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***C07D239/28 (2006.01)*** ***C07D241/14 (2006.01)***
***C07D249/10 (2006.01)*** ***C07D263/34 (2006.01)***
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***C07D487/08 (2006.01)*** ***C07D491/02 (2006.01)***
***A61K31/00 (2006.01)***

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(56)參考文獻：

WO 2010/123822A1

審查人員：陳世芹

申請專利範圍項數：45 項　　圖式數：1　　共 1589 頁

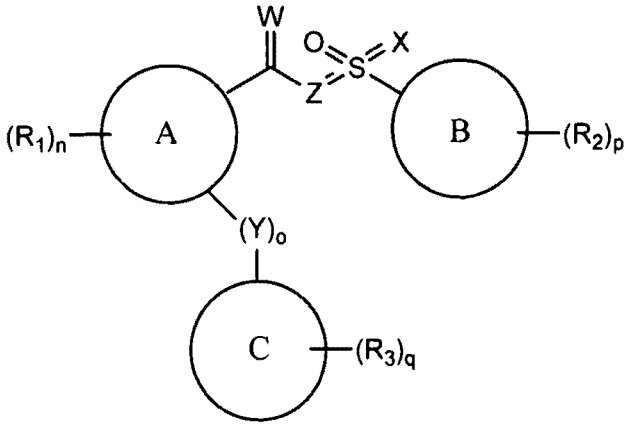
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(54)名稱

囊腫纖維化症跨膜傳導調節蛋白之調節劑

(57)摘要

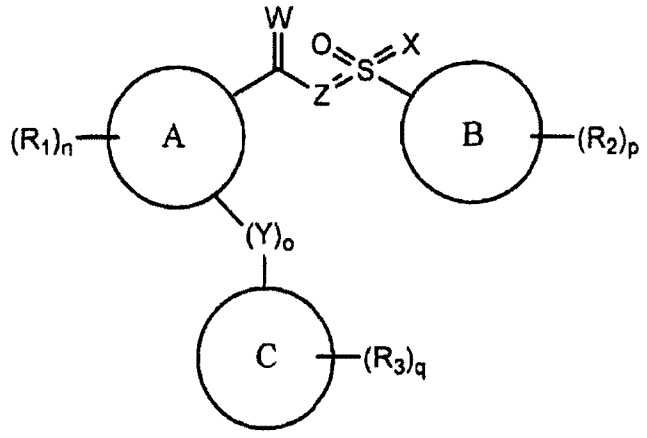
本發明之特徵在於一種式 I 化合物，




I，

或其醫藥學上可接受之鹽，其中 $R_1$、$R_2$、$R_3$、W、X、Y、Z、n、o、p 及 q 係如本文中定義，其用於治療 CFTR 介導之疾病，諸如囊腫纖維化症。本發明亦提供其醫藥組合物、治療方法及套組。

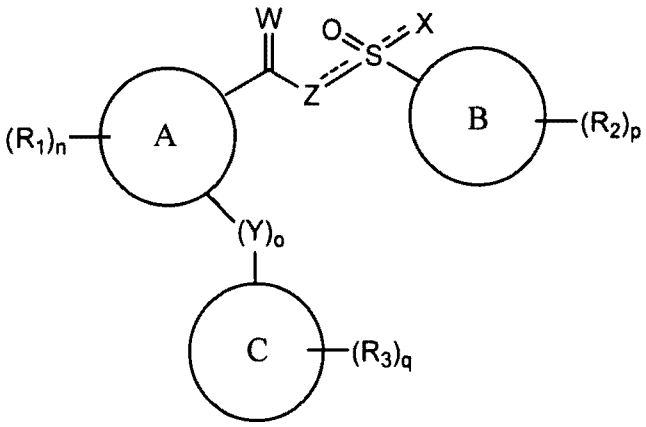
The present invention features a compound of formula I:




I,

or a pharmaceutically acceptable salt thereof, where $R_1$, $R_2$, $R_3$, W, X, Y, Z, n, o, p, and q are defined herein, for the treatment of CFTR mediated diseases, such as cystic fibrosis. The present invention also features pharmaceutical compositions, method of treating, and kits thereof.

特徵化學式：




I

公告本

I735416

# 發明摘要

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※ 申請日：104.10.06　　※IPC 分類：

C07C 311/38 (2006.01)
C07D 207/34 (2006.01)
C07D 209/02 (2006.01)
C07D 213/60 (2006.01)
C07D 215/16 (2006.01)
C07D 217/22 (2006.01)
C07D 223/16 (2006.01)
C07D 231/10 (2006.01)
C07D 233/66 (2006.01)
C07D 235/24 (2006.01)
C07D 453/06 (2006.01)
C07D 471/04 (2006.01)
C07D 487/08 (2006.01)
C07D 491/02 (2006.01)
A61K 31/00 (2006.01)
C07D 239/28 (2006.01)
C07D 241/14 (2006.01)
C07D 249/10 (2006.01)
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C07D 409/12 (2006.01)
C07D 413/14 (2006.01)
C07D 417/12 (2006.01)

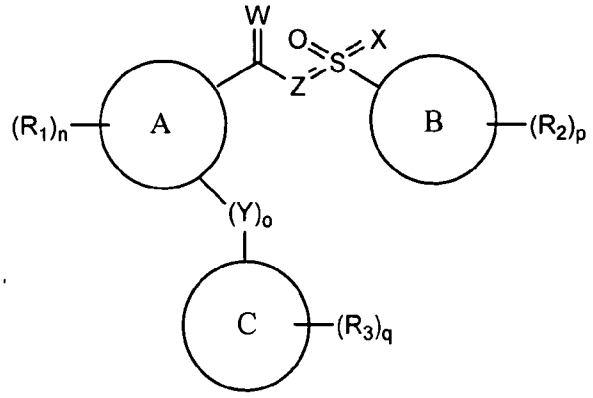
**【發明名稱】**

囊腫纖維化症跨膜傳導調節蛋白之調節劑

MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR

**【中文】**

本發明之特徵在於一種式I化合物，

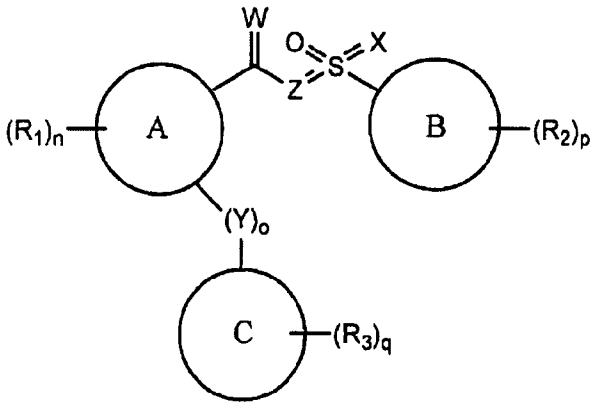



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或其醫藥學上可接受之鹽，其中$R_1$、$R_2$、$R_3$、W、X、Y、Z、n、o、p及q係如本文中定義，其用於治療CFTR介導之疾病，諸如囊腫纖維化症。本發明亦提供其醫藥組合物、治療方法及套組。

【英文】

The present invention features a compound of formula I:




I,

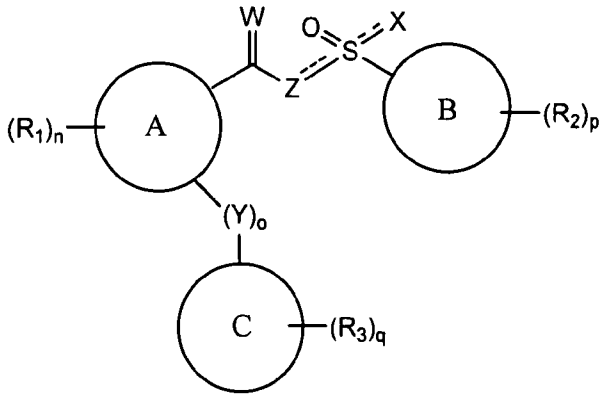
or a pharmaceutically acceptable salt thereof, where $R_1$, $R_2$, $R_3$, W, X, Y, Z, n, o, p, and q are defined herein, for the treatment of CFTR mediated diseases, such as cystic fibrosis. The present invention also features pharmaceutical compositions, method of treating, and kits thereof.

## 【代表圖】

【本案指定代表圖】：第（　　）圖。(無)

【本代表圖之符號簡單說明】：

【本案若有化學式時，請揭示最能顯示發明特徵的化學式】：




I

# 發明專利說明書

（本說明書格式、順序，請勿任意更動）

**【發明名稱】**

囊腫纖維化症跨膜傳導調節蛋白之調節劑

MODULATORS OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR

**相關申請案之交叉參考**

本申請案根據35 U.S.C.§ 119規定主張2014年10月6日申請之美國臨時專利申請案第62/060,182號、2015年2月11日申請之美國臨時專利申請案第62/114,767號及2015年4月27日申請之美國臨時專利申請案第62/153,120號的優先權益，所有申請案之整個內容以引用的方式併入本文中。

**【技術領域】**

本發明提供囊腫纖維化症跨膜傳導調節蛋白(CFTR)之調節劑、其醫藥組合物、治療方法及套組。

**【先前技術】**

囊腫纖維化症(CF)爲一種隱性基因疾病，其影響美國大約30,000名兒童及成人以及歐洲大約30,000名兒童及成人。儘管CF之治療有進展，但未治癒。

在患有CF之患者中，在呼吸上皮中內源性表現的CFTR之突變導致頂部陰離子分泌減少，引起離子及流體輸送不平衡。所引起的陰離子輸送減少引起肺中之黏液累積增加，伴隨微生物感染，最終導致CF患者死亡。除呼吸疾病之外，CF患者通常遭遇腸胃問題及胰臟功能不全，若不進行治療，則會引起死亡。另外，大部分患有囊腫纖維化症之男性不育且患有囊腫纖維化症之女性中生育力降低。與CF相

關基因之兩個複本的嚴重影響對比，具有CF相關基因之單個複本的個體顯示對霍亂及由腹瀉引起之脫水的抗性增加，此可能解釋該群體內CF基因之相對高頻率。

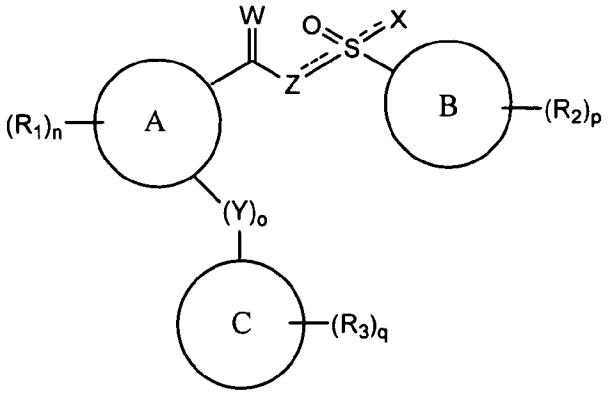
CF染色體之CFTR基因的序列分析已揭露引起突變之多種疾病(Cutting, G. R.等人(1990) Nature 346:366-369；Dean, M.等人(1990) Cell 61:863:870；以及Kerem, B-S.等人(1989) Science 245:1073-1080；Kerem, B-S等人(1990) Proc. Natl. Acad. Sci. USA 87:8447-8451)。迄今，已鑑別超過1000種引起CF基因突變之疾病(http://cftr2.org)。大部分流行突變爲CFTR胺基酸序列之位置508的苯丙胺酸缺失，且通常稱爲F508del。此突變發生在囊腫纖維化症大約70%病例中且與嚴重疾病相關。

F508del中殘基508之缺失阻止新生蛋白質正確摺疊。此使得突變蛋白質無法離開ER及輸送至質膜。因此，膜中存在之通道數遠低於表現野生型CFTR之細胞中觀測到之通道數。除削弱輸送外，突變亦引起有缺陷之通道閘控。總之，膜中通道數減少及有缺陷之閘控導致跨越上皮之陰離子輸送減少，引起有缺陷之離子及流體輸送(Quinton, P. M. (1990), FASEB J. 4: 2709-2727)。然而，研究已展示膜中減少數目之F508del爲功能性的，不過小於野生型CFTR (Dalemans等人(1991), Nature Lond. 354: 526-528；Denning等人，上述；Pasyk及Foskett (1995), J. Cell. Biochem. 270: 12347-50)。除F508del之外，引起CFTR突變，導致有缺陷之輸送、合成及/或通道閘控的其他疾病可經上調或下調以改變陰離子分泌且改善疾病進展及/或嚴重程度。

因此，需要CFTR介導之疾病的新穎治療。

**【發明內容】**

本發明提供式I化合物，




I，

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環A爲C6-C10芳基環；C3-C10環烷基環；或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C14雜芳基或雜環；

環B爲C3-C10環烷基環；C6-C10芳基環；或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C4-C10雜芳基或雜環；

環C爲C6-C10芳基環；其中1至4個環原子中任一個獨立地爲N、NR、O或S的C3-C14雜芳基或雜環；或C3-C10環烷基環；

W爲O、NR或S；

X爲O或NR；

Y獨立地爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

Z爲NR或CHR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜

芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元視情況且獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；OH；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

p爲0、1、2或3；且

q爲0、1、2、3、4或5；

┈┈爲單鍵或雙鍵；

其限制條件爲含有環B及環C之部分基團取代在環A上之相鄰位置上。

本發明亦提供可包括額外藥劑之其醫藥組合物，及治療CFTR介導之疾病(諸如囊腫纖維化症)之方法，該等方法包含向有需要之個體投與式I化合物。本發明亦提供包含式I化合物之套組。

【圖式簡單說明】

圖1藉由名稱、蛋白質名稱及傳統名稱揭示在本發明之一個態樣中患者可具有且可藉由本發明之化合物及組合物治療的CFTR突變之清單。

【實施方式】

定義

如本文所用，「CFTR」代表囊腫纖維化症跨膜傳導調節蛋白。

如本文所用，「突變」可指*CFTR*基因或CFTR蛋白質中之突變。「*CFTR*突變」係指*CFTR*基因中之突變，且「CFTR突變」係指CFTR蛋白質中之突變。基因缺陷或突變或基因中核苷酸之改變一般導致由該基因轉譯之CFTR蛋白質的突變。

如本文所用，「F508del突變」或「F508del」爲CFTR蛋白質內之特定突變。突變爲包含位置508之胺基酸苯丙胺酸之密碼子的三個核苷酸之缺失，產生缺乏此苯丙胺酸殘基之CFTR蛋白質。

如本文所用，術語「*CFTR*閘控突變」意謂產生其中主要缺陷爲與正常CFTR相比通道打開概率較低之CFTR蛋白質的*CFTR*突變(Van Goor, F., Hadida S.及Grootenhuis P.,「Pharmacological Rescue of Mutant CFTR function for the Treatment of Cystic Fibrosis」, Top. Med. Chem. 3: 91-120 (2008))。閘控突變包括(但不限於) G551D、G178R、S549N、S549R、G551S、G970R、G1244E、S1251N、S1255P及G1349D。

如本文所用，針對特定突變，例如F508del，「同種接合」之患者在各對偶基因上具有相同突變。

如本文所用，針對特定突變，例如F508del，「異種接合」之患者在一對偶基因上具有此突變，且在另一對偶基因上具有不同突變。

如本文所用，術語「調節劑」係指增加生物化合物，諸如蛋白

質之活性的化合物。舉例而言，CFTR調節劑爲增加CFTR活性之化合物。由CFTR調節劑引起的活性增加可經由如下所述之校正劑機制或增效劑機制。

如本文所用，術語「CFTR校正劑」係指增加細胞表面上功能CFTR蛋白質之量，增強離子輸送之化合物。

如本文所用，術語「CFTR增效劑」係指增加位於細胞表面之CFTR蛋白質之通道活性，增強離子輸送之化合物。

如本文所用，如在誘發CFTR活性中，術語「誘發」係指增加CFTR活性，無論藉由校正劑、增效劑還是其他機制。

如本文所用，術語「活性藥物成分」或「API」係指生物活性化合物。

術語「患者」、「個體(subject)」或「個體(individual)」可互換使用且係指人類或非人類動物。該術語包括哺乳動物，諸如人類。

術語「有效劑量」或「有效量」在本文中可互換使用且係指產生其投與所需作用(例如改善CF或CF症狀或減輕CF或CF症狀之嚴重程度)的量。準確量將視治療目的而定，且將藉由熟習此項技術者使用已知技術確定(參見例如Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding)。

如本文所用，術語「治療(treatment)」、「治療(treating)」及其類似術語一般意謂個體中CF或其症狀之改善或減輕CF或其症狀之嚴重程度。如本文所用，「治療」包括(但不限於)以下：個體生長增加、增加之重量增加、肺中黏液減少、改善胰臟及/或肝功能、減少胸部感染情況及/或減少咳嗽或呼吸短促情況。改善或減輕任一此等病狀之嚴重程度可容易根據此項技術中已知之標準方法及技術評估。

如本文所用，術語「與……組合」在提及兩種或兩種以上化合物或藥劑時意謂投與次序包括化合物或藥劑在彼此之前、彼此同時或

在彼此之後投與患者。

如本文所用，片語「視情況經取代」可與片語「經取代或未經取代」互換使用。

如本文所述，本發明之組合物內的化合物可視情況經一或多個取代基取代，諸如以上一般說明或如藉由本發明之特定類別、亞類及種類所例示(諸如表1中所列之化合物)。如本文在式I-Id-ii中所述，式I-Id-ii中之變數$R_1$-$R_4$涵蓋特定基團，諸如烷基、烯基、炔基、烷氧基、雜芳基、雜環基、環烷基及芳基等。除非另外指明，否則變數$R_1$-$R_4$之每一特定基團可視情況經一或多個選自以下各者之基團取代：鹵基、磷醯基、OH、環烷基、雜環烷基、芳基、雜芳基、氟烷基、烷基、烯基、炔基、硝基、CN、羥基及其中至多4個$CH_2$單元獨立地經O、S、$SO_2$、SO、CO、NH、*N*-烷基、*N*-烯基或*N*-炔基置換的(C1-C9伸烷基)-E，且E爲H、芳基、環烷基、雜環烷基、雜芳基、烷氧基、CN或$CF_3$，進一步其中芳基、環烷基、雜環烷基及雜芳基每一者視情況經一或多個選自鹵基、烷基、胺基、CN、烯基、炔基及烷氧基之基團取代。

如一般技術者將認識到，本發明所設想之取代基組合爲形成穩定或化學可行化合物之彼等組合。如本文所用，術語「穩定」係指當經受允許其產生、偵測及較佳其回收、純化及使用以達成本文所揭示之目的中之一或多者的條件時實質上不改變的化合物。在一些實施例中，穩定化合物或化學可行化合物爲當在不存在水分或其他化學反應性條件下保持於40℃或更低之溫度下時不實質上變化達至少一週的化合物。當兩個烷氧基結合於同一原子或相鄰原子時，兩個烷氧基可與其結合之原子一起形成環。

如本文所揭示，取代基或變數(諸如式I-Id-ii中之R及$R_1$-$R_4$)可選自一個以上特定基團。在變數之一個特定基團可包括同一變數之另一

特定基團或與其重疊的程度上，較窄特定基團由較寬特定基團限制條件而來。換言之，不可存在雙重包括。

一般而言，術語「經取代」無論之前是否有術語「視情況」，均係指既定結構中之氫基經規定取代基之基團置換。特定取代基在上文定義中及下文化合物及其實例之描述中描述。除非另有指示，否則視情況經取代之基團可在基團之各可取代位置處具有取代基，且當任何既定結構中之一個以上位置可經一個以上選自規定基團之取代基取代時，取代基在每一位置處可爲相同或不同。如一般技術者將認識到，本發明所設想之取代基組合爲形成穩定或化學可行化合物之彼等組合。

如本文所用，片語「至多」係指等於或小於片語之後之數字的零或任何整數數字。舉例而言，「至多3」意謂0、1、2及3中之任一者。

術語「約」及「大約」在與組合物或劑型之成分之劑量、量或重量百分比結合使用時意謂一般技術者認識到可提供等同於自指定劑量、量或重量百分比獲得之藥理學作用的藥理學作用的劑量、量或重量百分比。具體言之，術語「約」或「大約」意謂如由一般技術者所測定之特定值的可接受誤差，其部分視量測或測定該值之方式而定。在某些實施例中，術語「約」或「大約」意謂在1、2、3或4個標準差內。在某些實施例中，術語「約」或「大約」意謂在既定值或範圍之30%、25%、20%、15%、10%、9%、8%、7%、6%、5%、4%、3%、2%、1%、0.5%、0.1%或0.05%內。

如本文所用，術語「相鄰」係指環上兩個環原子彼此鍵結之位置。具有插入環原子之兩個環原子不視爲相鄰，即使當該插入原子因價數而不允許取代時。

如本文所用，術語「脂族」、「脂族基」意謂完全飽和或含有一

或多個不飽和單元之直鏈(亦即非分支鏈)或分支鏈烴鏈。除非另外規定，否則脂族基含有1-20個脂族碳原子。在一些實施例中，脂族基含有1-10個脂族碳原子。在其他實施例中，脂族基含有1至8個脂族碳原子。在其他實施例中，脂族基含有1至6個脂族碳原子，且在其他實施例中，脂族基含有1至4個脂族碳原子。適合脂族基包括(但不限於)直鏈或分支鏈、經取代或未經取代之烷基、烯基、炔基。

如本文所用，術語「螺」意謂兩個環僅僅共享一個共同原子之兩環系統。

術語「環脂基」或「環烷基」意謂具有單個與分子其餘部分之附接點，且完全飽和或含有一或多個不飽和單元之單環、雙環(稠合或螺)、三環(稠合或螺)或螺槳烷烴，但該單環、雙環或三環烴中之無一個別環爲芳族。單一附接點可在飽和或不飽和碳上。在一些實施例中，「環脂基」或「環烷基」係指完全飽和或含有一或多個不飽和單元之單環$C_3$-$C_8$烴或雙環$C_8$-$C_{12}$烴，但單環$C_3$-$C_8$烴或稠合雙環$C_8$-$C_{12}$烴中無一個別環爲芳族且具有單個與分子其餘部分之附接點，其中該雙環環系統中之任一個別環具有3-7個成員。

如本文所用，「烷基」係指含有1-20 (例如1-6或1至12)個碳原子之飽和烴基。烷基可爲直鏈或分支鏈。烷基之實例包括(但不限於)甲基、乙基、丙基、異丙基、丁基、異丁基、第二丁基、第三丁基、正戊基、正庚基或2-乙基己基。

如本文所用，「烯基」係指含有2-20 (例如2-12、2-6或2-4)個碳原子及至少一個雙鍵之烴基。如烷基，烯基可爲直鏈或分支鏈。附接點可在飽和碳或不飽和碳上。烯基之實例包括(但不限於)烯丙基、異戊二烯基、2-丁烯基及2-己烯基。

如本文所用，「炔基」係指含有2-20 (例如2-12、2-6或2-4)個碳原子且具有至少一個參鍵之烴基。炔基可爲直鏈或分支鏈。附接點可在

飽和碳或不飽和碳上。炔基之實例包括(但不限於)炔丙基及丁炔基。

如本文所用，「烷氧基」係指-O-烷基、O-烯基或O-炔基，其中烷基、烯基及炔基如上所定義。

如本文所用，「氟烷基」或「氟烷氧基」係指其中一或多個氫經氟取代之烷基或烷氧基。

如本文所用，「胺基」係指$NH_2$，其視情況經一或兩個獨立地選自烷基、環烷基及雜環烷基之基團取代。

如本文所用，術語「拉電子基團」意謂相對於氫具負電性之原子或基團。參見例如「Advanced Organic Chemistry: Reactions, Mechanisms, and Structure」, Jerry March, 第4版, John Wiley & Sons (1992), 例如第14-16、18-19頁等。示例性此類取代基包括鹵基(諸如Cl、Br或F)、CN、COOH、$CF_3$等。

除非另外說明，否則如本文所用，術語「雜環」、「雜環基」、「雜環脂族」、「雜環烷基」或「雜環」意謂單環、雙環(稠合或螺)、三環(稠合或螺)或螺槳烷環系統，其中一或多個環成員中之一或多個環原子爲獨立選擇之雜原子且系統中之個別環爲芳族。雜環可爲飽和或可含有一或多個不飽和鍵。在一些實施例中，「雜環」、「雜環基」、「雜環脂族」、「雜環烷基」或「雜環」基團具有三個至十四個環成員，其中一或多個環成員爲獨立地選自氧、硫、氮或磷之雜原子且環系統中之各環含有3至7個環成員。附接點可在碳或雜原子上。

術語「雜原子」意謂氧、硫、氮、磷或矽(包括氮、硫、磷或矽之任何氧化形式；任何鹼性氮之四級銨化形式；或雜環之可經取代氮，例如N (如在3,4-二氫-2*H*-吡咯基中)、NH (如在吡咯啶基中)或$NR^+$ (如在*N*經取代之吡咯啶基中))。

如本文所用，術語「不飽和」意謂部分具有一或多個不飽和單元，但非芳族。

如本文所用，術語「烷氧基」或「硫烷基」係指如先前所定義之烷基經由氧(「烷氧基」)或硫(「硫烷基」)原子附接於主碳鏈。

單獨或作爲如「芳烷基」、「芳烷氧基」或「芳氧基烷基」之較大部分之一部分使用的術語「芳基」係指具有總共五至十四個環碳原子之單環、雙環(稠合)及三環(稠合或螺)烴環系統，其中系統中之至少一個環爲芳族，且其中系統中之各環含有3至7個環碳原子。術語「芳基」可與術語「芳基環」互換使用。

單獨或作爲如「雜芳烷基」或「雜芳烷氧基」之較大部分之一部分使用的術語「雜芳基」係指具有總共五至十四個環成員之單環、雙環(稠合)及三環(稠合或螺)系統，其中系統中之至少一個環爲芳族，系統中之至少一個環含有一或多個雜原子，且其中系統中之各環含有3至7個環成員。術語「雜芳基」可與術語「雜芳基環」或術語「雜芳族基」互換使用。

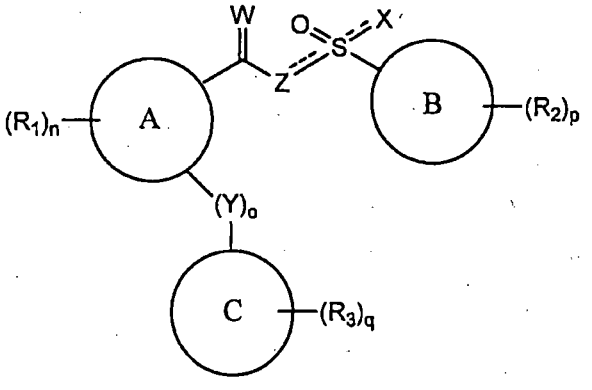
術語「伸烷基」係指可完全飽和或具有一或多個不飽和單元且具有兩個與分子其餘部分之附接點的直鏈或分支鏈烴鏈。

如本文所用，術語「前藥」表示在活體內轉化成根據本文中列出之任一式之化合物的化合物。此類轉化可例如藉由在血液中水解或在血液或組織中前藥形式經酶轉化成母體形式來實現。本發明之化合物之前藥可例如爲醯胺。在本發明中可用作前藥之醯胺爲苯基醯胺、脂族($C_1$-$C_{24}$)醯胺、醯氧基甲基醯胺、脲、胺基甲酸酯及胺基酸醯胺。舉例而言，含有NH基團之本發明之化合物可在其前藥形式中之此位置經醯化。其他前藥形式包括酯，諸如苯基酯、脂族($C_1$-$C_{24}$)酯、醯氧基甲基酯、碳酸酯、胺基甲酸酯及胺基酸酯。前藥之透徹論述提供於T. Higuchi及V. Stella, *Pro-drugs as Novel Delivery Systems*, the A.C.S. Symposium Series第14卷, Edward B. Roche編輯, *Bioreversible Carriers in Drug Design*, American Pharmaceutical

Association and Pergamon Press, 1987，及Judkins等人，*Synthetic Communications* 26(23):4351-4367, 1996，各文獻以全文引用的方式併入本文中。在一些實施例中，本發明提供本文中列出之任一式或化合物的前藥。

如本文所用，術語「電子等排體」或「生物電子等排體」係指由原子或原子基團交換產生之化合物，從而產生生物特性與母體化合物類似的新化合物。生物電子等排置換可基於物理化學或拓撲學。舉例而言，羧酸之電子等排置換爲$CONHSO_2$(烷基或芳基)，諸如$CONHSO_2Me$。電子等排性之進一步論述提供於R. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, 第二版, Elsevier Academic Press, 2004，其以全文引用的方式併入本文中。在一些實施例中，本發明提供本文中列出之任一式或化合物的電子等排體。

在式及圖式中，橫切環且鍵結於諸如下式中$R_2$之R基團的線




意謂在價數允許下R基團可鍵結於包括任何稠環之環之任何碳，或適用時，諸如N之雜原子。

在如例如$R_1$至$R_3$之術語定義內，當$CH_2$單元或可互換地亞甲基單元可經O、CO、S、SO、$SO_2$或NR置換時，其意謂包括任何$CH_2$單元，包括末端甲基或亞甲基內之$CH_2$。舉例而言，$-CH_2CH_2CH_2SH$在其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的C1-C9伸烷基-$R_4$之定義內，因爲末端甲基之$CH_2$單元已經S置換。類似適

用於諸如-$CH_2CH_2OH$、-$CH_2CH_2CN$或-$CH_2CH_2NH_2$之定義。

除非另有說明，否則本文中描繪之結構亦意謂包括該結構之所有異構(例如對映異構、非對映異構及幾何(或構形))形式；舉例而言，各不對稱中心之R及S組態、(Z)及(E)雙鍵異構體以及(Z)及(E)構形異構體。因此，本發明化合物之單一立體化學異構體以及對映異構、非對映異構及幾何異構(或構形)混合物在本發明之範疇內。在已分離外消旋混合物之對映異構體下，雖然尚未測定絕對化學，但化合物結構用波浪線描繪。

除非另有說明，否則本發明化合物之所有互變異構形式均在本發明之範疇內。由此，式I至Id-ii化合物之互變異構體包括在本發明之範疇內。

在本申請案中之定義不同於以引用的方式併入之申請案中之任何定義的程度上，本申請案中之定義代替。

CFTR爲在包括吸收及分泌上皮細胞之多種細胞類型中表現的cAMP/ATP介導之陰離子通道，其中其調控跨越膜之陰離子通量，以及其他離子通道及蛋白質之活性。上皮細胞中，CFTR之功能正常對維持全身(包括呼吸道及消化組織)電解質輸送至關重要。CFTR由編碼由串聯重複跨膜結構域組成之蛋白質的約1480個胺基酸構成，該等結構域各含有六個跨膜螺旋及核苷酸結合域。兩個跨膜結構域由具有調節通道活性及細胞輸送的多個磷酸化位點之大型極性調節(R)-結構域連接。

在患有囊腫纖維化症之患者中，內源性表現的CFTR之突變導致頂部陰離子分泌減少，引起離子及流體輸送不平衡。所引起的陰離子輸送減少引起肺中之黏液累積增加，伴隨微生物感染，最終導致CF患者死亡。除呼吸疾病之外，CF患者通常遭遇腸胃問題及胰臟功能不全，若不進行治療，則會引起死亡。另外，大部分患有囊腫纖維化

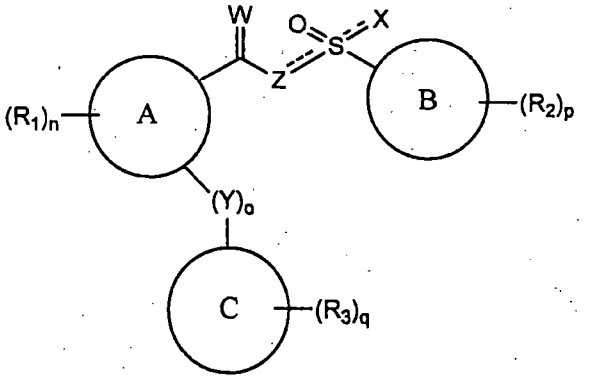
症之男性不育且患有囊腫纖維化症之女性中生育力降低。與CF相關基因之兩個複本的嚴重影響對比，具有CF相關基因之單個複本的個體顯示對霍亂及由腹瀉引起之脫水的抗性增加，此可能解釋該群體內CF基因之相對高頻率。

CF染色體之*CFTR*基因的序列分析已揭露引起突變之多種疾病(Cutting, G. R.等人(1990) Nature 346:366-369；Dean, M.等人(1990) Cell 61:863:870；及Kerem, B-S.等人(1989) Science 245:1073-1080；Kerem, B-S等人(1990) Proc. Natl. Acad. Sci. USA 87:8447-8451)。迄今，已如藉由科學及醫學文獻報導鑑別超過1000種引起CF基因突變之疾病。大部分流行突變爲CFTR胺基酸序列之位置508的苯丙胺酸缺失，且通常稱爲F508del。此突變發生在囊腫纖維化症大約70%病例中且與嚴重疾病相關。所鑑別突變之更完整列表可見於www.cftr2.org。

此等要素一起工作，經由其在細胞內之選擇性表現及定位實現跨越上皮細胞之定向輸送。氯離子吸收藉由存在於頂端膜上的ENaC及CFTR及在細胞底外側表面上表現之$Na^+$-$K^+$ATP酶泵及Cl-通道的協調活性發生。來自內腔側之氯離子的二級主動輸送導致胞內氯離子累積，其接著可經由$Cl^-$通道被動離開細胞，引起向量輸送。$Na^+/2Cl^-/K^+$共輸送體、$Na^+$-$K^+$-ATP酶泵及底外側膜$K^+$通道配置在底外側表面上及CFTR配置在內腔側上經由內腔側上之CFTR協調氯離子之分泌。因爲水決不可能自己主動輸送，所以其跨越上皮之流動視鈉及氯離子總體流動產生的微小經上皮滲透梯度而定。

**式I化合物**

在一些實施例中，本發明提供式I化合物：




I，

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環A爲C6-C10芳基環；C3-C10環烷基環；或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C14雜芳基或雜環；

環B爲C3-C10環烷基環；C6-C10芳基環；或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C4-C10雜芳基或雜環；

環C爲C6-C10芳基環；其中1至4個環原子中任一個獨立地爲N、NR、O或S的C3-C14雜芳基或雜環；或C3-C10環烷基環；

W爲O、NR或S；

X爲O或NR；

Y獨立地爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

Z爲NR或CHR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜

芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；OH；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基，其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

p爲0、1、2或3；且

q爲0、1、2、3、4或5；

┈┈爲單鍵或雙鍵；

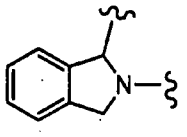
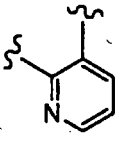
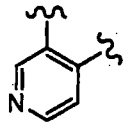
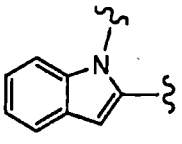
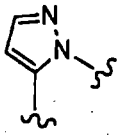
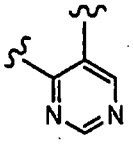
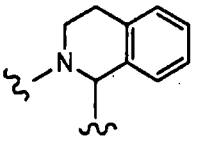
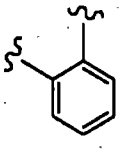
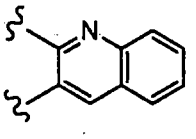
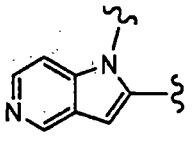
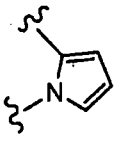
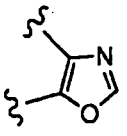
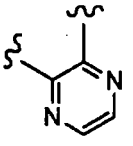
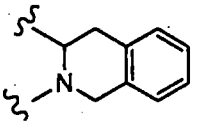
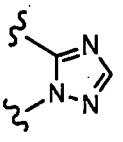
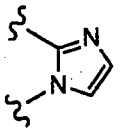
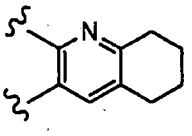
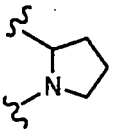
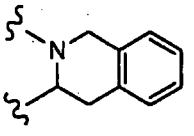
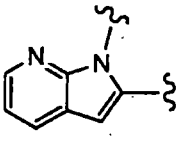
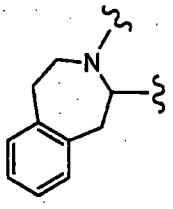
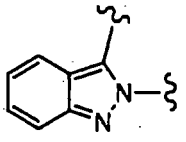
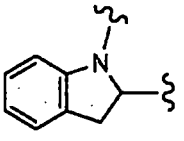
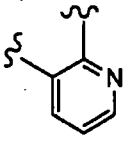
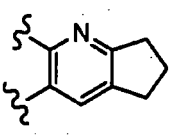
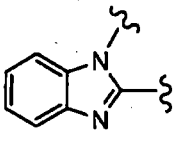
其限制條件爲含有環B及環C之部分基團取代在環A上之相鄰位置上。

在另一個實施例中，本發明之化合物具有式I及伴隨定義，其限制條件爲：i)當環A爲吲哚時，n不爲零且環B及C爲未經$CF_3$或鹵基取代之芳基；ii)當環A爲吡唑時，n不爲零；iii)當環A爲吡啶基時，環B

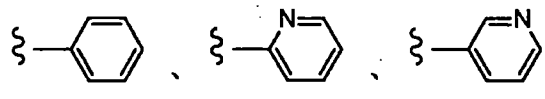
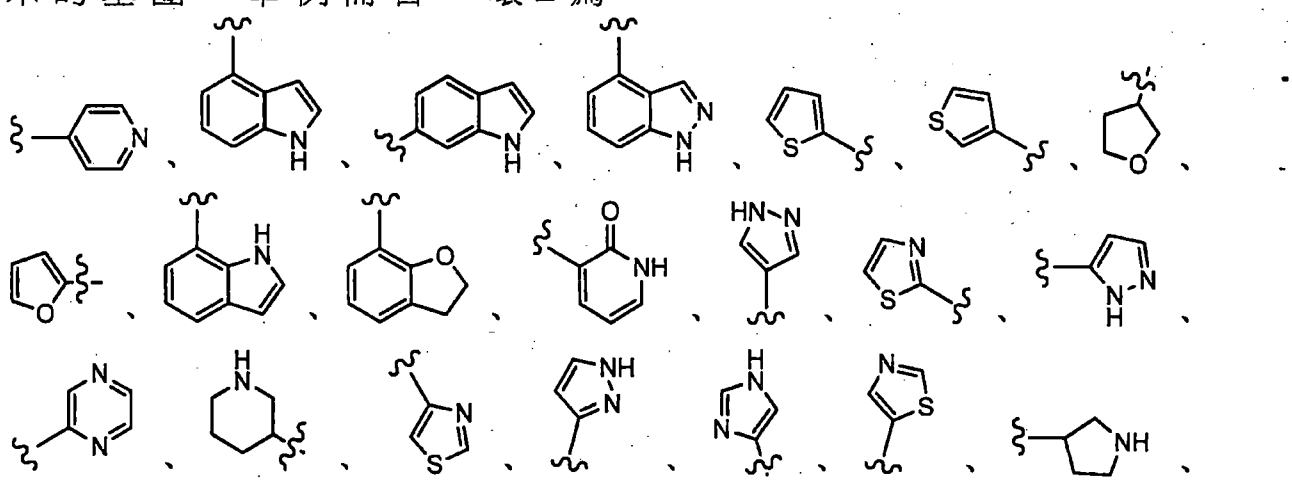
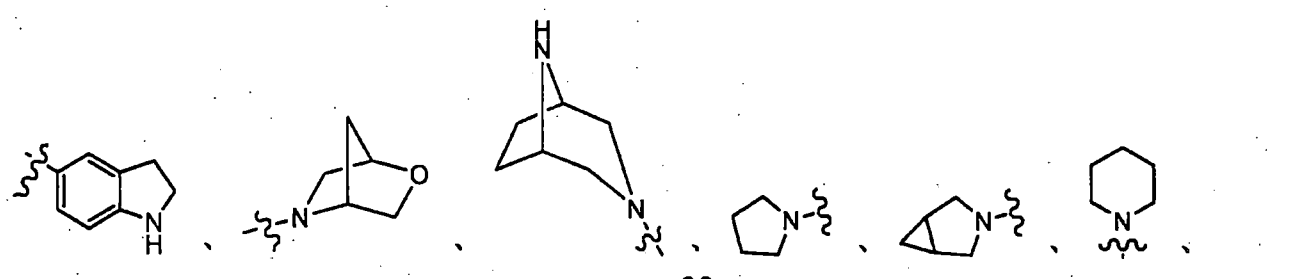
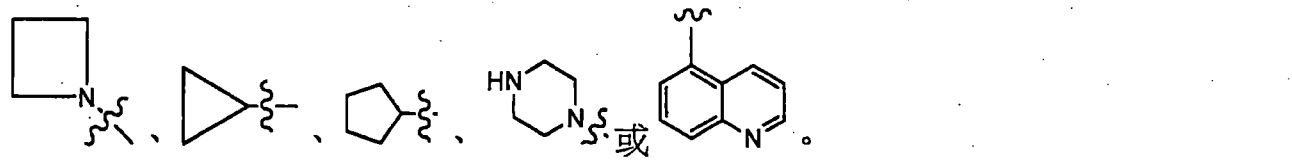
及環C部分在吡啶環之2及3位經取代，可互換地；以及iv)當環A爲咪唑時，環B部分在咪唑環之2位經取代。

在一些實施例中，本發明之化合物呈醫藥學上可接受之前藥形式。

在一些實施例中，環A爲C6-C10芳環，諸如苯基、茚滿、1,2,3,4-四氫化萘或萘。在一些實施例中，環A爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C11雜芳基或雜環，諸如吡啶基、吲哚、吲哚啉、異吲哚啉、吡唑、嘧啶、1,2,3,4-四氫喹啉、喹啉、5,6,7,8-四氫喹啉、1,2,3,4-四氫異喹啉、吡咯啶、氮雜吲哚、吡咯、噁唑、吡嗪、三唑、吲唑、2,3,4,5-四氫-1H-苯并[d]氮呯、1H-苯并[d]咪唑或咪唑環。

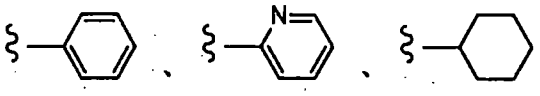
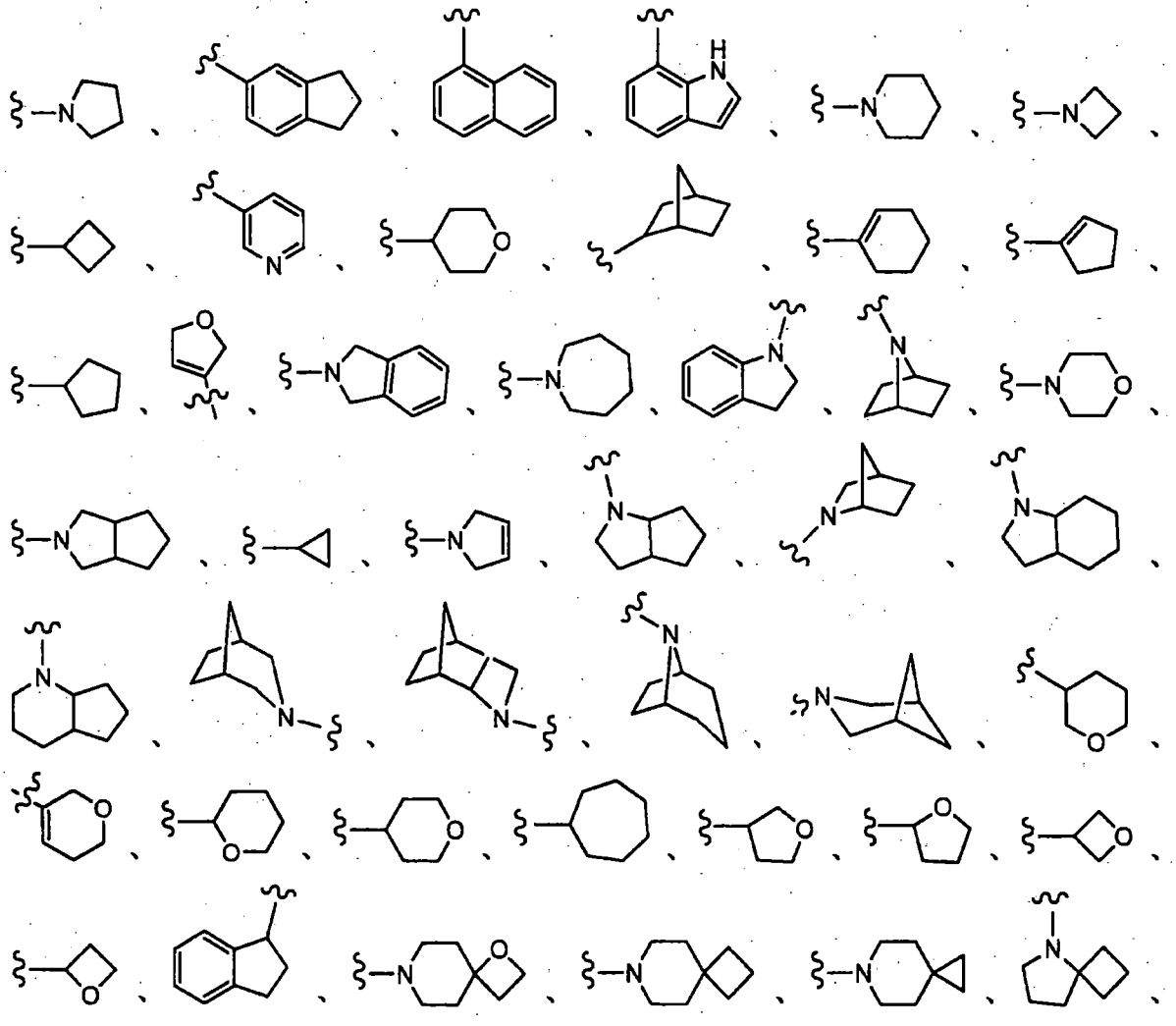
在一些實施例中，環A爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環A爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

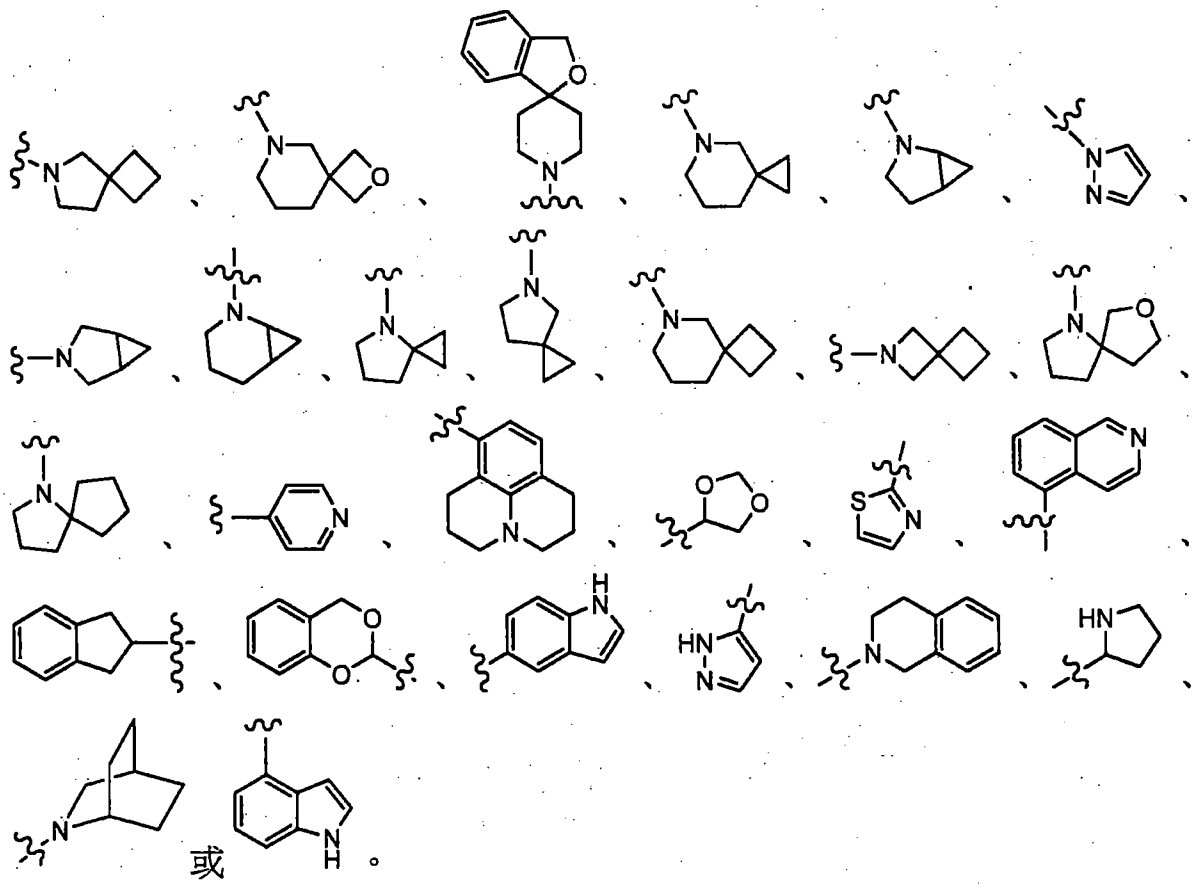
在一些實施例中，環B爲環烷基環，諸如環丙烷、環丁烷、環戊烷或環己烷。在一些實施例中，環B爲C6-C10芳基環，諸如苯基。在一些實施例中，環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的雜芳基或雜環，諸如吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、吲哚啉、噻吩、二氫苯并呋喃、四氫呋喃、呋喃、吡嗪、吲唑、噻唑、吡啶-4(1H)-酮、吡咯啶酮、3-氮雜雙環[3.1.0]己烷、(1R,4R)-2-氧雜-5-氮雜雙環[2.2.1]庚烷、吡咯啶、氮雜環丁烷、哌啶、哌嗪或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、  、、、  、、  或。

在一些實施例中，環C爲C6-C10芳基環，諸如苯基、茚滿或萘。在一些實施例中，環C爲C3-C10環烷基環，諸如環丙烷、環丁烷、環戊烷、環戊烯、環己烷、環己烯、環庚烷或(1s,4s)-雙環[2.2.1]庚烷。

在一些實施例中，環C爲其中1至4個環原子中任一個獨立地爲N、NR、O或S的C3-C10雜芳基或雜環，諸如吲哚、異吲哚啉、吲哚啉、吡啶基、吡咯啶、2,5-二氫-1H-吡咯、嗎啉、四氫-2H-哌喃、四氫呋喃、氧雜環丁烷、哌啶、哌嗪、氧雜環庚烷、氮雜環丁烷、八氫環戊并[c]吡咯、八氫環戊并[b]吡咯、八氫-1H-吲哚、八氫-1H-環戊并[b]吡啶、(1s,4s)-7-氮雜雙環[2.2.1]庚烷、2-氮雜雙環[4.1.0]庚烷、(1S,4R)-2-氮雜雙環[2.2.1]庚烷、(1R,5S)-8-氮雜雙環[3.2.1]辛烷、3,6-二氫-2H-哌喃或(1R,5S)-3-氮雜雙環[3.2.1]辛烷。

在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  

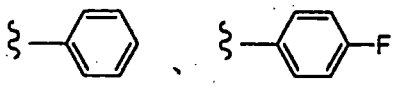
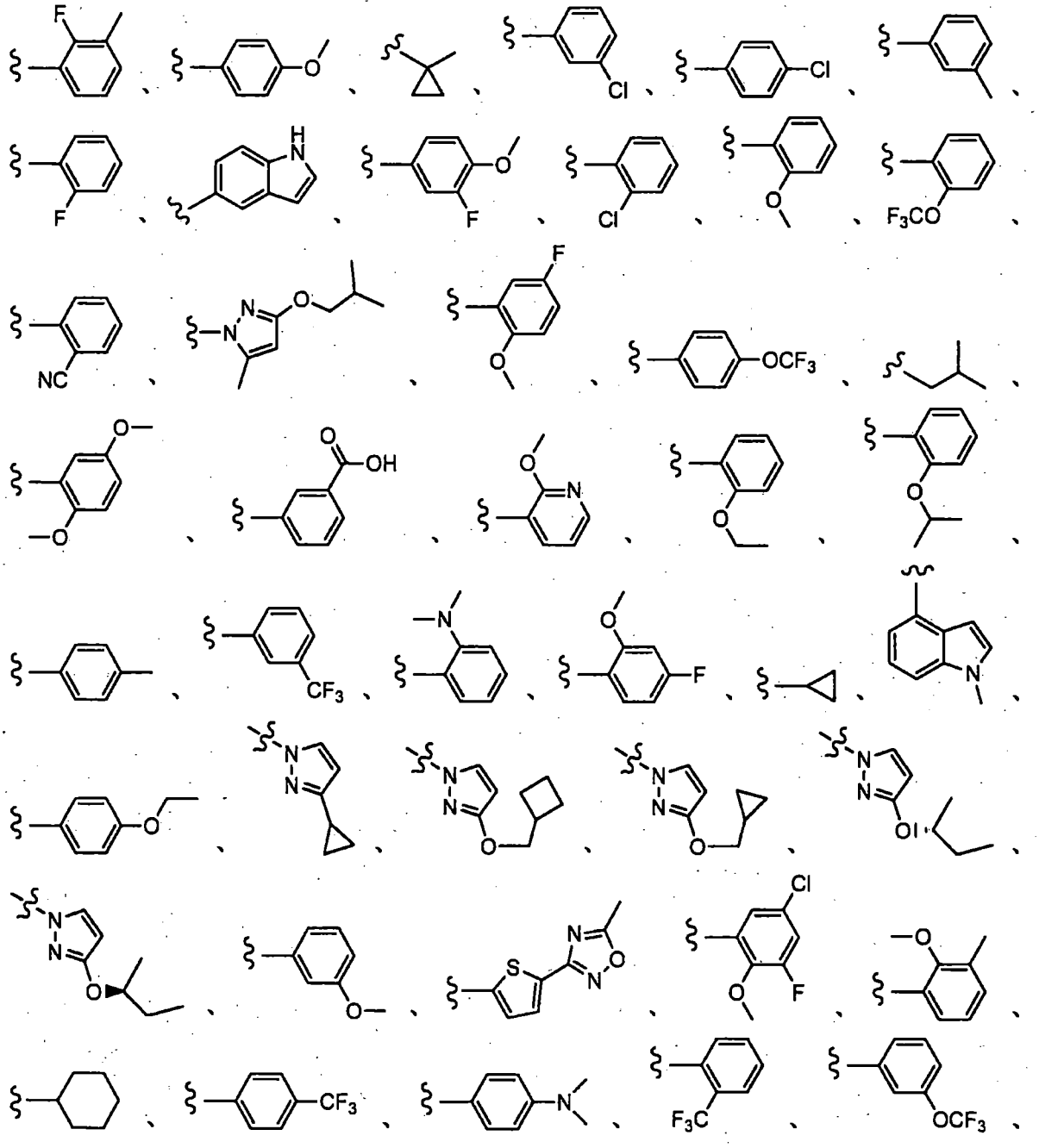


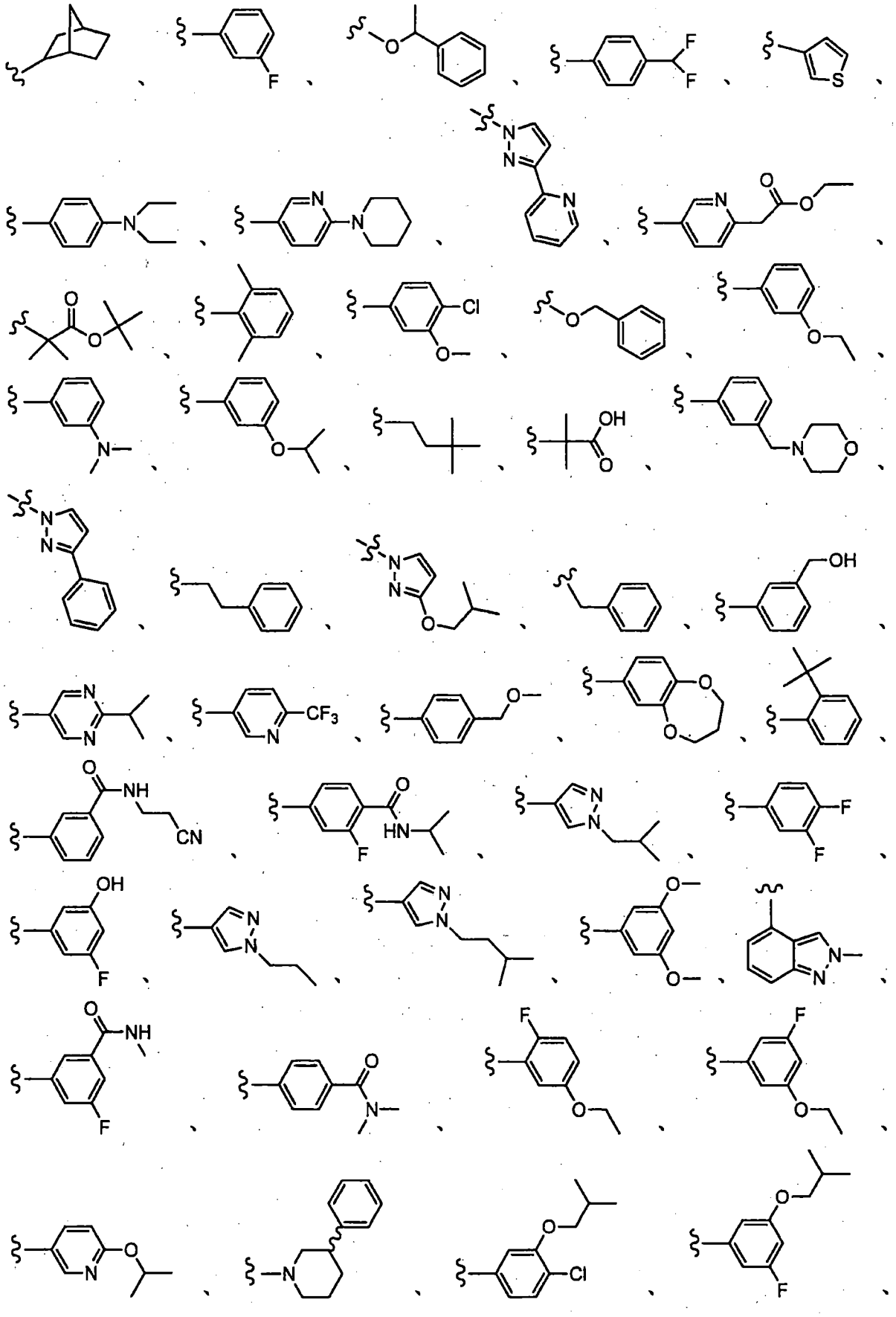
在一些實施例中，X爲O。在一些實施例中，X爲NR。在一些實施例中，X爲NH。

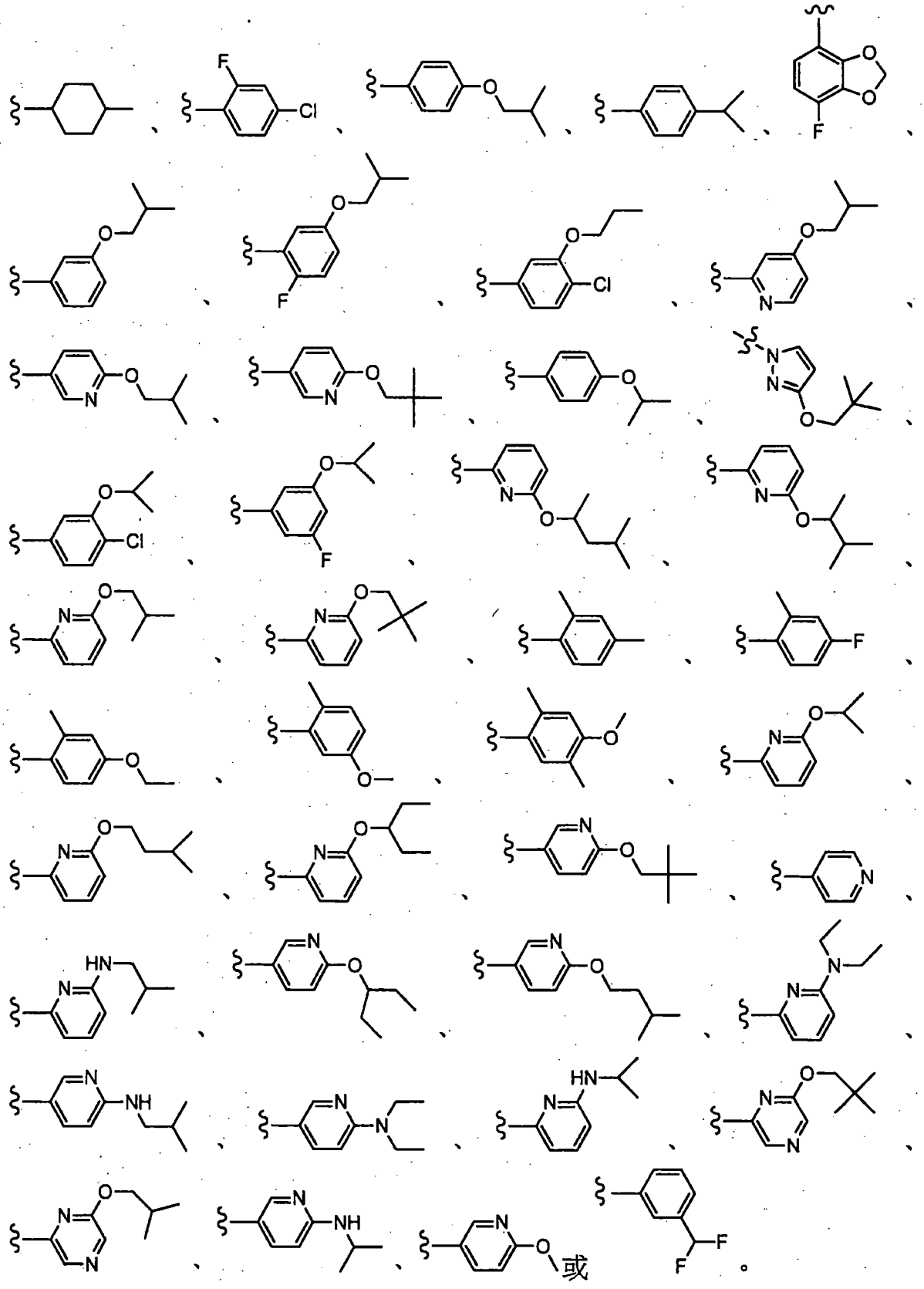
在一些實施例中，Y爲O。在一些實施例中，Y爲CRR，諸如$CH_2$、CH(C1-C6烷基)、$CH(CH_3)$或$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。在一些實施例中，$(Y)_o$爲一鍵、O、NH、$(CH_2)_m$、$O-(CH_2)_m$ (m=1-4)、$CH(CH_3)$、$O-CH(CH_3)$、$O-CH(CH_2CH_3)$、$O-CH(CH_3)CH_2$、$O-C(CH_3)_2CH_2$、$O-CH_2CH_2CH(CH_3)$、$N(CH_3)$、$NH-CH_2$、$N(CH_3)-CH_2$、$NCH(CH_3)_2-CH_2$、$N(CH_2CH_2CH_3)-CH_2$、$NH-CH(CH_3)$、$N(CH_3)-CH(CH_3)$或$N(CH_2CCH)-CH_2CH_2$。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、氮雜環丁烷、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、

SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

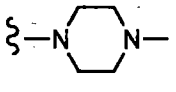
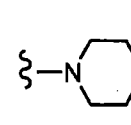
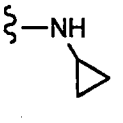
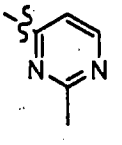
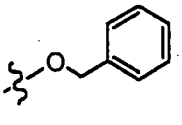
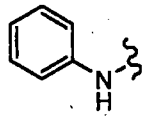
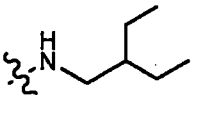
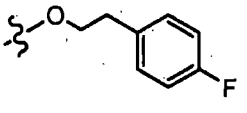
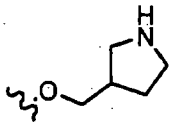
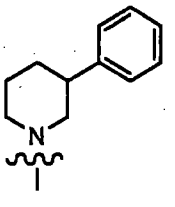
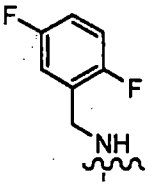
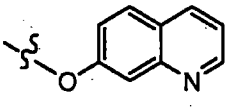
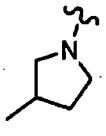
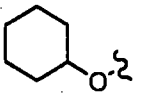
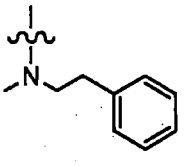
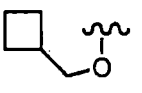
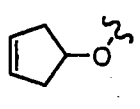
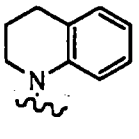
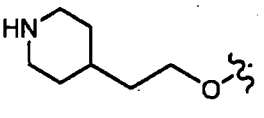
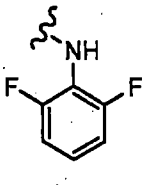
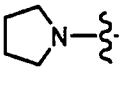
在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、、  、 

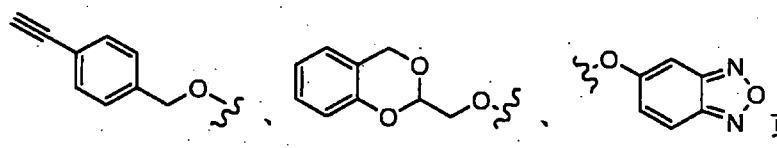




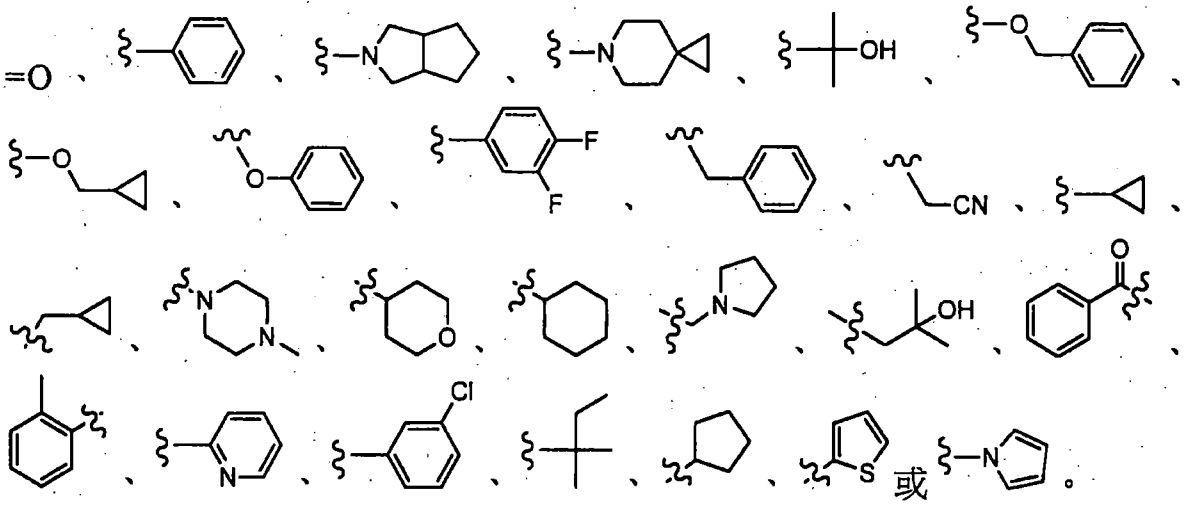
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任

一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元視情況且獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、


或$CO_2H$。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、

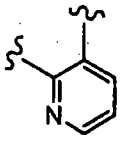
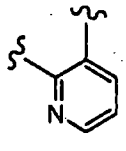
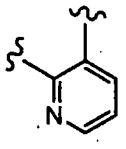

或

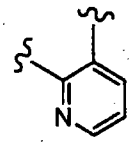
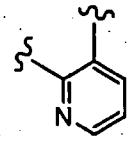
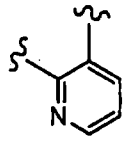

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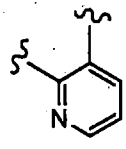
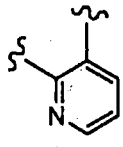
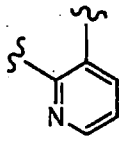
在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

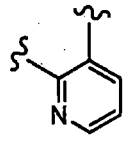
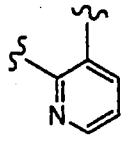
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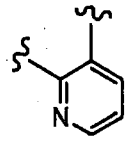
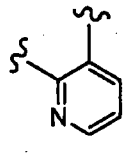
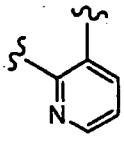
在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

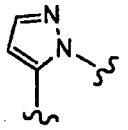
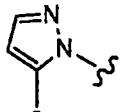
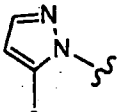
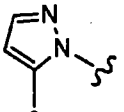
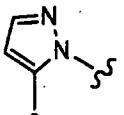
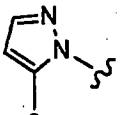
在一些實施例中，環A爲  ，且n爲1。在一些實施例中，環A爲  ，n爲1，且$R_1$爲tBu。在一些實施例中，環A爲  ，n

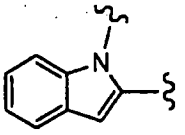
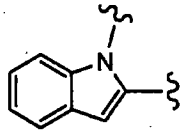
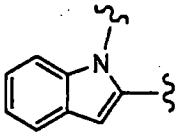
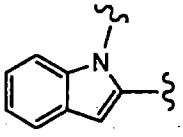
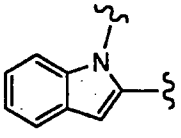
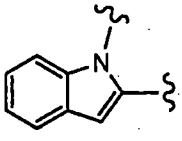
為1，且$R_1$為苯基。在一些實施例中，環A為  ，n為1，$R_1$為苯基，且Y為O。在一些實施例中，環A為  ，n為1，$R_1$為tBu，且Y為O。在一些實施例中，環A為  ，環B為吡啶基，且環C為苯基。在一些實施例中，$R_1$為苯基，且$R_2$為胺基，且$R_3$為$CH_3$。

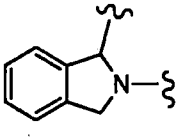
在一些實施例中，環A為  ，n為1，且$R_1$為吡啶基。在一些實施例中，環A為  ，n為1，$R_1$為吡啶基，且o為0。在一些實施例中，環A為  ，環B為吡啶基，且環C為吡咯啶。

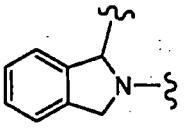
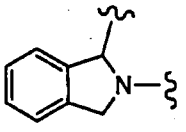
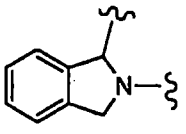
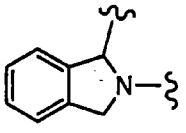
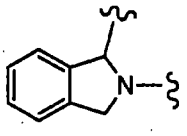
在一些實施例中，環A為  ，n為1，且$R_1$為吡唑。在一些實施例中，環A為  ，n為1，$R_1$為吡唑，且o為0。

在一些實施例中，環A為  ，n為1，且$R_1$為環烷基。在一些實施例中，環A為  ，n為1，$R_1$為環烷基，且Y為O。在一些實施例中，環A為  ，環B為吡啶基，且環C為環烷基。在一些實施例中，$R_1$為環烷基，且$R_2$為烷氧基，且$R_3$為$CH_3$。

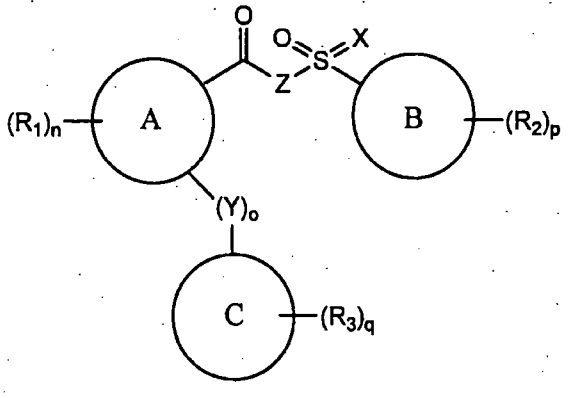
在一些實施例中，環A爲  ，且n爲1。在一些實施例中，環A爲  ，n爲1，且$R_1$爲苯基。在一些實施例中，環A爲  ，n爲1，且$R_1$爲tBu。在一些實施例中，環A爲  ，n爲1，$R_1$爲苯基，且Y爲O。在一些實施例中，環A爲  ，n爲1，$R_1$爲tBu，且Y爲O。在一個實施例中，環A爲  ，環B爲吡啶基，且環C爲苯基。

在一些實施例中，環A爲  ，且n爲1。在一些實施例中，環A爲  ，n爲1，且$R_1$爲苯基。在一些實施例中，環A爲  ，n爲1，且$R_1$爲tBu。在一些實施例中，環A爲  ，n爲1，$R_1$爲苯基，且Y爲O。在一些實施例中，環A爲  ，n爲1，$R_1$爲tBu，且Y爲O。在一些實施例中，環A爲  ，環B爲吡啶基，且環C爲苯基。

在一些實施例中，環A爲  ，且n爲1。在一些實施例

中，環A爲  ，n爲1，且$R_1$爲苯基。在一些實施例中，環A爲  ，n爲1，且$R_1$爲tBu。在一些實施例中，環A爲  ，n爲1，$R_1$爲苯基，且Y爲O。在一些實施例中，環A爲  ，n爲1，$R_1$爲tBu，且Y爲O。在一個實施例中，環A爲  ，環B爲吡啶基，且環C爲苯基。

在一些實施例中，本發明提供式I-i化合物：




I-i，

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環A爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C14雜芳基或雜環；

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

X爲O或NR；

Y為CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

Z為NR或CHR；

$R_1$為鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

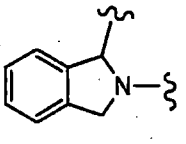
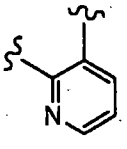
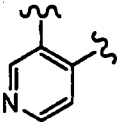
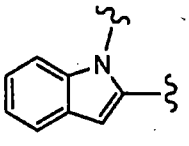
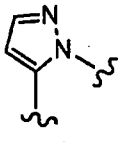
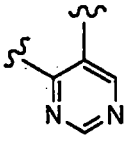
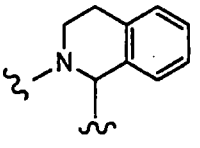
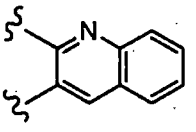
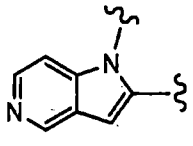
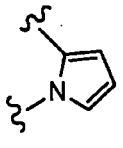
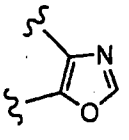
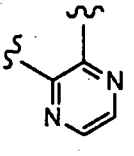
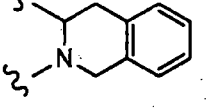
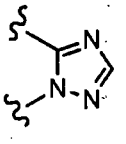
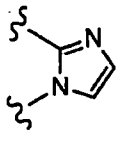
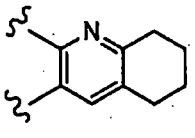
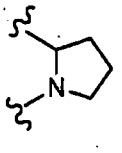
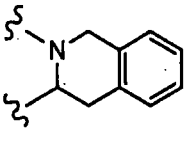
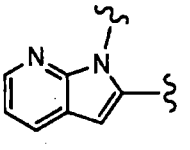
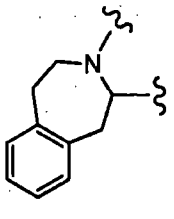
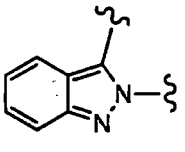
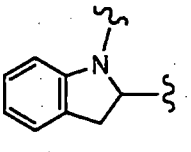
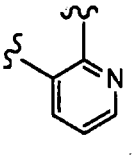
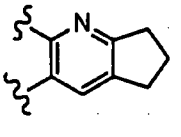
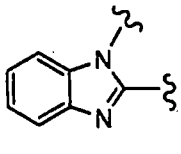
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q爲0、1、2、3、4或5；

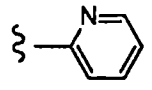
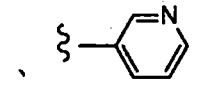
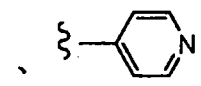
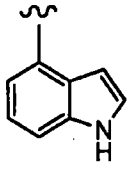
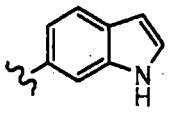
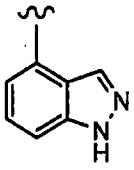
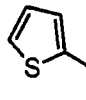
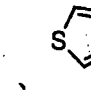
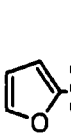
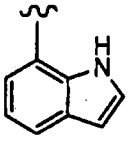
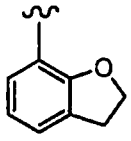
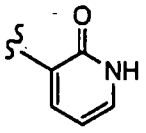
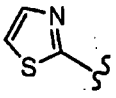
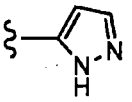
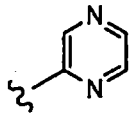
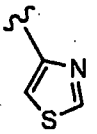
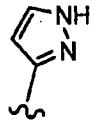
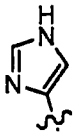
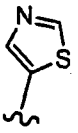
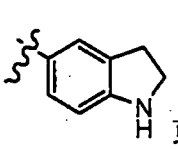
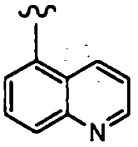
其限制條件爲含有環B及環C之部分基團取代在環A上之相鄰位置上。

在一些實施例中，式I-i化合物呈醫藥學上可接受之前藥形式存在。

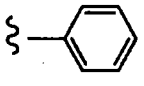
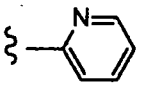
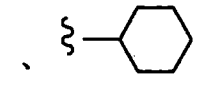
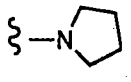
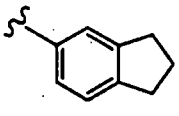
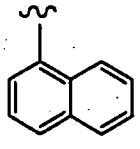
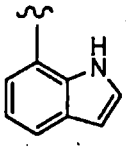
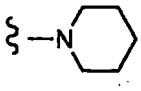
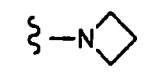
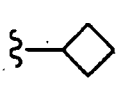
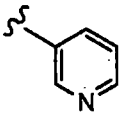
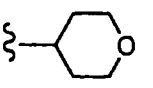
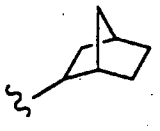
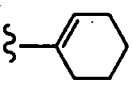
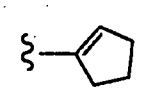
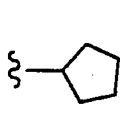
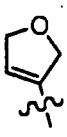
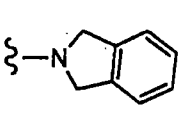
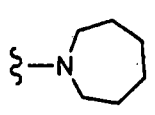
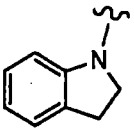
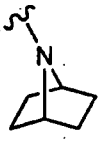
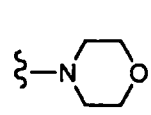
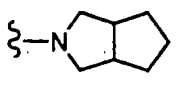
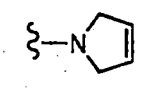
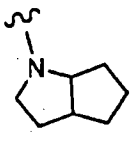
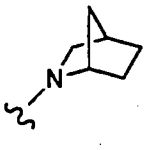
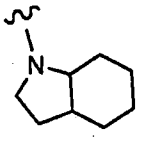
在一些實施例中，環A爲吡啶基、吲哚、吲哚啉、異吲哚啉、吡唑、嘧啶、喹啉、5,6,7,8-四氫喹啉、1,2,3,4-四氫異喹啉、吡咯啶、氮雜吲哚、吡咯、噁唑、吡嗪、三唑、吲唑或咪唑環。

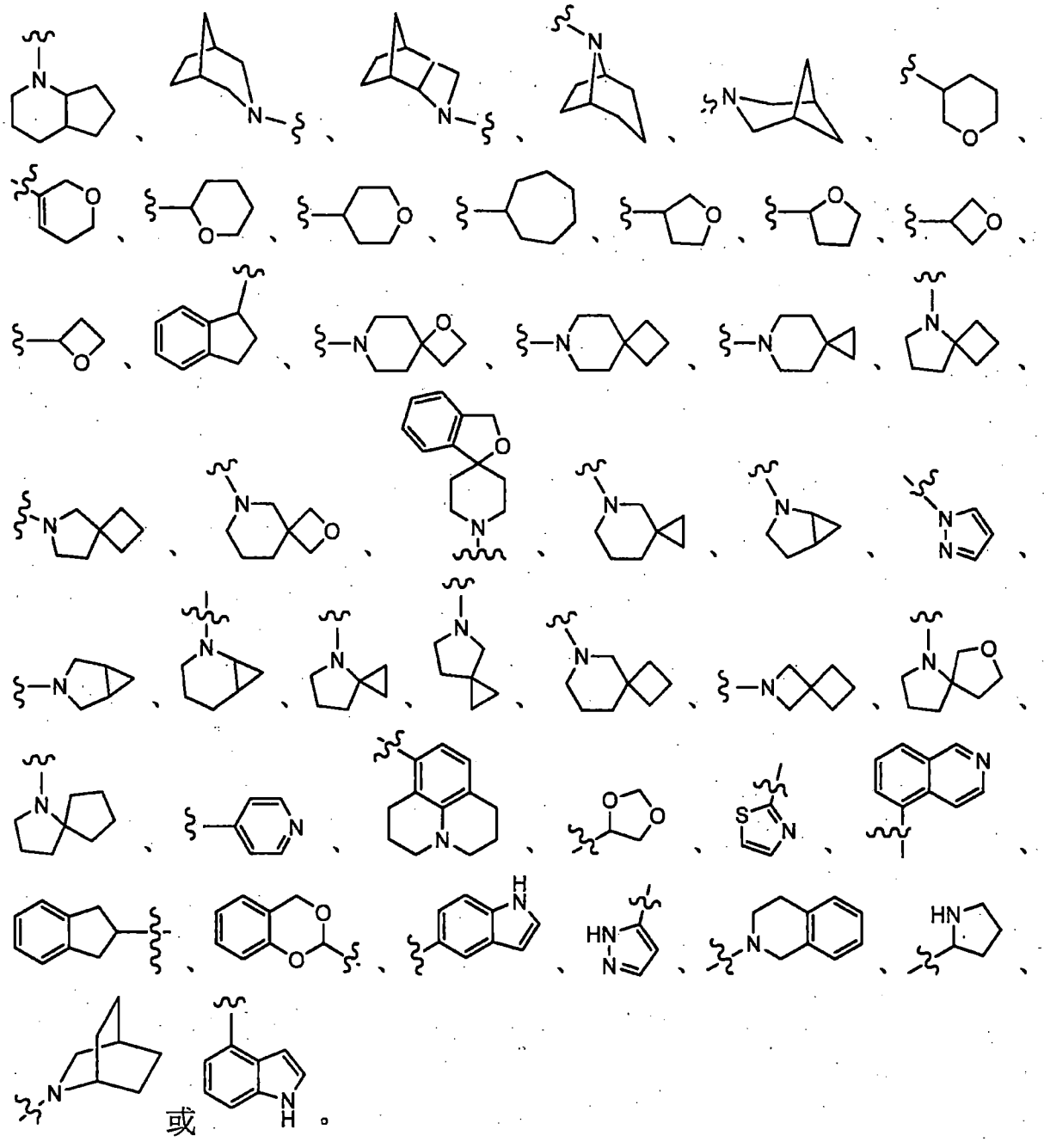
在一些實施例中，環A爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環A爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃、噻唑、吡咯啶酮或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、四氫-2H-哌喃、氧雜環庚烷、四氫呋喃、吡咯啶、萘、哌啶、氮雜環丁烷或二氫茚。

在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

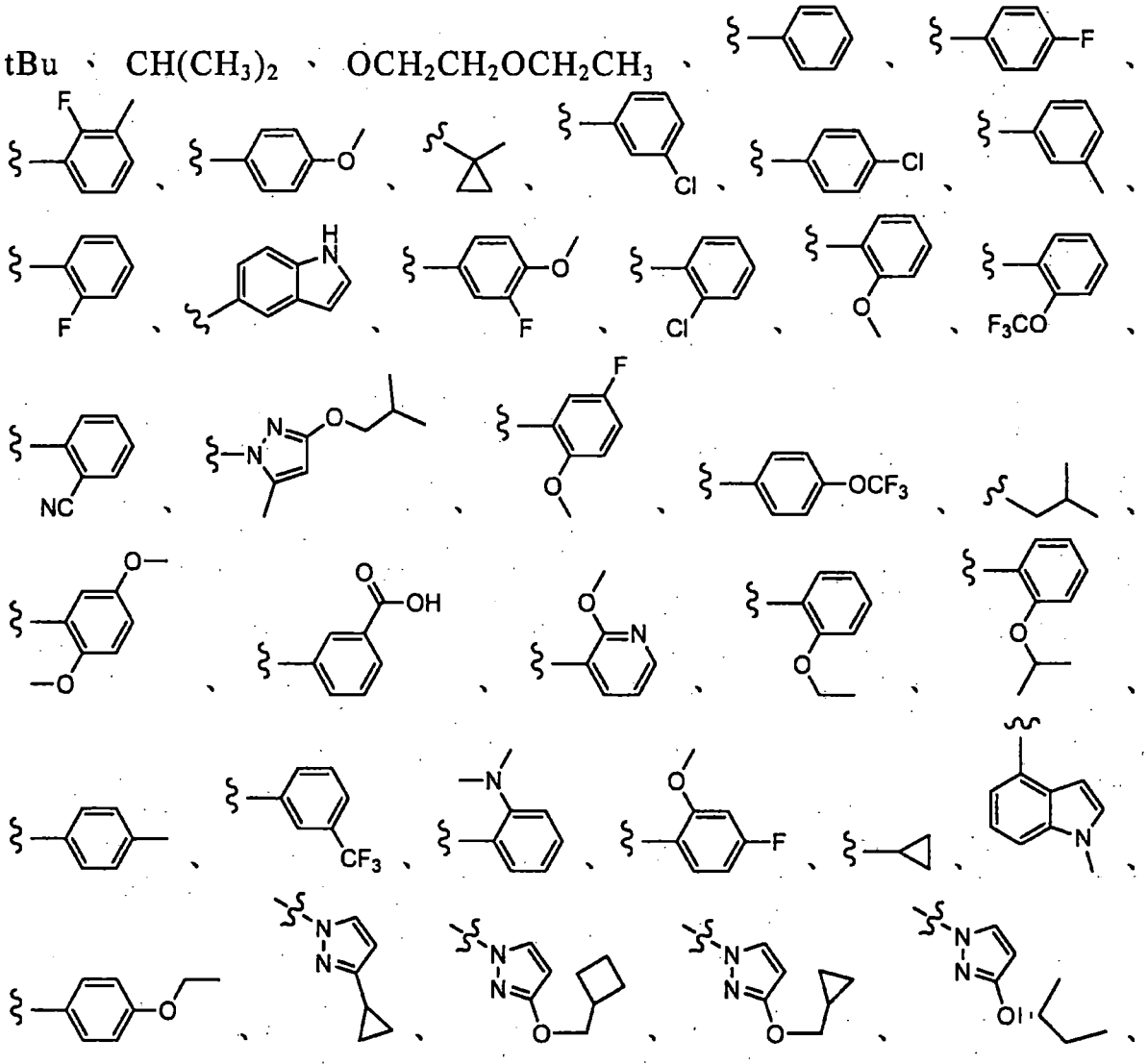


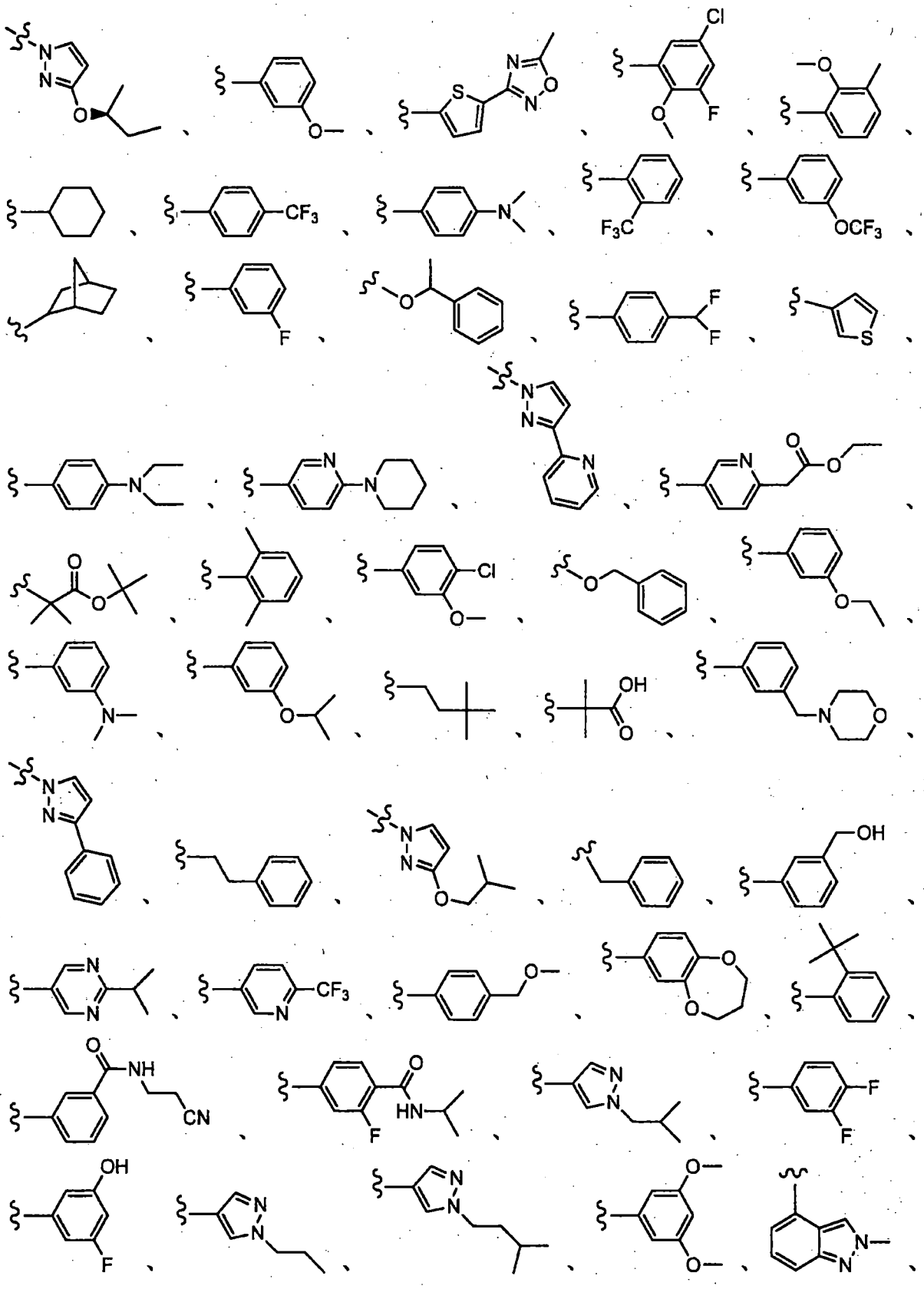
在一些實施例中，X爲O。在一些實施例中，X爲NR。在一些實施例中，X爲NH。

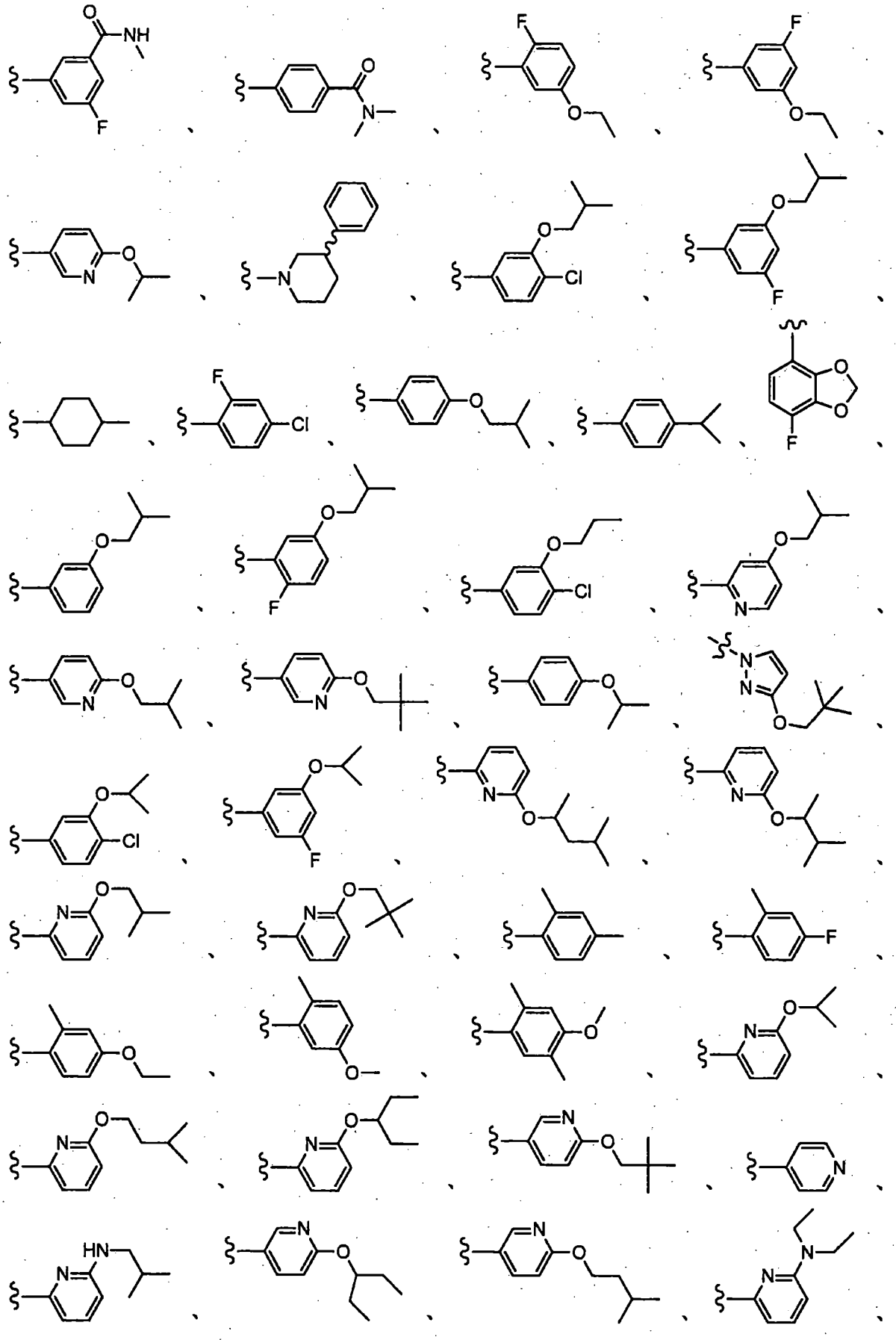
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

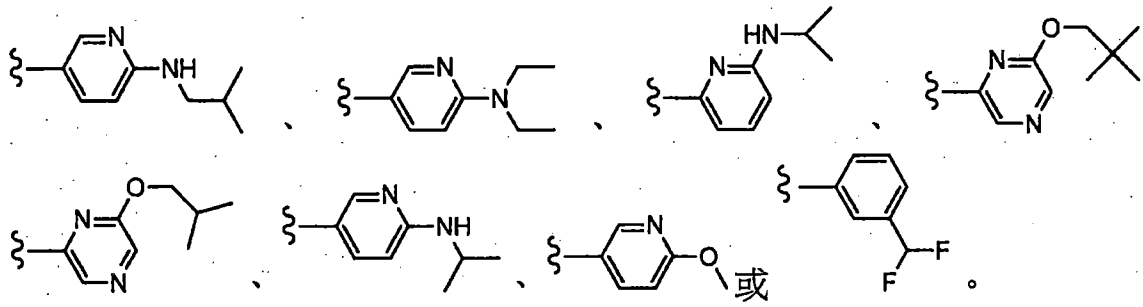
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、

C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、氮雜環丁烷、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、 

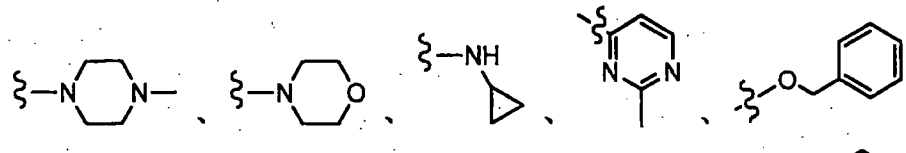


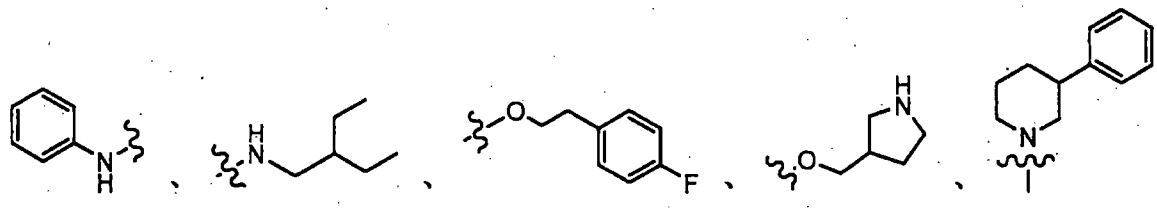


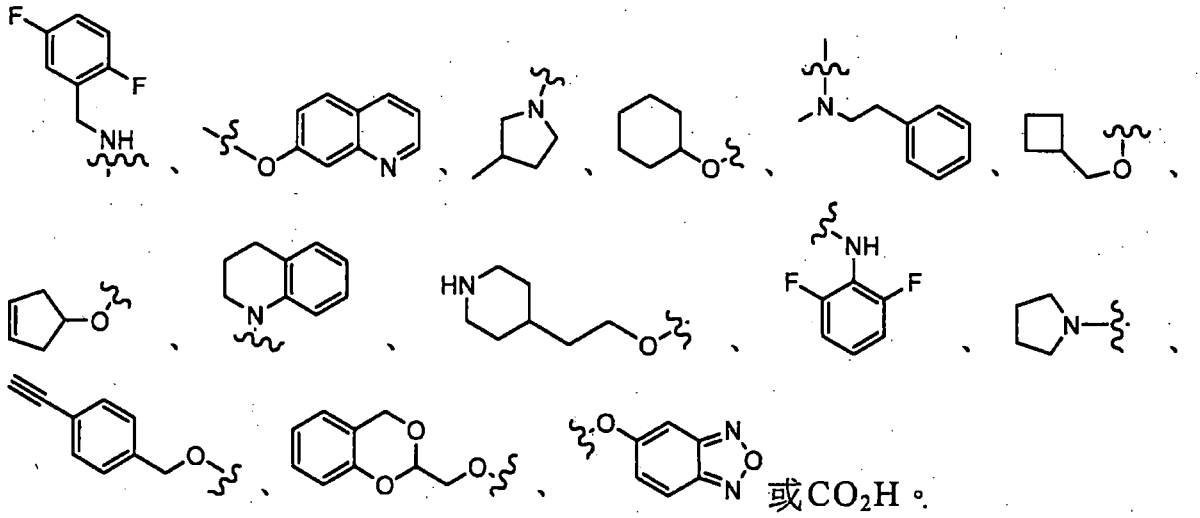


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個視情況爲O、S、N或NR的C3-C10雜環；及其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、

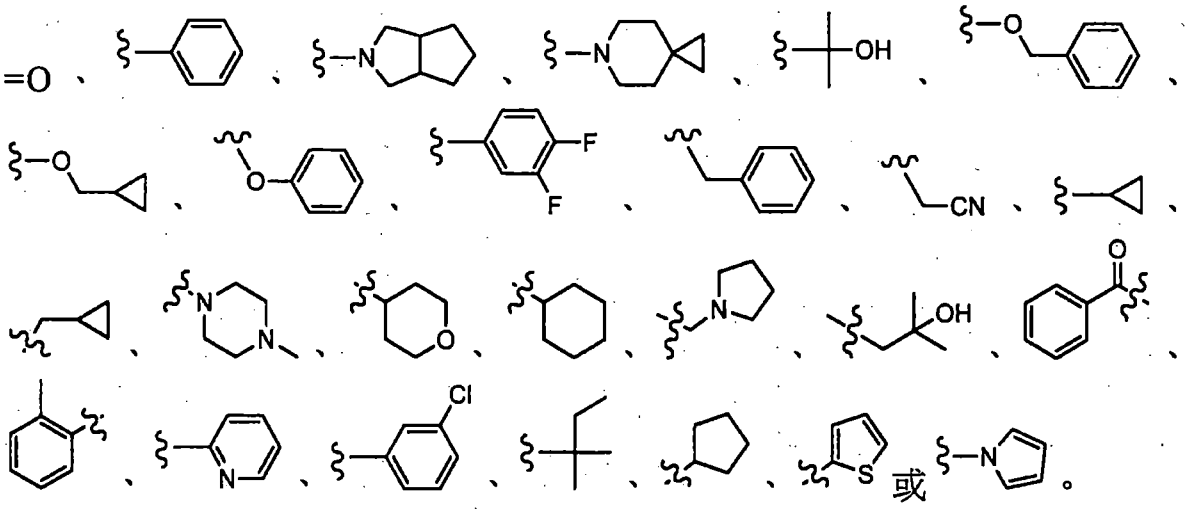






在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基、C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、



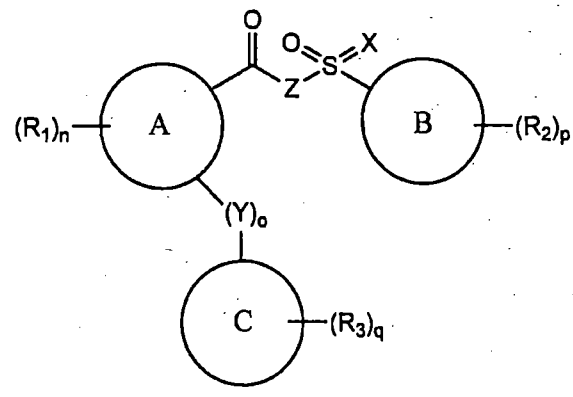
在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施

例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，式I化合物爲式I-ii化合物：




I-ii，

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環A爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C14雜芳基或雜環；

環B爲C6-C10芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

X爲O或NR；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

Z爲NR或CHR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟

烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

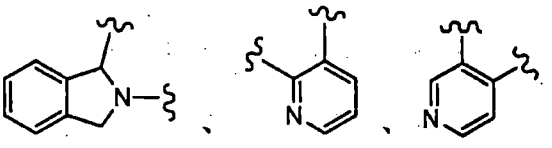
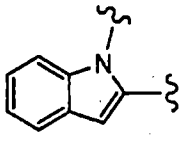
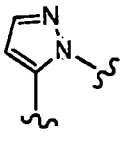
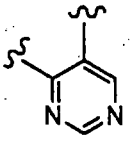
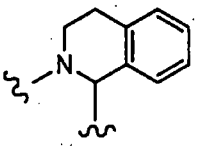
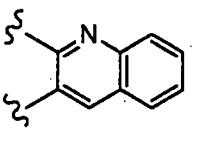
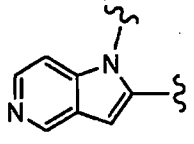
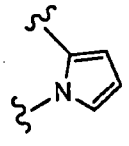
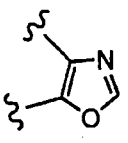
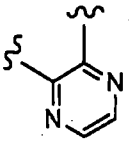
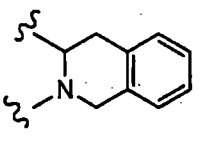
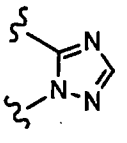
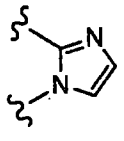
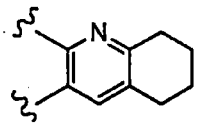
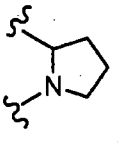
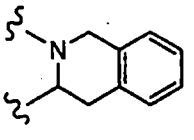
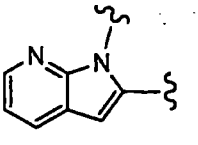
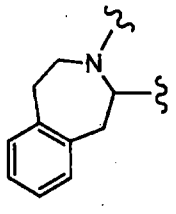
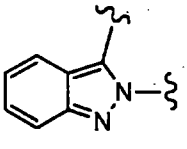
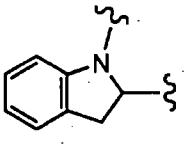
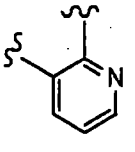
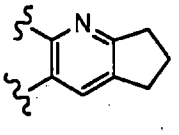
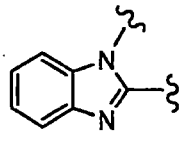
p爲0、1、2或3；且

q爲0、1、2、3、4或5；

其限制條件爲含有環B及環C之部分基團取代在環A上之相鄰位置上。

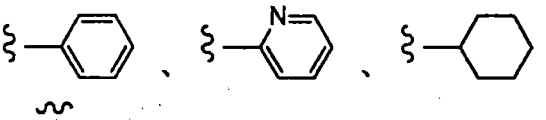
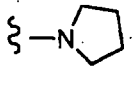
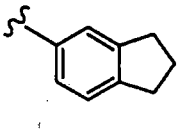
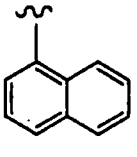
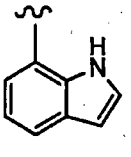
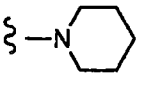
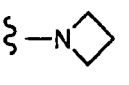
在一些實施例中，式I-ii化合物呈醫藥學上可接受之前藥形式存在。

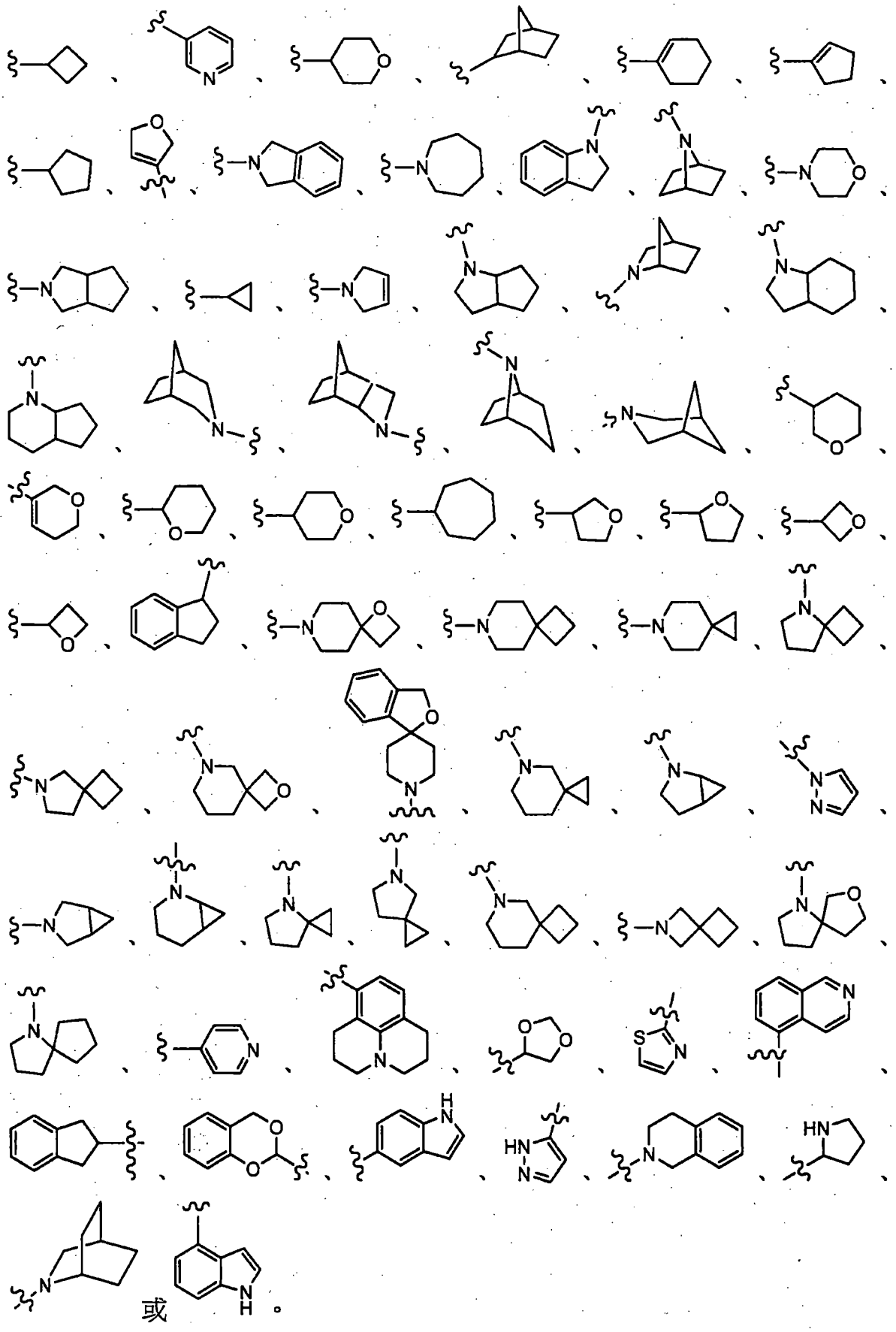
在一些實施例中，環A爲吡啶基、吲哚、吲哚啉、異吲哚啉、吡唑、嘧啶、喹啉、5,6,7,8-四氫喹啉、1,2,3,4-四氫異喹啉、吡咯啶、氮雜吲哚、吡咯、噁唑、吡嗪、三唑、吲唑或咪唑環。

在一些實施例中，環A爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環A爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，環B爲苯基或萘。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘、哌啶、氮雜環丁烷或二氫茚。

在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、



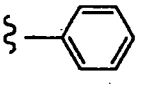
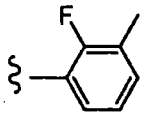
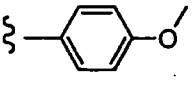
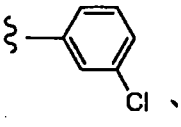
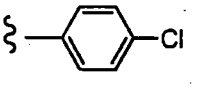
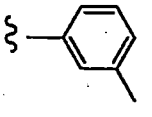
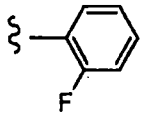
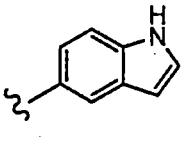
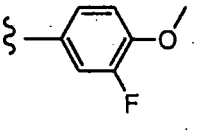
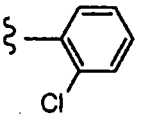
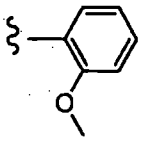
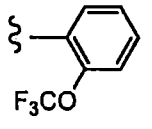
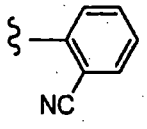
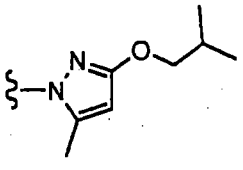
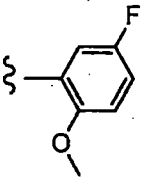
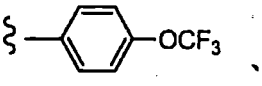
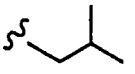
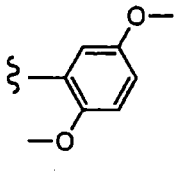
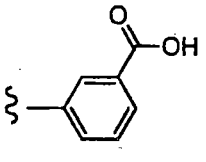
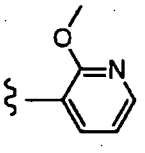
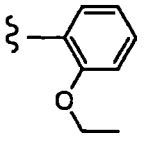
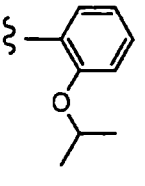
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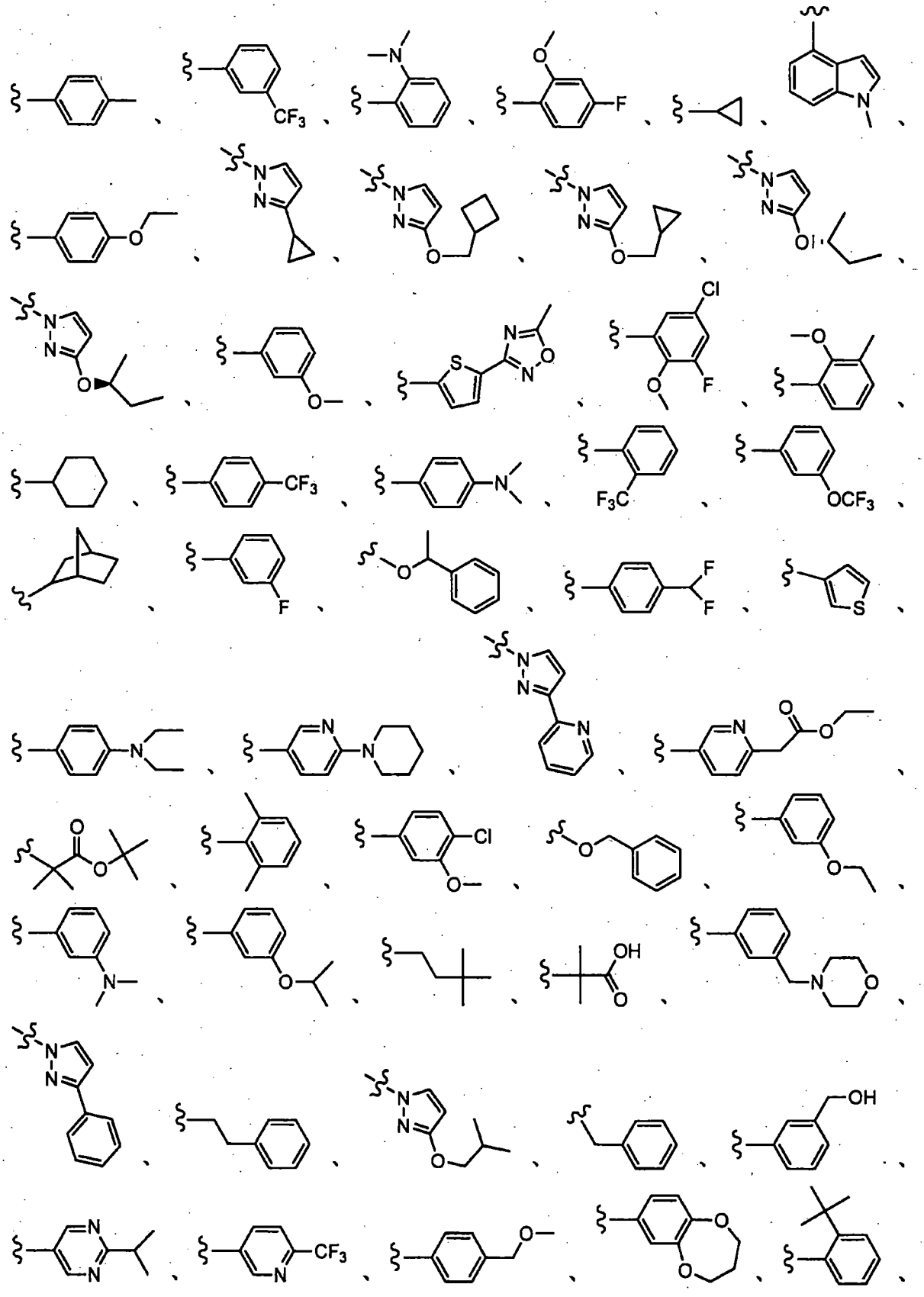
在一些實施例中，X爲O。在另一個實施例中，X爲NR。在一些

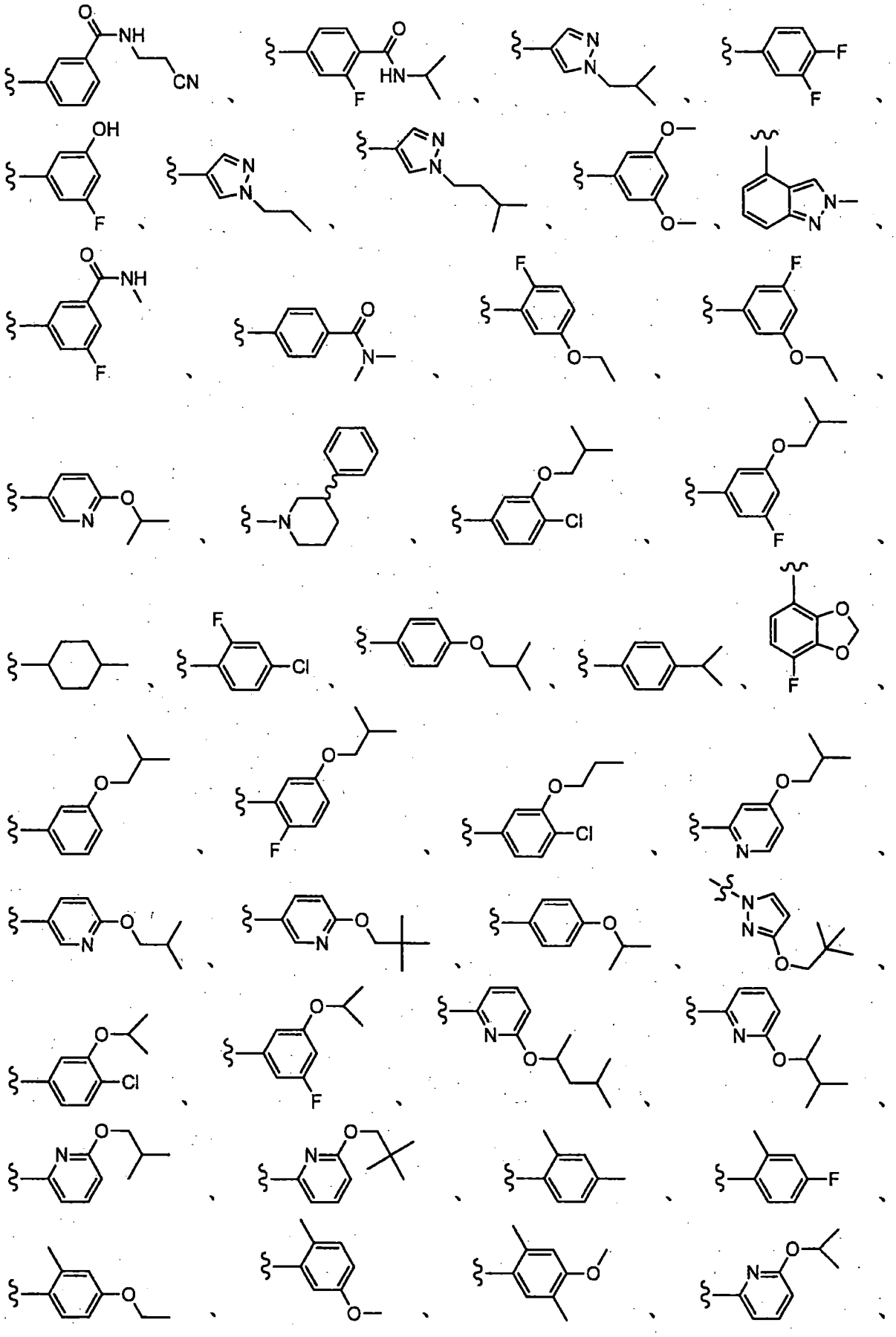
實施例中，X爲NH。

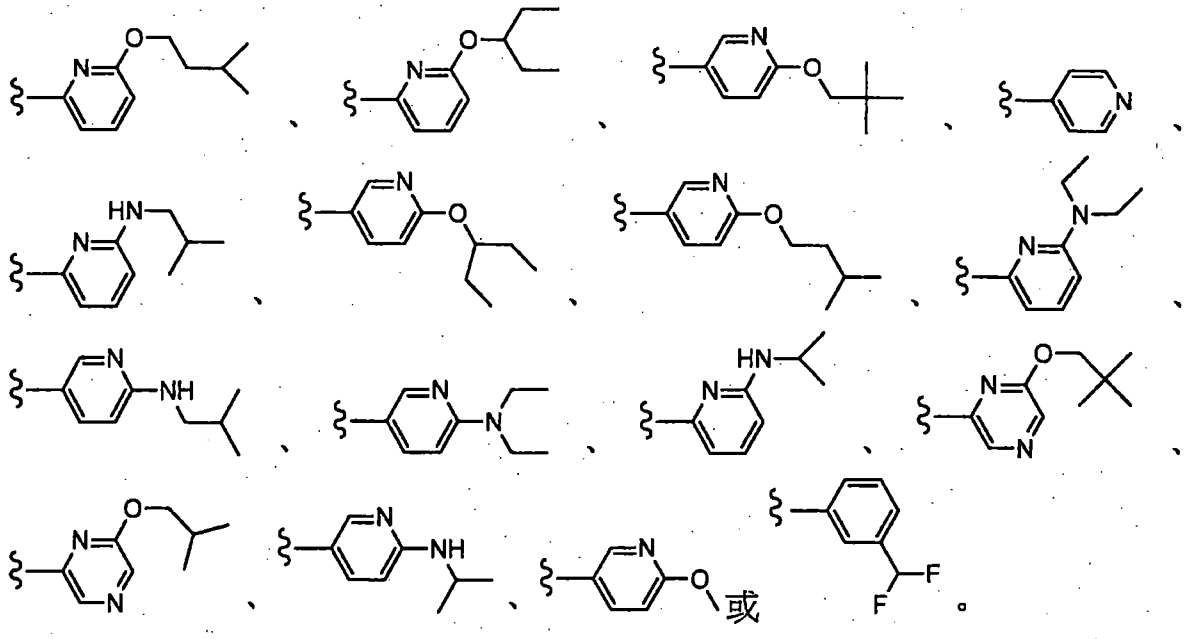
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、氮雜環丁烷、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

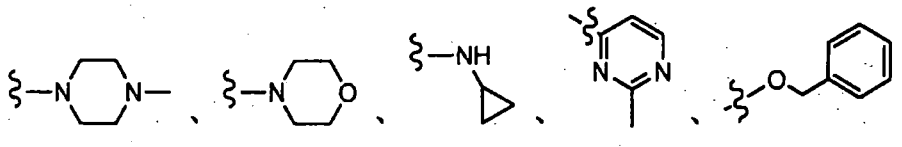


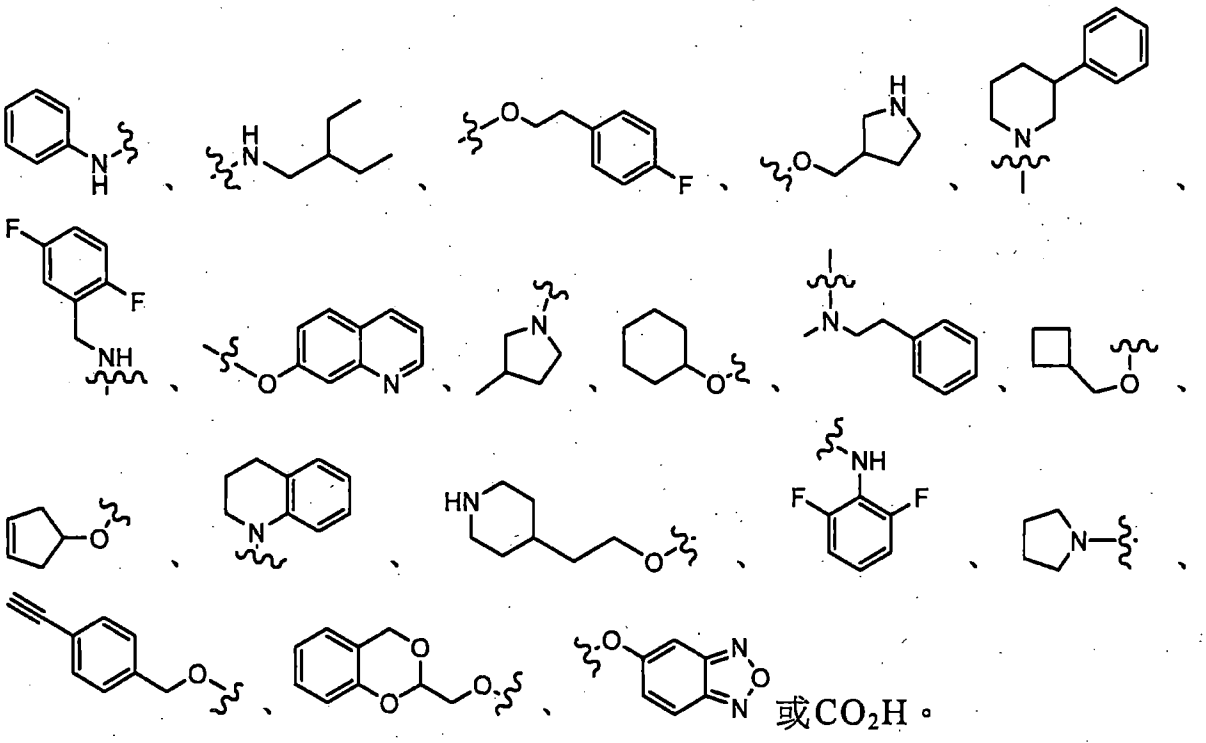




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

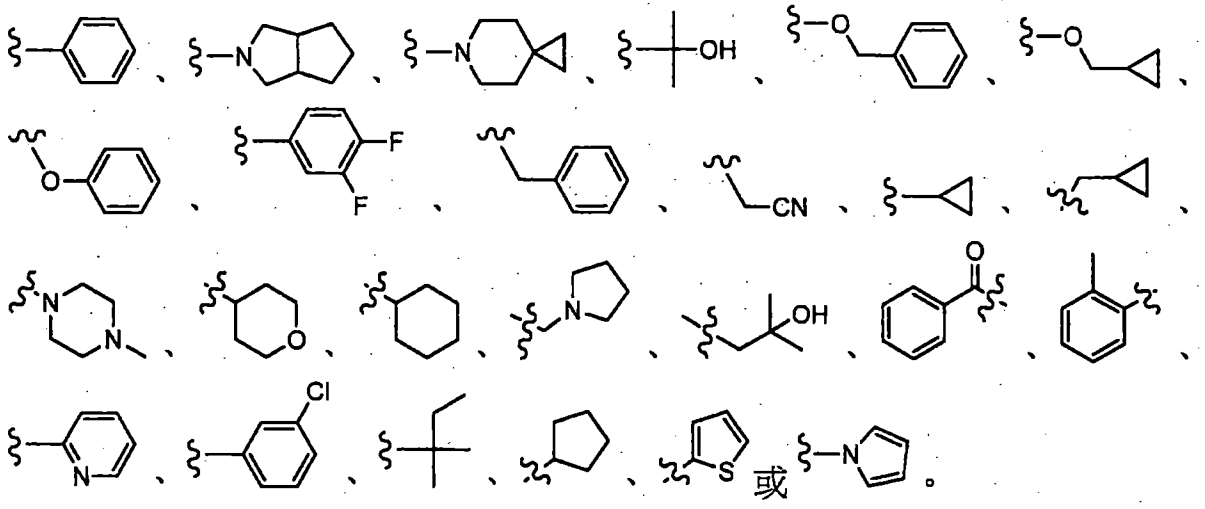
在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、




或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基、C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、


或

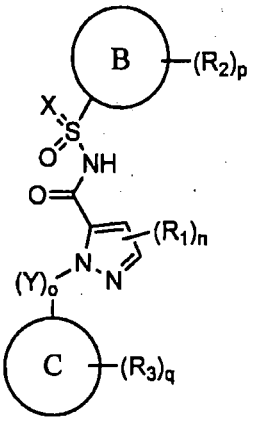

。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，本發明提供式Ia化合物：




**Ia**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

X爲O或NR；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n為0、1或2；

o為0、1、2、3、4或5；

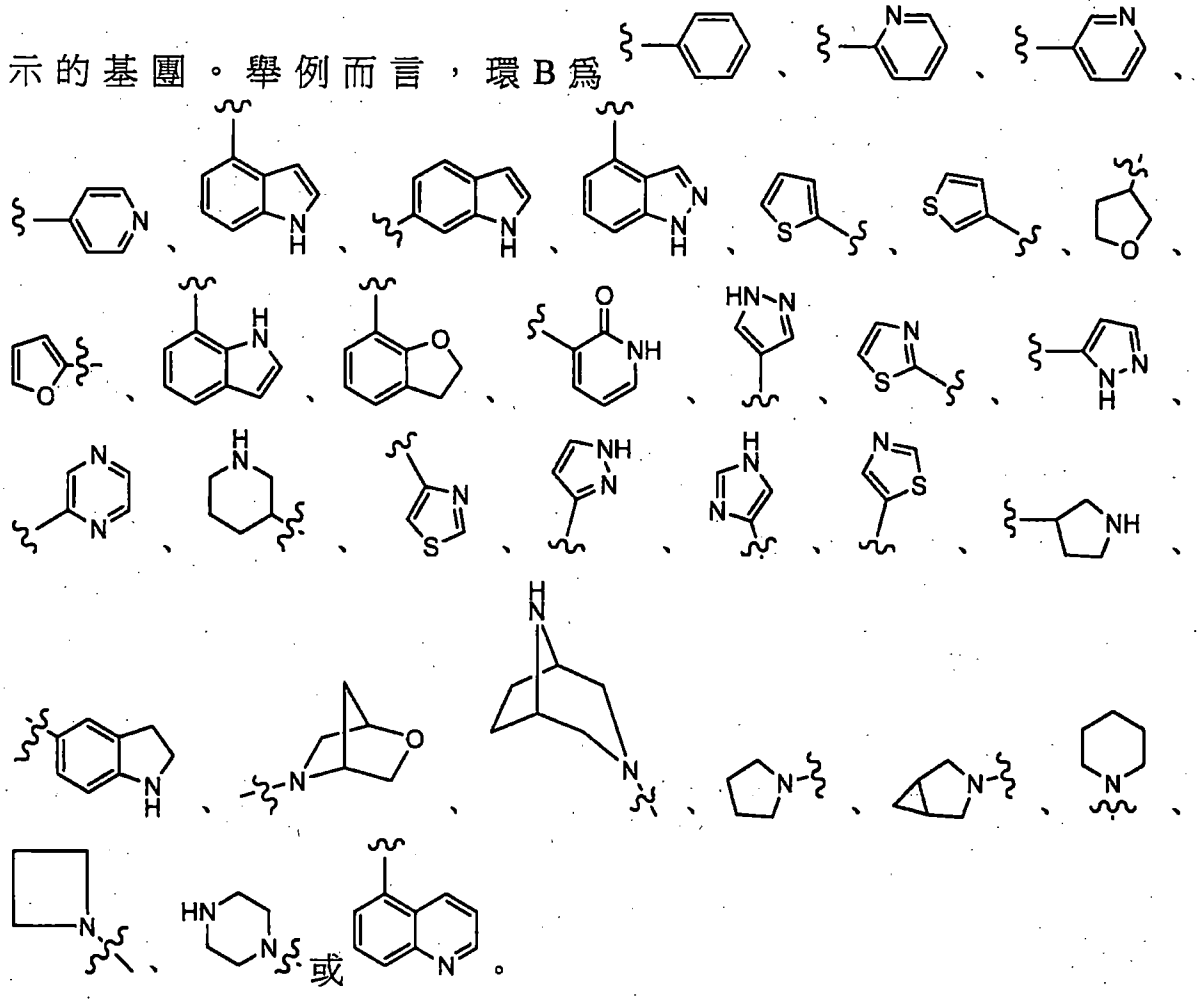
p為0、1、2或3；且

q為0、1、2、3、4或5。

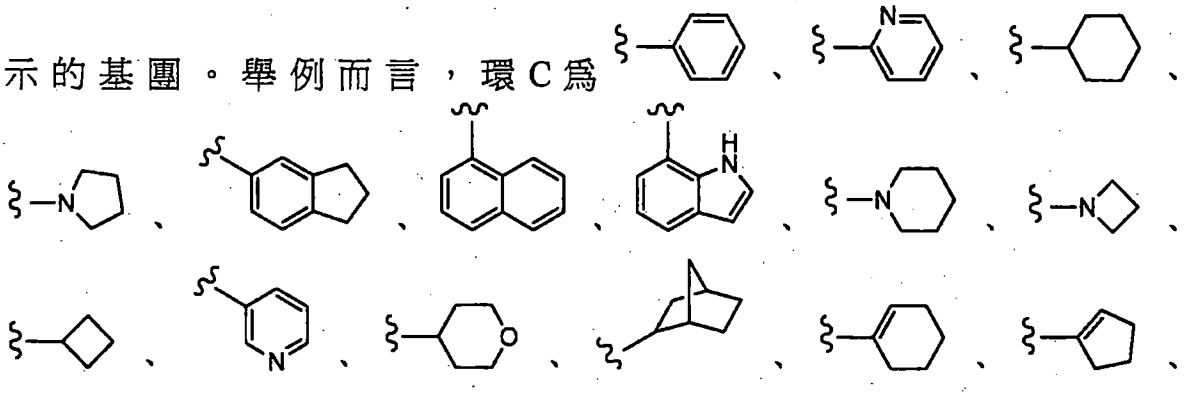
在一些實施例中，式Ia化合物呈醫藥學上可接受之前藥形式存在。

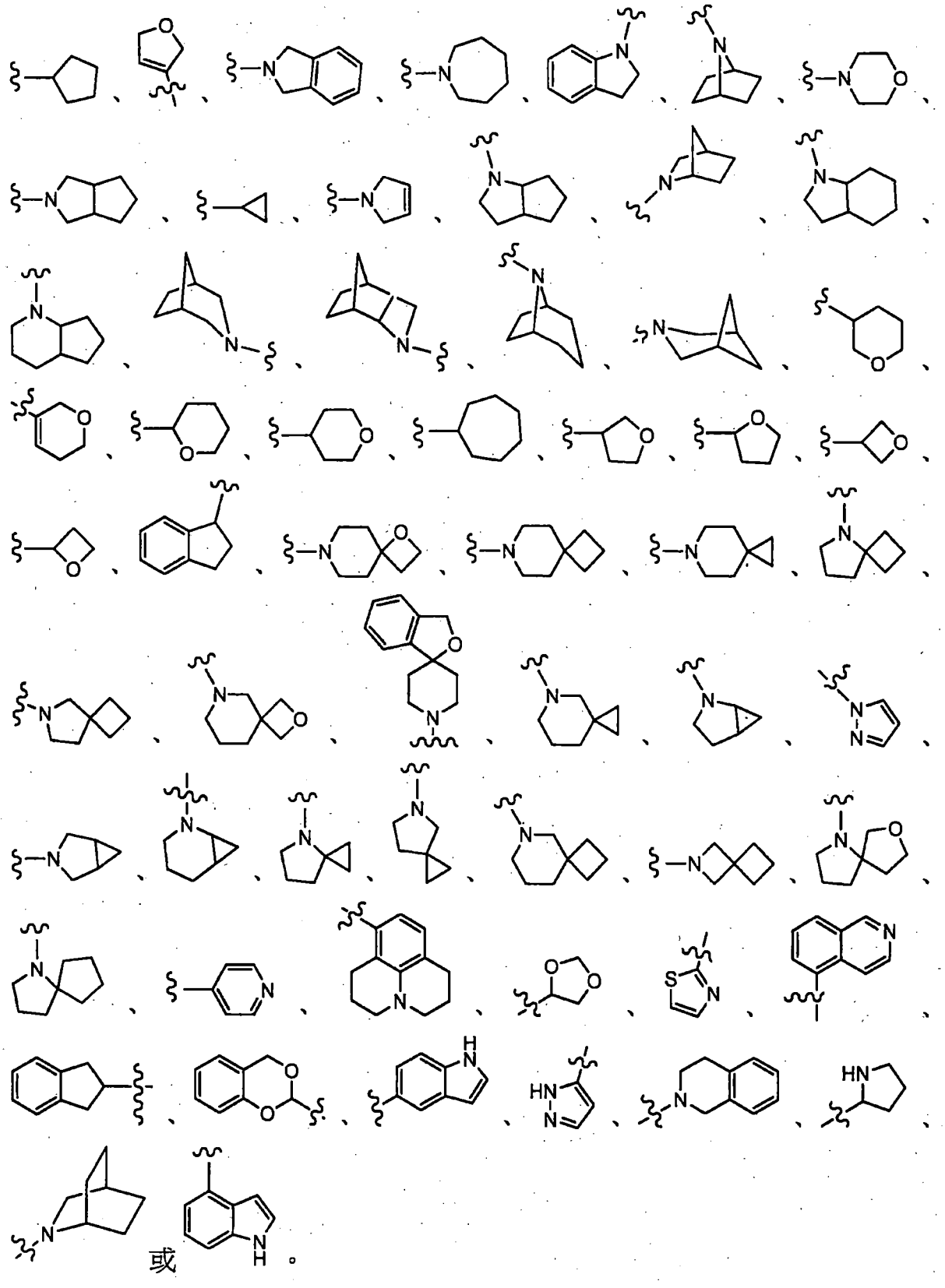
在一些實施例中，環B為苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、

吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  或。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘、哌啶或二氫茚。

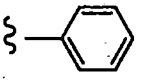
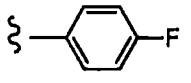
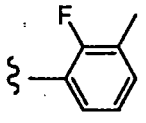
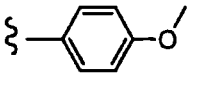
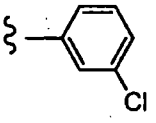
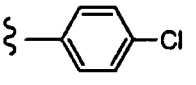
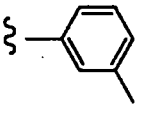
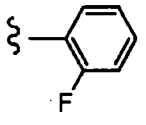
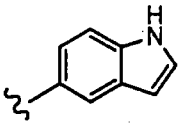
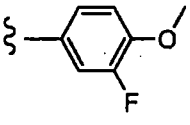
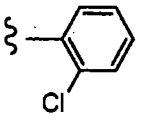
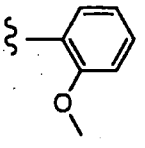
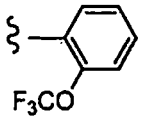
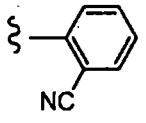
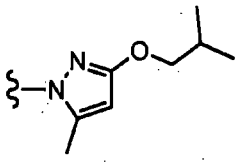
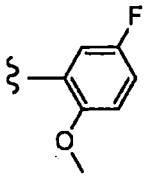
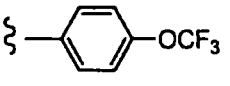
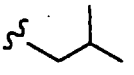
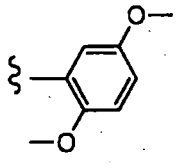
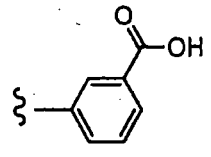
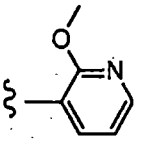
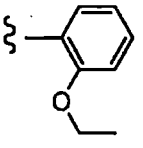
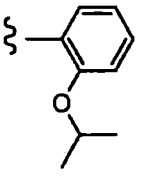
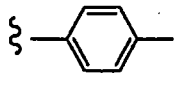
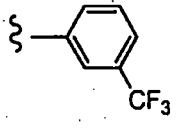
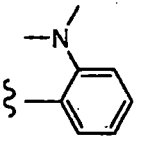
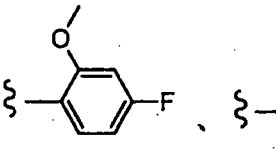
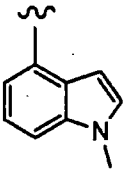
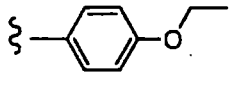
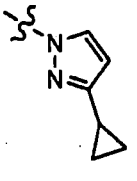
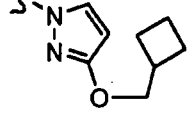
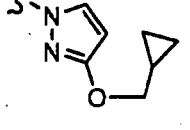
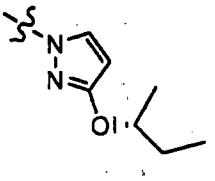
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲 

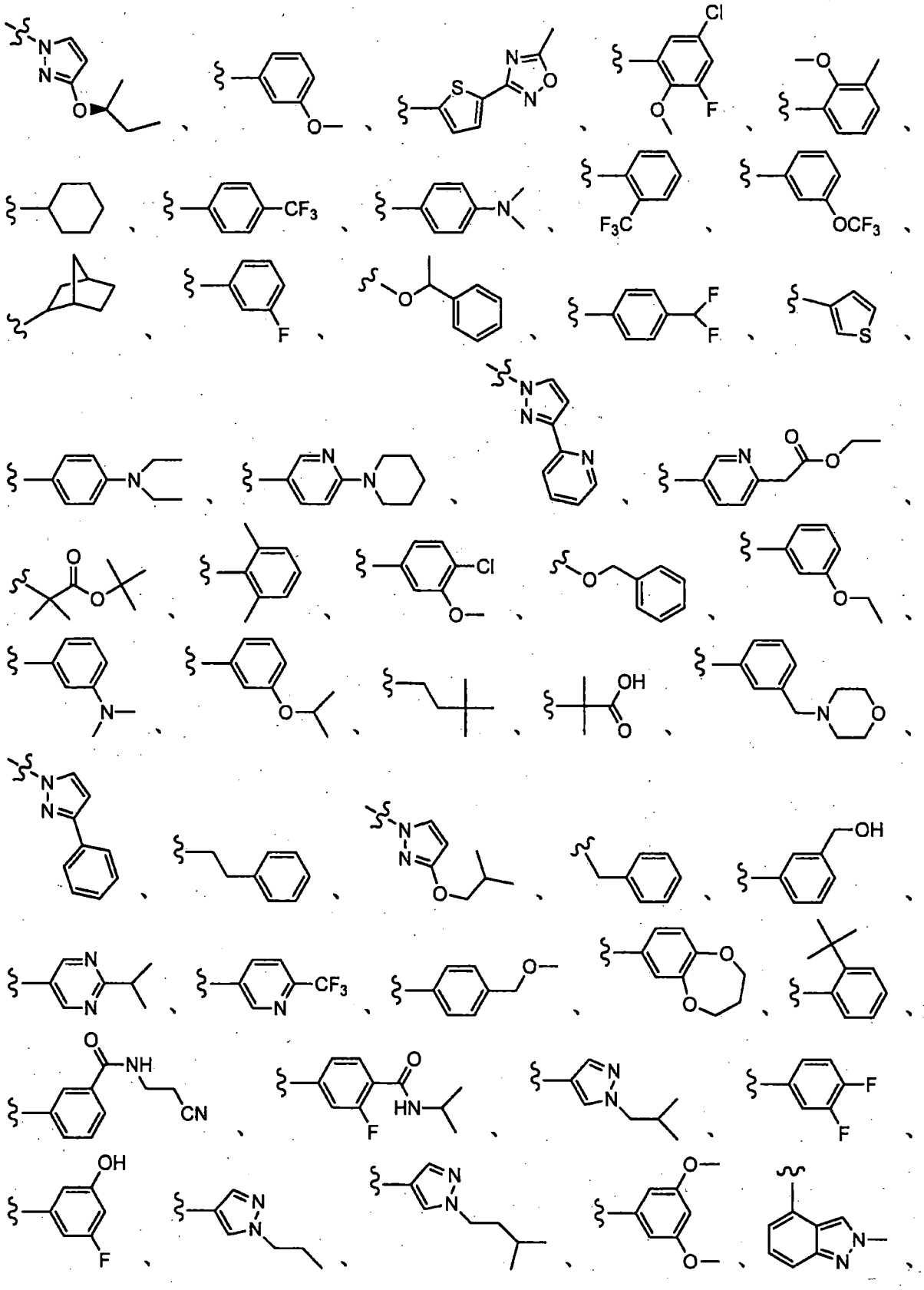


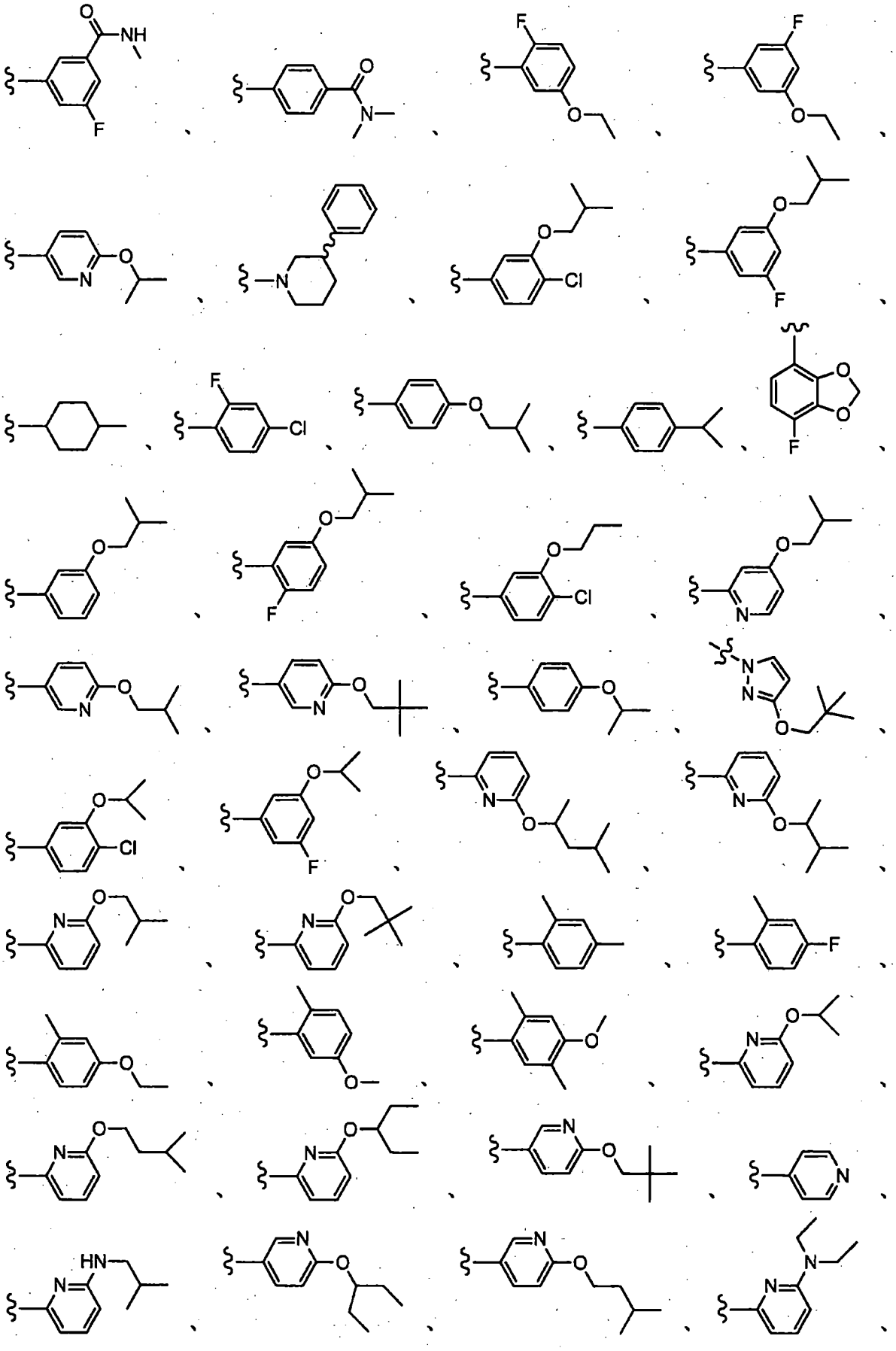
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如

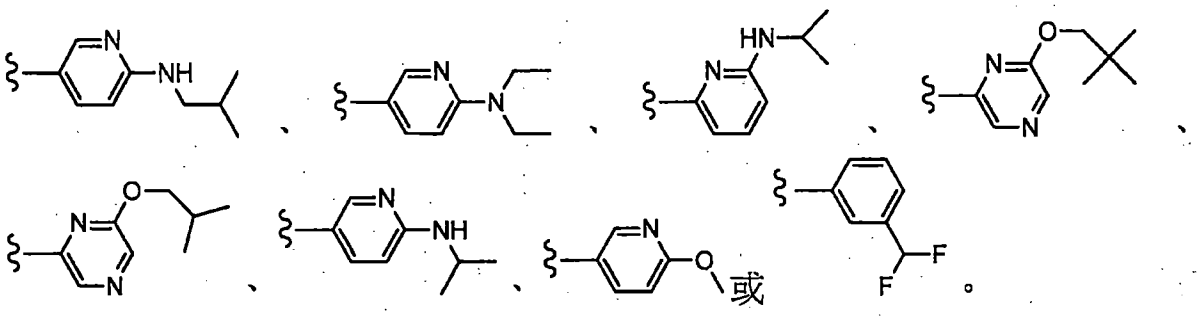
NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  。

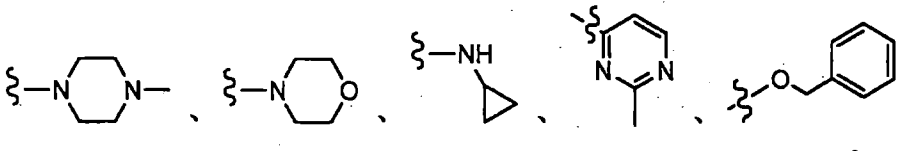


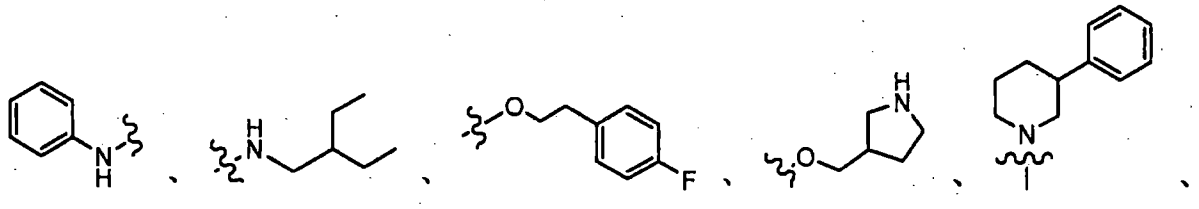


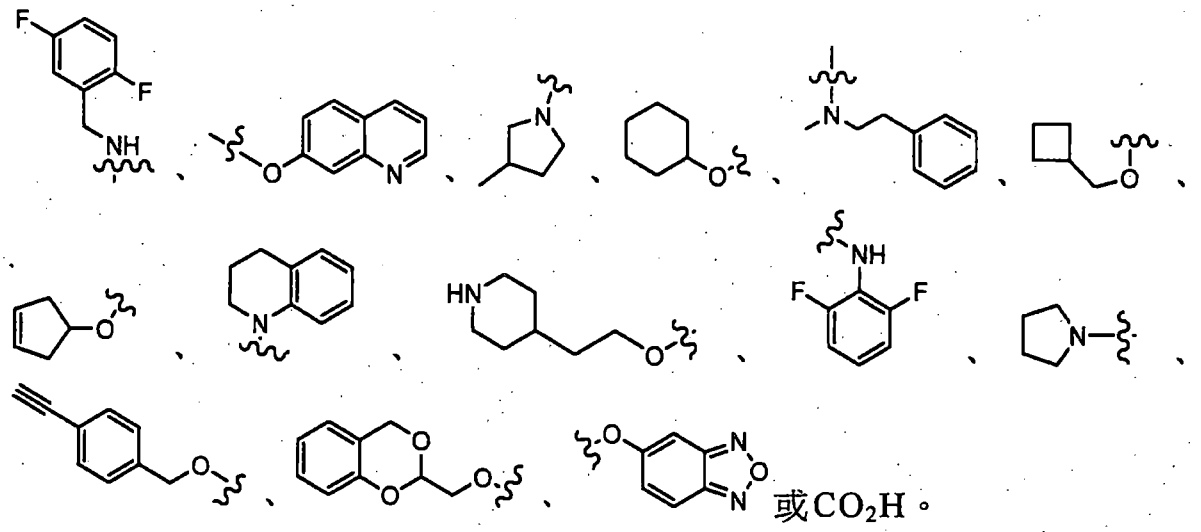


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、

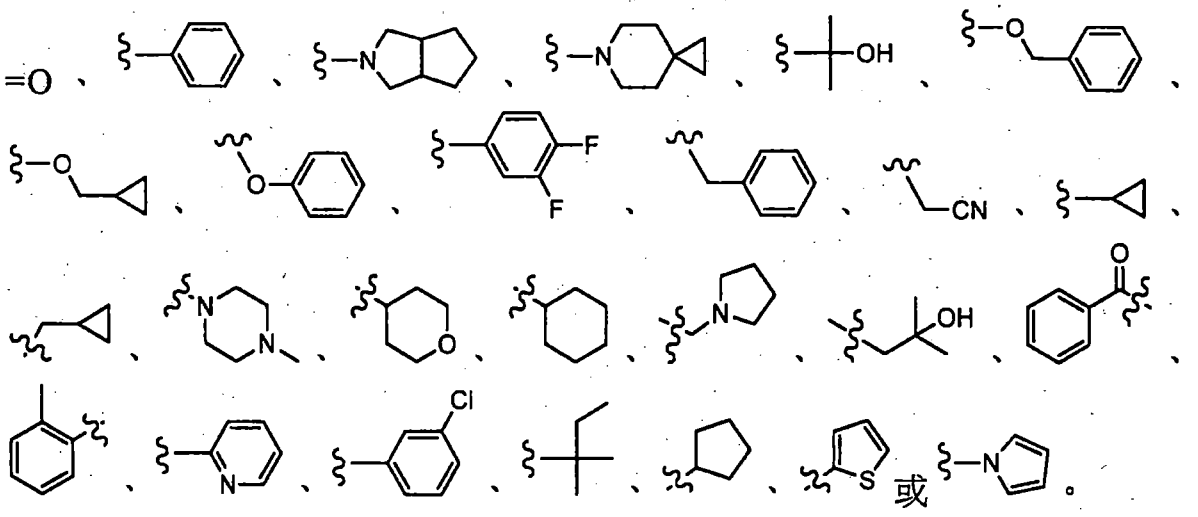





或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、


或

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

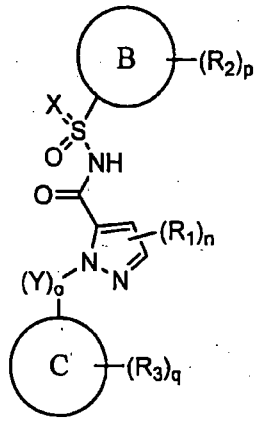
在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施

例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，環B爲苯基。在一些實施例中，環B及環C爲苯基。在一些實施例中，$R_1$爲tBu。在一些實施例中，環B及環C爲苯基且$R_1$爲tBu。在一些實施例中，Y爲$CH_2$。在一些實施例中，環B及環C爲苯基，$R_1$爲tBu，且Y爲$CH_2$。在一些實施例中，環B、環C及$R_1$爲苯基且Y爲$CH_2$。

在一些實施例中，本發明提供式Ia-i化合物：




**Ia-i**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

X爲O或NR；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-

$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1或2；

o爲0、1、2、3、4或5；

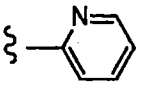
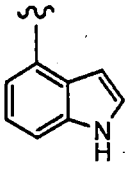
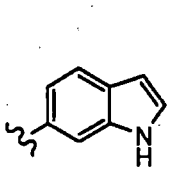
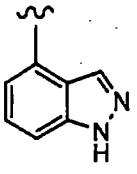
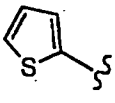
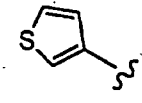
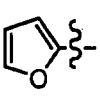
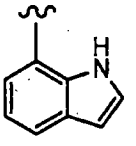
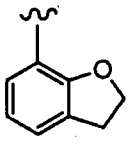
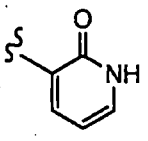
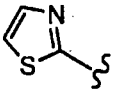
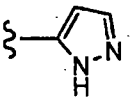
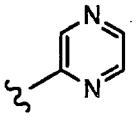
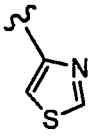
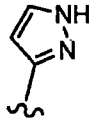
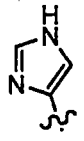
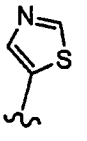
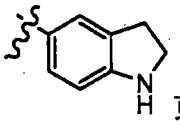
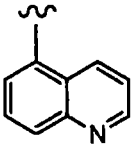
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

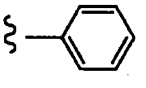
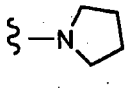
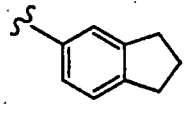
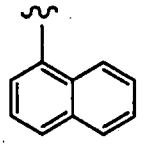
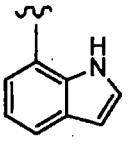
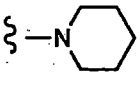
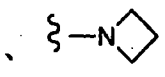
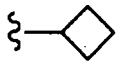
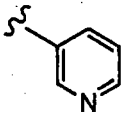
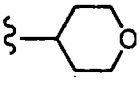
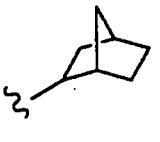
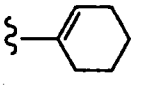
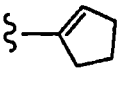
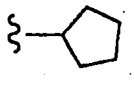
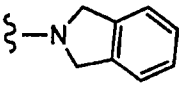
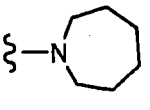
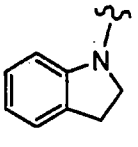
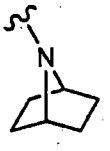
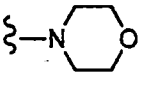
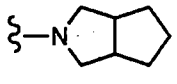
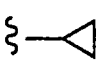
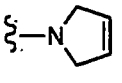
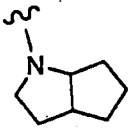
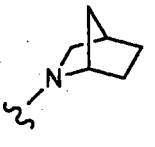
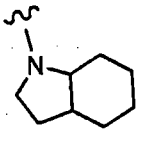
在一些實施例中，式Ia-i化合物呈醫藥學上可接受之前藥形式存

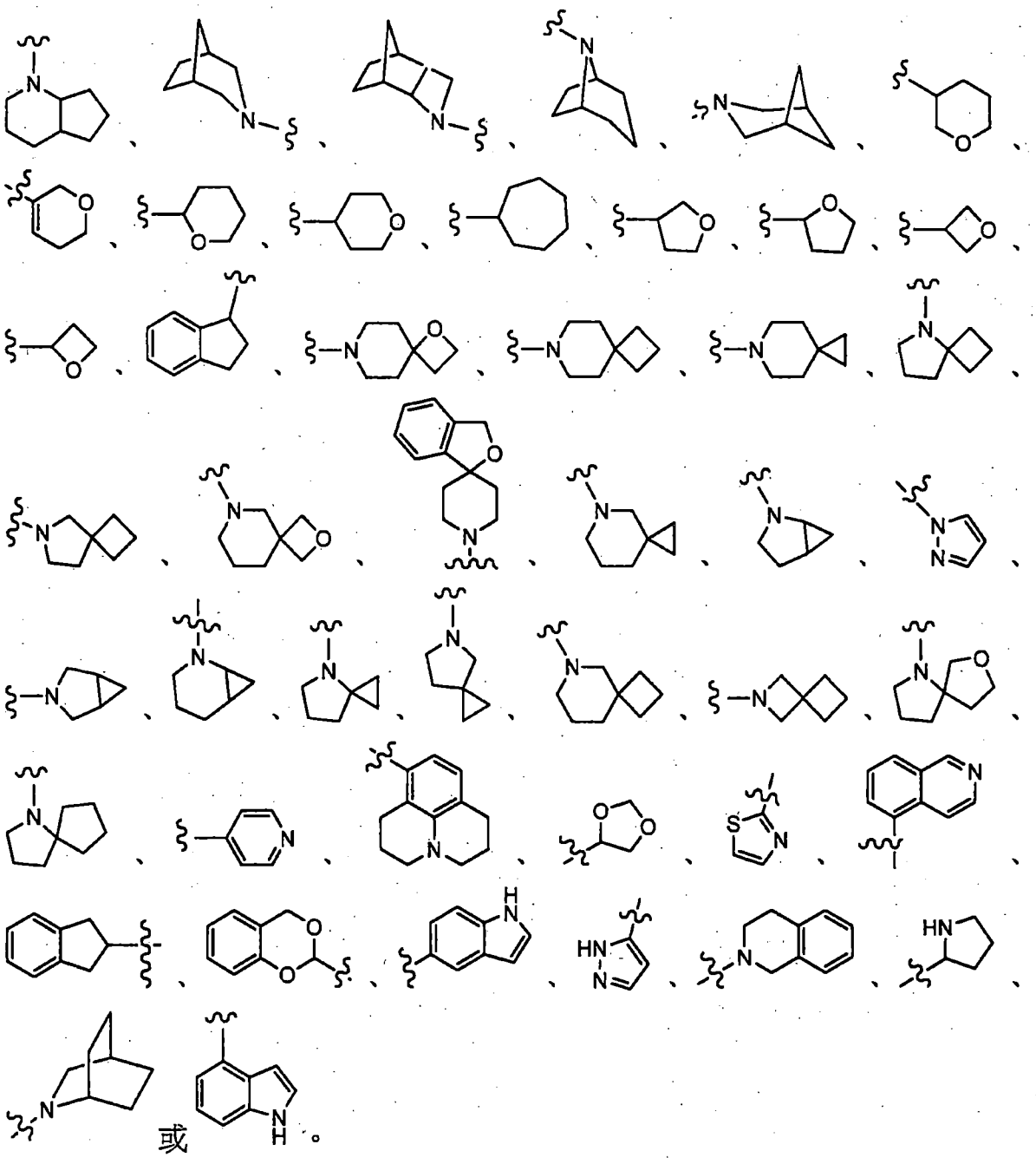
在。

在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘、哌啶或二氫茚。

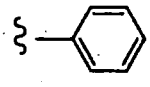
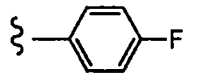
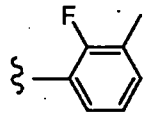
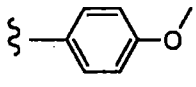
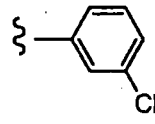
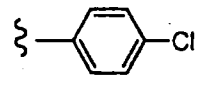
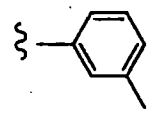
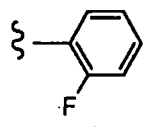
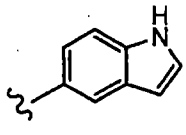
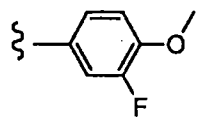
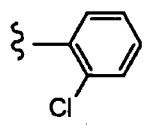
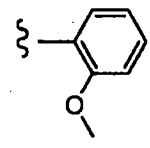
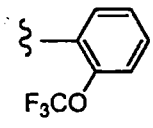
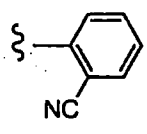
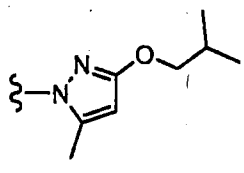
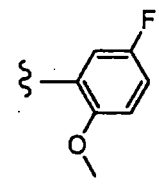
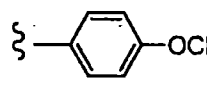
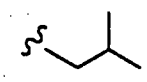
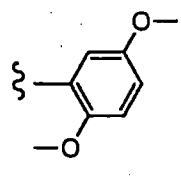
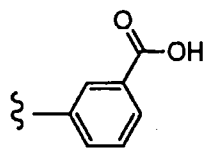
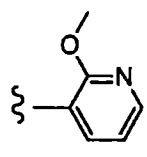
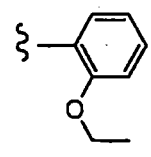
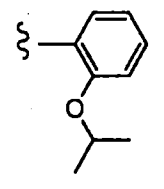
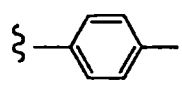
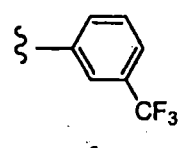
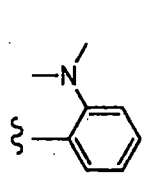
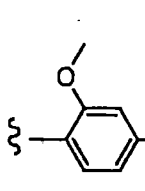
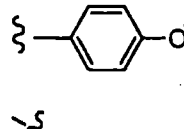
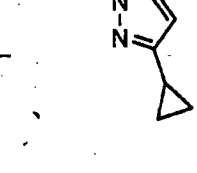
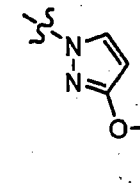
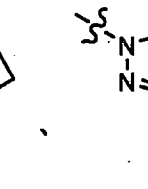
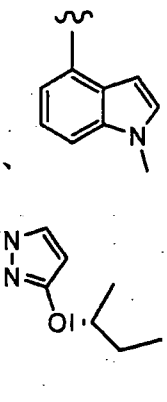
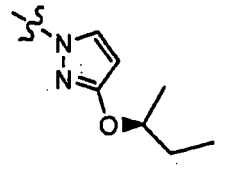
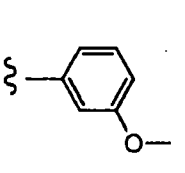
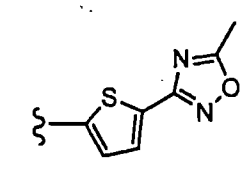
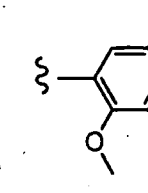
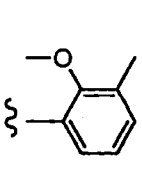
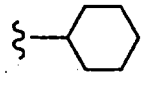
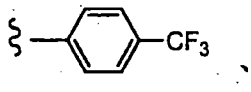
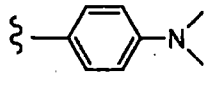
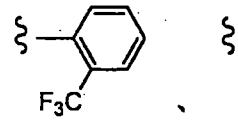
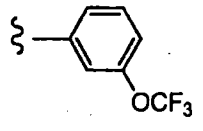
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  。

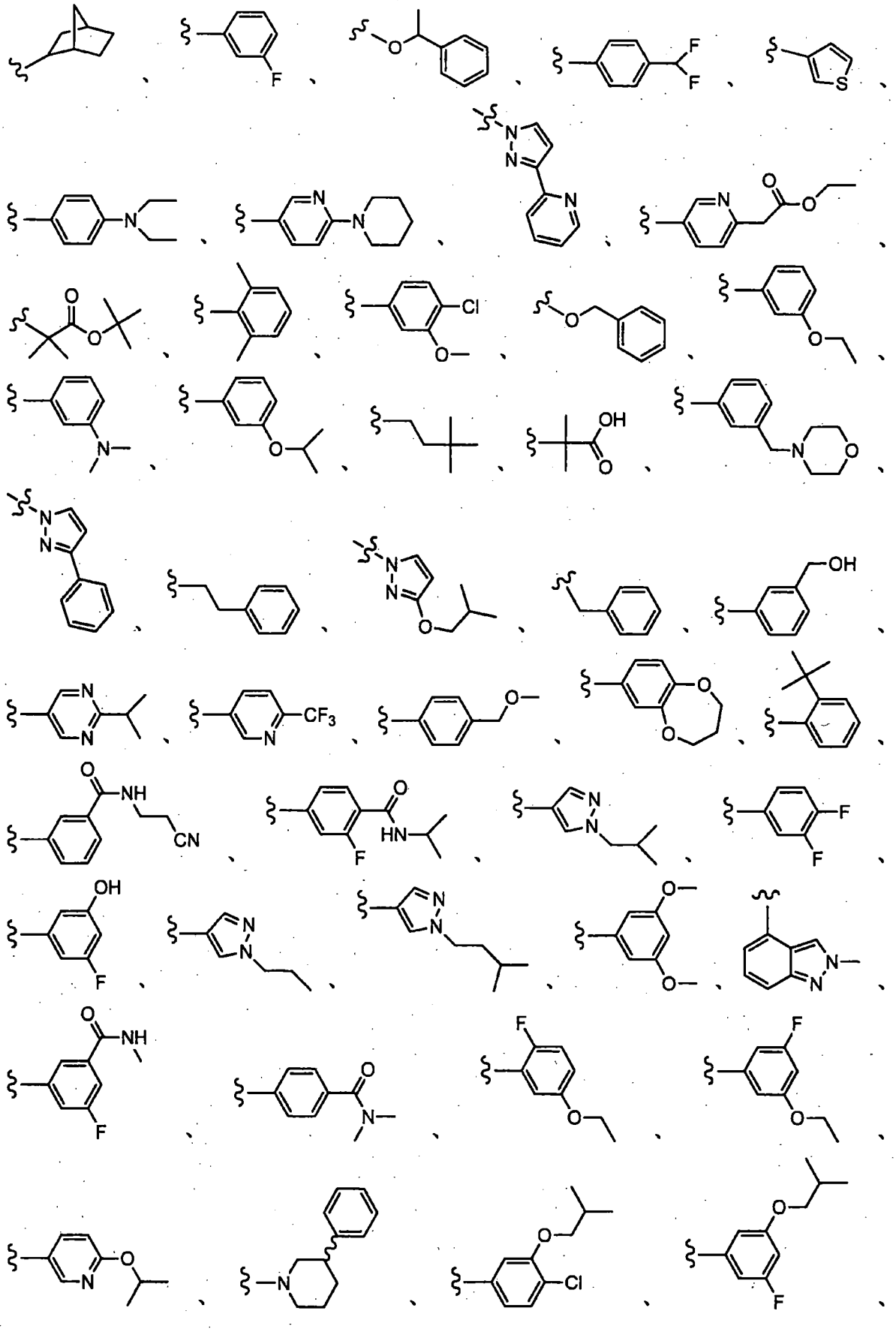


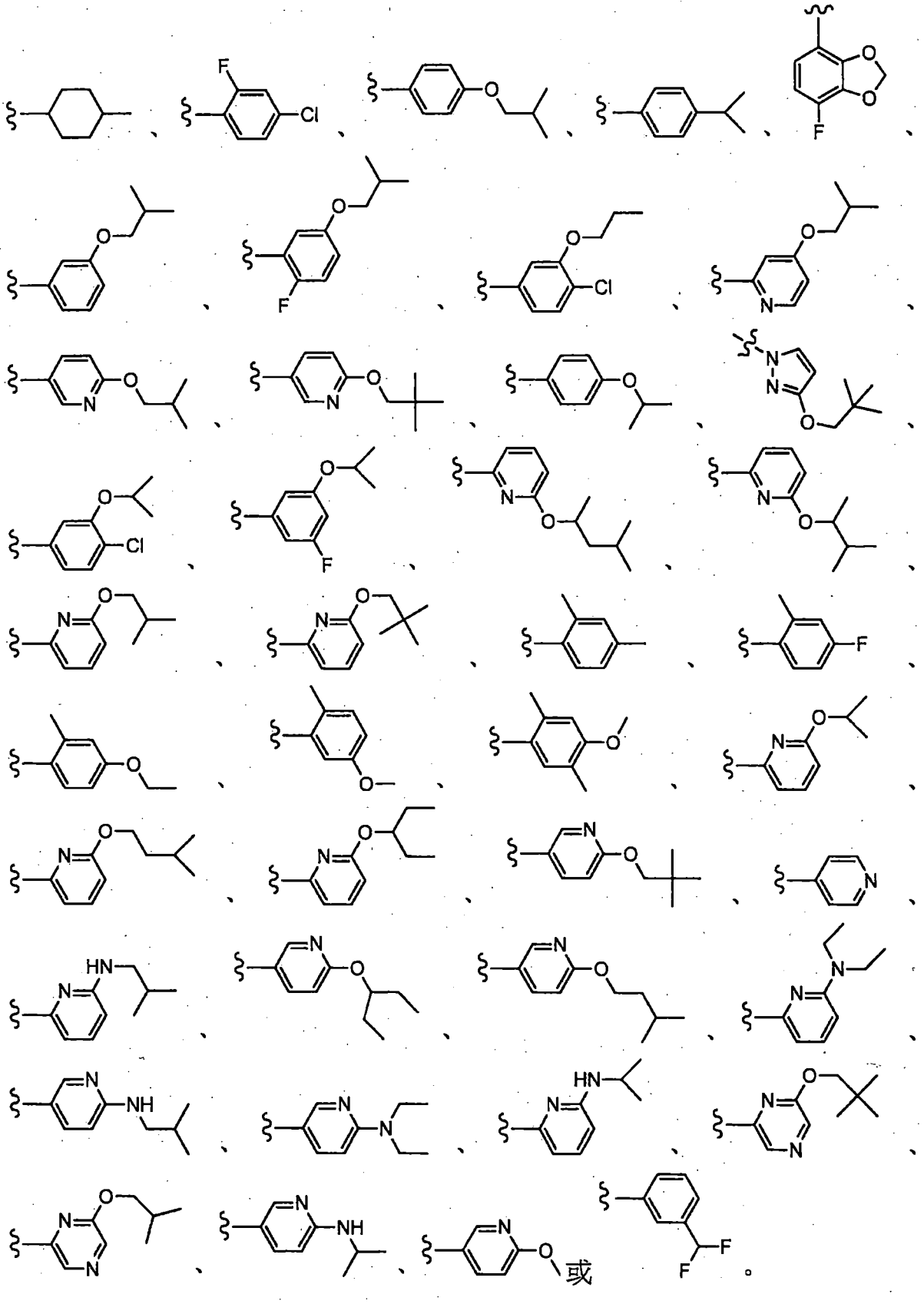
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換

的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

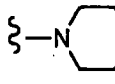
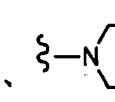
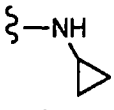
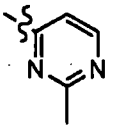
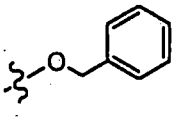
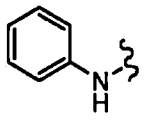
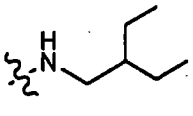
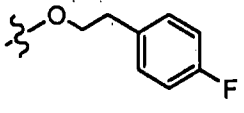
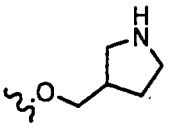
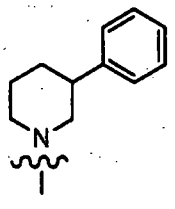
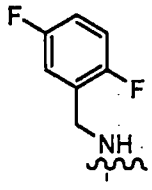
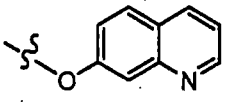
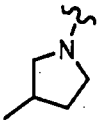
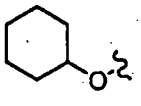
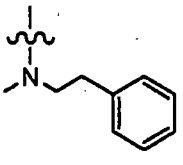
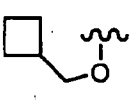
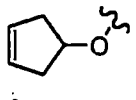
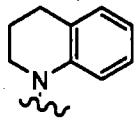
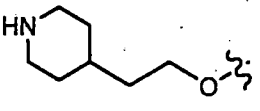
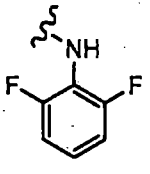
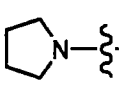
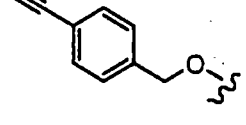
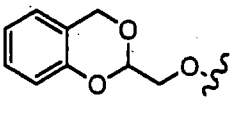
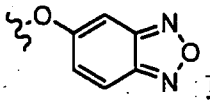
在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  。



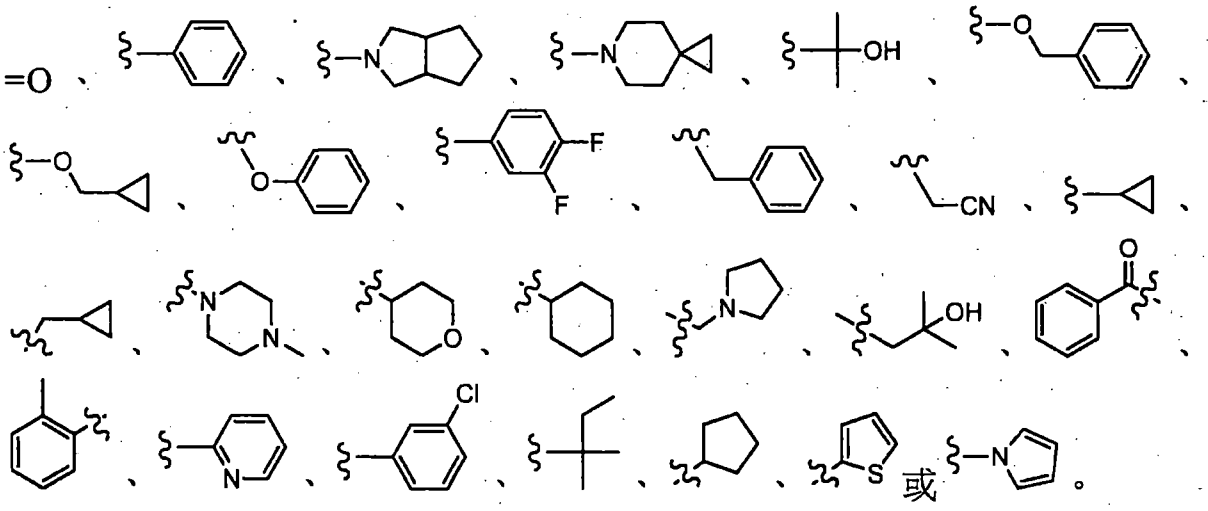


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任

一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

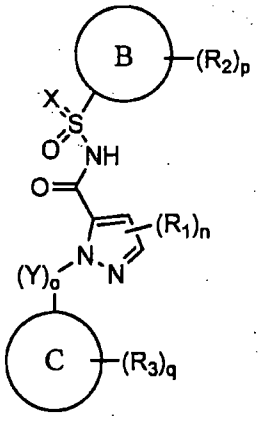
在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  或。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，本發明提供式Ia-ii化合物：




**Ia-ii**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

X爲O或NR；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原

子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1或2；

o爲0、1、2、3、4或5；

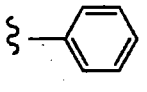
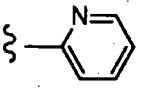
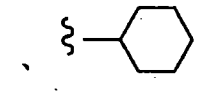
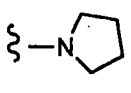
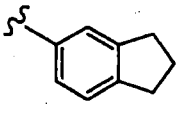
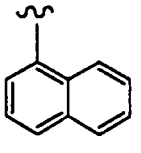
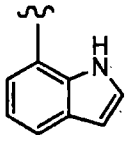
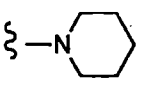
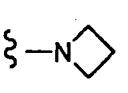
p爲0、1、2或3；且

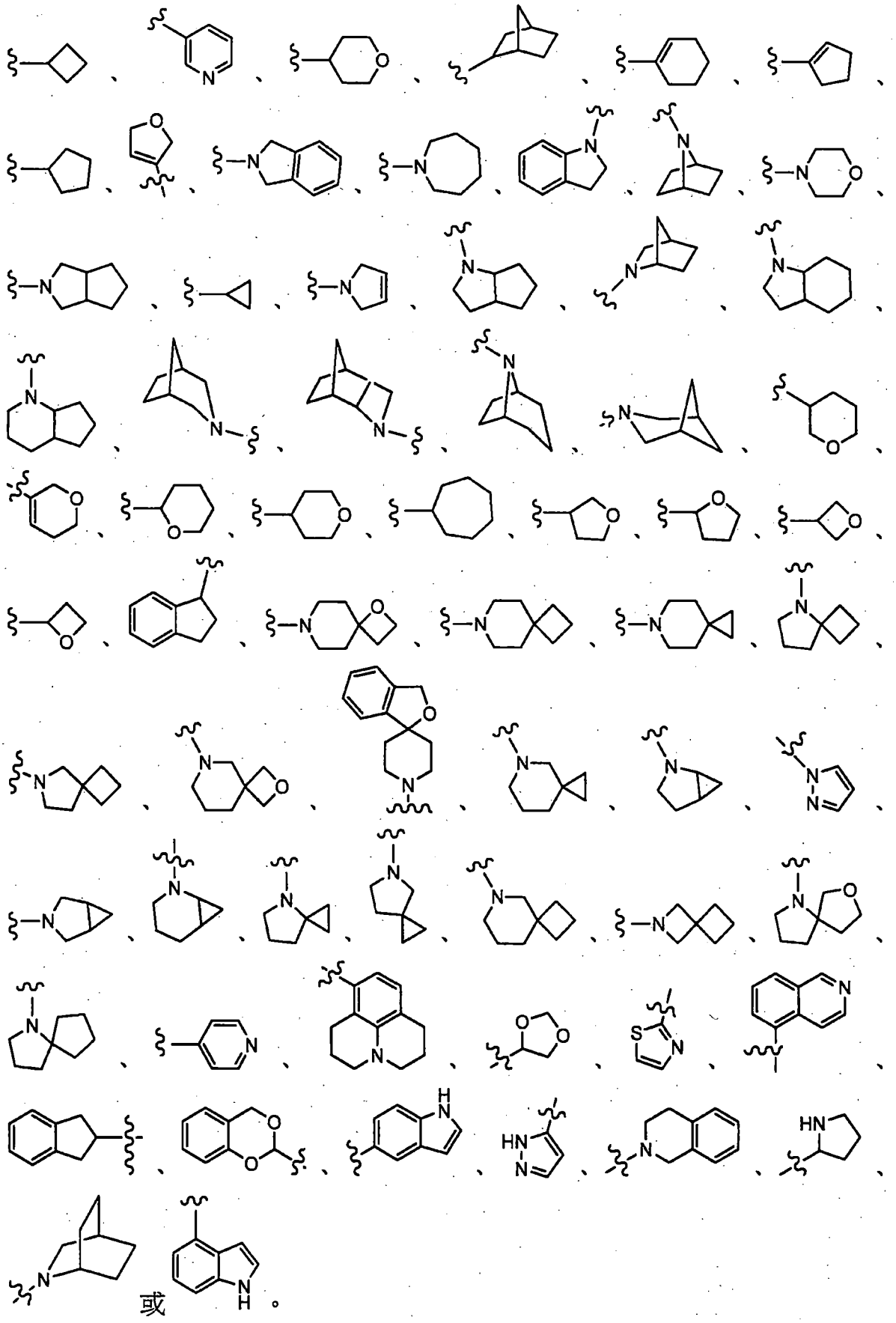
q爲0、1、2、3、4或5。

在一些實施例中，式Ia-ii化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基或萘。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘、哌啶或二氫茚。

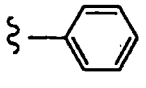
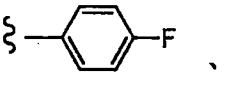
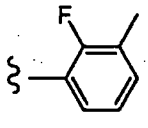
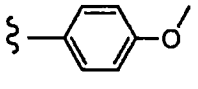
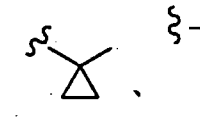
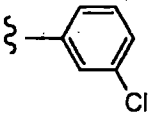
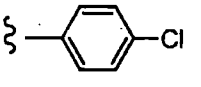
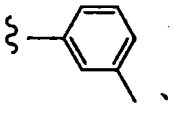
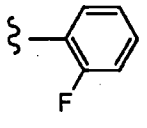
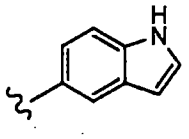
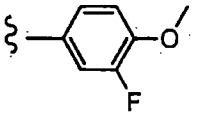
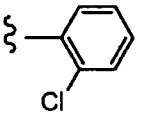
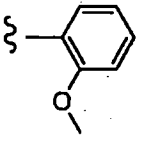
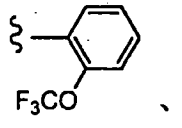
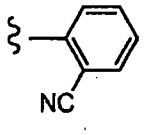
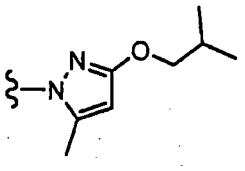
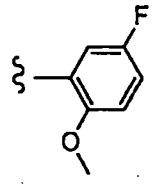
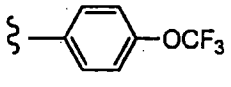
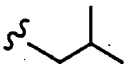
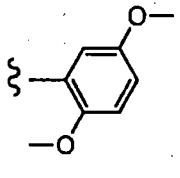
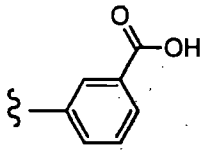
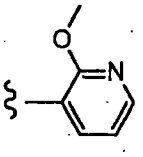
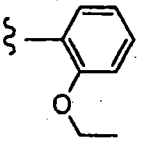
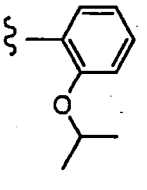
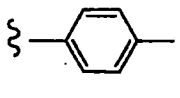
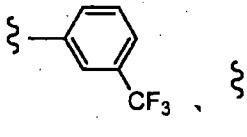
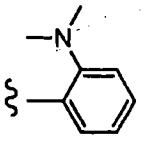
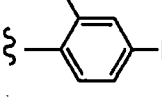
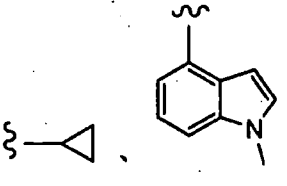
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、

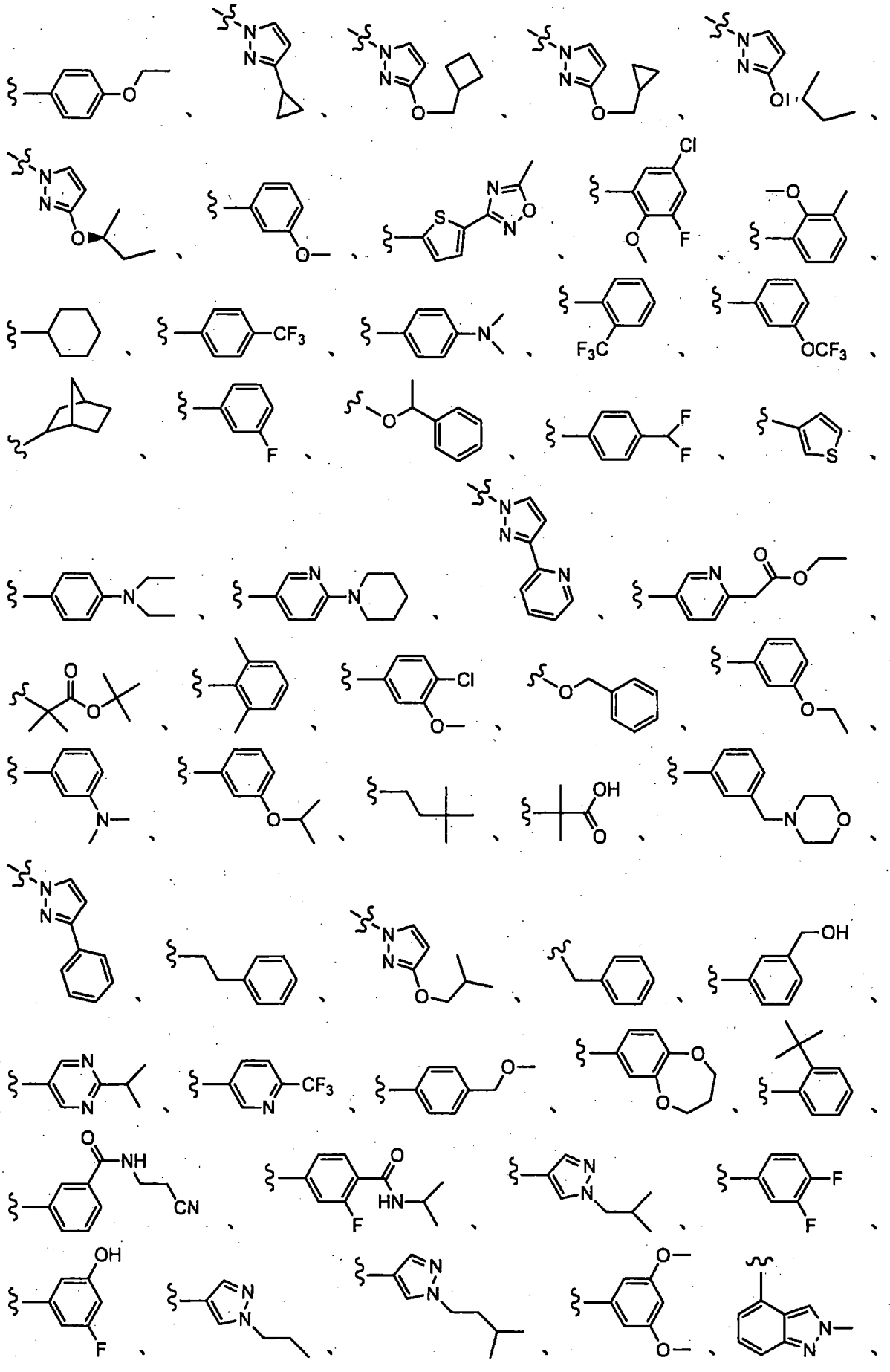


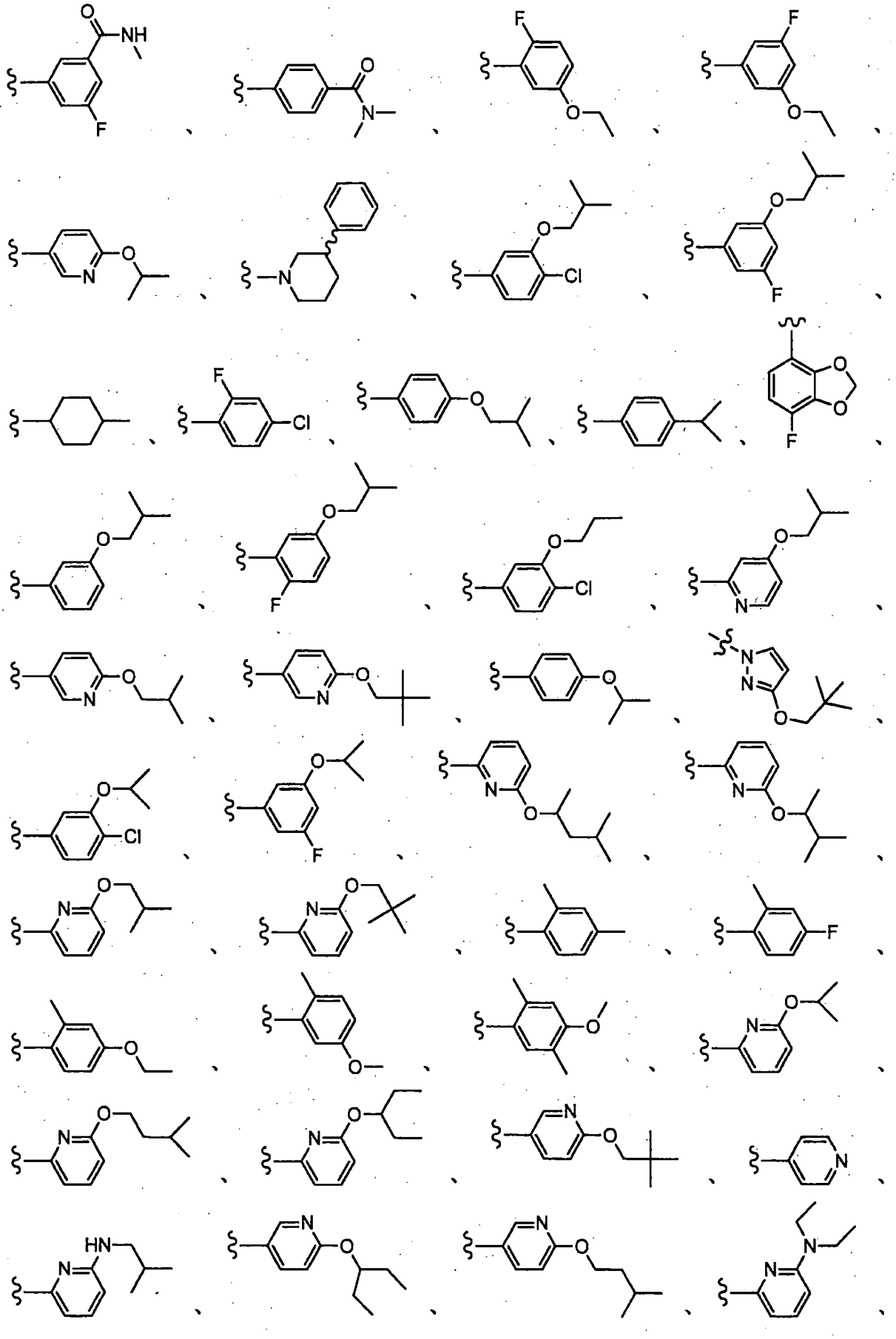
在一些實施例中，Y為O。在一些實施例中，Y為$CH_2$。在一些實

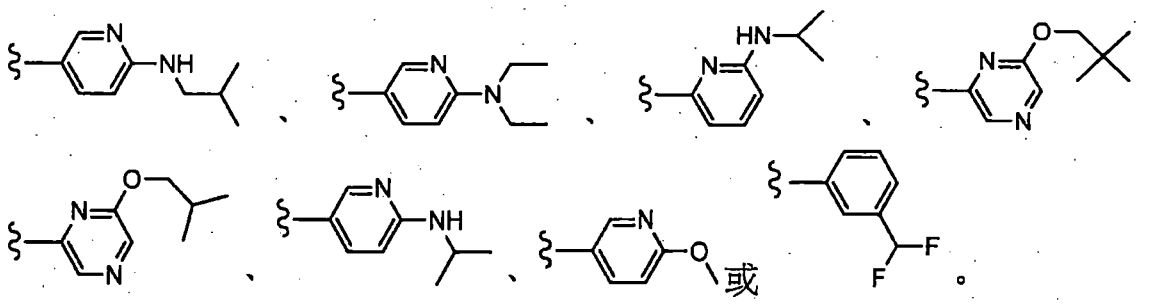
施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲CH($CH_3$)。在一些實施例中，Y爲CH($CH_2CH_3$)。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、 

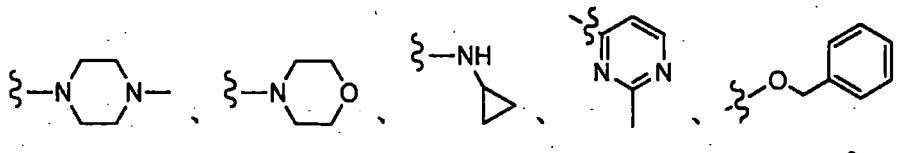


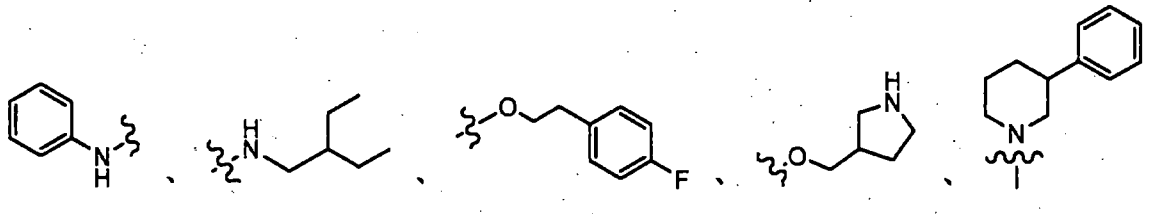


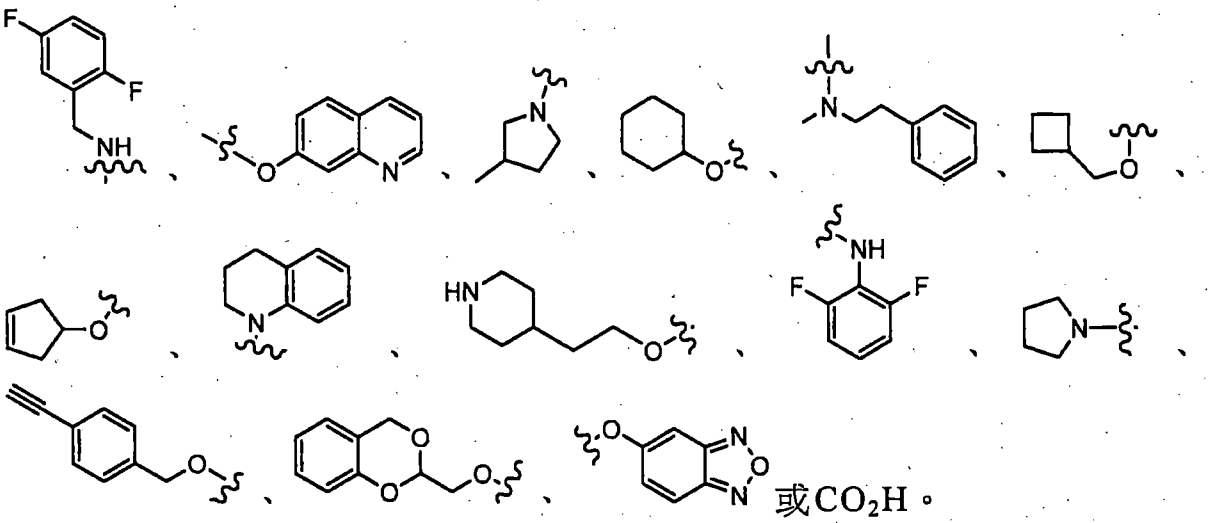


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、



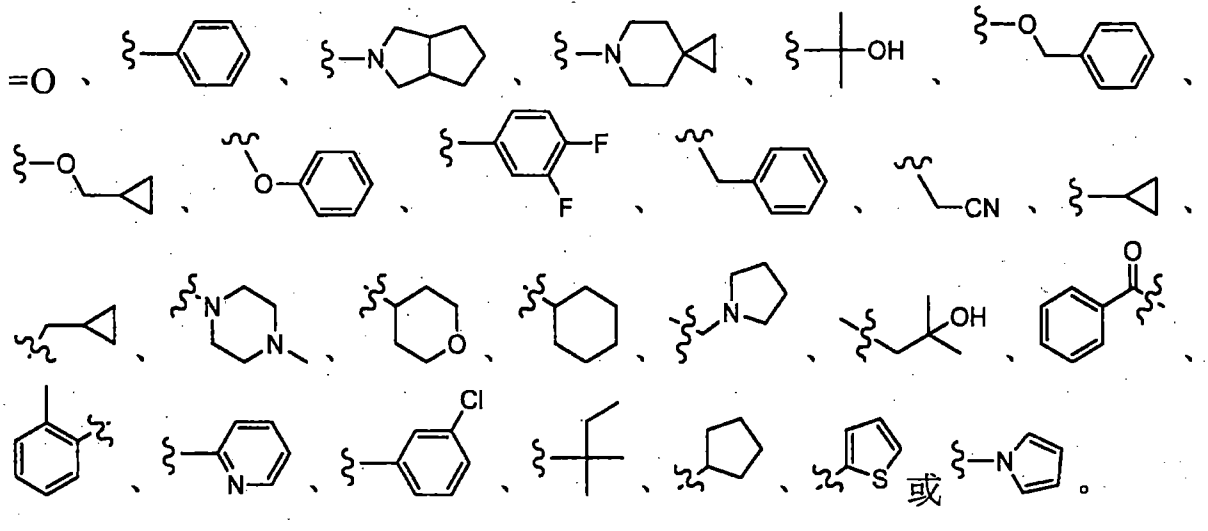




或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、



或



。

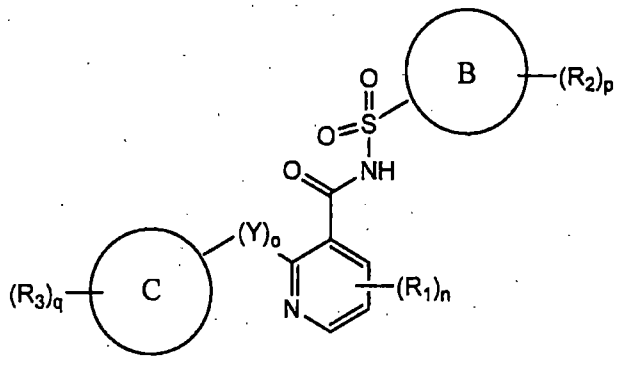
在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施

例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，式I化合物爲式Ib化合物：




**Ib**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10單環或雙環環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、

CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

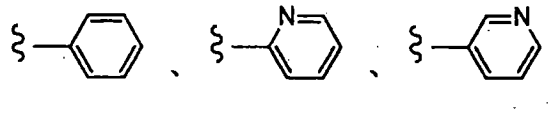
o爲0、1、2、3、4或5；

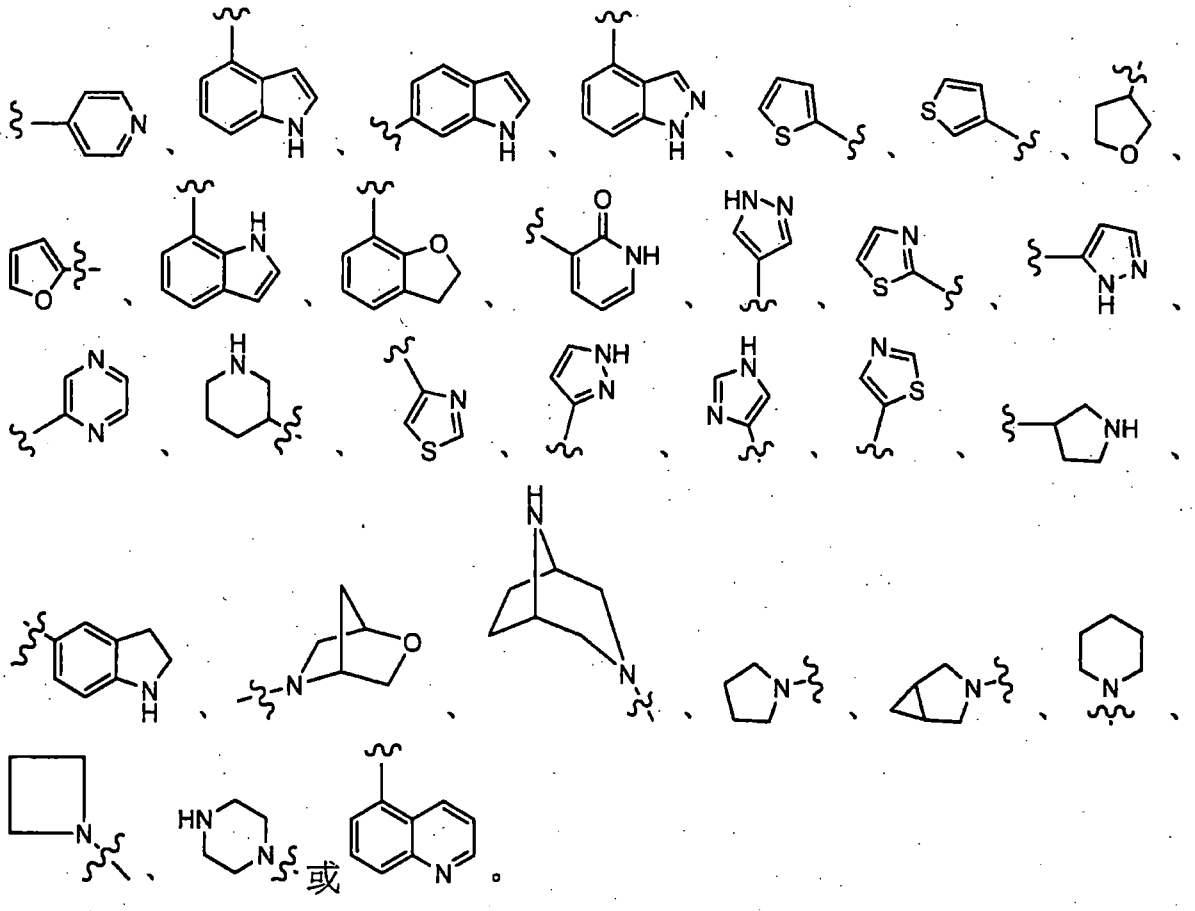
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ib化合物呈醫藥學上可接受之前藥形式存在。

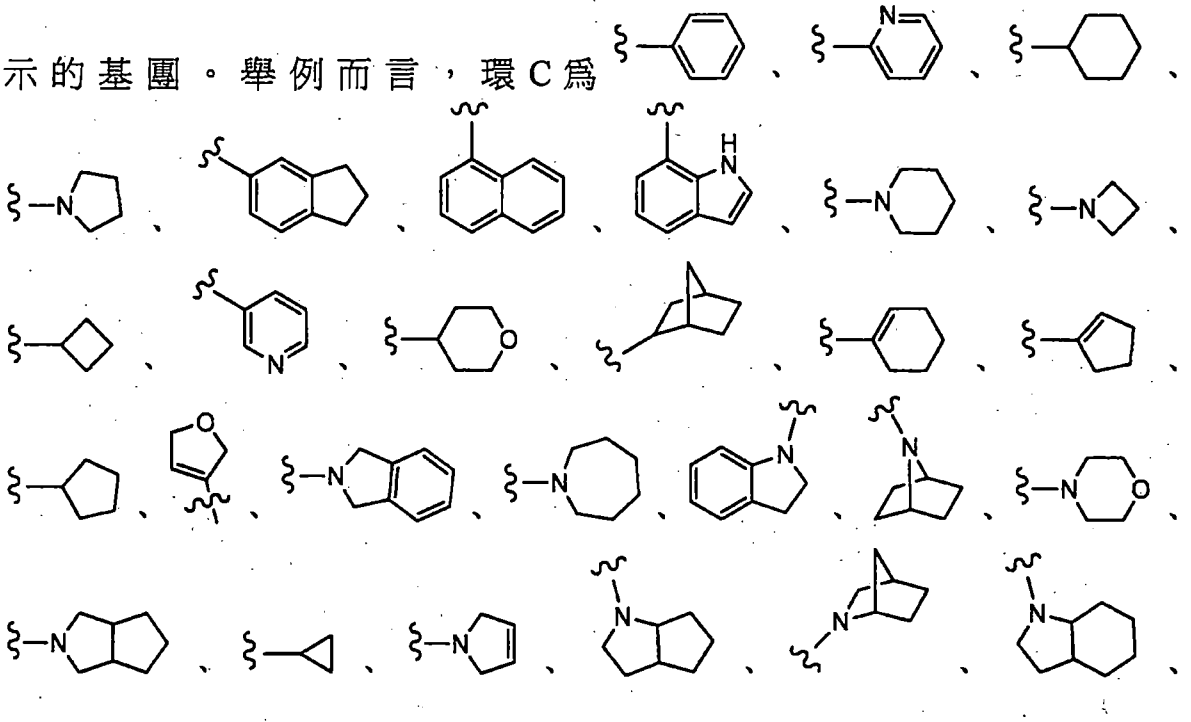
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

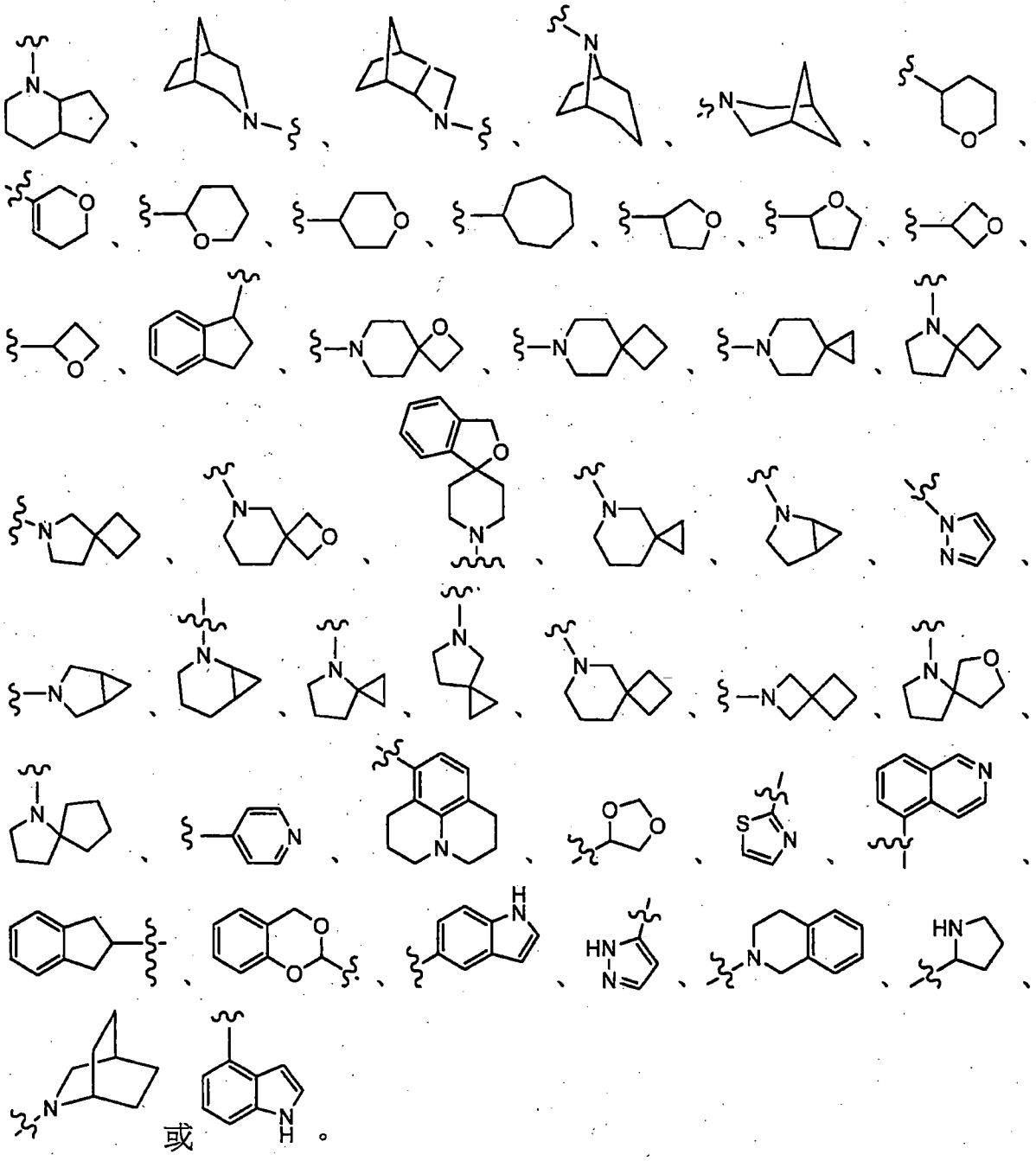
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、



在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、萘、吡咯啶或二氫茚。

在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲

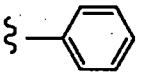
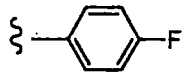
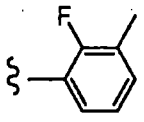
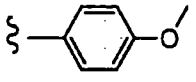
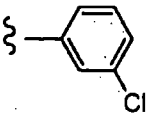
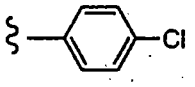
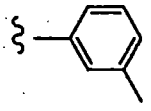
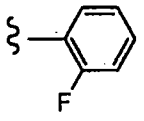
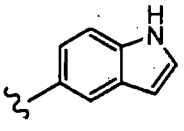
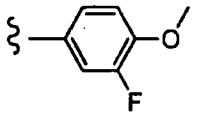
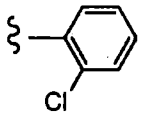
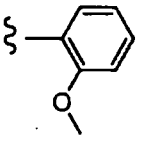
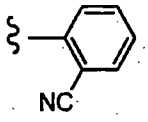
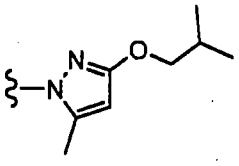
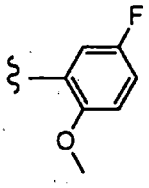
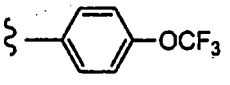
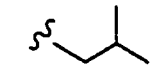
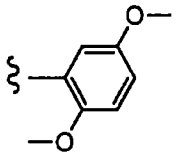
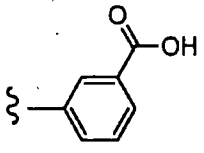
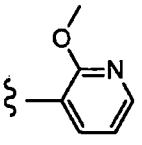
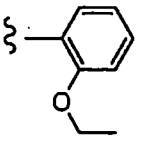
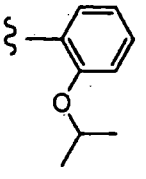
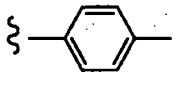
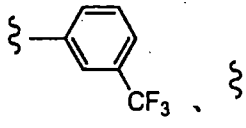
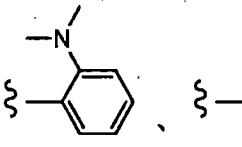
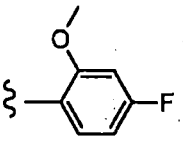
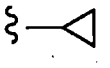
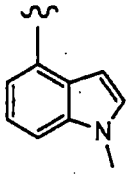
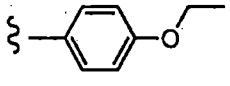
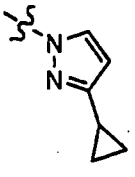
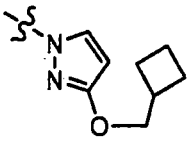
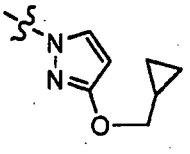
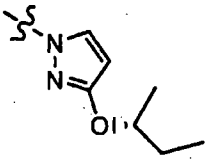
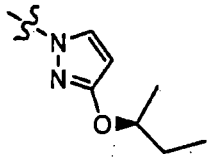
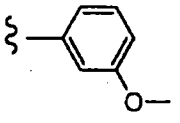
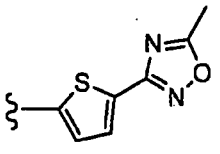
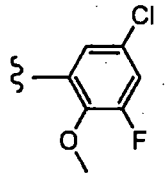
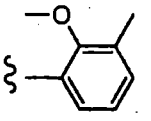
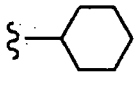
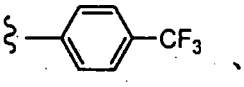
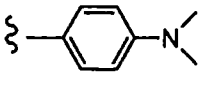
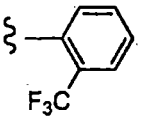
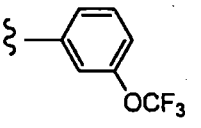


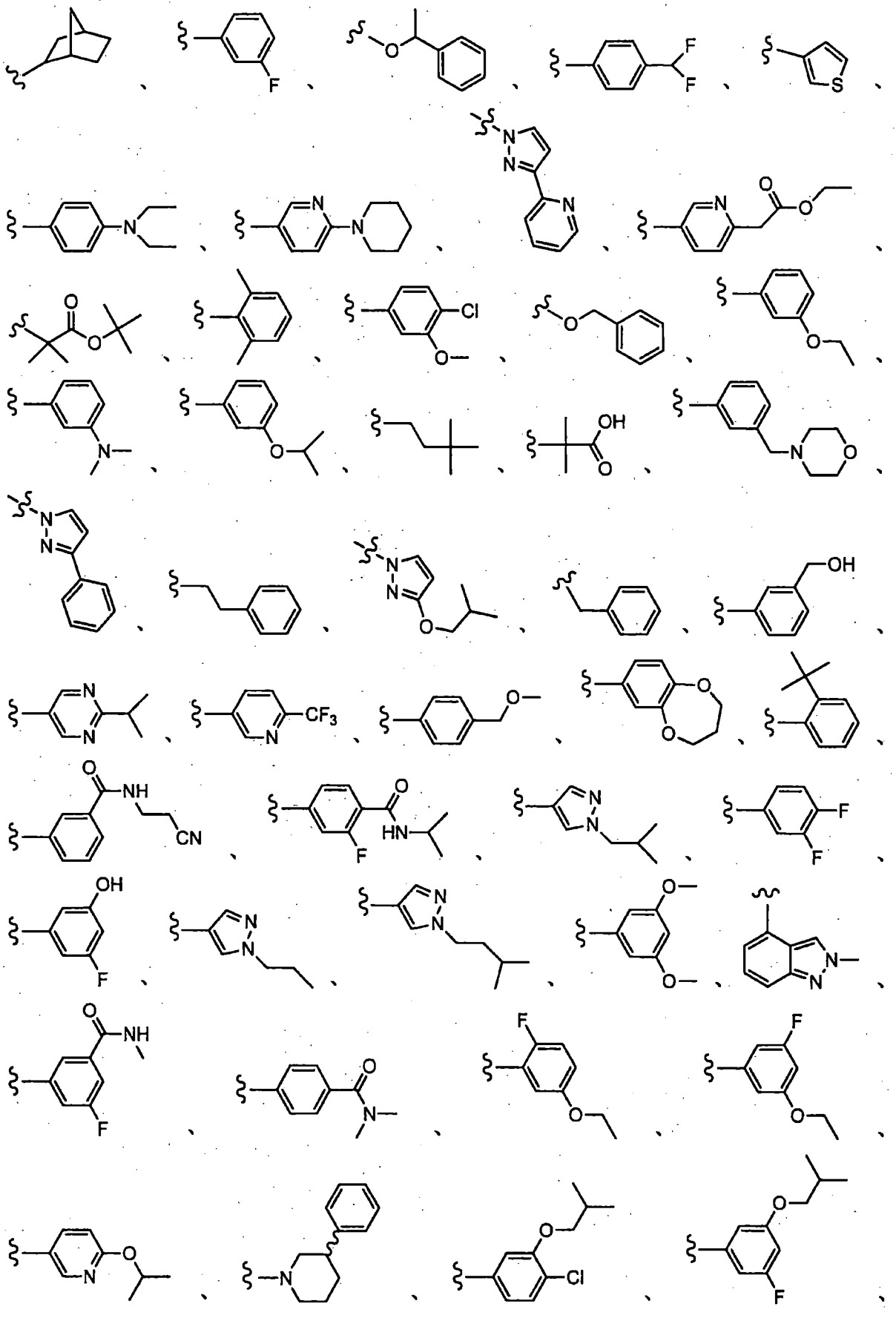


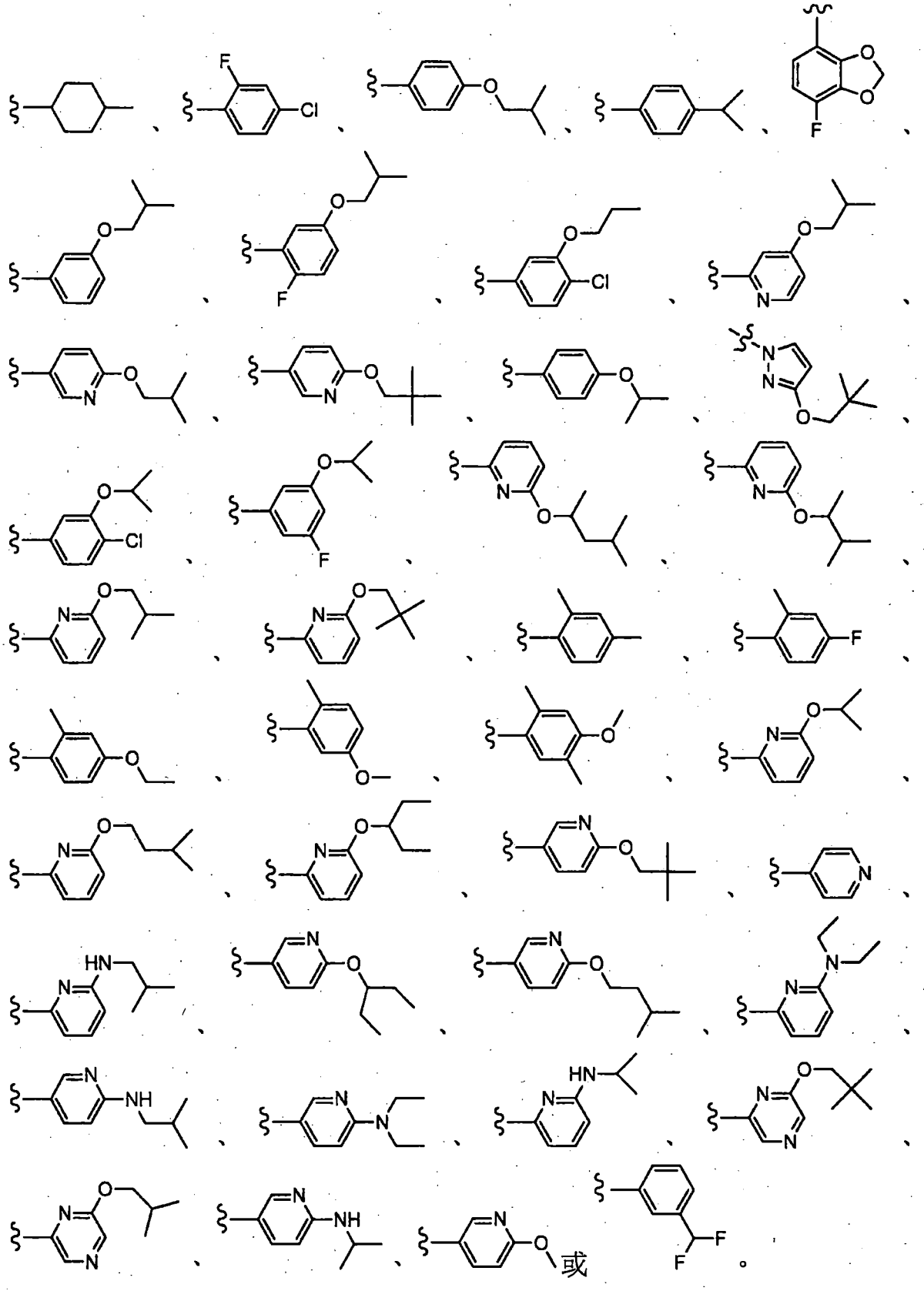
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換

的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

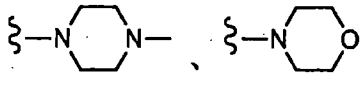
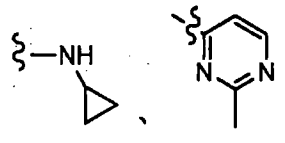
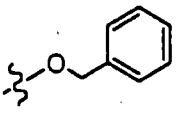
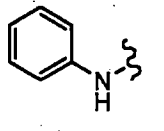
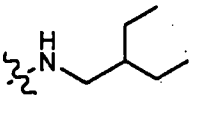
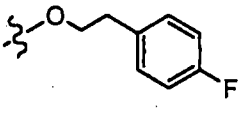
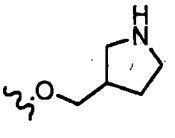
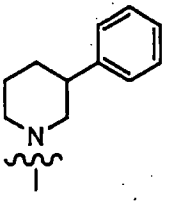
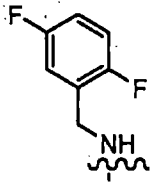
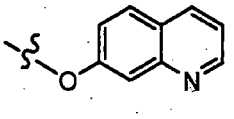
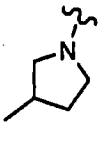
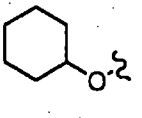
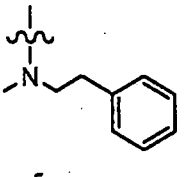
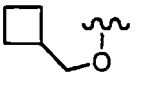
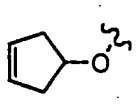
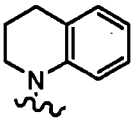
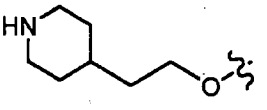
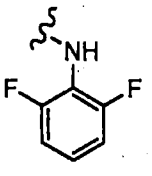
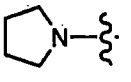
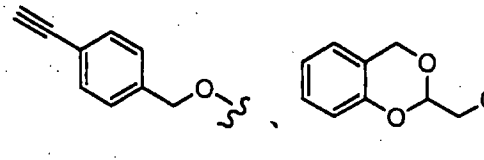
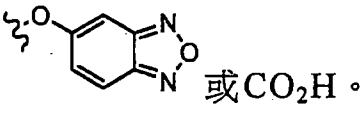
在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、 



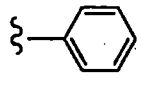
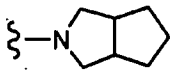
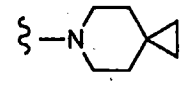
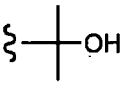
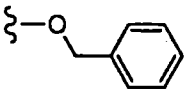
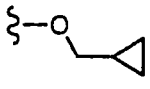
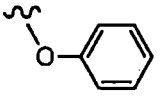
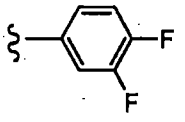
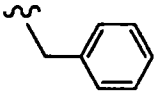
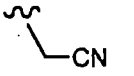
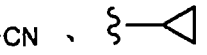
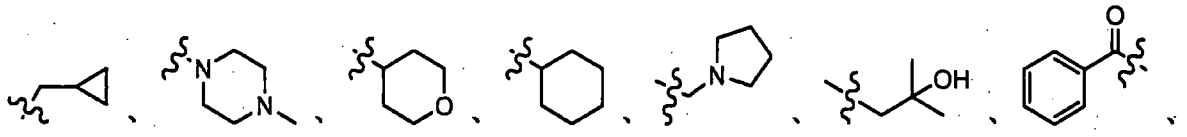
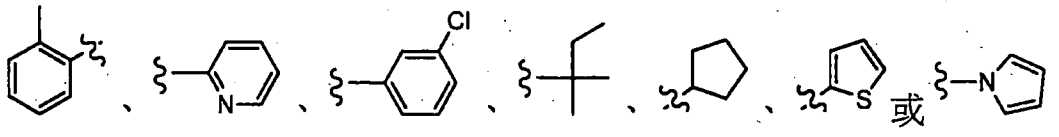


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨

立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  或。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，環B爲吡啶基。在一些實施例中，環B爲苯基。在一些實施例中，環B及環C爲苯基。在一些實施例中，環B爲吡啶基且環C爲苯基。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲O。

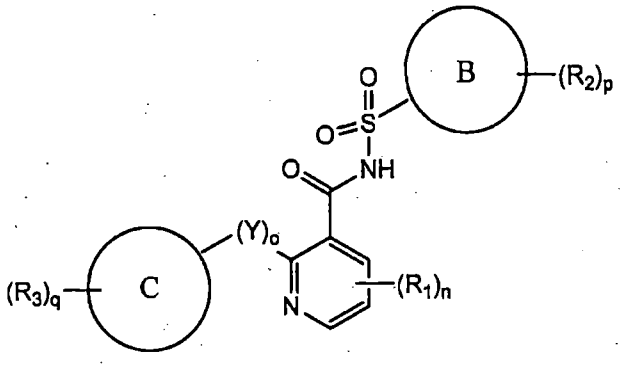
在一些實施例中，$R_1$爲芳基。在一些實施例中，環B、環C及$R_1$爲苯基。在一些實施例中，環B爲吡啶基，環C爲苯基，且$R_1$爲苯基。在一些實施例中，環B、環C及$R_1$爲苯基，且Y爲$CH_2$。在一些實施例中，環B、環C及$R_1$爲苯基，且Y爲O。在一些實施例中，環B爲吡啶基，環C爲苯基，$R_1$爲苯基，且Y爲$CH_2$。在一些實施例中，環B爲吡啶基，環C爲苯基，$R_1$爲苯基，且Y爲O。

在一些實施例中，環C爲雜環。在一些實施例中，環C爲吡咯啶。在一些實施例中，環C爲哌啶。在一些實施例中，環B爲吡啶基，環C爲雜環。在一些實施例中，環B爲吡啶基，環C爲雜環烷基，且$R_1$爲苯基。在一些實施例中，環B爲苯基，環C爲雜環烷基，且$R_1$爲苯基。

在一些實施例中，$R_1$爲雜芳基。在一些實施例中，環C爲吡咯啶且$R_1$爲雜芳基。在一些實施例中，環C爲吡咯啶且$R_1$爲吡唑。在一些實施例中，環B爲吡啶基，環C爲吡咯啶，且$R_1$爲雜芳基。在一些實施例中，環B爲吡啶基，環C爲雜環烷基，且$R_1$爲吡啶基。

在一些實施例中，$R_1$爲環烷基。在一些實施例中，環B爲吡啶基且$R_1$爲環烷基。

在一些實施例中，本發明提供式Ib-i化合物：




**Ib-i**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

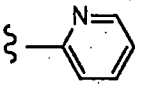
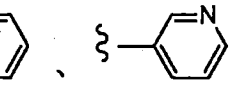
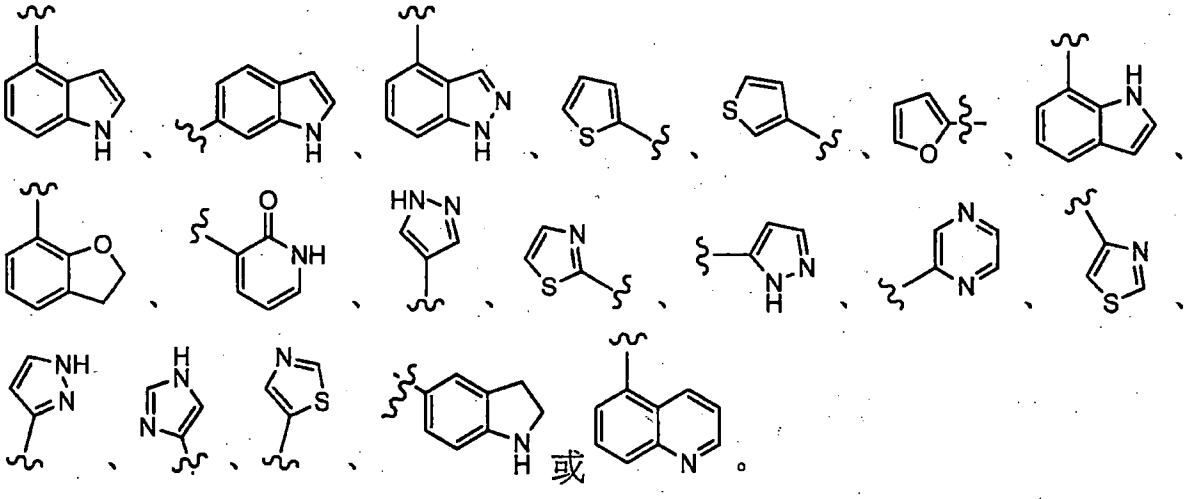
o爲0、1、2、3、4或5；

p爲0、1、2或3；且

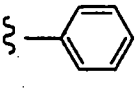
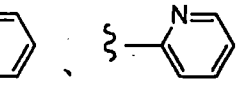
q爲0、1、2、3、4或5。

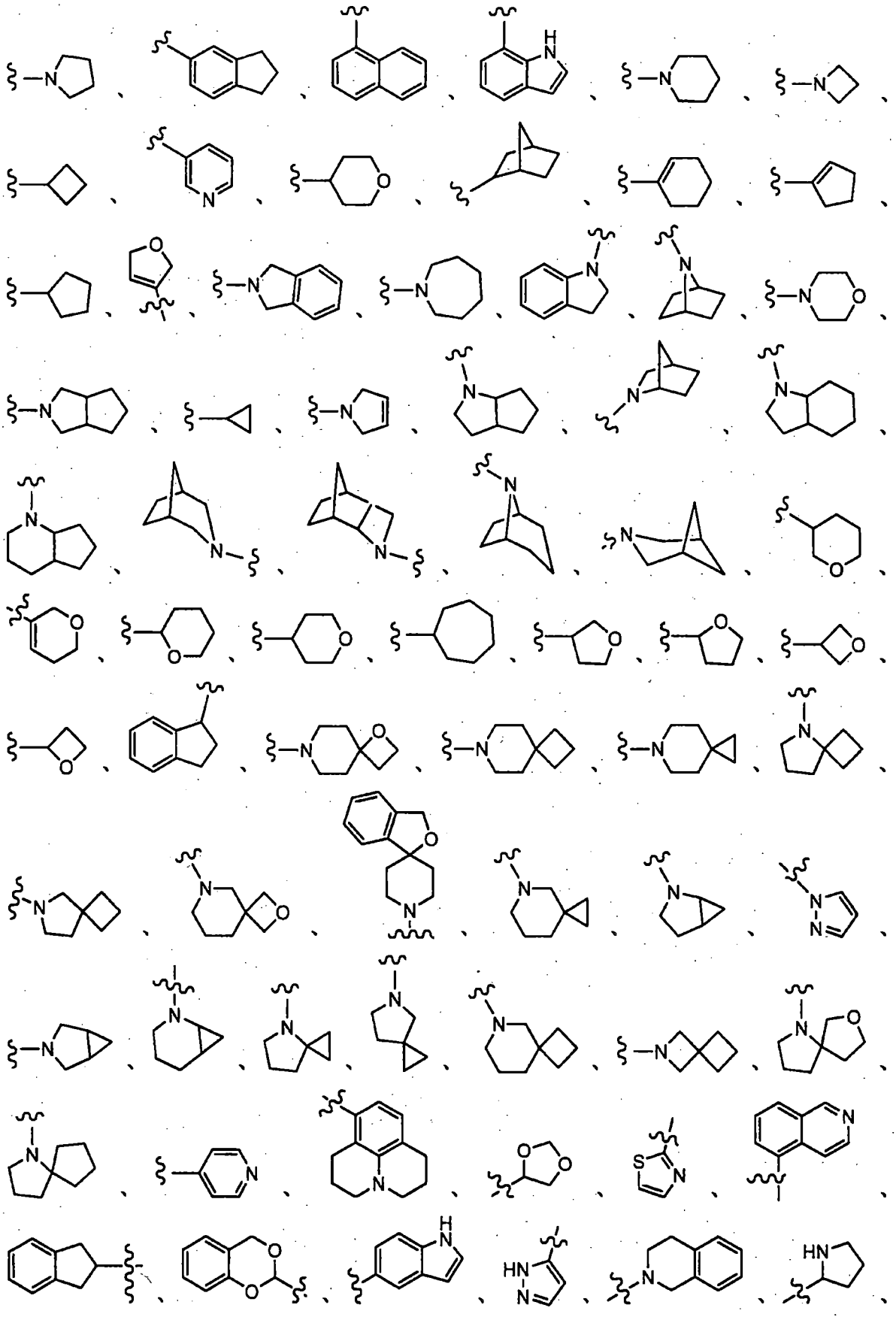
在一些實施例中，式Ib-i化合物呈醫藥學上可接受之前藥形式存在。

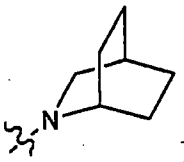
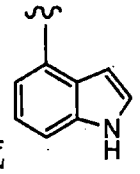
在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、  、  或。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、萘、吡咯啶或二氫茚。

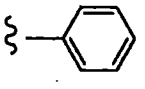
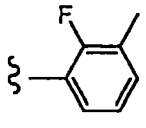
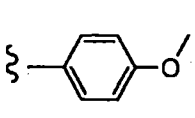
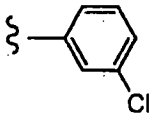
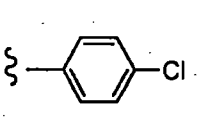
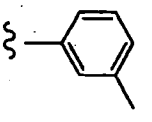
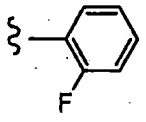
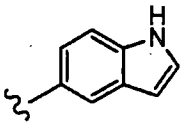
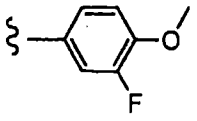
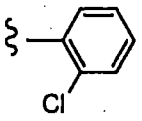
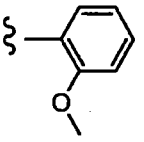
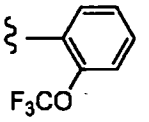
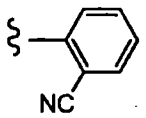
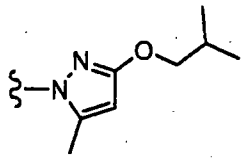
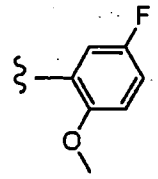
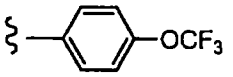
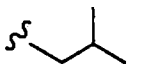
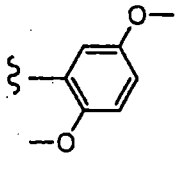
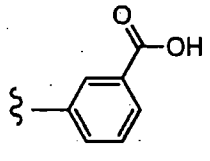
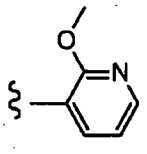
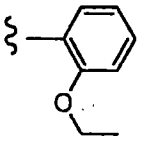
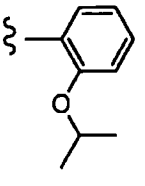
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、

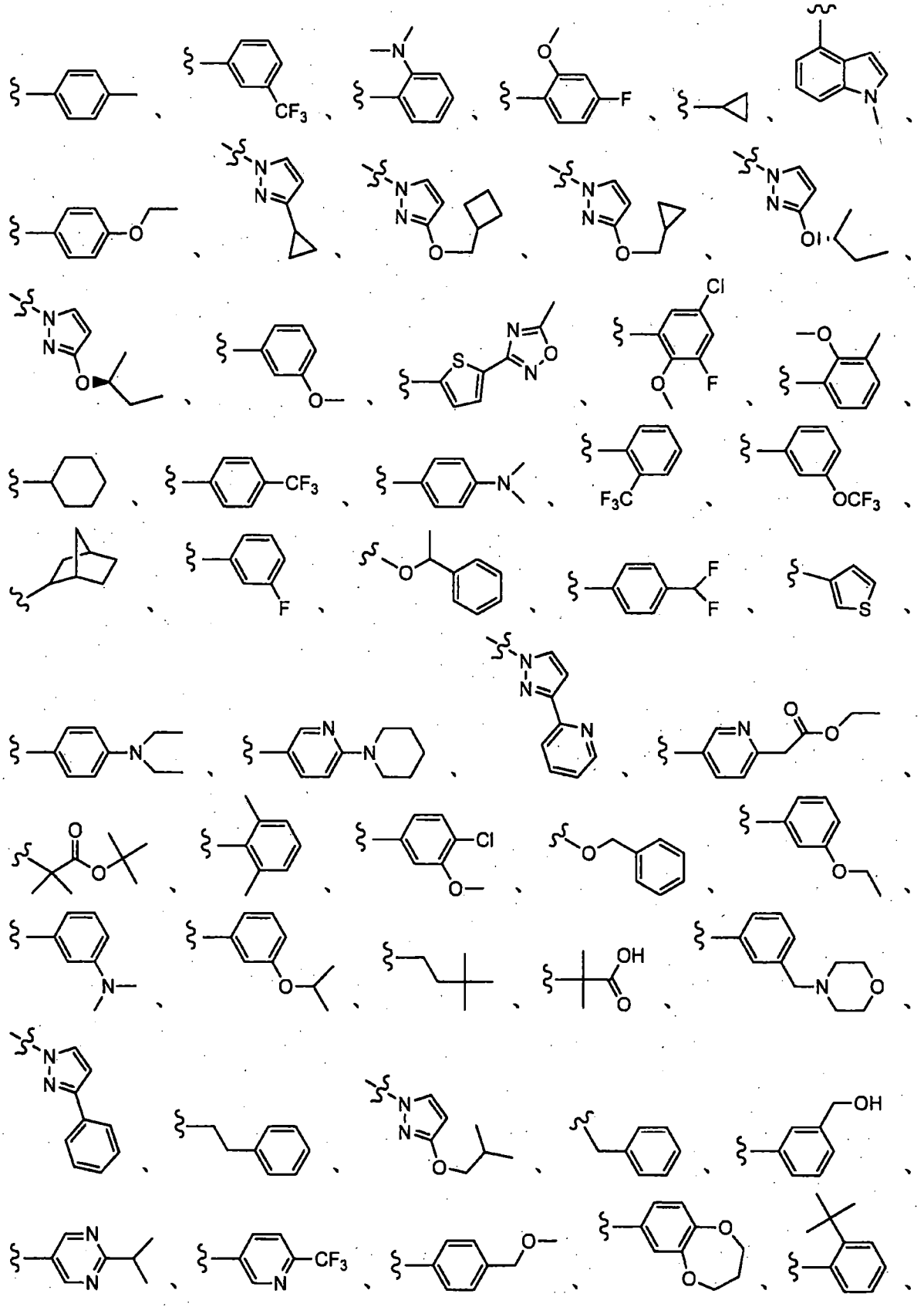


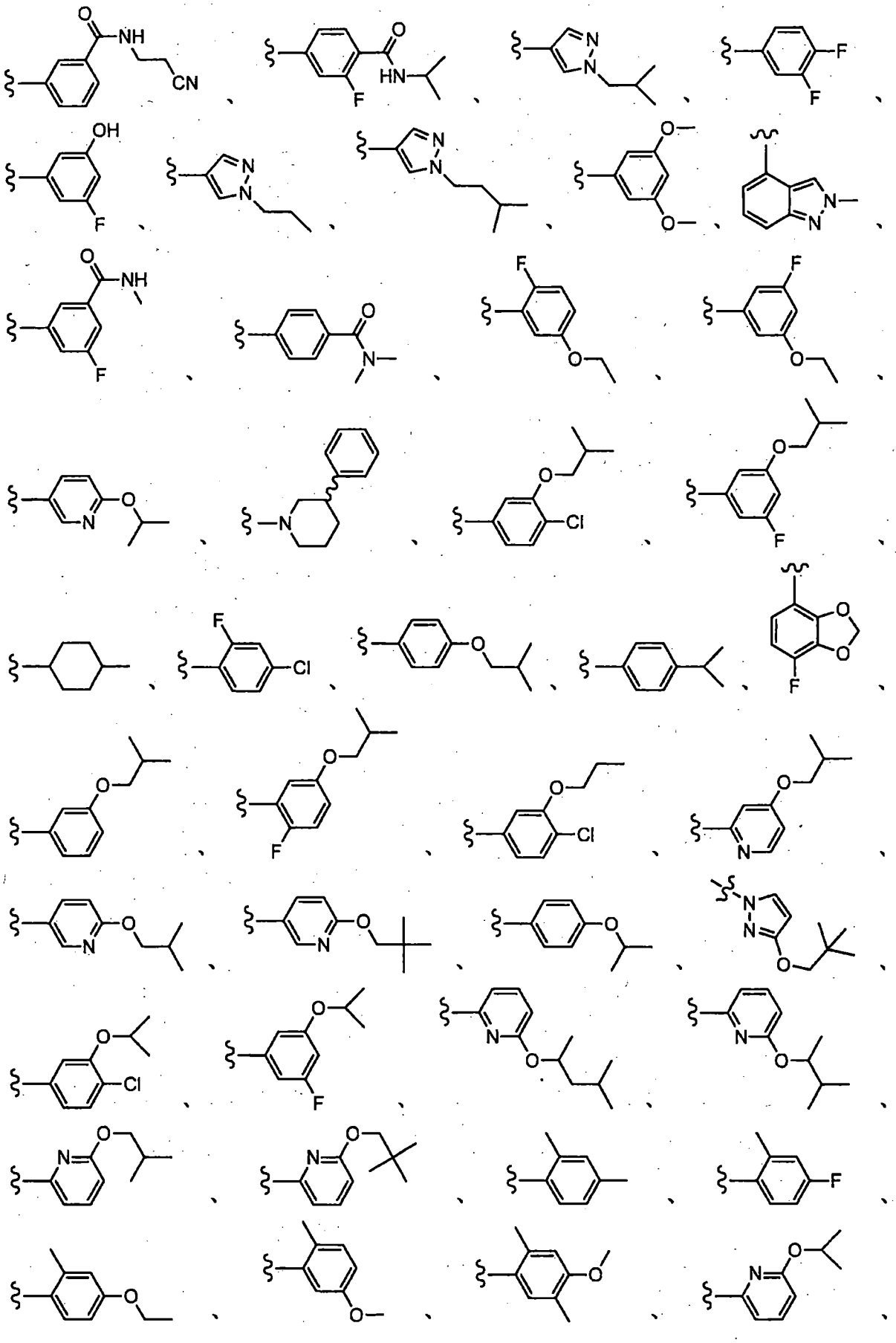

或

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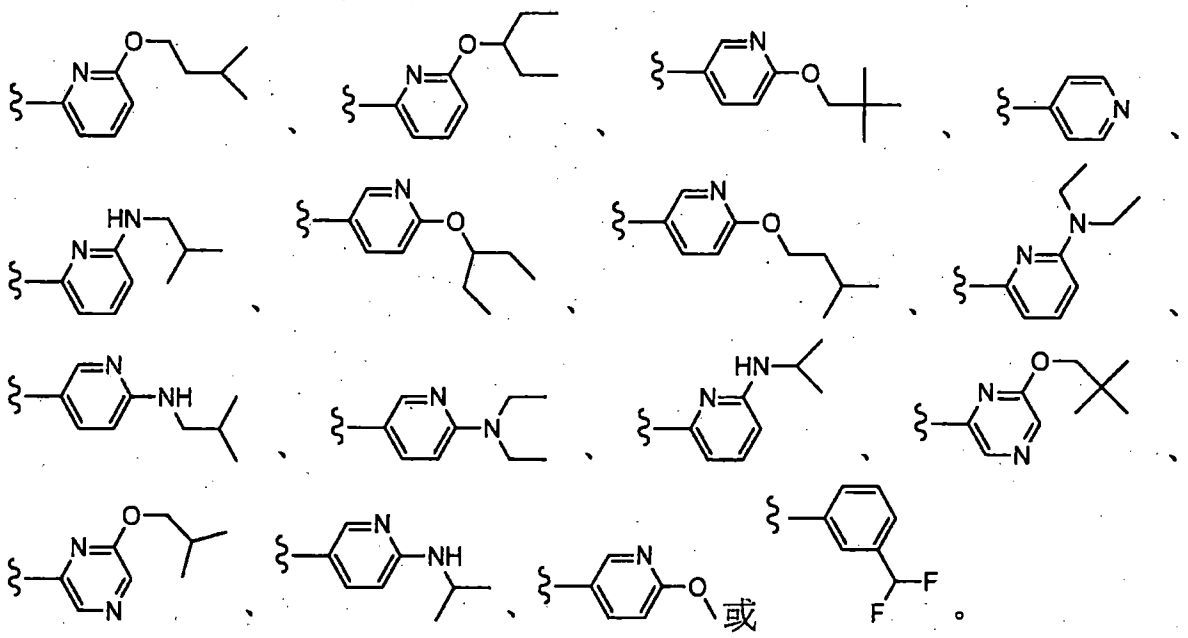
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

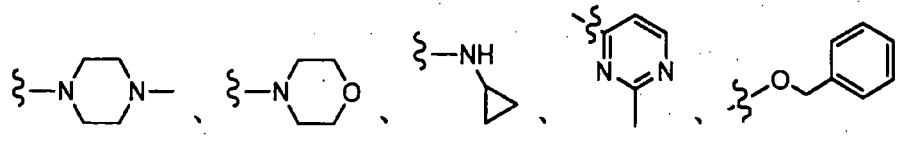


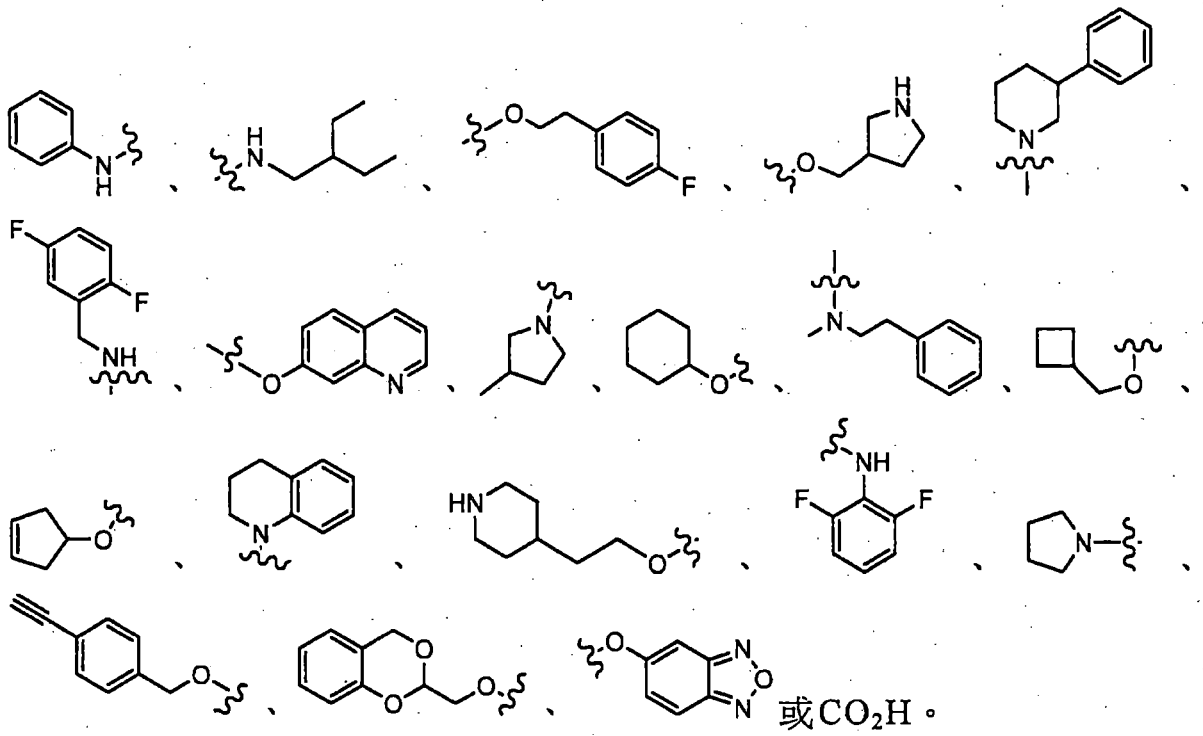




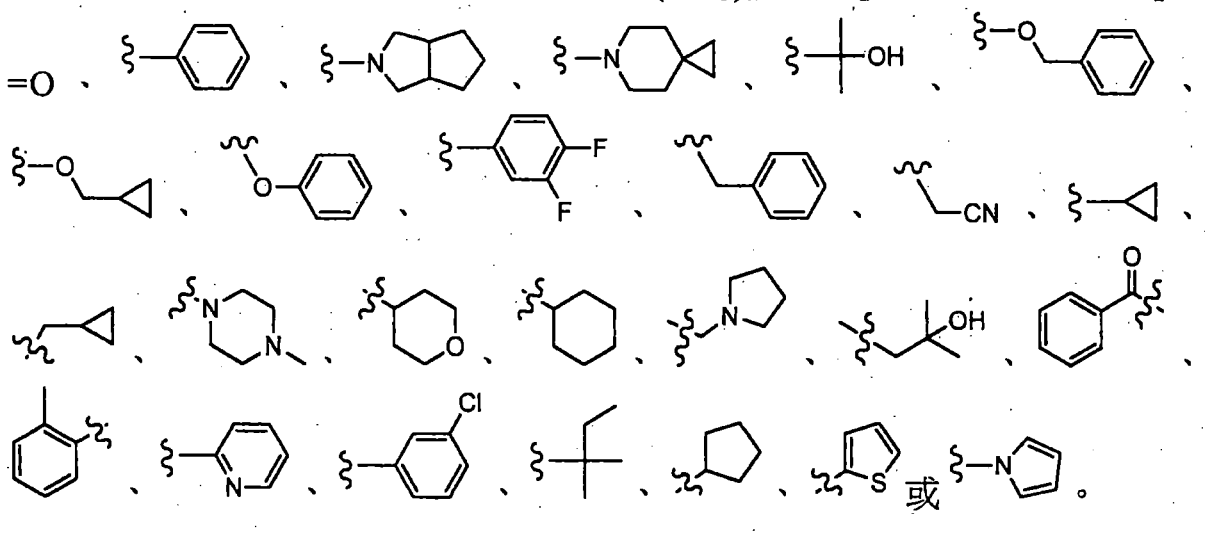
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、




或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

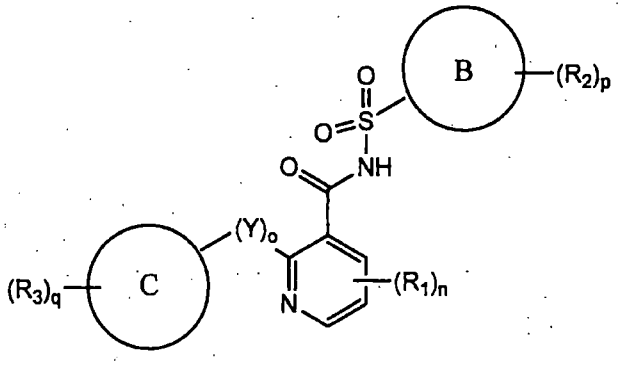
在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、 
或。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，本發明提供式Ib-ii化合物：




**Ib-ii**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳

基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

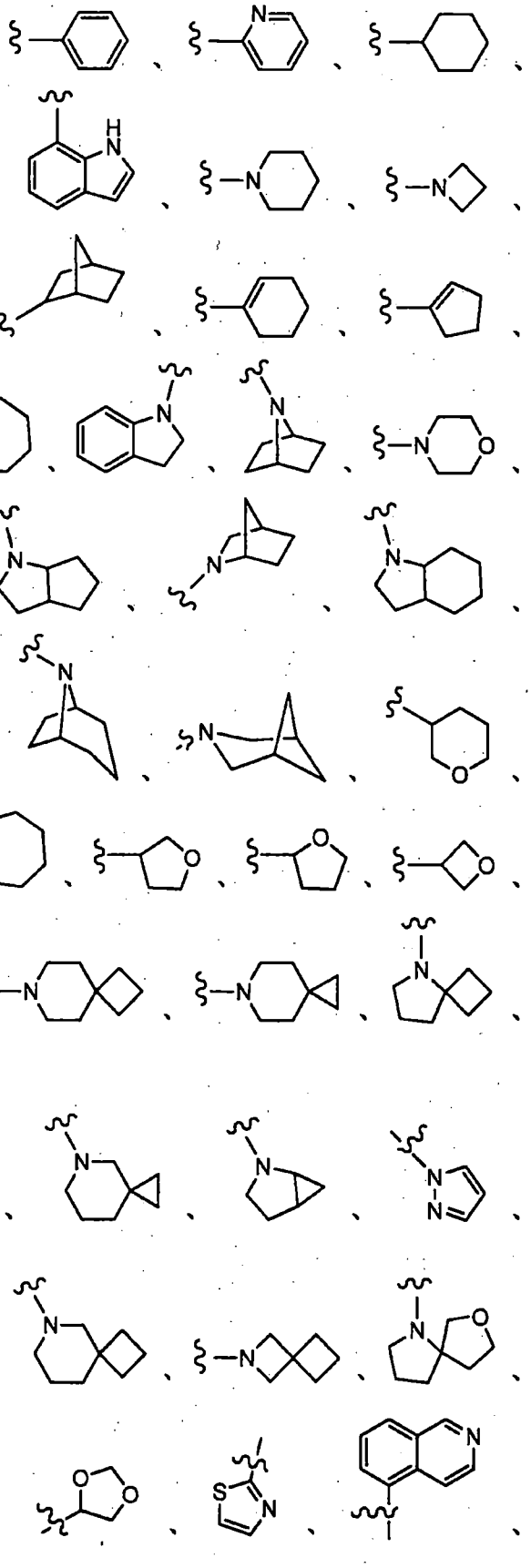
p爲0、1、2或3；且

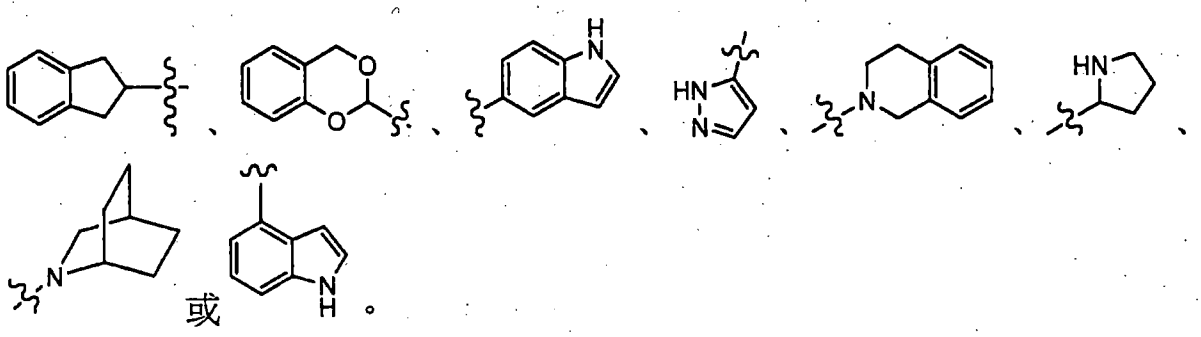
q爲0、1、2、3、4或5。

在一些實施例中，式Ib-ii 化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基或萘。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、萘、吡咯啶或二氫茚。

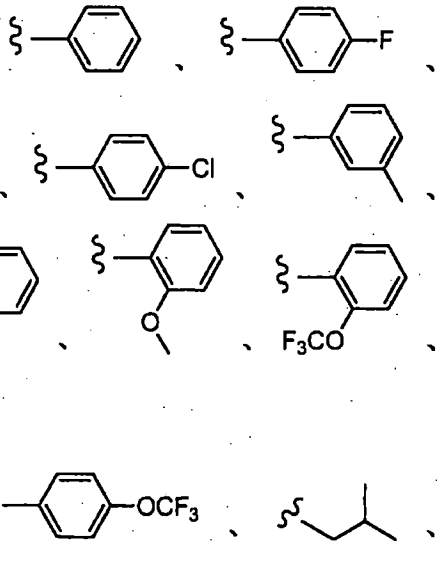
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲 

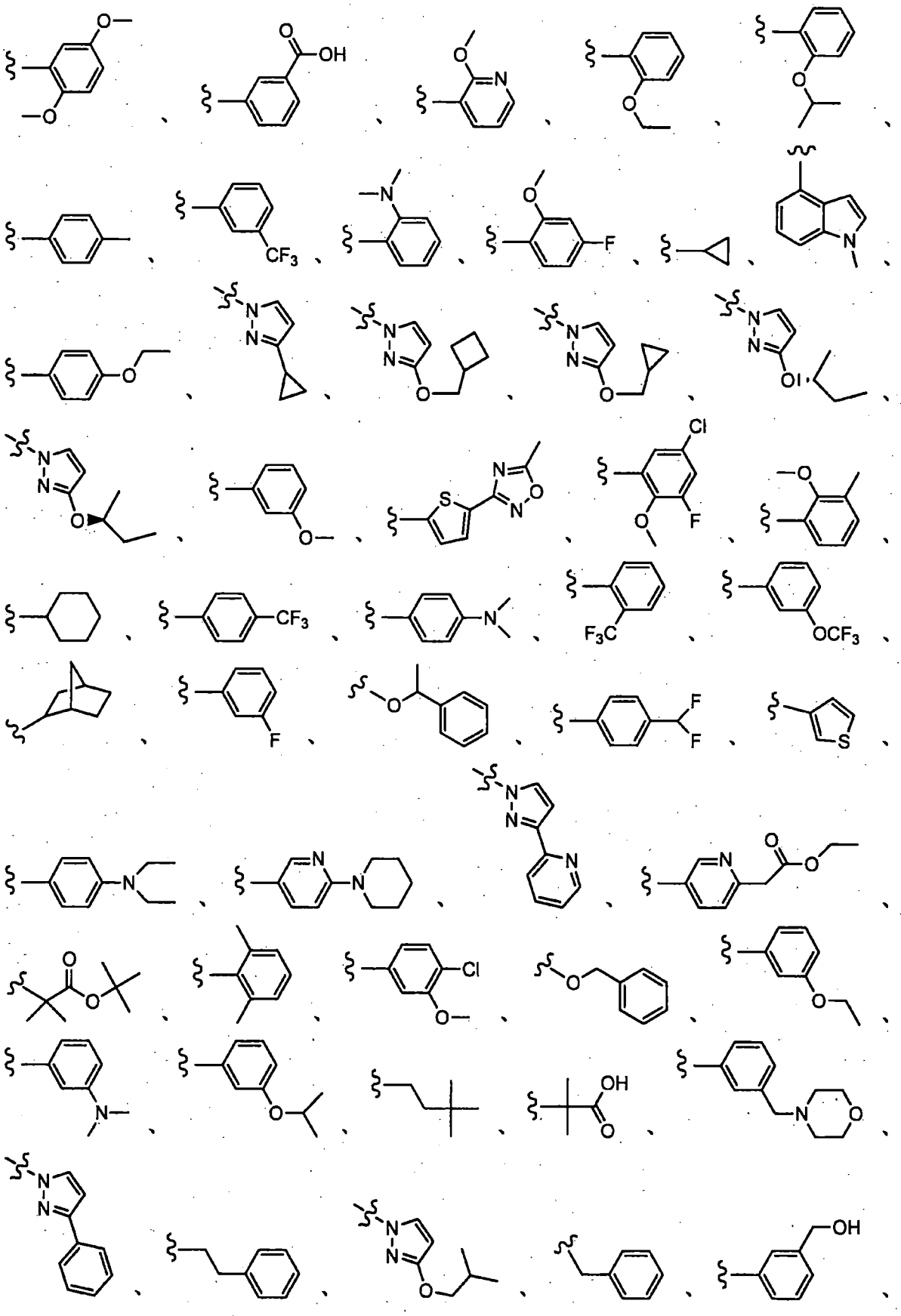


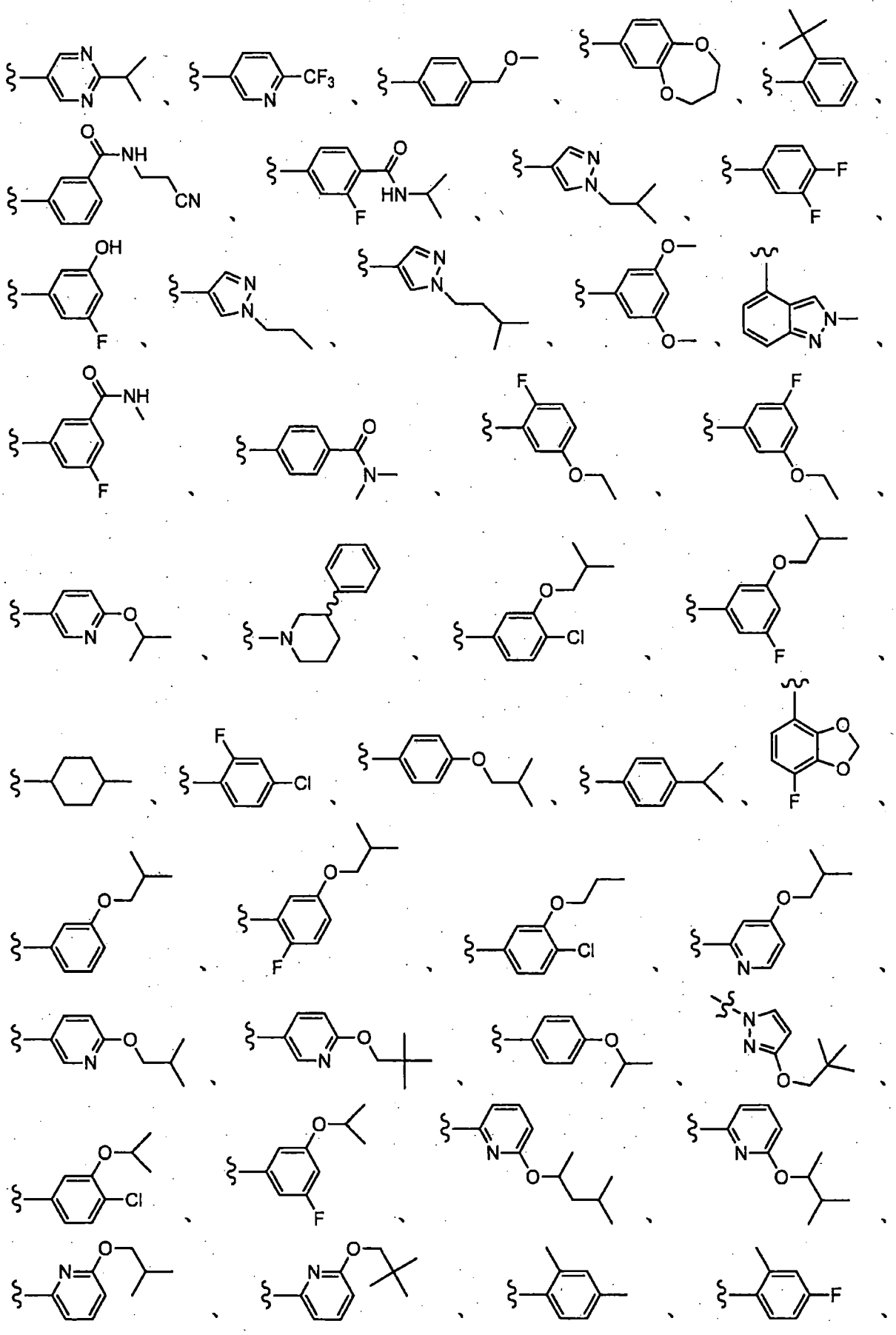
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

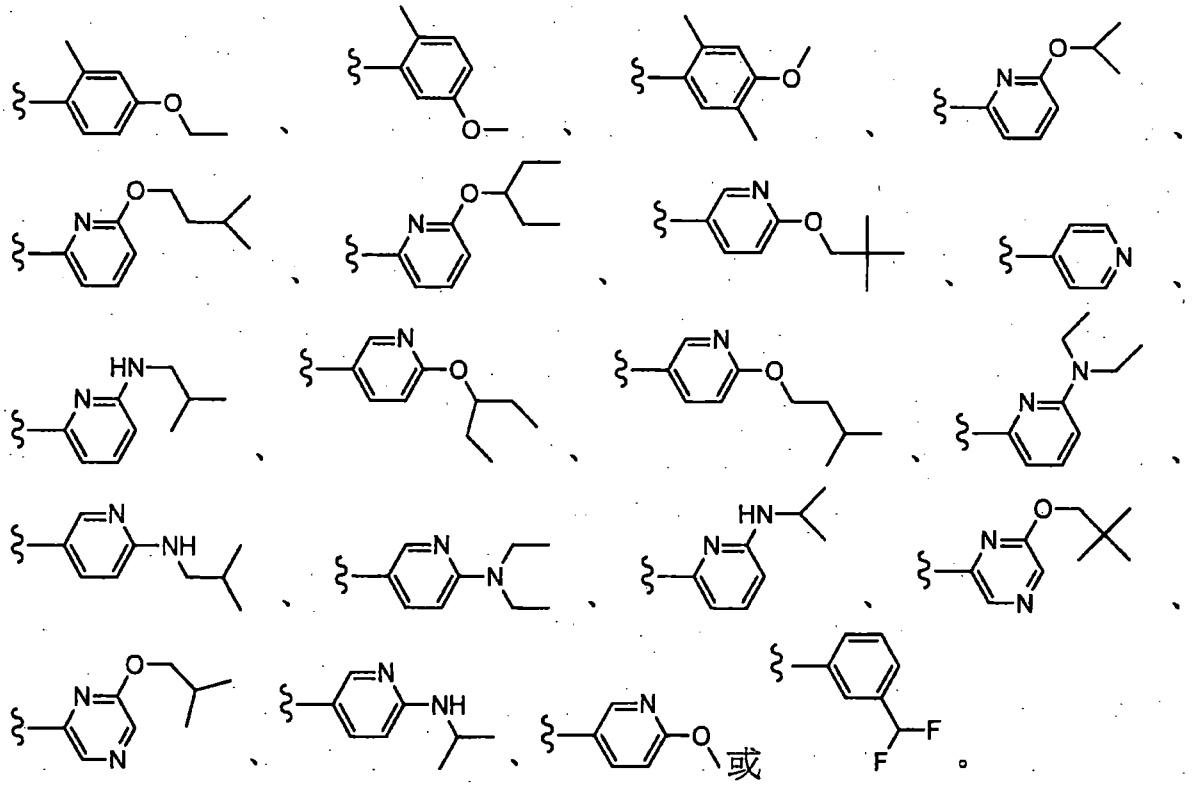
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、



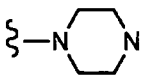
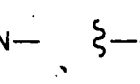
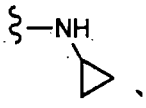
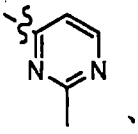
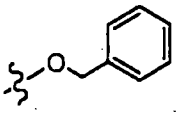
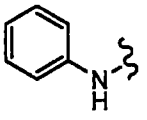
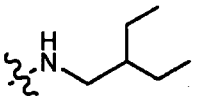
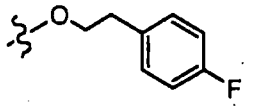
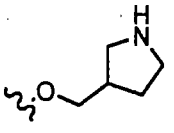
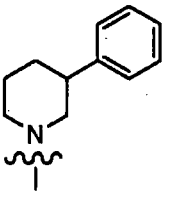
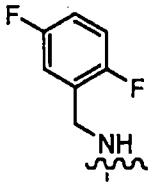
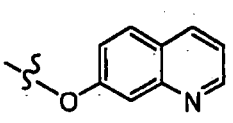
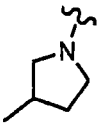
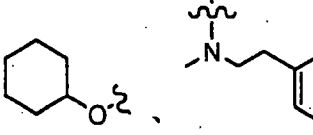
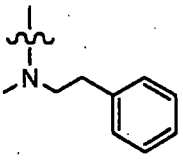
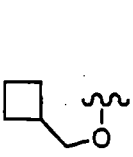
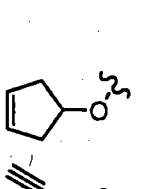
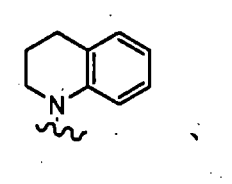
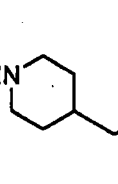
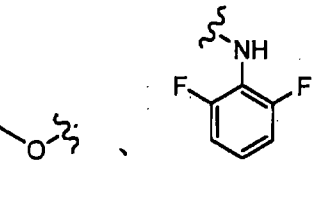
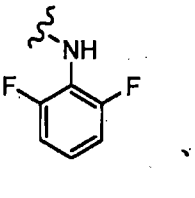
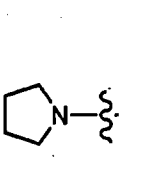
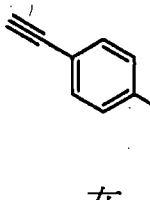
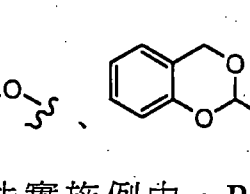
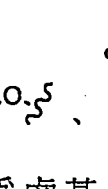
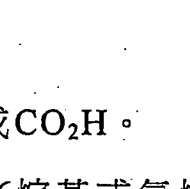
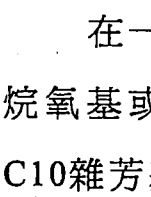
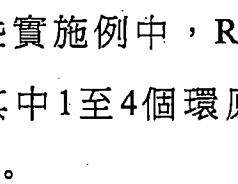
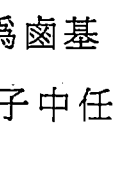
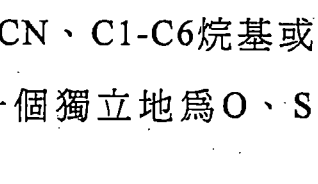
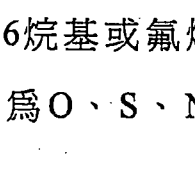
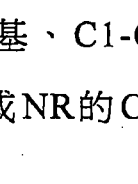
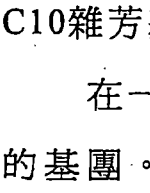
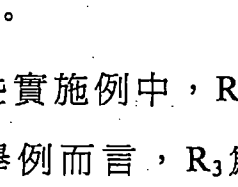
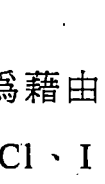
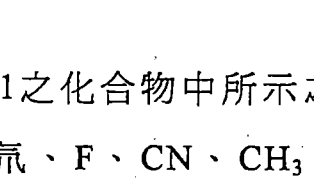
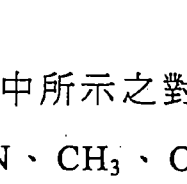
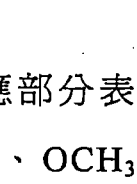
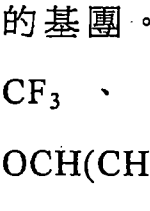
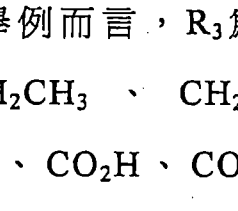
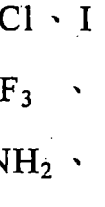
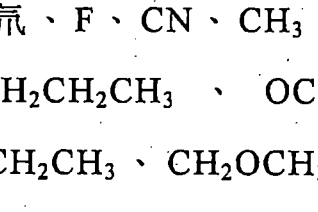
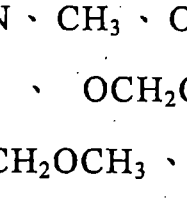
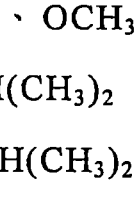
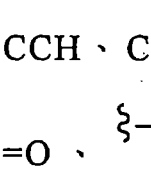
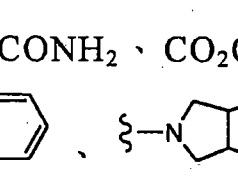
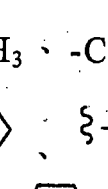
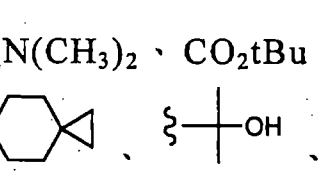
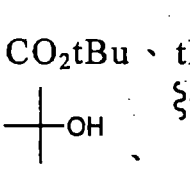
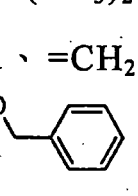
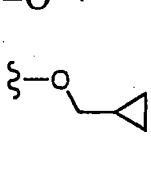
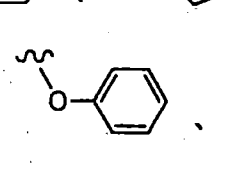
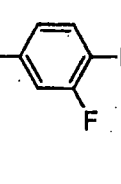
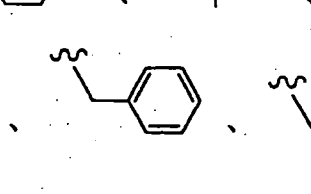
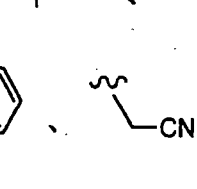
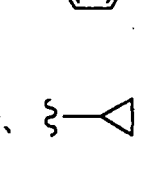




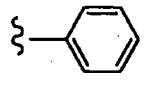
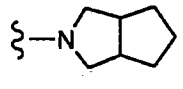
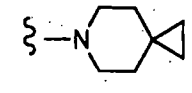
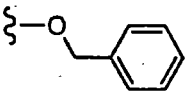
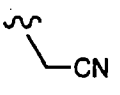


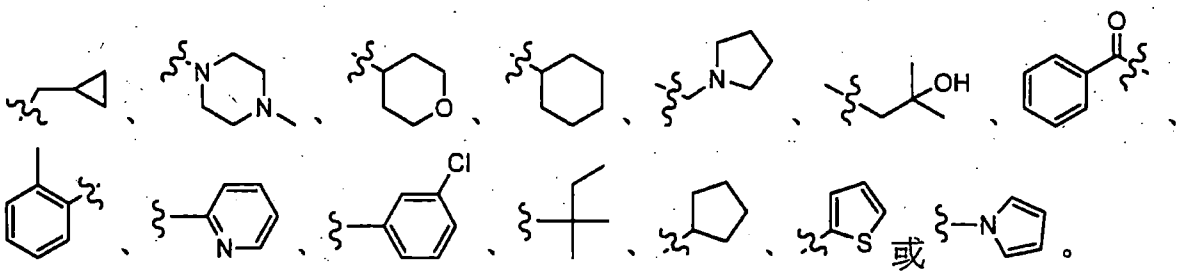
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、

$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、  、  、  、、、、、、、或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、、  、、、、、  、

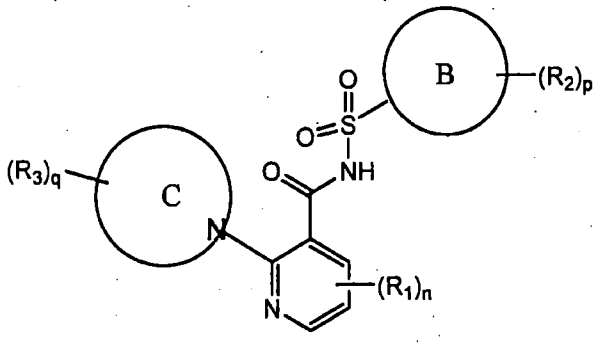


在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，本發明提供式Ib-iii化合物：



**Ib-iii**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

環C爲其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環，且其中環C上之一個氮爲與吡啶環之附接點；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或

NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

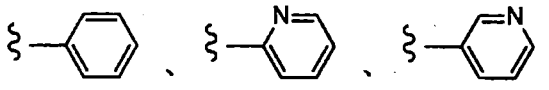
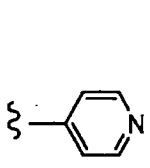
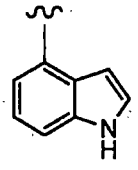
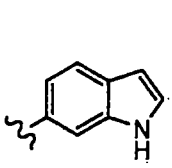
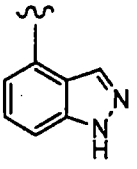
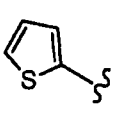
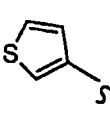
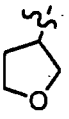
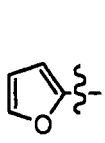
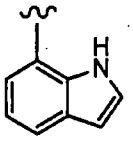
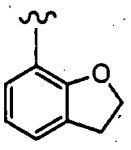
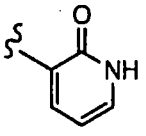
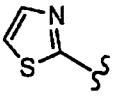
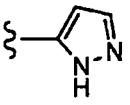
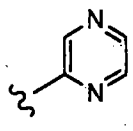
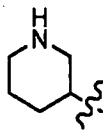
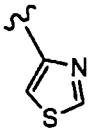
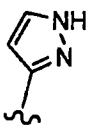
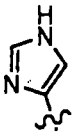
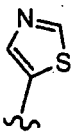
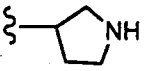
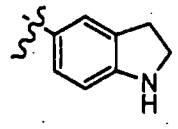
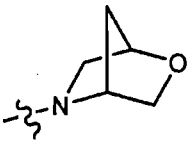
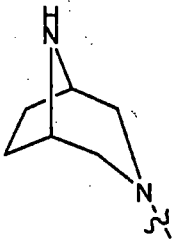
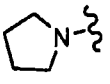
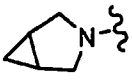
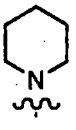
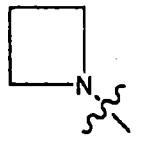
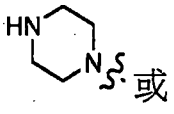
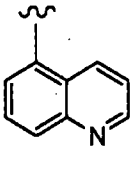
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

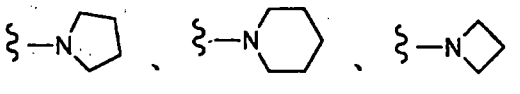
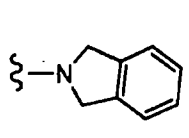
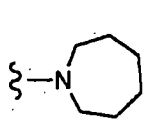
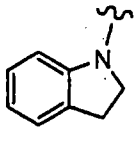
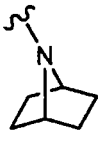
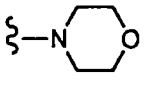
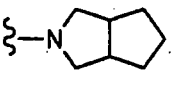
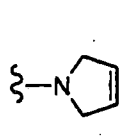
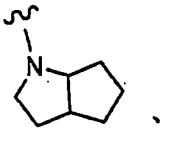
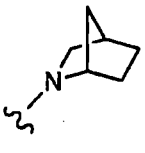
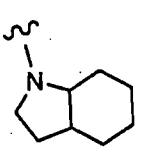
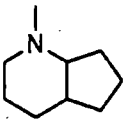
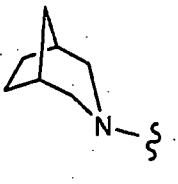
在一些實施例中，式Ib-iii化合物呈醫藥學上可接受之前藥形式存在。

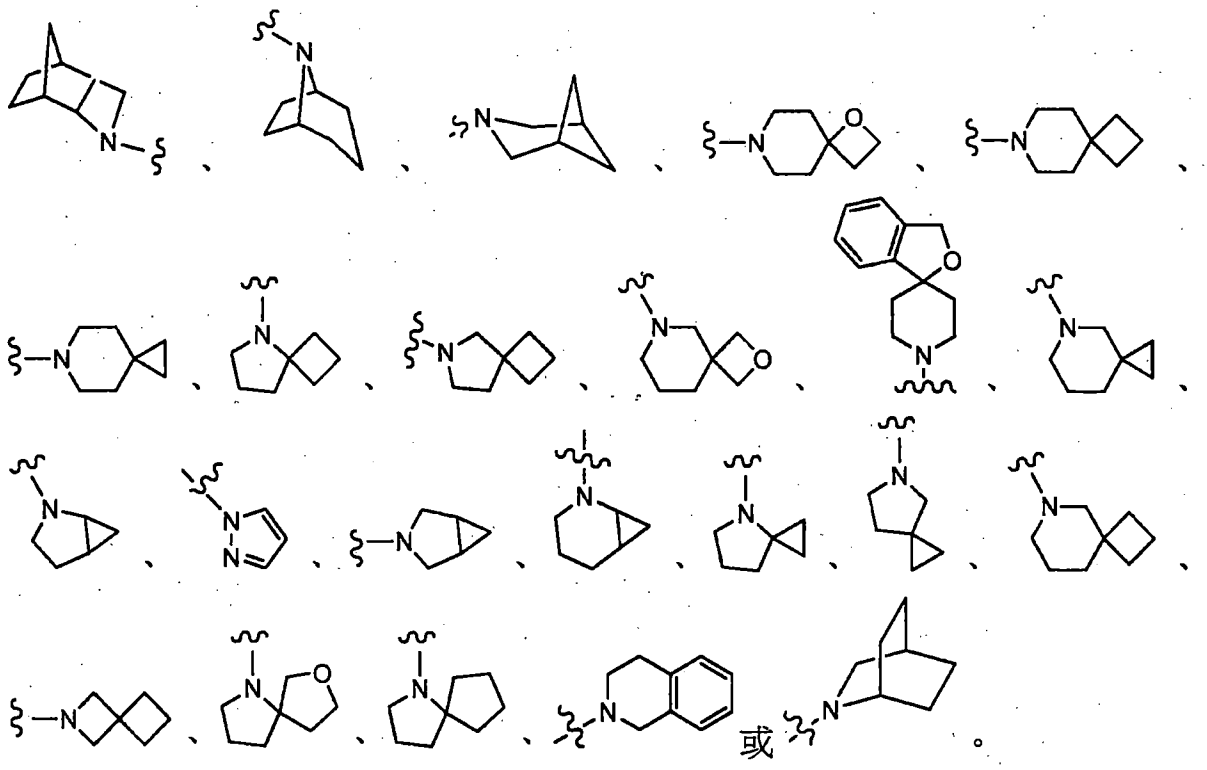
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、

吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或。

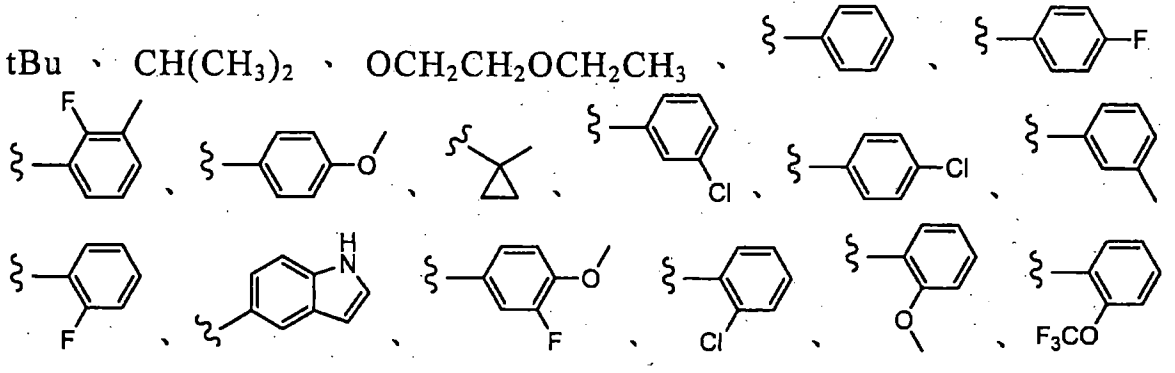
在一些實施例中，環C爲吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉或吡咯啶。

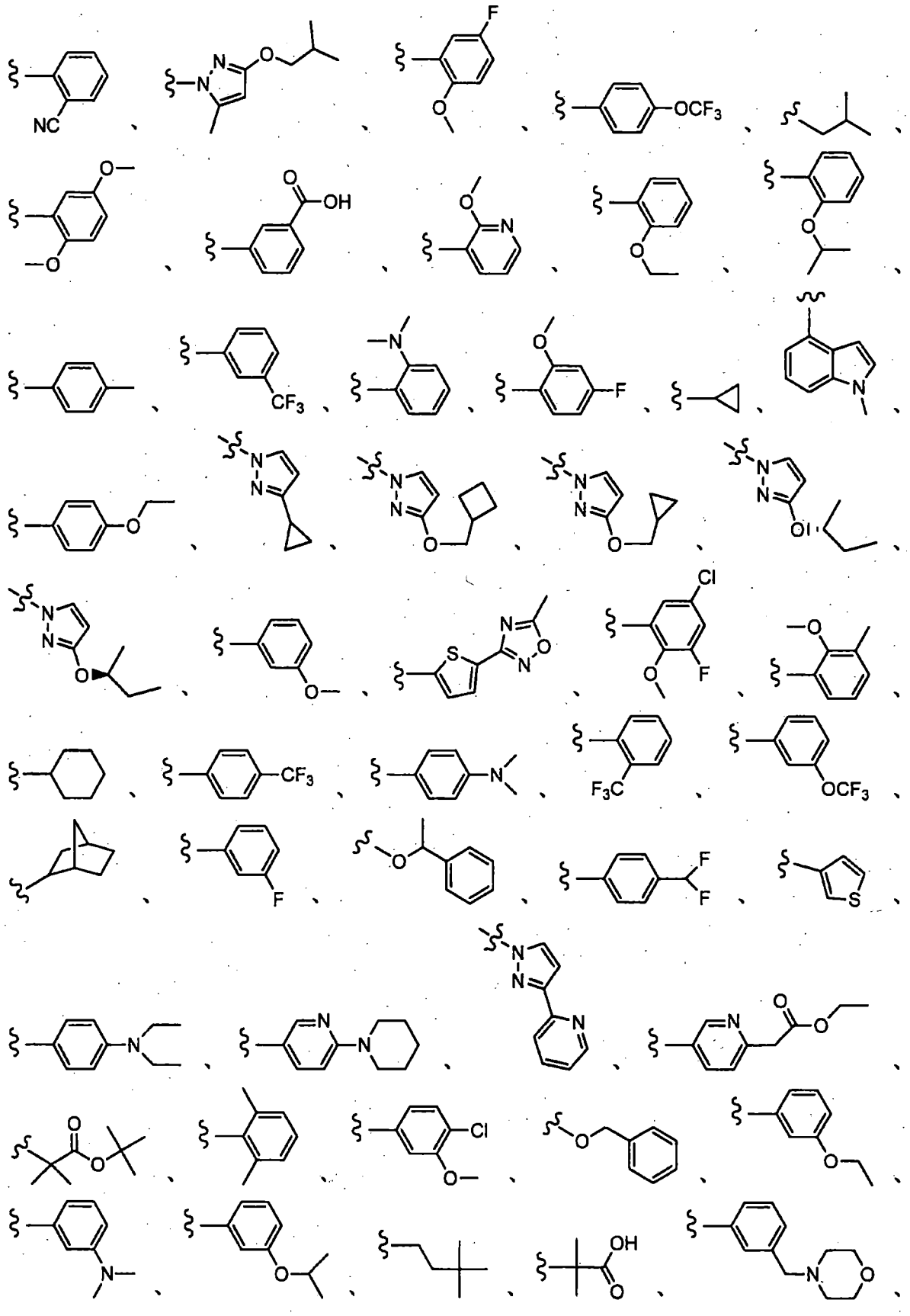
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、  、  、  、 

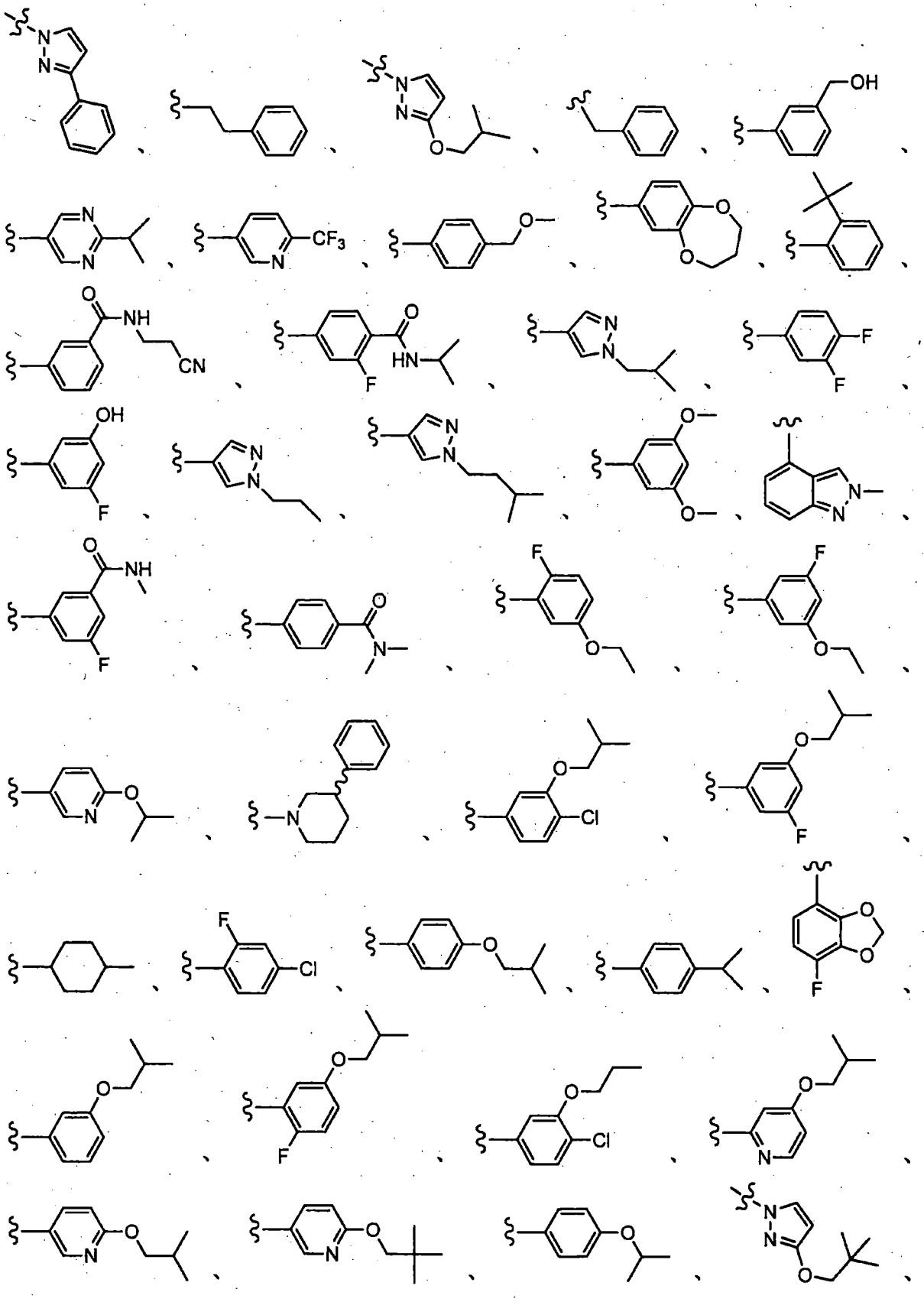


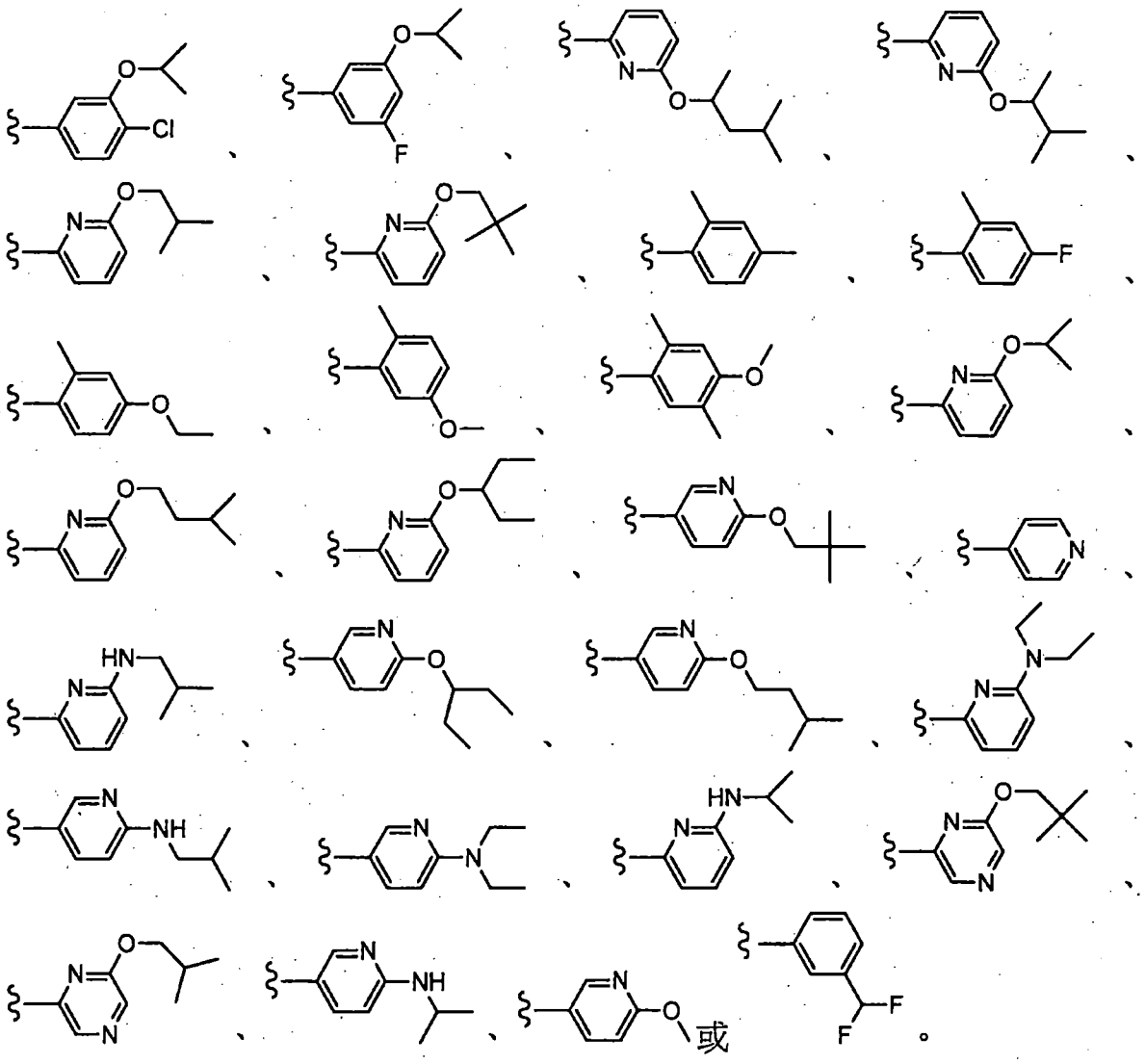
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、



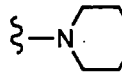
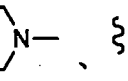
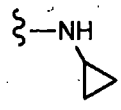


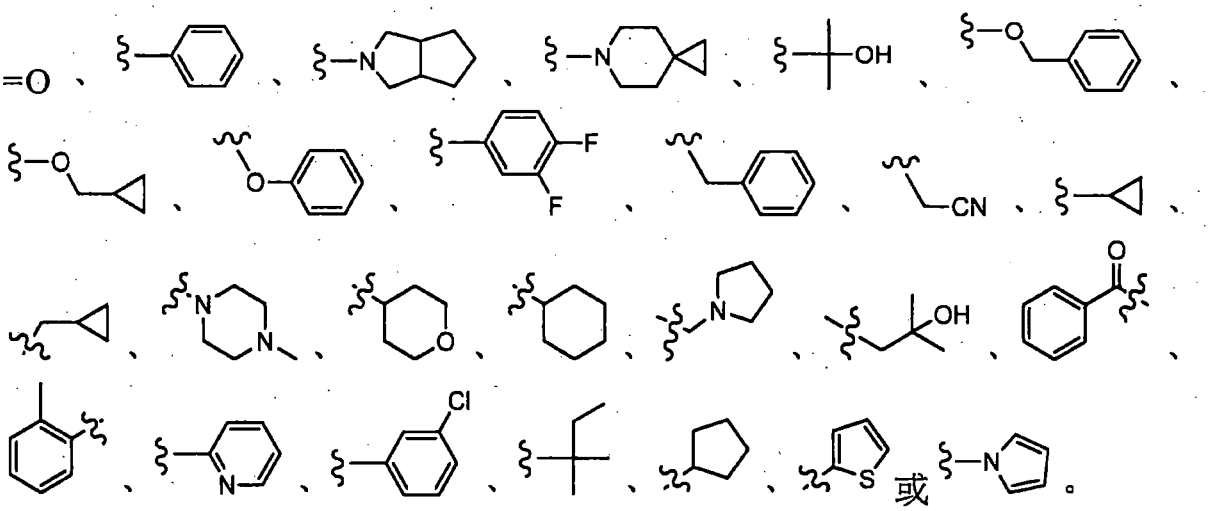




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、

$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 

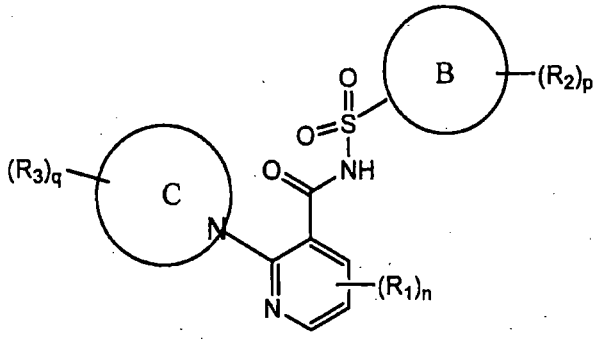


在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且n爲1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-iii-1化合物：



**Ib-iii-1**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜

芳基或雜環，且其中環C上之一個氮爲與吡啶環之附接點；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

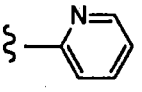
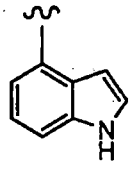
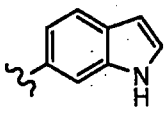
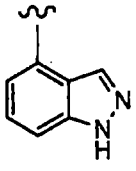
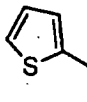
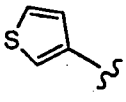
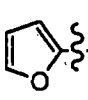
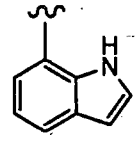
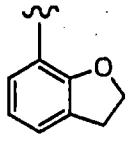
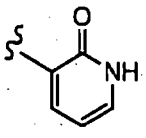
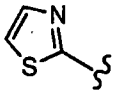
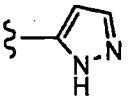
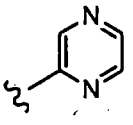
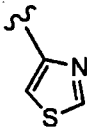
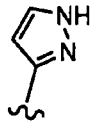
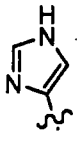
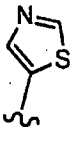
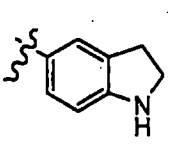
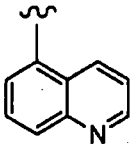
o爲0、1、2、3、4或5；

p爲0、1、2或3；且

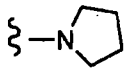
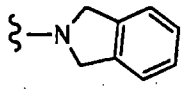
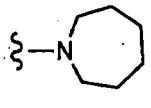
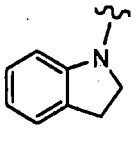
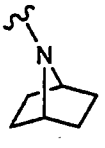
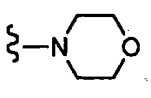
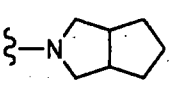
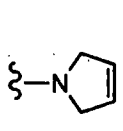
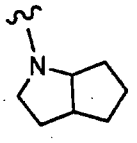
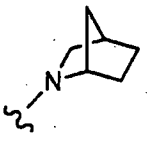
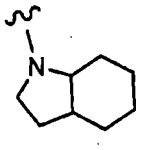
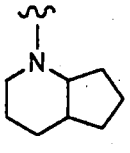
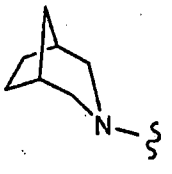
q爲0、1、2、3、4或5。

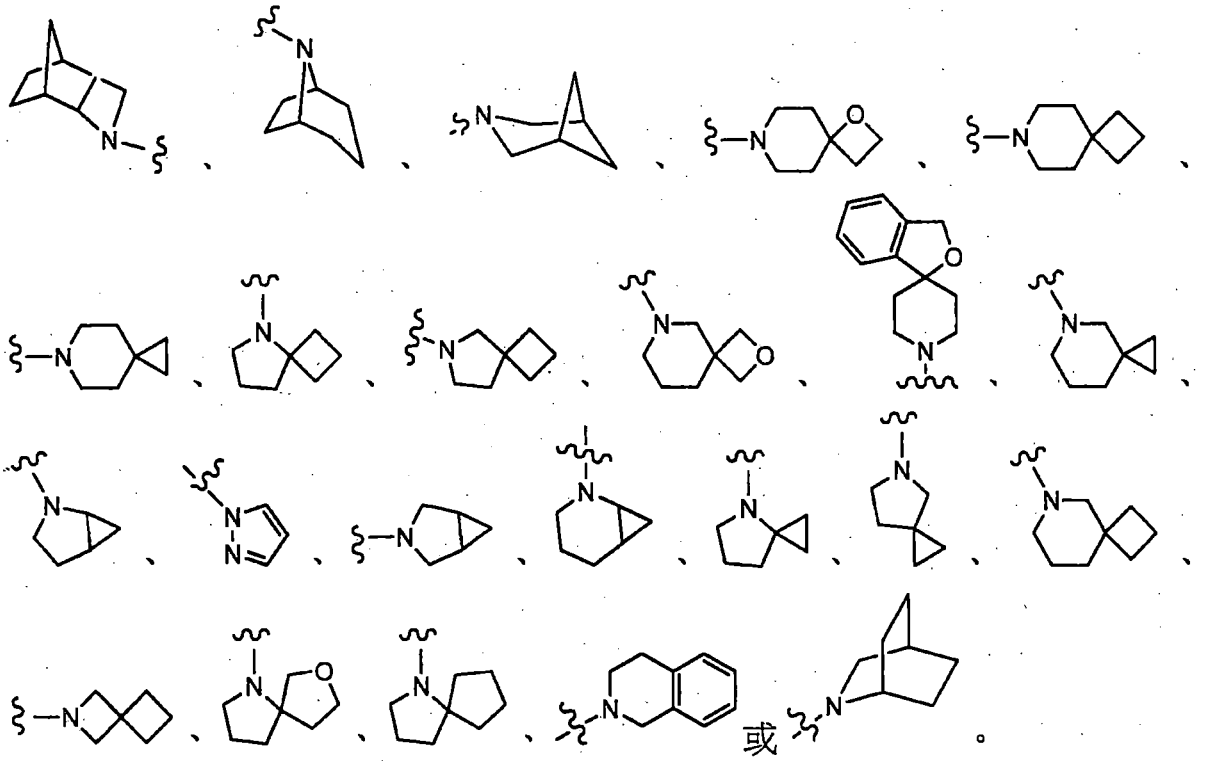
在一些實施例中，式Ib-iii-1化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

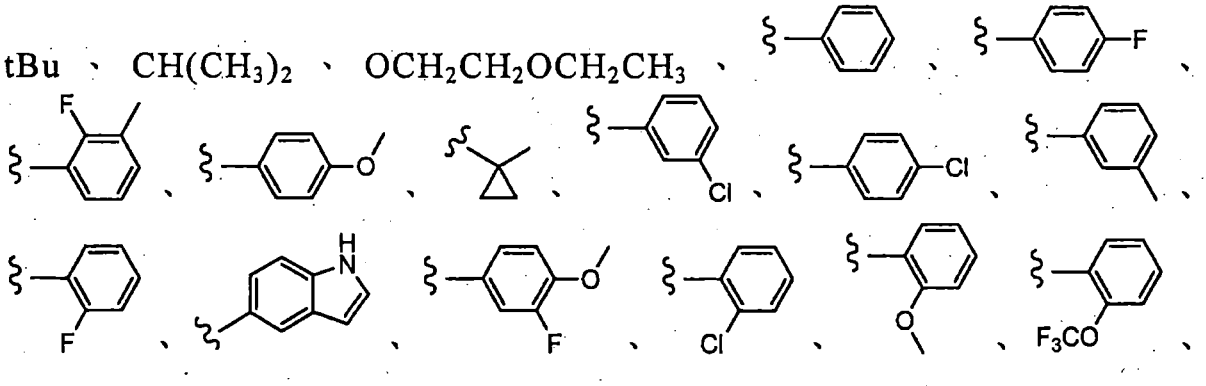
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

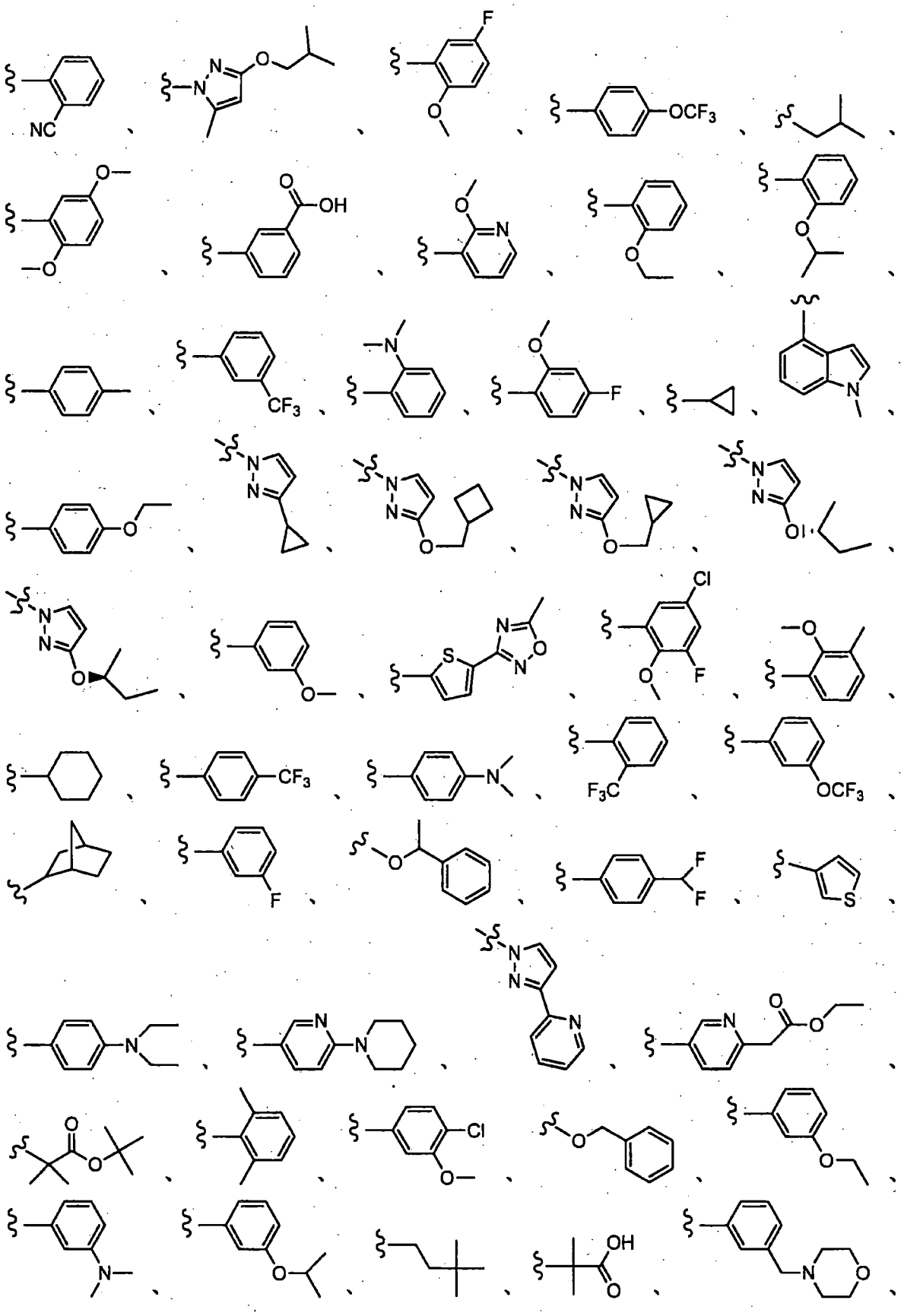
在一些實施例中，環C爲吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉或吡咯啶。

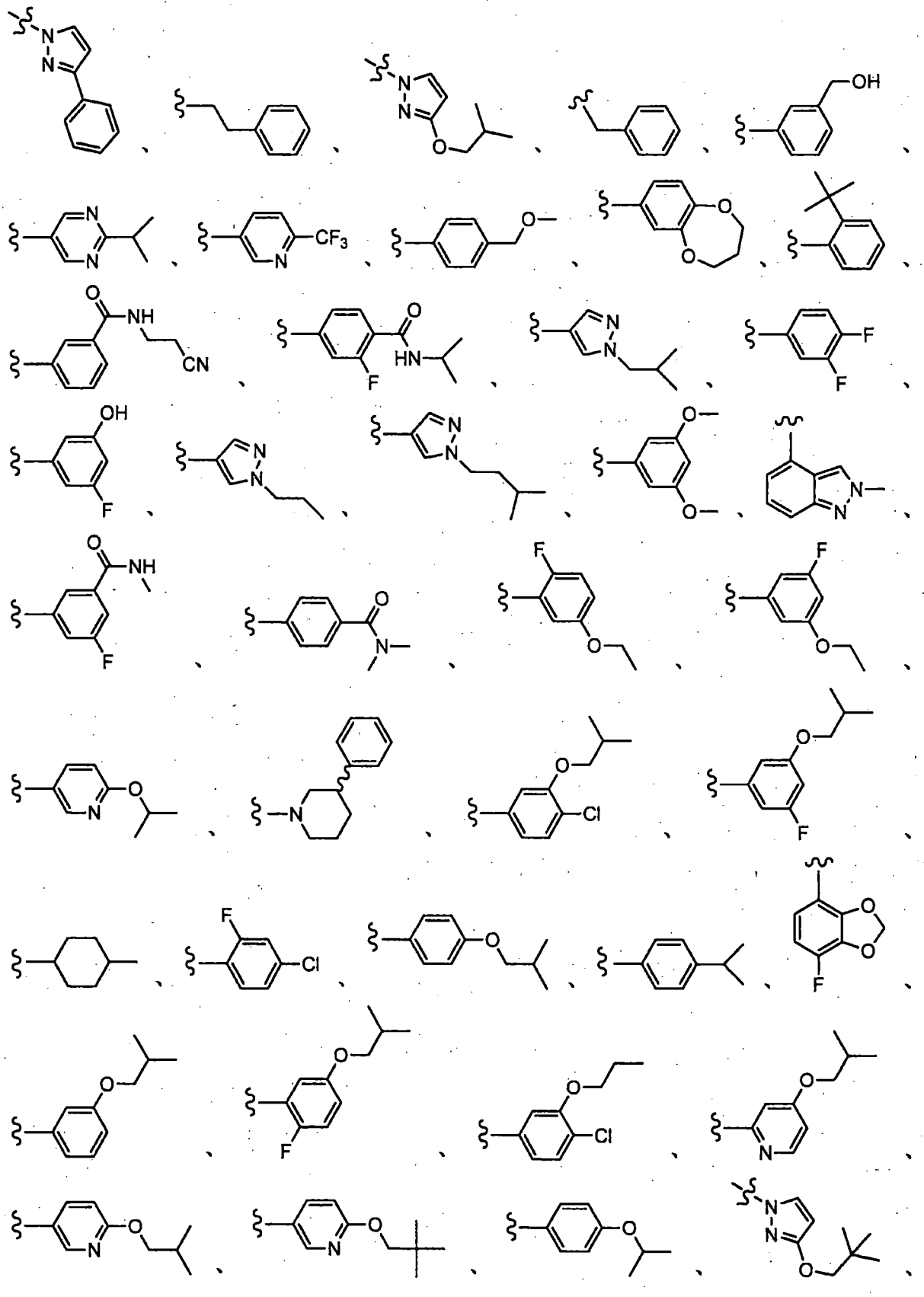
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

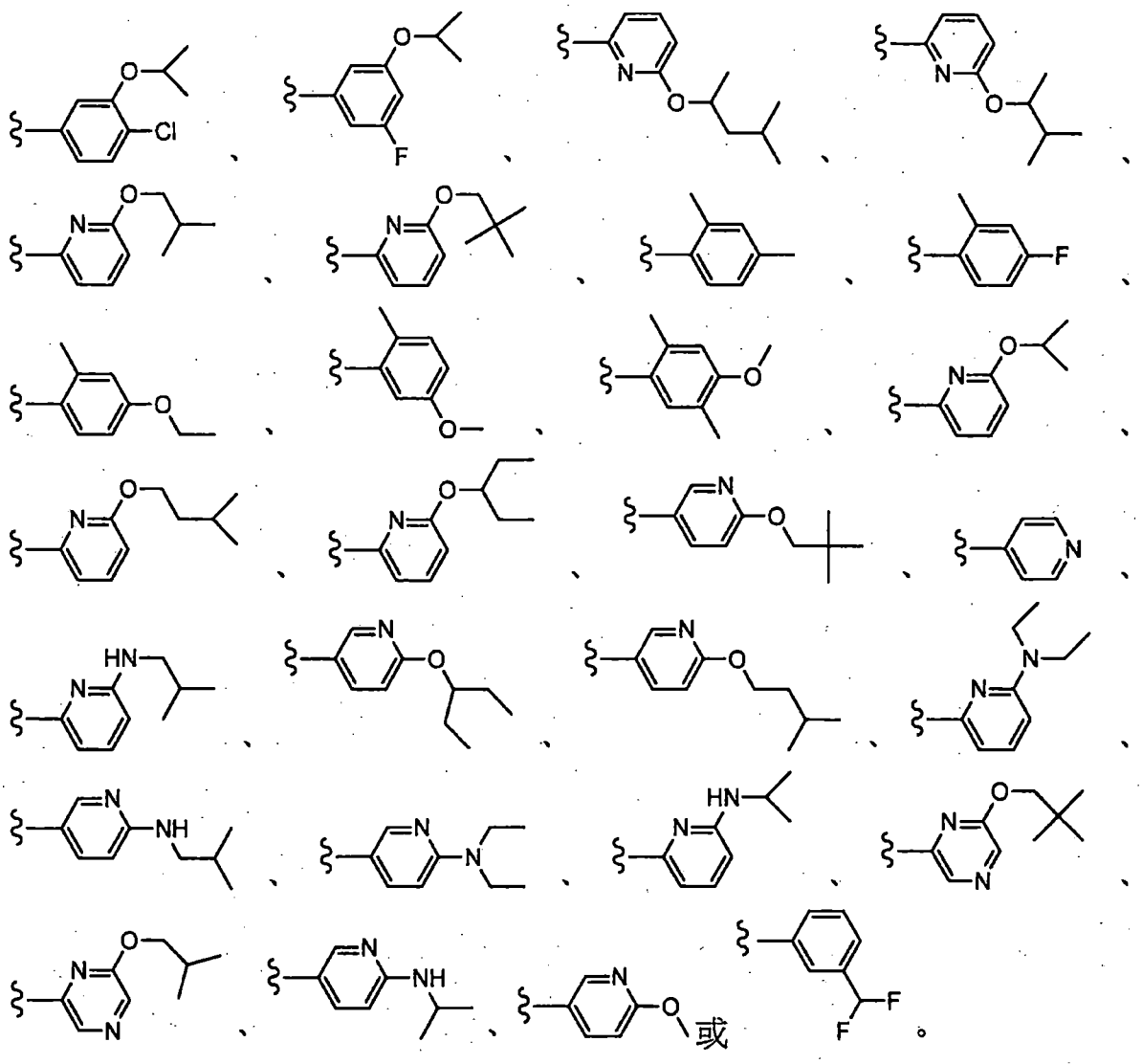


在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、 

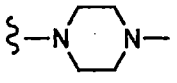
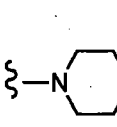
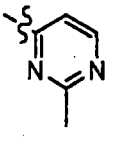


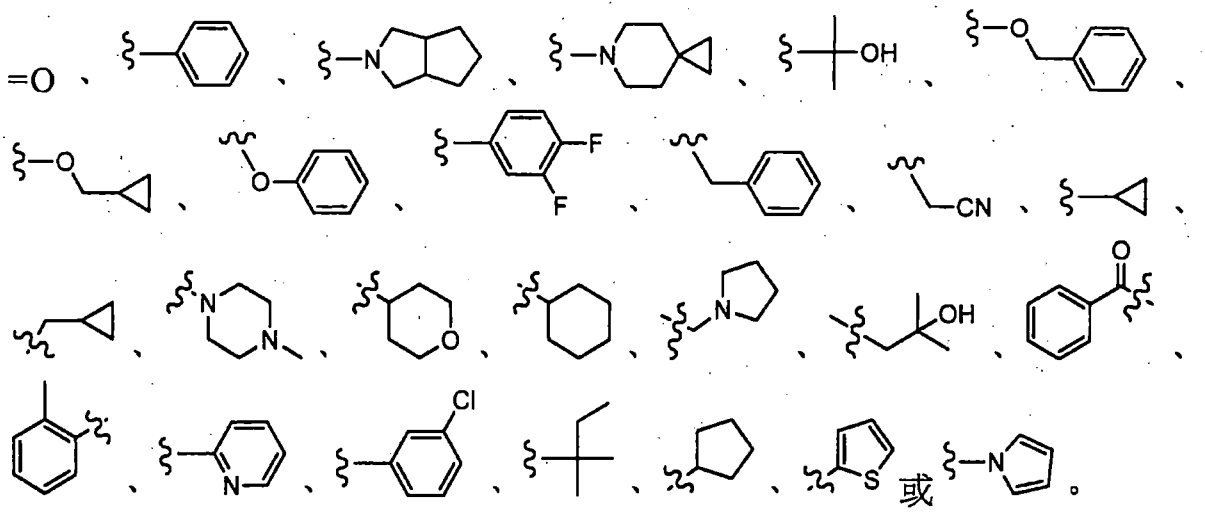




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、

$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 

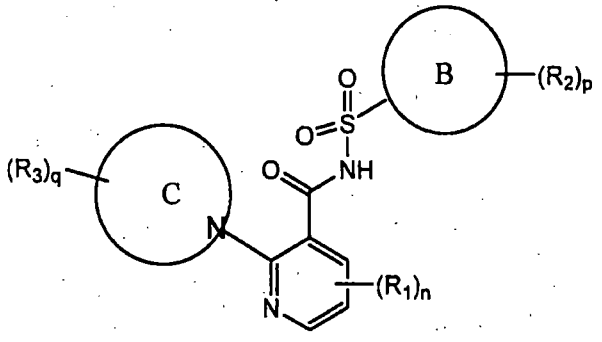


在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且n爲1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-iii-2化合物：



**Ib-iii-2**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

環C爲其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環，且其中環C上之一個氮爲與吡啶環之附接點；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

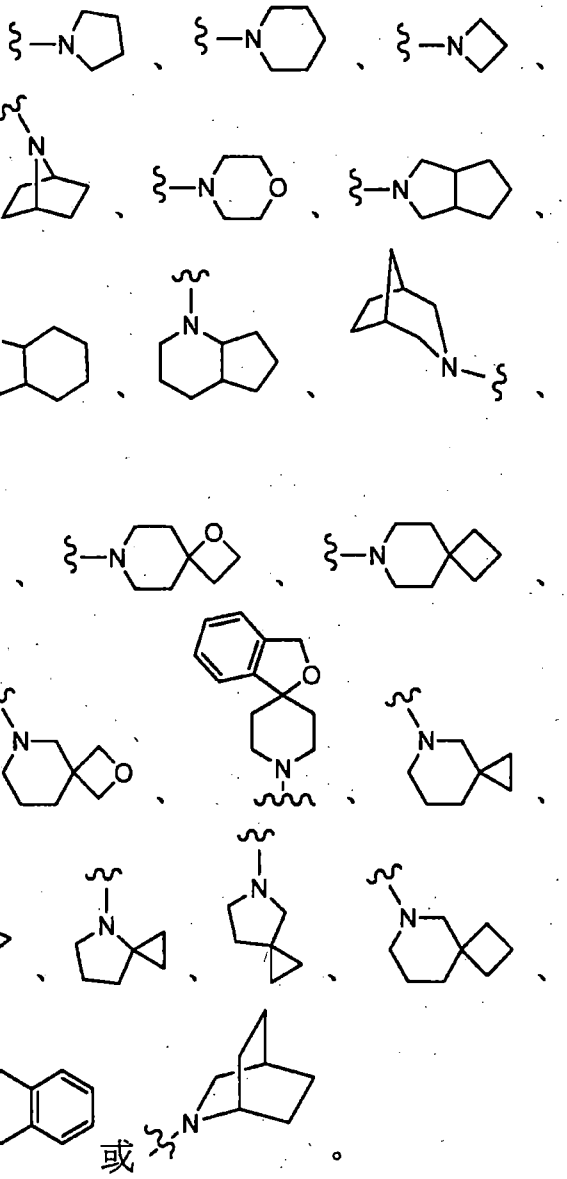
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ib-iii-2化合物呈醫藥學上可接受之前藥形式存在。

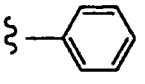
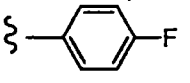
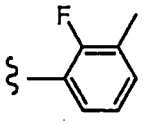
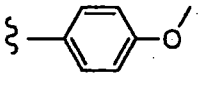
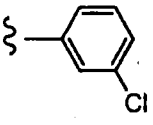
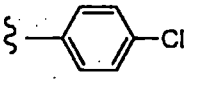
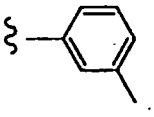
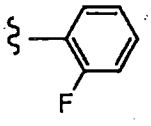
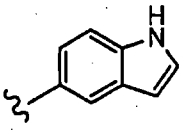
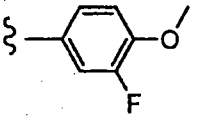
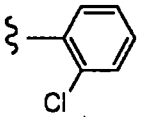
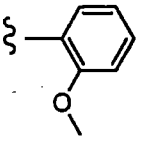
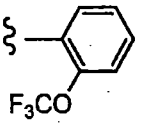
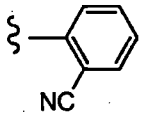
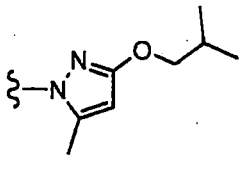
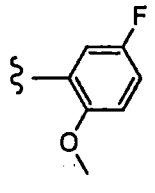
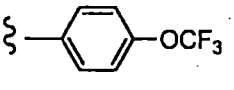
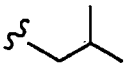
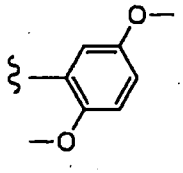
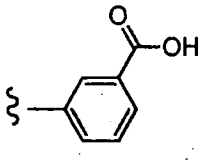
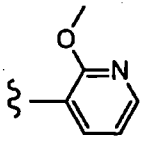
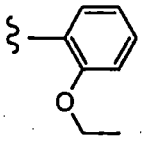
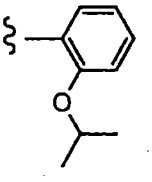
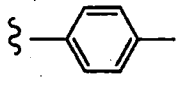
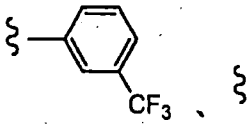
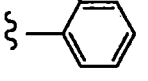
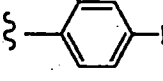
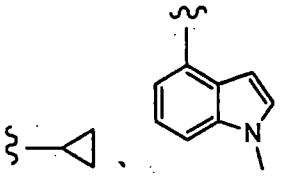
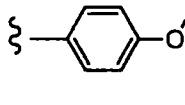
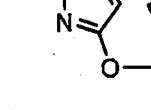
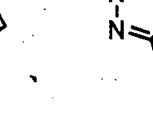
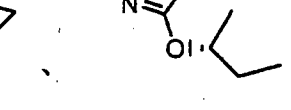
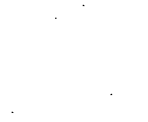
在一些實施例中，環B爲苯基或萘。

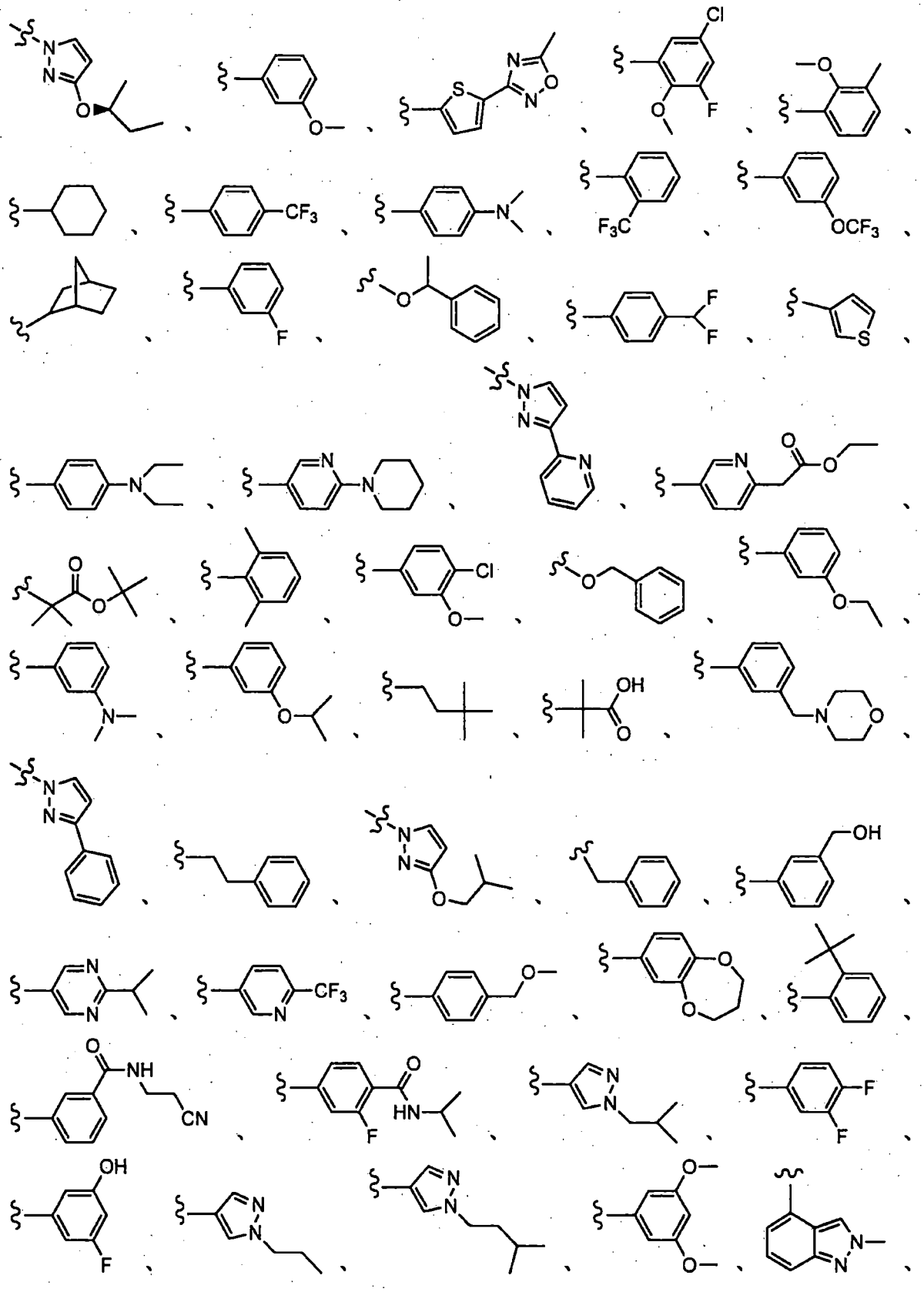
在一些實施例中，環C爲吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉或吡咯啶。

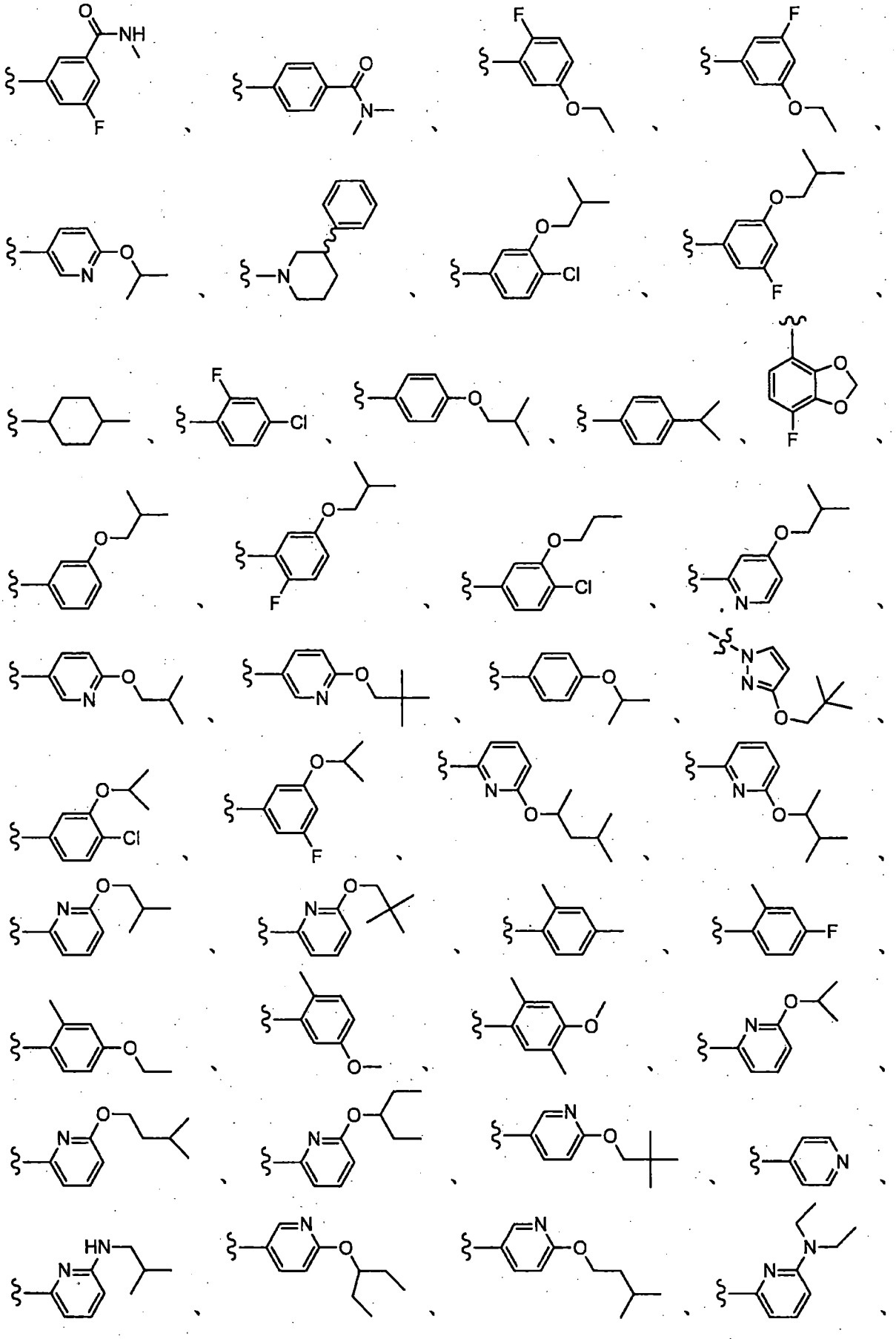
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  或 。

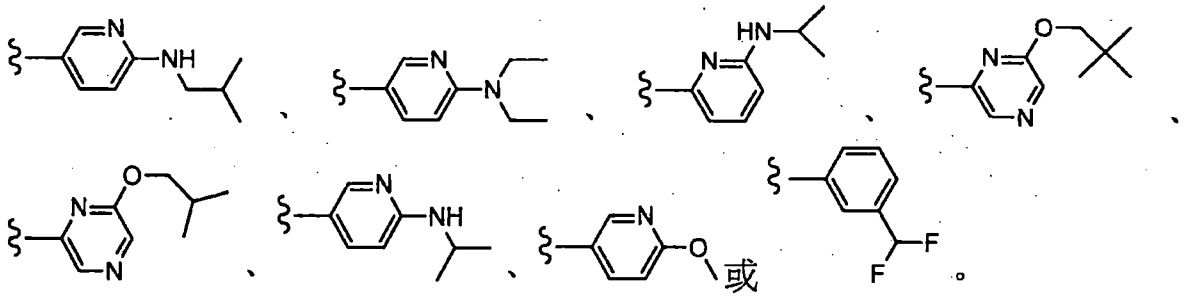
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、

C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

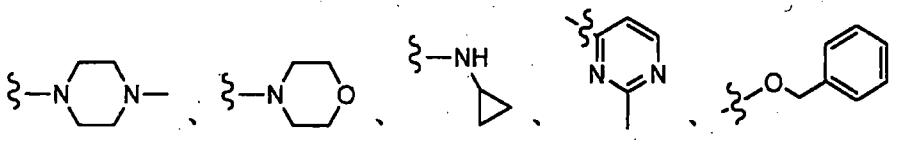


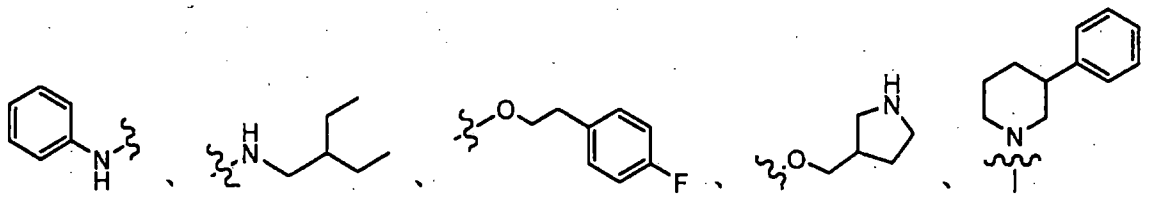


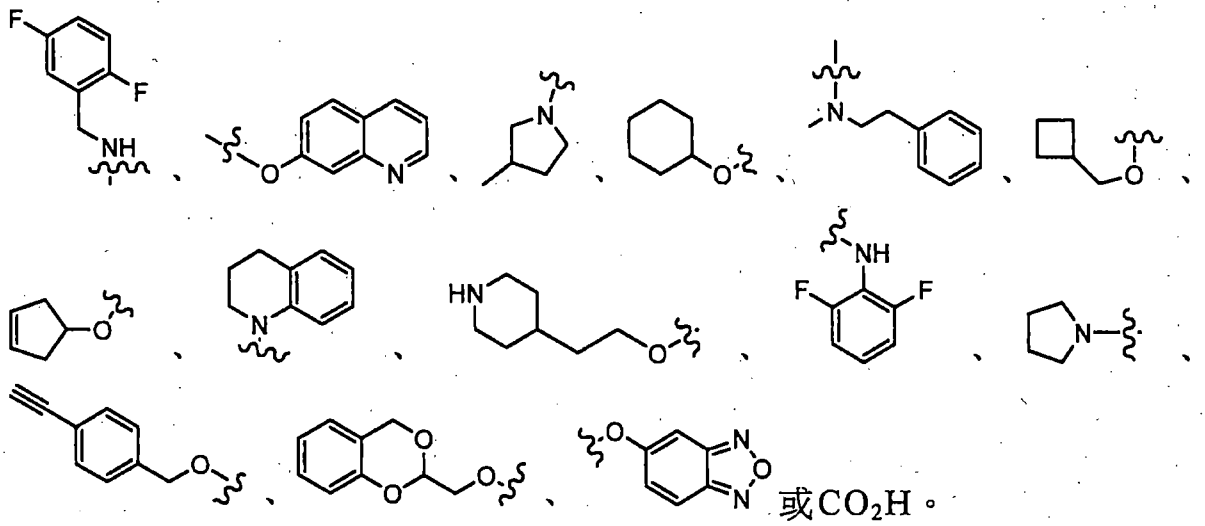


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、

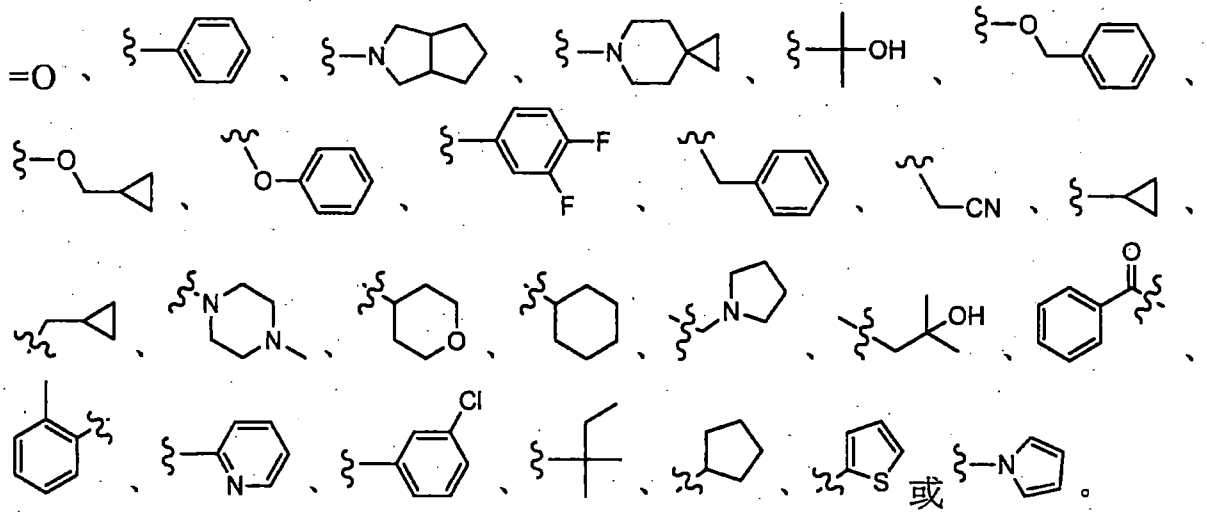







在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、



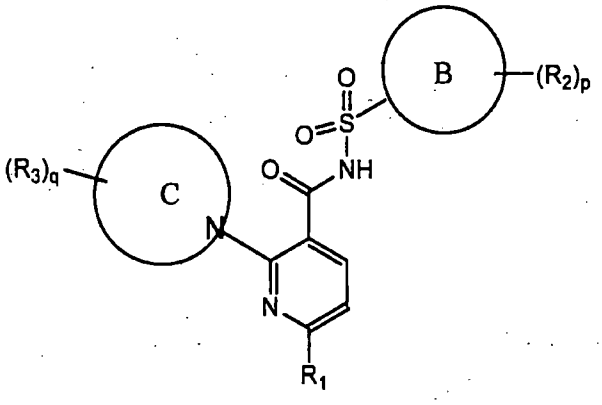

在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施

例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且n爲1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-iv化合物：




**Ib-iv**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

環C爲其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環，且其中環C上之一個氮爲與吡啶環之附接點；

$R_1$爲C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

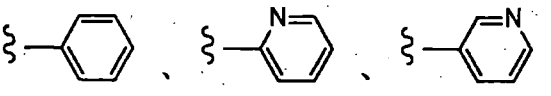
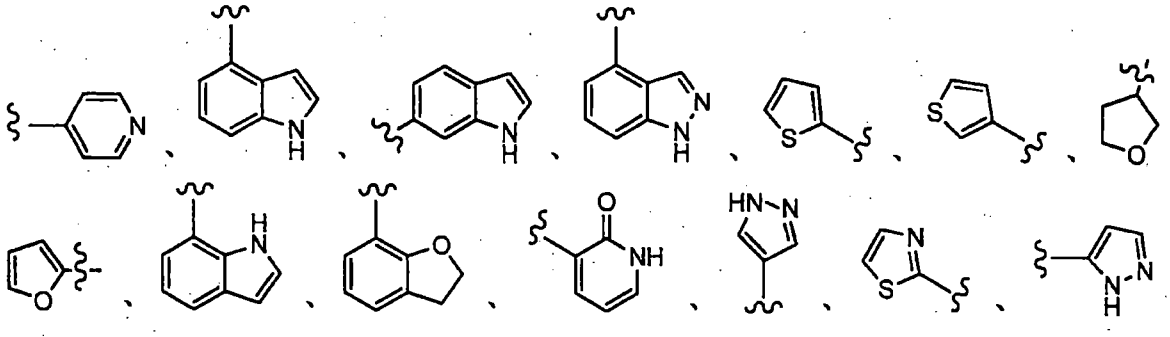
R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

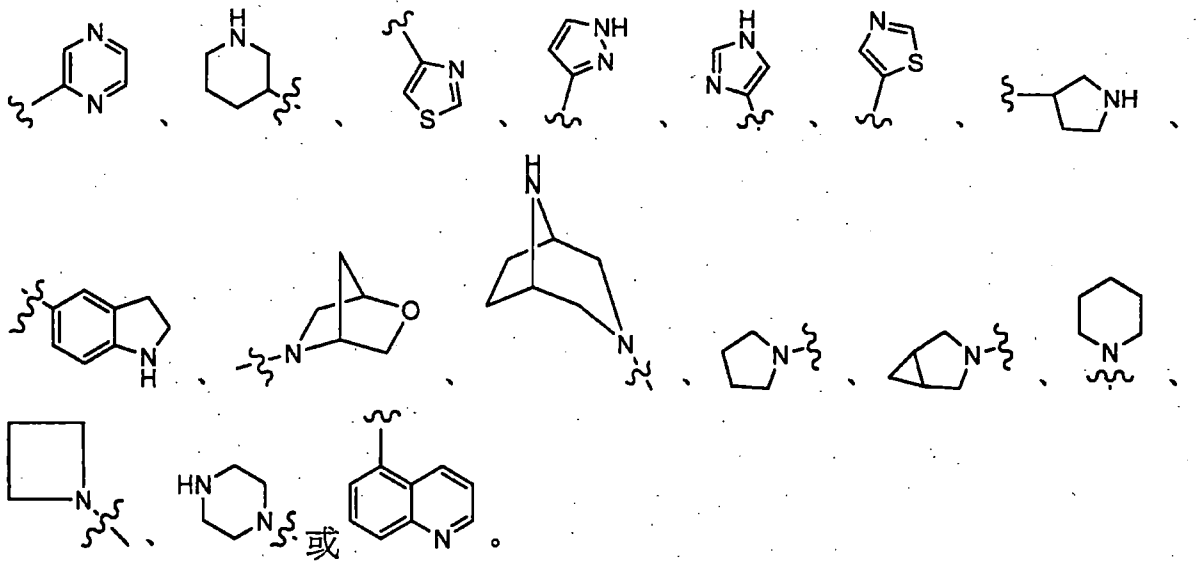
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ib-iv化合物呈醫藥學上可接受之前藥形式存在。

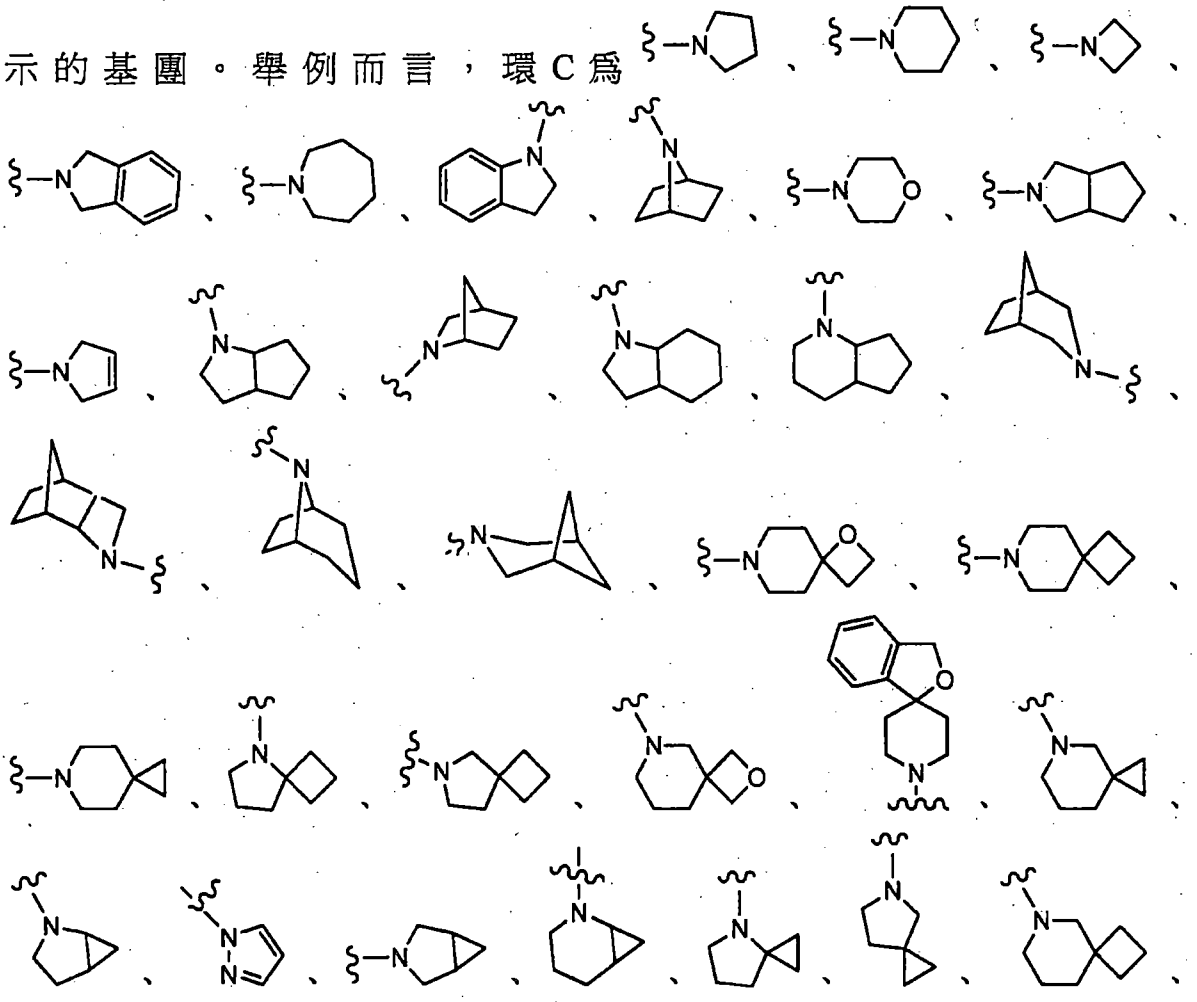
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

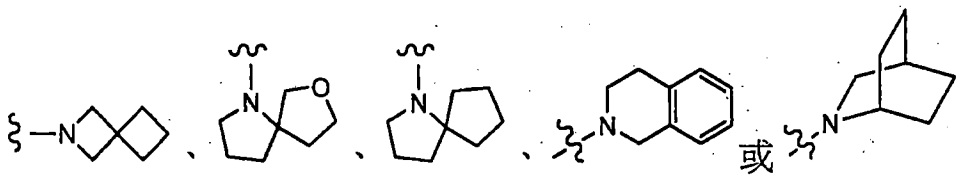
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、 



在一些實施例中，環C爲吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉或吡咯啶。

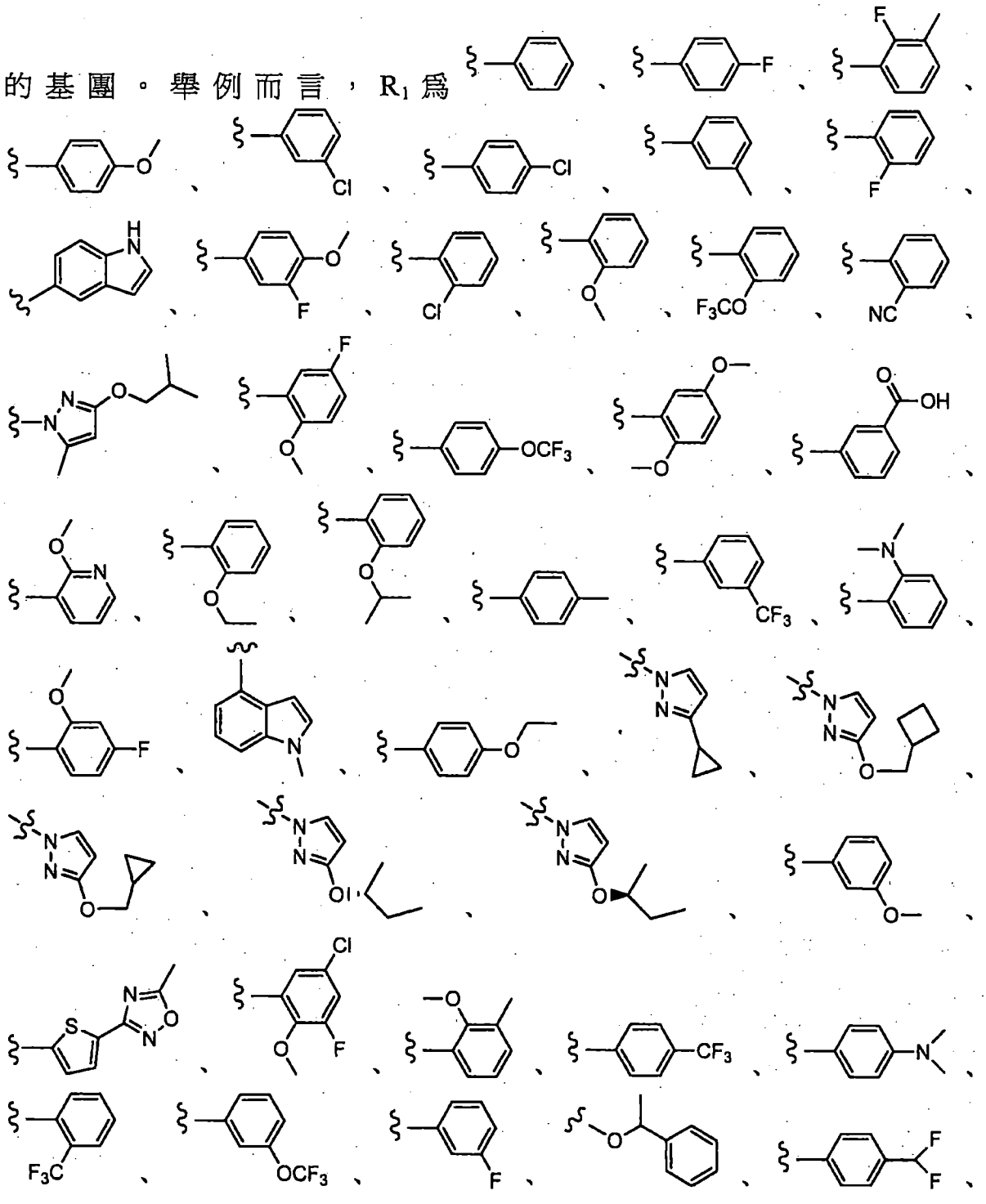
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲

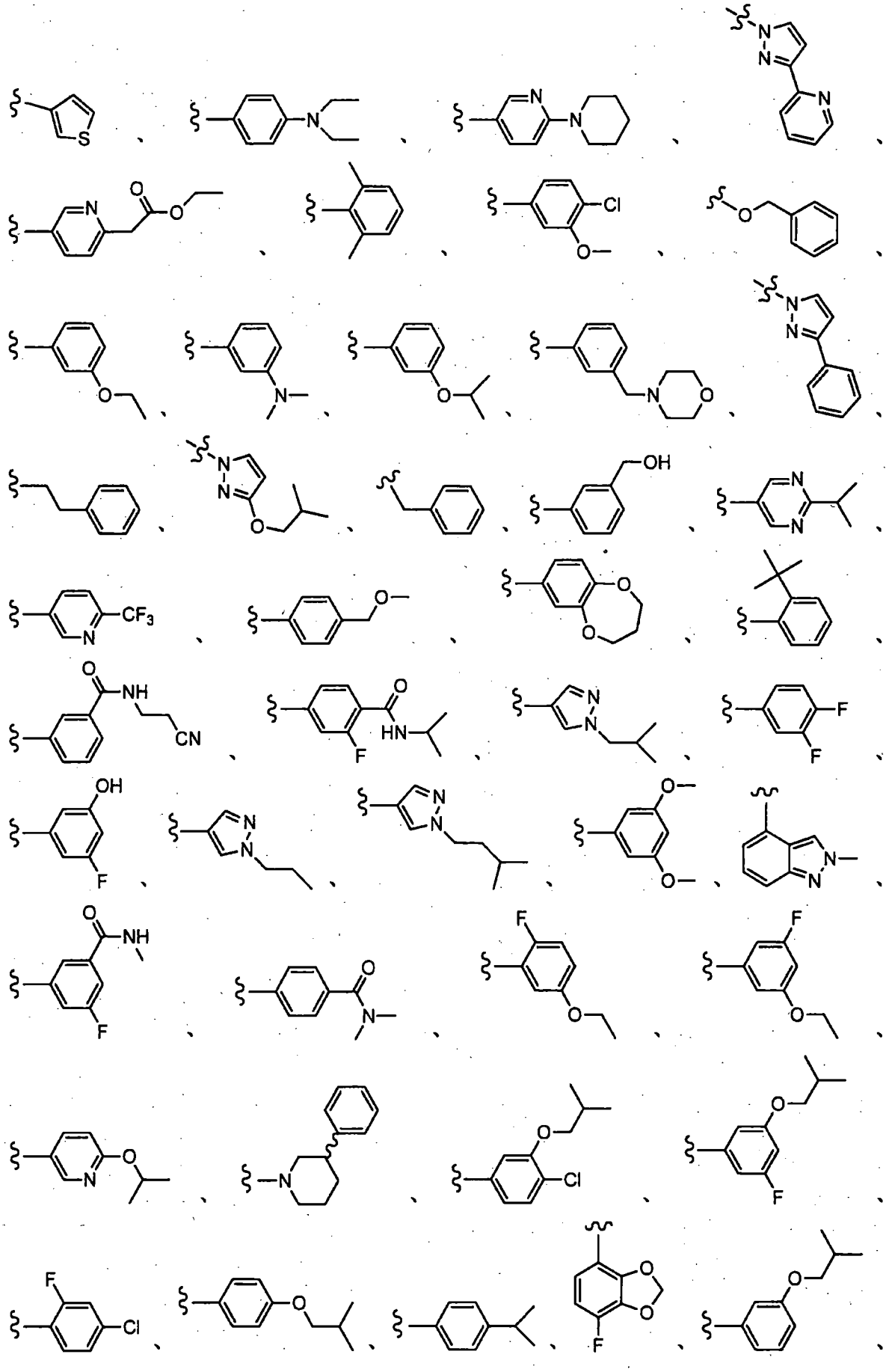


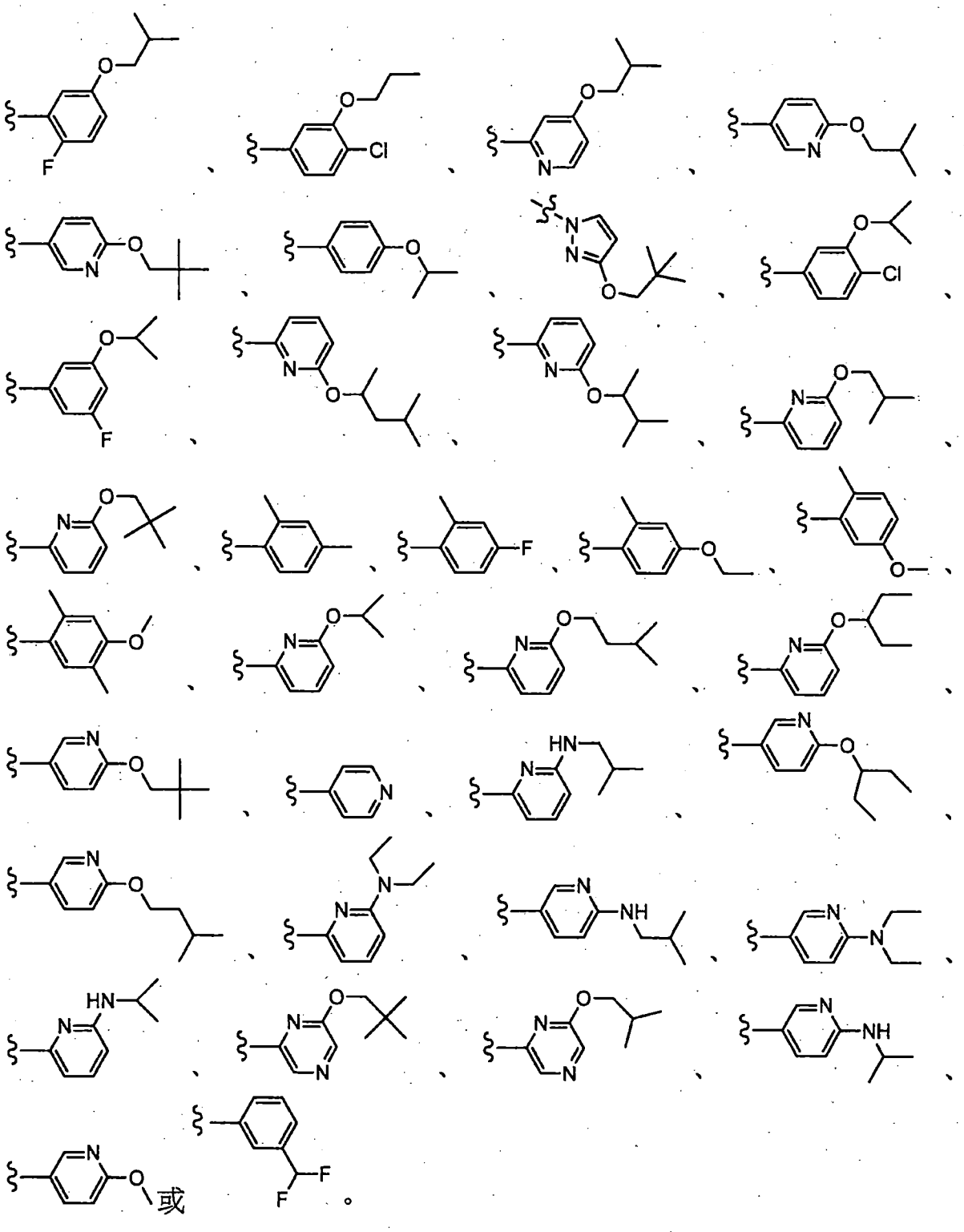


在一些實施例中，$R_1$為苯基、噻吩、吡啶或吡唑。

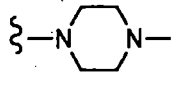
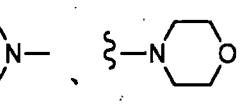
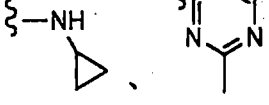
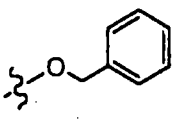
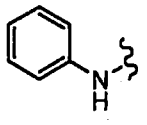
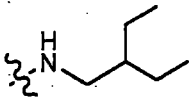
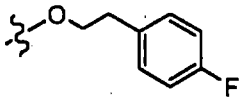
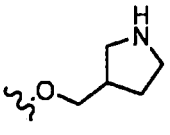
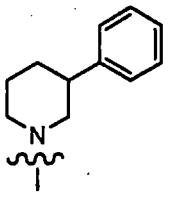
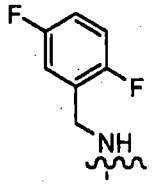
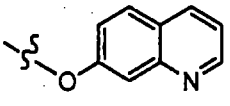
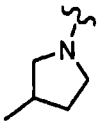
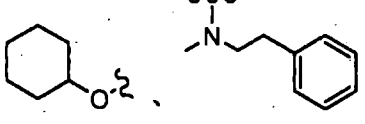
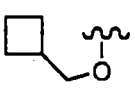
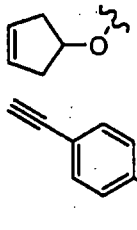
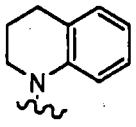
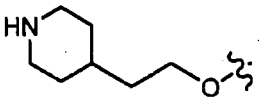
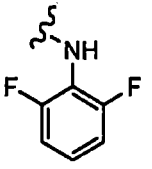
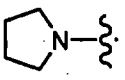
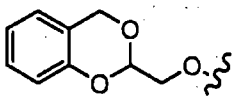
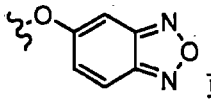
在一些實施例中，$R_1$為藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$為





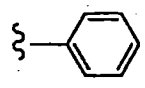
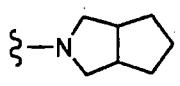
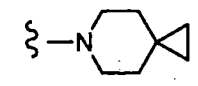
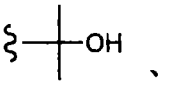
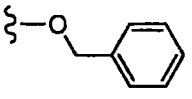
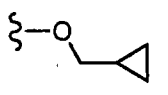
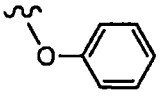
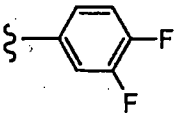
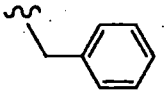
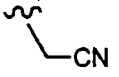
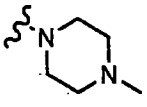
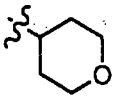
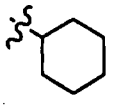
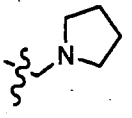
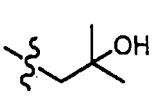
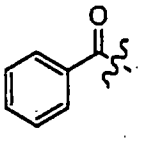
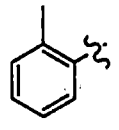
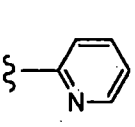
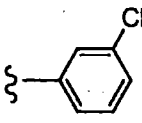
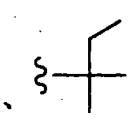
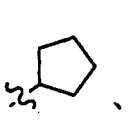
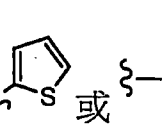
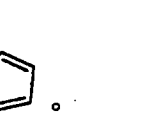
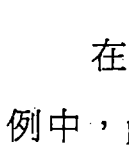
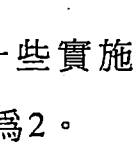
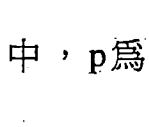
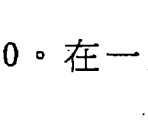
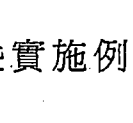
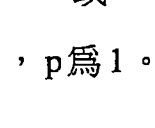
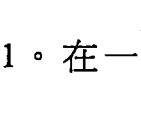


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、  、  、  、  、  、、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-

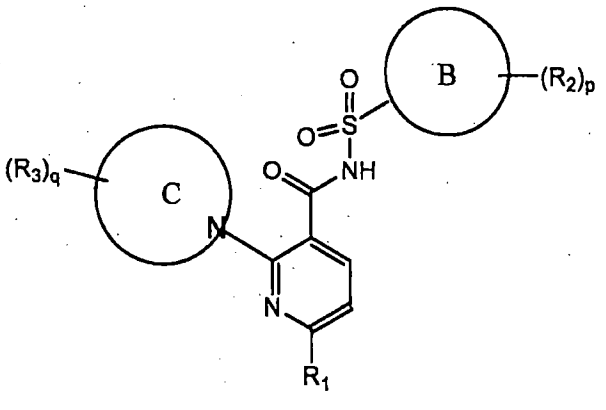
C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，R1爲苯基、吡啶或吡唑。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-iv-1化合物：



**Ib-iv-1**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環，且其中環C上之一個氮爲與吡啶環之附接點；

$R_1$爲C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

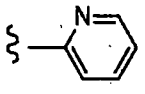
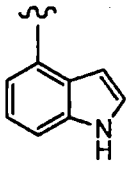
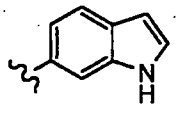
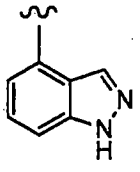
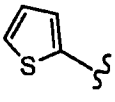
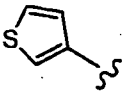
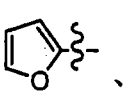
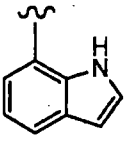
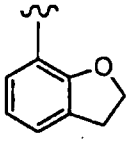
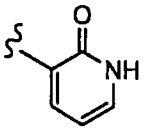
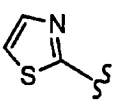
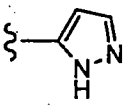
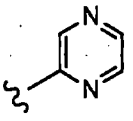
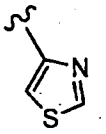
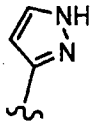
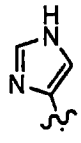
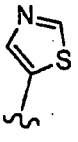
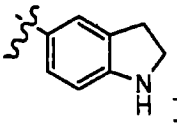
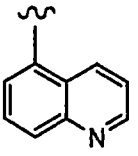
R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地

爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

p爲0、1、2或3；且

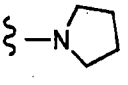
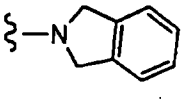
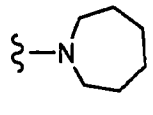
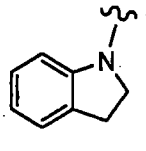
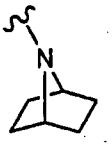
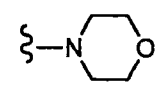
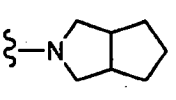
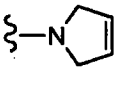
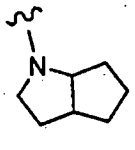
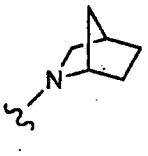
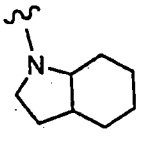
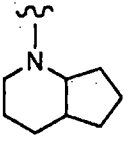
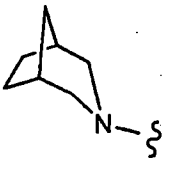
q爲0、1、2、3、4或5。

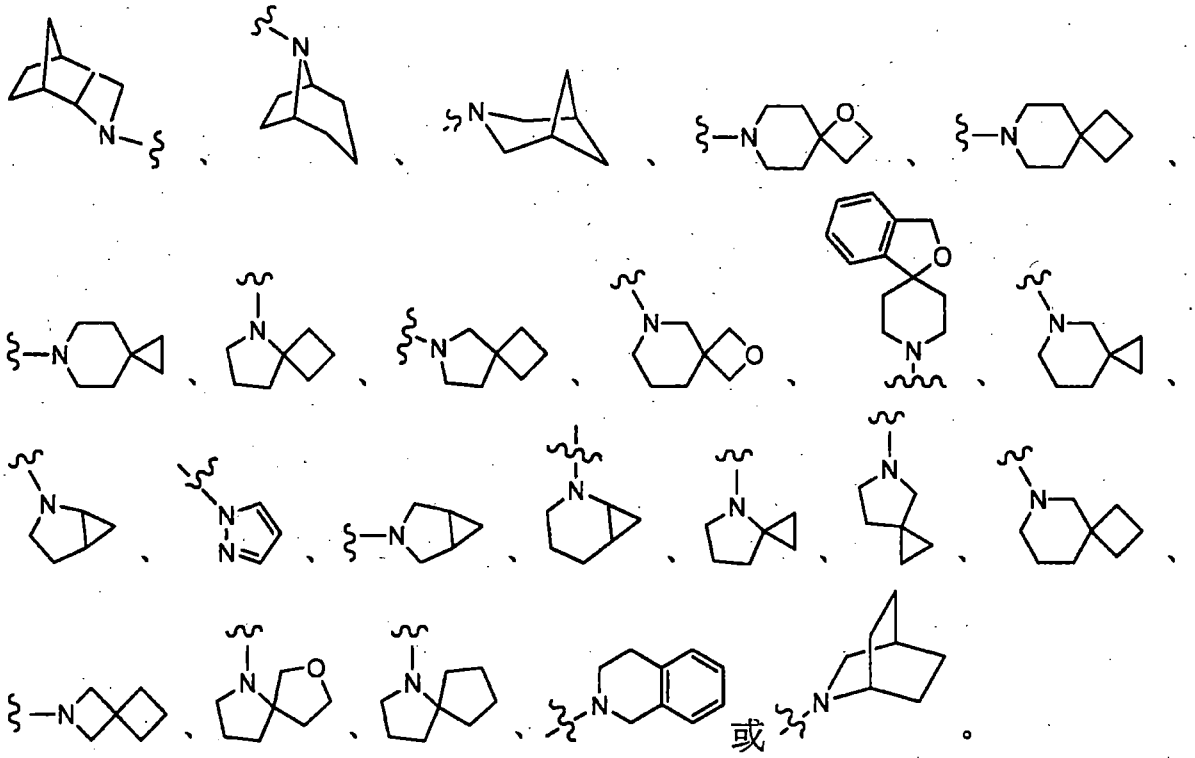
在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，式Ib-iv-1化合物呈醫藥學上可接受之前藥形式存在。

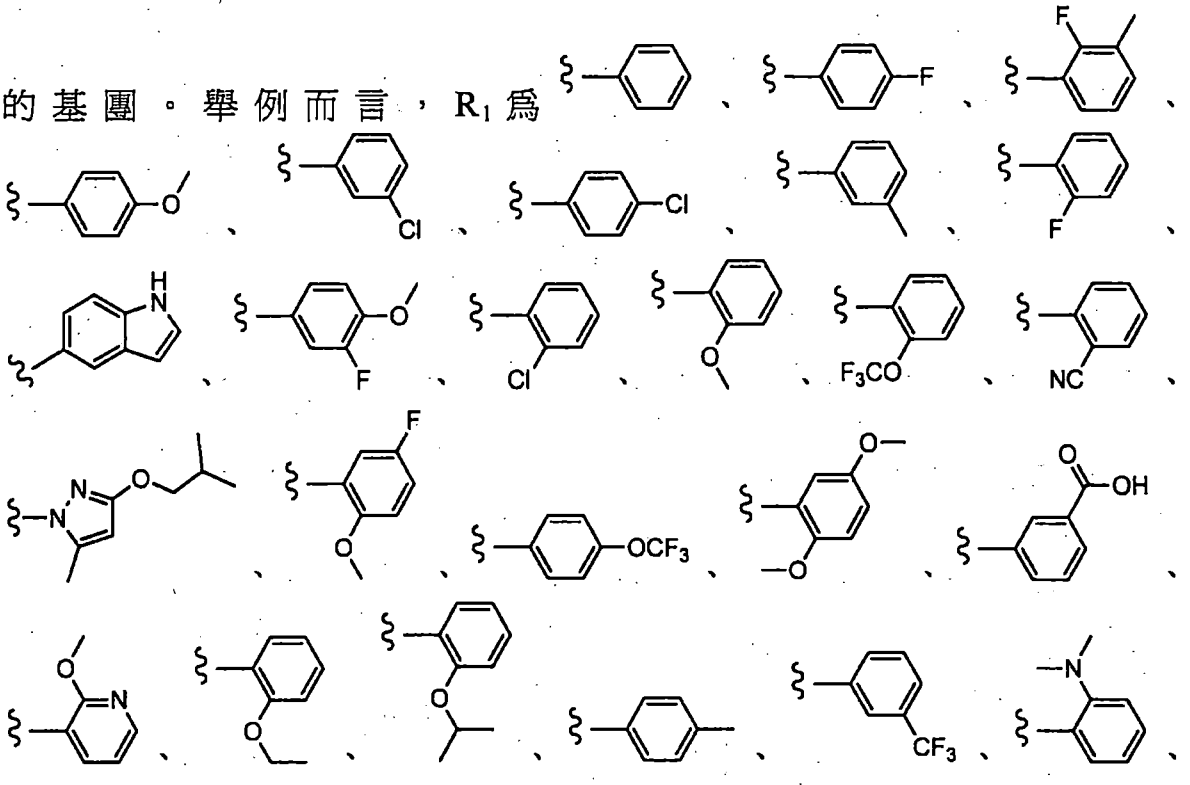
在一些實施例中，環C爲吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉或吡咯啶。

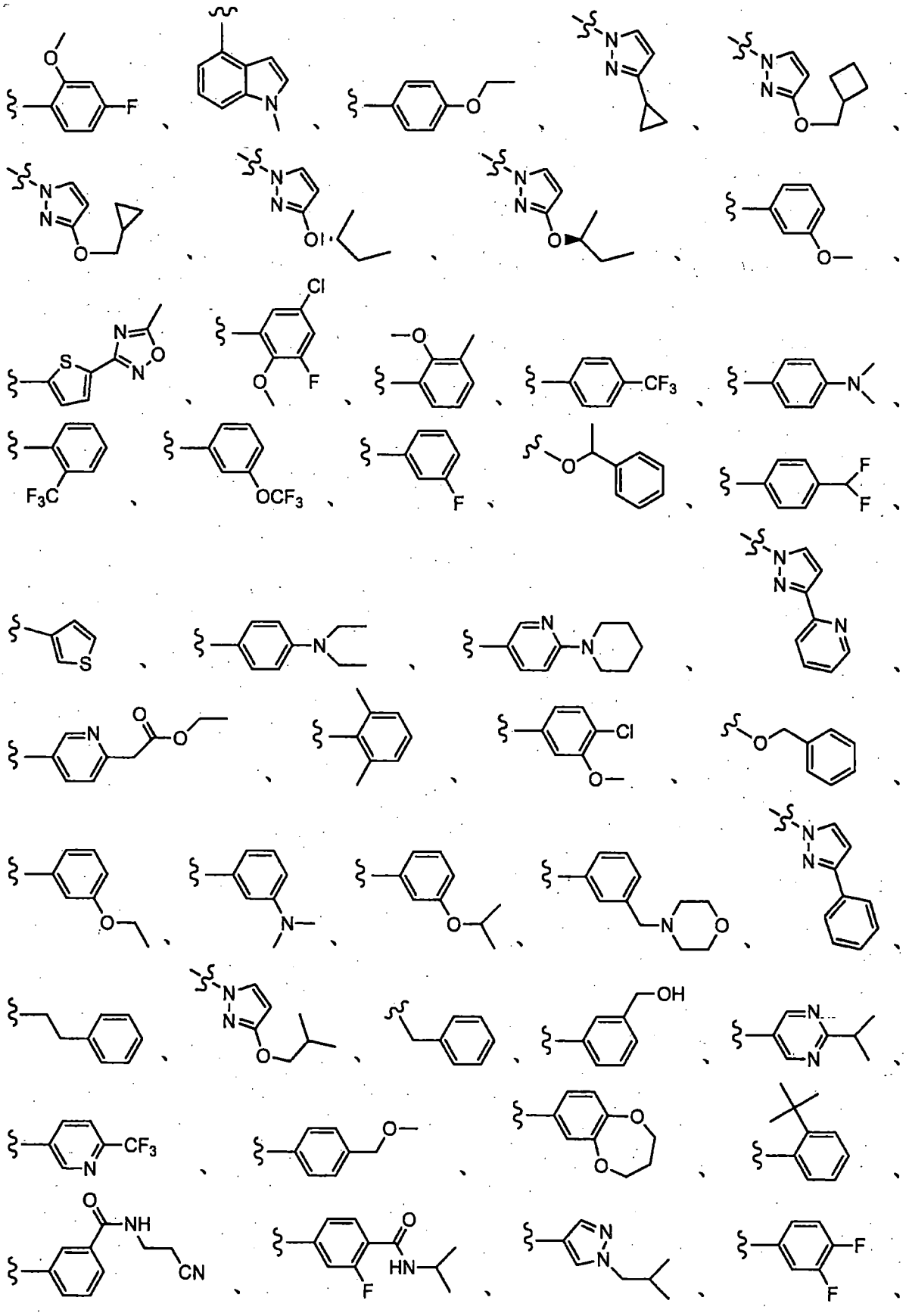
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、

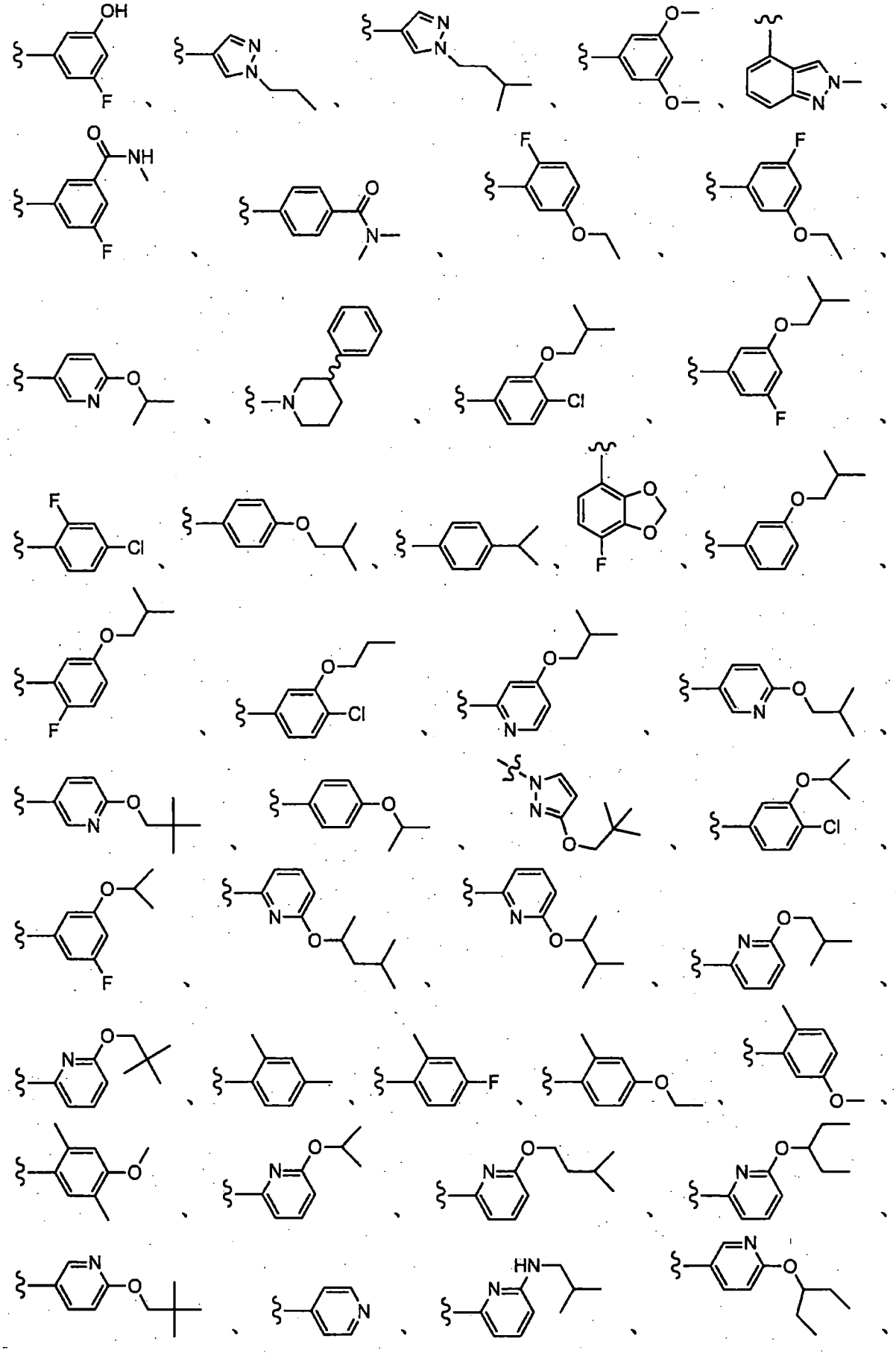


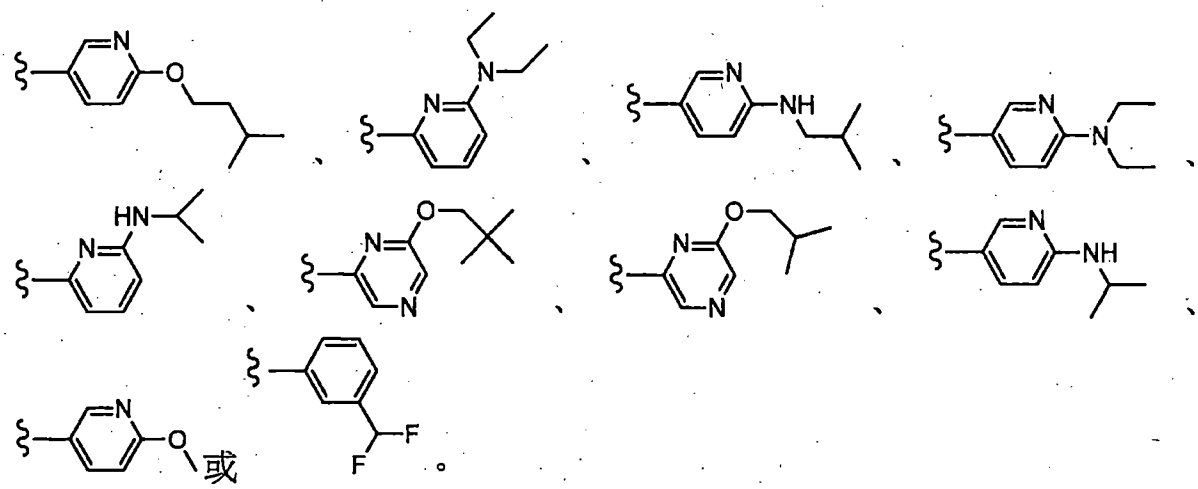
在一些實施例中，$R_1$為苯基、噻吩、吡啶或吡唑。

在一些實施例中，$R_1$為藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$為

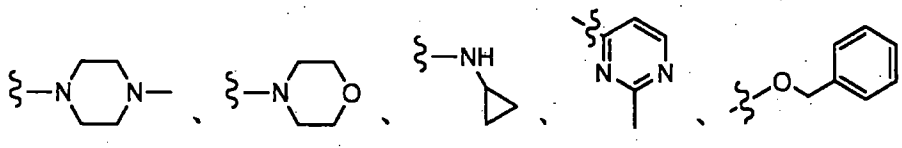


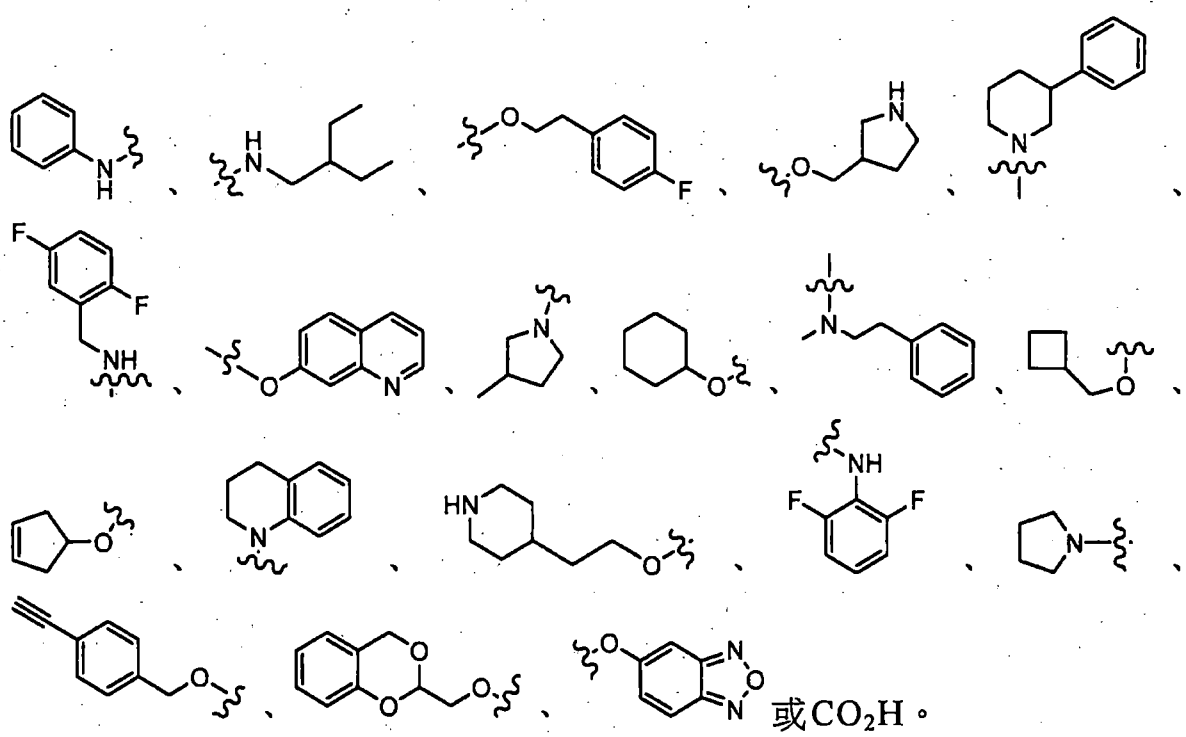




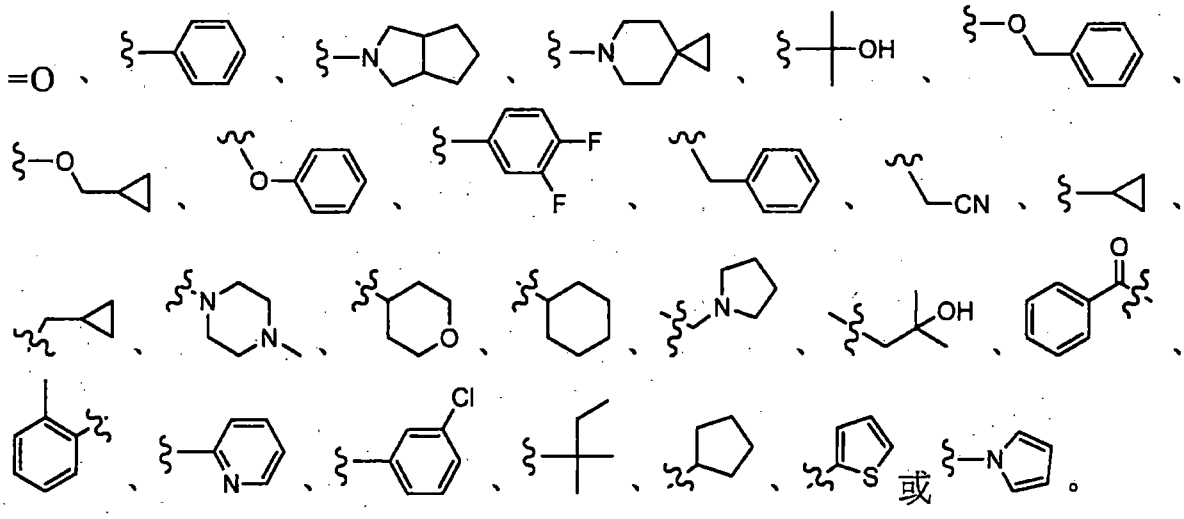


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、


或$CO_2H$。

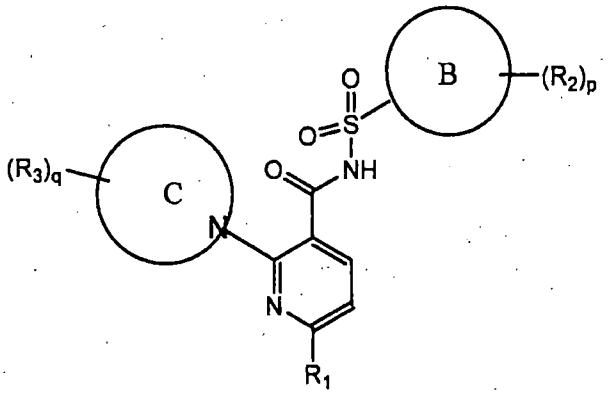
在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、 
或。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-iv-2化合物：




**Ib-iv-2**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

環C爲其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環，且其中環C上之一個氮爲與吡啶環之附接點；

$R_1$爲C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

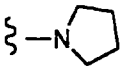
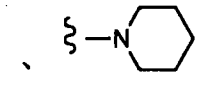
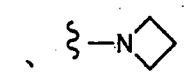
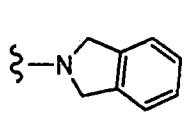
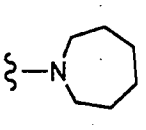
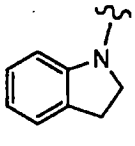
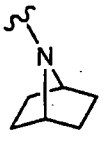
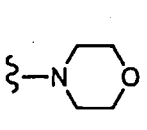
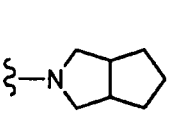
p爲0、1、2或3；且

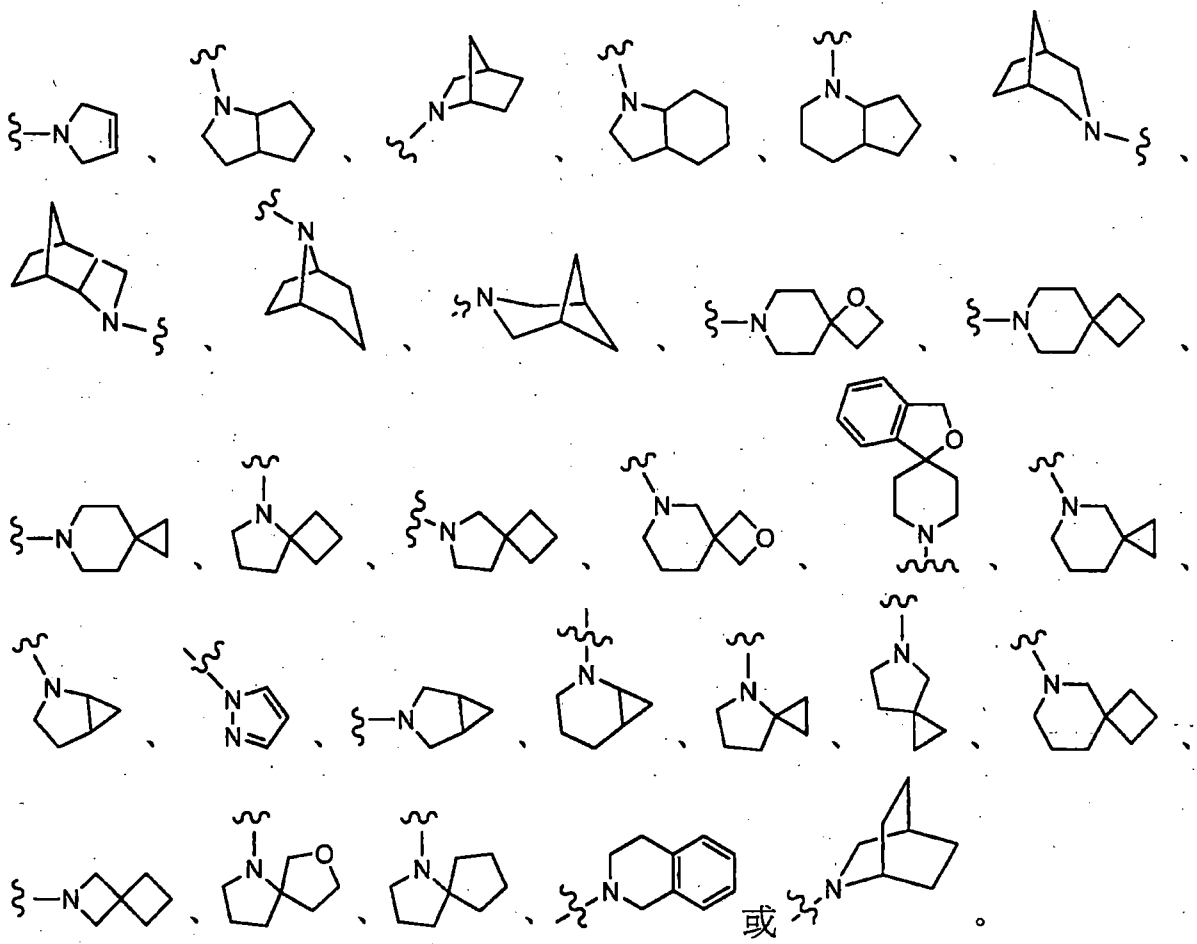
q爲0、1、2、3、4或5。

在一些實施例中，式Ib-iv-2化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基或萘。

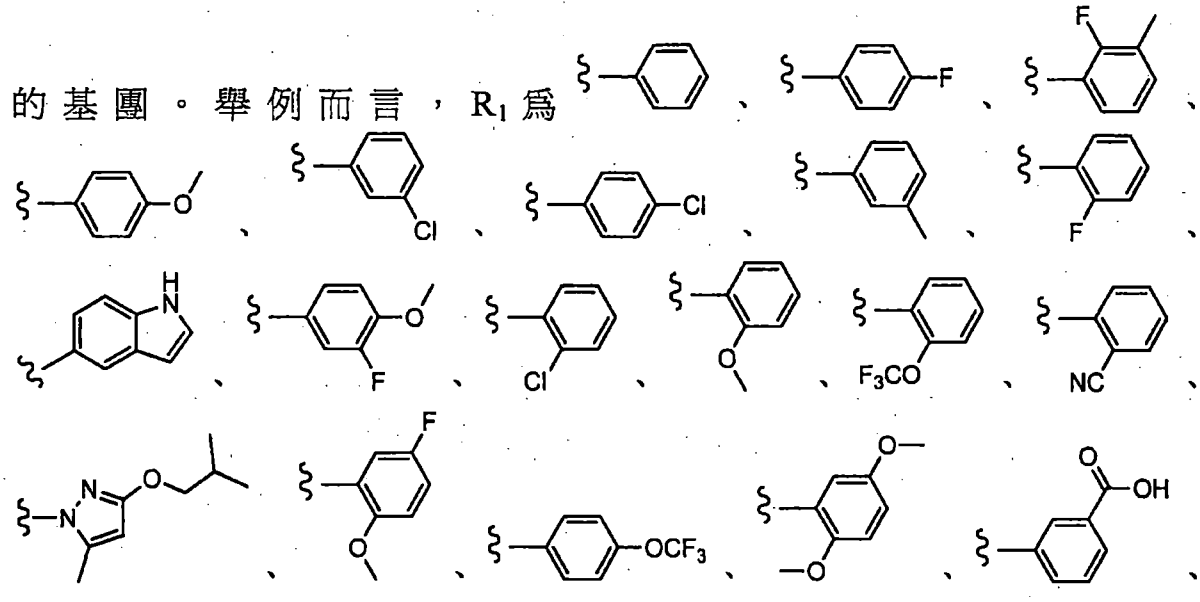
在一些實施例中，環C爲吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉或吡咯啶。

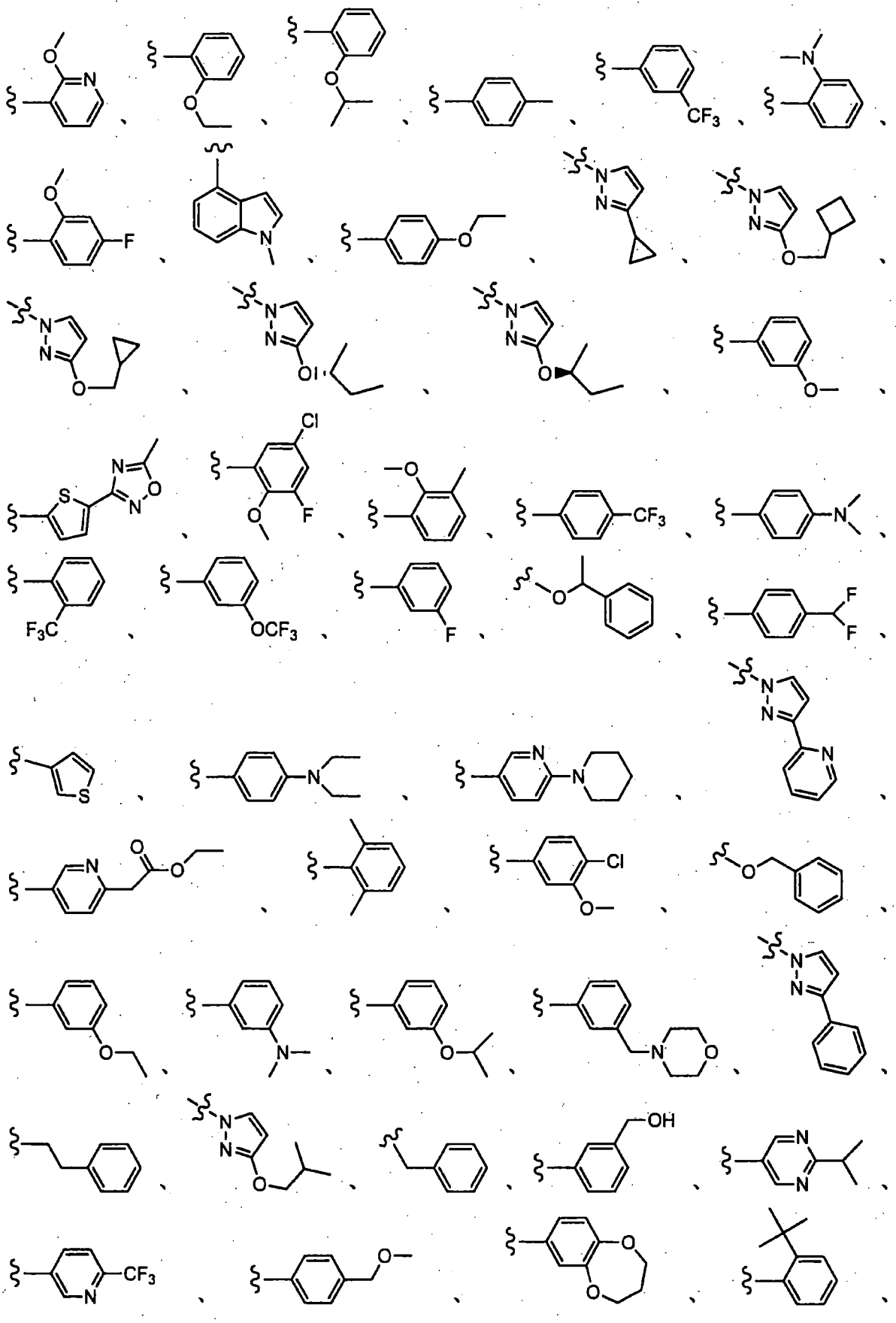
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、

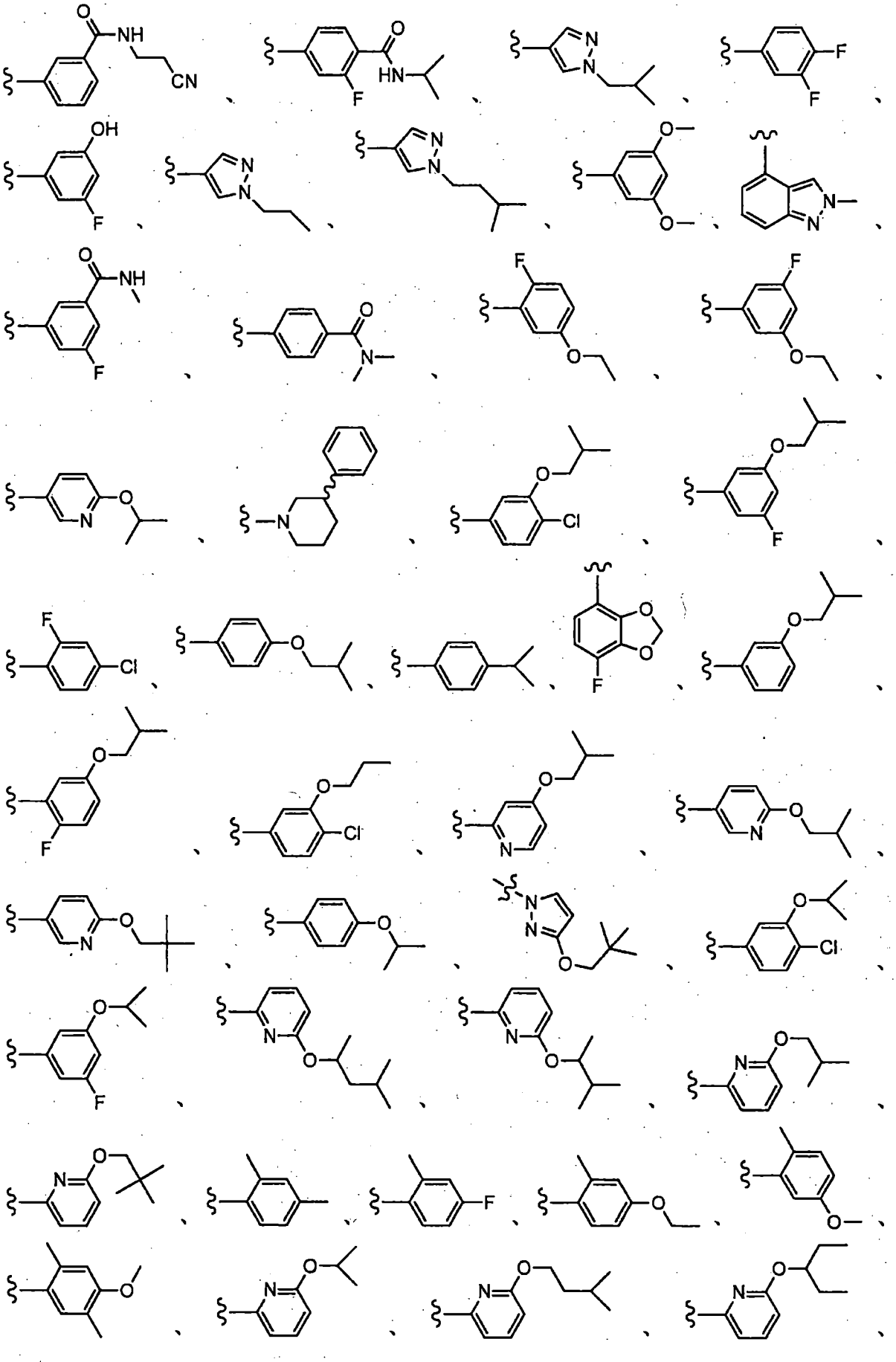


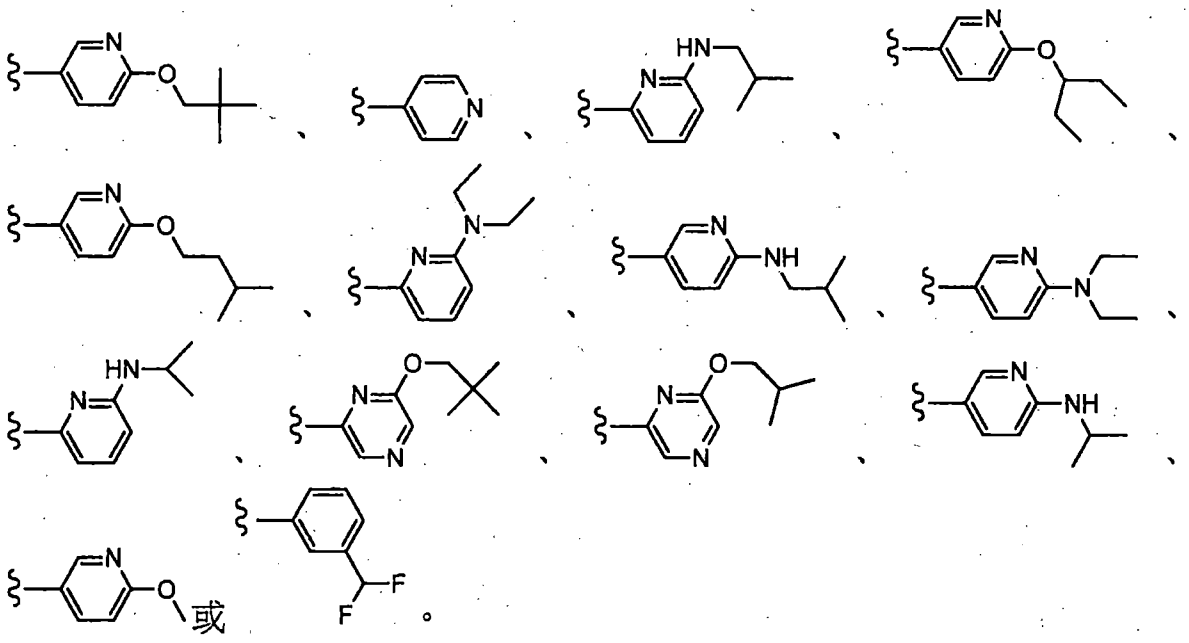
在一些實施例中，$R_1$為苯基、噻吩、吡啶或吡唑。

在一些實施例中，$R_1$為藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$為



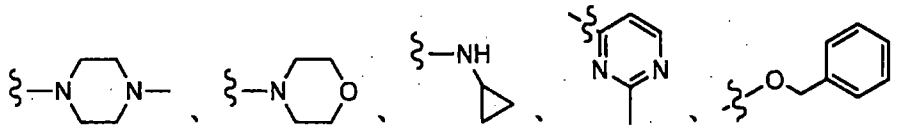


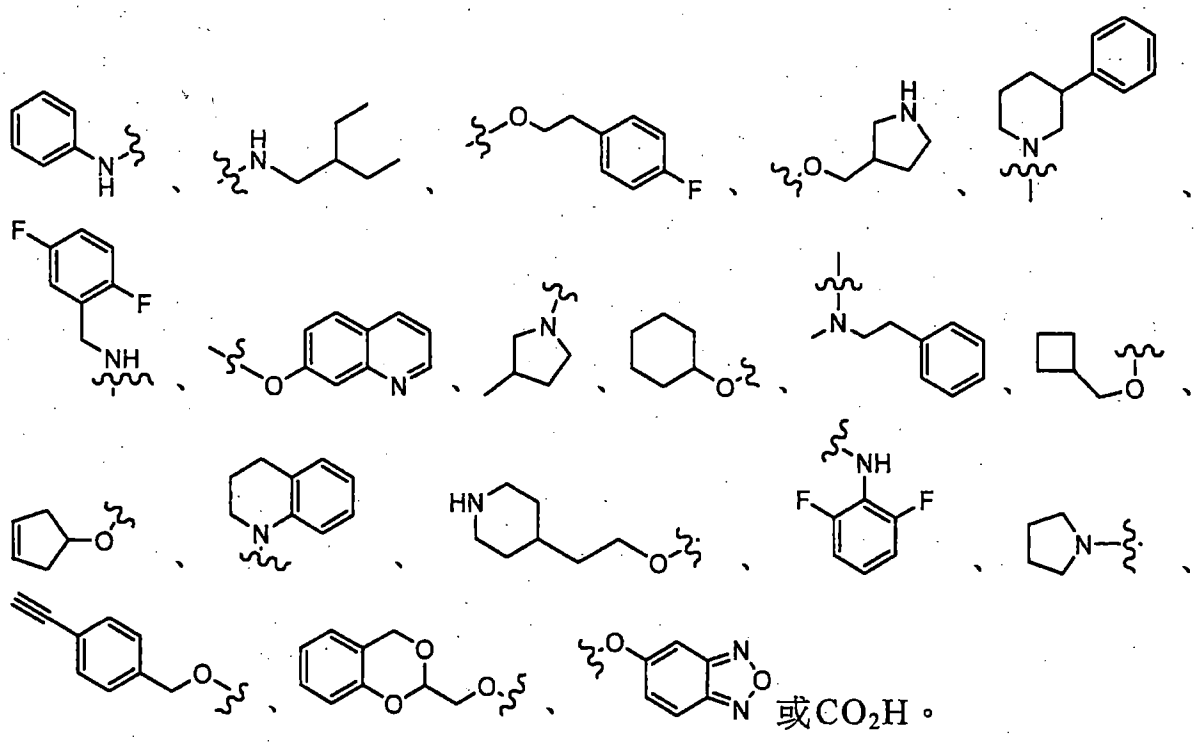




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

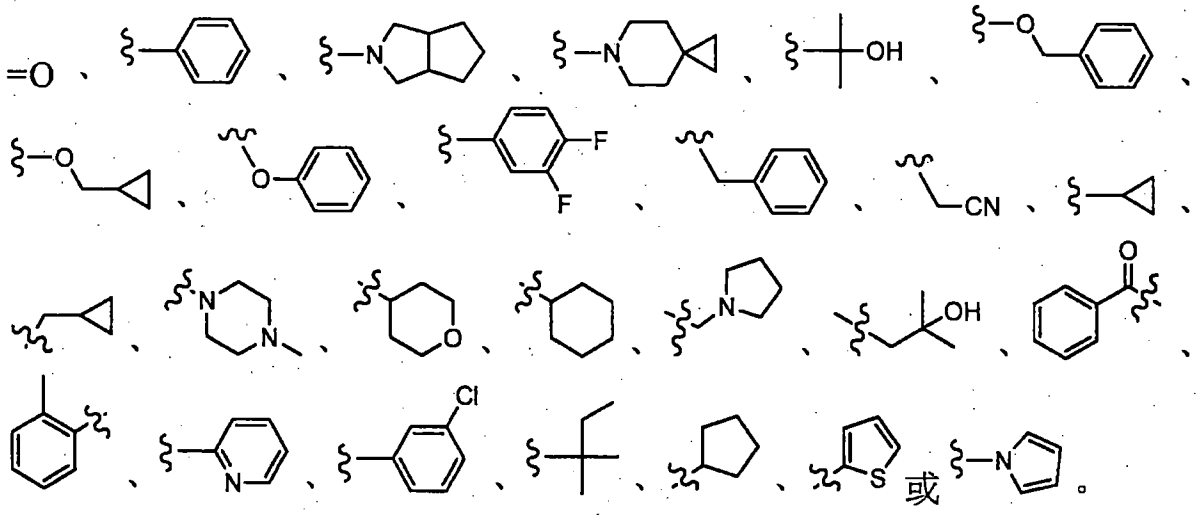
在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、





在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

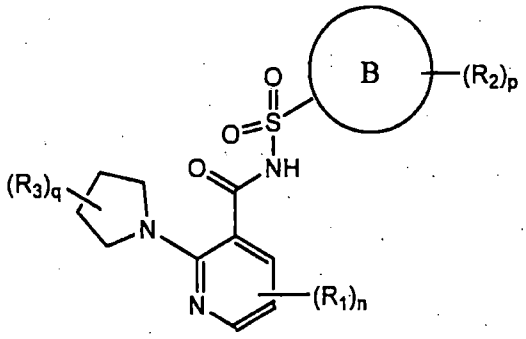
在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、



在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-v化合物：




**Ib-v**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

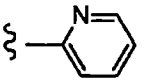
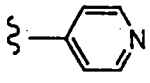
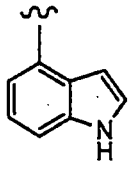
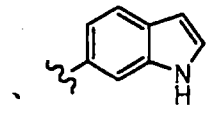
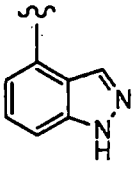
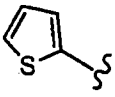
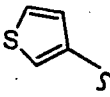
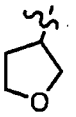
n爲0、1、2或3；

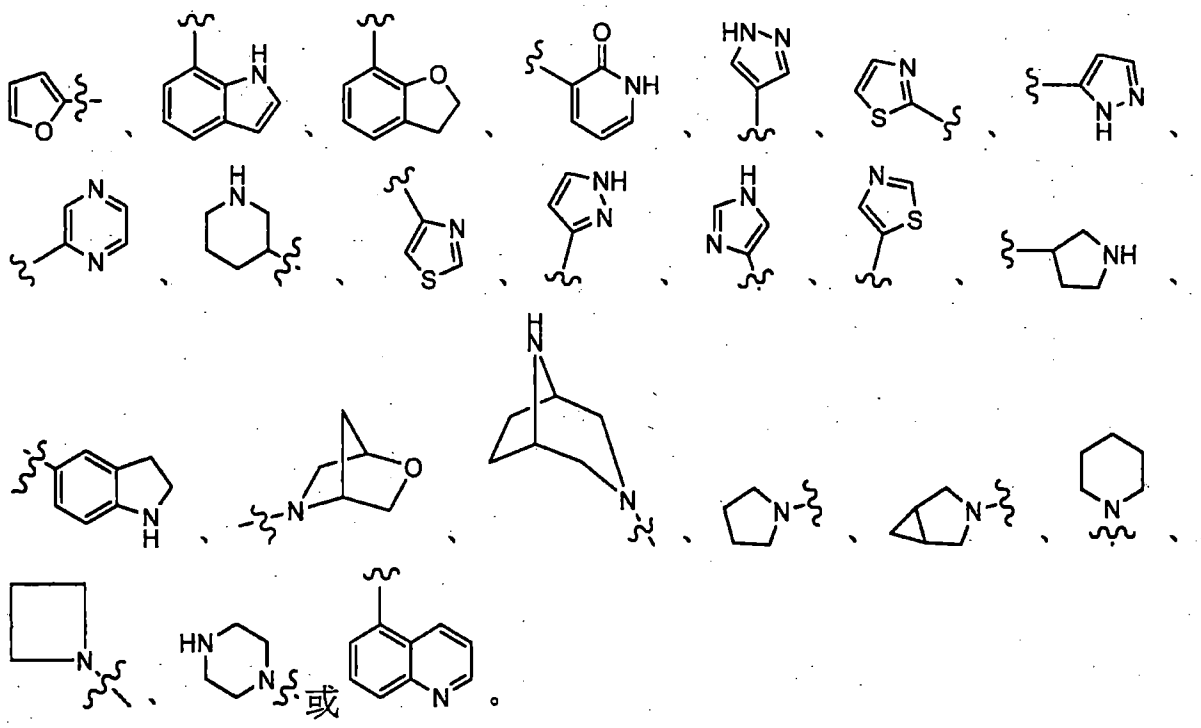
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ib-v化合物呈醫藥學上可接受之前藥形式存在。

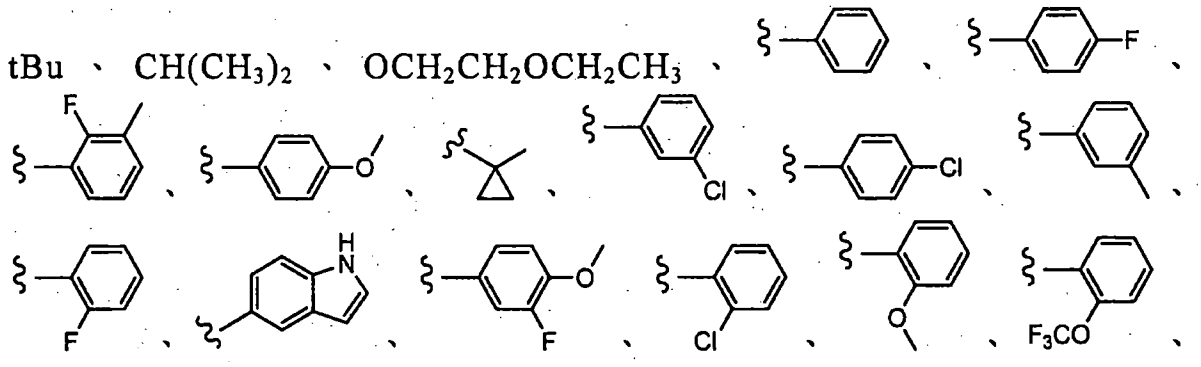
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

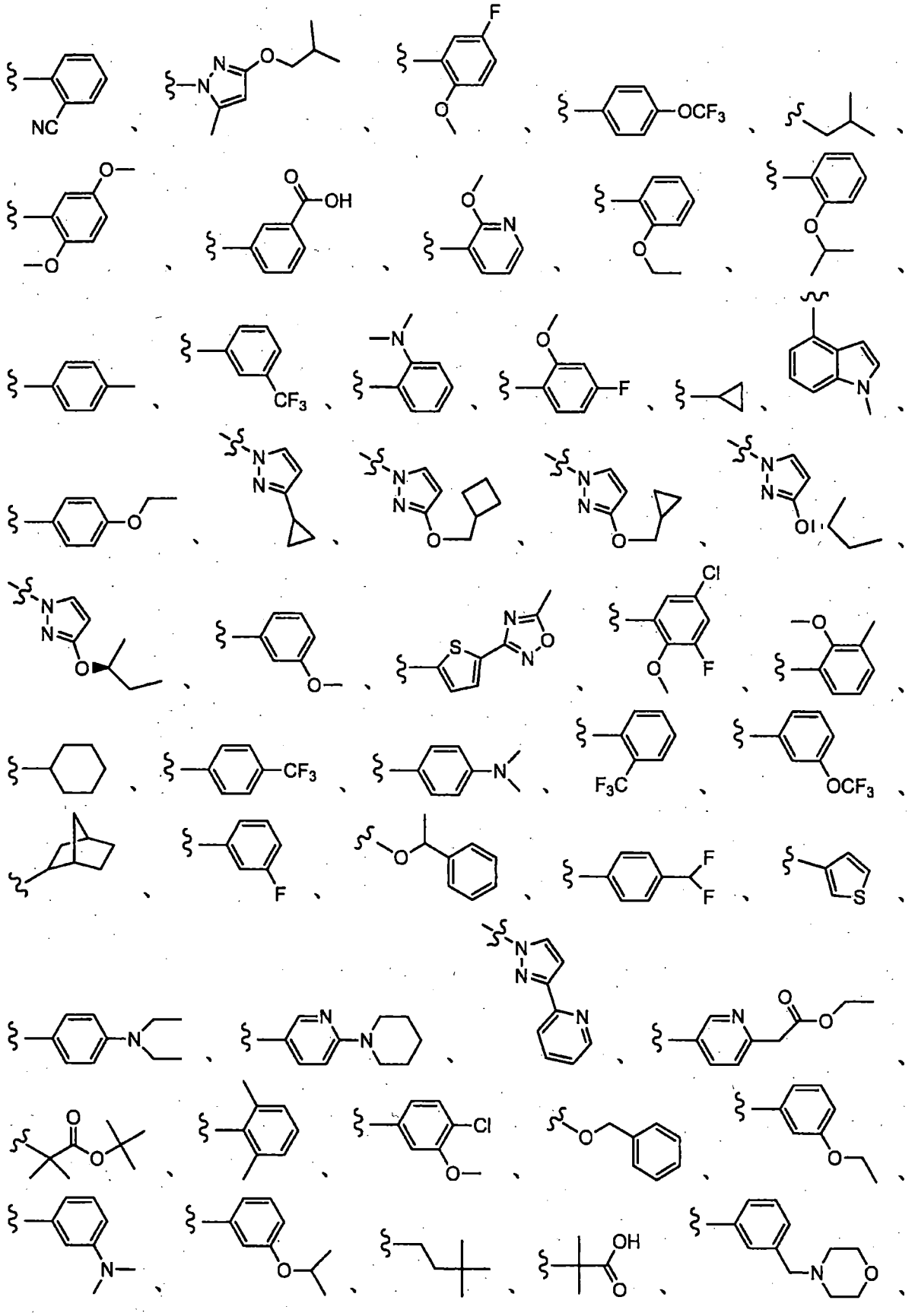
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、  、、  、  、  、  、  、  、  、

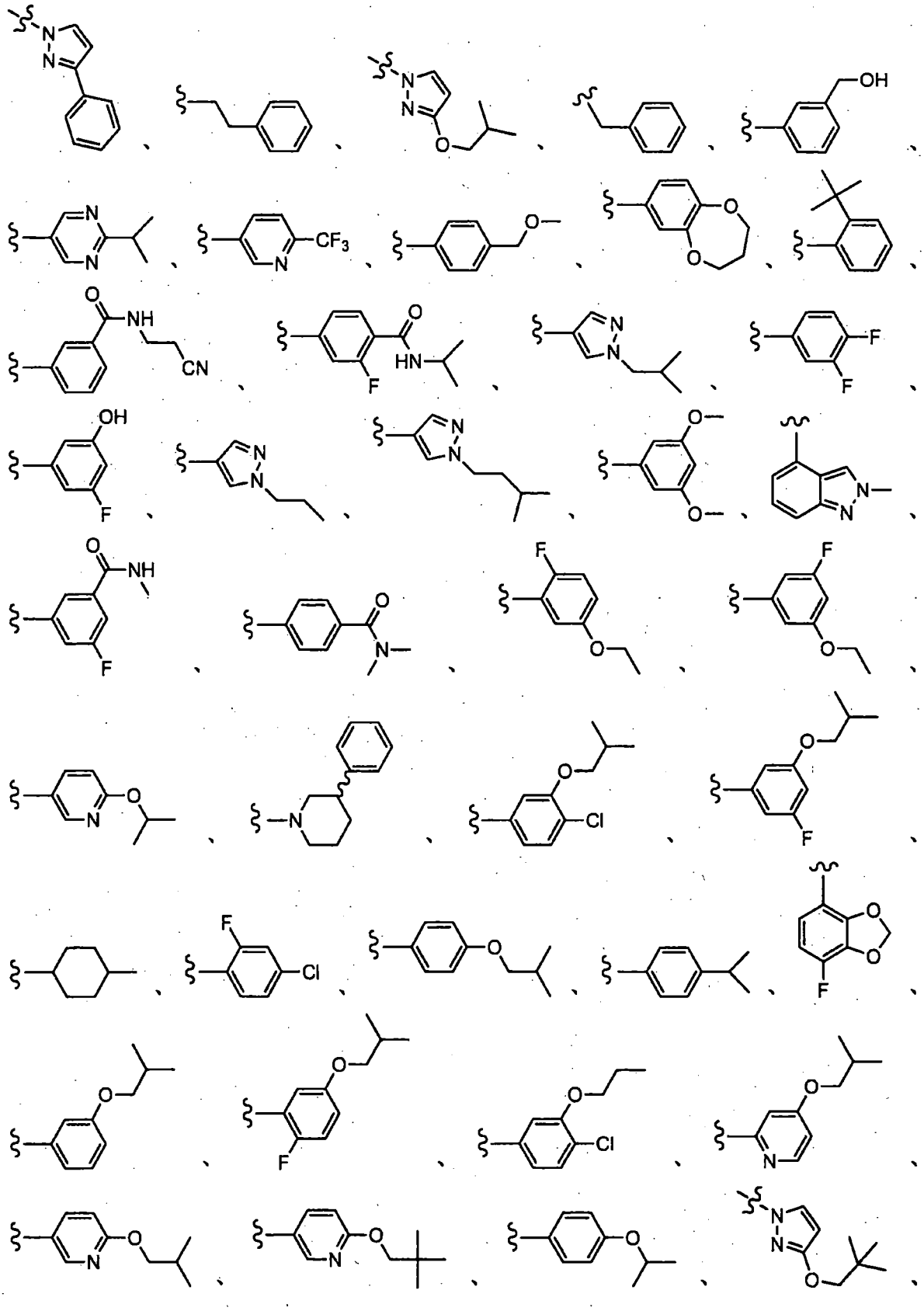


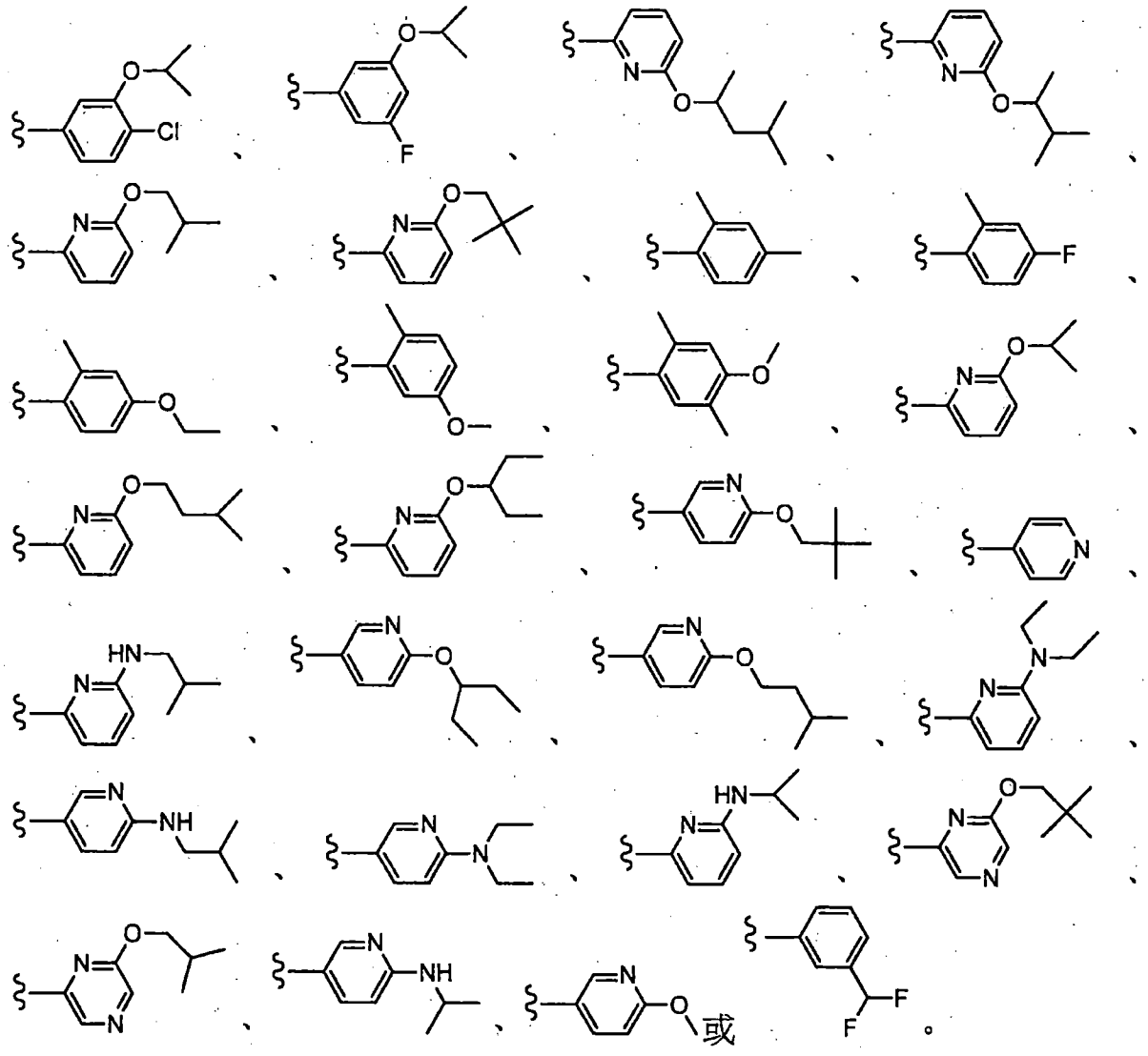
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、



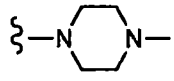
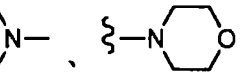
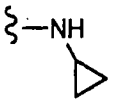


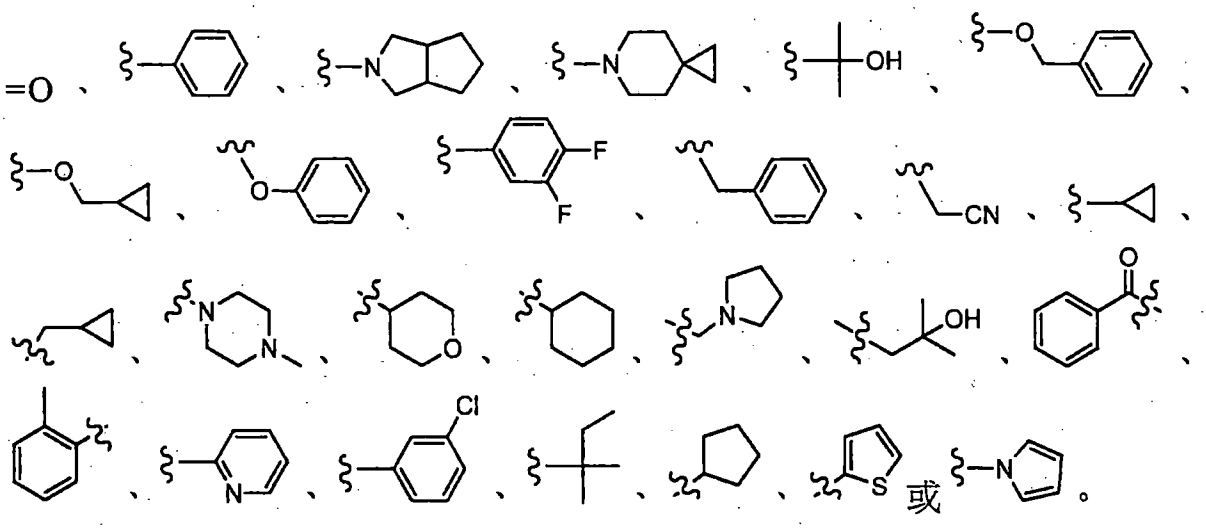




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、

$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 

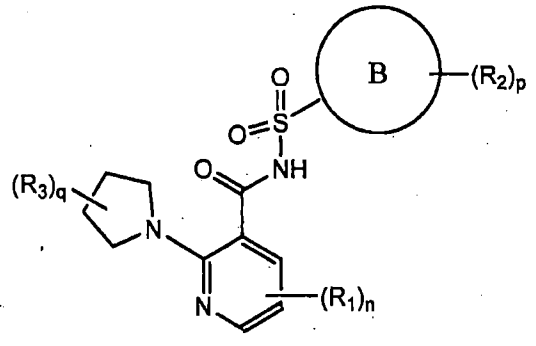


在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且n爲1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-v-1化合物：



**Ib-v-1**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；

C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

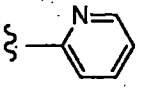
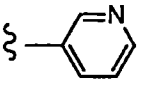
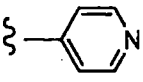
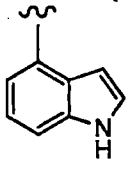
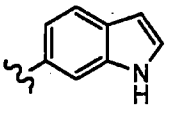
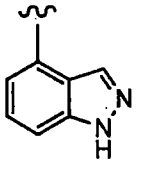
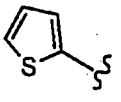
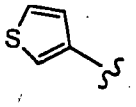
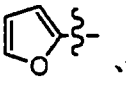
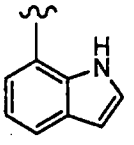
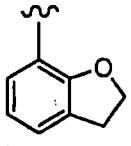
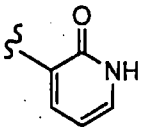
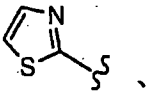
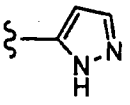
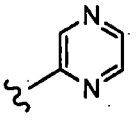
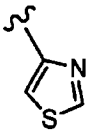
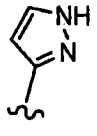
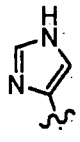
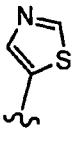
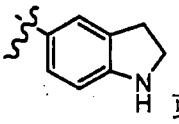
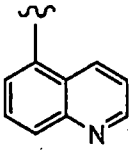
n爲0、1、2或3；

p爲0、1、2或3；且

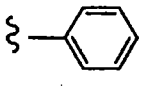
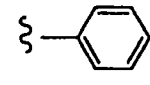
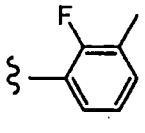
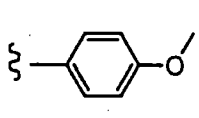
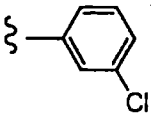
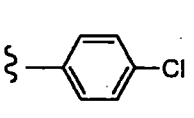
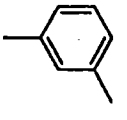
q爲0、1、2、3、4或5。

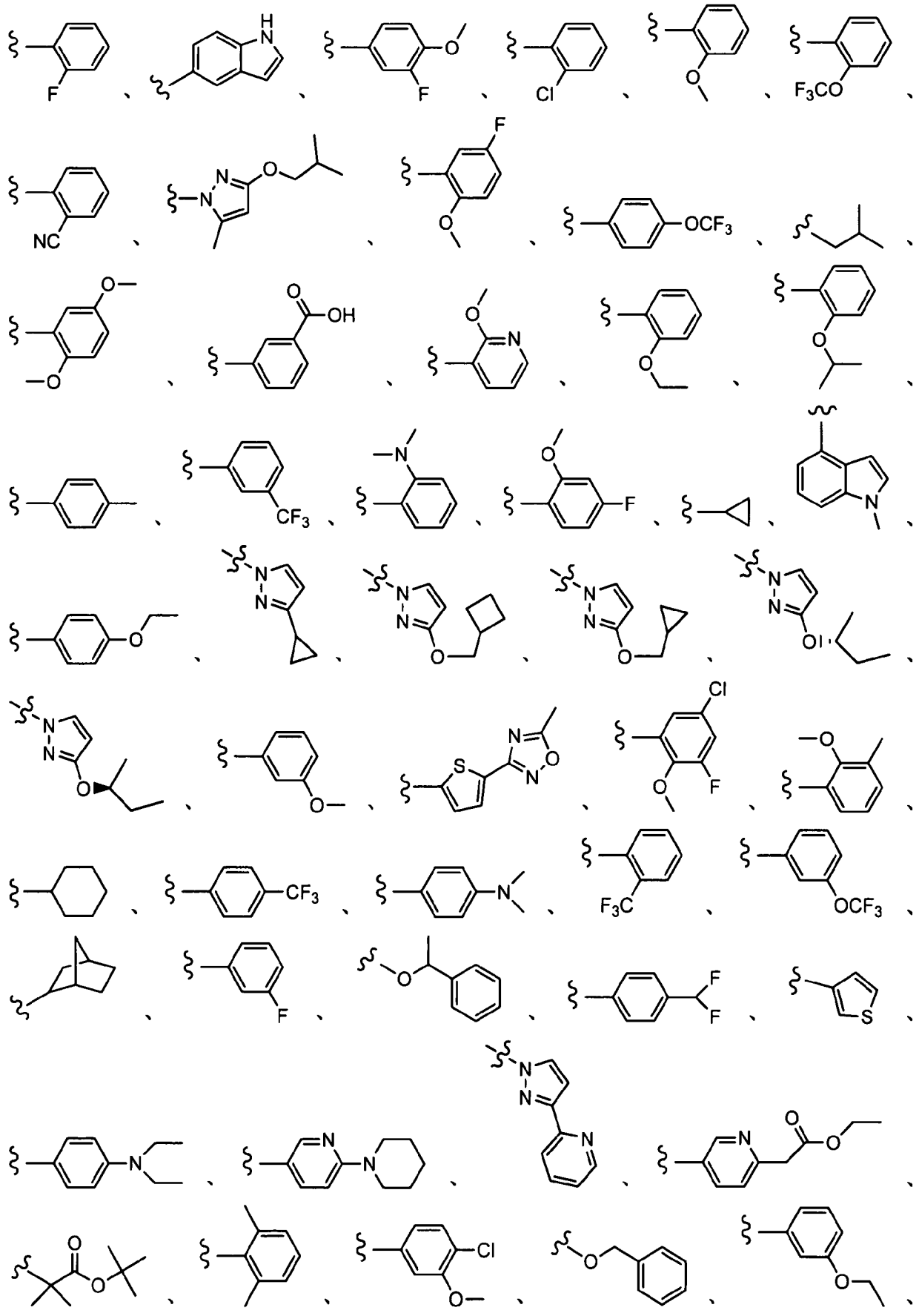
在一些實施例中，式Ib-v-1化合物呈醫藥學上可接受之前藥形式存在。

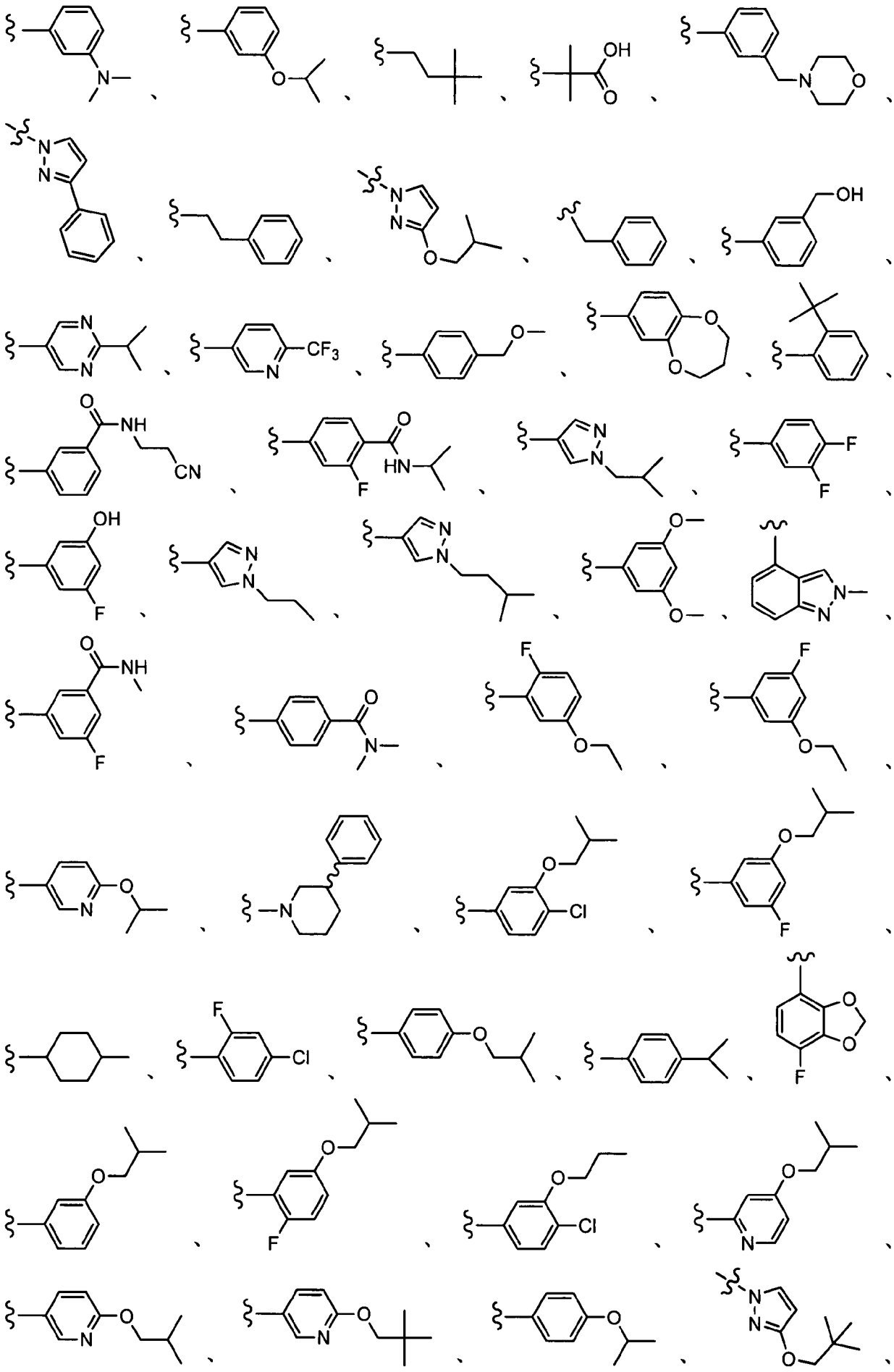
在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

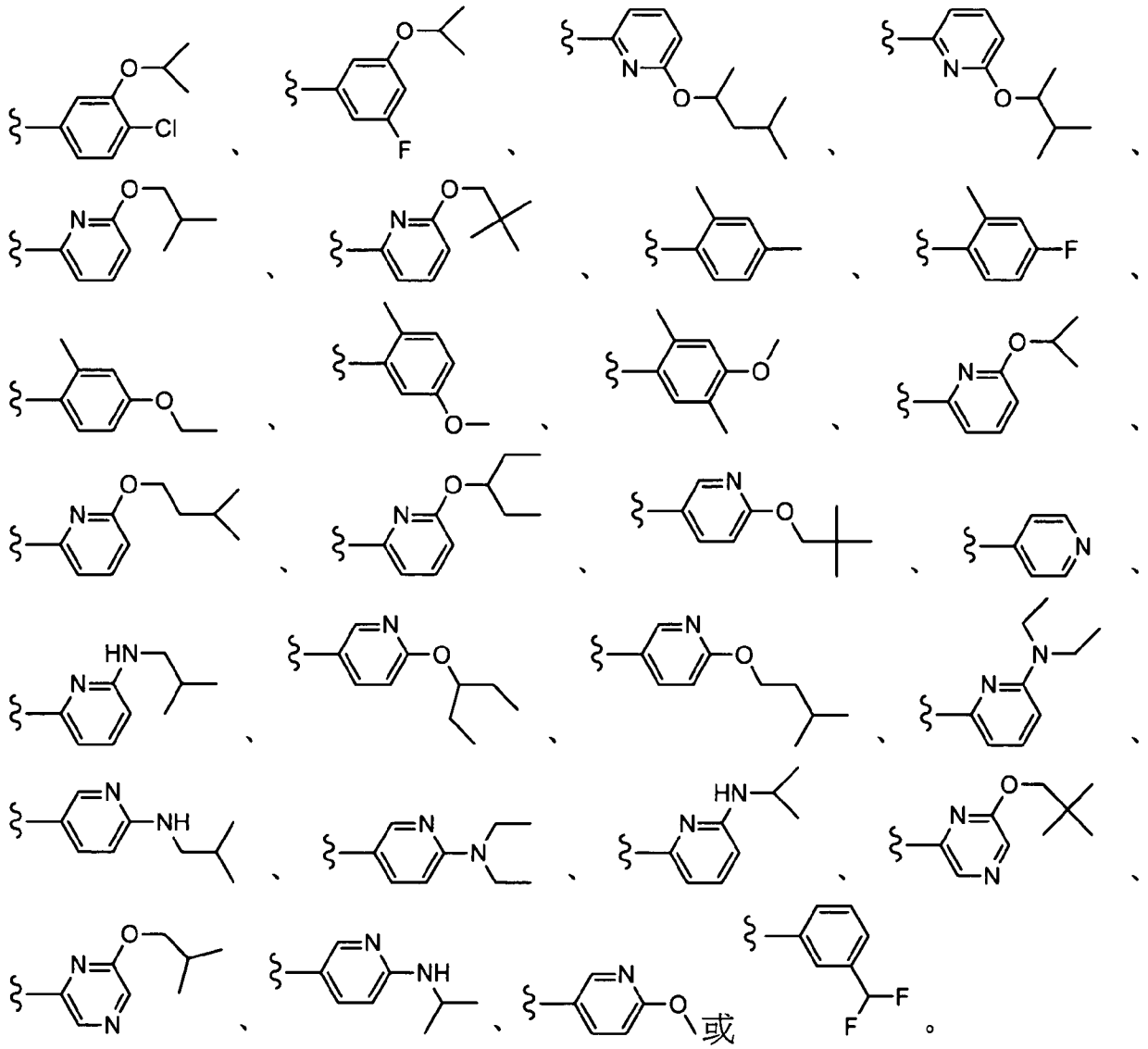
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、

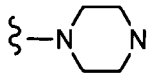
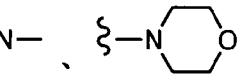
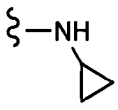


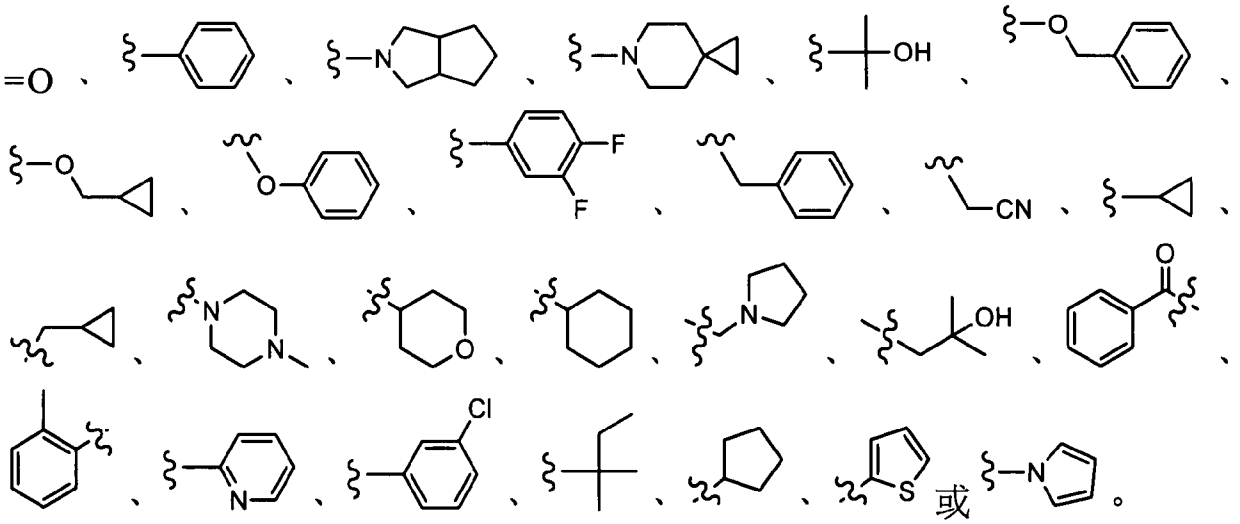




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、

$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 

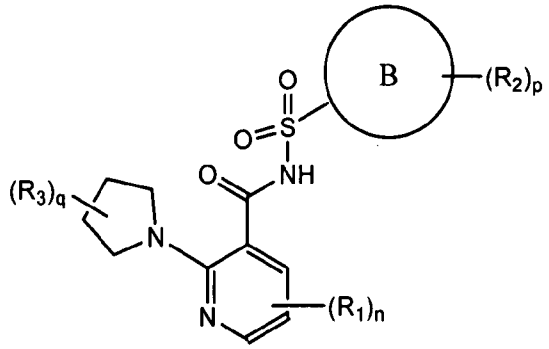


在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且n爲1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-v-2化合物：



**Ib-v-2**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個

$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

p爲0、1、2或3；且

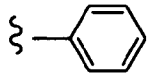
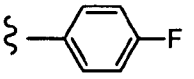
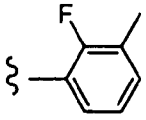
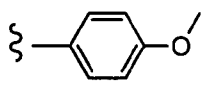
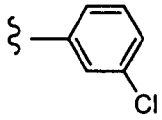
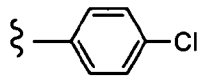
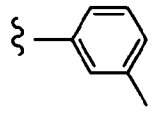
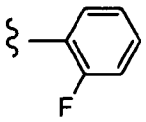
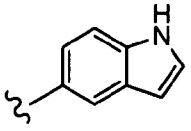
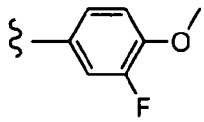
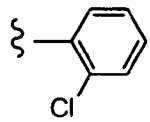
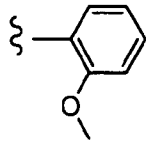
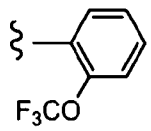
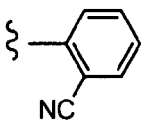
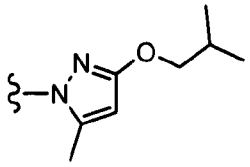
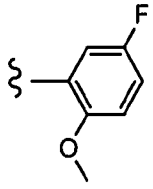
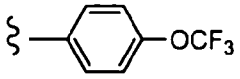
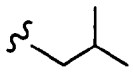
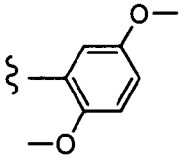
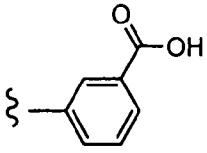
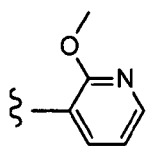
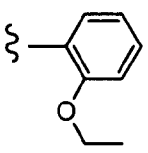
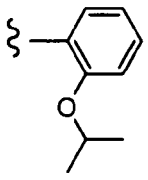
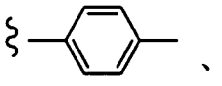
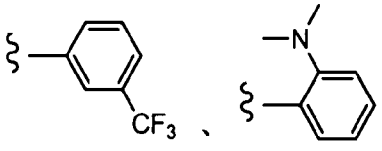
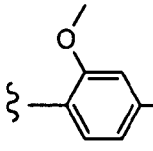
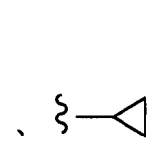
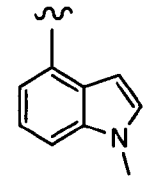
q爲0、1、2、3、4或5。

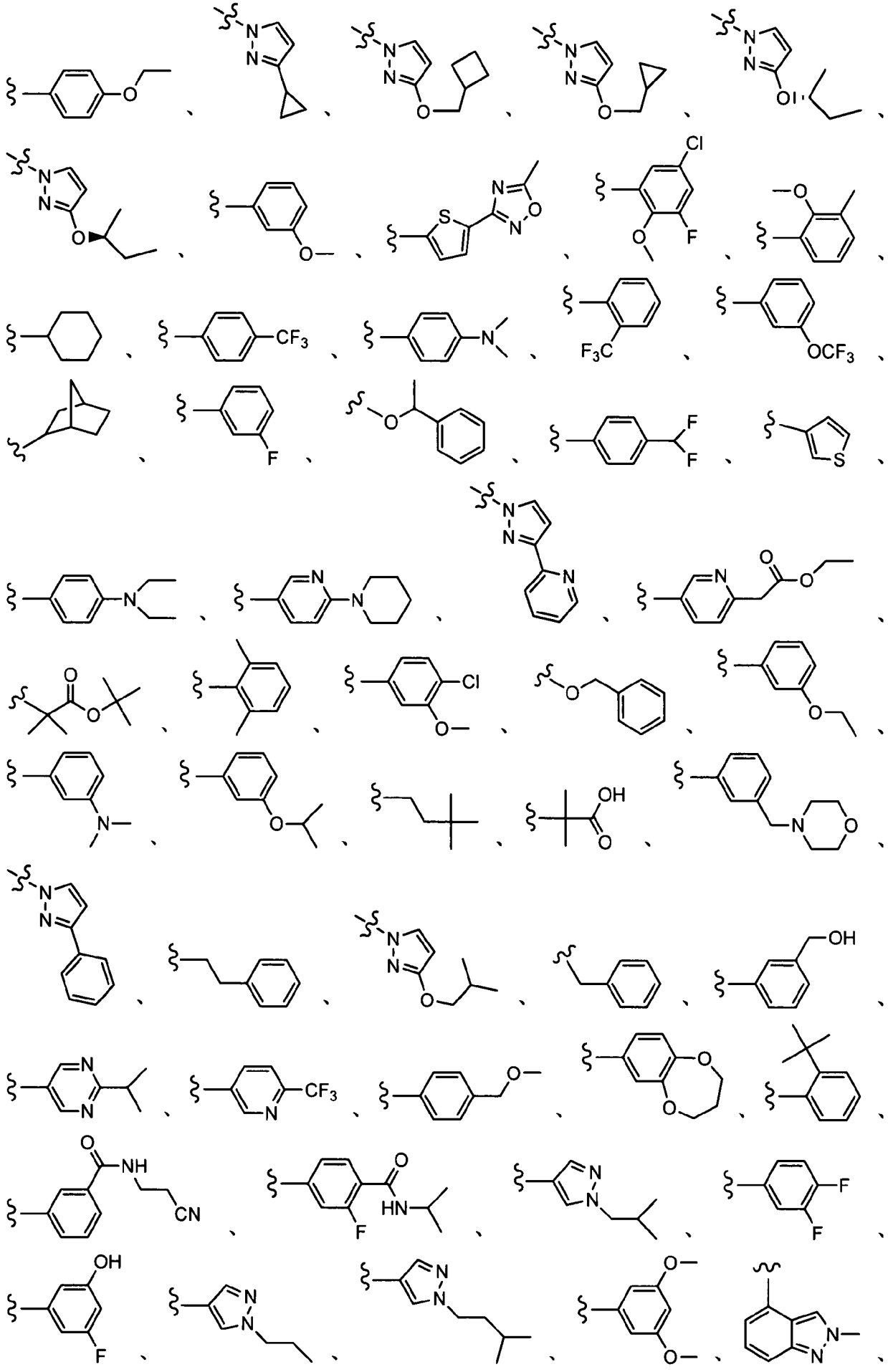
在一些實施例中，式Ib-v-2化合物呈醫藥學上可接受之前藥形式

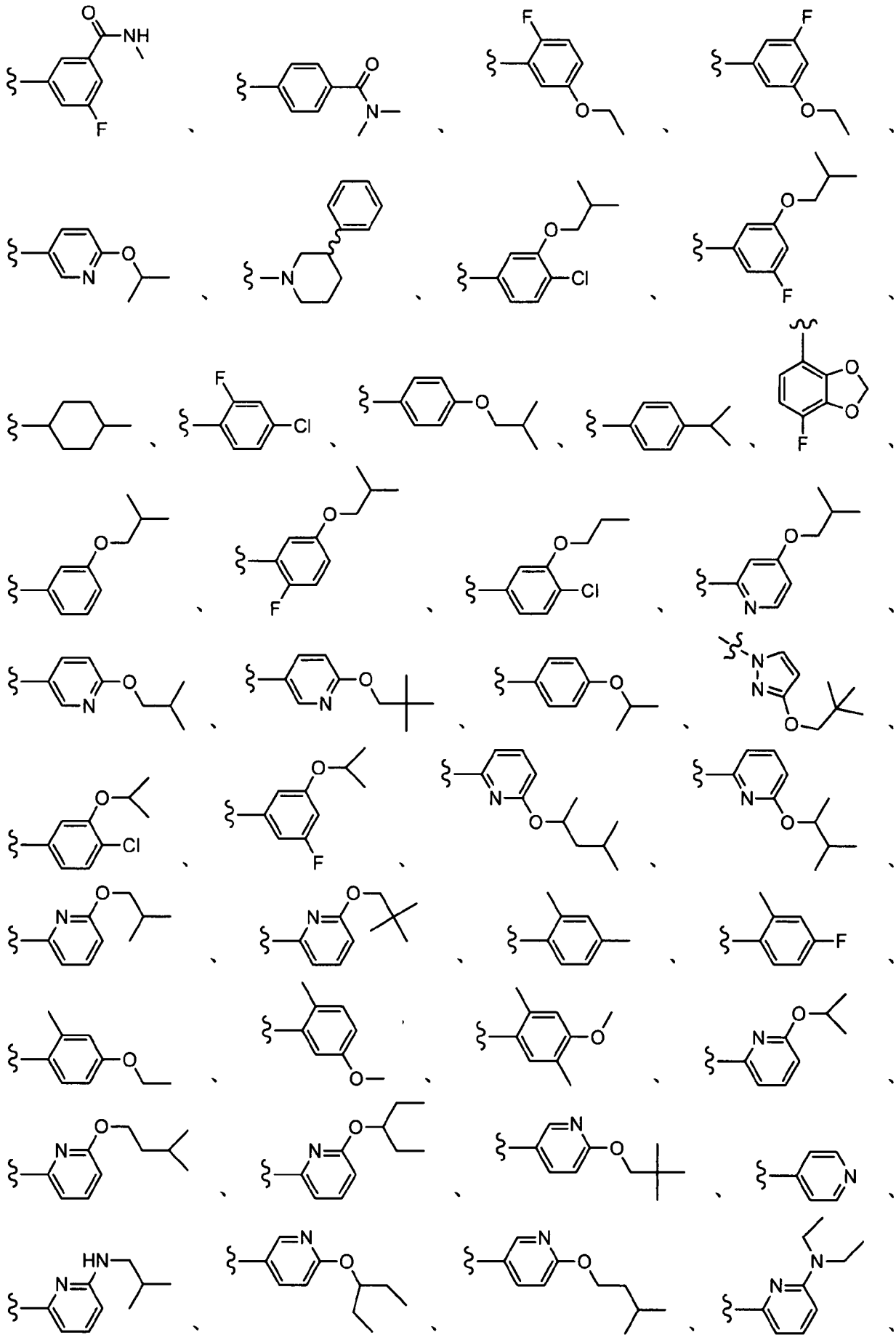
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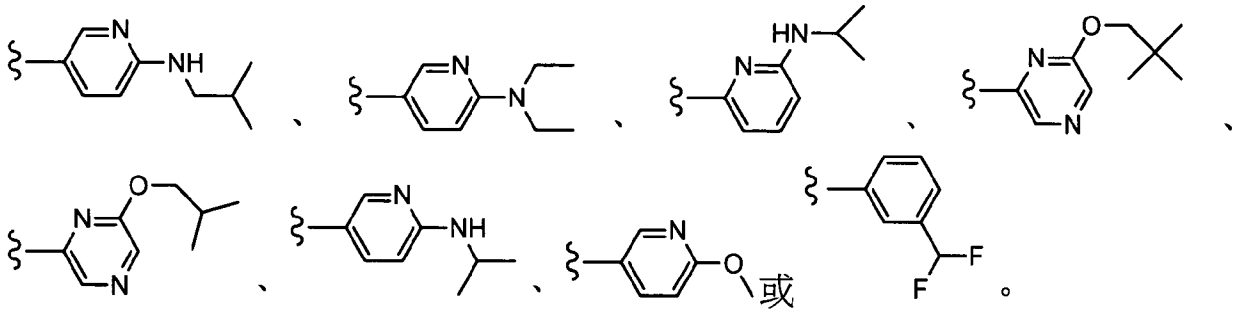
在一些實施例中，環B爲苯基或萘。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、  、  、、、、、、。

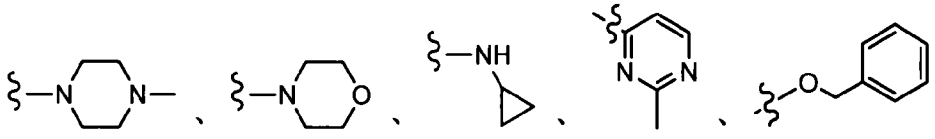


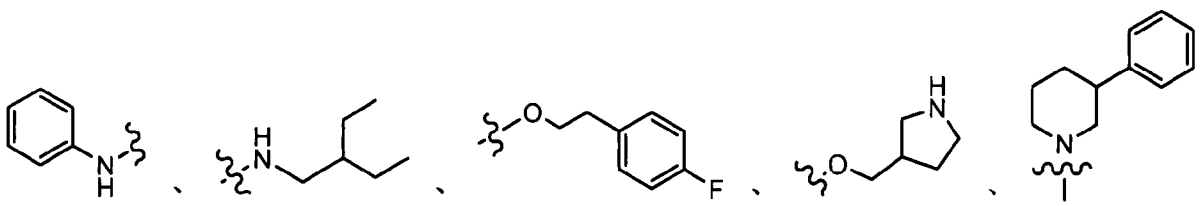


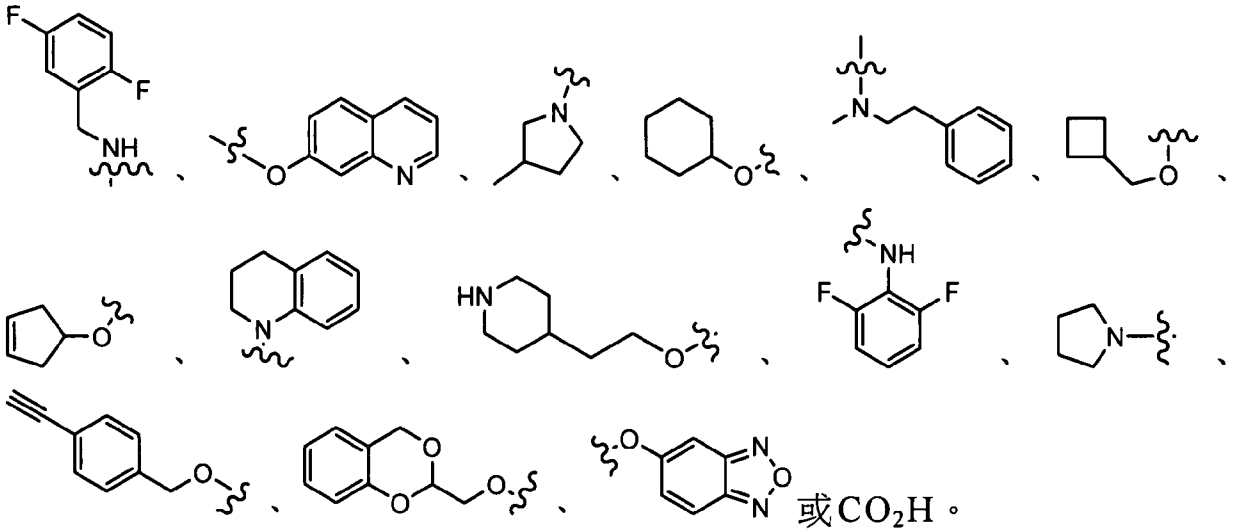


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、

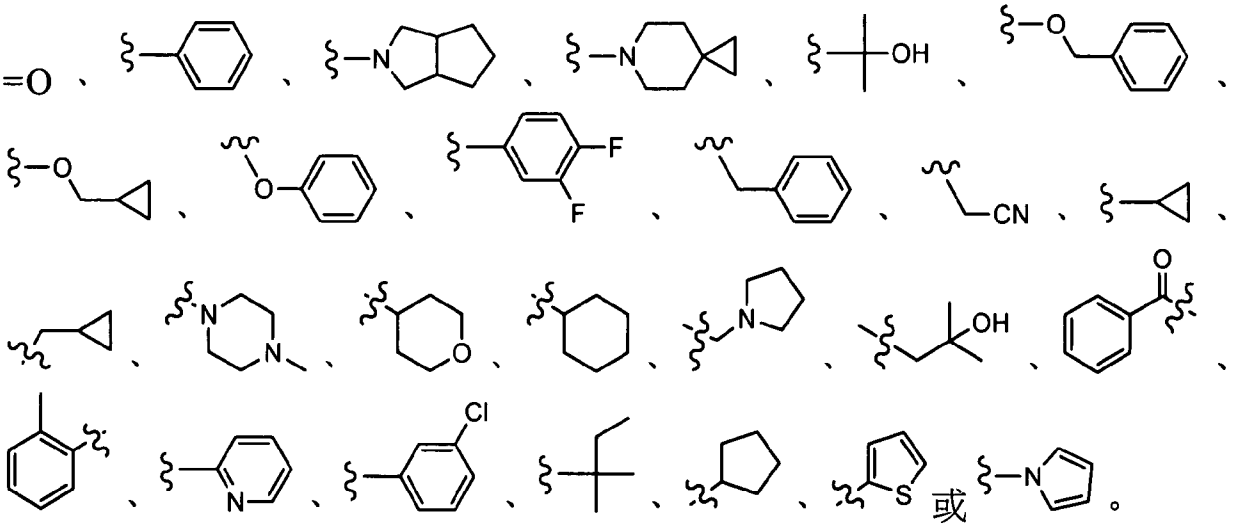






在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、



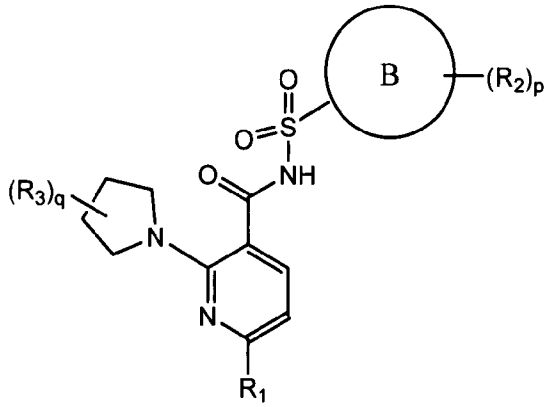
在一些實施例中，n爲0。在一些實施例中，n爲1。在一些實施例中，n爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施

例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且n爲1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，n爲1，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-vi化合物：




**Ib-vi**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

$R_1$爲C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原

子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

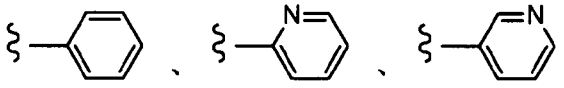
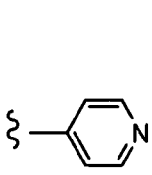
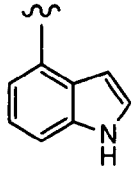
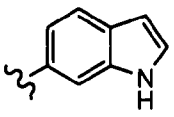
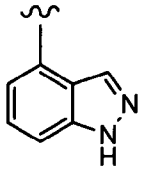
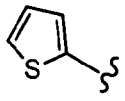
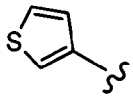
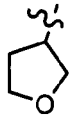
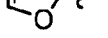
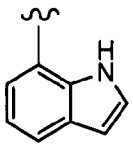
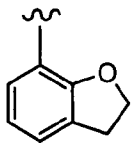
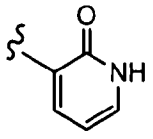
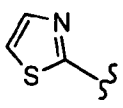
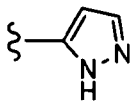
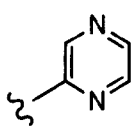
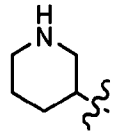
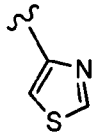
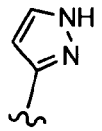
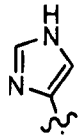
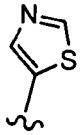
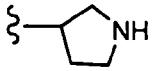
R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

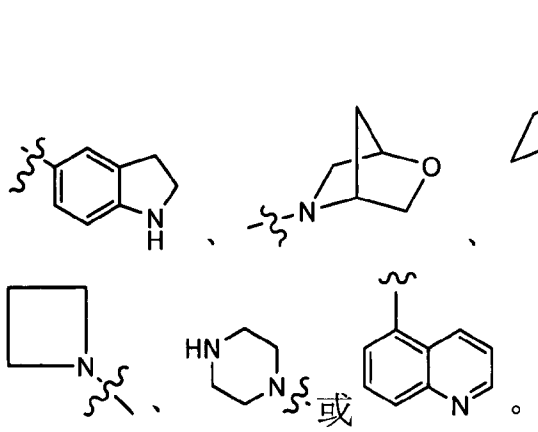
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ib-vi化合物呈醫藥學上可接受之前藥形式存在。

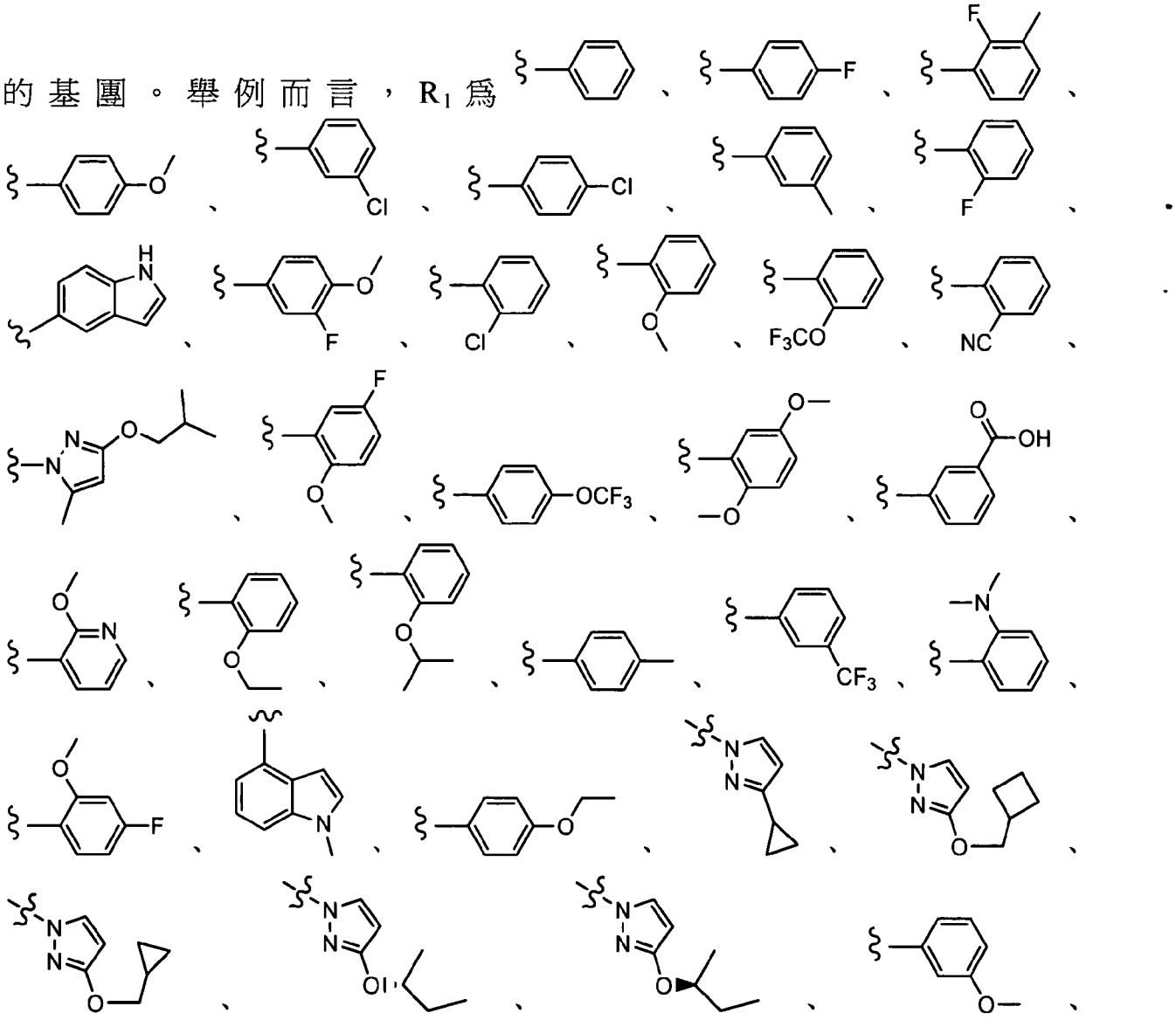
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

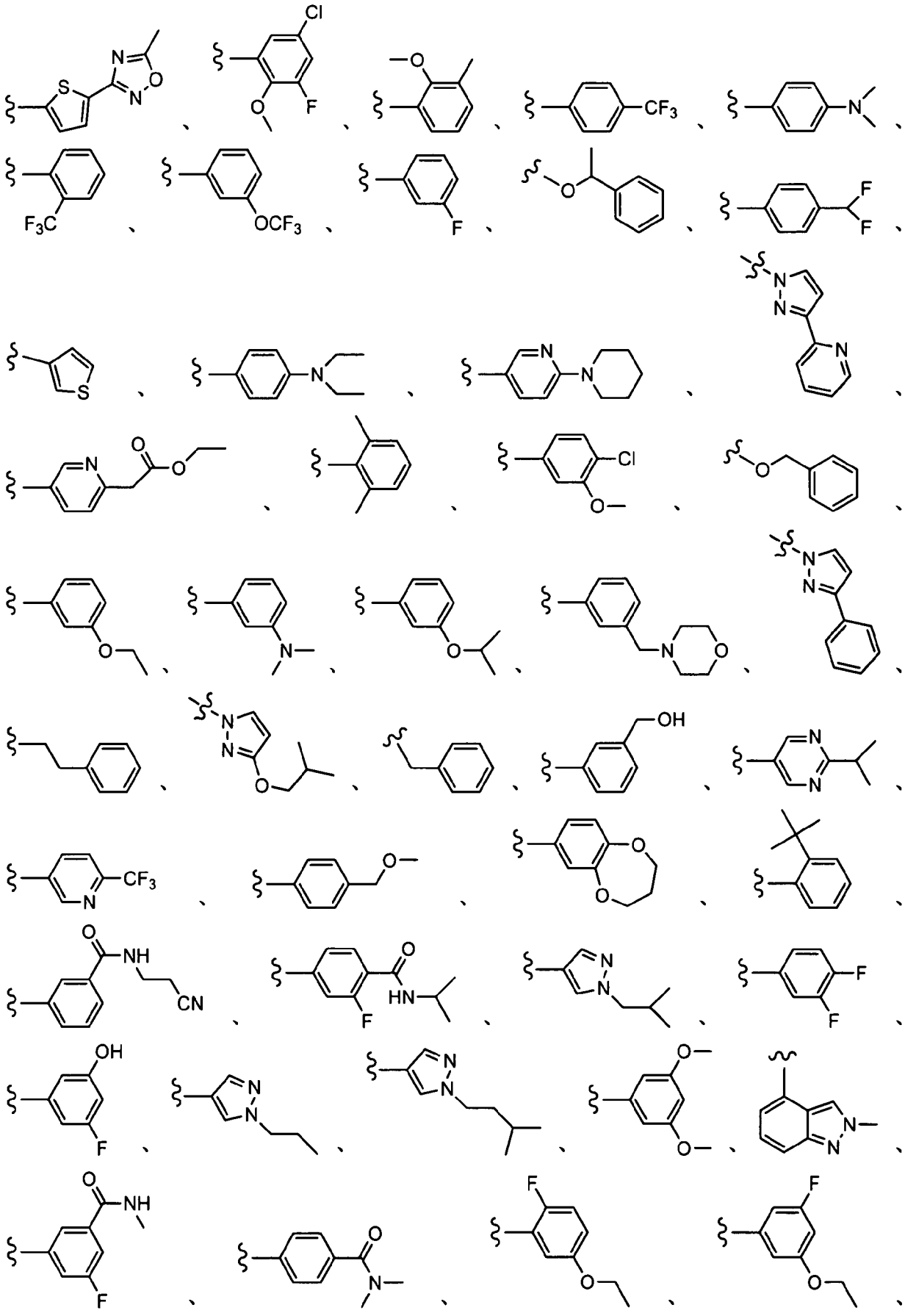
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

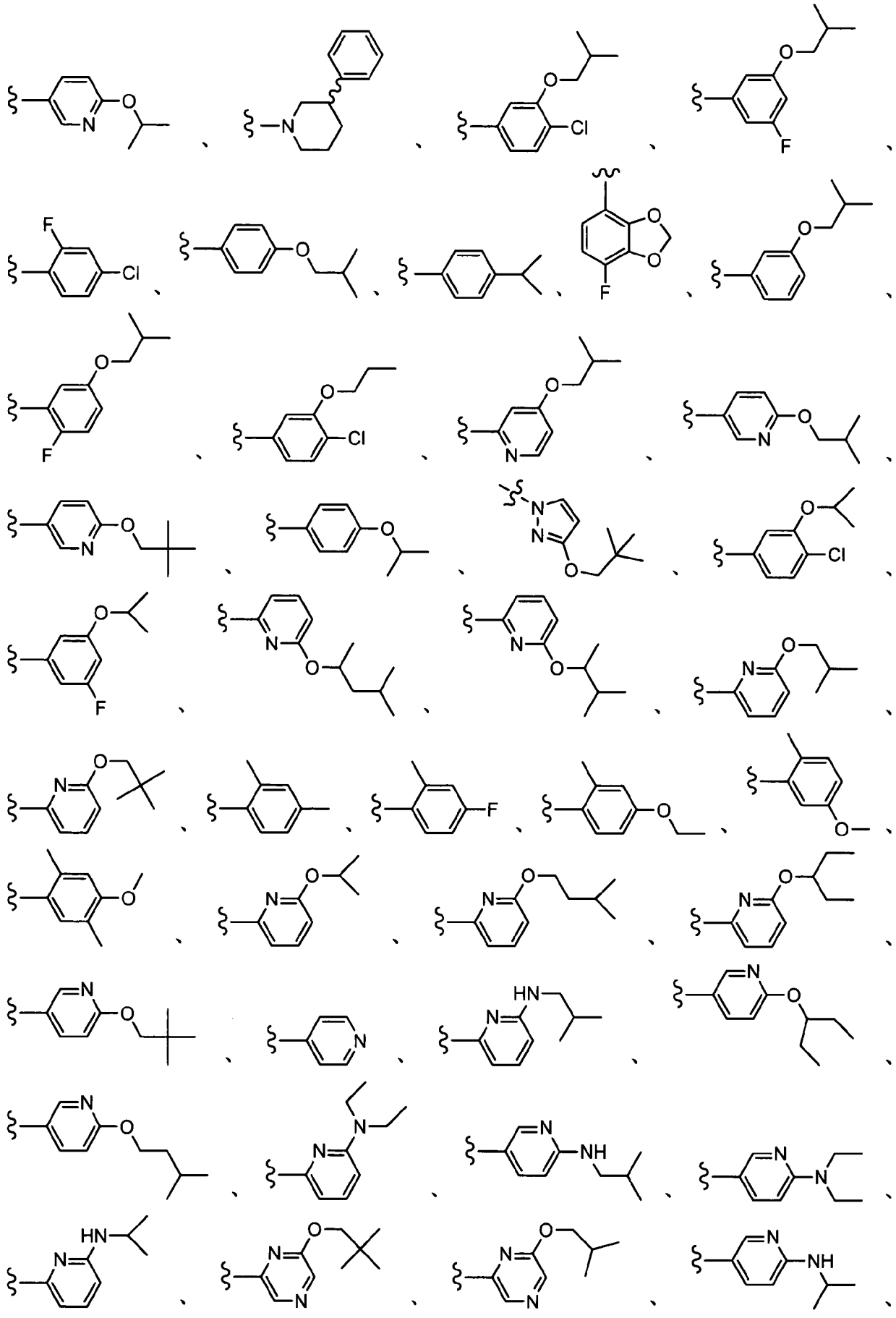


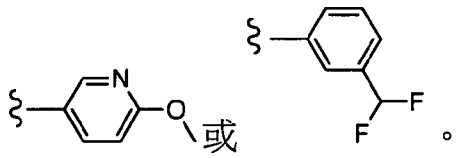
在一些實施例中，$R_1$為苯基、噻吩、吡啶或吡唑。

在一些實施例中，$R_1$為藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$為



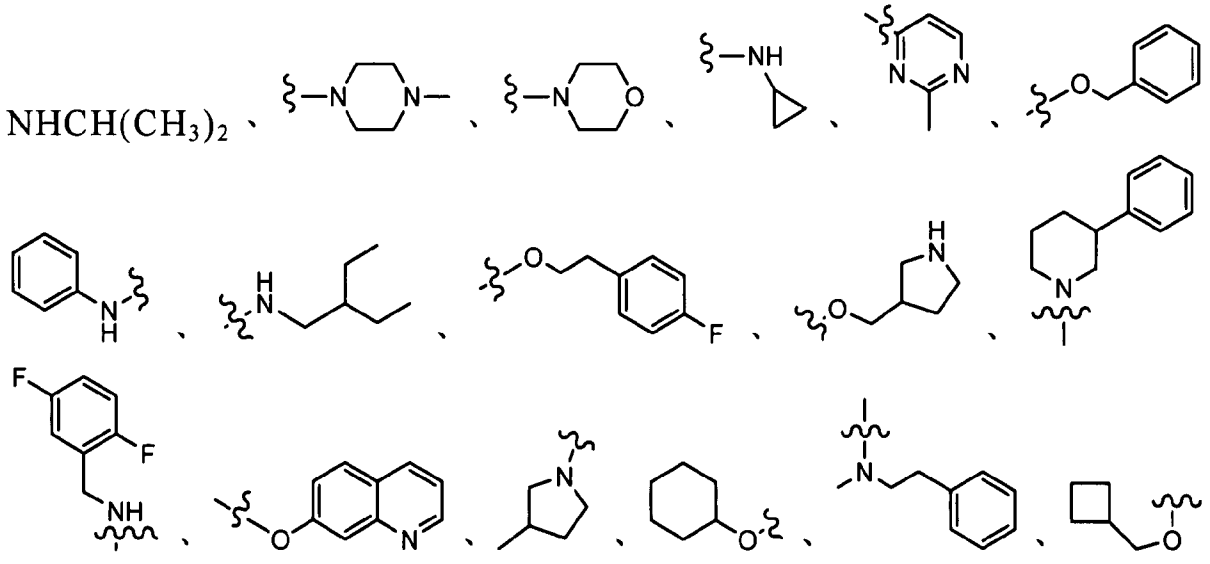


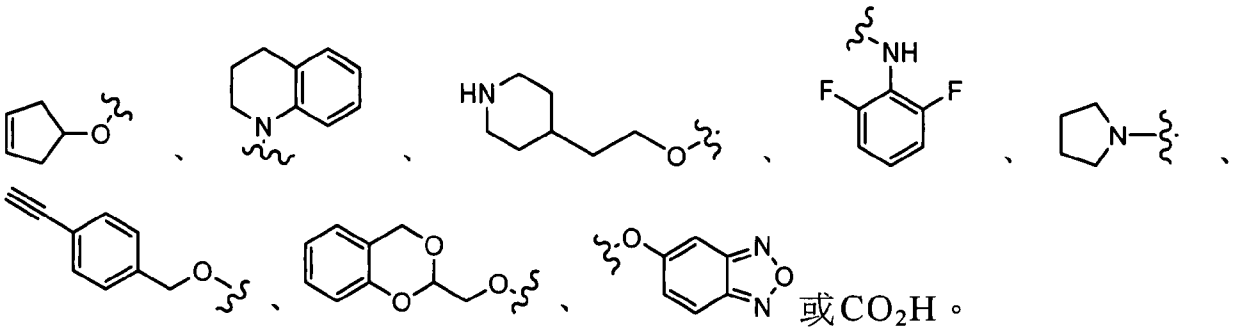




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

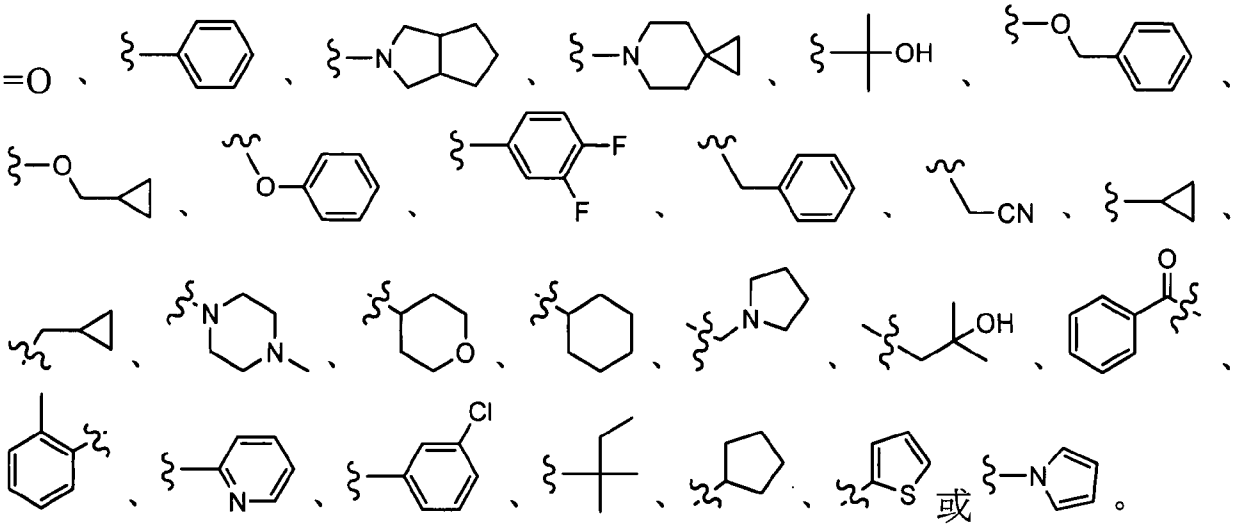
在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、






在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

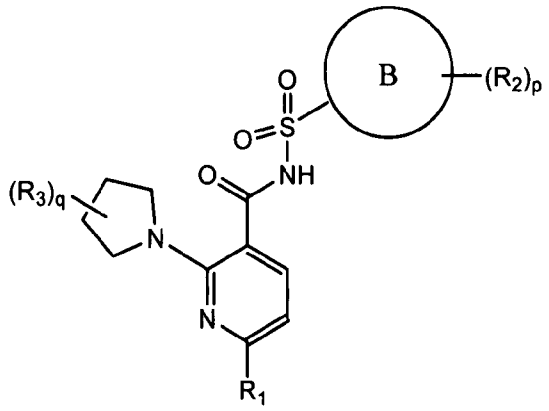
在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、




在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-vi-1化合物：



**Ib-vi-1**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

$R_1$爲C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-

C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

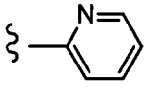
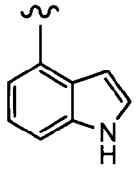
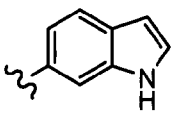
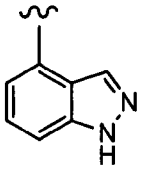
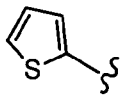
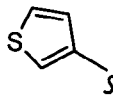
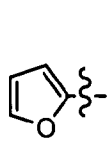
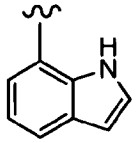
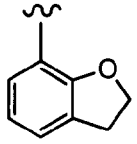
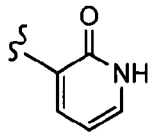
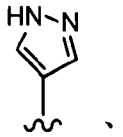
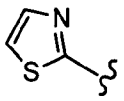
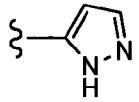
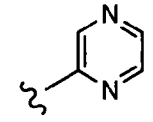
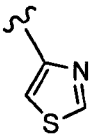
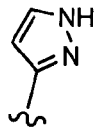
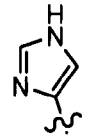
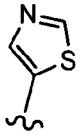
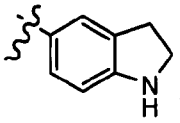
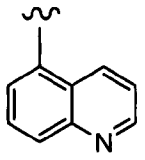
R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

p爲0、1、2或3；且

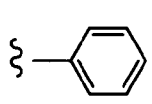
q爲0、1、2、3、4或5。

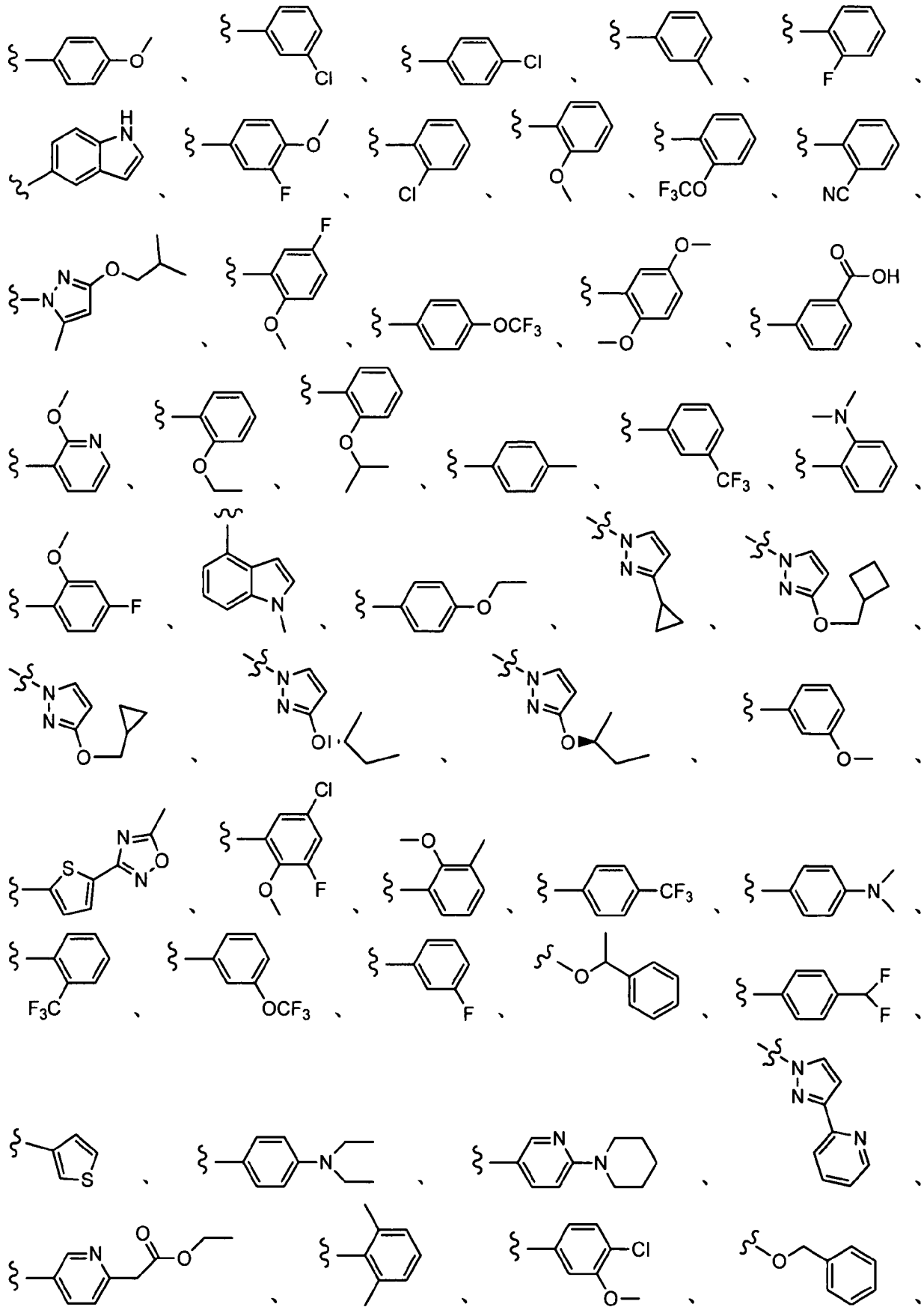
在一些實施例中，式Ib-vi-1化合物呈醫藥學上可接受之前藥形式存在。

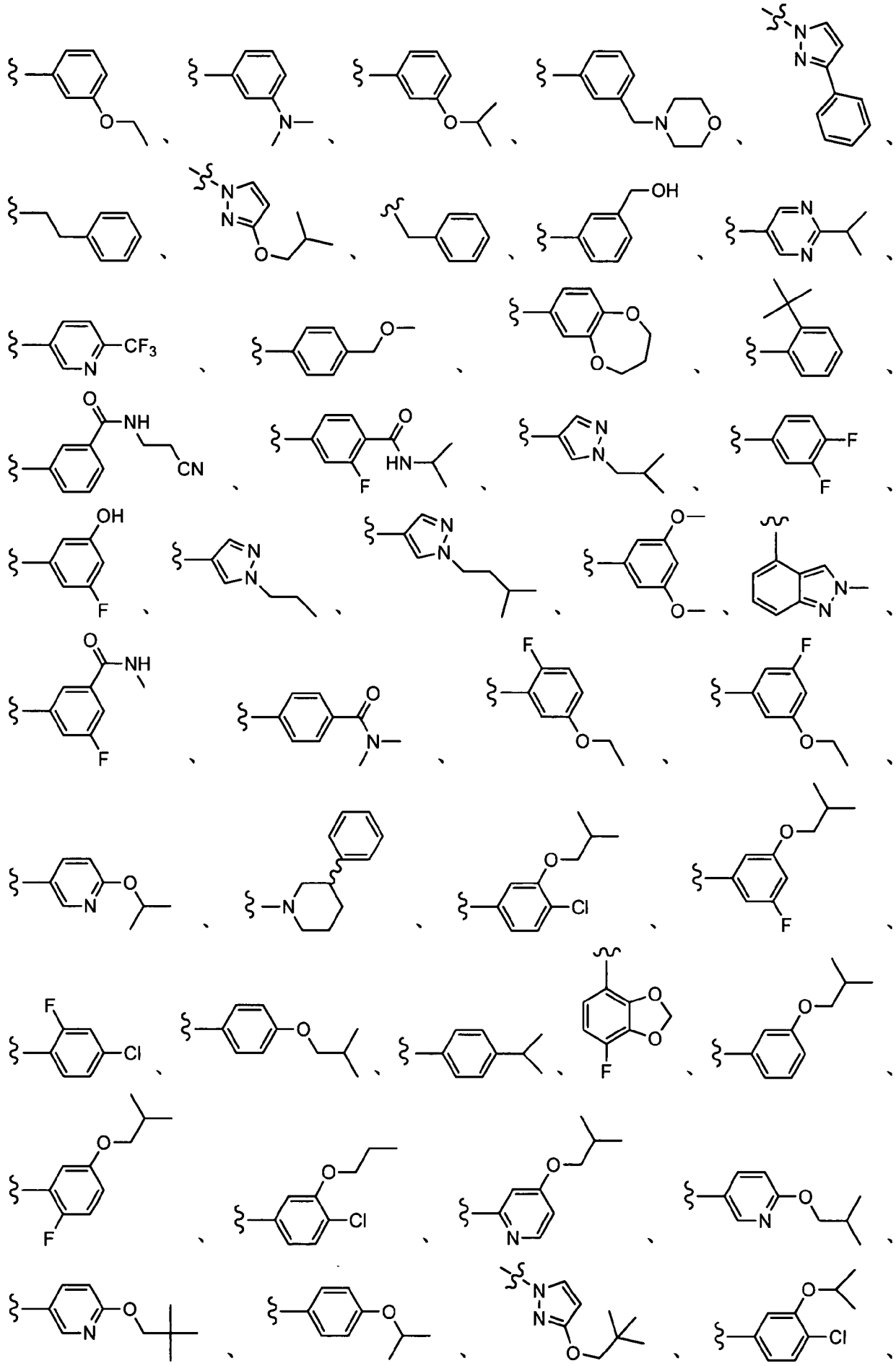
在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

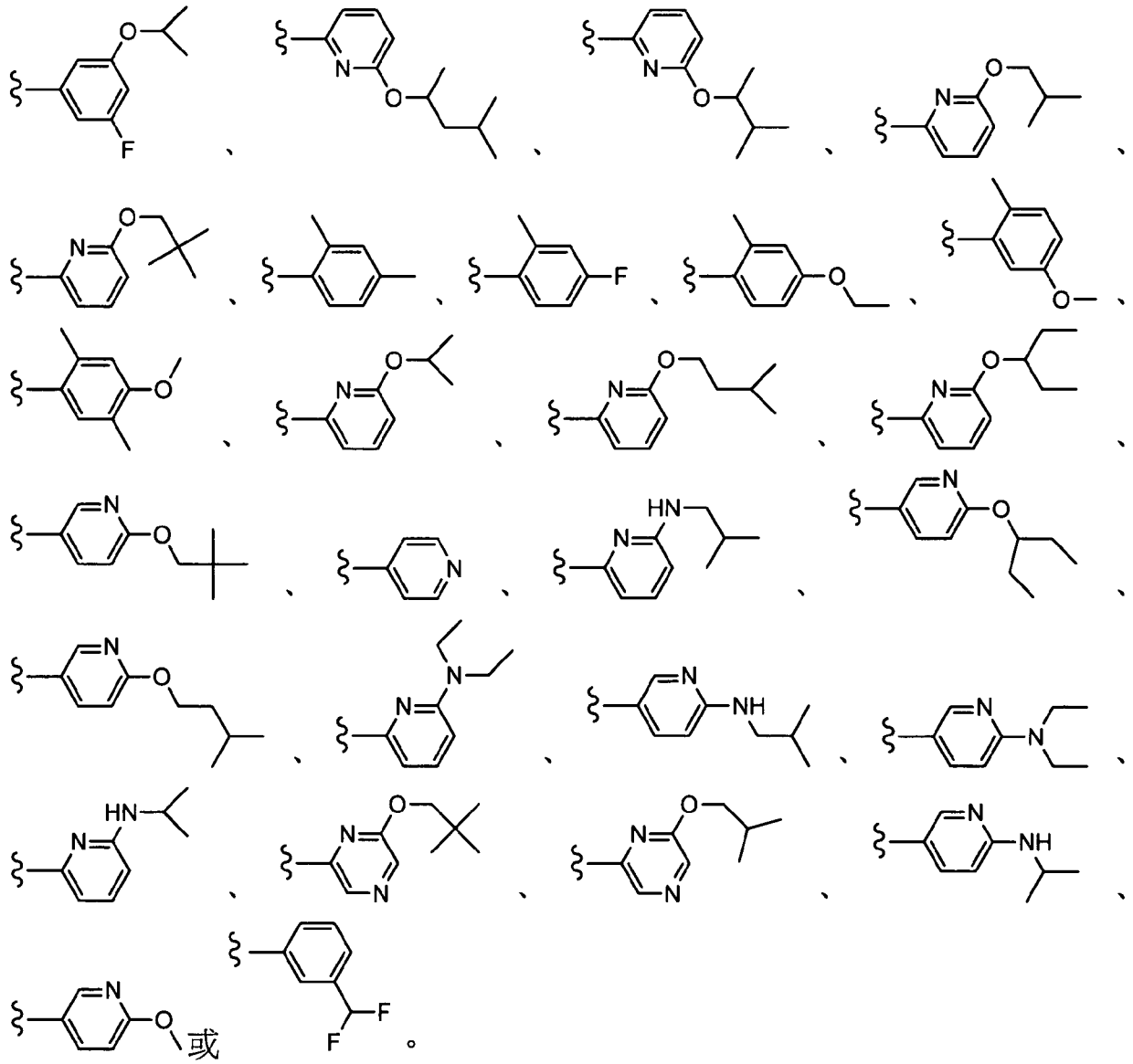
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，$R_1$爲苯基、噻吩、吡啶或吡唑。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲  、、、

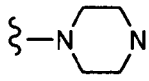
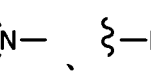
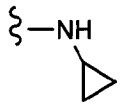


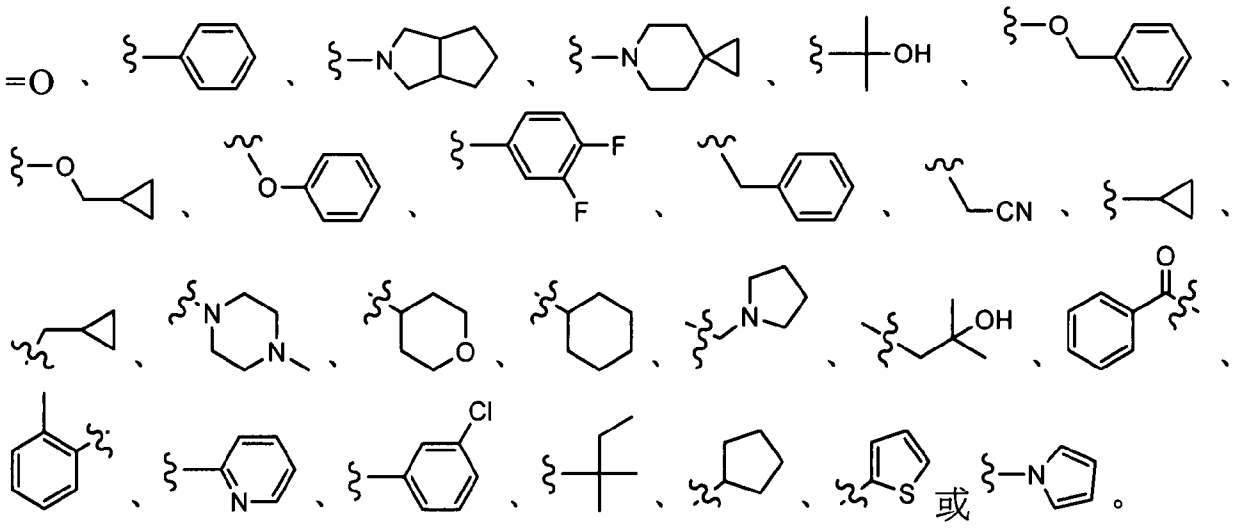




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、

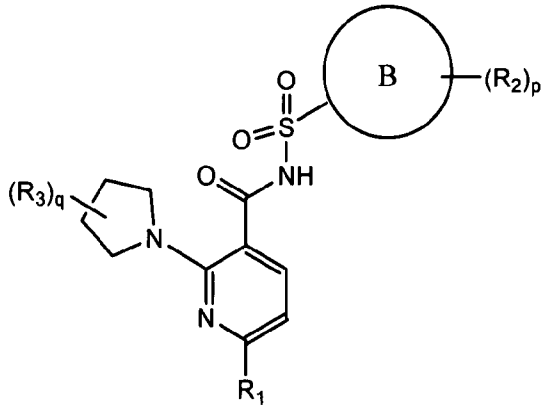
$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 



在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-vi-2化合物：



**Ib-vi-2**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

$R_1$爲C6-C10芳基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟

烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

p爲0、1、2或3；且

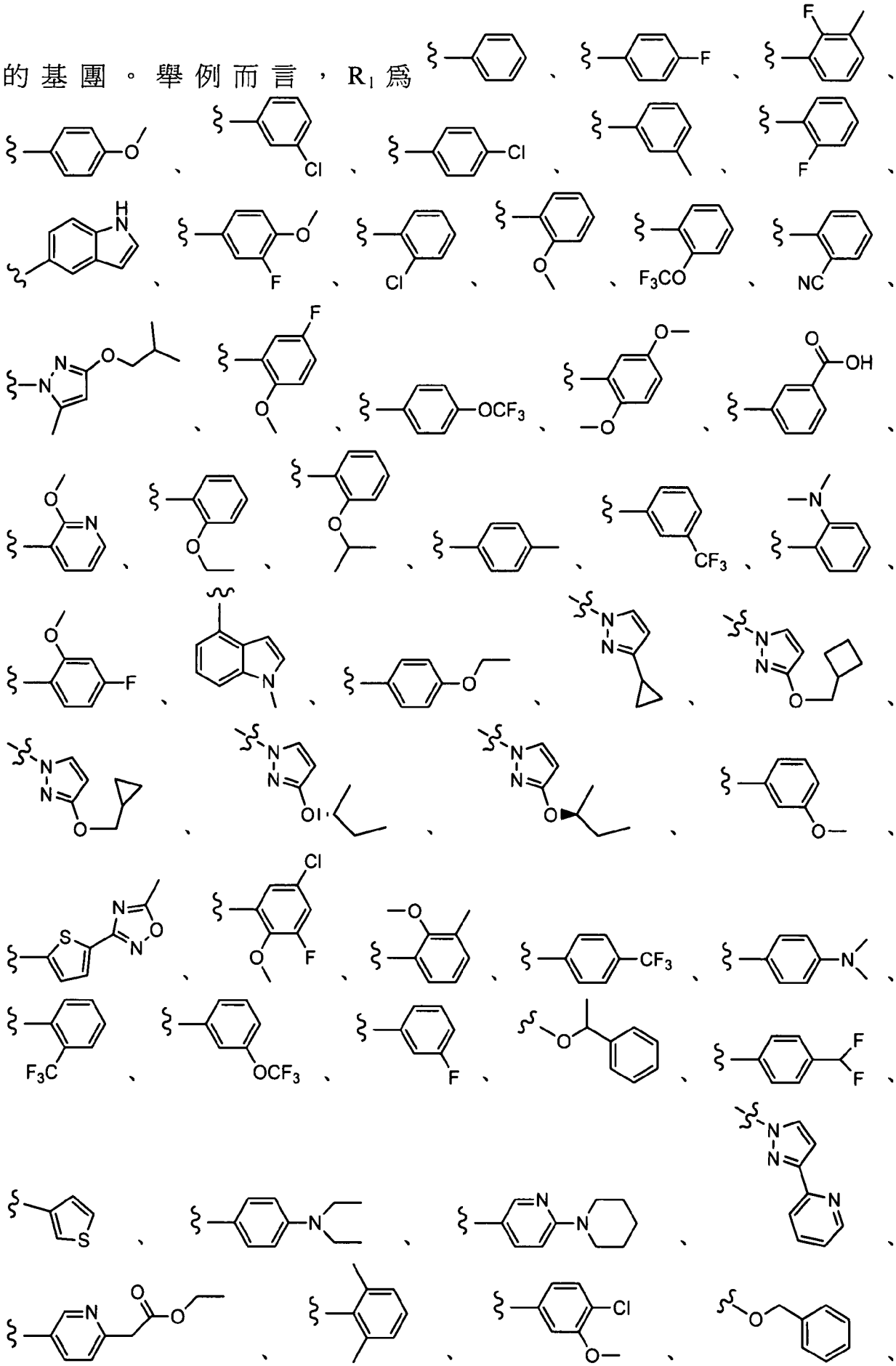
q爲0、1、2、3、4或5。

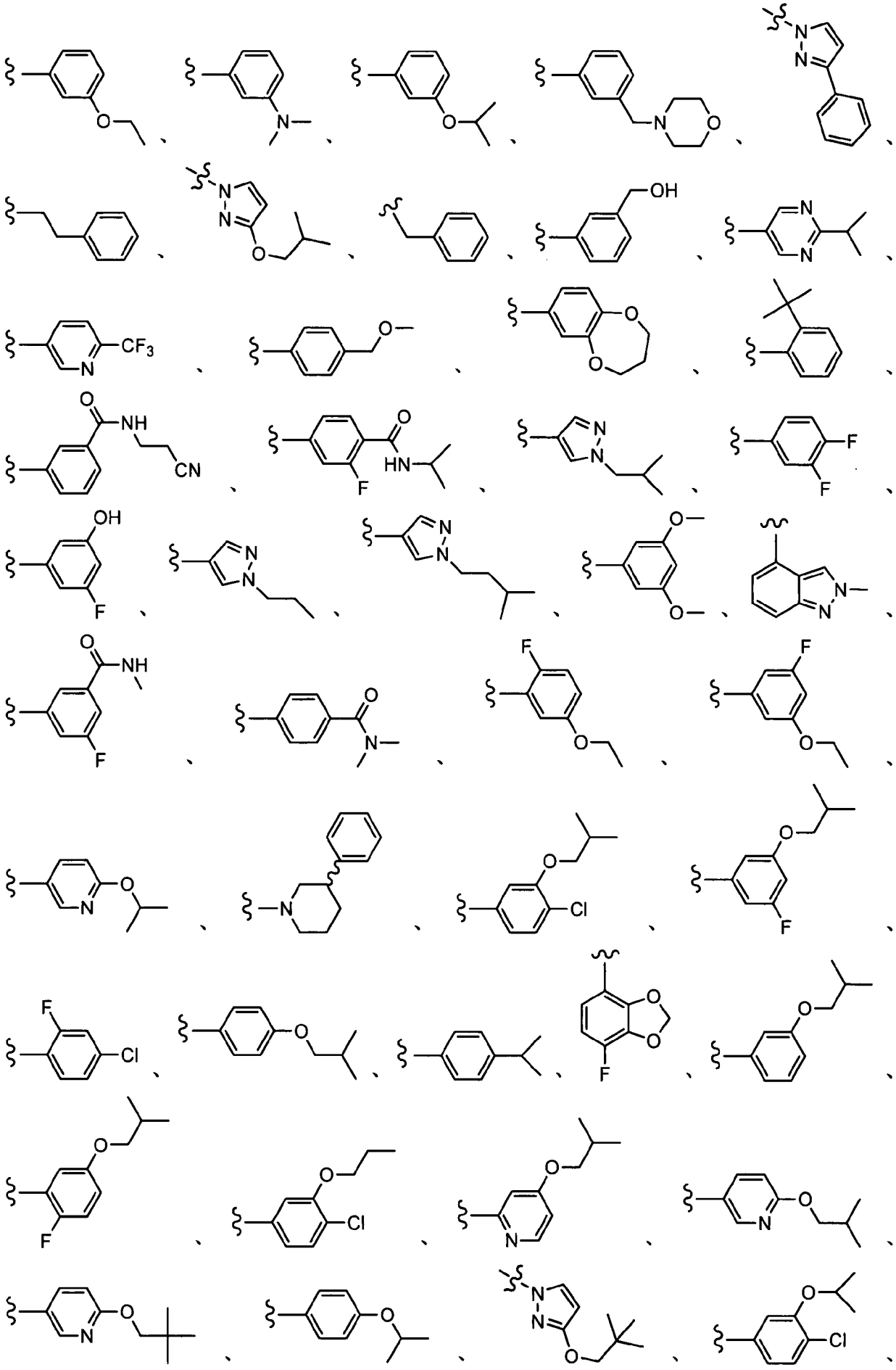
在一些實施例中，式Ib-vi-2化合物呈醫藥學上可接受之前藥形式存在。

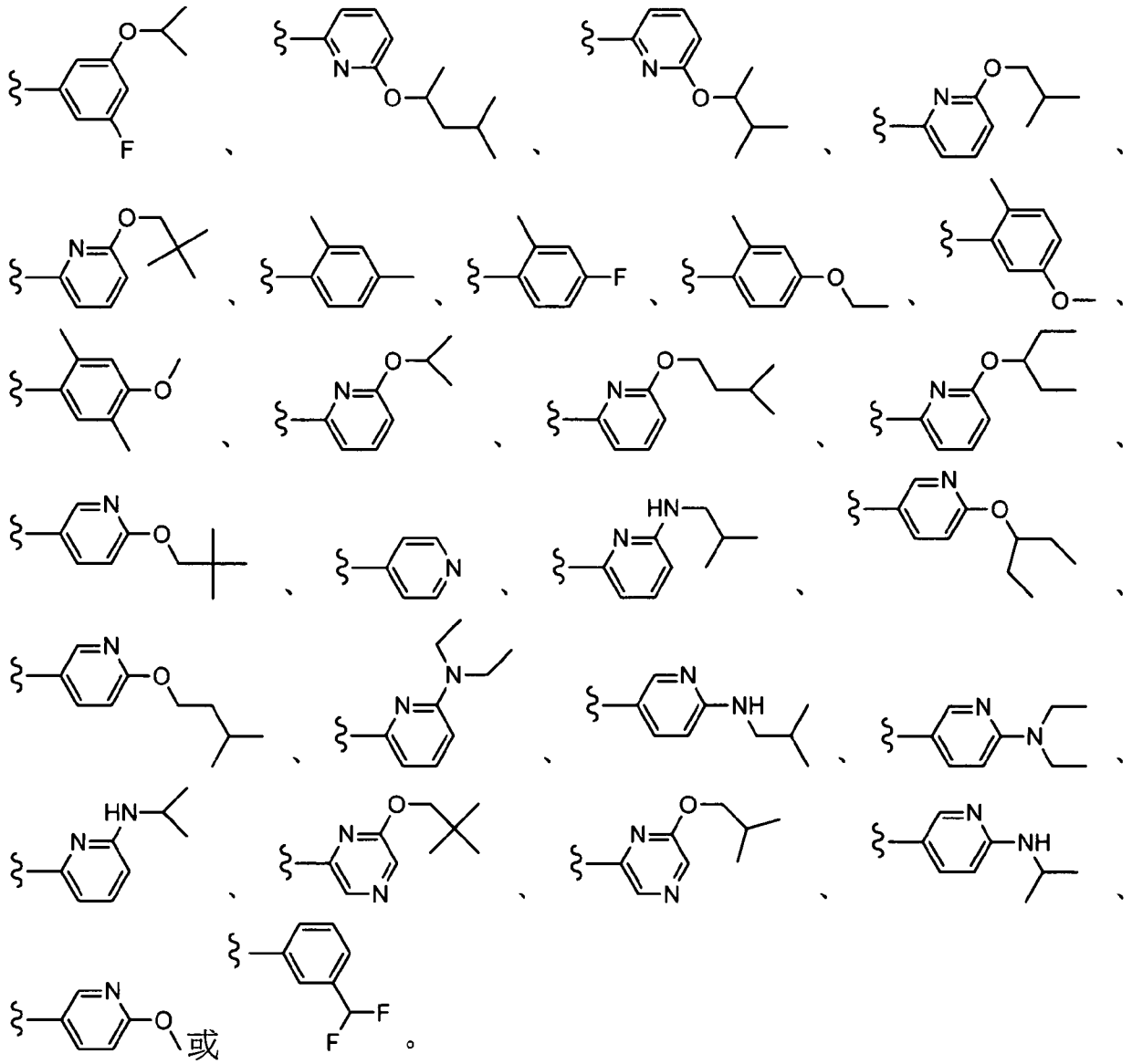
在一些實施例中，環B爲苯基或萘。

在一些實施例中，$R_1$爲苯基、噻吩、吡啶或吡唑。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示

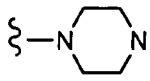
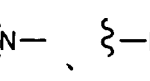
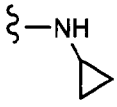
的基團。舉例而言，$R_1$為 

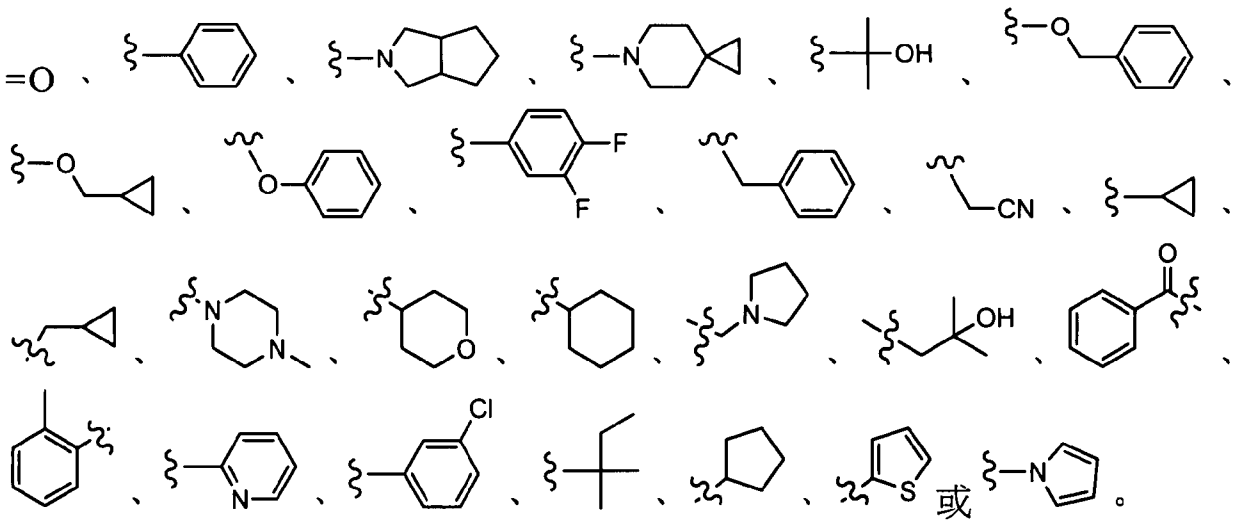




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、

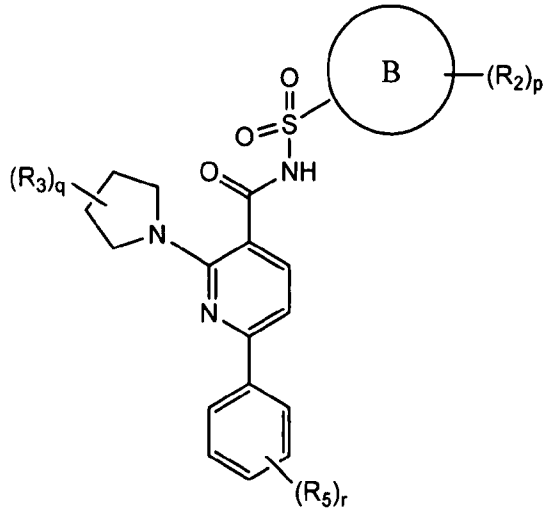
$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 



在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，$R_1$爲苯基、吡啶或吡唑。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，且$R_2$爲胺基或烷基，且p爲0或1。在一些實施例中，$R_1$爲苯基、吡啶或吡唑，$R_3$爲烷基，諸如甲基，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-vii化合物：



**Ib-vii**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

$R_5$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

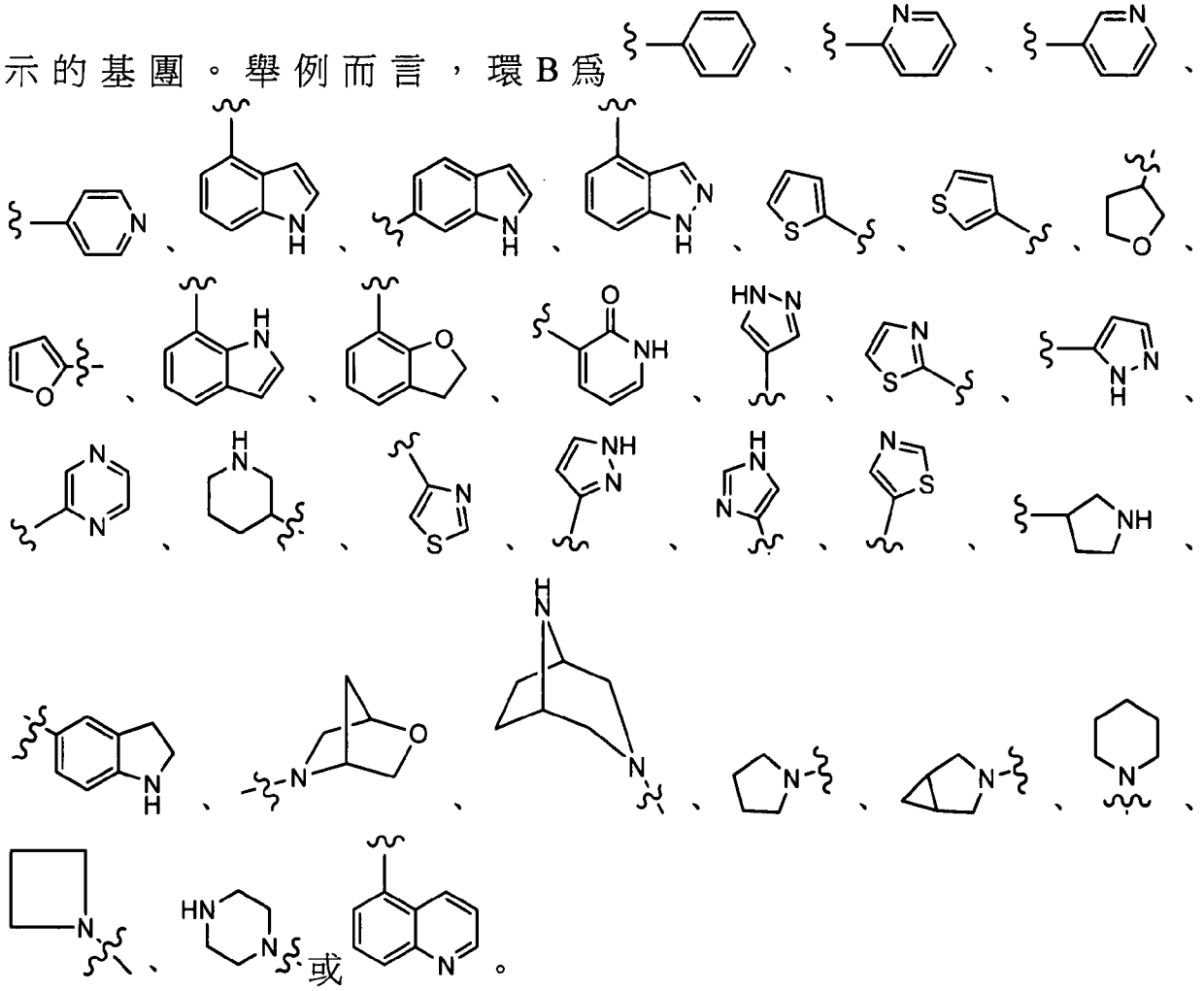
p爲0、1、2或3；

q爲0、1、2、3、4或5；且

r爲0、1、2、3、4或5。

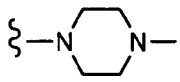
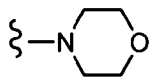
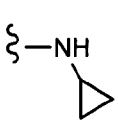
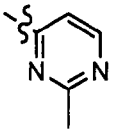
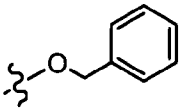
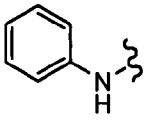
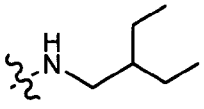
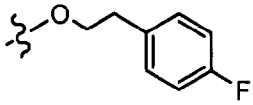
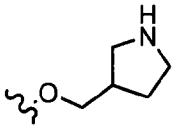
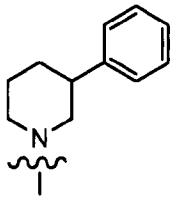
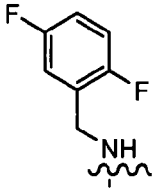
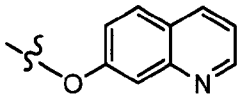
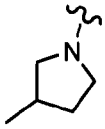
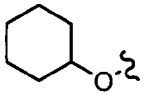
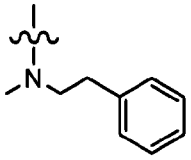
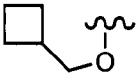
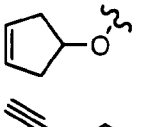
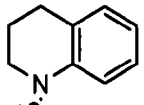
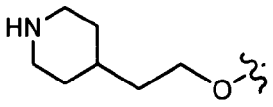
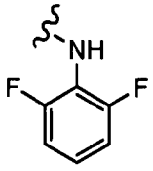
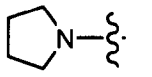
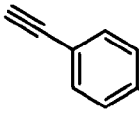
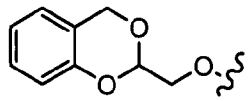
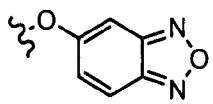
在一些實施例中，式Ib-vii化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  或。

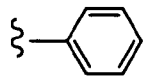
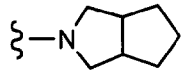
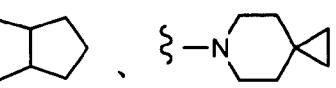
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

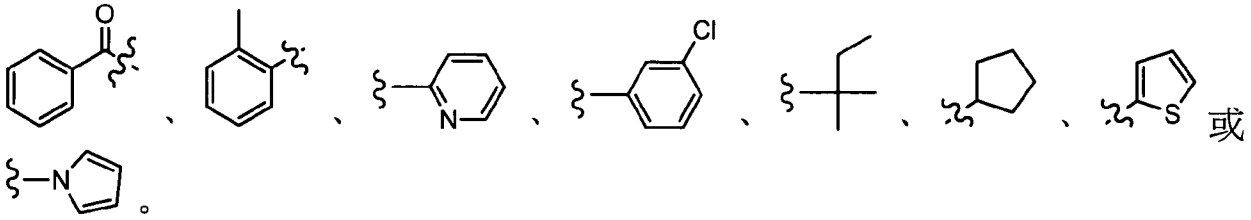
在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、

$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、  、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示

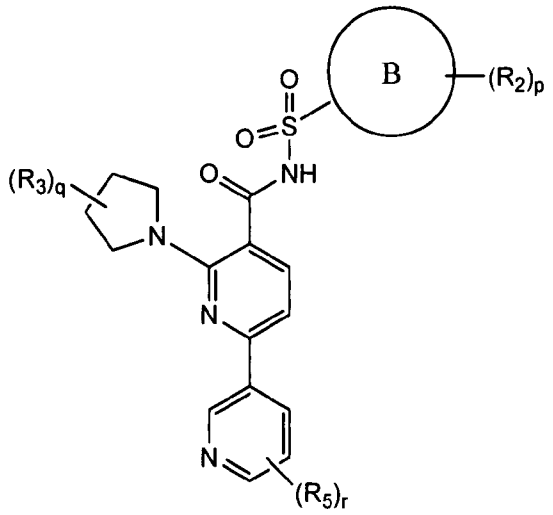
的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、 



在一些實施例中，r爲0。在一些實施例中，r爲1。在一些實施例中，r爲2。在一些實施例中，r爲3。在一些實施例中，r爲4。在一些實施例中，r爲5。

在一些實施例中，$R_5$爲鹵基或烷氧基。在一些實施例中，$R_2$爲胺基或烷基，$R_5$爲鹵基或烷氧基，r爲1或2，且p爲0或1。在一些實施例中，$R_5$爲鹵基或烷氧基，$R_3$爲烷基，諸如甲基，r爲1或2，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-viii化合物：



**Ib-viii**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜

芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

$R_5$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

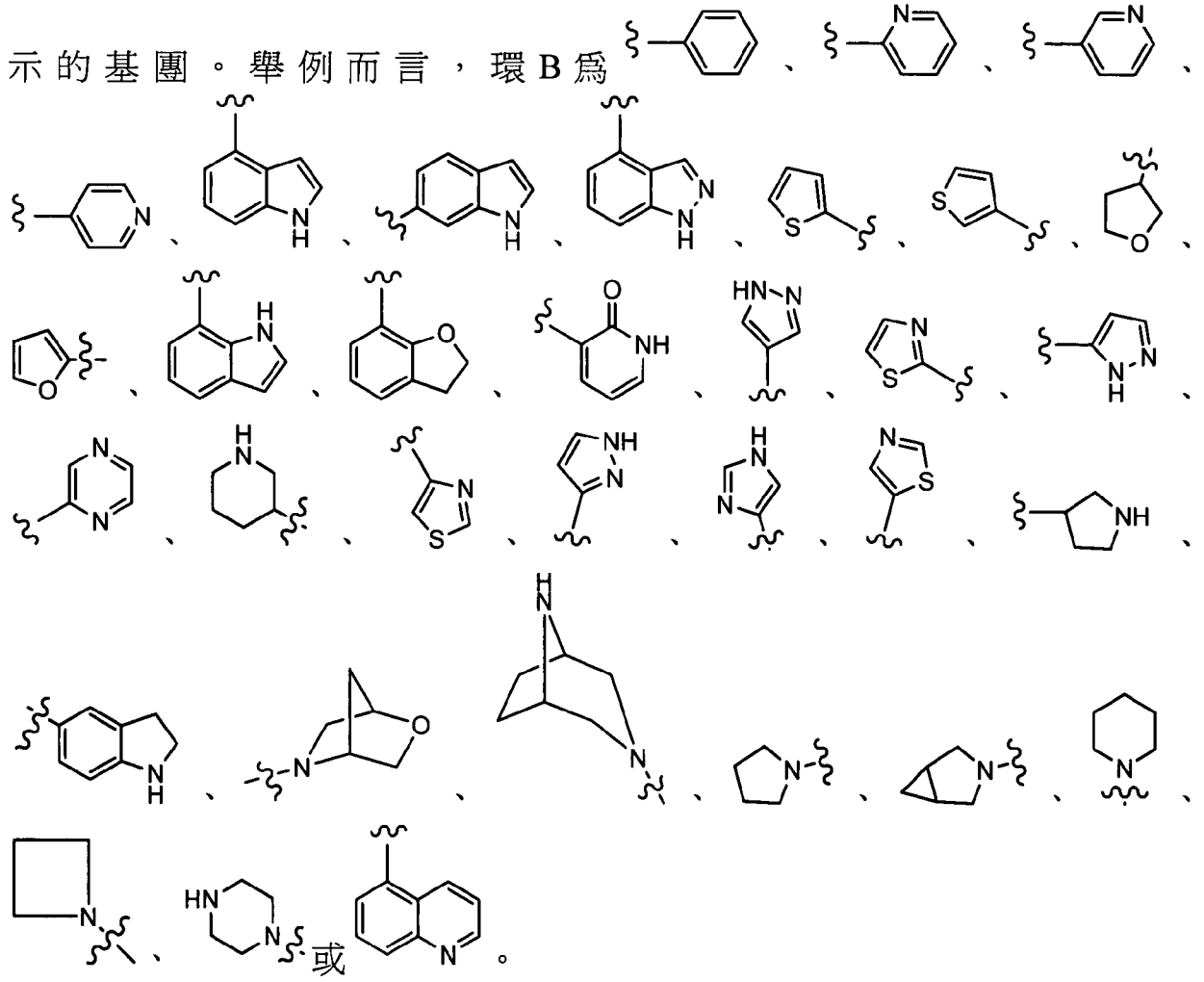
p爲0、1、2或3；

q爲0、1、2、3、4或5；且

r爲0、1、2、3、4或5。

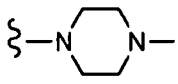
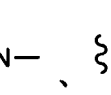
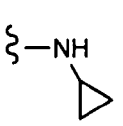
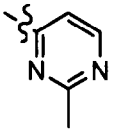
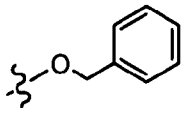
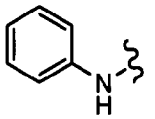
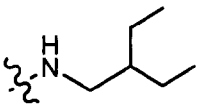
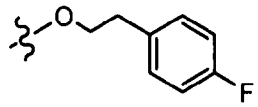
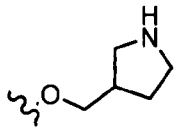
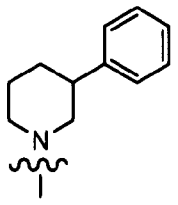
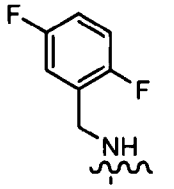
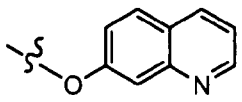
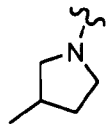
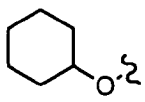
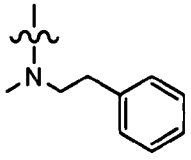
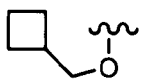
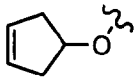
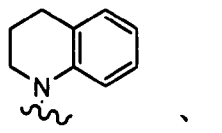
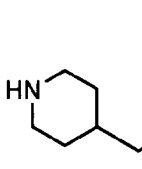
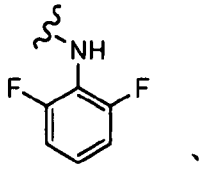
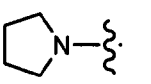
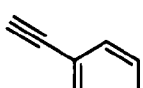
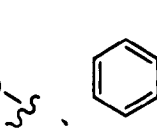
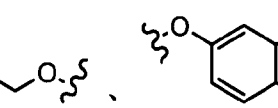
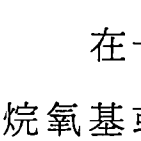
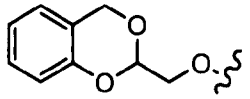
在一些實施例中，式Ib-viii化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  或。

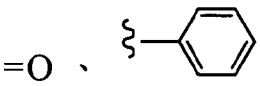
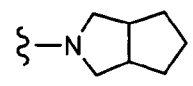
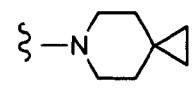
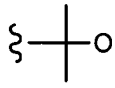
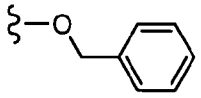
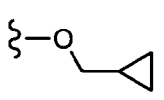
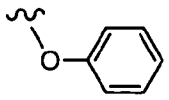
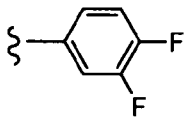
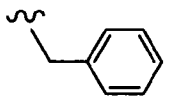
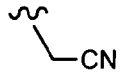
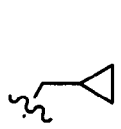
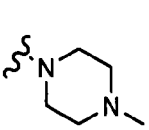
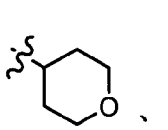
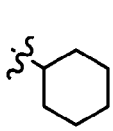
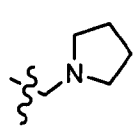
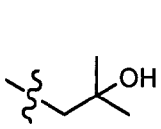
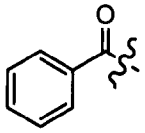
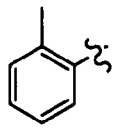
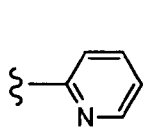
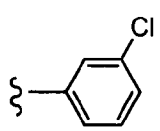
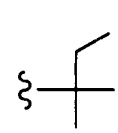
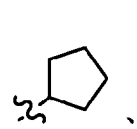
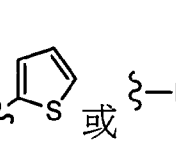
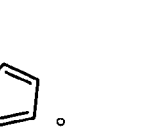
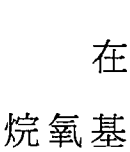
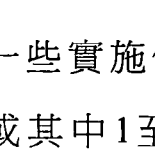
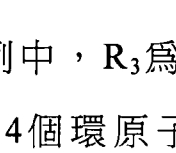
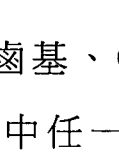
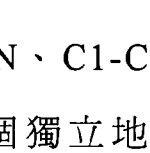
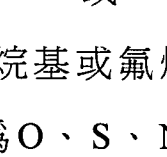
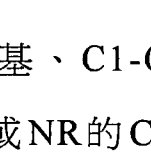
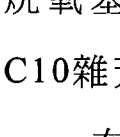
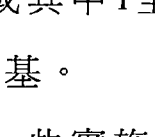
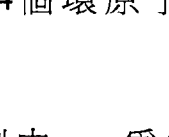
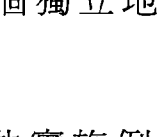
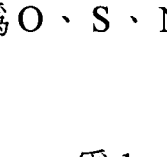
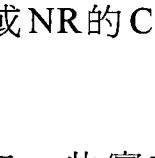
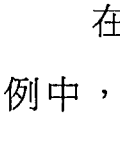
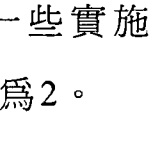
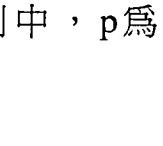
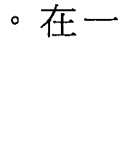
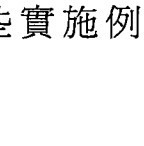
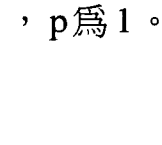
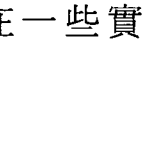
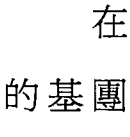
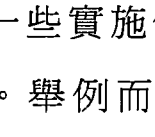
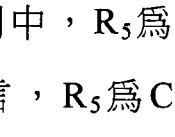
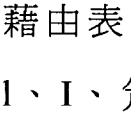
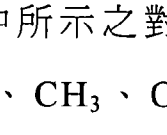
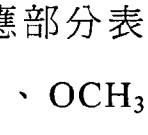
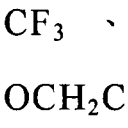
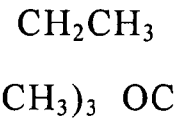
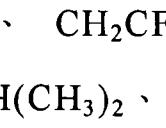
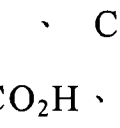
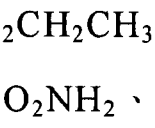
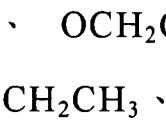
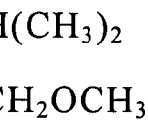
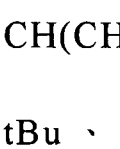
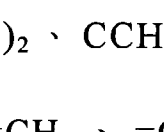
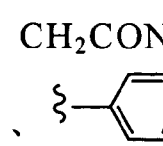
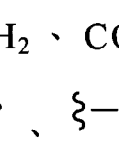
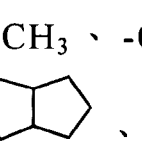
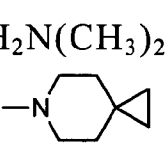
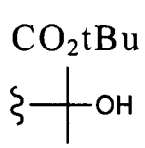
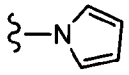
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、

$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、  、  、、、  、  、或$CO_2H$。

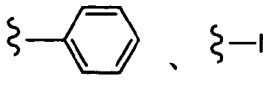
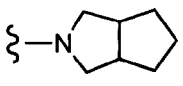
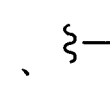
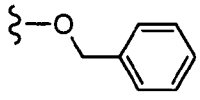
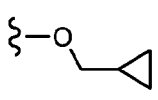
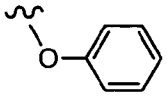
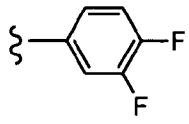
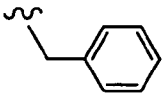
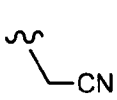
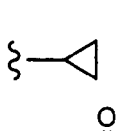
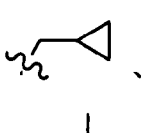
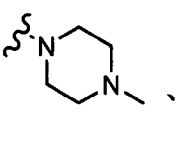
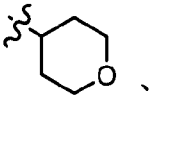
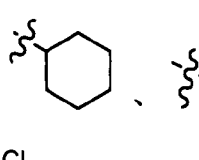
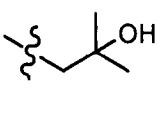
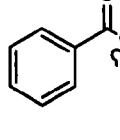
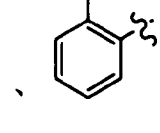
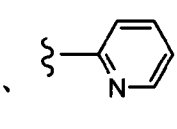
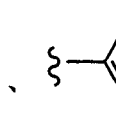
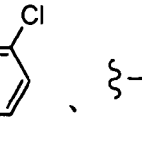
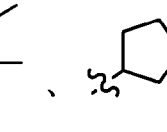
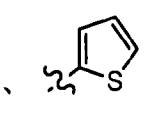
在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

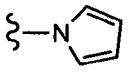
在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、

CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

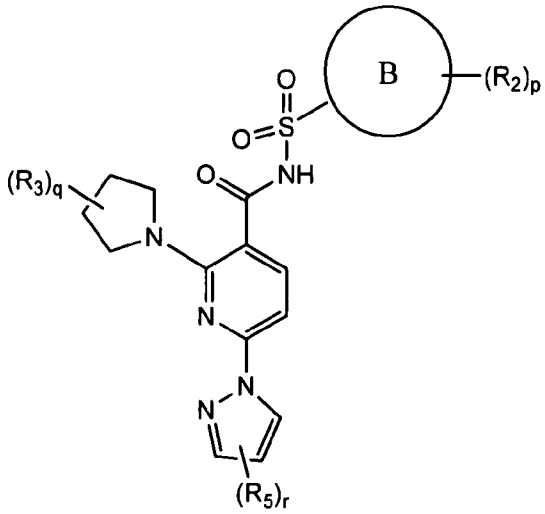
在一些實施例中，$R_5$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_5$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH_2C(CH_3)_3$ $OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或

 。

在一些實施例中，r爲0。在一些實施例中，r爲1。在一些實施例中，r爲2。在一些實施例中，r爲3。在一些實施例中，r爲4。在一些實施例中，r爲5。

在一些實施例中，$R_5$爲鹵基或烷氧基。在一些實施例中，$R_2$爲胺基或烷基，$R_5$爲鹵基或烷氧基，r爲1或2，且p爲0或1。在一些實施例中，$R_5$爲鹵基或烷氧基，$R_3$爲烷基，諸如甲基，r爲1或2，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ib-ix化合物：



**Ib-ix**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

$R_5$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

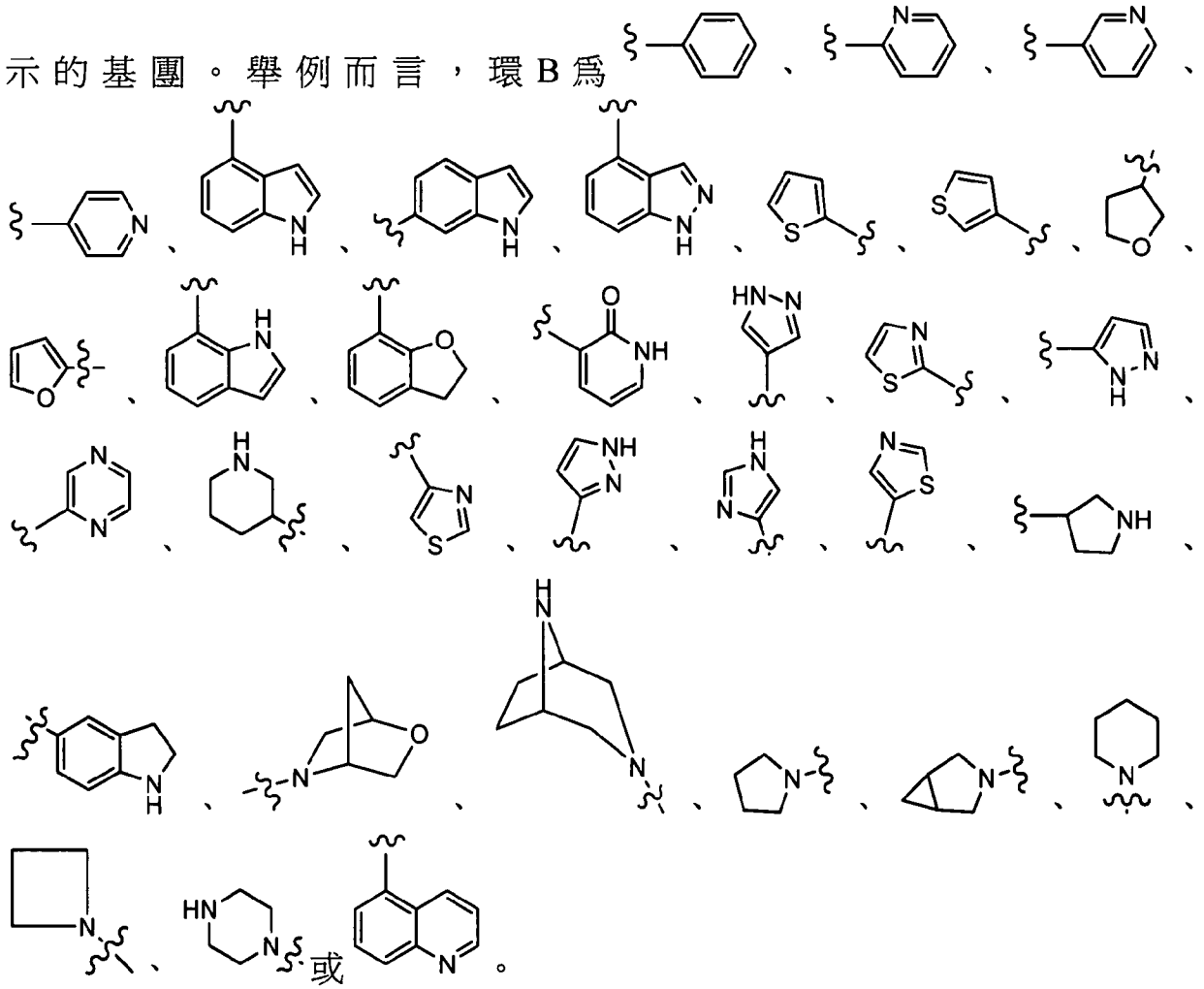
p爲0、1、2或3；

q爲0、1、2、3、4或5；且

r爲0、1、2、3、4或5。

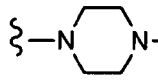
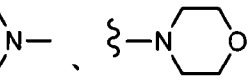
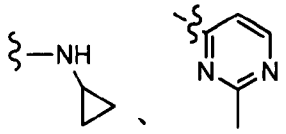
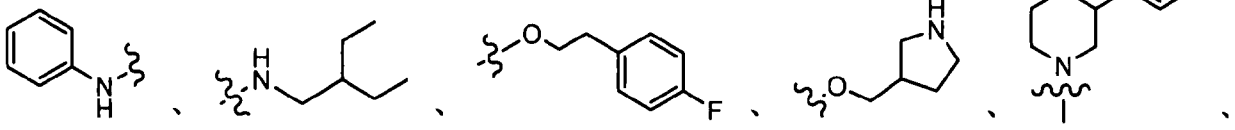
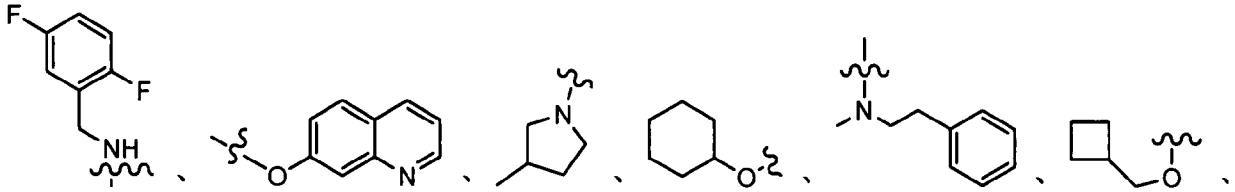
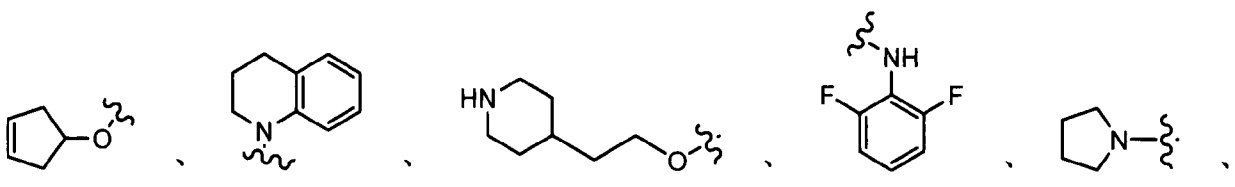
在一些實施例中，式Ib-ix化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

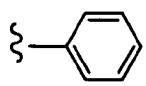
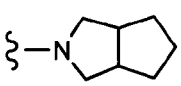
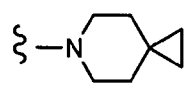
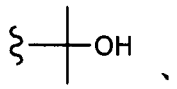
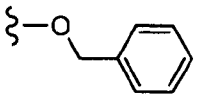
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  或。

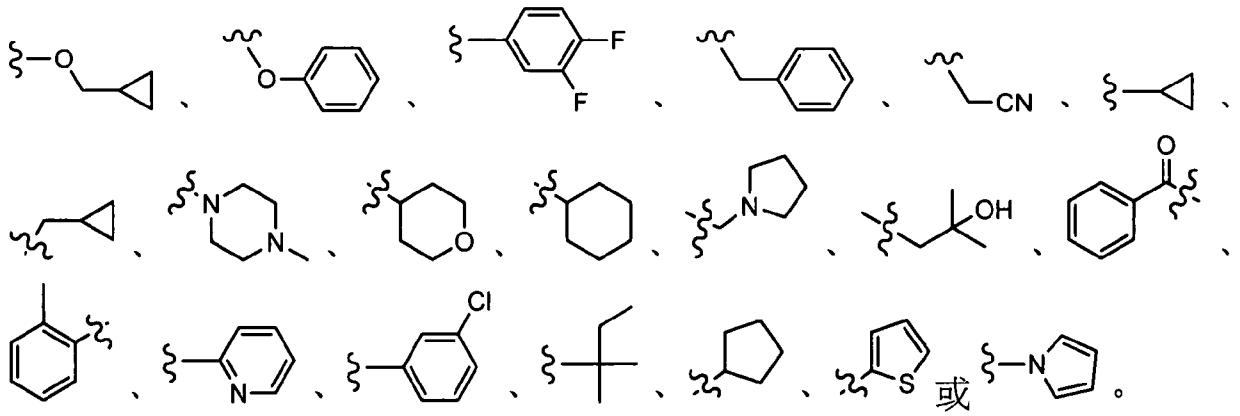
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、

$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

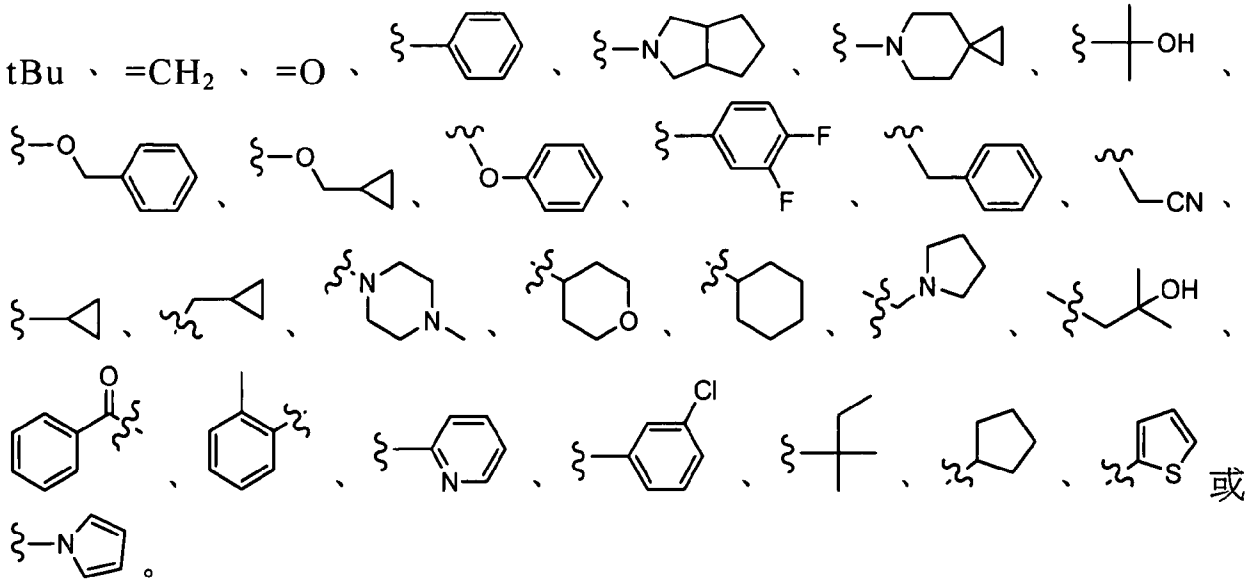
在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、



在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

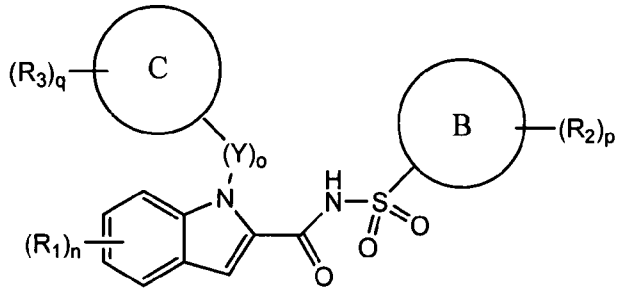
在一些實施例中，$R_5$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_5$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH_2C(CH_3)_3$ $OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、



實施例中，r爲5。

在一些實施例中，$R_5$爲鹵基或烷氧基。在一些實施例中，$R_2$爲胺基或烷基，$R_5$爲鹵基或烷氧基，r爲1或2，且p爲0或1。在一些實施例中，$R_5$爲鹵基或烷氧基，$R_3$爲烷基，諸如甲基，r爲1或2，且q爲1、2、3或4。

在一些實施例中，本發明提供式Ic化合物：




**Ic**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、

CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

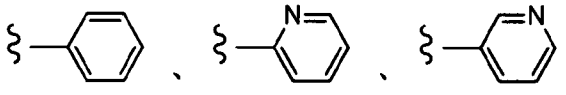
o爲0、1、2、3、4或5；

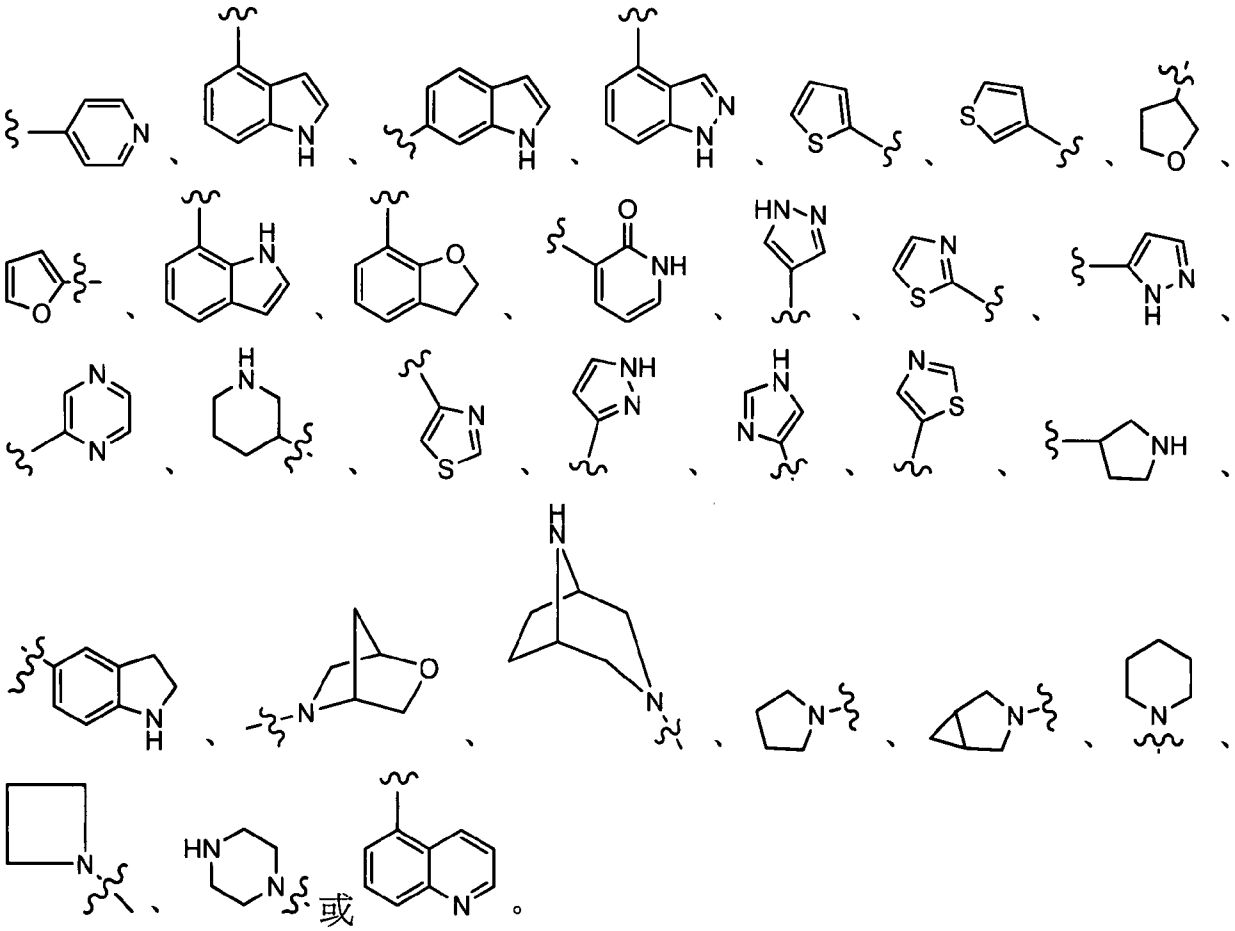
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ic化合物呈醫藥學上可接受之前藥形式存在。

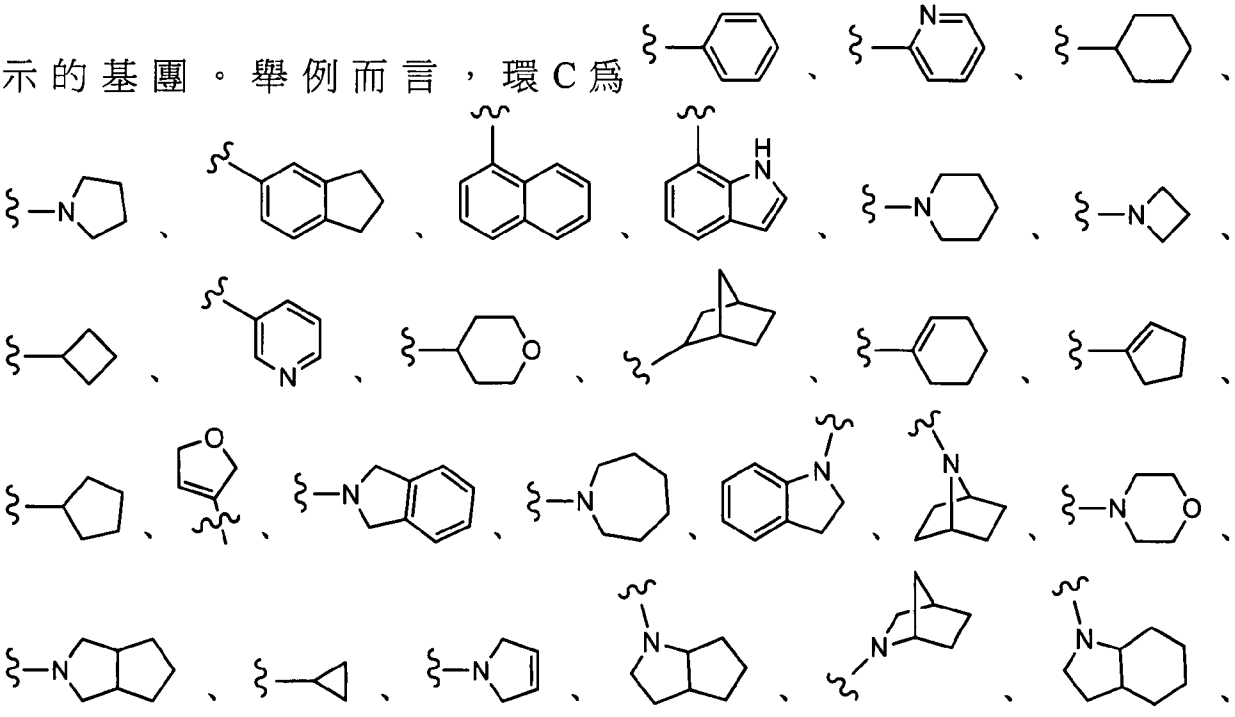
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

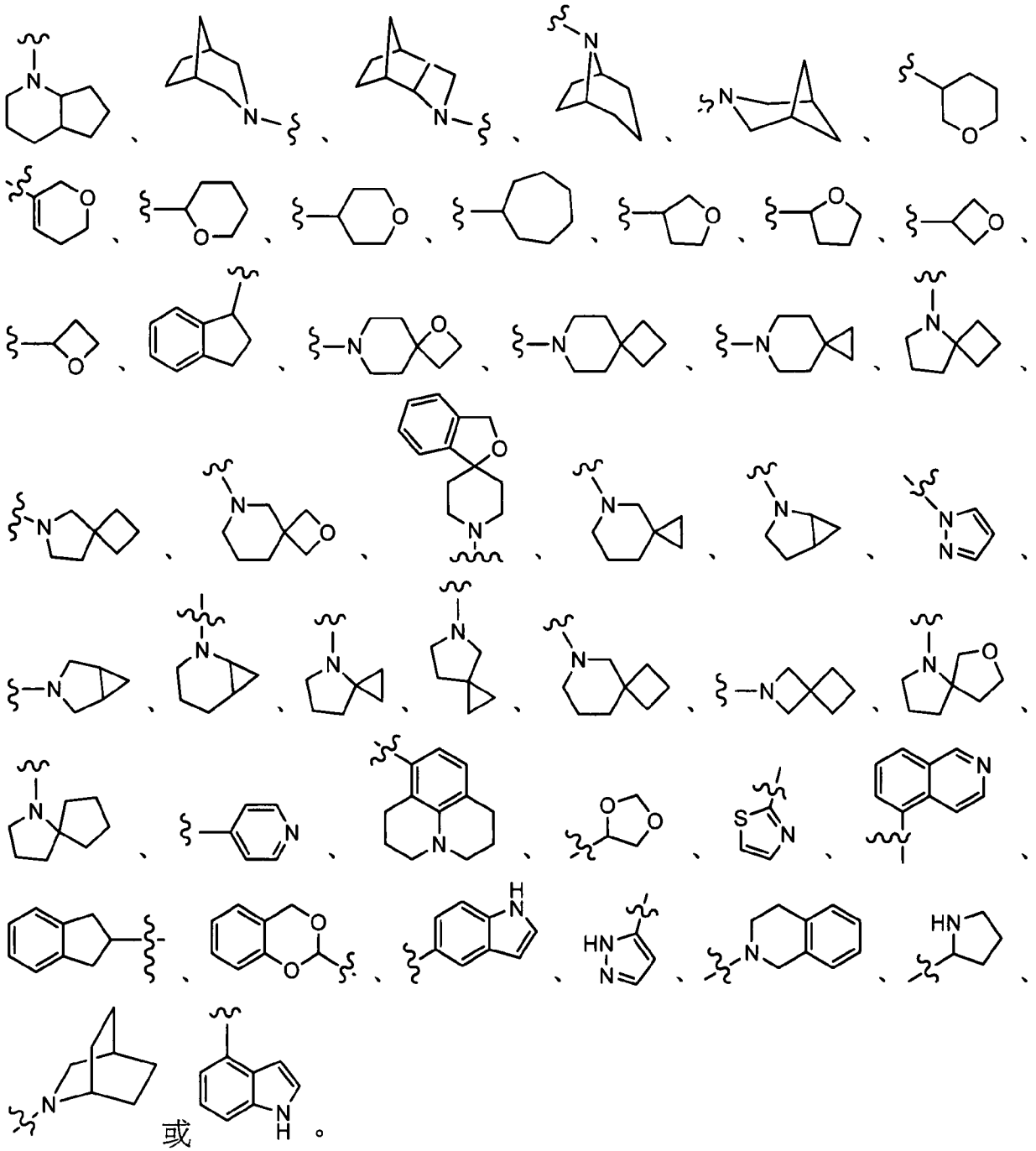
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、



在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲

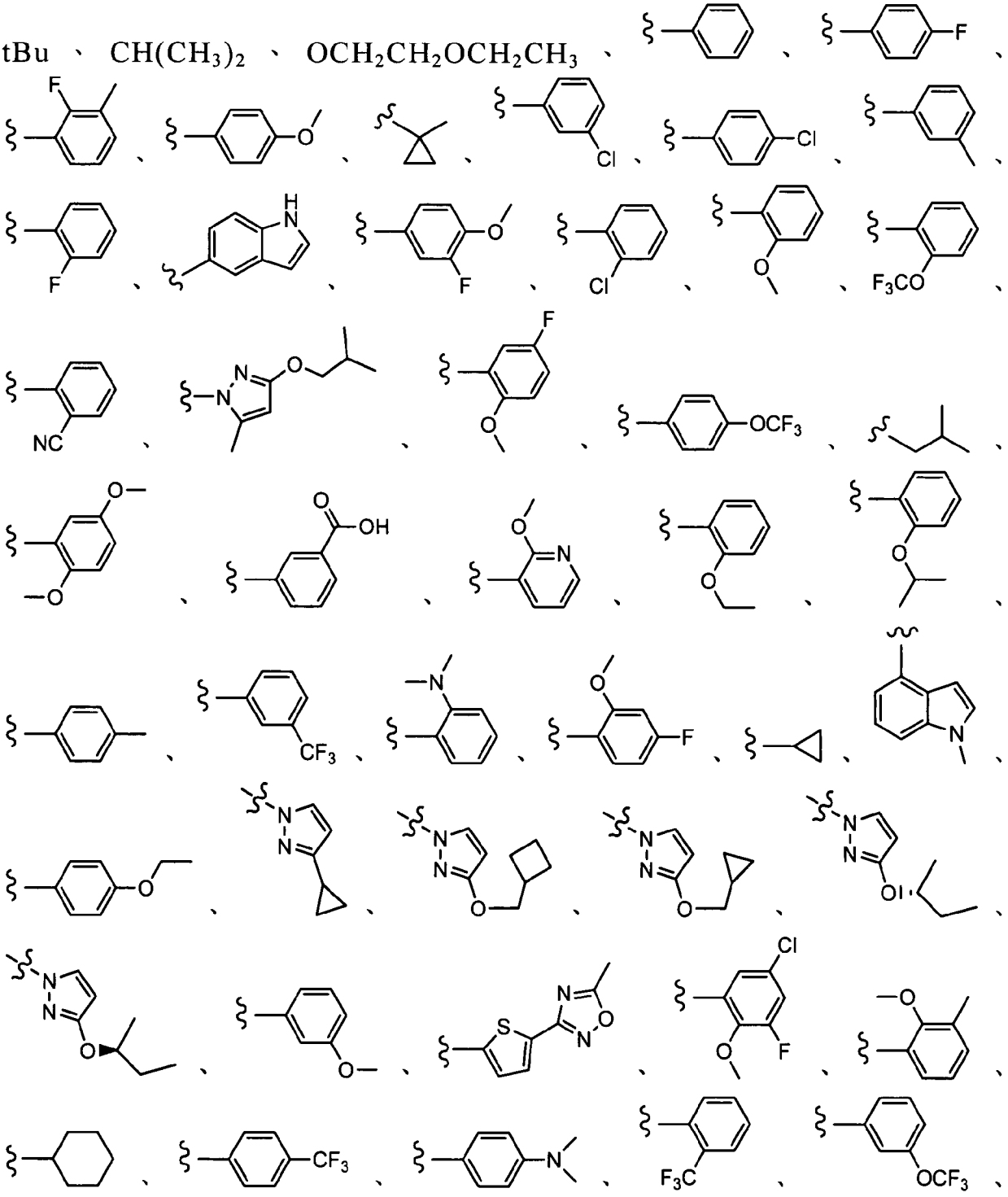


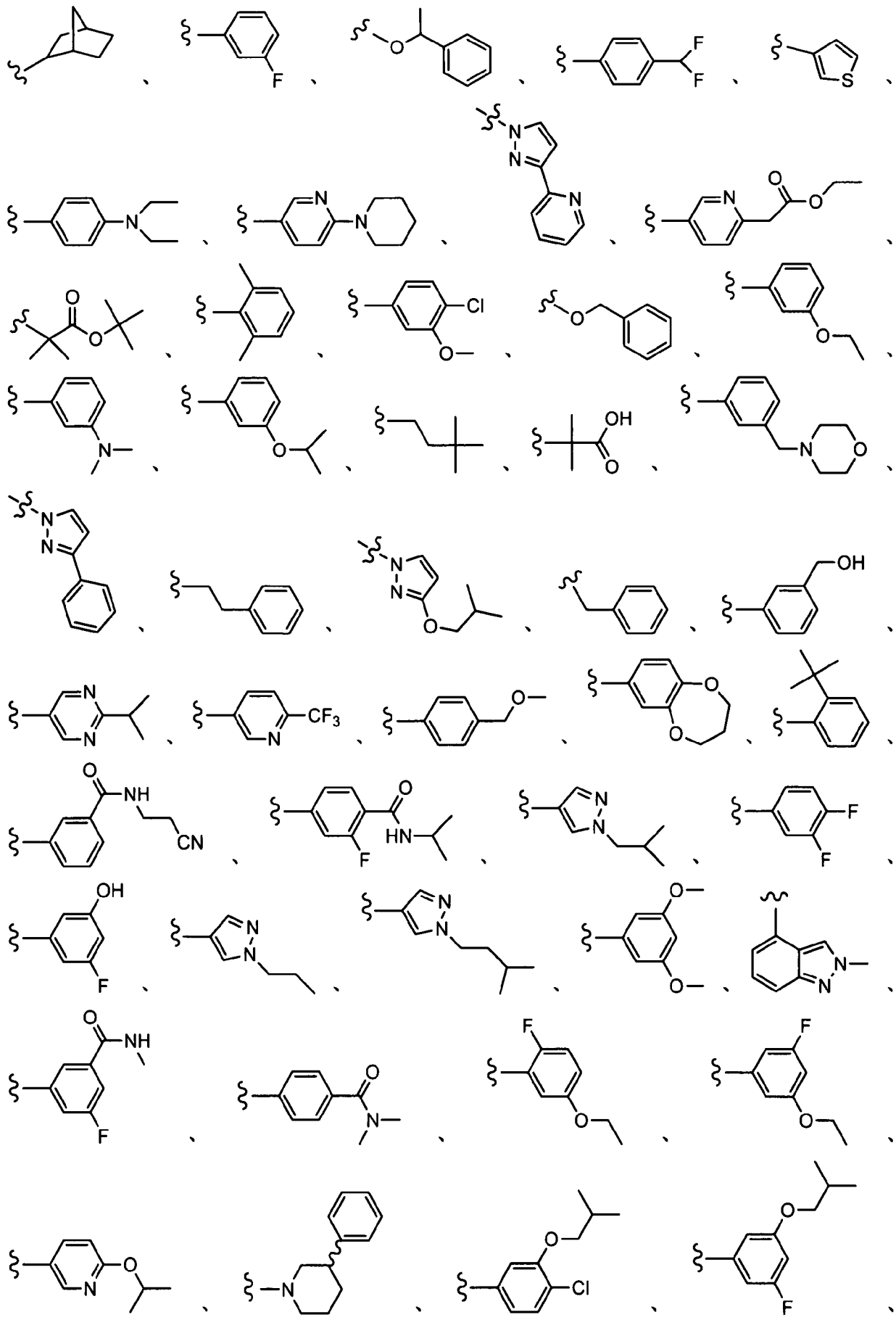


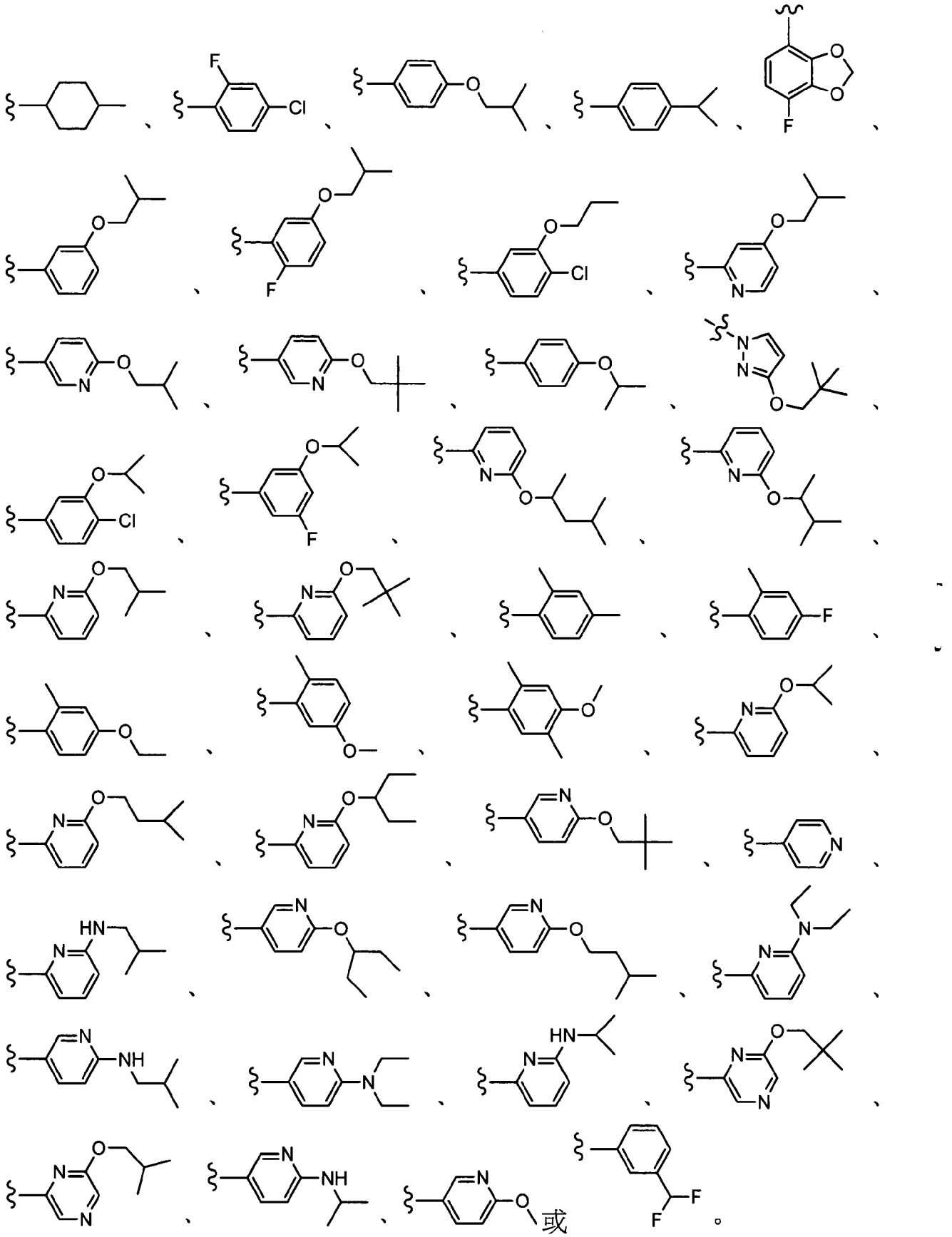
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換

的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

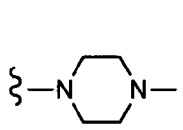
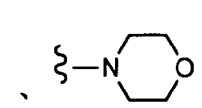
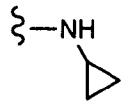
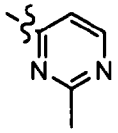
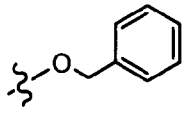
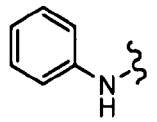
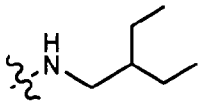
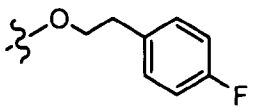
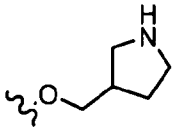
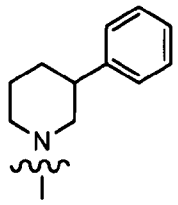
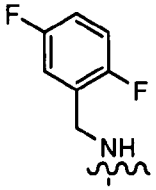
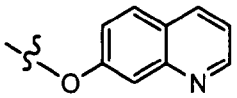
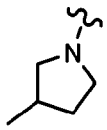
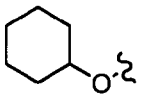
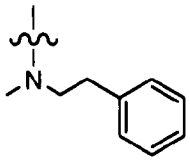
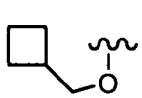
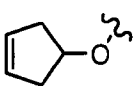
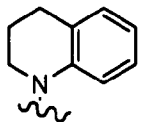
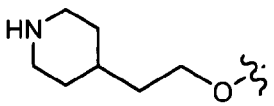
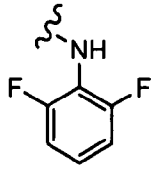
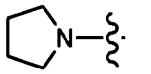
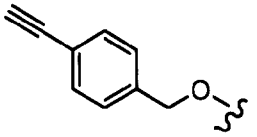
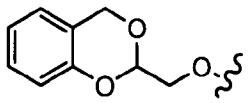
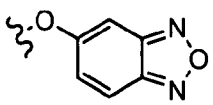
在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、 



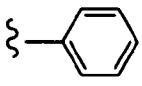
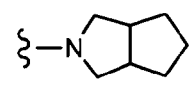
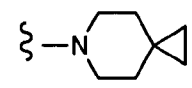
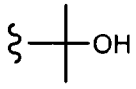
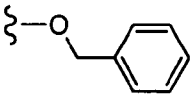
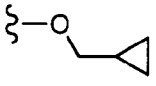
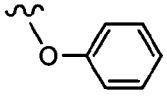
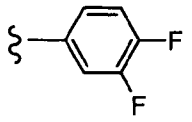
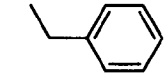
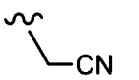
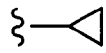
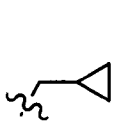
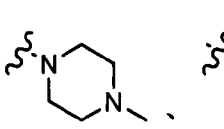
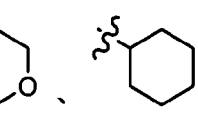
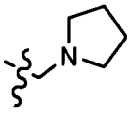
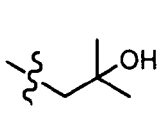
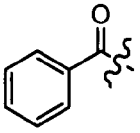
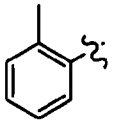
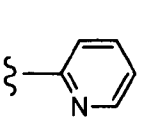
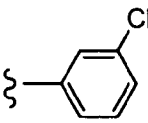
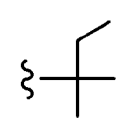
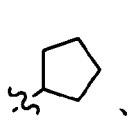
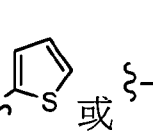
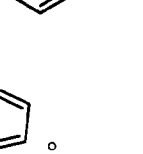
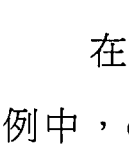
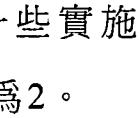
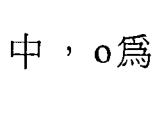
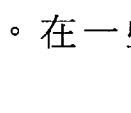
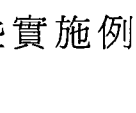
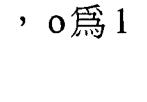
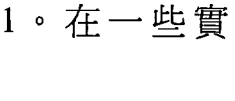


在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任

一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，，且$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

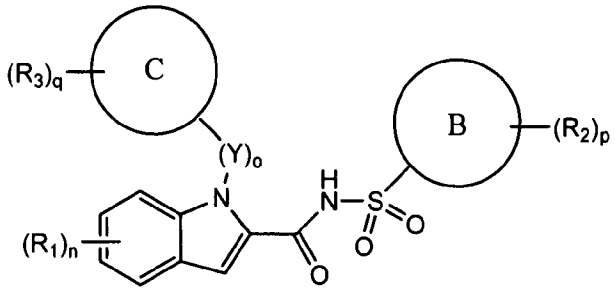
在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，環B爲苯基。在一些實施例中，環C爲苯基。在一些實施例中，環B及環C爲苯基。在一些實施例中，$R_1$爲鹵基。在一些實施例中，$R_1$爲F。在一些實施例中，$R_1$爲$OCH_3$。在一些實施例中，$R_2$爲胺基。在一些實施例中，$R_3$爲$CH_3$。在一些實施例中，$R_2$

爲胺基且$R_3$爲$CH_3$。在一些實施例中，Y爲$CH_3$。在一些實施例中，Y爲O。在一些實施例中，$R_1$爲F，且$R_2$爲胺基，$R_3$爲$CH_3$，且Y爲$CH_2$。在一些實施例中，Y爲O。在一些實施例中，$R_1$爲F，且$R_2$爲胺基，$R_3$爲$CH_3$，且Y爲O。

在一些實施例中，本發明提供式Ic-i化合物：




**Ic-i**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

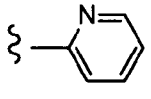
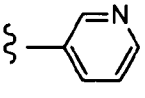
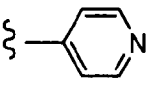
o爲0、1、2、3、4或5；

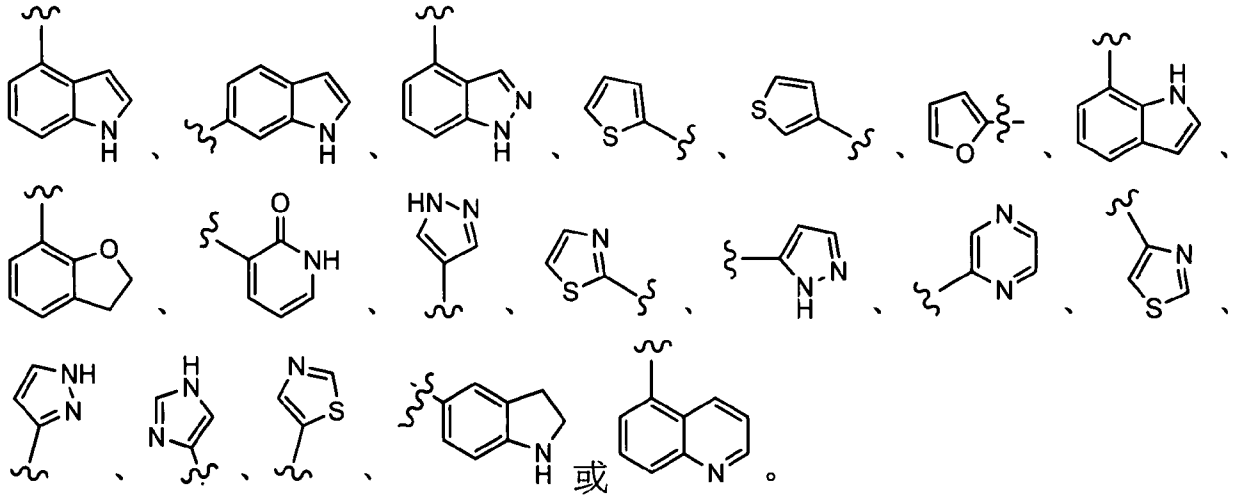
p爲0、1、2或3；且

q爲0、1、2、3、4或5。

在一些實施例中，式Ic-i化合物呈醫藥學上可接受之前藥形式存在。

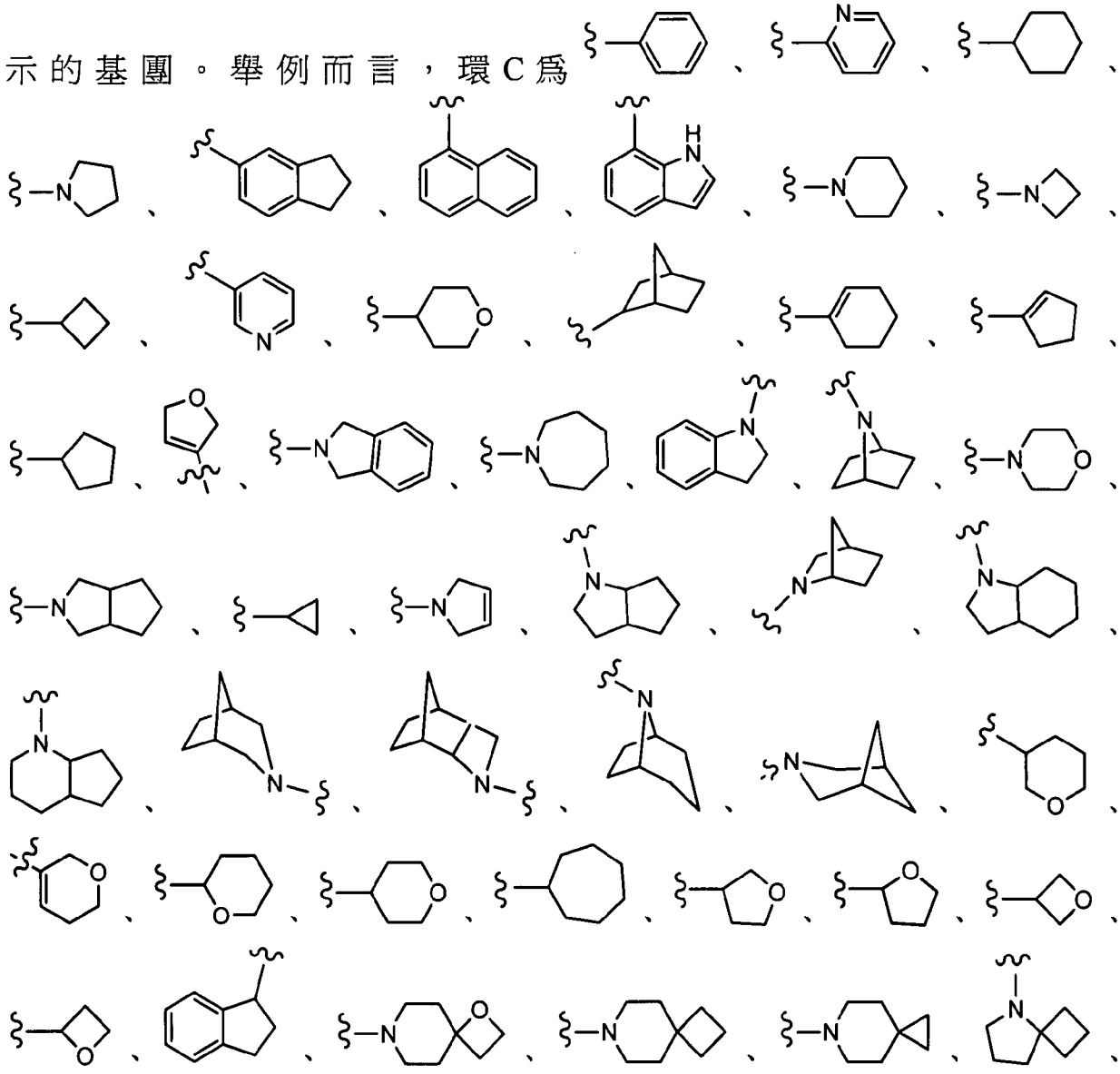
在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

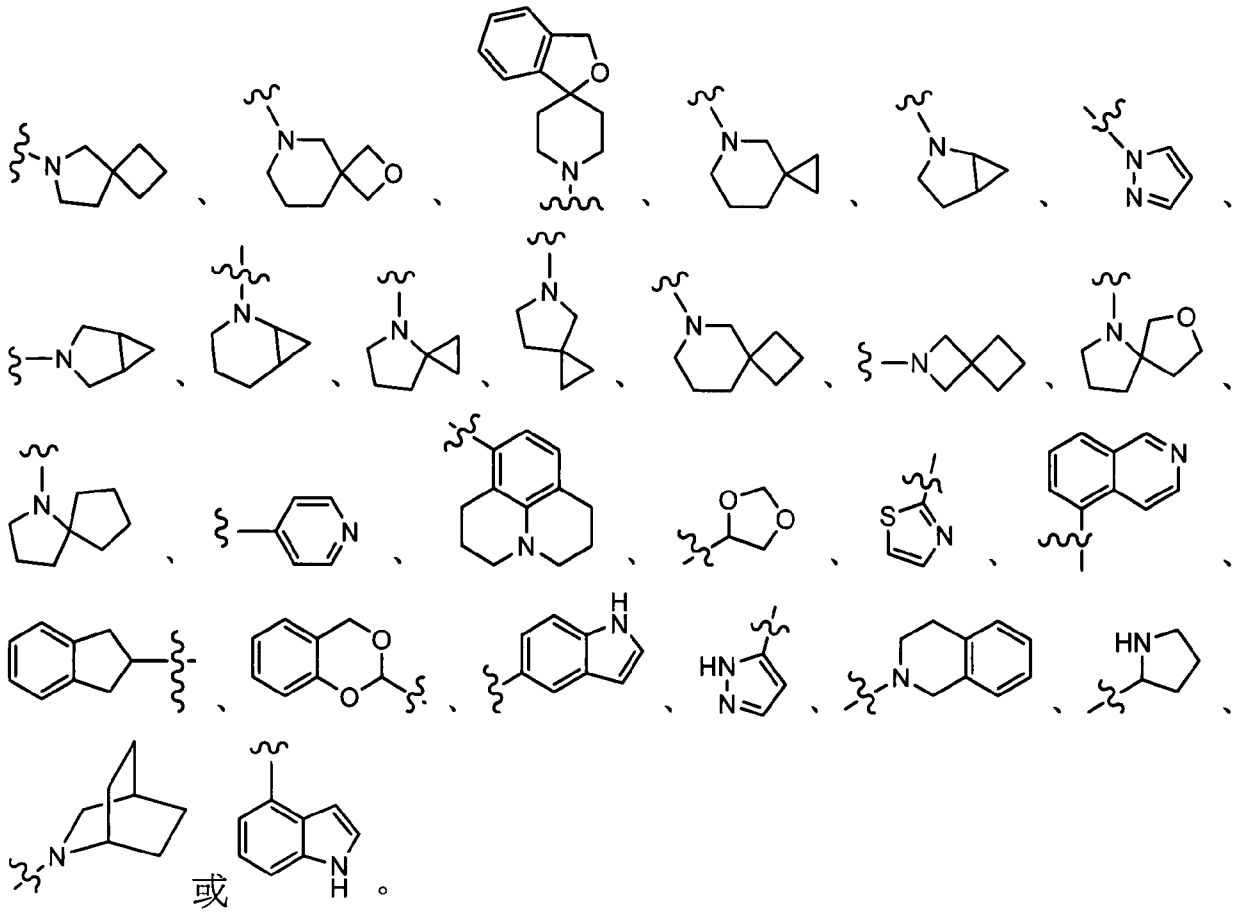
在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲、  、  、  、



在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲

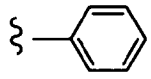
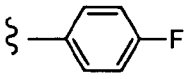
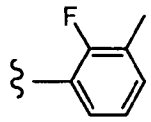
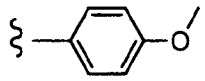
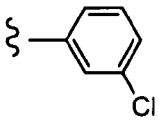
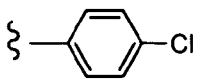
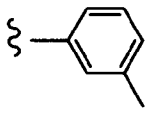
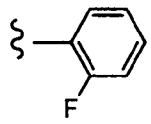
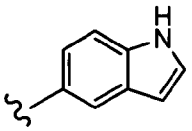
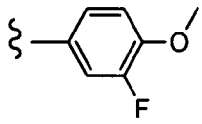
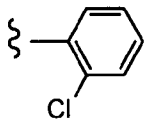
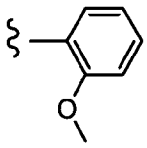
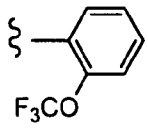
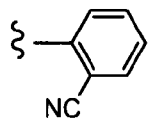
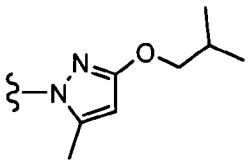
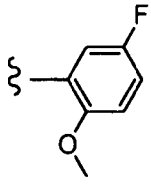
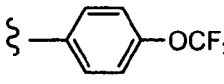
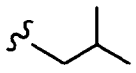
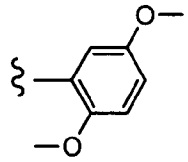
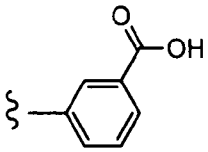
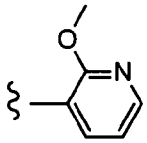
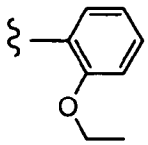
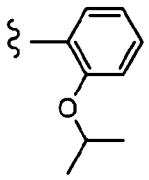
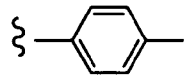
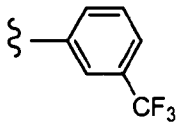
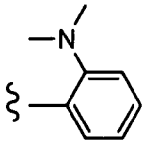
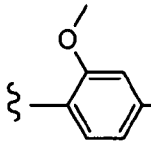
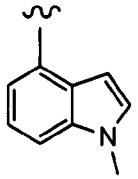
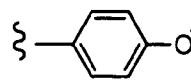


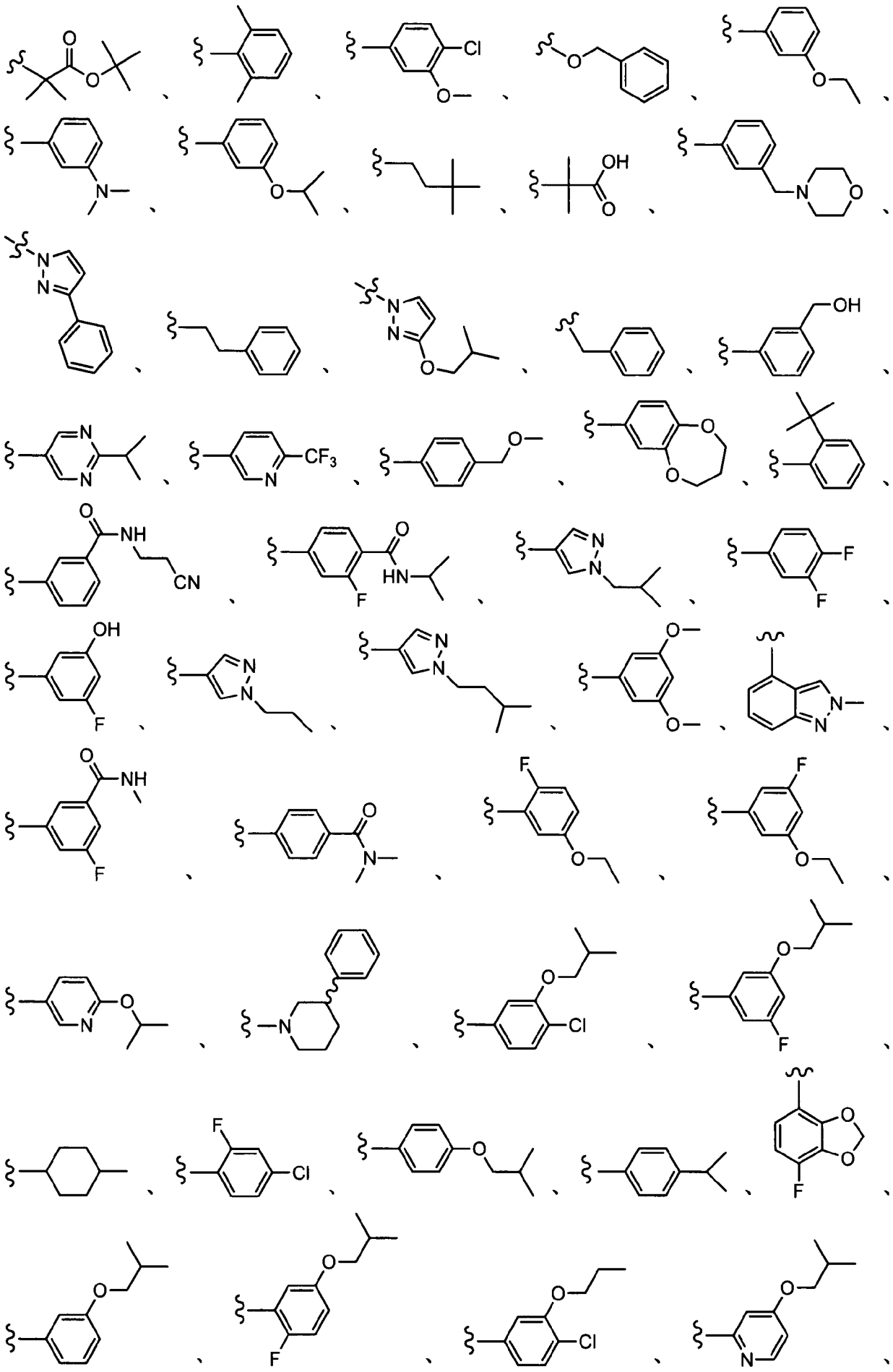


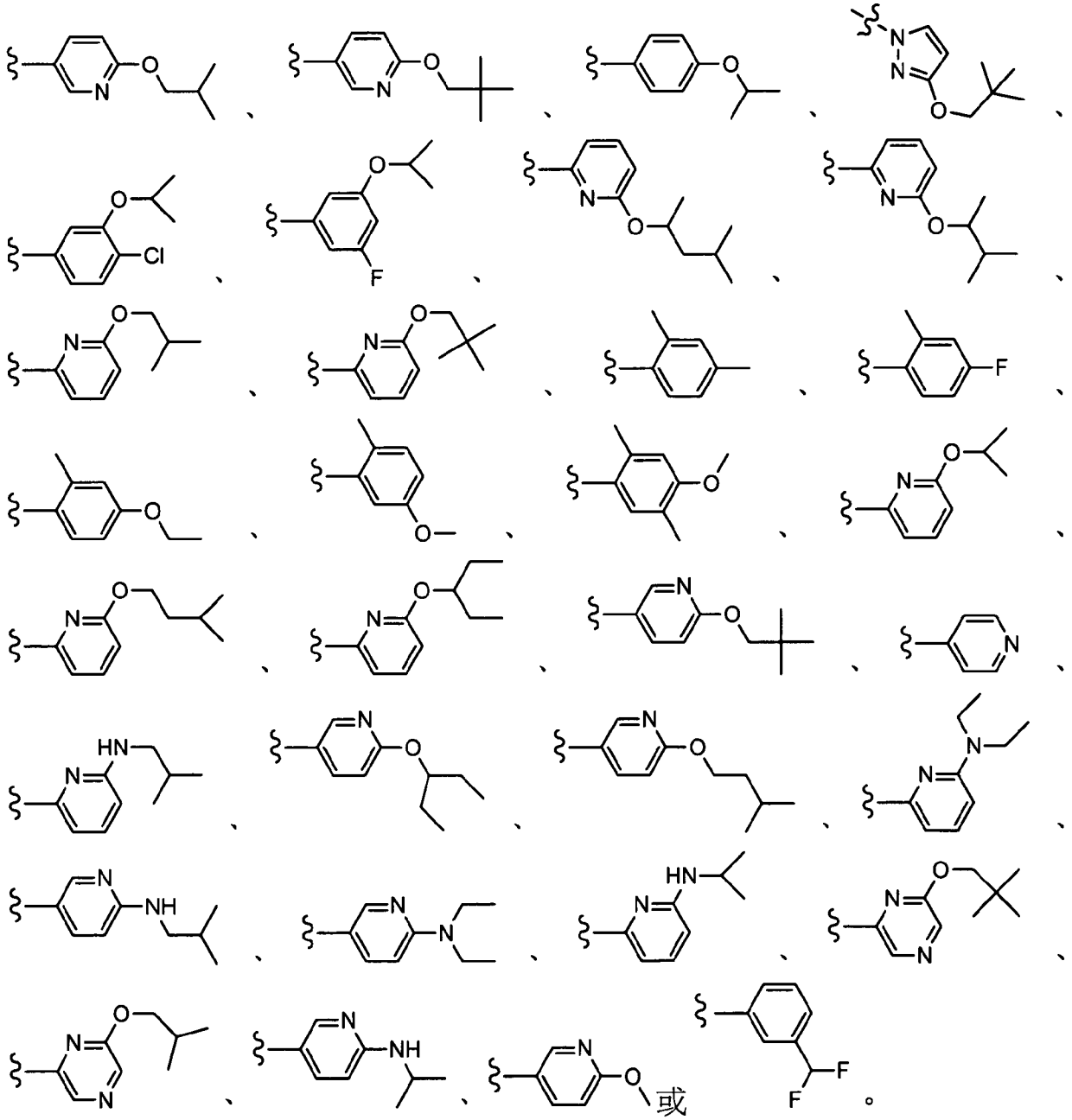
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、

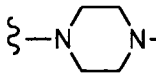
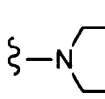
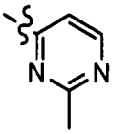
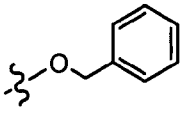
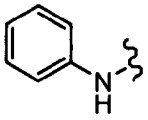
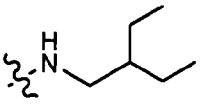
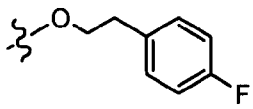
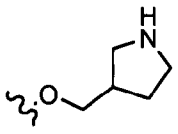
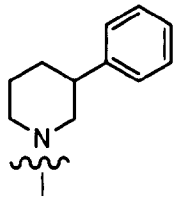
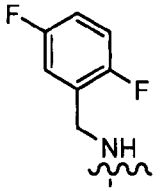
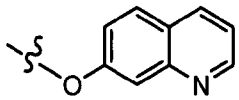
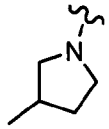
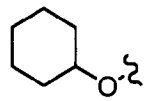
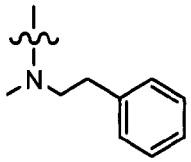
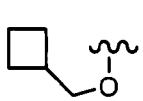
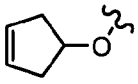
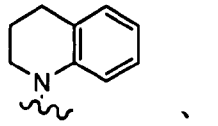
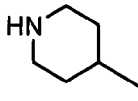
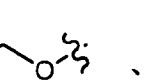
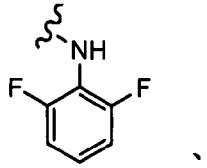
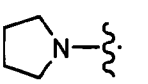
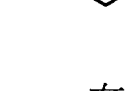
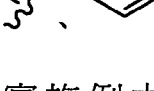
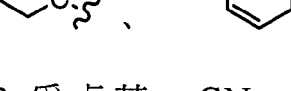
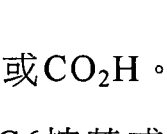
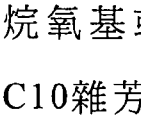
tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、  、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、





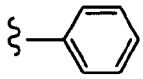
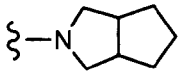
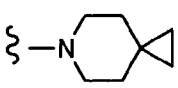
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、

$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、  、、或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、

$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、 

Y為CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$為鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n為0、1、2或3；

o爲0、1、2、3、4或5；

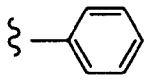
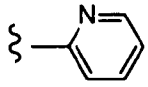
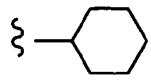
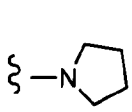
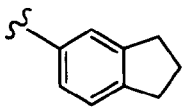
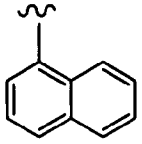
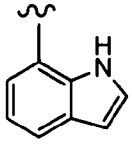
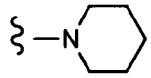
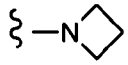
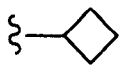
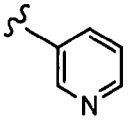
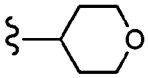
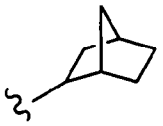
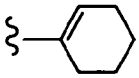
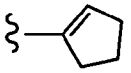
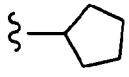
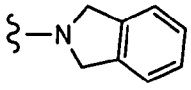
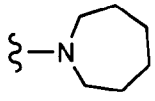
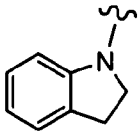
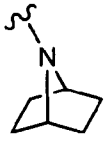
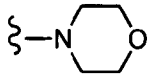
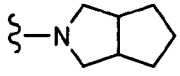
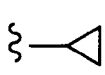
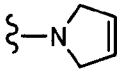
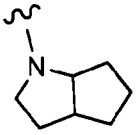
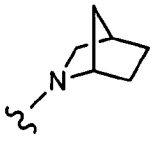
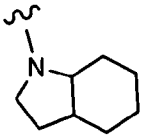
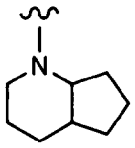
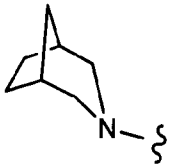
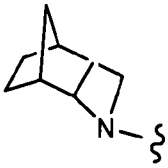
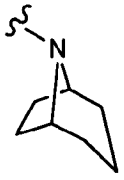
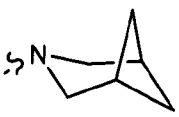
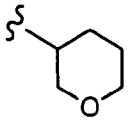
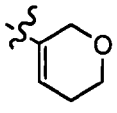
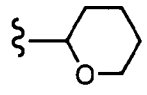
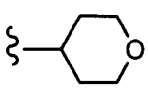
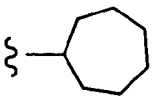
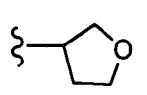
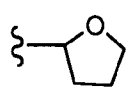
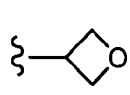
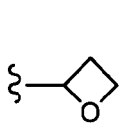
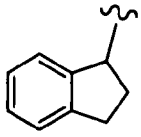
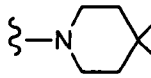
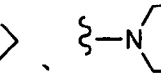
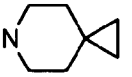
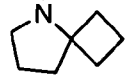
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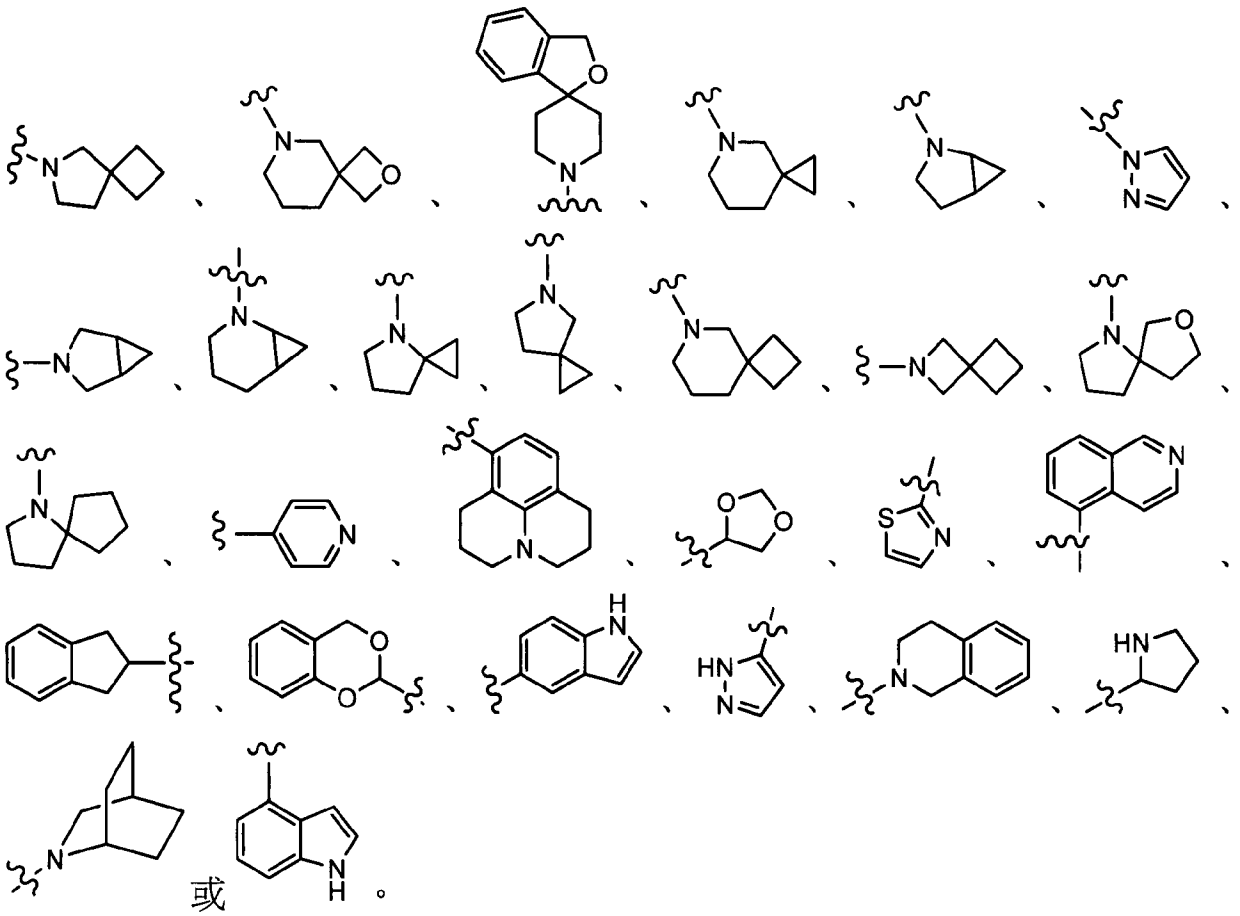
q爲0、1、2、3、4或5。

在一些實施例中，式Ic-ii化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基或萘。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

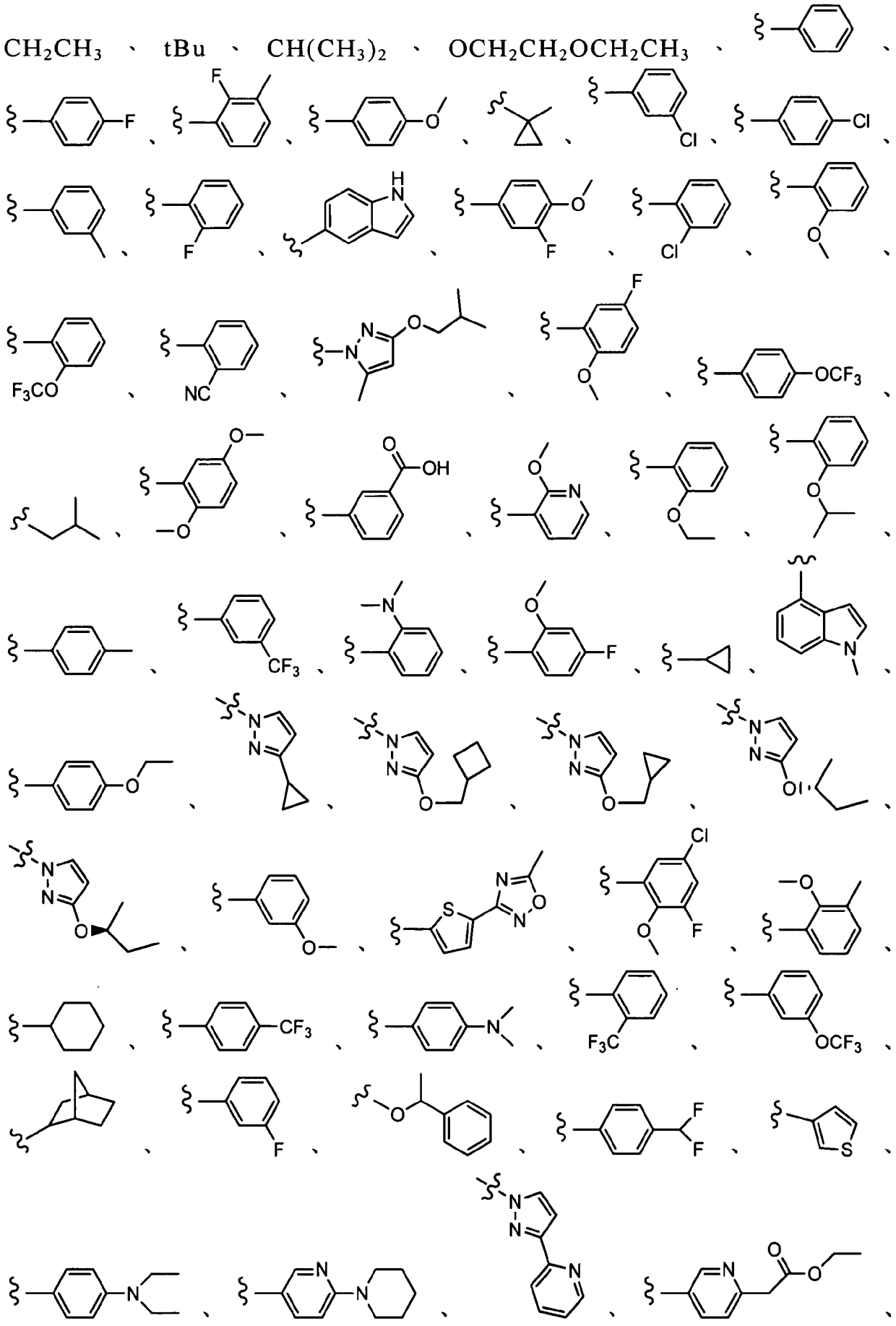
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

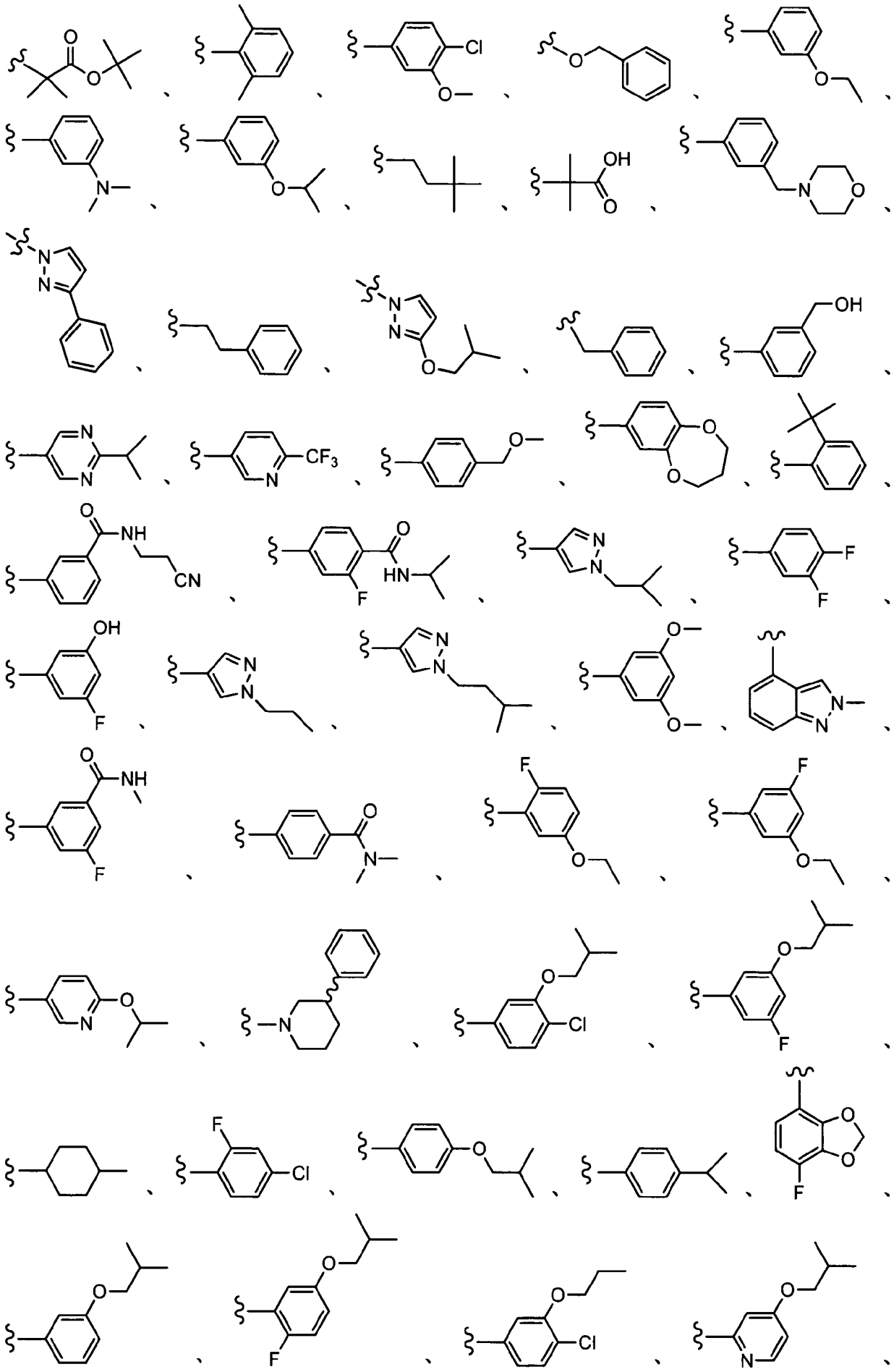


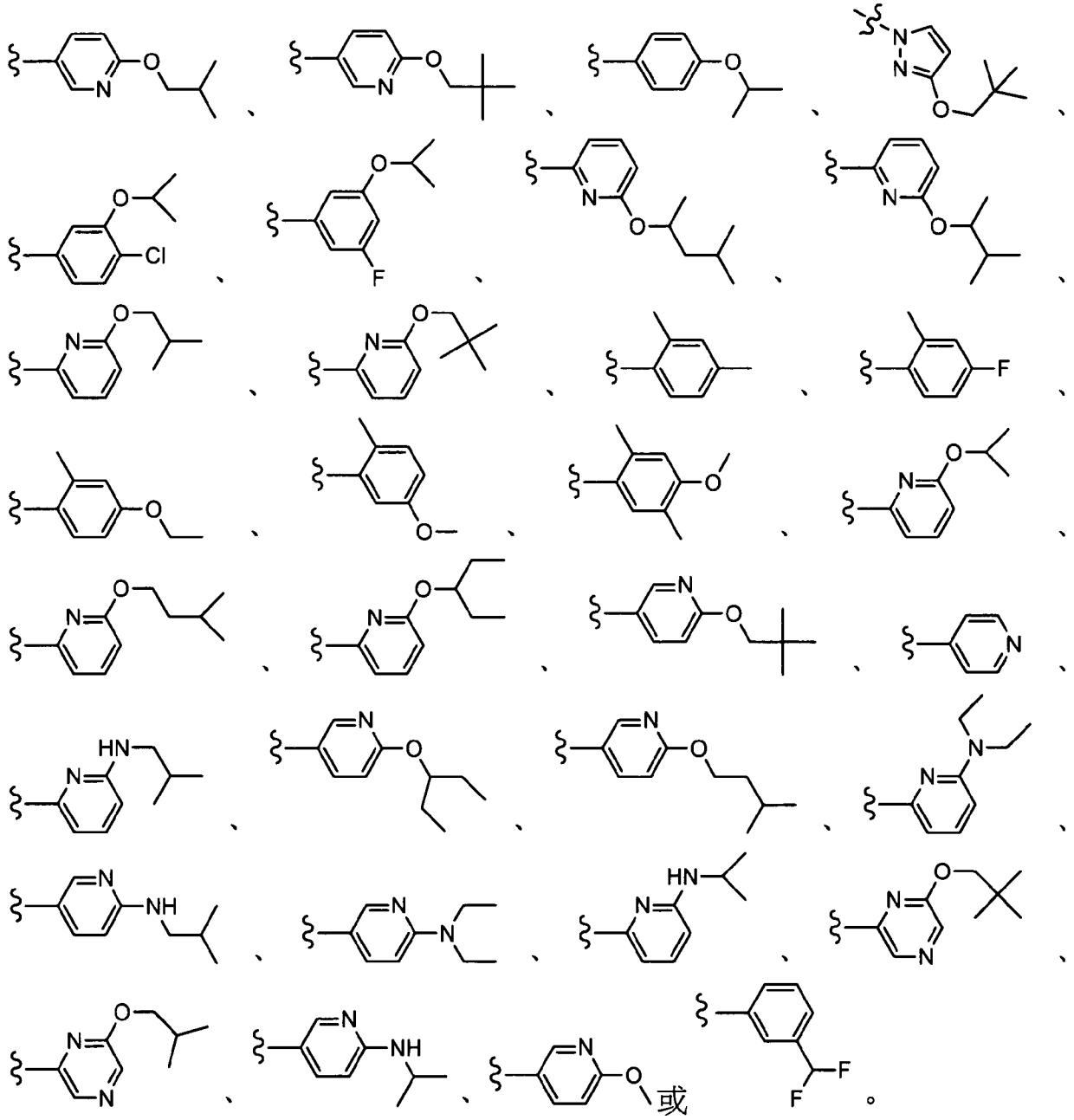
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、

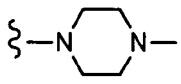
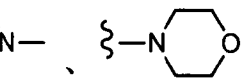
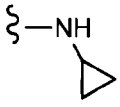
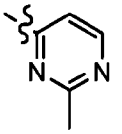
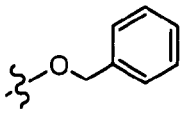
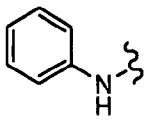
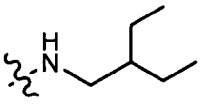
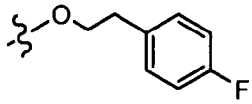
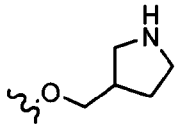
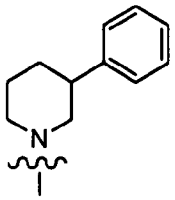
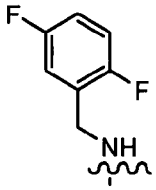
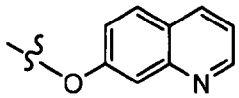
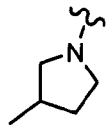
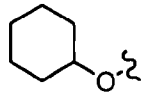
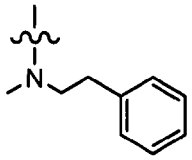
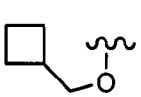
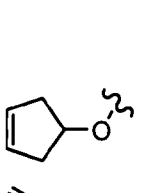
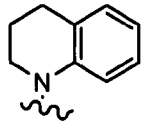
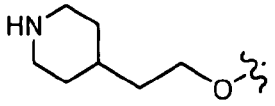
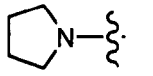
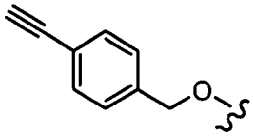
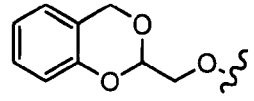
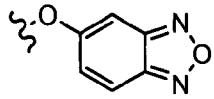






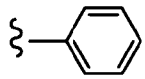
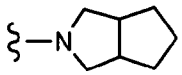
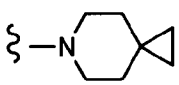
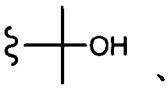
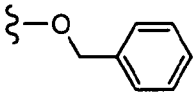
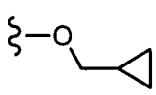
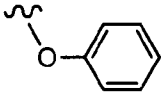
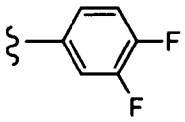
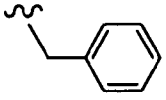
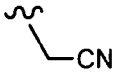
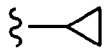
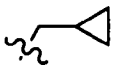
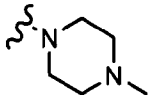
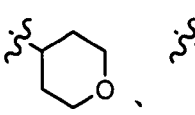
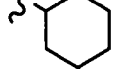
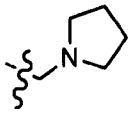
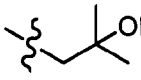
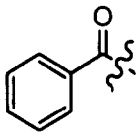
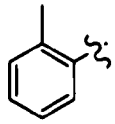
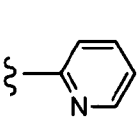
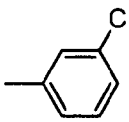
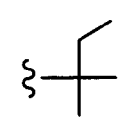
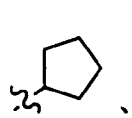
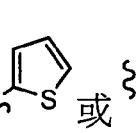
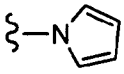
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、

$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、、  、  、  、  、  、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、

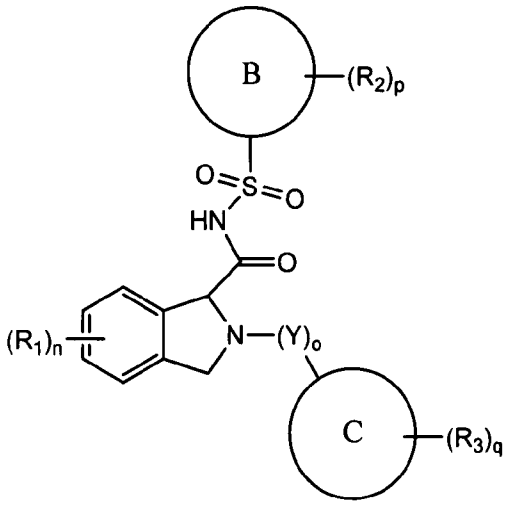
$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、或  。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，本發明提供式Id化合物：




**Id**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中1至4個環原子中任一個獨立地爲O、

S、N或NR的C3-C10雜芳基或雜環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6

烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

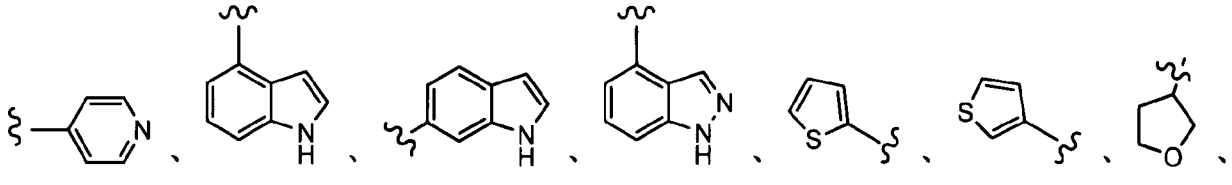
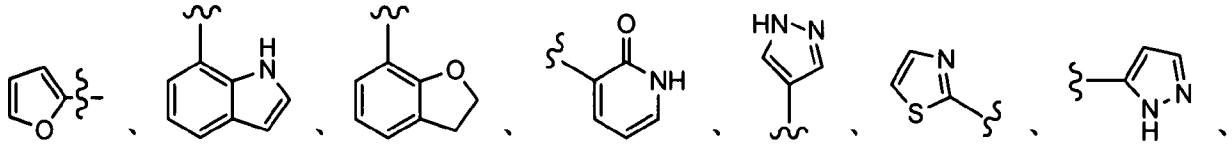
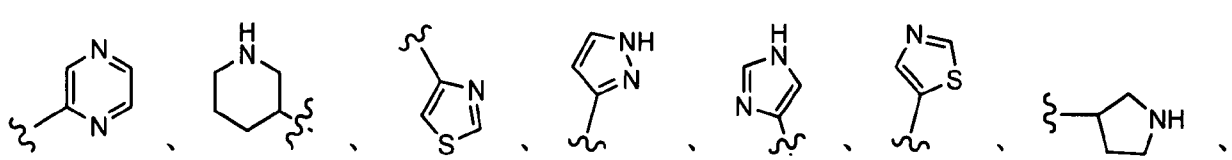
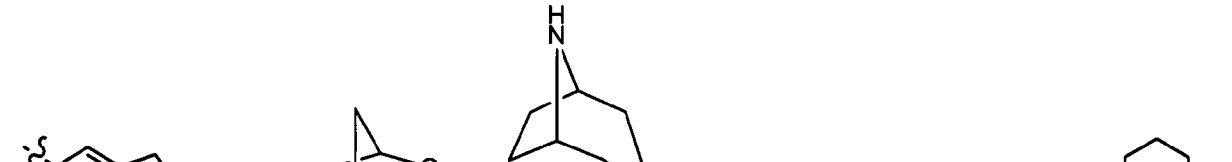
o爲0、1、2、3、4或5；

p爲0、1、2或3；且

q爲0、1、2、3、4或5。

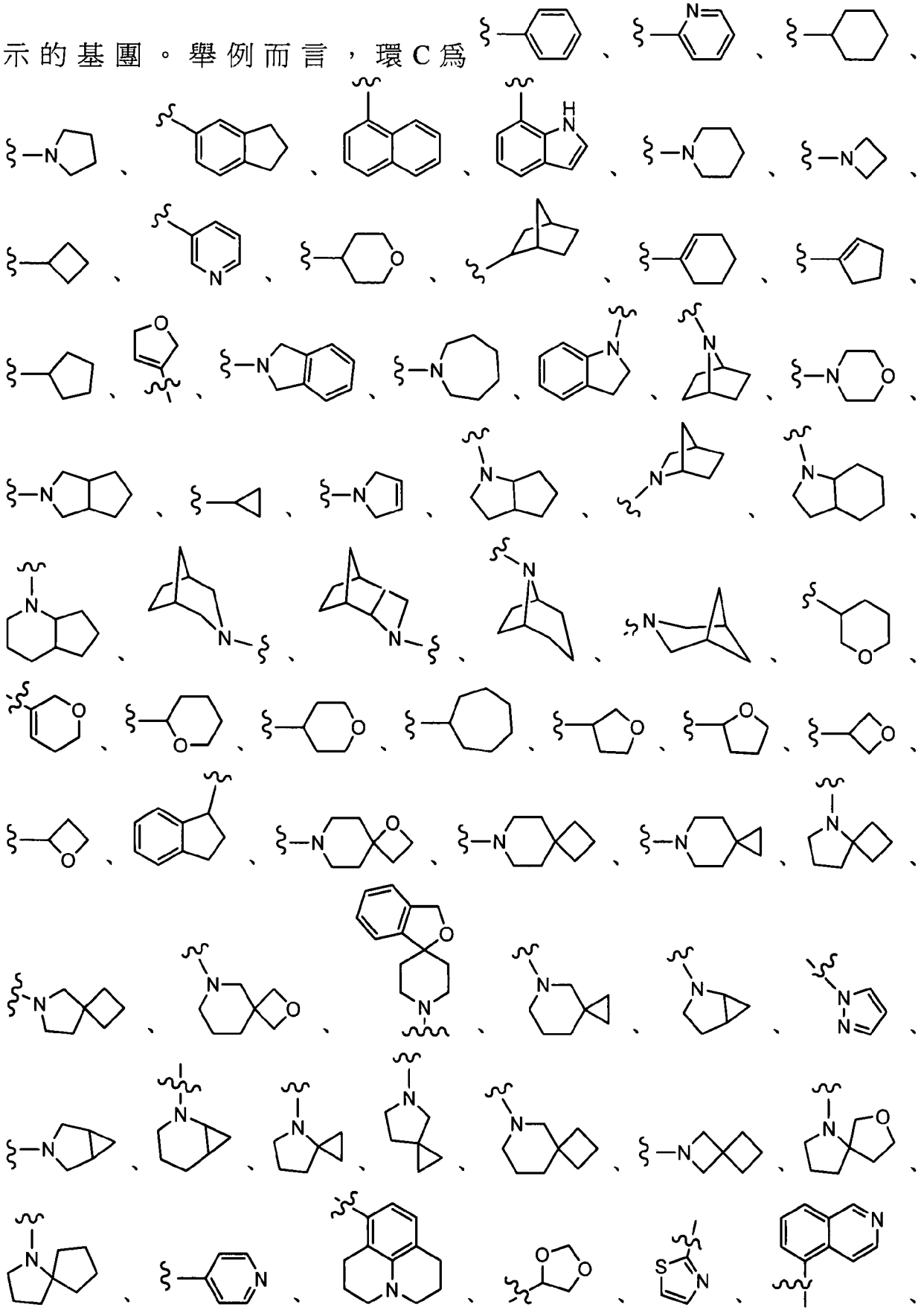
在一些實施例中，式Id化合物呈醫藥學上可接受之前藥形式存在。

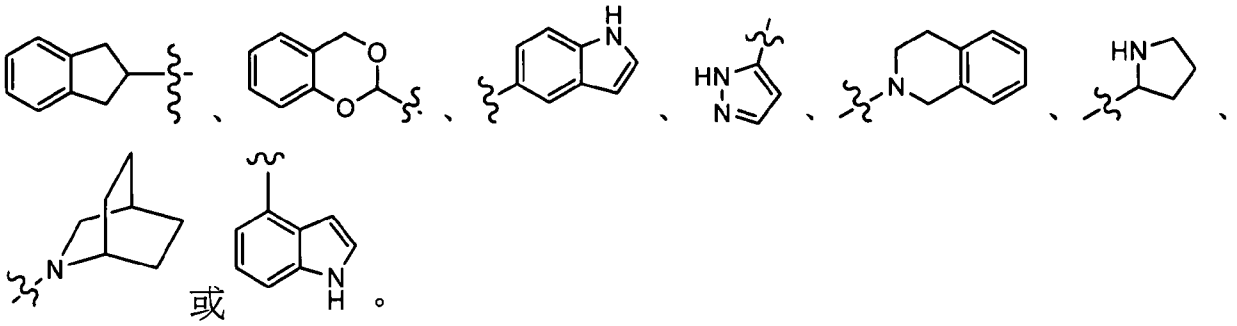
在一些實施例中，環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、  、  、  、  、  或。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯

啶、萘或二氫茚。

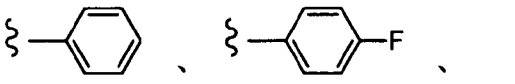
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲 

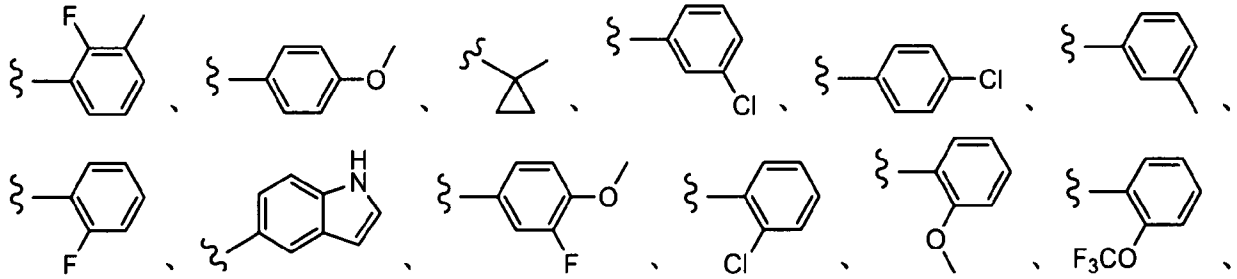


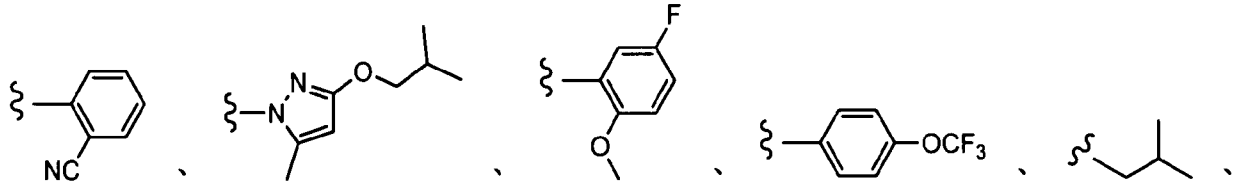
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

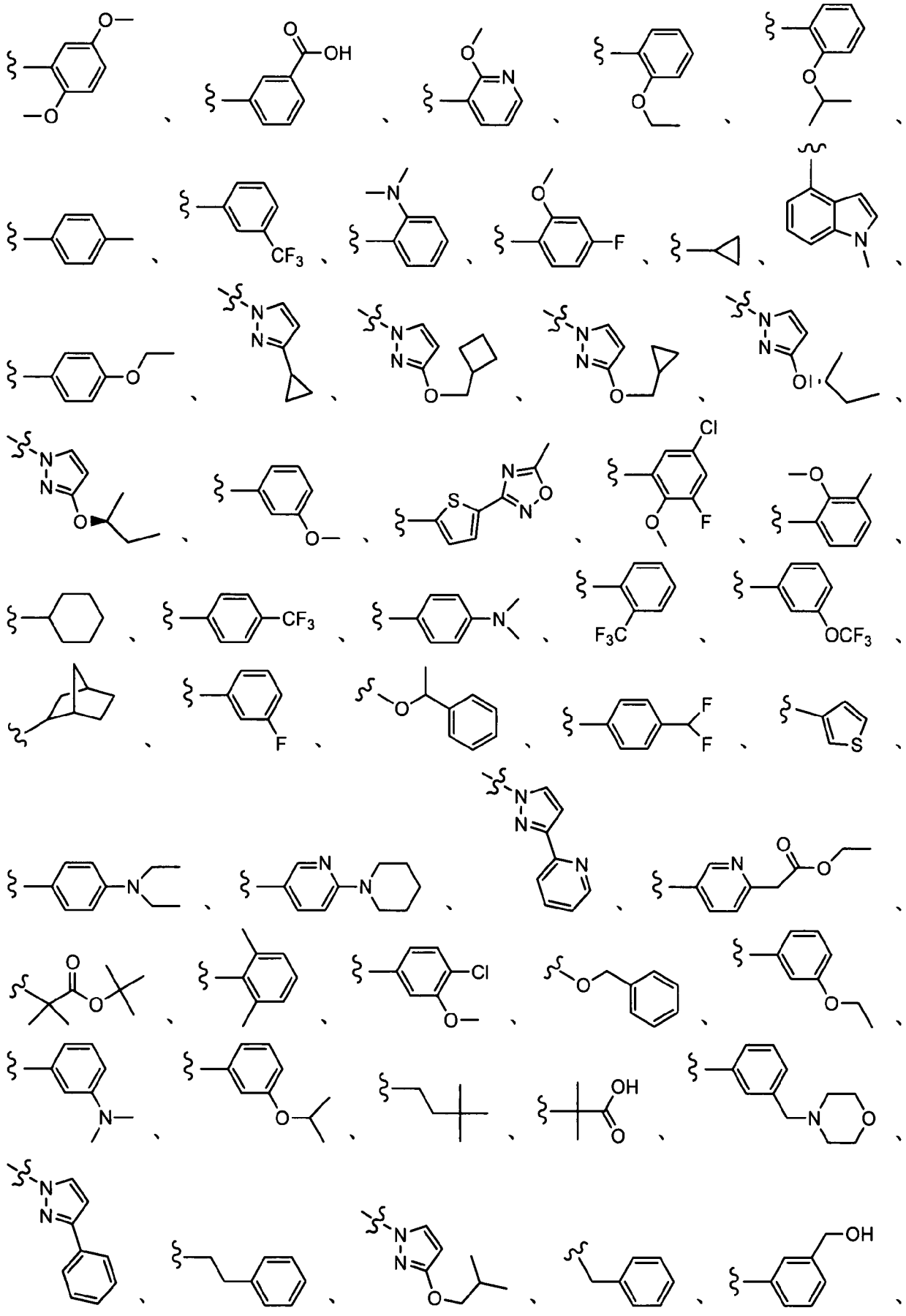
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

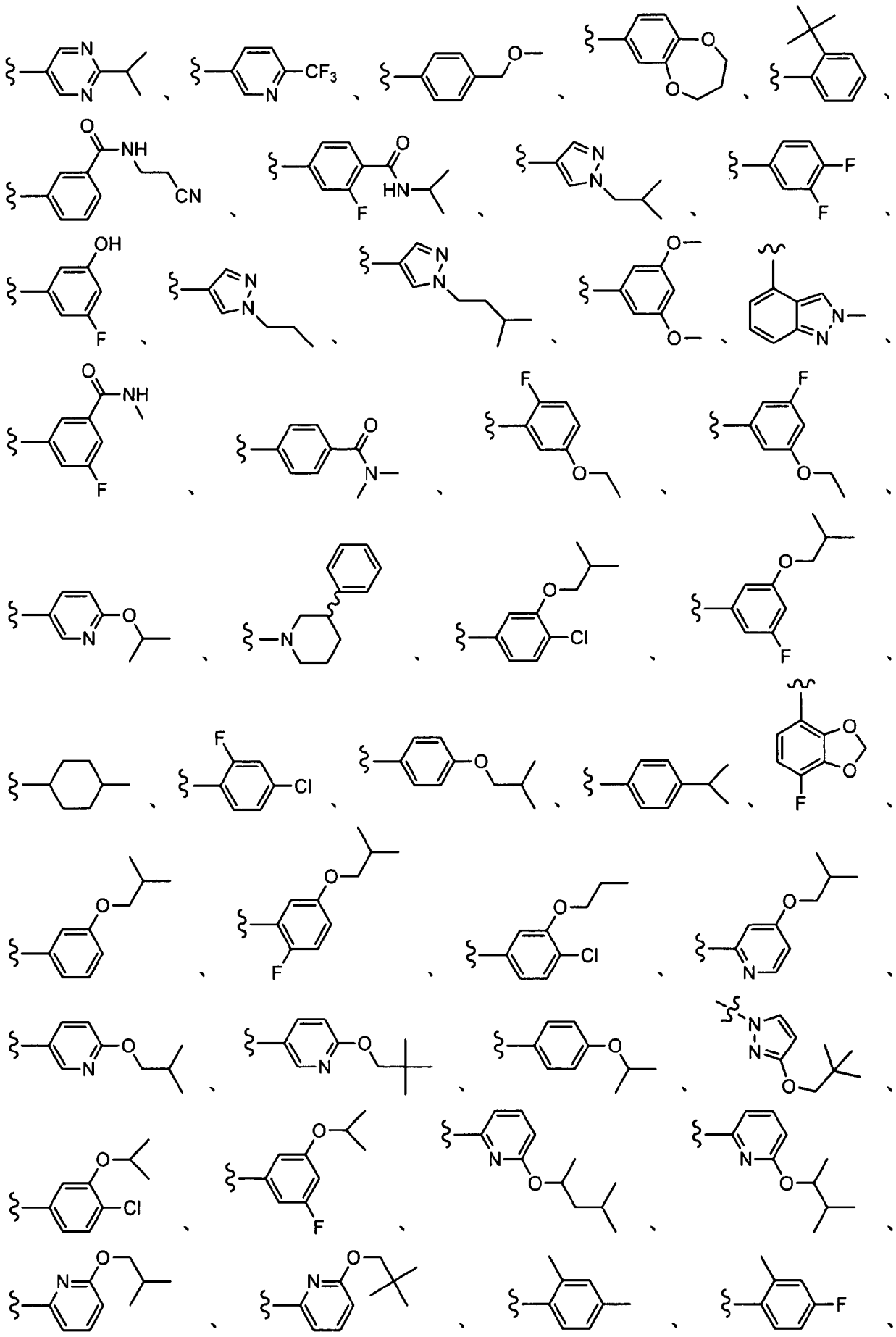
在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、

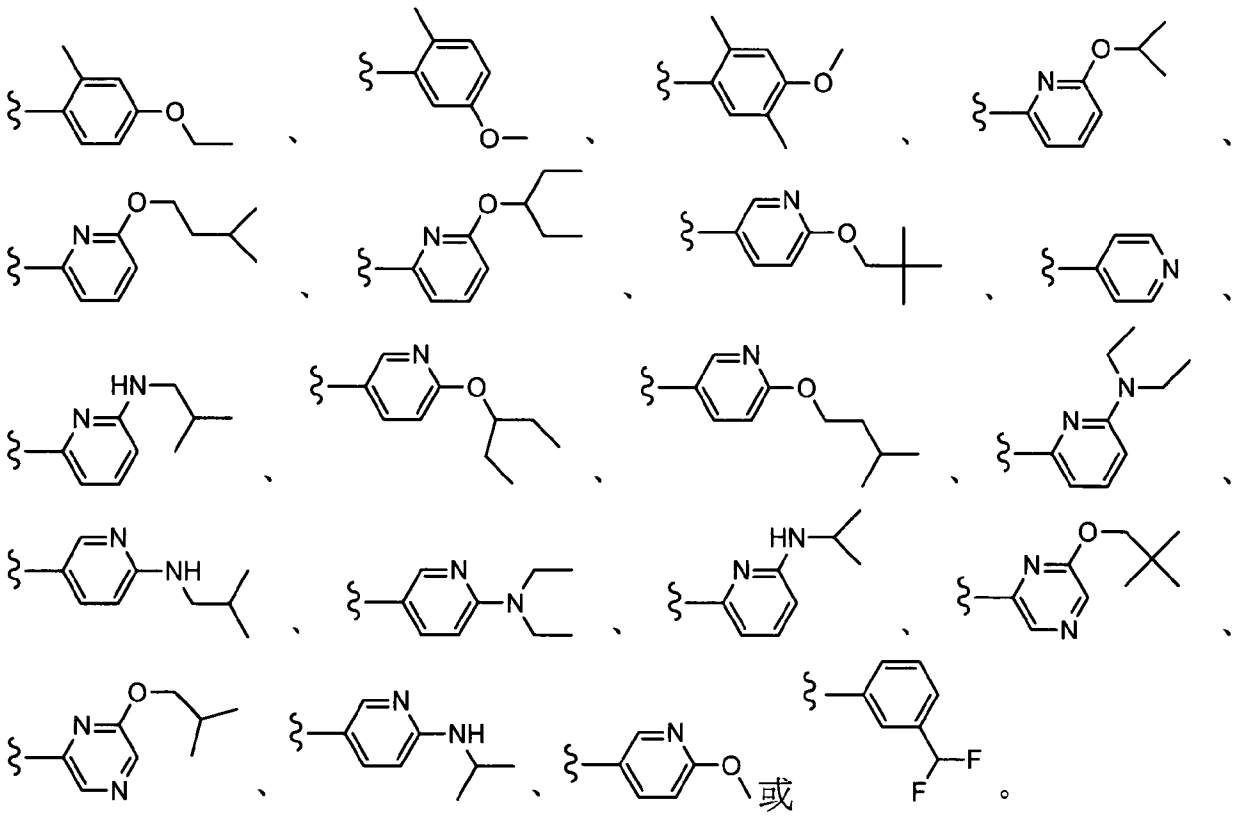






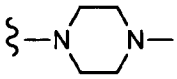
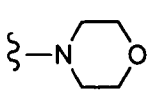
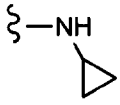


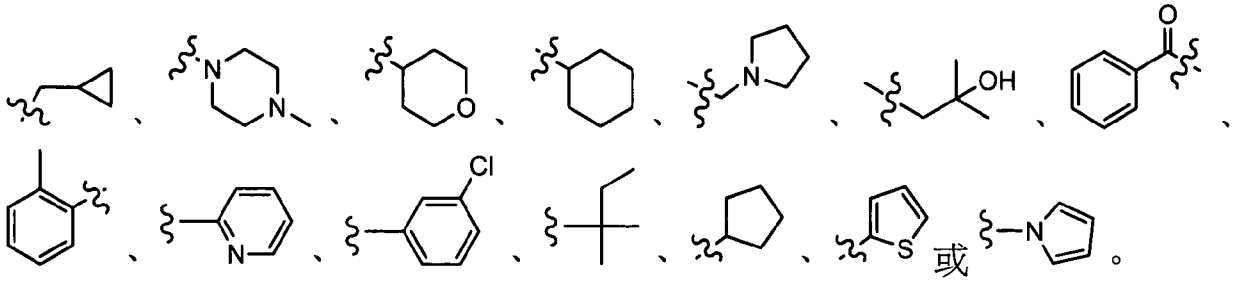




在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、

$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、 



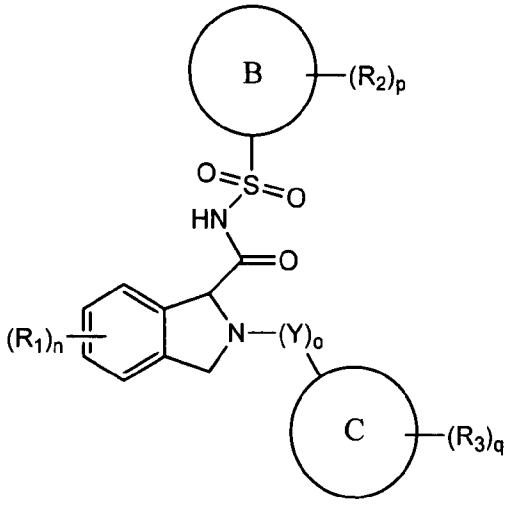
在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，環B爲苯基。在一些實施例中，環B爲吡啶基。在一些實施例中，環C爲苯基。在一些實施例中，環B及環C爲苯基。在一些實施例中，環B爲吡啶基且環C爲苯基。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲O。在一些實施例中，$R_2$爲胺基。在一些實施例中，$R_2$爲OH。在一些實施例中，$R_2$爲$OCH_3$。在一些實施例中，$R_3$爲$CH_3$。在一些實施例中，$R_2$爲胺基且$R_3$爲$CH_3$。在一些實施例中，環B爲吡啶基，環C爲苯基，且Y爲$CH_2$。在一些實施例中，環B爲吡啶基，環C爲苯基，且Y爲O。

在一些實施例中，本發明提供式Id-i化合物：



**Id-i**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-

C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

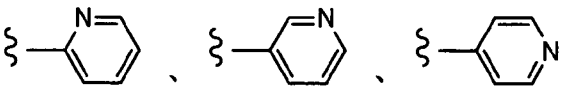
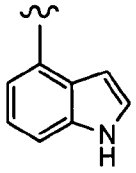
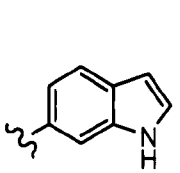
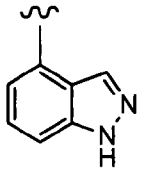
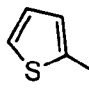
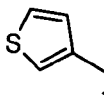
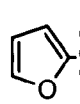
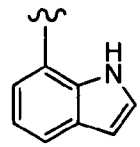
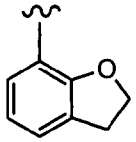
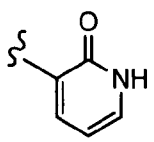
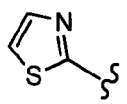
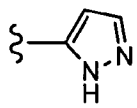
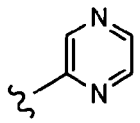
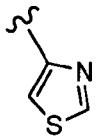
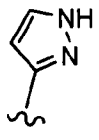
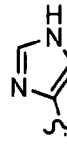
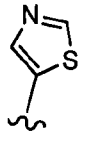
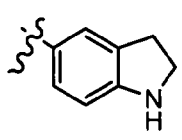
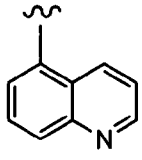
o爲0、1、2、3、4或5；

p爲0、1、2或3；且

q爲0、1、2、3、4或5。

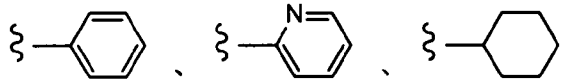
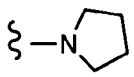
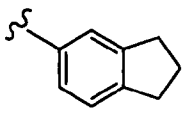
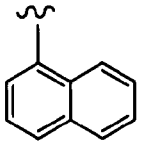
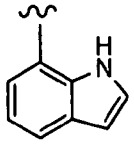
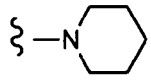
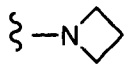
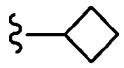
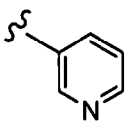
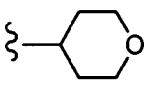
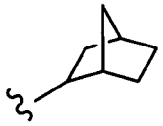
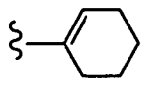
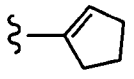
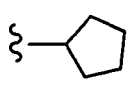
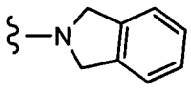
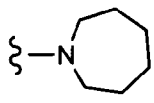
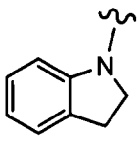
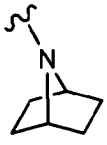
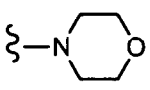
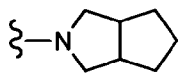
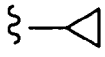
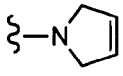
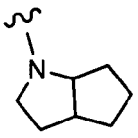
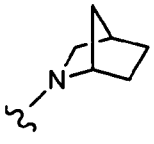
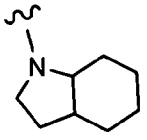
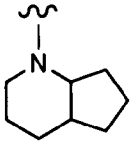
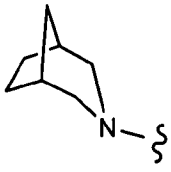
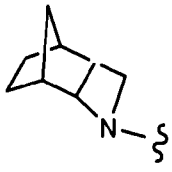
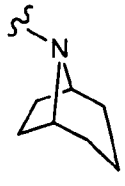
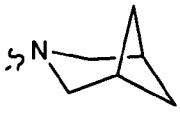
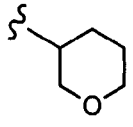
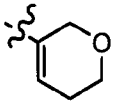
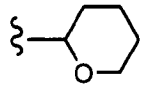
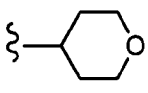
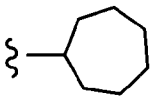
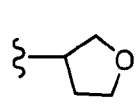
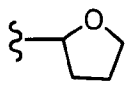
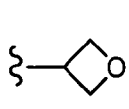
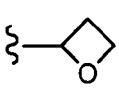
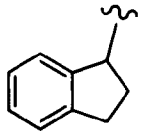
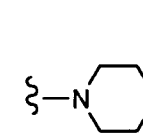
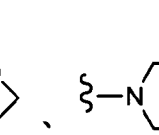
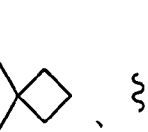
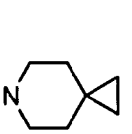
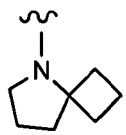
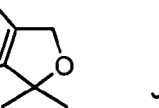
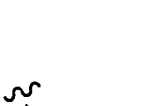
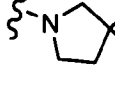
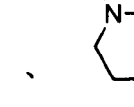
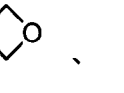
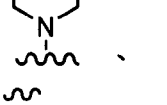
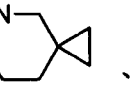
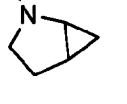
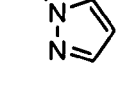
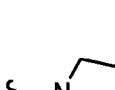
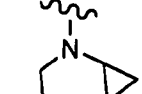
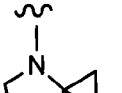
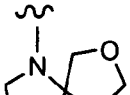
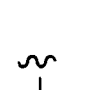
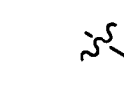
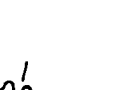
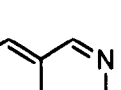
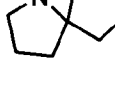
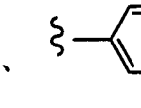
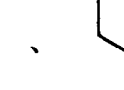
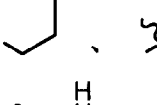
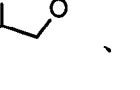
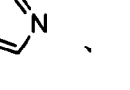
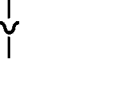
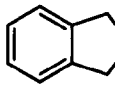
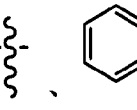
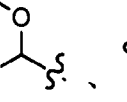
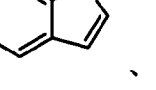
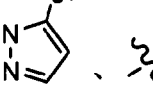
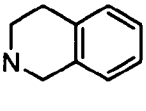
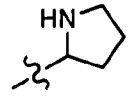
在一些實施例中，式Id-i化合物呈醫藥學上可接受之前藥形式存在。

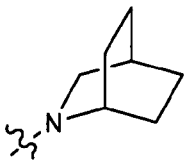
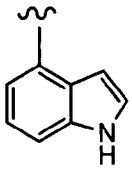
在一些實施例中，環B爲吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

在一些實施例中，環B爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環B爲  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

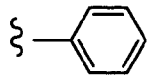
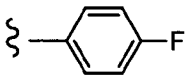
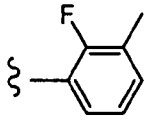
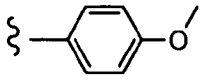
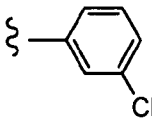
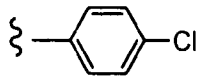
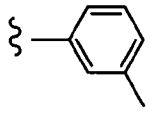
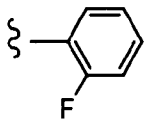
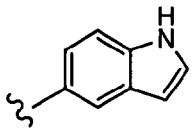
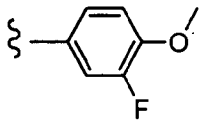
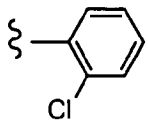
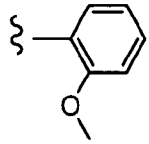
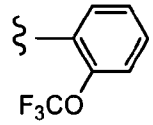
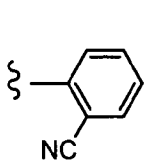
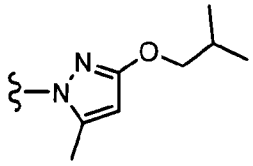
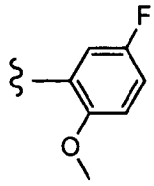
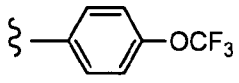
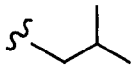
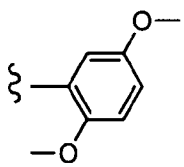
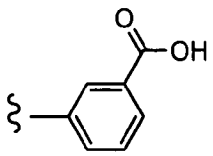
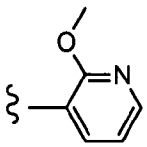
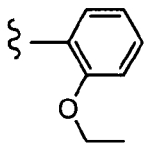
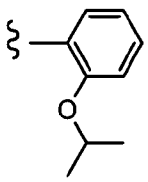
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表

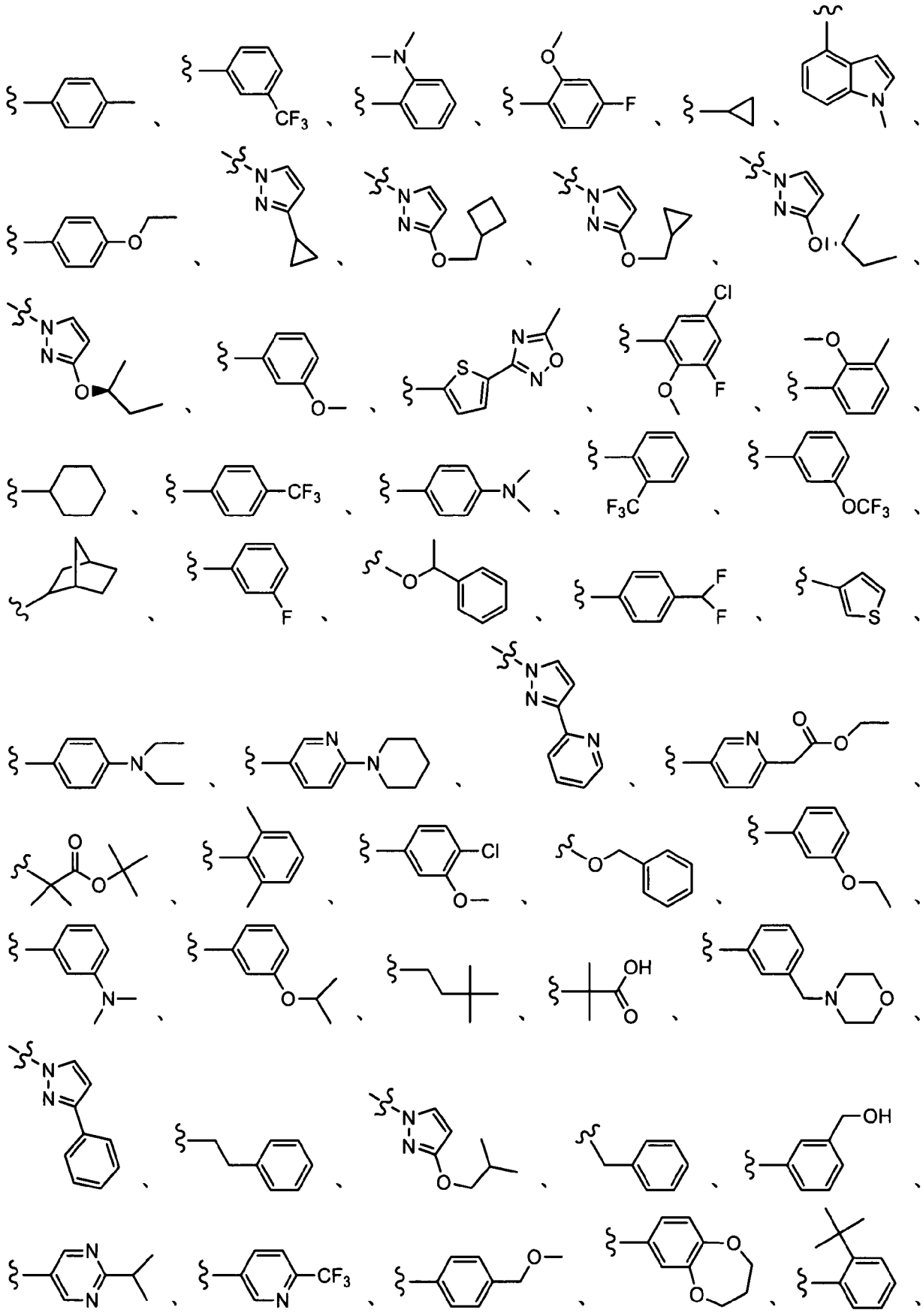
示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

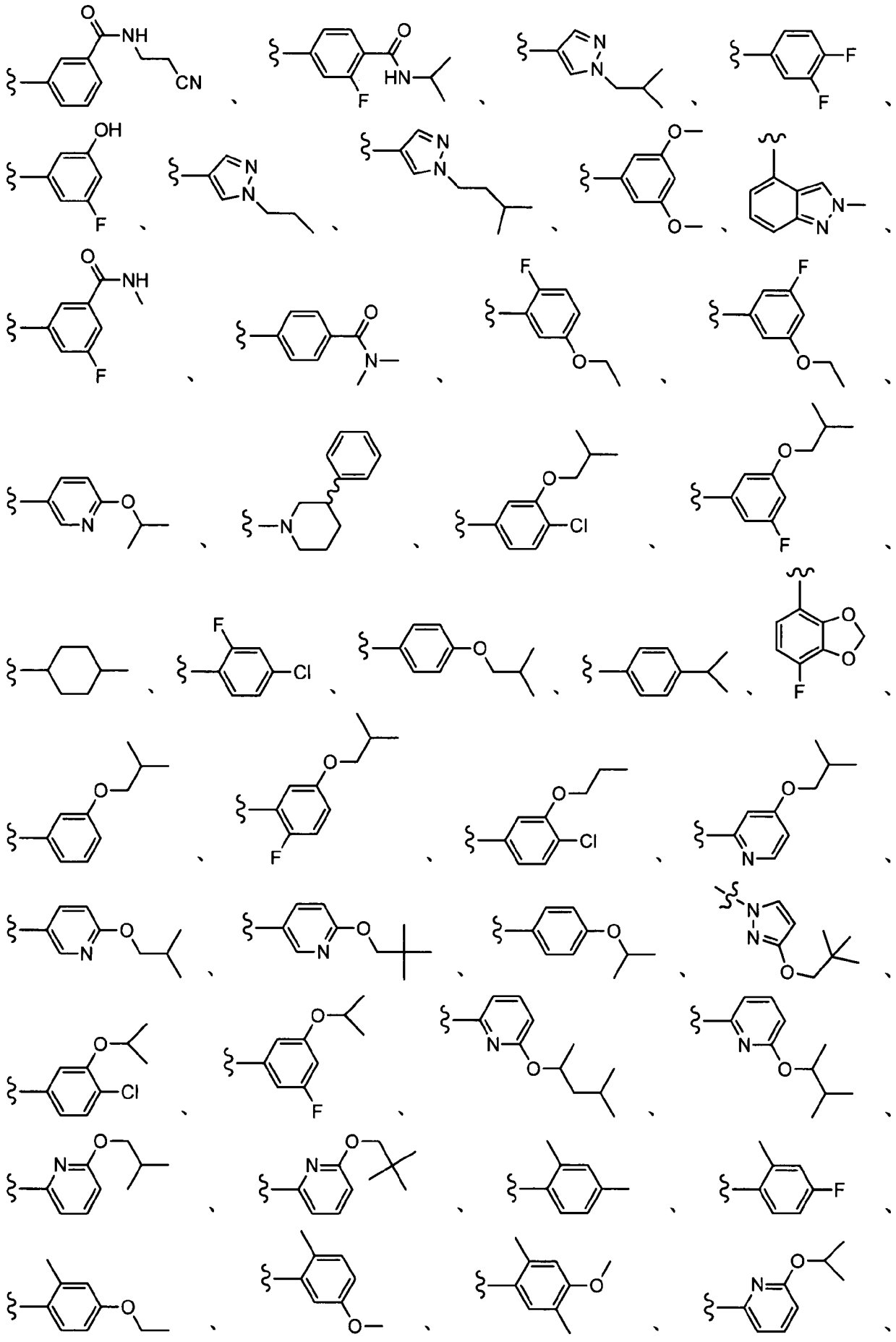

或

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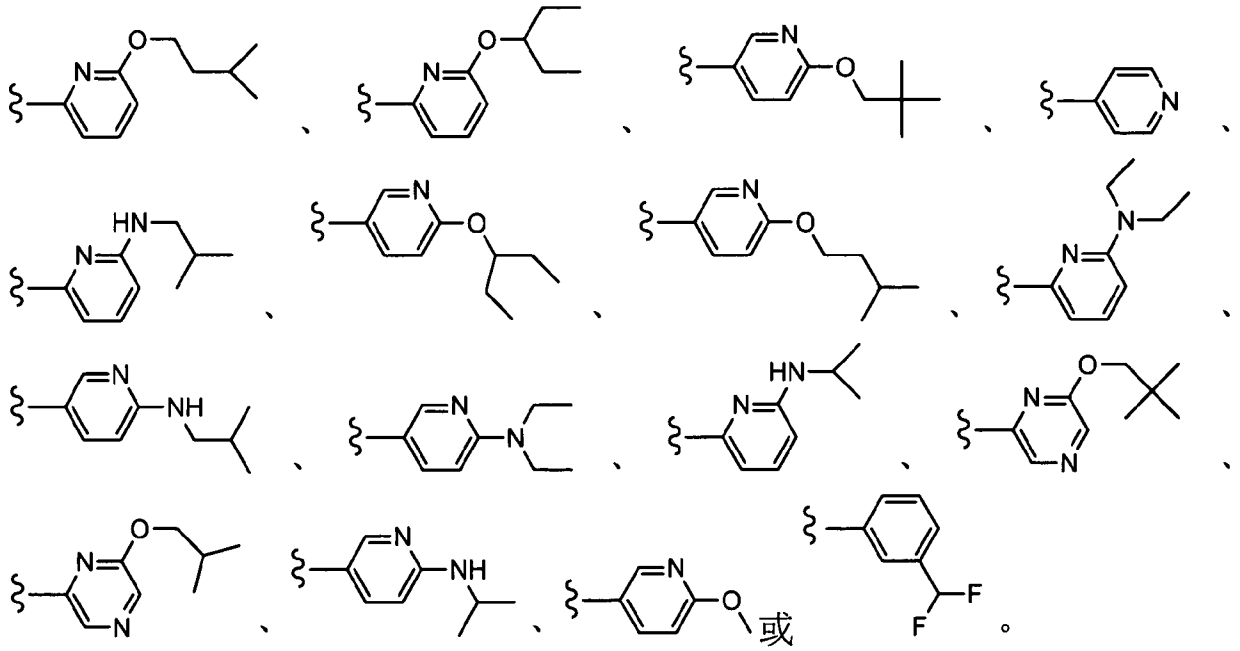
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

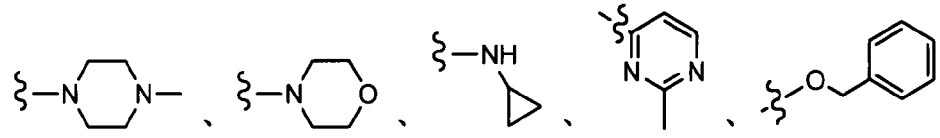
在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

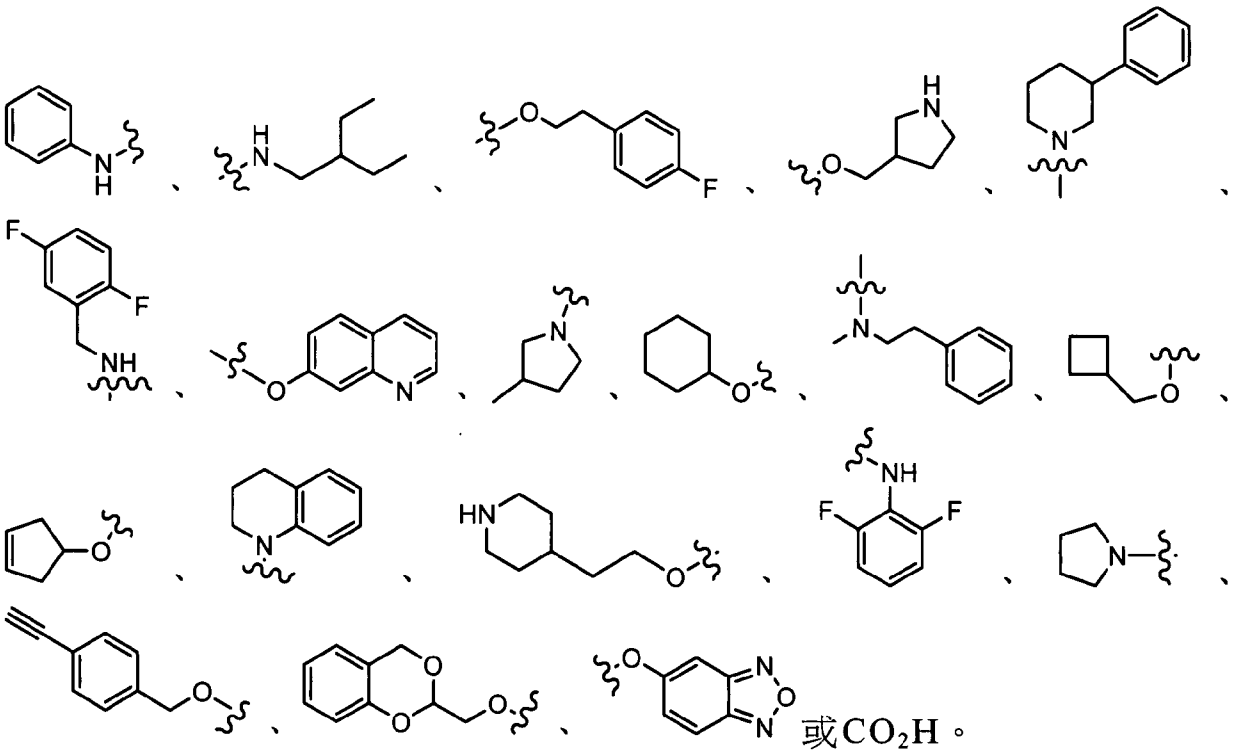






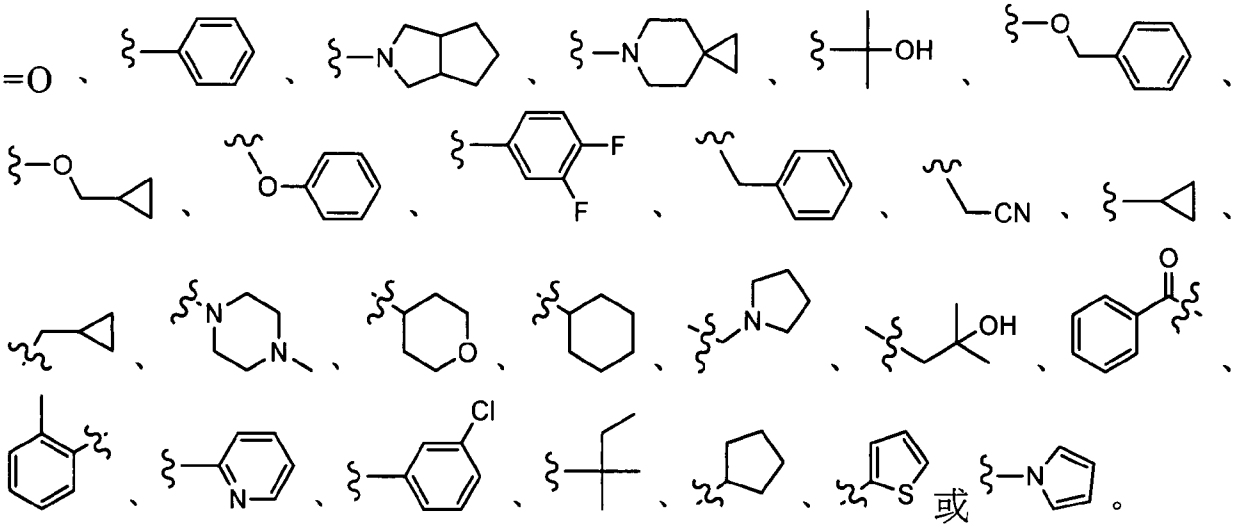
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、 


或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、


或

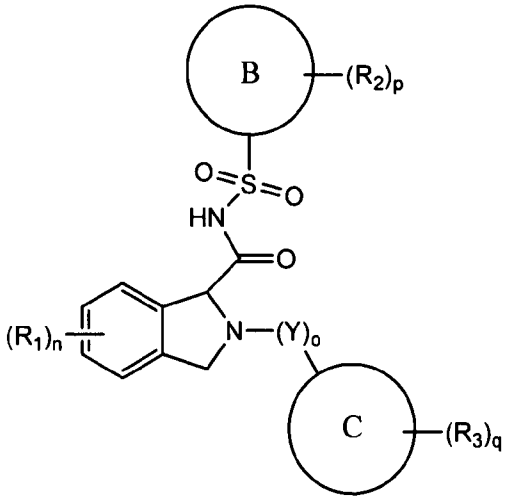

。

在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在一些實施例中，本發明提供式Id-ii化合物：




**Id-ii**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環；

環C爲C6-C10芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C3-C14雜芳基或雜環、或C3-C10環烷基環；

Y爲CRR、CO、O、S、SO、$SO_2$、S(O)NH或NR；

$R_1$爲鹵基；CN；$F_5S$；$SiR_3$；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$爲鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟

烷基；C1-C6烷氧基或氟烷氧基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$爲鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烯基；C1-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$爲H；疊氮化物；$CF_3$；$CHF_2$；OR；CCH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地爲H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C1-C6烯基；C1-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n爲0、1、2或3；

o爲0、1、2、3、4或5；

p爲0、1、2或3；且

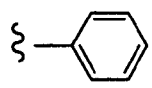
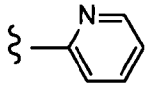
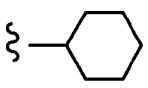
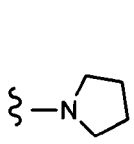
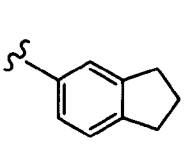
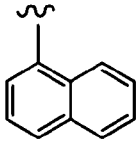
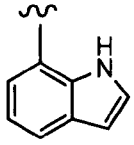
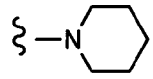
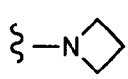
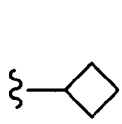
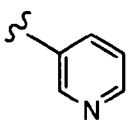
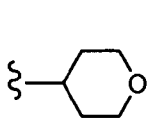
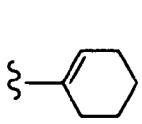
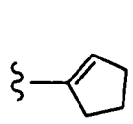
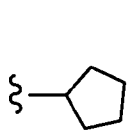
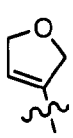
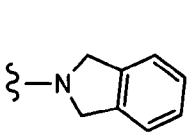
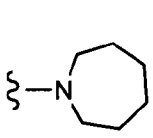
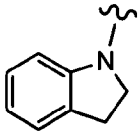
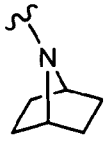
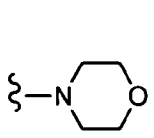
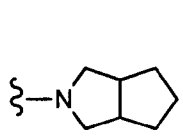
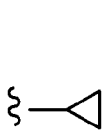
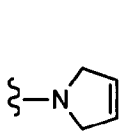
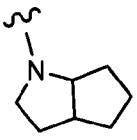
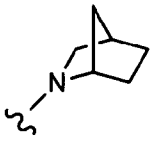
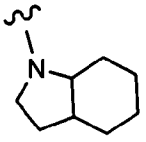
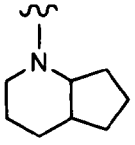
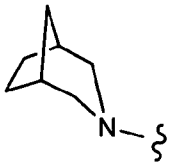
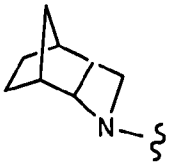
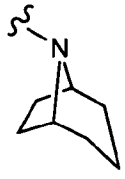
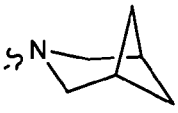
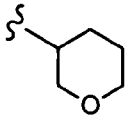
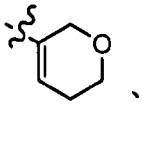
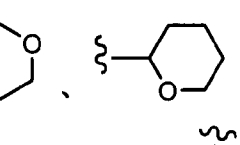
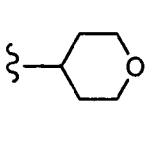
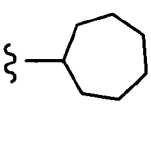
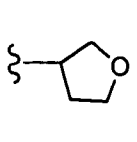
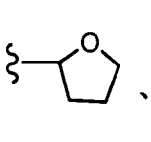
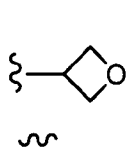
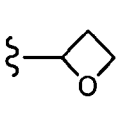
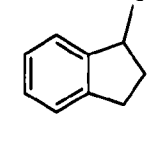
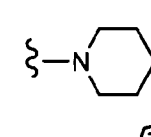
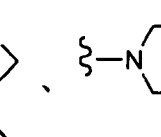
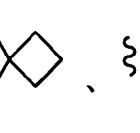
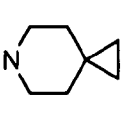
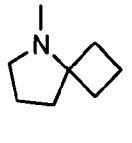
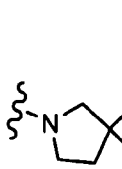
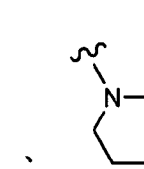
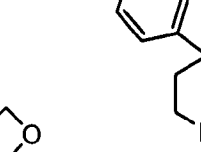
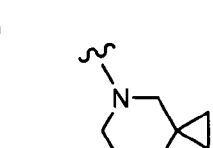
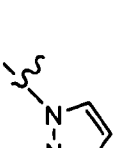
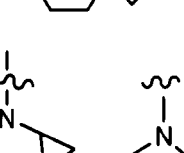
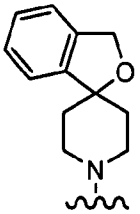
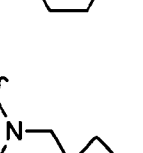
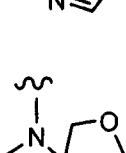
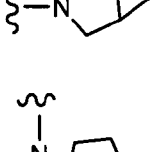
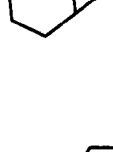
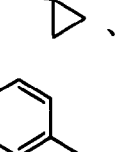
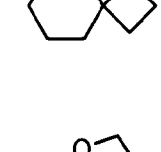
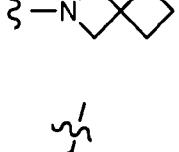
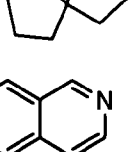
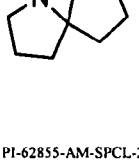
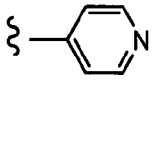
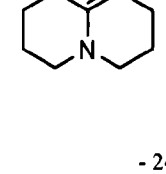
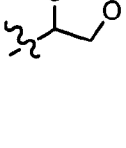
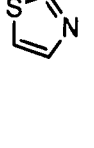
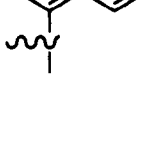
q爲0、1、2、3、4或5。

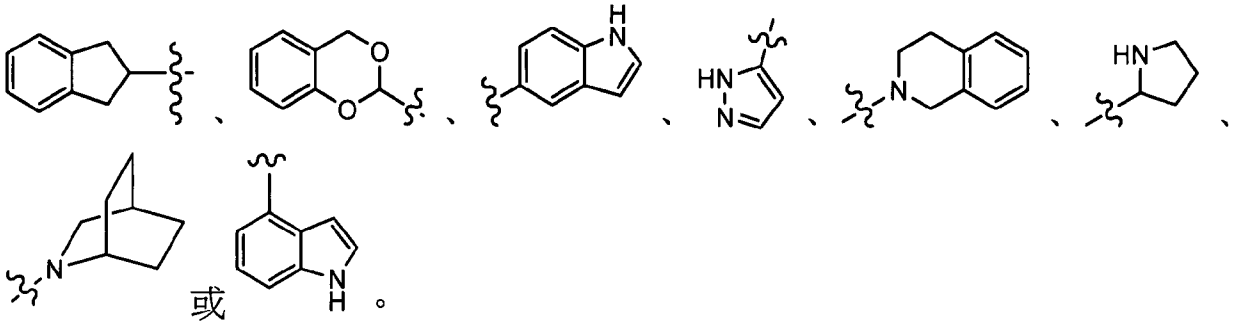
在一些實施例中，式Id-ii化合物呈醫藥學上可接受之前藥形式存在。

在一些實施例中，環B爲苯基或萘。

在一些實施例中，環C爲苯基、吲哚、環烷基、吡啶基、吡咯

啶、萘或二氫茚。

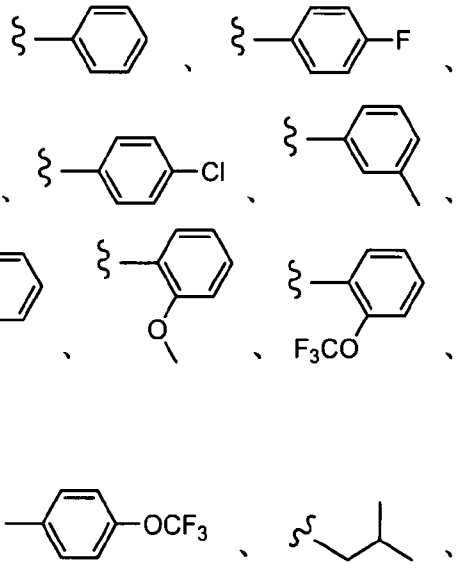
在一些實施例中，環C爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，環C爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、

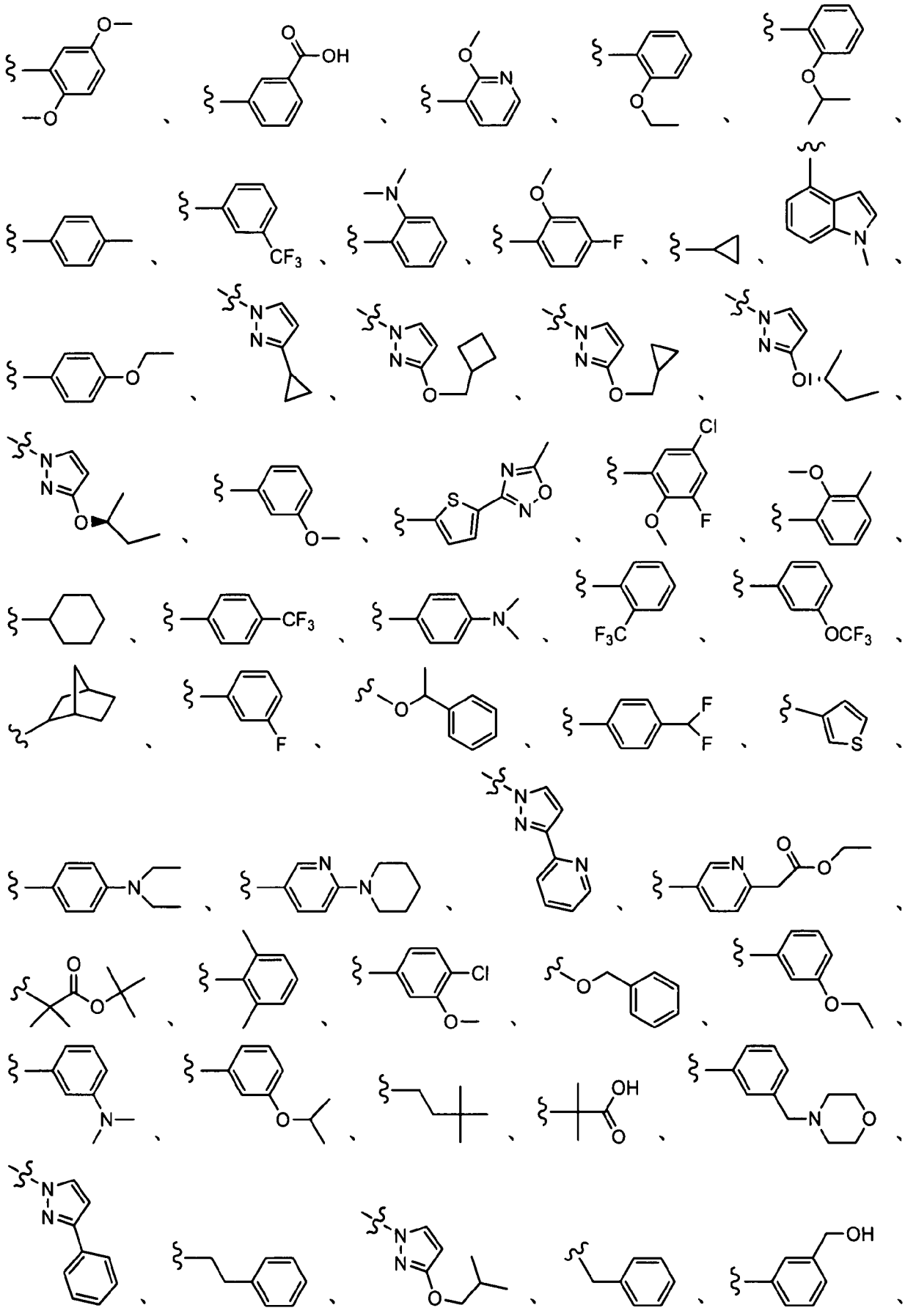


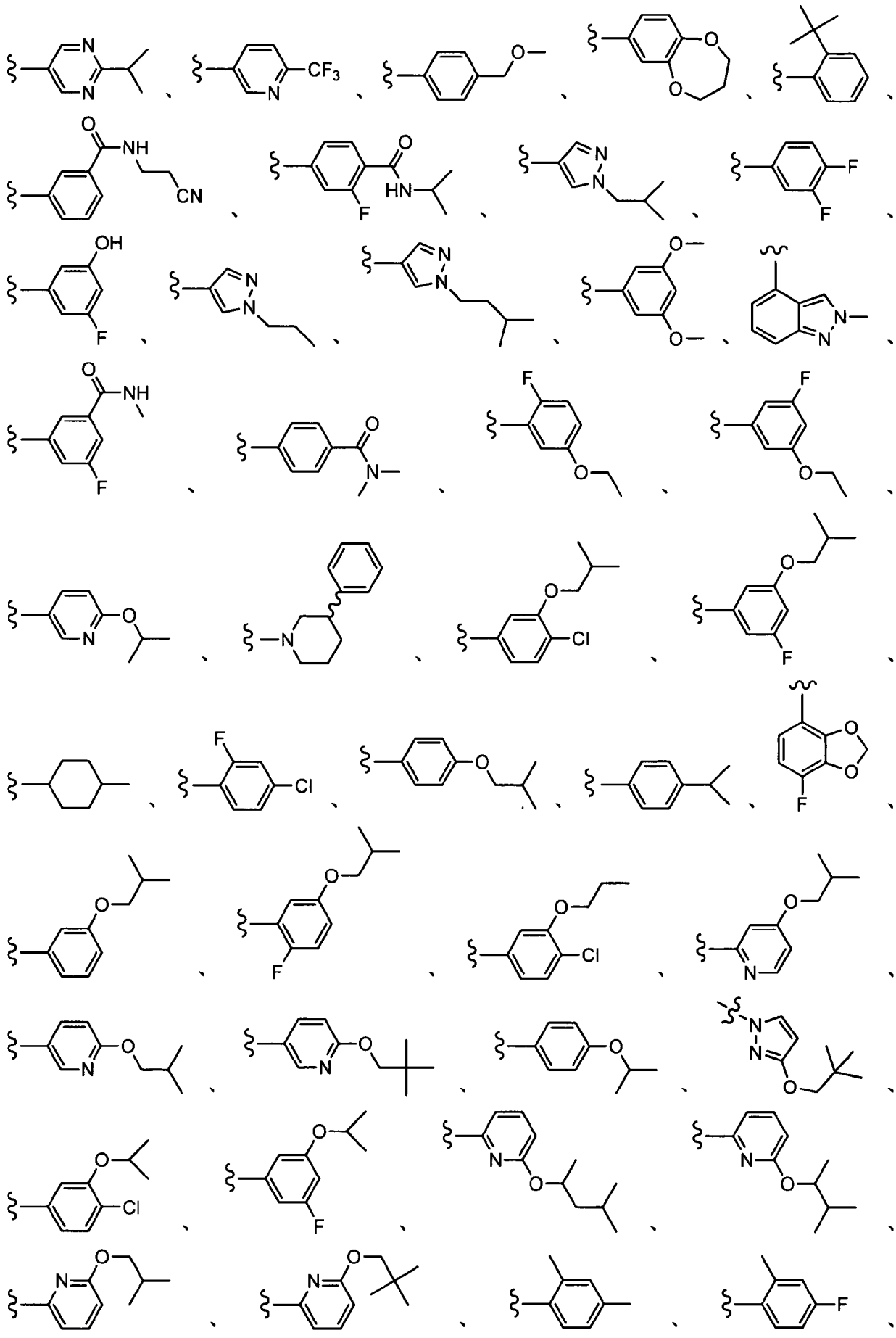
在一些實施例中，Y爲O。在一些實施例中，Y爲$CH_2$。在一些實施例中，Y爲CH(C1-C6烷基)。在一些實施例中，Y爲$CH(CH_3)$。在一些實施例中，Y爲$CH(CH_2CH_3)$。在一些實施例中，Y爲NR，諸如NH、N(C1-C6炔基)或N(C1-C6烷基)。

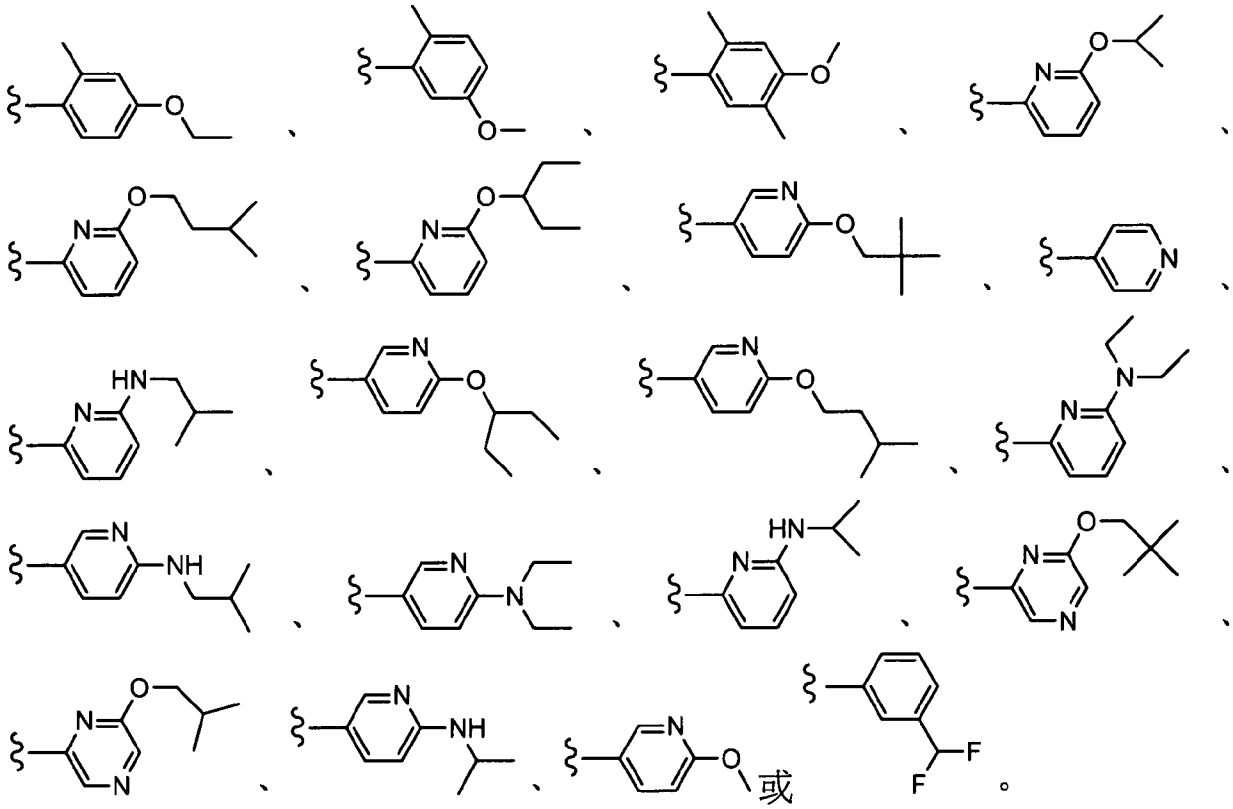
在一些實施例中，$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$，其中所有環視情況經一或多個選自以下各基之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

在一些實施例中，$R_1$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_1$爲$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、



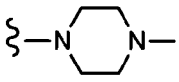
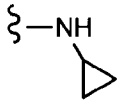
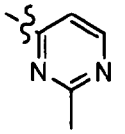
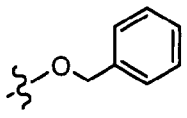
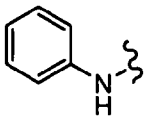
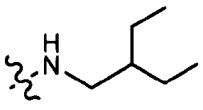
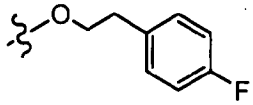
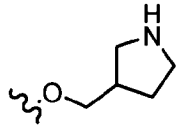
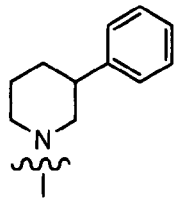
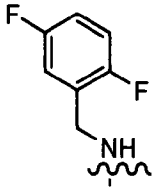
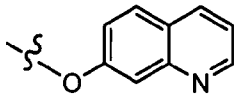
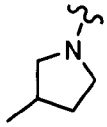
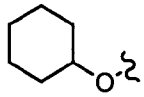
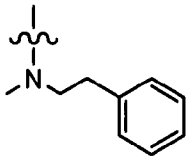
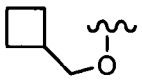
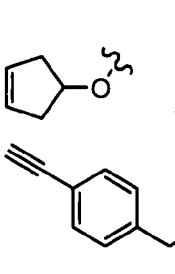
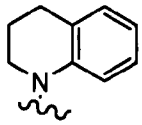
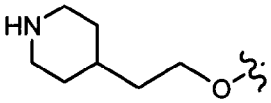
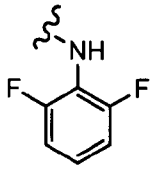
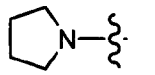
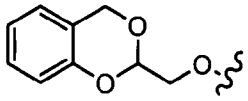
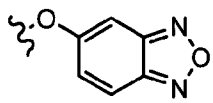




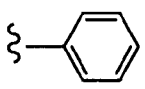
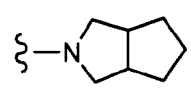
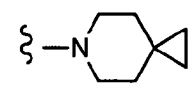
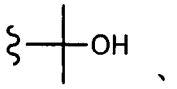
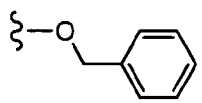
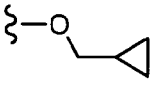
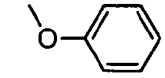
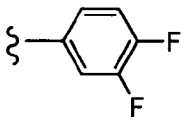
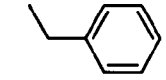
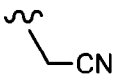
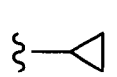


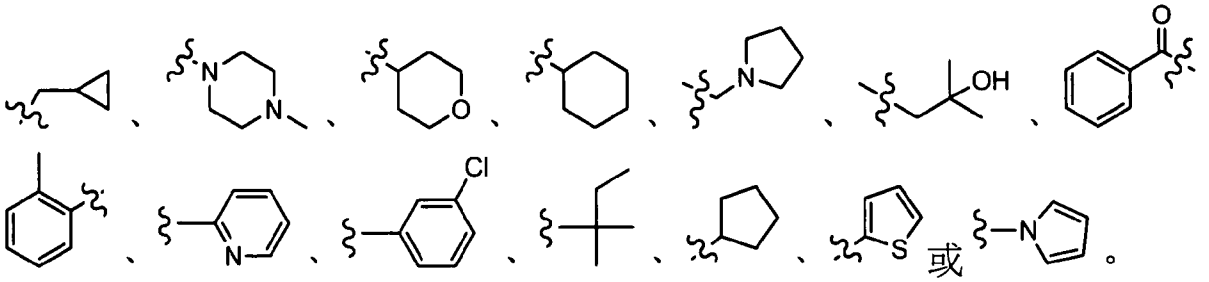
在一些實施例中，$R_2$爲鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜環；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

在一些實施例中，$R_2$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_2$爲Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、

$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、、  、  、  、  、、  、  或$CO_2H$。

在一些實施例中，$R_3$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中1至4個環原子中任一個獨立地爲O、S、N或NR的C3-C10雜芳基。

在一些實施例中，$R_3$爲藉由表1之化合物中所示之對應部分表示的基團。舉例而言，$R_3$爲Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、




在一些實施例中，o爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，n爲0。在一些實施例中，o爲1。在一些實施例中，o爲2。

在一些實施例中，p爲0。在一些實施例中，p爲1。在一些實施例中，p爲2。

在另一個實施例中，本發明提供含有其同位素標記形式之式I至Id-ii之化合物。式I至Id-ii之化合物之同位素標記形式與此化合物一致，除了化合物之一或多個原子已經原子質量或質量數不同於通常以更大天然豐度存在之原子之原子質量或質量數的原子置換。容易購得且可藉由熟知方法併入式I至Id-ii之化合物中的同位素之實例包括氫、碳、氮、氧、磷、氟及氯之同位素，分別例如$^{2}H$、$^{3}H$、$^{13}C$、$^{14}C$、$^{15}N$、$^{18}O$、$^{17}O$、$^{31}P$、$^{32}P$、$^{35}S$、$^{18}F$及$^{36}Cl$。含有一或多種以上提及之同位素及/或其他原子之其他同位素的式I至Id-ii之化合物、其前藥或每一者之醫藥學上可接受之鹽意欲爲本發明之一部分。式I至Id-ii之同位素標記化合物可以許多有益方式使用。舉例而言，已併入諸如$^{3}H$或$^{14}C$之放射性同位素的式I至In-i之同位素標記化合物適合於藥劑及/或受質組織分佈分析。此等放射性同位素，亦即氚($^{3}H$)及碳-14($^{14}C$)由於製備簡單及可偵測性優良而尤其較佳。例如氘($^{2}H$)之較重同位素併入式I至Id-ii之化合物由於此同位素標記化合物之代謝穩定性較高而具有治療優點。代謝穩定性較高直接轉換成活體內半衰期延長或劑量降低，此在大部分情形下將表示本發明之一個較佳實施例。式

I至Id-ii之同位素標記化合物可通常藉由進行本發明正文中實例部分及製備部分中合成流程及相關描述中所揭示之程序，用容易獲得之同位素標記反應物替換非同位素標記反應物來製備。

氘($^2H$)亦可併入式I至Id-ii之化合物中，以達成藉助於基本動力學同位素作用操縱化合物之氧化代謝的目的。基本動力學同位素作用爲由同位素核交換產生的化學反應之速率改變，同位素核交換又由此同位素交換後共價鍵形成所需之基態能量改變引起。較重同位素之交換通常降低化學鍵之基態能量且因此引起限速鍵斷裂的減少。若鍵斷裂發生在沿著多產物反應座標的鞍點區域中或附近，則可實質上改變產物分佈比率。出於解釋：若氘鍵結至不可交換位置之碳原子，則$k_M/k_D$ = 2-7之速率差異爲典型的。若此速率差異成功應用於易於氧化之式I至Id-ii之化合物，則此化合物在活體內之型態可大幅度改變且提高藥物動力學特性。關於另一論述，參見S. L. Harbeson及R. D. Tung, *Deuterium In Drug Discovery and Development*, Ann. Rep. Med. Chem. 2011, 46, 403-417，其以全文引用的方式併入本文中。

當發現及研發治療劑時，熟習此項技術者嘗試在保留所希望之活體外特性時使藥物動力學參數達至最佳。合理地假設許多具有不良藥物動力學型態之化合物易於氧化代謝。當前可用之活體外肝微粒體分析提供關於此類型氧化代謝過程之寶貴資訊，此又允許經由對此類氧化代謝之抗性合理設計具有提高穩定性之式I至Id-ii之氘化化合物。藉此獲得式I至Id-ii之化合物之藥物動力學型態的顯著改善，且可根據活體內半衰期($t_{1/2}$)、最大治療作用之濃度($C_{max}$)、劑量反應曲線下面積(AUC)及生物可用性的增加及根據清除率、劑量及材料成本之降低定量表述。

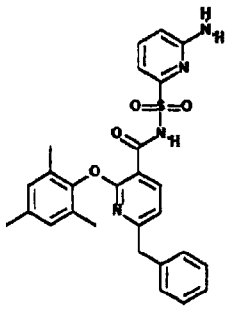
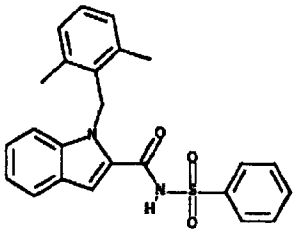
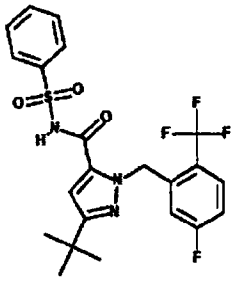
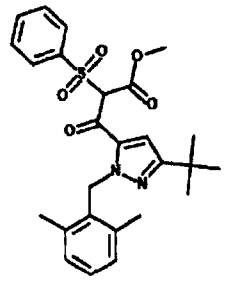
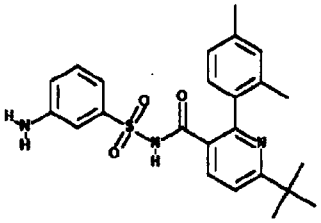
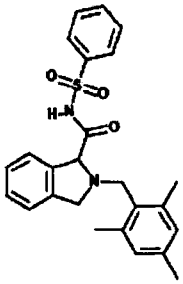
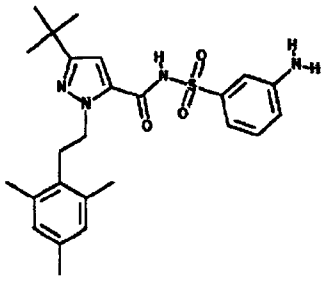
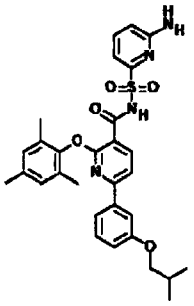
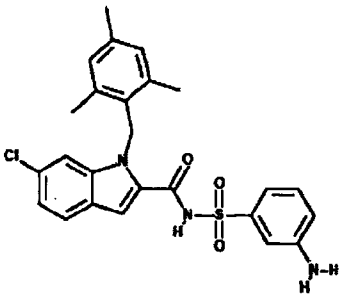
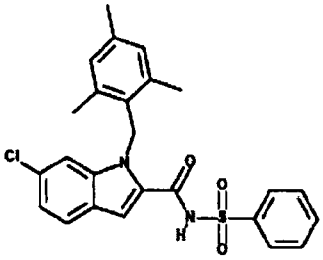
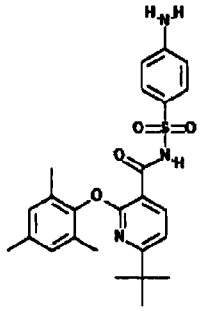
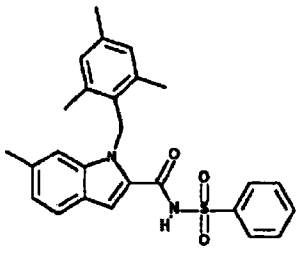
以下意欲說明以上：具有氧化代謝之多個潛在侵襲位點，例如苯甲基氫原子及鍵結至氮原子之氫原子的式I至Id-ii之化合物製備爲

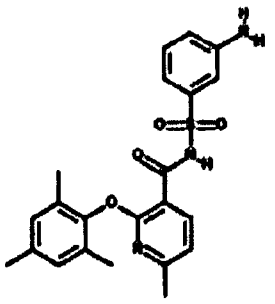
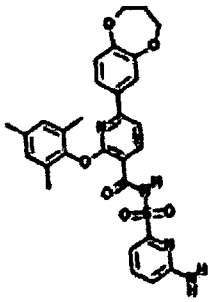
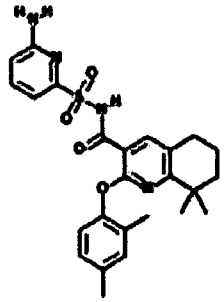
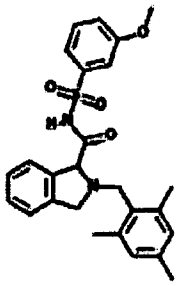
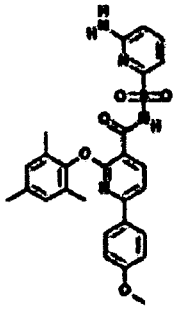
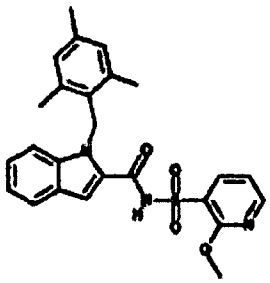
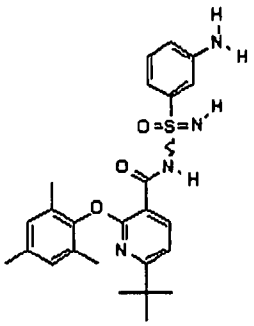
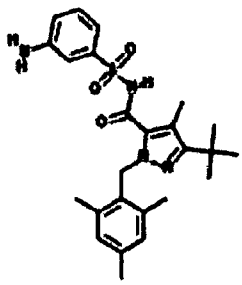
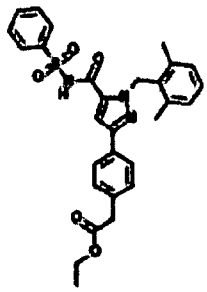
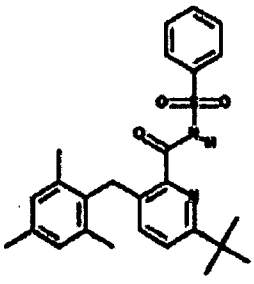
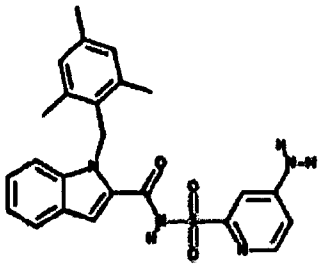
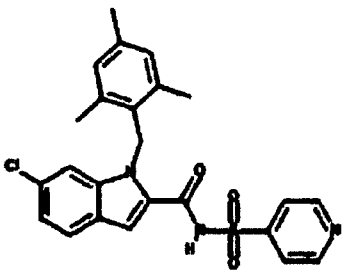
一系列類似物，其中氫原子之各種組合經氘原子置換，使得一些、大部分或所有此等氫原子經氘原子置換。半衰期之測定能夠有利且準確地測定對氧化代謝之抗性改善已改善的程度。以此方式，確定由於此類型之氘-氫交換，母體化合物之半衰期可延長多達100%。

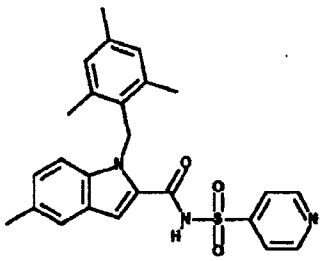
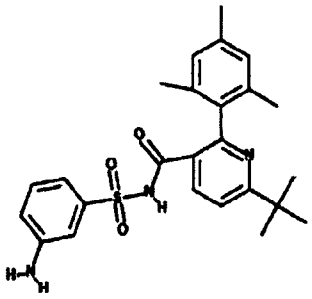
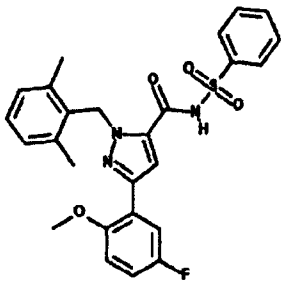
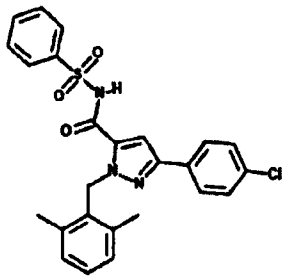
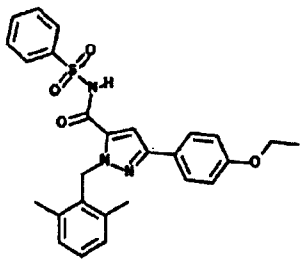
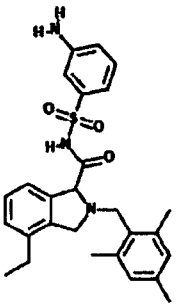
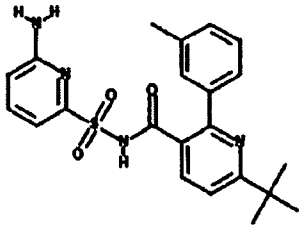
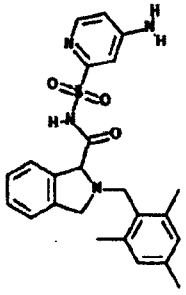
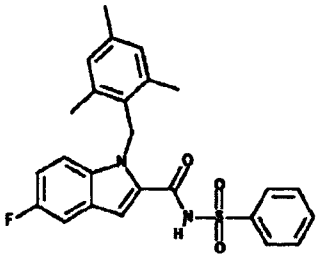
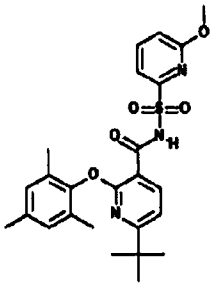
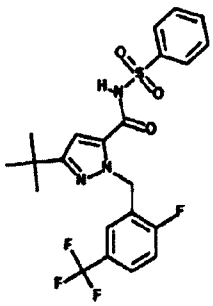
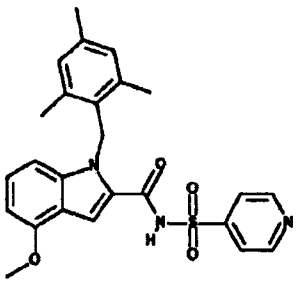
式I至Id-ii之化合物中的氘-氫交換亦可用於實現起始化合物之代謝物範圍的良好修改，從而減輕或消除不希望之毒性代謝物。舉例而言，若有毒代謝物經由氧化碳-氫(C-H)鍵裂解而出現，則可合理地假設，氘化類似物將大大減輕或消除不必要代謝物之產生，即使特定氧化不爲速率決定步驟亦如此。目前先進技術關於氘-氫交換之進一步資訊可見於例如Hanzlik等人, J. Org. Chem. 55, 3992-3997, 1990；Reider等人, J. Org. Chem. 52, 3326-3334, 1987；Foster, Adv. Drug Res. 14, 1-40, 1985；Gillette等人, Biochemistry 33(10) 2927-2937, 1994；及Jarman等人 Carcinogenesis 16(4), 683-688, 1993。

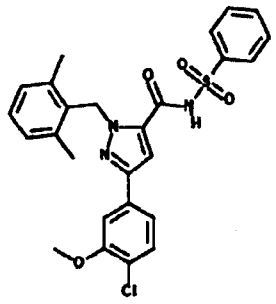
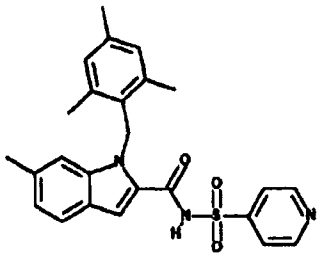
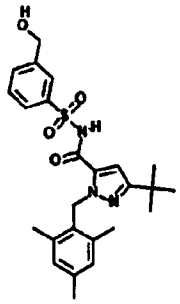
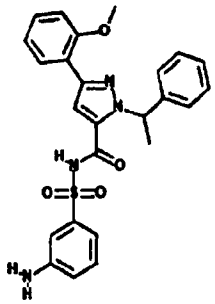
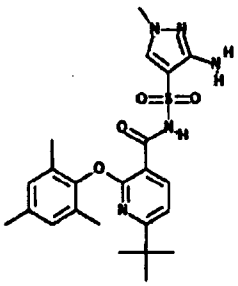
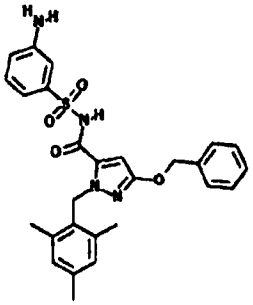
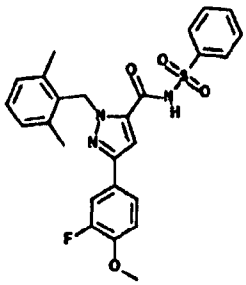
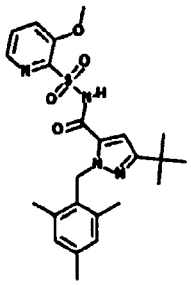
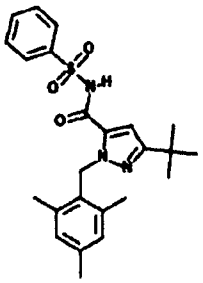
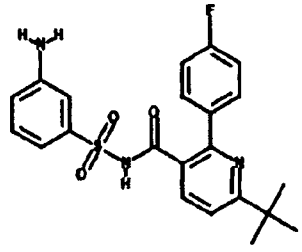
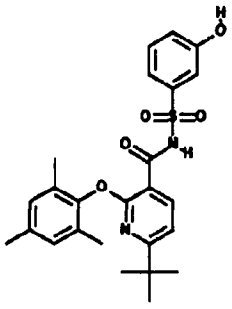
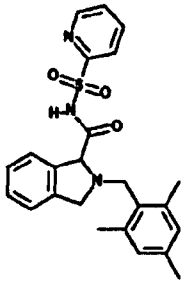
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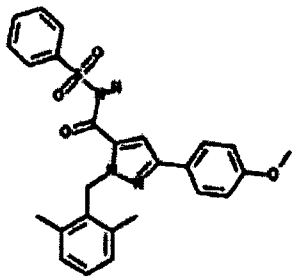
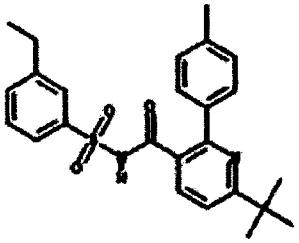
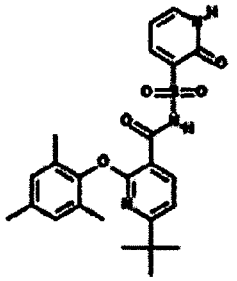
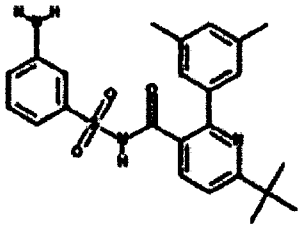
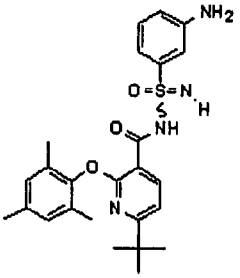
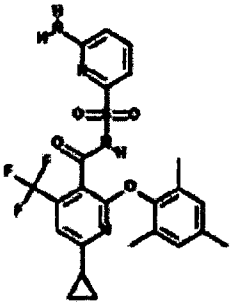
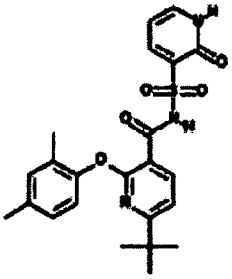
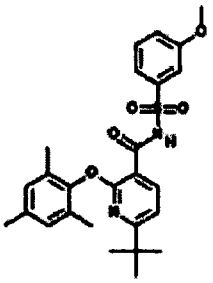
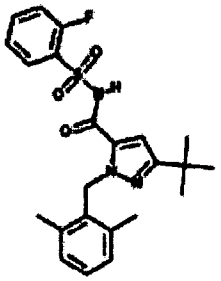
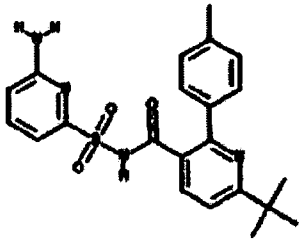
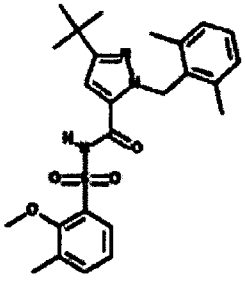
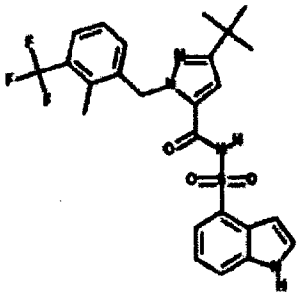
**表1.**

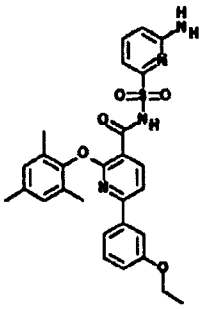
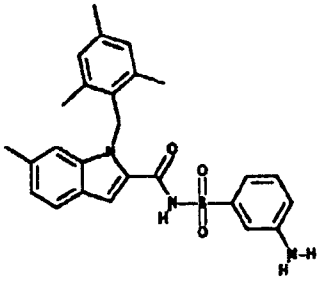
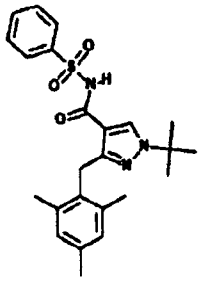
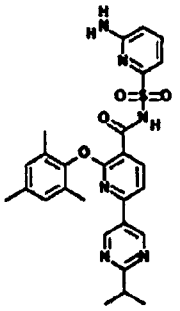
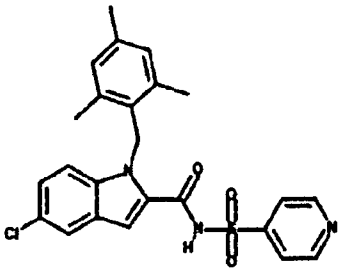
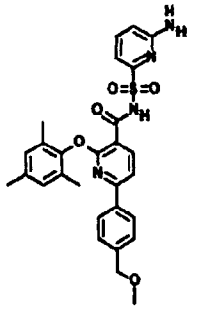
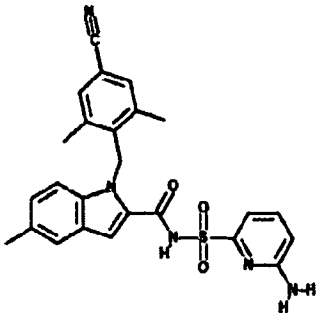
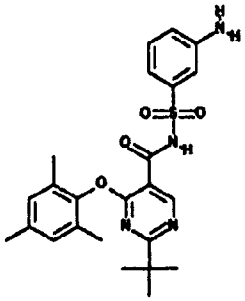
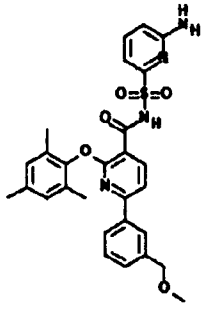
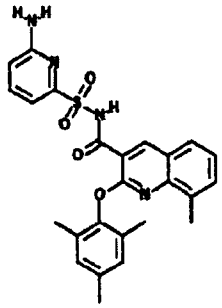
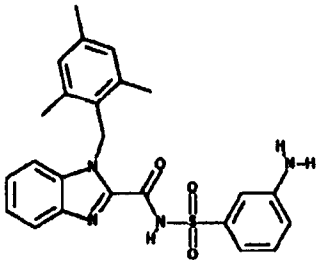
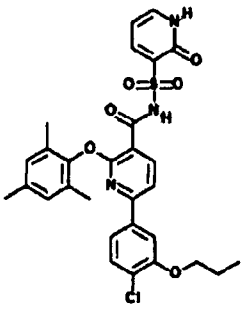
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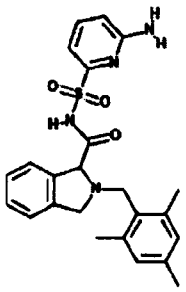
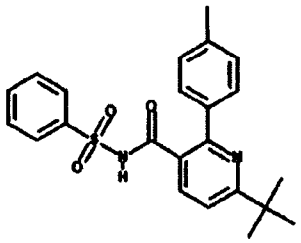
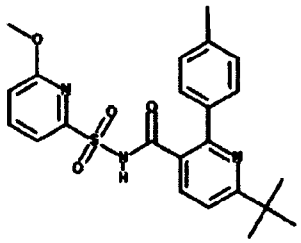
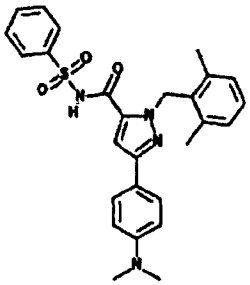
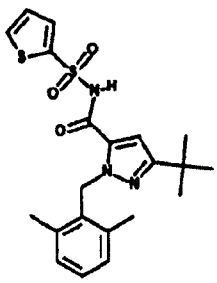
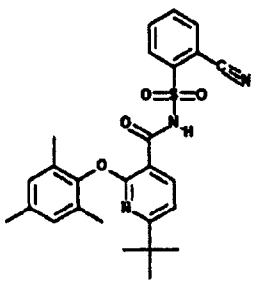
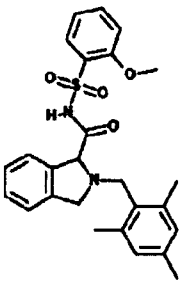
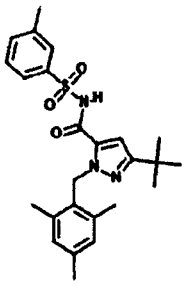
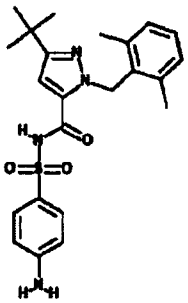
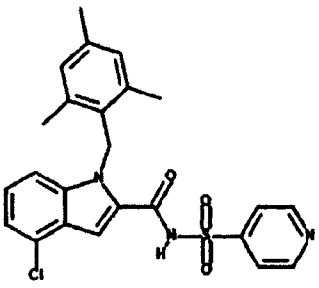
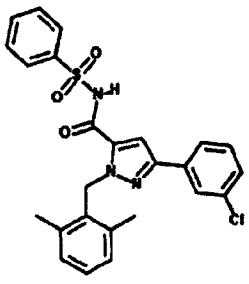
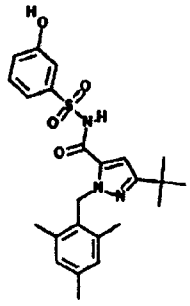
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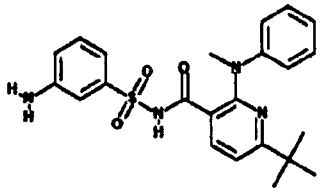
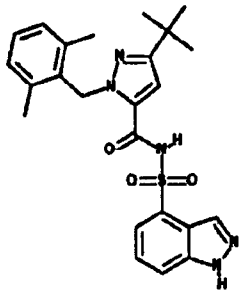
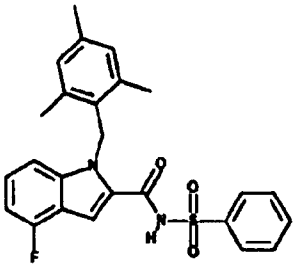
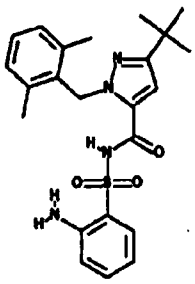
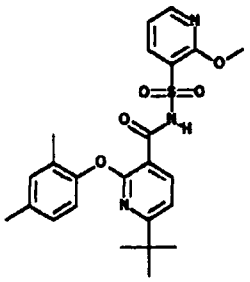
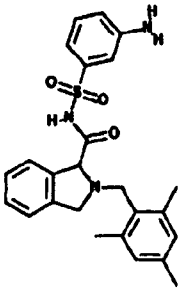
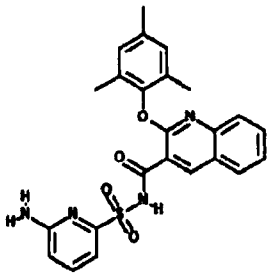
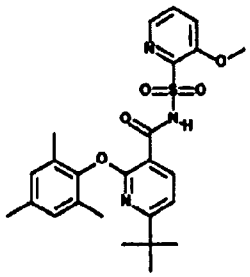
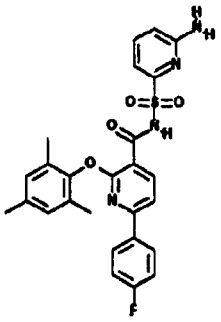
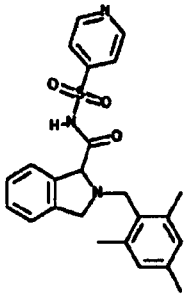
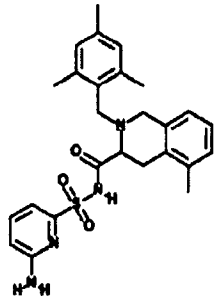
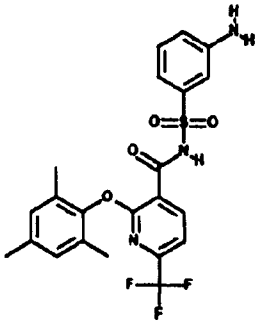
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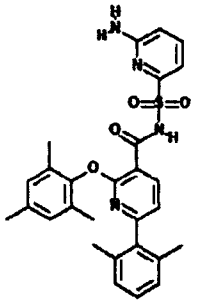
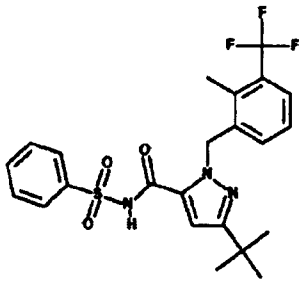
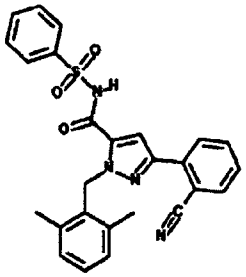
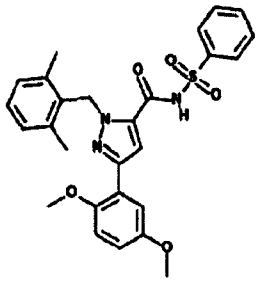
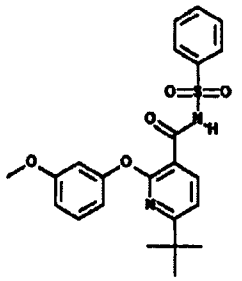
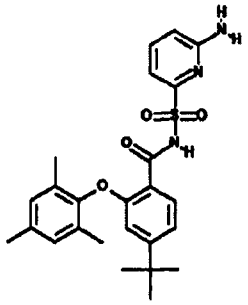
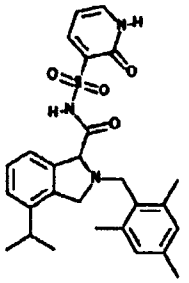
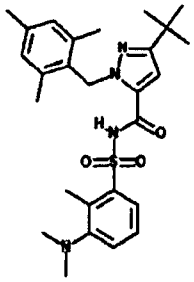
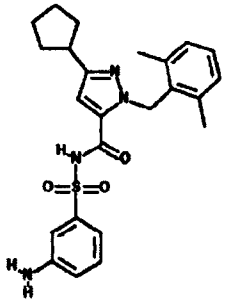
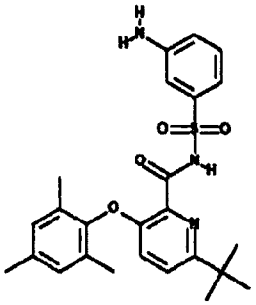
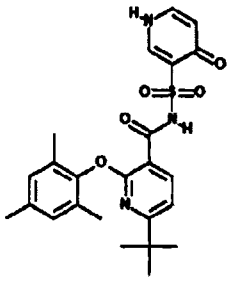
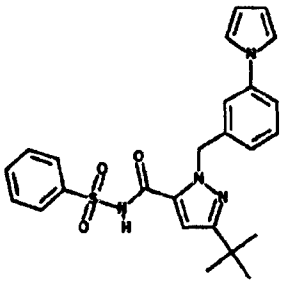
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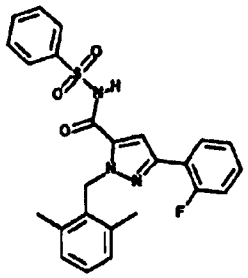
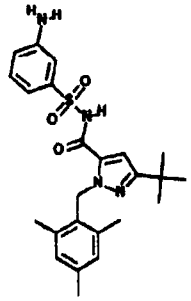
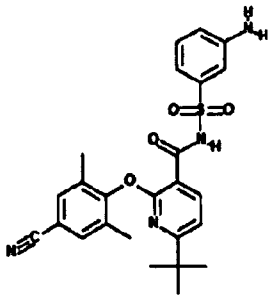
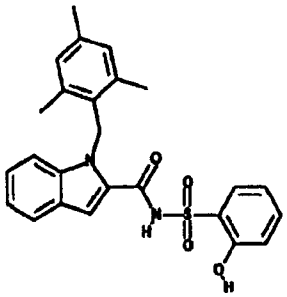
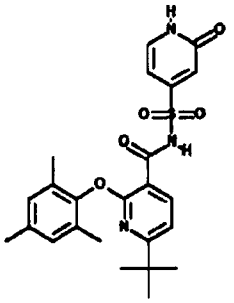
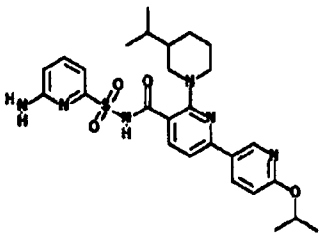
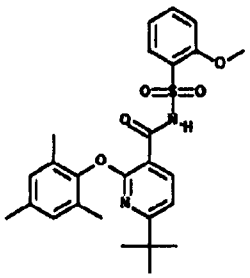
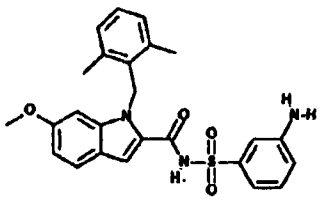
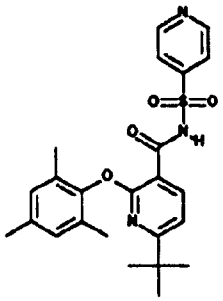
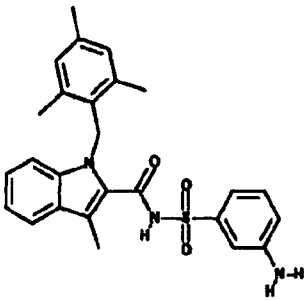
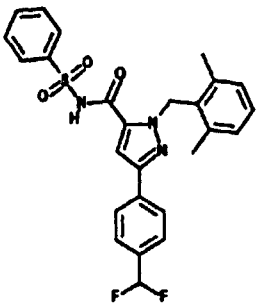
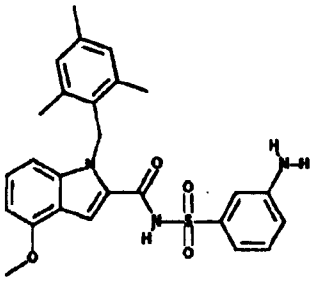
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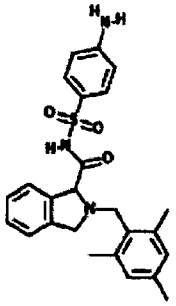
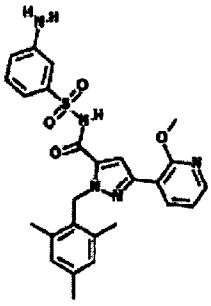
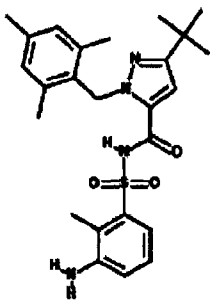
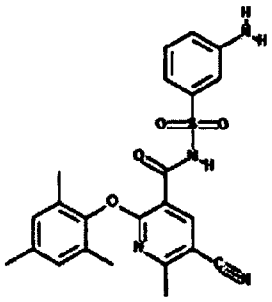
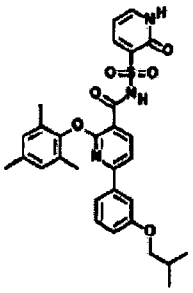
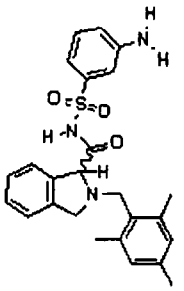
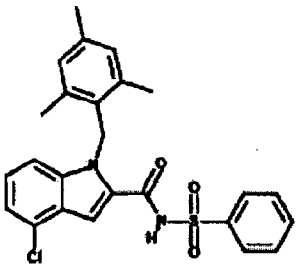
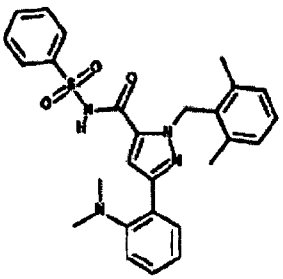
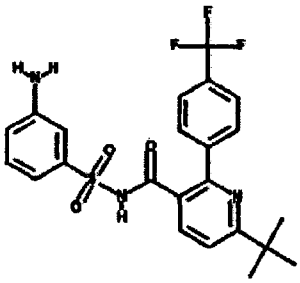
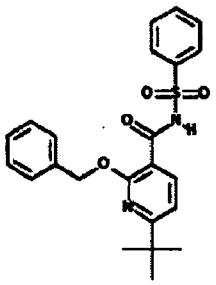
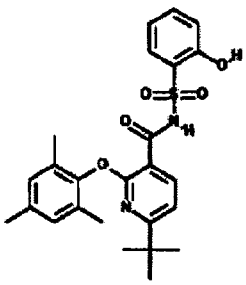
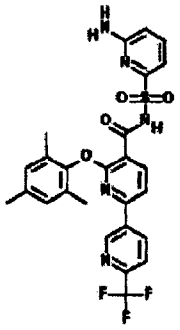
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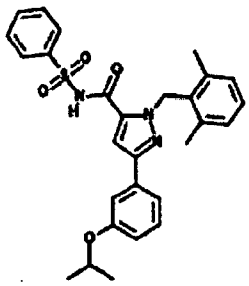
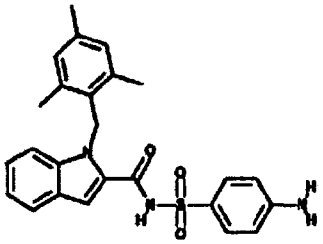
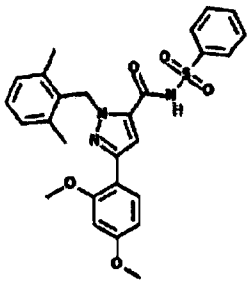
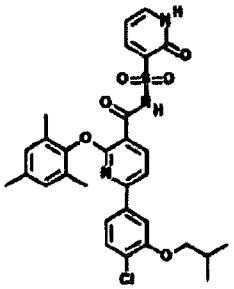
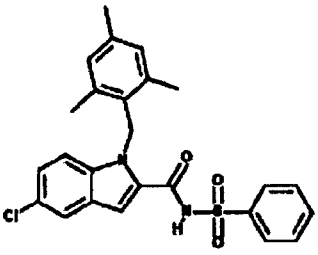
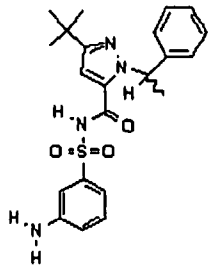
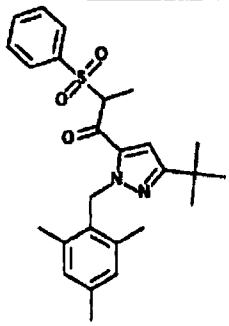
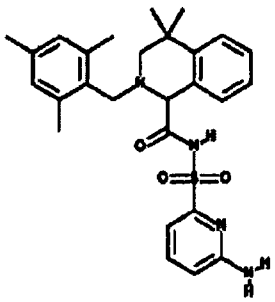
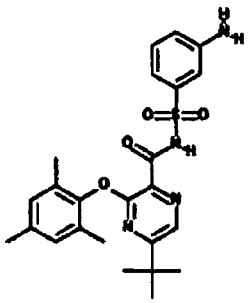
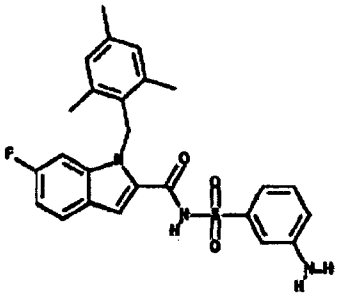
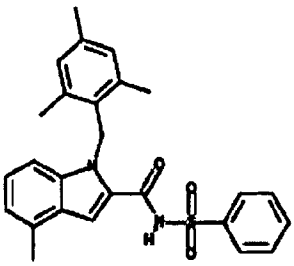
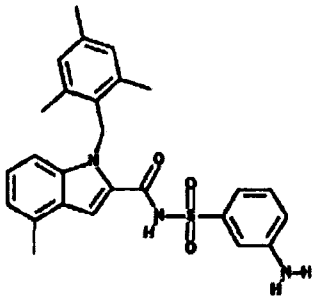
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| **76** | **77** | **78** |
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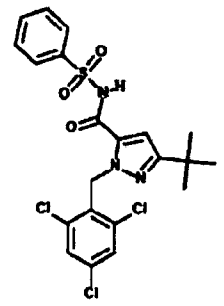
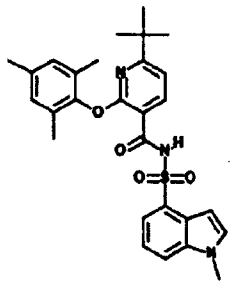
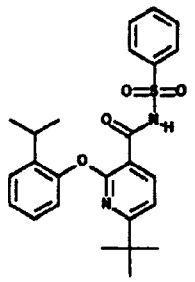
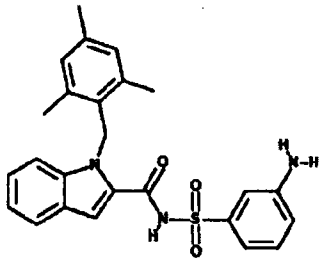
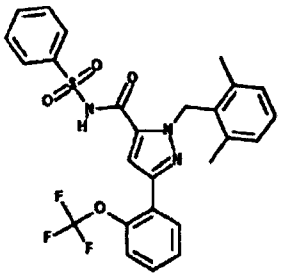
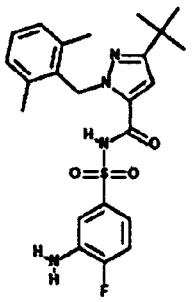
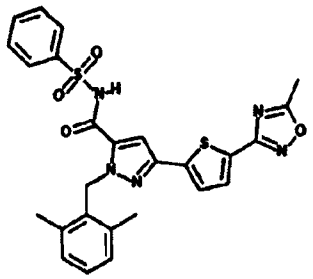
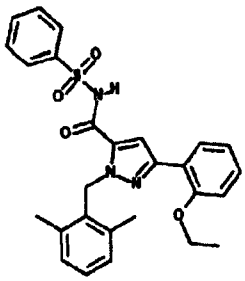
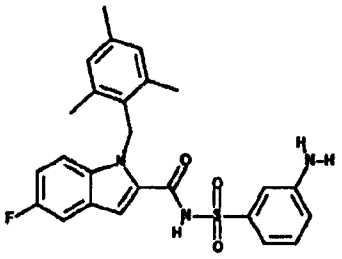
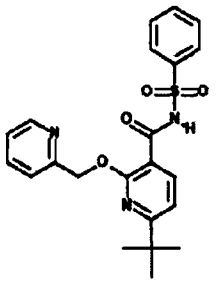
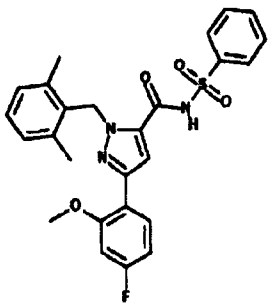
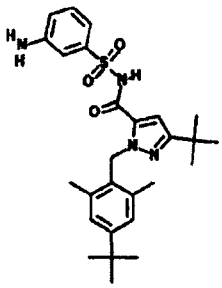
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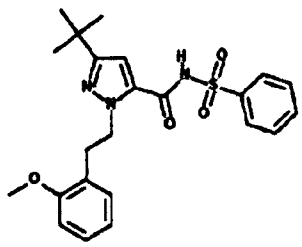
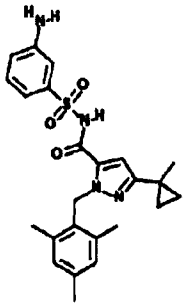
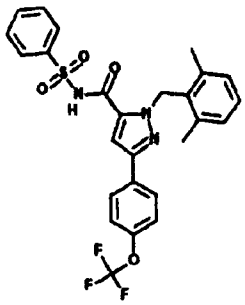
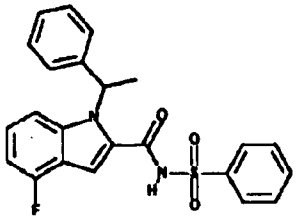
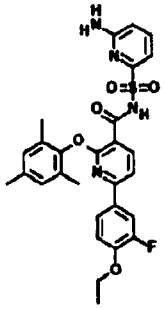
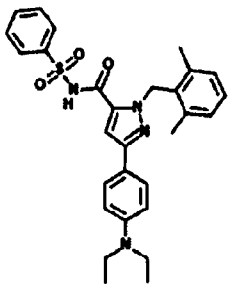
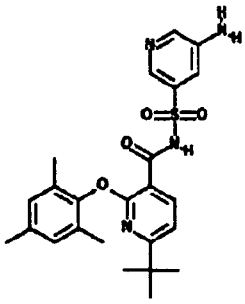
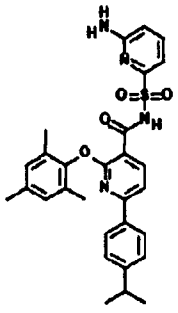
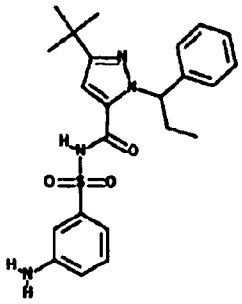
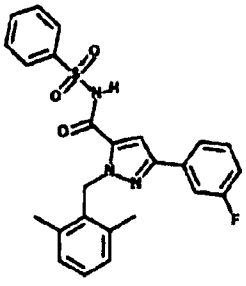
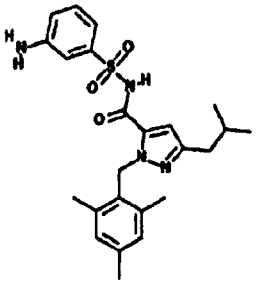
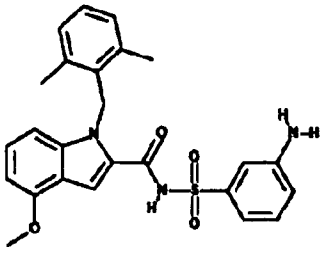
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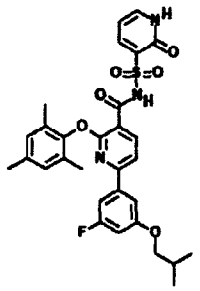
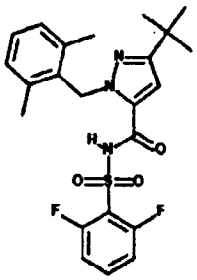
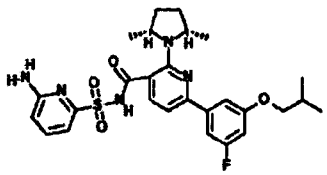
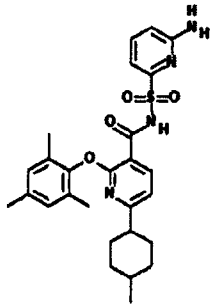
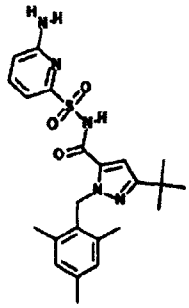
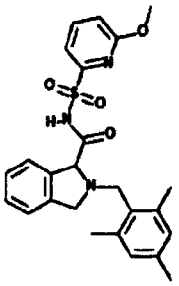
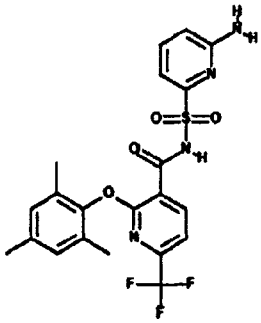
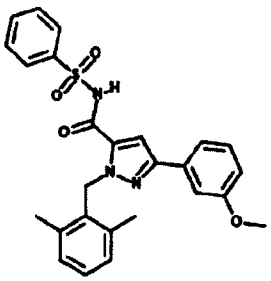
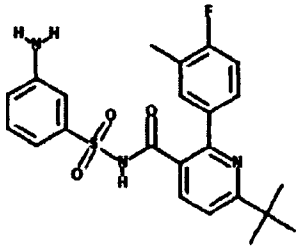
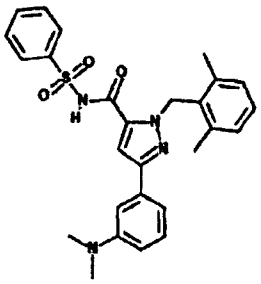
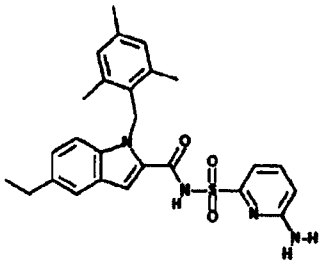
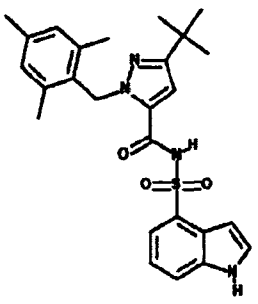
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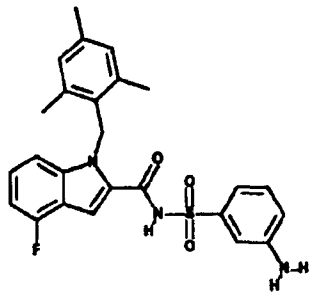
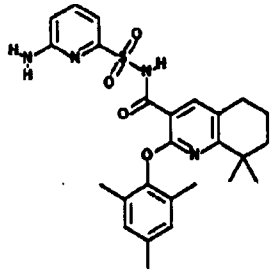
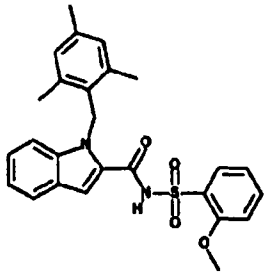
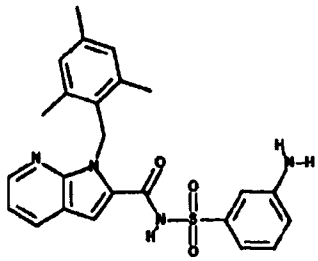
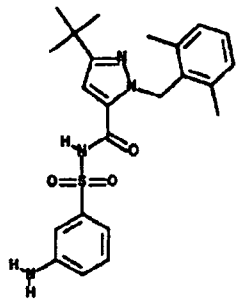
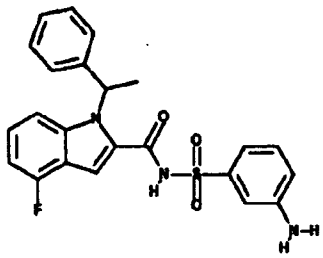
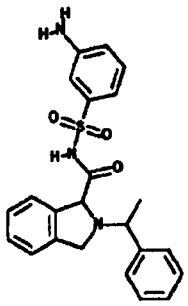
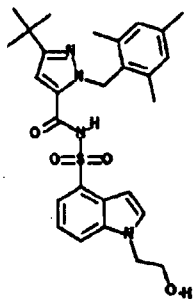
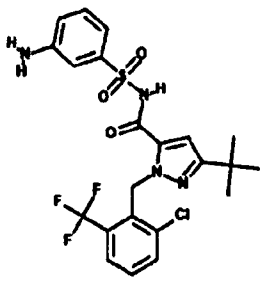
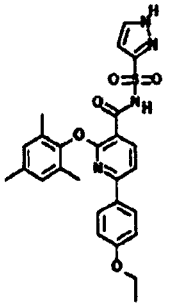
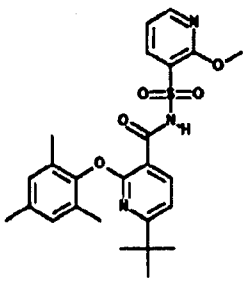
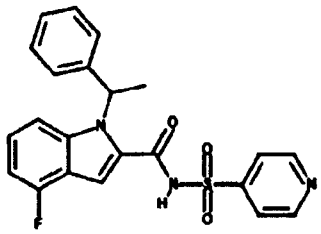
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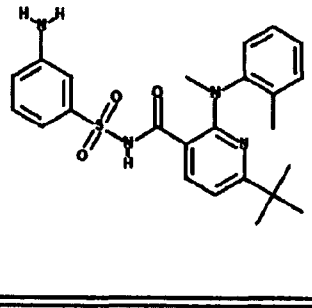
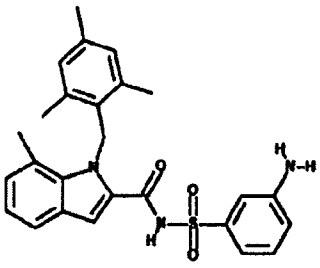
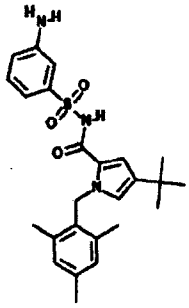
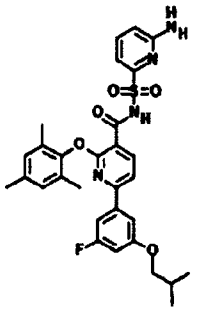
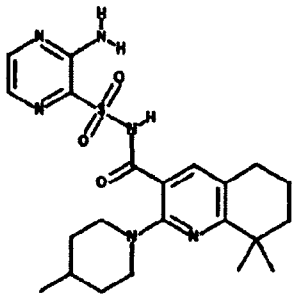
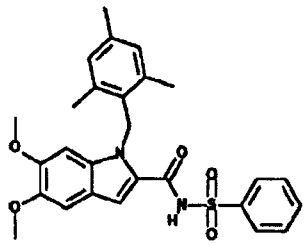
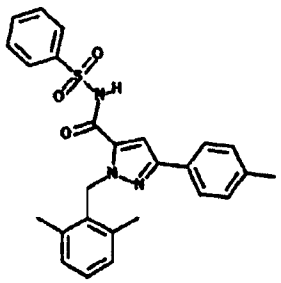
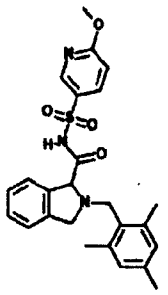
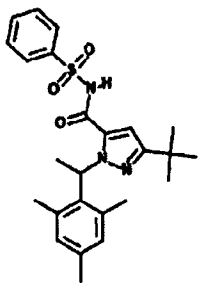
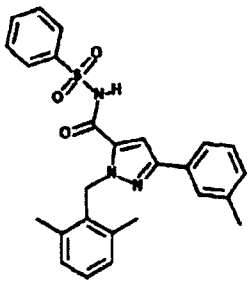
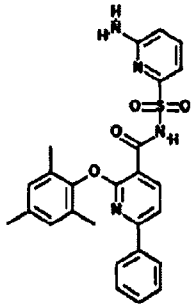
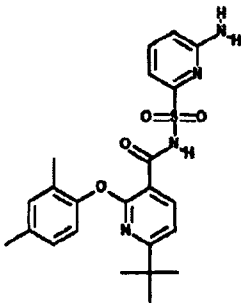
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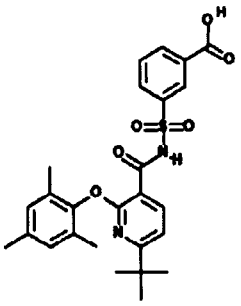
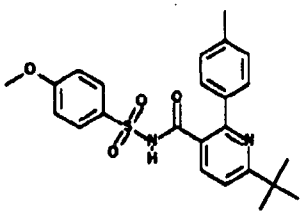
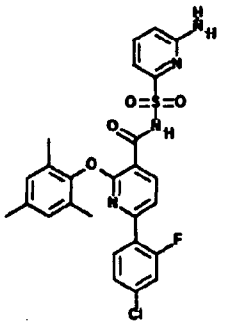
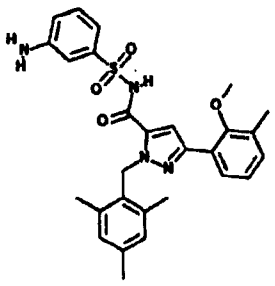
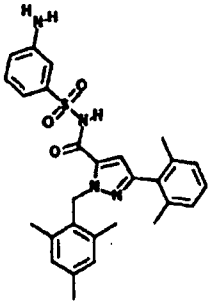
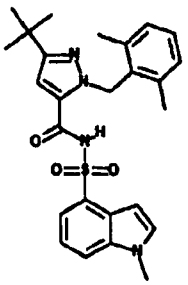
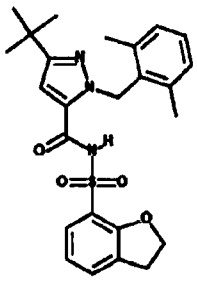
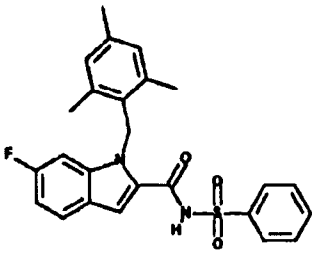
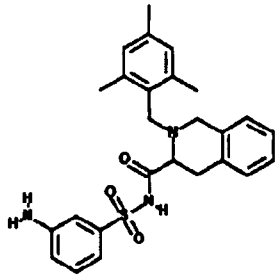
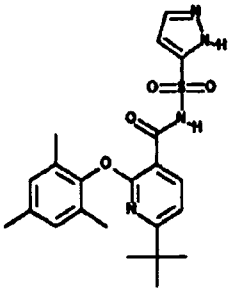
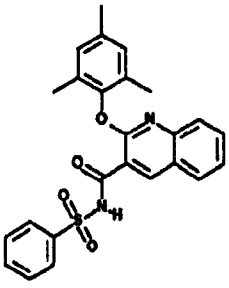
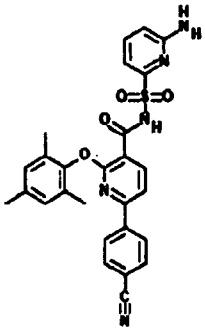
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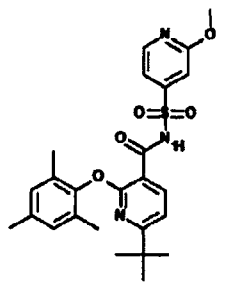
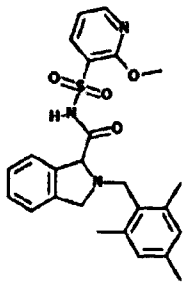
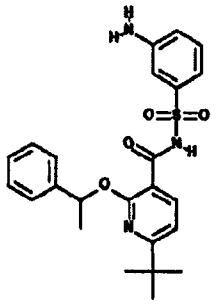
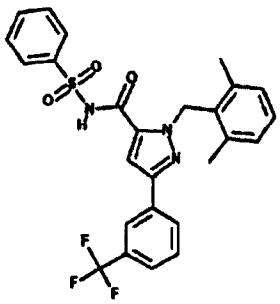
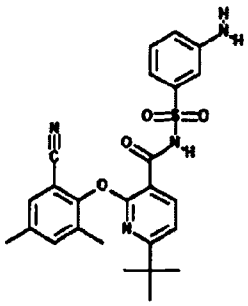
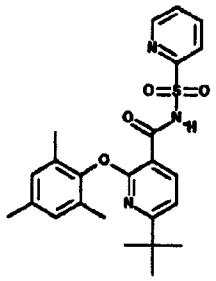
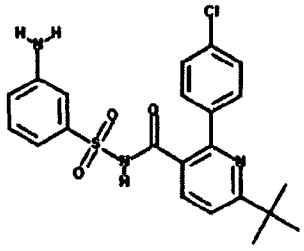
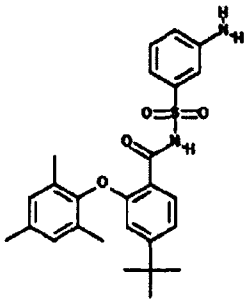
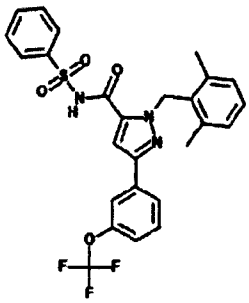
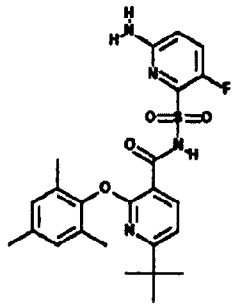
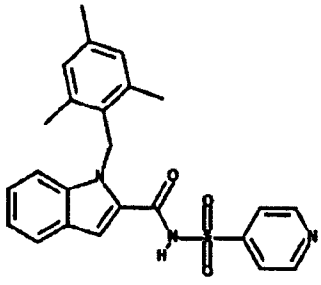
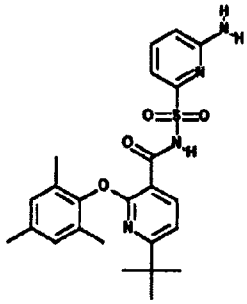
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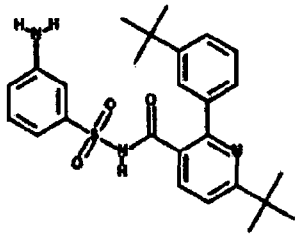
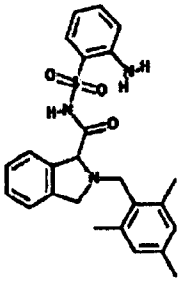
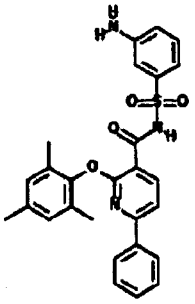
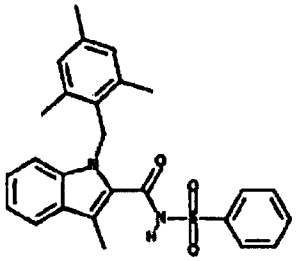
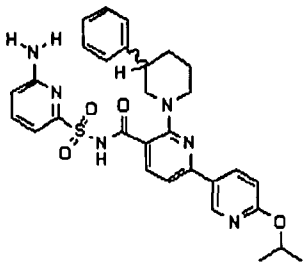
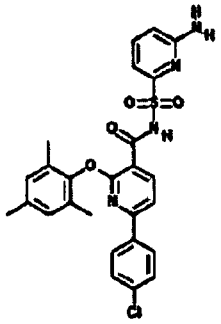
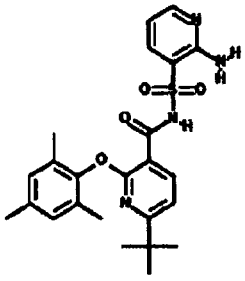
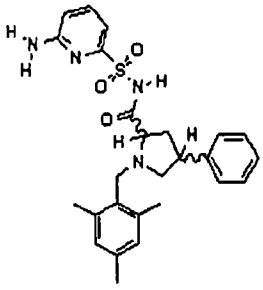
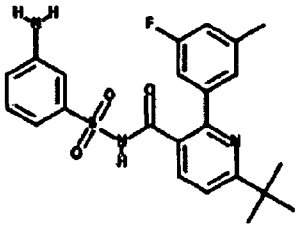
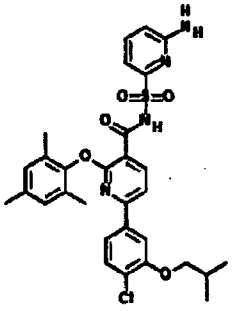
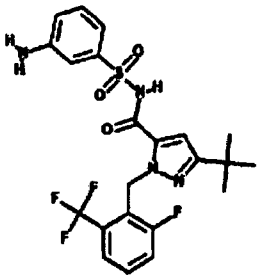
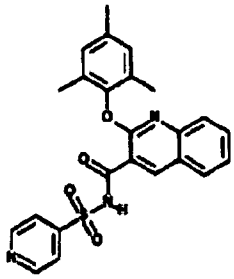
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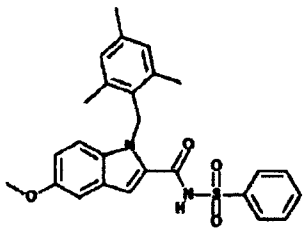
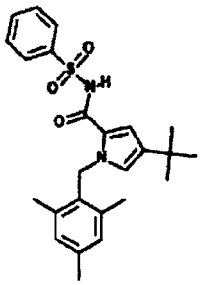
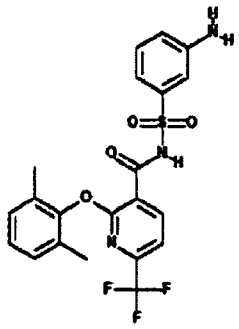
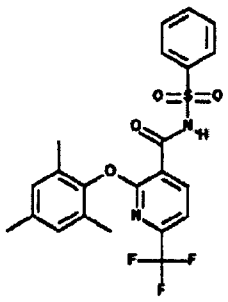
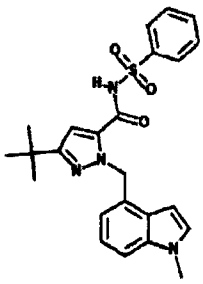
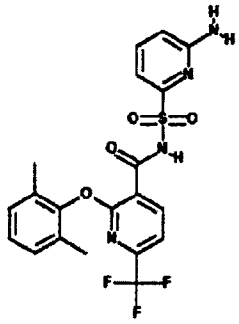
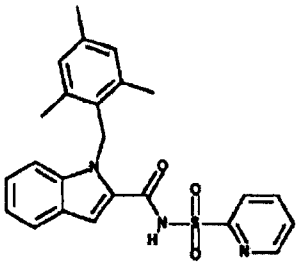
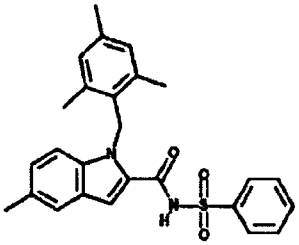
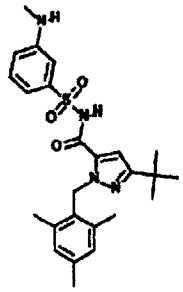
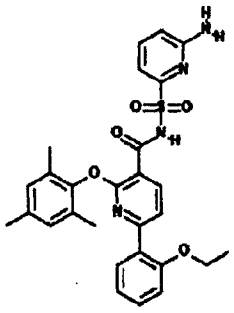
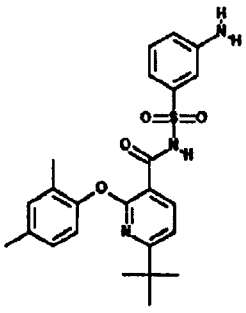
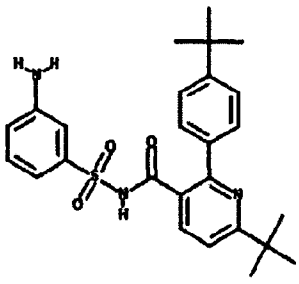
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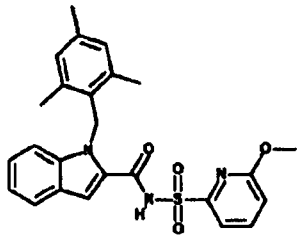
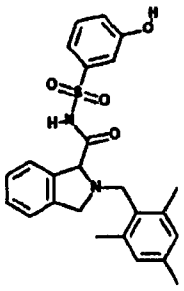
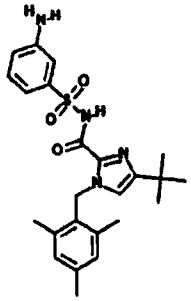
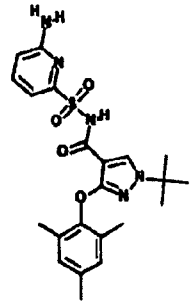
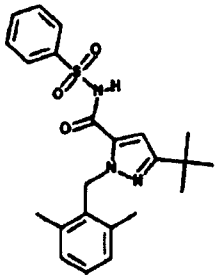
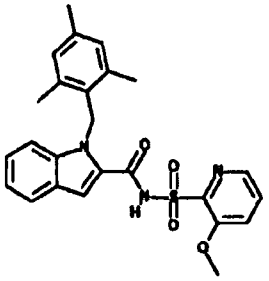
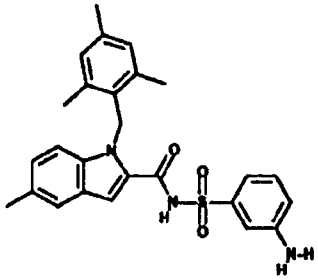
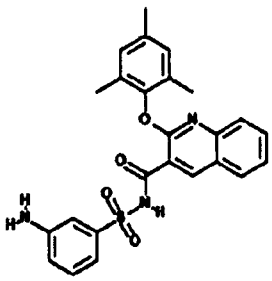
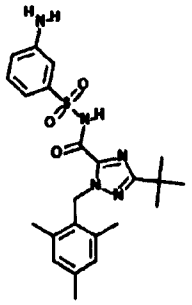
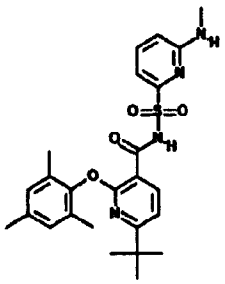
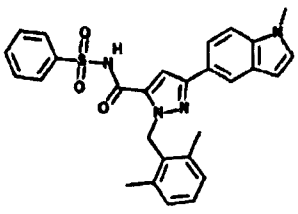
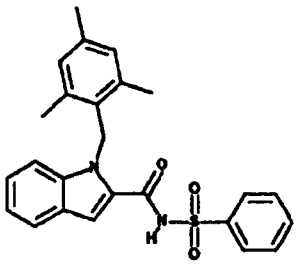
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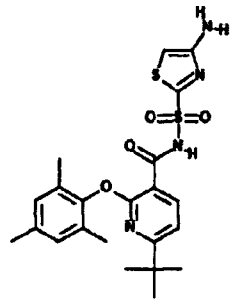
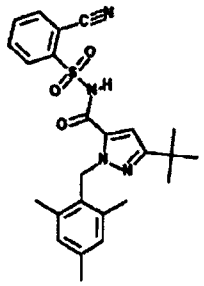
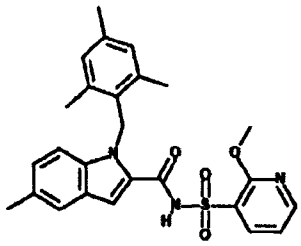
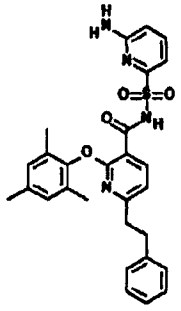
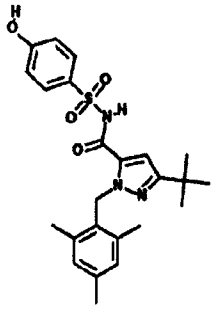
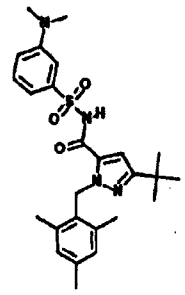
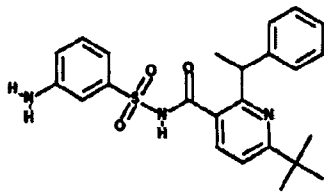
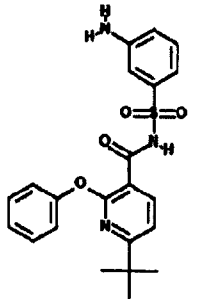
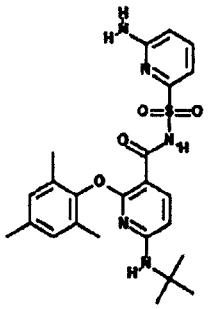
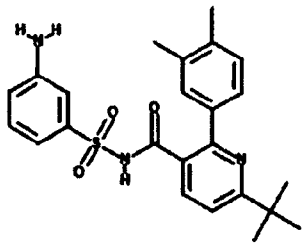
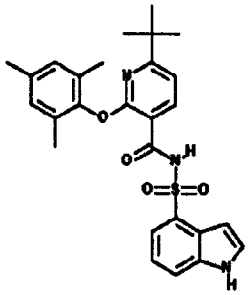
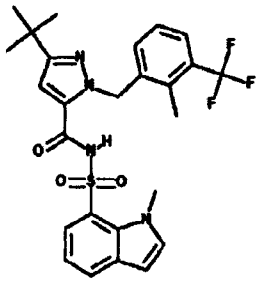
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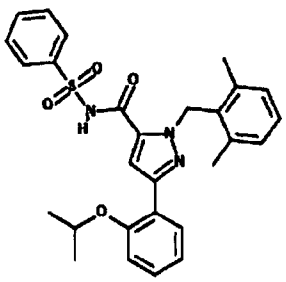
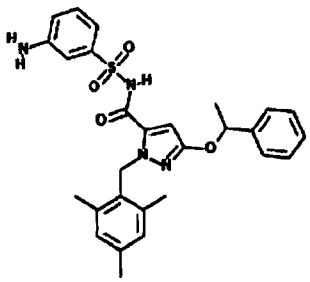
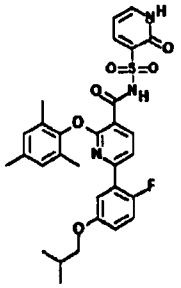
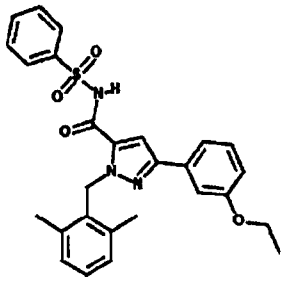
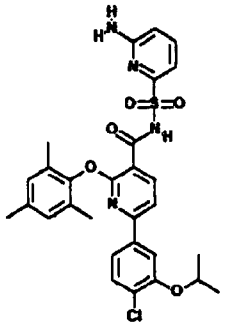
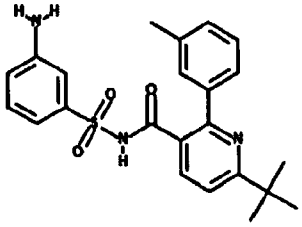
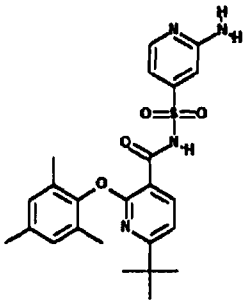
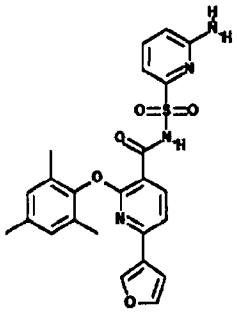
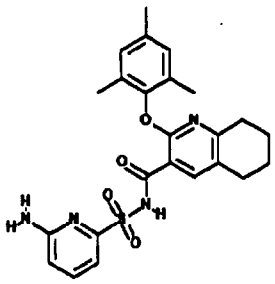
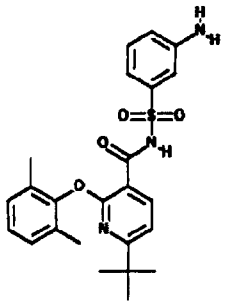
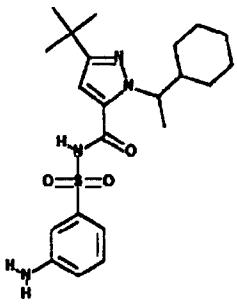
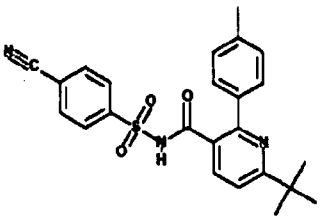
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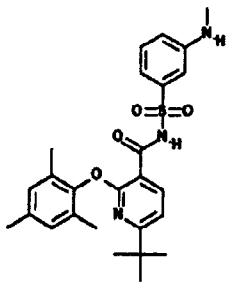
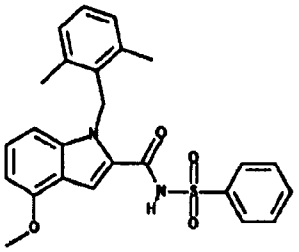
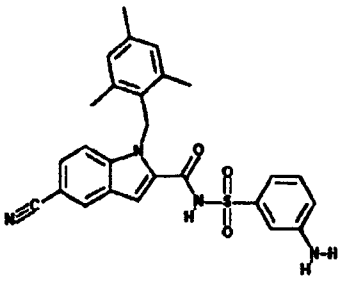
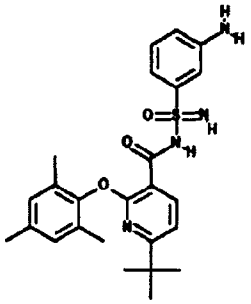
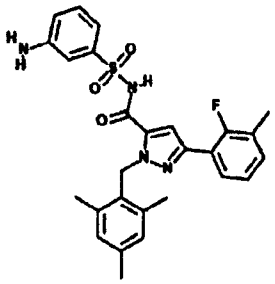
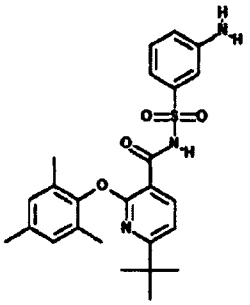
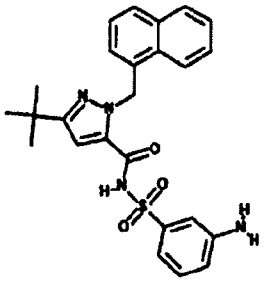
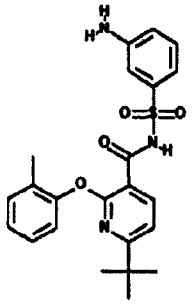
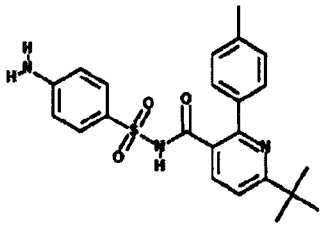
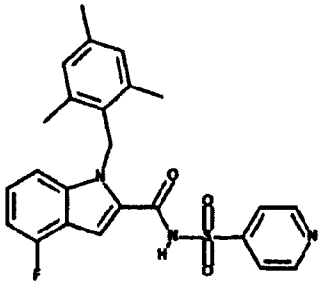
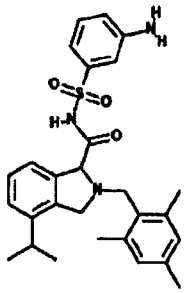
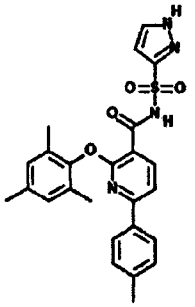
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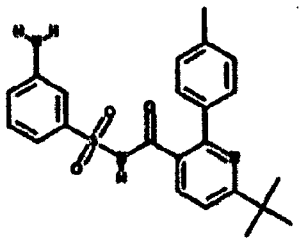
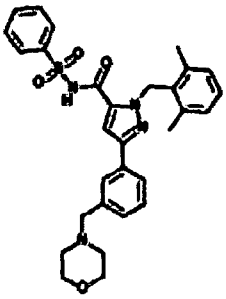
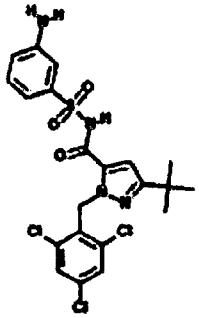
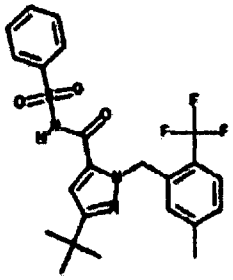
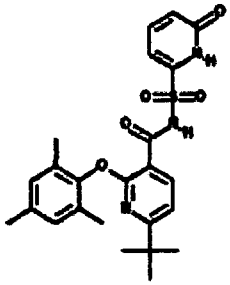
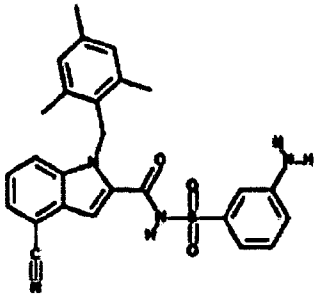
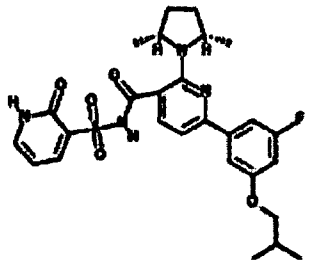
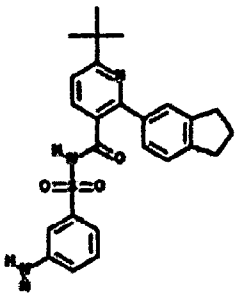
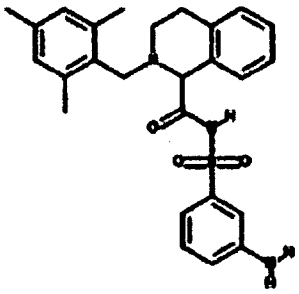
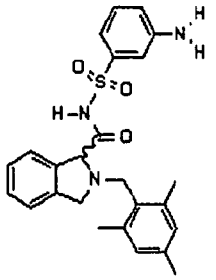
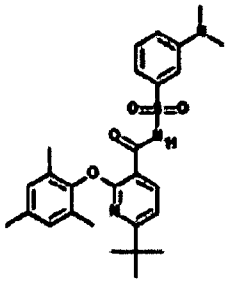
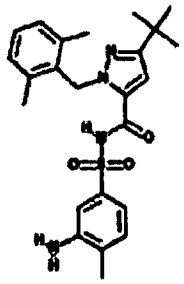
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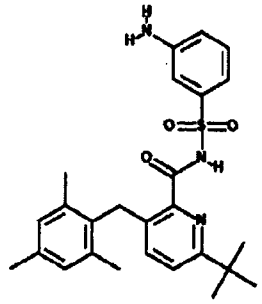
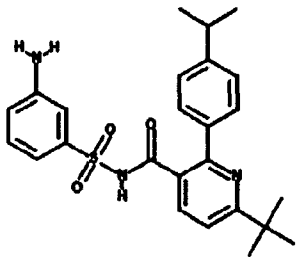
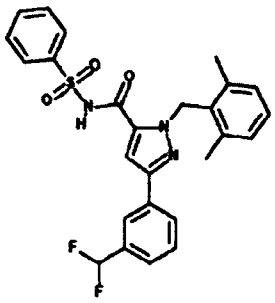
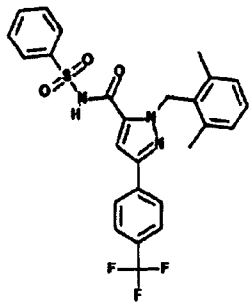
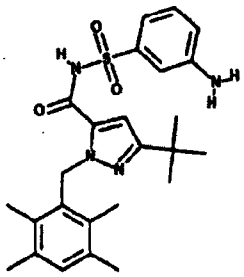
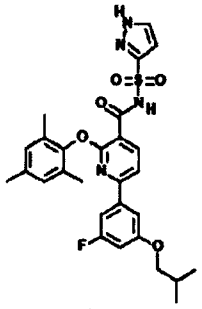
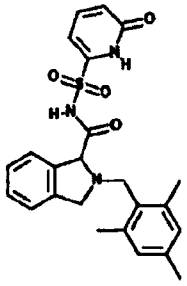
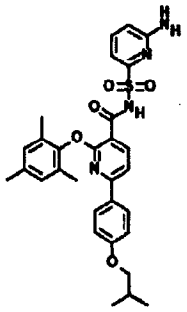
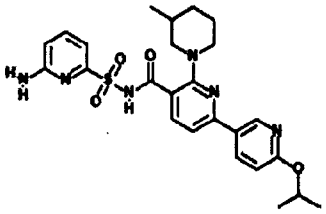
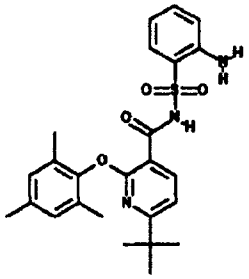
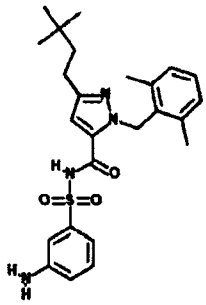
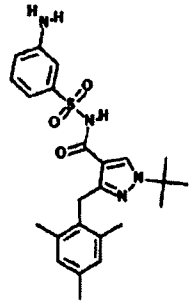
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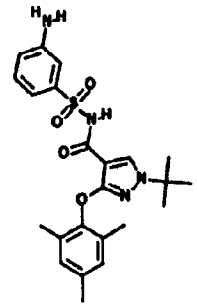
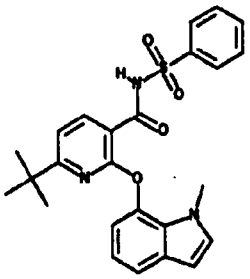
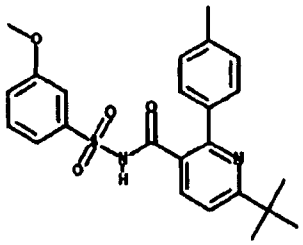
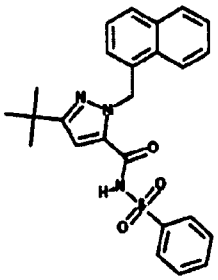
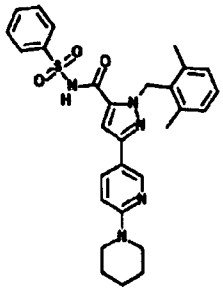
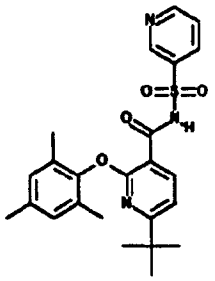
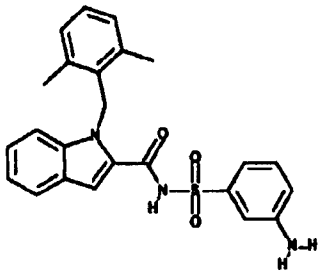
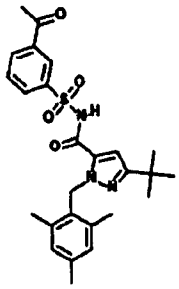
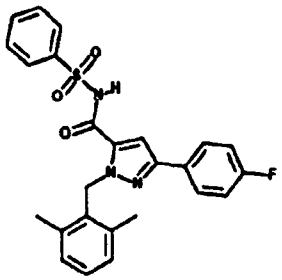
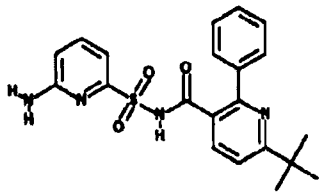
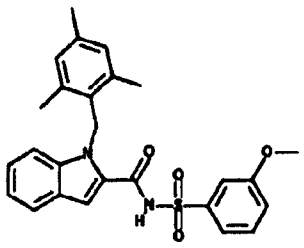
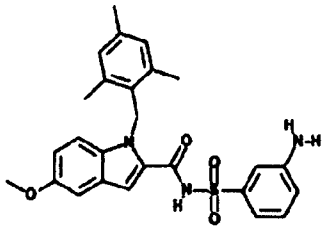
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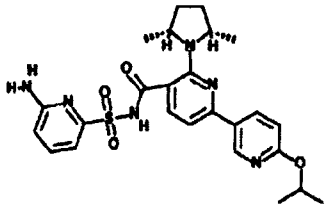
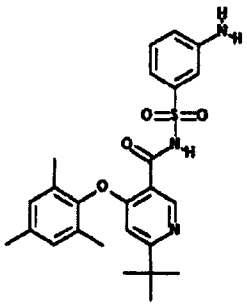
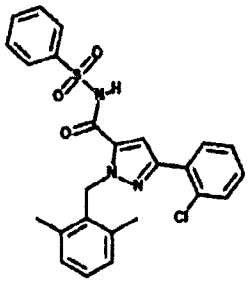
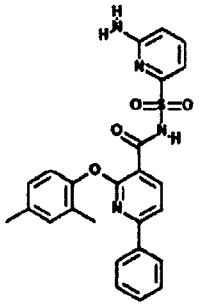
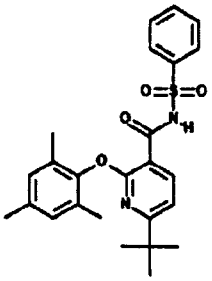
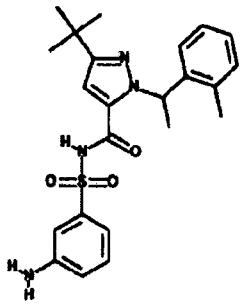
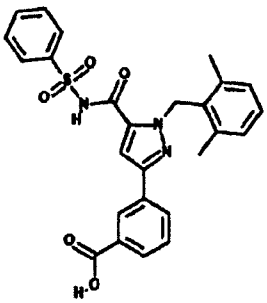
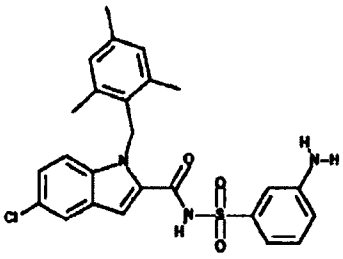
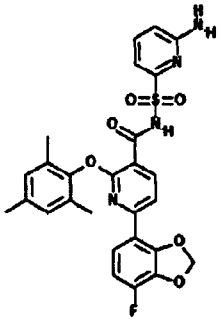
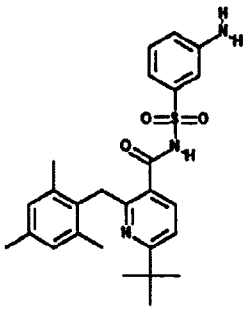
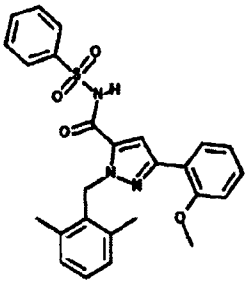
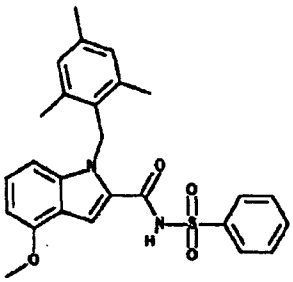
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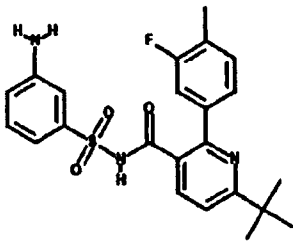
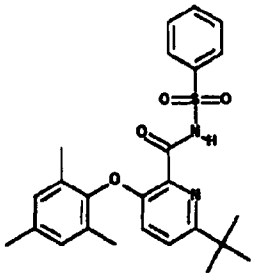
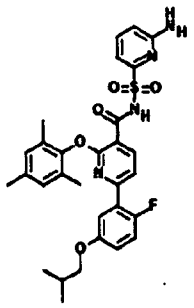
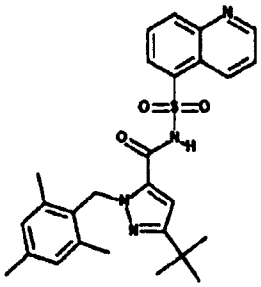
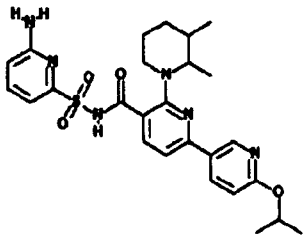
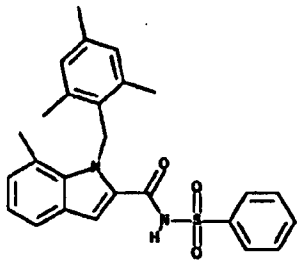
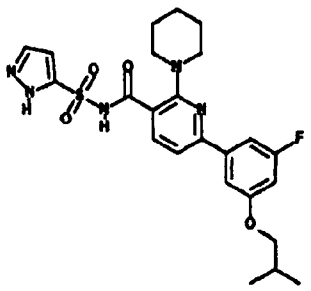
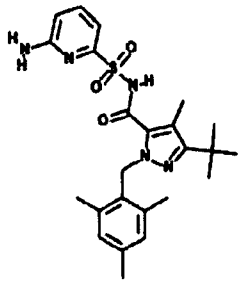
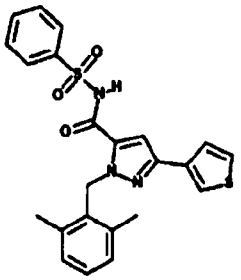
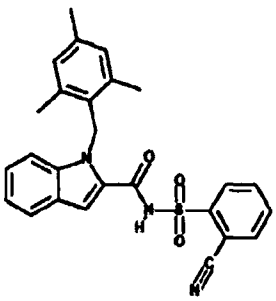
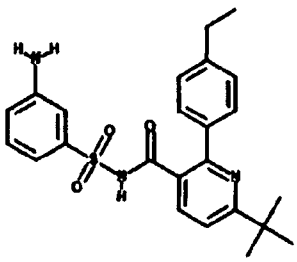
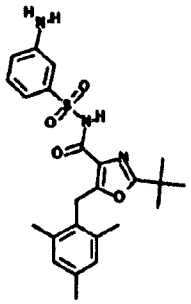
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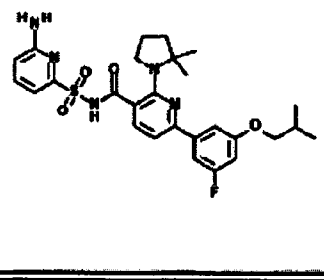
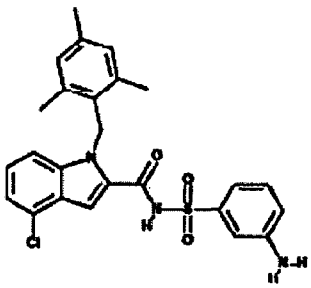
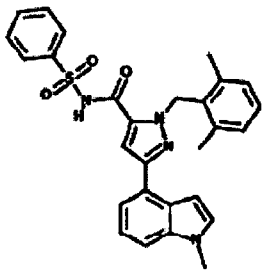
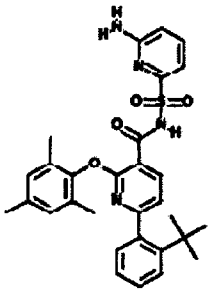
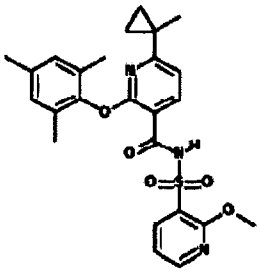
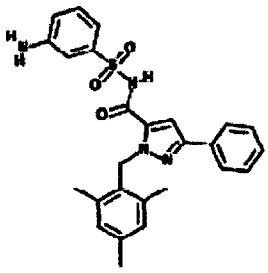
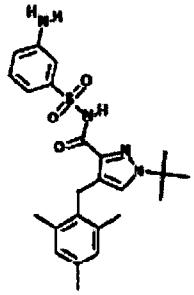
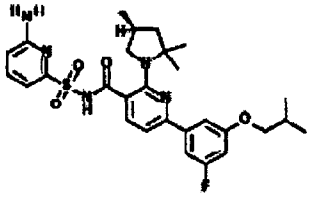
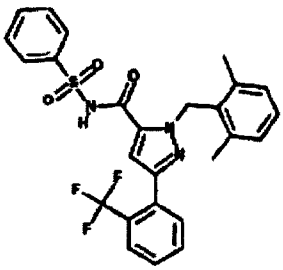
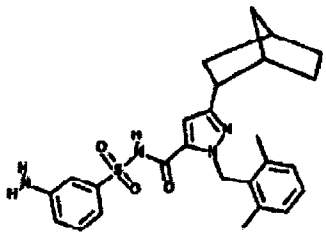
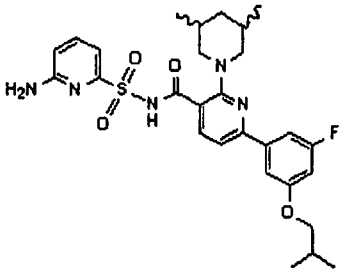
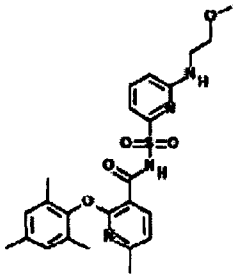
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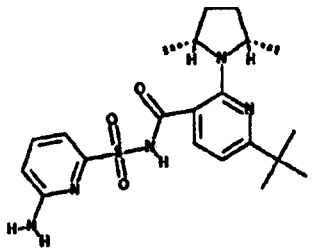
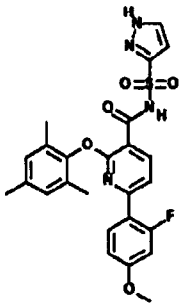
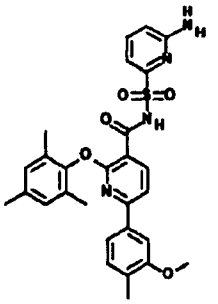
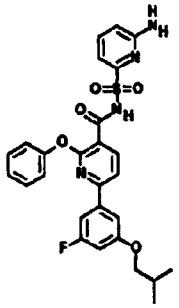
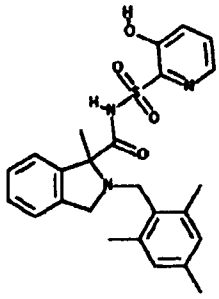
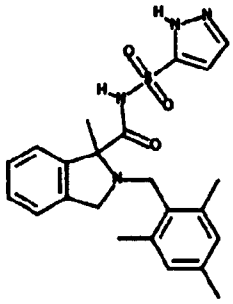
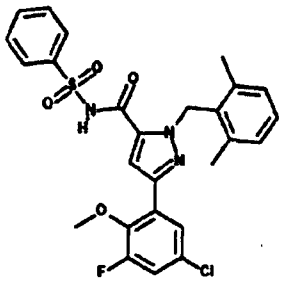
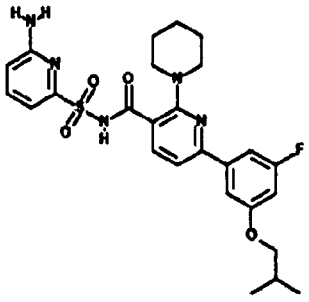
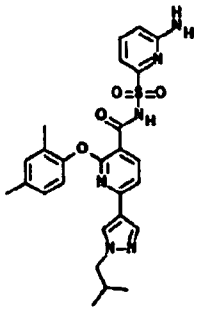
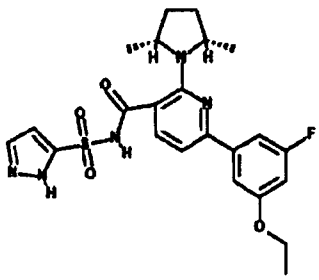
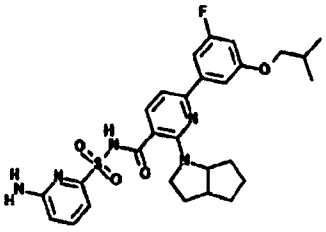
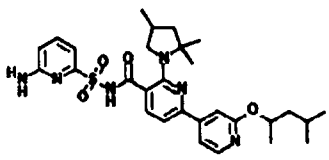
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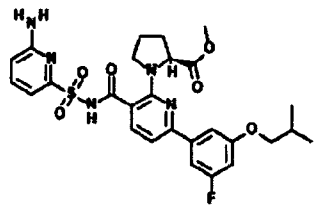
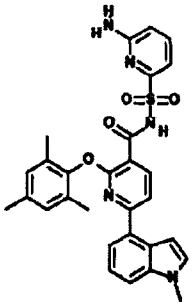
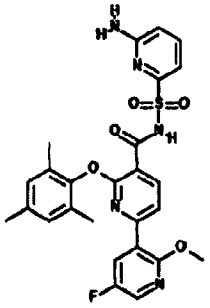
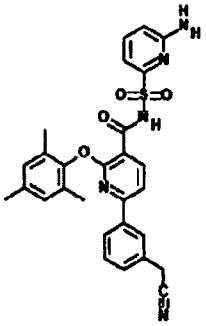
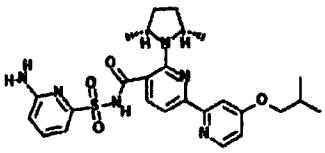
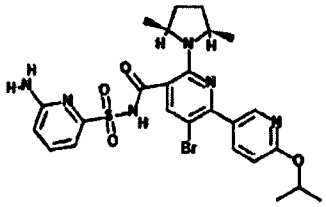
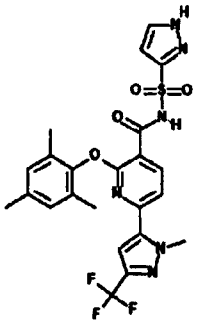
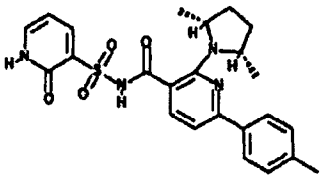
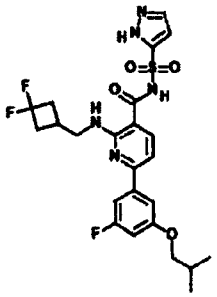
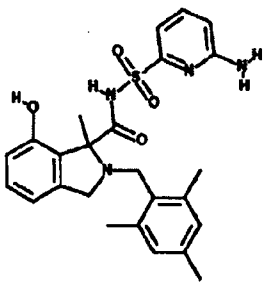
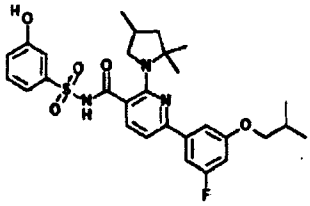
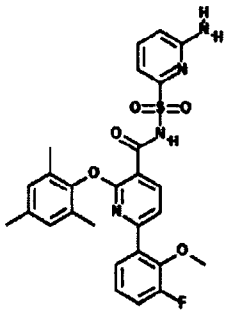
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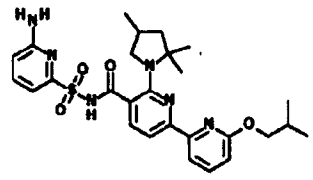
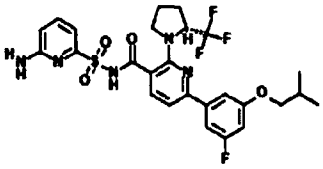
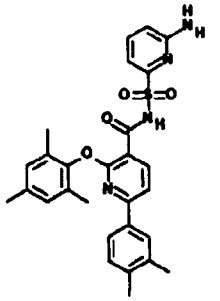
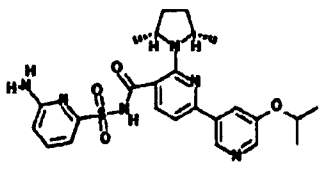
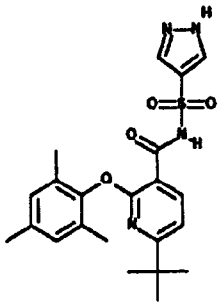
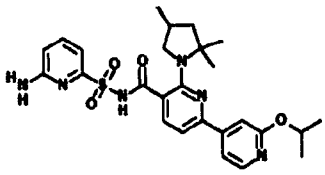
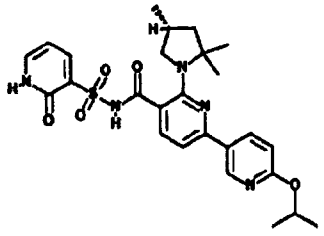
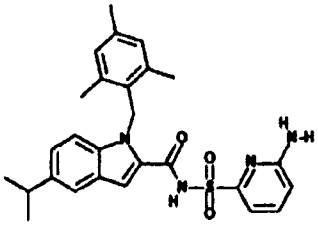
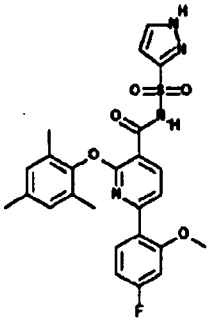
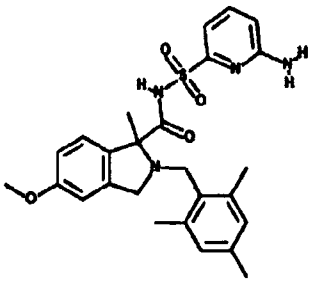
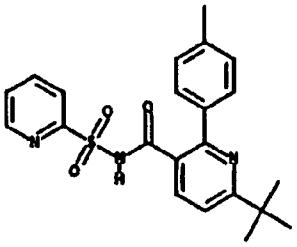
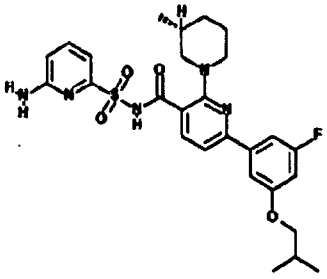
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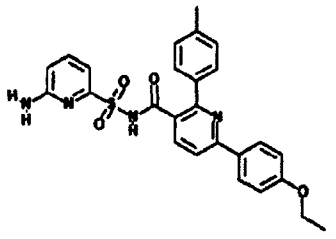
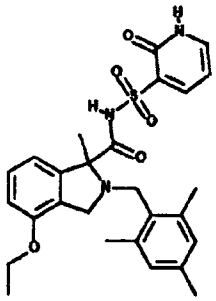
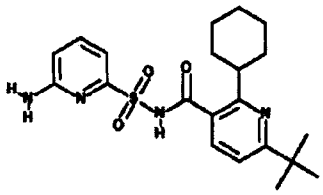
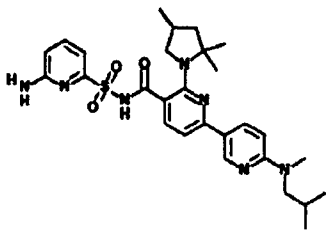
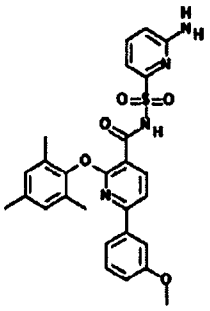
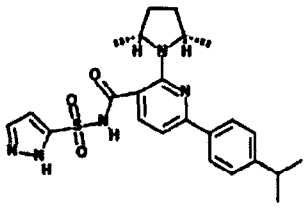
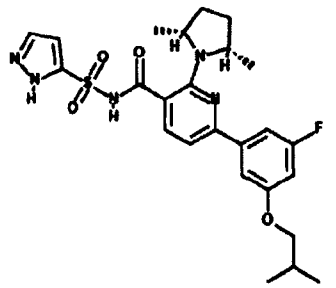
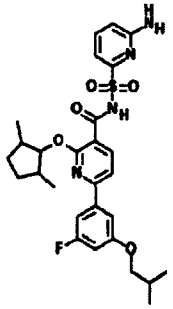
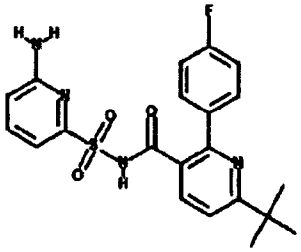
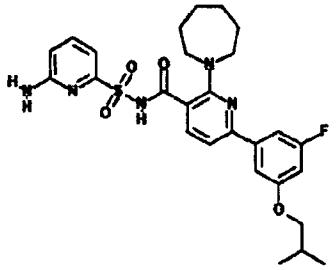
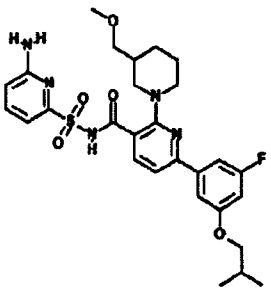
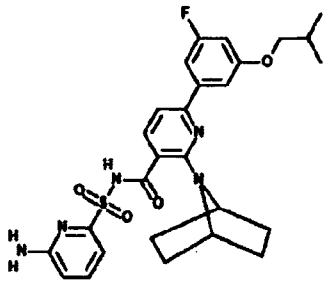
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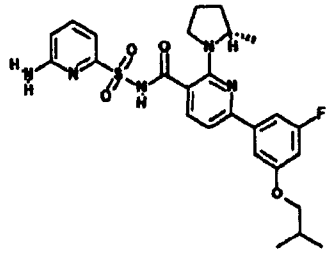
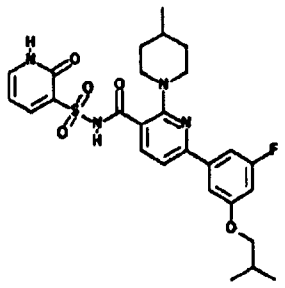
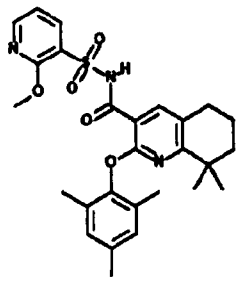
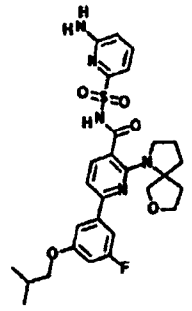
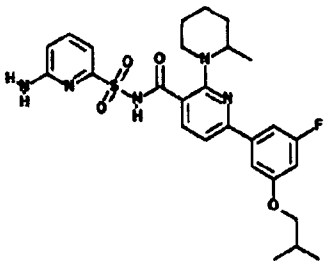
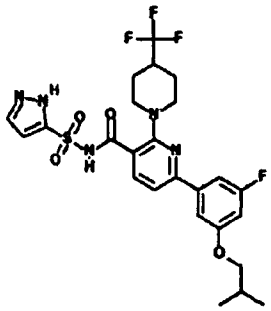
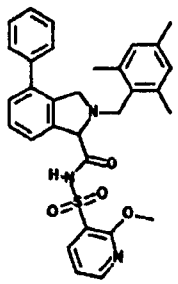
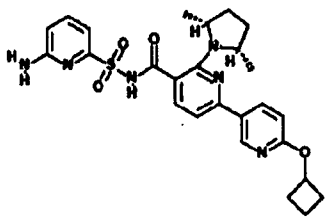
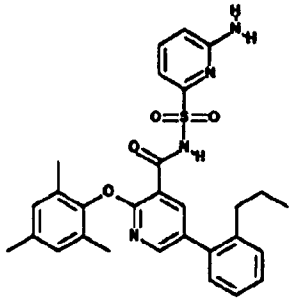
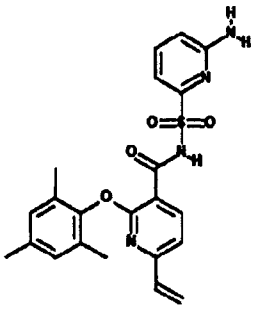
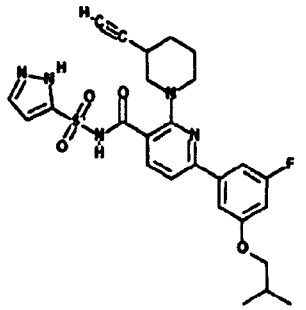
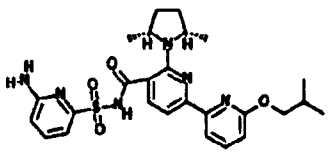
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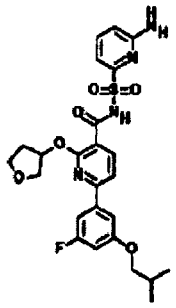
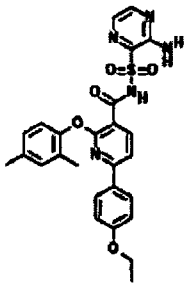
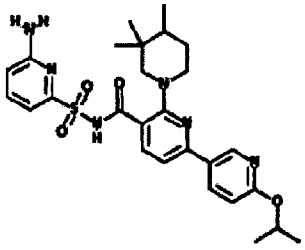
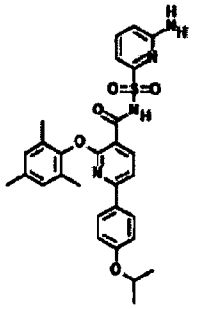
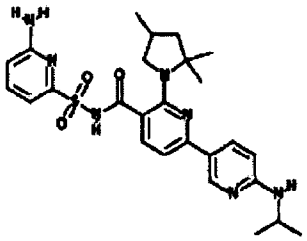
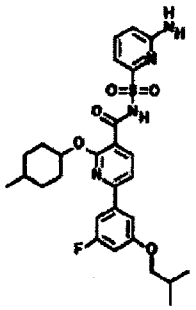
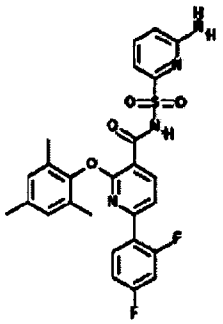
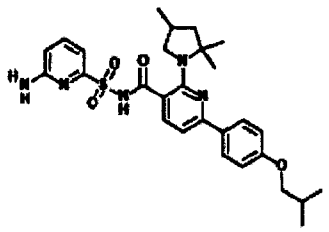
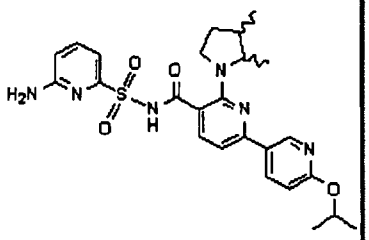
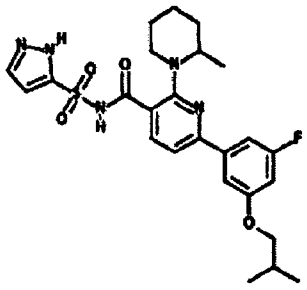
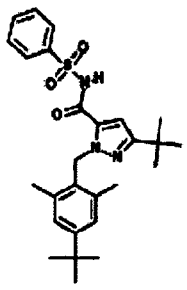
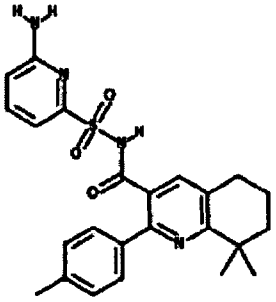
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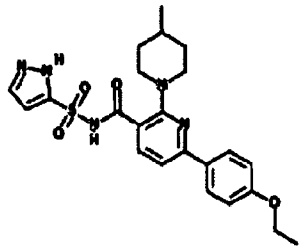
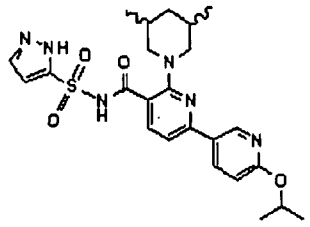
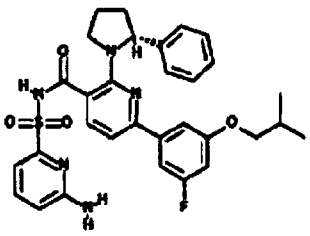
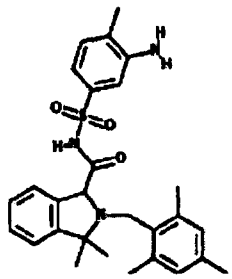
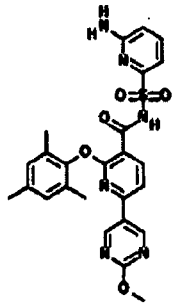
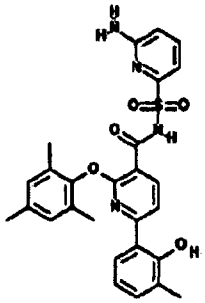
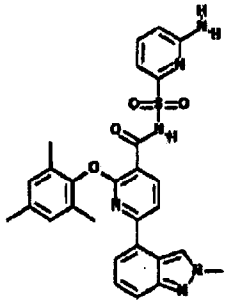
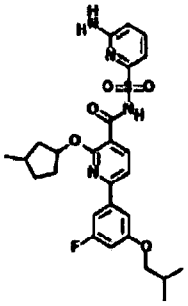
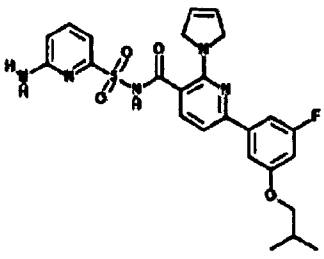
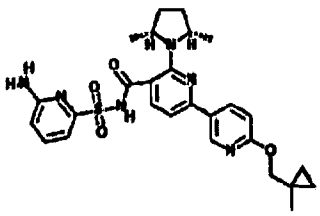
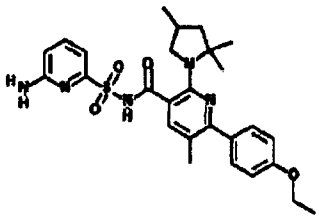
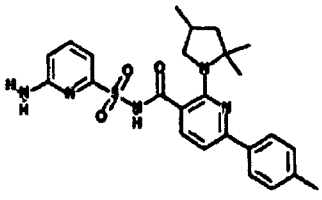
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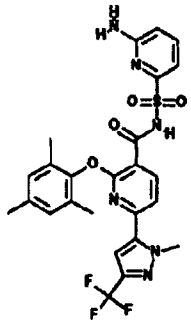
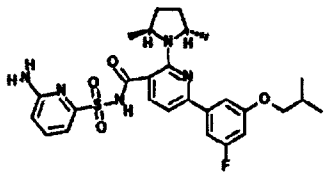
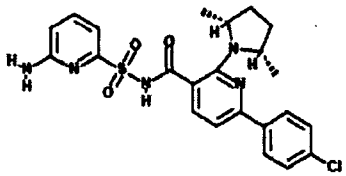
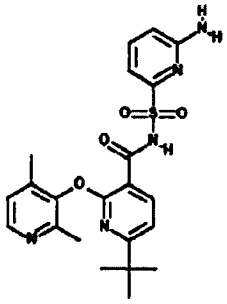
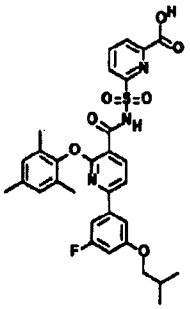
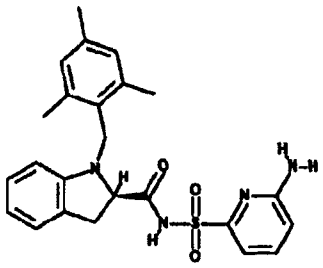
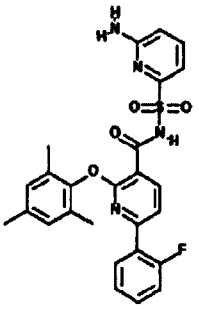
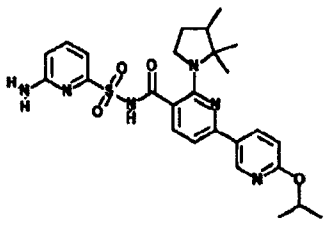
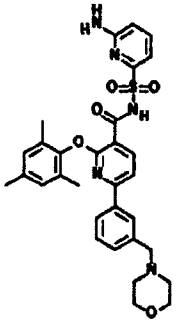
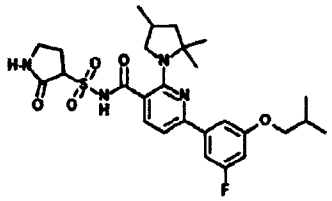
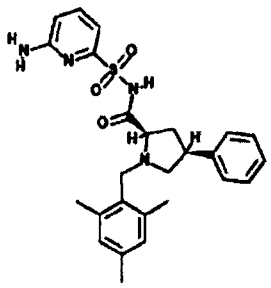
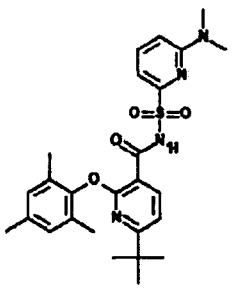
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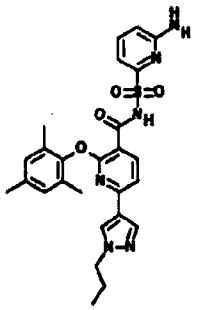
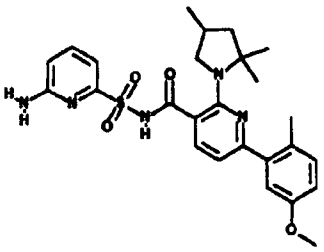
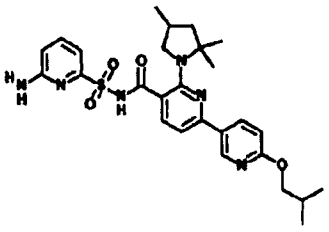
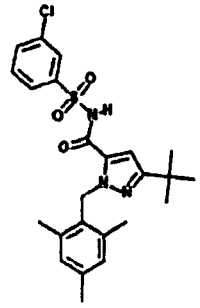
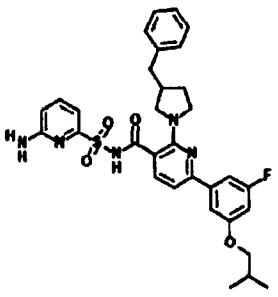
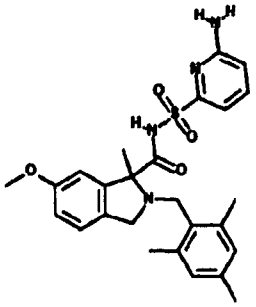
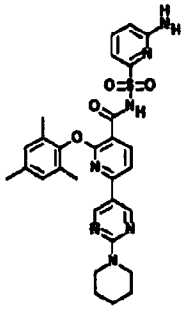
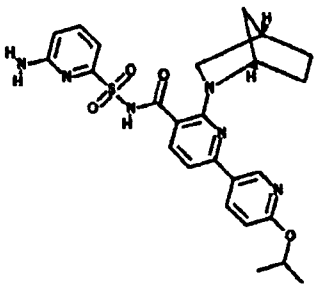
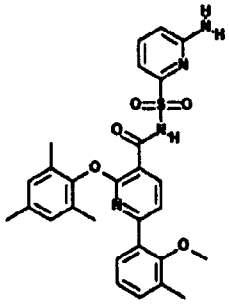
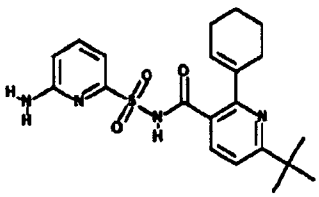
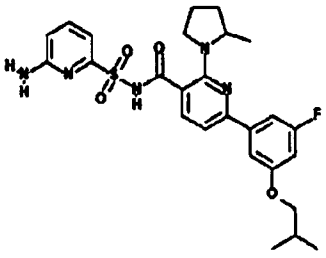
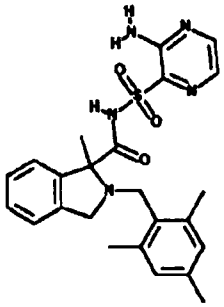
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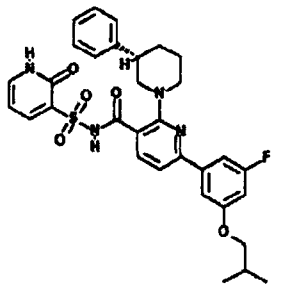
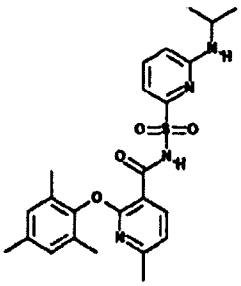
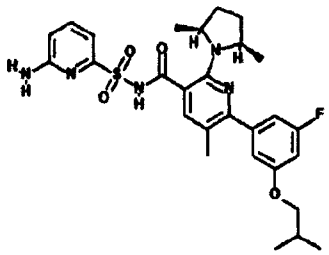
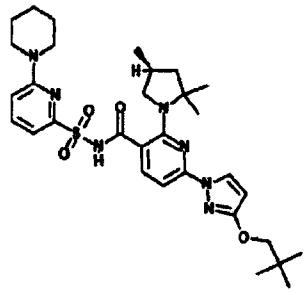
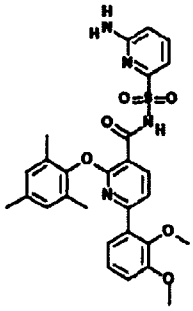
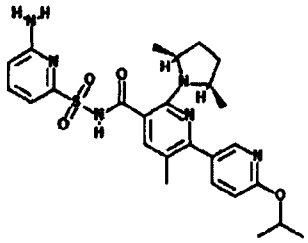
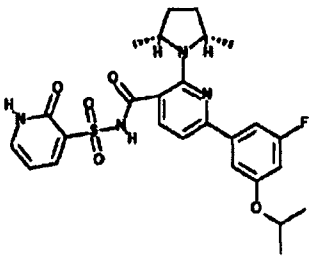
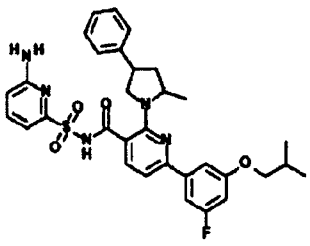
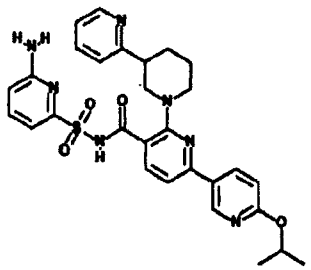
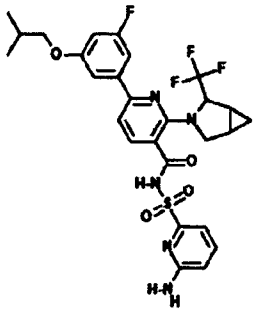
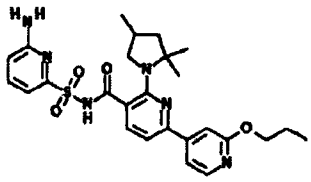
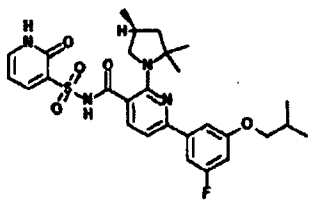
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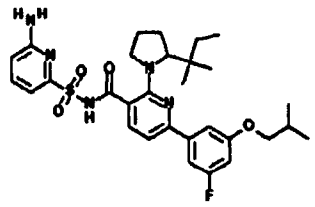
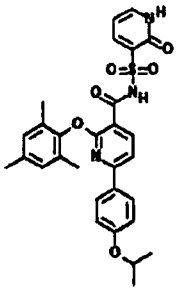
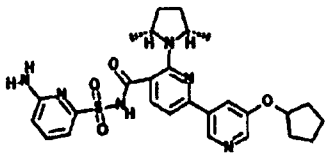
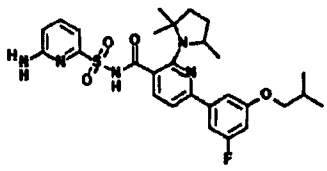
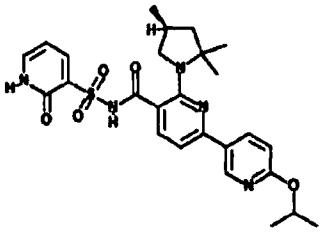
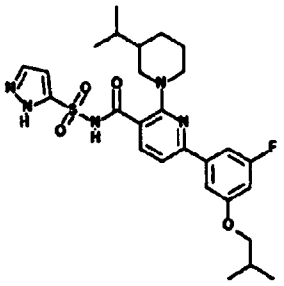
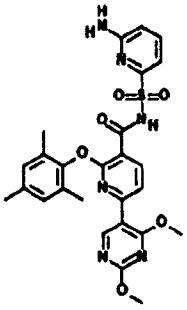
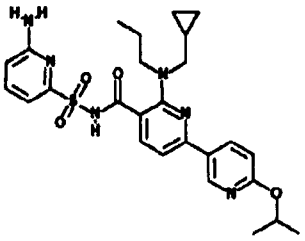
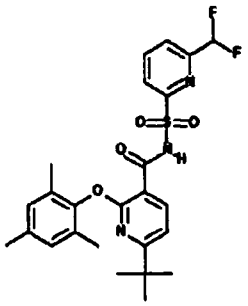
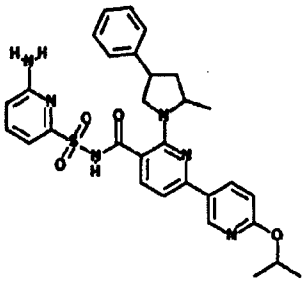
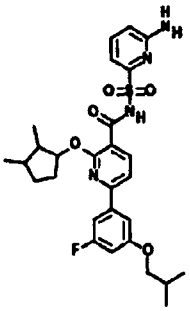
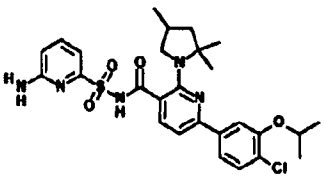
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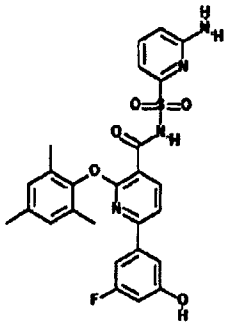
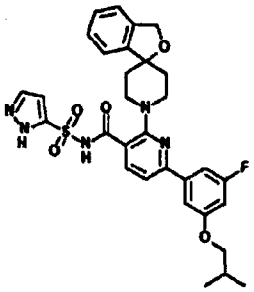
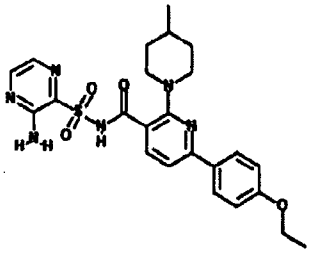
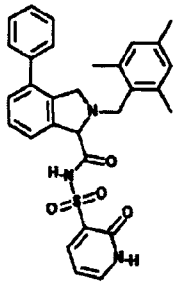
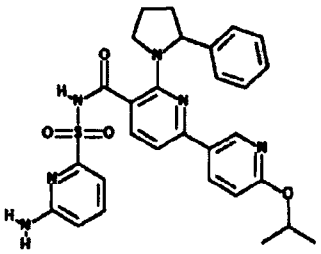
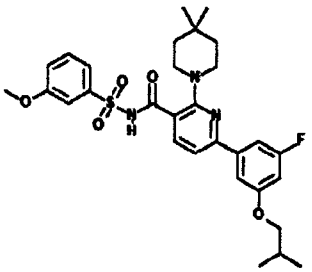
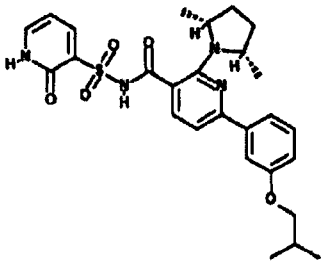
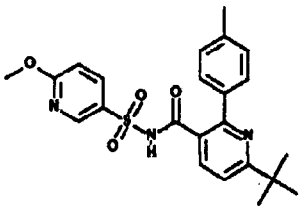
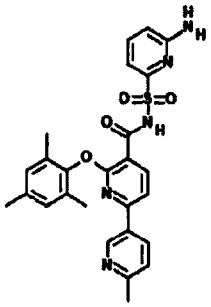
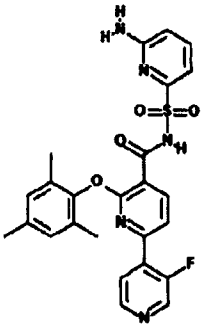
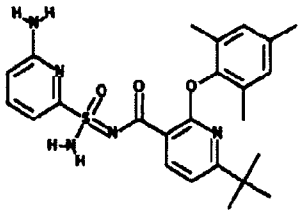
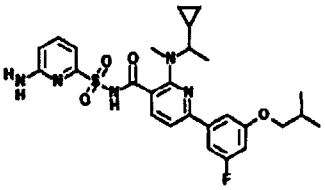
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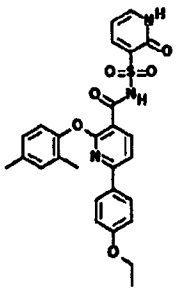
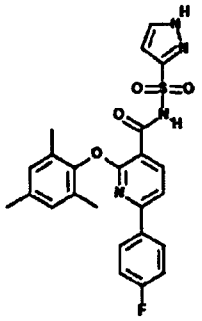
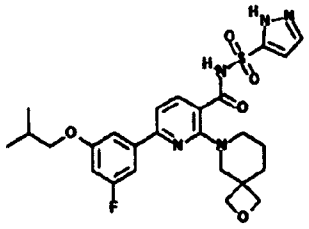
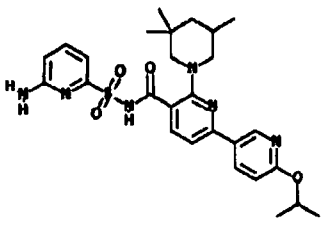
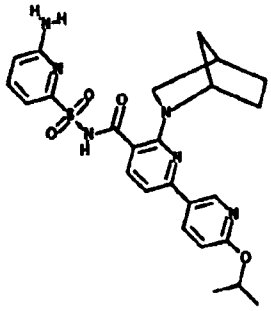
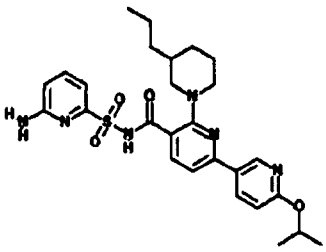
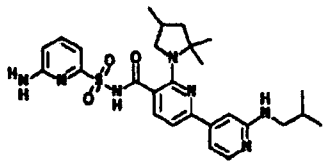
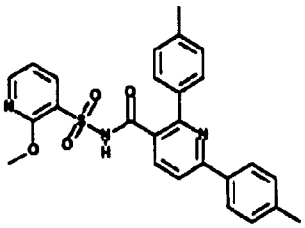
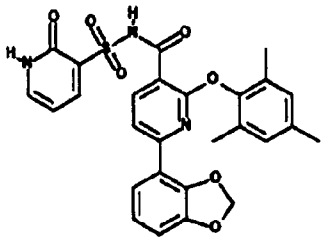
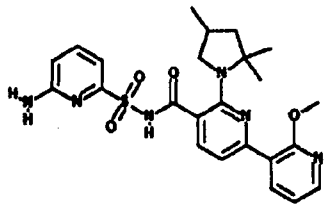
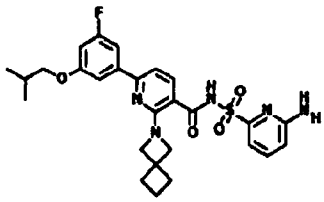
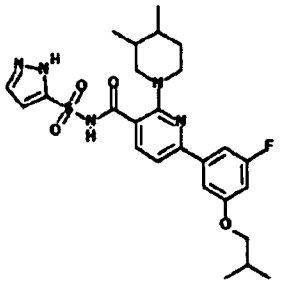
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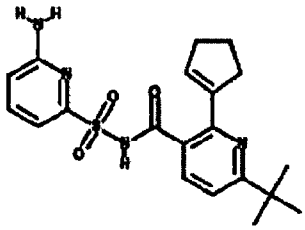
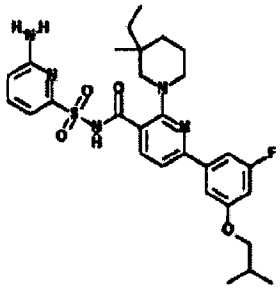
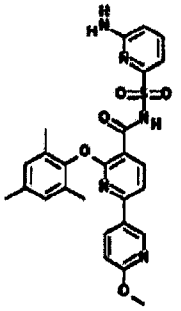
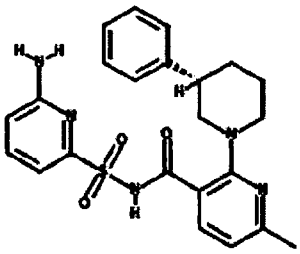
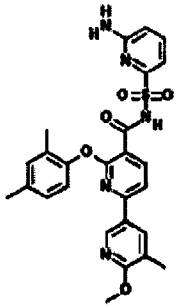
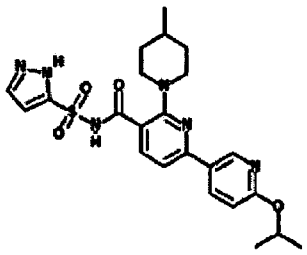
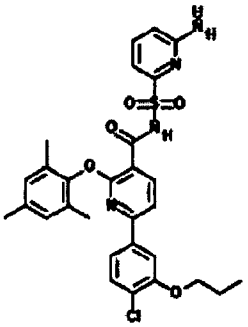
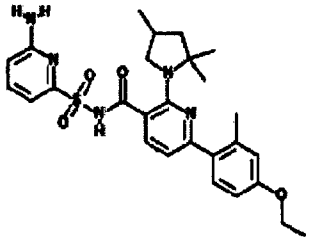
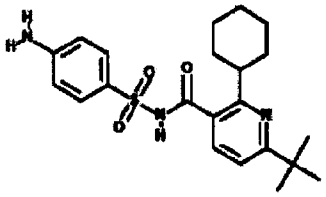
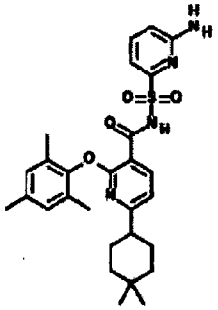
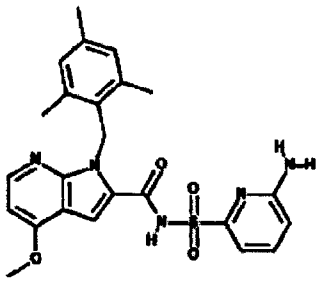
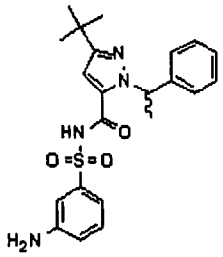
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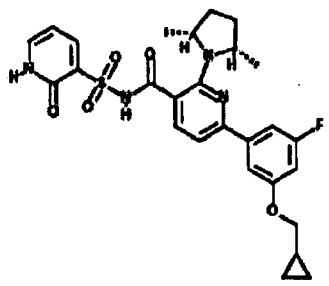
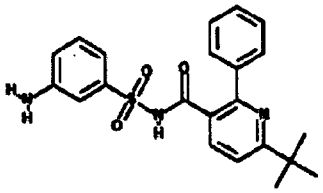
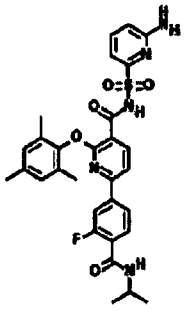
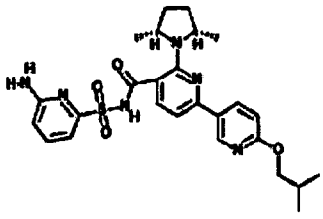
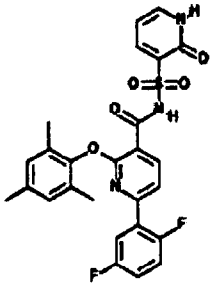
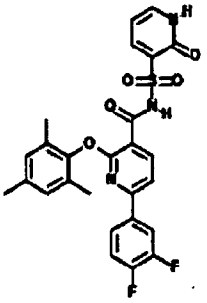
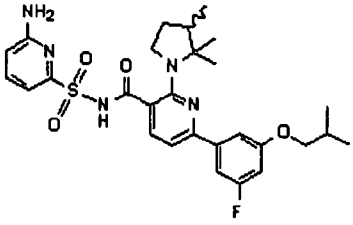
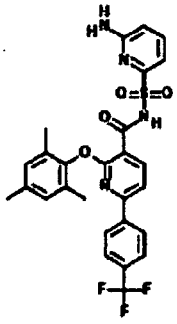
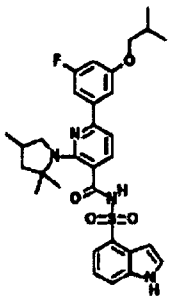
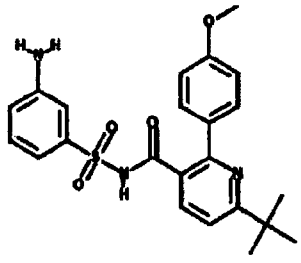
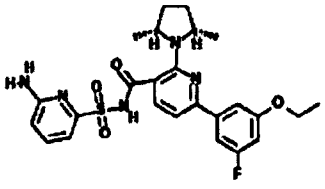
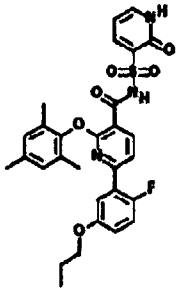
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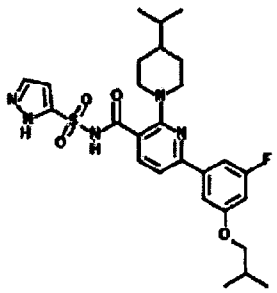
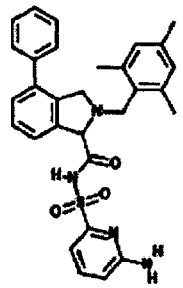
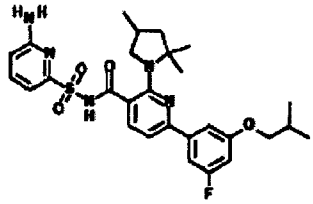
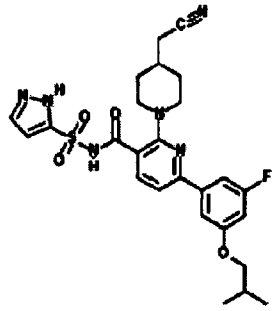
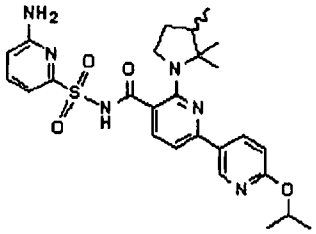
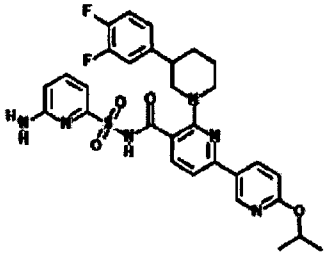
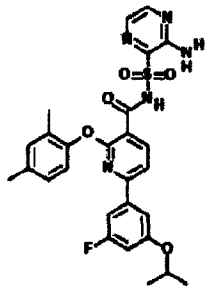
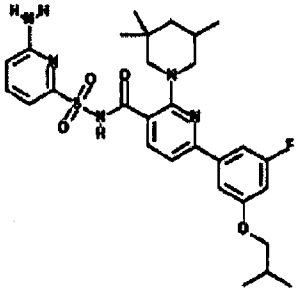
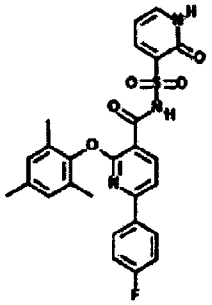
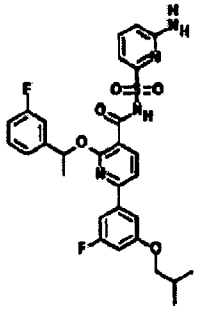
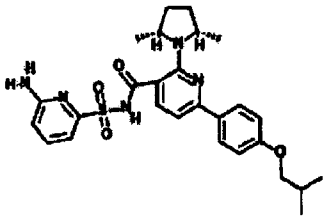
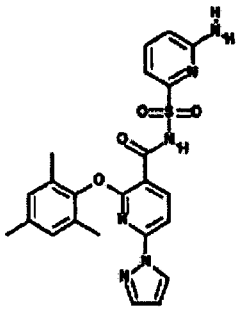
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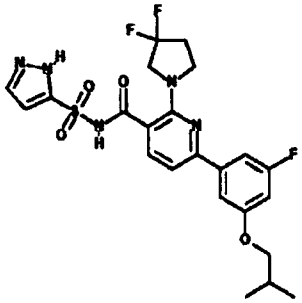
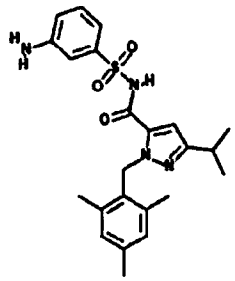
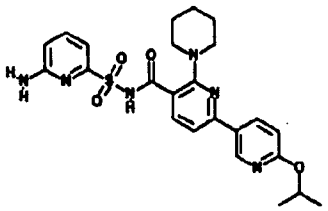
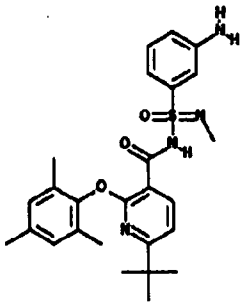
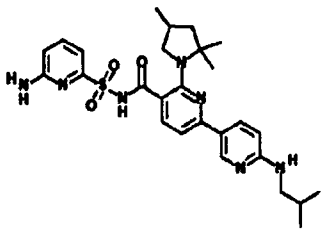
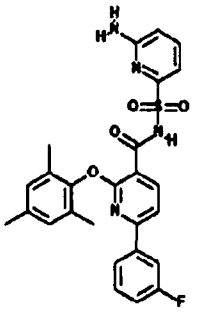
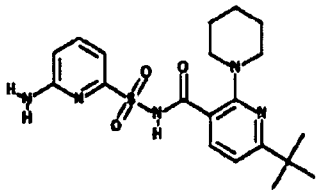
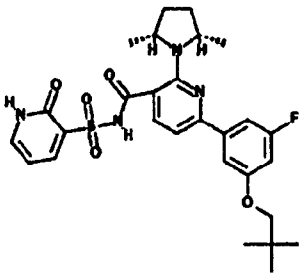
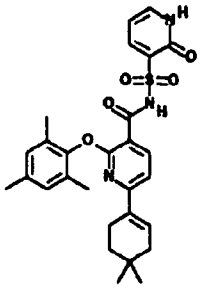
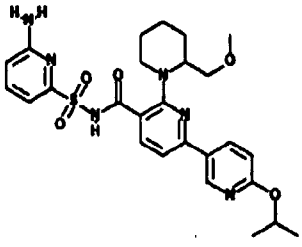
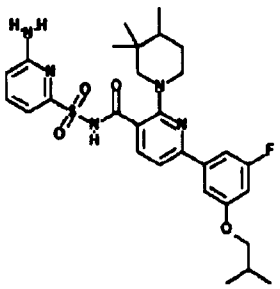
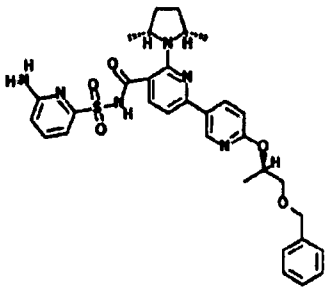
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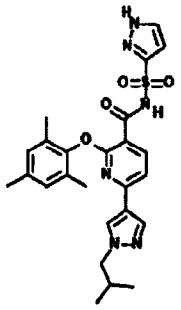
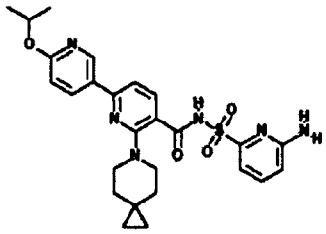
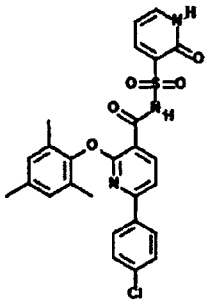
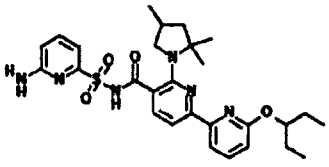
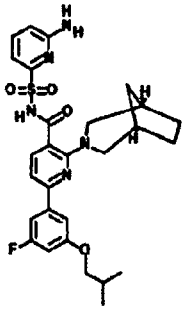
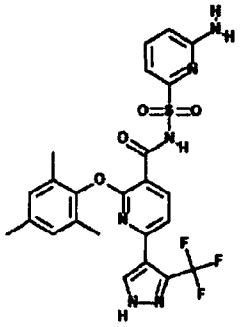
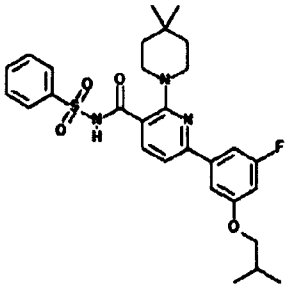
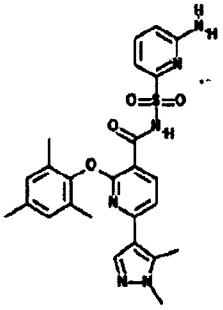
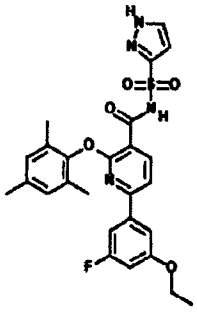
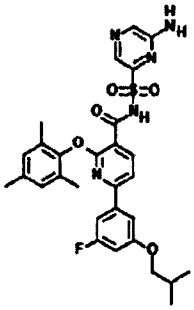
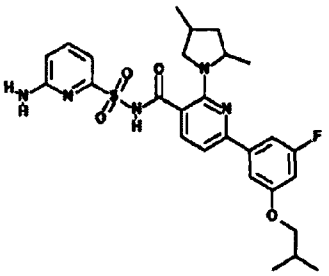
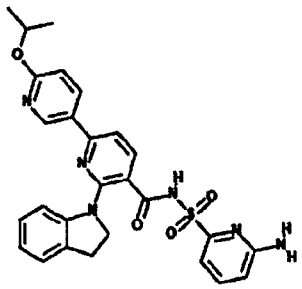
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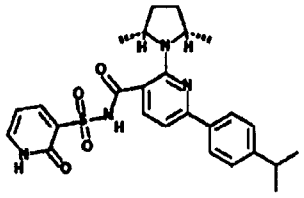
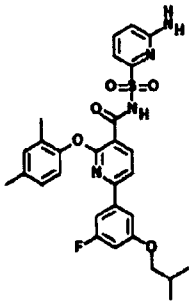
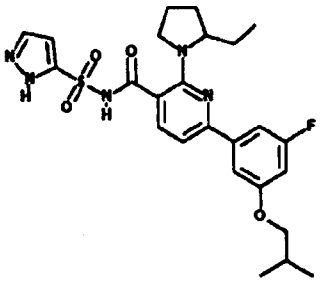
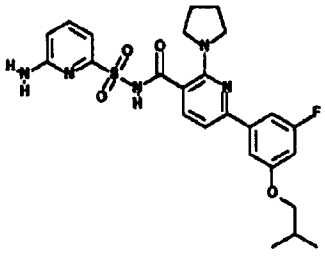
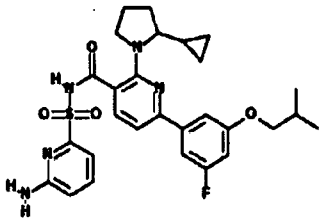
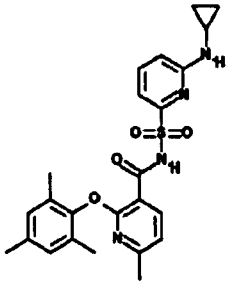
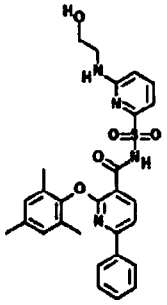
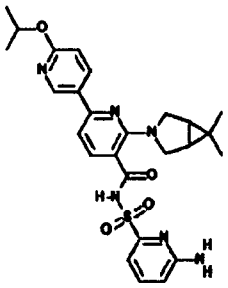
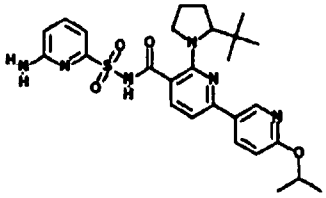
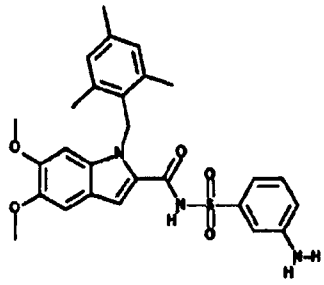
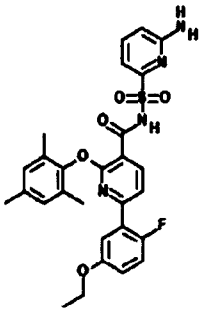
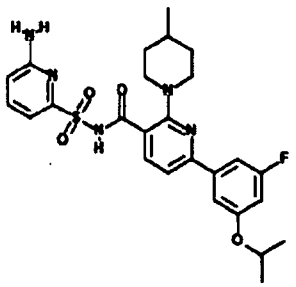
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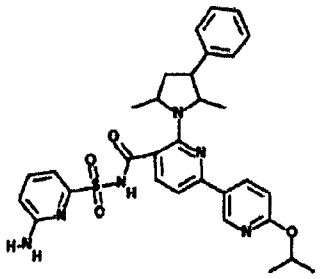
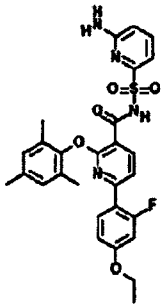
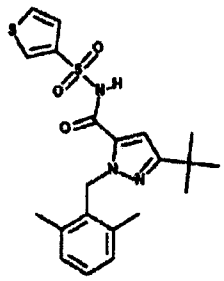
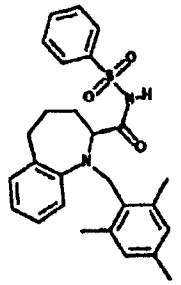
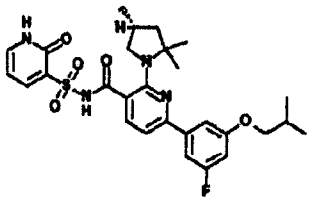
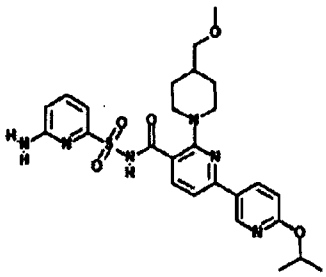
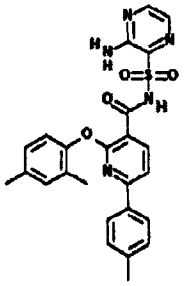
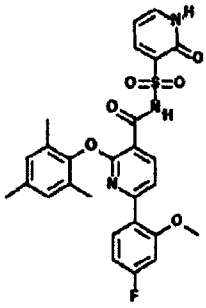
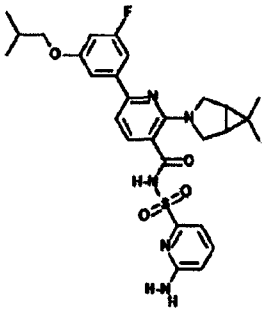
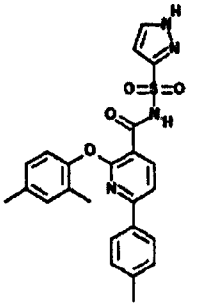
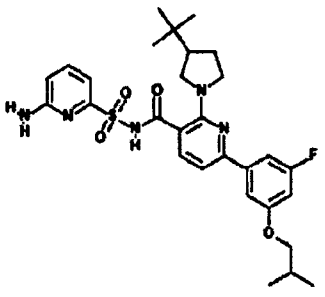
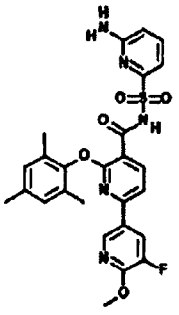
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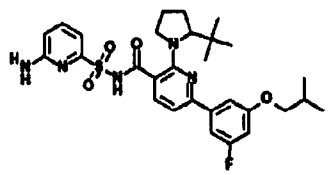
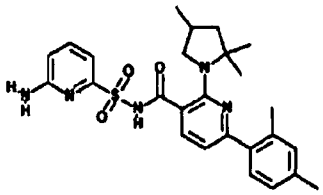
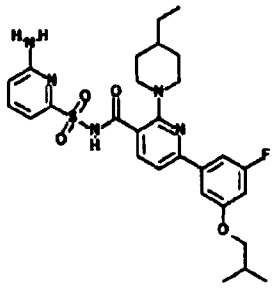
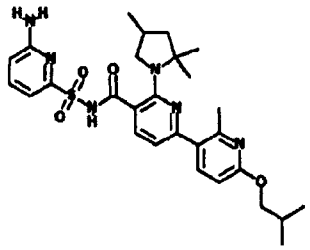
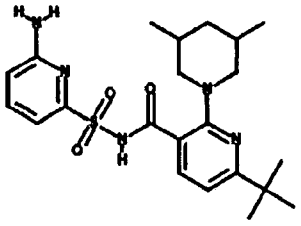
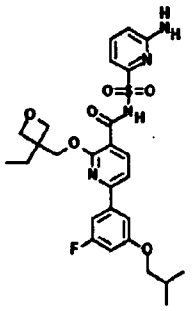
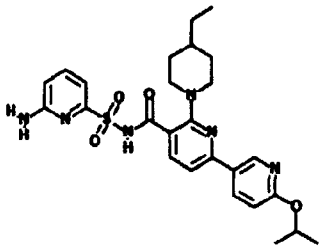
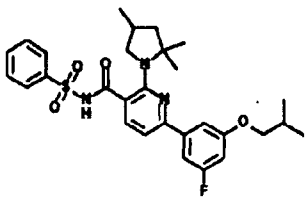
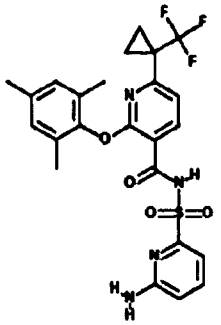
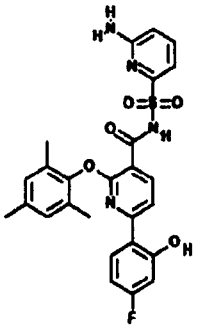
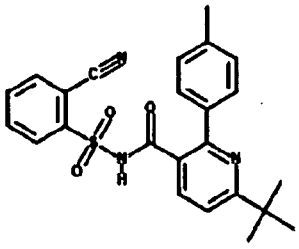
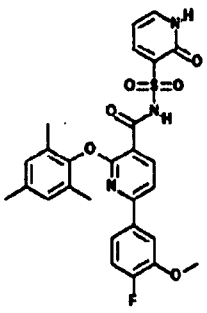
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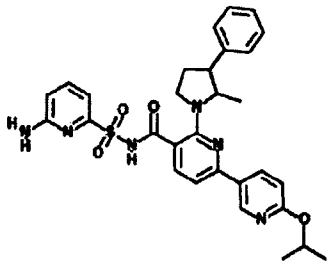
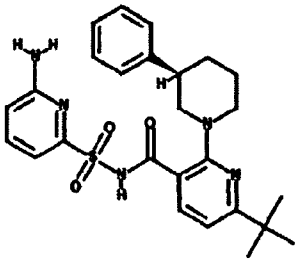
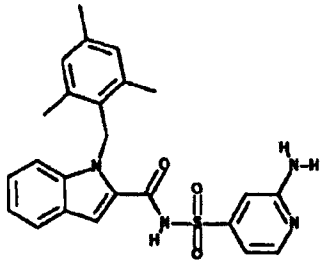
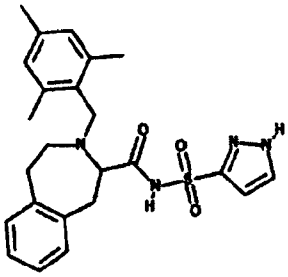
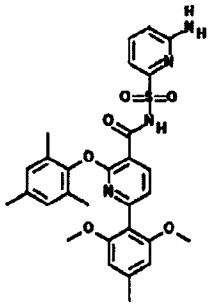
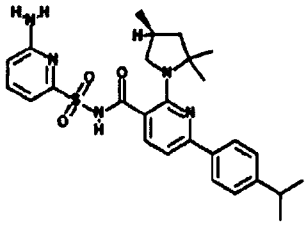
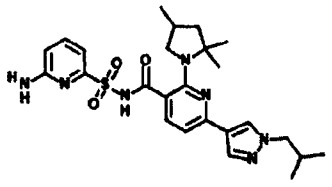
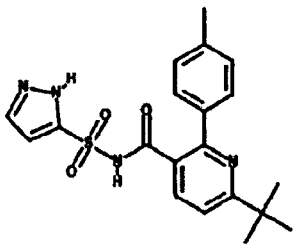
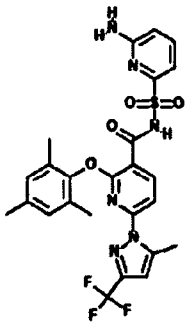
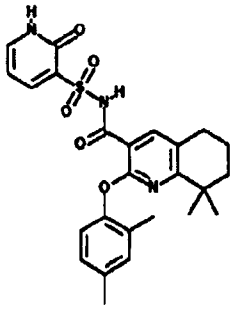
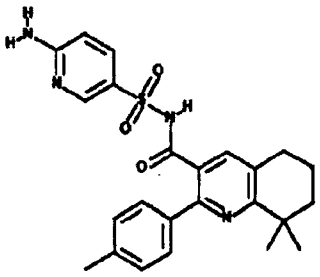
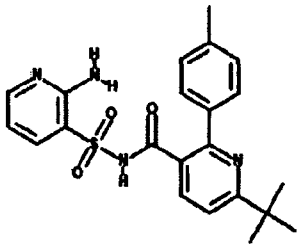
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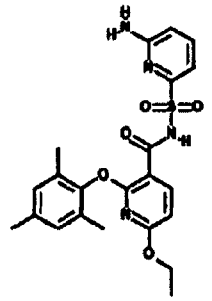
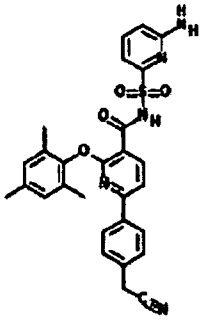
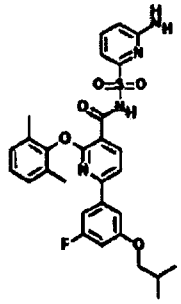
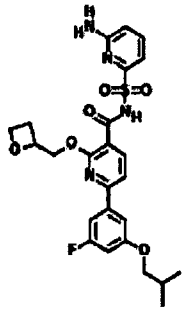
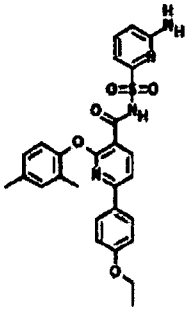
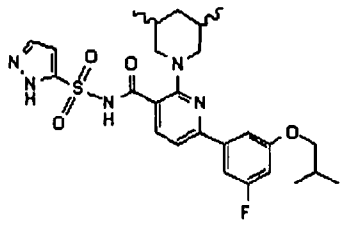
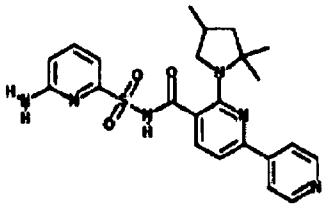
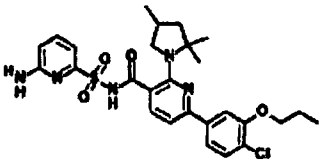
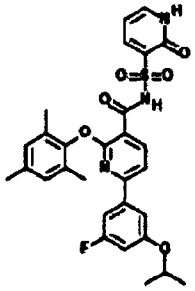
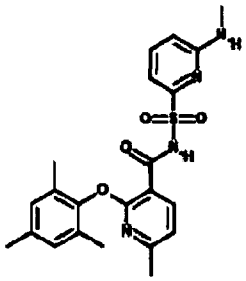
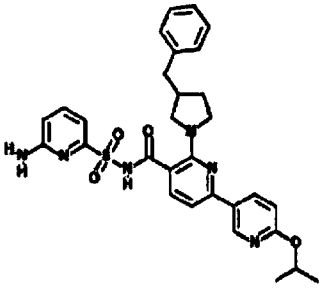
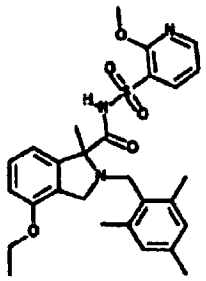
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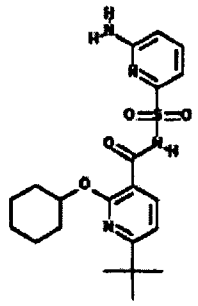
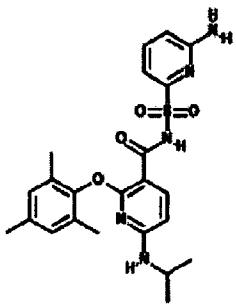
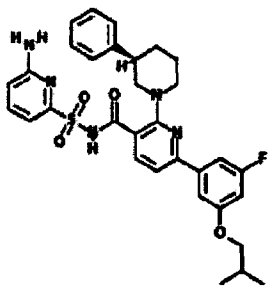
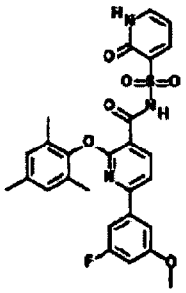
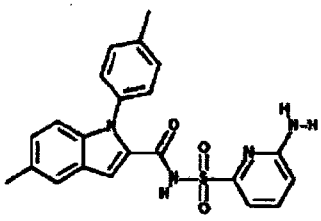
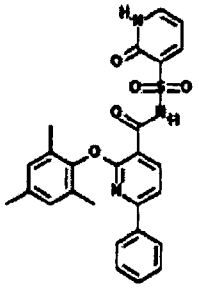
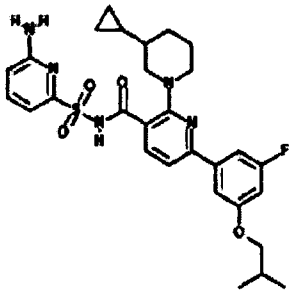
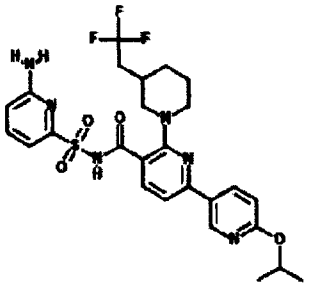
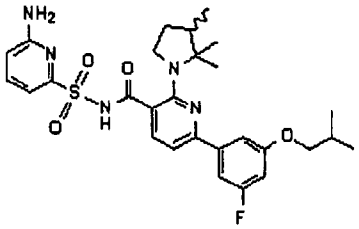
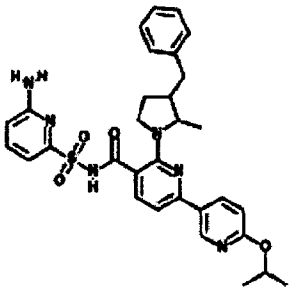
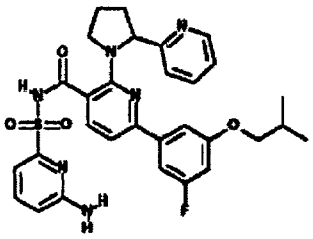
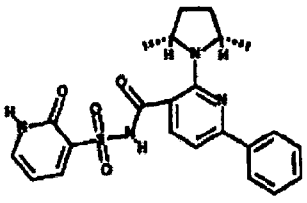
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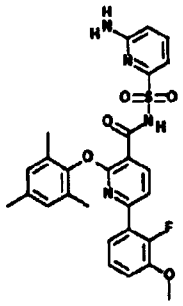
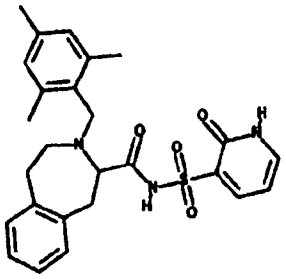
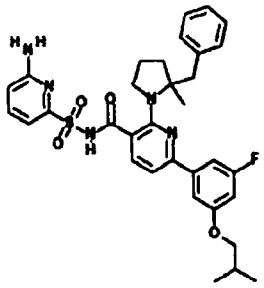
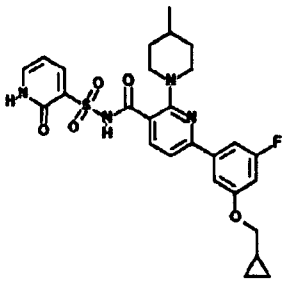
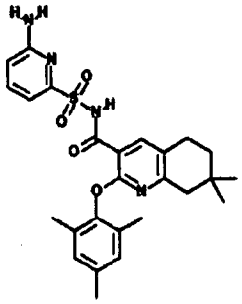
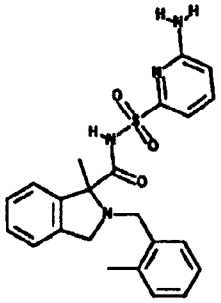
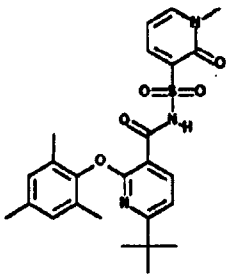
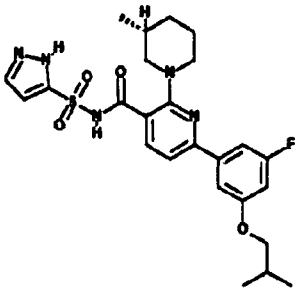
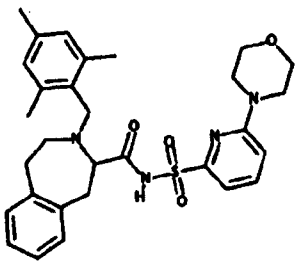
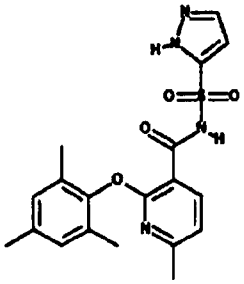
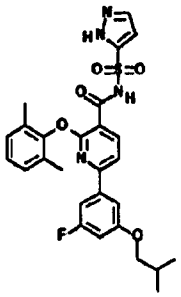
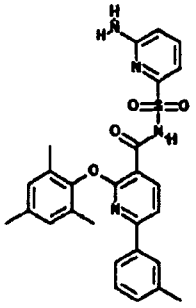
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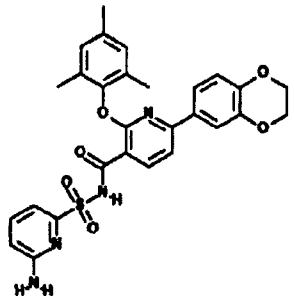
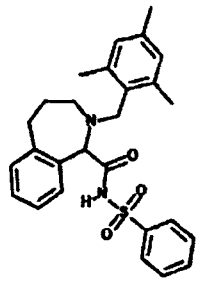
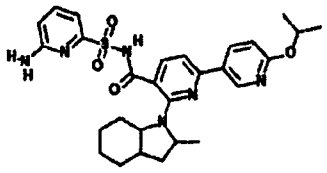
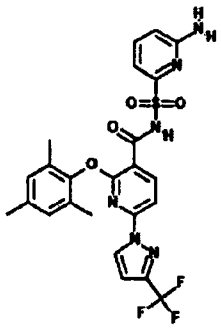
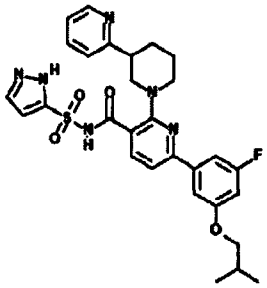
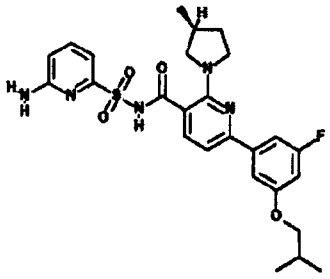
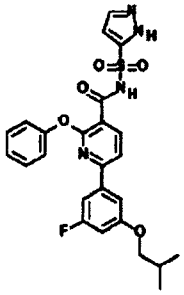
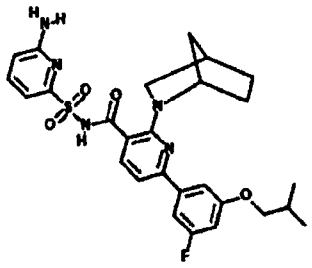
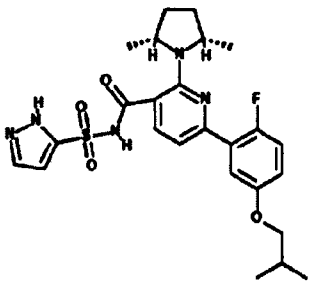
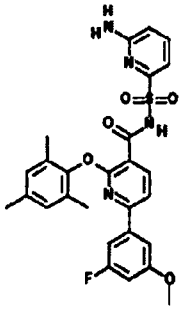
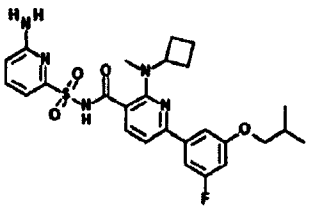
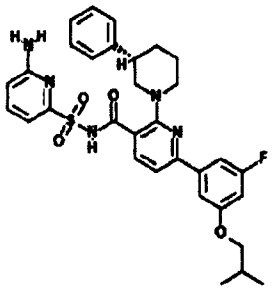
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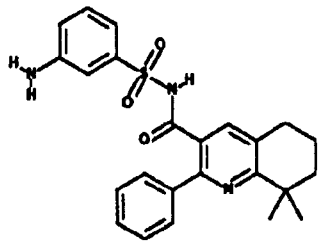
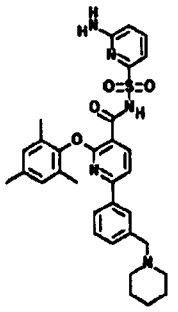
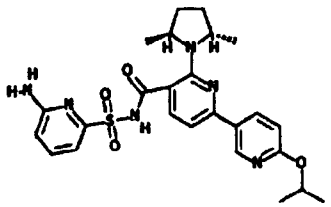
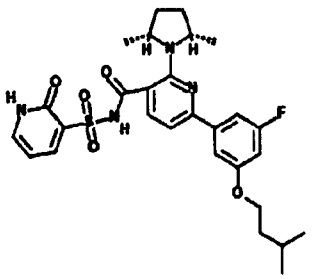
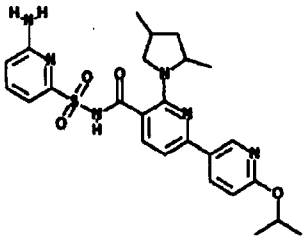
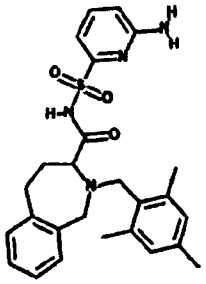
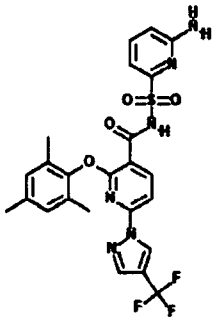
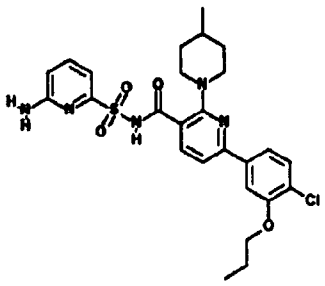
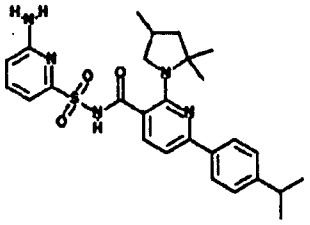
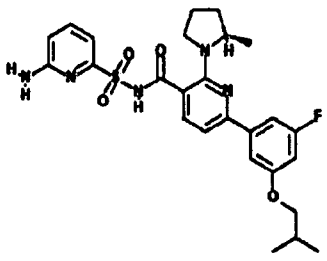
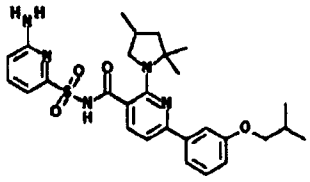
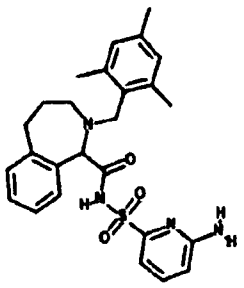
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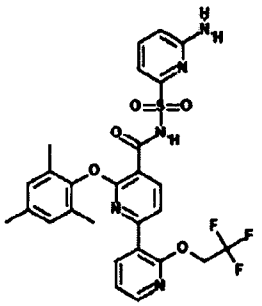
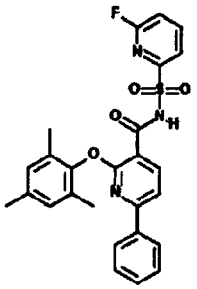
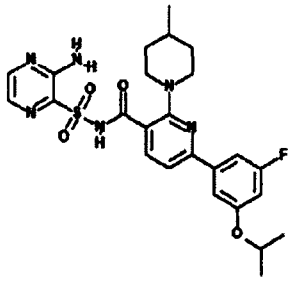
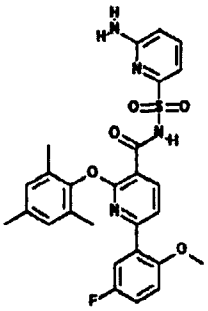
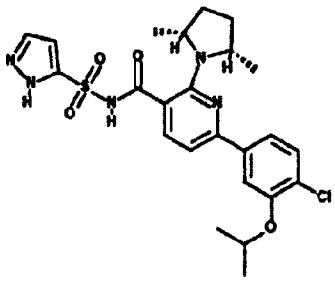
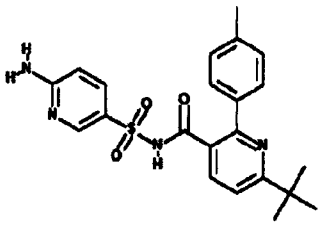
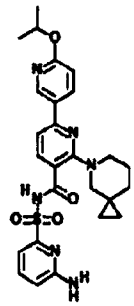
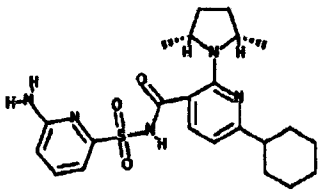
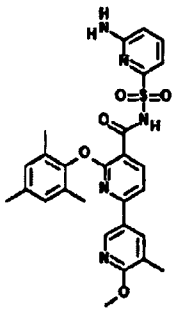
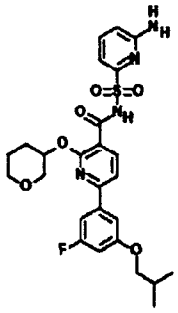
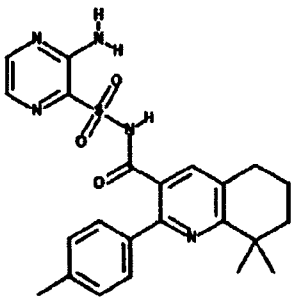
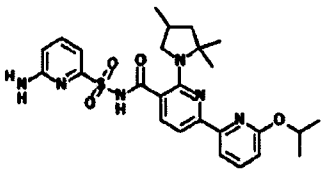
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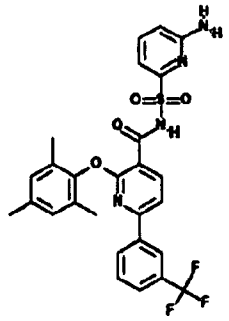
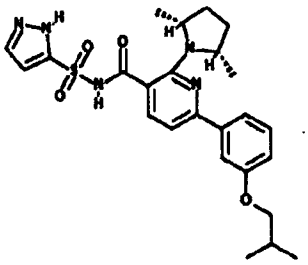
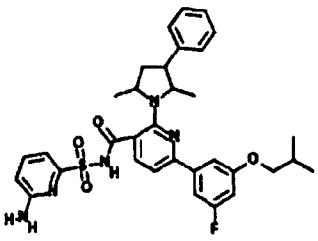
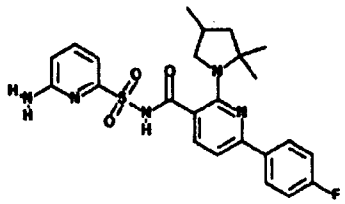
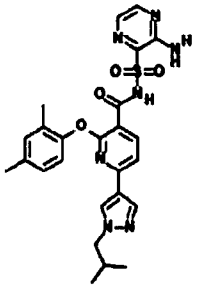
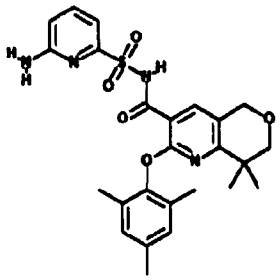
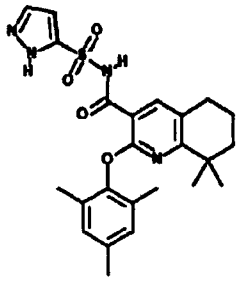
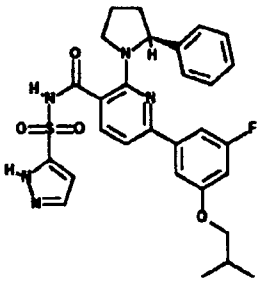
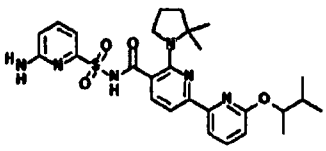
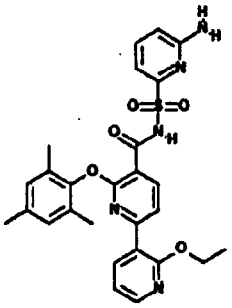
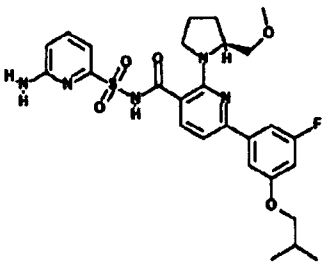
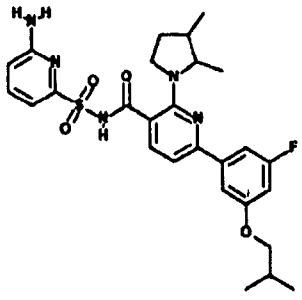
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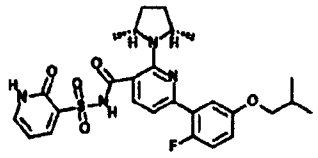
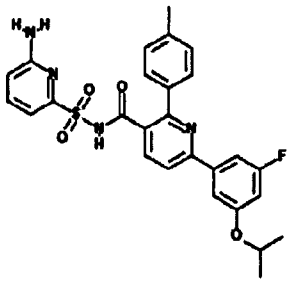
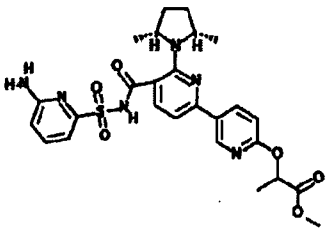
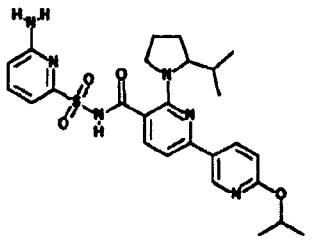
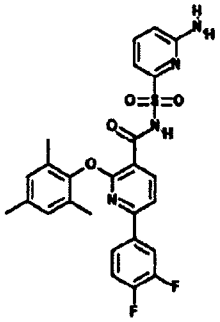
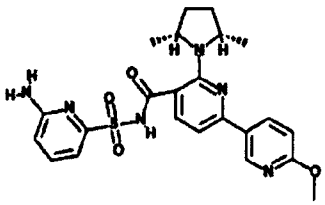
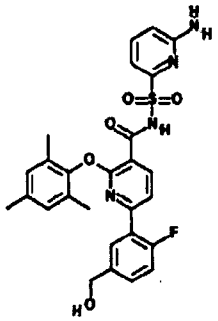
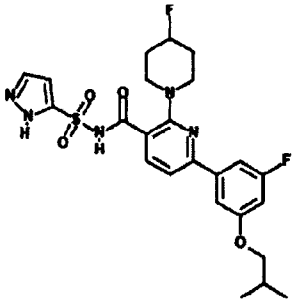
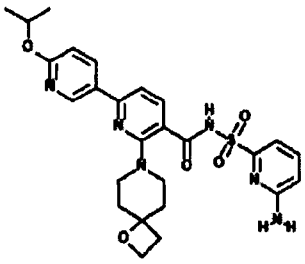
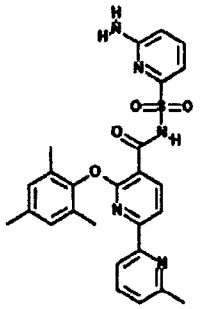
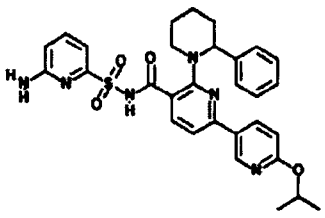
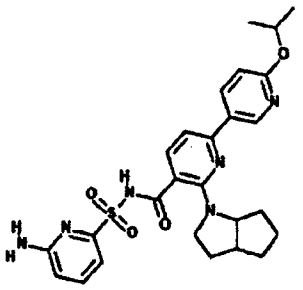
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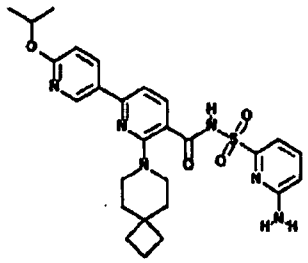
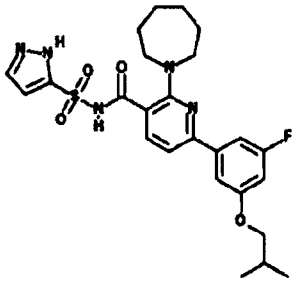
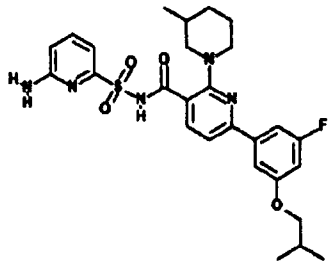
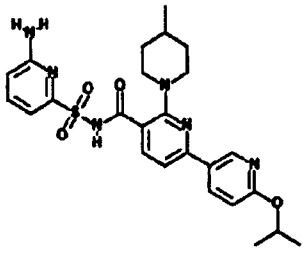
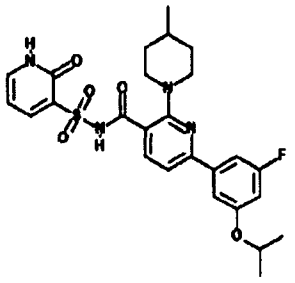
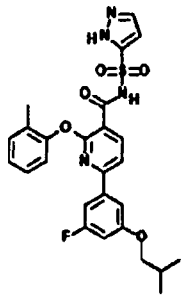
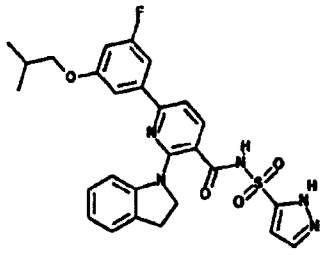
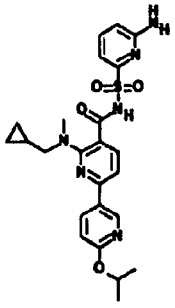
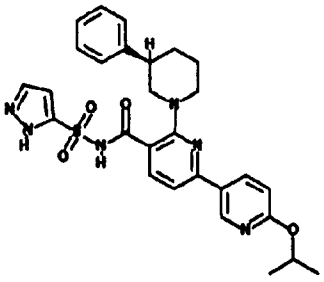
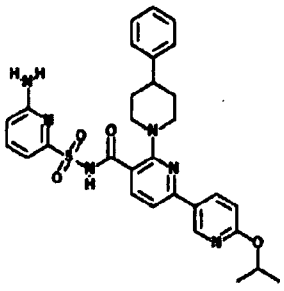
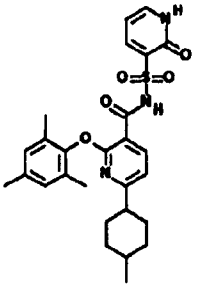
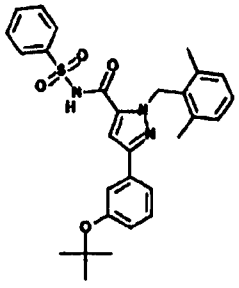
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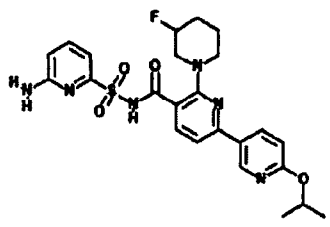
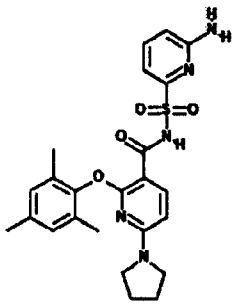
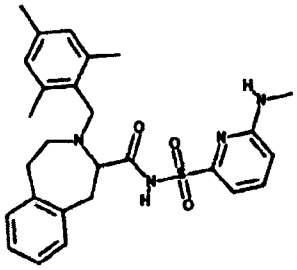
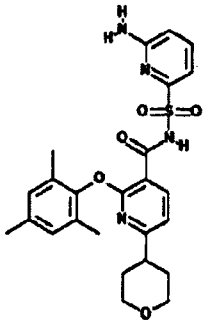
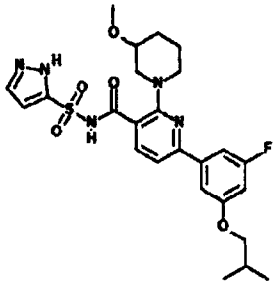
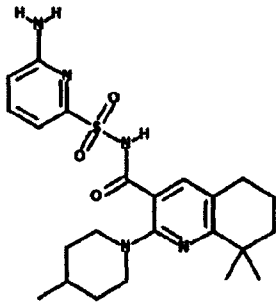
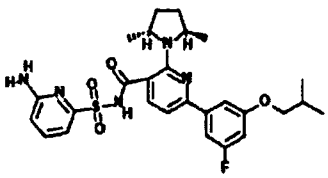
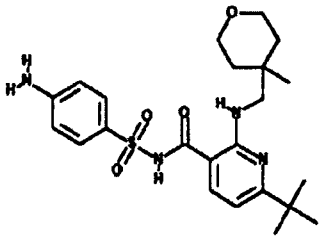
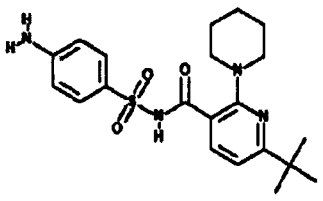
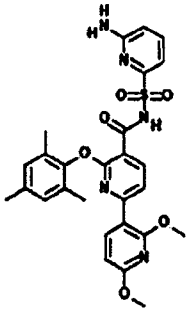
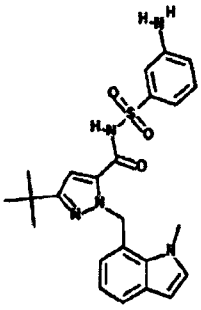
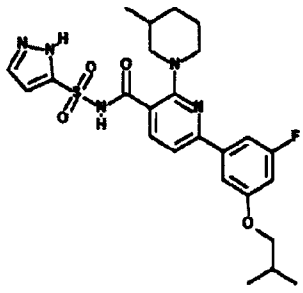
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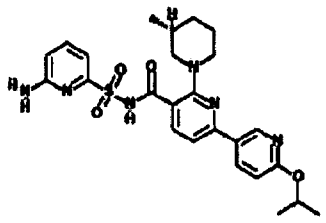
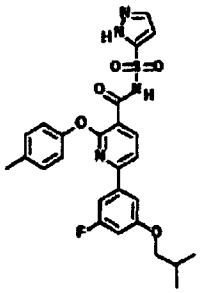
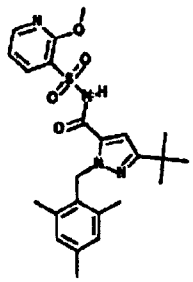
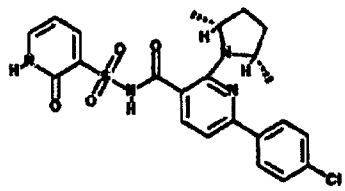
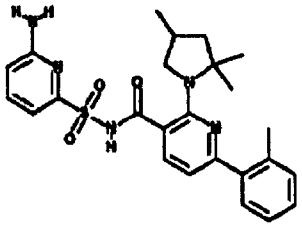
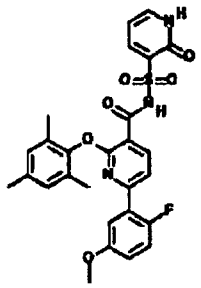
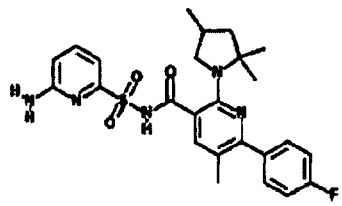
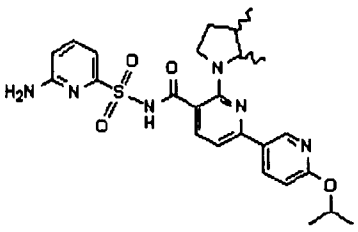
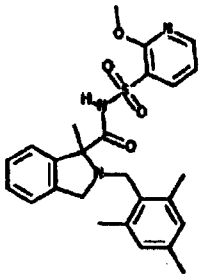
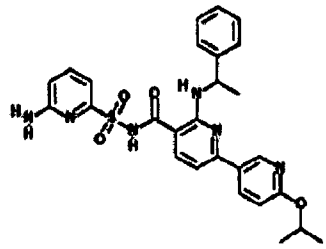
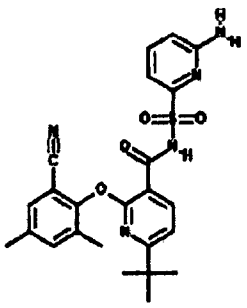
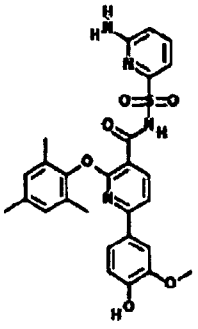
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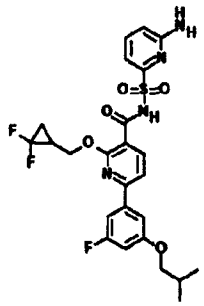
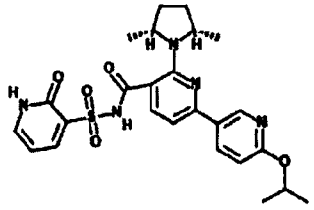
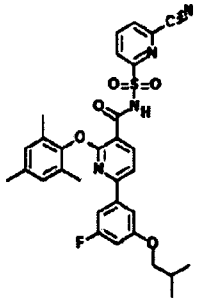
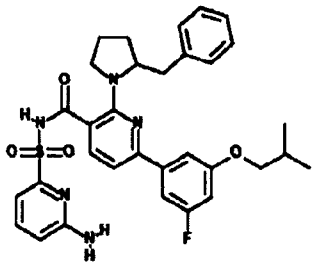
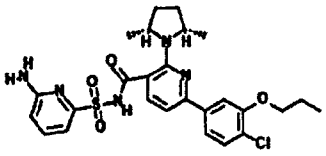
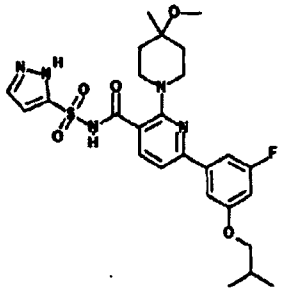
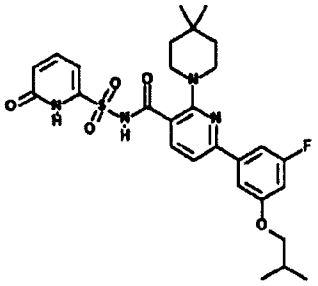
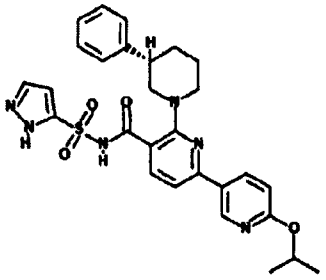
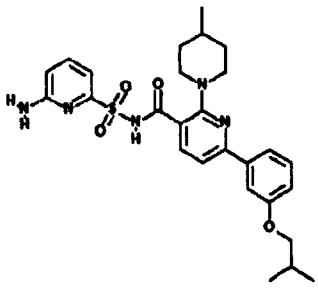
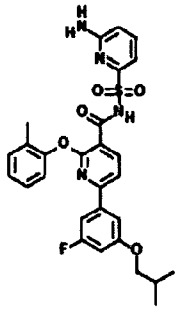
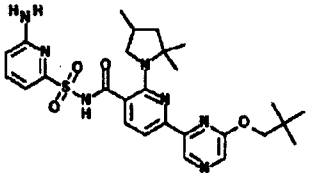
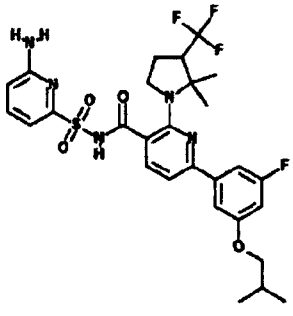
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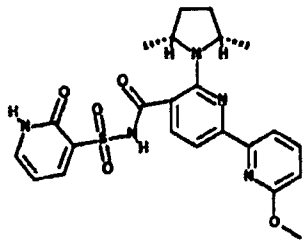
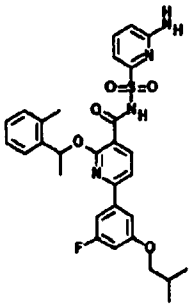
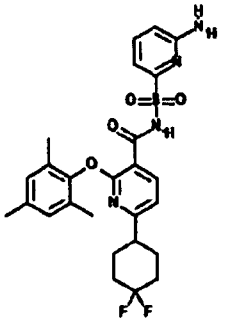
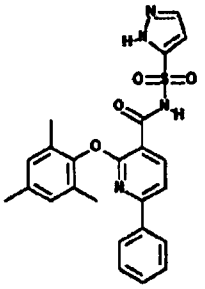
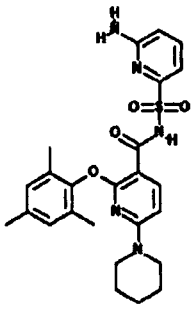
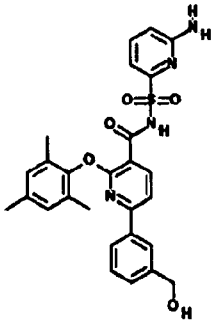
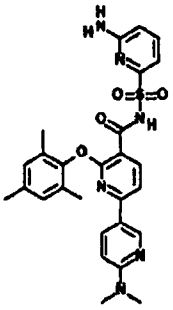
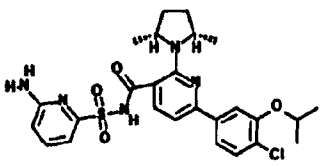
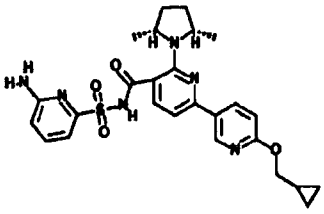
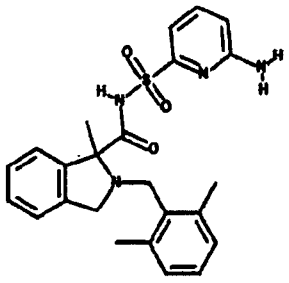
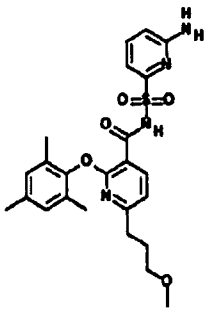
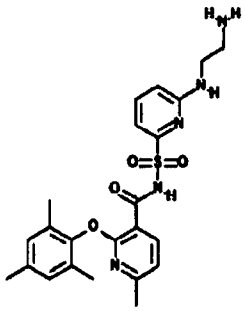
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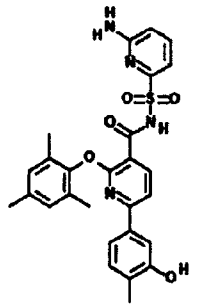
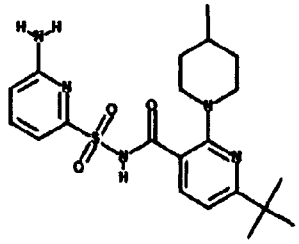
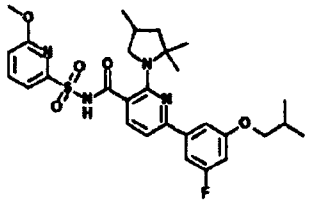
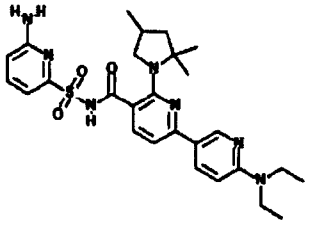
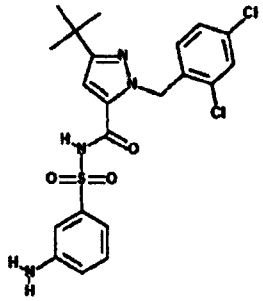
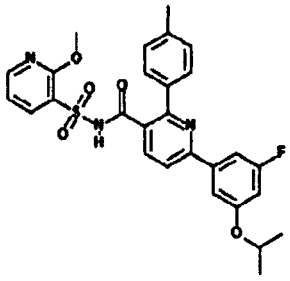
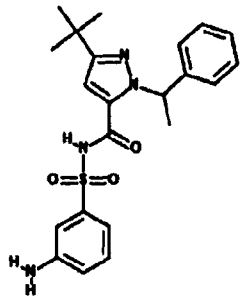
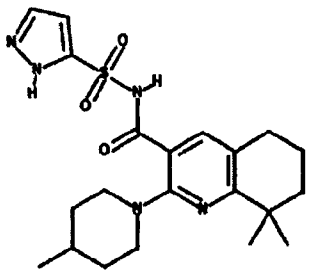
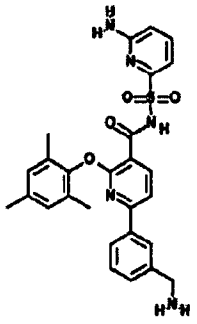
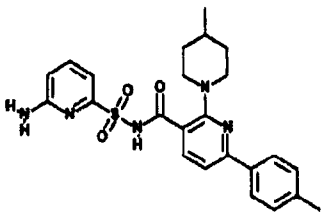
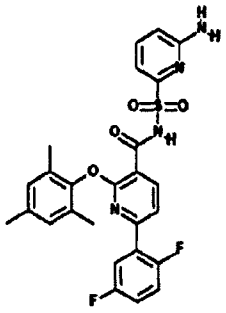
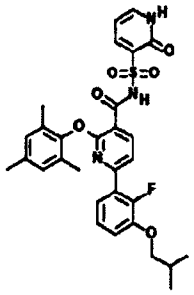
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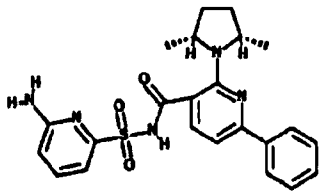
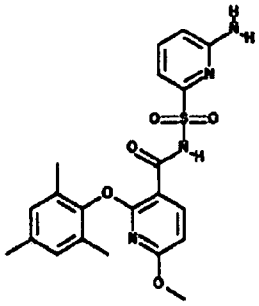
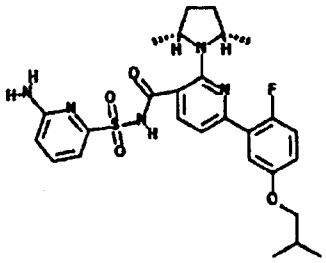
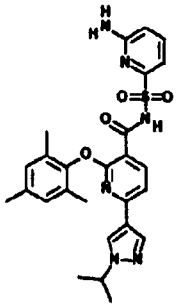
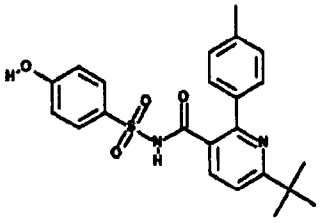
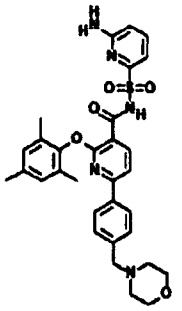
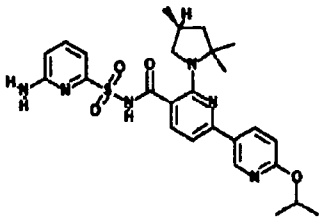
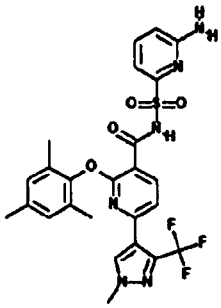
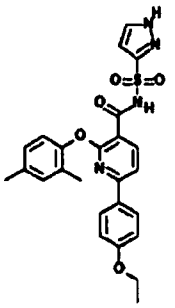
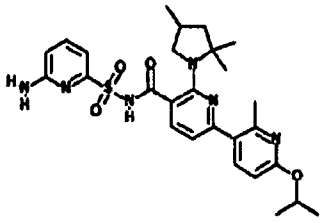
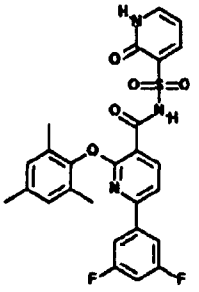
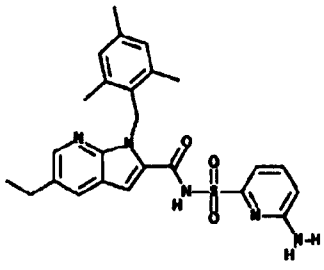
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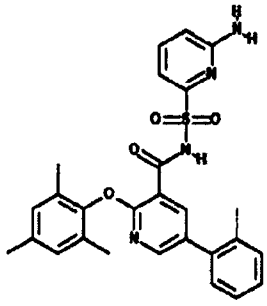
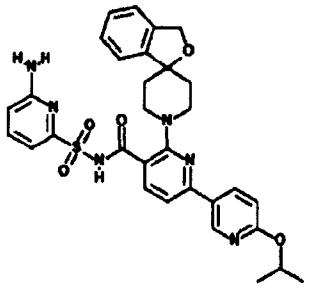
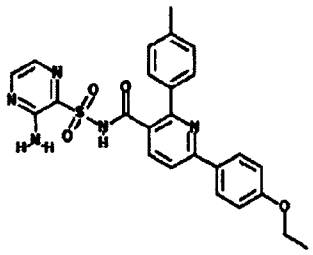
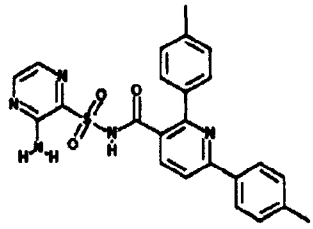
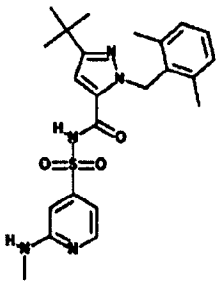
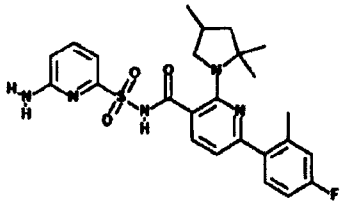
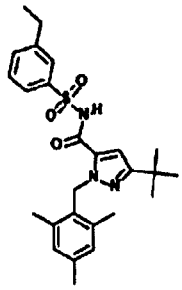
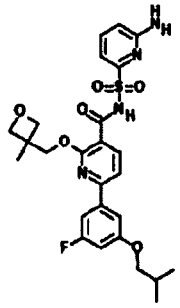
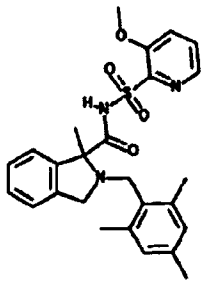
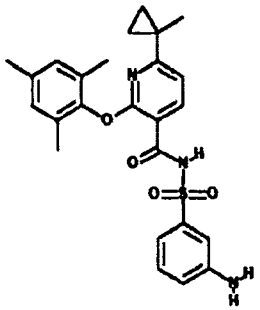
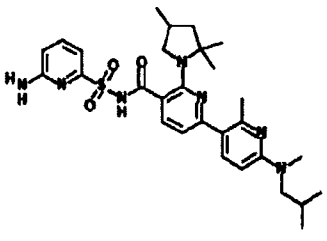
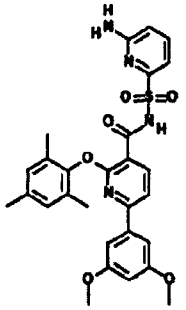
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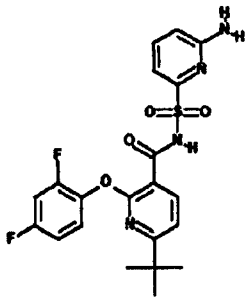
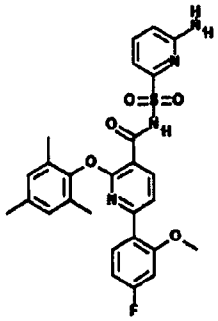
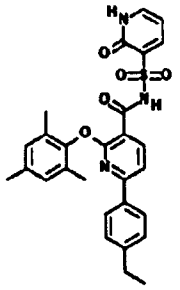
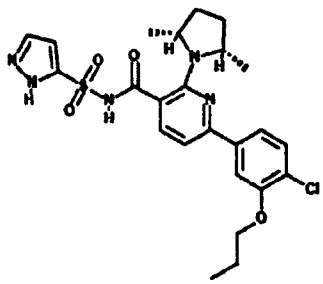
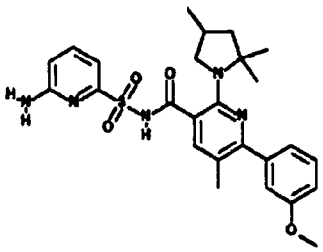
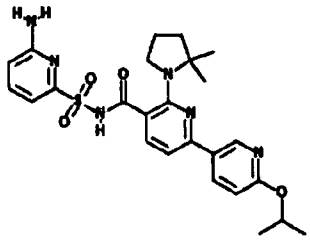
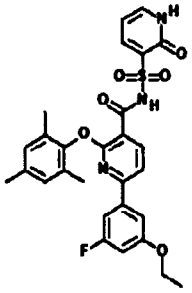
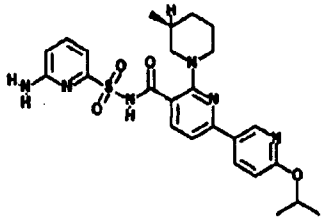
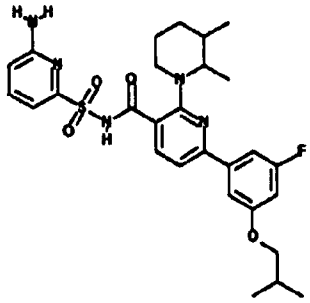
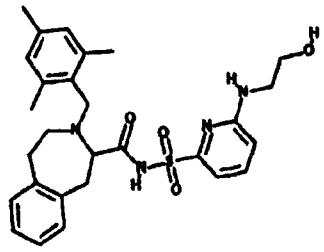
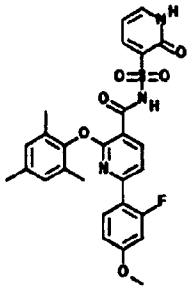
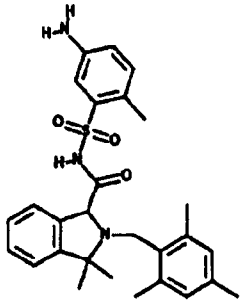
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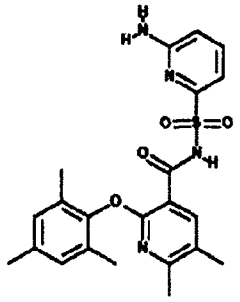
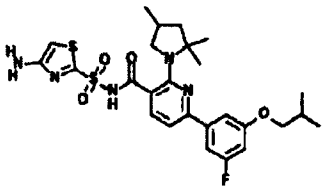
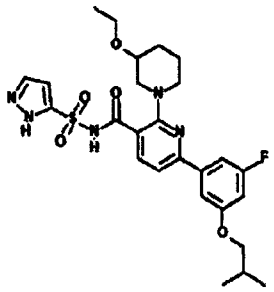
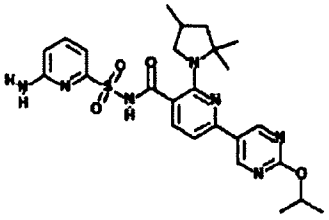
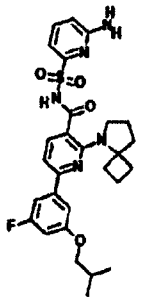
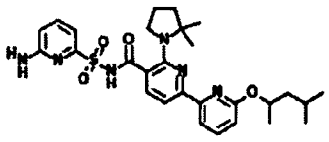
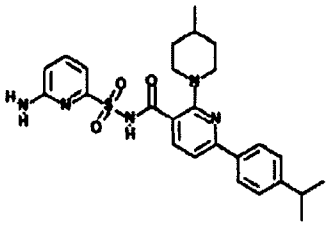
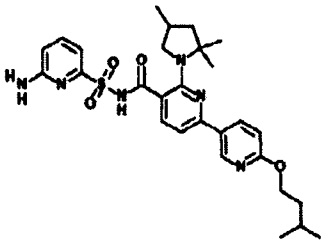
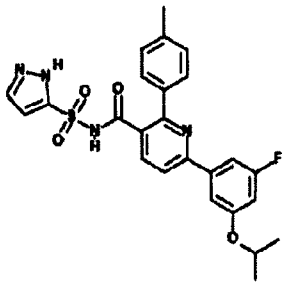
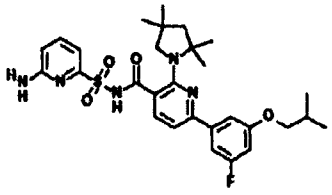
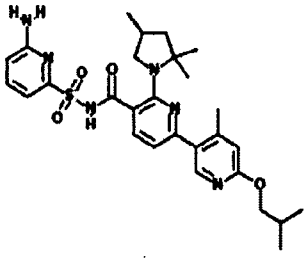
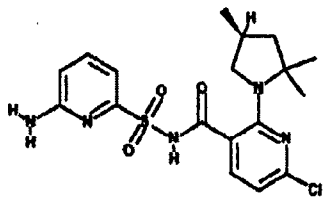
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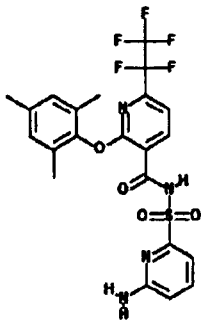
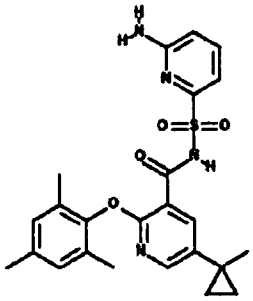
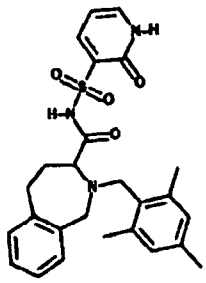
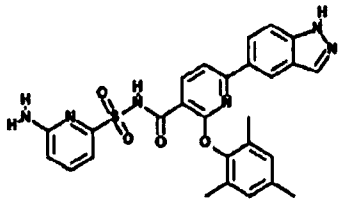
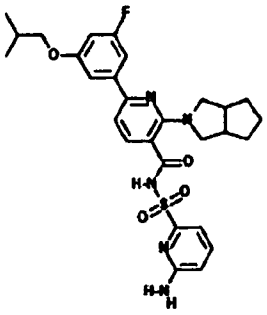
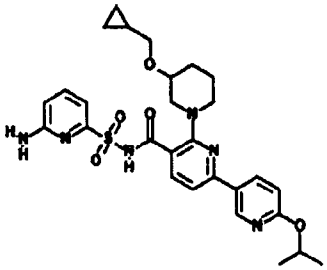
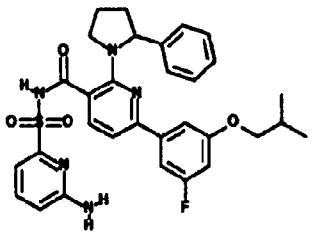
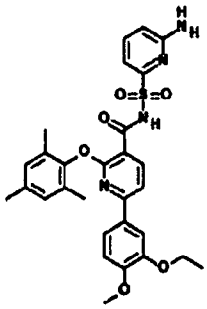
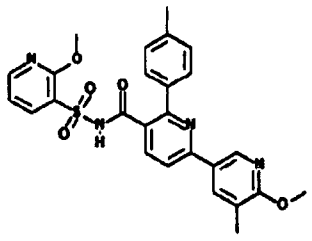
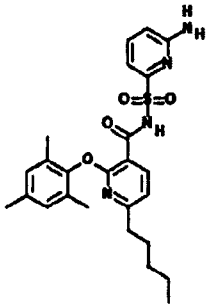
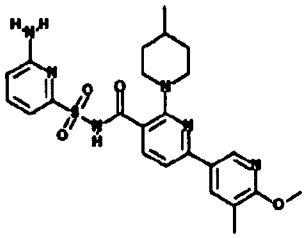
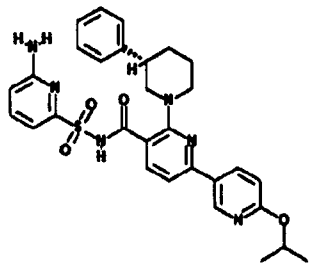
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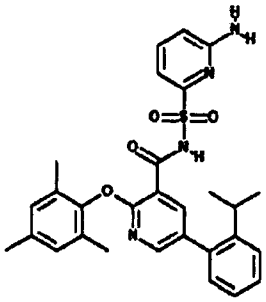
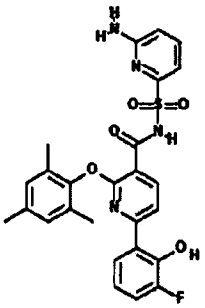
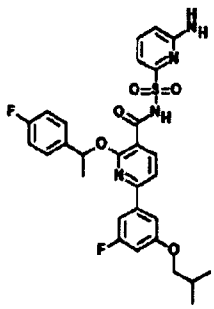
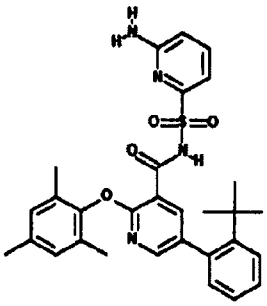
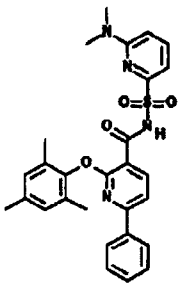
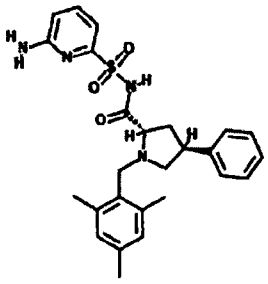
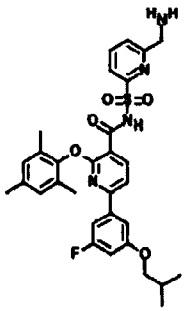
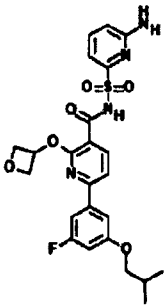
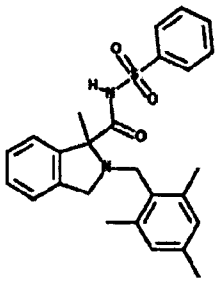
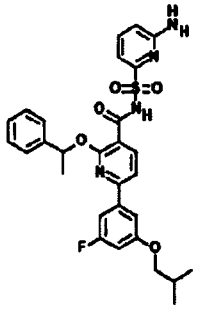
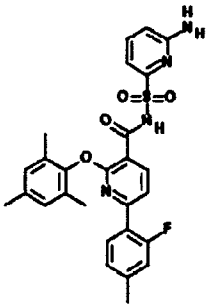
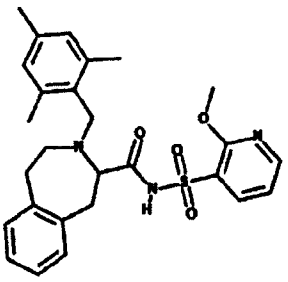
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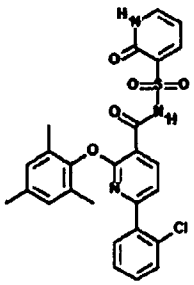
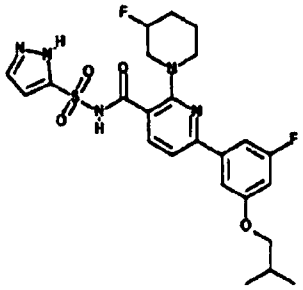
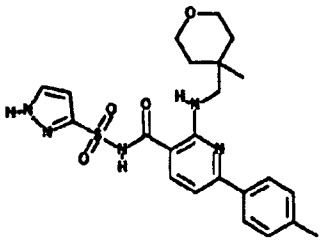
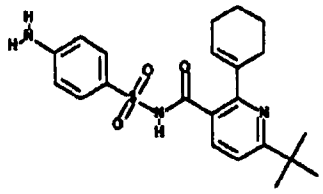
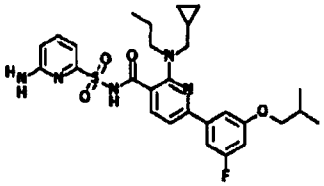
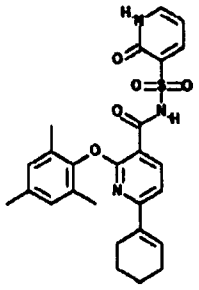
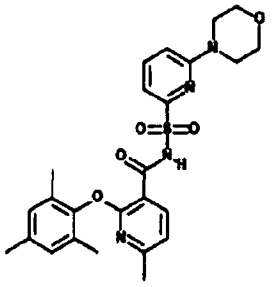
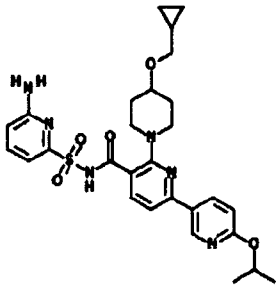
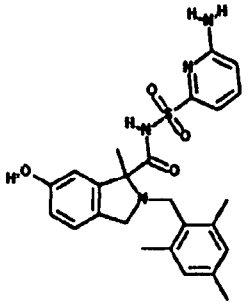
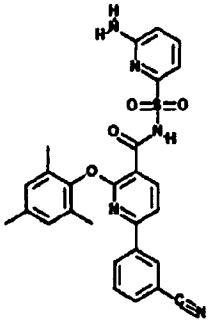
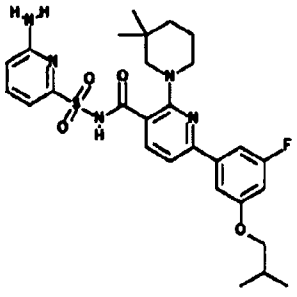
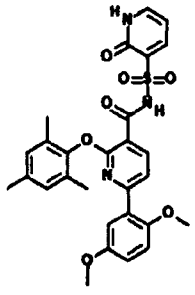
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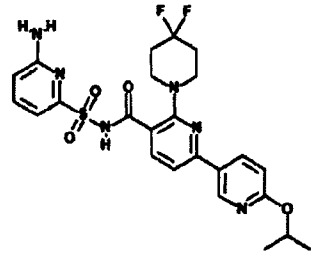
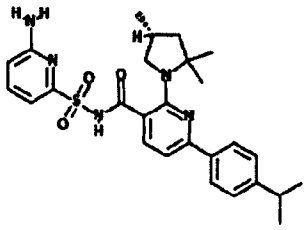
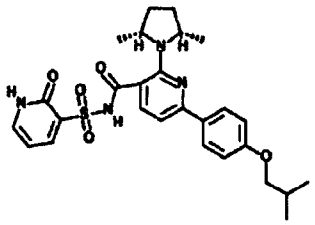
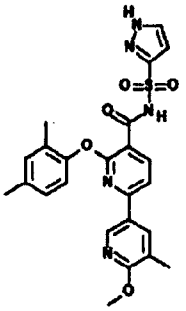
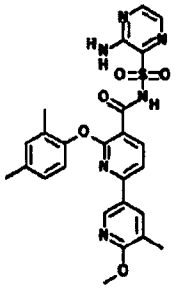
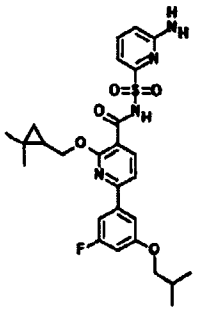
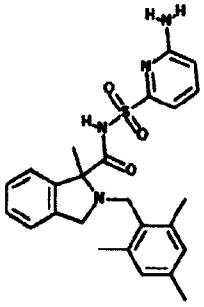
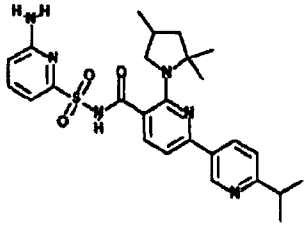
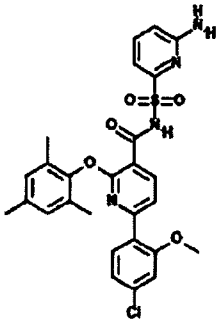
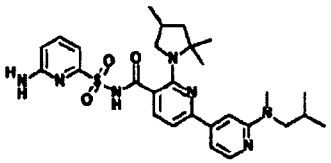
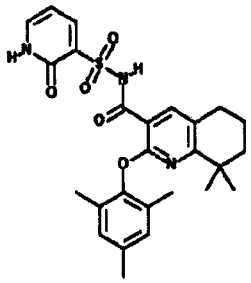
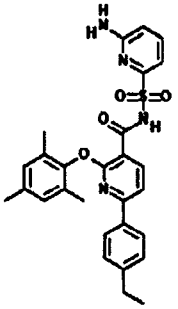
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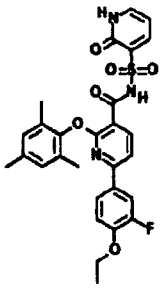
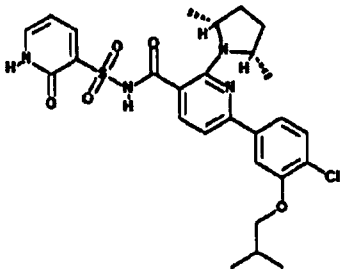
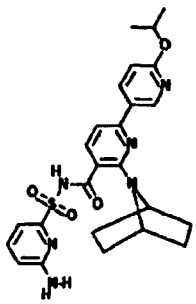
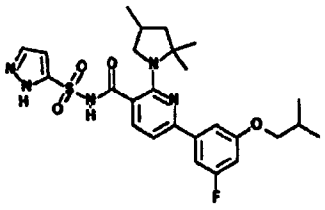
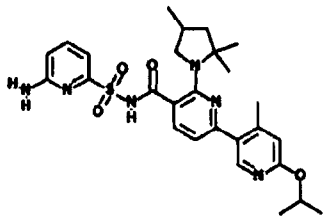
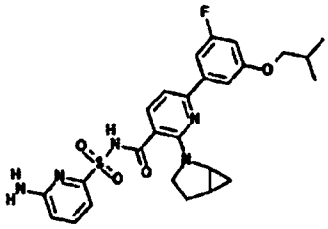
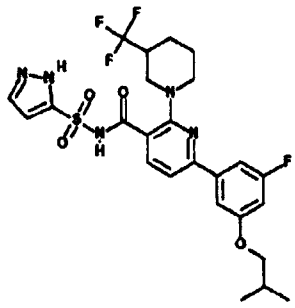
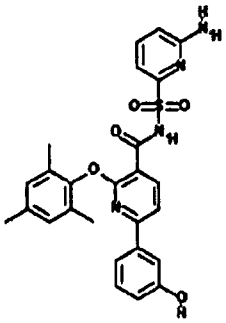
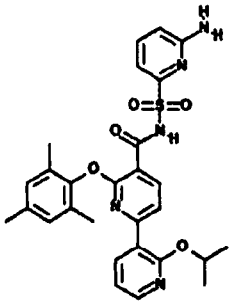
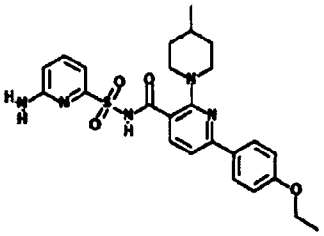
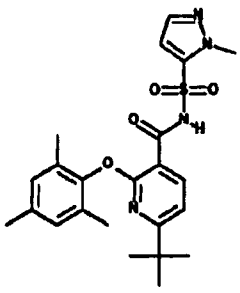
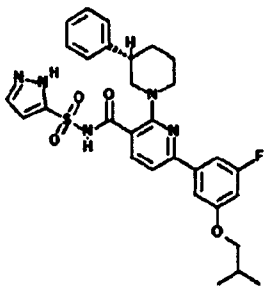
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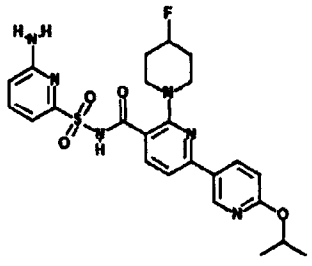
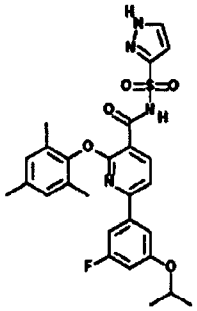
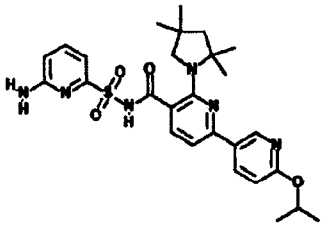
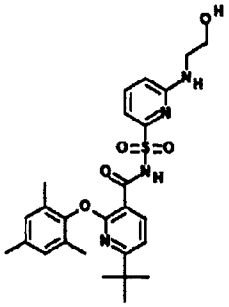
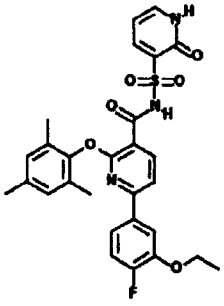
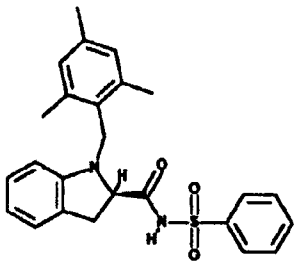
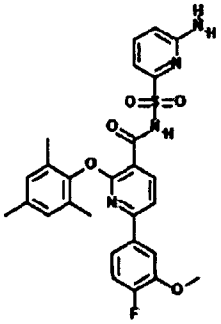
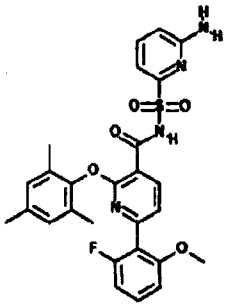
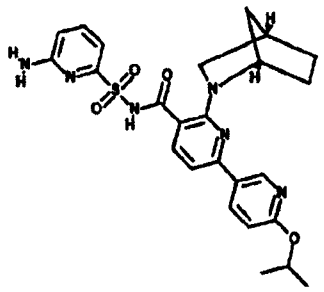
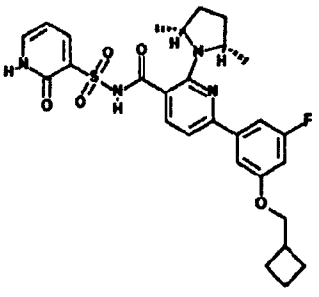
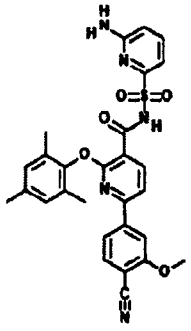
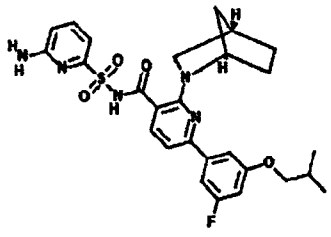
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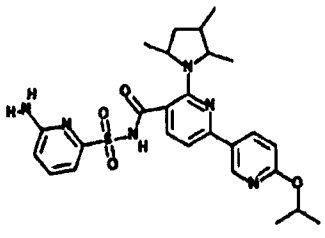
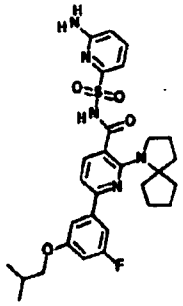
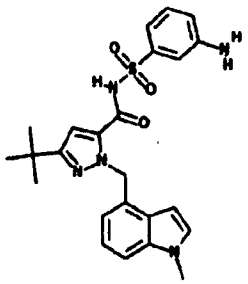
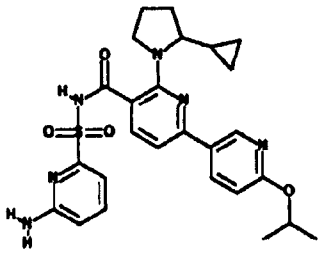
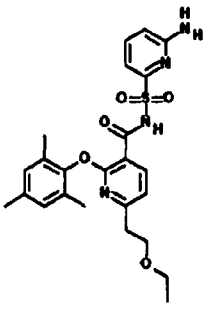
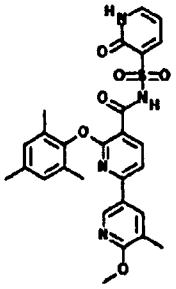
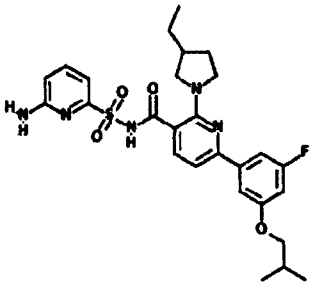
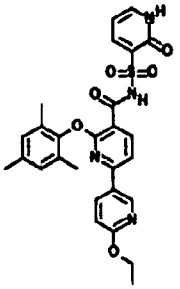
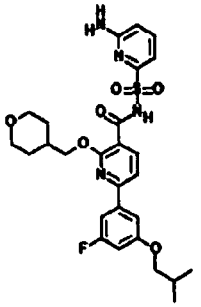
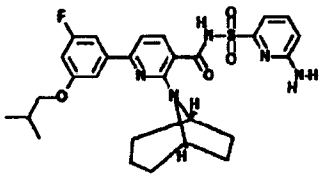
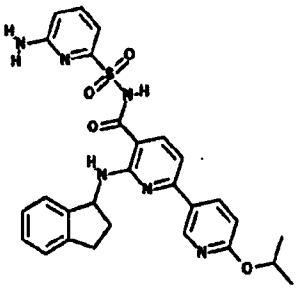
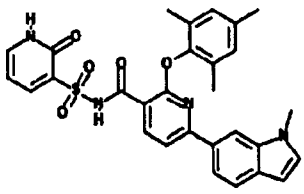
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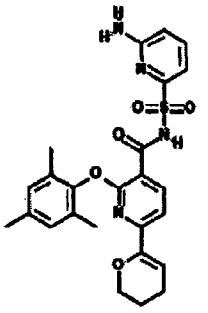
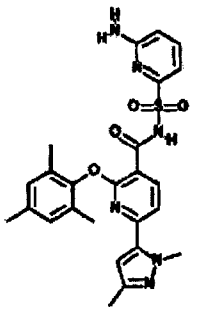
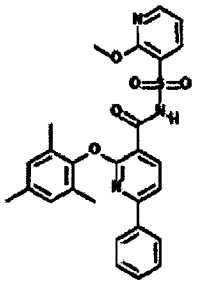
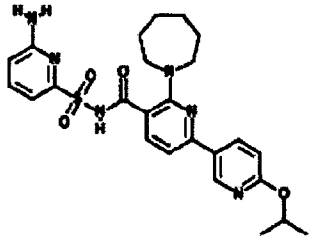
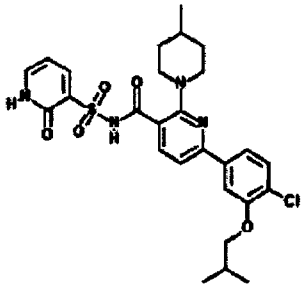
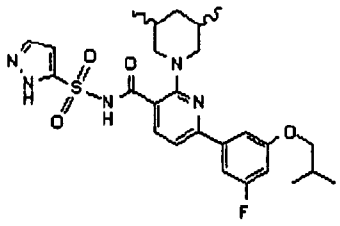
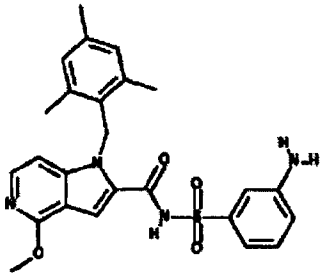
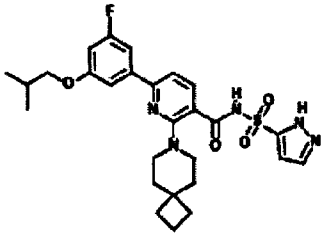
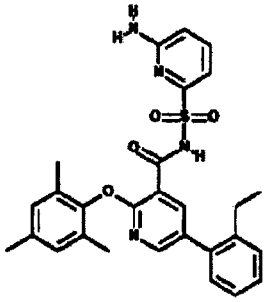
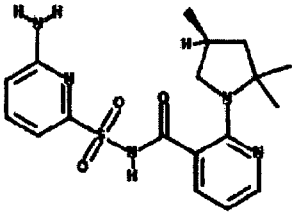
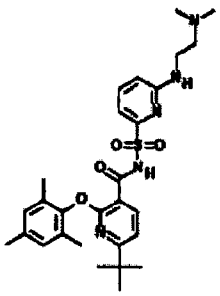
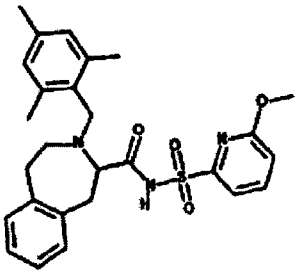
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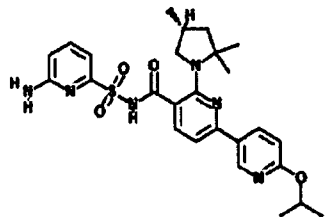
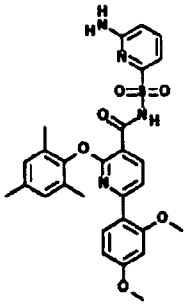
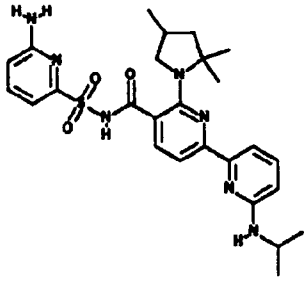
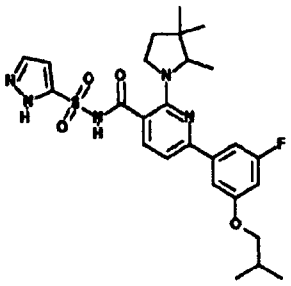
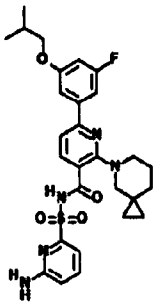
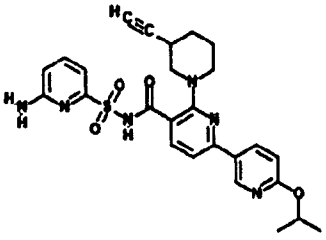
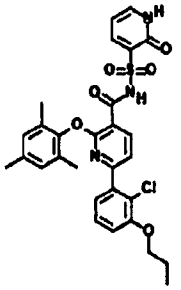
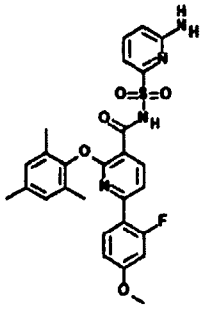
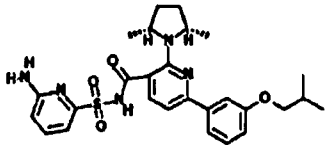
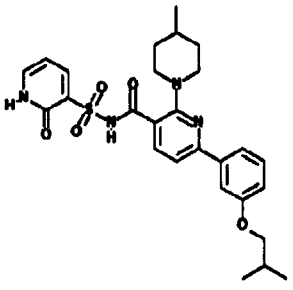
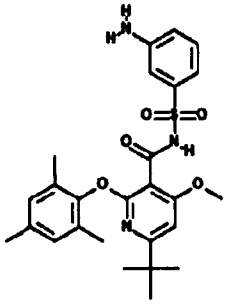
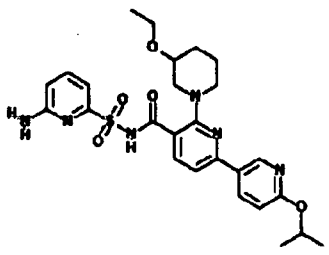
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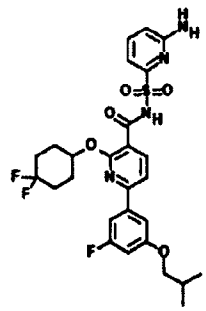
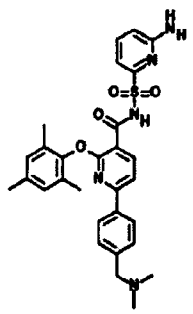
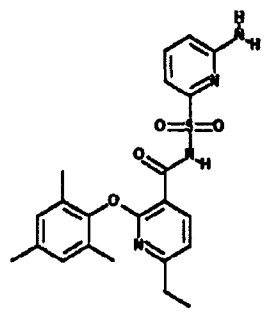
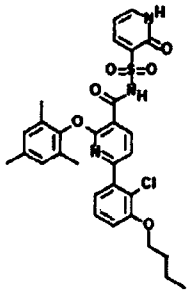
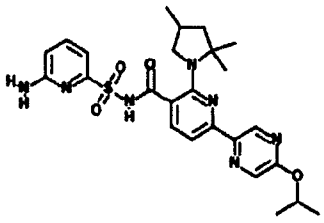
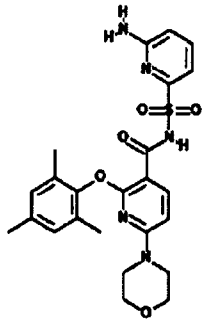
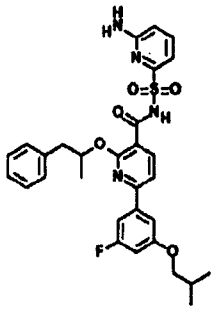
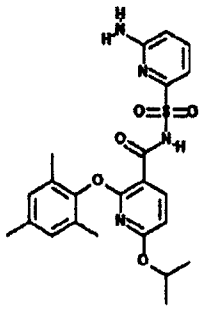
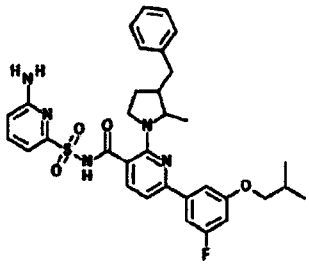
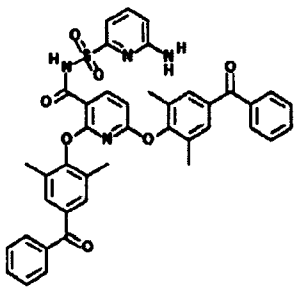
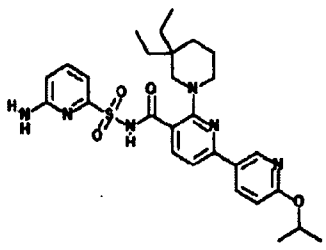
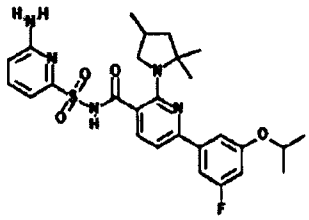
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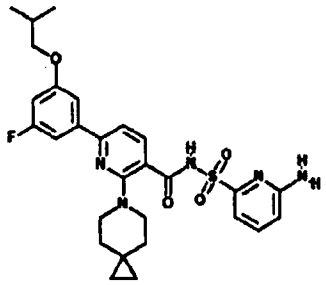
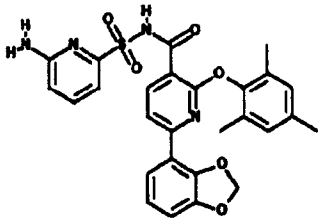
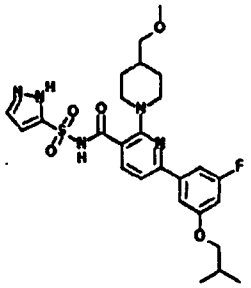
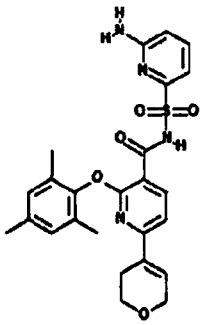
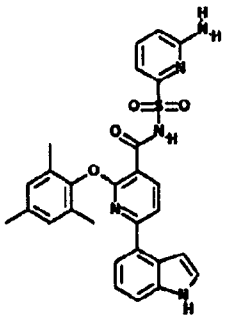
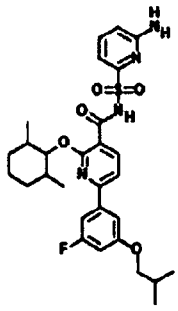
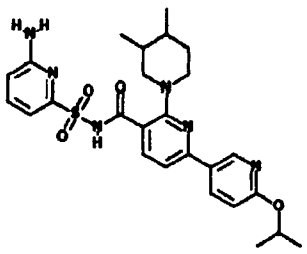
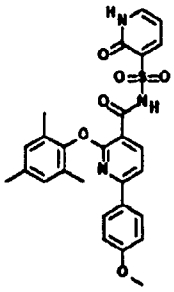
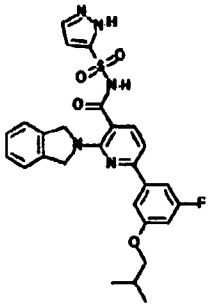
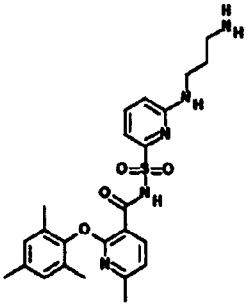
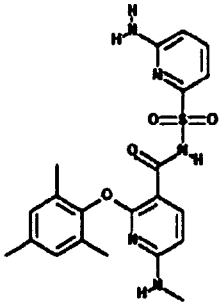
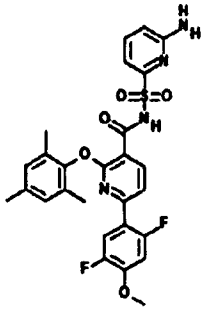
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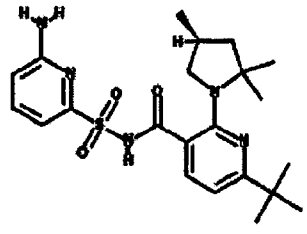
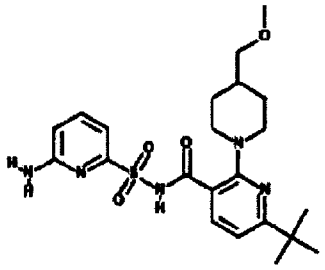
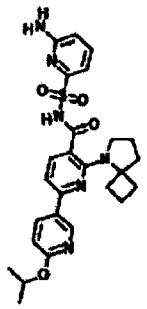
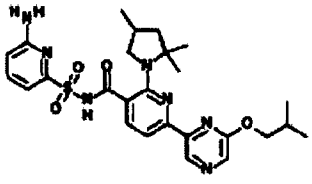
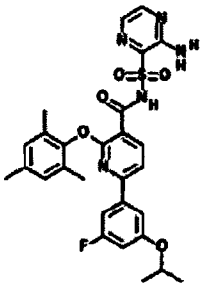
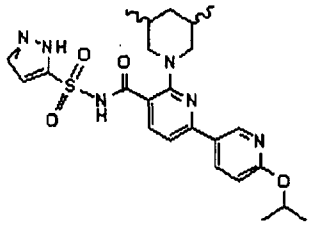
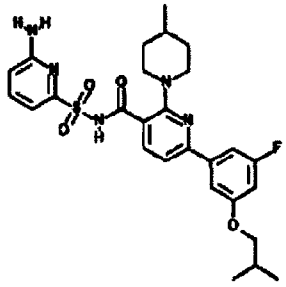
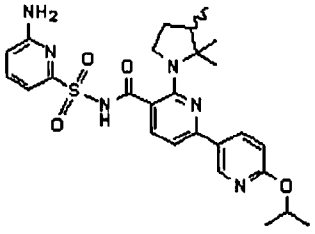
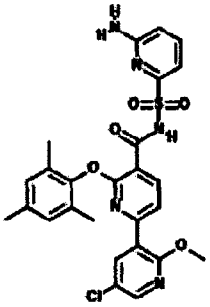
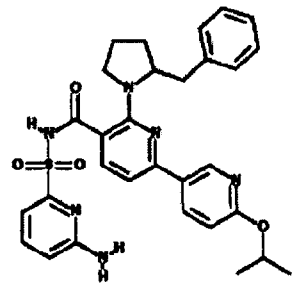
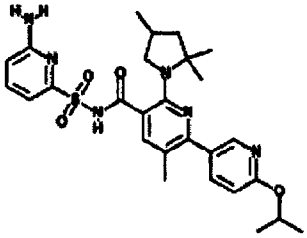
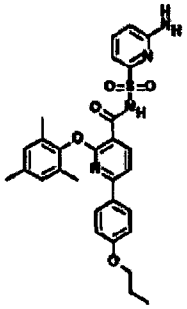
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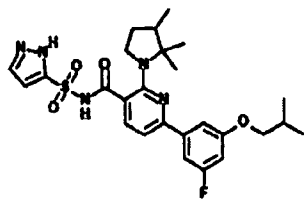
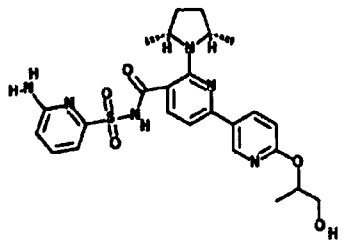
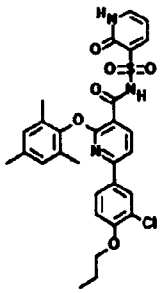
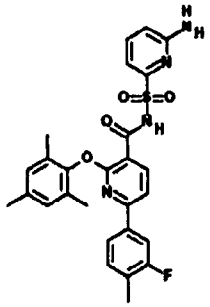
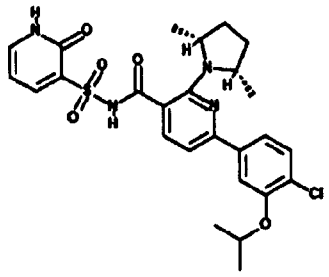
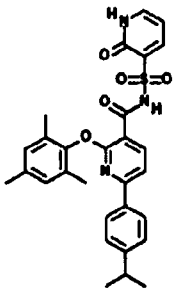
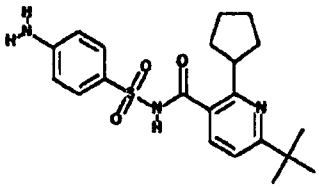
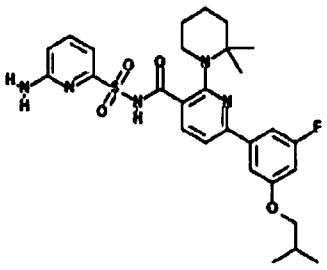
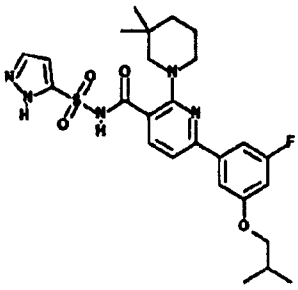
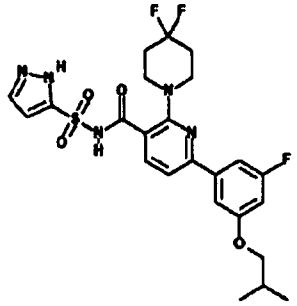
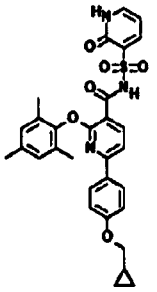
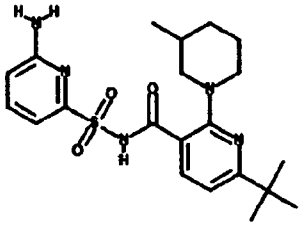
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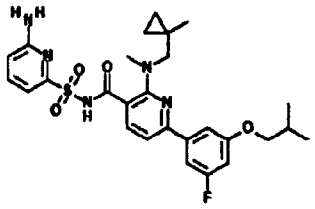
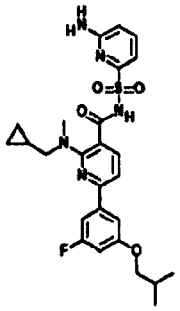
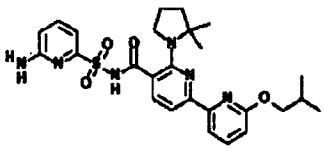
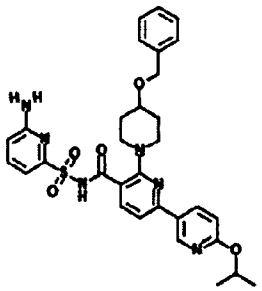
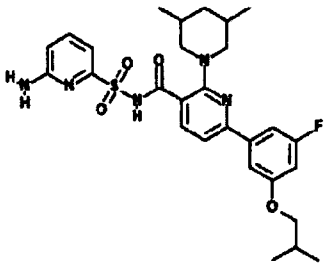
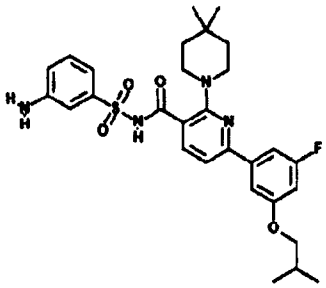
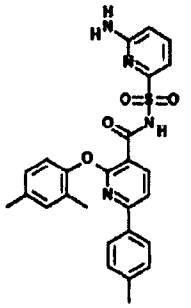
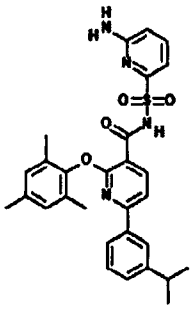
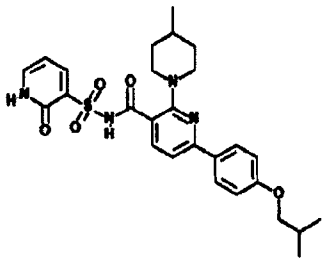
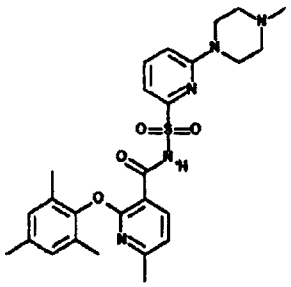
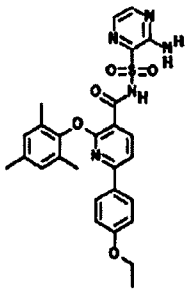
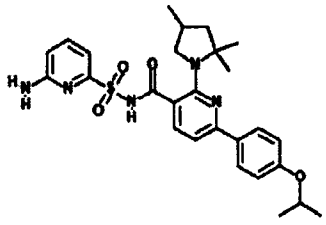
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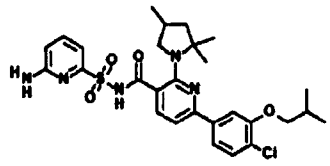
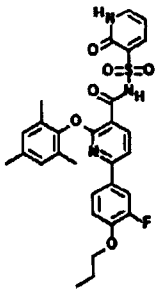
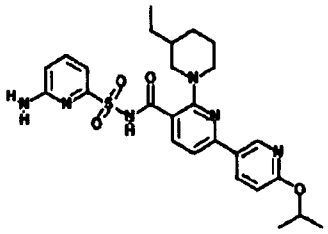
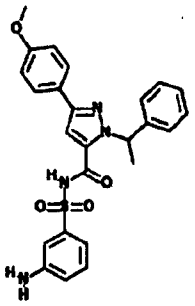
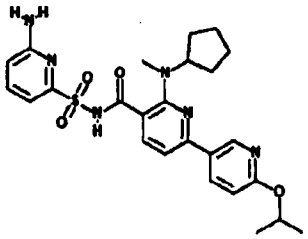
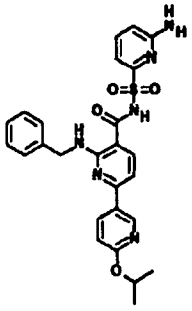
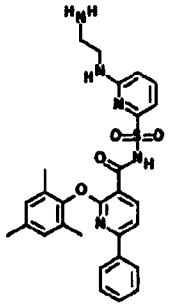
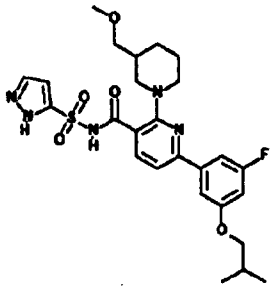
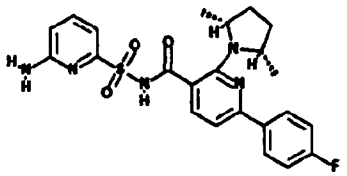
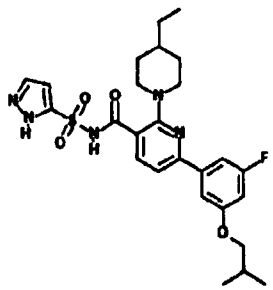
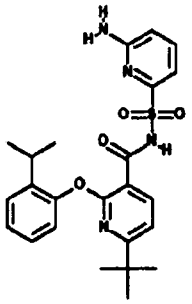
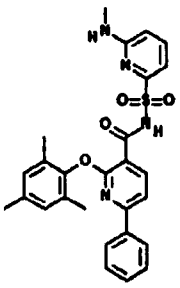
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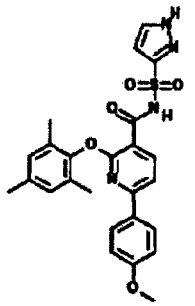
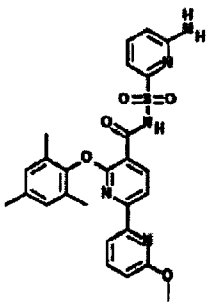
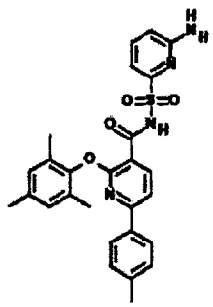
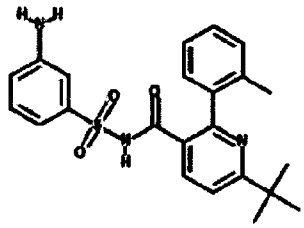
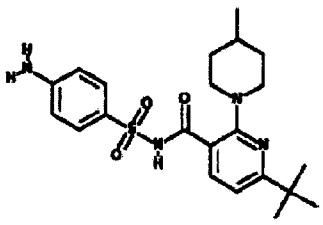
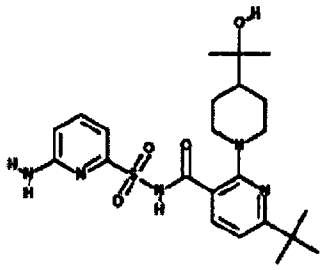
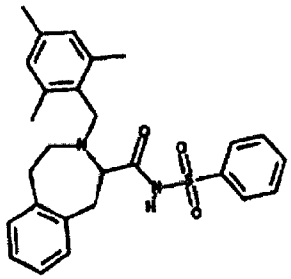
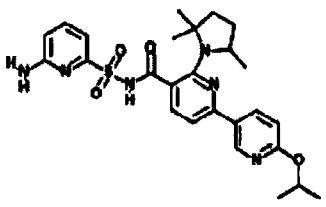
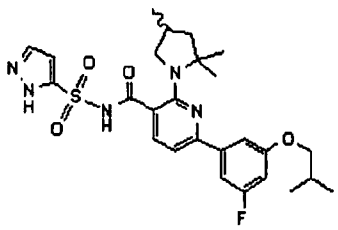
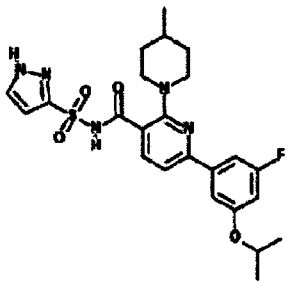
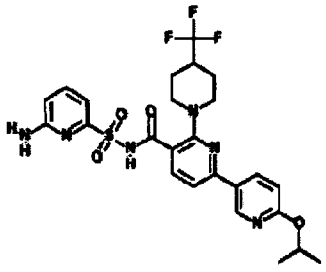
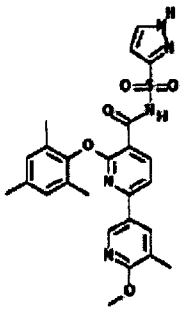
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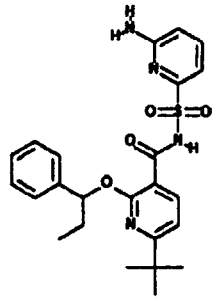
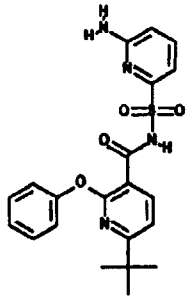
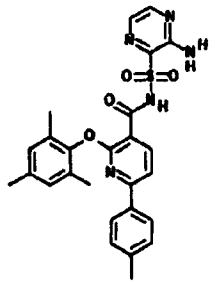
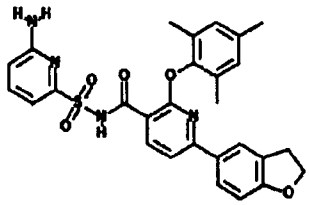
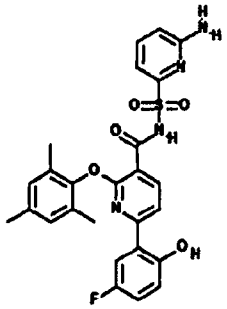
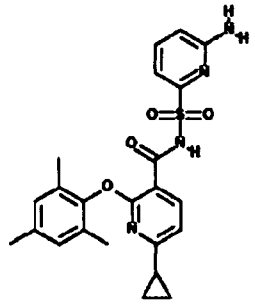
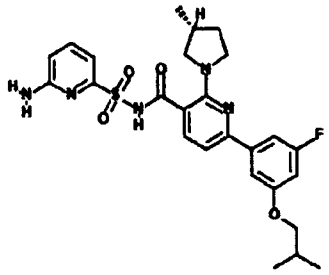
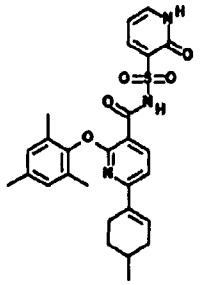
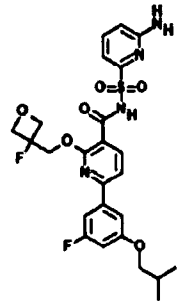
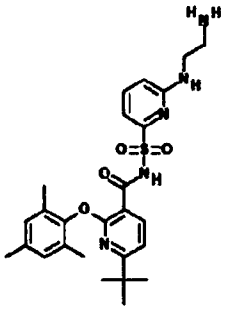
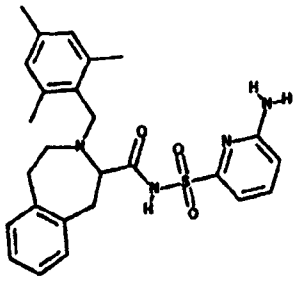
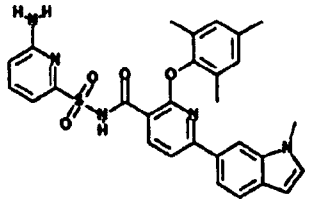
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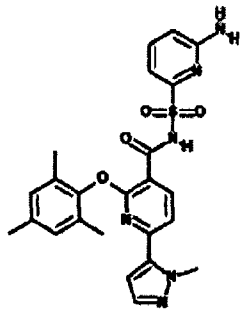
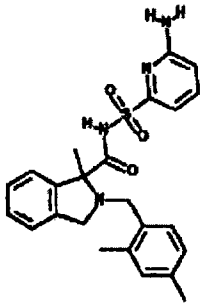
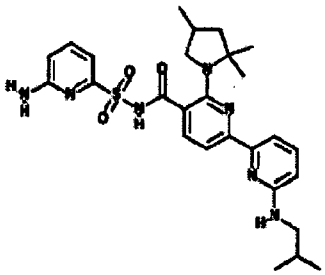
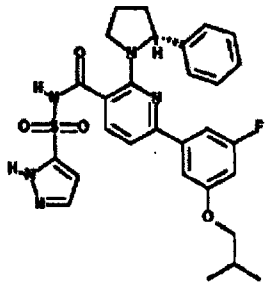
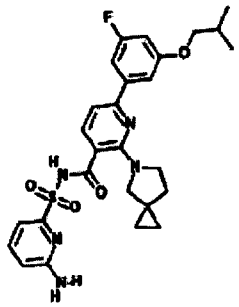
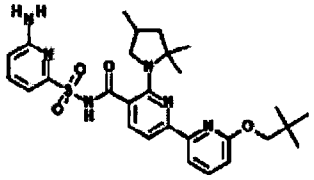
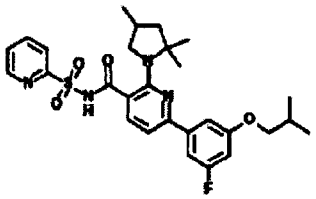
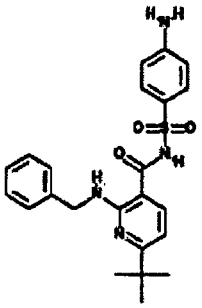
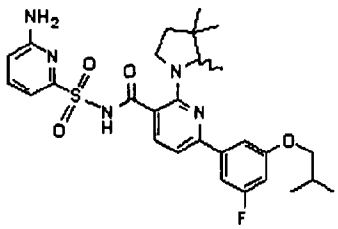
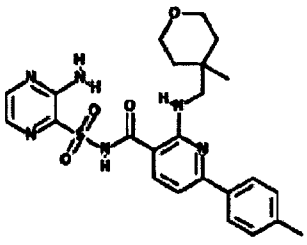
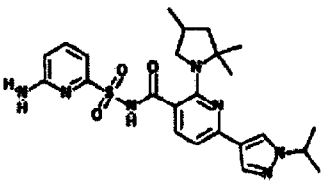
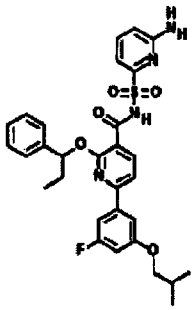
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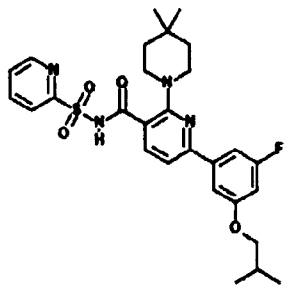
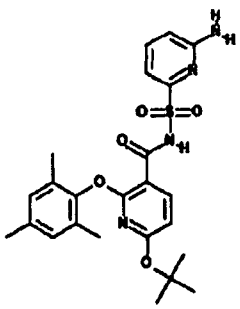
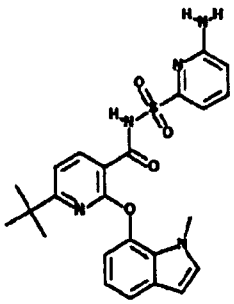
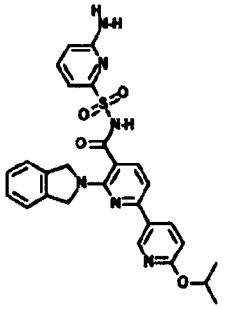
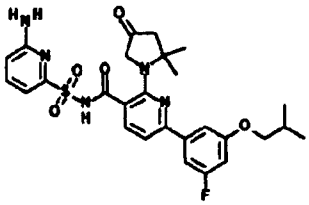
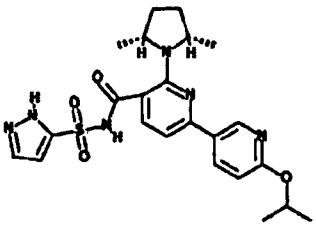
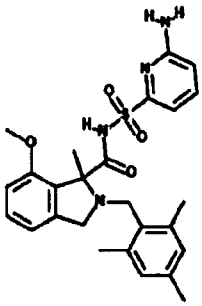
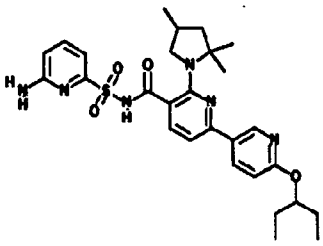
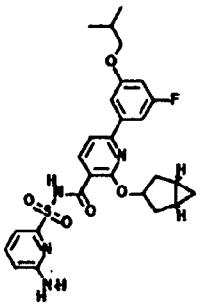
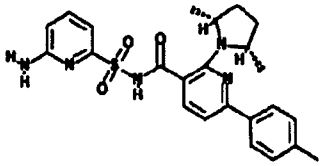
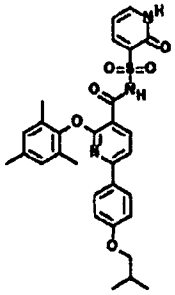
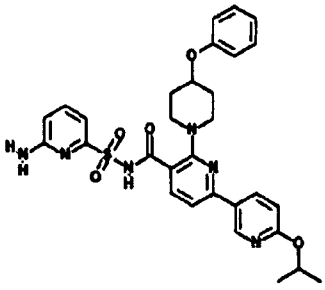
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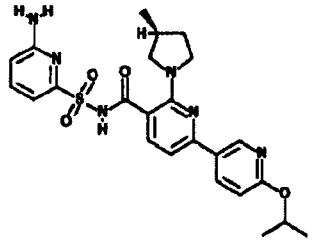
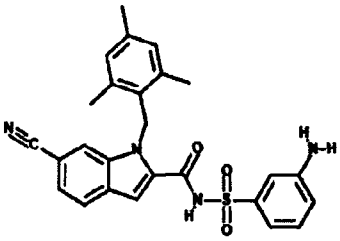
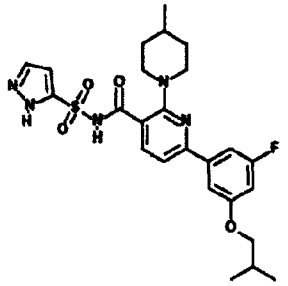
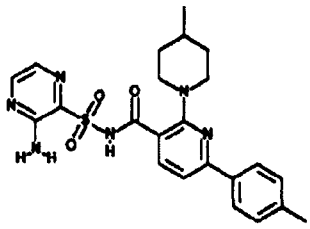
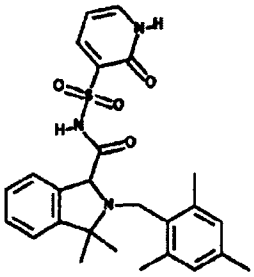
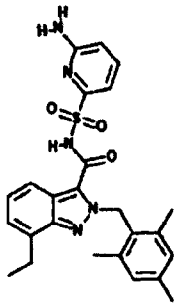
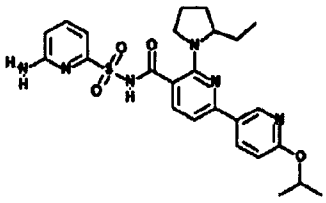
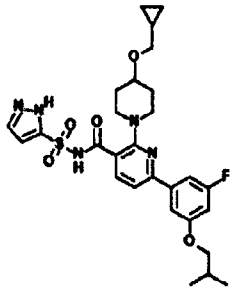
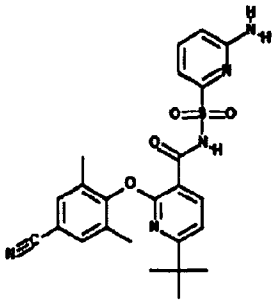
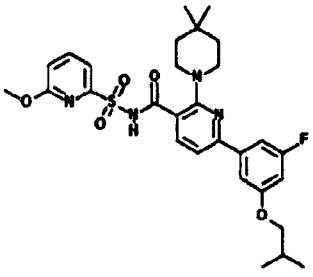
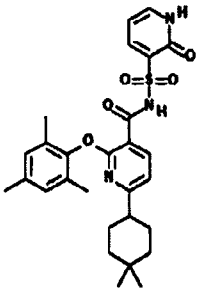
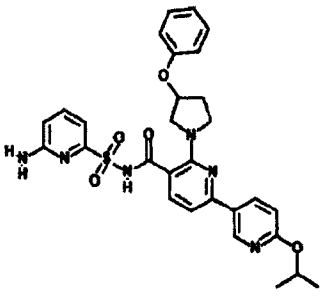
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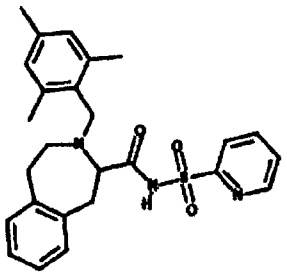
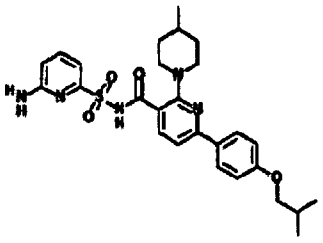
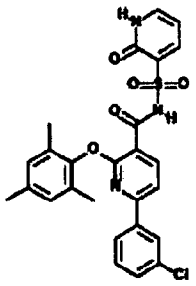
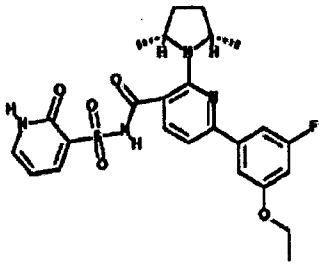
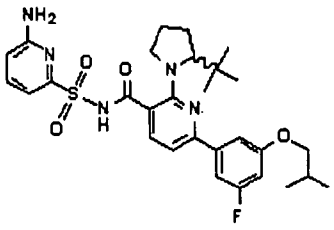
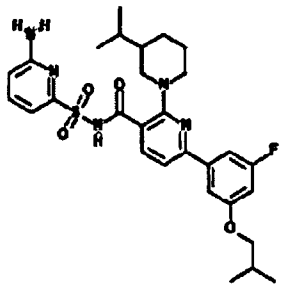
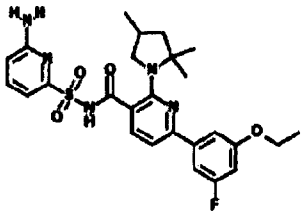
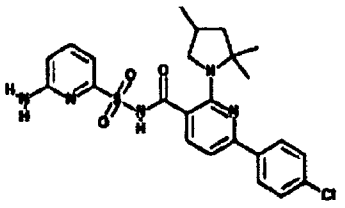
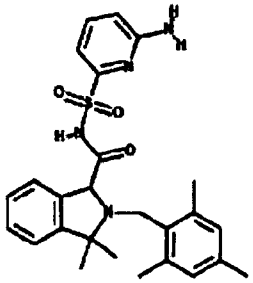
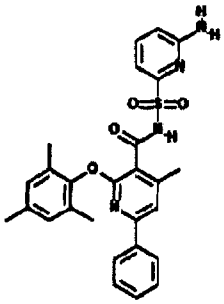
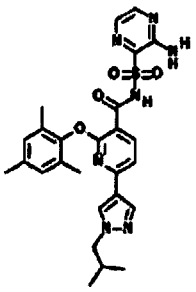
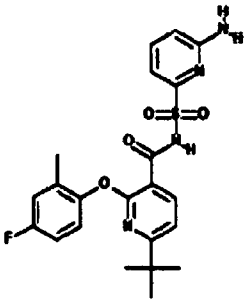
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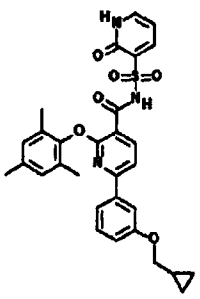
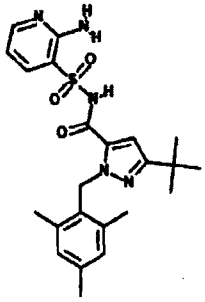
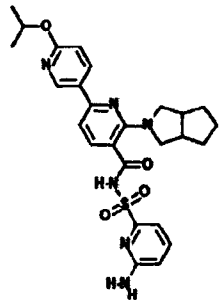
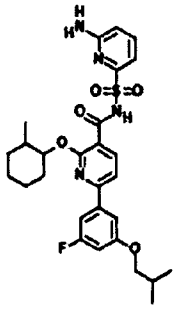
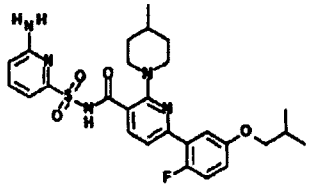
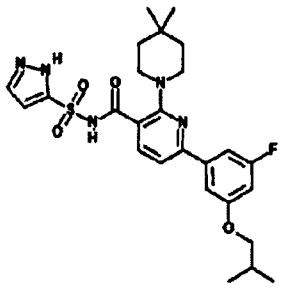
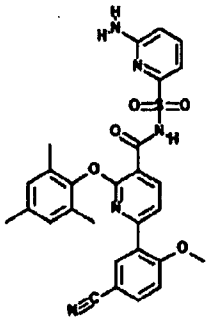
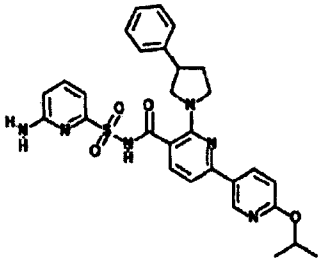
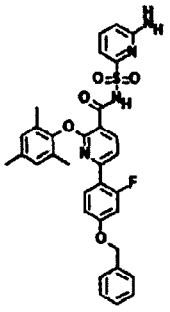
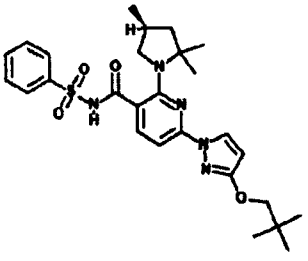
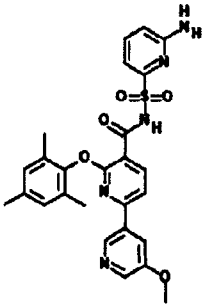
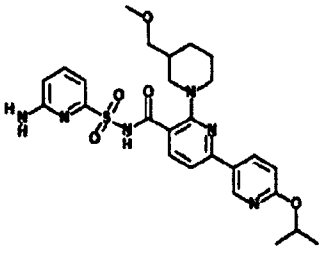
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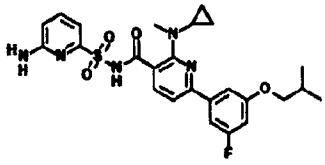
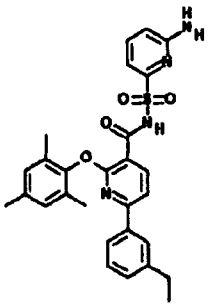
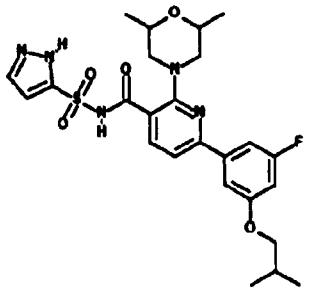
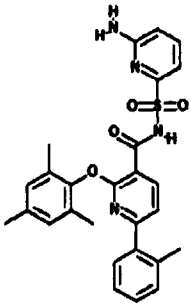
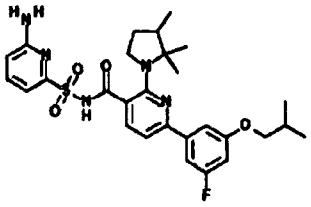
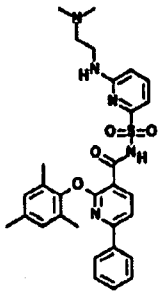
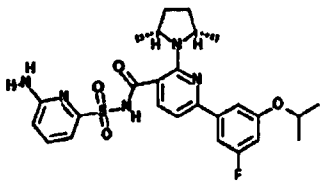
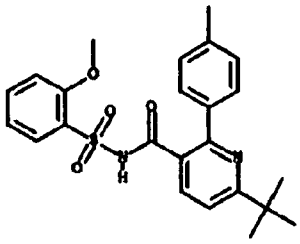
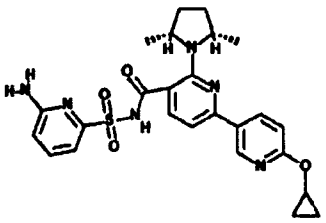
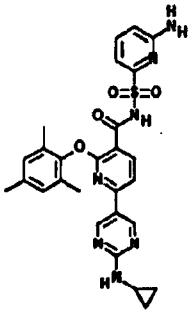
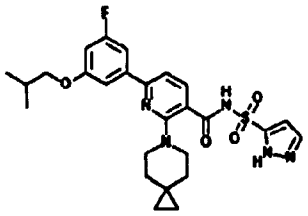
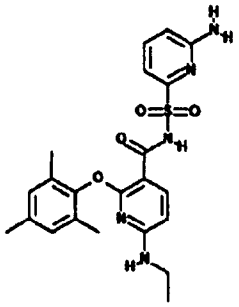
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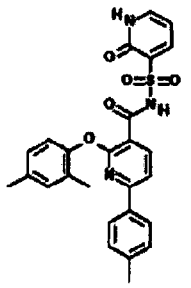
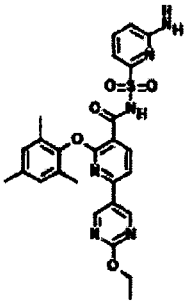
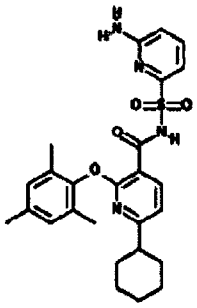
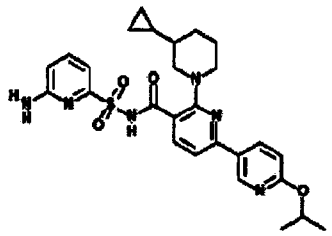
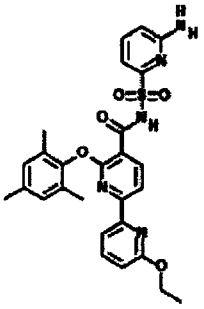
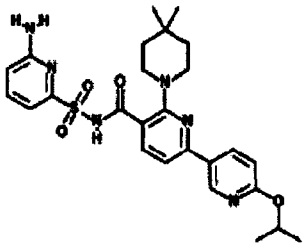
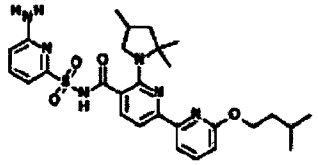
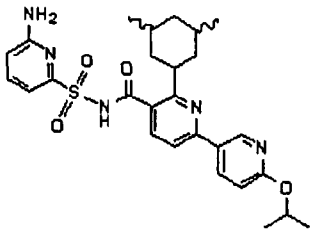
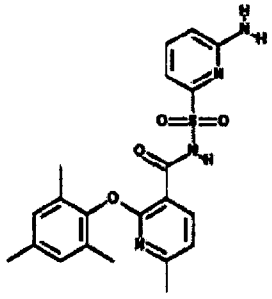
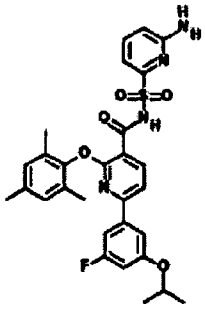
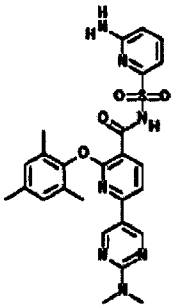
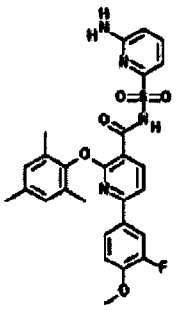
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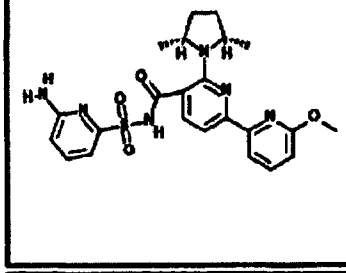
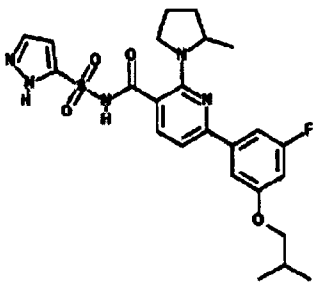
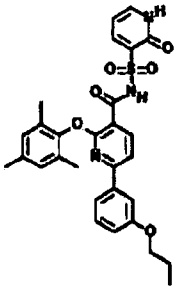
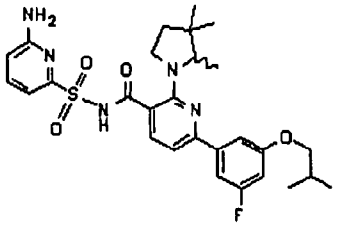
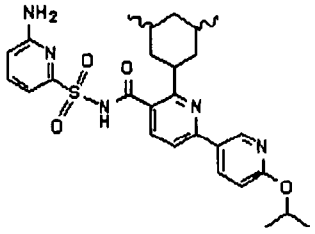
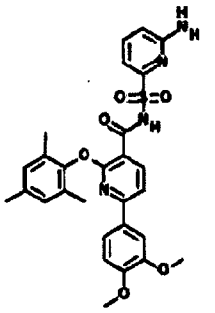
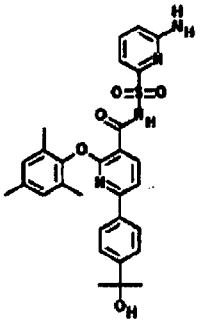
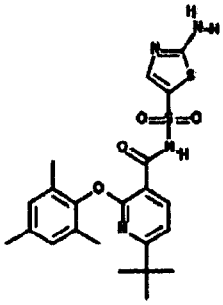
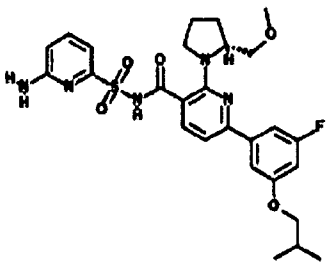
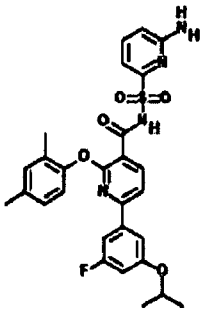
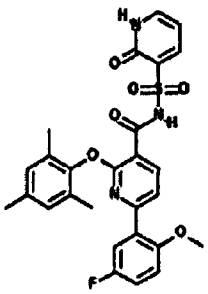
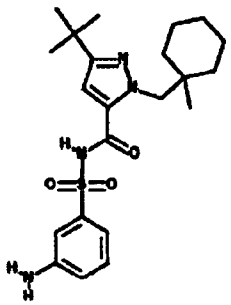
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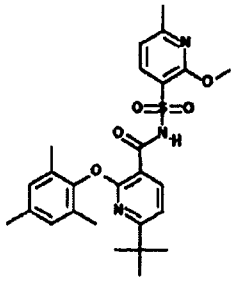
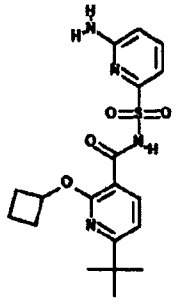
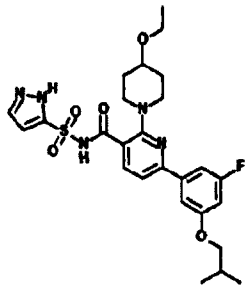
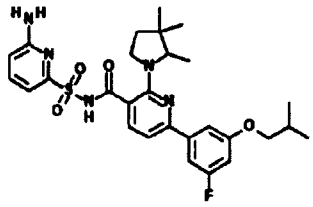
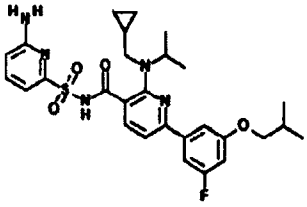
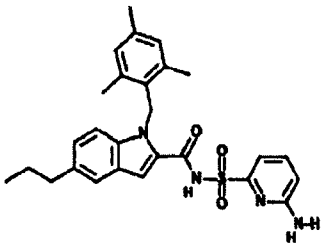
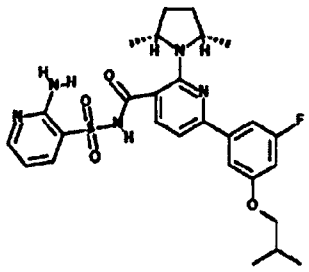
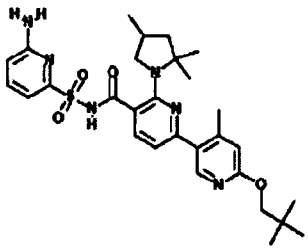
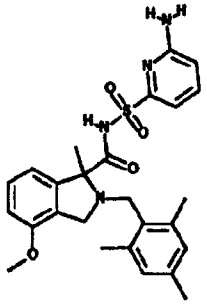
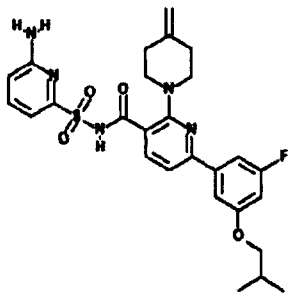
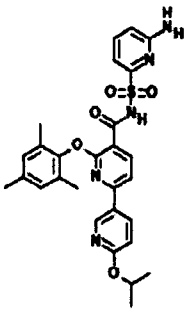
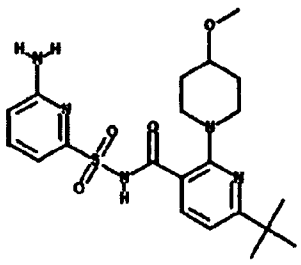
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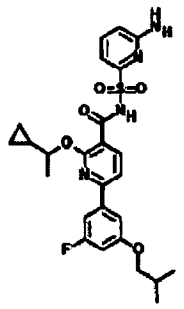
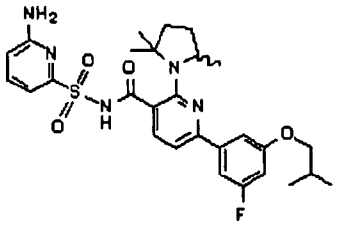
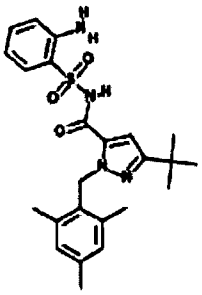
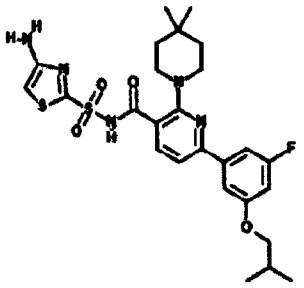
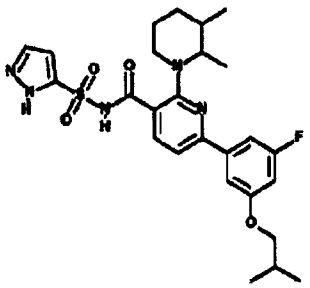
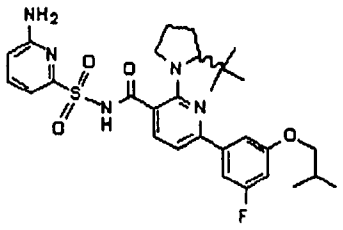
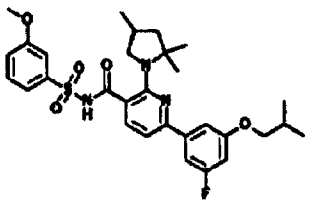
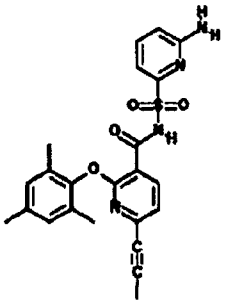
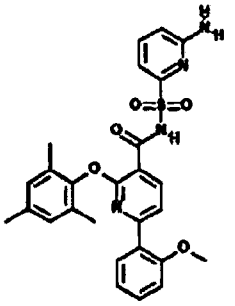
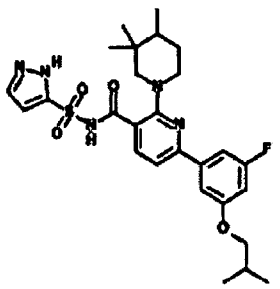
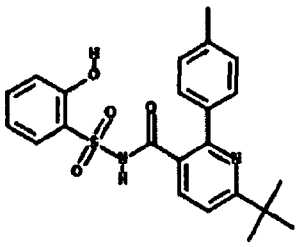
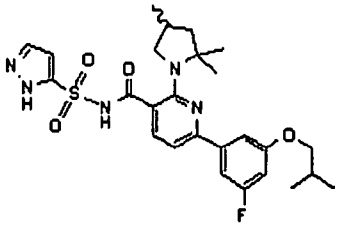
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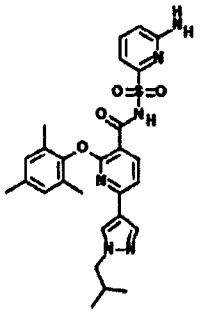
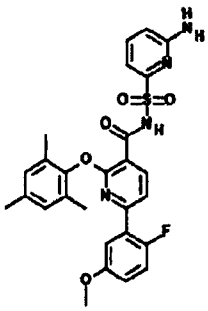
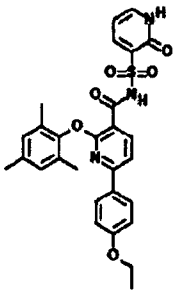
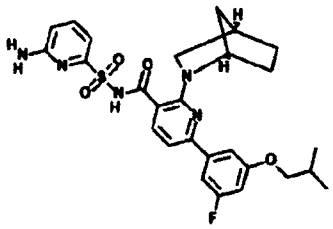
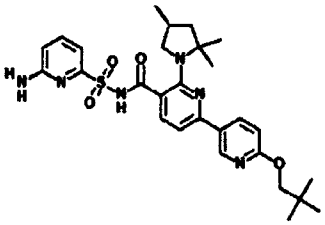
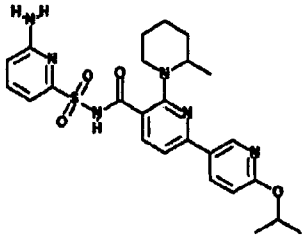
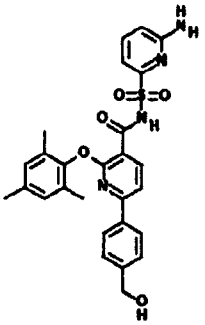
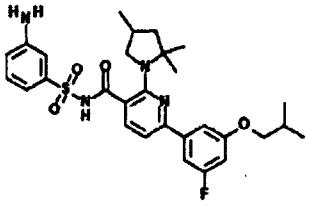
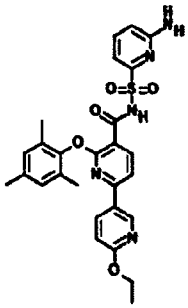
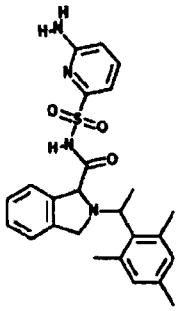
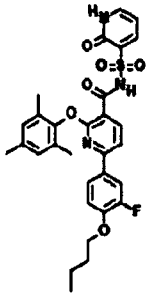
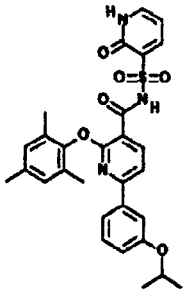
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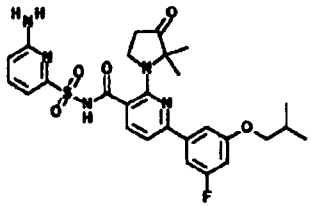
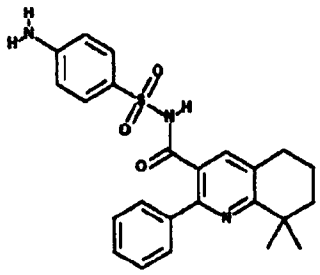
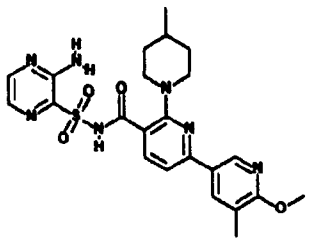
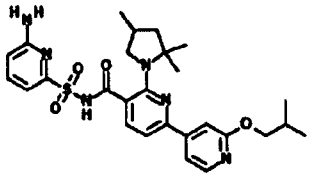
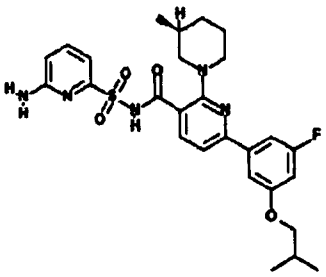
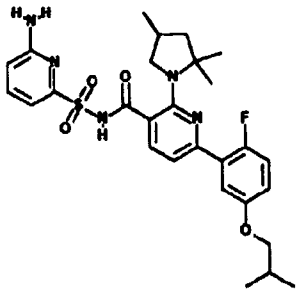
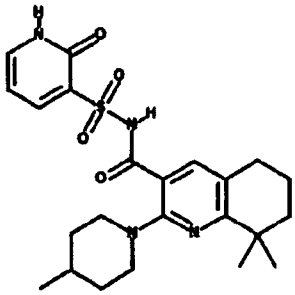
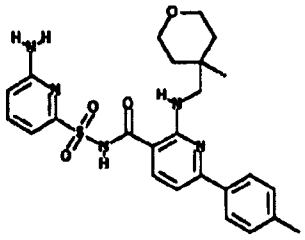
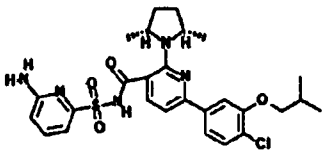
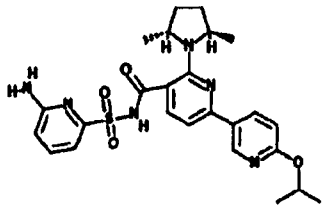
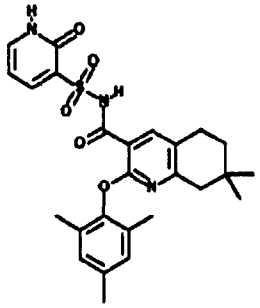
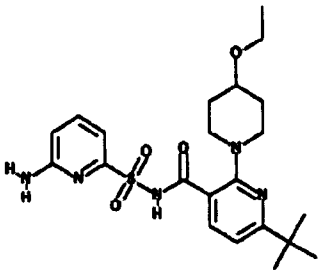
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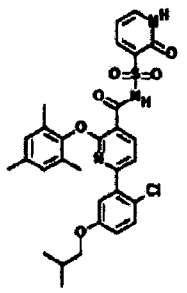
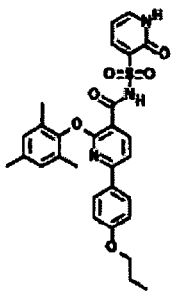
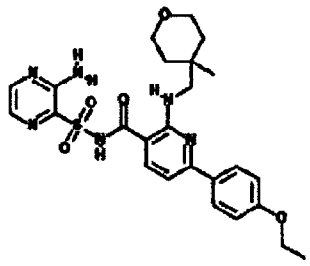
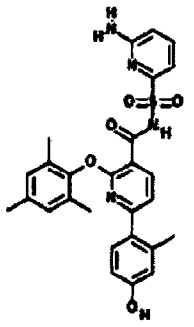
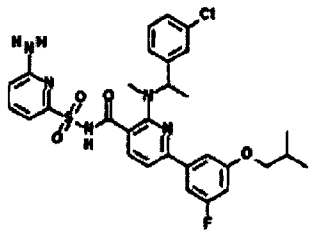
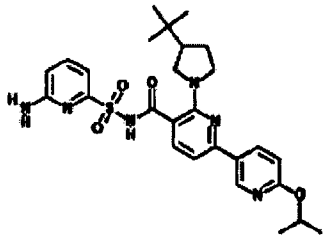
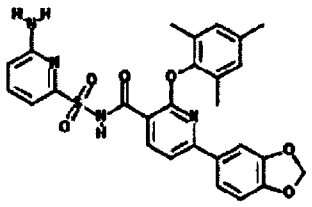
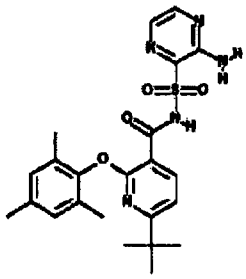
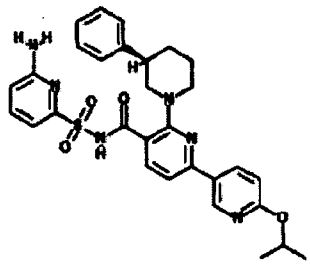
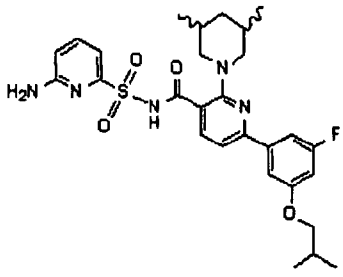
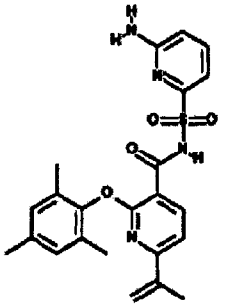
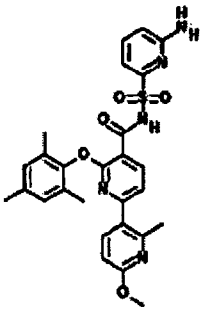
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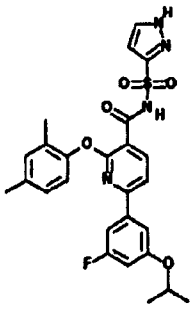
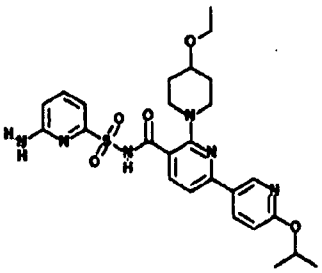
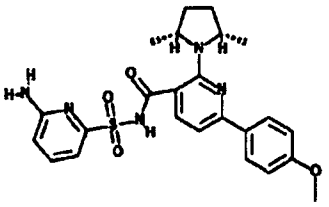
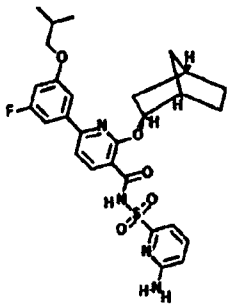
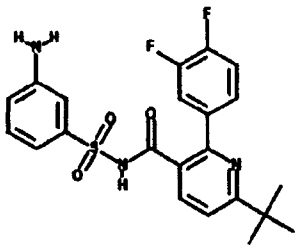
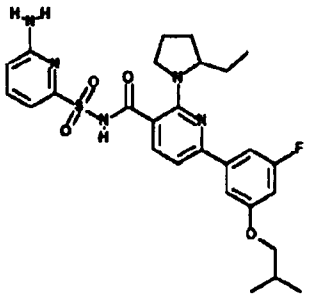
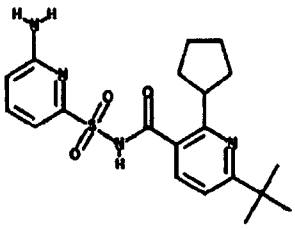
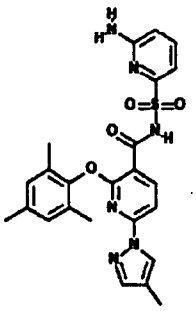
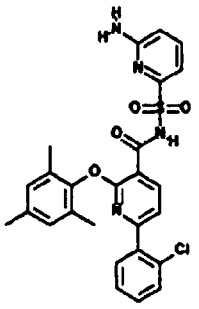
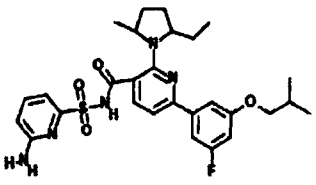
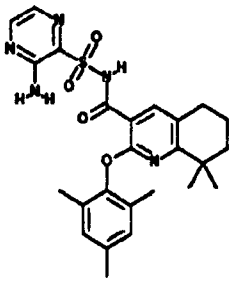
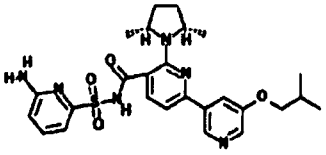
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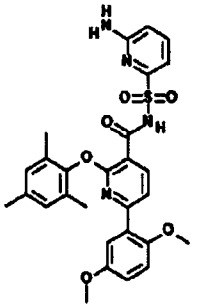
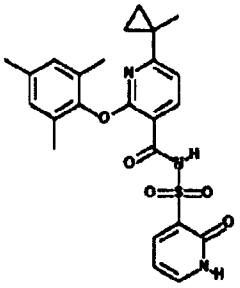
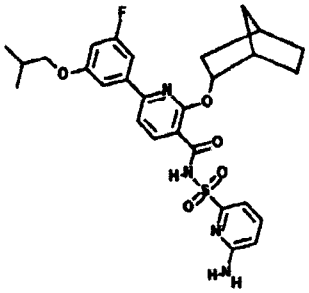
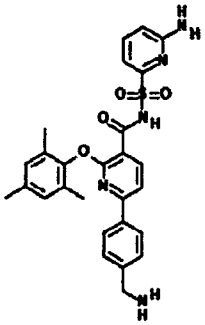
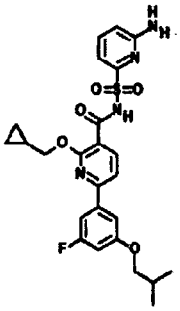
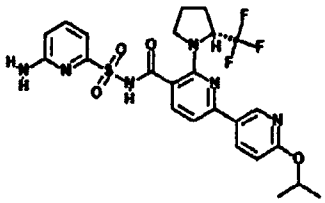
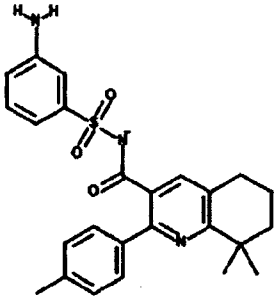
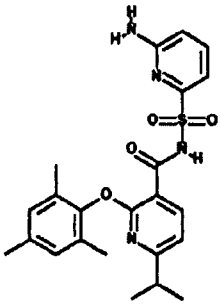
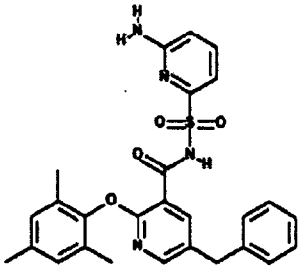
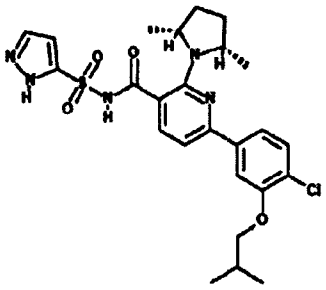
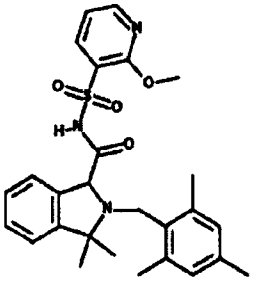
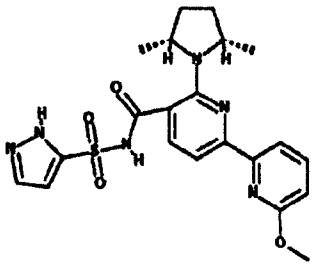
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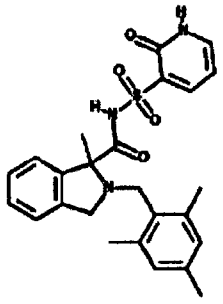
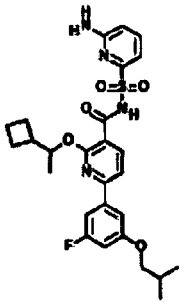
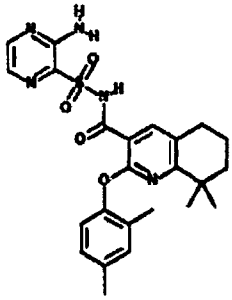
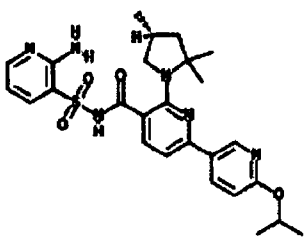
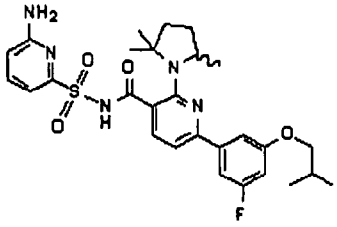
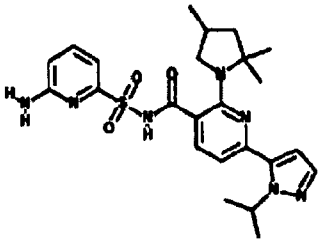
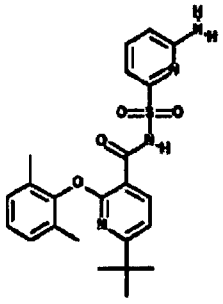
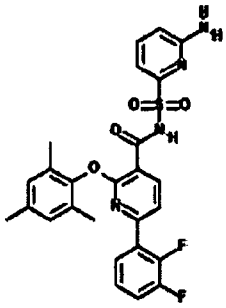
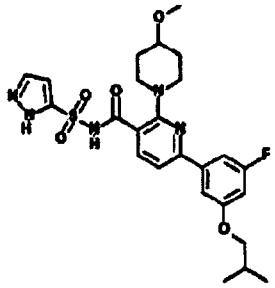
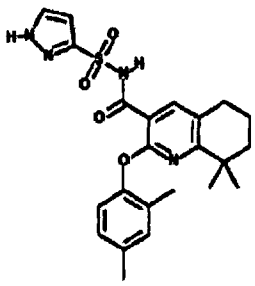
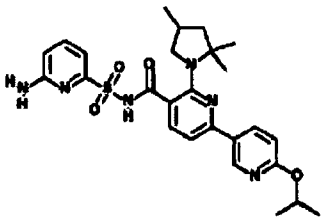
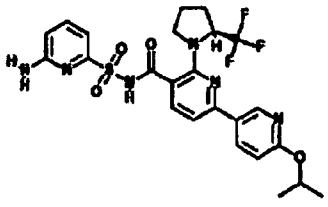
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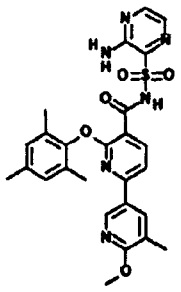
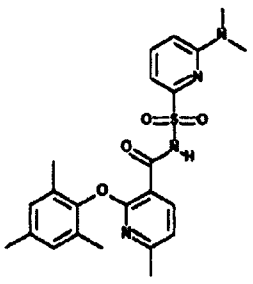
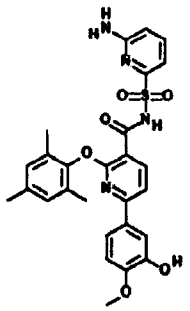
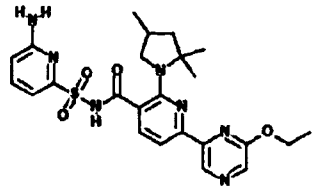
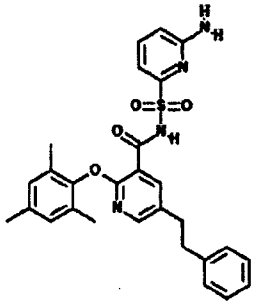
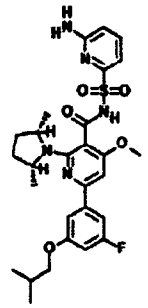
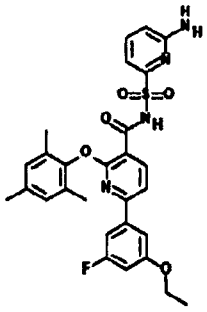
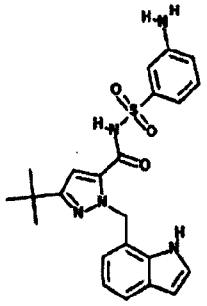
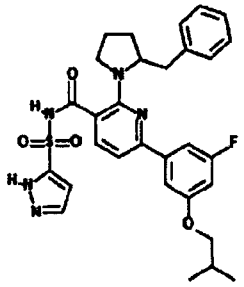
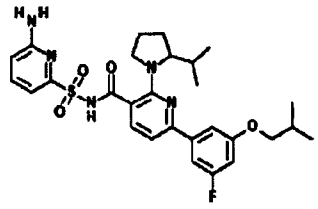
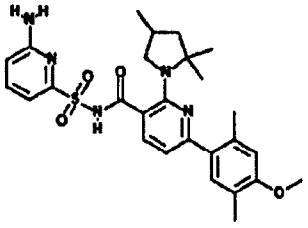
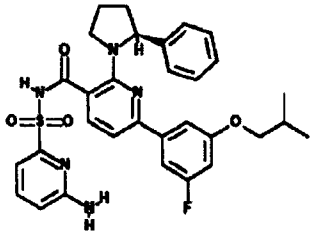
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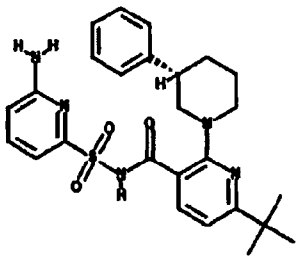
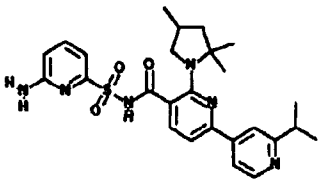
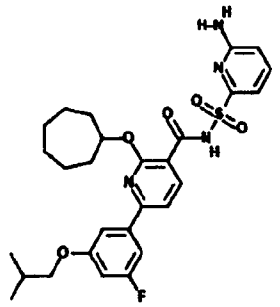
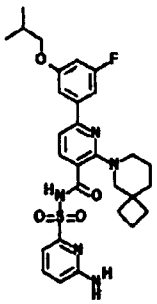
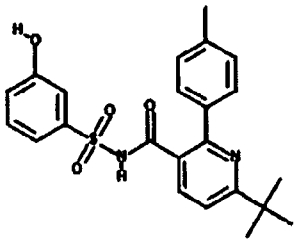
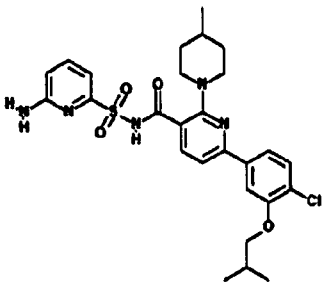
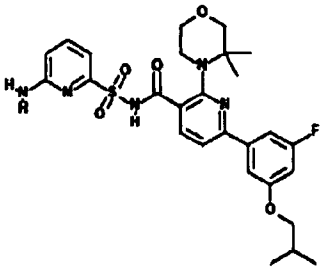
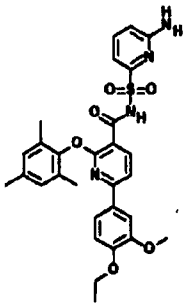
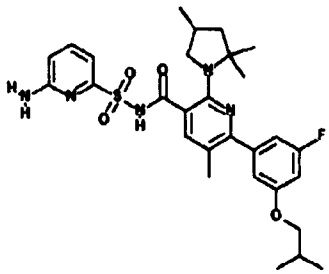
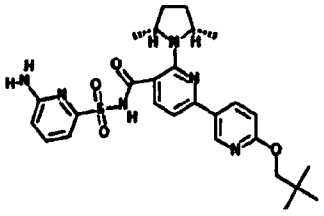
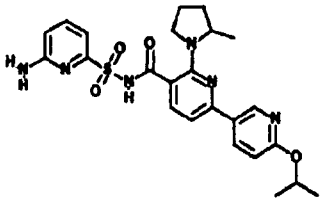
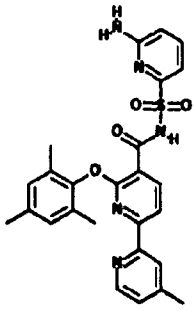
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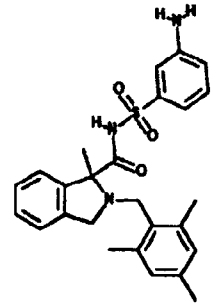
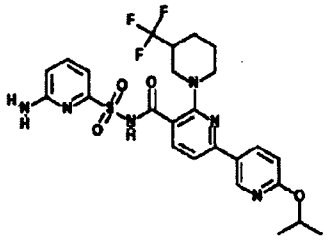
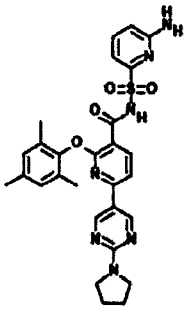
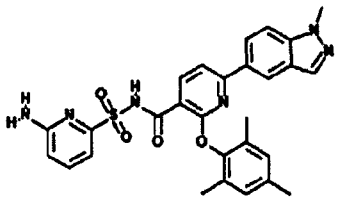
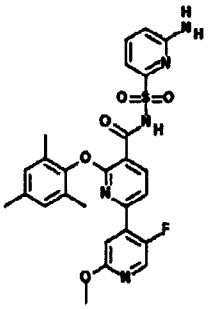
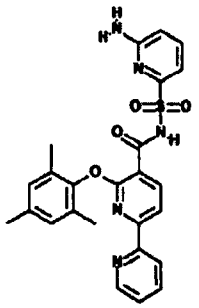
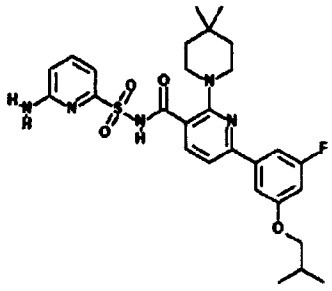
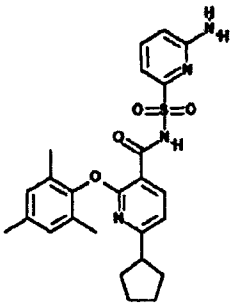
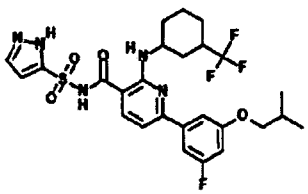
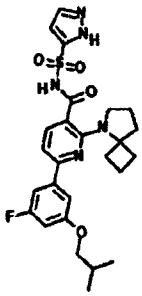
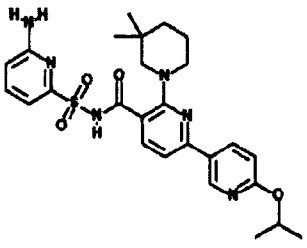
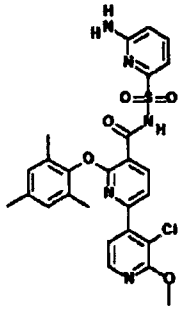
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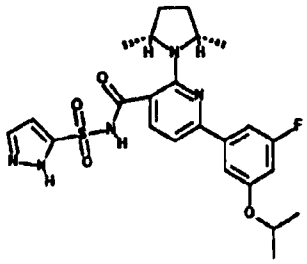
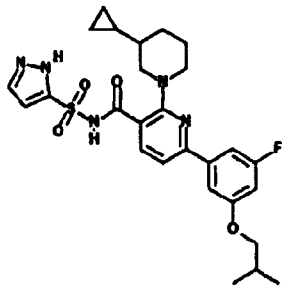
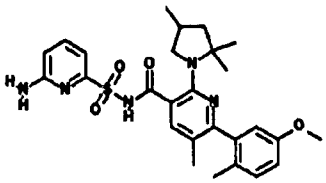
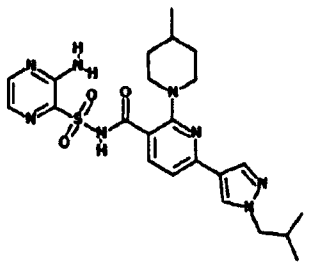
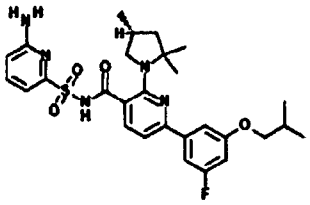
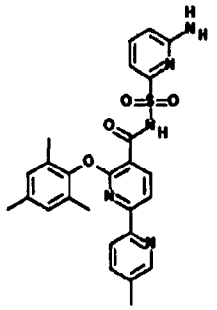
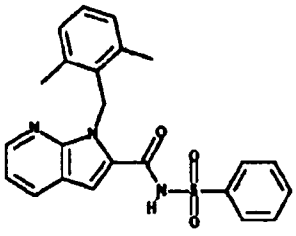
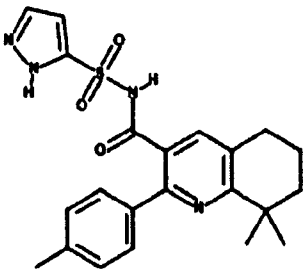
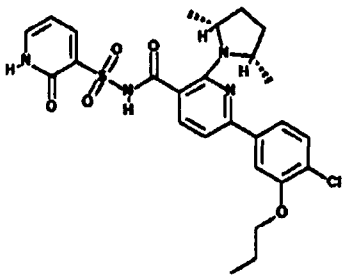
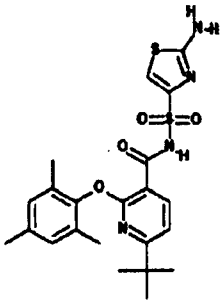
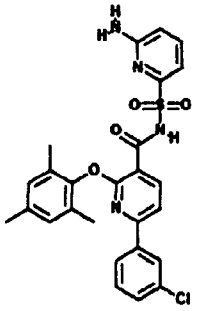
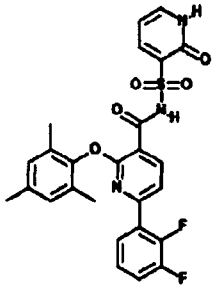
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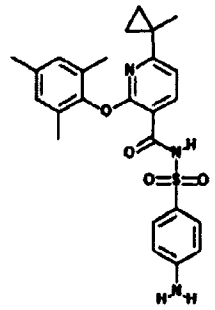
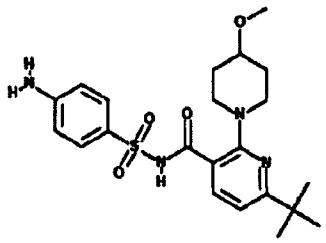
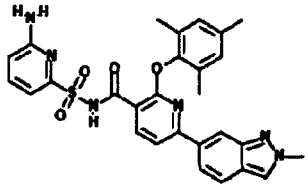
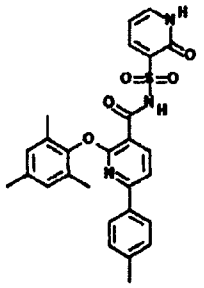
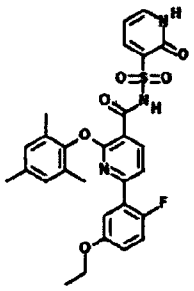
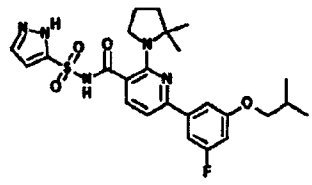
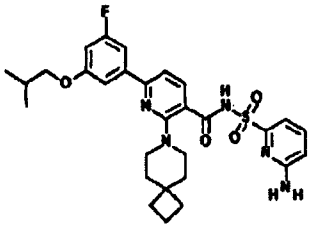
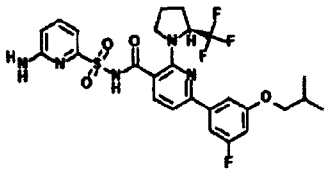
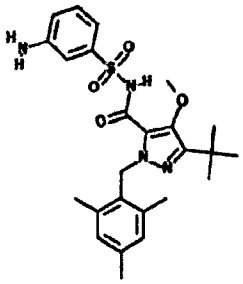
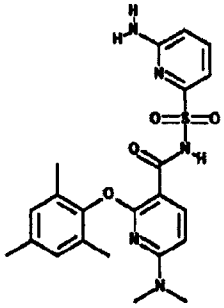
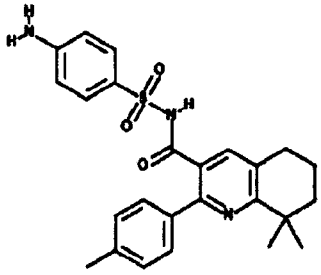
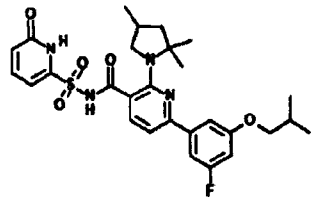
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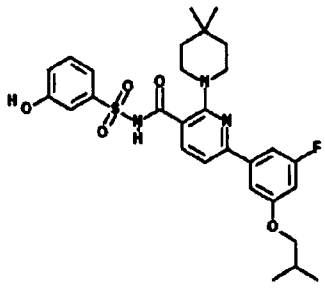
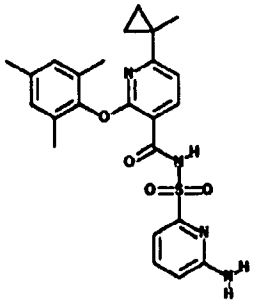
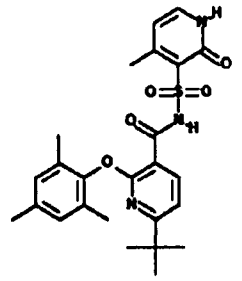
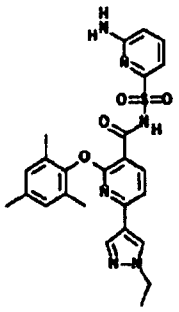
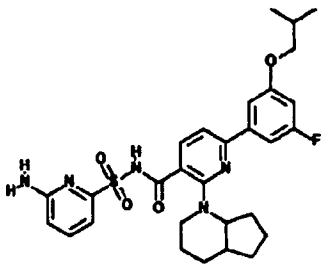
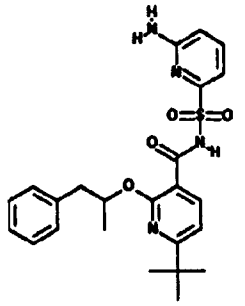
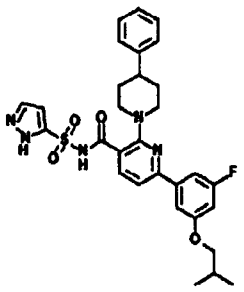
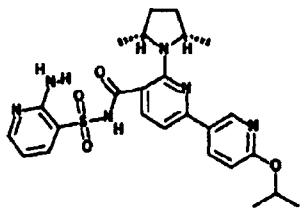
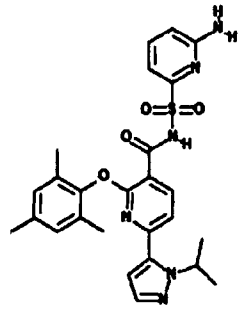
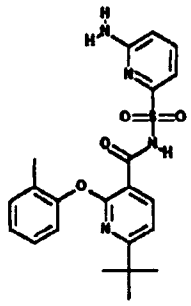
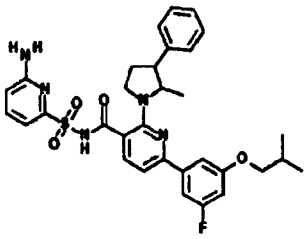
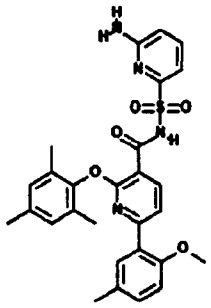
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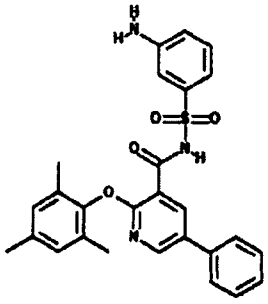
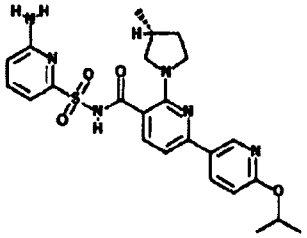
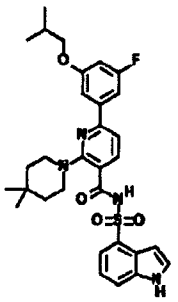
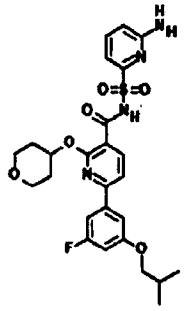
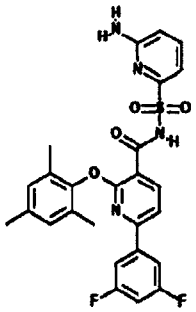
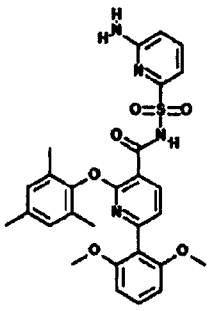
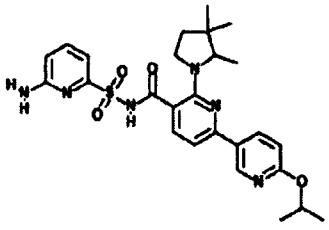
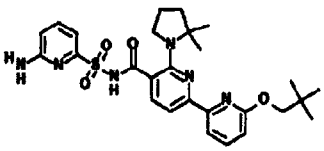
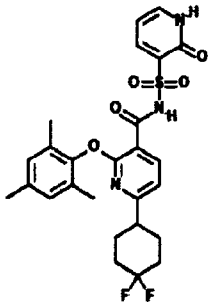
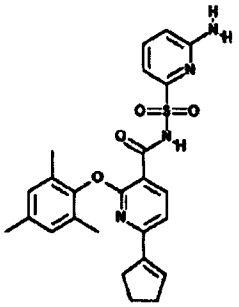
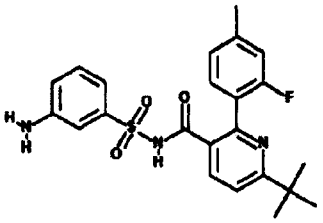
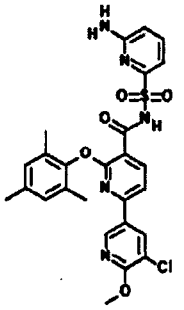
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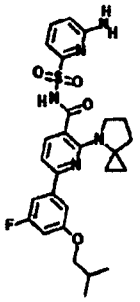
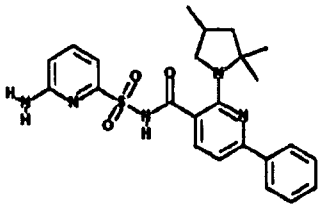
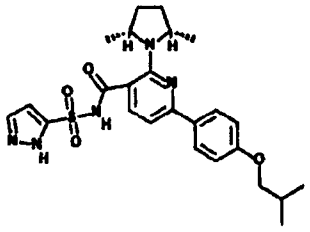
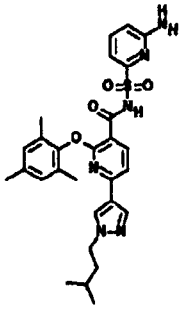
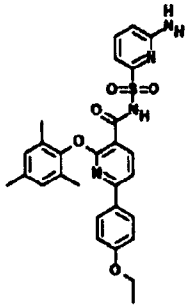
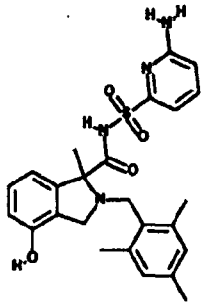
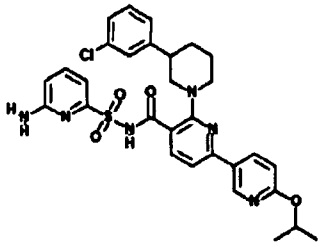
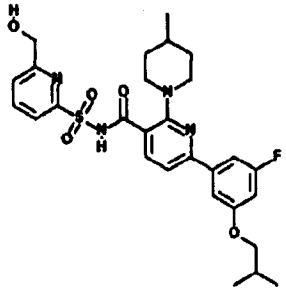
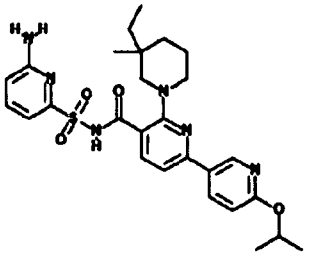
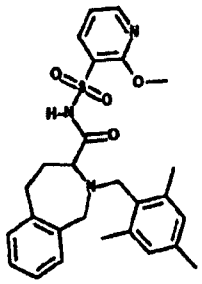
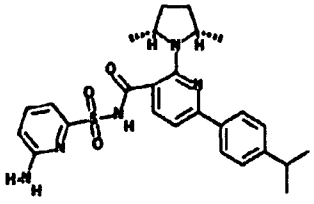
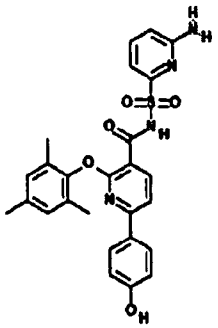
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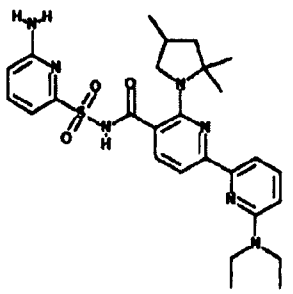
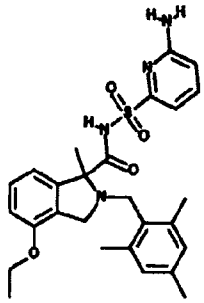
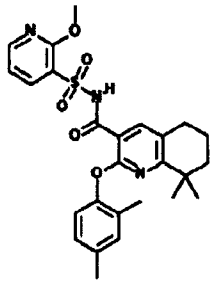
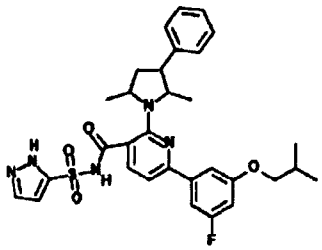
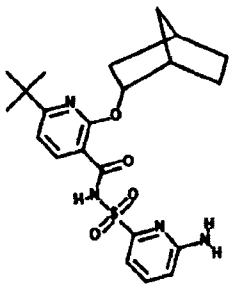
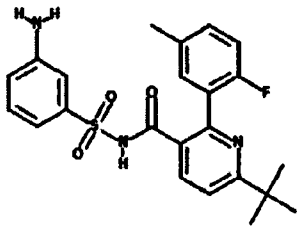
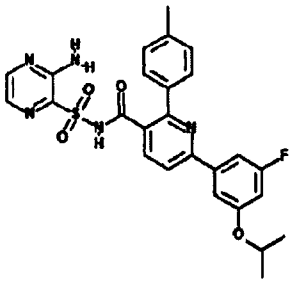
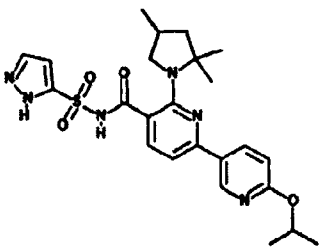
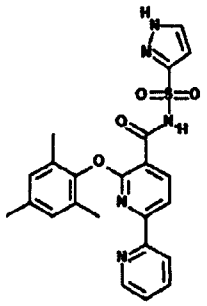
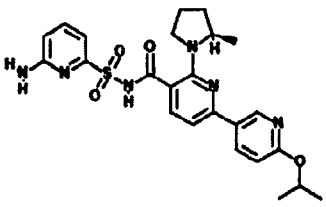
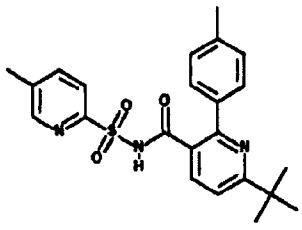
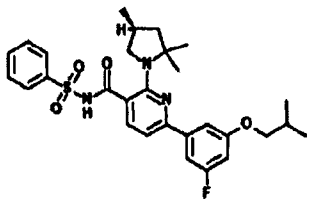
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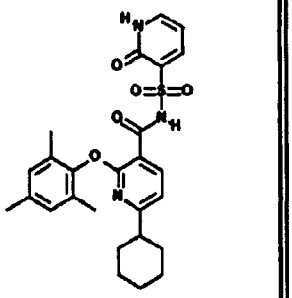
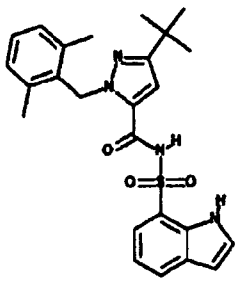
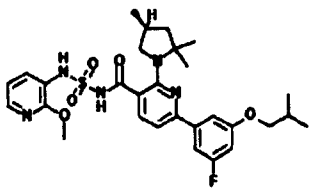
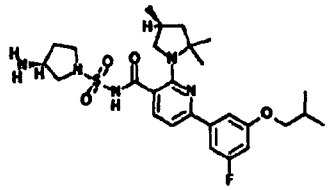
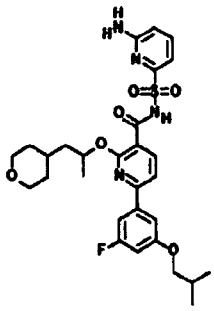
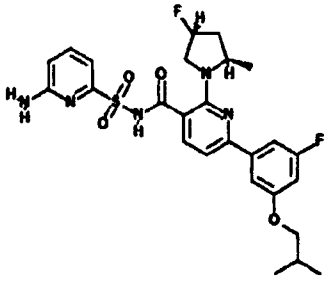
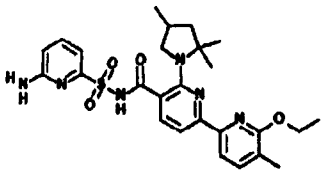
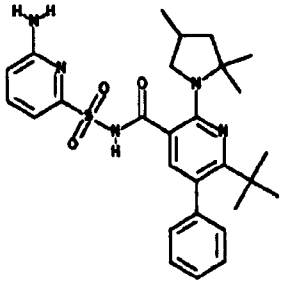
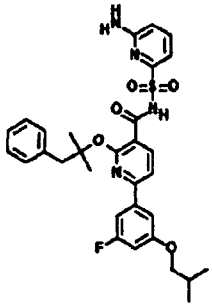
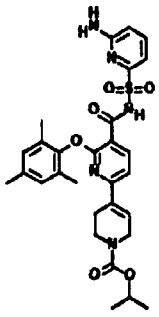
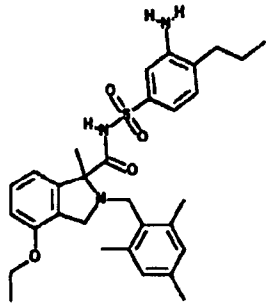
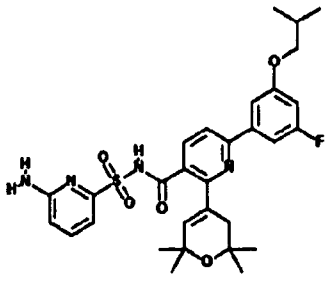
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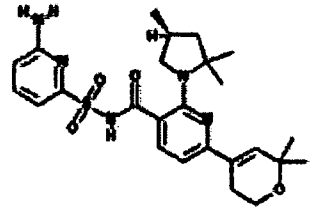
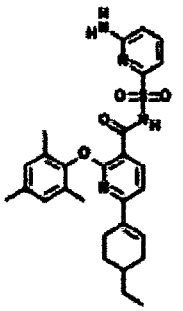
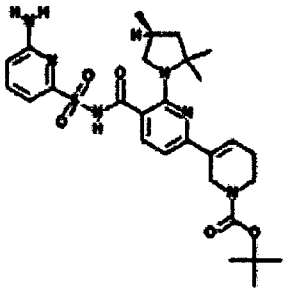
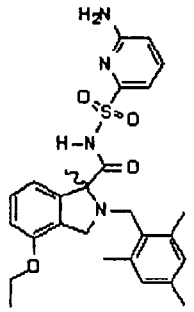
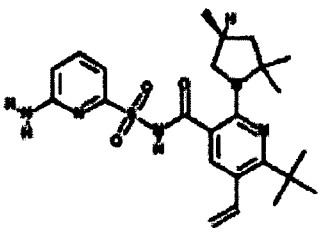
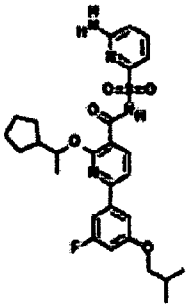
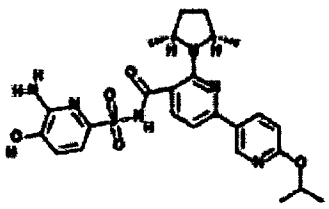
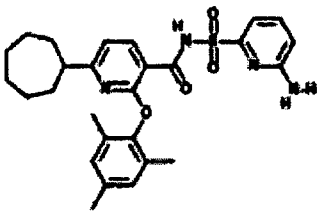
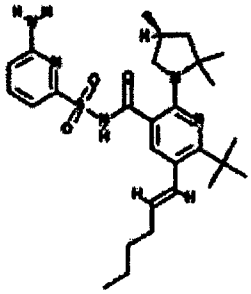
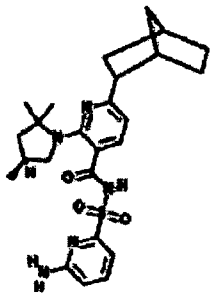
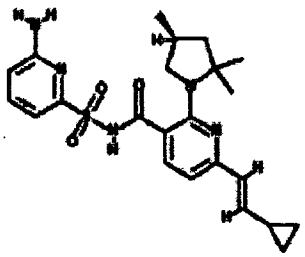
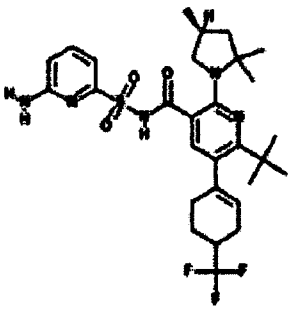
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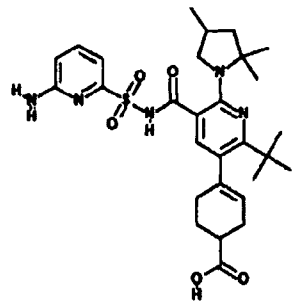
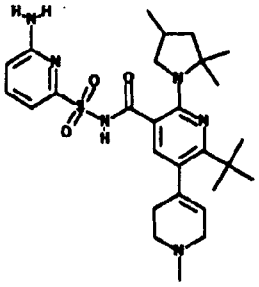
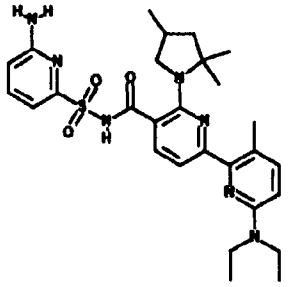
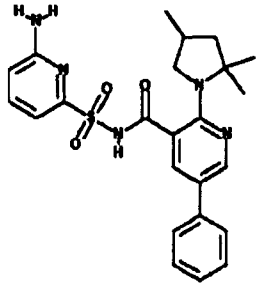
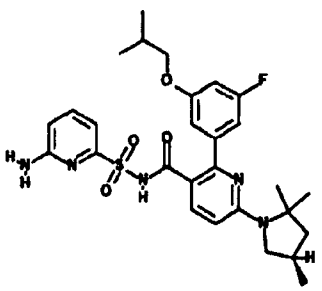
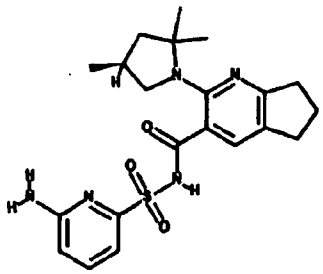
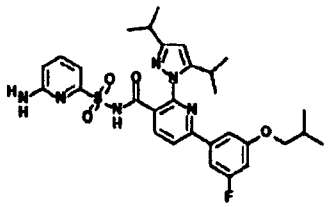
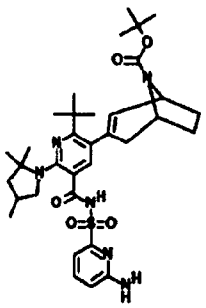
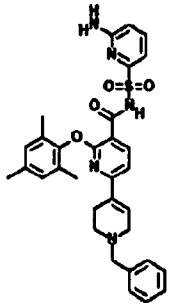
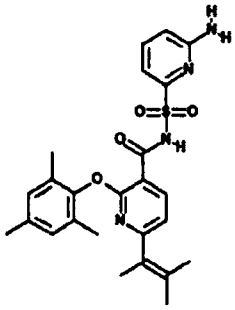
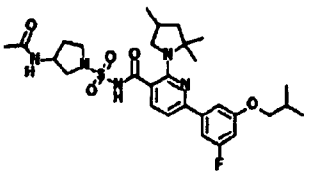
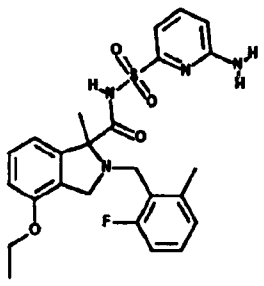
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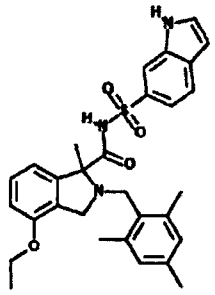
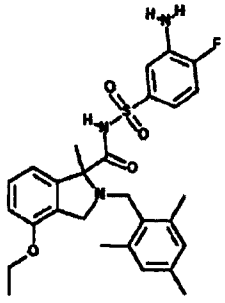
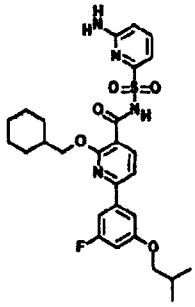
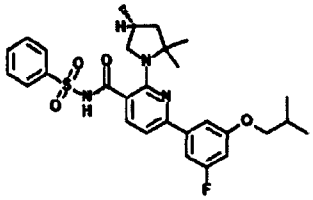
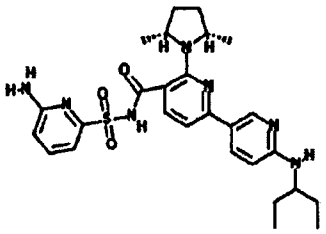
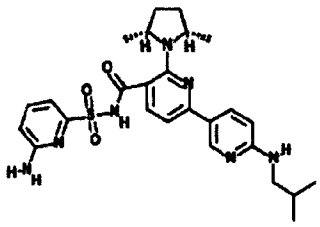
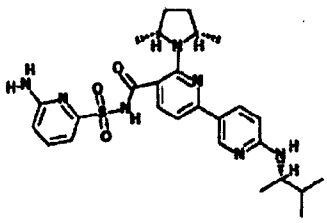
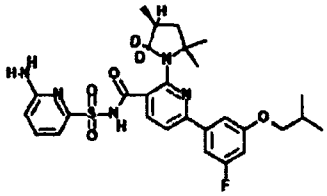
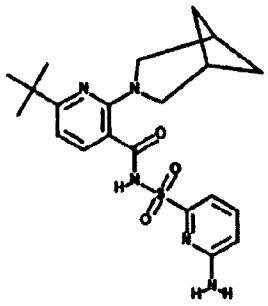
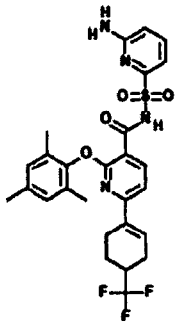
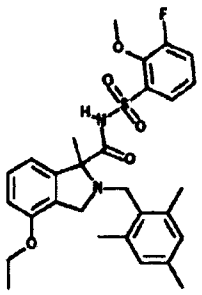
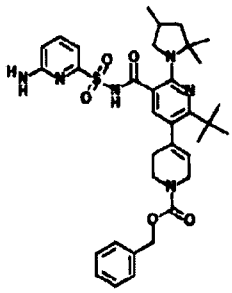
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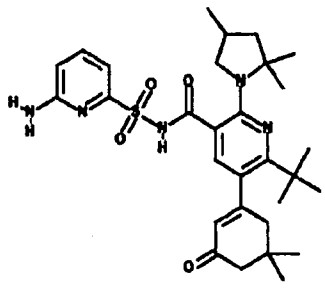
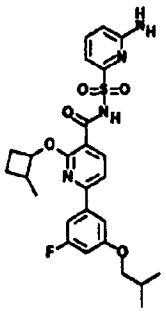
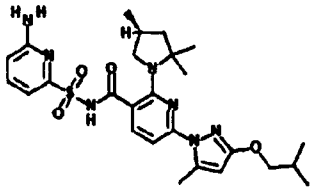
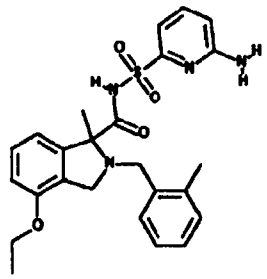
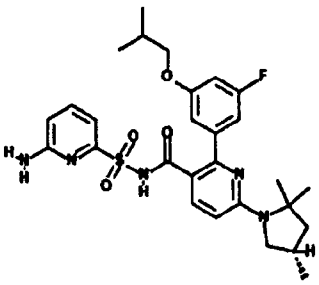
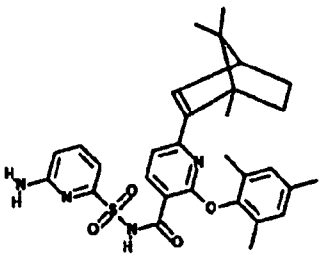
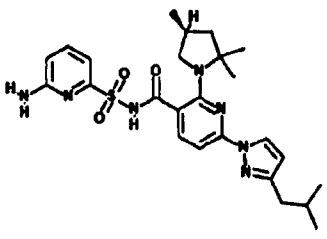
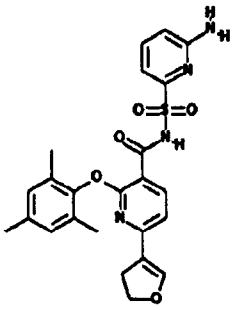
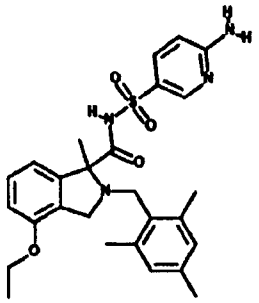
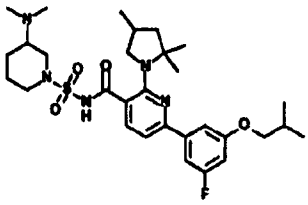
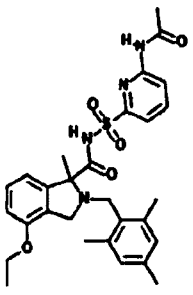
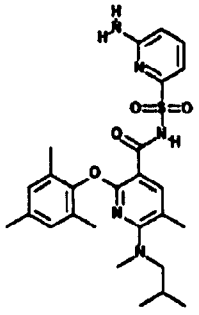
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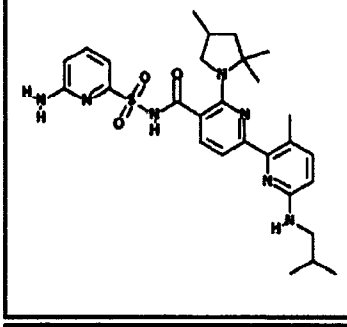
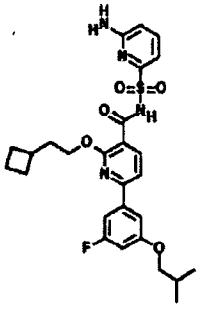
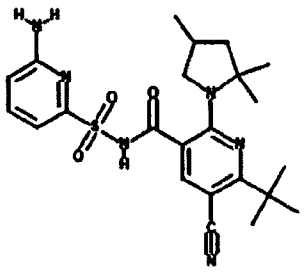
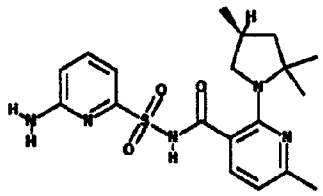
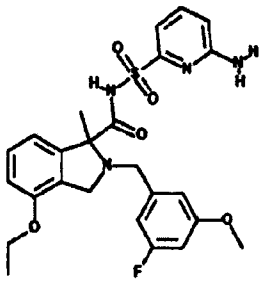
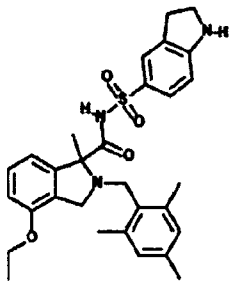
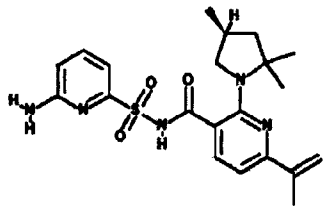
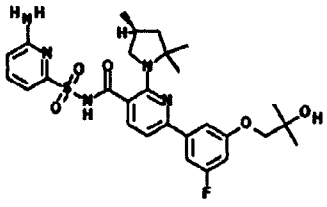
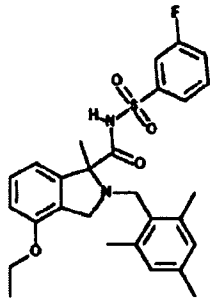
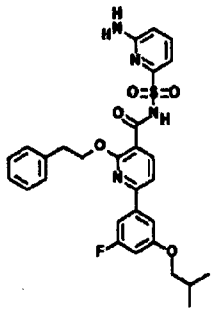
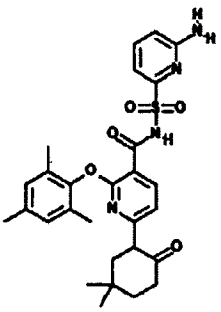
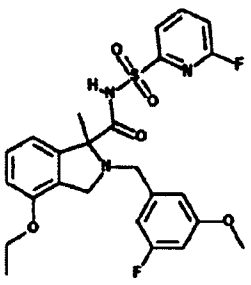
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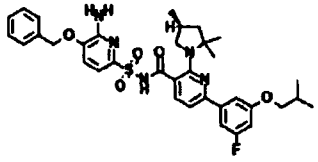
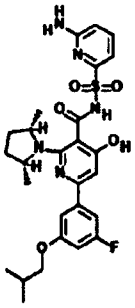
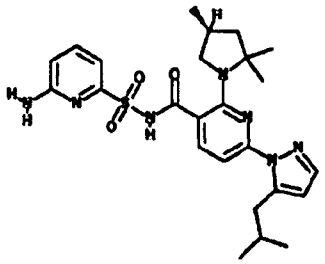
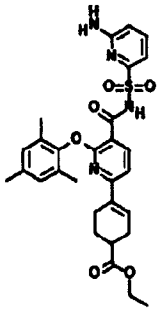
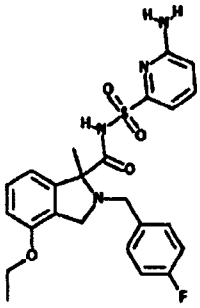
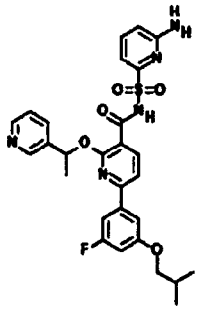
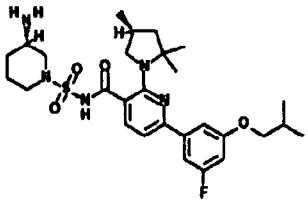
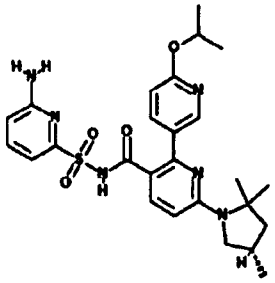
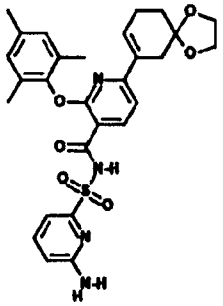
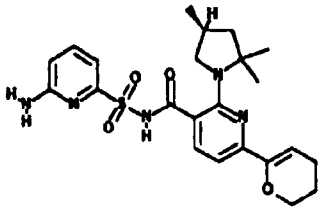
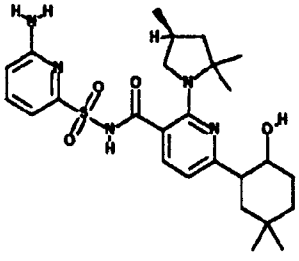
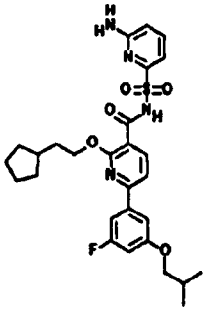
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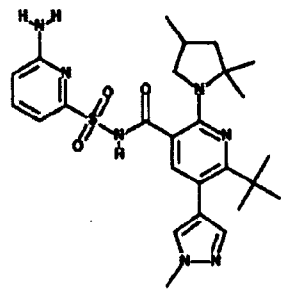
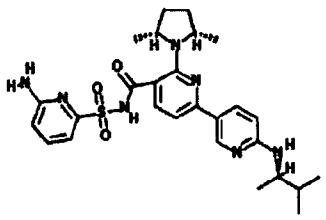
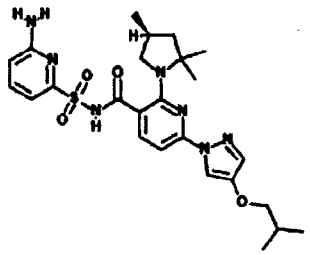
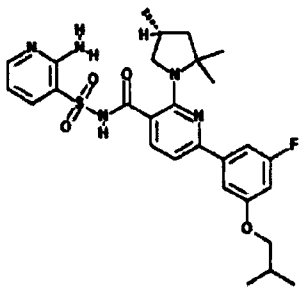
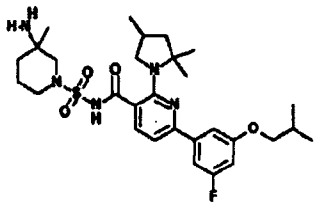
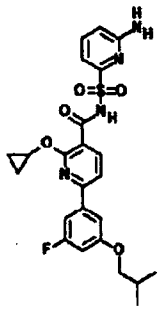
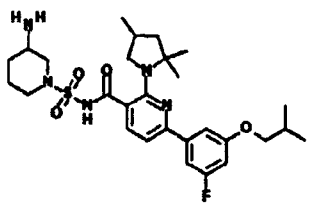
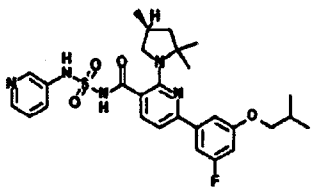
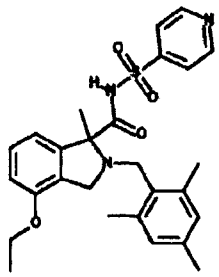
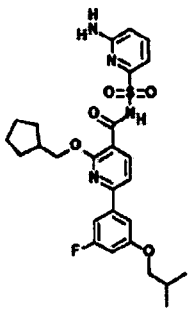
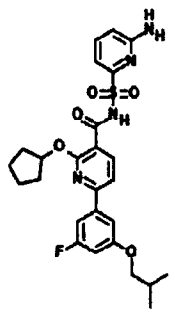
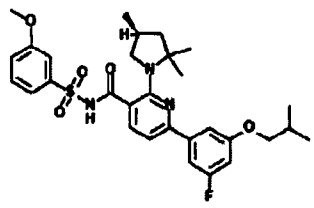
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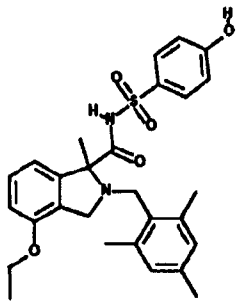
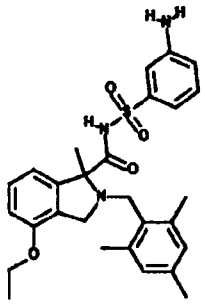
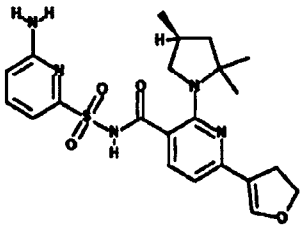
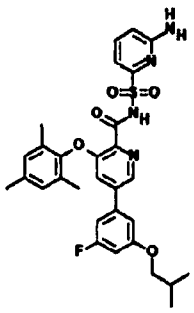
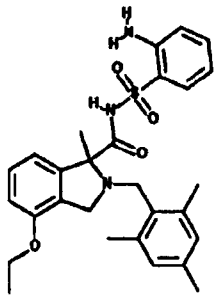
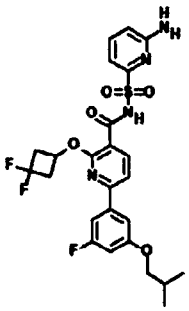
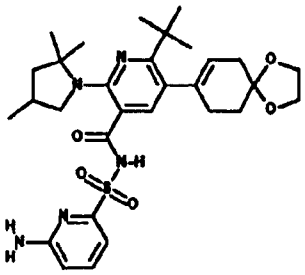
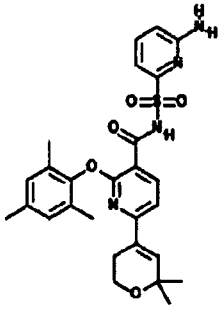
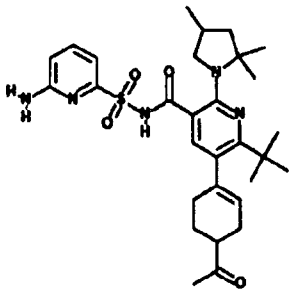
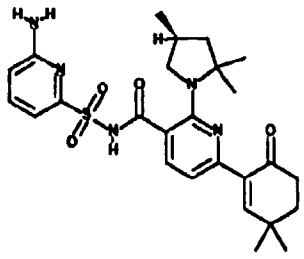
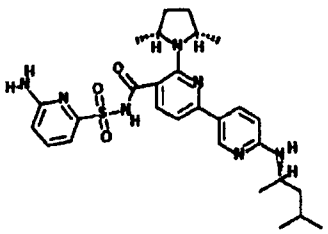
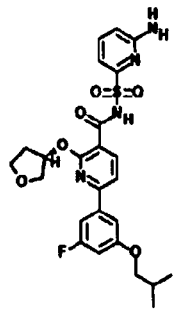
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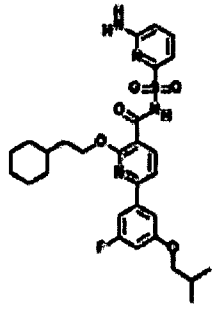
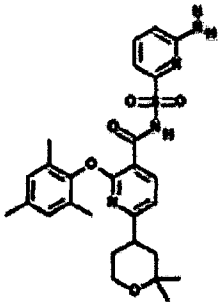
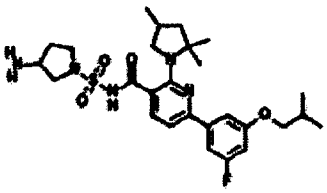
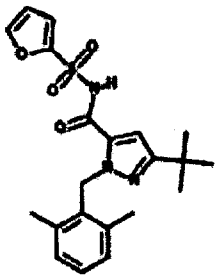
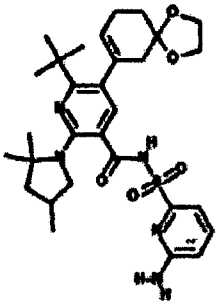
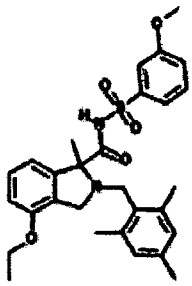
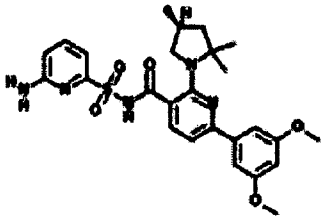
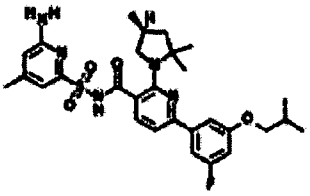
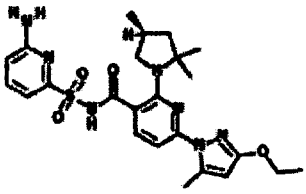
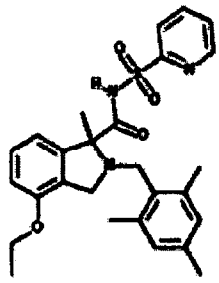
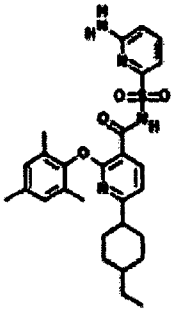
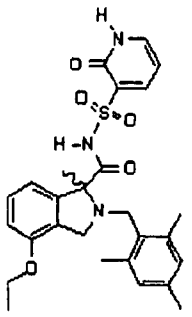
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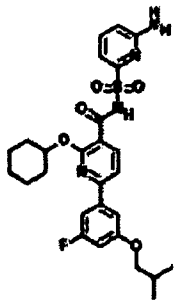
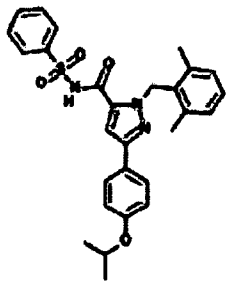
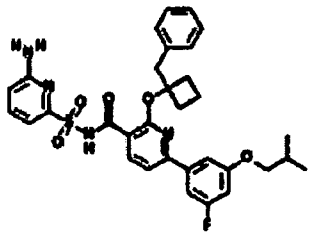
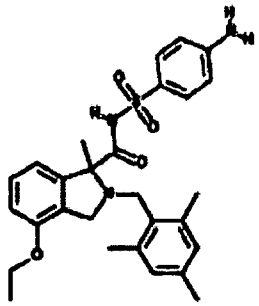
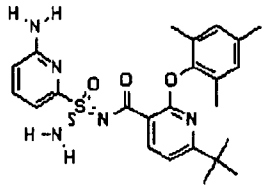
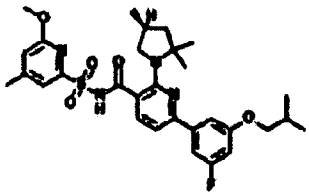
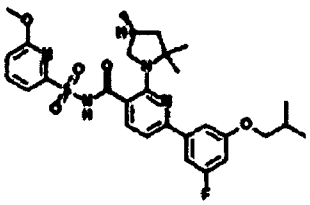
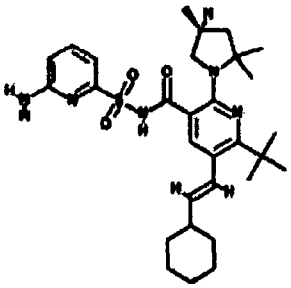
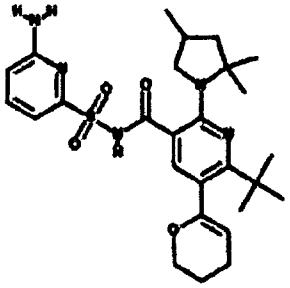
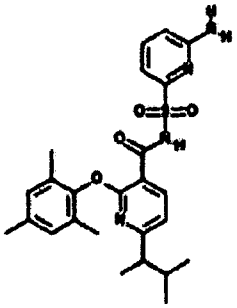
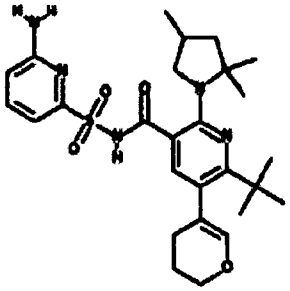
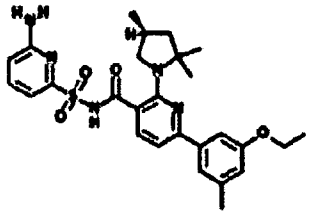
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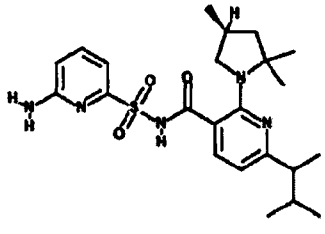
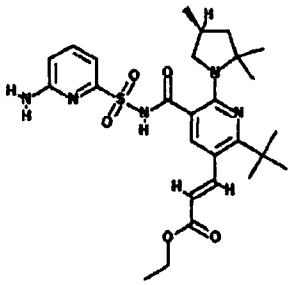
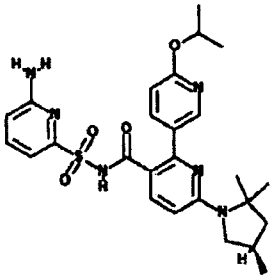
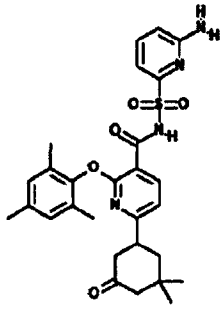
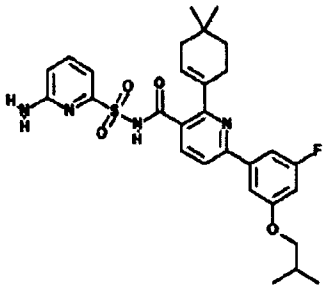
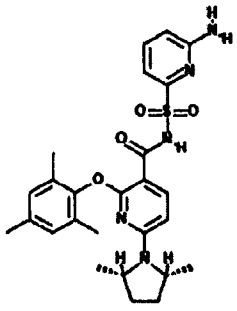
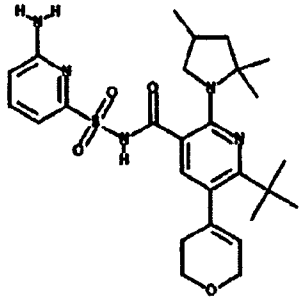
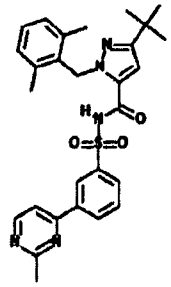
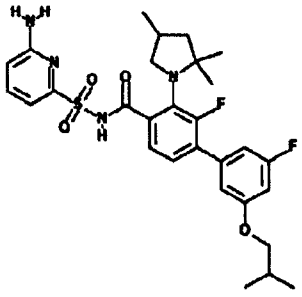
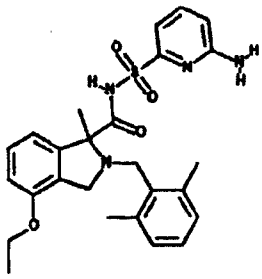
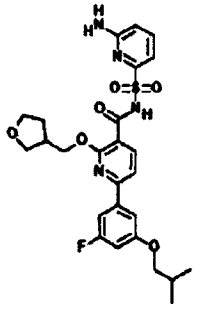
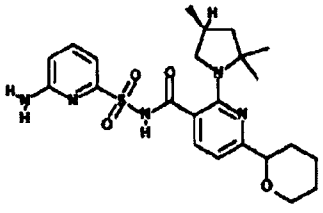
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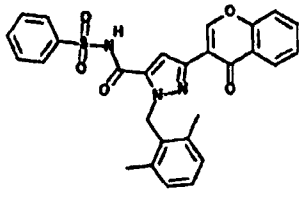
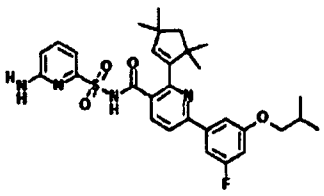
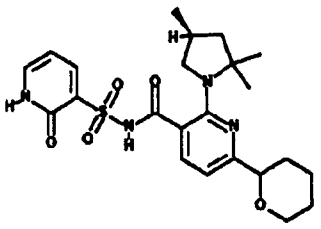
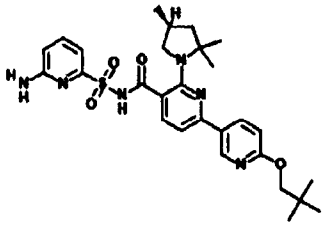
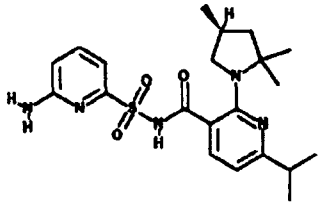
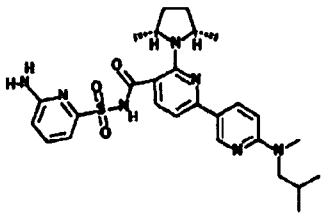
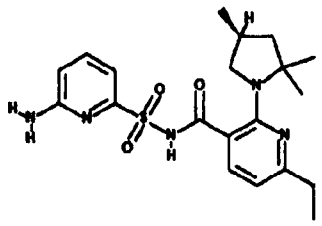
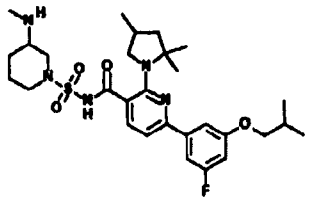
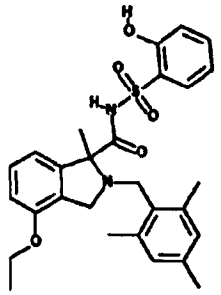
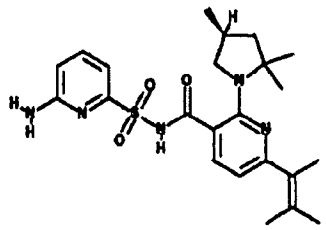
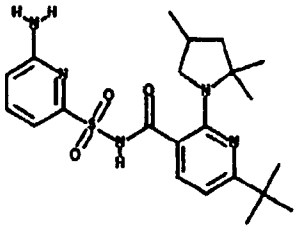
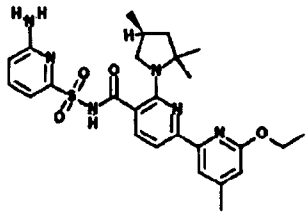
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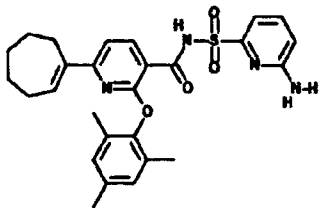
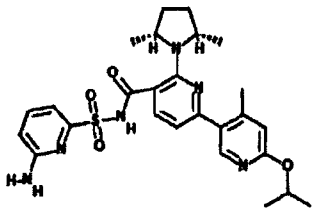
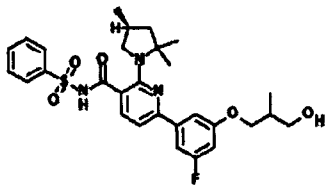
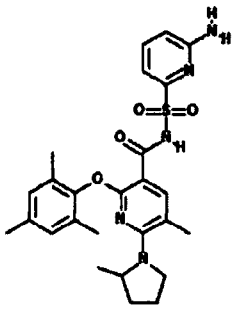
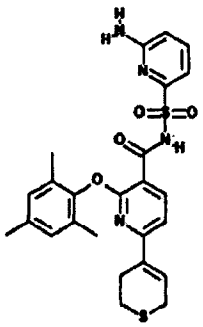
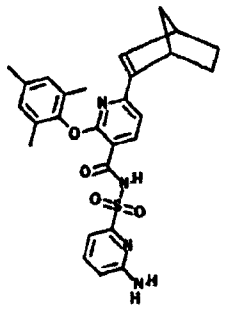
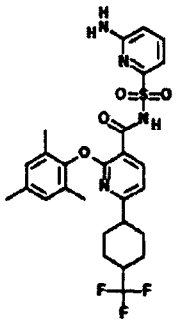
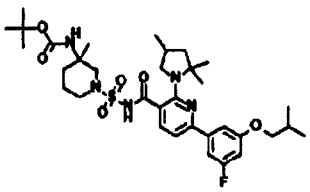
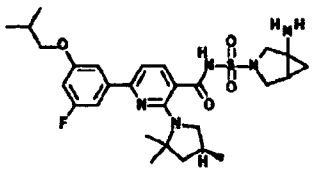
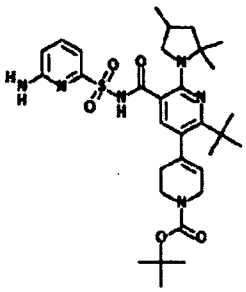
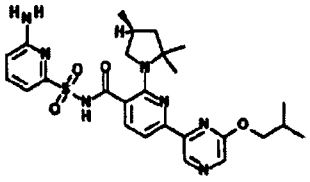
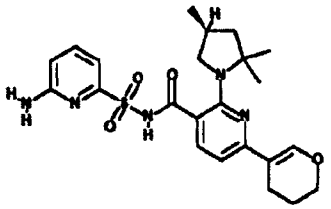
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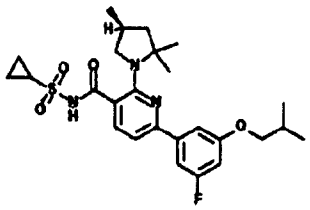
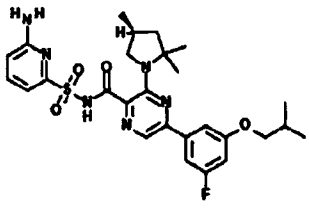
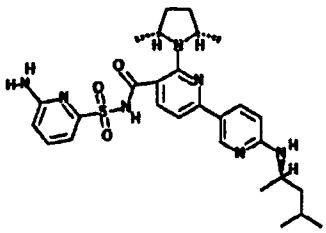
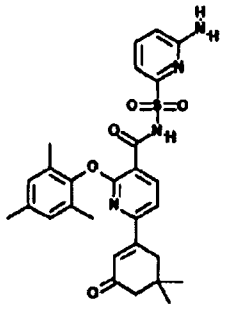
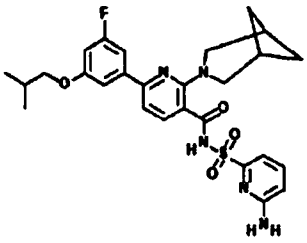
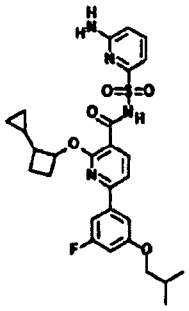
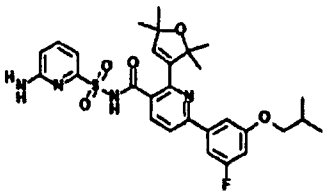
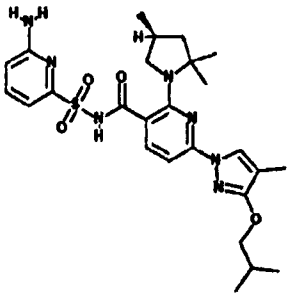
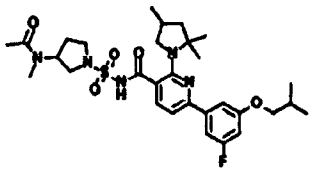
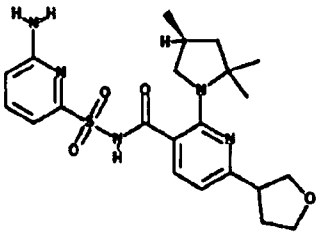
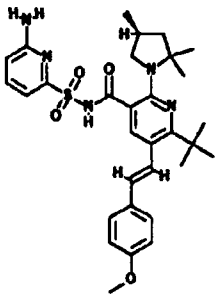
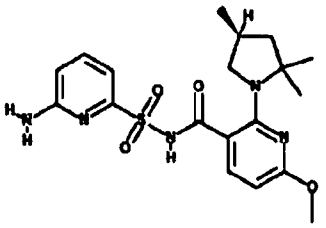
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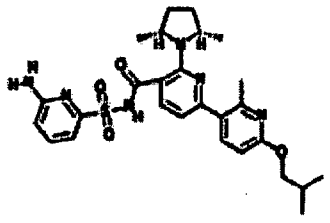
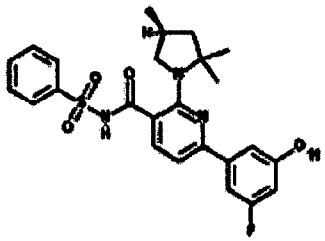
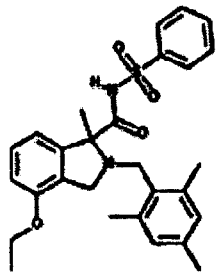
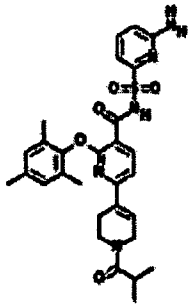
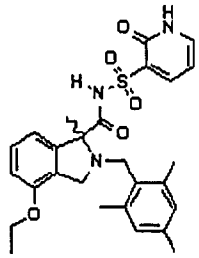
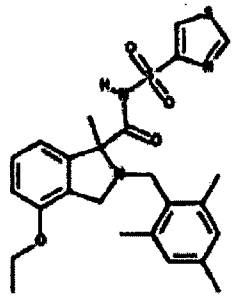
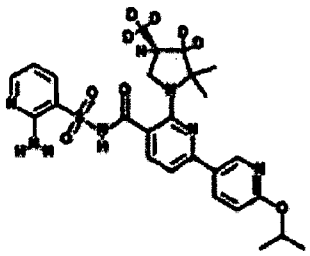
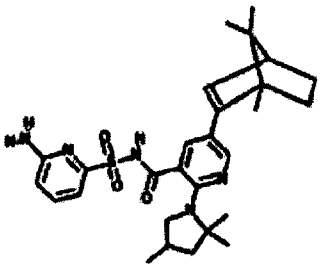
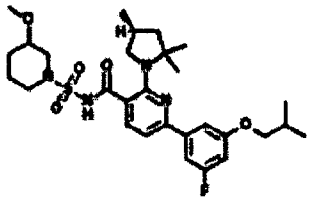
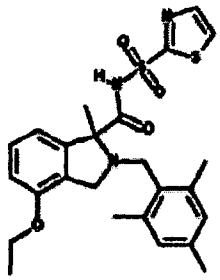
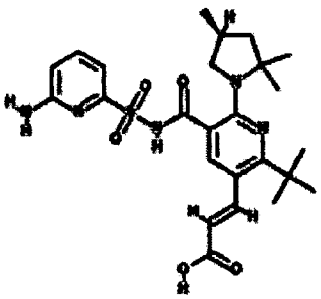
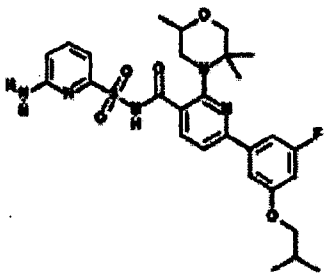
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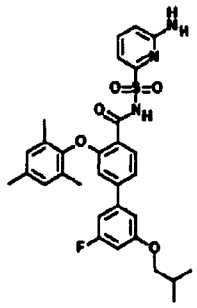
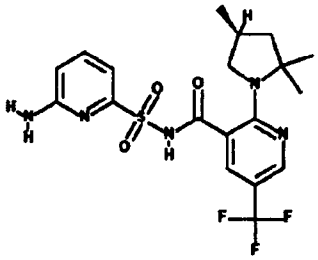
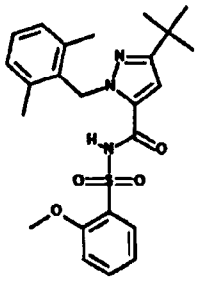
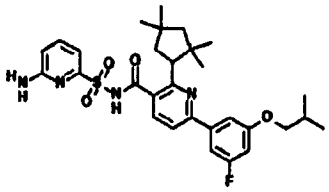
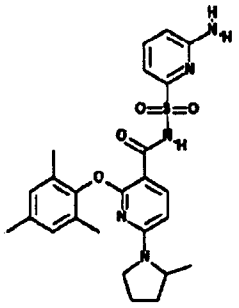
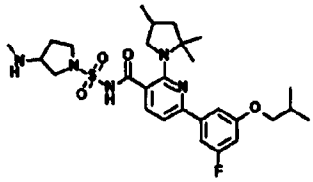
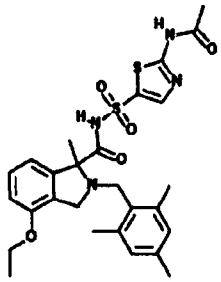
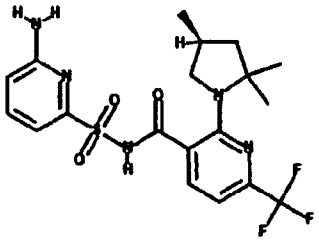
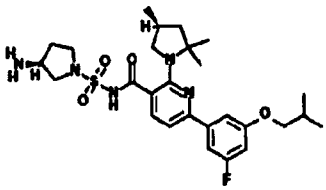
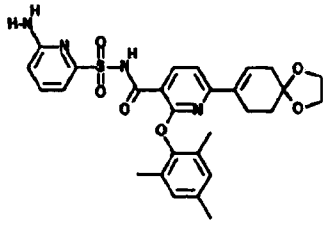
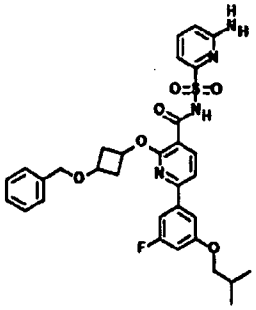
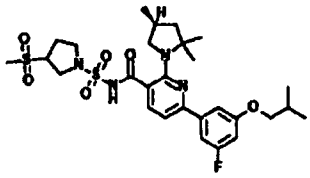
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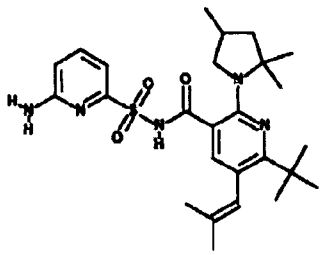
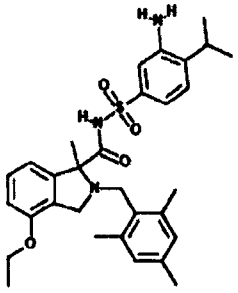
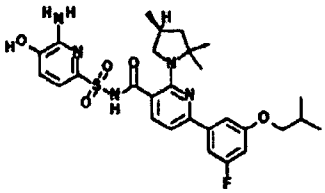
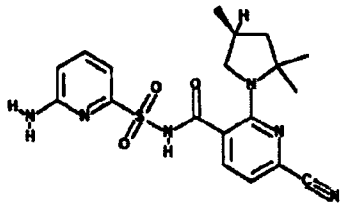
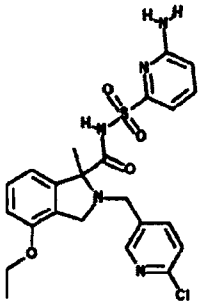
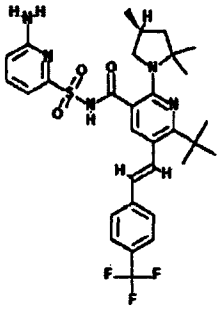
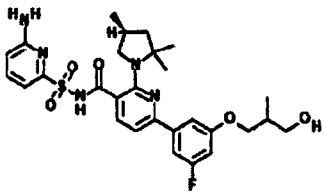
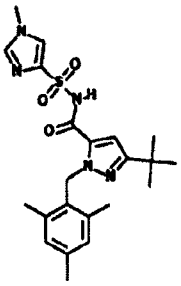
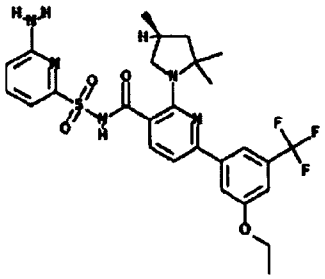
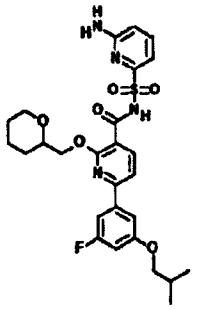
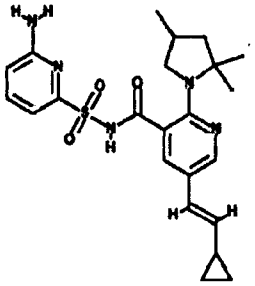
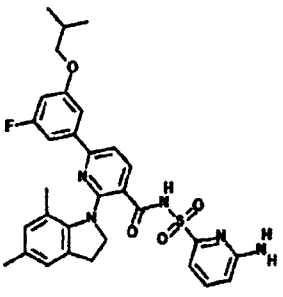
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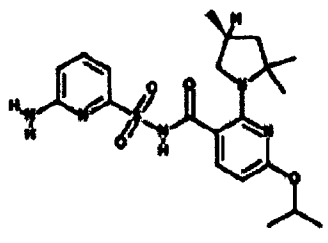
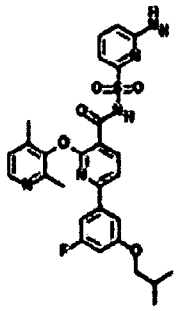
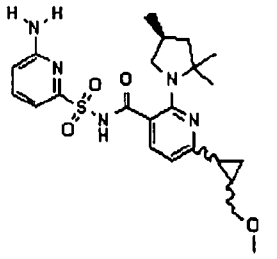
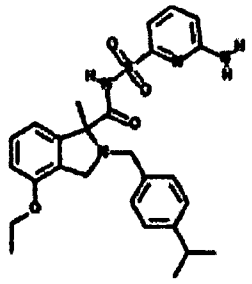
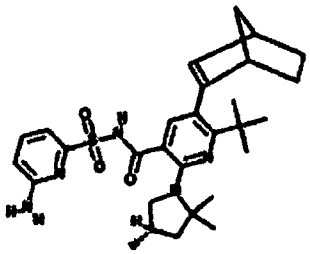
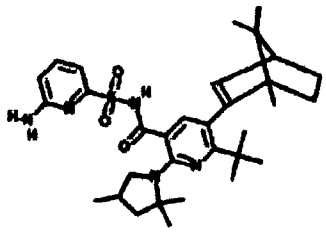
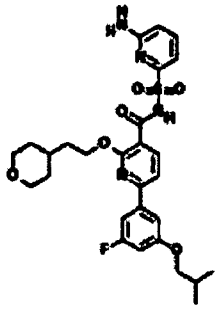
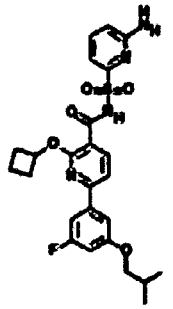
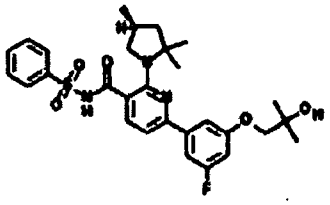
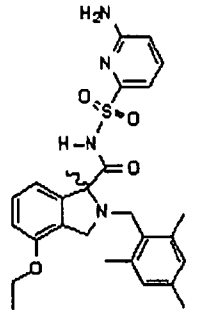
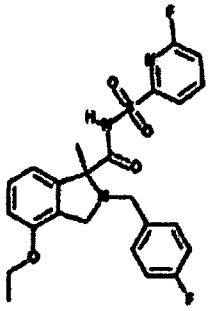
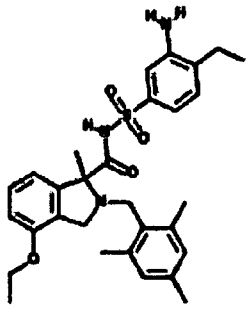
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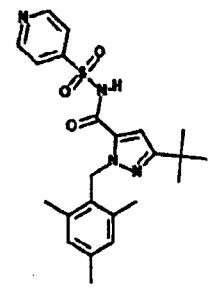
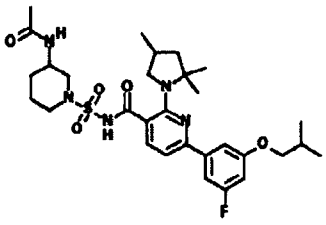
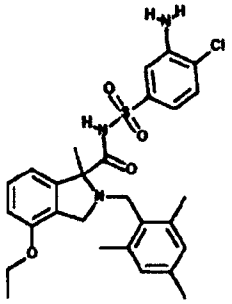
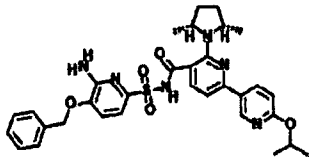
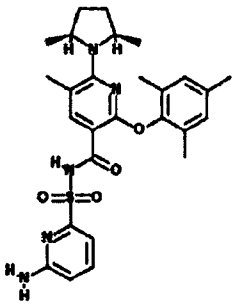
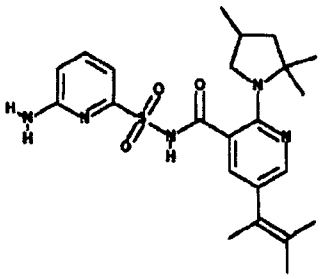
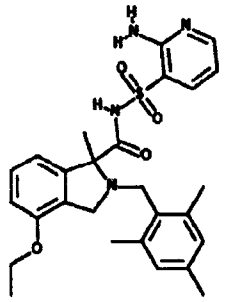
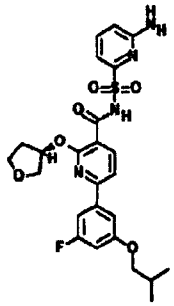
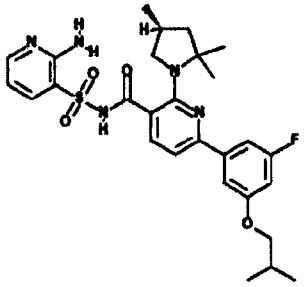
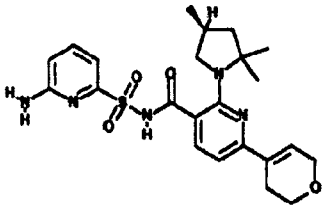
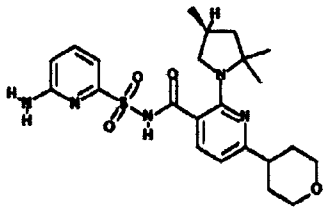
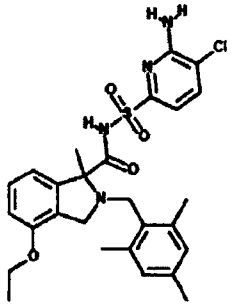
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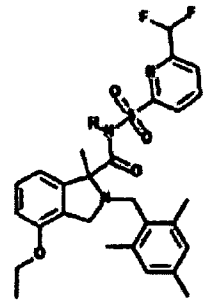
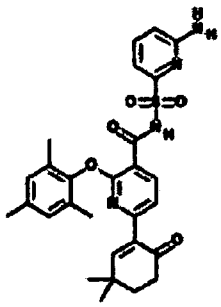
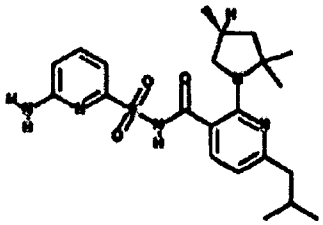
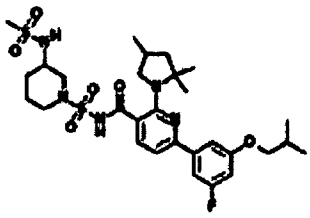
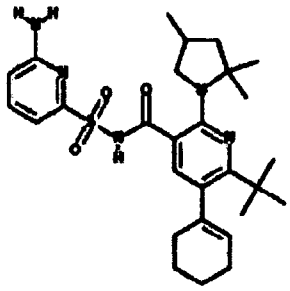
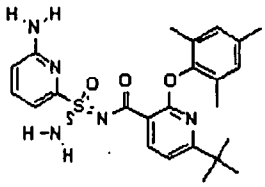
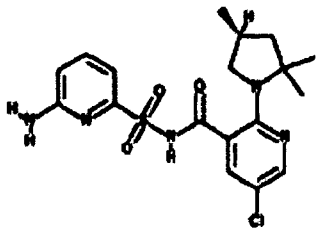
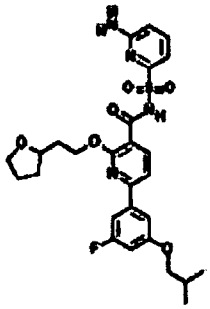
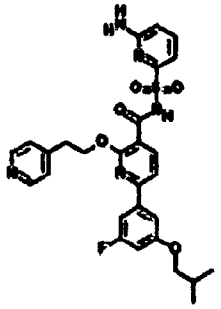
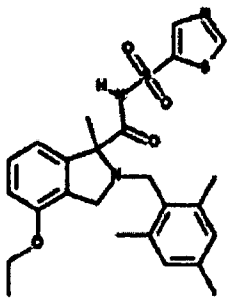
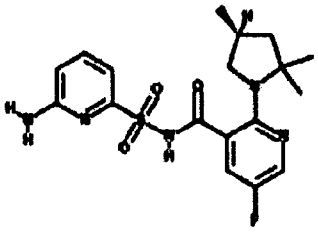
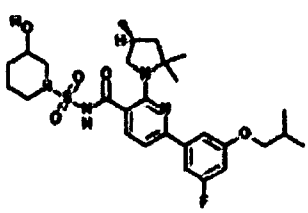
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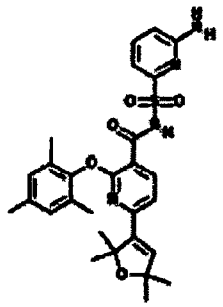
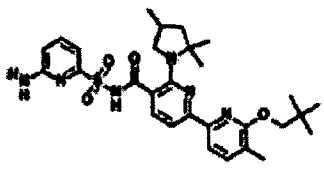
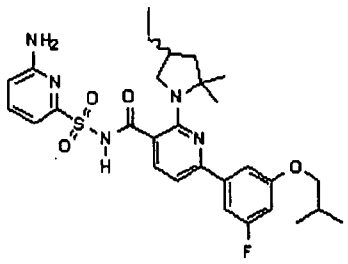
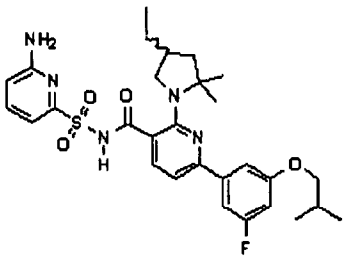
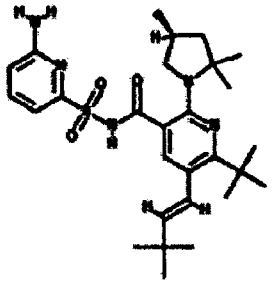
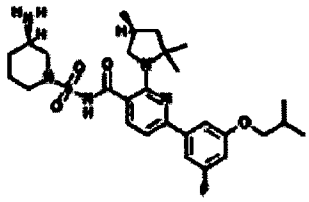
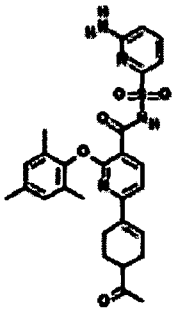
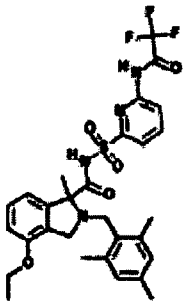
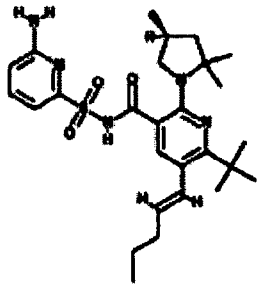
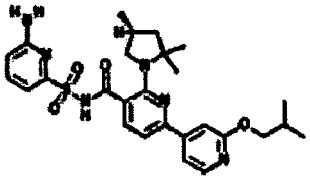
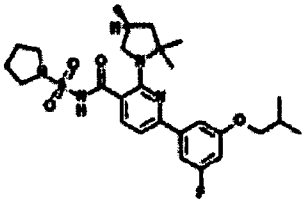
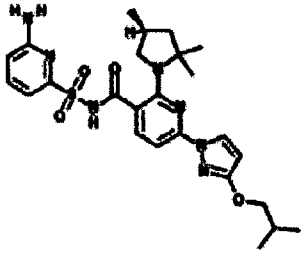
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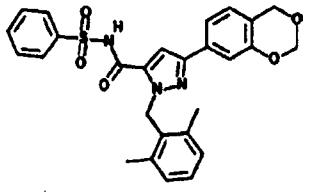
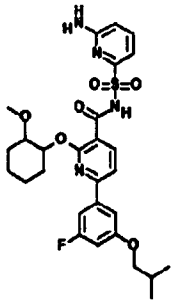
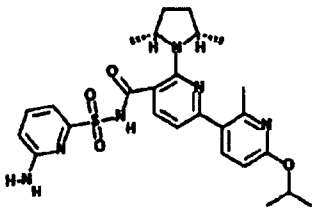
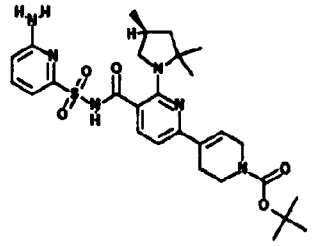
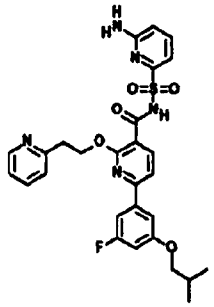
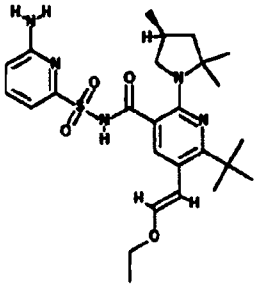
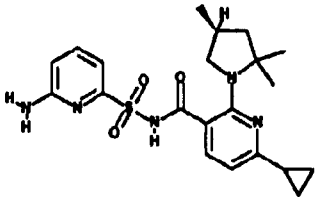
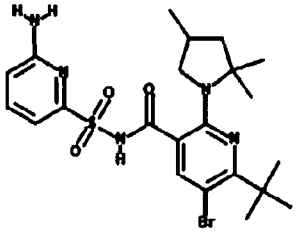
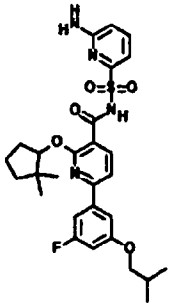
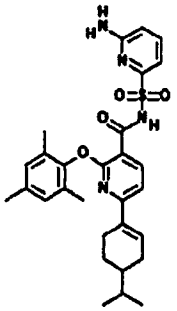
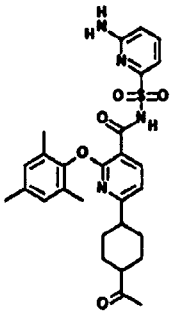
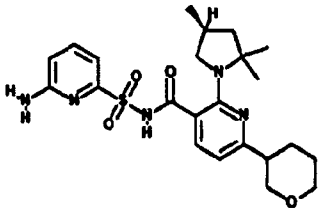
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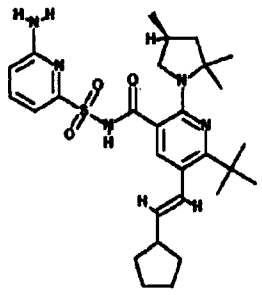
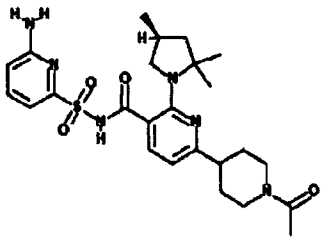
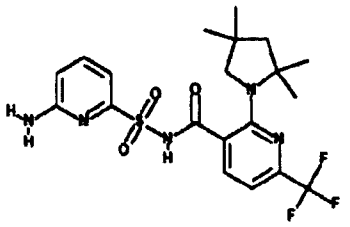
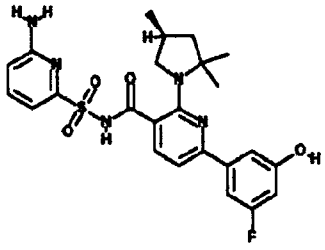
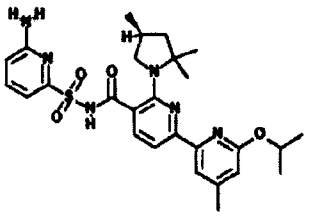
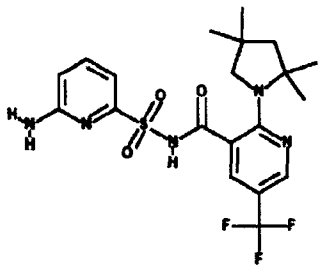
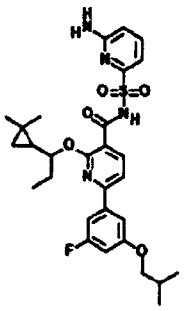
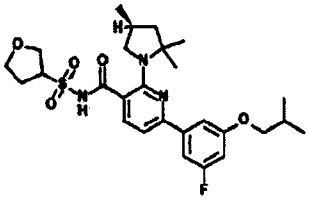
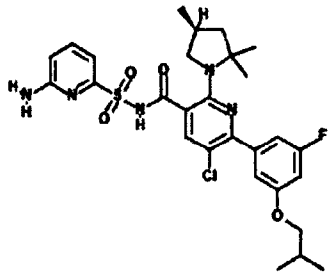
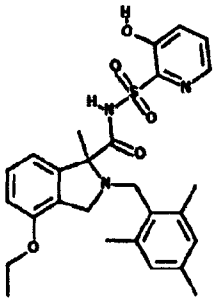
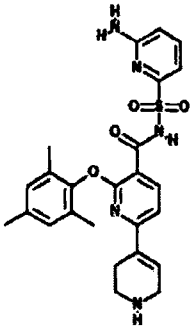
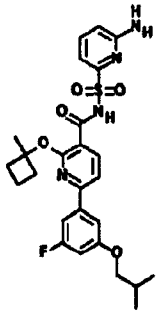
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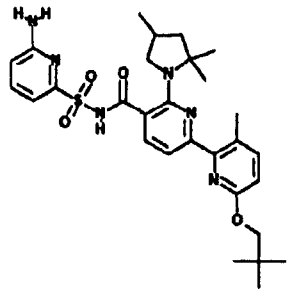
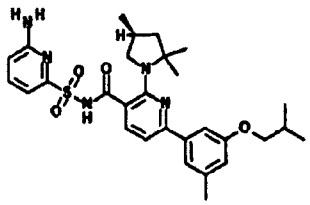
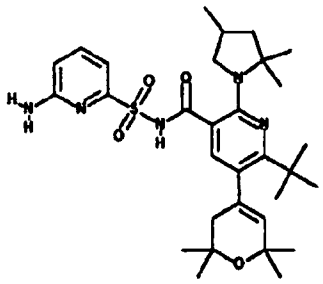
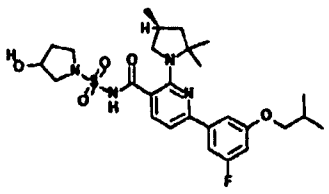
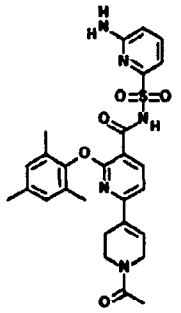
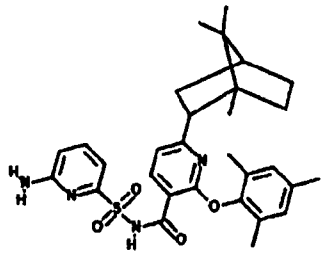
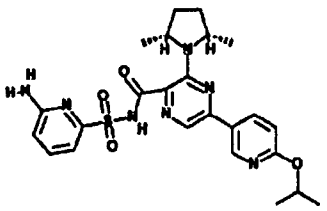
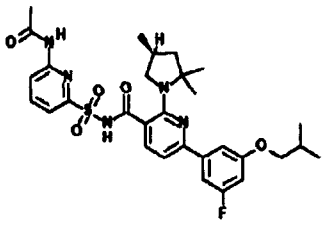
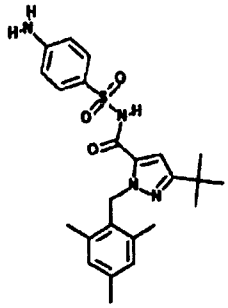
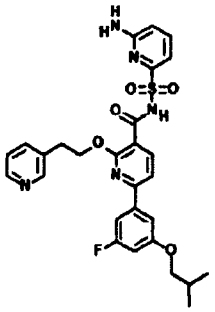
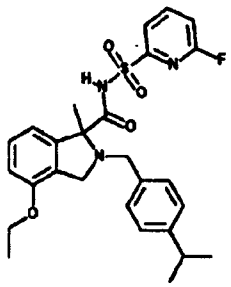
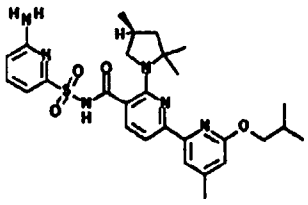
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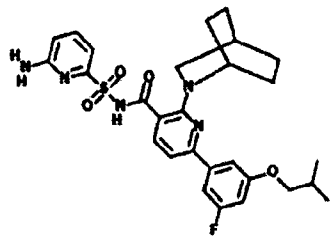
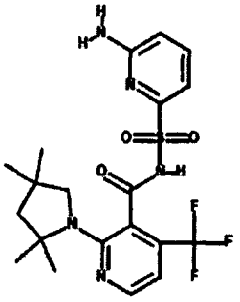
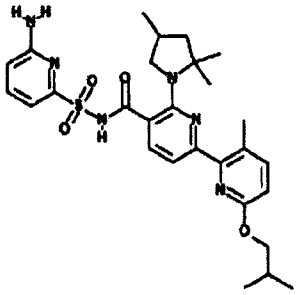
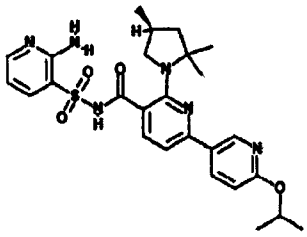
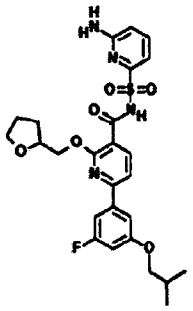
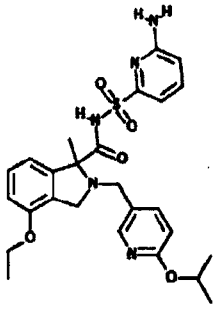
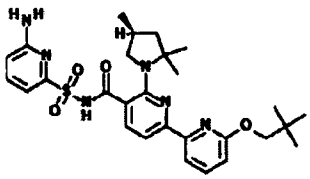
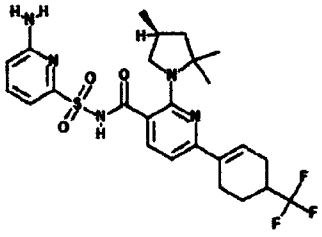
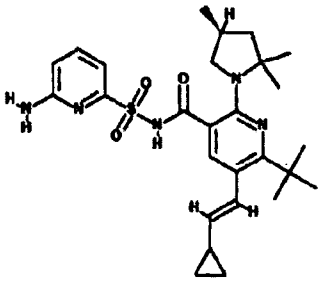
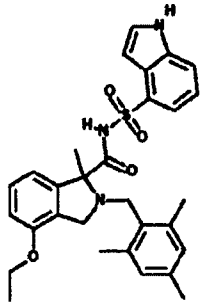
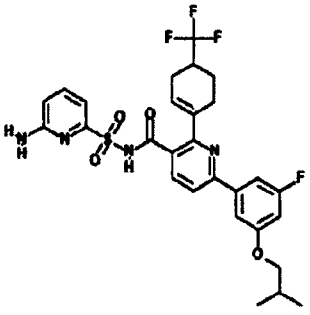
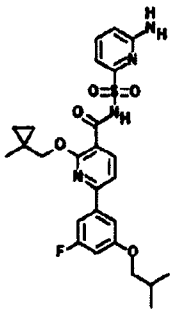
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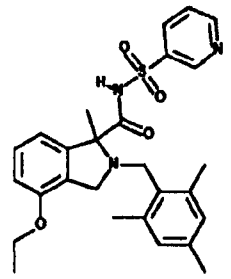
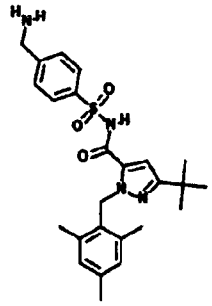
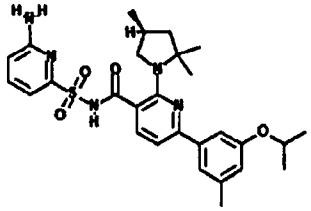
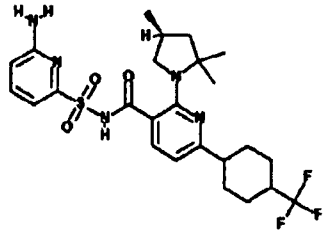
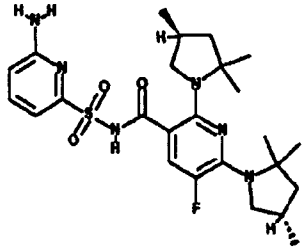
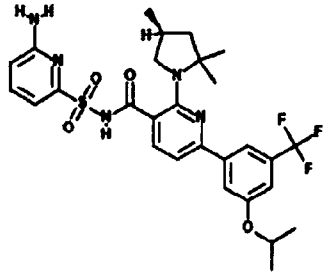
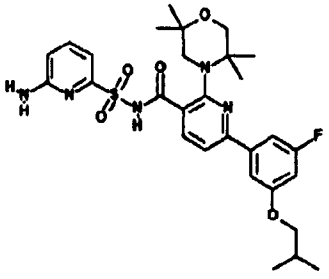
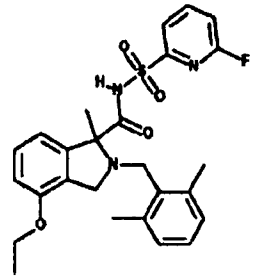
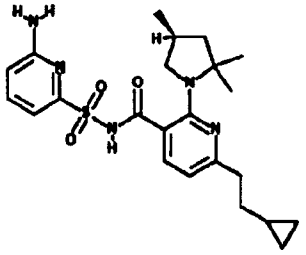
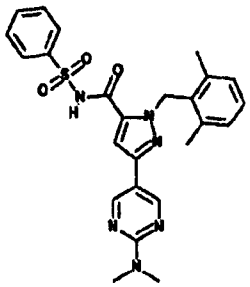
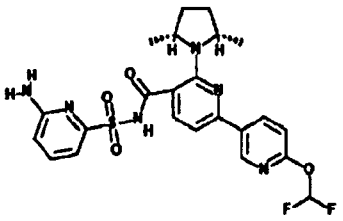
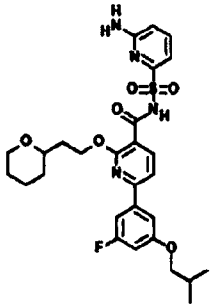
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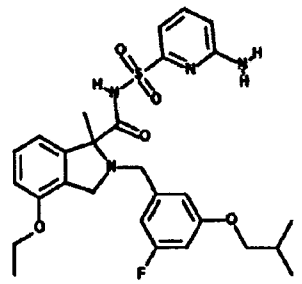
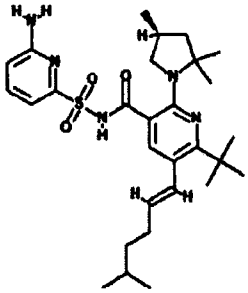
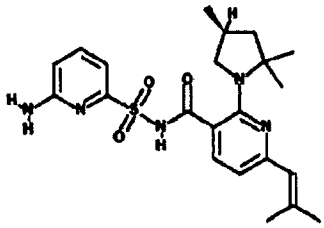
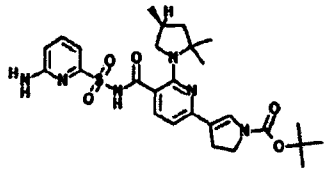
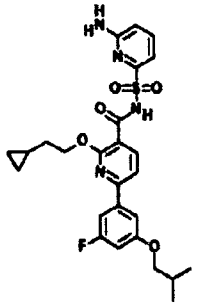
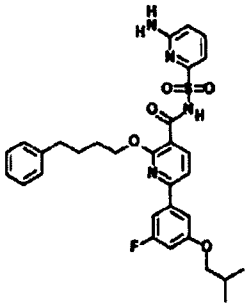
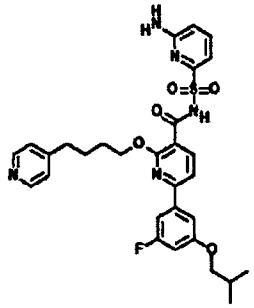
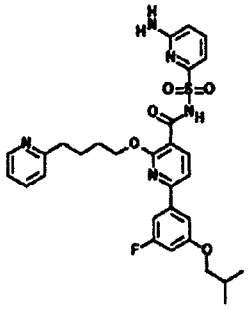
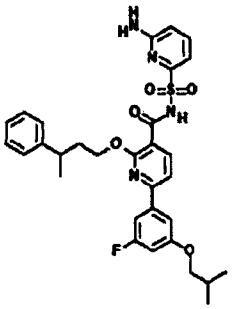
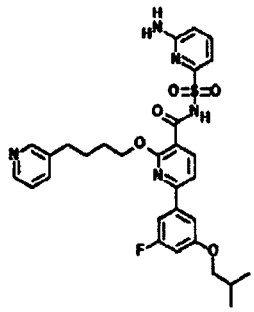
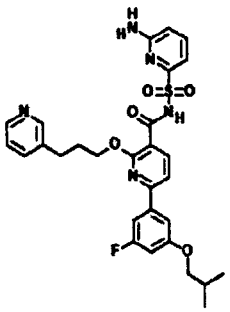
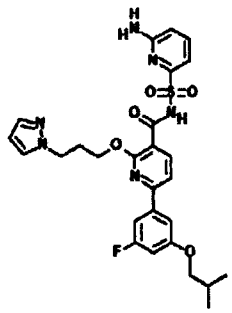
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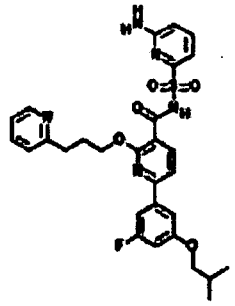
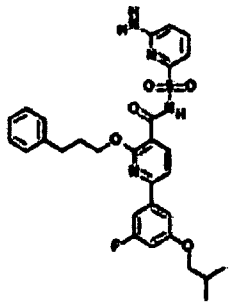
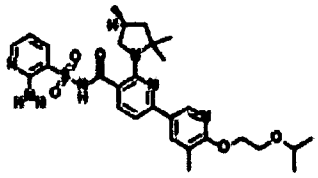
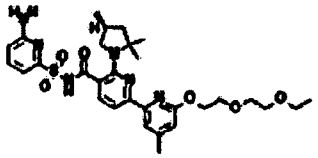
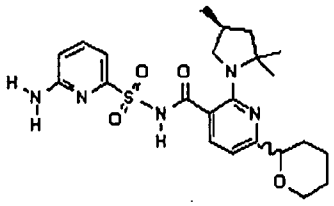
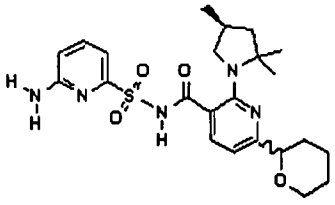
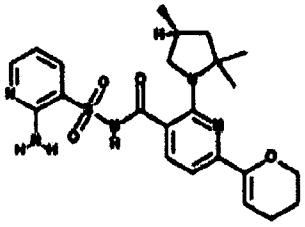
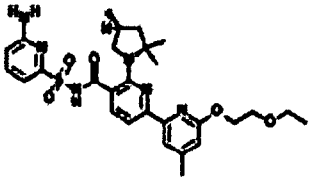
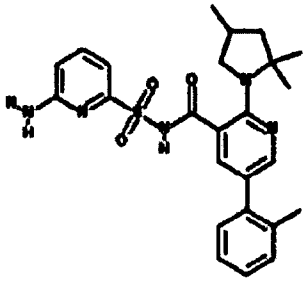
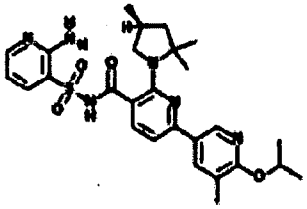
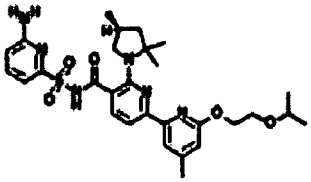
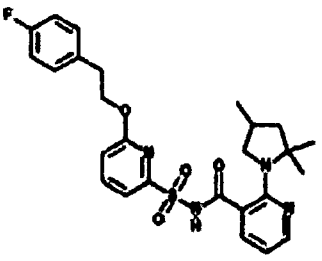
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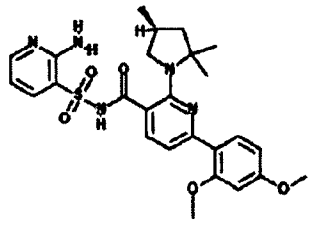
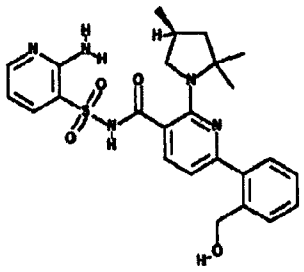
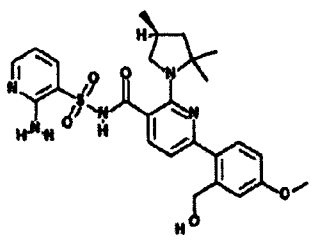
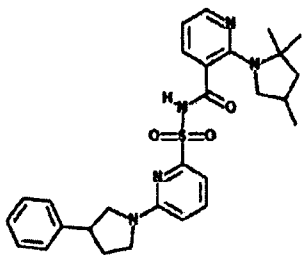
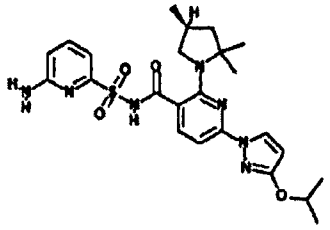
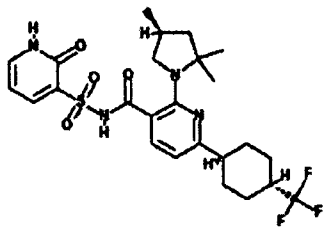
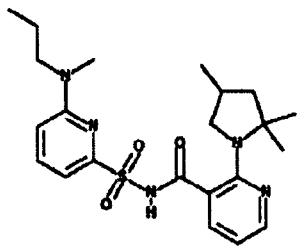
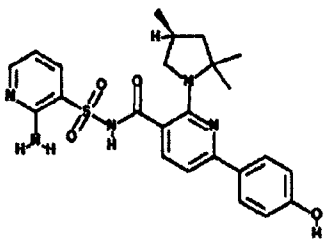
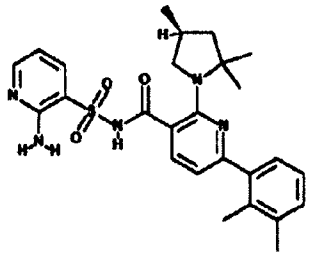
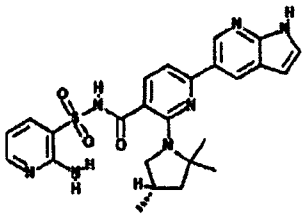
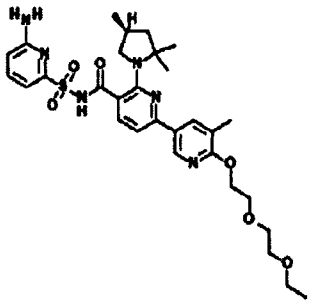
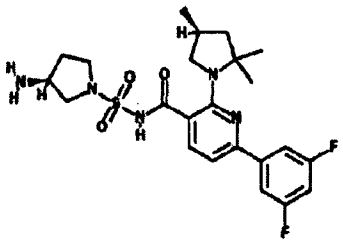
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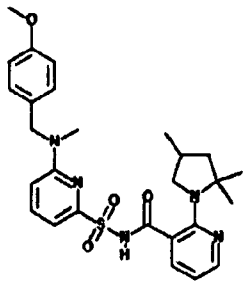
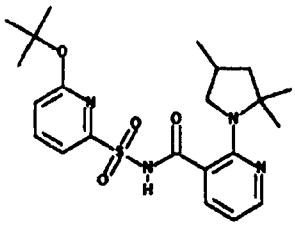
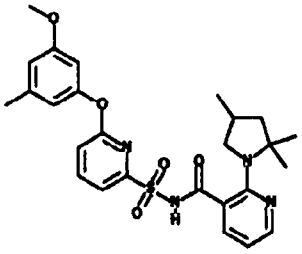
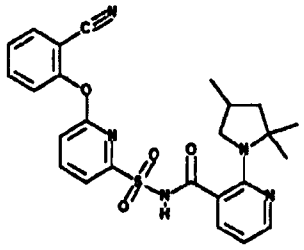
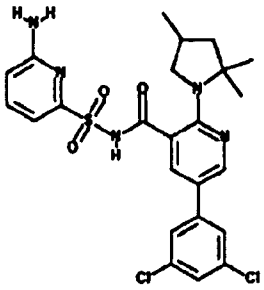
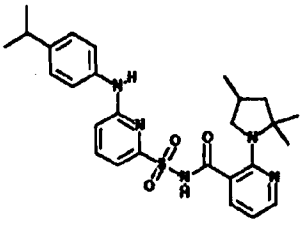
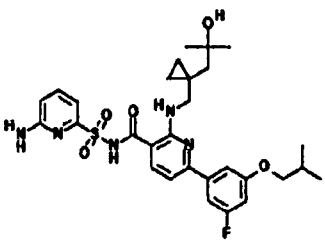
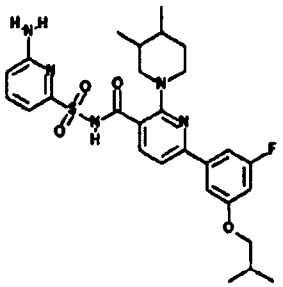
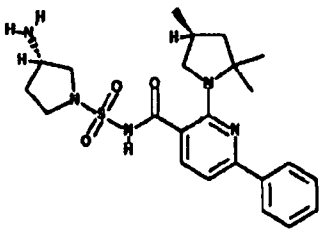
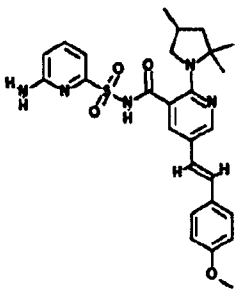
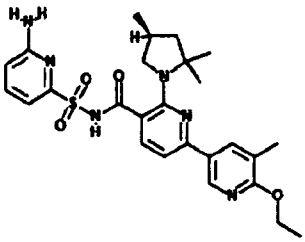
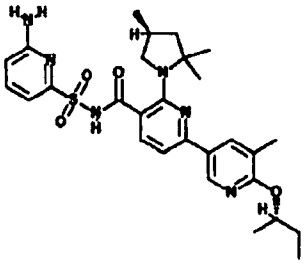
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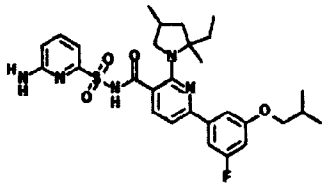
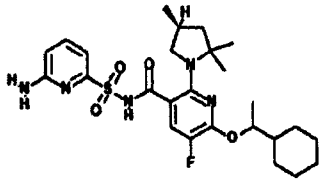
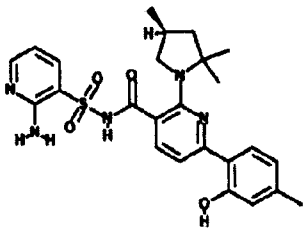
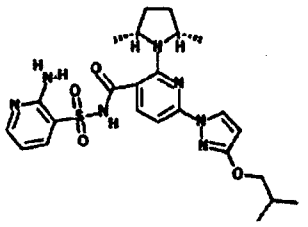
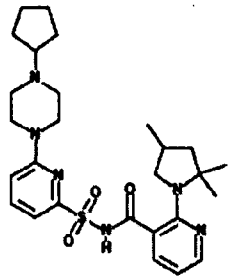
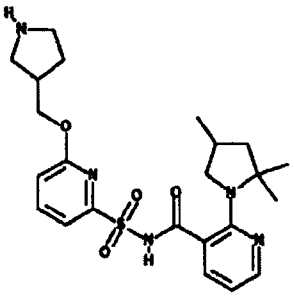
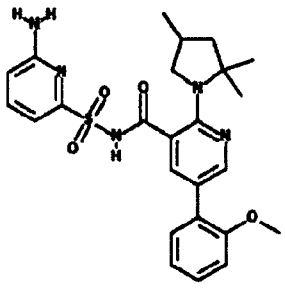
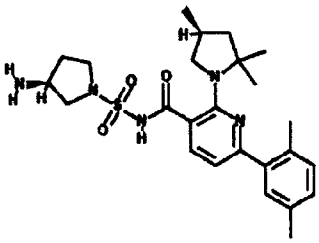
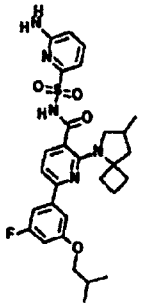
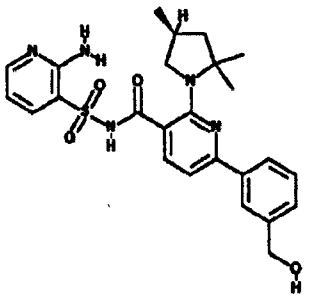
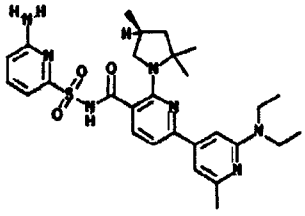
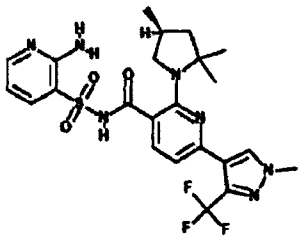
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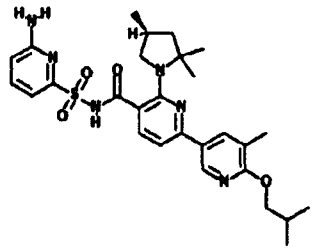
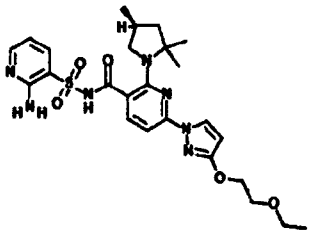
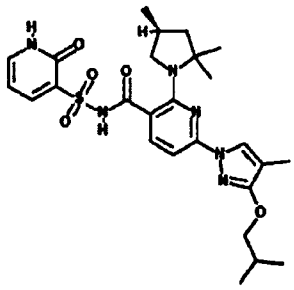
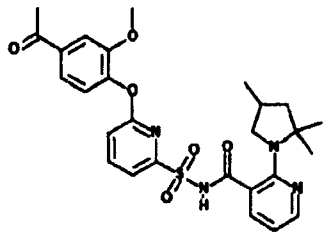
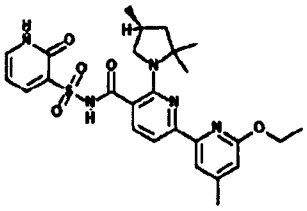
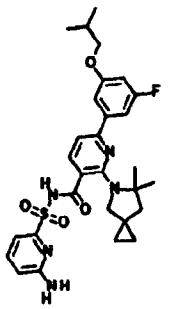
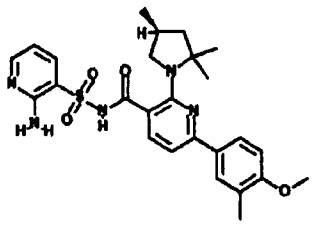
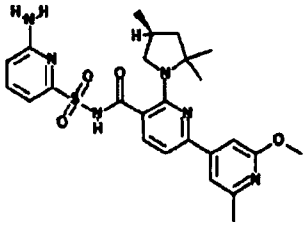
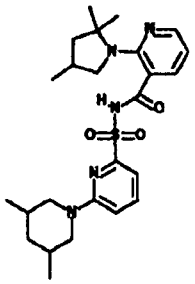
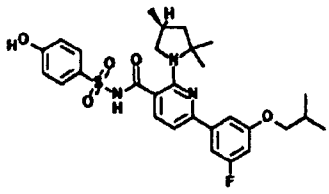
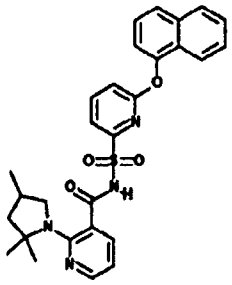
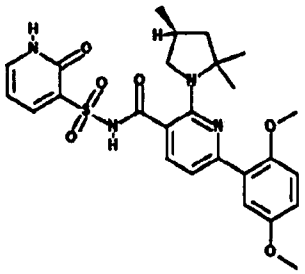
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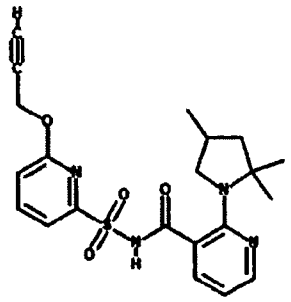
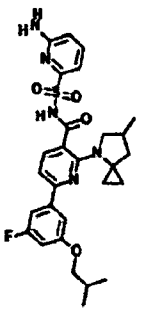
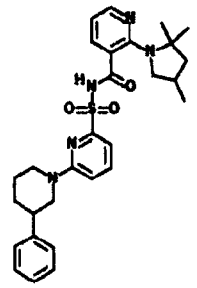
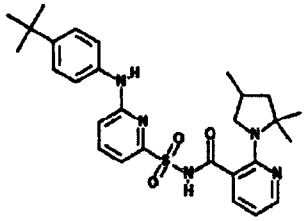
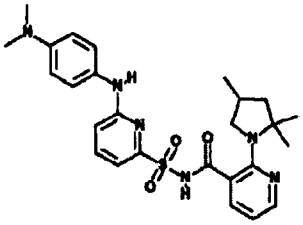
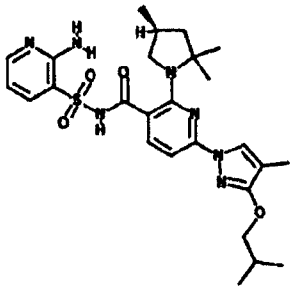
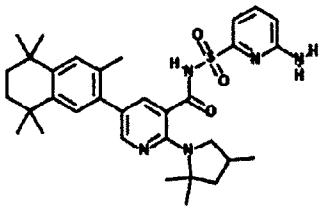
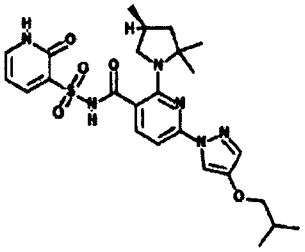
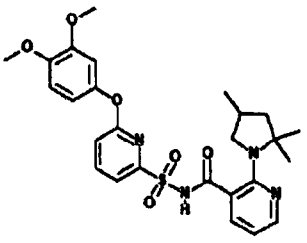
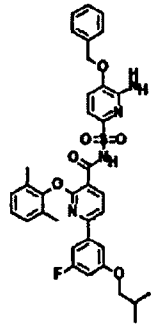
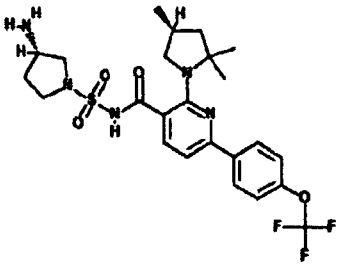
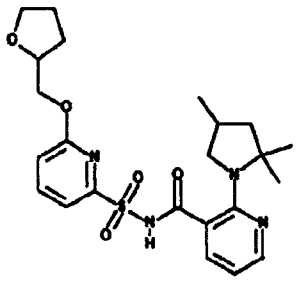
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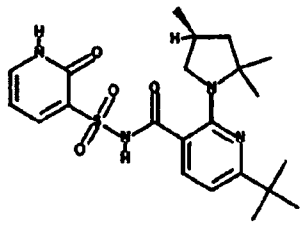
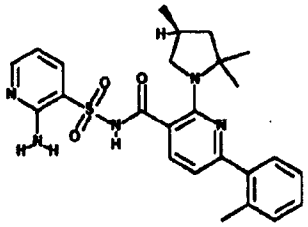
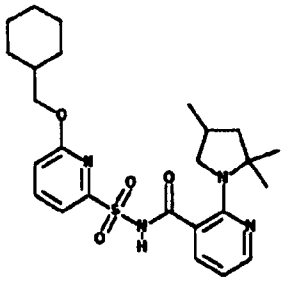
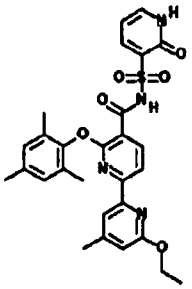
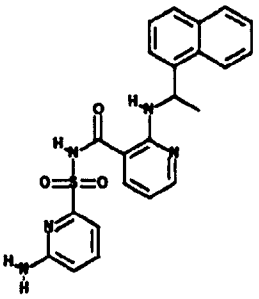
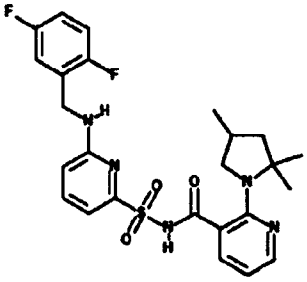
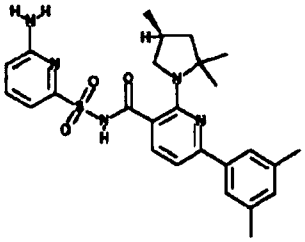
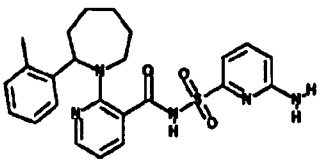
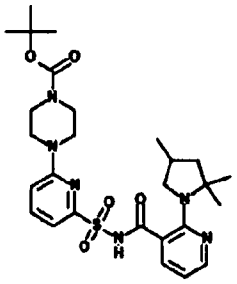
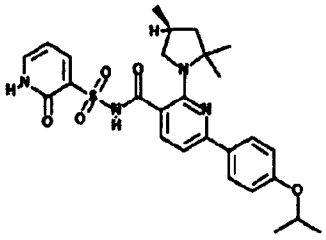
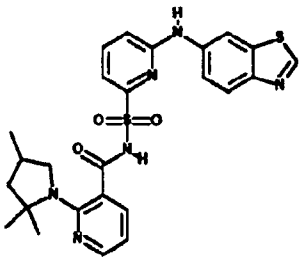
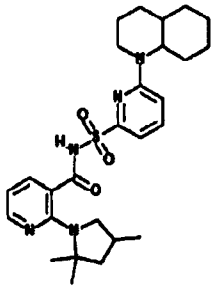
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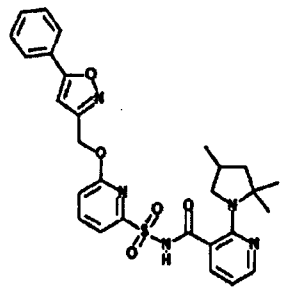
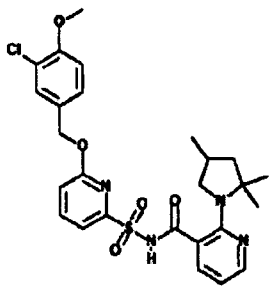
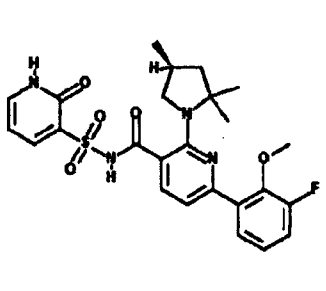
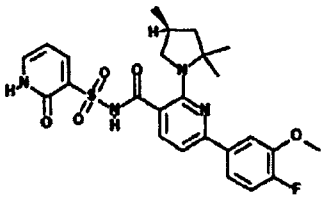
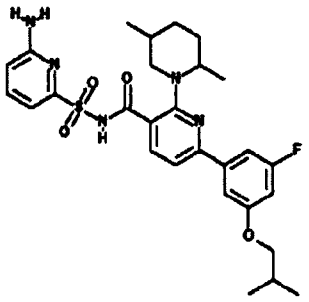
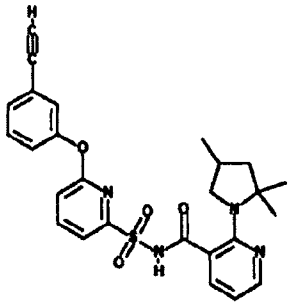
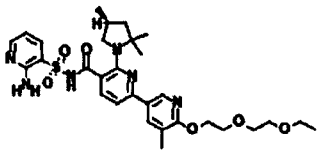
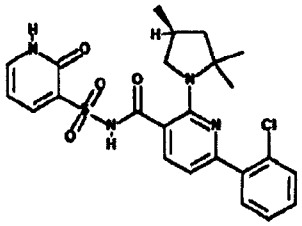
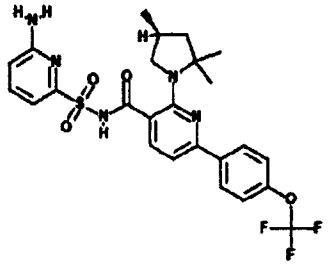
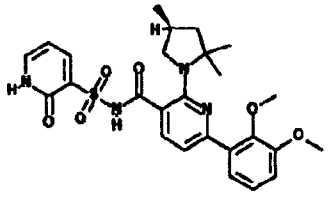
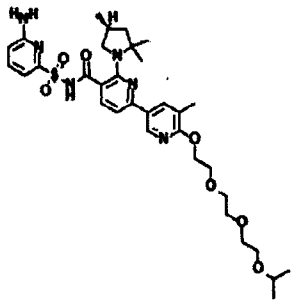
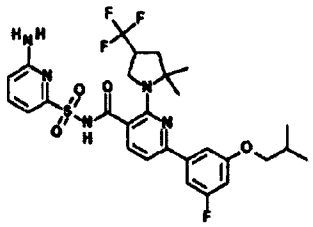
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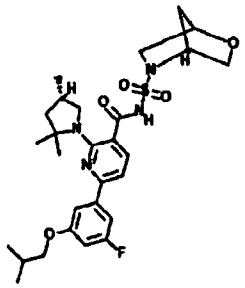
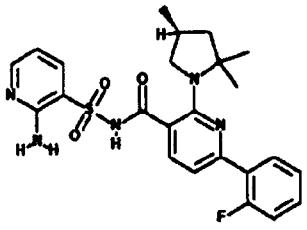
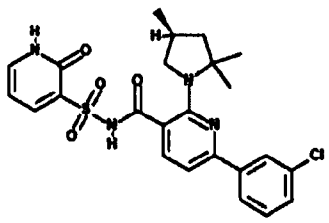
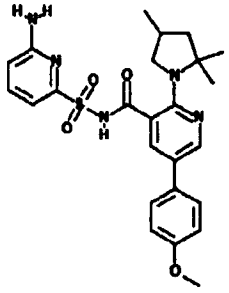
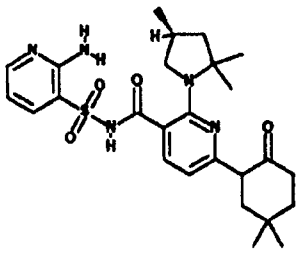
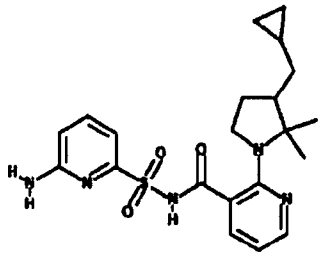
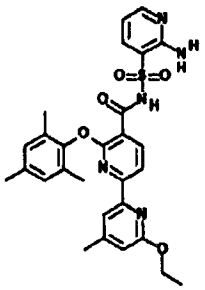
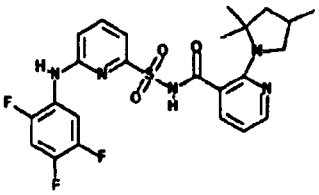
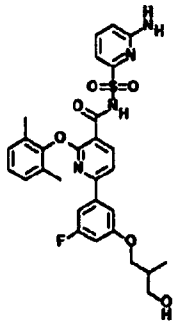
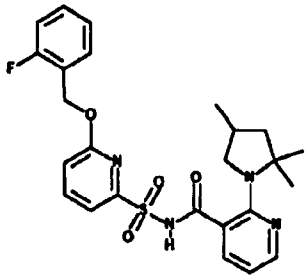
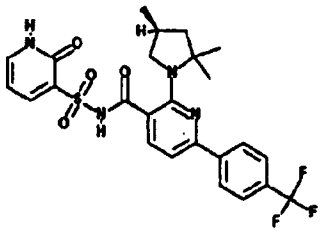
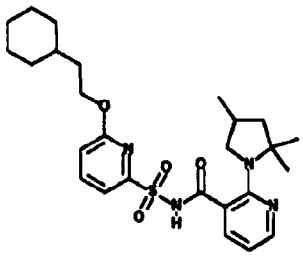
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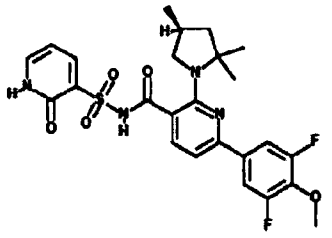
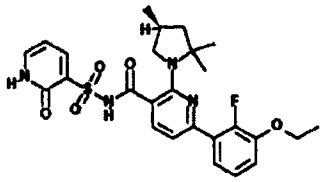
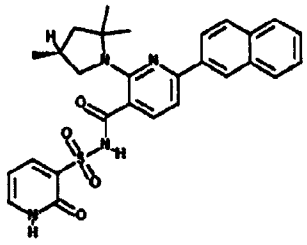
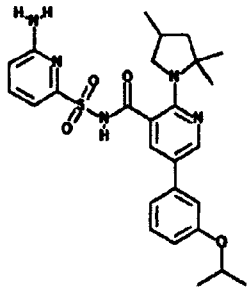
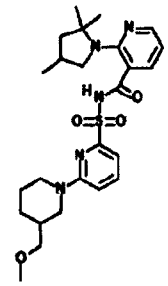
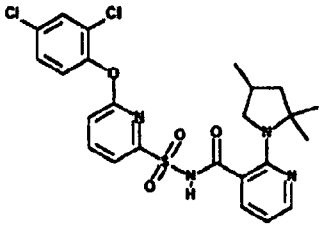
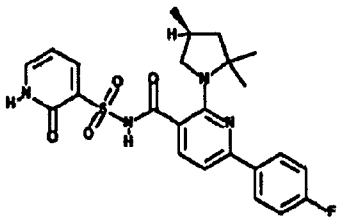
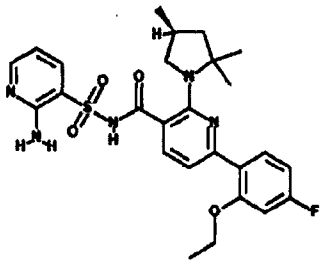
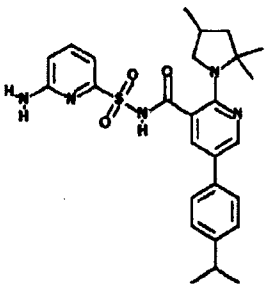
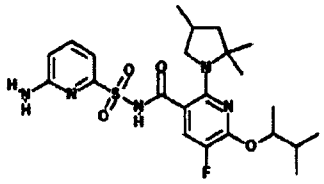
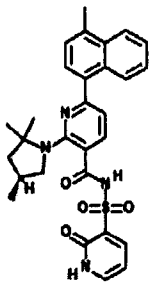
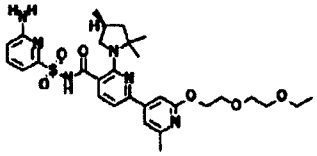
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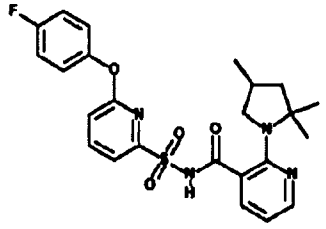
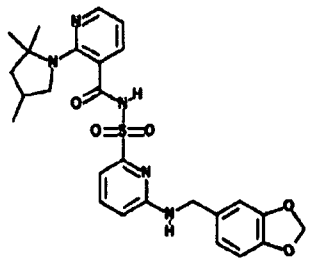
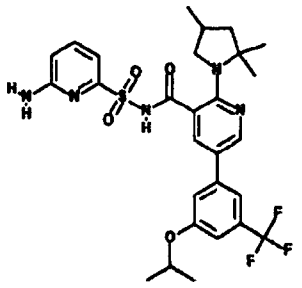
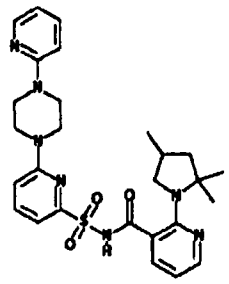
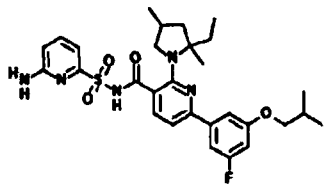
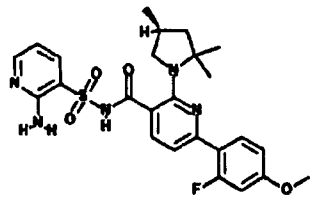
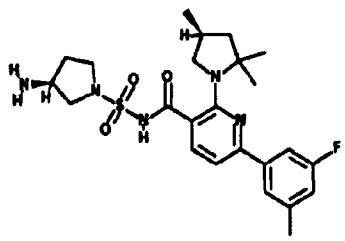
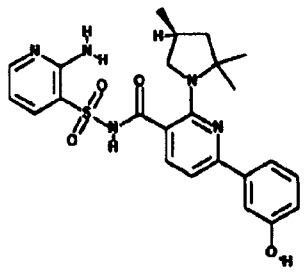
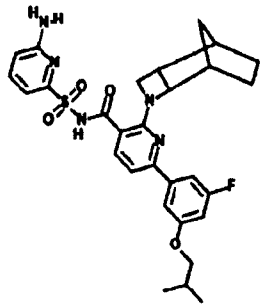
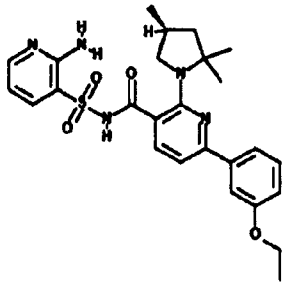
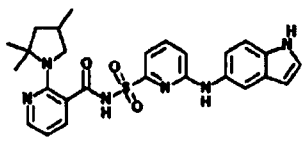
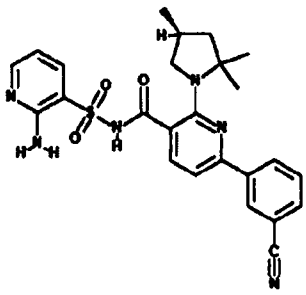
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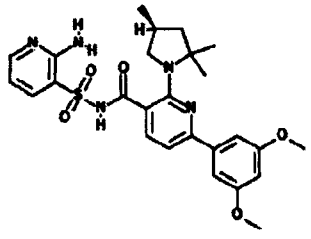
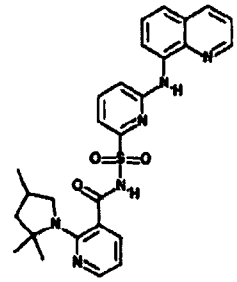
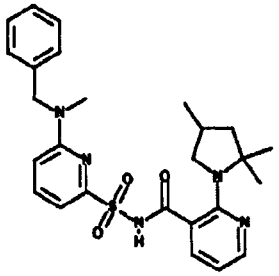
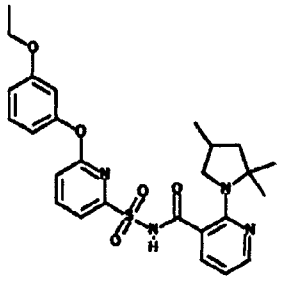
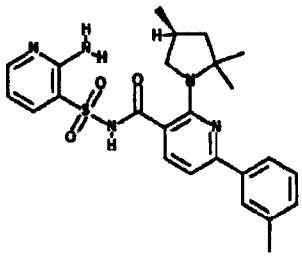
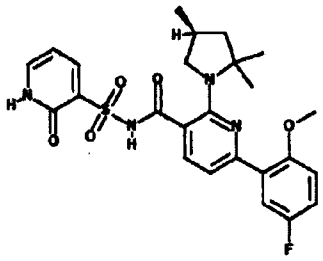
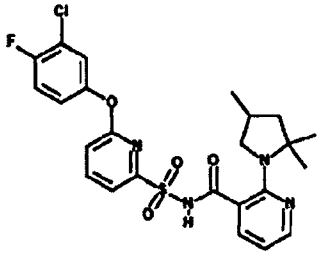
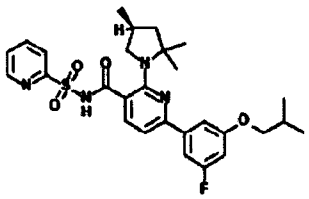
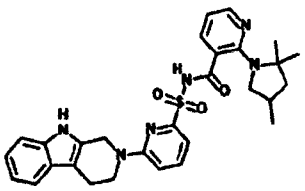
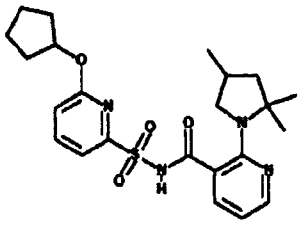
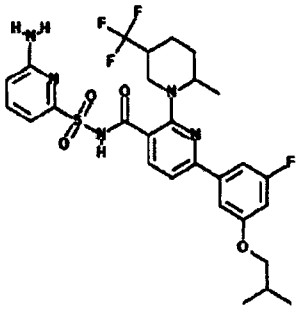
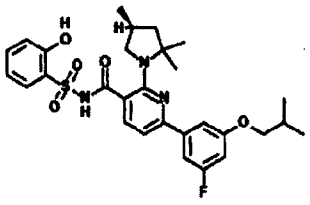
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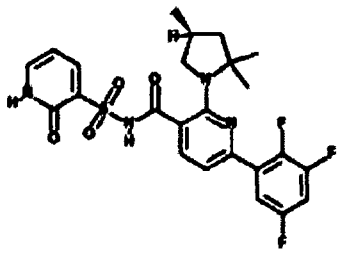
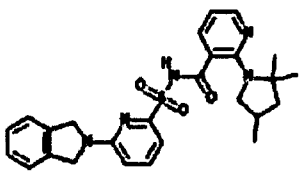
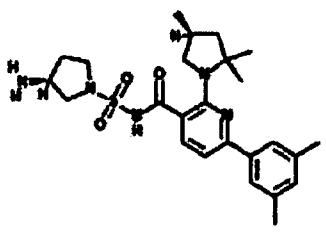
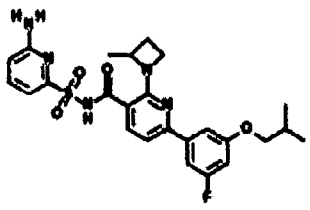
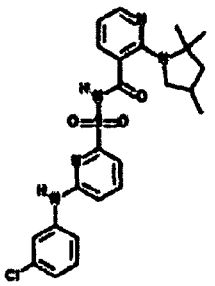
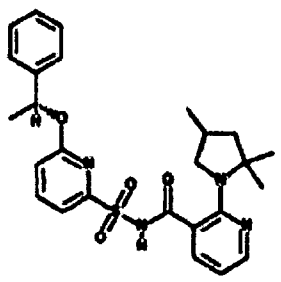
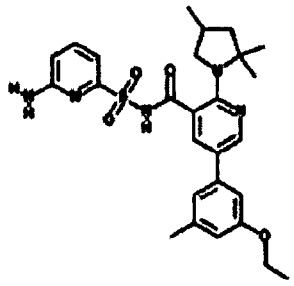
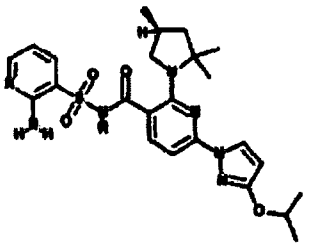
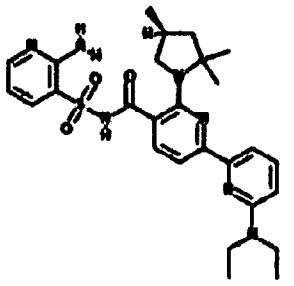
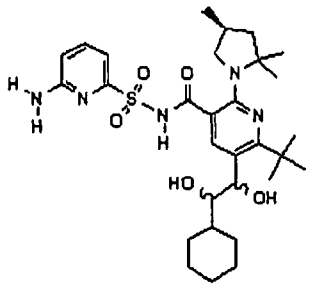
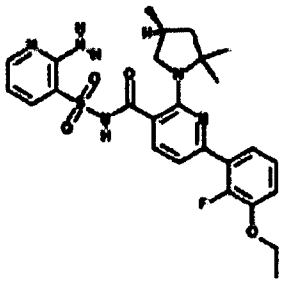
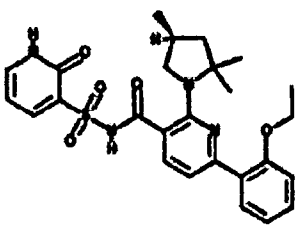
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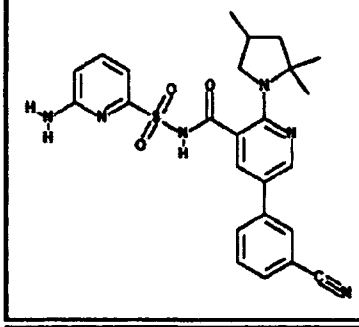
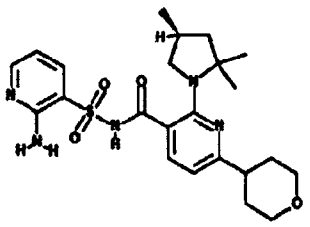
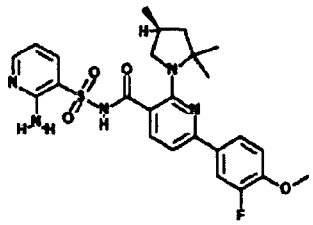
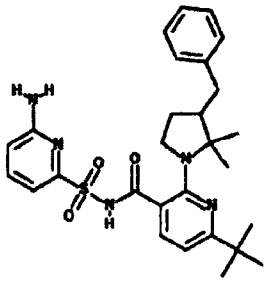
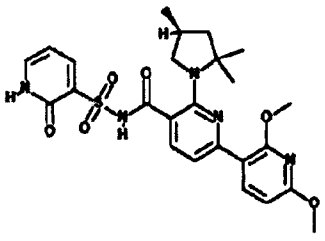
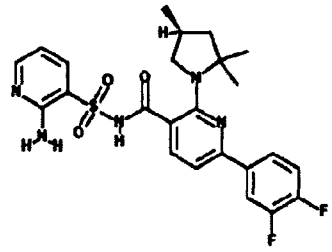
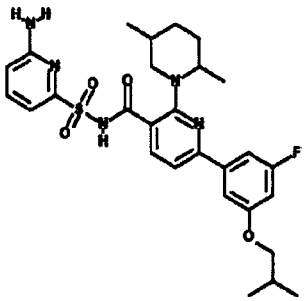
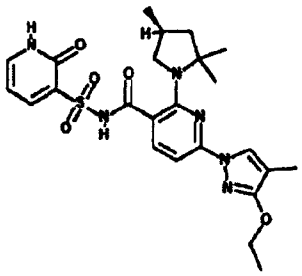
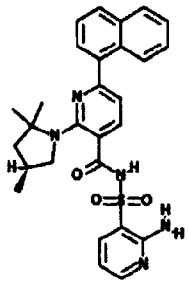
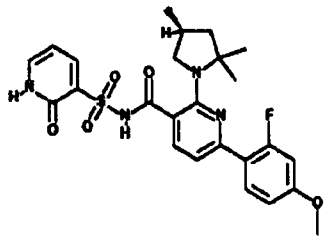
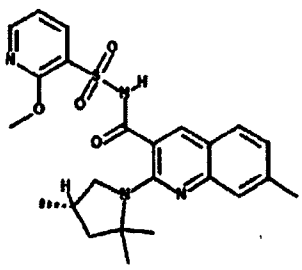
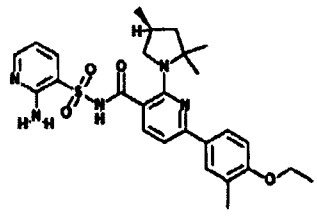
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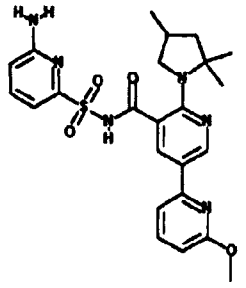
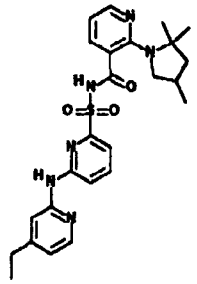
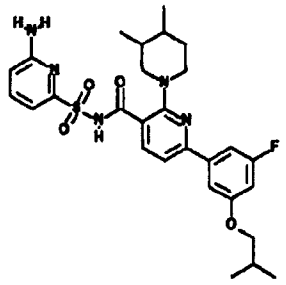
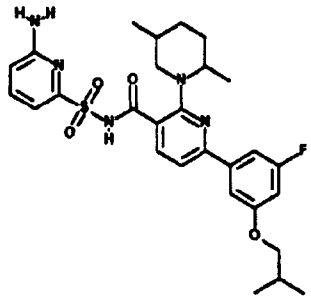
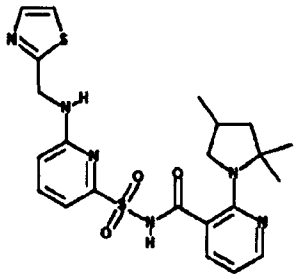
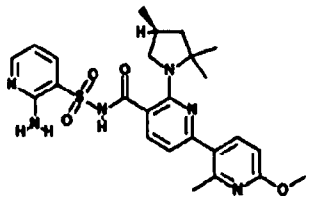
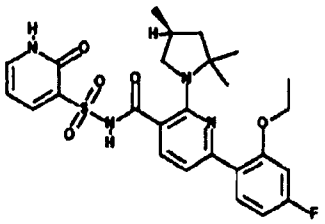
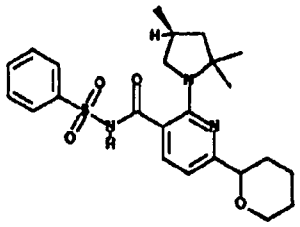
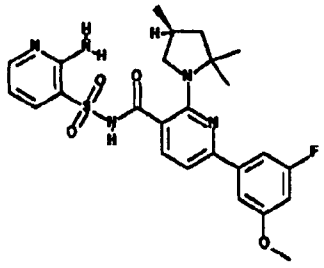
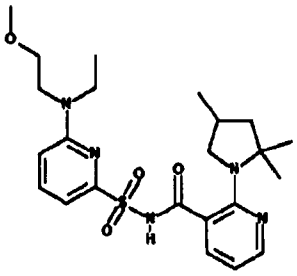
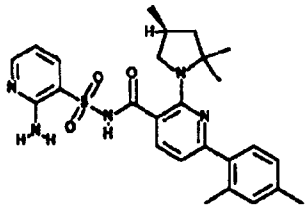
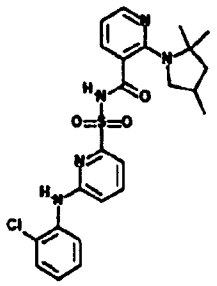
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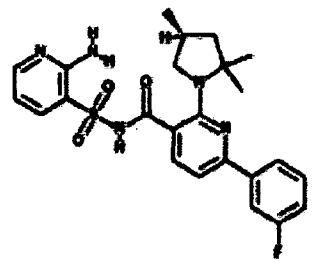
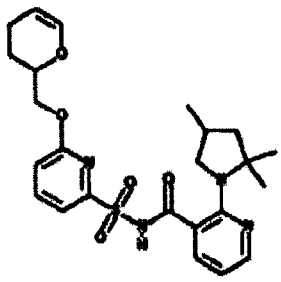
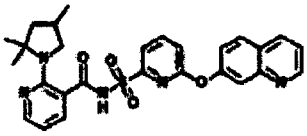
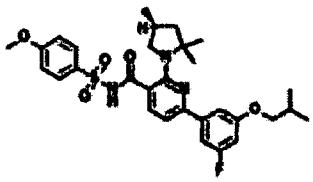
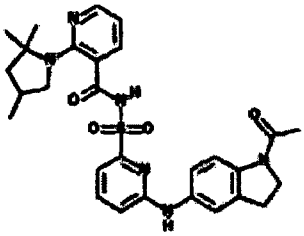
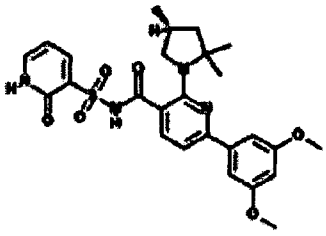
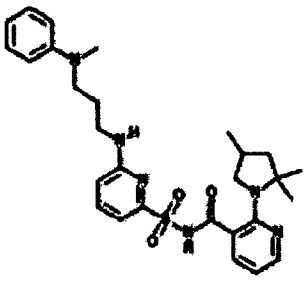
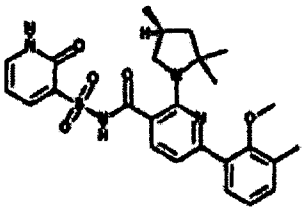
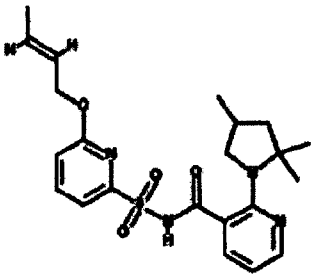
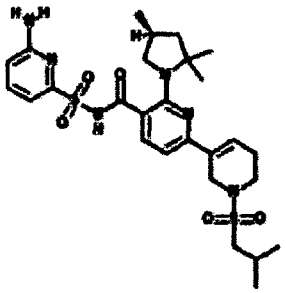
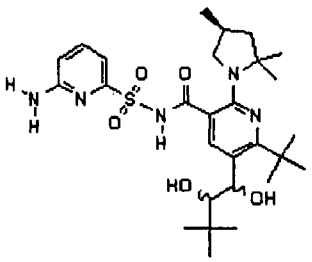
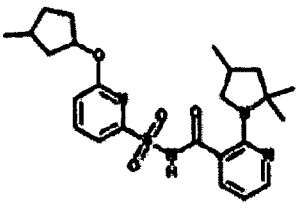
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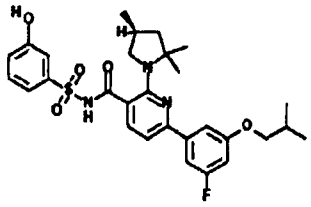
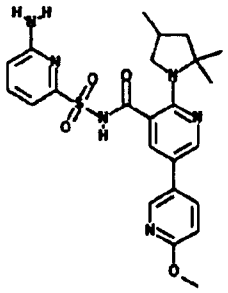
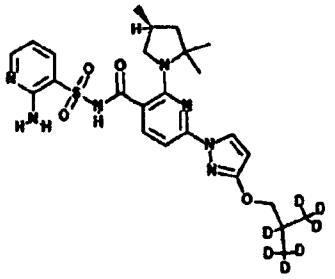
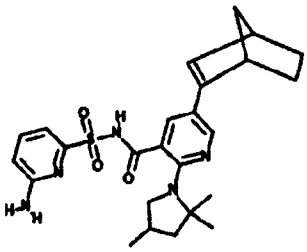
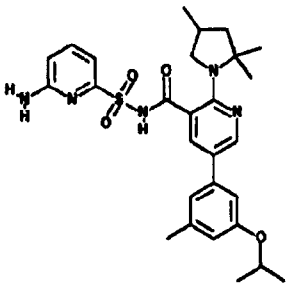
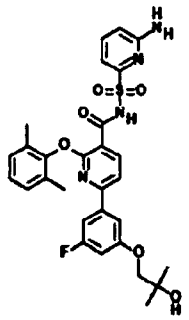
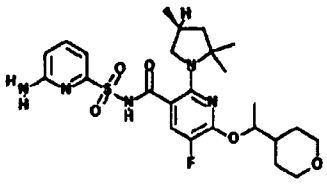
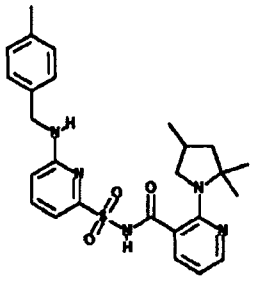
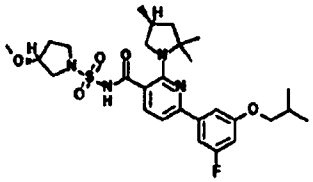
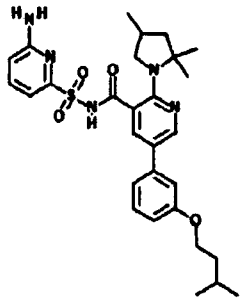
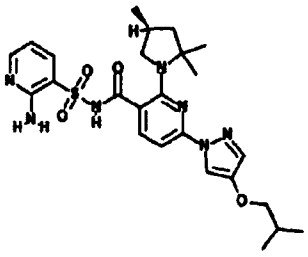
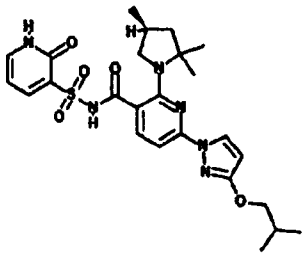
| 1825 | 1826 | 1827 |
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| **1828** | **1829** | **1830** |
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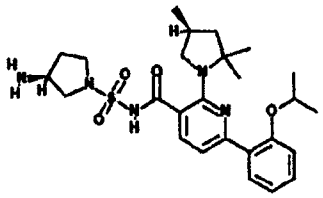
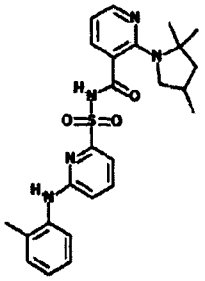
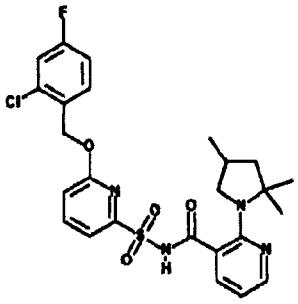
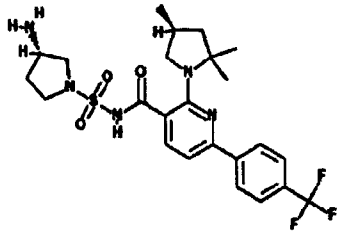
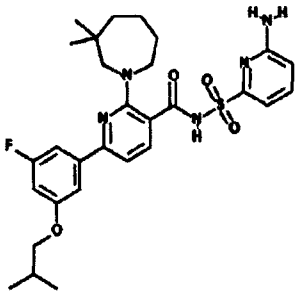
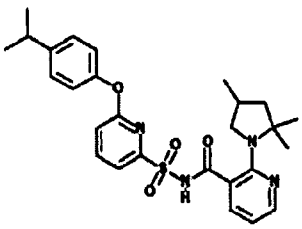
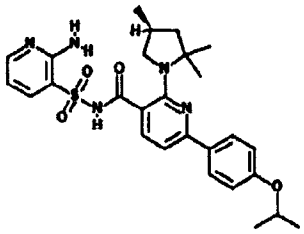
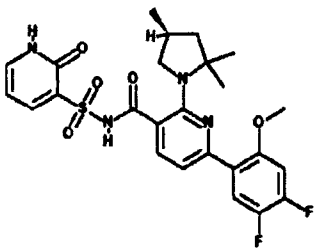
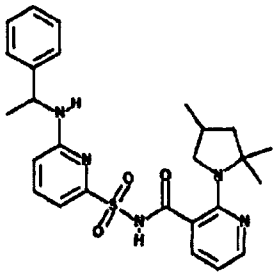
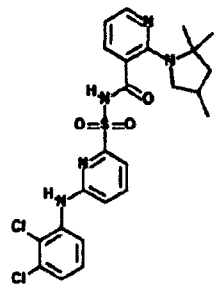
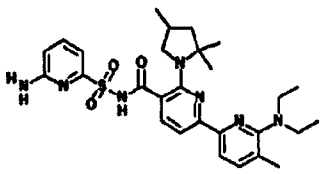
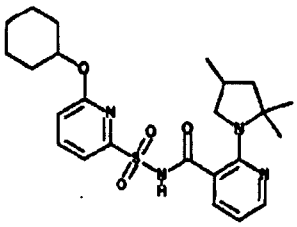
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| **1840** | **1841** | **1842** |
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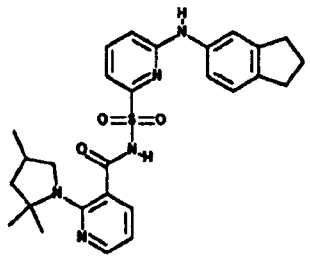
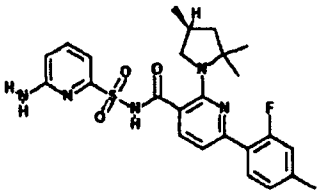
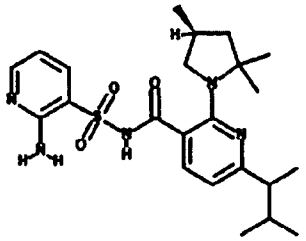
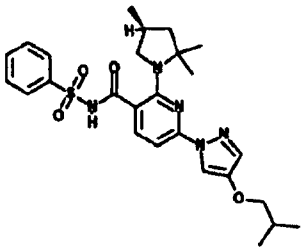
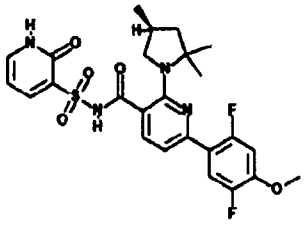
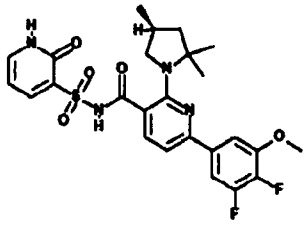
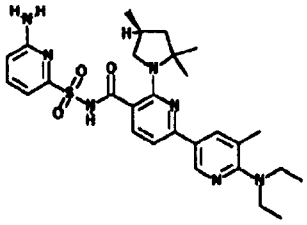
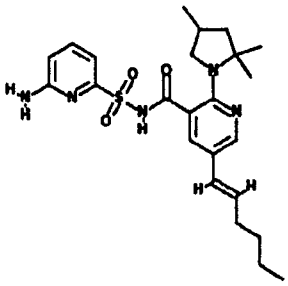
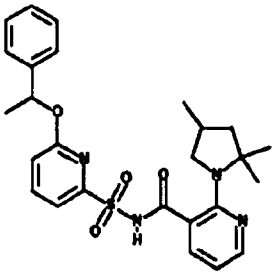
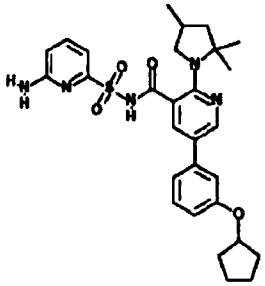
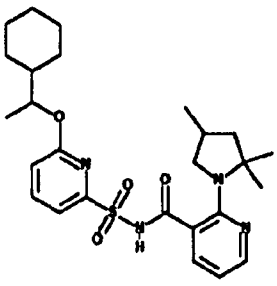
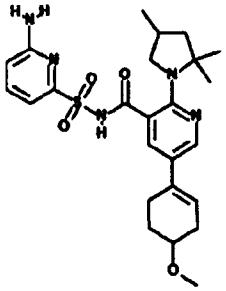
| 1849 | 1850 | 1851 |
|---|---|---|
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| **1852** | **1853** | **1854** |
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| **1855** | **1856** | **1857** |
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| **1858** | **1859** | **1860** |
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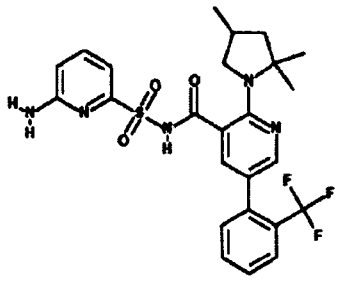
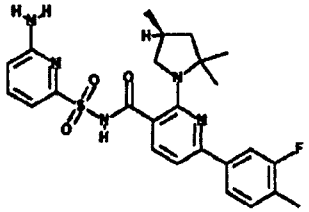
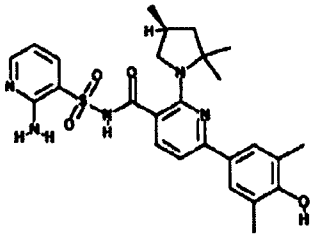
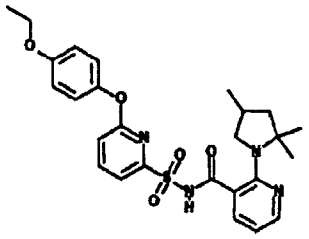
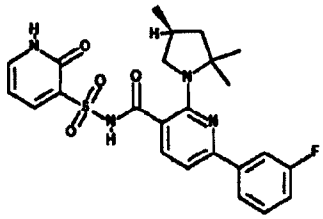
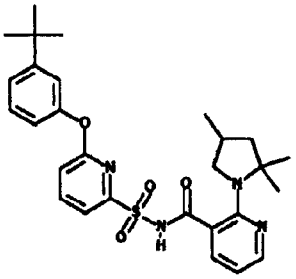
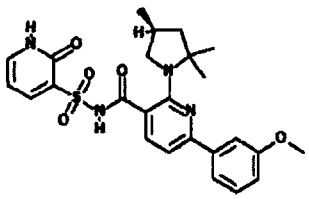
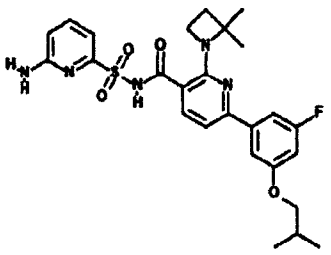
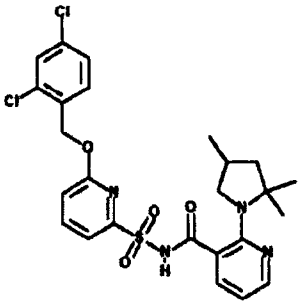
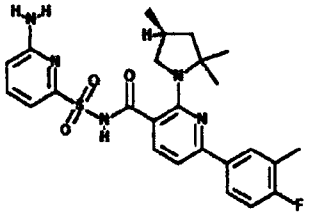
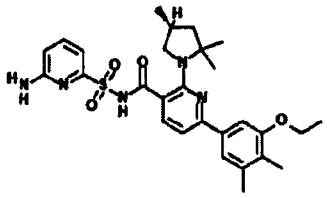
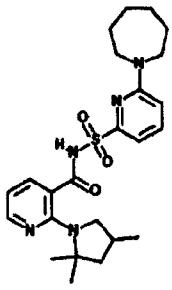
| 1861 | 1862 | 1863 |
|---|---|---|
|  |  |  |
| **1864** | **1865** | **1866** |
|  |  |  |
| **1867** | **1868** | **1869** |
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| **1870** | **1871** | **1872** |
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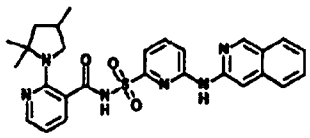
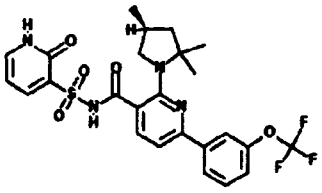
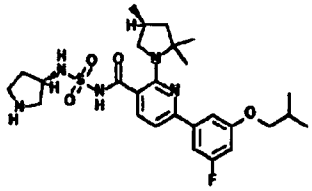
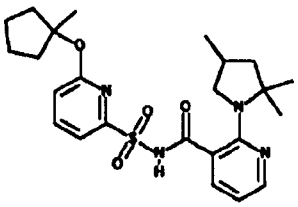
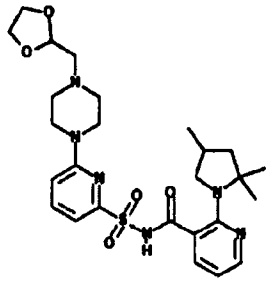
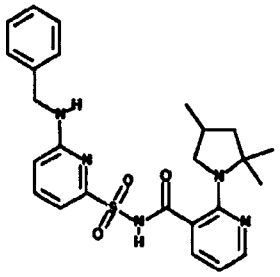
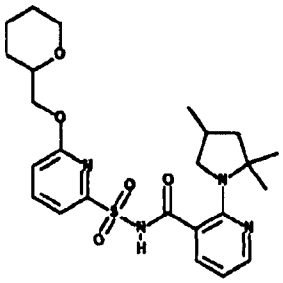
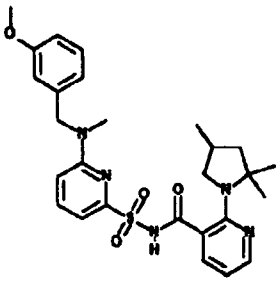
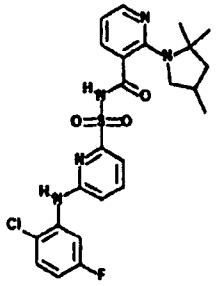
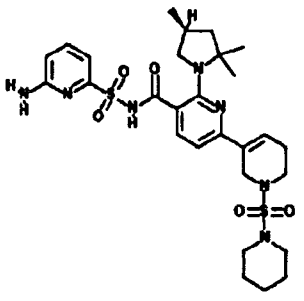
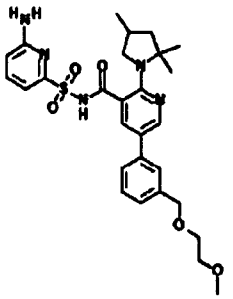
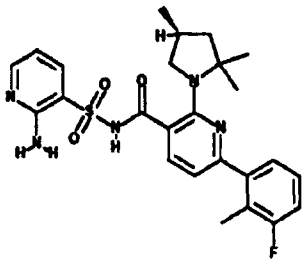
| 1873 | 1874 | 1875 |
|---|---|---|
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| **1876** | **1877** | **1878** |
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| **1879** | **1880** | **1881** |
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| **1882** | **1883** | **1884** |
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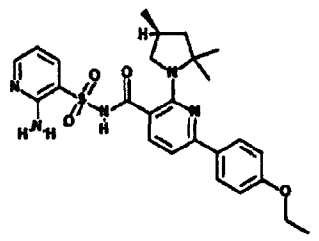
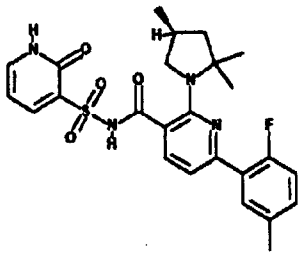
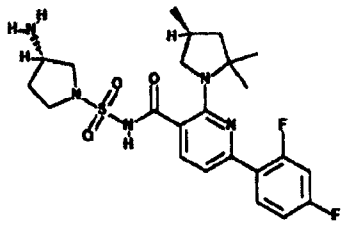
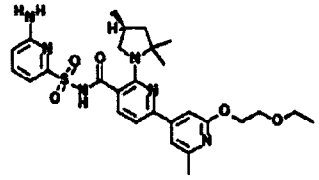
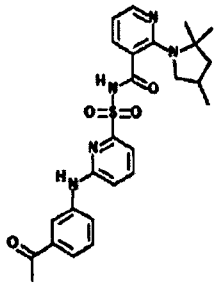
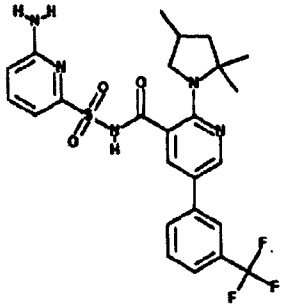
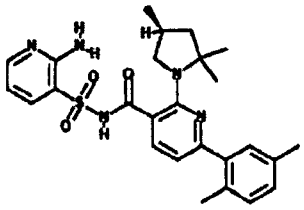
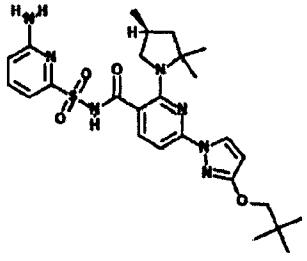
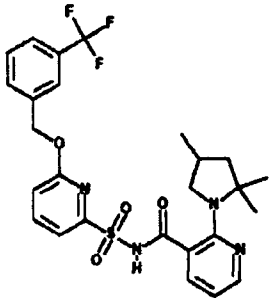
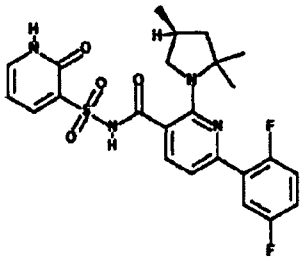
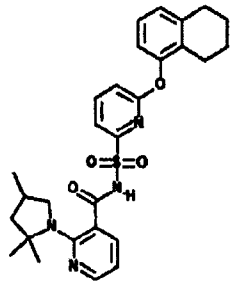
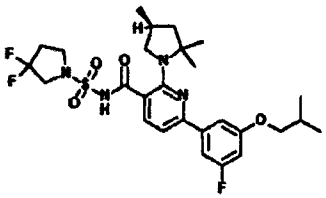
| 1885 | 1886 | 1887 |
|---|---|---|
|  |  |  |
| **1888** | **1889** | **1890** |
|  |  |  |
| **1891** | **1892** | **1893** |
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| **1894** | **1895** | **1896** |
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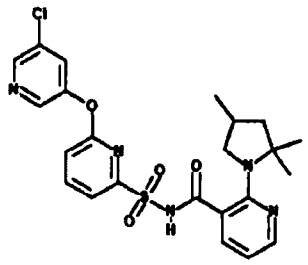
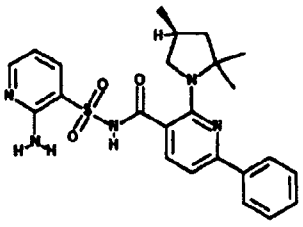
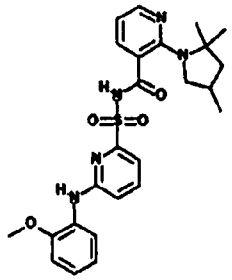
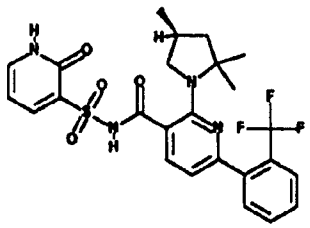
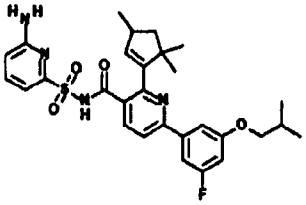
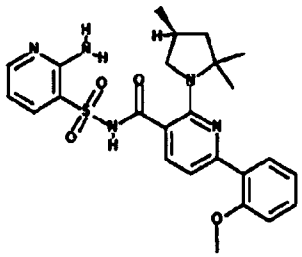
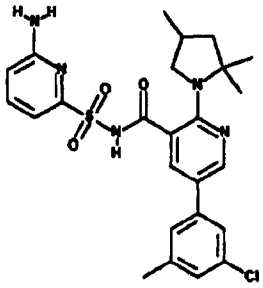
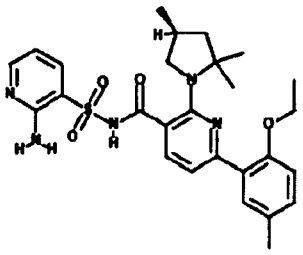
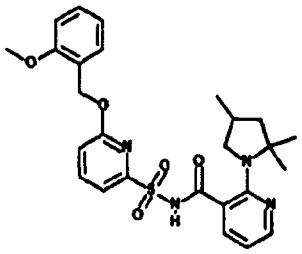
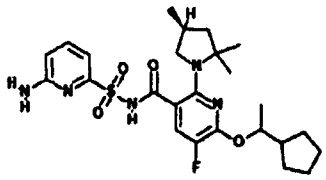
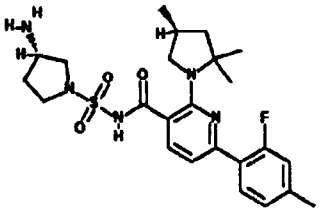
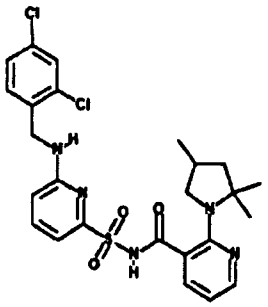
| 1897 | 1898 | 1899 |
|---|---|---|
|  |  |  |
| **1900** | **1901** | **1902** |
|  |  |  |
| **1903** | **1904** | **1905** |
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| **1906** | **1907** | **1908** |
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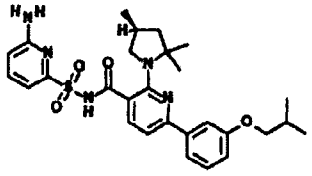
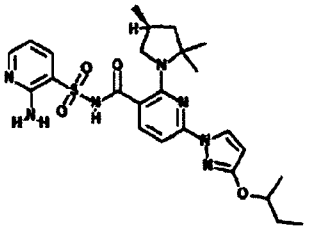
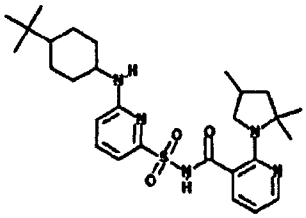
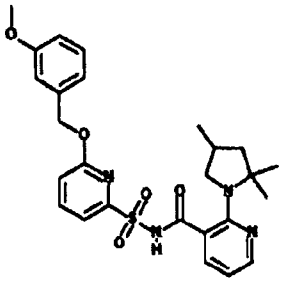
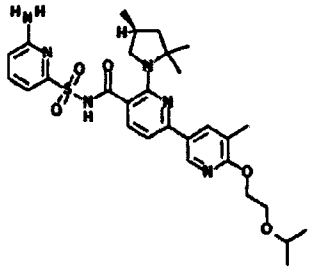
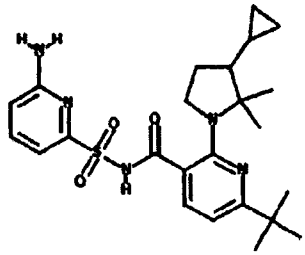
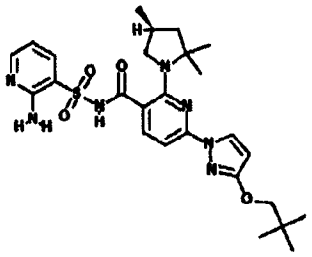
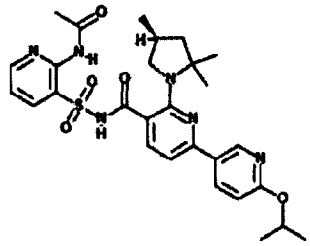
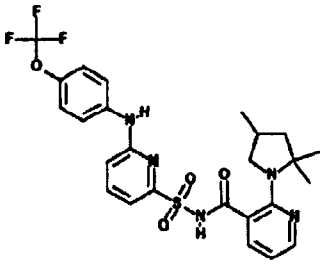
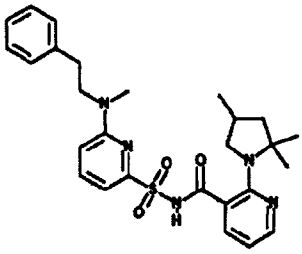
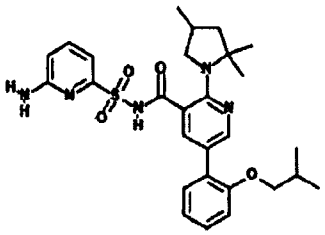
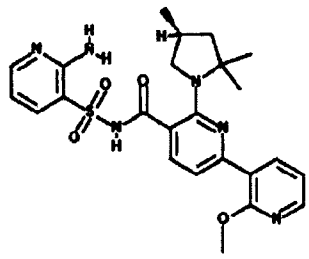
| 1909 | 1910 | 1911 |
|---|---|---|
|  |  |  |
| **1912** | **1913** | **1914** |
|  |  |  |
| **1915** | **1916** | **1917** |
|  |  |  |
| **1918** | **1919** | **1920** |
|  |  |  |

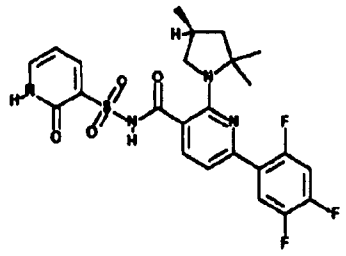
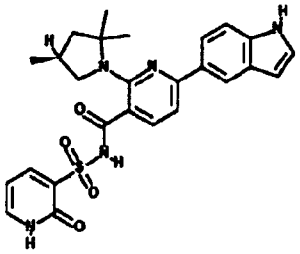
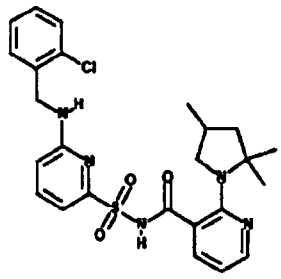
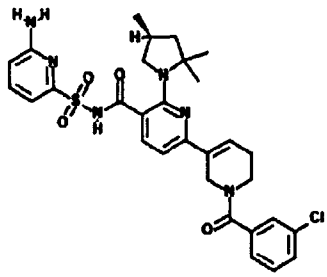
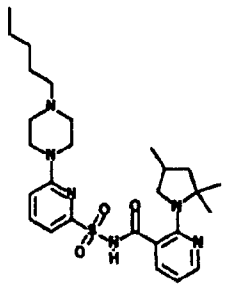
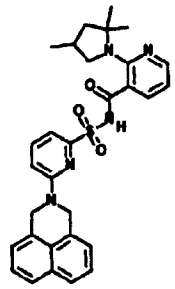
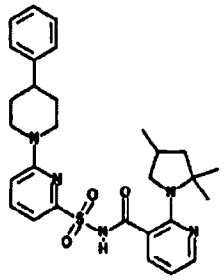
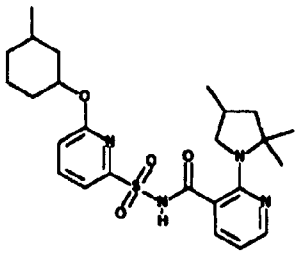
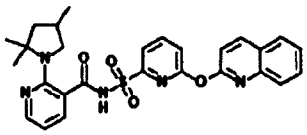
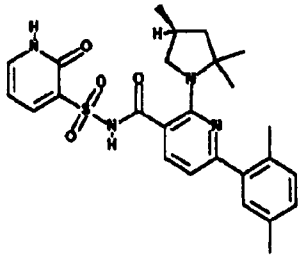
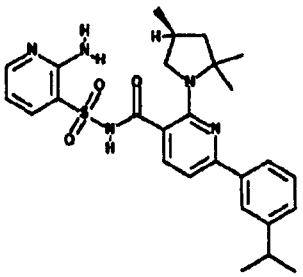
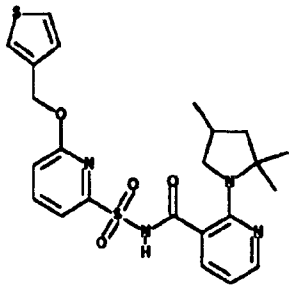
| 1921 | 1922 | 1923 |
|---|---|---|
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| **1924** | **1925** | **1926** |
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| **1927** | **1928** | **1929** |
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| **1930** | **1931** | **1932** |
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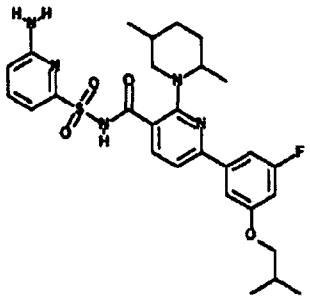
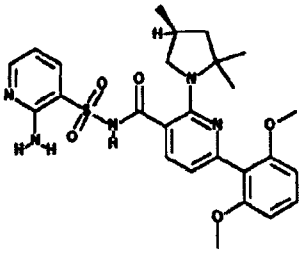
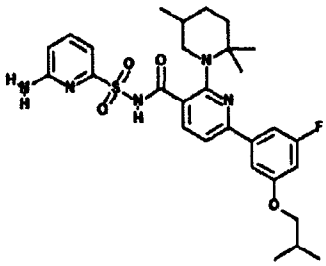
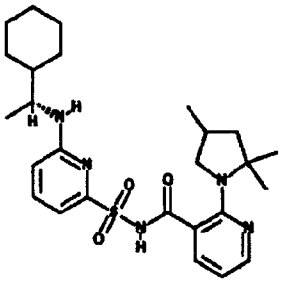
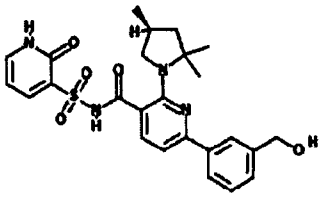
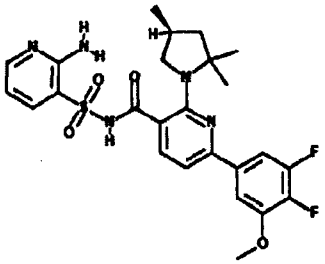
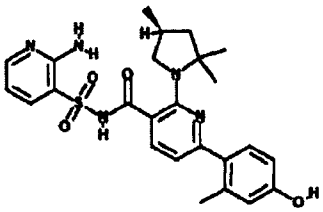
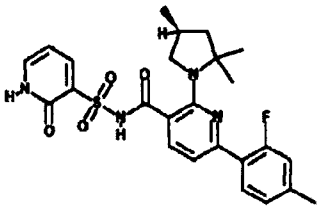
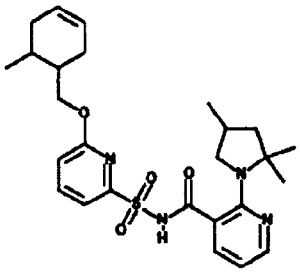
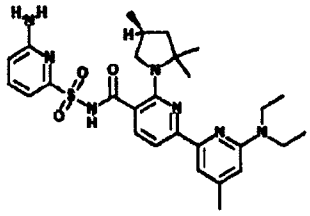
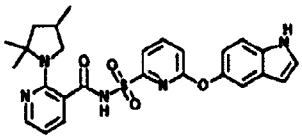
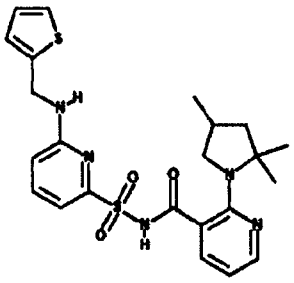
| 1933 | 1934 | 1935 |
|---|---|---|
|  |  |  |
| **1936** | **1937** | **1938** |
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| **1939** | **1940** | **1941** |
|  |  |  |
| **1942** | **1943** | **1944** |
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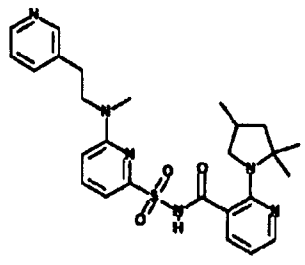
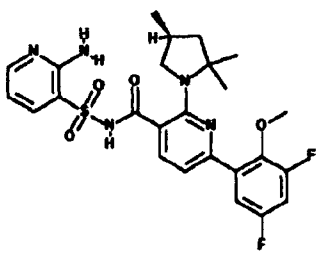
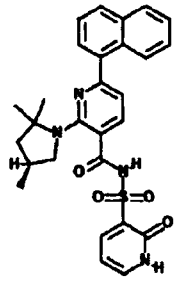
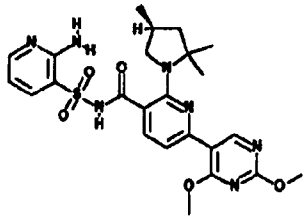
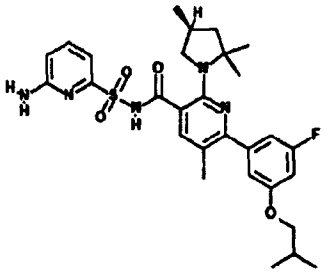
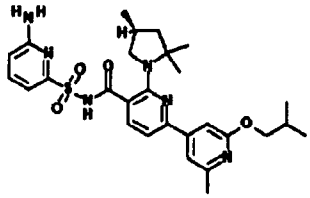
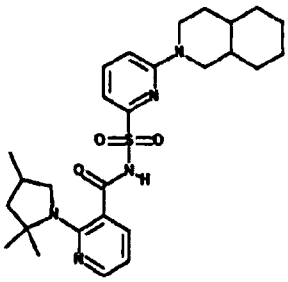
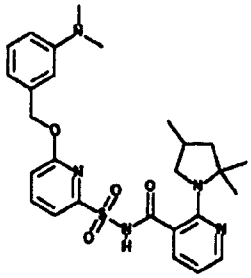
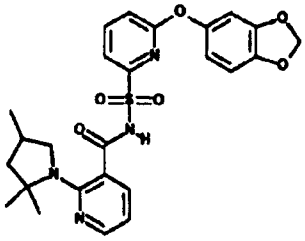
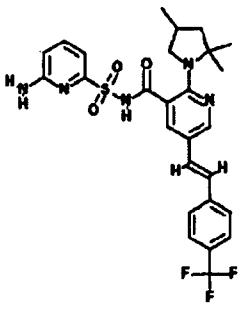
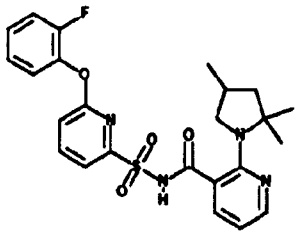
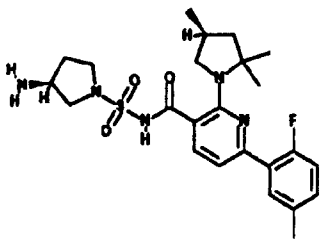
| 1945 | 1946 | 1947 |
|---|---|---|
|  |  |  |
| **1948** | **1949** | **1950** |
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| **1951** | **1952** | **1953** |
|  |  |  |
| **1954** | **1955** | **1956** |
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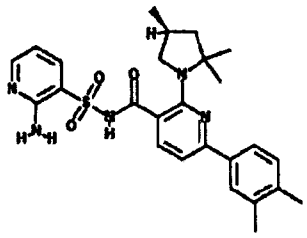
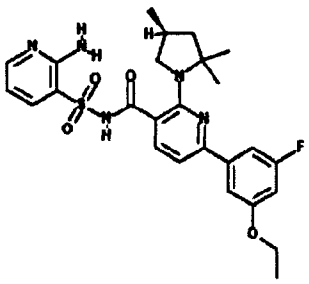
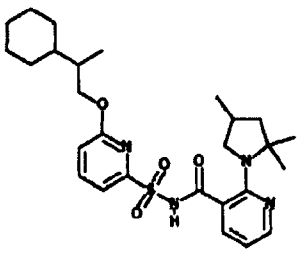
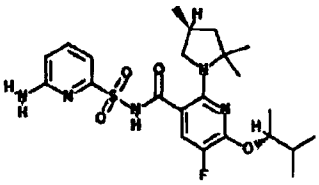
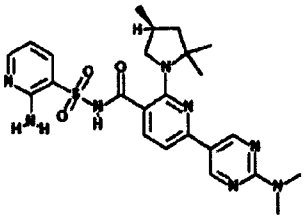
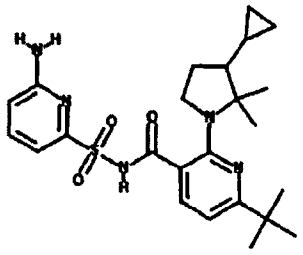
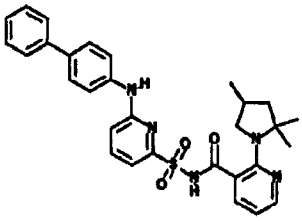
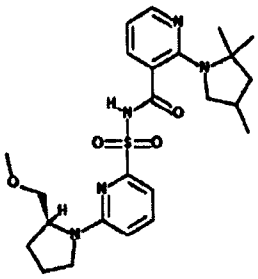
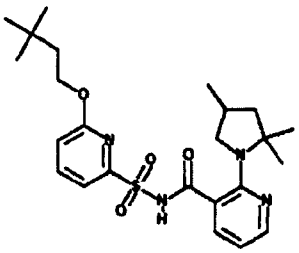
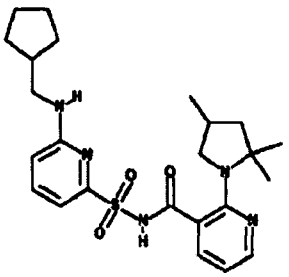
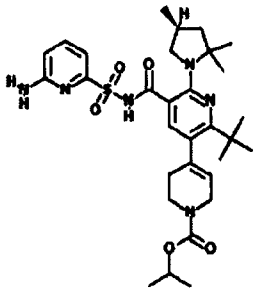
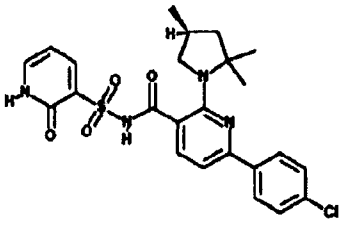
| 1957 | 1958 | 1959 |
|---|---|---|
|  |  |  |
| **1960** | **1961** | **1962** |
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| **1963** | **1964** | **1965** |
|  |  |  |
| **1966** | **1967** | **1968** |
|  |  |  |

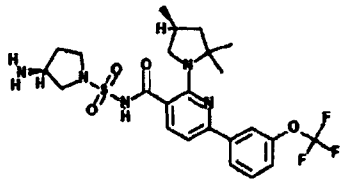
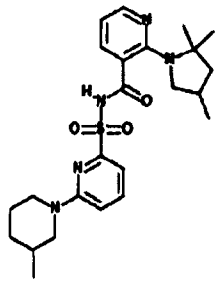
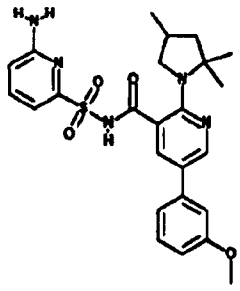
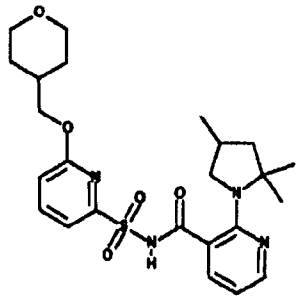
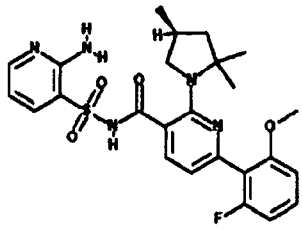
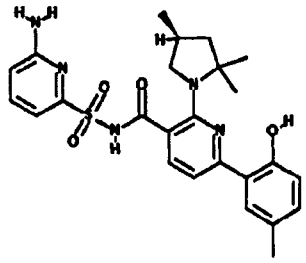
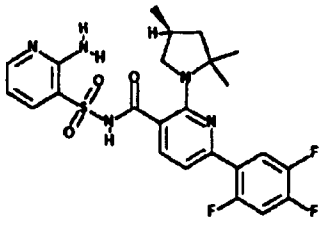
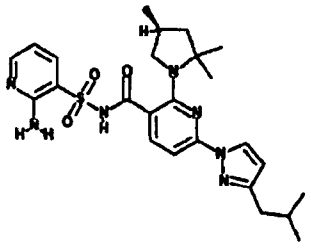
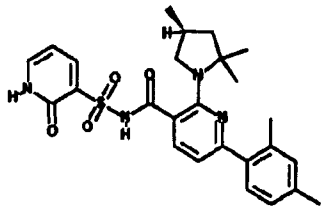
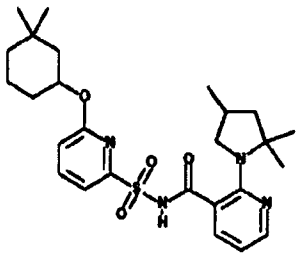
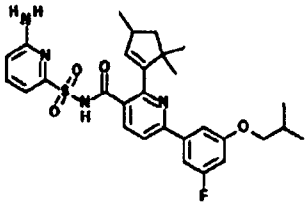
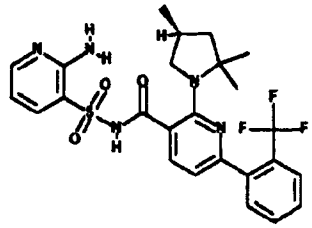
| 1969 | 1970 | 1971 |
|---|---|---|
|  |  |  |
| **1972** | **1973** | **1974** |
|  |  |  |
| **1975** | **1976** | **1977** |
|  |  |  |
| **1978** | **1979** | **1980** |
|  |  |  |

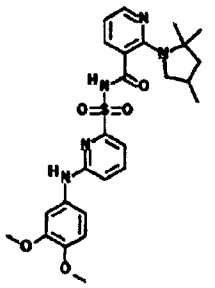
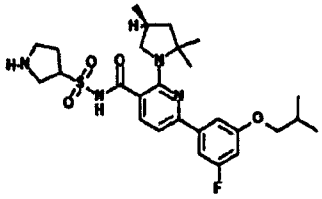
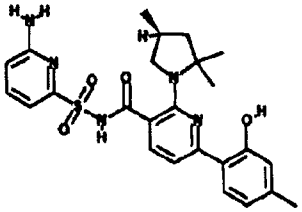
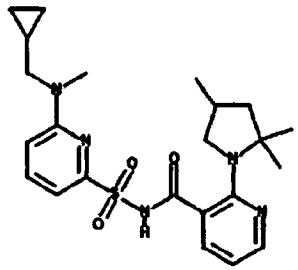
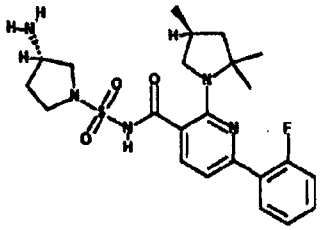
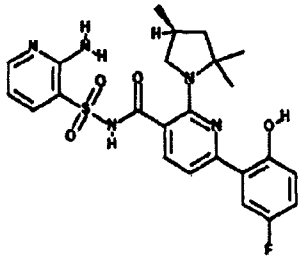
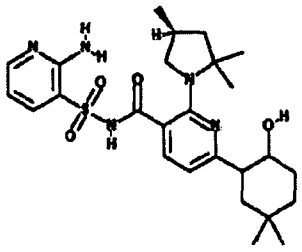
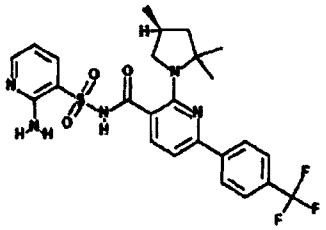
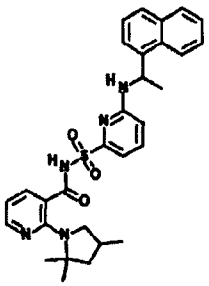
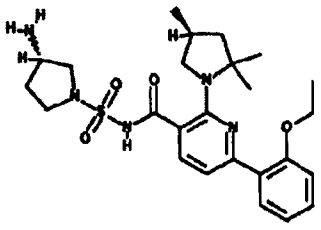
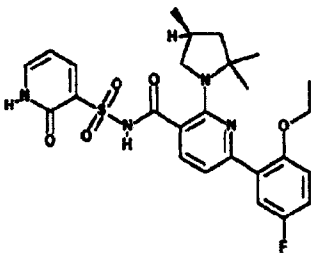
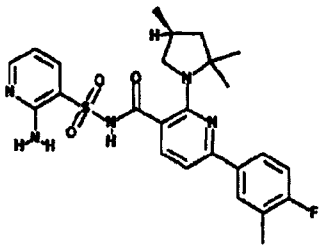
| 1981 | 1982 | 1983 |
|---|---|---|
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| **1984** | **1985** | **1986** |
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| **1987** | **1988** | **1989** |
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| **1990** | **1991** | **1992** |
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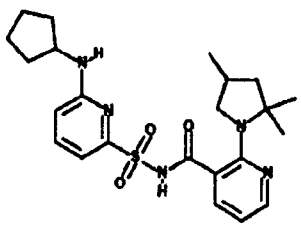
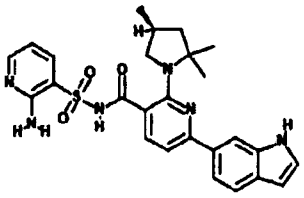
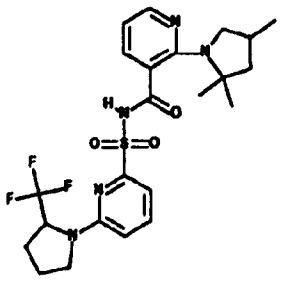
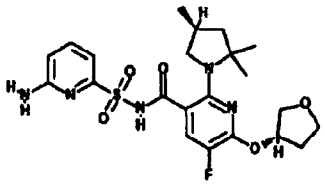
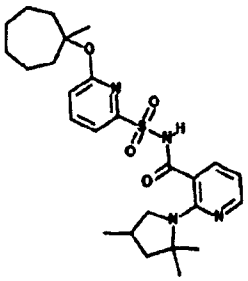
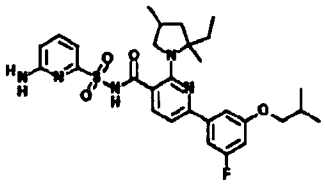
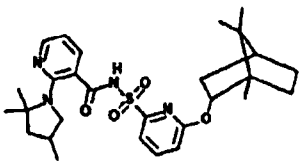
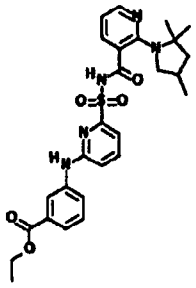
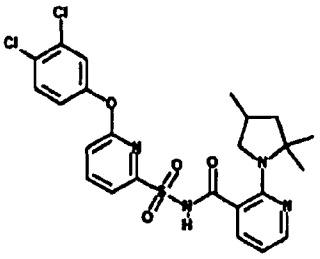
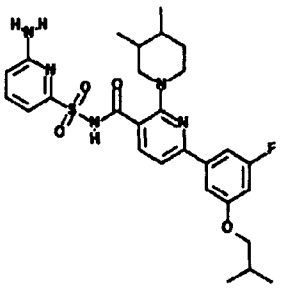
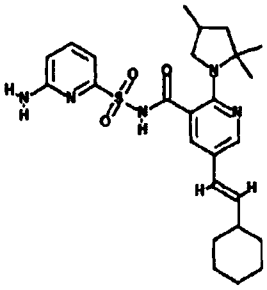
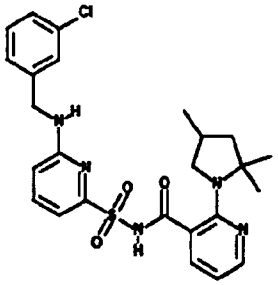
| 1993 | 1994 | 1995 |
|---|---|---|
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| **1996** | **1997** | **1998** |
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| **1999** | **2000** | **2001** |
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| **2002** | **2003** | **2004** |
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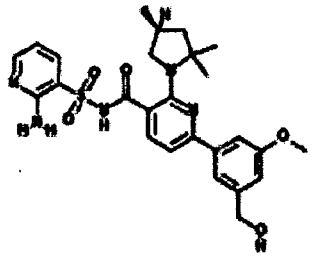
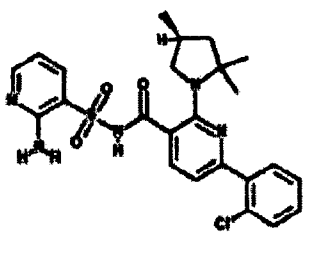
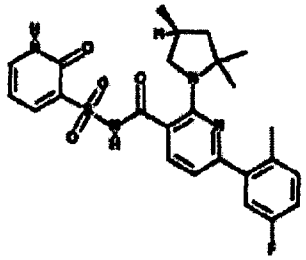
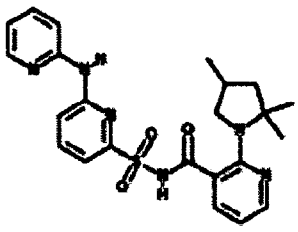
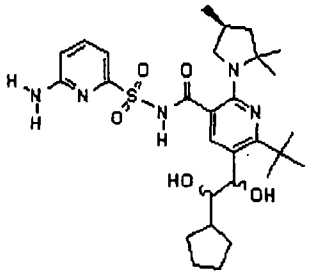
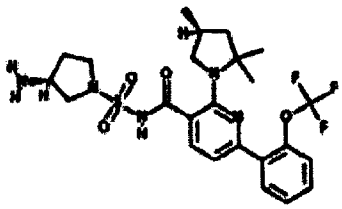
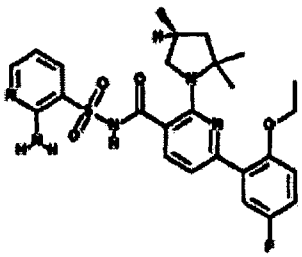
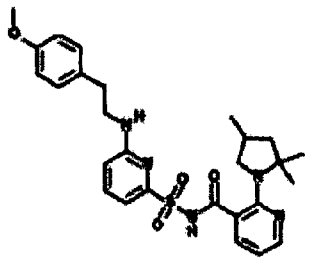
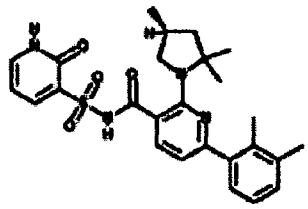
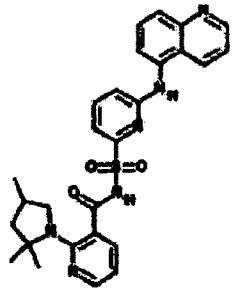
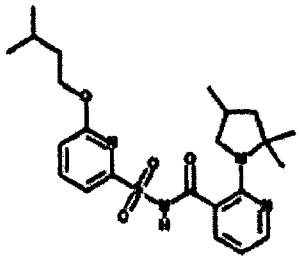
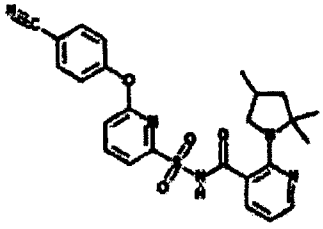
| 2005 | 2006 | 2007 |
|---|---|---|
|  |  |  |
| **2008** | **2009** | **2010** |
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| **2011** | **2012** | **2013** |
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| **2014** | **2015** | **2016** |
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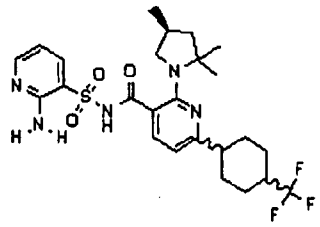
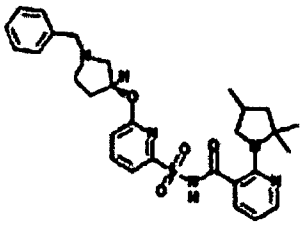
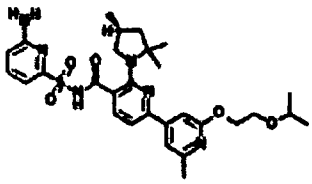
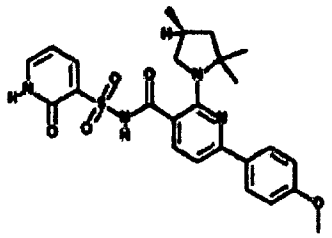
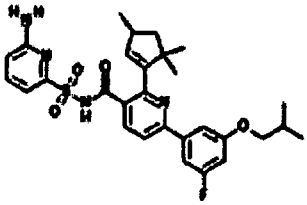
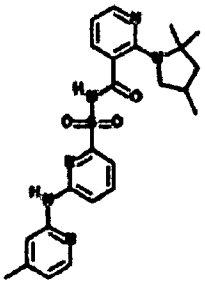
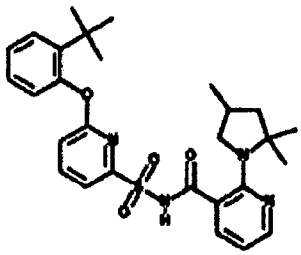
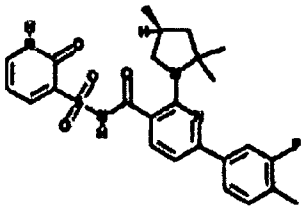
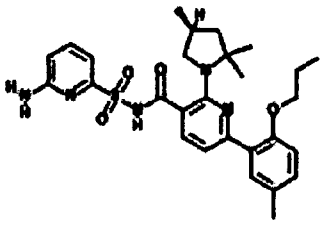
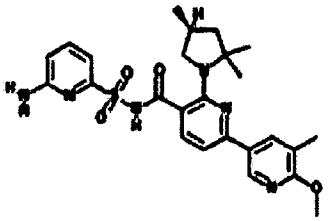
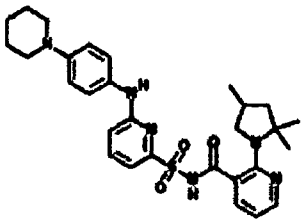
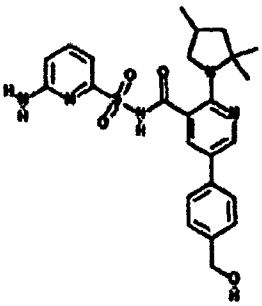
| 2017 | 2018 | 2019 |
|---|---|---|
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| **2020** | **2021** | **2022** |
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| **2023** | **2024** | **2025** |
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| **2026** | **2027** | **2028** |
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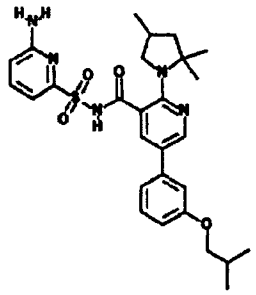
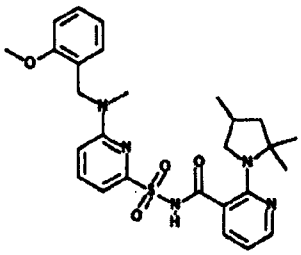
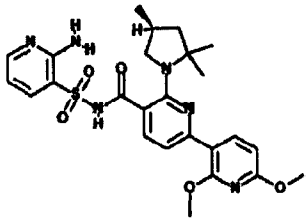
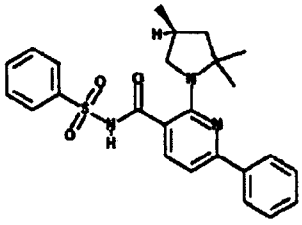
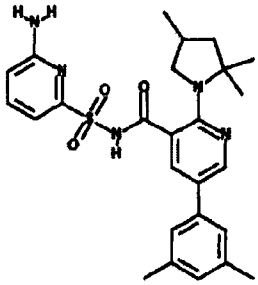
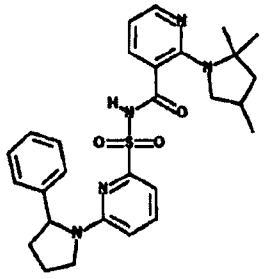
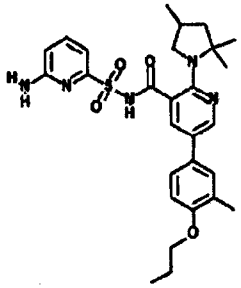
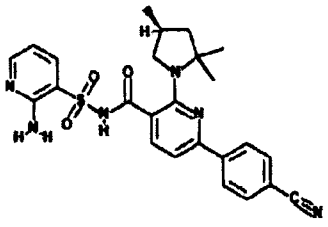
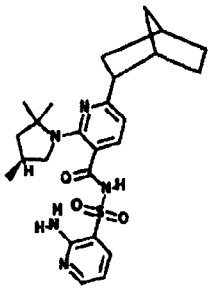
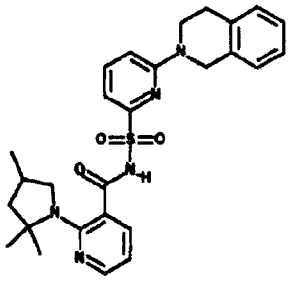
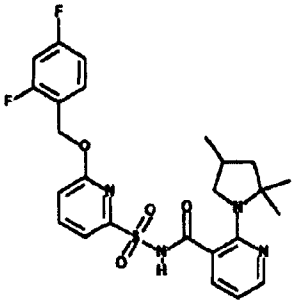
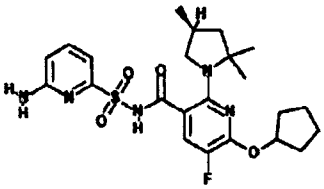
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| **2032** | **2033** | **2034** |
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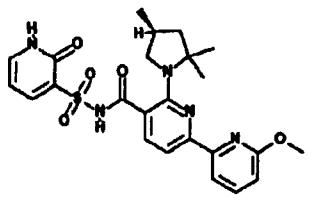
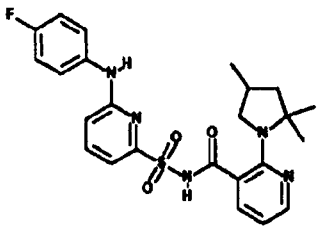
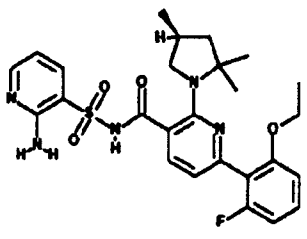
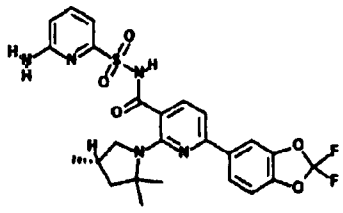
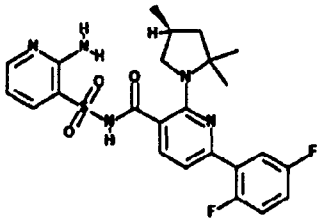
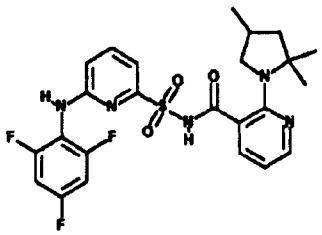
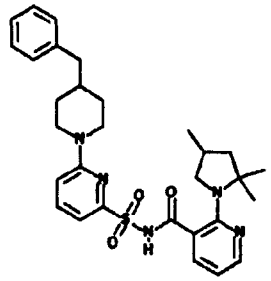
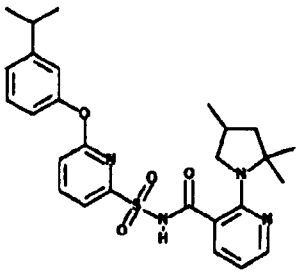
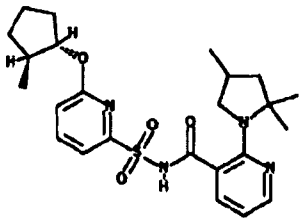
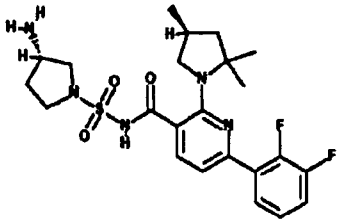
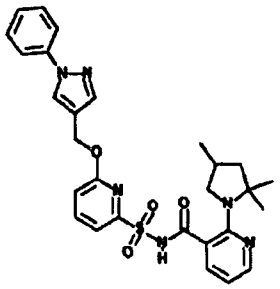
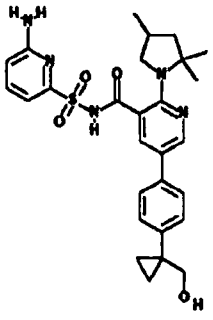
| 2041 | 2042 | 2043 |
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| **2044** | **2045** | **2046** |
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| **2047** | **2048** | **2049** |
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| **2050** | **2051** | **2052** |
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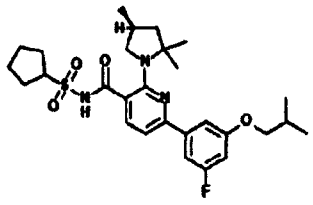
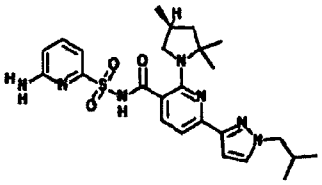
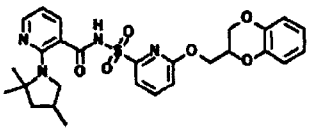
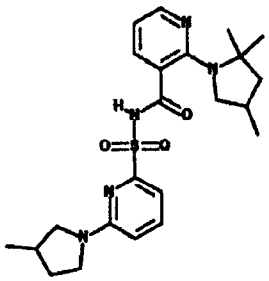
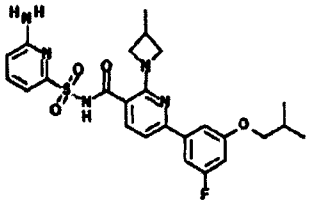
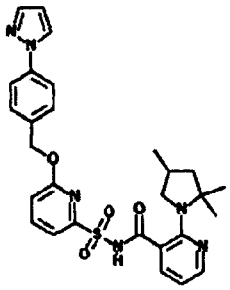
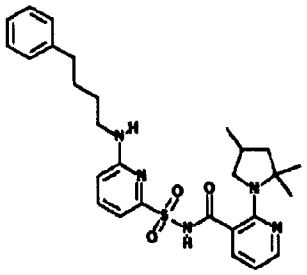
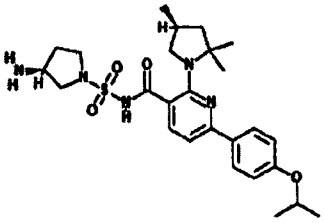
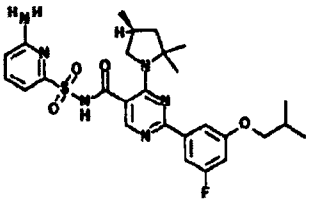
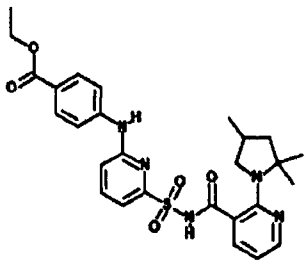
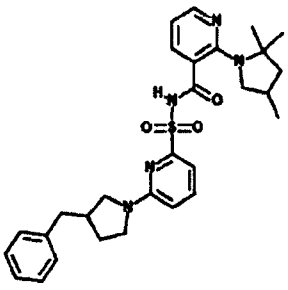
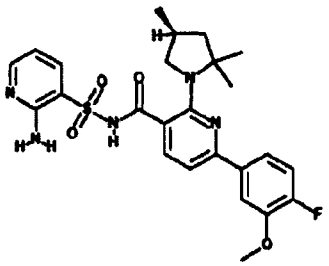
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| **2056** | **2057** | **2058** |
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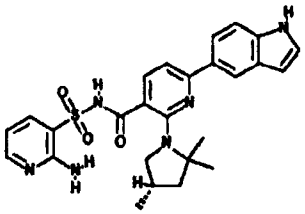
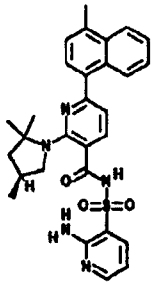
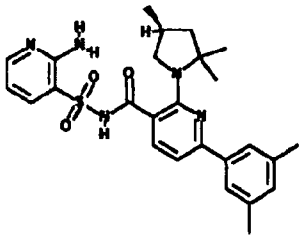
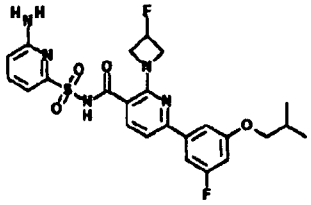
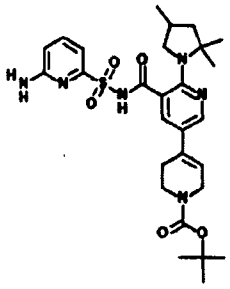
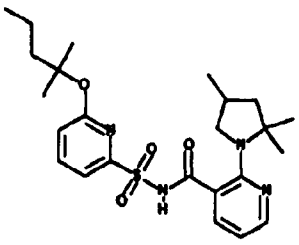
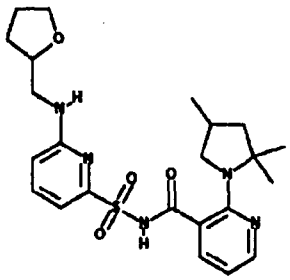
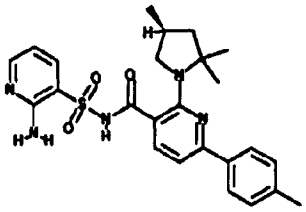
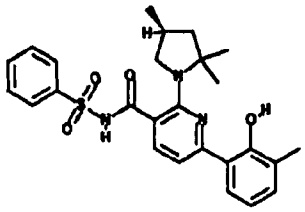
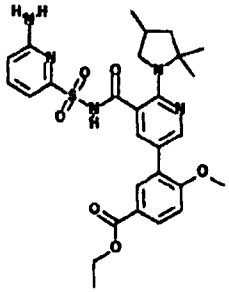
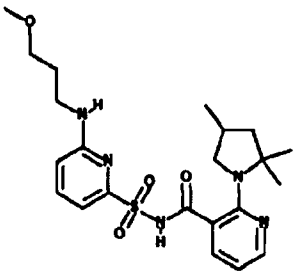
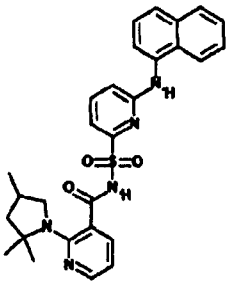
| 2065 | 2066 | 2067 |
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| **2068** | **2069** | **2070** |
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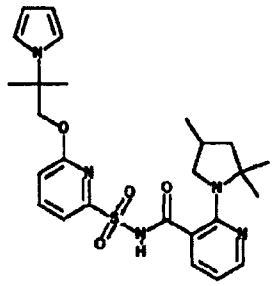
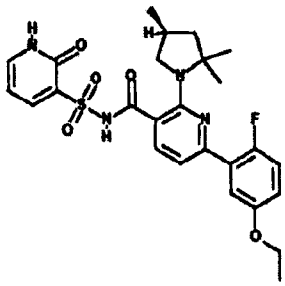
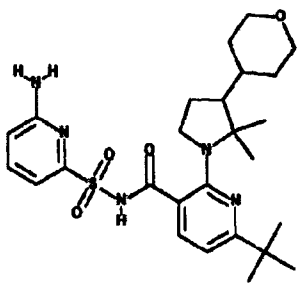
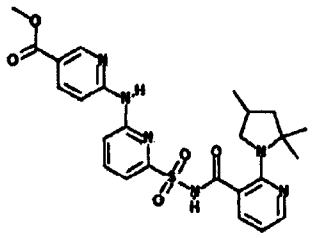
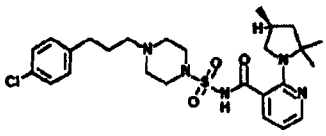
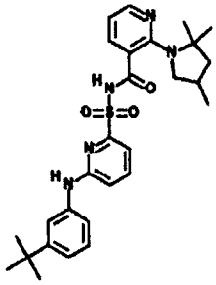
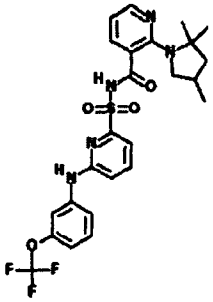
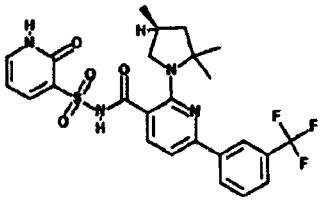
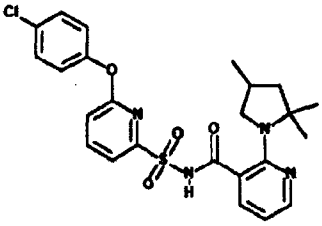
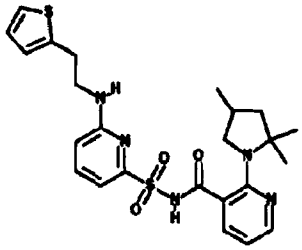
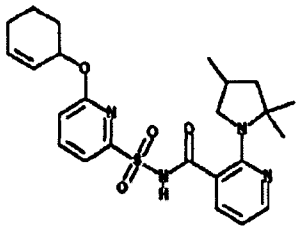
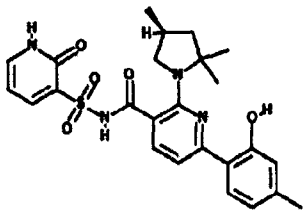
| 2077 | 2078 | 2079 |
|---|---|---|
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| **2080** | **2081** | **2082** |
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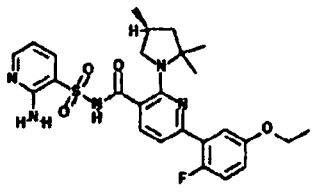
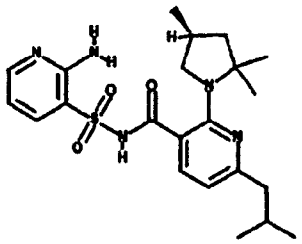
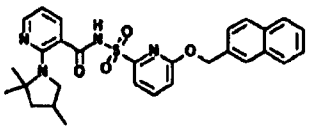
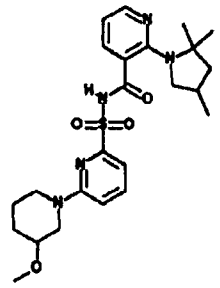
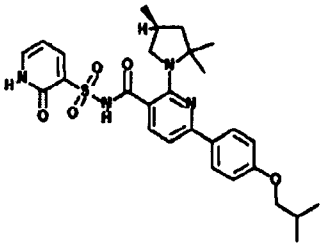
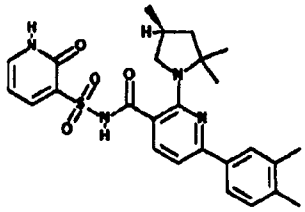
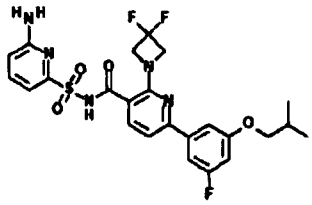
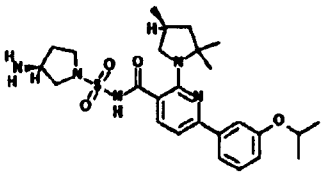
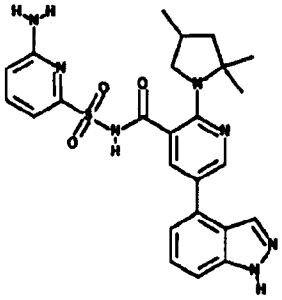
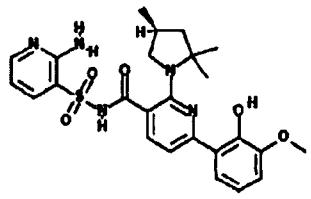
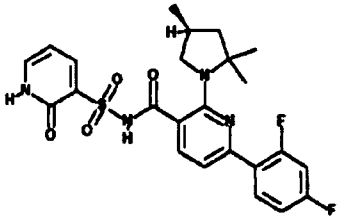
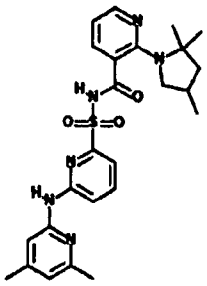
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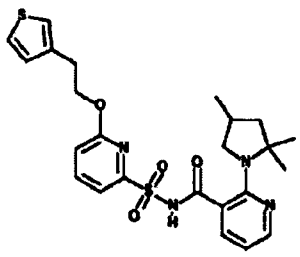
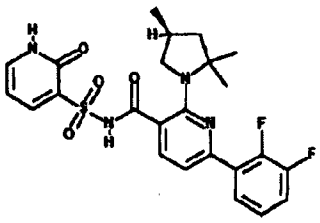
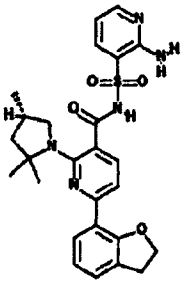
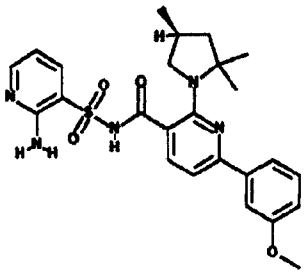
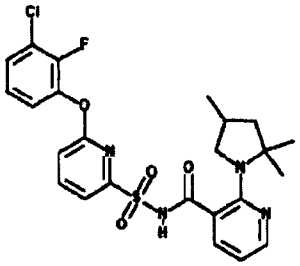
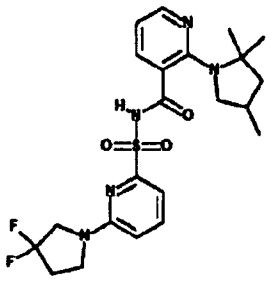
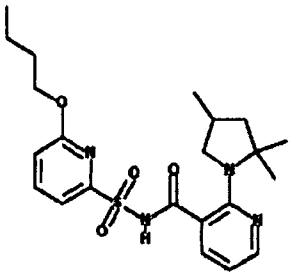
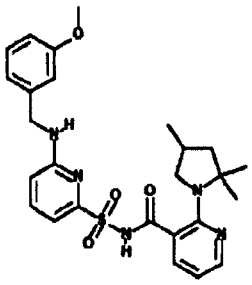
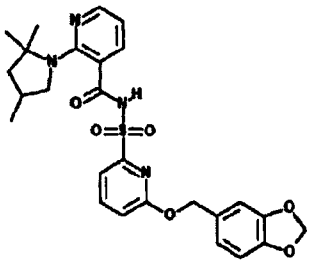
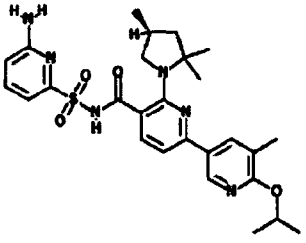
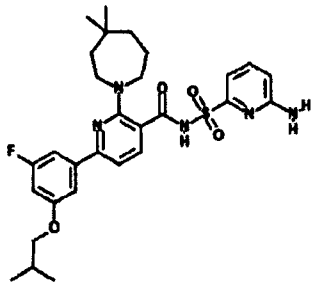
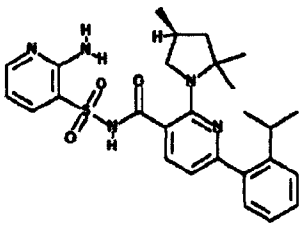
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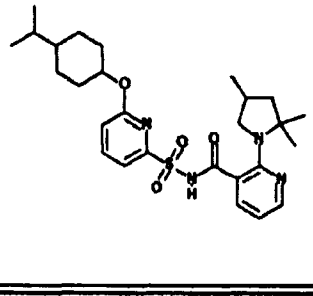
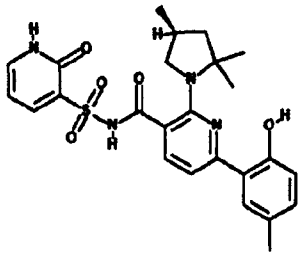
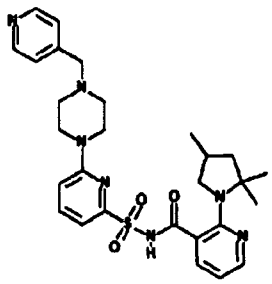
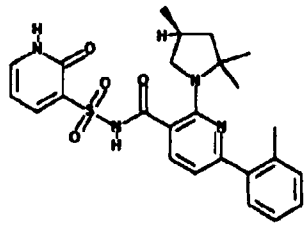
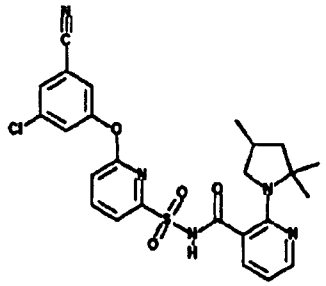
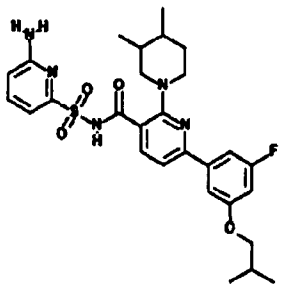
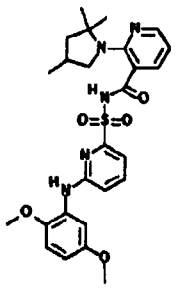
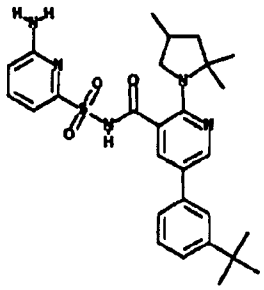
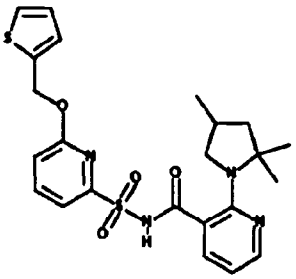
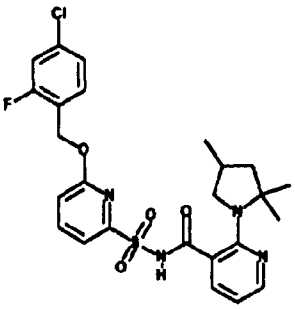
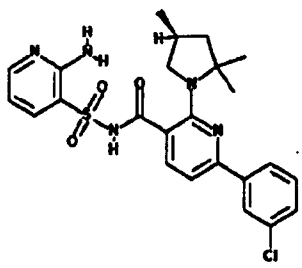
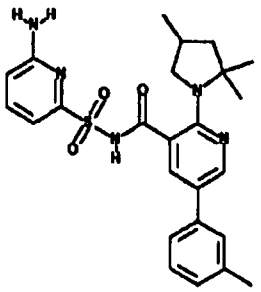
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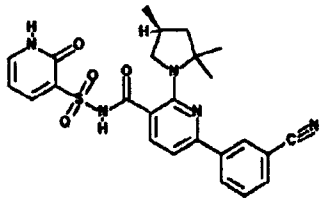
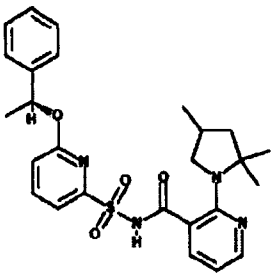
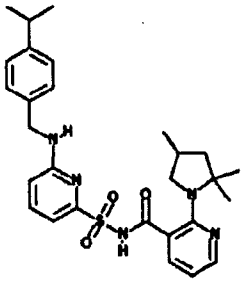
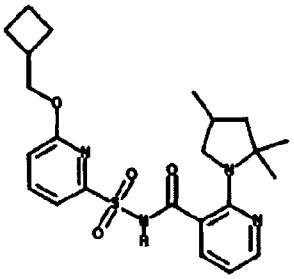
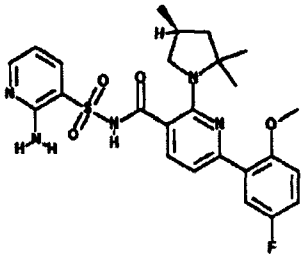
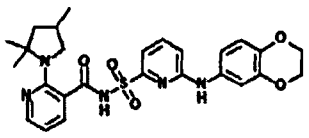
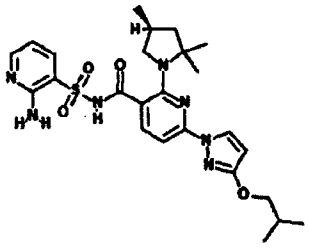
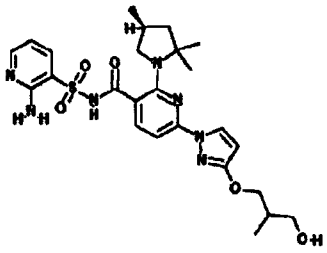
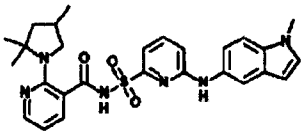
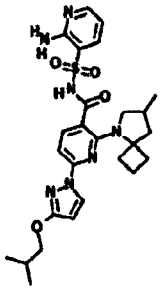
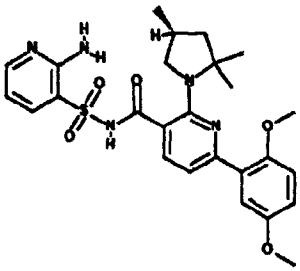
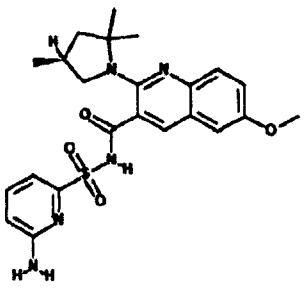
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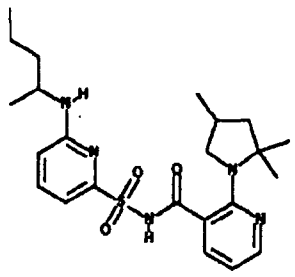
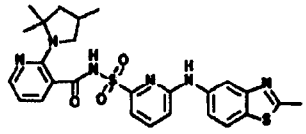
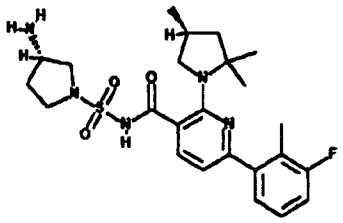
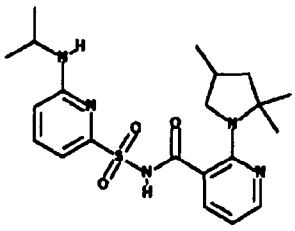
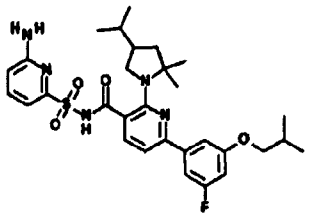
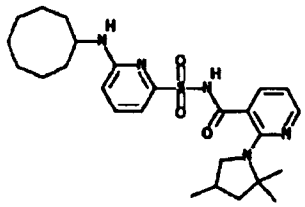
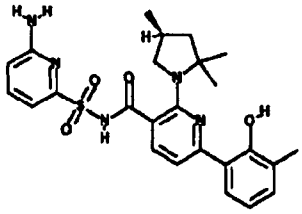
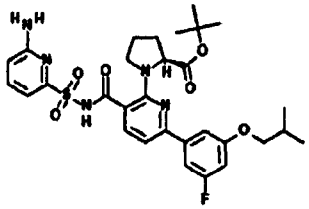
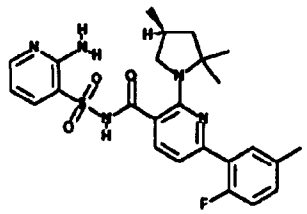
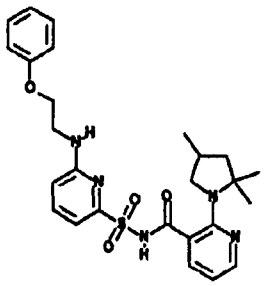
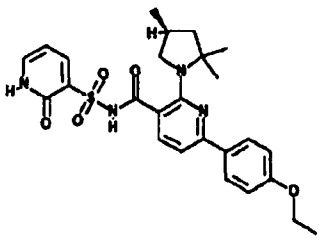
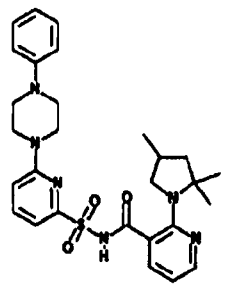
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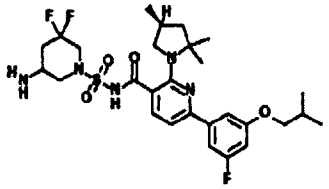
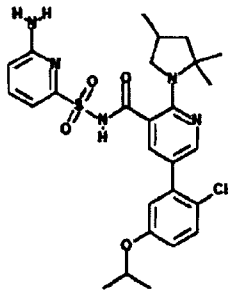
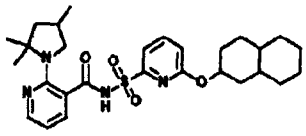
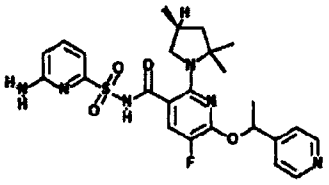
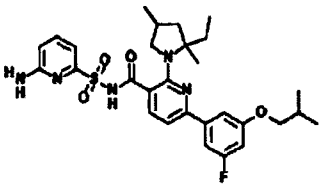
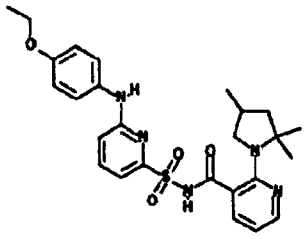
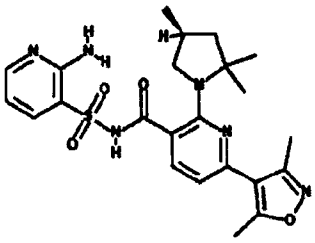
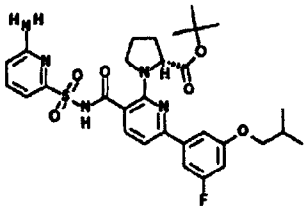
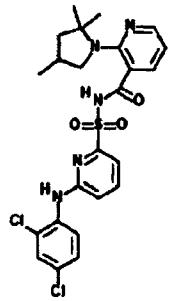
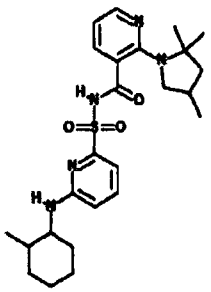
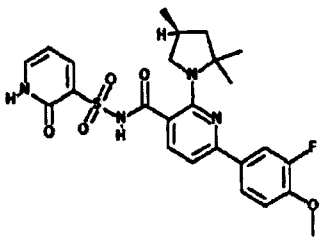
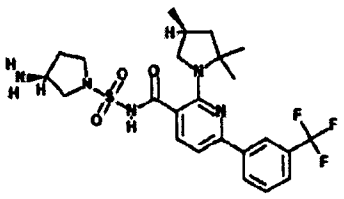
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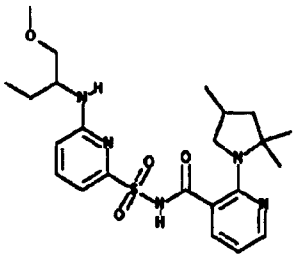
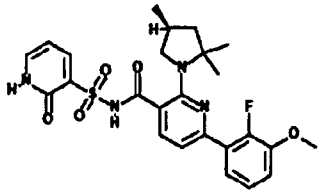
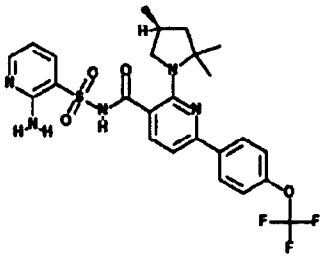
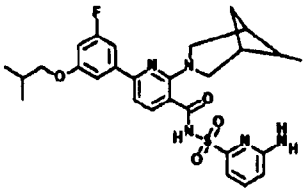
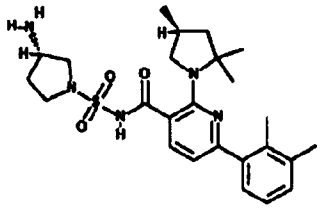
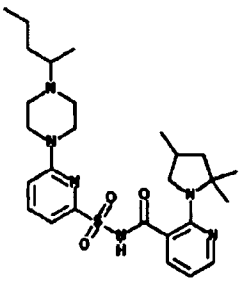
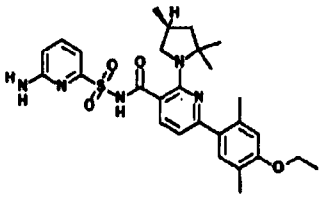
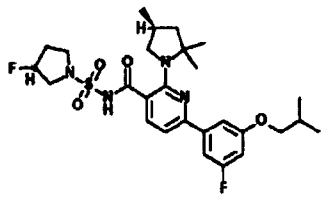
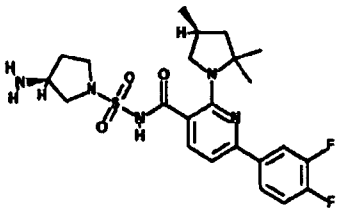
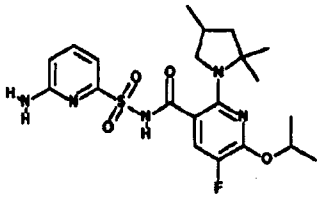
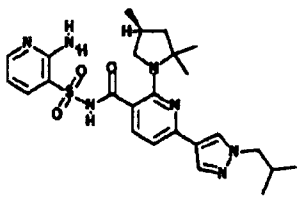
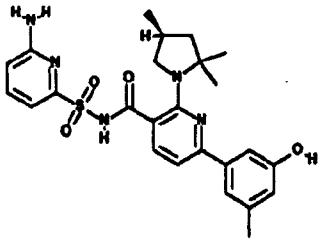
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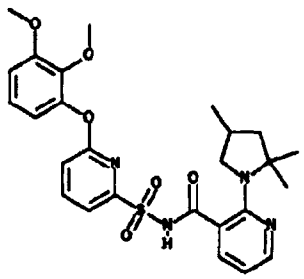
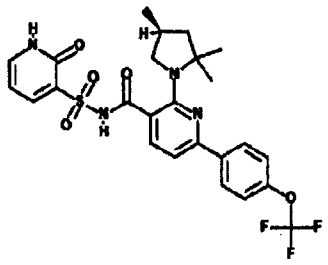
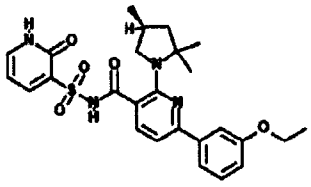
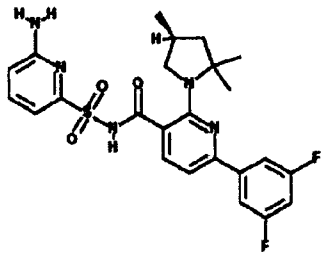
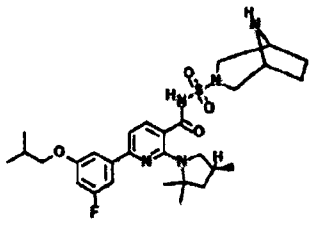
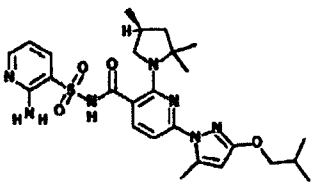
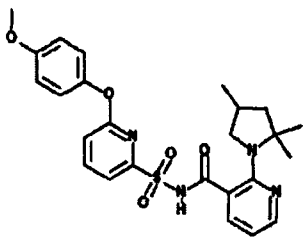
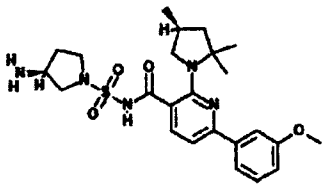
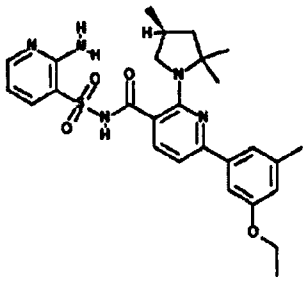
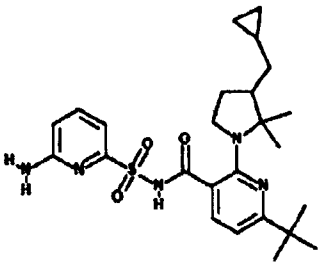
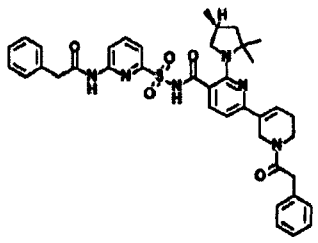
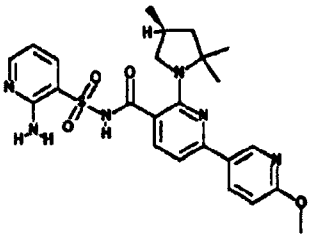
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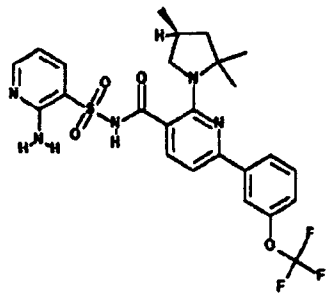
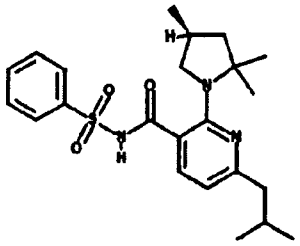
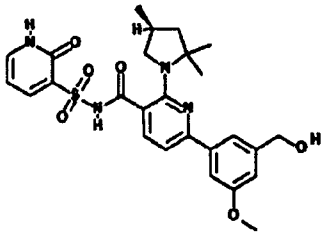
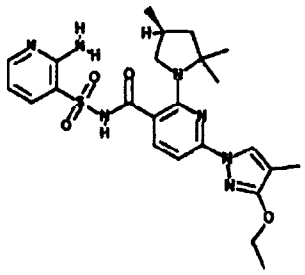
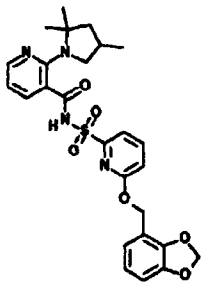
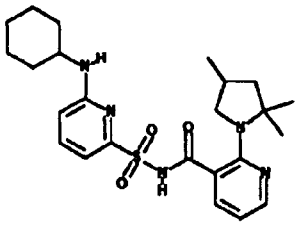
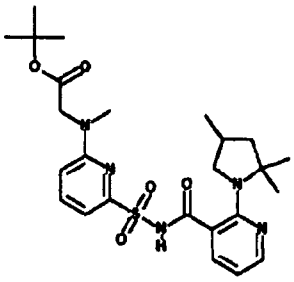
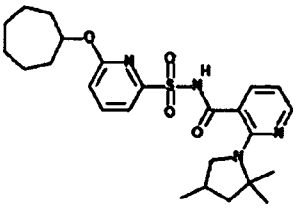
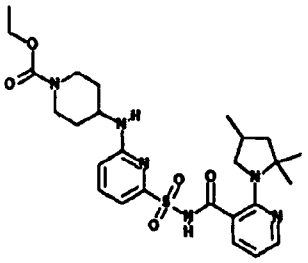
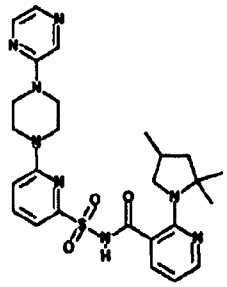
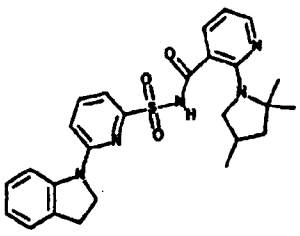
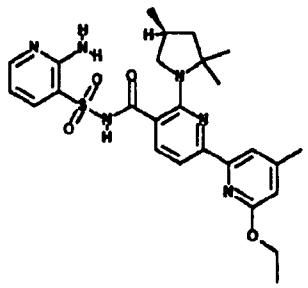
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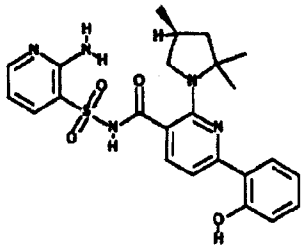
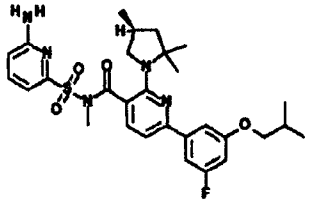
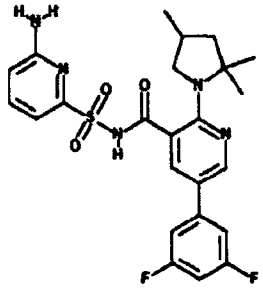
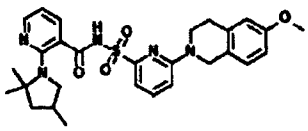
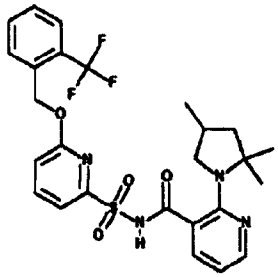
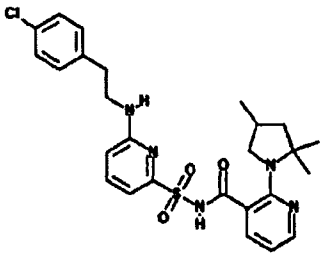
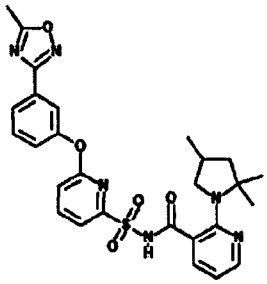
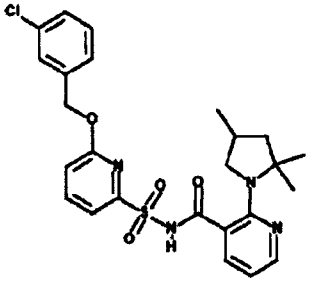
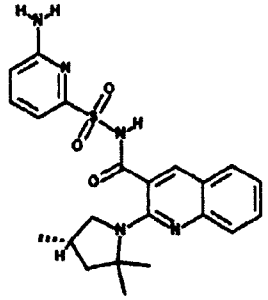
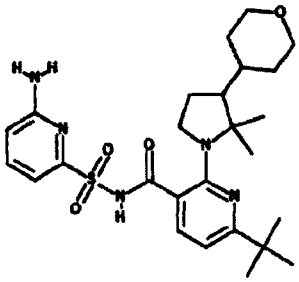
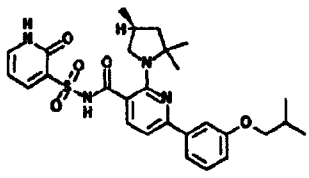
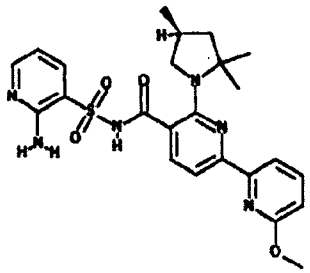
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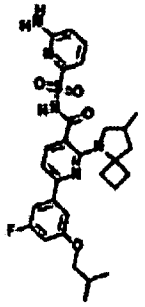
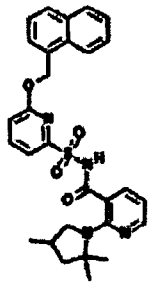
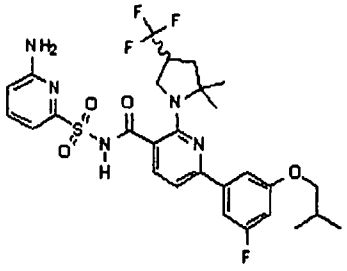
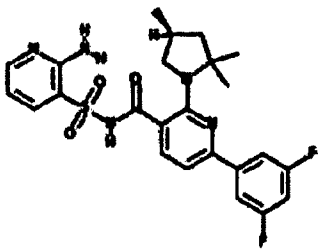
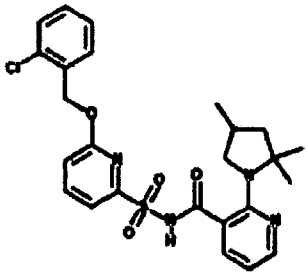
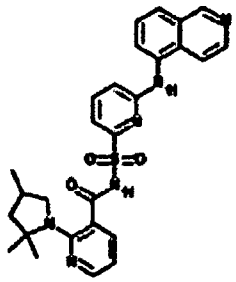
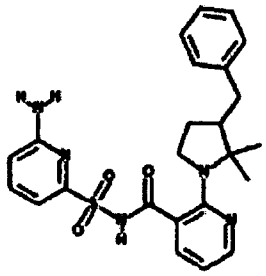
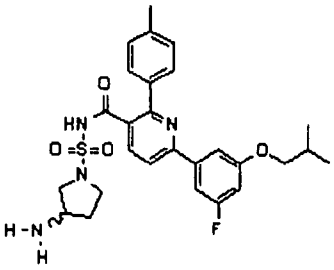
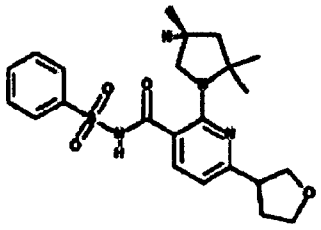
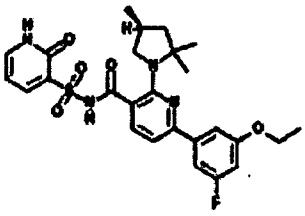
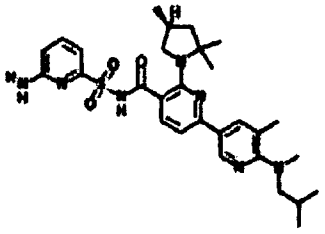
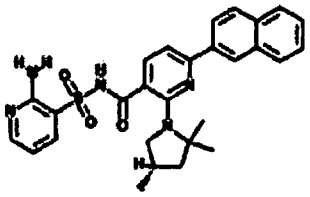
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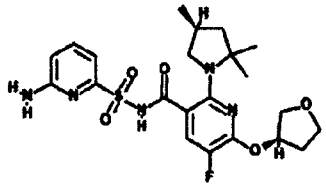
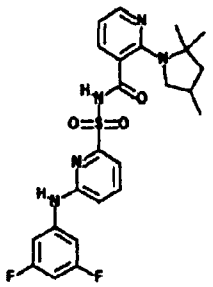
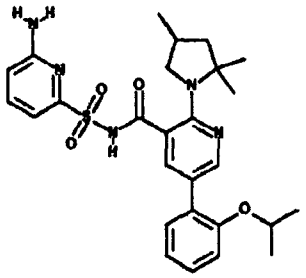
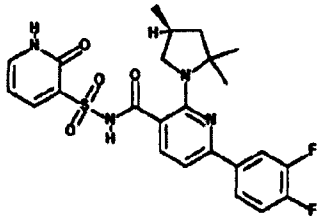
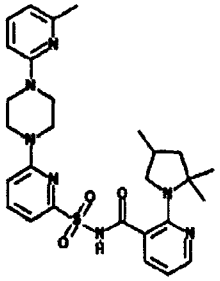
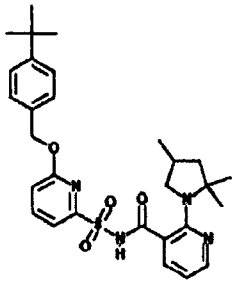
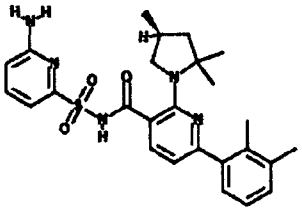
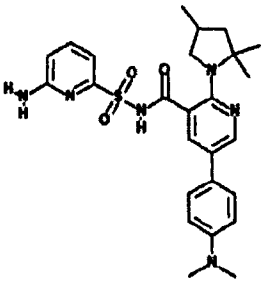
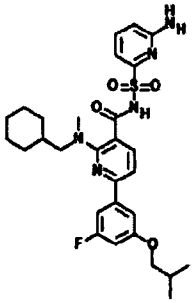
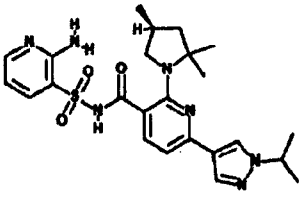
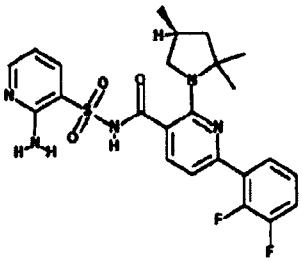
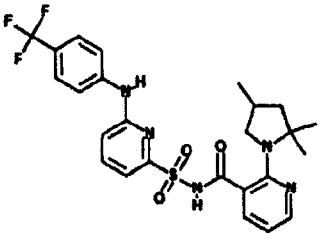
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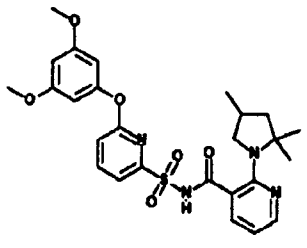
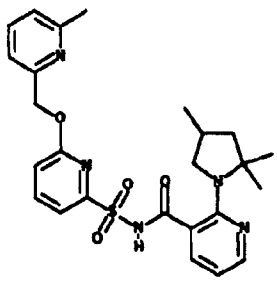
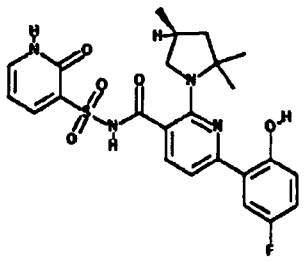
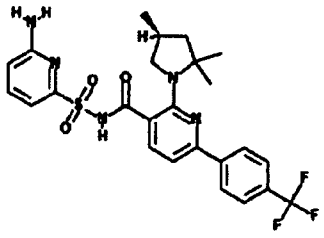
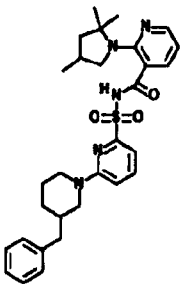
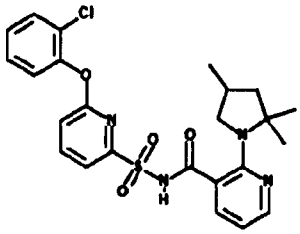
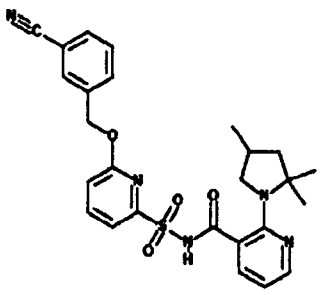
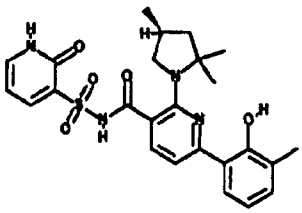
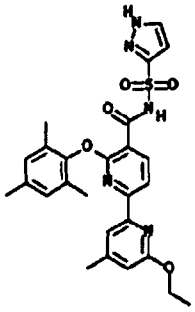
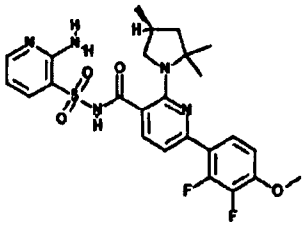
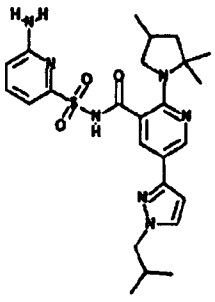
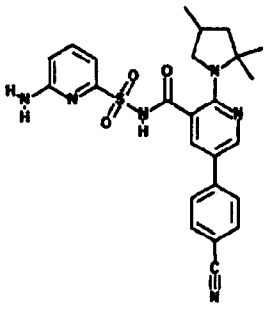
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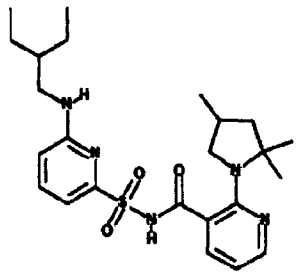
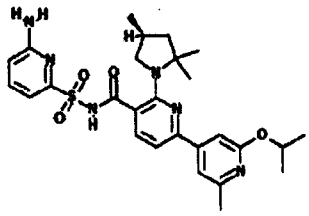
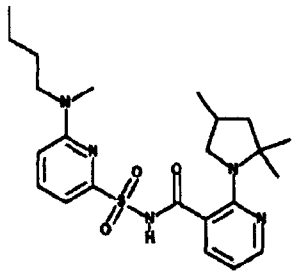
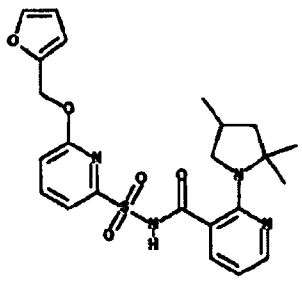
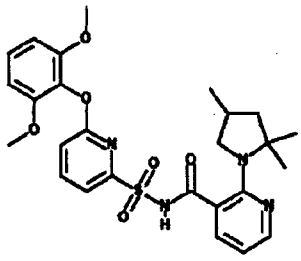
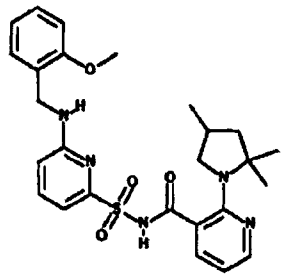
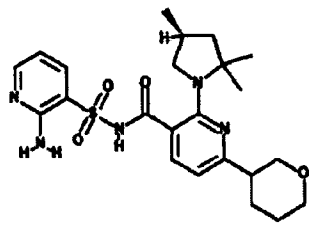
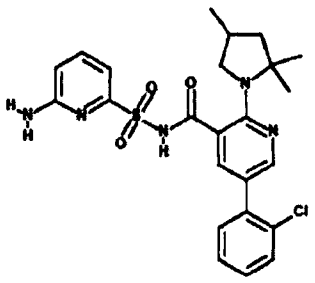
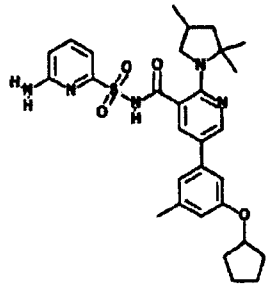
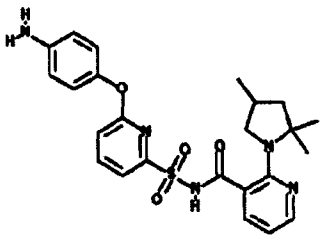
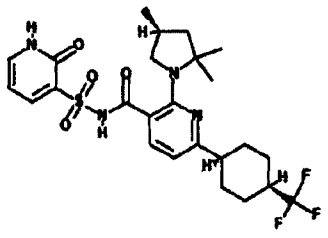
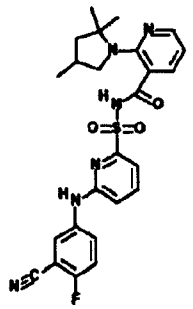
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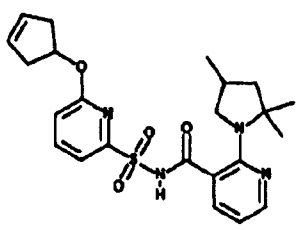
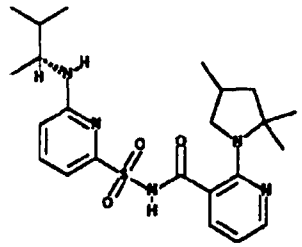
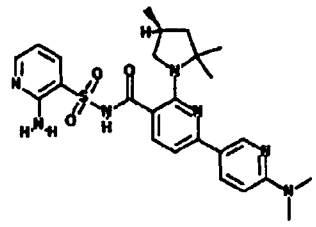
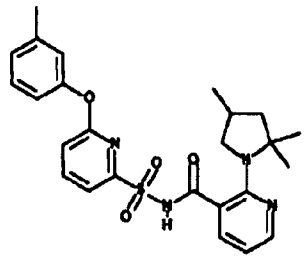
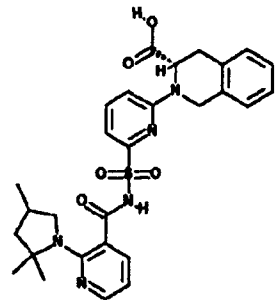
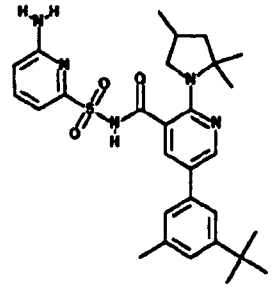
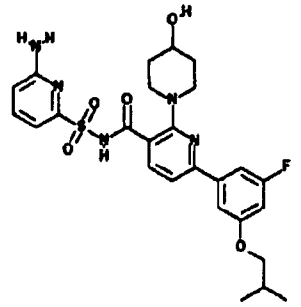
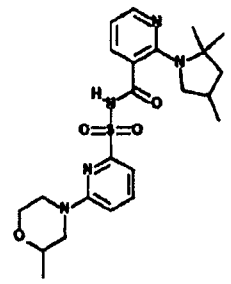
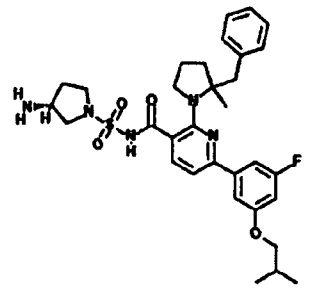
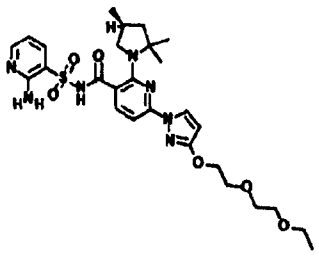
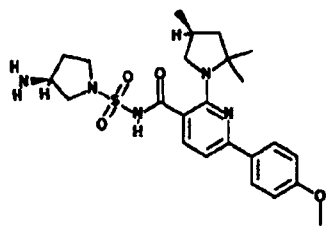
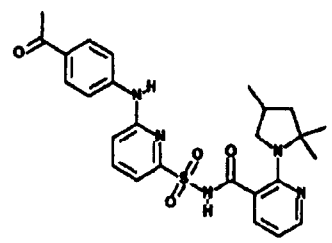
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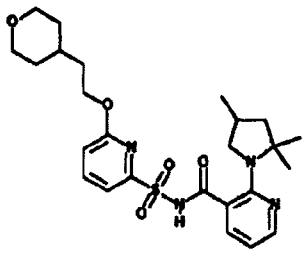
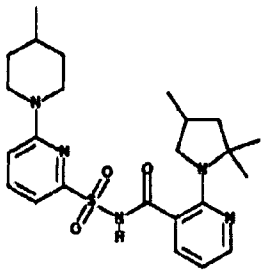
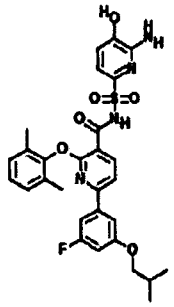
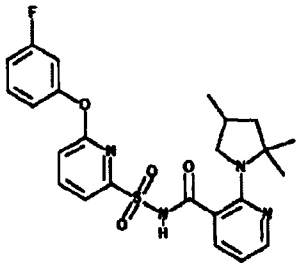
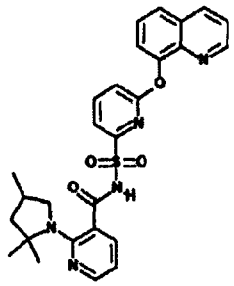
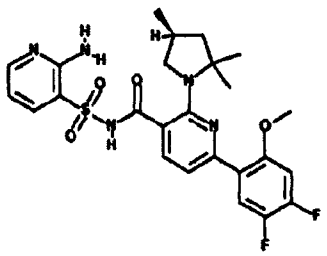
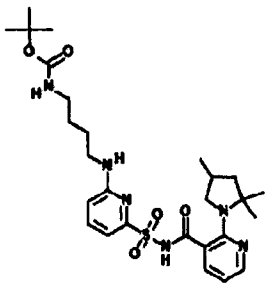
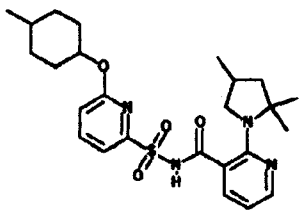
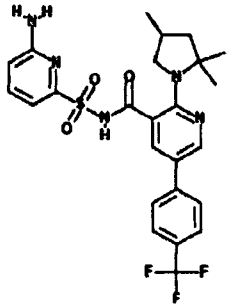
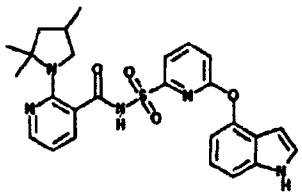
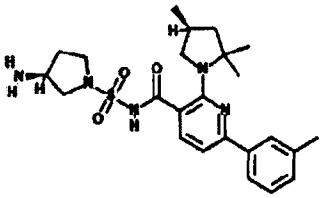
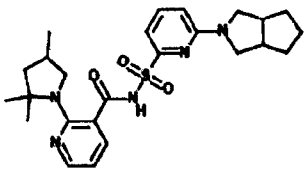
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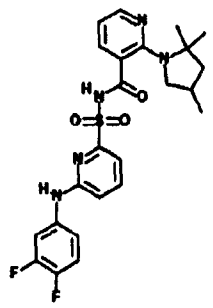
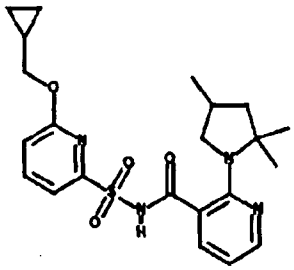
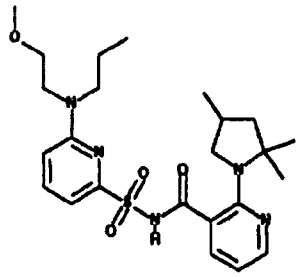
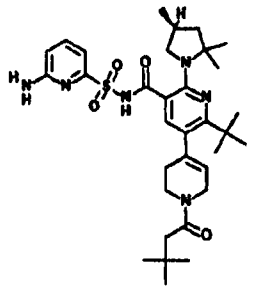
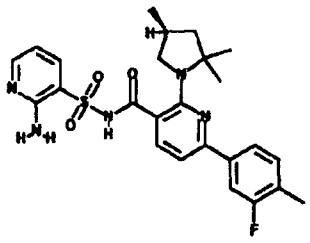
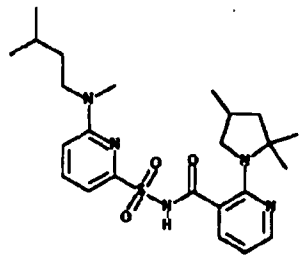
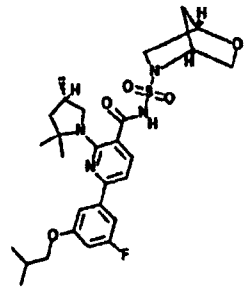
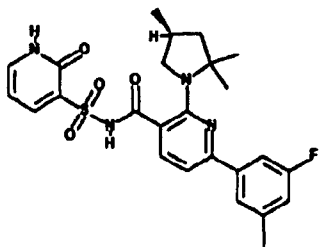
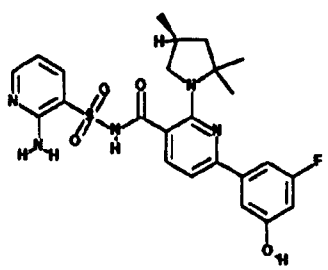
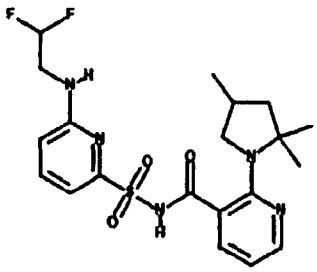
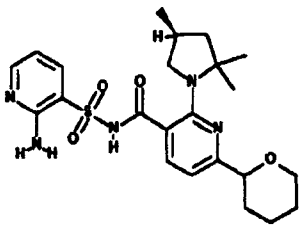
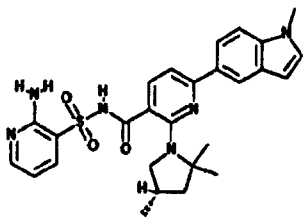
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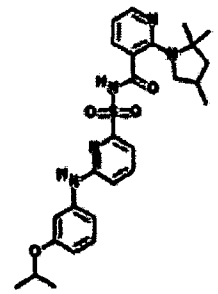
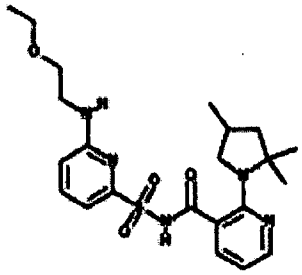
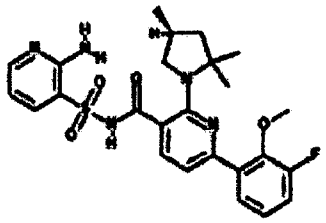
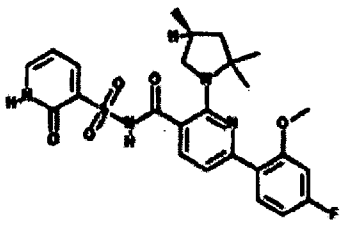
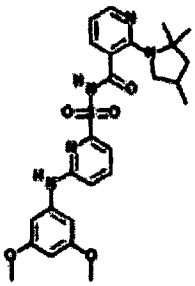
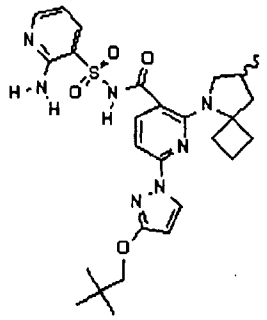
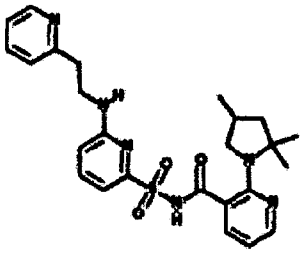
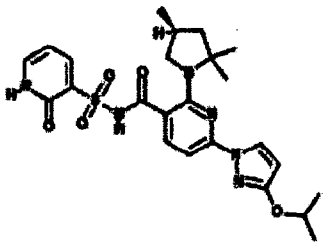
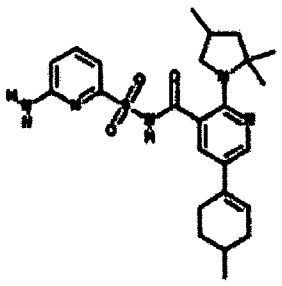
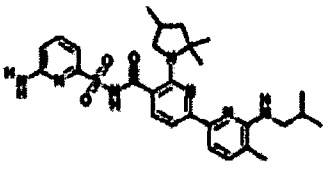
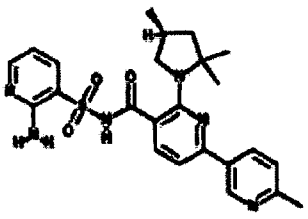
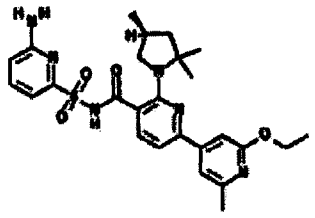
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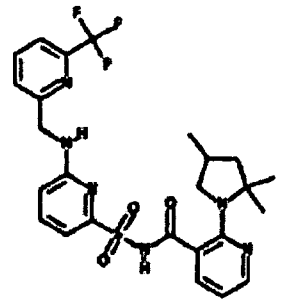
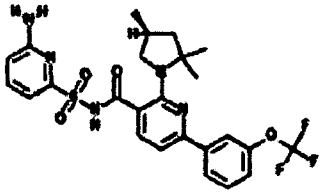
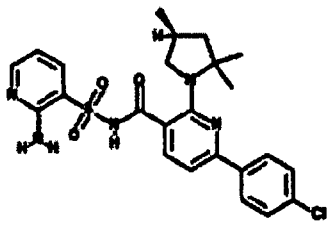
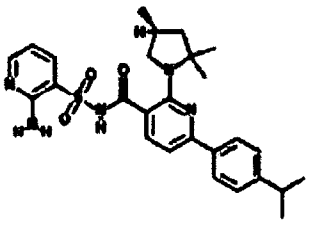
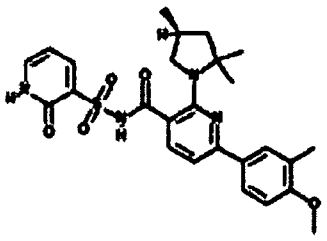
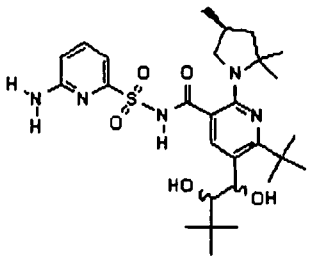
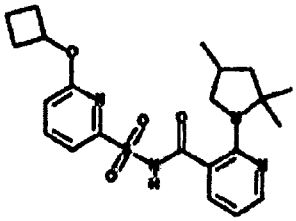
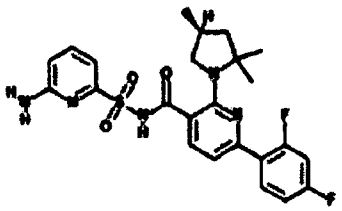
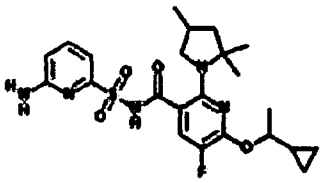
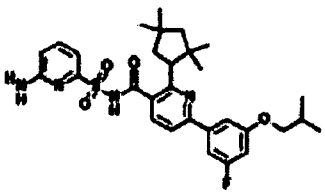
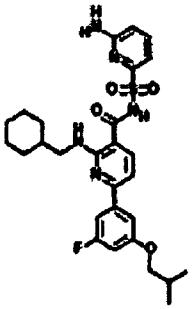
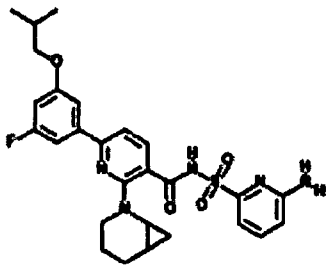
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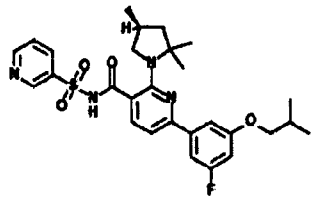
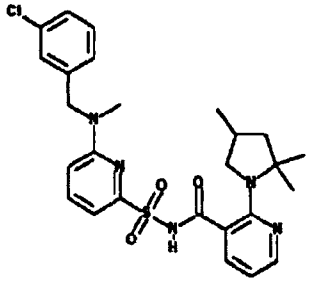
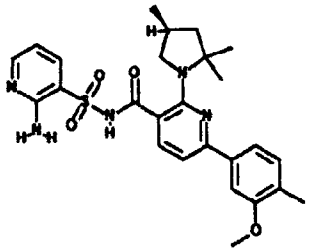
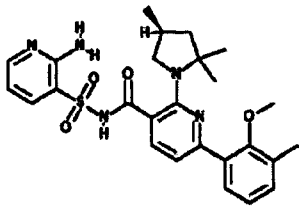
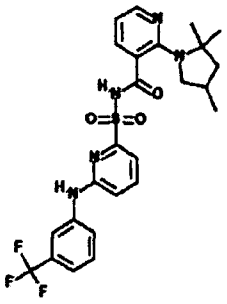
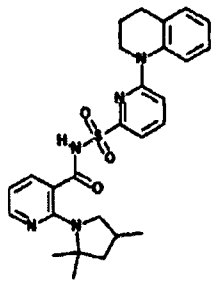
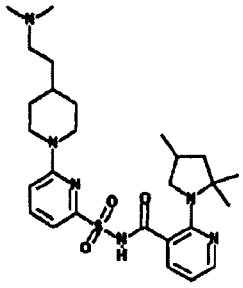
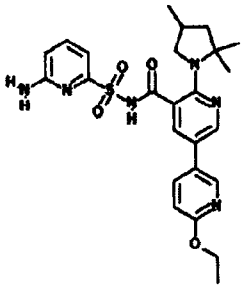
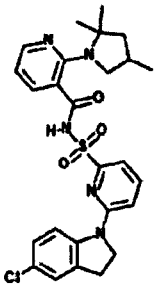
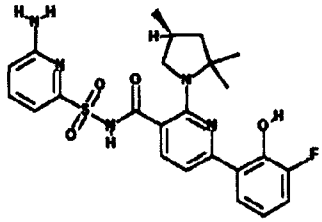
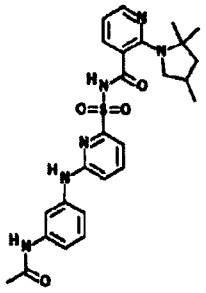
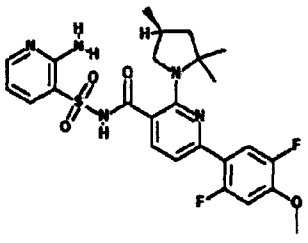
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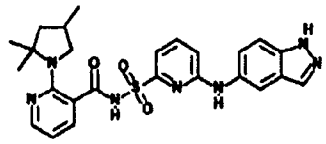
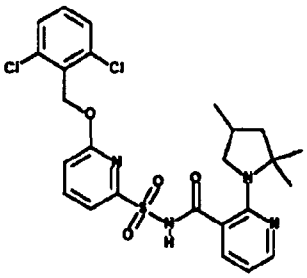
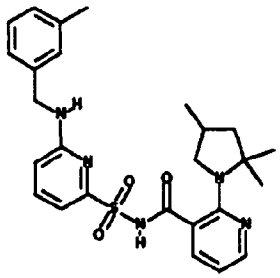
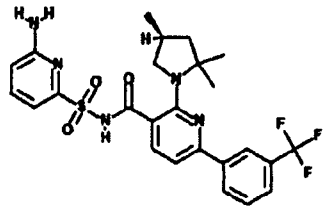
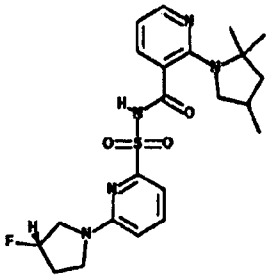
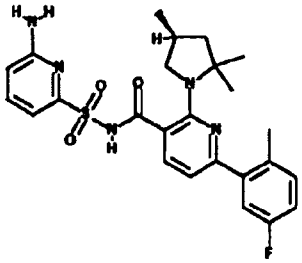
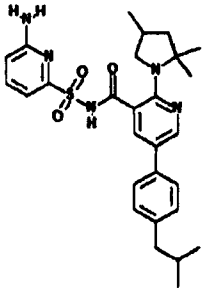
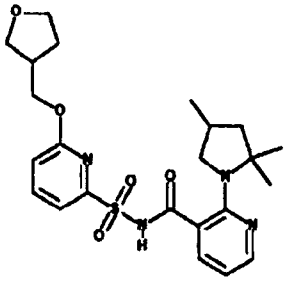
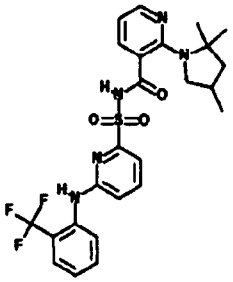
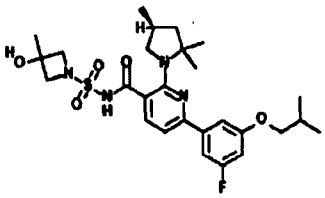
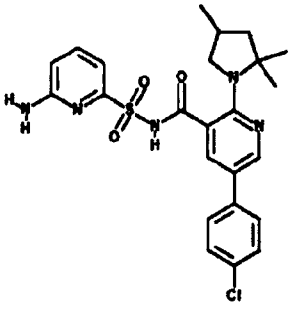
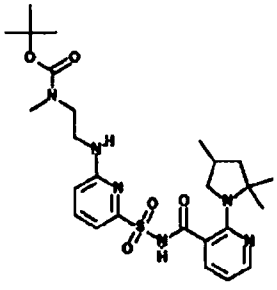
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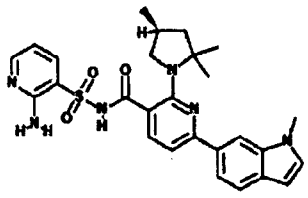
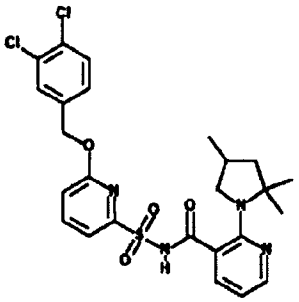
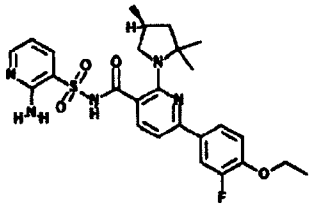
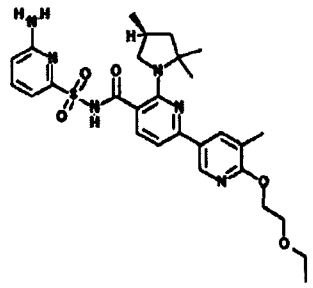
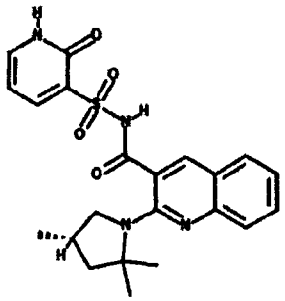
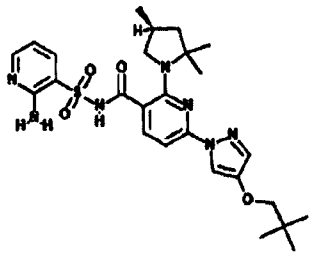
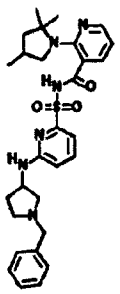
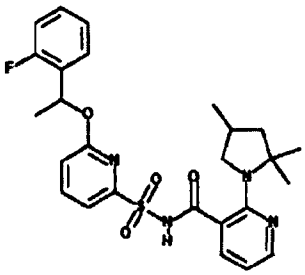
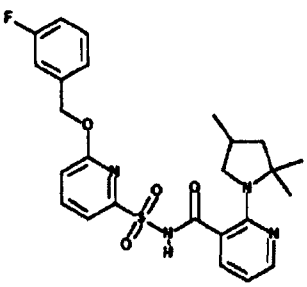
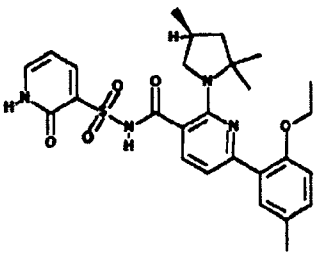
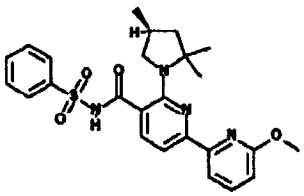
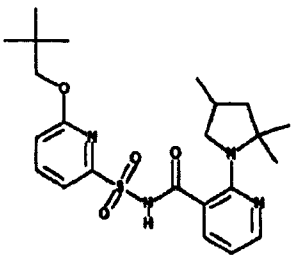
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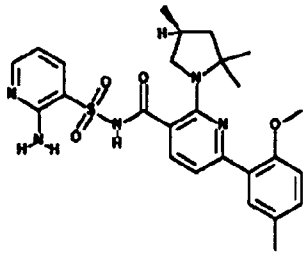
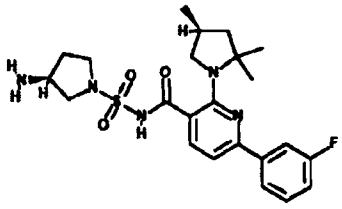
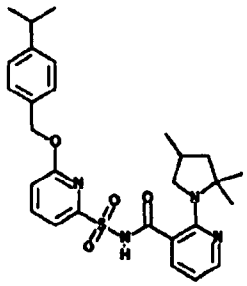
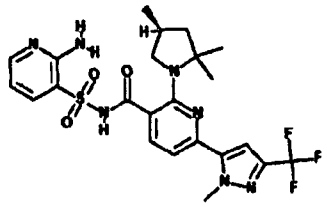
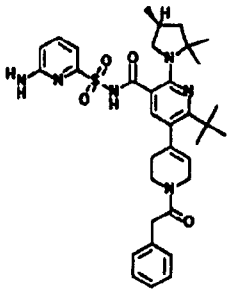
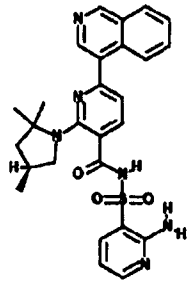
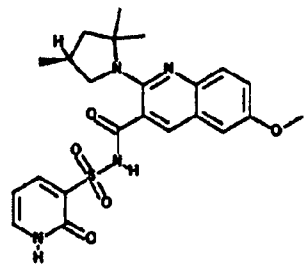
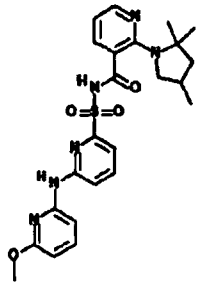
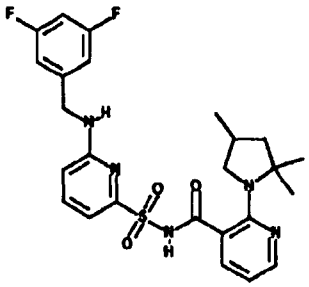
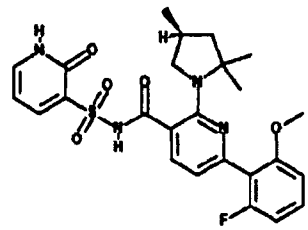
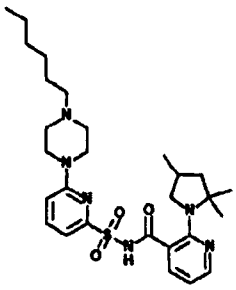
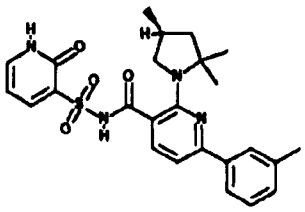
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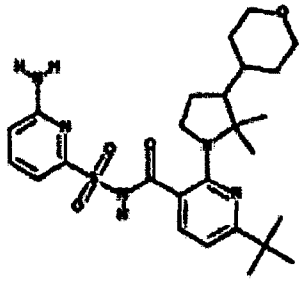
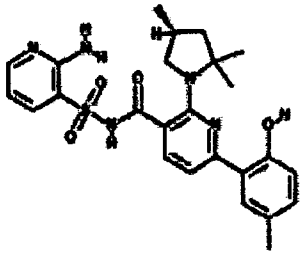
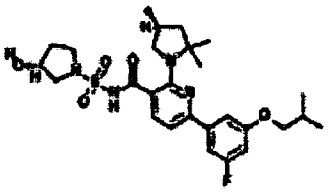
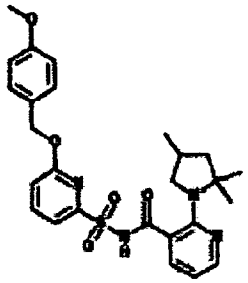
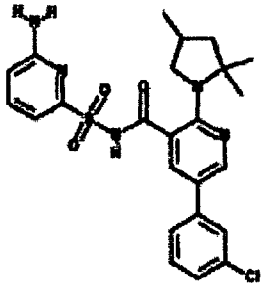
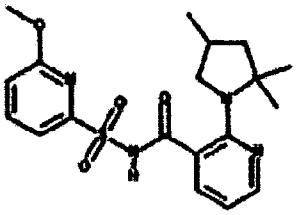
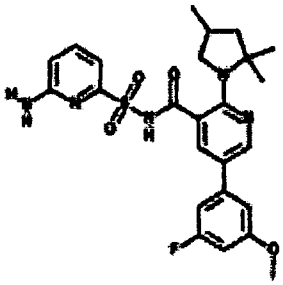
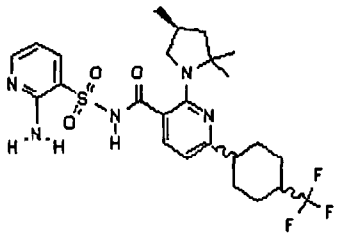
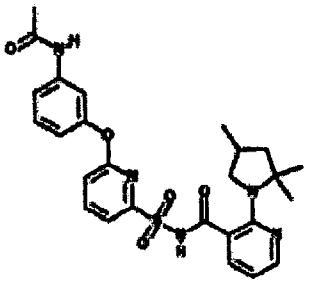
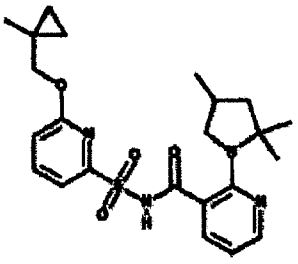
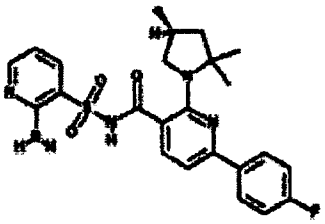
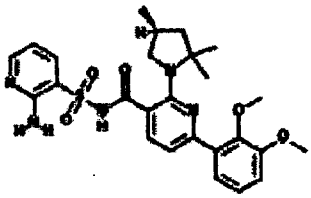
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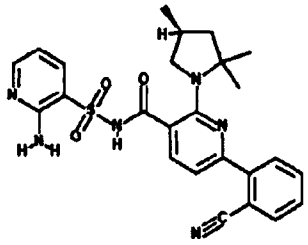
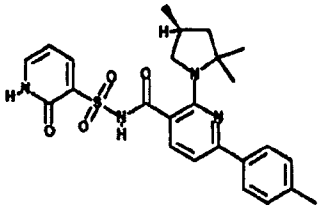
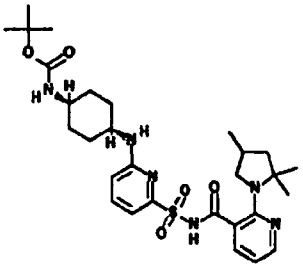
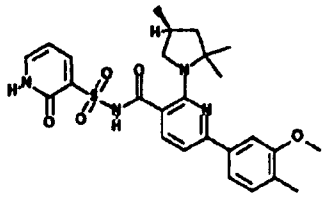
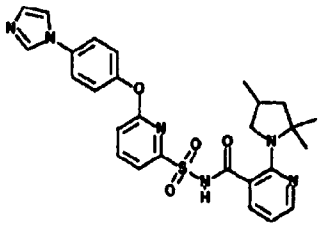
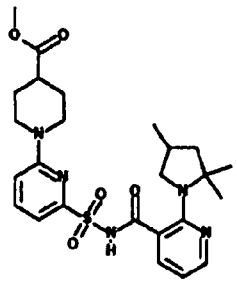
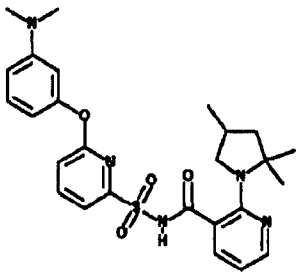
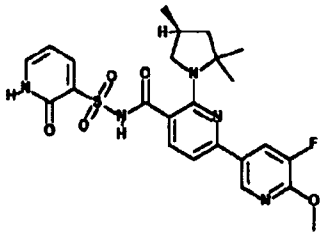
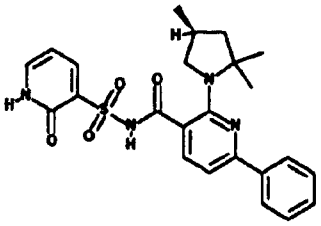
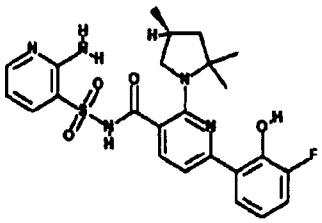
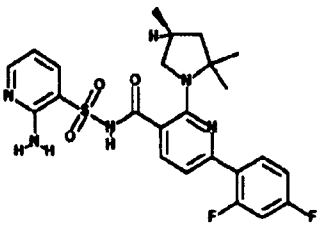
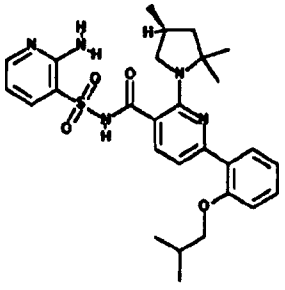
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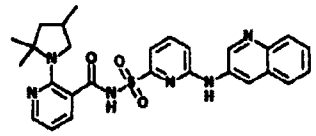
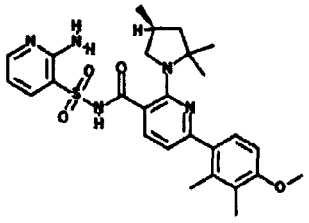
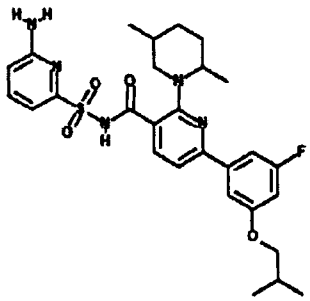
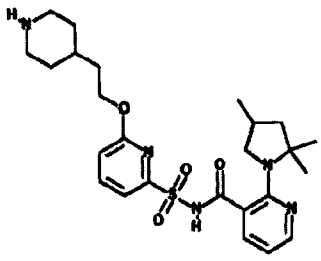
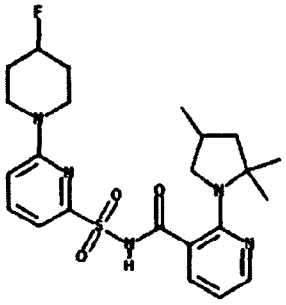
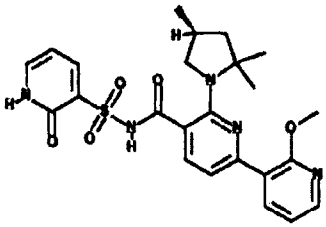
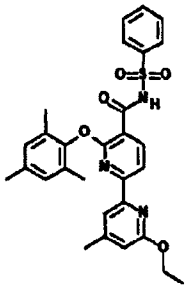
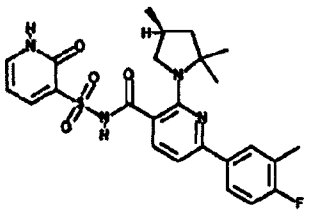
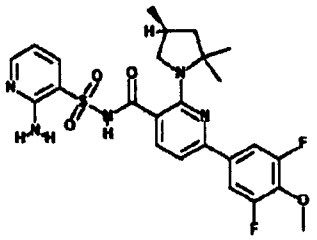
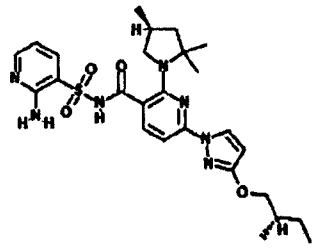
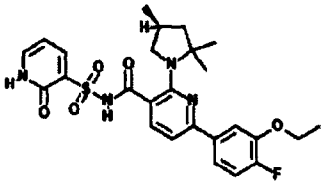
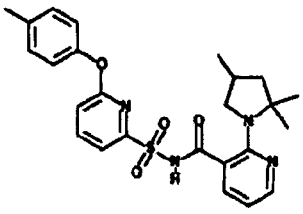
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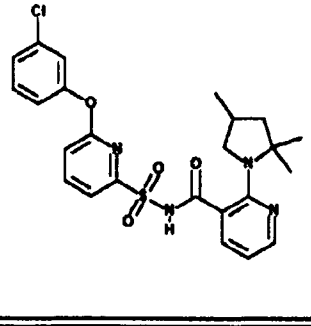
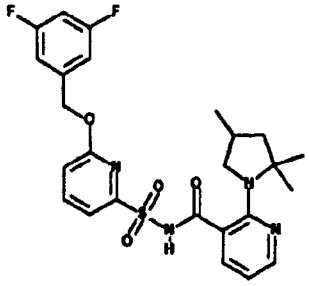
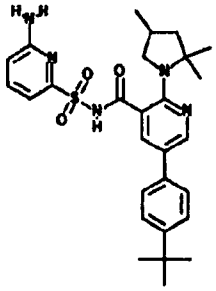
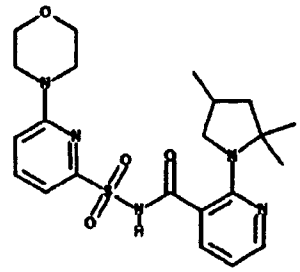
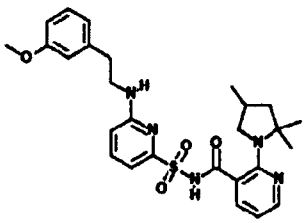
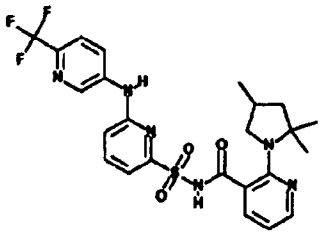
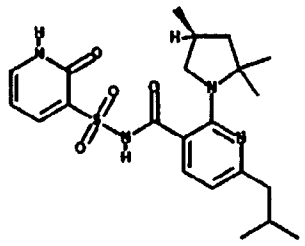
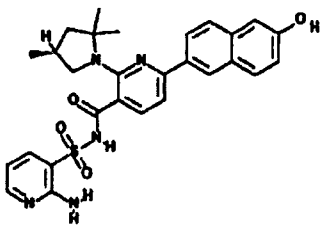
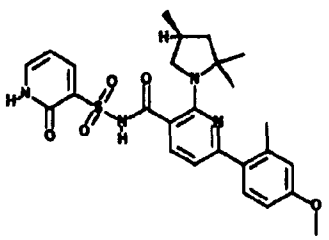
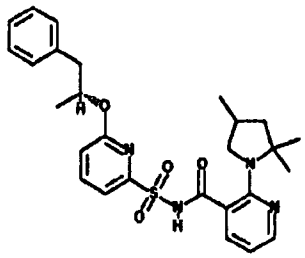
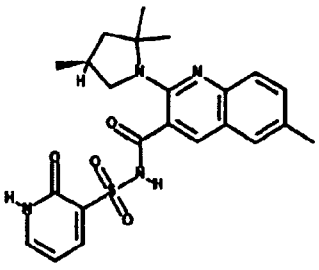
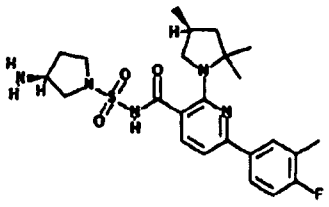
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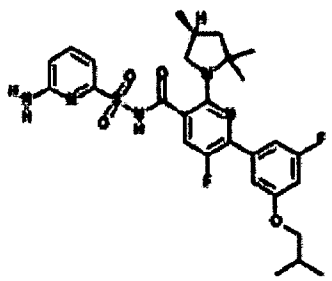
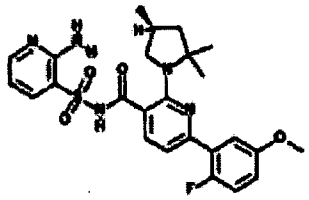
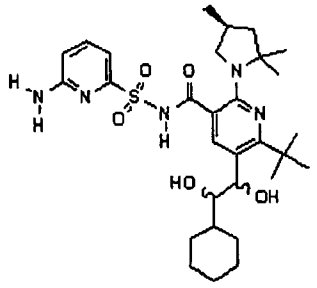
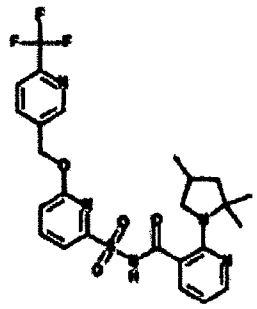
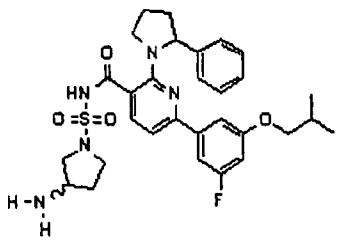
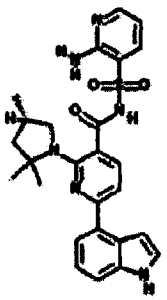
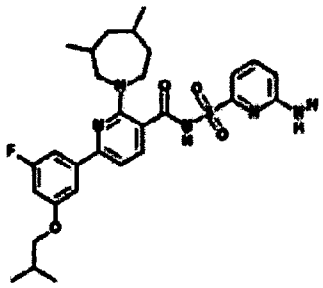
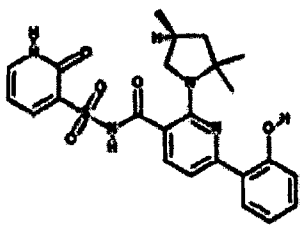
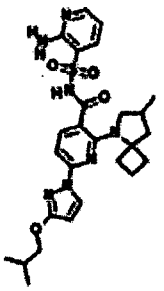
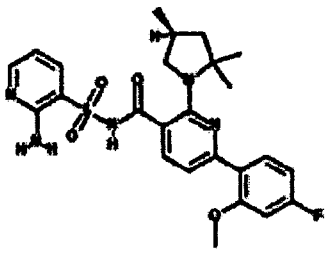
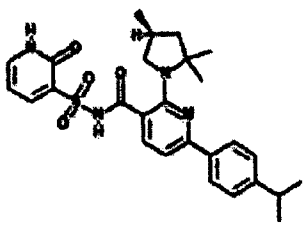
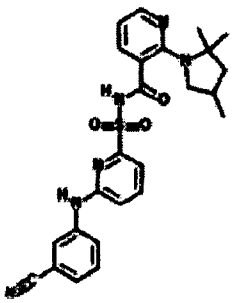
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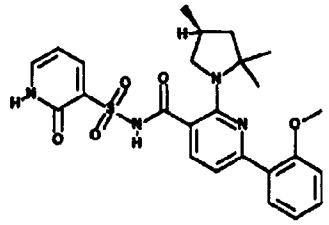
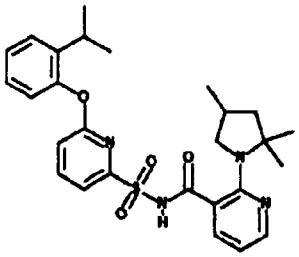
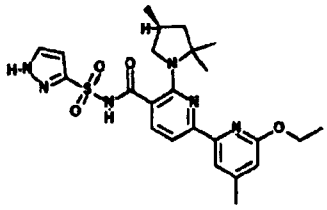
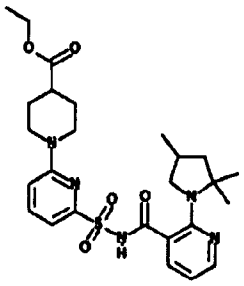
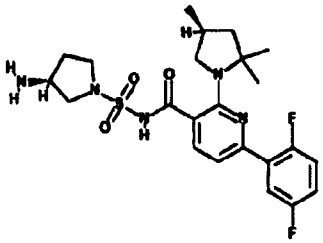
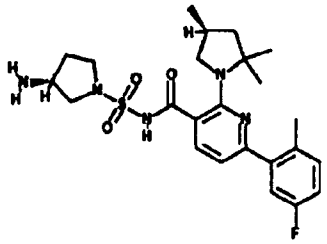
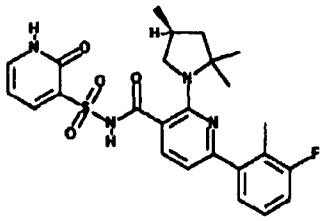
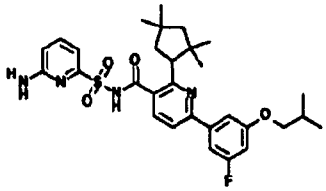
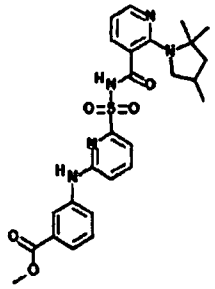
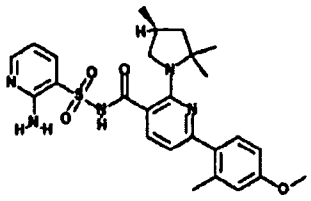
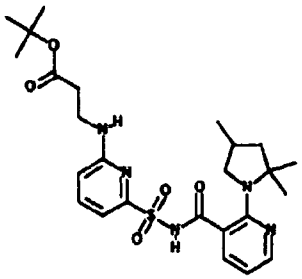
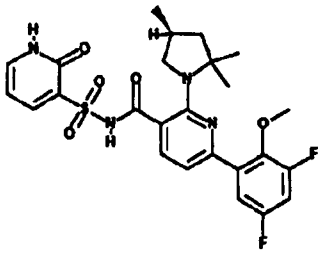
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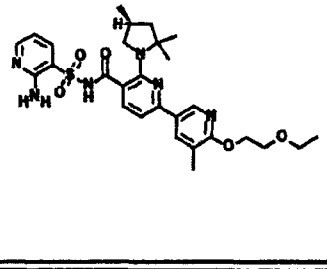
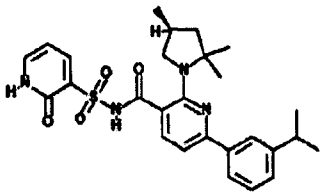
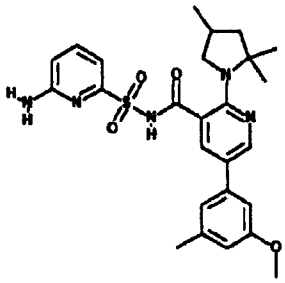
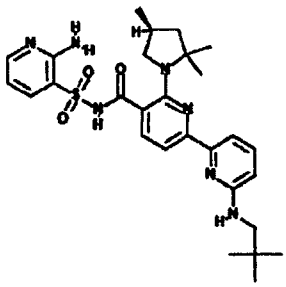
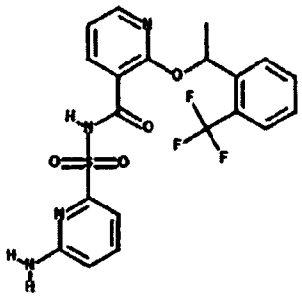
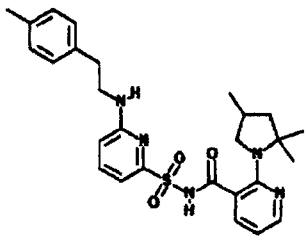
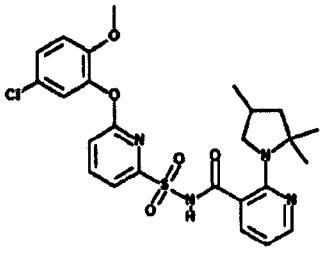
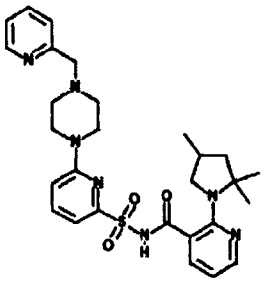
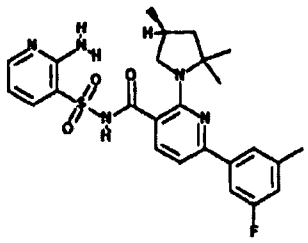
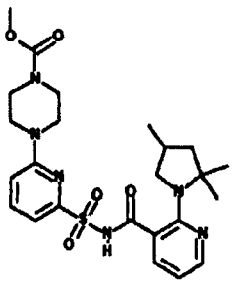
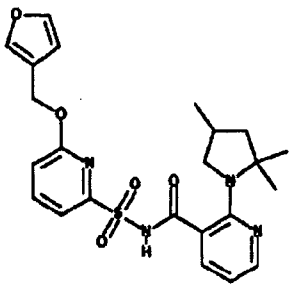
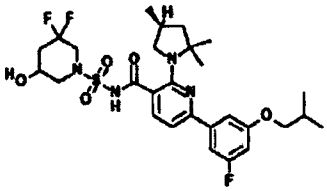
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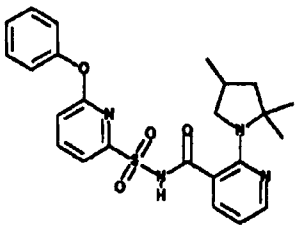
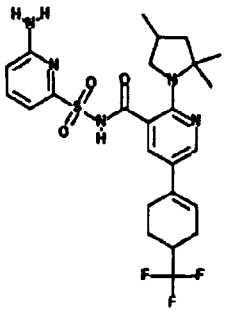
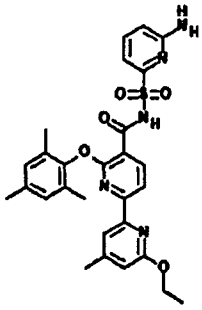
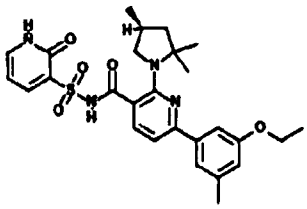
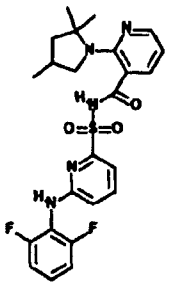
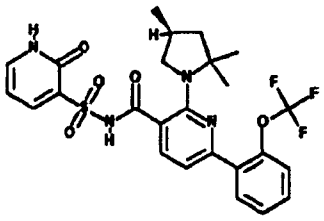
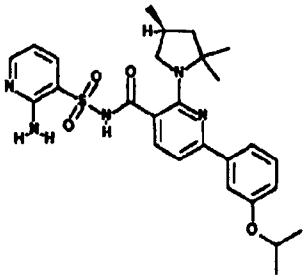
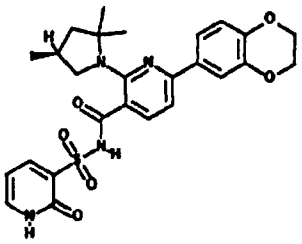
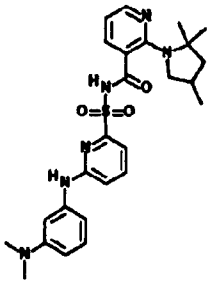
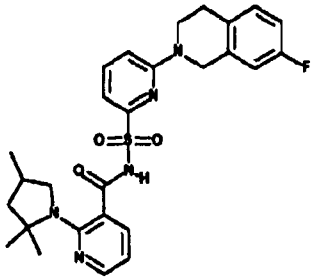
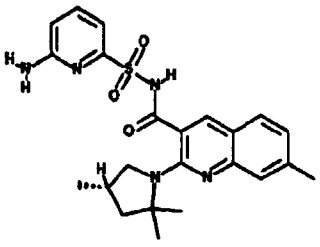
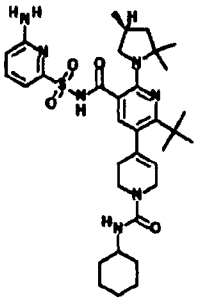
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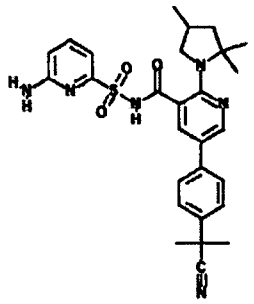
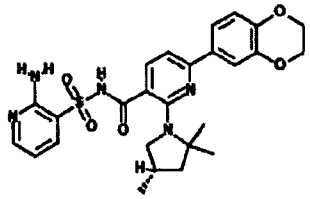
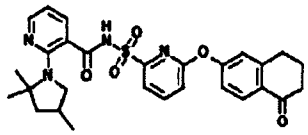
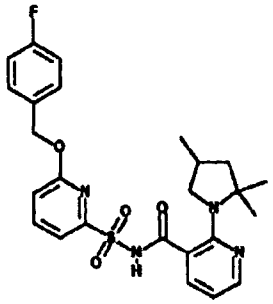
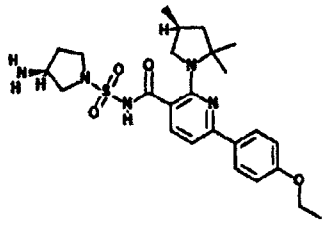
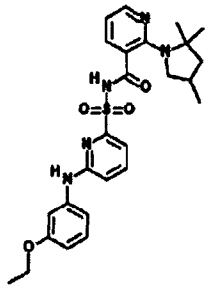
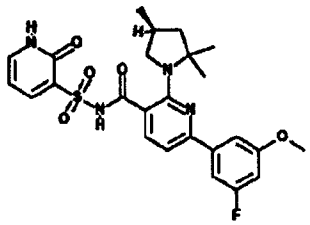
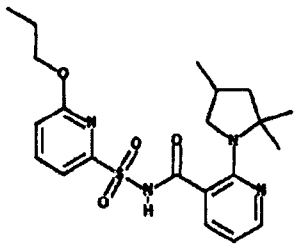
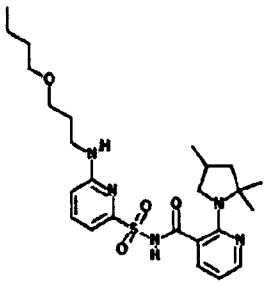
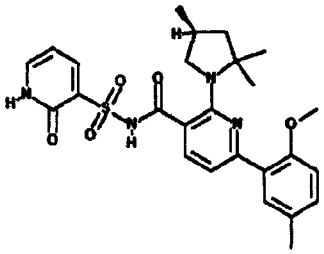
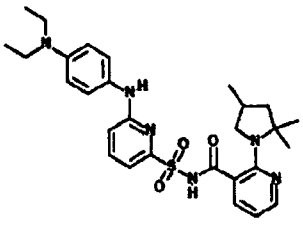
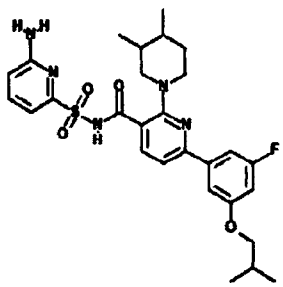
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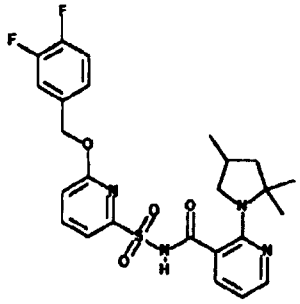
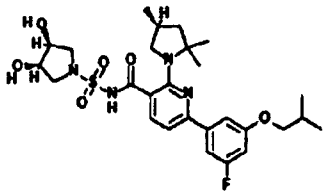
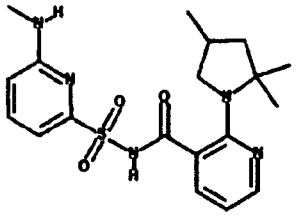
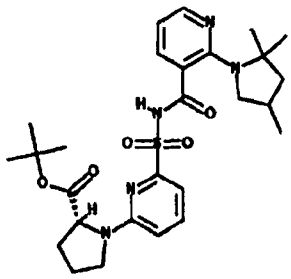
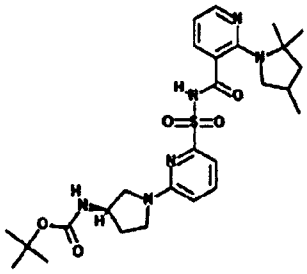
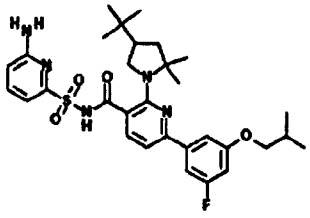
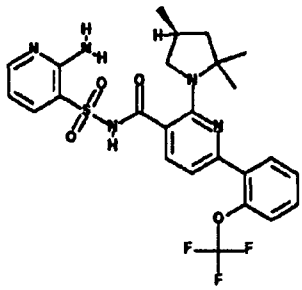
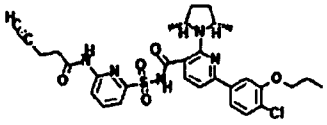
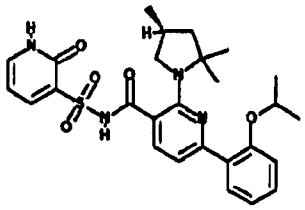
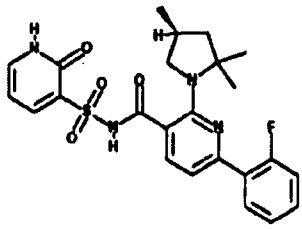
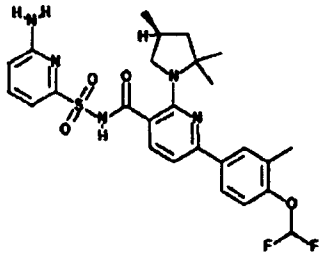
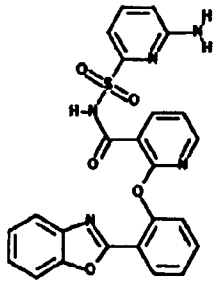
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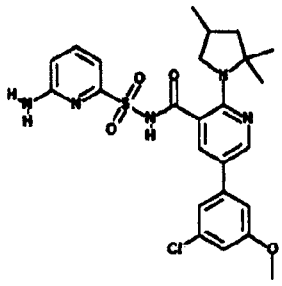
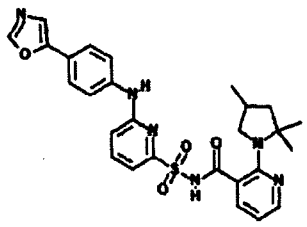
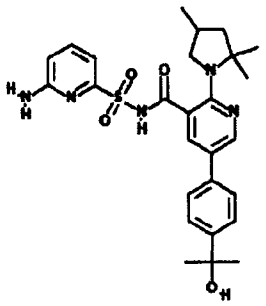
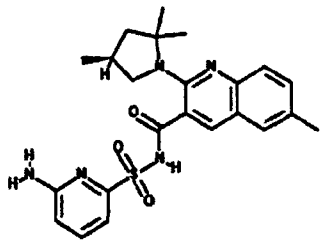
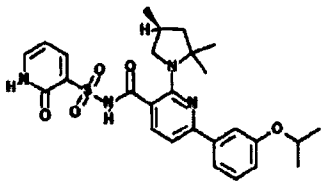
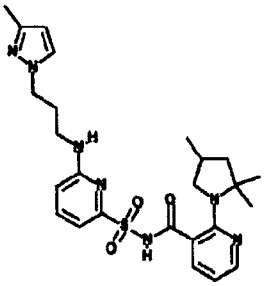
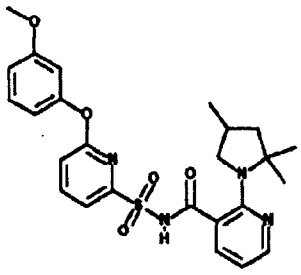
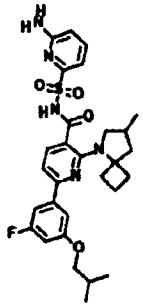
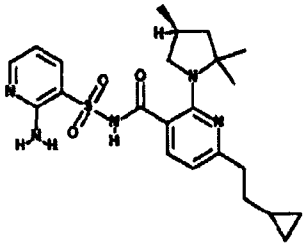
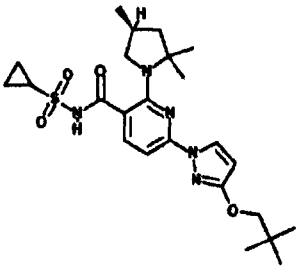
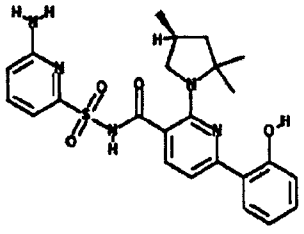
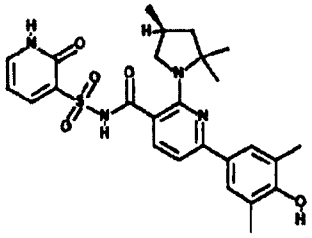
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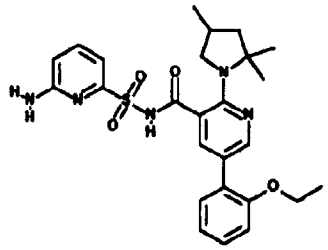
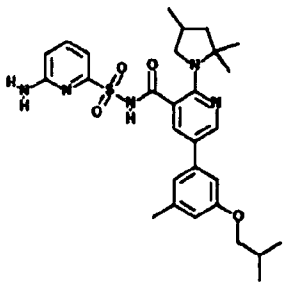
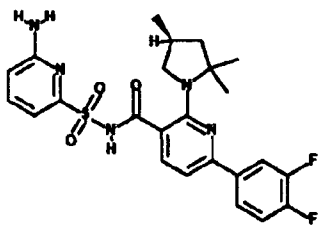
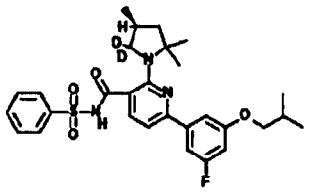
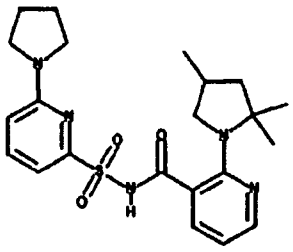
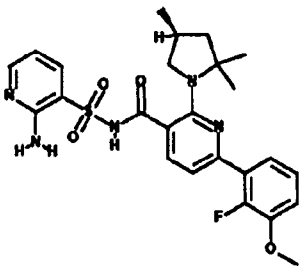
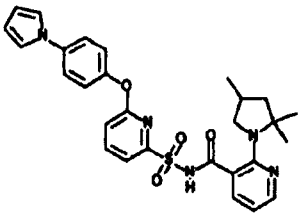
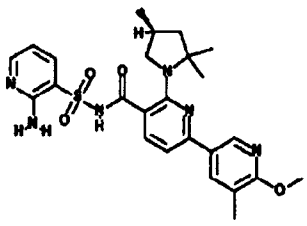
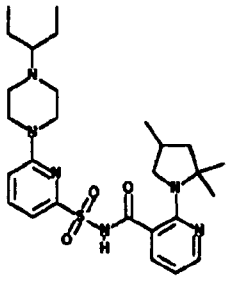
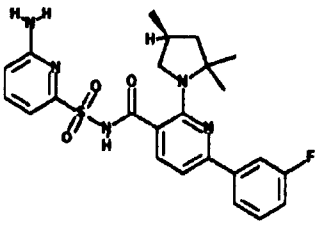
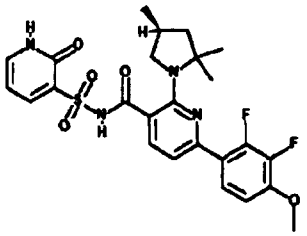
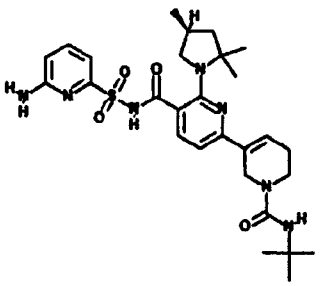
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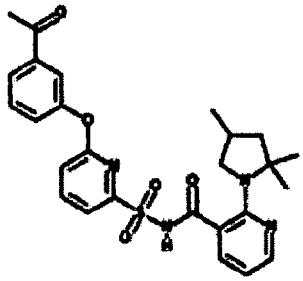
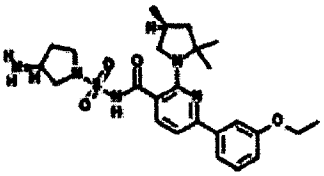
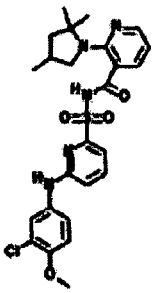
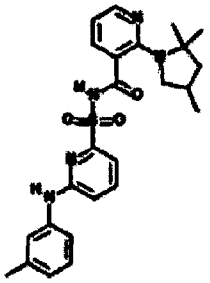
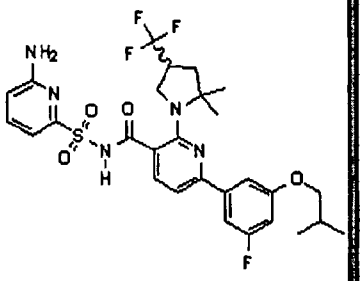
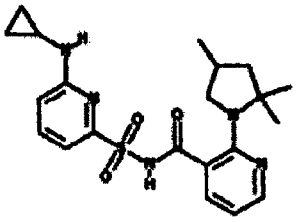
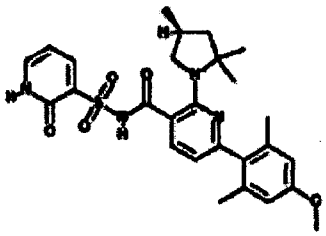
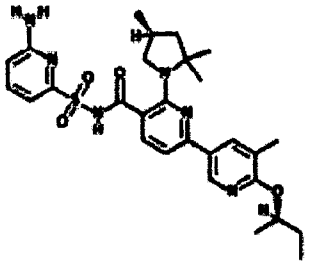
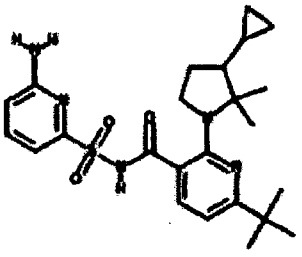
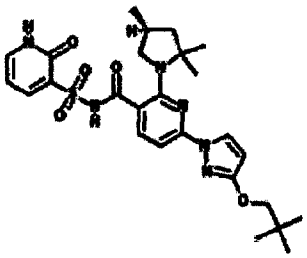
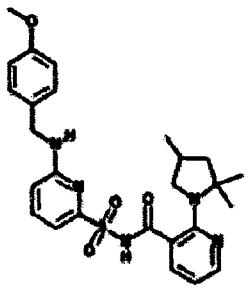
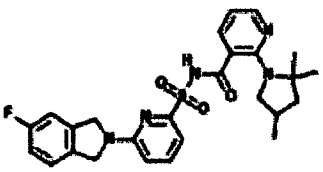
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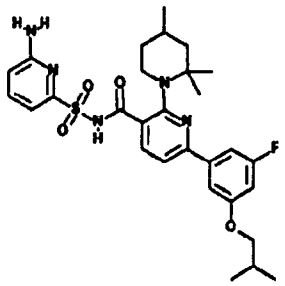
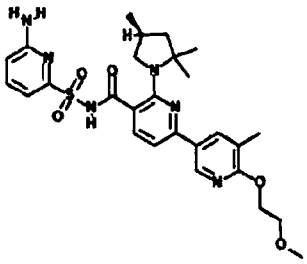
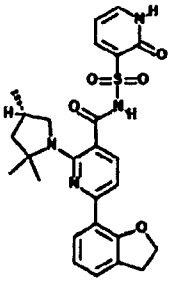
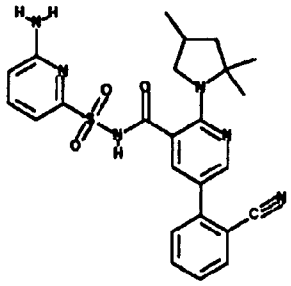
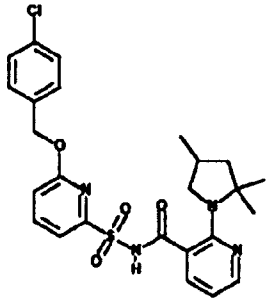
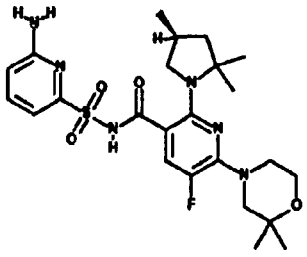
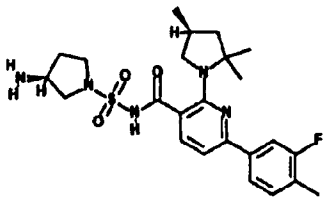
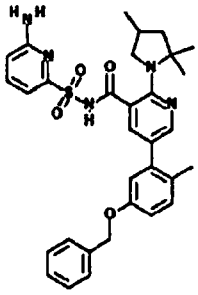
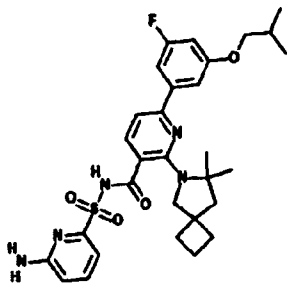
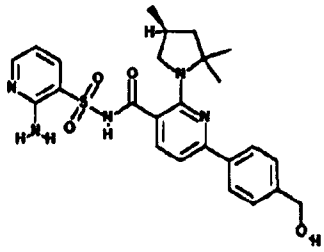
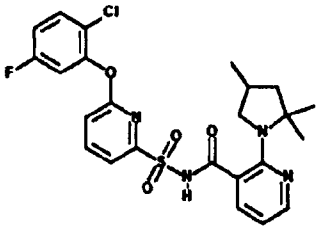
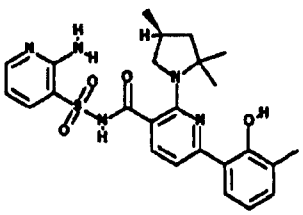
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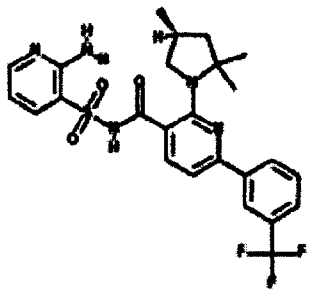
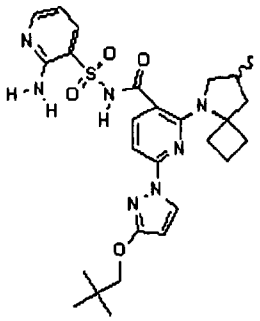
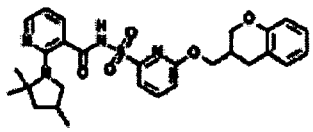
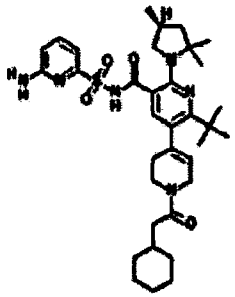
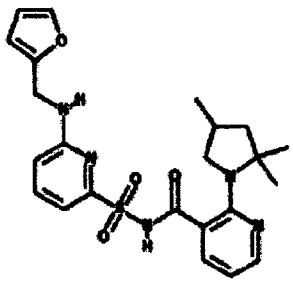
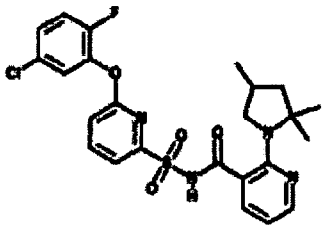
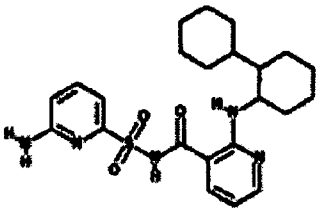
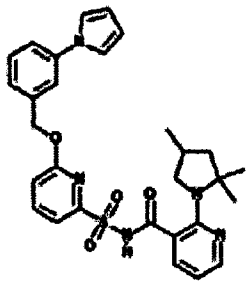
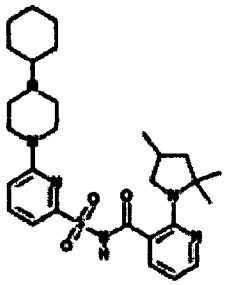
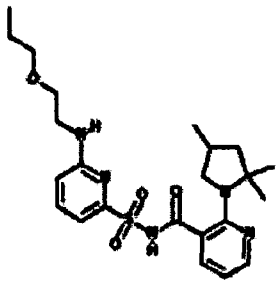
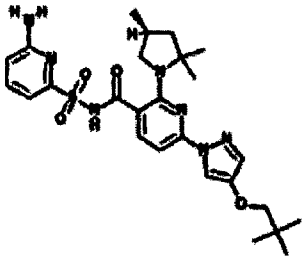
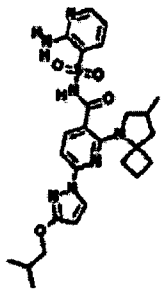
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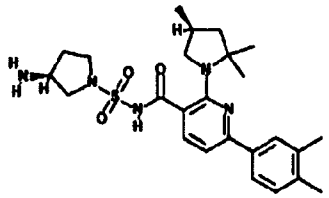
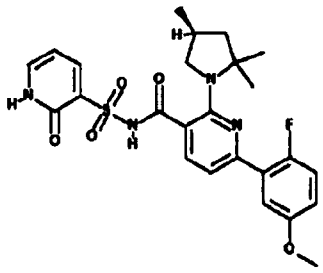
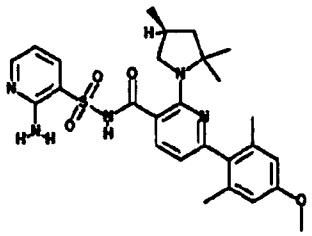
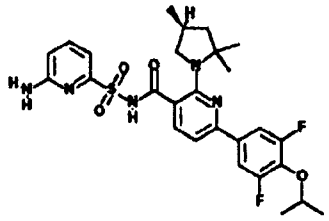
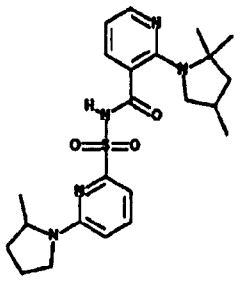
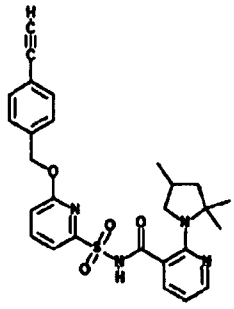
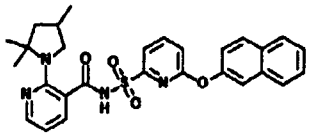
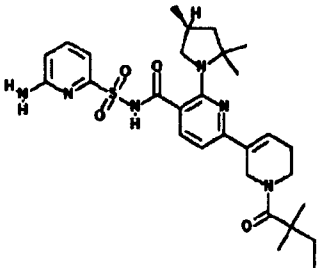
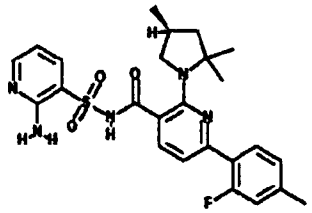
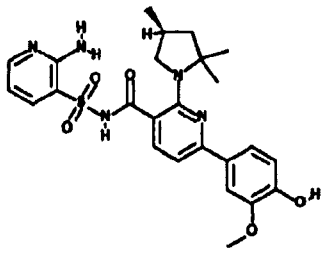
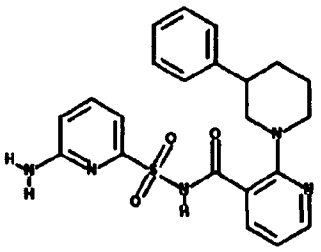
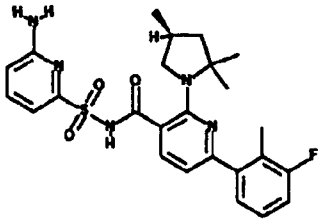
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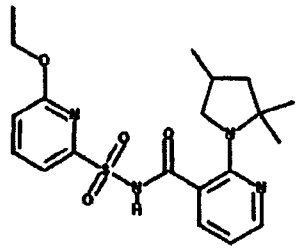
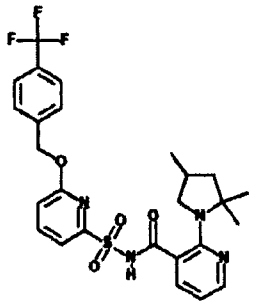
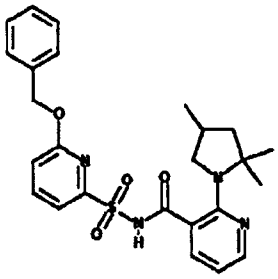
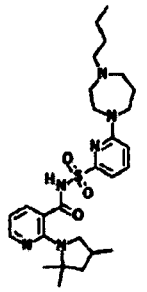
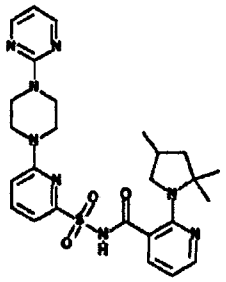
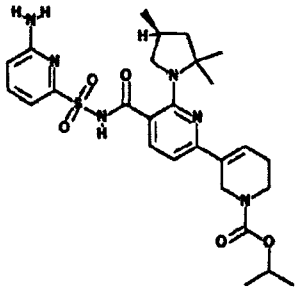
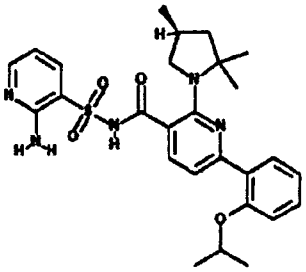
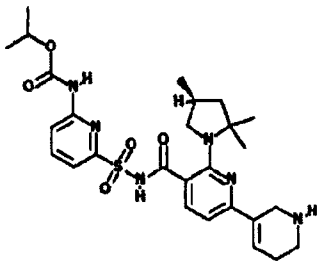
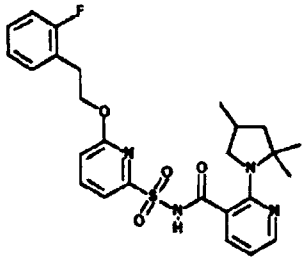
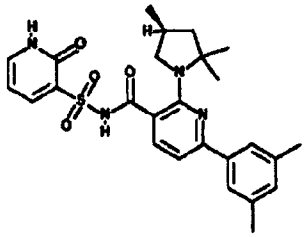
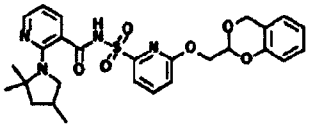
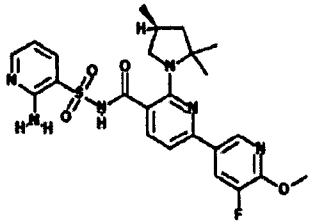
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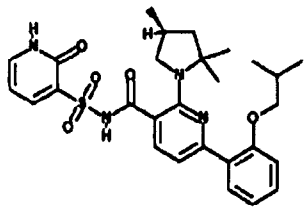
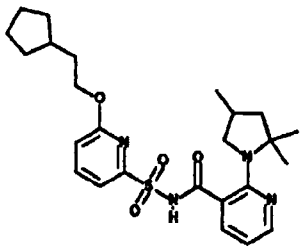
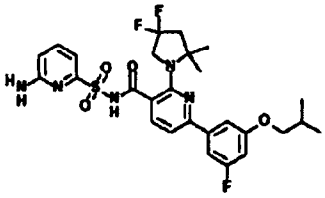
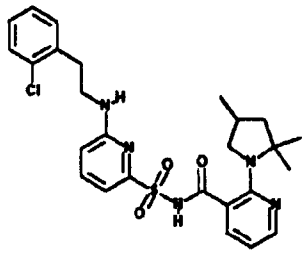
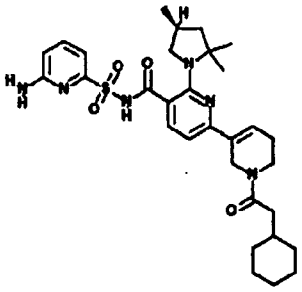
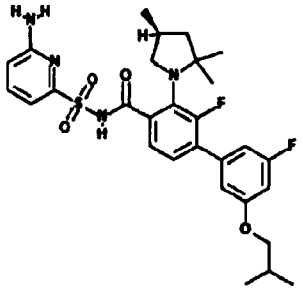
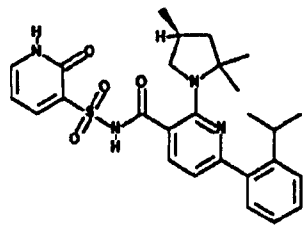
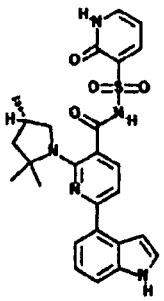
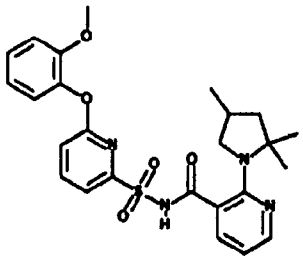
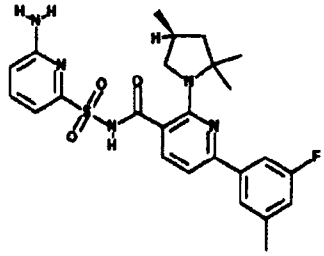
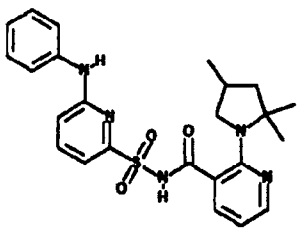
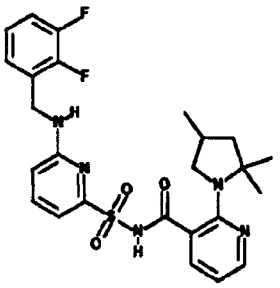
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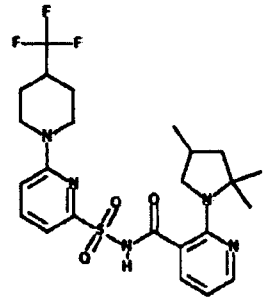
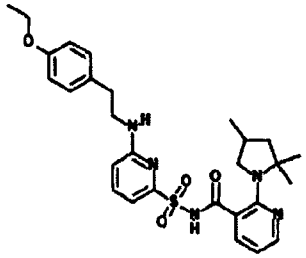
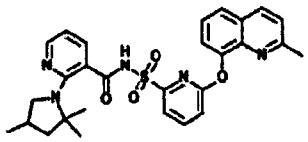
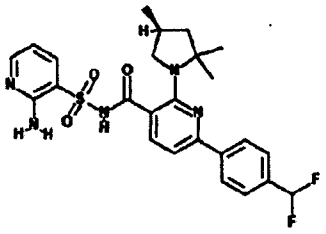
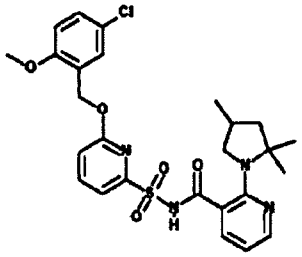
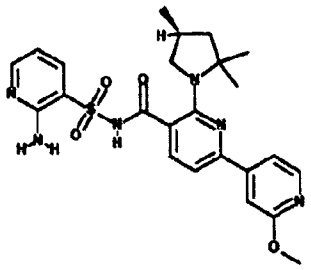
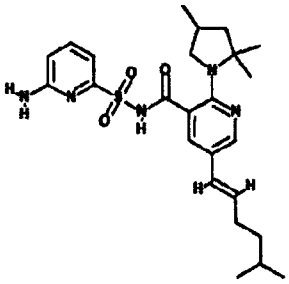
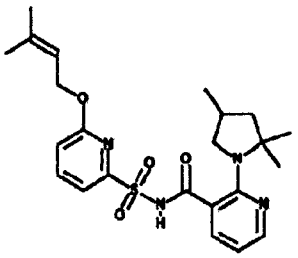
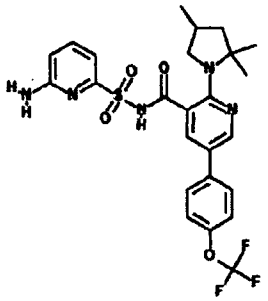
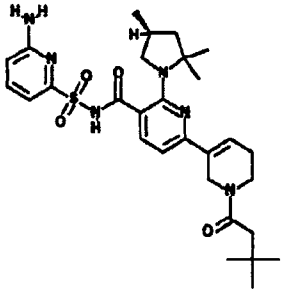
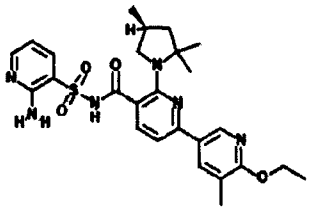
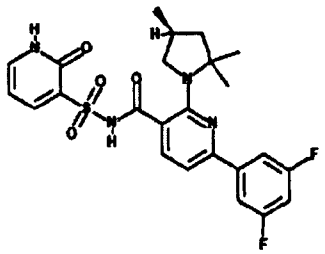
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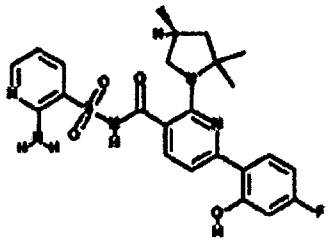
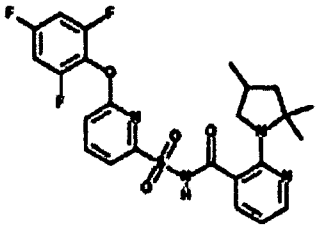
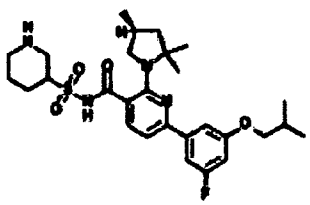
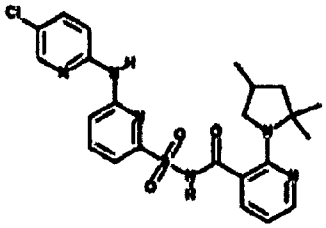
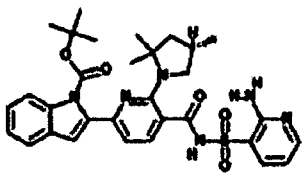
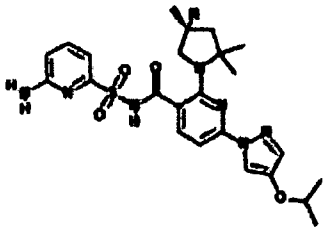
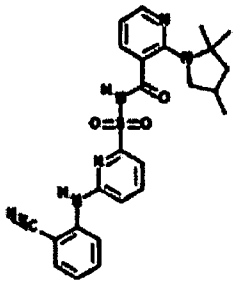
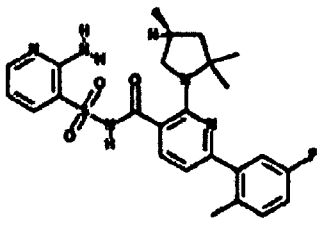
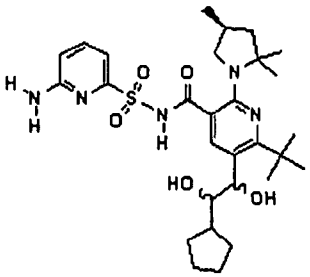
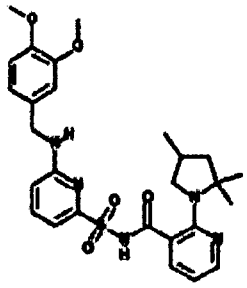
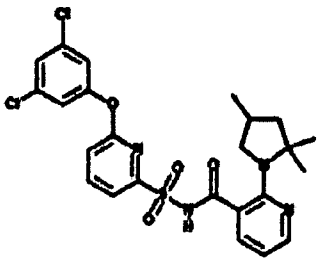
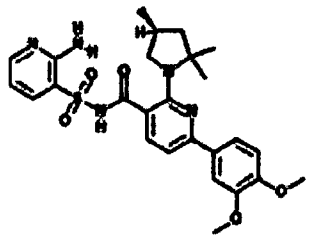
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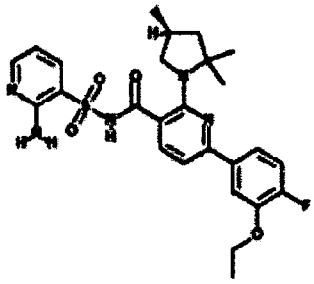
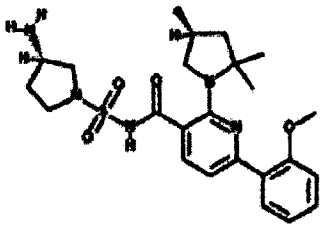
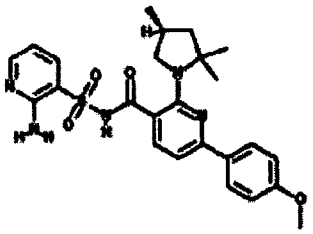
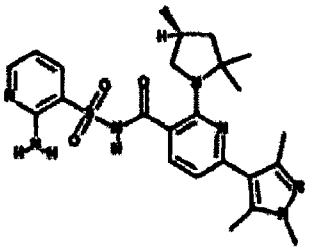
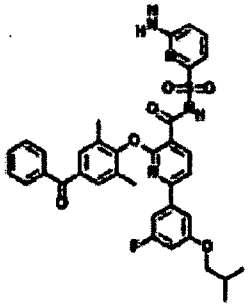
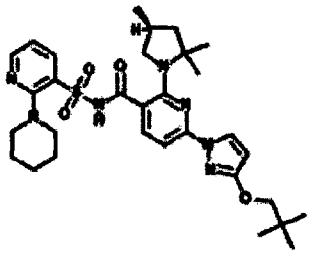
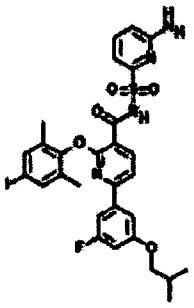
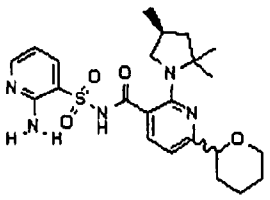
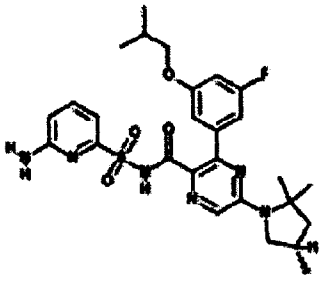
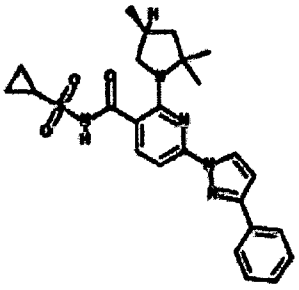
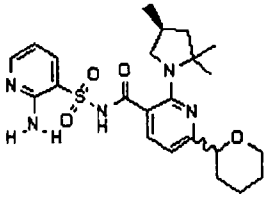
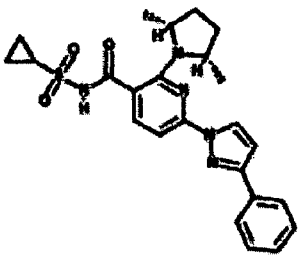
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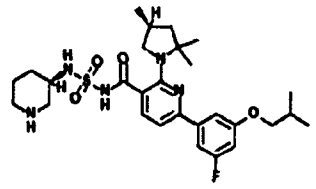
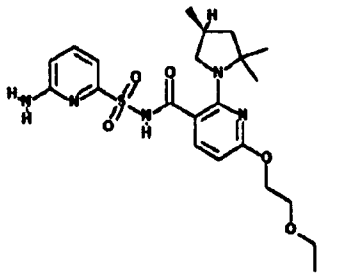
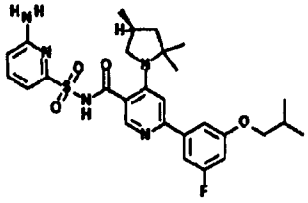
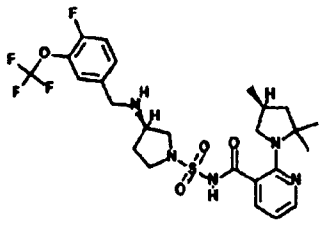
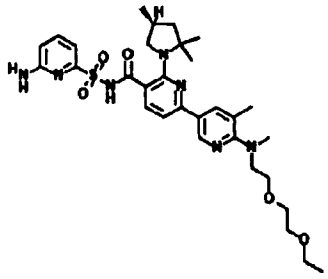
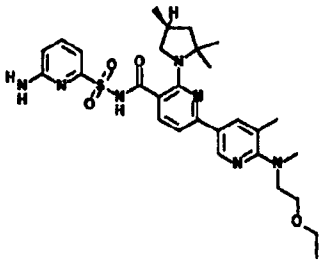
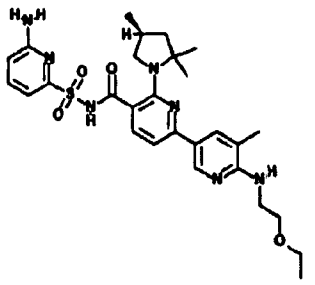
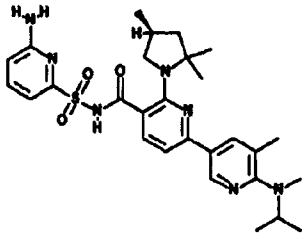
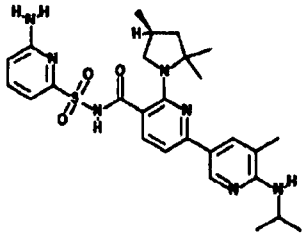
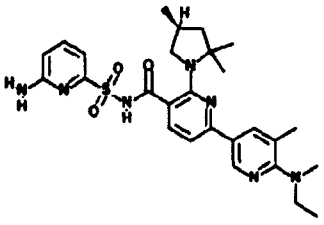
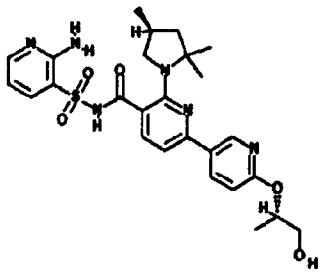
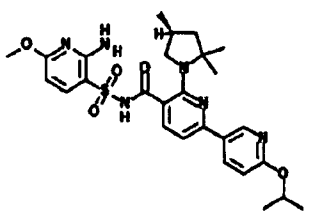
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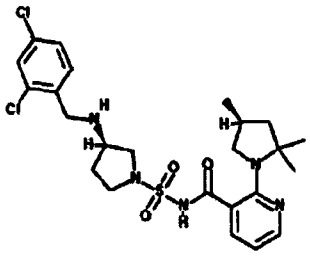
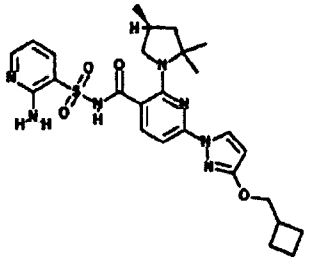
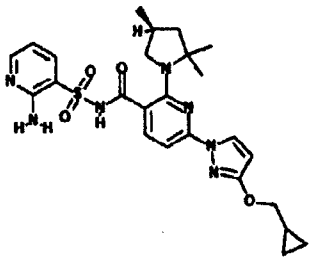
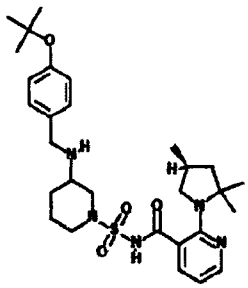
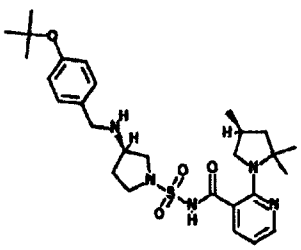
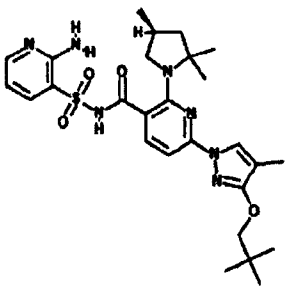
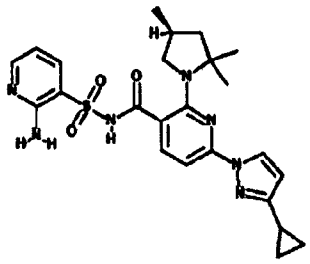
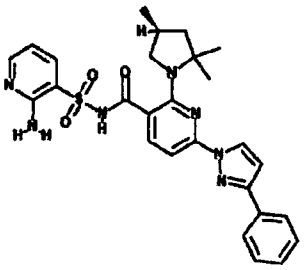
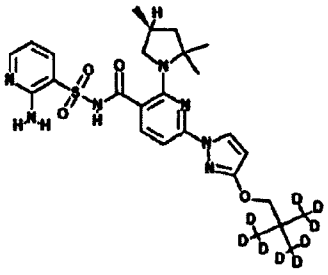
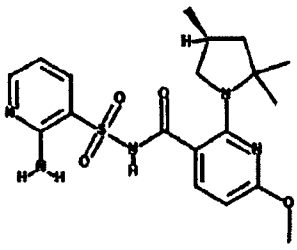
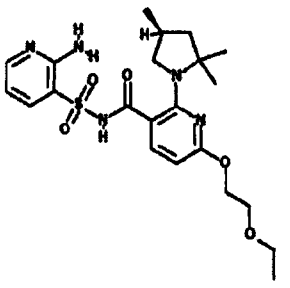
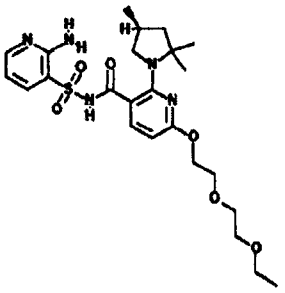
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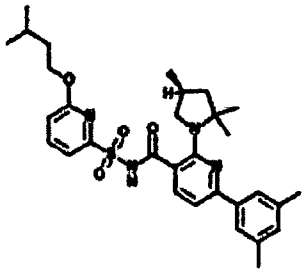
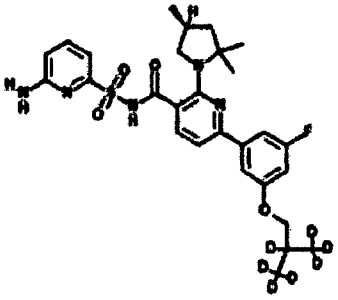
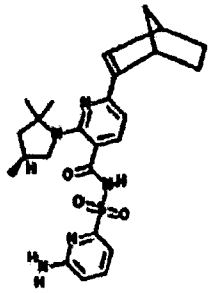
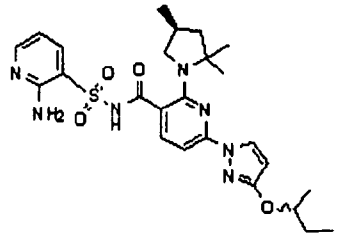
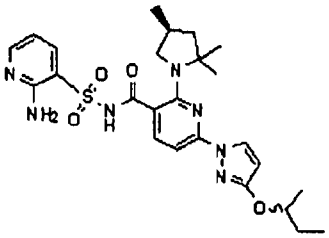
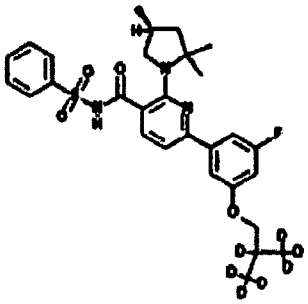
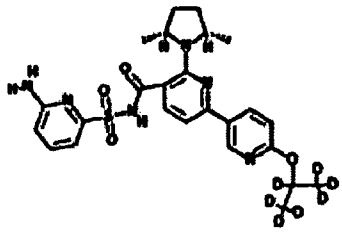
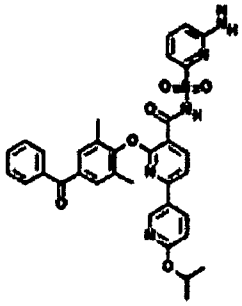
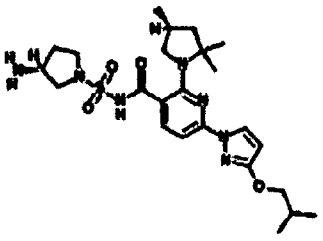
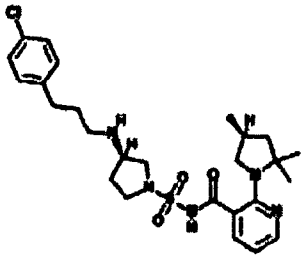
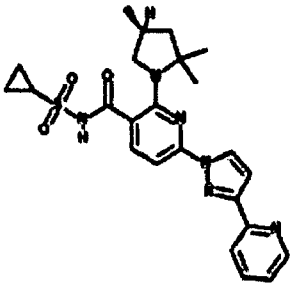
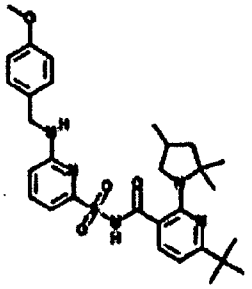
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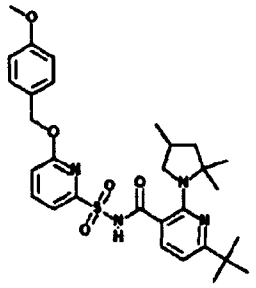
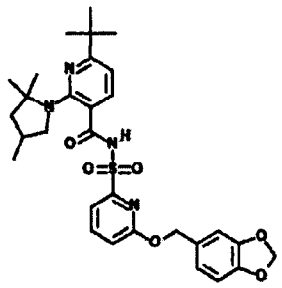
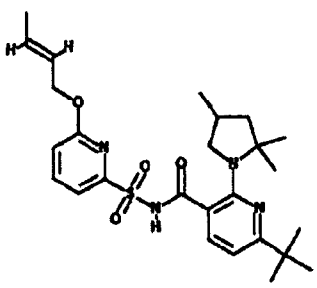
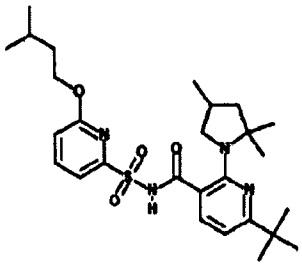
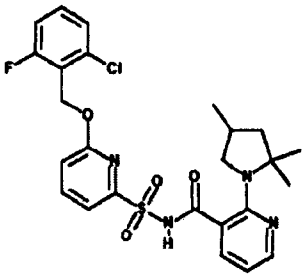
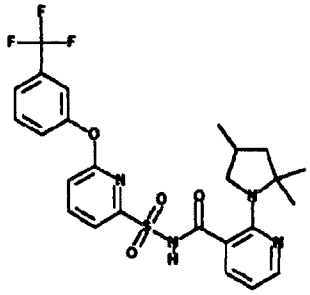
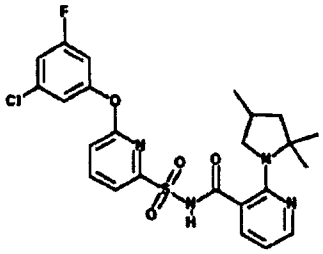
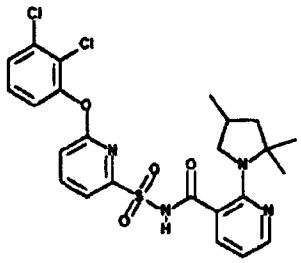
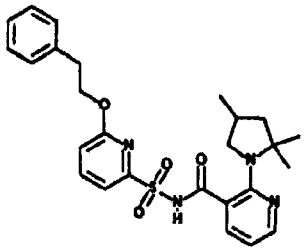
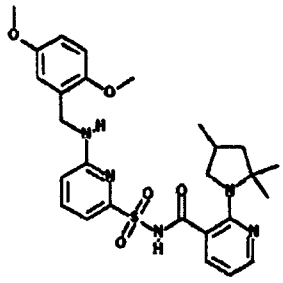
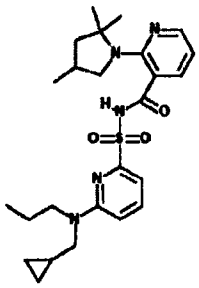
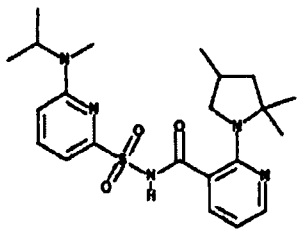
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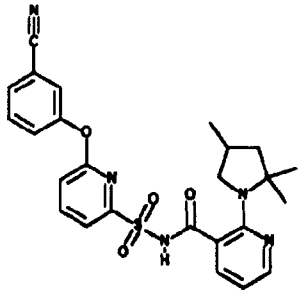
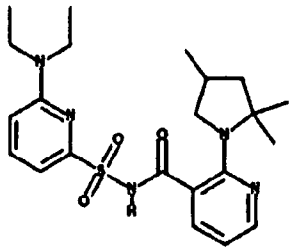
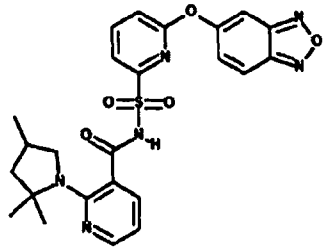
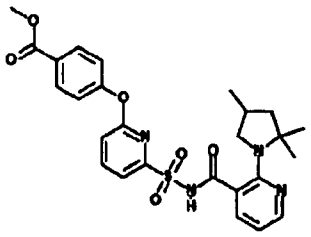
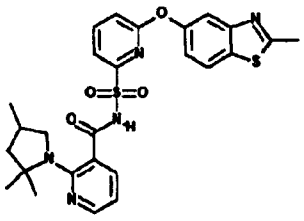
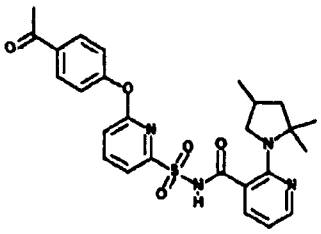
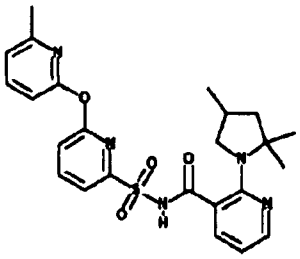
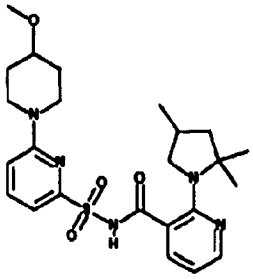
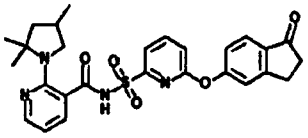
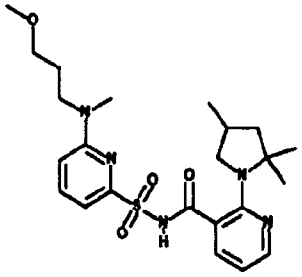
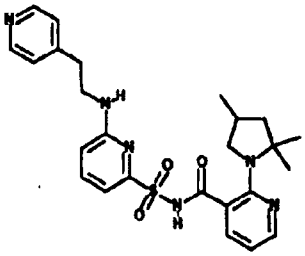
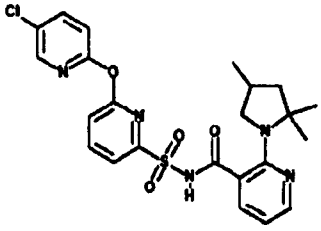
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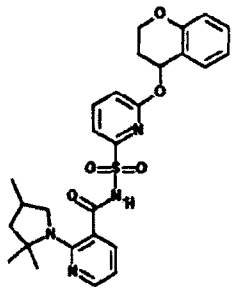
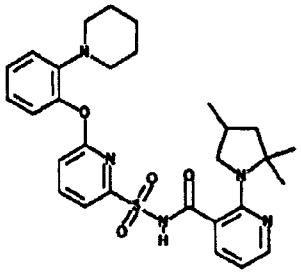
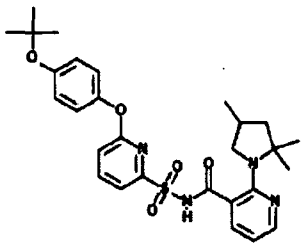
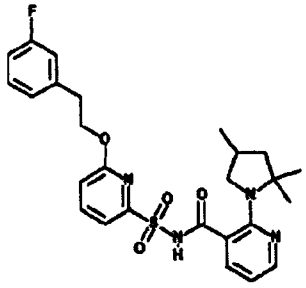
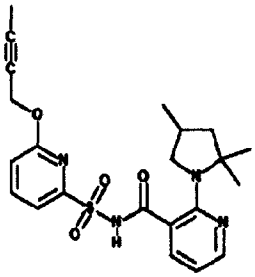
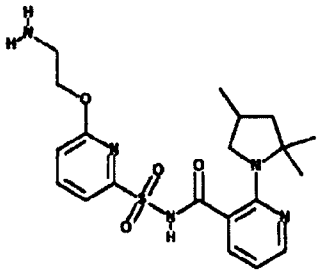
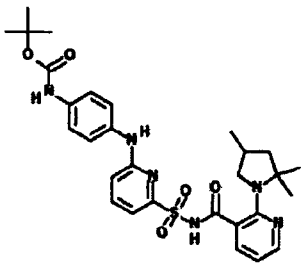
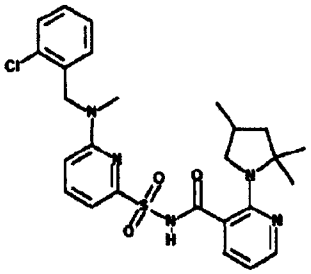
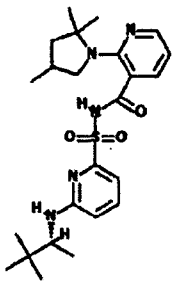
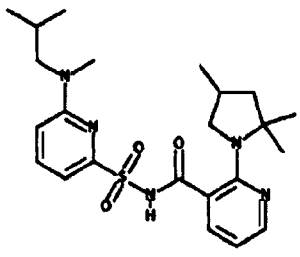
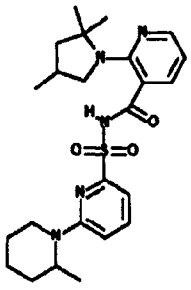
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| 2689 | 2690 | 2691 |
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| **2698** | **2699** | **2700** |
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| 2701 | 2702 | 2703 |
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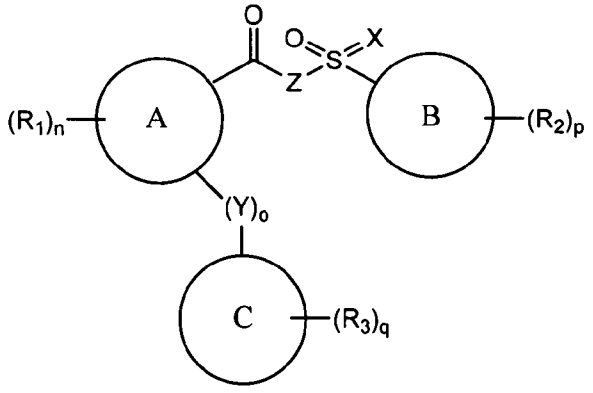
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| **2740** | **2741** | **2742** |
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| **2746** | **2747** | |
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在一個實施例中，本發明提供任一以下編號實施例。

1. 在一個實施例中，本發明提供式I化合物：




I，

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環A爲C6-C10單環或雙環芳基環或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環；

環B爲C6-C10芳基環或其中至多4個碳原子可經O、S、N或NR置換的C5-C10雜芳基或雜環；

環C爲C6-C10單環或雙環芳基環，其中1至4個環原子中任一個獨立地爲N、O或S的C4-C10單環或雙環雜芳基或雜環、或C3-C10單環或雙環環烷基環；

X爲O或NR；

Y爲$CR_2$、O、S、SO、$SO_2$或NR；

Z爲NR或$CR_2$；

$R_1$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環；或C3-C8環烷基，其中所有四者可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三

個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_1$連同其附接之原子一起形成C5-C8環或其中至多2個碳原子可經O、S或NR置換的C5-C8雜環；

$R_2$爲鹵基、OH、胺基、疊氮化物、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環、C3-C8環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；

$R_3$爲鹵基、CN、$CO_2R$、C1-C6烷基、烯烴、炔烴或氟烷基；C1-C6烷氧基、環烷氧基或氟烷氧基；C6-C10單環或雙環芳基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基，其中兩者均可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_3$可形成=$CH_2$或=O基團；

$R_4$爲H、$CF_3$、$CO_2R$、OH、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；$N(R)_2$、NRCOR、$CON(R)_2$、CN、鹵基或$SO_2R$；

R爲H、OH、C1-C6烷基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；

n爲0、1、2或3；

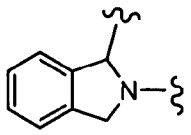
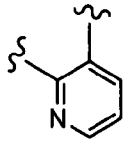
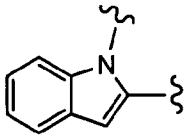
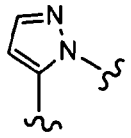
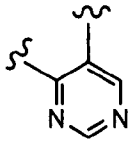
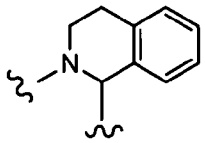
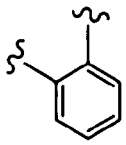
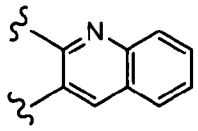
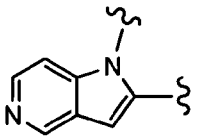
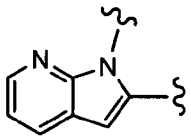
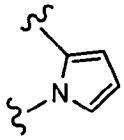
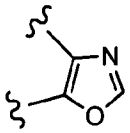
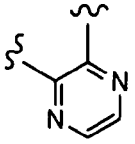
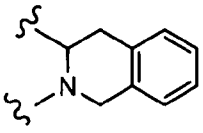
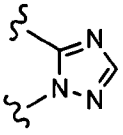
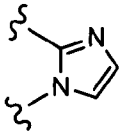
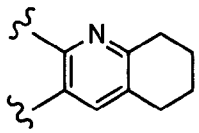
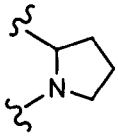
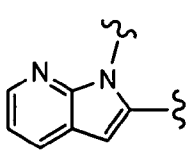
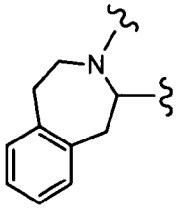
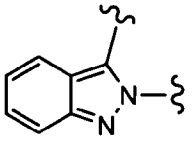
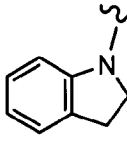
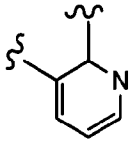
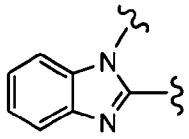
o爲0、1、2或3；

p爲0、1、2或3；且

q爲0、1、2、3、4或5；

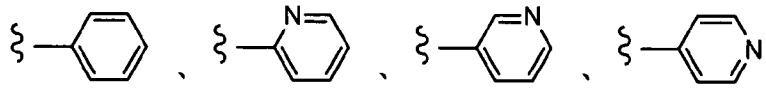
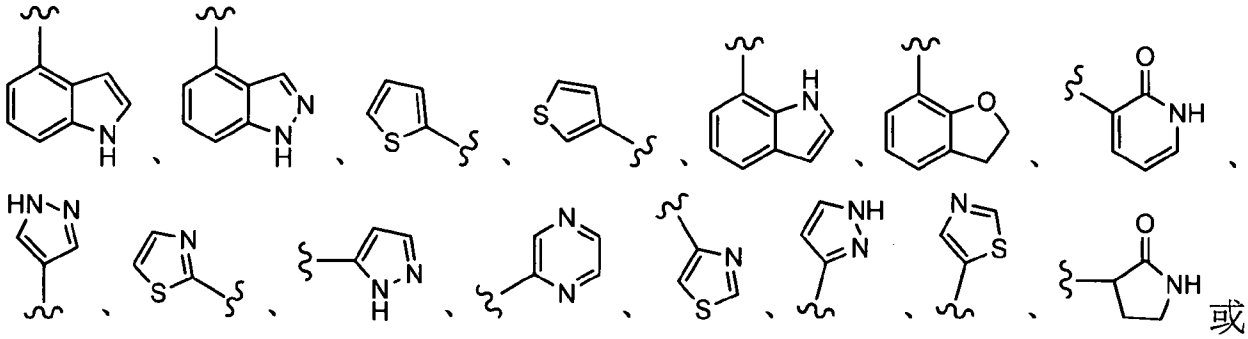
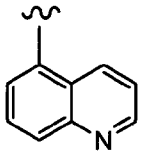
其限制條件爲含有環B及環C之部分基團取代在環A上之相鄰位置上。

2. 在另一個實施例中，本發明提供實施例1之化合物，其中環A爲吡啶基、吲哚、吲哚啉、異吲哚啉、吡唑、嘧啶、苯基、喹啉、5,6,7,8-四氫喹啉、1,2,3,4-四氫異喹啉、吡咯啶、氮雜吲哚、吡咯、噁唑、吡嗪、三唑、苯并咪唑、吲唑或咪唑環。

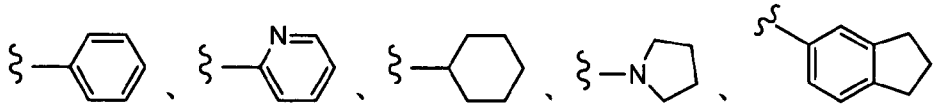
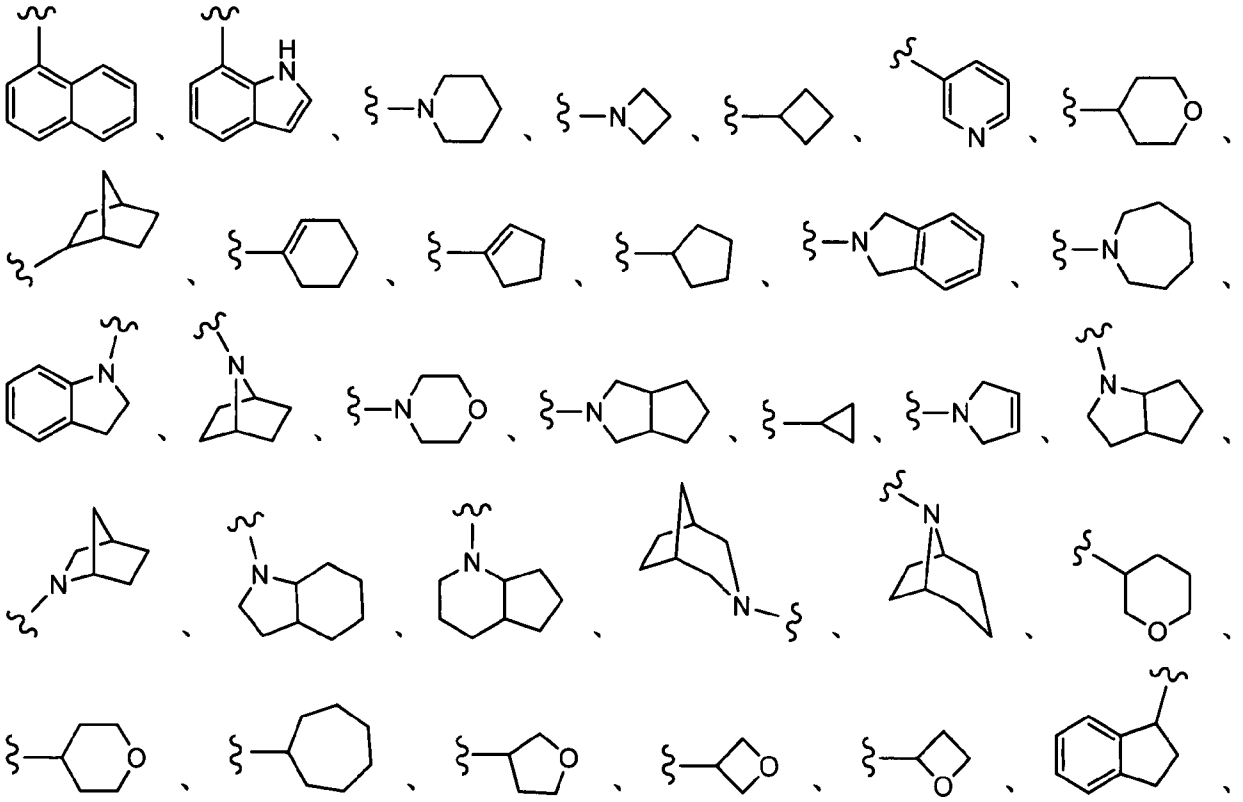
3. 一個實施例中，本發明提供實施例1或2之化合物，其中環A係選自  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

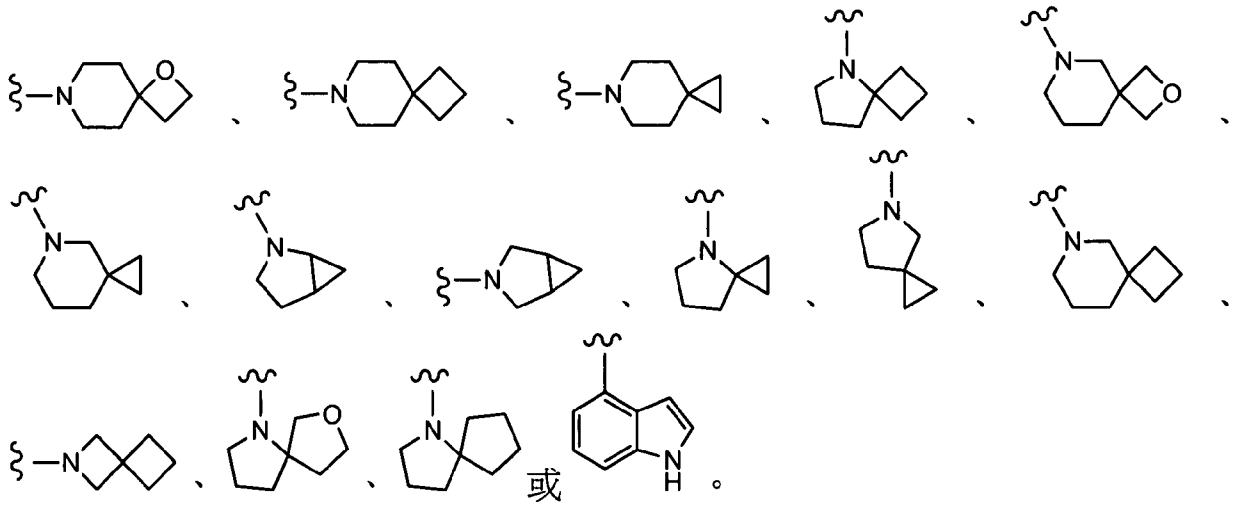
4. 在另一個實施例中，本發明提供實施例1至3中任一項之化合物，其中環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、噻吩、二氫苯并呋喃、吡嗪、吲唑、噻唑、吡啶-4(1H)-酮、吡咯啶酮或喹啉。

5. 在另一個實施例中，本發明提供實施例1至4中任一項之化合

物，其中環B係選自   或  。

6. 在另一個實施例中，本發明提供實施例1至5中任一項之化合物，其中環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘、哌啶、氮雜環丁烷或二氫茚。

7. 在另一個實施例中，本發明提供實施例1至6中任一項之化合物，其中環C爲  



8. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲O。

9. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲$CH_2$。

10. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲CH(C1-C6烷基)。

11. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲$CH(CH_3)$。

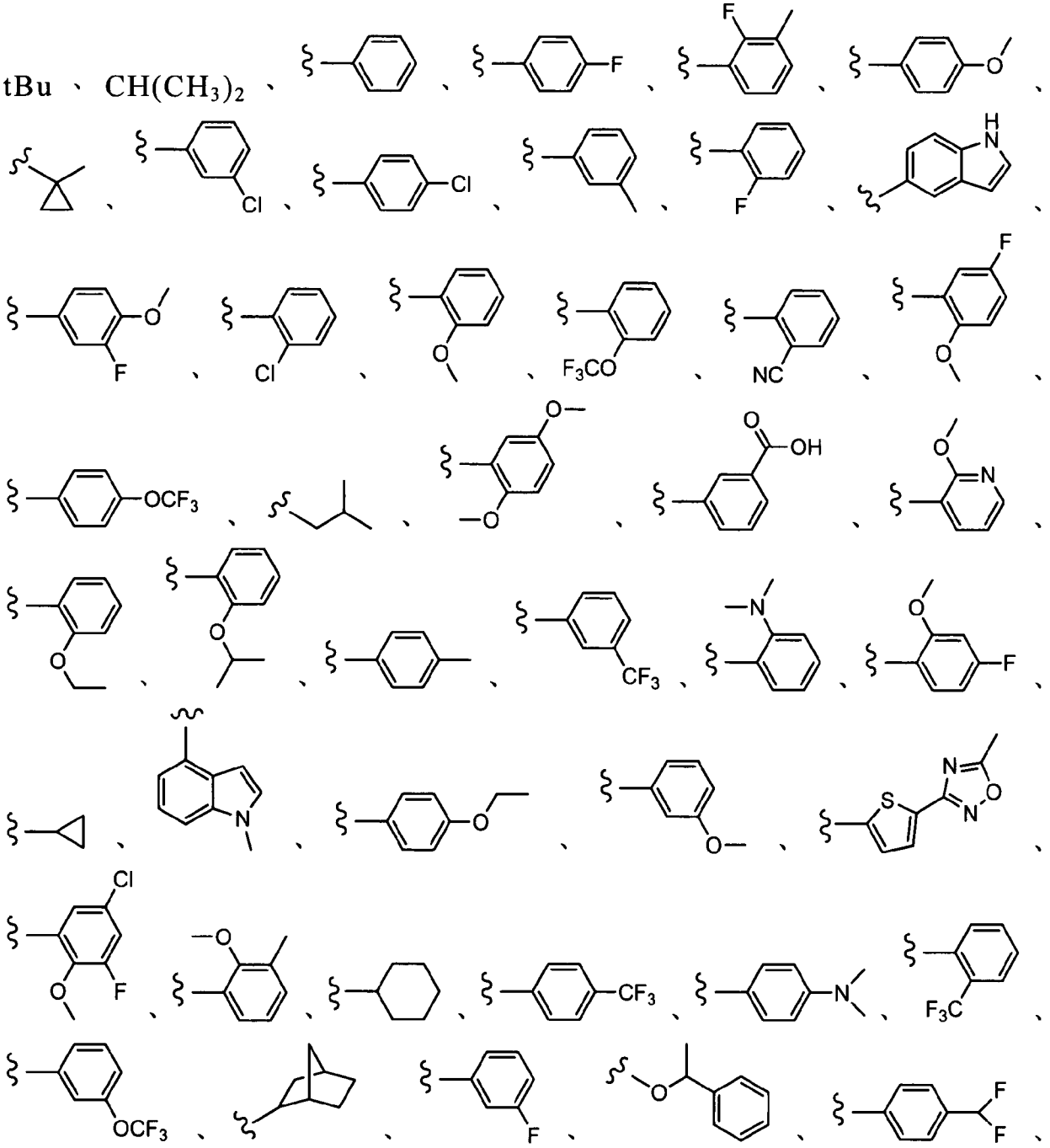
12. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲$CH(CH_2CH_3)$。

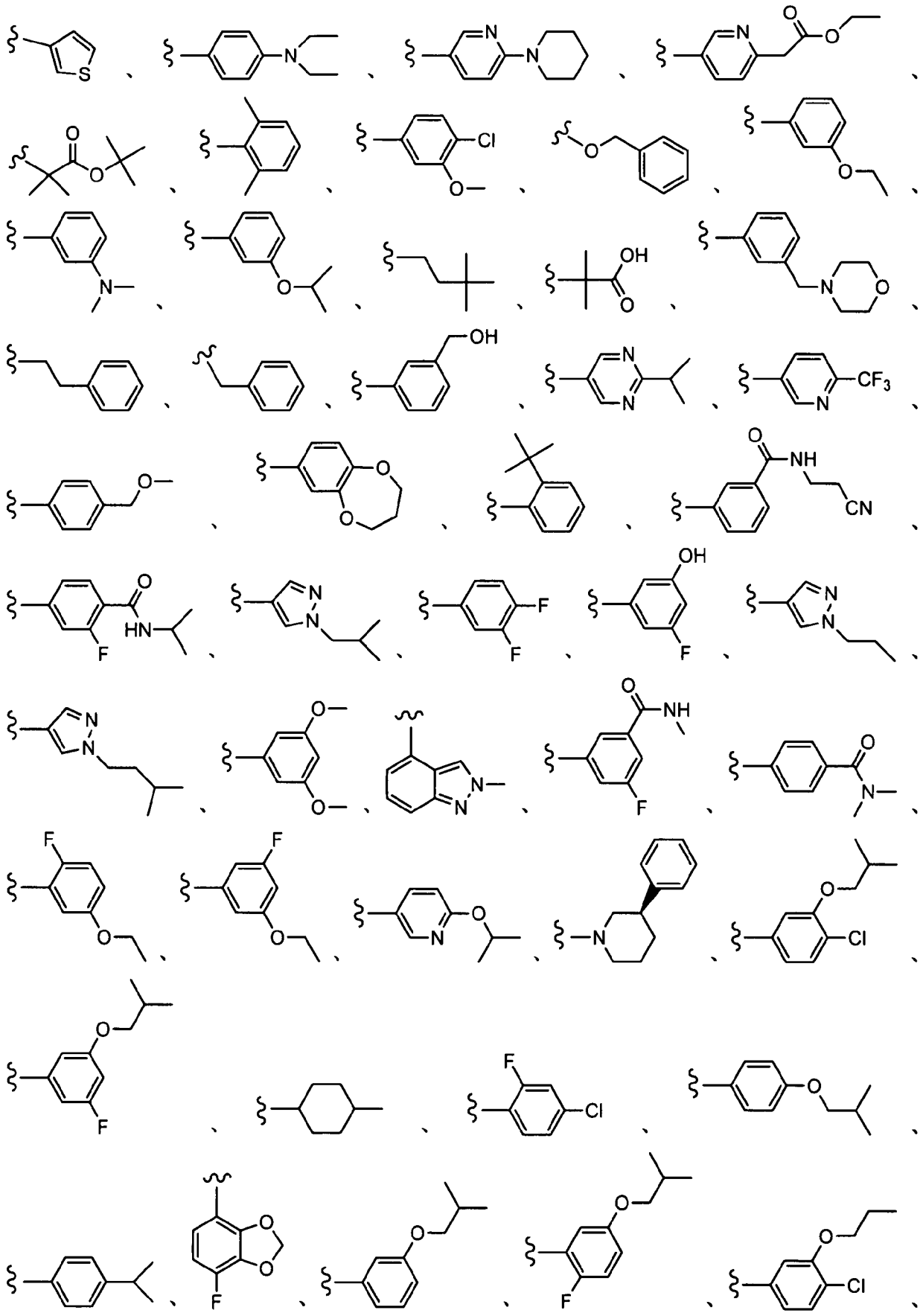
13. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲N(C1-C6烷基)。

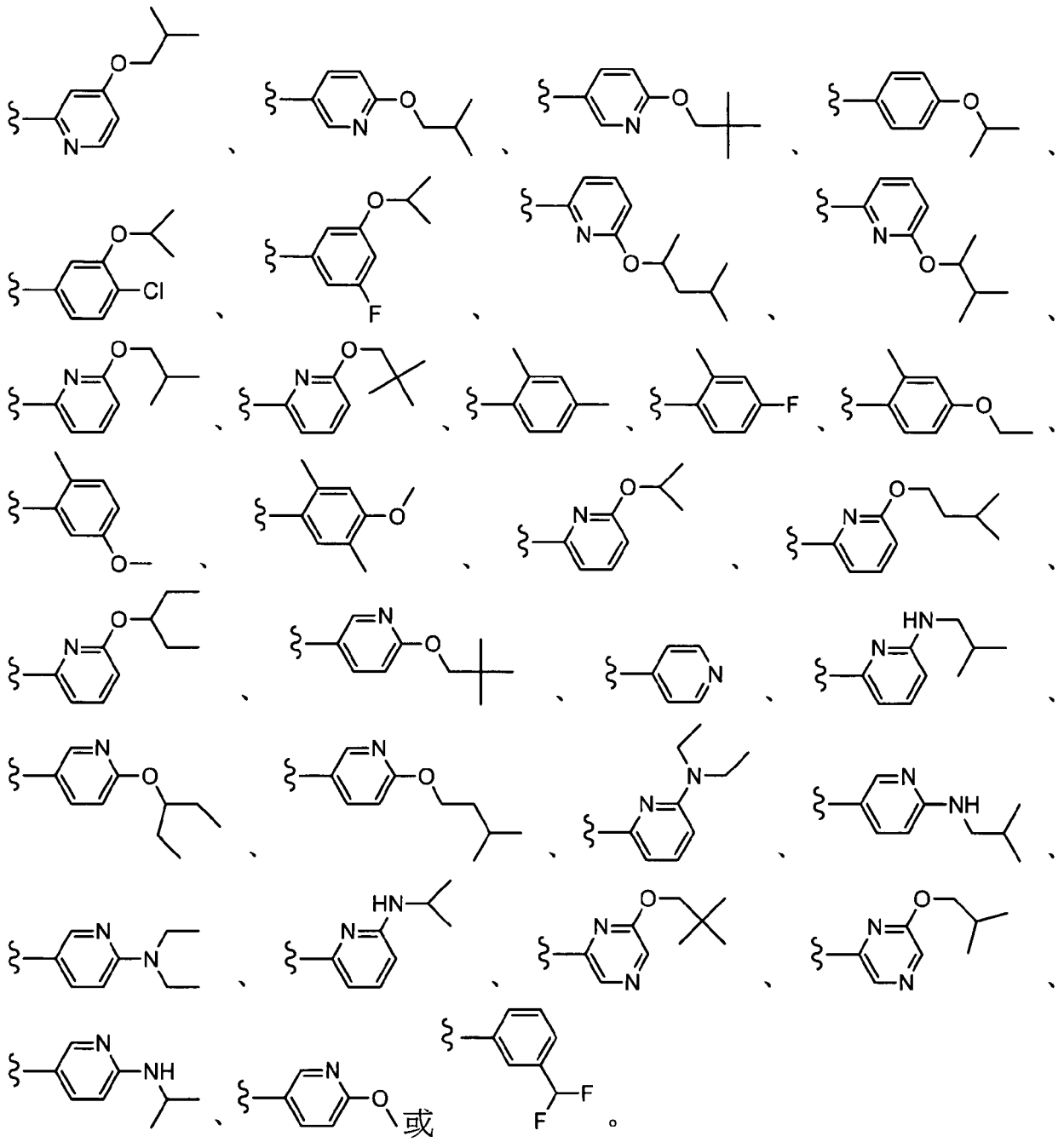
14. 在另一個實施例中，本發明提供實施例1至7中任一項之化合物，其中Y爲$N(CH_3)$。

15. 在另一個實施例中，本發明提供實施例1至14中任一項之化合物，其中$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、氮雜環丁烷或噻吩環，其中所有環可經以下基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、

C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C5-C10雜芳基、C5-C10雜環烷基或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

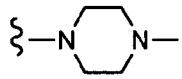
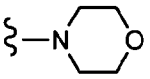
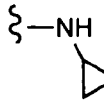
16. 在另一個實施例中，本發明提供實施例1至15中任一項之化合物，其中$R_1$係選自$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、 



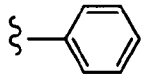
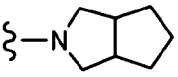
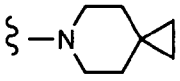
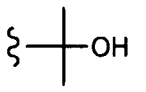
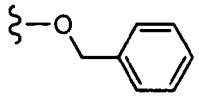
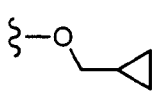
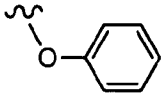
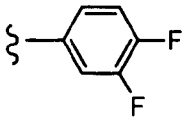
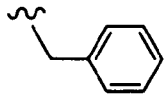
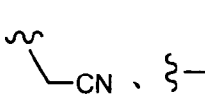
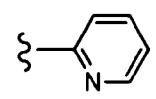
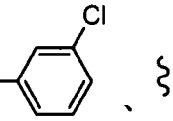
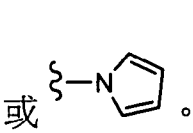
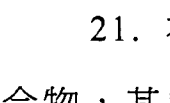
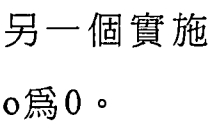
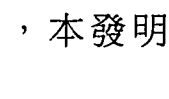
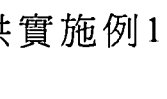
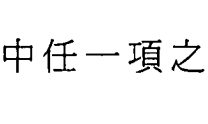
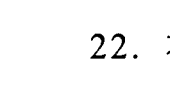
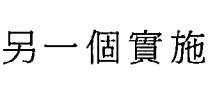
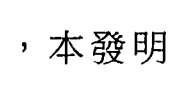
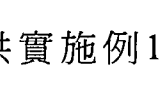
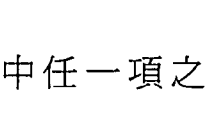


17. 在另一個實施例中，本發明提供實施例1至16中任一項之化合物，其中$R_2$係選自鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜環；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

18. 在另一個實施例中，本發明提供實施例1至17中任一項之化合物，其中$R_2$係選自Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、

$N(CH_3)_2$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCF_3$、$OCHF_2$、$OCH(CH_3)_2$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  或$CO_2H$。

19. 在另一個實施例中，本發明提供實施例1至18中任一項之化合物，其中$R_3$係選自鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環烷基。

20. 在另一個實施例中，本發明提供實施例1至19中任一項之化合物，其中$R_3$係選自Cl、F、CN、$CH_3$、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CO_2CH_3$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或。

21. 在另一個實施例中，本發明提供實施例1至20中任一項之化合物，其中o爲0。

22. 在另一個實施例中，本發明提供實施例1至20中任一項之化合物，其中o爲1。

23. 在另一個實施例中，本發明提供實施例1至20中任一項之化合物，其中o爲2。

24. 在另一個實施例中，本發明提供實施例1至23中任一項之化合物，其中n爲0。

25. 在另一個實施例中，本發明提供實施例1至23中任一項之化合物，其中n爲1。

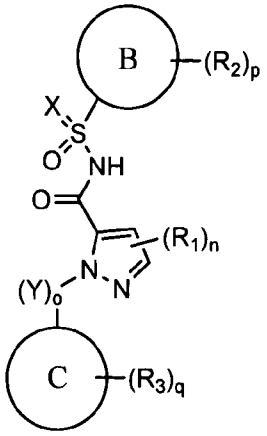
26. 在另一個實施例中，本發明提供實施例1至23中任一項之化合物，其中n爲2。

27. 在另一個實施例中，本發明提供實施例1至26中任一項之化合物，其中p爲0。

28. 在另一個實施例中，本發明提供實施例1至26中任一項之化合物，其中p爲1。

29. 在另一個實施例中，本發明提供實施例1至26中任一項之化合物，其中p爲2。

30. 在另一個實施例中，本發明提供實施例1之化合物，其中該化合物具有式Ia：




**Ia**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中至多4個碳原子可經O、S、N或NR置換的C5-C10雜芳基或雜環；

環C爲C6-C10單環或雙環芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C5-C10單環或雙環雜芳基或雜環、或C3-C10單環或雙環環烷基環；

X爲O或NR；

Y為$CR_2$、O、S、SO、$SO_2$、或NR；

$R_1$為鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環；或C3-C8環烷基，其中所有四者可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_1$連同其附接之原子一起形成C5-C8環或其中至多2個碳原子可經O、S或NR置換的C5-C8雜環；

$R_2$為鹵基、OH、胺基、疊氮化物、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環、C3-C8環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；

$R_3$為鹵基、CN、$CO_2R$、C1-C6烷基、烯烴、炔烴或氟烷基；C1-C6烷氧基、環烷氧基或氟烷氧基；C6-C10單環或雙環芳基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基，其中兩者均可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_3$可形成=$CH_2$或=O基團；

$R_4$爲H、$CF_3$、$CO_2R$、OH、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；$N(R)_2$、NRCOR、$CON(R)_2$、CN、鹵基或$SO_2R$；

R爲H、OH、C1-C6烷基、C6-C10單環或雙環芳基，其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；

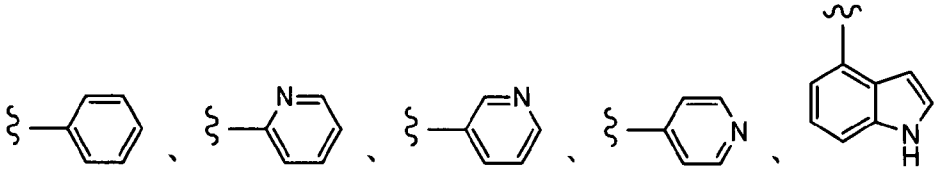
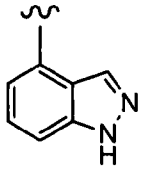
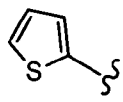
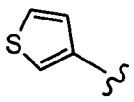
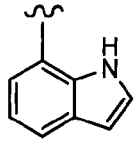
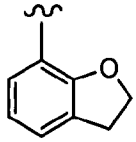
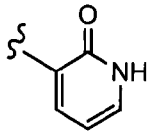
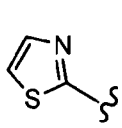
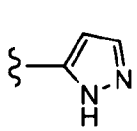
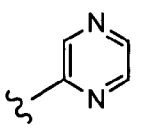
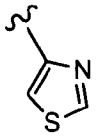
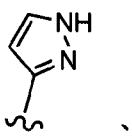
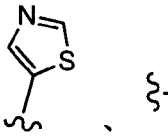
n爲0、1、2或3；

o爲0、1、2或3；

p爲0、1、2或3；且

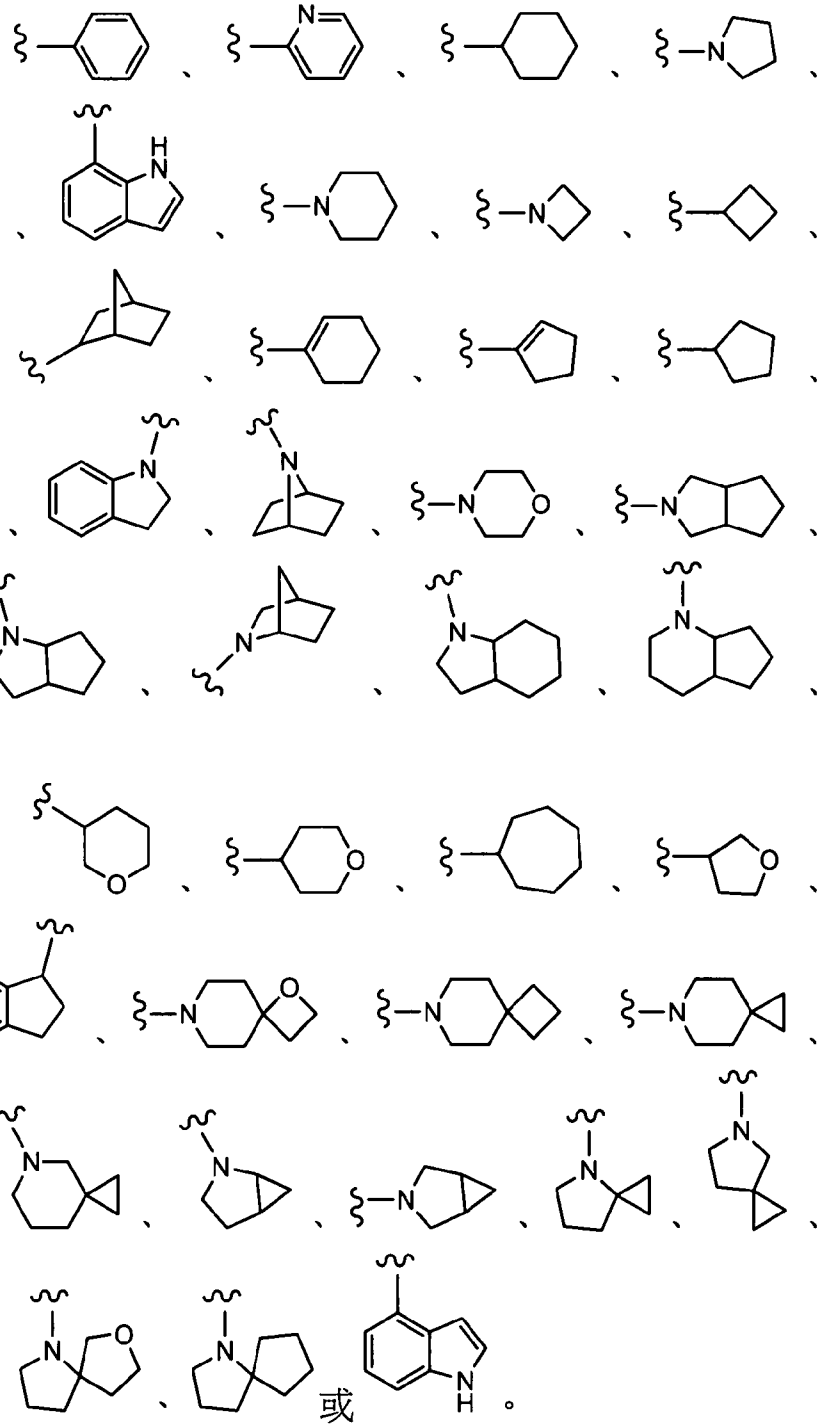
q爲0、1、2、3、4或5。

31. 在另一個實施例中，本發明提供實施例30之化合物，其中環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、噻吩、二氫苯并呋喃、吡嗪、吲唑、噻唑、吡啶-4(1H)-酮、吡咯啶酮或喹啉。

32. 在另一個實施例中，本發明提供實施例30或31之化合物，其中環B係選自  、、、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  或。

33. 在另一個實施例中，本發明提供實施例30至32中任一項之化

合物，其中環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘、哌啶或二氫茚。

34. 在另一個實施例中，本發明提供實施例30至33中任一項之化合物，其中環C爲  或。

35. 在另一個實施例中，本發明提供實施例30至34中任一項之化合物，其中Y爲O。

36. 在另一個實施例中，本發明提供實施例30至34中任一項之化

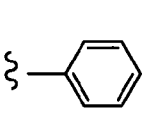
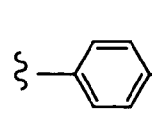
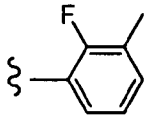
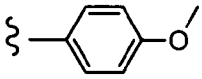
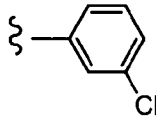
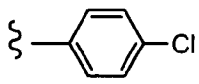
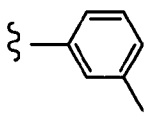
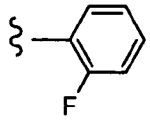
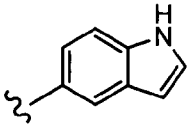
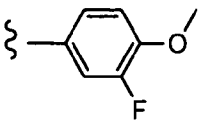
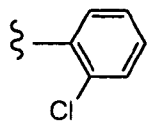
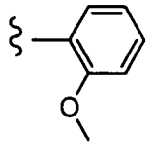
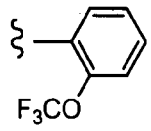
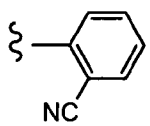
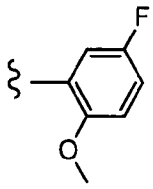
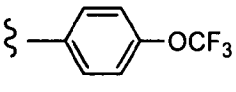
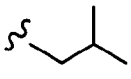
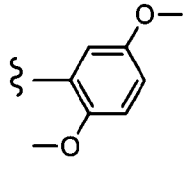
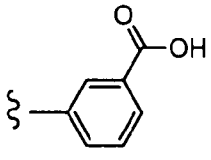
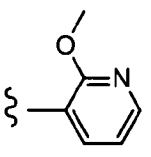
合物，其中Y爲$CH_2$。

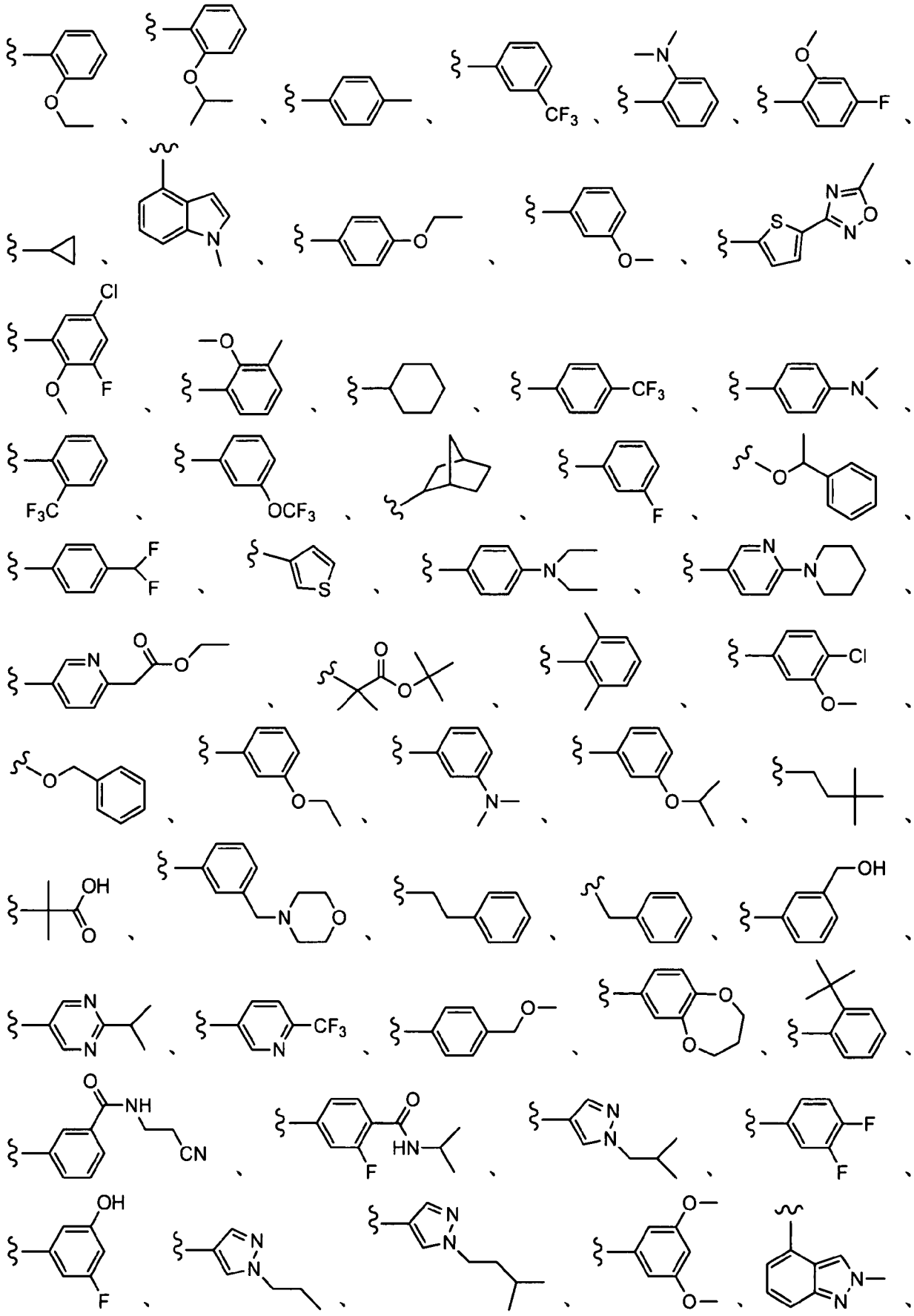
37. 在另一個實施例中，本發明提供實施例30至34中任一項之化合物，其中Y爲CH(C1-C6烷基)。

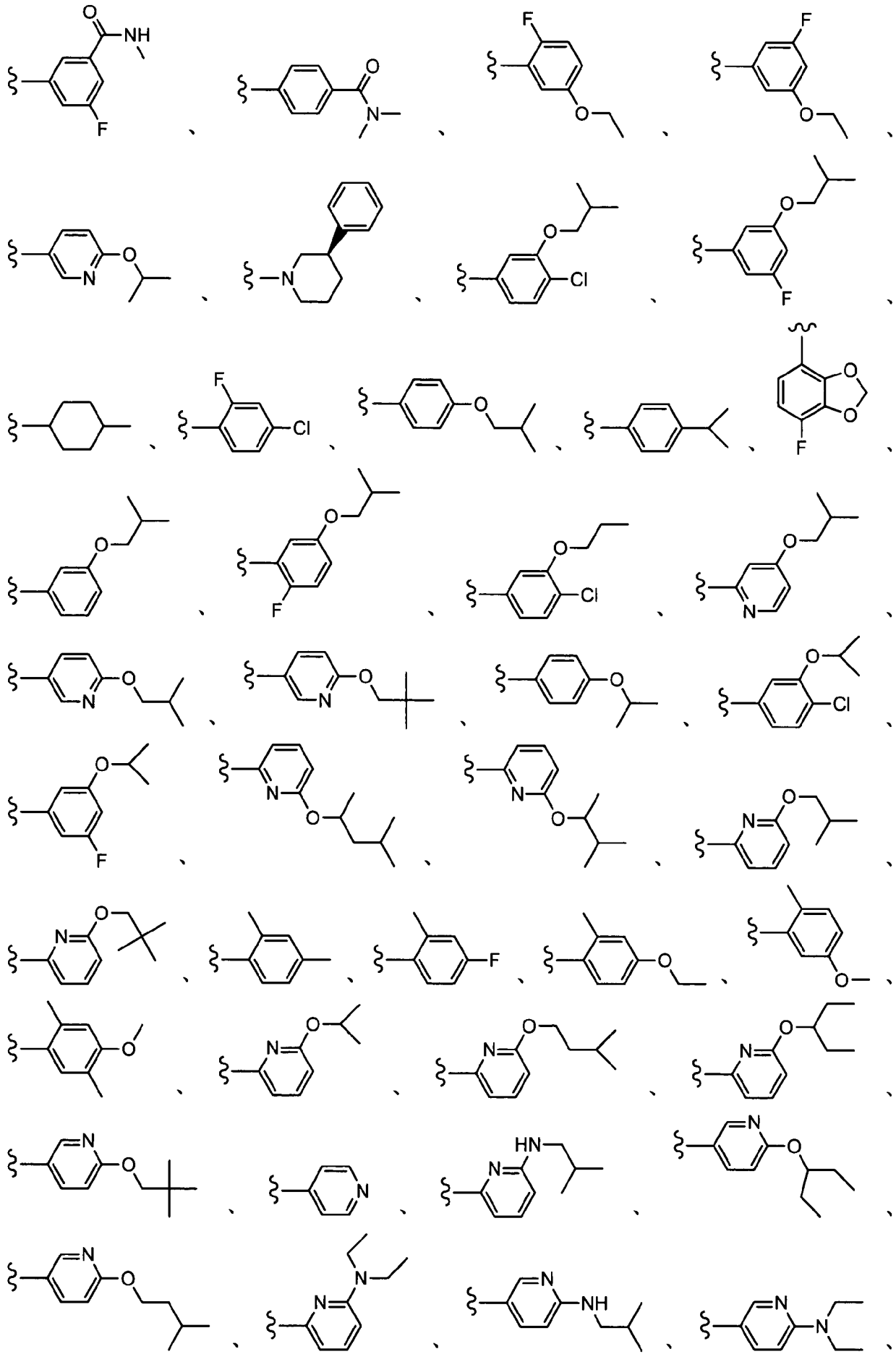
38. 如技術方案30之化合物，其中Y爲$CH(CH_3)$。

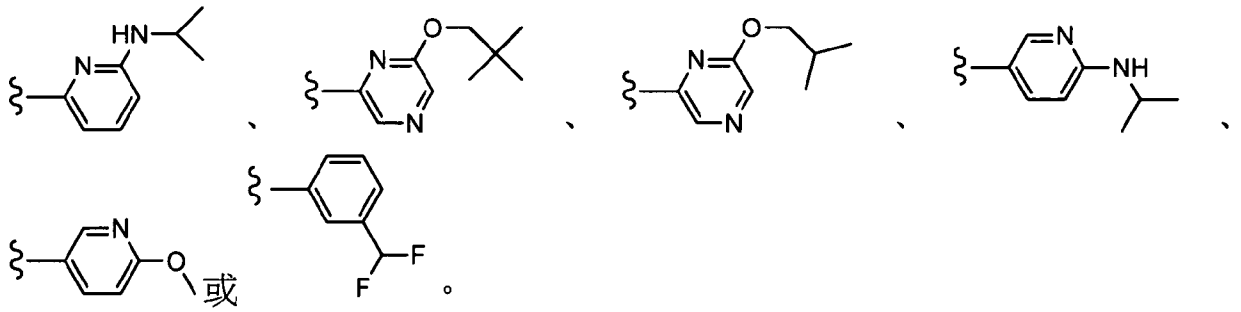
39. 在另一個實施例中，本發明提供實施例30至34中任一項之化合物，其中Y爲$CH(CH_2CH_3)$。

40. 在另一個實施例中，本發明提供實施例30至39中任一項之化合物，其中$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚或噻吩環，其中所有環可經以下基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C5-C10雜芳基、C5-C10雜環烷基或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

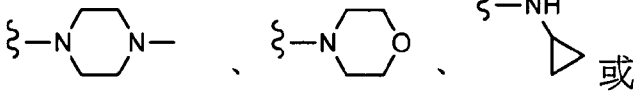
41. 在另一個實施例中，本發明提供實施例30至40中任一項之化合物，其中$R_1$係選自$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、 



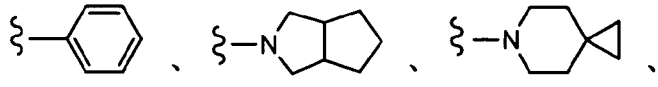


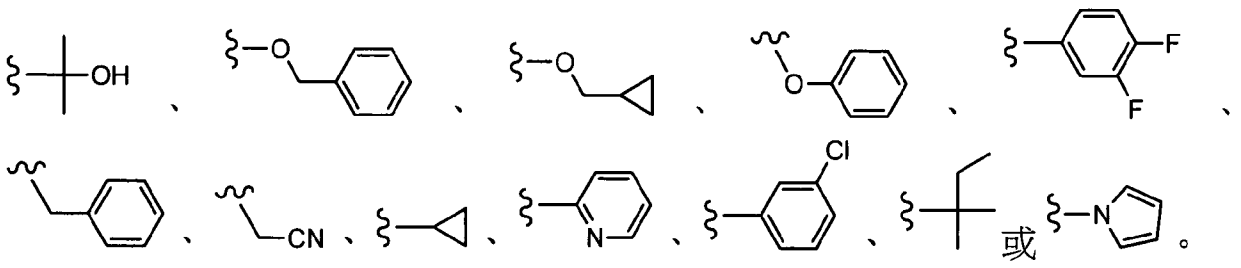


42. 在另一個實施例中，本發明提供實施例30至41中任一項之化合物，其中$R_2$係選自鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜環；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

43. 在另一個實施例中，本發明提供實施例30至中任一項之化合物42，其中$R_2$係選自Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCF_3$、$OCHF_2$、$OCH(CH_3)_2$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  或$CO_2H$。

44. 在另一個實施例中，本發明提供實施例30至43中任一項之化合物，其中$R_3$係選自鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基。

45. 在另一個實施例中，本發明提供實施例30至44中任一項之化合物，其中$R_3$係選自Cl、F、CN、$CH_3$、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CO_2CH_3$、tBu、$=CH_2$、=O、  、



46. 在另一個實施例中，本發明提供實施例30至45中任一項之化合物，其中o爲0。

47. 在另一個實施例中，本發明提供實施例30至45中任一項之化合物，其中o爲1。

48. 在另一個實施例中，本發明提供實施例30至47中任一項之化合物，其中n爲0。

49. 在另一個實施例中，本發明提供實施例30至47中任一項之化合物，其中n爲1。

50. 在另一個實施例中，本發明提供實施例30至47中任一項之化合物，其中n爲2。

51. 在另一個實施例中，本發明提供實施例30至50中任一項之化合物，其中p爲0。

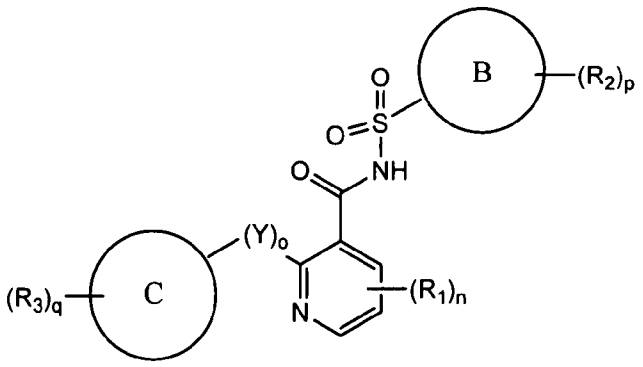
52. 在另一個實施例中，本發明提供實施例30至50中任一項之化合物，其中p爲1。

53. 在另一個實施例中，本發明提供實施例30至50中任一項之化合物，其中p爲2。

54. 在另一個實施例中，本發明提供實施例30至53中任一項之化合物，其中環B爲苯基。

55. 在另一個實施例中，本發明提供實施例30至54中任一項之化合物，其中環B及環C爲苯基。

56. 在另一個實施例中，本發明提供實施例1之化合物，其中該化合物具有式Ib：



**Ib**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中至多4個碳原子可經O、S、N或NR置換的C5-C10雜芳基或雜環；

環C爲C6-C10單環或雙環芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C5-C10單環或雙環雜芳基或雜環、或C3-C10單環或雙環環烷基環；

Y爲$CR_2$、O、S、SO、$SO_2$或NR；

$R_1$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環；或C3-C8環烷基，其中所有四者可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_1$連同其附接之原子一起形成C5-C8環或其中至多2個碳原子可經O、S或NR置換的C5-C8雜環；

$R_2$爲鹵基、OH、胺基、疊氮化物、CN、C1-C6烷基或氟烷基、

C1-C6烷氧基或氟烷氧基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環、C3-C8環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；

$R_3$爲鹵基、CN、$CO_2R$、C1-C6烷基、烯烴、炔烴或氟烷基；C1-C6烷氧基、環烷氧基或氟烷氧基；C6-C10單環或雙環芳基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基，其中兩者均可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_3$可形成=$CH_2$或=O基團；

$R_4$爲H、$CF_3$、$CO_2R$、OH、C6-C10單環或雙環芳基，其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；$N(R)_2$、NRCOR、$CON(R)_2$、CN、鹵基或$SO_2R$；

R爲H、OH、C1-C6烷基、C6-C10單環或雙環芳基，其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；

n爲0、1、2或3；

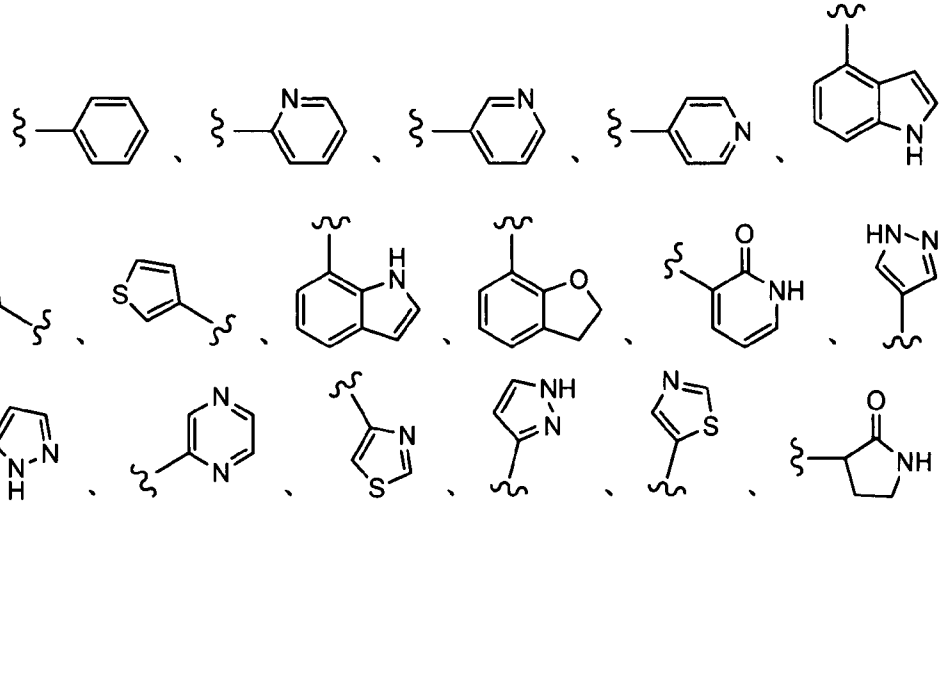
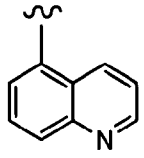
o爲0、1、2或3；

p爲0、1、2或3；且

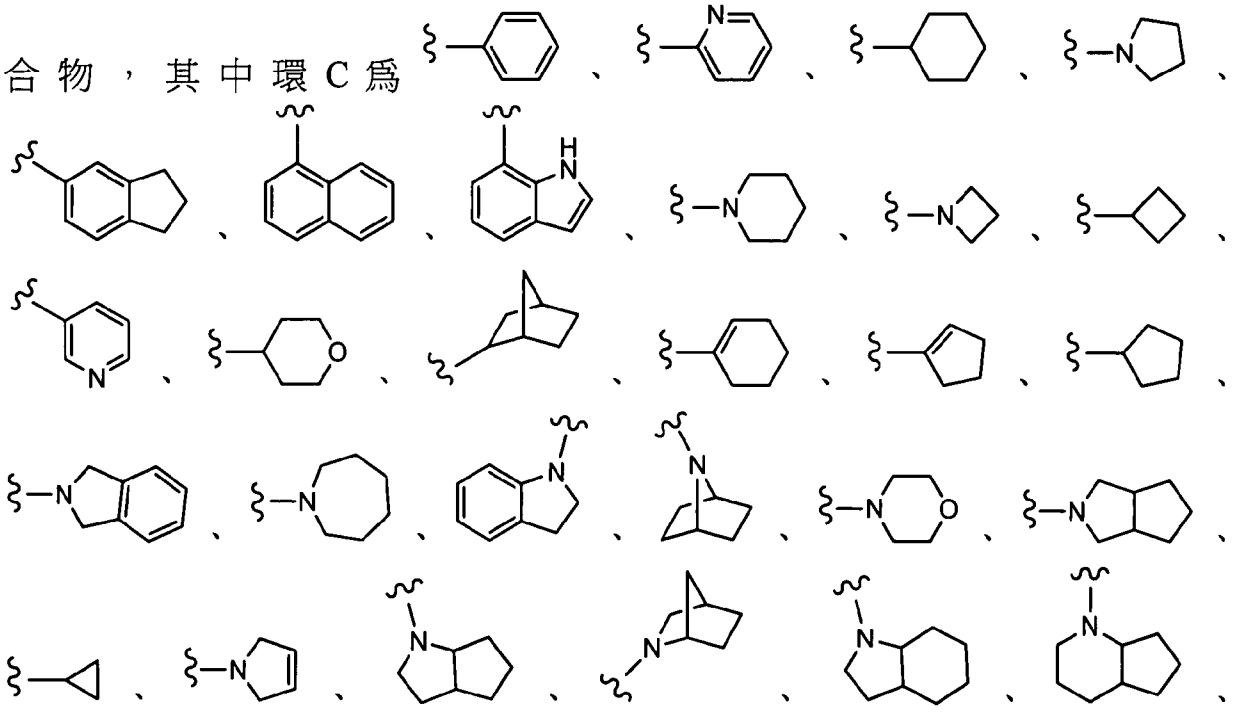
q爲0、1、2、3、4或5。

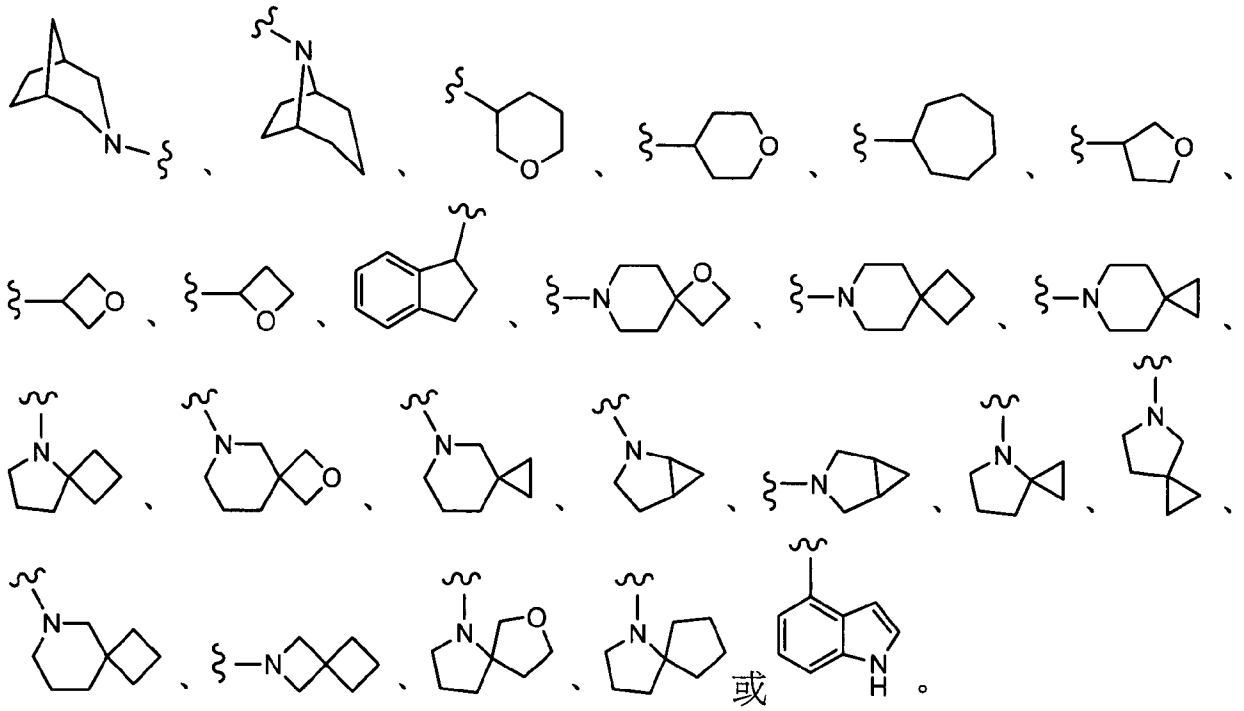
57. 在另一個實施例中，本發明提供實施例56之化合物，其中環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、噻吩、二氫苯并呋

喃、吡嗪、吲唑、噻唑、吡啶-4(1H)-酮、吡咯啶酮或喹啉。

58. 在另一個實施例中，本發明提供實施例56或57之化合物，其中環B係選自  或  。

59. 在另一個實施例中，本發明提供實施例56至58中任一項之化合物，其中環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

60. 在另一個實施例中，本發明提供實施例56至59中任一項之化合物，其中環C爲 



61. 在另一個實施例中，本發明提供實施例56至60中任一項之化合物，其中Y爲O。

62. 在另一個實施例中，本發明提供實施例56至60中任一項之化合物，其中Y爲$CH_2$。

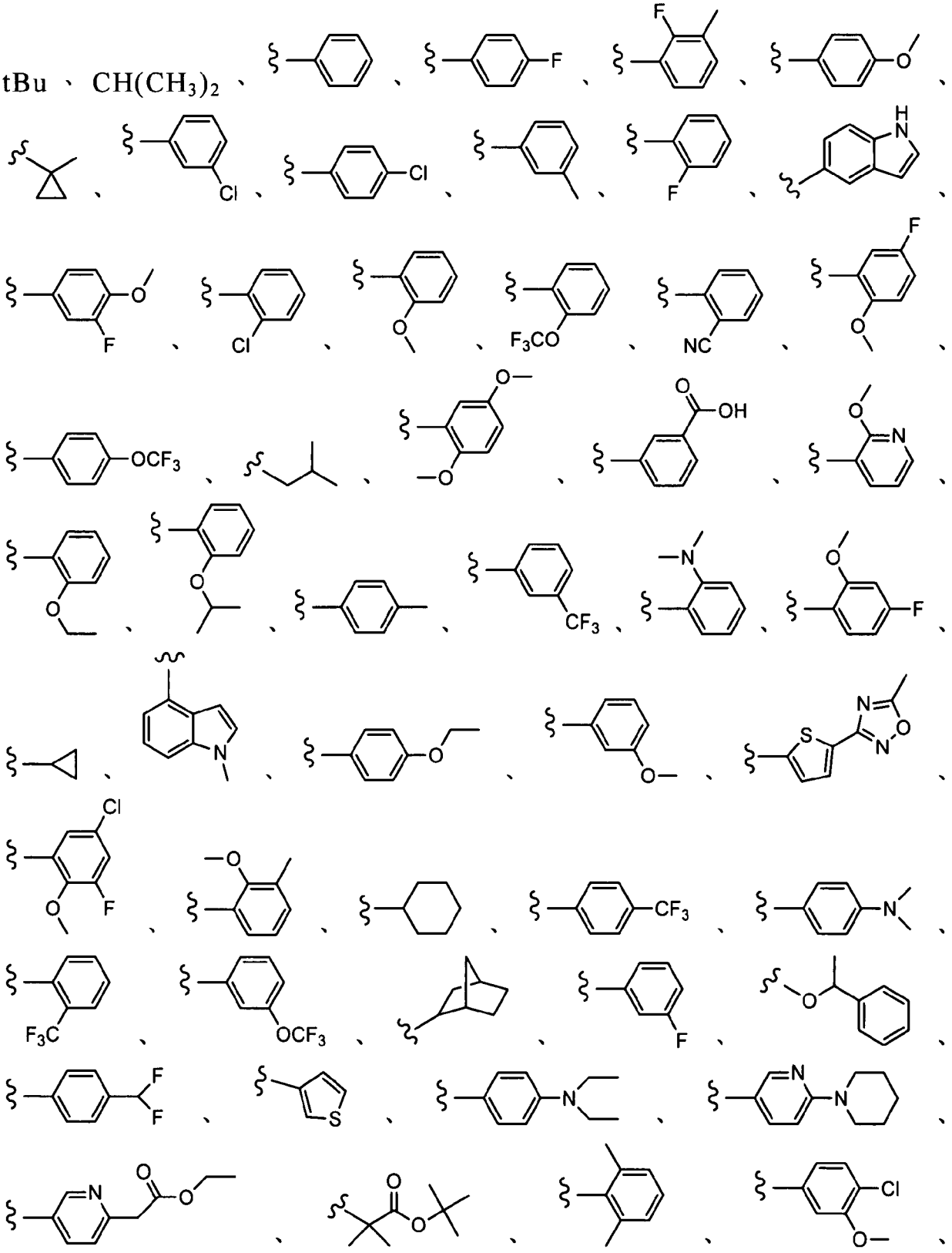
63. 在另一個實施例中，本發明提供實施例56至60中任一項之化合物，其中Y爲CH(C1-C6烷基)。

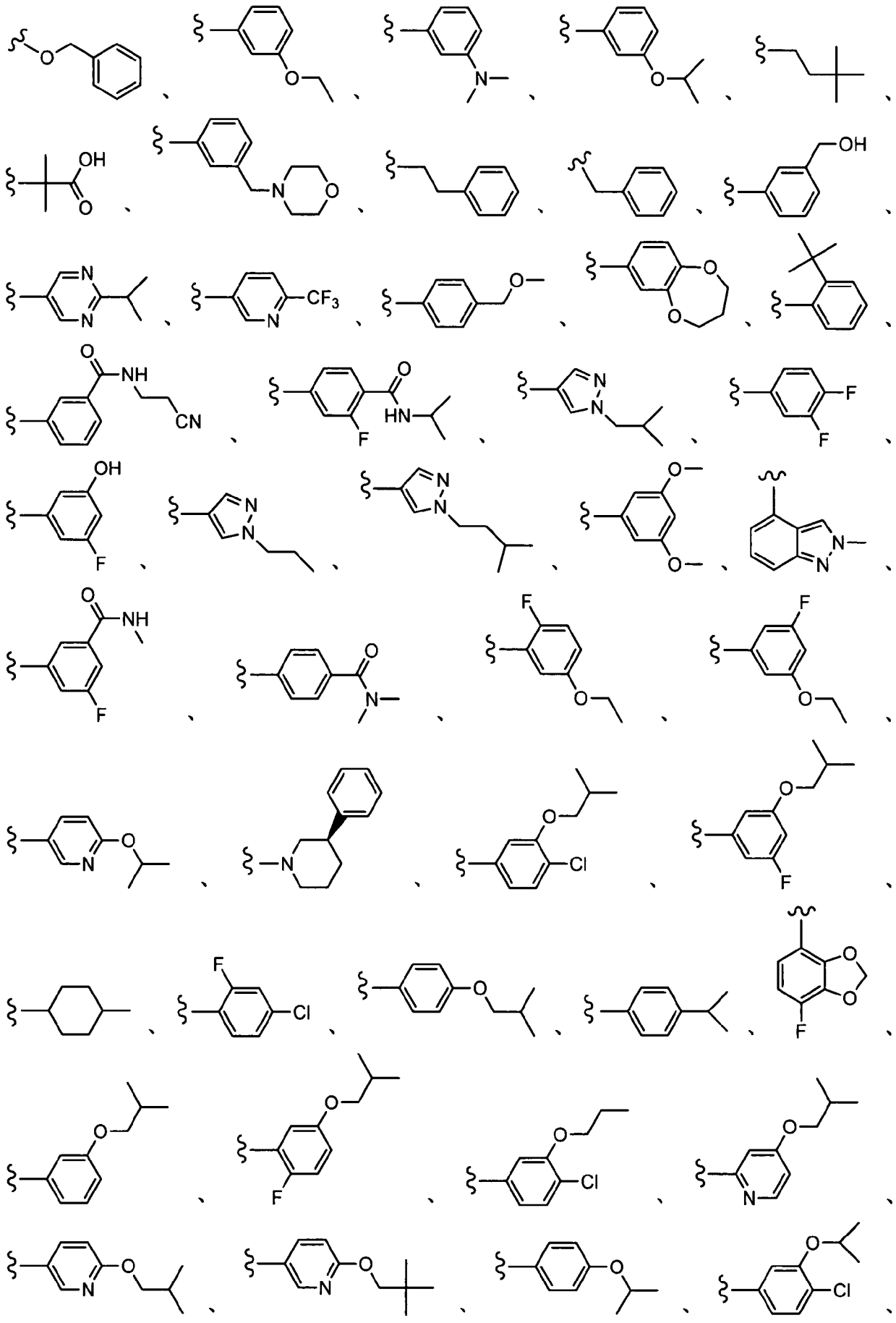
64. 在另一個實施例中，本發明提供實施例56至60中任一項之化合物，其中Y爲$CH(CH_3)$。

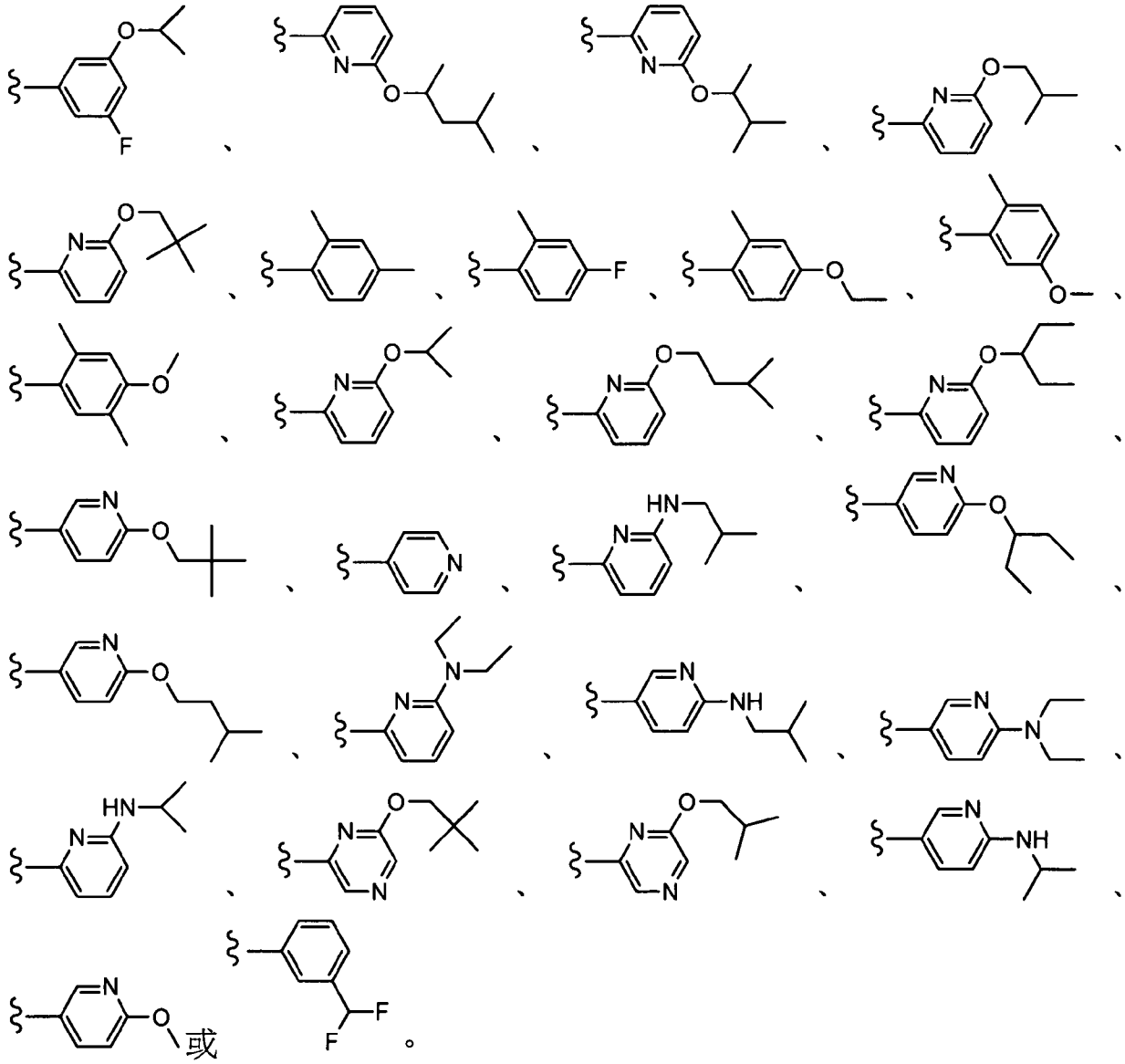
65. 在另一個實施例中，本發明提供實施例56至60中任一項之化合物，其中Y爲$CH(CH_2CH_3)$。

66. 在另一個實施例中，本發明提供實施例56至65中任一項之化合物，其中$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚或噻吩環，其中所有環可經以下基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C5-C10雜芳基、C5-C10雜環烷基或其中至多三個$CH_2$單元可經

O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

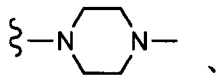
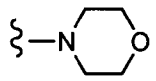
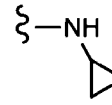
67. 在另一個實施例中，本發明提供實施例56至66中任一項之化合物，其中$R_1$係選自$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、 



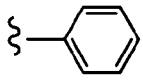
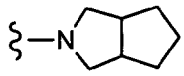
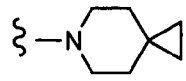
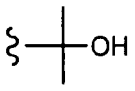
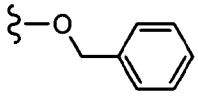
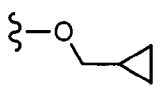
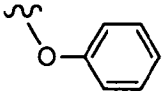
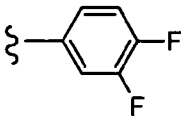
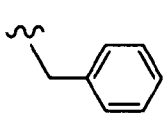
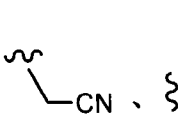
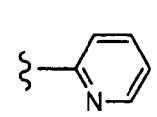
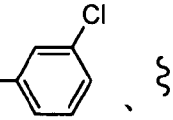
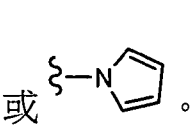


68. 在另一個實施例中，本發明提供實施例56至67中任一項之化合物，其中$R_2$係選自鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜環；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

69. 在另一個實施例中，本發明提供實施例56至68中任一項之化合物，其中$R_2$係選自Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCF_3$、$OCHF_2$、$OCH(CH_3)_2$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、

$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  或$CO_2H$。

70. 在另一個實施例中，本發明提供實施例56至69中任一項之化合物，其中$R_3$係選自鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基。

71. 在另一個實施例中，本發明提供實施例56至70中任一項之化合物，其中$R_3$係選自Cl、F、CN、$CH_3$、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CO_2CH_3$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、  、  、  、、、、、、、、、、、、、、、或。

72. 在另一個實施例中，本發明提供實施例56至71中任一項之化合物，其中o爲0。

73. 在另一個實施例中，本發明提供實施例56至71中任一項之化合物，其中o爲1。

74. 在另一個實施例中，本發明提供實施例56至71中任一項之化合物，其中o爲2。

75. 在另一個實施例中，本發明提供實施例56至74中任一項之化合物，其中n爲0。

76. 在另一個實施例中，本發明提供實施例56至74中任一項之化合物，其中n爲1。

77. 在另一個實施例中，本發明提供實施例56至74中任一項之化

合物，其中n爲2。

78. 在另一個實施例中，本發明提供實施例56至77中任一項之化合物，其中p爲0。

79. 在另一個實施例中，本發明提供實施例56至77中任一項之化合物，其中p爲1。

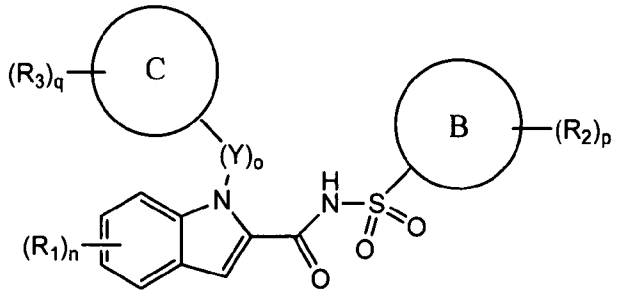
80. 在另一個實施例中，本發明提供實施例56至77中任一項之化合物，其中p爲2。

81. 在另一個實施例中，本發明提供實施例56至80中任一項之化合物，其中環B爲吡啶基。

82. 在另一個實施例中，本發明提供實施例56至81中任一項之化合物，其中環B爲苯基。

83. 在另一個實施例中，本發明提供實施例56至82中任一項之化合物，其中環B及環C爲苯基。

84. 在另一個實施例中，本發明提供實施例1之化合物，其中該化合物具有式Ic：




**Ic**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中至多4個碳原子可經O、S、N或NR置換的C5-C10雜芳基或雜環；

環C爲C6-C10單環或雙環芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C5-C10單環或雙環雜芳基或雜環、或C3-C10單環或雙環環烷基環；

Y為$CR_2$、O、S、SO、$SO_2$或NR；

$R_1$為鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環；或C3-C8環烷基，其中所有四者可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_1$連同其附接之原子一起形成C5-C8環或其中至多2個碳原子可經O、S或NR置換的C5-C8雜環；

$R_2$為鹵基、OH、胺基、疊氮化物、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環、C3-C8環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；

$R_3$為鹵基、CN、$CO_2R$、C1-C6烷基、烯烴、炔烴或氟烷基；C1-C6烷氧基、環烷氧基或氟烷氧基；C6-C10單環或雙環芳基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基，其中兩者均可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_3$可形成=$CH_2$或=O基團；

$R_4$爲H、$CF_3$、$CO_2R$、OH、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；$N(R)_2$、NRCOR、$CON(R)_2$、CN、鹵基或$SO_2R$；

R爲H、OH、C1-C6烷基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；

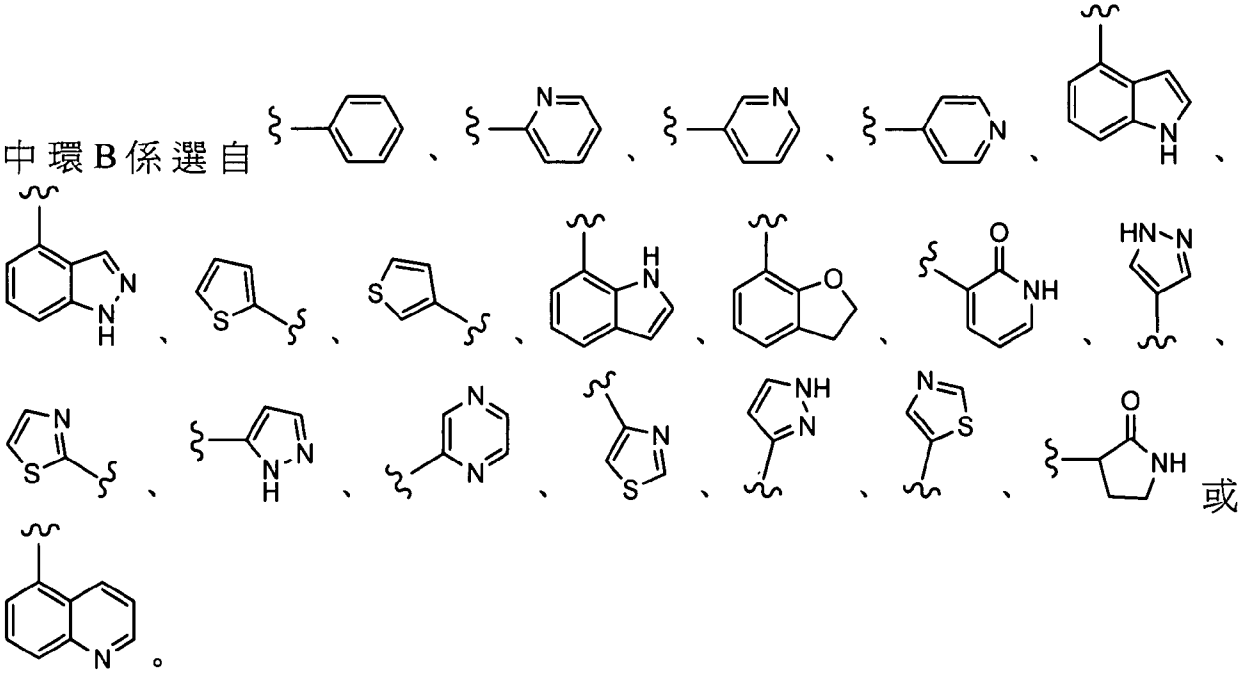
n爲0、1、2或3；

o爲0、1、2或3；

p爲0、1、2或3；且

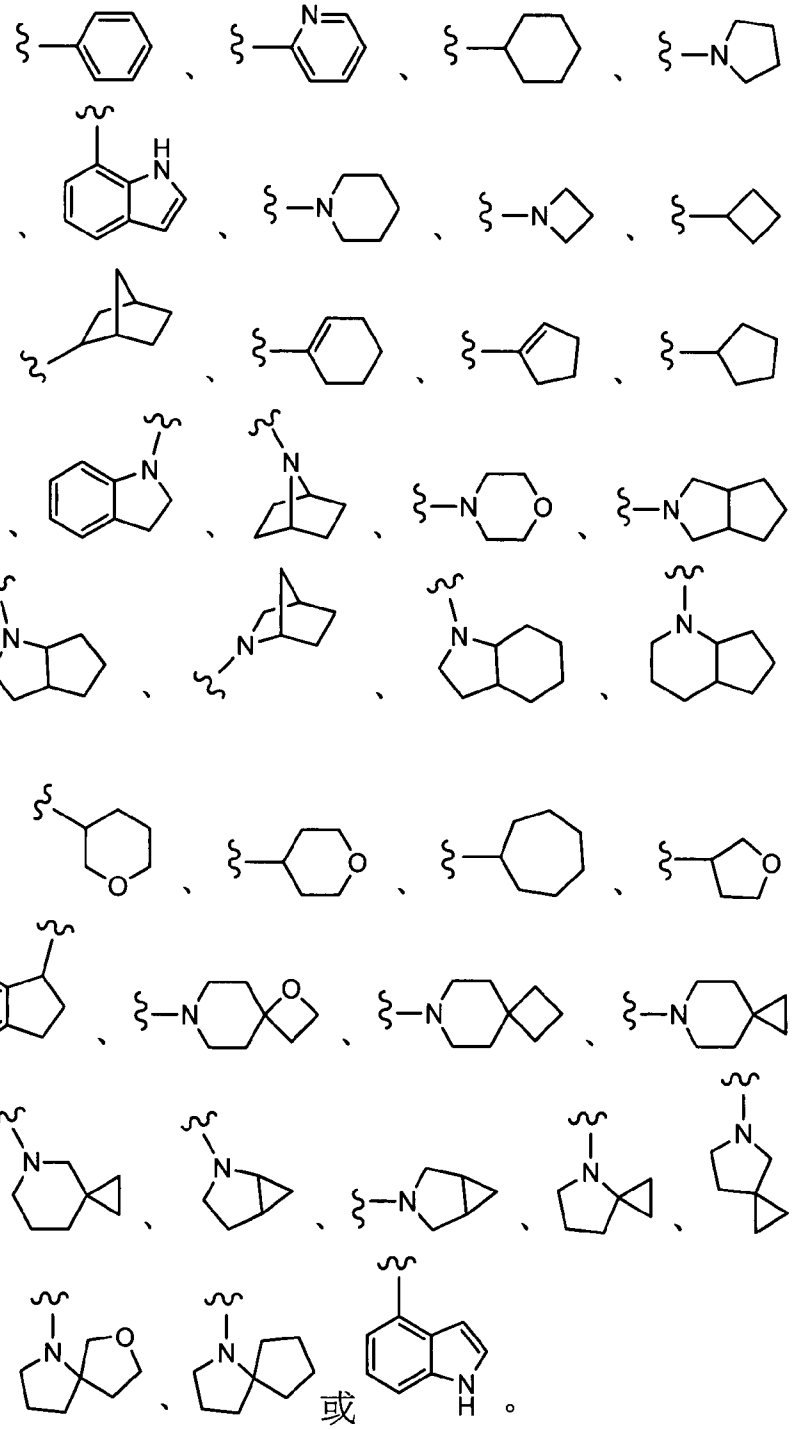
q爲0、1、2、3、4或5。

85. 在另一個實施例中，本發明提供實施例84之化合物，其中環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、噻吩、二氫苯并呋喃、吡嗪、吲唑、噻唑、吡啶-4(1H)-酮、吡咯啶酮或喹啉。

86. 在另一個實施例中，本發明提供實施例84或85之化合物，其中環B係選自  或。

87. 在另一個實施例中，本發明提供實施例84至86中任一項之化

合物，其中環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

88. 在另一個實施例中，本發明提供實施例84至87中任一項之化合物，其中環C爲  或  。

89. 在另一個實施例中，本發明提供實施例84至88中任一項之化合物，其中Y爲O。

90. 在另一個實施例中，本發明提供實施例84至88中任一項之化

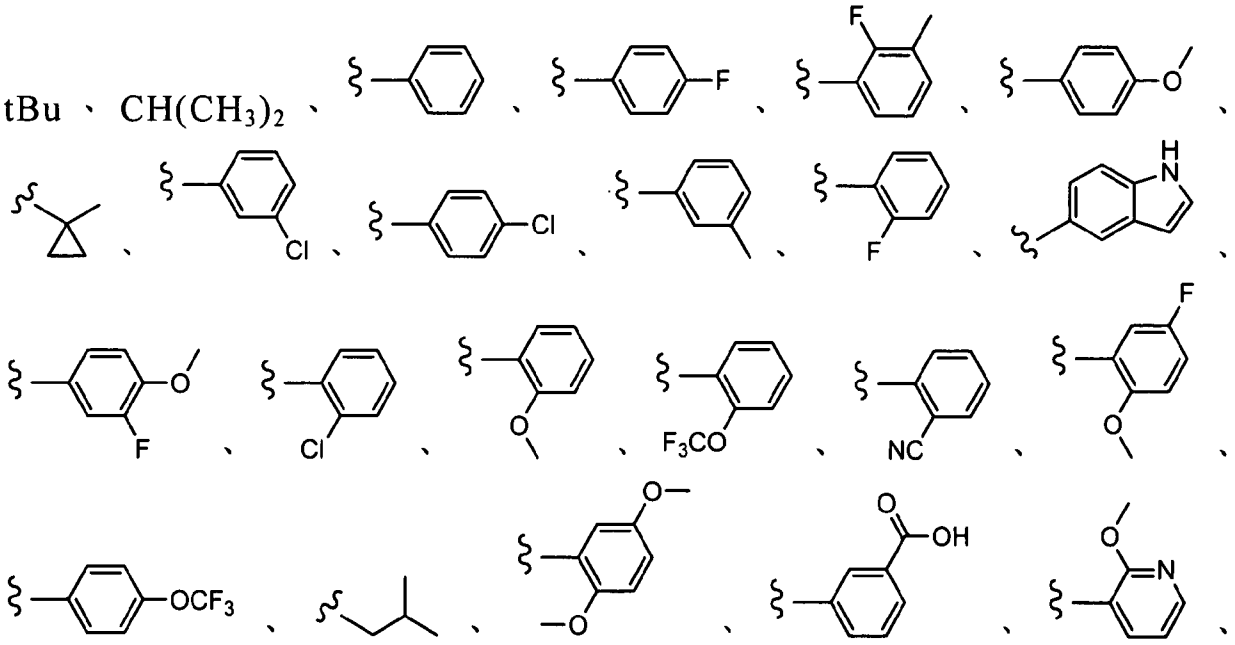
合物，其中Y爲$CH_2$。

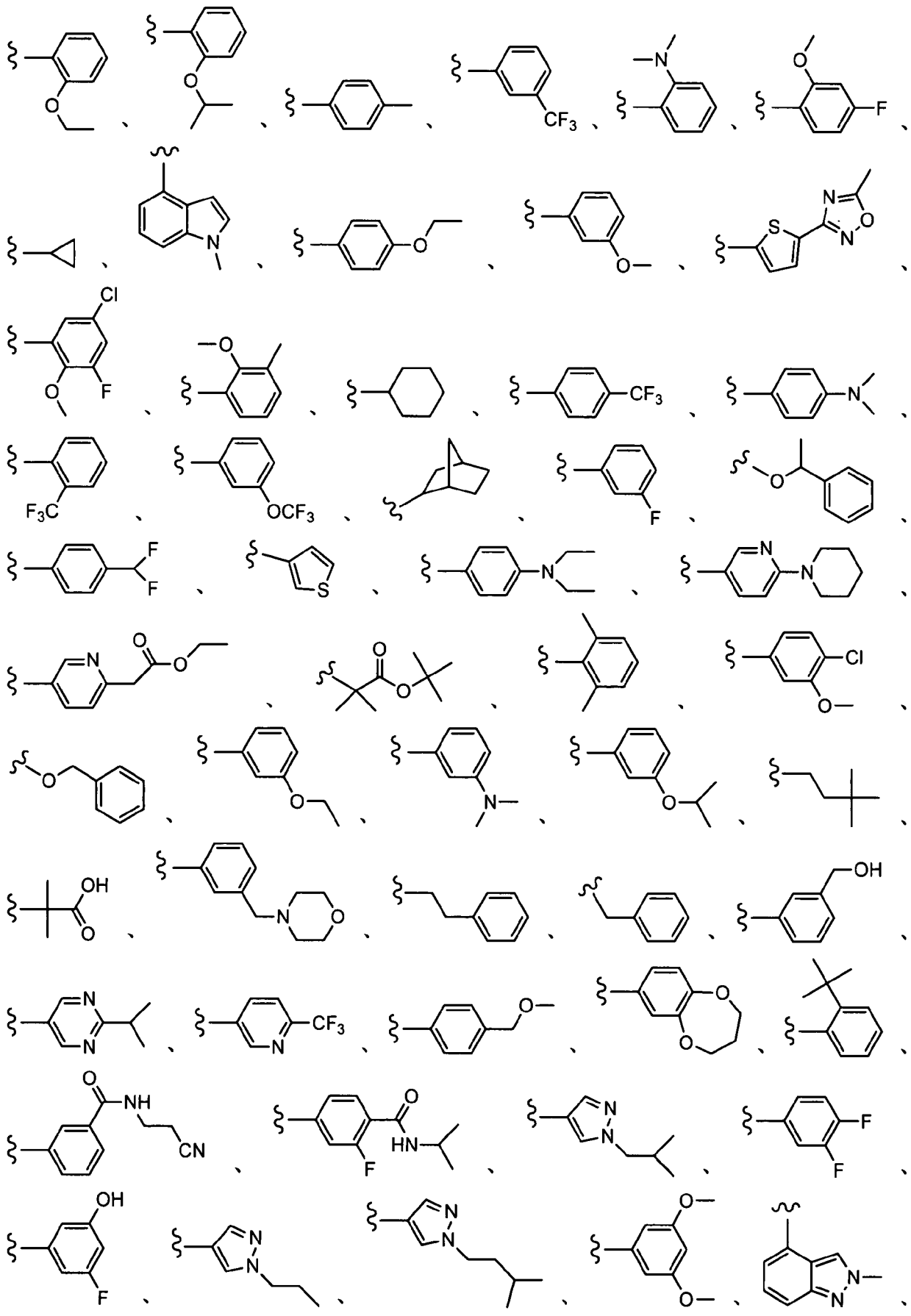
91. 在另一個實施例中，本發明提供實施例84至88中任一項之化合物，其中Y爲CH(C1-C6烷基)。

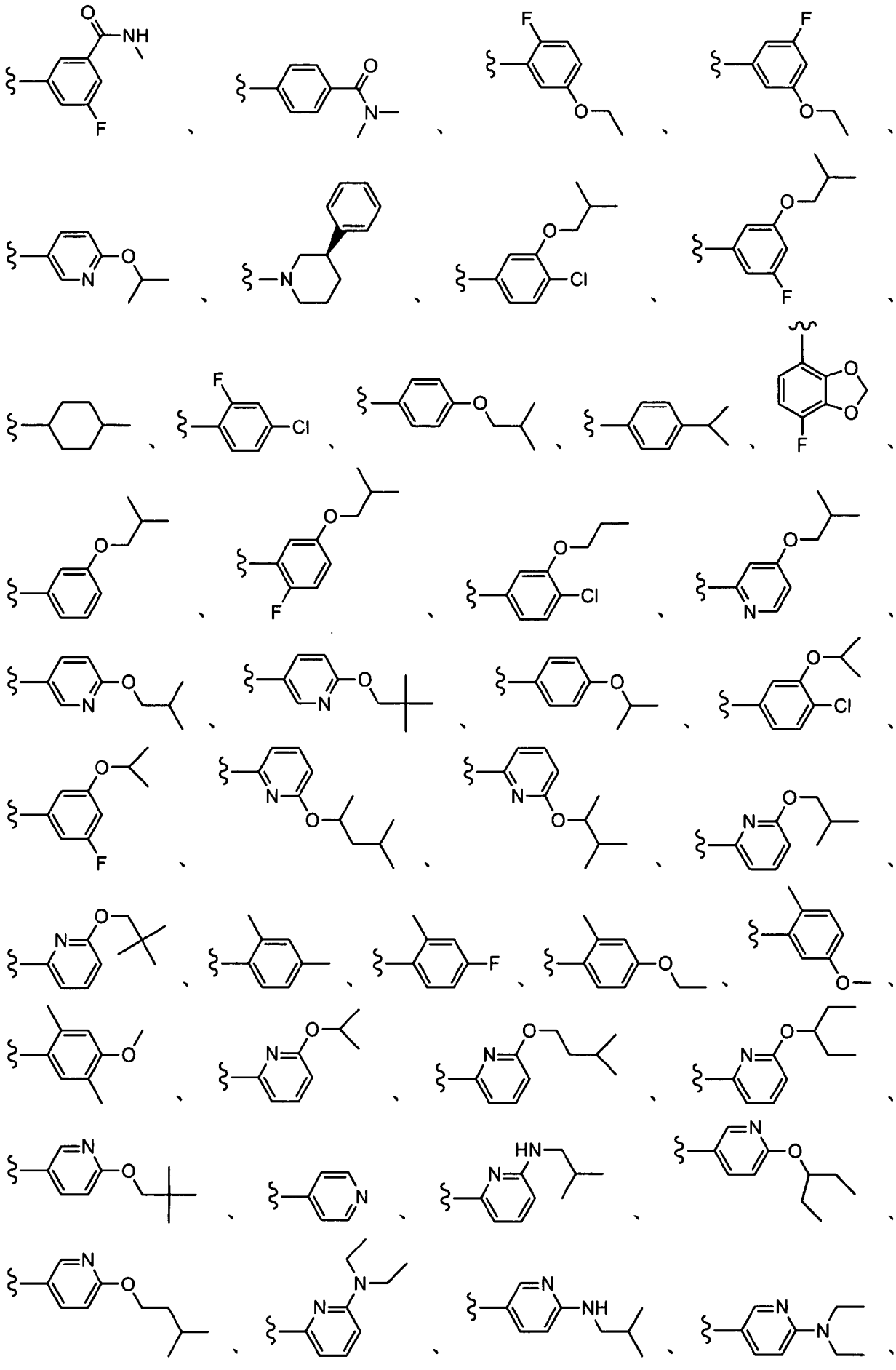
92. 在另一個實施例中，本發明提供實施例84至88中任一項之化合物，其中Y爲$CH(CH_3)$。

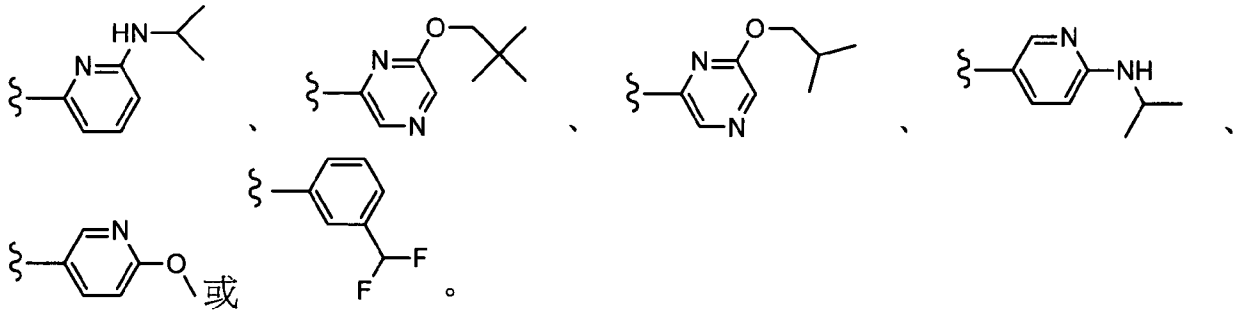
93. 在另一個實施例中，本發明提供實施例84至88中任一項之化合物，其中Y爲$CH(CH_2CH_3)$。

94. 在另一個實施例中，本發明提供實施例84至93中任一項之化合物，其中$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚或噻吩環，其中所有環可經以下基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C5-C10雜芳基、C5-C10雜環烷基或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

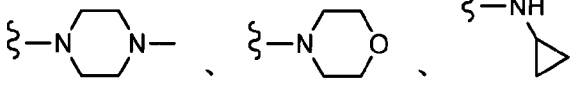
95. 在另一個實施例中，本發明提供實施例84至94中任一項之化合物，其中$R_1$係選自$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、 



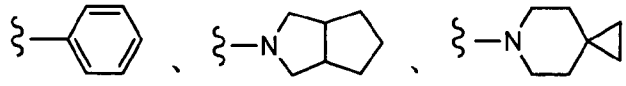


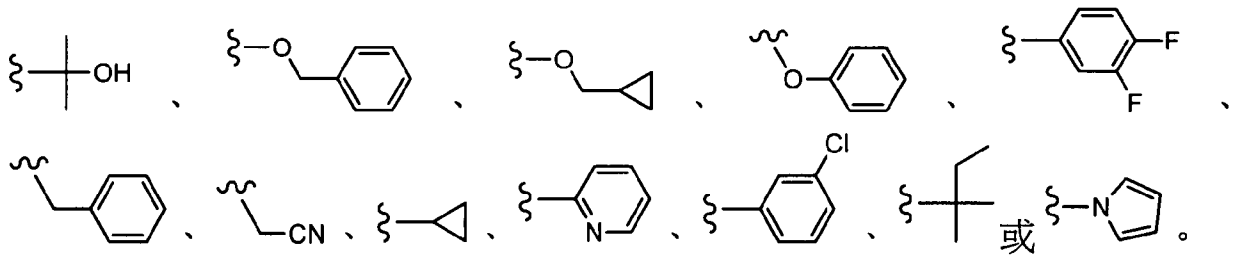


96. 在另一個實施例中，本發明提供實施例84至95中任一項之化合物，其中$R_2$係選自鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜環；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

97. 在另一個實施例中，本發明提供實施例84至96中任一項之化合物，其中$R_2$係選自Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCF_3$、$OCHF_2$、$OCH(CH_3)_2$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  或$CO_2H$。

98. 在另一個實施例中，本發明提供實施例84至97中任一項之化合物，其中$R_3$係選自鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基。

99. 在另一個實施例中，本發明提供實施例84至98中任一項之化合物，其中$R_3$係選自Cl、F、CN、$CH_3$、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CO_2CH_3$、tBu、$=CH_2$、=O、  、



100. 在另一個實施例中，本發明提供實施例84至99中任一項之化合物，其中o爲0。

101. 在另一個實施例中，本發明提供實施例84至99中任一項之化合物，其中o爲1。

102. 在另一個實施例中，本發明提供實施例84至99中任一項之化合物，其中o爲2。

103. 在另一個實施例中，本發明提供實施例84至102中任一項之化合物，其中n爲0。

104. 在另一個實施例中，本發明提供實施例84至102中任一項之化合物，其中n爲1。

105. 在另一個實施例中，本發明提供實施例84至102中任一項之化合物，其中n爲2。

106. 在另一個實施例中，本發明提供實施例84至105中任一項之化合物，其中p爲0。

107. 在另一個實施例中，本發明提供實施例84至105中任一項之化合物，其中p爲1。

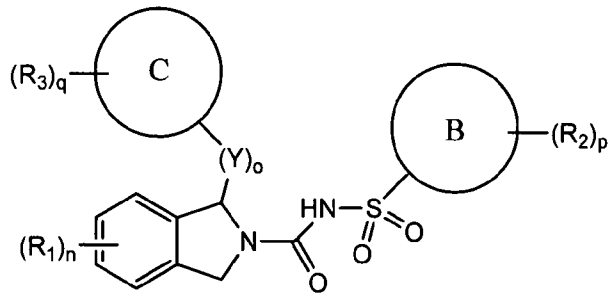
108. 在另一個實施例中，本發明提供實施例84至105中任一項之化合物，其中p爲2。

109. 在另一個實施例中，本發明提供實施例84至108中任一項之化合物，其中環B爲苯基。

110. 在另一個實施例中，本發明提供實施例84至109中任一項之化合物，其中環C爲苯基。

111. 在另一個實施例中，本發明提供實施例84至110中任一項之化合物，其中環B及環C爲苯基。

112. 在另一個實施例中，本發明提供實施例1之化合物，其中該化合物具有式Id：




**Id**

或其醫藥學上可接受之鹽，其中每次出現時獨立地：

環B爲C6-C10芳基環或其中至多4個碳原子可經O、S、N或NR置換的C5-C10雜芳基或雜環；

環C爲C6-C10單環或雙環芳基環、其中1至4個環原子中任一個獨立地爲N、O或S的C5-C10單環或雙環雜芳基或雜環、或C3-C10單環或雙環環烷基環；

Y爲$CR_2$、O、S、SO、$SO_2$或NR；

$R_1$爲鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環；或C3-C8環烷基，其中所有四者可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_1$連同其附接之原子一起形成C5-C8環或其中至多2個碳原子

可經O、S或NR置換的C5-C8雜環；

$R_2$爲鹵基、OH、胺基、疊氮化物、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基或雜環、C3-C8環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；

$R_3$爲鹵基、CN、$CO_2R$、C1-C6烷基、烯烴、炔烴或氟烷基；C1-C6烷氧基、環烷氧基或氟烷氧基；C6-C10單環或雙環芳基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基，其中兩者均可經以下基團取代：鹵基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、CN、$CO_2H$、胺基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；其中至多4個碳原子可經O、S或NR置換的C5-C10單環或雙環雜環烷基；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$；或兩個$R_3$可形成=$CH_2$或=O基團；

$R_4$爲H、$CF_3$、$CO_2R$、OH、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；$N(R)_2$、NRCOR、$CON(R)_2$、CN、鹵基或$SO_2R$；

R爲H、OH、C1-C6烷基、C6-C10單環或雙環芳基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基；C3-C8環烷基或其中至多4個碳原子可經O、S或NR置換的C3-C8雜環烷基；

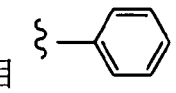
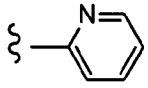
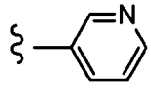
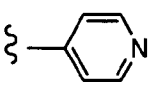
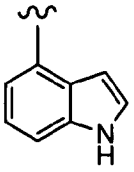
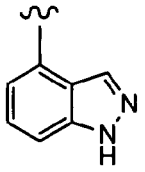
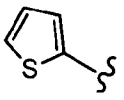
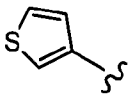
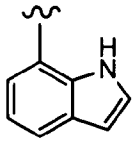
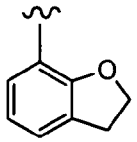
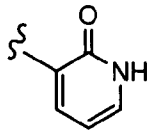
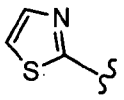
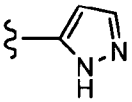
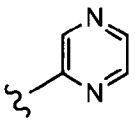
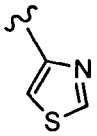
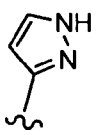
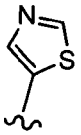
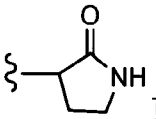
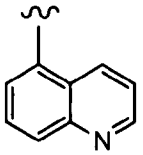
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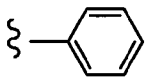
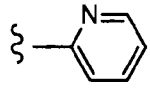
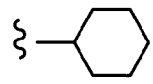
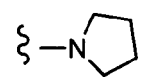
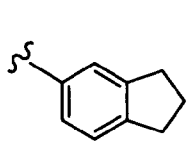
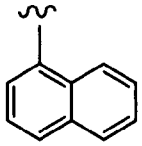
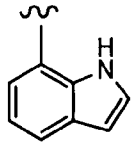
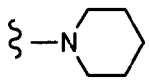
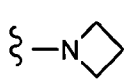
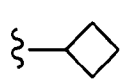
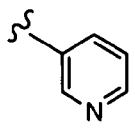
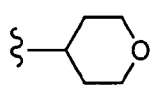
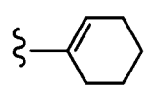
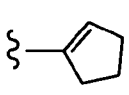
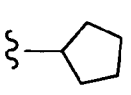
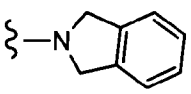
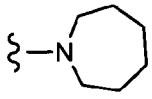
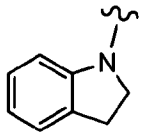
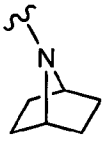
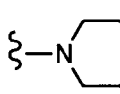
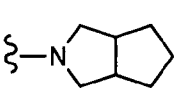
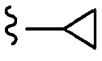
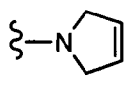
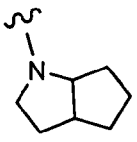
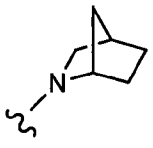
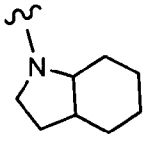
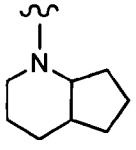
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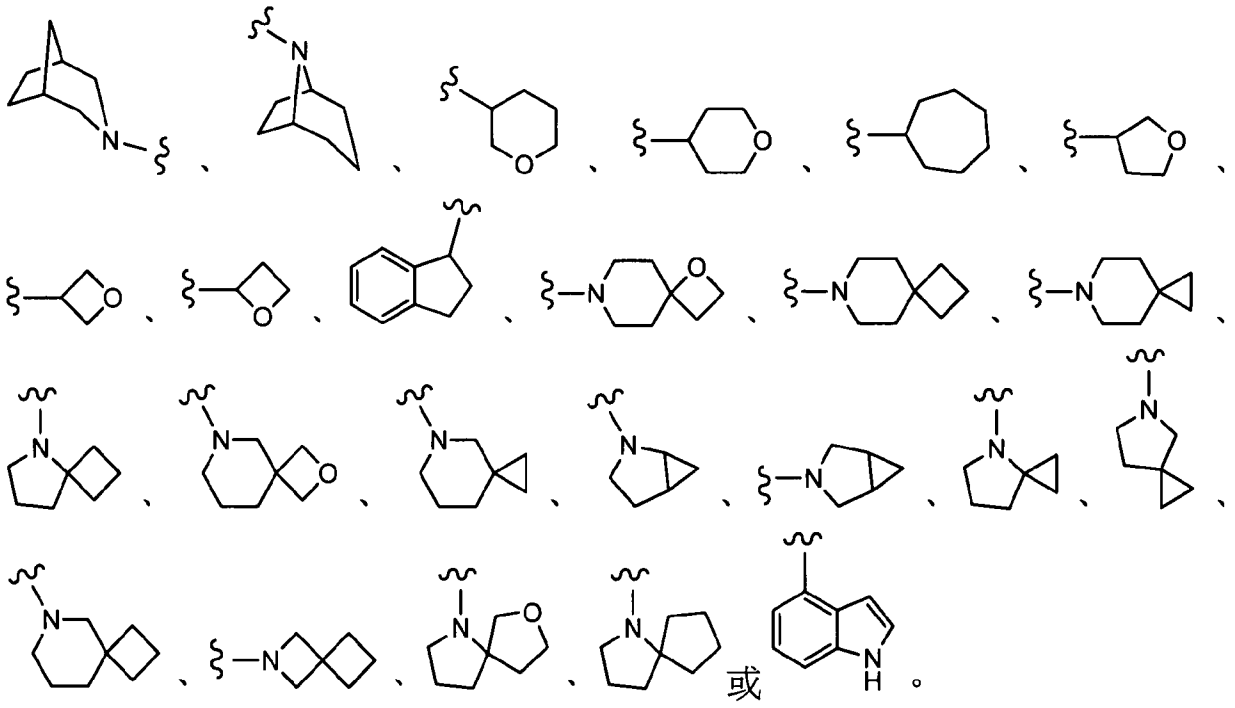
q爲0、1、2、3、4或5。

113. 在另一個實施例中，本發明提供實施例112之化合物，其中環B爲苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、噻吩、二氫苯并呋喃、吡嗪、吲唑、噻唑、吡啶-4(1H)-酮、吡咯啶酮或喹啉。

114. 在另一個實施例中，本發明提供實施例112或113之化合物，其中環B係選自  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或。

115. 在另一個實施例中，本發明提供實施例112至114中任一項之化合物，其中環C爲苯基、吲哚、環烷基、吡啶基、吡咯啶、萘或二氫茚。

116. 在另一個實施例中，本發明提供實施例112至115中任一項之化合物，其中環C爲  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、



117. 在另一個實施例中，本發明提供實施例112至116中任一項之化合物，其中Y爲O。

118. 在另一個實施例中，本發明提供實施例112至116中任一項之化合物，其中Y爲$CH_2$。

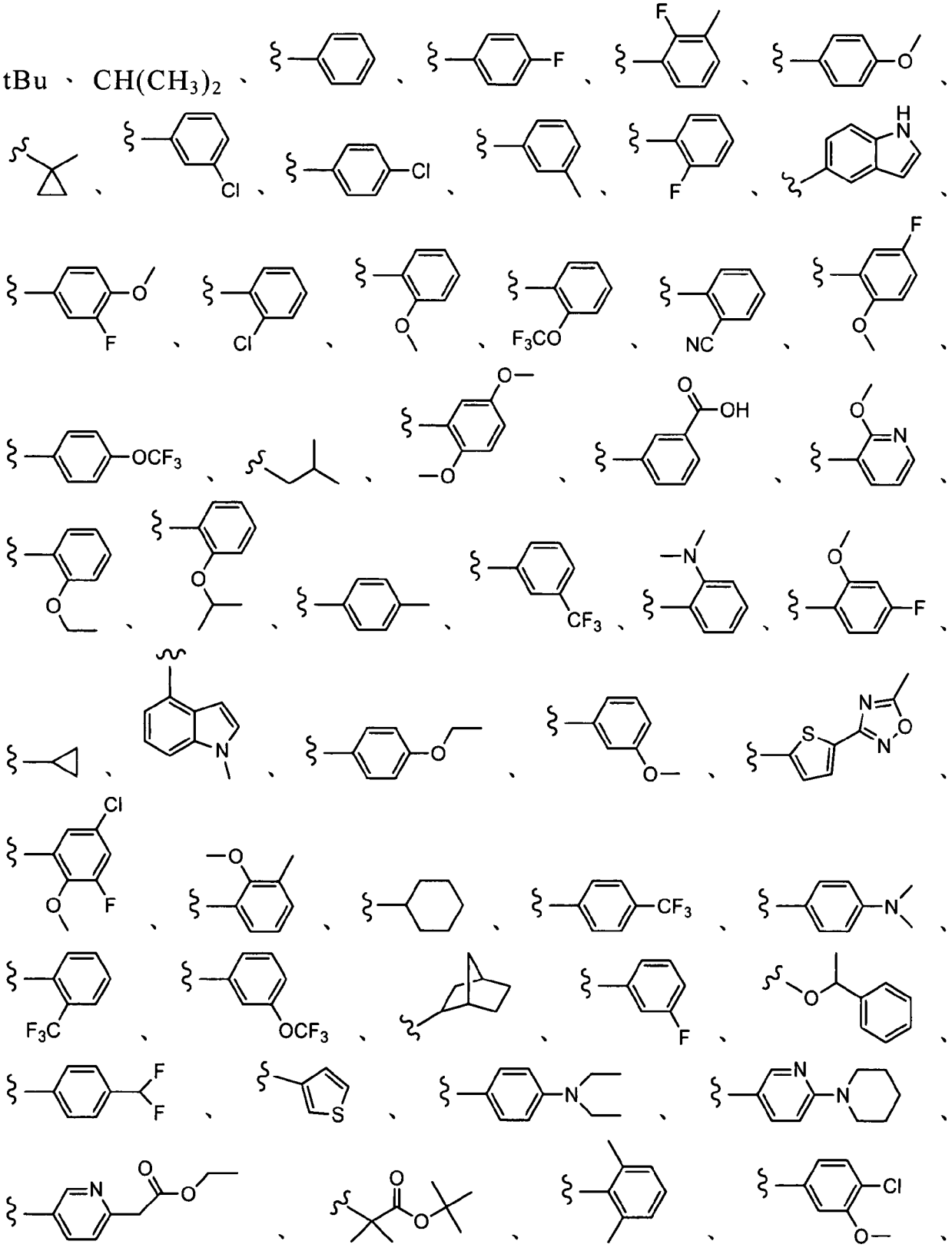
119. 在另一個實施例中，本發明提供實施例112至116中任一項之化合物，其中Y爲CH(C1-C6烷基)。

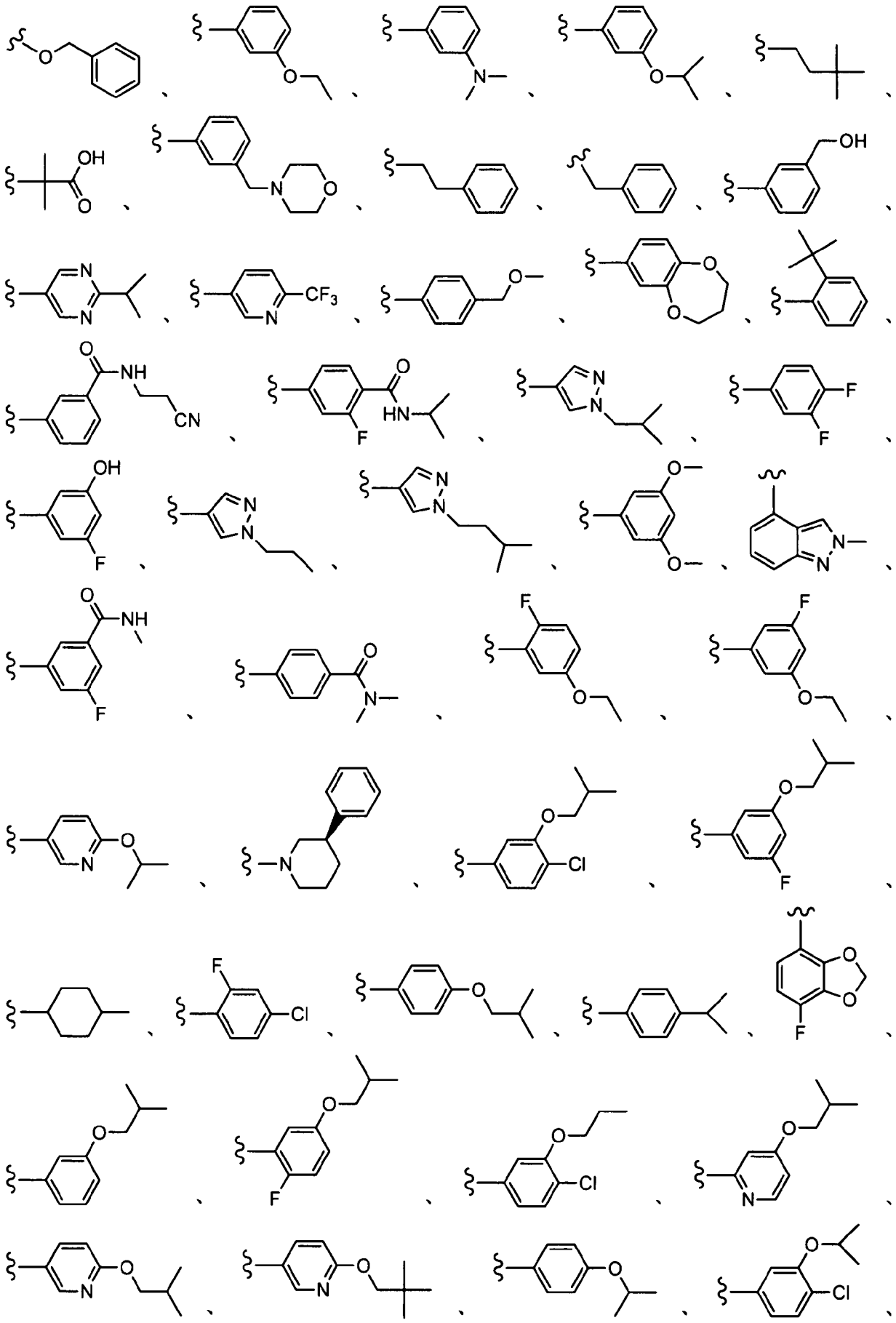
120. 在另一個實施例中，本發明提供實施例112至116中任一項之化合物，其中Y爲$CH(CH_3)$。

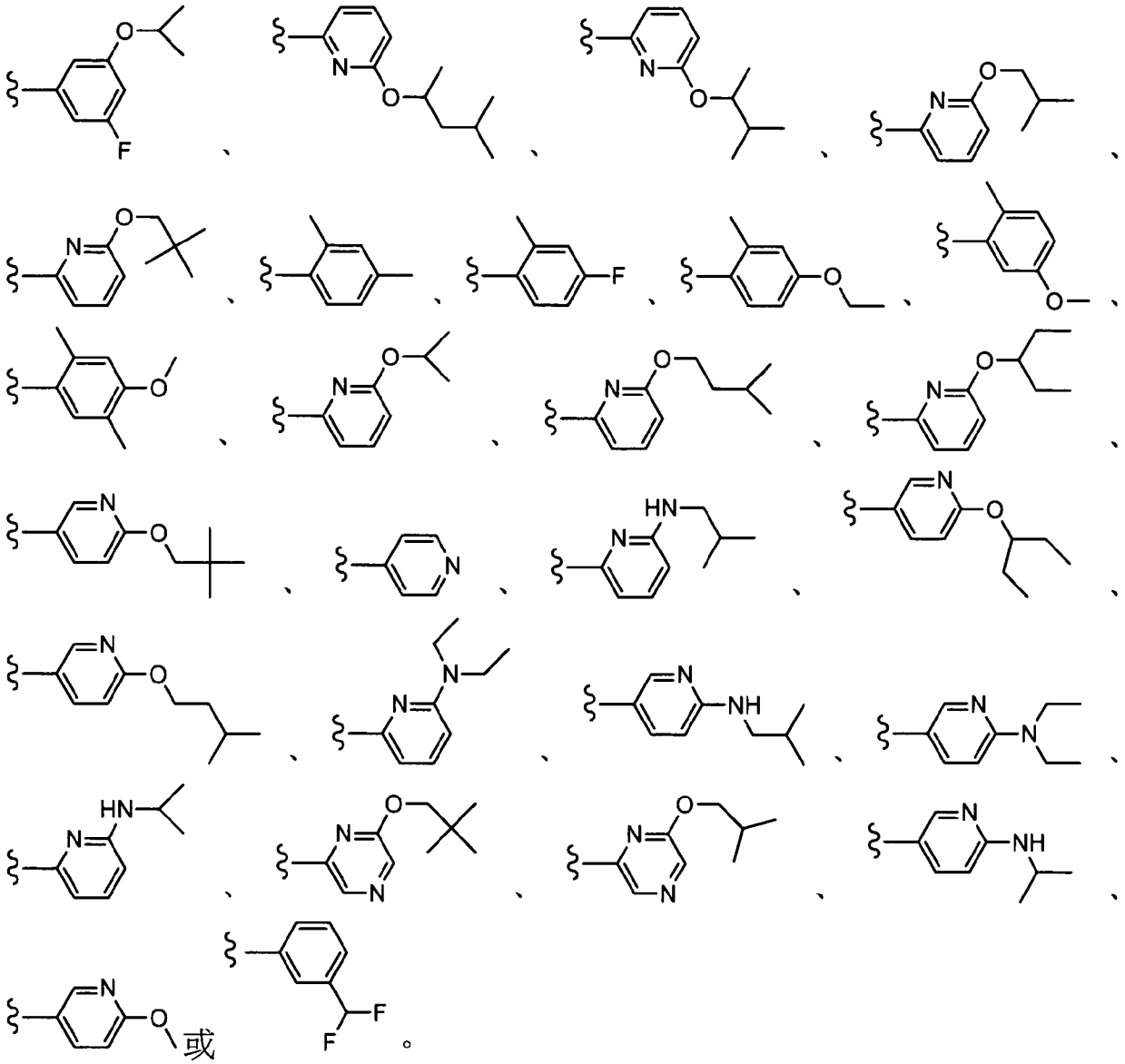
121. 在另一個實施例中，本發明提供實施例112至116中任一項之化合物，其中Y爲$CH(CH_2CH_3)$。

122. 在另一個實施例中，本發明提供實施例112至121中任一項之化合物，其中$R_1$爲鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚或噻吩環，其中所有環可經以下基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C5-C10雜芳基、C5-C10雜環烷基或其中至多三個$CH_2$單元可

經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

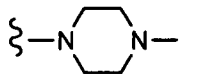
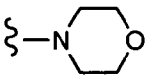
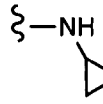
123. 在另一個實施例中，本發明提供實施例112至122中任一項之化合物，其中$R_1$係選自$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、 



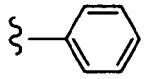
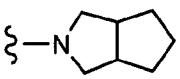
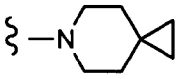
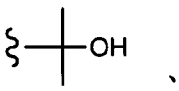
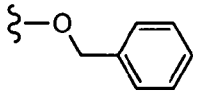
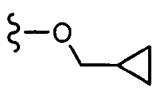
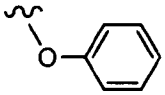
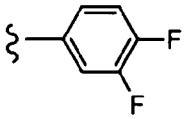
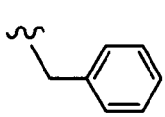
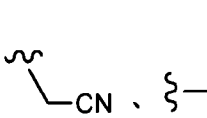
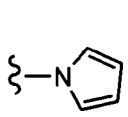


124. 在另一個實施例中，本發明提供實施例112至123中任一項之化合物，其中$R_2$係選自鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜環；或其中至多三個$CH_2$單元可經O、CO、S、SO、$SO_2$或NR置換的(C1-C8烷基)-$R_4$。

125. 在另一個實施例中，本發明提供實施例112至124中任一項之化合物，其中$R_2$係選自Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCF_3$、$OCHF_2$、$OCH(CH_3)_2$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、

$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、  、  、  或$CO_2H$。

126. 在另一個實施例中，本發明提供實施例112至125中任一項之化合物，其中$R_3$係選自鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基或其中至多4個碳原子可經O、S、N或NR置換的C5-C10單環或雙環雜芳基。

127. 在另一個實施例中，本發明提供實施例112至126中任一項之化合物，其中$R_3$係選自Cl、F、CN、$CH_3$、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、CCH、$CO_2CH_3$、tBu、$=CH_2$、=O、  、  、  、  、  、  、  、  、  、  、、或  。

128. 在另一個實施例中，本發明提供實施例112至127中任一項之化合物，其中o爲0。

129. 在另一個實施例中，本發明提供實施例112至127中任一項之化合物，其中o爲1。

130. 在另一個實施例中，本發明提供實施例112至127中任一項之化合物，其中o爲2。

131. 在另一個實施例中，本發明提供實施例112至130中任一項之化合物，其中n爲0。

132. 在另一個實施例中，本發明提供實施例112至130中任一項之化合物，其中n爲1。

133. 在另一個實施例中，本發明提供實施例112至130中任一項

之化合物，其中n爲2。

134. 在另一個實施例中，本發明提供實施例112至133中任一項之化合物，其中p爲0。

135. 在另一個實施例中，本發明提供實施例112至133中任一項之化合物，其中p爲1。

136. 在另一個實施例中，本發明提供實施例112至133中任一項之化合物，其中p爲2。

137. 在另一個實施例中，本發明提供實施例112至136中任一項之化合物，其中環B爲苯基。

138. 在另一個實施例中，本發明提供實施例112至137中任一項之化合物，其中環B爲吡啶基。

139. 在另一個實施例中，本發明提供實施例112至138中任一項之化合物，其中環C爲苯基。

140. 在另一個實施例中，本發明提供實施例112至139中任一項之化合物，其中環B及環C爲苯基。

141. 在另一個實施例中，本發明提供實施例112至140中任一項之化合物，其中環B爲吡啶基且環C爲苯基。

142. 在另一個實施例中，本發明提供實施例1之化合物，其中該化合物係選自表1。

143. 在另一個實施例中，本發明提供一種醫藥組合物，其包含實施例1至142中任一項之化合物及醫藥學上可接受之載劑。

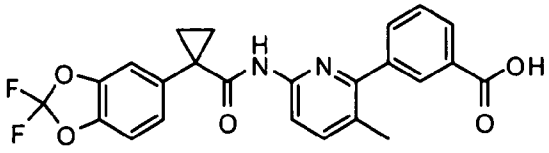
144. 在另一個實施例中，本發明提供實施例143之醫藥組合物，其進一步包含一或多種其他治療劑。

145. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑係選自黏液溶解劑、支氣管擴張藥、抗生素、抗感染劑、CFTR調節劑或消炎劑。

146. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲CFTR調節劑。

147. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲CFTR校正劑。

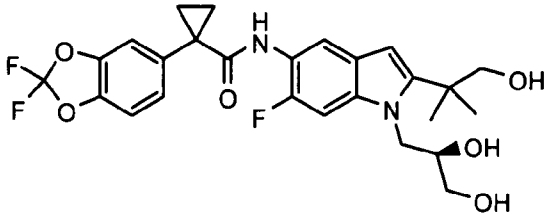
148. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲



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或其醫藥學上可接受之鹽。

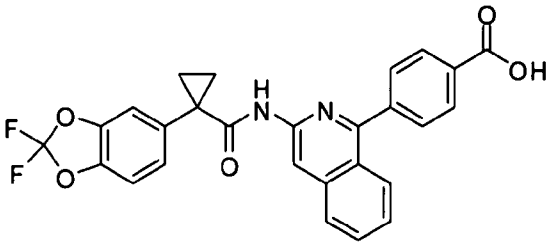
149. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲



，

或其醫藥學上可接受之鹽。

150. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲

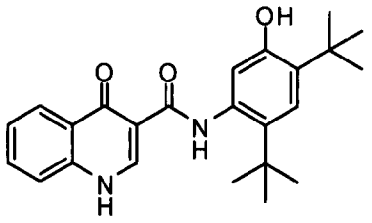


，

或其醫藥學上可接受之鹽。

151. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲CFTR增效劑。

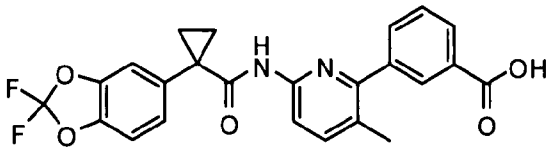
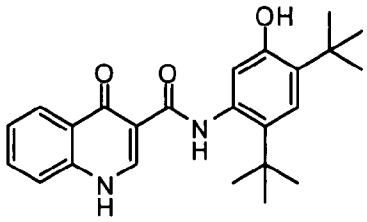
152. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該其他治療劑爲

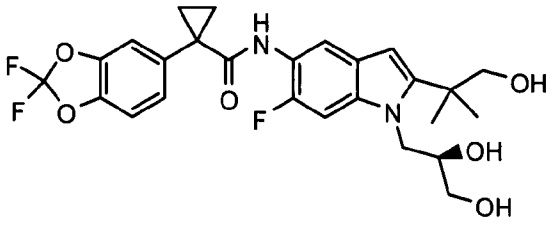
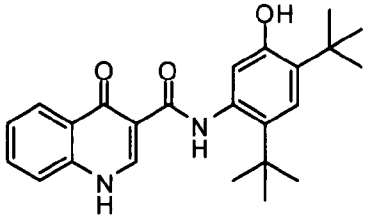


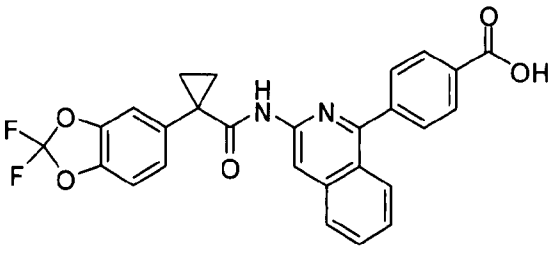
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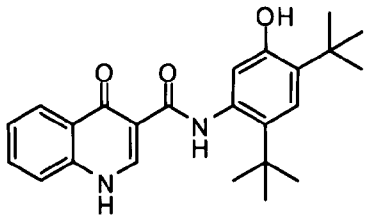
或其醫藥學上可接受之鹽。

153. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該等其他治療劑爲CFTR校正劑及CFTR增效劑。

154. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該等其他治療劑爲  及  ，或其醫藥學上可接受之鹽。

155. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該等其他治療劑爲  及  ，或其醫藥學上可接受之鹽。

156. 在另一個實施例中，本發明提供實施例144之醫藥組合物，其中該等其他治療劑爲  及



，或其醫藥學上可接受之鹽。

157. 在另一個實施例中，本發明提供一種治療患者之囊腫纖維化症的方法，其包含向該患者投與有效量之實施例1至142中任一項之化合物或實施例143至156中任一項之醫藥組合物。

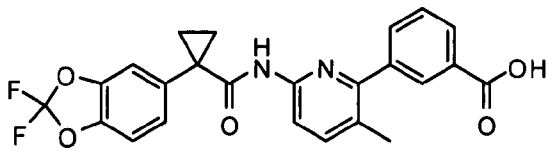
158. 在另一個實施例中，本發明提供實施例157之方法，其進一步包含在實施例1至137中任一項之化合物或實施例138至151中任一項之醫藥組合物之前、與其同時或在其之後向該患者投與一或多種其他治療劑。

159. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑係選自黏液溶解劑、支氣管擴張藥、抗生素、抗感染劑、CFTR調節劑或消炎劑。

160. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲CFTR調節劑。

161. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲CFTR校正劑。

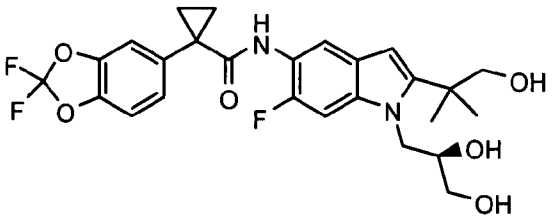
162. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲



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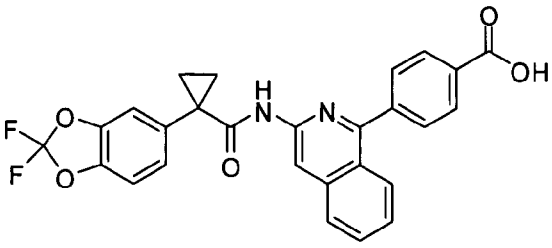
或其醫藥學上可接受之鹽。

163. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲



或其醫藥學上可接受之鹽。

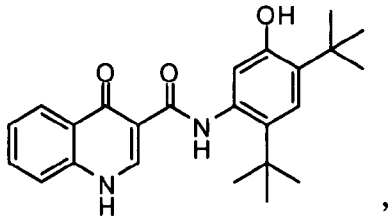
164. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲



或其醫藥學上可接受之鹽。

165. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲CFTR增效劑。

166. 在另一個實施例中，本發明提供實施例158之方法，其中該其他治療劑爲



或其醫藥學上可接受之鹽。

167. 在另一個實施例中，本發明提供實施例157至166中任一項之方法，其中該患者在F508del CFTR突變中同種接合。

168. 在另一個實施例中，本發明提供實施例157至166中任一項之方法，其中該患者在F508del CFTR突變中異種接合。

169. 在另一個實施例中，本發明提供一種套組，其包含實施例1至142中任一項之化合物或實施例143至156中任一項之醫藥組合物及其使用說明書。

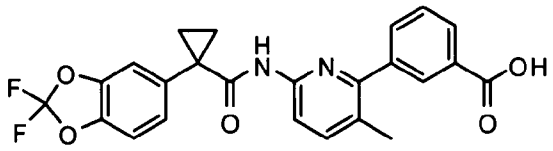
170. 在另一個實施例中，本發明提供實施例169之套組，其進一步包含一或多種其他治療劑。

171. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑係選自黏液溶解劑、支氣管擴張藥、抗生素、抗感染劑、CFTR調節劑或消炎劑。

172. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲CFTR調節劑。

173. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲CFTR校正劑。

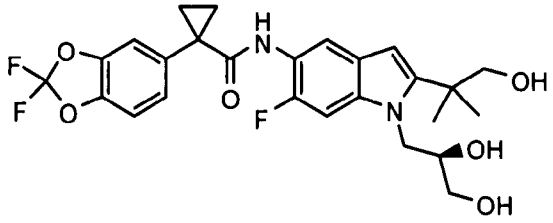
174. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲



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或其醫藥學上可接受之鹽。

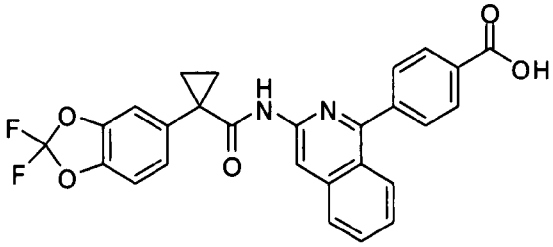
175. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲



，

或其醫藥學上可接受之鹽。

176. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲

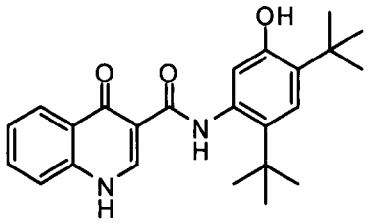


，

或其醫藥學上可接受之鹽。

177. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲CFTR增效劑。

178. 在另一個實施例中，本發明提供實施例170之套組，其中該其他治療劑爲

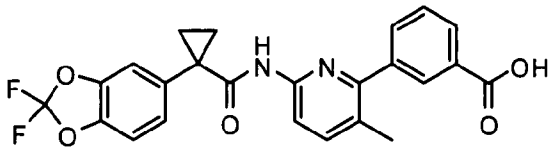


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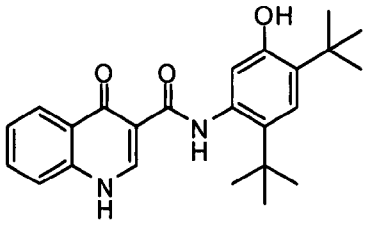
或其醫藥學上可接受之鹽。

179. 在另一個實施例中，本發明提供實施例170之套組，其中該等其他治療劑爲CFTR校正劑及CFTR增效劑。

180. 在另一個實施例中，本發明提供實施例170之套組，其中該等其他治療劑爲

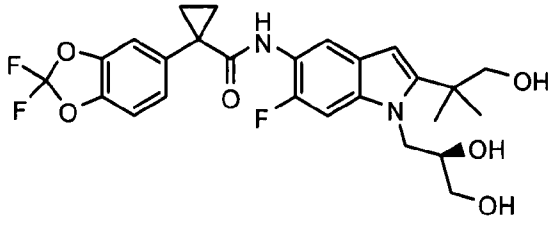


及

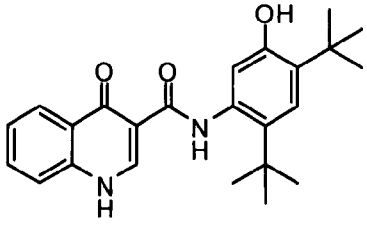


，或其醫藥學上可接受之鹽。

181. 在另一個實施例中，本發明提供實施例170之套組，其中該等其他治療劑爲

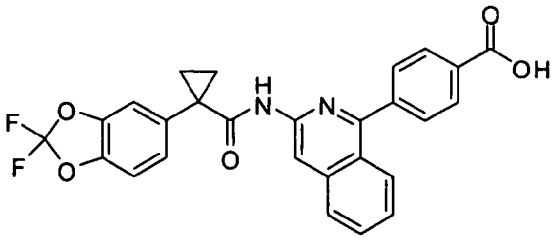


及

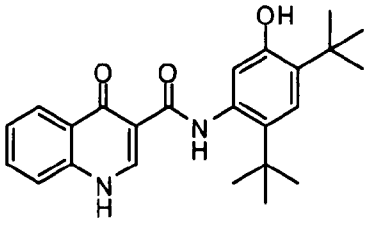


，或其醫藥學上可接受之鹽。

182. 在另一個實施例中，本發明提供實施例170之套組，其中該



等其他治療劑爲



及

，或其醫藥學上可接受之鹽。

183. 在另一個實施例中，本發明提供實施例169至182中任一項之套組，其中實施例1至142中任一項之化合物或實施例143至156中任一項之醫藥組合物及該一或多種其他治療劑在分開容器中。

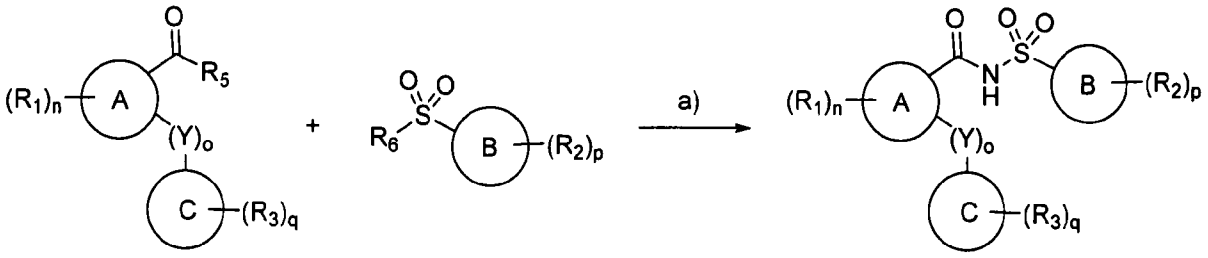
184. 在另一個實施例中，本發明提供實施例169至182中任一項之套組，其中實施例1至142中任一項之化合物或實施例143至156中任一項之醫藥組合物及該一或多種其他治療劑在同一容器中。

185. 在另一個實施例中，本發明提供實施例183或184之套組，其中該容器爲瓶、小瓶或泡殼包裝或其組合。

**製備式I化合物之方法**

本發明之化合物可藉由已知方法且如流程I-XX1所繪示來製備，除非下文針對各個別流程所提及，否則環A、B、C及R、$R_1$、$R_2$、$R_3$、$R_4$、X、Y、Z及n、o、p、q如在本說明書中所定義。

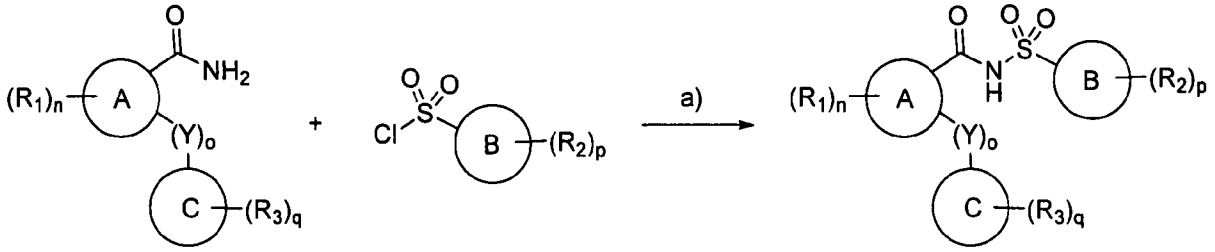
**流程I**



a) $R_5$ = OH，$R_6$ = $NH_2$：HATU、$Et_3N$或$(i\text{-}Pr)_2NEt$或$K_2CO_3$或$Na_2CO_3$、DMF或$CH_2Cl_2$或NMP；$R_5$ = OH、$R_6$ = $NH_2$：$SOCl_2$、

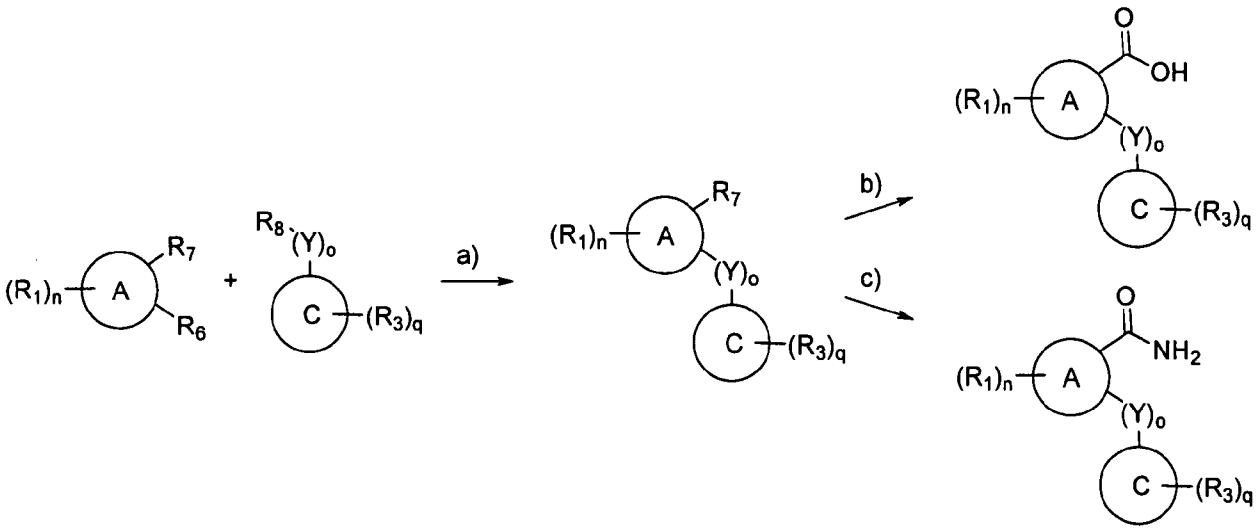
$CH_2Cl_2$及DMF (催化量)，接著 $Et_3N$、$CH_2Cl_2$；$R_5$ = $NH_2$，$R_6$ = Cl：NaH或$Cs_2CO_3$、DMF或THF；或吡啶、$CH_2Cl_2$。

**流程II**



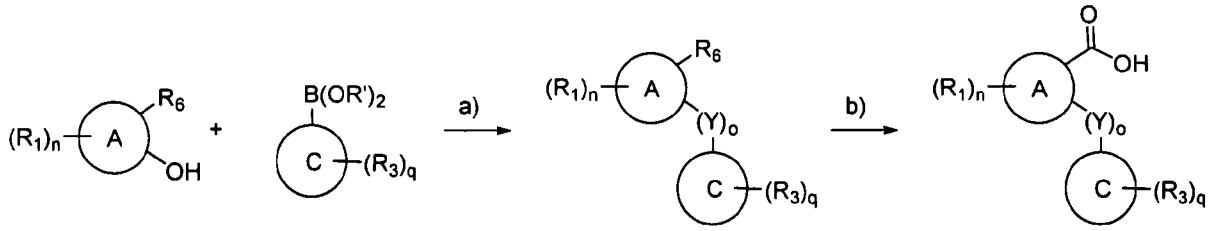
a) NaH或$Cs_2CO_3$、DMF或THF；或吡啶、$CH_2Cl_2$。

**流程III**



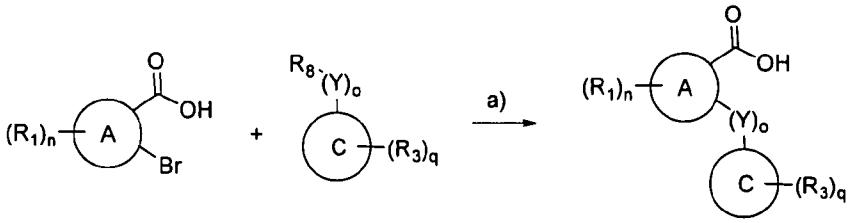
a) $R_7$ = CN或$CO_2R'$，$R_6$ = 鹵素(Cl或Br)，Y = 鍵，$R_8$ = 硼酸或硼酸酯：$Pd(dppf)Cl_2*CH_2Cl_2$、$NaHCO_3$或$Na_2CO_3$、水、DMA或DME；Y = O或N(R')，$R_8$ = H：NaH或$Cs_2CO_3$或KHMDS；DMF或DMSO或二噁烷或DMF/THF；Y = O，$R_8$ = H：$Cu(OTf)_2$、$Cs_2CO_3$、甲苯；Y = C(R')(R")，$R_8$ = ZnBr：$Pd(dppf)Cl_2*CH_2Cl_2$或$Pd(PPh_3)_4$或$Pd(OAc)_2$及$tBu_3P*HBF_4$、THF；Y = C(R')(R")，$R_8$ = Cl或Br：$K_2CO_3$或KOH、DMF或*i*-PrOH。b) KOH或NaOH或LiOH、水、*i*-PrOH或EtOH或MeOH；或含HCl之AcOH。c) $H_2O_2$、NaOH、EtOH；或KOH、EtOH。

**流程IV**



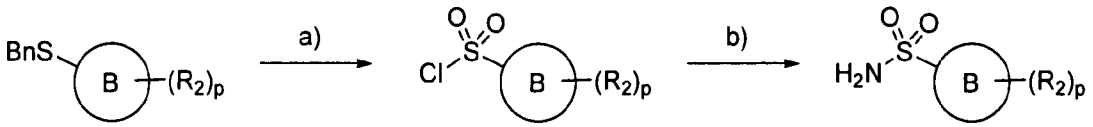
a) $R_6$ = Br、CN或$CO_2R''$：$Cu(OAc)_2$、吡啶、DCE；b) $R_6$ = Br或不存在：*n*-BuLi、THF、$CO_2$。

**流程V**



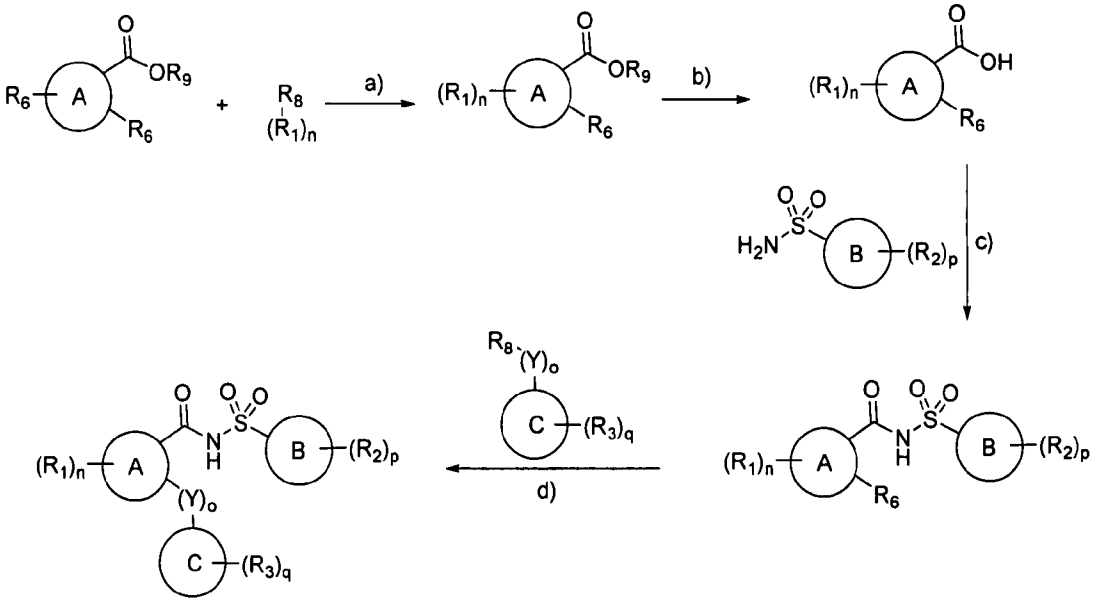
a) $Cu(OTf)_2$、$Cs_2CO_3$、甲苯。Y = O、$R_8$= H。

**流程VI**



a) $Cl_2$、水、$CHCl_3$；b) $NH_3$或$NH_4OH$、MeOH或$CH_2Cl_2$或二噁烷。

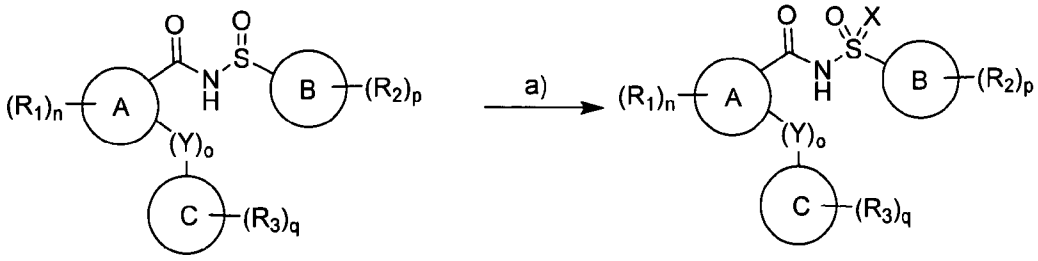
**流程VII**



a) $R_6$= 鹵素(Cl)，$R_8$ = $B(OR'')_2$，$R_9$ = 保護基(第三丁基)或當$R_8$

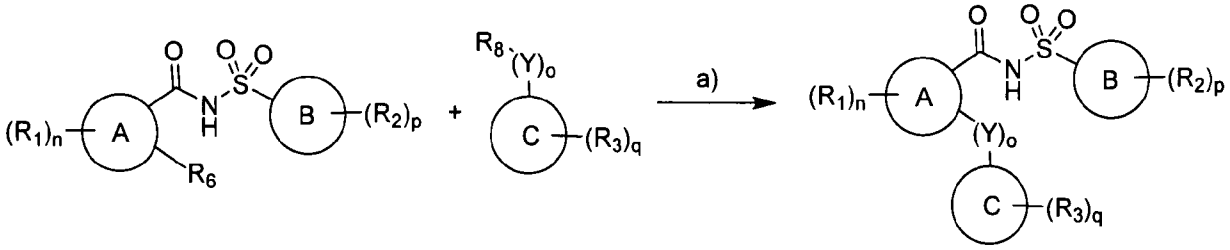
不存在時$R_1$= 含有N之部分：EtOH、甲苯、水、$Na_2CO_3$、$Pd(PPh_3)_4$或NaH及DMF；b) TFA、$CH_2Cl_2$；c) CDI、NaH、DMF；d) C=含有N之部分，Y及$R_8$不存在或$R_8$ = NHR、$NH_2$或NRR：$K_2CO_3$、DMSO或CsF、$K_2CO_3$、DMSO。

**流程VIII**



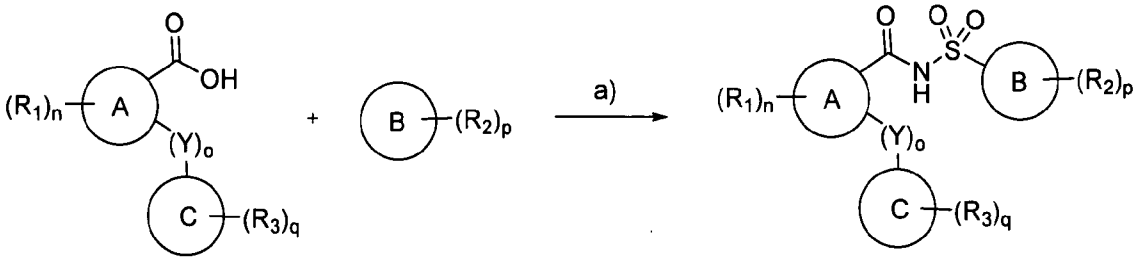

a) X= NH：$(CH_3)_3COK$、$CH_3CN$、HMDS、*N*-氯琥珀醯亞胺；X = $NCH_3$或NR：$CH_3NH_2$或$RNH_2$、$CH_3CN$、*N*-氯琥珀醯亞胺。

**流程IX**



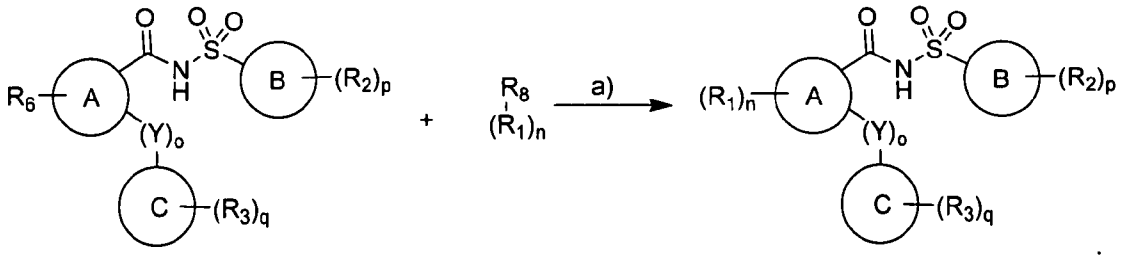

a) $R_6$= 鹵素(Cl)，Y = 鍵，$R_8$= $B(OR'')_2$：$Pd(PPh_3)_4$或$Pd(dppf)Cl_2*CH_2Cl_2$、$Na_2CO_3$、DMF、水或二噁烷或DMA。

**流程X**



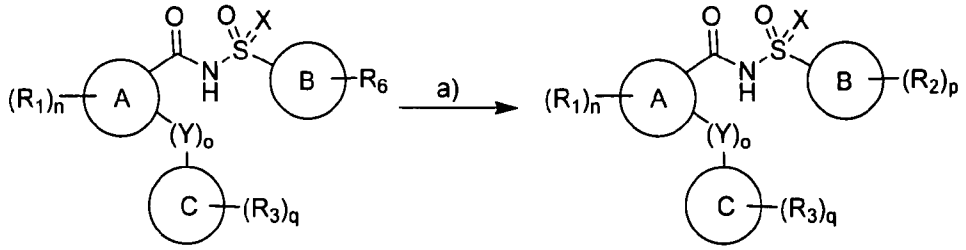

a) CSI、$CH_2Cl_2$、45分鐘，接著$Et_3N$、B=含有N之部分。

**流程XI**



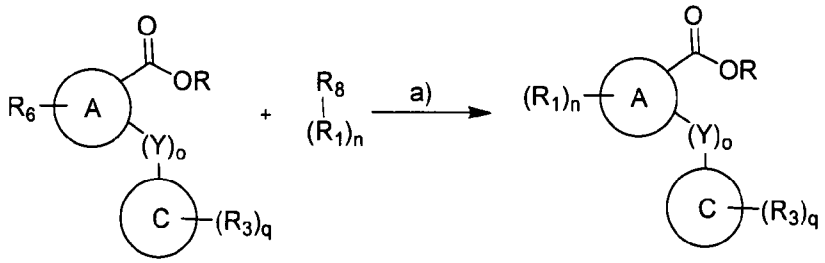
a) $R_6$ = 鹵素(Cl)，Y = 鍵或Y = O，$R_8$ = $B(OR'')_2$：$Pd(PPh_3)_4$、$Na_2CO_3$、$K_2CO_3$或$K_3PO_4$、DMF；$R_6$ = 鹵素(Cl)，Y = 鍵，$R_8$ = H：CsF、DMSO，接著$R_1$= 含有N之部分；$R_6$ = $B(OR'')_2$，Y = C(R')(R'')，$R_8$ = 鹵素(Br)：$Pd(dppf)Cl_2*CH_2Cl_2$、$K_2CO_3$、DMF；$R_6$ = 鹵素(Cl)，$R_8$ = H或$R_8$不存在，$R_1$= 含有N之部分：反-二胺基環己烷、DMF、CuI；$R_6$= 鹵素(Cl)，Y = 鍵，$R_8$ = $B(OR'')_2$，$R_1$= 含有視情況經取代之C3-C8環烷基之部分：PEPPSI™-IPr催化劑、$K_2CO_3$、二噁烷。

**流程XII**



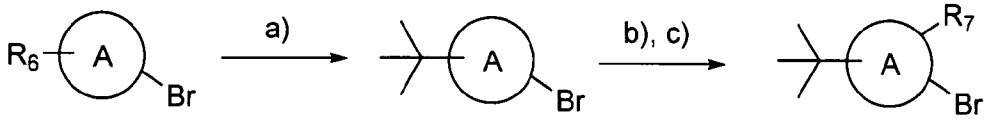
a) $R_6$ = 鹵素(F、Cl)，Y = 鍵或Y = O，$R_2$ = $NH_2$，p = 1，X= O：$NH_4OH$；$R_6$ = $NO_2$，Y = O，$R_2$ = $NH_2$，p = 1，X = O：$CH_3COOH$、Zn；$R_6$ = OMe，Y = C(R')(R'')，且$R_2$爲=O，p = 1，X = O：$CH_3COOH$或二噁烷、HBr或HCl；$R_6$ = $NO_2$，$R_2$ = $NH_2$，p = 1，X = NH：MeOH、Pd/C；$R_6$ = 醛，X = O，Y = C(R')(R'')，$R_2$= 羥基烷基：$NaBH_4$、MeOH。

**流程XIII**



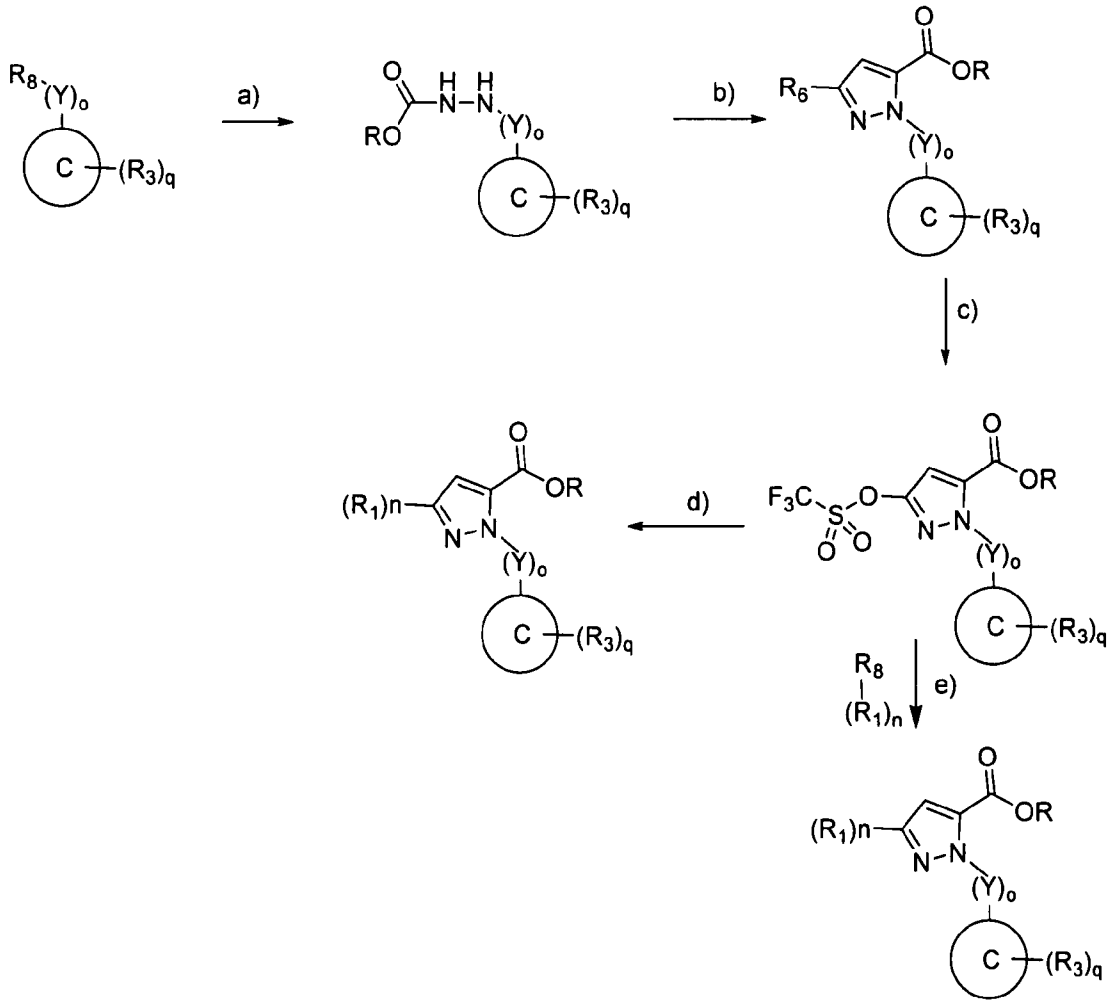
a) R =烷基或H，$R_6$ = 鹵素(Cl)，$R_8$ = $NH_2$或OH，Y = O：DMA或NaH及DMF；R =烷基，$R_6$= 鹵素(Cl)，$R_8$= 炔烴：DMF、$Et_3N$、$PdCl_2(PPh_3)_2$、CuI、$PPh_3$；R =烷基，$R_6$= 鹵素(Cl)，Y = O，$R_8$ = ZnBr：$Pd(dppf)Cl_2*CH_2Cl_2$，接著EDTA二鈉鹽飽和水溶液及$NH_4Cl$飽和水溶液。

**流程XIV**



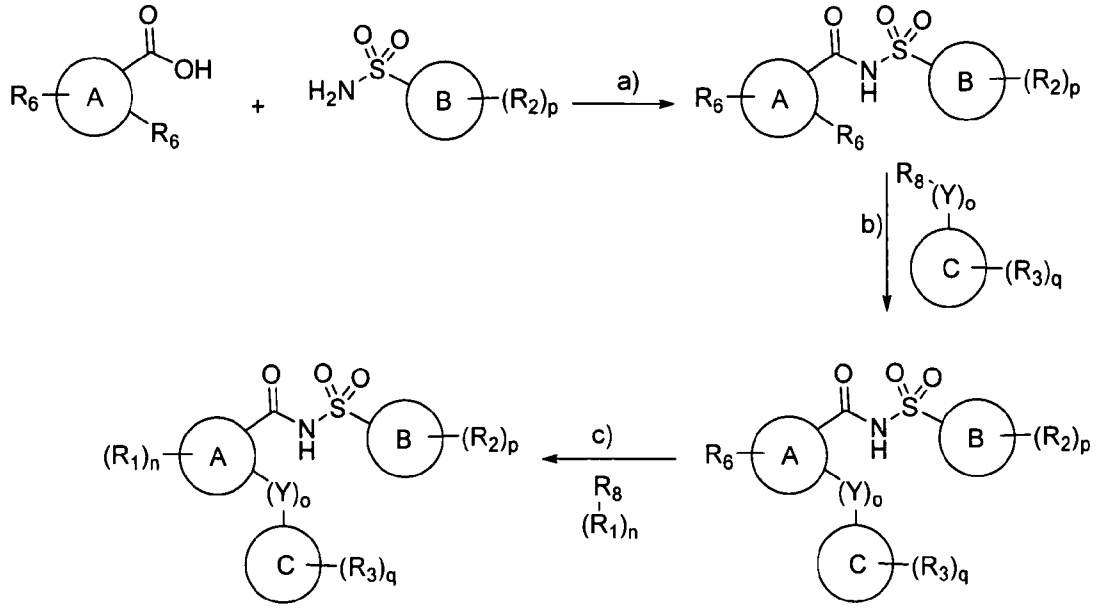
a) $R_6$ = 鹵素(I)：$(CH_3)_3CMgCl$、CuCN、THF；b) 3-氯過氧苯甲酸、$CH_2Cl_2$；c) $R_7$ = CN：TMSCN、$Et_3N$、$CH_3CN$。

**流程XV**



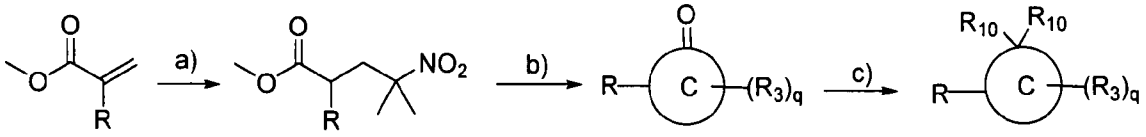
a) $R_8$ = Cl，Y = C(R')(R")，o = 1，R =烷基(例如甲基)：*N*-胺基胺基甲酸甲酯、$K_2CO_3$、DMF；b) $R_6$ = OH：丁-2-炔二酸二甲酯、MeOH，接著NaOMe；c)吡啶、甲苯、三氟甲磺酸；d) $R_1$= 硼酸酯：雙(頻哪醇根基)二硼、KOAc、二噁烷、$Pd(dppf)Cl_2*CH_2Cl_2$、DPPF；e) Y = C(R')(R")，o = 1，R =烷基(例如甲基)：$R_8$ = 硼酸、$K_2CO_3$、二噁烷、$Pd(dppf)Cl_2*CH_2Cl_2$。

**流程XVI**



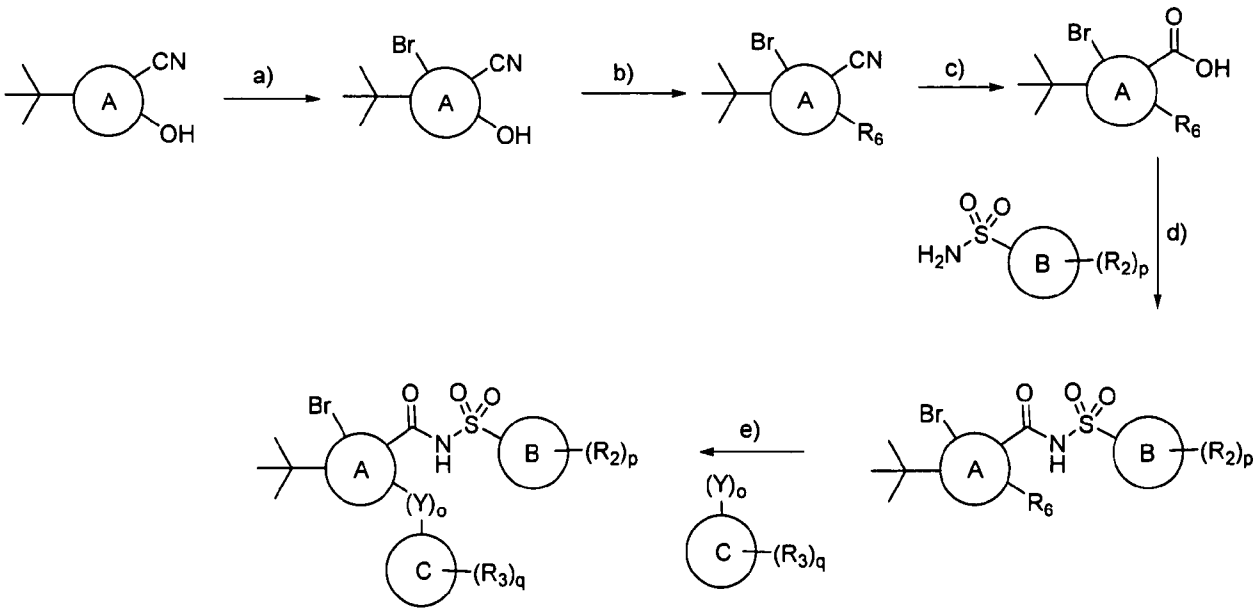
a) $R_6$= 鹵素(Cl)：CDI、NaH、DMF；b) $R_8$不存在，Y或o = 0：C=含有N之部分或$R_8$= $B(OR'')_2$，Y或o = 0：$K_2CO_3$、DMSO或$Na_2CO_3$、DMF、水、$Pd(PPh_3)_4$；c) $R_8$ = $B(OR'')_2$、$Pd(PPh_3)_4$、$K_2CO_3$、DMF或$R_8$不存在：$R_1$=含有N之部分，n = 1：CsF、DMSO。

**流程XVII**



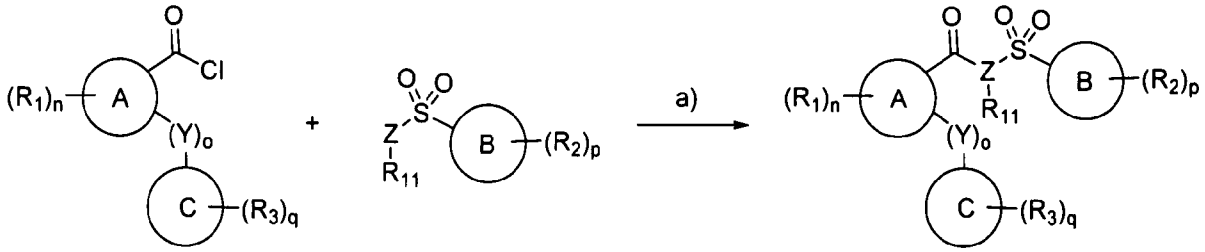
a) R =烷基(甲基、乙基)：2-硝基丙烷、二噁烷、氫氧化苯甲基三甲基銨；b) $R_3$ = 孿-二甲基基團，q = 1，C = 含有N之部分：$NiCl_2$ $6H_2O$、水、MeOH、$NaBH_4$；c) $R_{10}$ = H或D：$LiAlH_4$、THF或$LiAlD_4$、THF。

**流程XVIII**



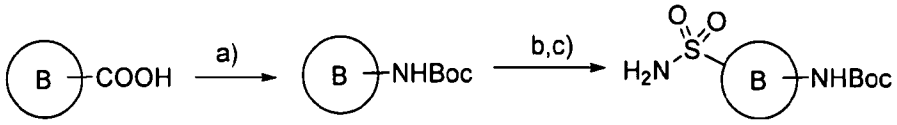
a) NBS、DCE；b) $R_6$ = Cl：$POCl_3$、$PCl_5$；c) $R_6$ = Cl：KOH、水、*i*-PrOH；d) CDI及DMF，接著含有所需磺醯胺及含NaH之DMF的混合物；e) C=含有N之部分，Y或o = 0：$K_2CO_3$、DMSO。

**流程XIX**



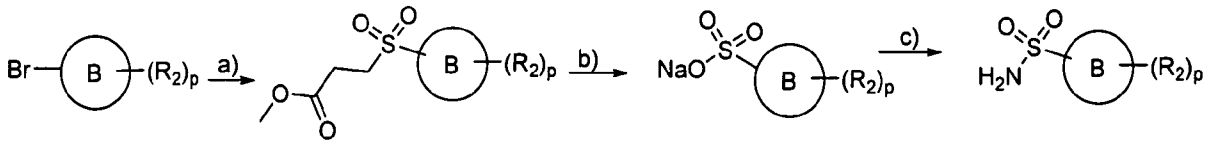
a) Z = $CH_2$、$R_{11}$ = $CO_2R$、R =烷基(甲基)：NaH、DMF。

**流程XX**



a)$Et_3N$、$(CH_3)_3COH$、DPPA；b) MTBE、含$(CH_3)_2CHMgCl$之THF、接著$SO_2$；c) $CH_3COONa$、$H_2NOSO_3H$。

**流程XXI**



a) DMSO、SMOPS；b) THF/MeOH 1:1、含NaOMe之MeOH；c)

DMSO、$H_2NOSO_3H$、$CH_3COONa$。

**式I-Id之化合物的醫藥學上可接受之鹽及前藥**

亦瞭解，本發明之組合物的某些化合物可以游離形式存在供治療，或適當時，呈其醫藥學上可接受之衍生物或前藥形式存在。根據本發明，醫藥學上可接受之衍生物或前藥包括(但不限於)醫藥學上可接受之鹽、酯、此類酯之鹽或任何其他加合物或衍生物，其在向有需要之患者投與後能夠直接或間接提供如本文中另外所述之化合物或其代謝物或殘餘物。

如本文所用，術語「醫藥學上可接受之鹽」係指在合理醫學判斷範疇內適用於與人類及低等動物之組織接觸而無異常毒性、刺激、過敏反應及其類似情況且與合理益處/風險比相稱的彼等鹽。「醫藥學上可接受之鹽」意謂本發明化合物之任何無毒鹽或酯之鹽，其在向接受者投與後能夠直接或間接提供本發明化合物或其抑制活性代謝物或殘餘物。

醫藥學上可接受之鹽爲此項技術中熟知。舉例而言，S. M. Berge等人在*J. Pharmaceutical Sciences*, 1977, *66*, 1-19 (以引用的方式併入本文中)中詳細描述醫藥學上可接受之鹽。本發明化合物之醫藥學上可接受之鹽包括衍生自適合無機酸及鹼及有機酸及鹼之鹽。醫藥學上可接受之無毒酸加成鹽之實例爲胺基與無機酸(諸如鹽酸、氫溴酸、磷酸、硫酸及過氯酸)或有機酸(諸如乙酸、草酸、順丁烯二酸、酒石酸、檸檬酸、丁二酸或丙二酸)形成之鹽，或藉由使用此項技術中所用之其他方法(諸如離子交換)形成之鹽。其他醫藥學上可接受之鹽包括己二酸鹽、海藻酸鹽、抗壞血酸鹽、天冬胺酸鹽、苯磺酸鹽、苯甲酸鹽、硫酸氫鹽、硼酸鹽、丁酸鹽、樟腦酸鹽、樟腦磺酸鹽、檸檬酸鹽、環戊烷丙酸鹽、二葡糖酸鹽、十二烷基硫酸鹽、乙烷磺酸鹽、甲酸鹽、反丁烯二酸鹽、葡庚糖酸鹽、甘油磷酸鹽、葡糖酸鹽、半硫酸

鹽、庚酸鹽、己酸鹽、氫碘酸鹽、2-羥基-乙烷磺酸鹽、乳糖酸鹽、乳酸鹽、月桂酸鹽、月桂基硫酸鹽、蘋果酸鹽、順丁烯二酸鹽、丙二酸鹽、甲烷磺酸鹽、2-萘磺酸鹽、菸鹼酸鹽、硝酸鹽、油酸鹽、草酸鹽、棕櫚酸鹽、雙羥萘酸鹽、果膠酸鹽、過硫酸鹽、3-苯基丙酸鹽、磷酸鹽、苦味酸鹽、特戊酸鹽、丙酸鹽、硬脂酸鹽、丁二酸鹽、硫酸鹽、酒石酸鹽、硫氰酸鹽、對甲苯磺酸鹽、十一烷酸鹽、戊酸鹽及其類似鹽。衍生自適當鹼之鹽包括鹼金屬鹽、鹼土金屬鹽、銨鹽及$N^+(C_{1-4}$烷基$)_4$鹽。本發明亦預見本文中所揭示化合物之任何鹼性含氮基團的四級銨化。可藉由此類四級銨化來獲得水或油溶性或可分散性產物。代表性鹼金屬或鹼土金屬鹽包括鈉、鋰、鉀、鈣、鎂及其類似鹽。其他醫藥學上可接受之鹽包括(適當時)無毒銨、四級銨及使用相對離子(諸如鹵離子、氫氧根、羧酸根、硫酸根、磷酸根、硝酸根、低碳烷基磺酸根及芳基磺酸根)形成之胺陽離子。

**醫藥組合物**

**醫藥學上可接受之媒劑、佐劑或載劑**

在一個態樣中，本發明提供一種醫藥組合物，其包含式I化合物或其醫藥學上可接受之鹽或前藥，及醫藥學上可接受之媒劑、佐劑或載劑。

如上所述，本發明之醫藥組合物另外包含醫藥學上可接受之載劑、佐劑或媒劑，如本文所用，其包括任何及所有溶劑、稀釋劑或其他液體媒劑、分散或懸浮助劑、表面活性劑、等張劑、增稠或乳化劑、防腐劑、固體黏合劑、潤滑劑及其類似物，如所需特定劑型所適合。Remington: *The Science and Practice of Pharmacy*, 第21版, 2005, 編輯D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, 及 *Encyclopedia of Pharmaceutical Technology*, 編輯J. Swarbrick及J. C. Boylan, 1988-1999, Marcel Dekker, New York (每一者之內容以引用的

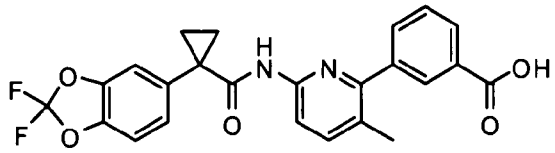
方式併入本文中)揭示用於調配醫藥學上可接受之組合物的各種載劑及用於其製備之已知技術。除非任何習知載劑介質諸如因產生任何不合需要之生物效應或另外以有害方式與醫藥學上可接受之組合物之任何其他組分相互作用而與本發明化合物不相容，否則預期其使用屬於本發明範疇內。可充當醫藥學上可接受之載劑之物質的一些實例包括(但不限於)離子交換劑、氧化鋁、硬脂酸鋁；卵磷脂；血清蛋白，諸如人類血清白蛋白；緩衝物質，諸如磷酸鹽、甘胺酸、山梨酸或山梨酸鉀；飽和植物脂肪酸之部分甘油酯混合物；水、鹽或電解質，諸如硫酸魚精蛋白、磷酸氫二鈉、磷酸氫鉀、氯化鈉、鋅鹽；膠態二氧化矽；三矽酸鎂；聚乙烯吡咯啶酮；聚丙烯酸酯；蠟；聚乙烯-聚氧化丙烯嵌段聚合物；羊毛脂；糖，諸如乳糖、葡萄糖及蔗糖；澱粉，諸如玉米澱粉及馬鈴薯澱粉；纖維素及其衍生物，諸如羧甲基纖維素鈉、乙基纖維素及乙酸纖維素；粉末狀黃蓍膠；麥芽；明膠；滑石；賦形劑，諸如可可脂及栓劑蠟；油，諸如花生油、棉籽油、紅花油、芝麻油、橄欖油、玉米油及大豆油；二醇，諸如丙二醇或聚乙二醇；酯，諸如油酸乙酯及月桂酸乙酯；瓊脂；緩衝劑，諸如氫氧化鎂及氫氧化鋁；海藻酸；無熱原質水；等張生理食鹽水；林格氏溶液(Ringer's solution)；乙醇及磷酸鹽緩衝溶液；以及其他無毒性相容潤滑劑，諸如月桂基硫酸鈉及硬脂酸鎂；以及著色劑、釋放劑、包衣劑、甜味劑、調味劑及芳香劑、防腐劑及抗氧化劑亦可根據調配者之判斷而存在於組合物中。

**其他治療劑**

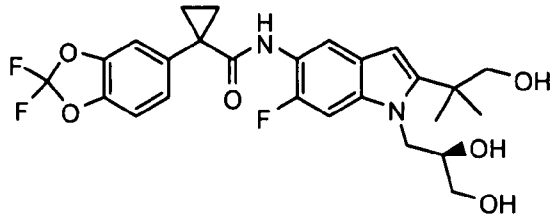
在另一個實施例中，本發明之醫藥組合物進一步包含一或多種其他治療劑。在一個實施例中，其他治療劑爲CFTR調節劑。在一個實施例中，其他治療劑爲CFTR校正劑。在一個實施例中，其他治療劑爲CFTR增效劑。在另一個實施例中，醫藥組合物包含式I化合物及

一或多種以下其他治療劑。

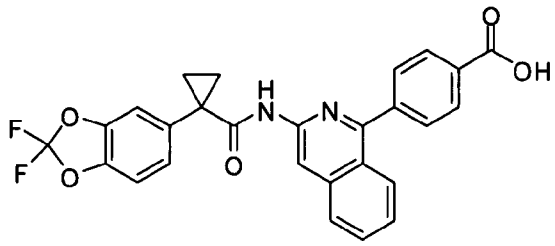
在另一個實施例中，其他治療劑係選自：



3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽；



(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽；或



4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽及4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽及4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥

基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-

5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物196)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物337)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二

氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物182)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1356)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-

5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物639)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1660)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物262)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶

基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶

基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5H-喹啉-3-甲醯胺(化合物15)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二

氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物164)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間

二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物110)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物281)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-

吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物197)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-

基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環

戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-

(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物365)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)或其醫藥學上可接受之鹽；及選自以下之化合物：3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸或其醫藥學上可接受之鹽。

在一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-

甲醯胺(化合物196)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物337)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物182)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1356)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并

[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物639)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1660)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-

3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物262)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5H-喹啉-3-甲醯胺(化合物15)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶

基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物164)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物110)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-

甲醯胺(化合物281)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物197)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-

二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物365)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲

酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)或其醫藥學上可接受之鹽；及3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-

2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物196)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物337)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶

基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物182)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1356)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物639)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-

2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1660)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺

(化合物262)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶

基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5H-喹啉-3-甲醯胺(化合物15)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧

雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物164)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物110)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧

雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物281)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物197)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)或其醫藥

學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物365)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)或其醫藥學上可接受之鹽；及(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明之醫藥組合物包含式I化合物或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含表1之化合物或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-

1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物196)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物337)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物182)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1356)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物639)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶

基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1660)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物262)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5H-喹啉-3-甲醯胺(化合物15)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(4-胺基噻唑-2-

基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物164)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物110)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-

甲醯胺(化合物281)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物197)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(4-氯-3-丙氧基-

苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

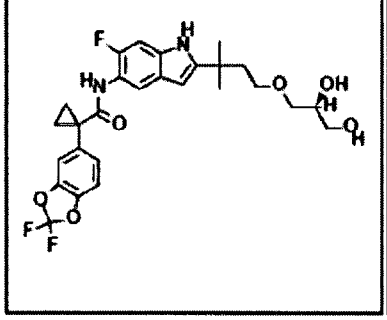
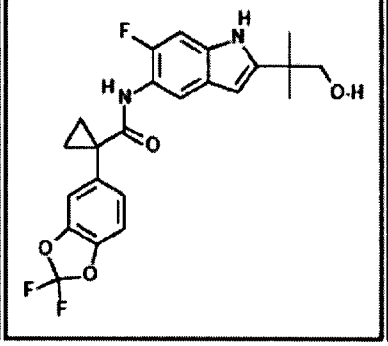
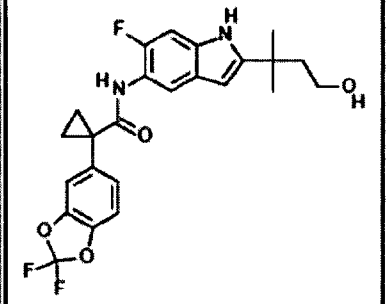
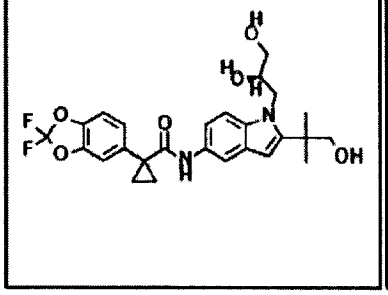
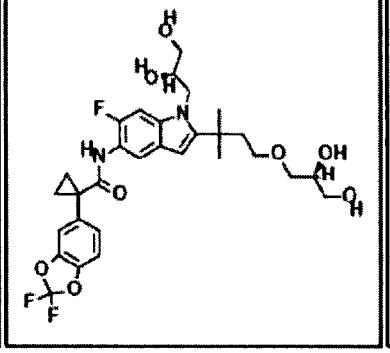
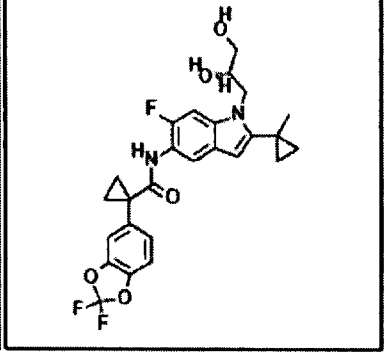
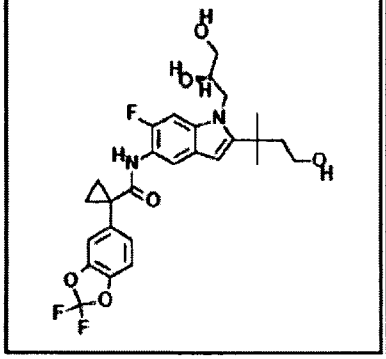
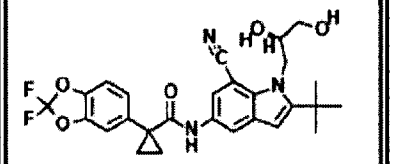
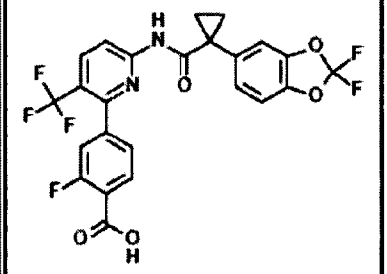
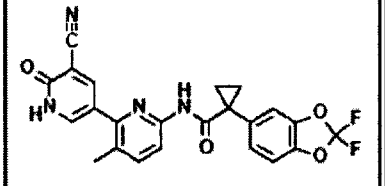
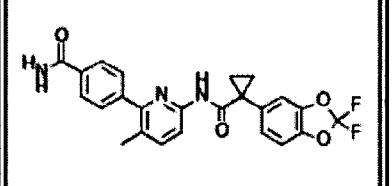
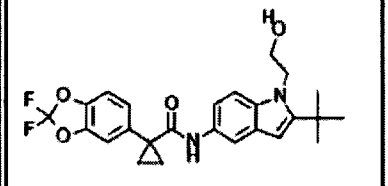
在另一個實施例中，本發明之醫藥組合物包含*N*-(3-胺基苯基)磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

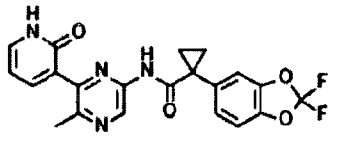
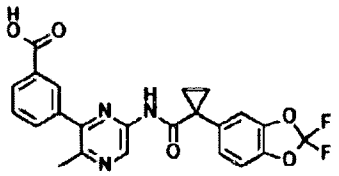
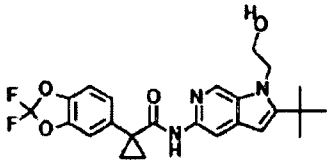
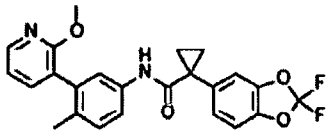
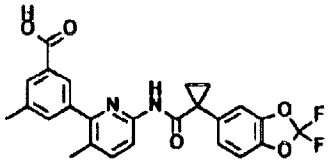
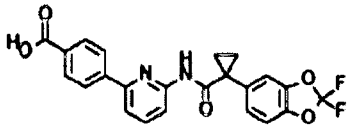
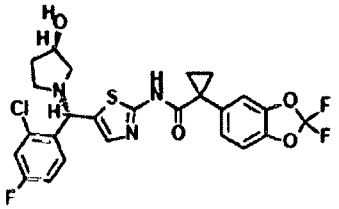
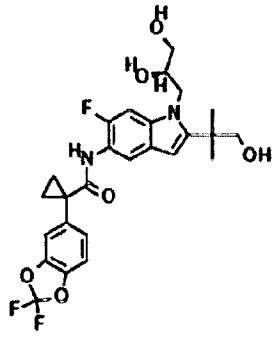
在另一個實施例中，本發明之醫藥組合物包含*N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物365)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)或其醫藥學上可接受之鹽；及*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，其他治療劑係選自下表：

| | | |
|---|---|---|
| 1  | 2  | 3  |
| 4  | 5  | 6  |
| 7  | 8  | 9  |
| 10  | 11  | 12  |

| 13 | 14 | 15 |
|---|---|---|
|  |  |  |
| **16** | **17** | **18** |
|  |  |  |
| **19** | **20** | |
|  |  | |

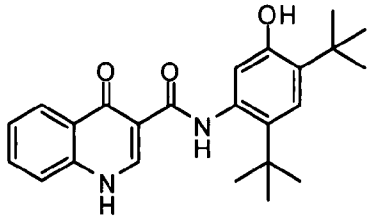
。

在一個實施例中，其他治療劑係選自下表：

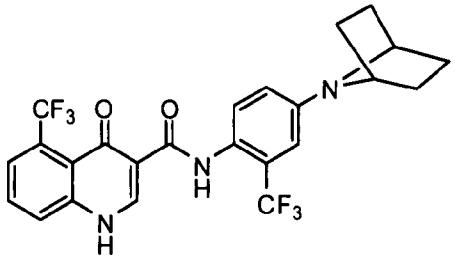
| |
|---|
| 美國專利第7,407,976號中揭示之化合物(第13欄第35行-第66欄第67行；表1中第67欄第1行-第127欄第42行化合物1-100) |
| 美國專利第7,645,789號中揭示之化合物(第16欄第52行-第50欄第22行；表1中第50欄第24行-第167欄第42行化合物1-322) |
| 美國專利第7,659,268號中揭示之化合物(第16欄第20行-第70欄第52行；表1中第70欄第53行-第331欄第34行化合物1-528) |
| 美國專利第7,671,221號中揭示之化合物(第16欄第12行-第54欄第48行；表1中第54欄第49行-第699欄第27行化合物1-1216) |
| 美國專利第7,691,902號中揭示之化合物(第16欄第11行-第54欄第29行；表1中第54欄第29行-第683欄第44行化合物1-959) |
| 美國專利第7,741,321號中揭示之化合物(第16欄第25行-第72欄第17行；表1中第72欄第20行-第279欄第15行化合物1-422) |
| 美國專利第7,754,739號中揭示之化合物(第16欄第1行-第22欄第47行；表1中第18欄第26-65行化合物1-2) |
| 美國專利第7,776,905號中揭示之化合物(第16欄第23行-第38欄第40行；表1中第38欄 |

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| 第45行-第96欄第40行化合物1-306) |
| 美國專利第7,973,169號中揭示之化合物(第9欄第16行-第40欄第40行；表1中第40欄第41行-第289欄第39行化合物1-289) |
| 美國專利第7,977,322號中揭示之化合物(第6欄第26行-第37欄第47行；表1中第37欄第50行-第141欄第40行化合物1-498) |
| 美國專利第7,999,113號中揭示之化合物(第6欄第13行-第10欄第67行；表1中第11欄第5行-第13欄第65行化合物1-13) |
| 美國專利第8,227,615號中揭示之化合物(第6欄第10行-第29欄第66行；表1中第30欄第1行-第46欄第48行化合物1-78) |
| 美國專利第8,299,099號中揭示之化合物(第6欄第10行-第34欄第18行；表1中第34欄第20行-第42欄第35行化合物1-47) |
| 美國公開申請案第2006-0052358號中揭示之化合物(段落[0034]-[0056]；[0077]-[0240]；段落[0241]表1中化合物1-320) |
| 美國公開申請案第2009-0143381號中揭示之化合物(段落[0102]-[0263]；段落[0264]表1中化合物1-28) |
| 美國公開申請案第2009-0170905號中揭示之化合物(段落[0012]-[0013]；[0030]-[0051]) |
| 美國公開申請案第2009-0253736號中揭示之化合物(段落[0031]-[0162]；段落[0163]表1中化合物1-15) |
| 美國公開申請案第2011-0263654號中揭示之化合物(段落[0012]-[0013]；[0066]-[0141]) |
| 美國公開申請案第2011-0251253號中揭示之化合物(段落[0012]-[0013]；[0054]-[0079]) |
| PCT申請案WO2008141119中揭示之化合物(段落[0100]-[0339]；段落[0340]表1中化合物1-117) |
| 美國申請案第11/047,361號中揭示之化合物 |
| 美國公開申請案第2013-0116238號中揭示之化合物(段落[0028]-[0044]；[0117]-[0128])或其組合 |

在另一個實施例中，其他治療劑係選自



*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；或



*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)選自*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)選自*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺之化合物。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環

丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，其他治療劑係選自下表：

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| 美國公開申請案第2005-0113423號中揭示之化合物(段落[00146]；段落[0391]-[0392]表1及2中化合物IA-1-IA-136及化合物I-1-I-21) |
| 美國公開申請案第2005-0059687號中揭示之化合物(段落[00100]-[00101]；段落[0169]表1中化合物1-405) |
| 美國專利第7,598,412號中揭示之化合物1-108 (第22欄第14行-第79欄第20行；表1) |

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| 美國專利第7,495,103號中揭示之化合物1-485 (第51欄第1行-第63欄第43行；表1) |
| 美國專利第8,354,427號中揭示之化合物1-718 (第51欄第3行-第71欄第46行；表1) |
| 美國公開申請案第2007-0105833號中揭示之化合物1-233 (段落[00145]；表1) |
| 美國專利第8,242,149號中揭示之化合物1-26 (第46欄第47行-第57欄第37行；表1) |
| 美國專利第8,314,256號中揭示之化合物1-18 (第21欄第1行-第26欄第19行) |
| 美國專利第8,399,479號中揭示之化合物1-14 (第36欄第20行-第38欄第40行；表1) |
| 美國專利第8,188,283號中揭示之化合物1-18 (第38欄第43行-第43欄第36行；表1) |
| 美國公開申請案第2010-0249180號中揭示之化合物1-16 (段落[0173]；表1) |
| 美國公開申請案第2011-0008259號中揭示之化合物1-19 (段落[0172]；表1) |
| 美國專利第8,367,660號中揭示之化合物1-129 (第57欄第31行-第81欄第24行；表1) |

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)選自*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)選自*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺之化合物。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)選自以下各者之化合物：某些黃酮及異黃酮，諸如金雀異黃酮 ，其能夠以與環狀-AMP無關之方式刺激上皮組織中CFTR介導之氯離子輸送(參見美國專利第6,329,422號，以全文引用的方式併入本文中)；苯基甘胺酸-01 (2-[(2-1H-吲哚-3-基-乙醯基)-甲基胺基]-*N*-(4-異丙基苯基)-2-苯基乙醯胺)；非洛地平(4-(2,3-二氯苯基)-2,6-二甲基-1,4-二氫-3,5-吡啶二甲酸乙酯甲酯)；磺醯胺SF-01 (6-(乙基苯基胺磺醯基)-4-側氧基-1,4-二氫喹啉-3-甲酸環庚基醯胺)；及UCCF-152 (3-[2-(苯甲氧基)苯基]-5-(氯甲基)異噁唑)。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-

3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之

鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物196)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物337)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物182)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1356)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-

甲醯胺(化合物639)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1660)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其

醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物262)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-

3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡

啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5H-喹啉-3-甲醯胺(化合物15)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物164)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)或其醫藥學上可接受之鹽；b) *N*-(5-

羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基] 吡唑-3-甲醯胺(化合物110)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物281)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之

鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物197)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(4-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(3-胺基苯基)磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯

胺(化合物365)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸或其醫藥學上可接受之鹽。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物196)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物337)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-

(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物182)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1356)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲唑-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-

苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物639)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1660)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡

啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物262)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環

丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可

接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5H-喹啉-3-甲醯胺(化合物15)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合

物265)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物164)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基] 吡唑-3-甲醯胺(化合物110)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物281)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-

二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5H-喹啉-3-甲醯胺(化合物197)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)或其醫藥學上可接受之鹽；b) *N*-(5-羥基

-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(4-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) 6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-(3-胺基苯基)

磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物365)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之醫藥組合物包含a) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)或其醫藥學上可接受之鹽；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或其醫藥學上可接受之鹽；及c) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基

丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)其他CFTR校正劑。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合物；及c)其他CFTR校正劑。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在另一個實施例中，來自以上之其他CFTR校正劑爲(*N*-(2-(5-氯-2-甲氧基-苯基胺基)-4'-甲基-[4,5']聯噻唑-2'-基)-苯甲醯胺(corr-4a)。在另一個實施例中，其他CFTR校正劑爲以全文引用的方式併入本文中的公開之國際專利申請案WO2014081820中揭示之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺；及選自以下之CFTR校正劑：(*N*-(2-(5-氯-2-甲氧基-苯基胺基)-4'-甲基-[4,5']聯噻唑-2'-基)-苯甲醯胺(corr-4a)、以全文引用的方式併入本文中的公開之國際專利申請案WO2014081820中揭示之化合物、公開之國際專利申請案第WO2014086687號中揭示之化合物或美國專利第8,247,436號或第8,476,269號、美國專利申請案第13/923,349號或公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、

第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b)選自以下之化合物：某些黃酮及異黃酮，諸如金雀異黃酮，其能夠以與環狀-AMP無關之方式刺激上皮組織中CFTR介導之氯離子輸送(參見美國專利第6,329,422號，以全文引用的方式併入本文中)；苯基甘胺酸-01 (2-[(2-1H-吲哚-3-基-乙醯基)-甲基胺基]-*N*-(4-異丙基苯基)-2-苯基乙醯胺)；非洛地平(4-(2,3-二氯苯基)-2,6-二甲基-1,4-二氫-3,5-吡啶二甲酸乙酯甲酯)；磺醯胺SF-01 (6-(乙基苯基胺磺醯基)-4-側氧基-1,4-二氫喹啉-3-甲酸環庚基醯胺)；及UCCF-152 (3-[2-(苯甲氧基)苯基]-5-(氯甲基)異噁唑)；及c)選自以下之CFTR校正劑：(*N*-(2-(5-氯-2-甲氧基-苯基胺基)-4'-甲基-[4,5']聯噻唑-2'-基)-苯甲醯胺(corr-4a)、以全文引用的方式併入本文中的公開之國際專利申請案WO2014081820中揭示之化合物或美國專利第8,247,436號或第8,476,269號、美國專利申請案第13/923,349號或公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中。

在另一個實施例中，本發明提供上述醫藥組合物，其包含a)式I化合物；b)選自3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸、(*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺或4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸之化合

物；及c)其他CFTR校正劑，諸如上文特別列出之彼等CFTR校正劑；且進一步包含d) CFTR增效劑。

在另一個實施例中，來自以上之CFTR增效劑爲*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺或*N*-(4-(7-氮雜雙環[2.21]庚-7-基)-2-(三氟甲基)苯基)-4-側氧基-5-(三氟甲基)-1,4-二氫喹啉-3-甲醯胺。在另一個實施例中，來自以上之CFTR增效劑爲*N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，來自以上之CFTR增效劑係選自某些黃酮及異黃酮，諸如金雀異黃酮 ，其能夠以與環狀-AMP無關之方式刺激上皮組織中CFTR介導之氯離子輸送(參見美國專利第6,329,422號，以全文引用的方式併入本文中)；苯基甘胺酸-01 (2-[(2-1H-吲哚-3-基-乙醯基)-甲基胺基]-*N*-(4-異丙基苯基)-2-苯基乙醯胺)；非洛地平(4-(2,3-二氯苯基)-2,6-二甲基-1,4-二氫-3,5-吡啶二甲酸乙酯甲酯)；磺醯胺SF-01 (6-(乙基苯基胺磺醯基)-4-側氧基-1,4-二氫喹啉-3-甲酸環庚基醯胺)；及UCCF-152 (3-[2-(苯甲氧基)苯基]-5-(氯甲基)異噁唑)。

在一個實施例中，其他治療劑係選自公開之國際專利申請案第WO2014078842號或第WO2012158885號或美國公開之申請案第US20140073667號中揭示之化合物；所有公開之國際專利申請案及公開之美國專利申請案均以全文引用的方式併入本文中。

在一個實施例中，其他治療劑係選自公開之國際專利申請案第WO2012078909號、第WO2012154880號、第WO2012154888號、第WO2012154967號、第WO2013112651號、第WO2013112699號或第WO2012078902號中揭示之化合物；所有公開之國際專利申請案均以全文引用的方式併入本文中。

在一個實施例中，其他治療劑係選自美國專利第8,247,436號或第8,476,269號、美國專利申請案第13/923,349號及公開之國際專利申

請案第WO2011113894號、第WO2013038373號、第WO2013038378號、第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中。

在一個實施例中，其他治療劑係選自WO2014210159或WO2014152213中揭示之化合物；所有公開之國際專利申請案均以全文引用的方式併入本文中。

在一個實施例中，其他治療劑係選自公開之國際專利申請案第WO2014210159號或第WO2014152213號中揭示之化合物；所有公開之國際專利申請案均以全文引用的方式併入本文中。

在一個實施例中，其他治療劑係選自公開之國際專利申請案第WO2015003083號、第WO2015007517號、第WO2015007519或第WO2015007516號中揭示之化合物；所有公開之國際專利申請案均以全文引用的方式併入本文中。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c)美國專利第8,247,436號或第8,476,269號；美國專利申請案第13/923,349號及公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c)美國專利第8,247,436號或第8,476,269號、美國專利申

請案第13/923,349號及公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c)美國專利第8,247,436號或第8,476,269號、美國專利申請案第13/923,349號及公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中。

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在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；c)美國專利第8,247,436號或第8,476,269號、美國專利申請案第13/923,349號及公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、

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在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；c)美國專利第8,247,436號或第8,476,269號、美國專利申請案第13/923,349號及公開之國際專利申請案第WO2011113894號、第WO2013038373號、第WO2013038378號、第WO2013038381號、第WO2013038386號或第WO2013038390號中揭示之化合物；所有美國專利、美國專利申請案及公開之國際專利申請案均以全文引用的方式併入本文中；及d) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

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WO2012078909號、第WO2012154880號、第WO2012154888號、第WO2012154967號、第WO2013112651號、第WO2013112699號或第WO2012078902號中揭示之化合物；所有公開之國際專利申請案均以全文引用的方式併入本文中。

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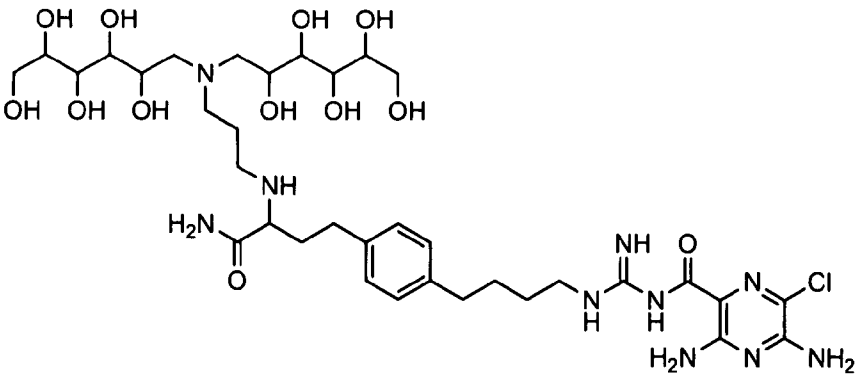
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4-側氧基-1H-喹啉-3-甲醯胺。

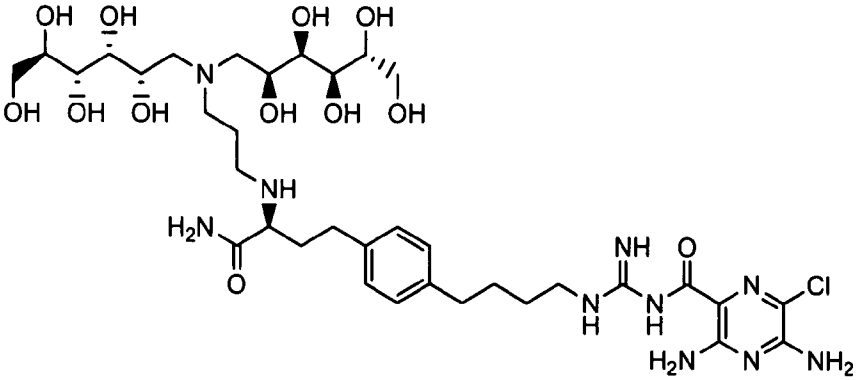
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在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；c)公開之國際專利申請案第WO2012078909號、第WO2012154880號、第WO2012154888號、第WO2012154967號、第WO2013112651號、第WO2013112699號或第WO2012078902號中揭示之化合物；所有公開之國際專利申請案均以全文引用的方式併入本文中；及d) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

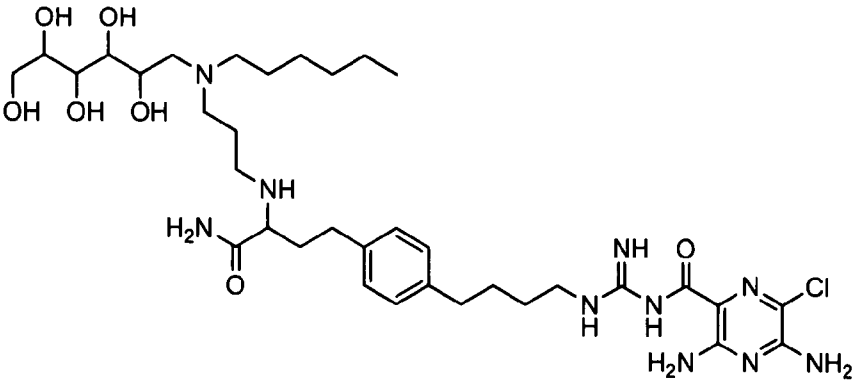
在另一個實施例中，其他治療劑爲以全文引用的方式併入本文中的公開之國際專利申請案第WO2014099673號中揭示之化合物，包括但不限於以下化合物：



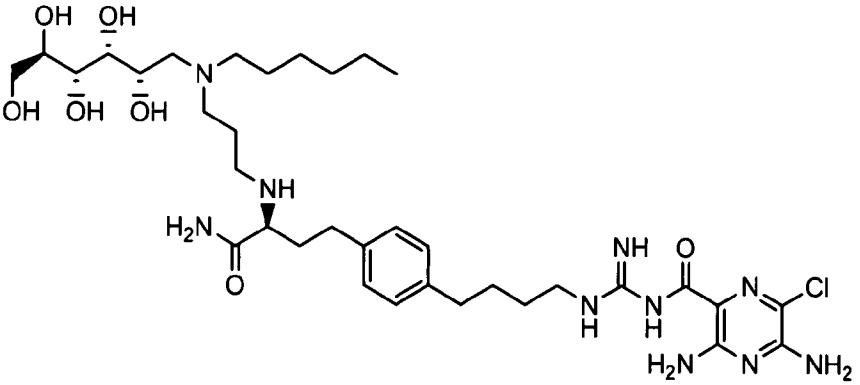
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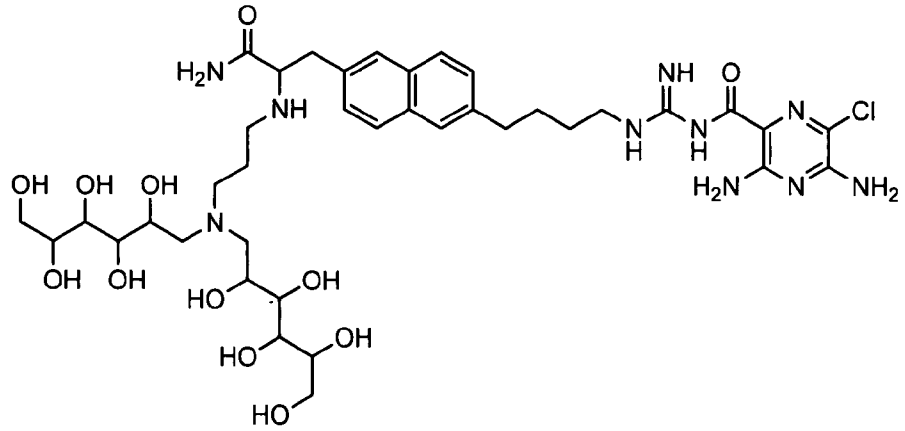
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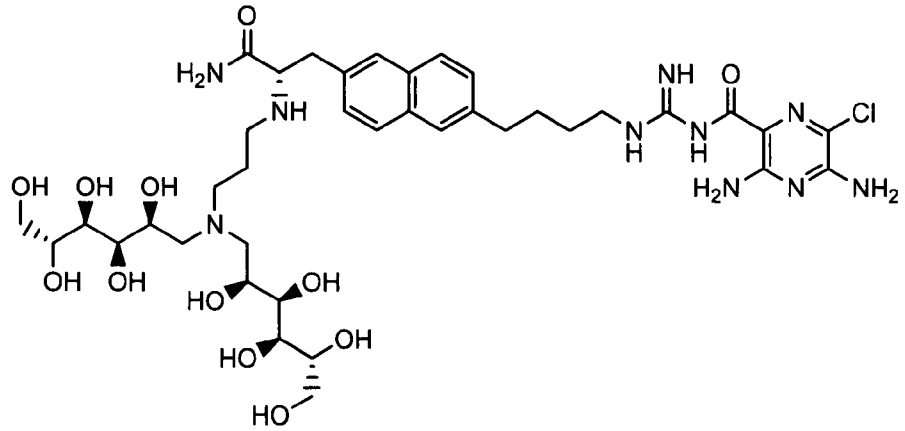
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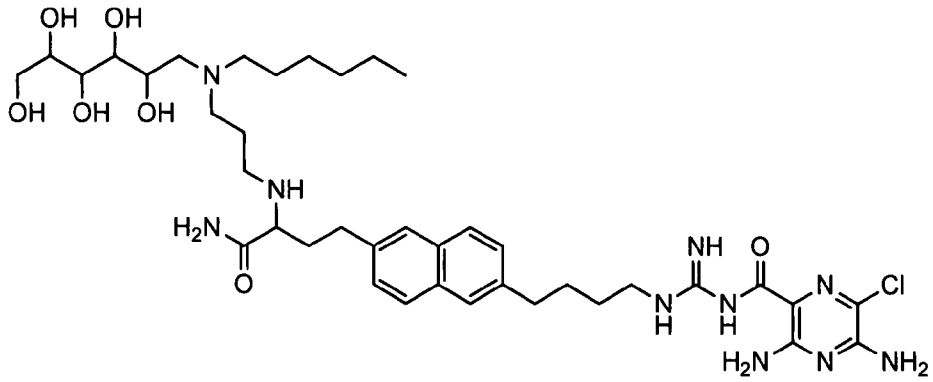
P-4 ;



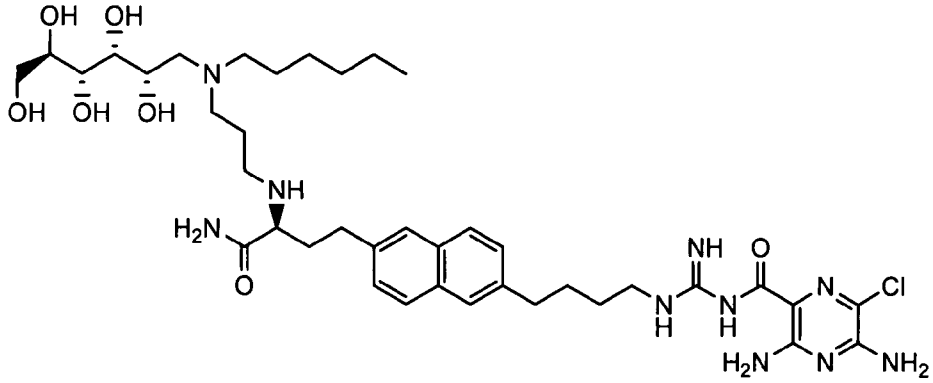
P-5 ;



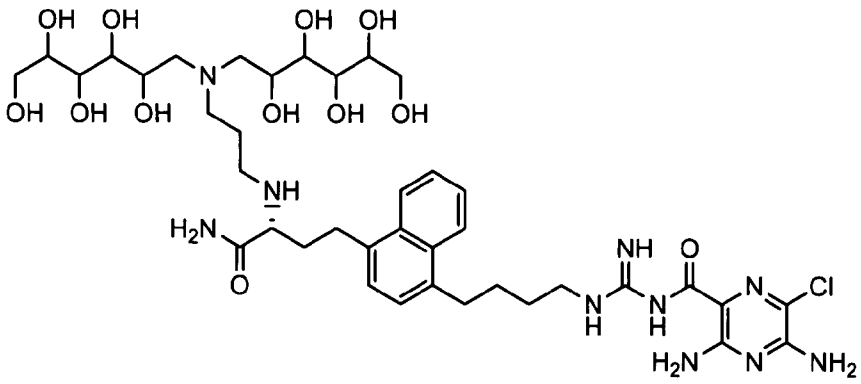
P-6 ;



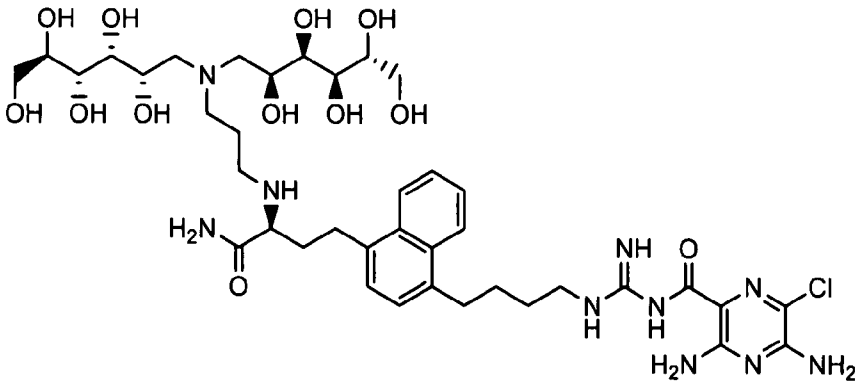
P-7 ;



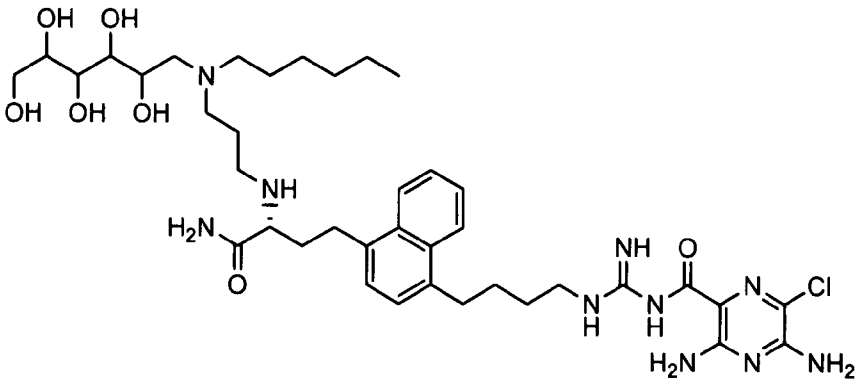
P-8 ;



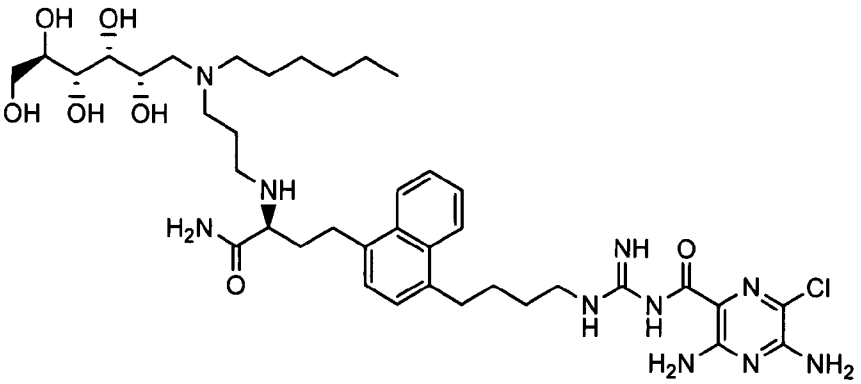
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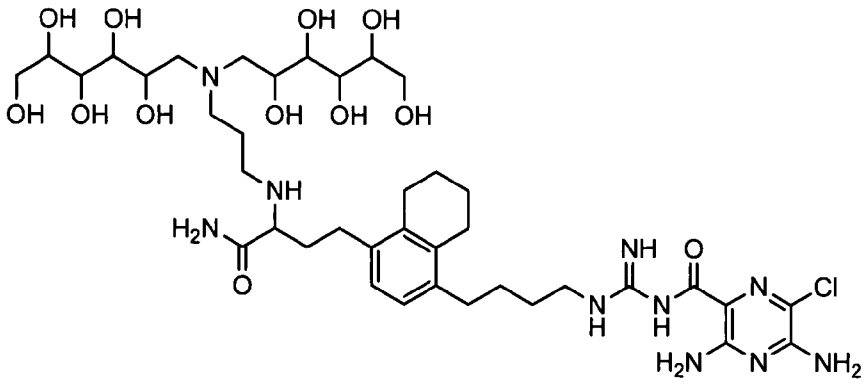
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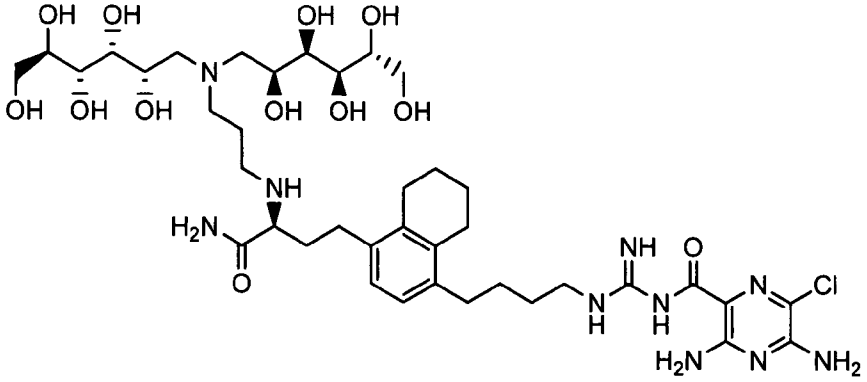
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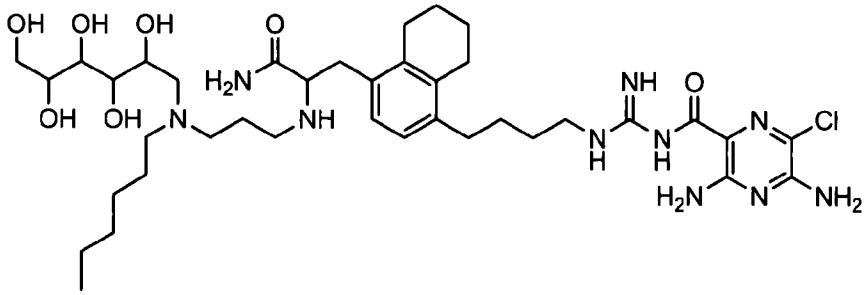
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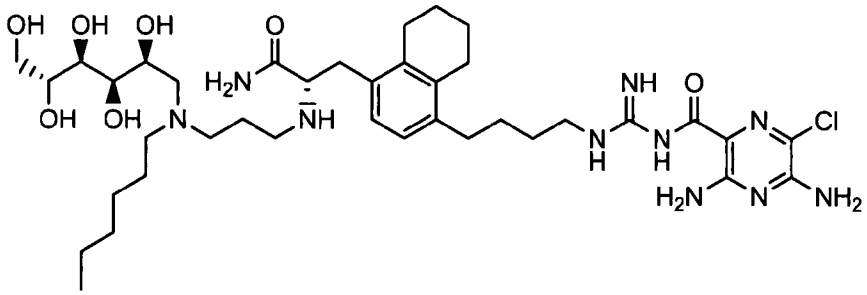
P-13；



P-14；



P-15；或



P-16。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c)選自以上揭示之P-1至P-

16之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c)選自以上揭示之P-1至P-16之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c)選自以上揭示之P-1至P-16之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c)選自以上揭示之P-1至P-16之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c)選自以上揭示之P-1至P-16之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；及c)選自以上揭示之P-1至P-16之化合物。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；c)選自以上揭示之P-1至P-16之化合物；及d) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

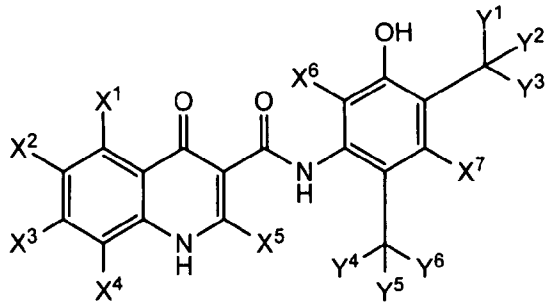
在另一個實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；c)選自以上揭示之P-1至P-16之化合物；及d) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；c)選自以上揭示之P-1至P-16之化合物；及d) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸；c)選自以上揭示之P-1至P-16之化合物；及d) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在一些實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；及b)美國專利第8,865,902號中揭示之化合物。在一些實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；及b)美國專利第8,865,902號中揭示之化合物。在另一個實施例中，美國專利第8,865,902號中揭示之化合物具有以下結構：



其中美國專利第8,865,902號中揭示之化合物爲下表化合物中之任一者：

| $X^1$ | $X^2$ | $X^3$ | $X^4$ | $X^5$ | $X^6$ | $X^7$ | $Y^1$ | $Y^2$ | $Y^3$ | $Y^4$ | $Y^5$ | $Y^6$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D | D | D | D | D | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | D | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | D | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | D | H | H | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | D | H | H | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | H | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | H | H | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |

在另一個實施例中，美國專利第8,865,902號中揭示之化合物爲下表化合物中之任一者：

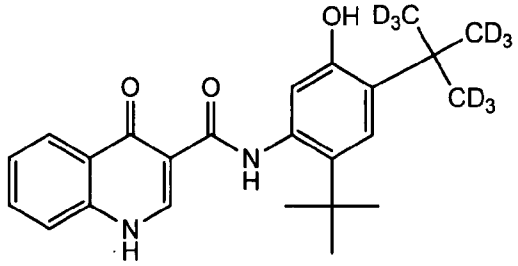
| $X^1$ | $X^2$ | $X^3$ | $X^4$ | $X^5$ | $X^6$ | $X^7$ | $Y^1$ | $Y^2$ | $Y^3$ | $Y^4$ | $Y^5$ | $Y^6$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | H | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | D | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | D | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | D | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | D | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| D | D | D | D | D | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| D | D | D | D | D | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| D | D | D | D | D | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| D | D | D | D | D | H | H | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | H | H | D | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | H | H | D | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | H | D | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | H | D | H | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| H | H | H | H | H | D | H | $CD_3$ | $CD_3$ | $CD_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | D | H | $CH_3$ | $CH_3$ | $CH_3$ | $CD_3$ | $CD_3$ | $CD_3$ |

在另一個實施例中，美國專利第8,865,902號中揭示之化合物爲下表化合物中之任一者：

| $X^1$ | $X^2$ | $X^3$ | $X^4$ | $X^5$ | $X^6$ | $X^7$ | $Y^1$ | $Y^2$ | $Y^3$ | $Y^4$ | $Y^5$ | $Y^6$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D | D | D | D | D | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| D | D | D | D | D | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| D | D | D | D | D | H | H | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |

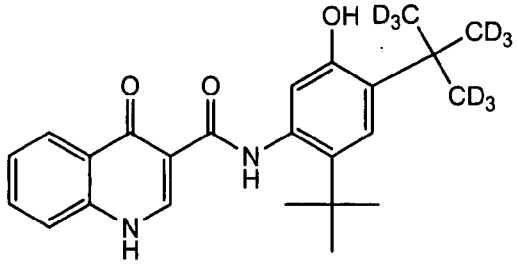
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D | D | D | D | H | D | D | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| D | D | D | D | H | H | H | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ | $CD_3$ |
| D | D | D | D | H | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| D | D | D | D | H | H | H | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| H | H | H | H | H | D | D | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |

在一些實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；及b)化合物：



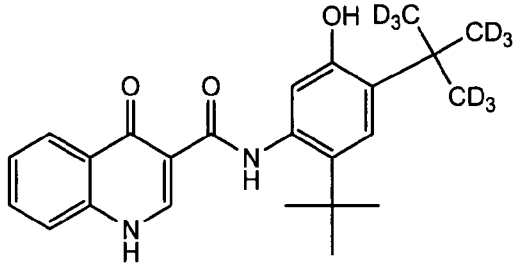
。

在一些實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；及b)化合物：



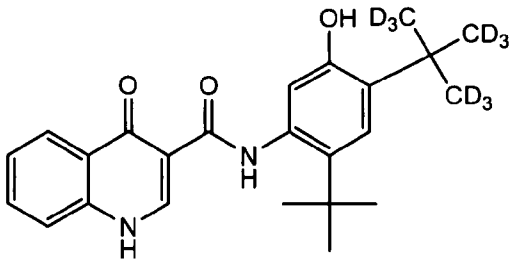
。

在一些實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c)化合物：



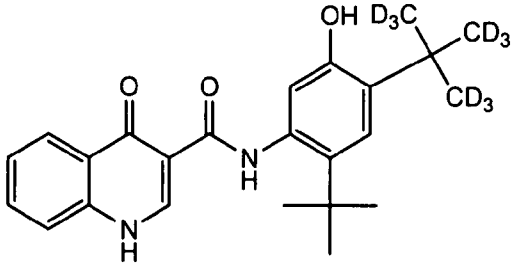
。

在一些實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c)化合物：



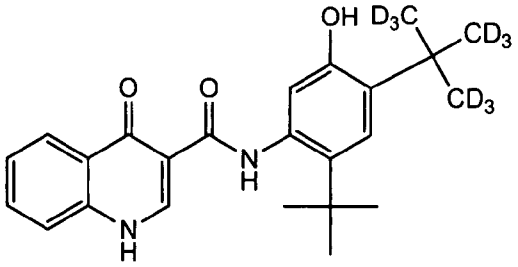
。

在一些實施例中，本發明提供一種醫藥組合物，其包含a)選自化合物233、化合物238、化合物318、化合物228、化合物196、化合物337、化合物368、化合物182、化合物1356、化合物172、化合物639、化合物300、化合物1660、化合物234、化合物1975、化合物262、化合物2191、化合物207、化合物320、化合物353、化合物171、化合物114、化合物321、化合物15、化合物265、化合物164、化合物214、化合物345、化合物8、化合物110、化合物281、化合物351、化合物197、化合物136、化合物307、化合物279、化合物72、化合物125、化合物45、化合物299、化合物365或化合物361之化合物；b) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸；及c)化合物：

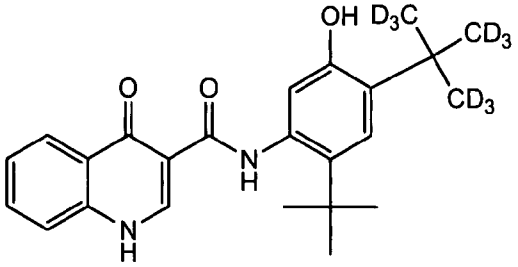


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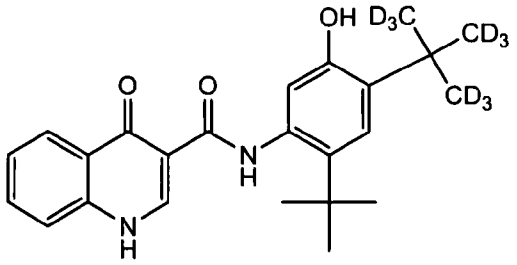
在一些實施例中，本發明提供一種醫藥組合物，其包含a)式I化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c)化合物：



在一些實施例中，本發明提供一種醫藥組合物，其包含a)表1之化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c)化合物：



在一些實施例中，本發明提供一種醫藥組合物，其包含a)選自化合物233、化合物238、化合物318、化合物228、化合物196、化合物337、化合物368、化合物182、化合物1356、化合物172、化合物639、化合物300、化合物1660、化合物234、化合物1975、化合物262、化合物2191、化合物207、化合物320、化合物353、化合物171、化合物114、化合物321、化合物15、化合物265、化合物164、化合物214、化合物345、化合物8、化合物110、化合物281、化合物351、化合物197、化合物136、化合物307、化合物279、化合物72、化合物125、化合物45、化合物299、化合物365或化合物361之化合物；b) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺；及c)化合物：



。

在另一個實施例中，上述醫藥組合物含有本發明化合物之醫藥學上可接受之前藥。

在一個實施例中，任一以下治療劑可單獨與式I或Id之化合物使用，或與任一上述醫藥組合物組合使用，或作爲任一上述醫藥組合物中之組分使用。

在一個實施例中，其他治療劑係選自黏液溶解劑、支氣管擴張藥、抗生素、抗感染劑、CFTR調節劑或消炎劑。

在一個實施例中，主要治療CFTR介導之疾病，諸如囊腫纖維化症的症狀，而非其根本病因之任一以下治療劑可單獨與式I化合物使用，或與任一上述醫藥組合物組合使用，或作爲任一上述醫藥組合物中之組分使用。

在一個實施例中，其他治療劑爲抗生素。適用於本文中之示例性抗生素包括托普黴素(tobramycin)(包括托普黴素吸入粉末(TIP))、阿奇黴素(azithromycin)、凱斯通(cayston)、安曲南(aztreonam)(包括安曲南之氣溶膠化形式)、阿米卡星(amikacin)(包括其脂質體調配物)、環丙沙星(ciprofloxacin)(包括其適合於藉由吸入投與之調配物)、左氧氟沙星(levoflaxacin)(包括其氣溶膠化調配物)及兩種抗生素，例如磷黴素(fosfomycin)與托普黴素之組合。

在另一個實施例中，其他治療劑爲黏液溶解劑。適用於本文中之示例性黏液溶解劑包括Pulmozyme®。

在另一個實施例中，其他治療劑爲支氣管擴張藥。示例性支氣管擴張藥包括沙丁胺醇(albuterol)、硫酸奧西那林(metaprotenerol

sulfate)、乙酸吡布特羅(pirbuterol acetate)、沙美特羅(salmeterol)或硫酸特布林(tetrabuline sulfate)。

在另一個實施例中，其他治療劑有效恢復肺呼吸道表面液體。此類藥劑提高鹽移入細胞及移出細胞，允許黏液在肺呼吸道中更多地水合，且因此更容易清除。示例性此類藥劑包括高滲透壓生理食鹽水、德福索爾四鈉(denufosol tetrasodium)([[(3S,5R)-5-(4-胺基-2-側氧基嘧啶-1-基)-3-羥基氧雜環戊烷-2-基]甲氧基-羥基磷醯基][[[(2R,3S,4R,5R)-5-(2,4-二側氧基嘧啶-1-基)-3, 4-二羥基氧雜環戊烷-2-基]甲氧基-羥基磷醯基]氧基-羥基磷醯基]磷酸氫鹽)或布諾托(bronchitol)(甘露糖醇之吸入調配物)。

在另一個實施例中，其他治療劑爲消炎劑，亦即可減輕肺中發炎之藥劑。適用於本文中之示例性此類藥劑包括布洛芬(ibuprofen)、二十二碳六烯酸(docosahexanoic acid，DHA)、西地那非(sildenafil)、吸入麩胱甘肽、吡格列酮(pioglitazone)、羥基氯奎(hydroxychloroquine)或辛伐他汀(simavastatin)。

在另一個實施例中，其他治療劑爲除式I化合物外加強或誘發CFTR活性的化合物。示例性此類藥劑包括阿塔路壬(ataluren)(「PTC124®」；3-[5-(2-氟苯基)-1,2,4-噁二唑-3-基]苯甲酸)、西那普肽(sinapultide)、蘭考韋泰(lancovutide)、地來司他(depelestat) (人類重組嗜中性白血球彈性蛋白酶抑制劑)及可普斯通(cobiprostone) (7-{(2R, 4aR, 5R, 7aR)-2-[(3S)-1,1-二氟-3-甲基戊基]-2-羥基-6-側氧基八氫環戊并[b]哌喃-5-基}庚酸)。

在另一個實施例中，其他治療劑爲營養劑。示例性營養劑包括胰脂肪酶(胰化酶替換)，包括Pancrease®、Pancreacarb®、Ultrase®或Creon®、Liprotomase® (前稱爲Trizytek®)、Aquadeks®或麩胱甘肽吸入。在一個實施例中，其他營養劑爲胰脂肪酶。

在另一個實施例中，其他治療劑爲選自以下之化合物：慶大黴素(gentamicin)、薑黃素(curcumin)、環磷醯胺(cyclophosphamide)、4-苯丁酸鹽(4-phenylbutyrate)、美格魯特(miglustat)、非洛地平(felodipine)、尼莫地平(nimodipine)、非洛新B (Philoxin B)、金雀異黃酮 (geniestein)、芹黃素(Apigenin)、cAMP/cGMP加強劑或誘導劑(諸如咯利普蘭(rolipram)、西地那非(sildenafil)、米利酮(milrinone)、他達拉非(tadalafil)、胺利酮(amrinone)、異丙腎上腺素(isoproterenol)、沙丁胺醇(albuterol)及沙美特羅(almeterol))、去氧斯匹胍素(deoxyspergualin)、HSP 90抑制劑、HSP 70抑制劑、蛋白酶體抑制劑(諸如埃普黴素(epoxomicin))、雷克塔西汀(lactacystin)等。

在其他實施例中，其他治療劑爲以全文引用的方式併入本文中的WO 2004028480、WO 2004110352、WO 2005094374、WO 2005120497或WO 2006101740中揭示之化合物。在另一個實施例中，其他藥劑爲顯示誘發或加強CFTR活性之苯并[c]喹嗪衍生物或顯示誘發或加強CFTR活性之苯并哌喃衍生物。在另一個實施例中，其他藥劑爲以全文引用的方式併入本文中的美國專利第7,202,262號、美國專利第6,992,096號、US20060148864、US20060148863、US20060035943、US20050164973、WO2006110483、WO2006044456、WO2006044682、WO2006044505、WO2006044503、WO2006044502或WO2004091502中揭示之化合物。在另一個實施例中，其他藥劑爲以全文引用的方式併入本文中的WO2004080972、WO2004111014、WO2005035514、WO2005049018、WO2006099256、WO2006127588或WO2007044560中揭示之化合物。

在另一個實施例中，其他治療劑爲以全文引用的方式併入本文中的WO2014180562或US20140274933中揭示之化合物。

在另一個實施例中，其他治療劑係選自以下類別：ENaC抑制

劑、β模擬劑、抗膽鹼激導性劑、皮質類固醇、PDE4抑制劑、LTD4拮抗劑、EGFR抑制劑、多巴胺促效劑、H1抗組織胺、PAF拮抗劑、MAP激酶抑制劑、MPR4抑制劑、iNOS抑制劑或SYK抑制劑或其雙重或三重組合。

在另一個實施例中，其他治療劑爲選自以下之ENaC抑制劑：3-胺基-6-(4-氟-苯基)-5-三氟甲基-吡啶-2-甲酸(3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

5-胺基-6'-甲基-3-三氟甲基-[2,3]聯吡啶-6-甲酸(3,3,3-三氟-2-羥基 -2-甲基-丙基)-醯胺；

3-胺基-6-環丙基-*N*-(3,3,3-三氟-2-羥基-2-甲基丙基)-5-(三氟甲基)吡啶甲醯胺；3-胺基-6-甲氧基-*N*-(3,3,3-三氟-2-羥基-2-(三氟甲基)丙基)-5-(三氟甲基)吡啶甲醯胺；

3-胺基-6-(4-氟-苯基)-5-三氟甲基-吡啶-2-甲酸((S)-3,3,3-三氟-2-羥基 -2-甲基-丙基)-醯胺；

3-胺基-6-甲氧基-5-三氟甲基-吡啶-2-甲酸((S-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-6-甲氧基-5-三氟甲基-吡啶-2-甲酸((R)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-6-(2,4-二氯-苯基)-5-三氟甲基-吡啶-2-甲酸((S)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-6-(2,4-二氯-苯基)-5-三氟甲基-吡啶-2-甲酸((R)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-6-(4-氟-苯基)-5-三氟甲基-吡啶-2-甲酸(2-羥基-2-甲基-丙基)-醯胺；

3-胺基-5,6-雙-三氟甲基-吡啶-2-甲酸((S)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-5,6-雙-三氟甲基-吡啶-2-甲酸((R)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

(S)-3-胺基-6-乙氧基-*N*-(3,3,3-三氟-2-羥基-2-甲基丙基)-5-(三氟甲基)吡啶甲醯胺；

3-胺基-6-甲氧基-5-三氟甲基-吡啶-2-甲酸((S)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-6-甲氧基-5-三氟甲基-吡啶-2-甲酸((R)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-6-(4-氟-苯基)-5-三氟甲基-吡啶-2-甲酸(3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-5,6-雙-三氟甲基-吡啶-2-甲酸((S)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺；

3-胺基-5,6-雙-三氟甲基-吡啶-2-甲酸((R)-3,3,3-三氟-2-羥基-2-甲基-丙基)-醯胺或其醫藥學上可接受之鹽。

在另一個實施例中，其他藥劑爲以全文引用的方式併入本文中的美國專利第8,247,436號及國際PCT公開案WO 2011113894中揭示之化合物。

在另一個實施例中，其他治療劑爲選自以下各者之β模擬劑：阿布特羅(Albuterole)、阿福莫特羅(Arformoterole)、班布特羅(Bambuterole)、比托特羅(Bitolterole)、溴沙特羅(Broxaterole)、卡布特羅(Carbuterole)、克侖特羅(Clenbuterole)、非諾特羅(Fenoterole)、福莫特羅(Formoterole)、海索那林(Hexoprenaline)、異丁特羅(Ibuterole)、異他林(Isoetharine)、異丙腎上腺素、左旋沙丁胺醇(Levosalbutamole)、馬布特羅(Mabuterole)、美盧君(Meluadrine)、美它特羅(Metaproterenole)、米沃特羅(Milveterol)、奧西那林(Orciprenaline)、吡布特羅(Pirbuterole)、丙卡特羅(Procaterole)、瑞普

特羅(Reproterole)、瑞米特羅(Rimiterole)、利托君(Ritodrine)、沙甲胺醇(Salmefamole)、沙美特羅(Salmeterole)、索特瑞醇(Soterenole)、磺特羅(Sulphonterole)、特布他林(Terbutaline)、噻拉米特(Tiaramide)、托布特羅(Tolubuterole)、新特羅(Zinterole)、諾米羅(Nolomirole)及

1-(2-氯-4-羥基苯基)-第三丁基胺基乙醇；

(-)-2-[7(S)-[2(R)-羥基-2-(4-羥基苯基)-乙基胺基]-5,6,7,8-四氫-2-萘氧基]-N,*N*-二甲基乙醯胺鹽酸鹽單水合物；

3-(4-{6-[2-羥基-2-(4-羥基-3-羥基甲基-苯基)-乙基胺基]-己基-氧基}-丁基)-苯甲基-磺醯胺；

5-[2-(5,6-二乙基-茚滿-2-基胺基)-1-羥基-乙基]-8-羥基-1H-喹啉-2-酮；

4-羥基-7-[2-{[2-{[3-(2-苯基乙氧基)丙基]磺醯基}乙基]-胺基}乙基-l]-2(3H)-苯并噻唑酮；

1-(2-氟-4-羥基苯基)-2-[4-(1-苯并咪唑基)-2-甲基-2-丁基胺基]乙醇；

1-[3-(4-甲氧基苯甲基-胺基)-4-羥基苯基]-2-[4-(1-苯并咪唑基)-2-甲基-2-丁基胺基]乙醇；

1-[2H-5-羥基-3-側氧基-4H-1,4-苯并噁嗪-8-基]-2-[3-(4-N,*N*-二甲基胺基苯基)-2-甲基-2-丙基胺基]乙醇；

1-[2H-5-羥基-3-側氧基-4H-1,4-苯并噁嗪-8-基]-2-[3-(4-甲氧基苯基)-2-甲基-2-丙基胺基]乙醇；

1-[2H-5-羥基-3-側氧基-4H-1,4-苯并噁嗪-8-基]-2-[3-(4-正丁氧基苯基)-2-甲基-2-丙基胺基]乙醇；

1-[2H-5-羥基-3-側氧基-4H-1,4-苯并噁嗪-8-基]-2-{4-[3-(4-甲氧基苯基)-1,2,4-三唑-3-基]-2-甲基-2-丁基胺基}乙醇；

5-羥基-8-(1-羥基-2-異丙基胺基丁基)-2H-1,4-苯并噁嗪-3-(4H)-酮；

1-(4-胺基-3-氯-5-三氟甲基苯基)-2-第三丁基胺基)乙醇；

6-羥基-8-{1-羥基-2-[2-(4-甲氧基-苯基)-1,1-二甲基-乙基胺基]-乙基}-4H-苯并[1,4]噁嗪-3-酮；

6-羥基-8-{1-羥基-2-[2-(4-苯氧基-乙酸乙酯)-1,1-二甲基-乙基胺基]-乙基}-4H-苯并[1,4]噁嗪-3-酮；

6-羥基-8-{1-羥基-2-[2-(4-苯氧基-乙酸)-1,1-二甲基-乙基胺基]-乙基}-4H-苯并[1,4]噁嗪-3-酮；

8-{2-[1,1-二甲基-2-(2,4,6-三甲基苯基)-乙基胺基]-1-羥基-乙基}-6-羥基-4H-苯并[1,4]噁嗪-3-酮；

6-羥基-8-{1-羥基-2-[2-(4-羥基-苯基)-1,1-二甲基-乙基胺基]-乙基}-4H-苯并[1,4]噁嗪-3-酮；

6-羥基-8-{1-羥基-2-[2-(4-異丙基-苯基)-1,1二甲基-乙基胺基]-乙基}-4H-苯并[1,4]噁嗪-3-酮；

8-{2-[2-(4-乙基-苯基)-1,1-二甲基-乙基胺基]-1-羥基-乙基}-6-羥基-4H-苯并[1,4]噁嗪-3-酮；

8-{2-[2-(4-乙氧基-苯基)-1,1-二甲基-乙基胺基]-1-羥基-乙基}-6-羥基-4H-苯并[1,4]噁嗪-3-酮；

4-(4-{2-[2-羥基-2-(6-羥基-3-側氧基-3,4-二氫-2H-苯并[1,4]噁嗪-8-基)-乙基胺基]-2-甲基-丙基}-苯氧基)-丁酸；

8-{2-[2-(3,4-二氟-苯基)-1,1-二甲基-乙基胺基]-1-羥基-乙基}-6-羥基-4H-苯并[1,4]噁嗪-3-酮；

1-(4-乙氧基-羰基胺基-3-氰基-5-氟苯基)-2-(第三丁基胺基)乙醇；

*N*-[2-羥基-5-(1-羥基-2-{2-[4-(2-羥基-2-苯基-乙基胺基)-苯基]-乙

基胺基}-乙基)-苯基]-甲醯胺；

8-羥基-5-(1-羥基-2-{2-[4-(6-甲氧基-聯苯-3-基胺基)-苯基]-乙基胺基}-乙基)-1H-喹啉-2-酮；

8-羥基-5-[1-羥基-2-(6-苯乙基胺基-己基胺基)-乙基]-1H-喹啉-2-酮；

5-[2-(2-{4-[4-(2-胺基-2-甲基-丙氧基)-苯基胺基]-苯基}-乙基胺基)-1-羥基-乙基]-8-羥基-1H-喹啉-2-酮；

[3-(4-{6-[2-羥基-2-(4-羥基-3-羥基甲基-苯基)-乙基胺基]己基-氧基}-丁基)-5-甲基-苯基]-脲；

4-(2-{6-[2-(2,6-二氯-苯甲氧基)-乙氧基]-己基胺基}-1-羥基-乙基)-2-羥基甲基-苯酚；

3-(4-{6-[2-羥基-2-(4-羥基-3-羥基甲基-苯基)-乙基胺基]-己基-氧基}-丁基)-苯磺醯胺；

3-(3-{7-[2-羥基-2-(4-羥基-3-羥基甲基-苯基)-乙基胺基]-庚氧基}-丙基)-苯磺醯胺；

4-(2-{6-[4-(3-環戊烷磺醯基-苯基)-丁氧基]-己基胺基}-1-羥基-乙基)-2-羥基甲基-苯酚；

*N*-金剛烷-2-基-2-(3-{2-[2-羥基-2-(4-羥基-3-羥基甲基-苯基)-乙基胺基]-丙基}-苯基)-乙醯胺；

(R,S)-4-(2-{[6-(2,2-二氟-4-苯基丁氧基)己基]胺基}-1-羥基-乙基)-2-(羥基甲基)苯酚；

(R,S)-4-(2-{[6-(2,2-二氟-2-苯基乙氧基)己基]胺基}-1-羥基-乙基)-2-(羥基甲基)苯酚；

(R,S)-4-(2-{[4,4-二氟-6-(4-苯基丁氧基)己基]胺基}-1-羥基-乙基)-2-(羥基-甲基)苯酚；

(R,S)-4-(2-{[6-(4,4-二氟-4-苯基丁氧基)己基]胺基}-1-羥基-乙基)-

2-(羥基甲基)苯酚；

(R,S)-5-(2-{[6-(2,2-二氟-2-苯基乙氧基)己基]胺基}-1-羥基-乙基)-8-羥基喹啉-2(1H)-酮；

(R,S)-[2-({6-[2,2-二氟-2-(3-甲基苯基)乙氧基]己基}胺基)-1-羥基乙基]-2-(羥基甲基)苯酚；

4-(1R)-2-{[6-(2,2-二氟-2-苯基乙氧基)己基]胺基}-1-羥基乙基)-2-(羥基甲基)苯酚；

(R,S)-2-(羥基甲基)-4-(1-羥基-2-{[4,4,515-四氟-6-(3-苯基丙氧基)-己基]胺基}乙基)苯酚；

(R,S)-[5-(2-{[6-(2,2-二氟-2-苯基乙氧基)己基]胺基}-1-羥基-乙基-)-2-羥基-苯基]甲醯胺；

(R,S)-4-[2-({6-[2-(3-溴苯基)-2,2-二氟乙氧基]己基}胺基)-1-羥基乙基]-2-(羥基甲基)苯酚；

(R,S)-*N*-[3-(1,1-二氟-2-{[6-({2-羥基-2-[4-羥基-3-(羥基甲基)- 苯基]-乙基}胺基)己基]氧基}乙基)苯基]脲；

3-[3-(1,1-二氟-2-{[6-({2-羥基-2-[4-羥基-3-(羥基甲基)苯基]乙基}-胺基)己基]氧基}乙基)苯基]咪唑啶-2,4-二酮；

(R,S)-4-[2-({6-[2,2-二氟-2-(3-甲氧基苯基)乙氧基]己基}胺基)-1-羥基乙基]-2-(羥基甲基)苯酚；

5-((1R)-2-{[6-(2,2-二氟-2-苯基乙氧基)己基]胺基}-1-羥基乙基)-8-羥基喹啉-2(1H)-酮；

4-((1R)-2-{[4,4-二氟-6-(4-苯基丁氧基)己基]胺基}-1-羥基-乙基)-2-(羥基甲基)苯酚；

(R,S)-4-(2-{[6-(3,3-二氟-3-苯基丙氧基)己基]胺基}-1-羥基-乙基-)-2-(羥基甲基)苯酚；

(R,S)-(2-{[6-(2,2-二氟-2-苯基乙氧基)-4,4-二氟己基]胺基}-1-羥

基乙基)-2-(羥基甲基)苯酚；

(R,S)-4-(2-{[6-(2,2-二氟-3-苯基丙氧基)己基]胺基}-1-羥基乙基)-2-(羥基-甲基)苯酚；

3-[2-(3-氯-苯基)-乙氧基]-*N*-(2-二乙基胺基-乙基)-*N*-{2-[2-(4-羥基-2-側氧基-2,3-二氫-苯并噻唑-7-基)-乙基胺基]-乙基}-丙醯胺；

*N*-(2-二乙基胺基-乙基)-*N*-{2-[2-(4-羥基-2-側氧基-2,3-二氫-苯并噻唑-7-基)-乙基胺基]-乙基}-3-(2-萘-1-基-乙氧基)-丙醯胺；

7-[2-(2-{3-[2-(2-氯-苯基)-乙基胺基]-丙基硫基}-乙基胺基)-1-羥基-乙基]-4-羥基-3H-苯并噻唑-2-酮；或

7-[(1R)-2-(2-{3-[2-(2-氯-苯基)-乙基胺基]-丙基硫基}-乙基胺基)-1-羥基乙基]-4-羥基-3H-苯并噻唑-2-酮；視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在一個實施例中，其他治療劑爲選自以下之抗膽鹼激導性劑：噻托銨(Tiotropium)鹽(較佳溴化物鹽)、氧托銨(Oxitropium)鹽(較佳溴化物鹽)、氟托銨(Flutropium)鹽(較佳溴化物鹽)、異丙托銨(Ipratropium)鹽(較佳溴化物鹽)、阿地銨(Aclidinium)鹽(較佳溴化物鹽)、格隆銨(Glycopyrronium)鹽(較佳溴化物鹽)、曲司銨(Trospium)鹽(較佳氯化物鹽)、托特羅定(Tolterodin)。自上述鹽，醫藥活性部分爲陽離子，可能陰離子爲氯離子、溴離子、碘離子、硫酸根、磷酸根、甲烷磺酸根、硝酸根、順丁烯二酸根、乙酸根、檸檬酸根、反丁烯二酸根、酒石酸根、乙二酸根、丁二酸根、苯甲酸根或對甲苯磺酸根。較佳抗膽鹼激導性劑之其他實例係選自以下各者：

2,2-二苯基丙酸托品醇酯-甲溴化物；

2,2-二苯基丙酸莨菪品鹼酯-甲溴化物；

2-氟-2,2-二苯基乙酸莨菪品鹼酯-甲溴化物；

2-氟-2,2-二苯基乙酸托品醇酯-甲溴化物；

3,3',4,4'-四氟苯甲酸托品醇酯-甲溴化物；

3,3',4,4'-四氟苯甲酸莨菪品鹼酯-甲溴化物；

4,4'-二氟苯甲酸托品醇酯-甲溴化物；

4,4'-二氟苯甲酸莨菪品鹼酯-甲溴化物；

3,3'-二氟苯甲酸托品醇酯-甲溴化物；

3,3'-二氟苯甲酸莨菪品鹼酯-甲溴化物；

9-羥基-芴-9-碳氫酸托品醇酯-甲溴化物；

9-氟-芴-9-碳氫酸托品醇酯-甲溴化物；

9-羥基-芴-9-碳氫酸莨菪品鹼酯-甲溴化物；

9-氟-芴-9-碳氫酸莨菪品鹼酯甲溴化物；

9-甲基-芴-9-碳氫酸托品醇酯甲溴化物；

9-甲基-芴-9-碳氫酸莨菪品鹼酯甲溴化物；

苯甲酸環丙基托品鹼酯-甲溴化物；

2,2-二苯基丙酸環丙基托品鹼酯-甲溴化物；

9-羥基-二苯并哌喃-9-碳氫酸環丙基托品鹼酯-甲溴化物；

9-甲基-芴-9-碳氫酸環丙基托品鹼酯-甲溴化物；

9-甲基-二苯并哌喃-9-碳氫酸環丙基托品鹼酯-甲溴化物；

9-羥基-芴-9-碳氫酸環丙基托品鹼酯-甲溴化物；

4,4'-二氟苯甲酸甲基酯環丙基托品鹼酯-甲溴化物；

9-羥基-二苯并哌喃-9-碳氫酸托品醇酯-甲溴化物；

9-羥基-二苯并哌喃-9-碳氫酸莨菪品鹼酯甲溴化物；

9-甲基-二苯并哌喃-9-碳氫酸托品醇酯-甲溴化物；

9-甲基-二苯并哌喃-9-碳氫酸莨菪品鹼酯甲溴化物；

9-乙基-二苯并哌喃-9-碳氫酸托品醇酯甲溴化物；

9-二氟甲基-二苯并哌喃-9-碳氫酸托品醇酯-甲溴化物；或

9-羥基甲基-二苯并哌喃-9-碳氫酸莨菪品鹼酯甲溴化物。

在一個實施例中，其他治療劑爲選自以下之皮質類固醇：倍氯米松(Beclomethasone)、倍他米松(Betamethasone)、布地奈德(Budesonide)、布替可特(Butixocorte)、環索奈德(Ciclesonide)、德拉可特(Deflazacorte)、地塞米松(Dexamethasone)、伊替皮諾(Etiprednole)、氟尼縮松(Flunisolide)、氟替卡松(Fluticasone)、羅特皮諾(Loteprednole)、莫米松(Mometasone)、潑尼松龍(Prednisolone)、潑尼松(Prednisone)、羅氟奈德(Rofleponide)、去炎松(Triamcinolone)、替潑尼旦(Tipredane)，

{20R-16α,17α-[亞丁基雙(氧基)]-6α,9α-二氟-11β-羥基-17β-(甲基硫基)雄甾-4-烯-3-酮}；

9-氟-11β,17,21-三羥基-16α-甲基孕甾-1,4-二烯-3,20-二酮21-環己烷甲酸酯17-環丙烷甲酸酯；

16,17-亞丁基二氧基-6,9-二氟-11-羥基-17-(甲基硫基)雄甾-4-烯-3-酮；

氟尼縮松-21-[4'-(硝基氧基甲基)苯甲酸酯]；

6,9-二氟-17-[(2-呋喃基羰基)氧基]-11-羥基-16-甲基-3-側氧基-雄甾-1,4-二烯-17-硫代甲酸(S)-氟甲基酯；

6,9-二氟-11-羥基-16-甲基-3-側氧基-17-丙醯基氧基-雄甾-1,4-二烯-17-硫代甲酸(S)-(2-側氧基-四氫-呋喃-3S-基)酯；或

6α,9α-二氟-11β-羥基-16α-甲基-3-側氧基-17α-(2,2,3,3-四甲基環丙基羰基)氧基-雄甾-1,4-二烯-17β-甲酸氰基甲基酯；視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑

合物或水合物。較佳鹽及衍生物之實例爲鹼金屬鹽，亦即鈉或鉀鹽、磺基苯甲酸鹽、磷酸鹽、異菸酸鹽、乙酸鹽、二氯乙酸鹽、丙酸鹽、磷酸二氫鹽、棕櫚酸鹽、特戊酸鹽或糠酸鹽。

在一個實施例中，其他治療劑爲選自以下各者之PDE4抑制劑：恩丙茶鹼(Enprofylline)、茶鹼(Theophylline)、羅氟司特(Roflumilaste)、艾利福(Ariflo)(西洛司特(Cilomilaste))、托米司特(Tofimilaste)、普馬芬群(Pumafentrine)、利米司特(Lirimilaste)、阿普斯特(Apremilaste)、阿羅茶鹼(Arofylline)、阿左瑞姆(Atizorame)、奧米司特(Oglemilastum)、特米司特(Tetomilaste)；

5-[(*N*-(2,5-二氯-3-吡啶基)-甲醯胺]-8-甲氧基-喹啉；

5-[*N*-(3,5-二氯-1-氧離子基-4-吡啶基)-甲醯胺]-8-甲氧基-2-(三氟甲基)-喹啉；

*N*-(3,5-二氯吡啶-4-基)-[1-(4-氟苯甲基)-5-羥基-吲哚-3-基]乙醛醯胺)；

9-[(2-氟苯基)甲基]-*N*-甲基-2-(三氟甲基)-9H-嘌呤-6-胺；

4-[(2R)-2-[3-(環戊基氧基)-4-甲氧基苯基]-2-苯基乙基]-吡啶；

*N*-[(3R)-3,4,6,7-四氫-9-甲基-4-側氧基-1-苯基吡咯并[3,2,1-jk-][1,4]苯并二氮呯-3-基]-4-吡啶甲醯胺；

4-[6,7-二乙氧基-2,3-雙(羥基甲基)-1-萘基]-1-(2-甲氧基乙基)-2(1H)-吡啶酮；

2-[4-[6,7-二乙氧基-2,3-雙(羥基甲基)-1-萘基]-2-吡啶基]-4-(3-吡啶基)-1 (2H)-酞嗪酮；

(3-(3-環戊基氧基-4-甲氧基苯甲基)-6-乙基胺基-8-異丙基-3H-嘌呤；

β-[3-(環戊基氧基)-4-甲氧基苯基]-1,3-二氫-1,3-二側氧基-2H-異吲哚-2-丙醯胺；

9-乙基-2-甲氧基-7-甲基-5-丙基-咪唑并[1,5-a]吡啶并[3,2-e]吡嗪-6(-5H)-酮；

5-[3-(環戊基氧基)-4-甲氧基苯基]-3-[(3-甲基苯基)甲基](3S,5S)-2-哌啶酮；

4-[1-[3,4-雙(二氟甲氧基)苯基]-2-(3-甲基-1-氧離子基-4-吡啶基)乙基]-α,α-雙(三氟甲基)-苯甲醇；

*N*-(3,5-二氯-1-側氧基-吡啶-4-基)-4-二氟甲氧基-3-環丙基甲氧基-苯甲醯胺；

(-)p-[(4aR*,10bS*)-9-乙氧基-1,2,3,4,4a,10b-六氫-8-甲氧基-2-甲基-苯并[s][1,6]嗦啶-6-基]-N,*N*-二異丙基苯甲醯胺；

(R)-(+)-1-(4-溴苯甲基)-4-[(3-環戊基氧基)-4-甲氧基苯基]-2-吡咯啶酮；

3-(環戊基氧基-4-甲氧基苯基)-1-(4-N'-[*N*-2-氰基-S-甲基-異硫脲基]-苯甲基)-2-吡咯啶酮；

順[4-氰基-4-(3-環戊基氧基-4-甲氧基苯基)環己烷-1-碳氫酸]；

2-甲氧羰基-4-氰基-4-(3-環丙基甲氧基-4-二氟甲氧基苯基)-環己烷-1-酮；

順[4-氰基-4-(3-環丙基甲氧基-4-二氟甲氧基苯基)環己-1-醇]；

(R)-(+)-[4-(3-環戊基氧基-4-甲氧基苯基)吡咯啶-2-亞基]乙酸乙酯；

(S)-(-)-[4-(3-環戊基氧基-4-甲氧基苯基)吡咯啶-2-亞基]乙酸乙酯；

9-環戊基-5,6-二氫-7-乙基-3-(2-噻吩基)-9H-吡唑并[3,4-c]-1,2,4-三唑并[4,3-a]吡啶；或

9-環戊基-5,6-二氫-7-乙基-3-(第三丁基)-9H-吡唑并[3,4-c]-1,2,4-三唑并[4,3-a]吡啶；視情況呈外消旋形式，呈對映異構體、非對映異

構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在一個實施例中，其他治療劑爲選自以下各者之LTD4拮抗劑：孟魯司特(Montelukast)、普魯司特(Pranlukast)、紮魯司特(Zafirlukast)、馬斯司特(Masikulast)、L-733321（參見D. Guay等人Bioorg. Med. Chem. Lett. 8 (1998) 453-458之化合物2ab)；

(E)-8-[2-[4-[4-(4-氟苯基)丁氧基]苯基]乙烯基]-2-(1H-四唑-5-基)-4H-1-苯并哌喃-4-酮；

4-[6-乙醯基-3-[3-(4-乙醯基-3-羥基-2-丙基苯基硫基)丙氧基]-2-丙基- 苯氧基]-丁酸；

1-(((R)-(3-(2-(6,7-二氟-2-喹啉基)乙烯基)苯基)-3-(2-(2-羥基-2-丙基)苯基)硫基)甲基環丙烷-乙酸；

1-(((1(R)-3(3-(2-(2,3-二氯噻吩并[3,2-b]吡啶-5-基)-(E)-乙烯基)苯基)-3-(2-(1-羥基-1-甲基乙基)苯基)丙基)硫基)甲基)環丙烷乙酸；或

[2-[[2-(4-第三丁基-2-噻唑基)-5-苯并呋喃基]氧基甲基]苯基]乙酸；視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。視情況較佳鹽及衍生物之其他實例爲鹼金屬鹽，亦即鈉或鉀鹽、磺基苯甲酸鹽、磷酸鹽、異菸酸鹽、乙酸鹽、丙酸鹽、磷酸二氫鹽、棕櫚酸鹽、特戊酸鹽或糠酸鹽。

在一個實施例中，其他治療劑爲選自以下各者之EGFR抑制劑：西妥昔單抗(Cetuximab)、曲妥珠單抗(Trastuzumab)、帕尼單抗(Panitumumab)、吉非替尼(Gefitinib)、卡奈替尼(Canertinib)、埃羅替尼(Erlotinib)、Mab ICR-62；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-7-環丙基甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二乙基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-環丙基甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-環丙基甲氧基-喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-{[4-(嗎啉-4-基)-1-側氧基-2-丁烯-1-基- ]胺基}-7-環戊基氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-((R)-6-甲基-2-側氧基-嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-7-環丙基甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-((R)-6-甲基-2-側氧基-嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-7-[(S)-(四氫呋喃-3-基)氧基]-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-((R)-2-甲氧基甲基-6-側氧基-嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-7-環丙基甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[2-((S)-6-甲基-2-側氧基-嗎啉-4-基)-乙氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-({4-[*N*-(2-甲氧基-乙基)-*N*-甲基-胺基]-1-側氧基-2-丁烯-1-基}胺基)-7-環丙基甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-環戊基氧基-喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-{[4-(N,*N*-雙-(2-甲氧基-乙基)-胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-環丙基甲氧基-喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-({4-[*N*-(2-甲氧基-乙基)-*N*-乙基-胺基]-1-側氧基-2-丁烯-1-基}胺基)-7-環丙基甲氧基-喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-({4-[*N*-(2-甲氧基-乙基)-*N*-甲基-胺基]-1-側氧基-2-丁烯-1-基}胺基)-7-環丙基甲氧基-喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-({4-[*N*-(四氫哌喃-4-基)-*N*-甲基-胺基]-1-側氧基-2-丁烯-1-基}胺基)-7-環丙基甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-((R)-四氫呋喃-3-基氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-((S)-四氫呋喃-3-基氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-({4-[*N*-(2-甲氧基-乙基)-*N*-甲基-胺基]-1-側氧基-2-丁烯-1-基}胺基)-7-環戊基氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(*N*-環丙基-*N*-甲基-胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-環戊基氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-[(R)-(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-[(S)-(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6,7-雙-(2-甲氧基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-7-[3-(嗎啉-4-基)-丙基氧基]-6-[(乙烯基羰基)胺基]-喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-(4-羥基-苯基)-7H-吡咯并[2,3-d]嘧啶；

3-氰基-4-[(3-氯-4-氟苯基)胺基]-6-{[4-(N,*N*-二甲基胺基)-1-側氧基-2-丁烯-1-基]胺基}-7-乙氧基-喹啉；

4-{[3-氯-4-(3-氟-苯甲氧基)-苯基]胺基}-6-(5-{[(2-甲磺醯基- 乙

基)胺基]甲基}-呋喃-2-基)喹唑啉；

4-[(R)-(1-苯基-乙基)胺基]-6-{[4-((R)-6-甲基-2-側氧基-嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{[4-(嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-7-[(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-({4-[N,*N*-雙-(2-甲氧基-乙基)-胺基]-1-側氧基-2-丁烯-1-基}胺基)-7-[(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-{[4-(5,5-二甲基-2-側氧基-嗎啉-4-基)-1-側氧基-2-丁烯-1-基]胺基}-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[2-(2,2-二甲基-6-側氧基-嗎啉-4-基)-乙氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[2-(2,2-二甲基-6-側氧基-嗎啉-4-基)-乙氧基]-7-[(R)-(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-7-[2-(2,2-二甲基-6-側氧基-嗎啉-4-基)-乙氧基]-6-[(S)-(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{2-[4-(2-側氧基-嗎啉-4-基)-哌啶-1-基]-乙氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[1-(第三丁基氧基羰基)-哌啶-4-基氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(反-4-胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(反-4-甲磺醯基胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(四氫哌喃-3-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-甲基-哌啶-4-基氧基)-7-甲氧基-喹

唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(嗎啉-4-基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(甲氧基甲基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(哌啶-3-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[1-(2-乙醯基胺基-乙基)-哌啶-4-基氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(四氫哌喃-4-基氧基)-7-乙氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-((S)-四氫呋喃-3-基氧基)-7-羥基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(四氫哌喃-4-基氧基)-7-(2-甲氧基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{反-4-[(二甲基胺基)磺醯基胺基]-環己烷-1-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{反-4-[(嗎啉-4-基)羰基胺基]-環己烷-1-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{反-4-[(嗎啉-4-基)磺醯基胺基]-環己烷-1-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(四氫哌喃-4-基氧基)-7-(2-乙醯基-胺基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(四氫哌喃-4-基氧基)-7-(2-甲磺醯基胺基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(哌啶-1-基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-胺基羰基甲基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-{*N*-[(四氫哌喃-4-基)羰基]-*N*-甲基-胺基}-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-{*N*-[(嗎啉-4-基)羰基]-*N*-甲基-胺基}-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-{*N*-[(嗎啉-4-基)磺醯基]-*N*-甲基-胺基}-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(反-4-乙磺醯基胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-甲磺醯基-哌啶-4-基氧基)-7-乙氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-甲磺醯基-哌啶-4-基氧基)-7-(2-甲氧基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[1-(2-甲氧基-乙醯基)-哌啶-4-基-氧基]-7-(2-甲氧基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-乙醯基胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-[1-(第三丁基氧基羰基)-哌啶-4-基氧基]-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-(四氫哌喃-4-基氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-{*N*-[(哌啶-1-基)羰基]-*N*-甲基-胺基}-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-{*N*-[(4-甲基-哌嗪-1-基)-羰基]-*N*-甲基-胺基}-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{順-4-[(嗎啉-4-基)羰基胺基]-環己烷-1-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[2-(2-側氧基吡咯啶-1-基)乙基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(嗎啉-4-基)羰基]-哌啶-4-基氧基}-7-(2-甲氧基-乙氧基)-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-(1-乙醯基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-(1-甲基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-(1-甲磺醯基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-甲基-哌啶-4-基氧基)-7-(2-甲氧基-乙氧基)-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-異丙基氧基羰基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(順-4-甲基胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{順-4-[*N*-(2-甲氧基-乙醯基)-*N*-甲基-胺基]-環己烷-1-基氧基}-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-(哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-[1-(2-甲氧基-乙醯基)-哌啶-4-基氧基]-7-甲氧基-喹唑啉；

4-[(3-乙炔基-苯基)胺基]-6-{1-[(嗎啉-4-基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[順-2,6-二甲基-嗎啉-4-基)- 羰基]-

哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(2-甲基-嗎啉-4-基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(S,S)-(2-氧雜-5-氮雜-雙環[2.2.1]-庚-5-基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(*N*-甲基-*N*-2-甲氧基乙基-胺基)-羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-乙基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(2-甲氧基乙基)羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-{1-[(3-甲氧基丙基-胺基)-羰基]-哌啶-4-基氧基}-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[順-4-(*N*-甲磺醯基-*N*-甲基-胺基)-環己烷-1-基氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[順-4-(*N*-乙醯基-*N*-甲基-胺基)-環己烷-1-基氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(反-4-甲基胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[反-4-(*N*-甲磺醯基-*N*-甲基-胺基)-環己烷-1-基氧基]-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(反-4-二甲基胺基-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(反-4-{*N*-[(嗎啉-4-基)羰基]-*N*-甲基-胺基}-環己烷-1-基氧基)-7-甲氧基-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-[2-(2,2-二甲基-6-側氧基-嗎啉-4-基)-

乙氧基]-7-[(S)-(四氫呋喃-2-基)甲氧基]-喹唑啉；

4-[(3-氯-4-氟苯基)胺基]-6-(1-甲磺醯基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；或

4-[(3-氯-4-氟苯基)胺基]-6-(1-氰基-哌啶-4-基氧基)-7-甲氧基-喹唑啉；視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在另一個實施例中，其他治療劑爲選自以下各者之多巴胺拮抗劑：溴麥角環肽(Bromocriptine)、卡麥角林(Cabergoline)、α-二氫麥角隱亭(Alpha-Dihydroergocryptine)、麥角乙脲(Lisuride)、培高利特(Pergolide)、普拉克索(Pramipexole)、羅克吲哚(Roxindole)、羅匹尼洛(Ropinirole)、他利克索(Talipexole)、特麥角脲(Terguride)及維紮尼(Viozane)，視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在另一個實施例中，其他治療劑爲選自以下各者之抗過敏劑：依匹斯汀(Epinastine)、西替利嗪(Cetirizine)、氮拉斯汀(Azelastine)、菲索芬那定(Fexofenadine)、左卡巴司汀(Levocabastine)、洛拉他定(Loratadine)、咪唑司汀(Mizolastine)、甲哌噻庚酮(Ketotifene)、依美斯汀(Emedastine)、二甲茚定(Dimetindene)、氯馬斯汀(Clemastine)、

巴米品(Bamipine)、右氯苯拉敏(Cexchlorpheniramine)、苯吡胺(Pheniramine)、苯吡拉明(Doxylamine)、氯苯安明(Chlorphenoxamine)、茶苯海明(Dimenhydrinate)、苯海拉明(Diphenhydramine)、普敏太定(Promethazine)、依巴司汀(Ebastine)、奧洛他定(Olopatadine)、地氯雷他定(Desloratidine)及美克洛嗪(Meclozine)，視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在一個實施例中，其他治療劑爲選自以下各者之MAP激酶抑制劑：倍它莫德(Bentamapimod)、達馬莫德(Doramapimod)、5-卡巴莫德(5-Carbamoylindole)、5-胺甲醯基吲哚、6-[(胺基羰基)(2,6-二氟苯基)胺基]-2-(2,4-二氟苯基)-3-吡啶甲醯胺、α-[2-[[2-(3-吡啶基)乙基]胺基]-4-嘧啶基]-2-苯并噻唑乙腈、9,12-環氧基-1H-二吲哚并[1,2,3-fg:3',2',1'-kl]吡咯并[3,4-i][1,6]苯并二氮-咔-10-甲酸或4-[3-(4-氯苯基)-5-(1-甲基-4-哌啶基)-1H-吡唑-4-基]-嘧啶，視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在一個實施例中，其他治療劑爲選自以下各者之MRP4抑制劑：N-乙醯基-二硝基苯基-半胱胺酸、cGMP、膽酸鹽、雙氯芬酸(Diclofenac)、脫氫表雄酮3-葡萄糖苷酸(Dehydroepiandrosterone 3-

glucuronide)、脫氫表雄酮3-硫酸鹽(Dehydroepiandrosterone 3-sulphate)、地拉齊普(Dilazep)、二硝基苯基-S-麩胱甘肽(Dinitrophenyl-S-glutathione)、雌二醇17-β-葡萄糖苷酸(Estradiol 17-beta-glucuronide)、雌二醇3,17-硫酸氫鹽(Estradiol 3,17-disulphate)、雌二醇3-葡萄糖苷酸(Estradiol 3-glucuronide)、雌二醇3-硫酸鹽(Estradiol 3-sulphate)、雌酮3-硫酸鹽(Estrone 3-sulphate)、氟比洛芬(Flurbiprofen)、葉酸鹽(Folate)、N5-甲醯基-四氫葉酸(N5-formyl-tetrahydrofolate)、甘膽酸鹽(Glycocholate)、葡糖石膽酸硫酸鹽(Glycolithocholic acid sulphate)、布洛芬(Ibuprofen)、吲哚美辛(Indomethacin)、吲哚洛芬(Indoprofen)、酮基布洛芬(Ketoprofen)、石膽酸硫酸鹽(Lithocholic acid sulphate)、甲胺喋呤(Methotrexate)、((E)-3-[[[3-[2-(7-氯-2-喹啉基)乙烯基]苯基]-[3-二甲胺基)-3-側氧基丙基]硫基]甲基]硫基]-丙酸)、α-萘基-β-D-葡萄糖苷酸、硝基苯甲基甦基嘌呤核糖苷、丙磺舒(Probenecid)、伐司撲達(Valspodar)、西地那非(Sildenafil)、苯磺唑酮(Sulfinpyrazone)、牛磺鵝去氧膽酸鹽(Taurochenodeoxycholate)、牛磺膽酸鹽(Taurocholate)、牛磺去氧膽酸鹽(Taurodeoxycholate)、牛磺石膽酸鹽(Taurolithocholate)、牛磺石膽酸硫酸鹽(Taurolithocholic acid sulphate)、拓朴替康(Topotecan)、曲喹辛(Trequinsin)、紮普司特(Zaprinast)或雙嘧達莫(Dipyridamol)，視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在一個實施例中，其他治療劑爲選自以下各者之iNOS抑制劑：

S-(2-胺基乙基)異硫脲、胺基胍、2-胺基甲基吡啶、5,6-二氫-6-甲基-4H-1,3-噻嗪-2-胺(AMT)、L-刀豆胺酸、2-亞胺基哌啶、S-異丙基異硫脲、S-甲基異硫脲、S-乙基異硫脲、S-甲基硫基瓜胺酸、S-乙基硫基瓜胺酸、L-NA (N$^{\omega}$-硝基-L-精胺酸)、L-NAME (N$^{\omega}$-硝基-L-精胺酸甲酯)、L-NMMA (N$^{\omega}$-單甲基-L-精胺酸)、L-NIO (N$^{\omega}$-亞胺基乙基-L-鳥胺酸)、L-NIL (N$^{\omega}$-亞胺基乙基-離胺酸)，

(S)-6-乙醯亞胺醯基胺基-2-胺基-己酸(1H-四唑-5-基)-醯胺；

*N*-[[3-(胺基甲基)苯基]甲基]-乙醯亞胺；

(S)-4-(2-乙醯亞胺醯基胺基-乙基硫基)-2-胺基-丁酸；

2-[2-(4-甲氧基-吡啶-2-基)-乙基]-3H-咪唑并[4,5-b]吡啶；

2-((R)-3-胺基-1-苯基-丙氧基)-4-氯-5-氟苯甲腈；

2-((1R,3S)-3-胺基-4-羥基-1-噻唑-5-基-丁基硫基)-6-三氟甲基-菸鹼腈；

2-((1R,3S)-3-胺基-4-羥基-1-噻唑-5-基-丁基硫基)-4-氯-苯甲腈；

2-((1R,3S)-3-胺基-4-羥基-1-噻唑-5-基-丁基硫基)-5-氯-苯甲腈；

(2S,4R)-2-胺基-4-(2-氯-5-三氟甲基-苯基硫基)-4-噻唑-5-基-丁-1-醇；

2-((1R,3S)-3-胺基-4-羥基-1-噻唑-5-基-丁基硫基)-5-氯-菸鹼腈；

4-((S)-3-胺基-4-羥基-1-苯基-丁基硫基)-6-甲氧基-菸鹼腈；或經取代之3-苯基-3,4-二氫-1-異喹啉胺，例如(1S,5S,6R)-7-氯-5-甲基-2-氮雜-雙環[4.1.0]伸庚-2-基-3-基胺、(4R,5R)-5-乙基-4-甲基-噻唑啶-2-亞基胺、(1S,5S,6R)-7-氯-5-甲基-2-氮雜-雙環[4.1.0]伸庚-2-基-3-基胺、(4R,5R)-5-乙基-4-甲基-噻唑啶-2-亞基胺、(4R,5R)-5-乙基-4-甲基-硒唑啶-2-亞基胺、4-胺基四氫生物喋呤、(E)-3-(4-氯-苯基)-*N*-(1-{2-側氧基-2-[4-(6-三氟甲基-嘧啶-4-基氧基)-哌啶-1-基]-乙基胺甲醯基}-2-吡啶-2-基-乙基)-丙烯醯胺、3-(2,4-二氟-苯基)-6-[2-(4-咪唑-1-基甲

基-苯氧基)-乙氧基]-2-苯基-吡啶、3-{[(苯并[1,3]間二氧雜環戊烯-5-基甲基)-胺甲醯基]-甲基}-4-(2-咪唑-1-基-嘧啶-4-基)-哌嗪-1-碳氫酸甲基酯或(R)-1-(2-咪唑-1-基-6-甲基-嘧啶-4-基)-吡咯啶-2-碳氫酸(2-苯并[1,3]二側氧基1-5-基-乙基)-醯胺，視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。可提及之較佳iNOS抑制劑之其他實例包括反義寡核苷酸，尤其結合iNOS編碼核酸之彼等反義寡核苷酸，其實例揭示於以全文引用的方式併入本文中的WO 01/52902中。

在另一個實施例中，其他治療劑爲選自以下各者之SYK抑制劑：

2-[(2-胺基乙基)胺基]-4-[(3-溴苯基)胺基]-5-嘧啶甲醯胺；

2-[[7-(3,4-二甲氧基苯基)咪唑并[1,2-c]嘧啶-5-基]胺基]-3-吡啶甲醯胺；

6-[[5-氟-2-[3,4,5-三甲氧基苯基)胺基]-4-嘧啶基]胺基]-2,2-二甲基-2H-吡啶并[3,2-b]-1,4-噁嗪-3(4H)-酮；

*N*-[3-溴-7-(4-甲氧基苯基)-1,6-啶啶-5-基]-1,3-丙二胺；

7-(4-甲氧基苯基)-*N*-甲基-1,6-啶啶-5-胺；

*N*-[7-(4-甲氧基苯基)-1,6-啶啶-5-基]-1,3-丙二胺；

*N*-[7-(2-噻吩基)-1,6-啶啶-5-基-1,3-丙二胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-啶啶-5-基]-1,2-乙二胺；

*N*-[7-(4-甲氧基苯基)-2-(三氟甲基)-1,6-啶啶-5-基]-1,3-丙二胺；

*N*-[7-(4-甲氧基苯基)-3-苯基-1,6-啶啶-5-基]-1,3-丙二胺；

*N*-(7-苯基-1,6-啶啶-5-基)-1,3-丙二胺；

*N*-[7-(3-氟苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(3-氯苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[3-(三氟甲氧基)苯基]-1,6-萘啶-5基]-1,3-丙二胺；

*N*-[7-(4-氟苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(4-氟苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(4-氯苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(4'-甲基[1,1'-聯苯]-4-基)-1,6-萘啶-1,3-丙二胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(二乙基胺基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(4-嗎啉基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-[[2-(二甲基胺基)乙基]甲基胺基]苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(4-溴苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(4-甲基苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(甲基硫基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(1-甲基乙基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

7-[4-(二甲基胺基)苯基]-*N*-甲基-1,6-萘啶-5-胺；

7-[4-(二甲基胺基)苯基]-N,*N*-二甲基-1,6-萘啶-5-胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,4-丁二胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,5-戊二胺；

3-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]氧基]-1-丙醇；

4-[5-(4-胺基丁氧基)-1,6-萘啶-7-基]-N,*N*-二甲基-苯胺；

4-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]胺基]-1-丁醇；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-*N*-甲基-1,3-丙二胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-N'-甲基-1,3-丙二胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-N,N'-二甲基-1,3-丙二

胺；

1-胺基-3-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]胺基]-2-丙醇；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-2,2-二甲基-1,3-丙二胺；

7-[4-(二甲基胺基)苯基]-*N*-(3-吡啶基甲基)-1,6-萘啶-5-胺；

*N*-[(2-胺基苯基)甲基]-7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-胺；

*N*-[7-[6-(二甲基胺基)[1,1'-聯苯]-3-基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[3-氯-4-(二乙基胺基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(二甲基胺基)-3-甲氧基苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(二乙基胺基)苯基]-3-甲基-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(3'-氟[1,1'-聯苯]-3-基)-1,6-萘啶-5-基]-1,2-乙二胺；

*N*-[7-(4-甲氧基苯基)-1,6-萘啶-5-基]-1,6-萘啶-1,3-丙二胺；

N,N'-雙(3-胺基丙基)-7-(4-甲氧基苯基)-2,5-二胺；

*N*-[7-(4-甲氧基苯基)-2-(苯基甲氧基)-1,6-萘啶-5-基]-1,6-萘啶-1,3-丙二胺；

N5-(3-胺基丙基)-7-(4-甲氧基苯基)-N2-(苯基甲基)-2,5-二胺；

*N*-[7-(2-萘基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(2'-氟[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(3,4,5-三甲氧基苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(3,4-二甲基苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

1-胺基-3-[[7-(2-萘基)-1,6-萘啶-5-基]胺基]-2-丙醇；

1-胺基-3-[[7-(2'-氟[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]胺基]-2-丙醇；

1-胺基-3-[[7-(4'-甲氧基[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]胺基]-2-丙醇；

1-胺基-3-[[7-(3,4,5-三甲氧基苯基)-1,6-萘啶-5-基]胺基]-2-丙醇；

1-胺基-3-[[7-(4-溴苯基)-1,6-萘啶-5-基]胺基]-2-丙醇；

*N*-[7-(4'-甲氧基[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]-2,2-二甲基-1,3-丙二胺；

1-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]胺基]-2-丙醇；

2-[[2-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]胺基]-乙基]硫基]-乙醇；

7-[4-(二甲基胺基)苯基]-*N*-(3-甲基-5-異噁唑基)-1,6-萘啶-5-胺；

7-[4-(二甲基胺基)苯基]-*N*-4-嘧啶-1,6-萘啶-5-胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,3-環己烷 二胺；

N,*N*-二甲基-4-[5-(1-哌嗪基)-1,6-萘啶-7-基]-苯胺；

4-[5-(2-甲氧基乙氧基)-1,6-萘啶-7-基]-N,*N*-二甲基-苯胺；

1-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-4-哌啶醇；

1-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-3-吡咯啶醇；

7-[4-(二甲基胺基)苯基]-*N*-(2-呋喃基甲基)-1,6-萘啶-5-胺；

7-[4-(二甲基胺基)苯基]-*N*-[3-(1H-咪唑-1-基)丙基]-1,6-萘啶-5-胺；

1-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-4-哌啶甲醯胺；

1-[3-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]胺基]丙基]-2-吡咯啶酮；

*N*-[3'-[5-[(3-胺基丙基)胺基]-1,6-萘啶-7-基][1,1'-聯苯]-3-基]-乙醯胺；

*N*-[7-(4'-氟[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[4'-[5-[(3-胺基丙基)胺基]-1,6-萘啶-7-基][1,1'-聯苯]-3-基]-乙醯

胺；

*N*-[7-[4-(1,3-苯并間二氧雜環戊烯-5-基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(2-噻吩基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-氟-3-(三氟甲基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(3-吡啶基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(1,3-苯并間二氧雜環戊烯-5-基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(6-甲氧基-2-萘基)-1,6-萘啶-5-基]-1,3-丙二胺；

7-[4-(二甲基胺基)苯基]-*N*-(4-吡啶基甲基)-1,6-萘啶-5-胺；

3-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]甲基胺基]-丙腈；

7-[4-(二甲基胺基)苯基]-*N*-[1-(苯基甲基)-4-哌啶基]-1,6-萘啶-5-胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,2-環己烷二胺；

(1R,2S)-rel-*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,2-環己烷二胺；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,2-苯二甲胺；

*N*-[7-[4-(二乙基胺基)苯基]-1,6-萘啶-5-基]-1,4-丁二胺；

*N*-[7-[3',5'-雙(三氟甲基)[1,1'-聯苯]-4-基]-1,6-萘啶-5-基]-,3-丙二胺；

*N*-[7-(3'-甲氧基[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(3'-氟[1,1'-聯苯]-4-基)-1,6-萘啶-5-基]-1,3-丙二胺；

4-[[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]氧基]-1-丁醇；

*N*-[7-[4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,4-環己烷二胺；

7-[4-(二甲基胺基)苯基]-*N*-(2,2,6,6-四甲基-4-哌啶基)-1,6-萘啶-5-胺；

*N*-[7-[3-溴-4-(二甲基胺基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(1-甲基-1H-吲哚-5-基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[3-(三氟甲基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-(三氟甲基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-(3-溴-4-甲氧基苯基)-1,6-萘啶-5-基]-1,3-丙二胺；

*N*-[7-[4-[[3-(二甲基胺基)丙基]甲基胺基]苯基]-1,6-萘啶-5-基]-1,4-環己烷二胺；

*N*-[7-[4-[[2-(二甲基胺基)乙基]甲基胺基]苯基]-1,6-萘啶-5-基]-1,4-環己烷二胺；

*N*-[7-[4-(二甲基胺基)-3-甲氧基苯基]-1,6-萘啶-5-基]-1,4-環己烷二胺；

*N*-[7-[4-(4-嗎啉基)苯基]-1,6-萘啶-5-基]-1,4-環己烷二胺；

*N*-[7-[3-溴-4-(4-嗎啉基)苯基]-1,6-萘啶-5-基]-1,4-環己烷-二胺；

4-[[7-[4-[[2-(二甲基胺基)乙基]甲基胺基]苯基]-1,6-萘啶-5-基]氧基]-環己醇；

*N*-[7-[3-溴-4-(4-嗎啉基)苯基]-1,6-萘啶-5-基]-1,3-丙二胺；

N,*N*-二甲基-4-[5-(4-甲基-1-哌嗪基)-1,6-萘啶-7-基]-苯胺；

4-[[7-[4-[[3-(二甲基胺基)丙基]甲基胺基]苯基]-1,6-萘啶-5-基]氧基]-環己醇；

*N*-[7-[4-[[2-(二甲基胺基)乙基]甲基胺基]苯基]-1,6-萘啶-5-基]-1,4-丁二胺；或

[3-[[5-[(3-胺基丙基)胺基]-7-(4-甲氧基苯基)-1,6-萘啶-2-基]- 胺基]丙基]-胺基甲酸-1,1-二甲基乙基酯，視情況呈外消旋形式，呈對映異構體、非對映異構體或呈醫藥學上可接受之鹽、溶劑合物或水合物。較佳鹽選自由以下各者組成之群：鹽酸鹽、氫溴酸鹽、氫碘酸鹽、硫酸氫鹽、磷酸氫鹽、甲烷磺酸氫鹽、硝酸氫鹽、順丁烯二酸氫

鹽、乙酸氫鹽、檸檬酸氫鹽、反丁烯二酸氫鹽、酒石酸氫鹽、草酸氫鹽、丁二酸氫鹽、苯甲酸氫鹽及對甲苯磺酸氫鹽。

在另一個實施例中，其他治療劑爲抑制CAL (亦稱爲CFTR相關配位體)與突變CFTR蛋白質之間的相互作用之藥劑。在一個實施例中，抑制CAL與突變CFTR蛋白質之間的相互作用之藥劑爲肽或肽模擬物(例如長度爲6至20個殘基)。在另一個實施例中，抑制CAL與突變CFTR蛋白質之間的相互作用之藥劑爲以全文引用的方式併入本文中的美國公開專利申請案第US2014/0100155 A1號中所揭示之肽或肽模擬物。

在另一個實施例中，上述醫藥組合物含有本發明之化合物的醫藥學上可接受之前藥。

在一個態樣中，本發明之醫藥組合物可每天或約每二十四小時投與患者一次。或者，本發明之醫藥組合物可每天投與患者兩次。或者，本發明之醫藥組合物可約每十二小時投與。此等醫藥組合物呈含有約25 mg、50 mg、100 mg、125 mg、150 mg、200 mg、250 mg、300 mg或400 mg式I化合物之口服調配物投與。在此態樣中，醫藥組合物進一步包含填充劑；崩解劑；界面活性劑；黏合劑；或潤滑劑或其組合。

亦應瞭解，本發明之醫藥組合物，包括包含前述組合之醫藥組合物，可用於組合療法中；亦即，組合物可與一或多種其他所需治療劑或醫學程序同時、在其之前或在其之後。

此等組合適用於治療本文所述之疾病，包括囊腫纖維化症。此等組合亦適用於本文所述之套組。

存在於本發明之組合物中之其他治療劑的量將不超過將在包含該治療劑作爲唯一活性劑之組合物中投與的量。目前所揭示之組合物中其他治療劑之量較佳將在包含該藥劑作爲唯一治療活性劑之組合物

中正常存在之量的約50%至100%的範圍內。

**式I-Ij之化合物及其醫藥組合物的治療用途**

在一個態樣中，本發明亦提供一種治療患者之疾病、減輕疾病之嚴重程度或症狀上治療疾病的方法，該方法包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物，其中該疾病係選自囊腫纖維化症、哮喘、抽菸誘發之COPD、慢性支氣管炎、鼻竇炎、便秘、胰臟炎、胰臟功能不全、由先天性雙側輸精管缺乏(CBAVD)引起之男性不育、輕度肺部疾病、特發性胰臟炎、過敏性支氣管肺麴黴病(ABPA)、肝病、遺傳性肺氣腫、遺傳性血色素沉著病、凝血-纖維蛋白溶解不足(諸如蛋白質C不足及1型遺傳性血管性水腫)、脂質處理不足(諸如家族性高膽固醇血症、1型乳糜微粒血症及β-脂蛋白缺乏症)、溶酶體儲存疾病(諸如I-細胞疾病/假賀勒(pseudo-Hurler))、黏多醣症、山多夫/泰-薩池(Sandhof/Tay-Sachs)、II型克果納傑氏症候群(Crigler-Najjar type II)、多內分泌腺病/高胰島素血症、糖尿病、勞倫侏儒症(Laron dwarfism)、髓過氧化酶缺乏症、原發性副甲狀腺低能症、黑色素瘤、1型醣酵解CDG、先天性甲狀腺高能症、成骨不全、遺傳性低纖維蛋白原血症、ACT缺乏症、尿崩症(DI)、垂體神經部DI、腎源性DI、恰克-馬里耶杜斯症候群(Charcot-Marie Tooth syndrome)、佩利措伊斯-梅茨巴赫病(Pelizaeus-Merzbacher disease)、神經退化性疾病(諸如阿茲海默氏病(Alzheimer's disease)、帕金森氏症(Parkinson's disease)、肌肉萎縮性側索硬化、進行性核上麻痺及皮克病(Pick's disease))、若干聚麩醯胺酸神經病症(諸如亨廷頓氏(Huntington's)、I型脊髓小腦失調、脊髓延髓肌肉萎縮、齒狀核紅核蒼白球路易體萎縮症(dentatorubral pallidoluysian atrophy)及肌緊張性營養不良)、海綿狀腦病(諸如遺傳性庫賈氏病(hereditary Creutzfeldt-Jakob disease)(歸因於朊病毒蛋白質處理缺陷))、法布立病(Fabry

disease)、格斯曼-斯托斯勒-謝恩克爾症候群(Gerstmann-Straussler-Scheinker syndrome)、COPD、乾眼病或休格連氏病(Sjogren's disease)、骨質疏鬆、骨質減少、骨骼癒合及骨骼生長(包括骨骼修復、骨骼再生、減少骨骼再吸收及增加骨骼沈積)、戈漢症候群(Gorham's Syndrome)、氯離子通道病(諸如先天性肌強直(湯姆森(Thomson)及貝克爾(Becker)形式)、III型巴特症候群(Bartter's syndrome type III)、登特病(Dent's disease)、癲癇症、溶酶體儲存疾病、安格爾曼症候群(Angelman syndrome)及原發性睫運動障礙(PCD，睫毛結構及/或功能之遺傳性病症的術語，包括具有逆位之PCD (亦稱爲卡塔基納症候群(Kartagener syndrome)、不具有逆位之PCD及睫發育不全)。

在另一個實施例中，本發明之治療患者疾病、減輕其嚴重程度或症狀上治療其的方法包含投與有效量之本發明之醫藥組合物，其限制條件爲在式I及伴隨定義中：i)當環A爲吲哚時，n不爲零且環B及C爲未經$CF_3$或鹵基取代之芳基；ii)當環A爲吡唑時，n不爲零；iii)當環A爲吡啶基時，可互換地，環B及環C部分在吡啶環之2及3位經取代；以及iv)當環A爲咪唑時，環B部分在咪唑環之2位經取代。

在一個態樣中，本發明亦提供一種治療患者疾病、減輕其嚴重程度或症狀上治療其的方法，其包含向該患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該疾病係選自全身型癲癇伴熱性驚厥附加症(GEFS+)、全身型癲癇伴熱驚厥及非熱驚厥、肌強直、先天性肌強直病、鉀加重肌強直、高鉀血性週期性癱瘓、LQTS、LQTS/布魯加達症候群(Brugada syndrome)、伴有耳聾的常染色體顯性LQTS、常染色體隱性LQTS、伴有畸形特徵之LQTS、先天性及獲得性LQTS、蒂莫西症候群(Timothy syndrome)、嬰兒持續性高胰島素低血糖、擴張型心肌症、常染色體顯性LQTS、登特病(Dent

disease)、骨質石化病、III型巴特症候群、中央軸空病、惡性高熱及兒茶酚胺激導性多形性室性心動過速。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有CFTR基因突變N1303K、ΔI507或R560T。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有CFTR基因突變G551D。在另一個實施例中，患者爲G551D中同種接合。在另一個實施例中，患者爲G551D中異種接合。在另一個實施例中，患者爲G551D中異種接合，其中另一CFTR基因突變爲以下中之任一者：F508del、G542X、N1303K、W1282X、R117H、R553X、1717-1G->A、621+1G->T、2789+5G->A、3849+10kbC->T、R1162X、G85E、3120+1G->A、ΔI507、1898+1G->A、3659delC、R347P、R560T、R334W、A455E、2184delA或711+1G->T。在另一個實施例中，患者爲G551D中異種接合，其中另一CFTR基因突變爲F508del。在另一個實施例中，患者爲G551D中異種接合，其中另一CFTR基因突變爲R117H。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有CFTR基因突變F508del。在另一個實施例中，患者爲F508del中同種接合。在另一個實施例中，患者爲F508del中異種接合。在另一個實施例中，患者爲F508del中異種接合，其中另一CFTR基因突變爲以下中之任一者：G551D、G542X、N1303K、W1282X、R117H、R553X、1717-

1G->A、621+1G->T、2789+5G->A、3849+10kbC->T、R1162X、G85E、3120+1G->A、ΔI507、1898+1G->A、3659delC、R347P、R560T、R334W、A455E、2184delA或711+1G->T。在另一個實施例中，患者爲F508del中異種接合，其中另一CFTR基因突變爲G551D。在另一個實施例中，患者爲F508del中異種接合，其中另一CFTR基因突變爲R117H。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：G178R、G551S、G970R、G1244E、S1255P、G1349D、S549N、S549R、S1251N、E193K、F1052V、G1069R、R117C、D110H、R347H、R352Q、E56K、P67L、L206W、A455E、D579G、S1235R、S945L、R1070W、F1074L、D110E、D1270N、D1152H、1717-1G->A、621+1G->T、3120+1G->A、1898+1G->A、711+1G->T、2622+1G->A、405+1G->A、406-1G->A、4005+1G->A、1812-1G->A、1525-1G->A、712-1G->T、1248+1G->A、1341+1G->A、3121-1G->A、4374+1G->T、3850-1G->A、2789+5G->A、3849+10kbC->T、3272-26A->G、711+5G->A、3120G->A、1811+1.6kbA->G、711+3A->G、1898+3A->G、1717-8G->A、1342-2A->C、405+3A->C、1716G/A、1811+1G->C、1898+5G->T、3850-3T->G、IVS14b+5G->A、1898+1G->T、4005+2T->C及621+3A->G。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：G178R、G551S、G970R、G1244E、S1255P、G1349D、S549N、S549R、S1251N、E193K、F1052V及G1069R。在

此態樣之一個實施例中，本發明提供一種治療CFTR之方法，其包含向具有選自以下各者之人類CFTR突變的患者投與化合物1：G178R、G551S、G970R、G1244E、S1255P、G1349D、S549N、S549R及S1251N。在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：E193K、F1052V及G1069R。在此態樣之一些實施例中，該方法使得氯離子輸送相對於基線氯離子輸送增加超過10倍。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：R117C、D110H、R347H、R352Q、E56K、P67L、L206W、A455E、D579G、S1235R、S945L、R1070W、F1074L、D110E、D1270N及D1152H。在此態樣之一個實施例中，該方法使得氯離子輸送增加超過基線氯離子輸送10%或大於10%。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：1717-1G->A、621+1G->T、3120+1G->A、1898+1G->A、711+1G->T、2622+1G->A、405+1G->A、406-1G->A、4005+1G->A、1812-1G->A、1525-1G->A、712-1G->T、1248+1G->A、1341+1G->A、3121-1G->A、4374+1G->T、3850-1G->A、2789+5G->A、3849+10kbC->T、3272-26A->G、711+5G->A、3120G->A、1811+1.6kbA->G、711+3A->G、1898+3A->G、1717-8G->A、1342-2A->C、405+3A->C、1716G/A、1811+1G->C、1898+5G->T、

3850-3T->G、IVS14b+5G->A、1898+1G->T、4005+2T->C及621+3A->G。在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：1717-1G->A、1811+1.6kbA->G、2789+5G->A、3272-26A->G及3849+10kbC->T。在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：2789+5G->A及3272-26A->G。

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在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：1717-1G->A、621+1G->T、3120+1G->A、1898+1G->A、711+1G->T、2622+1G->A、405+1G->A、406-1G->A、4005+1G->A、1812-1G->A、1525-1G->A、712-1G->T、1248+1G-

>A、1341+1G->A、3121-1G->A、4374+1G->T、3850-1G->A、2789+5G->A、3849+10kbC->T、3272-26A->G、711+5G->A、3120G->A、1811+1.6kbA->G、711+3A->G、1898+3A->G、1717-8G->A、1342-2A->C、405+3A->C、1716G/A、1811+1G->C、1898+5G->T、3850-3T->G、IVS14b+5G->A、1898+1G->T、4005+2T->C及621+3A->G，及一或多個選自以下各者之人類CFTR突變：F508del、R117H及G551D。在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：1717-1G->A、1811+1.6kbA->G、2789+5G->A、3272-26A->G及3849+10kbC->T，及一或多個選自以下各者之人類CFTR突變：F508del、R117H及G551D。在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自以下之CFTR基因突變：2789+5G->A及3272-26A->G，及一或多個選自以下各者之人類CFTR突變：F508del、R117H及G551D。

在一個態樣中，本發明係針對一種治療患者囊腫纖維化症、減輕其嚴重程度或症狀上治療其的方法，其包含向患者，較佳哺乳動物投與有效量之本發明之醫藥組合物或錠劑，其中該患者具有選自圖1之CFTR基因突變。

在某些實施例中，本發明之組合物適用於治療顯示呼吸及非呼吸上皮之頂端膜中殘餘CFTR活性的患者之囊腫纖維化症、減輕其嚴重程度或症狀上治療其。上皮表面上殘餘CFTR活性之存在可容易使用此項技術中已知之方法，例如標準電生理學、生物化學或組織化學技術偵測。此類方法使用活體內或離體電生理學技術、汗水或唾液

$Cl^-$濃度之量測或離體生物化學或組織化學技術監測細胞表面密度來鑑別CFTR活性。使用此類方法，殘餘CFTR活性可容易在多種不同突變異種接合或同種接合的患者，包括最常見突變F508del以及諸如G551D突變或R117H突變之其他突變同種接合或異種接合的患者中偵測到。在某些實施例中，本發明之組合物適用於治療幾乎不顯示殘餘CFTR活性之患者的囊腫纖維化症、減輕其嚴重程度或症狀上治療其。在某些實施例中，本發明之組合物適用於治療幾乎不顯示呼吸及非呼吸上皮之頂端膜中殘餘CFTR活性的患者之囊腫纖維化症、減輕其嚴重程度或症狀上治療其。

在另一個實施例中，本發明之組合物適用於使用藥理學方法治療顯示殘餘CFTR活性之患者的囊腫纖維化症或減輕其嚴重程度。在另一個實施例中，本發明之組合物適用於使用基因療法治療具有殘餘CFTR活性之患者的囊腫纖維化症或減輕其嚴重程度。此類方法增加細胞表面上存在之CFTR的量，藉此誘發患者中迄今不存在之CFTR活性或加強患者中殘餘CFTR活性之現有水準。

在一個實施例中，本發明之組合物適用於治療具有顯示殘餘CFTR活性之某些基因型，例如I類突變(非合成)、II級突變(錯誤摺疊)、III類突變(調控或閘控減弱)、IV類突變(傳導改變)或V類突變(合成減少)的患者之囊腫纖維化症或減輕其嚴重程度。

在一個實施例中，本發明之組合物適用於治療具有某些臨床表現型，例如通常與上皮頂端膜中殘餘CFTR活性之量相關的中度至輕度臨床表現型之患者的囊腫纖維化症、減輕其嚴重程度或症狀上治療其。此類表現型包括顯示胰臟充足性之患者。

在一個實施例中，本發明之組合物適用於治療經診斷患有胰臟充足性、特發性胰臟炎及先天性雙側輸精管缺乏或其中患者顯示殘餘CFTR活性之輕度肺病的患者、減輕其嚴重程度或症狀上治療其。

在一個實施例中，本發明之組合物適用於治療經診斷患有胰臟充足性、特發性胰臟炎及先天性雙側輸精管缺乏或其中患者具有野生型CFTR之輕度肺病的患者、減輕其嚴重程度或症狀上治療其。

除囊腫纖維化症之外，CFTR活性之調節可有益於不直接由CFTR突變引起之其他疾病，諸如分泌性疾病及藉由CFTR介導之其他蛋白質摺疊疾病。此等包括(但不限於)慢性阻塞性肺病(COPD)、乾眼病及休格連氏症候群。COPD之特徵爲限制氣流，其爲進展性的且不完全可逆。氣流限制係歸因於黏液分泌過多、肺氣腫及細支氣管炎。突變或野生型CFTR之活化劑可治療黏液分泌過多且減弱在COPD中常見之黏液纖毛清除。特定言之，提高跨越CFTR之陰離子分泌可促進流體輸送至氣道表面液體中，使黏液與水化合且使纖周流體黏度最佳。此將增強黏液纖毛清除且減少與COPD相關之症狀。乾眼病特徵在於眼淚產生減少，及淚膜脂質、蛋白質及黏蛋白型態異常。乾眼存在許多病因，其中一些包括年齡、萊斯克眼睛手術(Lasik eye surgery)、關節炎、藥物治療、化學/熱燒傷、過敏及諸如囊腫纖維化症及休格連氏症候群之疾病。增加穿過CFTR之陰離子分泌將增強流體自眼睛周圍之角膜內皮細胞及分泌腺體輸送以增加角膜水合。此將幫助緩解與乾眼病相關之症狀。休格連氏症候群爲一種自體免疫疾病，其中免疫系統損害全身產生水分的腺體，包括眼睛、口、皮膚、呼吸道組織、肝臟、陰道及腸道。症狀包括乾眼、口及陰道，以及肺病。該疾病亦與類風濕性關節炎、系統性狼瘡、全身性硬化症及多肌炎/皮肌炎有關。咸信疾病起因在於有缺陷之蛋白質輸送，其治療選擇有限。CFTR活性之加強劑或誘導劑可水合罹患該疾病之各種器官且幫助改善相關症狀。

在一個實施例中，本發明係關於一種活體外或活體內加強或誘發陰離子通道活性之方法，其包含使通道與本發明之組合物接觸。在

另一個實施例中，陰離子通道爲氯離子通道或碳酸氫根通道。在另一個實施例中，陰離子通道爲氯離子通道。

所需的精確量將隨各個體而變化，視個體之物種、年齡及整體狀況、感染之嚴重程度、特定藥劑、其投與模式及其類似因素而定。爲便於投與及劑量均一，較佳以單位劑型調配本發明之化合物。如本文所用，表述「單位劑型」係指適於待治療患者之藥劑的物理離散單元。然而，應瞭解，本發明之化合物及組合物每日總用量將由主治醫師在合理醫學判斷範疇內來決定。任何特定患者或生物體之特定有效劑量將視多種因素而定，該等因素包括待治療病症及病症嚴重強度；所用特定化合物之活性；所用特定組合物；患者之年齡、體重、一般健康、性別及膳食；投與時間、投與途徑及所用特定化合物之排泄比率；治療持續時間；與所用特定化合物組合或同時使用之藥物；及如醫學技術中熟知之因素。如本文所用，術語「患者」意謂動物，較佳爲哺乳動物且最佳爲人類。

近年來，已多次嘗試使用基因療法治療囊腫纖維化症。基因療法爲個體細胞及生物組織內基因之插入、改變或移除以治療疾病。其爲一項用於校正引起疾病出現之缺陷基因的技術。基因療法之最常見形式包括功能基因插入未指定基因組位置以替換突變基因，但其他形式包括直接校正突變或修飾能夠進行病毒感染之正常基因。雖然技術仍然處於起步階段，其已取得一些成功。

囊腫纖維化症爲基因療法優良的候選病症，因爲其主要由單一基因之突變引起。基因之正常複製可經由局部傳遞至肺來傳遞至患者，不需要侵入性技術或手術。基因互補方法亦將直接靶向疾病病因，且可校正複雜肺病理學之許多態樣。

在選殖CFTR基因之後不久，當在人類野生型CFTR DNA之功能複本傳遞至自囊腫纖維化症患者分離之細胞之後校正Cl-傳導缺陷時

建立原理驗證。迄今，已在人類中測試囊腫纖維化症基因療法之許多試驗。此等早期研究主要涉及安全性問題。

在一個實施例中，本發明提供一種治療囊腫纖維化症之方法，其包含向患者投與式I至Id之化合物以及基因療法。基因療法可如以全文引用的方式併入本文中的國際公開專利申請案第WO2013061091號中所揭示。投與可在式I-Id之化合物或任一本發明之醫藥組合物之前、與其同時或之後投與。

在另一個實施例中，基因療法提供向患者投與1 mL至小於10 mL以下各物之複合物：(i)非病毒性無CpG二核苷酸的質體，其包含可操作地連接於hCEF1啓動子之編碼CFTR多肽的核酸，其中質體濃度爲2 mg/mL至3 mg/mL；及(ii) 10 mg/mL至20 mg/mL之濃度的GL67A脂質混合物。

在一個實施例中，基因療法在投與包含(i)式I-Id之化合物及包含(i)式I-Id之化合物及(ii) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-3-甲基吡啶-2-基)苯甲酸的醫藥組合物之前、與其同時或之後投與囊腫纖維化症患者。

在一個實施例中，基因療法在投與包含(i)式I-Id之化合物及及(ii) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺的醫藥組合物之前、與其同時或之後投與囊腫纖維化症患者。

在一個實施例中，基因療法在投與包含(i)式I-Id之化合物及及(ii) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸的醫藥組合物之前、與其同時或之後投與囊腫纖維化症患者。

在一個實施例中，基因療法在投與包含(i)式I-Id之化合物，(ii) 3-(6-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)-

3-甲基吡啶-2-基)苯甲酸，及(iii) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺的醫藥組合物之前、與其同時或之後投與囊腫纖維化症患者。

在一個實施例中，基因療法在投與包含(i)式I-Id之化合物，(ii) (*R*)-1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)-*N*-(1-(2,3-二羥基丙基)-6-氟-2-(1-羥基-2-甲基丙-2-基)-1H-吲哚-5-基)環丙烷甲醯胺及(iii) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺的醫藥組合物之前、與其同時或之後投與囊腫纖維化症患者。

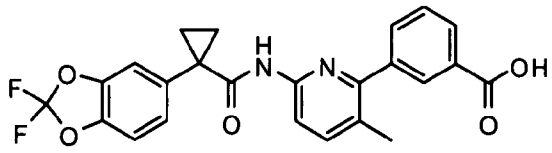
在一個實施例中，基因療法在投與包含(i)式I-Id之化合物，(ii) 4-(3-(1-(2,2-二氟苯并[d][1,3]間二氧雜環戊烯-5-基)環丙烷甲醯胺基)異喹啉-1-基)苯甲酸及(iii) *N*-(5-羥基-2,4-二第三丁基-苯基)-4-側氧基-1H-喹啉-3-甲醯胺的醫藥組合物之前、與其同時或之後投與囊腫纖維化症患者。

**套組**

在另一個態樣中，本發明提供一種套組，其包含本發明之化合物及/或醫藥組合物及其使用說明書。

在另一個實施例中，本發明之套組進一步包含一或多種其他治療劑。在另一個實施例中，其他治療劑係選自黏液溶解劑、支氣管擴張藥、抗生素、抗感染劑、CFTR調節劑或消炎劑。在另一個實施例中，其他治療劑爲CFTR調節劑。在另一個實施例中，其他治療劑爲CFTR校正劑。

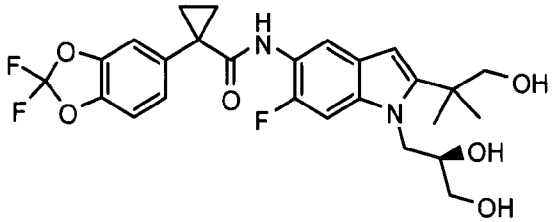
在另一個實施例中，其他治療劑爲



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或其醫藥學上可接受之鹽。

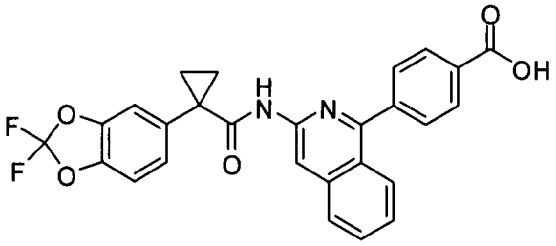
在另一個實施例中，其他治療劑爲



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或其醫藥學上可接受之鹽。

在另一個實施例中，其他治療劑爲

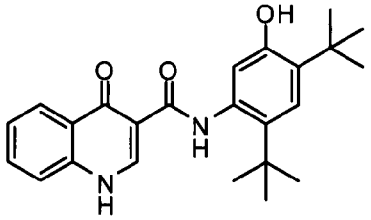


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或其醫藥學上可接受之鹽。

在另一個實施例中，其他治療劑爲CFTR增效劑。

在另一個實施例中，其他治療劑爲

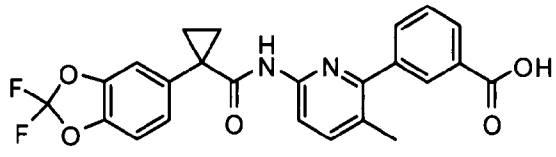


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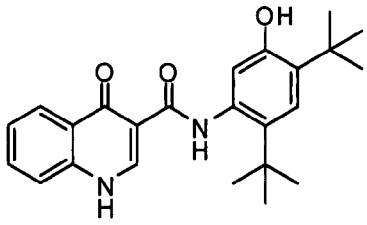
或其醫藥學上可接受之鹽。

在另一個實施例中，該等其他治療劑爲CFTR校正劑及CFTR增效劑。

在另一個實施例中，該等其他治療劑爲

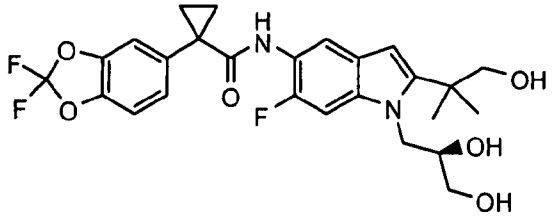
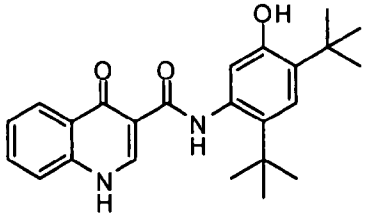


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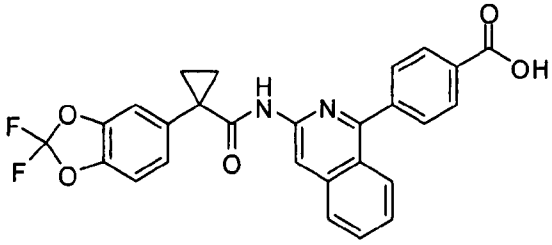
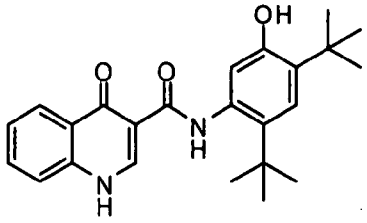


或其醫藥學上可接受之鹽。

在另一個實施例中，該等其他治療劑爲


及

或其醫藥學上可接受之鹽。

在另一個實施例中，該等其他治療劑爲


及

或其醫藥學上可接受之鹽。

在另一個實施例中，本發明之套組包括其中本發明之化合物或醫藥組合物及一或多種其他治療劑在分開容器中之套組。

在另一個實施例中，本發明之套組包括其中本發明之化合物或醫藥組合物及一或多種其他治療劑在相同容器中之套組。

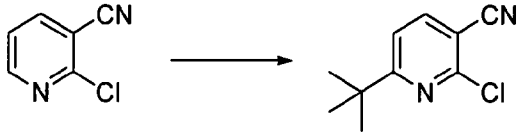
在另一個實施例中，容器爲瓶、小瓶或泡殼包裝或其組合。

在本申請案中化合物之名稱可能未正確描述化合物結構之任何地方，結構取代名稱且爲準。

**實例**

**製備1：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲醯胺(化合物26)**

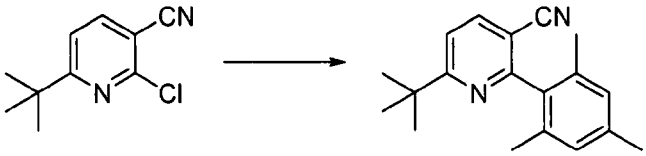
**步驟1：6-第三丁基-2-氯-吡啶-3-甲腈**



使2,2-二甲基丙酸(50. mL，870 mmol)、2-氯吡啶-3-甲腈(30 g，220 mmol)及$AgNO_3$ (9.2 g，54 mmol)懸浮於10% $H_2SO_4$水溶液(300 mL)中。經由加料漏斗將過氧硫酸氫銨(91 g，430 mmol)及水(480 mL)

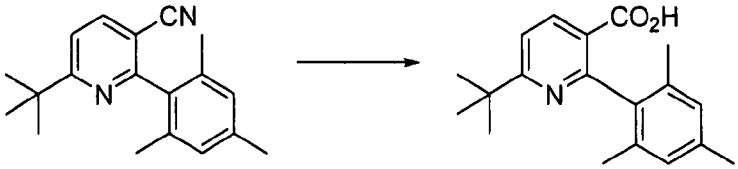
之溶液逐滴添加至混合物中。將混合物在室溫下攪拌隔夜。用30% $NH_4OH$ (約250 mL)將反應混合物之pH值調至約8-9且混合物用乙酸乙酯(3×300 mL)萃取。合併之有機層用鹽水洗滌，經硫酸鈉乾燥，且濃縮。殘餘物進行矽膠管柱層析(0-25%乙酸乙酯/己烷)，得到呈透明油狀之6-第三丁基-2-氯-吡啶-3-甲腈(37 g，83%)，其在靜置後凝固。$^1H$ NMR (400 MHz, $CDCl_3$) δ 7.83 (d, $J$ = 8.1 Hz, 1H), 7.30 (d, $J$ = 8.1 Hz, 1H), 1.29 (s, 9H)。ESI-MS *m/z*計算值194.1，實驗值195.0 $(M+1)^+$；滯留時間: 1.66 min (3分鐘操作)。

**步驟2：6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲腈**




將6-第三丁基-2-氯-吡啶-3-甲腈(400. mg，2.06 mmol)、(2,4,6-三甲基苯基)硼酸(506 mg，3.08 mmol)、$Pd(dppf)_2Cl_2*CH_2Cl_2$ (75 mg，0.10 mmol)、$NaHCO_3$ (173 mg，2.06 mmol)及DME (2 mL)之混合物在微波反應器中在120℃下加熱30分鐘。混合物分溶於$CH_2Cl_2$與水之間。分離各層且水層用$CH_2Cl_2$ (2次)萃取。合併之有機物經硫酸鈉乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-20%乙酸乙酯/己烷)，得到6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲腈(225 mg，39%)。ESI-MS *m/z*計算值278.2，實驗值279.4 $(M+1)^+$；滯留時間: 0.84 min (3分鐘操作)。

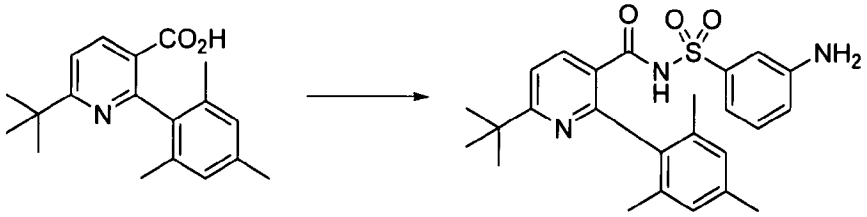
**步驟3：6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲酸**




將6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲腈(225 mg，0.808 mmol)、KOH (2.0 mL 4.0 M，8.0 mmol)及EtOH (2.3 mL)之混合物在

90℃下加熱2.5天。將混合物用濃HCl酸化至約pH 2，接著其在減壓下濃縮。殘餘物進行製備型HPLC (含0.05 mM HCl之10-99%乙腈/水)，得到呈白色固體狀之6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲酸(40 mg，17%)。ESI-MS *m/z*計算值297.2，實驗值298.4 $(M+1)^+$；滯留時間: 1.77 min (3分鐘操作)。

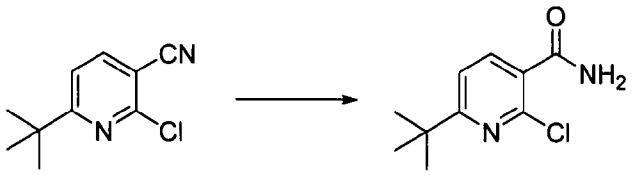
**步驟4：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲醯胺(化合物26)**



在室溫下將(3-硝基苯基)磺醯基胺基鈉(60. mg，0.27 mmol)添加至6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲酸(40. mg，0.13 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(51 mg，0.13 mmol)及*N,N*-二甲基甲醯胺(800.0 μL)之混合物中。將混合物在70℃下攪拌隔夜，接著過濾且經受製備型HPLC (10-99%含0.05% HCl之乙腈/水)，得到硝基中間物6-第三丁基-*N*-(3-硝基苯基)磺醯基-2-(2,4,6-三甲基苯基)吡啶-3-甲醯胺。硝基中間物溶解於乙酸(1 mL)中，接著添加Zn (8.8 mg，0.13 mmol)。將混合物在室溫下攪拌30分鐘，接著過濾。濾液進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯基)吡啶-3-甲醯胺(化合物26) (13 mg，22%)。ESI-MS *m/z*計算值451.2，實驗值452.5 $(M+1)^+$；滯留時間: 1.81 min (3分鐘操作)。

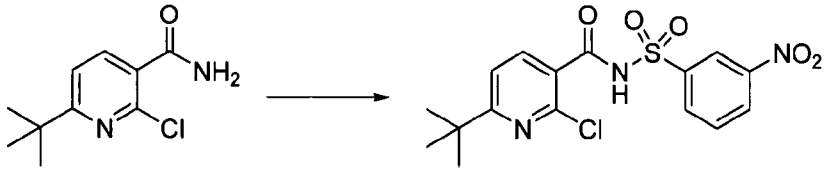
**製備2：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-氯苯基)吡啶-3-甲醯胺(化合物223)**

**步驟1：6-第三丁基-2-氯-吡啶-3-甲醯胺**



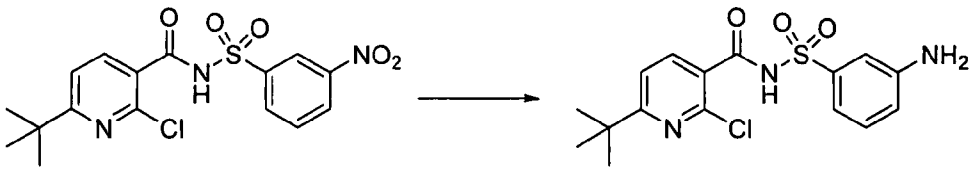
向6-第三丁基-2-氯-吡啶-3-甲腈(6.81 g，35.0 mmol)及NaOH (38.5 mL 1.0 M，38.5 mmol)於EtOH (175 mL)中之混合物中緩慢添加過氧化氫(19.9 mL 30% w/v，175 mmol)。將反應混合物在室溫下攪拌45分鐘，接著添加額外過氧化氫(19.9 mL 30% w/v，175 mmol)。1小時後，混合物用飽和亞硫酸氫鈉溶液緩慢淬滅，用水稀釋，且用乙酸乙酯萃取。合併之萃取物用水洗滌，經硫酸鈉乾燥，且蒸發，得到呈白色固體狀之6-第三丁基-2-氯-吡啶-3-甲醯胺(7.21 g，97%)。ESI-MS *m/z*計算值212.1，實驗值212.9 $(M+1)^+$；滯留時間: 0.46 min (1分鐘操作)。

**步驟2：6-第三丁基-2-氯-*N*-(3-硝基苯基)磺醯基-吡啶-3-甲醯胺**



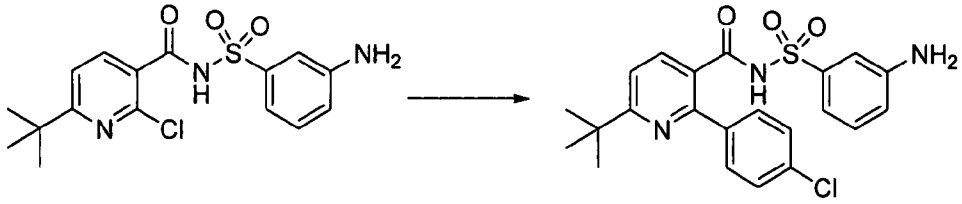
向6-(第三丁基)-2-氯菸鹼醯胺(3.19 g，15.0 mmol)及3-硝基苯磺醯氯(3.32 g，15.0 mmol)於THF (100.0 mL)中之溶液中緩慢分部分添加NaH (1.80 g，60% w/w，45.0 mmol)。將混合物在室溫下攪拌2小時，接著其用飽和氯化銨水溶液淬滅。混合物用乙酸乙酯(3次)萃取。合併之萃取物用水洗滌，經硫酸鈉乾燥，且蒸發。殘餘物溶解於二乙醚中。過濾固體，用二乙醚洗滌，且真空乾燥。蒸發濾液且殘餘物藉由矽膠層析(1-11%甲醇/$CH_2Cl_2$)來純化。合併兩批(來自乙醚之固體及來自管柱之產物)，得到呈淡黃色固體狀之6-(第三丁基)-2-氯-*N*-((3-硝基苯基)磺醯基)菸鹼醯胺(3.56 g，60%)。ESI-MS *m/z*計算值397.1，實驗值398.0 $(M+1)^+$；滯留時間: 0.66 min (1分鐘操作)。

**步驟3：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-氯-吡啶-3-甲醯胺**



向6-(第三丁基)-2-氯-*N*-((3-硝基苯基)磺醯基)菸鹼醯胺(1.40 g，3.52 mmol)於冰醋酸(140 mL)中之溶液中添加鋅(5.76 g，88.0 mmol)。將反應混合物在室溫下攪拌1小時，接著過濾且在減壓下濃縮。粗產物進行矽膠管柱層析(0-5%甲醇/$CH_2Cl_2$)，得到呈橙色黏性泡沫狀之*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-氯-吡啶-3-甲醯胺(1.12 g，87%)。ESI-MS *m/z*計算值367.1，實驗值368.6 $(M+1)^+$；滯留時間：1.09 min (3分鐘操作)。

**步驟4：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-氯苯基)吡啶-3-甲醯胺(化合物223)**



向(4-氯苯基)硼酸(26 mg，0.16 mmol)中添加*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-氯-吡啶-3-甲醯胺(50. mg，0.14 mmol)於DMA (0.5 mL)中之溶液。添加$Na_2CO_3$ (136 μL，2.0 M，0.27 mmol)及二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(5 mg，0.007 mmol)且將容器在氮氣下密封且在微波照射下在120℃下加熱20分鐘。反應混合物冷卻至室溫，過濾且經受製備型HPLC (10-99%含0.05 mM HCl之水/$CH_3CN$)，得到*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-氯苯基)吡啶-3-甲醯胺(化合物223) (15 mg，25%)。ESI-MS *m/z*計算值443.1，實驗值444.1 $(M+1)^+$；滯留時間：1.81 min (3分鐘操作)。

以下化合物使用以下所述之程序合成：

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-第三丁基苯基)吡啶-3-甲

醯胺(化合物252)，

*N*-(3-胺基苯基)磺醯基-8,8-二甲基-2-苯基-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物685)，

(3-胺基苯基)磺醯基-[8,8-二甲基-2-(對甲苯基)-6,7-二氫-5*H*-喹啉-3-羰基]胺化物(化合物1231)，

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-(環己烯-1-基)吡啶-3-甲醯胺(化合物880)，

*N*-(4-胺基苯基)磺醯基-8,8-二甲基-2-苯基-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1190)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-氟苯基)吡啶-3-甲醯胺(化合物417)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-茚滿-5-基-吡啶-3-甲醯胺(化合物308)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3,4-二甲基苯基)吡啶-3-甲醯胺(化合物274)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3-第三丁基苯基)吡啶-3-甲醯胺(化合物229)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3,5-二甲基苯基)吡啶-3-甲醯胺(化合物52)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-異丙基苯基)吡啶-3-甲醯胺(化合物314)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-乙基苯基)吡啶-3-甲醯胺(化合物359)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-[4-(三氟甲基)苯基]吡啶-3-甲醯胺(化合物129)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3-氟-5-甲基-苯基)吡啶-3-

甲醯胺(化合物237)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物301)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-氟-3-甲基-苯基)吡啶-3-甲醯胺(化合物177)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3-氟-4-甲基-苯基)吡啶-3-甲醯胺(化合物349)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2,4-二甲基苯基)吡啶-3-甲醯胺(化合物5)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(間甲苯基)吡啶-3-甲醯胺(化合物282)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-氟苯基)吡啶-3-甲醯胺(化合物46)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2-氟-5-甲基-苯基)吡啶-3-甲醯胺(化合物1350)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3,4-二氟苯基)吡啶-3-甲醯胺(化合物1217)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(o-tol基)吡啶-3-甲醯胺(化合物1036)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-甲氧基苯基)吡啶-3-甲醯胺(化合物550)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2-氟-4-甲基-苯基)吡啶-3-甲醯胺(化合物1331)，

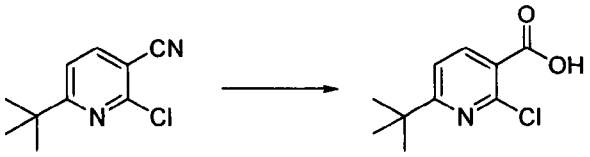
*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-苯基-吡啶-3-甲醯胺(化合物542)，及

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(3,4-二氟苯基)吡啶-3-甲醯

胺(化合物1217)。

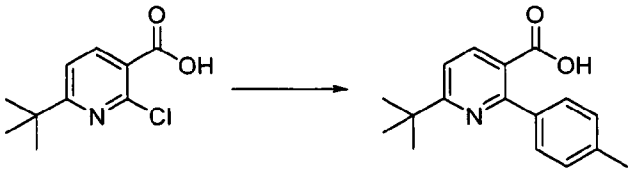
**製備3：*N*-(苯磺醯基)-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物74)**

**步驟1：6-第三丁基-2-氯-吡啶-3-甲酸**



將KOH (8.65 g，154 mmol)於水(25 mL)中之溶液添加至6-第三丁基-2-氯-吡啶-3-甲腈(5.00 g，25.7 mmol)於異丙醇(25 mL)中之溶液中。將反應混合物在90℃下攪拌隔夜。冷卻至室溫後，將反應混合物用乙酸乙酯(75 mL)稀釋且用NaOH水溶液(1 N，3×75 mL)萃取。藉由添加HCl水溶液(1 N，200 mL)將合併之水層酸化至pH 3且用乙酸乙酯(2×75 mL)萃取。合併之有機層經硫酸鈉乾燥，過濾且濃縮，得到呈黃色固體狀之6-第三丁基-2-氯-吡啶-3-甲酸(5.25 g，96%)。ESI-MS *m/z*計算值213.1, 實驗值214.4 $(M+1)^+$；滯留時間: 1.09 min (3分鐘操作)。$^1$H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.26 (d, $J$ = 8.1 Hz, 1H), 7.36 (d, $J$ = 8.1 Hz, 1H), 1.38 (s, 9H)。

**步驟2：6-第三丁基-2-(對甲苯基)吡啶-3-甲酸**



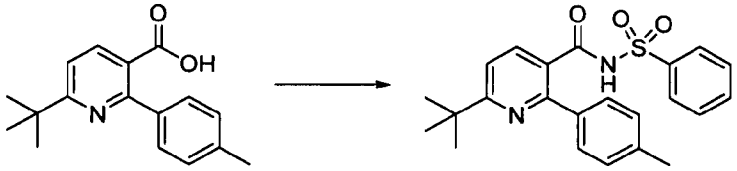
使6-第三丁基-2-氯-吡啶-3-甲酸(1.35 g，6.32 mmol)及對甲苯基硼酸(1.03 g，7.58 mmol)懸浮於DMA (14 mL)中。添加碳酸鈉水溶液(6.3 mL 2.0 M，13 mmol)，接著添加二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(231 mg，0.312 mmol)。將反應容器密封在氮氣下且在微波反應器中加熱至140℃，保持1.5小時。將反應混合物用乙酸乙酯(50 mL)稀釋且用NaOH水溶液(1 M，4×50 mL)洗滌。用1

N HCl將合併之水層酸化至pH 3且接著用乙酸乙酯(5×50 mL)萃取。合併有機層，經硫酸鈉乾燥，過濾，且在減壓下濃縮。殘餘物進行矽膠管柱層析(0-30%乙酸乙酯/己烷)，得到呈白色固體狀之6-第三丁基-2-(對甲苯基)吡啶-3-甲酸(740 mg，43%)。ESI-MS *m/z*計算值269.1，實驗值270.5 $(M+1)^+$；滯留時間: 1.53 min (3分鐘操作)。

以下化合物可使用以下所述之程序合成：

8,8-二甲基-2-(對甲苯基)-5,6,7,8-四氫喹啉-3-甲酸。

**步驟3：*N*-(苯磺醯基)-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物74)**



向苯磺醯胺(23 mg，0.14 mmol)中添加含6-第三丁基-2-(對甲苯基)吡啶-3-甲酸(35 mg，0.13 mmol)之*N,N*-二甲基甲醯胺(400 μL)。添加六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(54 mg，0.14 mmol)於*N,N*-二甲基甲醯胺(125 μL)中之溶液，接著添加固體碳酸鈉(54 mg，0.39 mmol)。將反應混合物在80℃下攪拌1小時。添加額外六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(0.5當量)且將反應混合物在80℃下攪拌隔夜。冷卻混合物，過濾且經受製備型HPLC (10-99%含0.05 mM HCl之水/乙腈)，得到*N*-(苯磺醯基)-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物74) (28 mg，53%)。ESI-MS *m/z*計算值408.2，實驗值409.3 $(M+1)^+$；滯留時間: 1.93 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

6-第三丁基-*N*-(3-乙基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物50)，

6-第三丁基-*N*-(3-甲氧基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物327)，

6-第三丁基-*N*-(4-甲氧基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物206)，

6-第三丁基-*N*-(4-氰基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物288)，

6-第三丁基-2-(對甲苯基)-*N*-(2-吡啶基磺醯基)吡啶-3-甲醯胺(化合物407)，

6-第三丁基-2-(對甲苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物632)，

6-第三丁基-*N*-[(5-甲基-2-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺(化合物1355)，

6-第三丁基-*N*-(2-氰基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物623)，

6-第三丁基-*N*-(2-甲氧基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物1124)，

*N*-(4-胺基苯基)磺醯基-8,8-二甲基-2-(對甲苯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1307)，

6-第三丁基-*N*-(2-羥基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物1175)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(對甲苯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物444)，

8,8-二甲基-2-(對甲苯基)-*N*-(1H-吡唑-5-基磺醯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1292)，

6-第三丁基-*N*-(4-羥基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物809)，

6-第三丁基-*N*-(3-羥基苯基)磺醯基-2-(對甲苯基)吡啶-3-甲醯胺(化合物1265)，

6-第三丁基-*N*-[(6-甲氧基-3-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺(化合物512)，

*N*-[(6-胺基-3-吡啶基)磺醯基]-8,8-二甲基-2-(對甲苯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物635)，

6-(3-氟-5-異丙氧基-苯基)-2-(對甲苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物849)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丙氧基-苯基)-2-(對甲苯基)吡啶-3-甲醯胺(化合物722)，

6-(3-氟-5-異丙氧基-苯基)-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺(化合物798)，

6-第三丁基-*N*-(1H-吡唑-4-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物401)，

6-(4-氟苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物518)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物423)，

6-第三丁基-*N*-[[6-(二氟甲基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物501)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2,6-雙(對甲苯基)吡啶-3-甲醯胺(化合物524)，

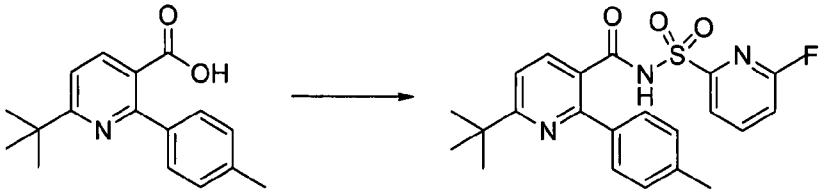
6-(6-甲氧基-5-甲基-3-吡啶基)-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺(化合物861)，

6-第三丁基-*N*-[(6-甲氧基-2-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺(化合物75)，及

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物297)。

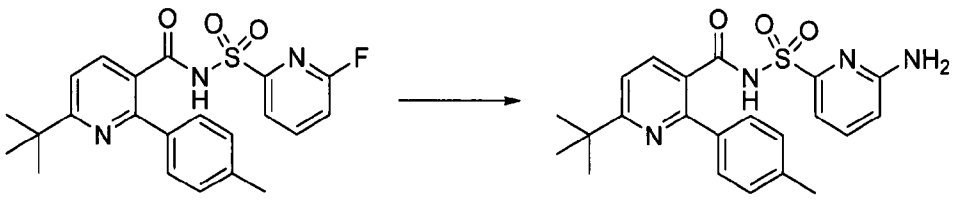
**製備4：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物58)**

**步驟1：6-第三丁基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺**



在室溫下將*N,N*-二異丙基乙胺(104 μL，0.5940 mmol)添加至 6-第三丁基-2-(對甲苯基)吡啶-3-甲酸(80. mg，0.30 mmol)、6-氟吡啶-2-磺醯胺(58 mg，0.33 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(136 mg，0.356 mmol)及*N,N*-二甲基甲醯胺(800 μL)之混合物中。將混合物在70℃下加熱隔夜，接著其冷卻。混合物分溶於乙酸乙酯與1N HCl之間。分離各層且水層用乙酸乙酯(3次)萃取。合併之有機物用鹽水洗滌，經硫酸鈉乾燥，過濾，且濃縮。殘餘物進行矽膠管柱層析(0-20%乙酸乙酯/己烷)，得到呈微黃色固體狀之6-第三丁基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲醯胺(66 mg，38%)。ESI-MS *m/z*計算值427.1，實驗值428.4 $(M+1)^+$；滯留時間: 0.7 min (1分鐘操作)。

**步驟2：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物58)**



將6-第三丁基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(對甲苯基)吡啶-3-甲

醯胺(55 mg，0.13 mmol)及$NH_4OH$ (30%，860 μL)之混合物在微波反應器中在150℃下加熱30分鐘。濃縮混合物且殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物58) (17 mg，31%)。ESI-MS *m/z*計算值424.2，實驗值425.4 $(M+1)^+$；滯留時間: 1.63 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(間甲苯基)吡啶-3-甲醯胺(化合物31)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(環戊烯-1-基)吡啶-3-甲醯胺(化合物529)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(環己烯-1-基)吡啶-3-甲醯胺(化合物478)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基苯基)-2-(對甲苯基)吡啶-3-甲醯胺(化合物409)，

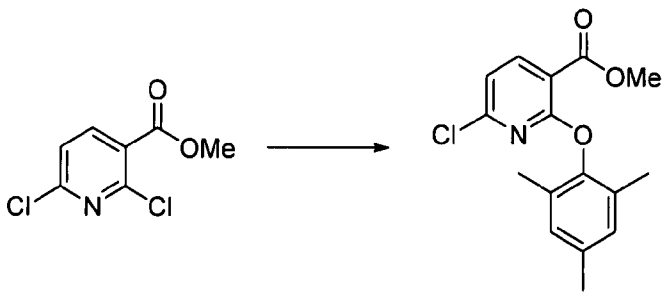
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-氟苯基)吡啶-3-甲醯胺(化合物417)，

及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-苯基-吡啶-3-甲醯胺(化合物334)。

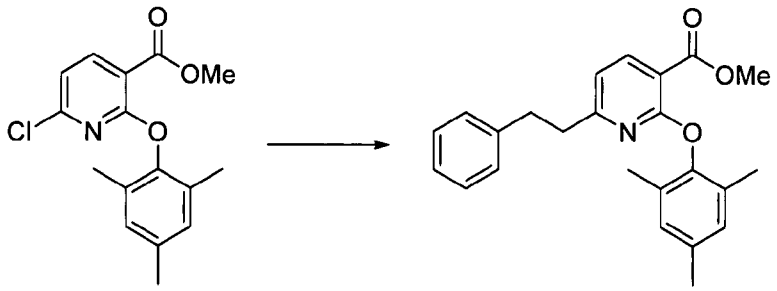
**製備5：6-苯乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸**

**步驟1：6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯**



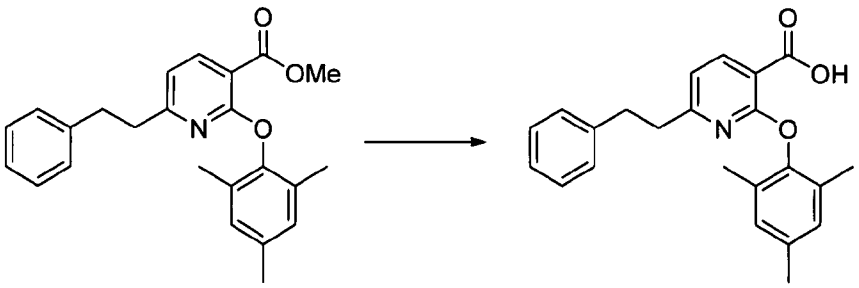
在0℃下將NaH (60%，2.13 g，53.3 mmol)添加至2,4,6-三甲基苯酚(6.60 g，48.5 mmol)及*N,N*-二甲基甲醯胺(150 mL)之溶液中。將混合物攪拌15分鐘，接著逐滴添加2,6-二氯菸鹼酸甲酯(10.0 g，48.5 mmol)於*N,N*-二甲基甲醯胺(20 mL)中之溶液。在室溫下將混合物攪拌1小時，接著添加水。混合物用乙酸乙酯(2次)萃取。合併之萃取物用水及鹽水洗滌，經硫酸鈉乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-50% $CH_2Cl_2$/已烷)，得到6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(3.58 g，24%)。ESI-MS *m/z*計算值305.1，實驗值306.2 $(M+1)^+$；滯留時間: 0.87 min (1分鐘操作)。

**步驟2：6-苯乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯**




將溴-(2-苯基乙基)鋅(3.9 mL 0.5 M，2.0 mmol)及二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(36 mg，0.049 mmol)在室溫下在氮氣下攪拌20分鐘。將6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(150 mg，0.49 mmol)添加至反應混合物中且接著其在微波反應器中在150℃下加熱10分鐘。將飽和乙二胺四乙酸二鈉鹽水溶液(2 mL)及飽和氯化銨水溶液添加至反應混合物。在攪拌30分鐘後，分離各層且水層用二氯甲烷萃取。合併之有機層蒸發至乾且殘餘物進行製備型HPLC (含5 mM HCl之20-80%乙腈/水)，得到6-(2-苯基乙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(56 mg，31%)。ESI-MS *m/z*計算值375.2，實驗值376.4 $(M+1)^+$；滯留時間: 0.87 min (1分鐘操作)。

**步驟3：6-苯乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸**

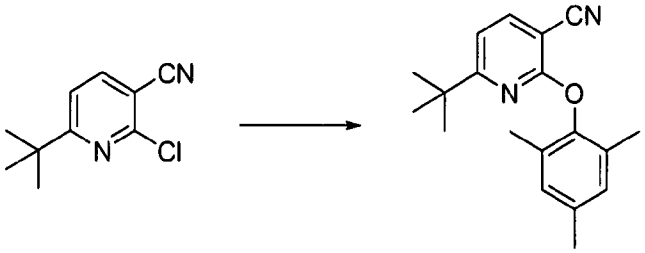


6-(2-苯基乙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(56 mg，0.15 mmol)溶於甲醇(5mL)中。添加NaOH (245 μL 4.0 M，0.98 mmol)且將混合物在室溫下攪拌隔夜。移除溶劑且用1N HCl將殘餘物之pH值調至約3。過濾沈澱，用水洗滌且乾燥，得到6-苯乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(21 mg，36%)。ESI-MS *m/z*計算值361.2，實驗值362.5 $(M+1)^+$；滯留時間: 0.77 min (1分鐘操作)。

以下化合物可使用本文所述之程序合成：6-苯甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸。

**製備6：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)**

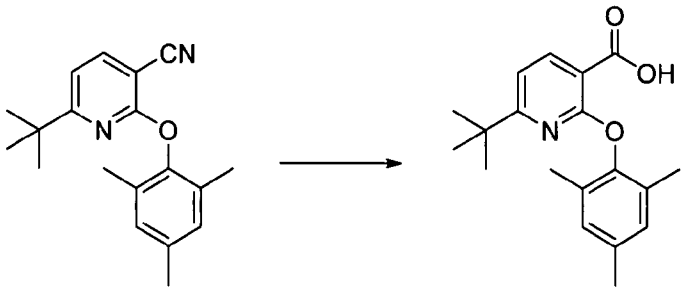
**步驟1：6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲腈**



將6-第三丁基-2-氯-吡啶-3-甲腈(5.00 g，25.7 mmol)、2,4,6-三甲基苯酚(3.50 g，25.7 mmol)、$K_2CO_3$ (3.91 g，28.3 mmol)及*N,N*-二甲基甲醯胺(10 mL)添加至40 mL小瓶。將混合物在95℃下攪拌隔夜。將反應混合物用$H_2O$ (10 mL)稀釋且用乙酸乙酯(3×20 mL)萃取。合併之有機層用鹽水洗滌，經硫酸鈉乾燥且濃縮。殘餘物進行矽膠管柱層析(0-20%乙酸乙酯/己烷)，得到呈白色固體狀之6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲腈(6.70 g，84%)。ESI-MS *m/z*計算值294.2，實

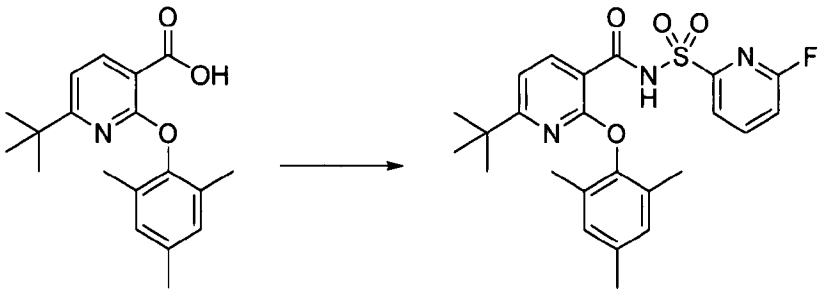
驗值295.2 $(M+1)^+$；滯留時間: 2.31 min (3分鐘操作)。$^1$H NMR (400 MHz, DMSO) δ 8.31 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 6.96 (s, 2H), 2.27 (s, 3H), 2.00 (s, 6H), 1.07 (s, 9H)。

**步驟2：6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸**




將6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲腈(4.50 g，15.3 mmol)、KOH (5.15 g，91.7 mmol)、EtOH (135 mL)及$H_2O$ (32 mL)之混合物在90℃下加熱隔夜。添加額外KOH (2.00 g，35.6 mmol)且將混合物在90℃下加熱隔夜。混合物冷卻至室溫，濃縮且用2N HCl酸化至約pH 2。固體經由過濾收集且置於真空烘箱中50℃下隔夜，得到6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(4.64 g，96%)。$^1$H NMR (400 MHz, DMSO) δ 8.14 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H), 1.04 (s, 9H)。

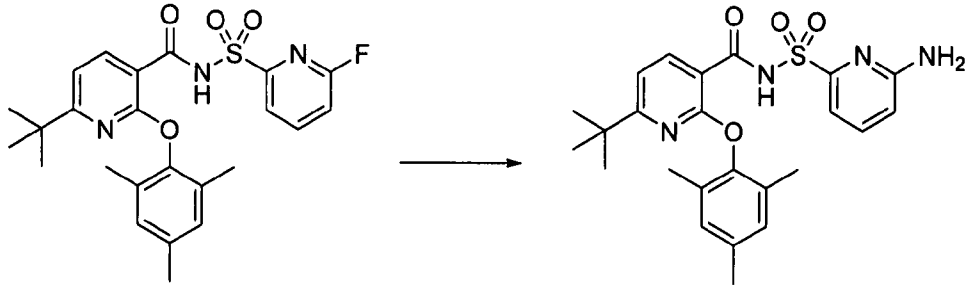
**步驟3：6-第三丁基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**




在室溫下將*N*-乙基-*N*-異丙基丙-2-胺(560 μL，3.19 mmol)添加至6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(500. mg，1.56 mmol)、6-氟吡啶-2-磺醯胺(309 mg，1.76 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化

物(728 mg，1.91 mmol)及*N,N*-二甲基甲醯胺(5 mL)之混合物中。將混合物在70℃下加熱隔夜，接著其冷卻。混合物分溶於乙酸乙酯與1N HCl之間。分離各層且水層用乙酸乙酯(3次)萃取。合併之有機物用鹽水洗滌，經硫酸鈉乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-20%乙酸乙酯/己烷)，接著藉由矽膠管柱層析(0-10%乙酸乙酯/己烷)進行第二次純化，得到呈白色固體狀之6-第三丁基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(230 mg，23%)。ESI-MS *m/z*計算值471.2，實驗值472.4 $(M+1)^+$；滯留時間: 2.32 min (3分鐘操作)。

**步驟4：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228)**



6-第三丁基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(77 mg，0.16 mmol)溶於氫氧化銨(10 mL 30 %w/w)中且在微波反應器中在150℃下照射1小時。混合物蒸發且粗物質藉由製備型HPLC (10-99%含5 μM HCl之乙腈/水)來純化。物質藉由矽膠層析(0-100%乙酸乙酯/己烷)進一步純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物228) (27 mg，35%)。$^1$H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.67 - 7.58 (m, 1H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.90 (s, 2H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.49 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H), 1.05 (s, 9H)。ESI-MS *m/z*計算值468.2，實驗值469.3 $(M+1)^+$；滯留時間: 2.11 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：6-第三丁基-*N*-(1H-吲唑-4-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物275)，

*N*-(苯磺醯基)-6-第三丁基-2-(2-異丙基苯氧基)吡啶-3-甲醯胺(化合物147)，

6-第三丁基-*N*-[[6-(二甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物468)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,1,2,2,2-五氟乙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物853)，

*N*-(4-胺基苯基)磺醯基-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1297)，

*N*-(2-胺基噻唑-4-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1294)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1310)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物854)，

*N*-(3-胺基苯基)磺醯基-6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物826)，

6-(3-氟-5-異丙氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物914)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-丙-1-炔基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1172)，

6-第三丁基-*N*-(2-甲基吡唑-3-基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物911)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5,6-二甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物841)，

*N*-[[6-(2-羥基乙基胺基)-2-吡啶基]磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物595)，

*N*-[[6-(二甲基胺基)-2-吡啶基]磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物869)，

*N*-[[6-(2-胺基乙基胺基)-2-吡啶基]磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1027)，

*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1032)，

*N*-[[6-(2-二甲基胺基乙基胺基)-2-吡啶基]磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1122)，

*N*-[(6-氰基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物771)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-甲基-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1102)，

6-第三丁基-*N*-[[6-(2-羥基乙基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物916)，

6-第三丁基-*N*-[[6-(2-二甲基胺基乙基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物947)，

6-[[6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-羰基]胺磺醯基]吡啶-2-甲酸(化合物461)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[6-(羥基甲基)-2-吡啶基]磺醯基]-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1340)，

*N*-[[6-(2-胺基乙基胺基)-2-吡啶基]磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1054)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1137)，

*N*-(2-疊氮基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺，

6-甲基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物670)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-苯乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1253)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(三氟甲基)環丙基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物621)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-苯甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1233)，

*N*-[[6-(異丙基胺基)-2-吡啶基]磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物482)，

*N*-[[6-(2-甲氧基乙基胺基)-2-吡啶基]磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物372)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物182)，

*N*-(苯磺醯基)-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物341)，

6-第三丁基-*N*-[3-(甲基胺基)苯基]磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物289)，

6-第三丁基-*N*-[3-(二甲基胺基)苯基]磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物311)，

6-第三丁基-*N*-(2-氰基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物78)，

*N*-(苯磺醯基)-6-第三丁基-2-(1-甲基吲哚-7-基)氧基-吡啶-3-甲醯胺(化合物326)，

6-第三丁基-*N*-(1-甲基吲哚-4-基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物146)，

*N*-[(6-胺基-5-氟-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺，

6-第三丁基-*N*-[(6-甲氧基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物34)，

6-第三丁基-*N*-(4-吡啶基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物117)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物235)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物590)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基苯氧基)吡啶-3-甲醯胺(化合物778)，

6-第三丁基-*N*-(2-甲氧基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物115)，

6-第三丁基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物191)，

6-第三丁基-*N*-(2-吡啶基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物222)，

*N*-[(2-胺基-4-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物283)，

6-第三丁基-*N*-[(2-甲氧基-4-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物217)，

6-第三丁基-*N*-(3-吡啶基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物330)，

6-第三丁基-*N*-(3-甲氧基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物56)，

*N*-(苯磺醯基)-6-(三氟甲基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物244)，

6-第三丁基-*N*-[(3-甲氧基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物92)，

*N*-(苯磺醯基)-2-苯甲氧基-6-第三丁基-吡啶-3-甲醯胺(化合物130)，

6-第三丁基-2-(2,4-二甲基苯氧基)-*N*-[(2-甲氧基-3-吡啶基)磺醯基]吡啶-3-甲醯胺(化合物89)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4-二甲基苯氧基)吡啶-3-甲醯胺(化合物204)，

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物11)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(1-苯基乙氧基)吡啶-3-甲醯胺(化合物219)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)-5,6,7,8-四氫喹啉-3-甲醯胺(化合物285)，

*N*-[(5-胺基-3-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物163)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2-甲基苯氧基)吡啶-3-甲醯胺(化合物296)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(4-氯基-2,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物111)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2,4-二甲基苯氧基)吡啶-3-甲醯胺(化合物251)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基環戊氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物503)，

*N*-(苯磺醯基)-6-第三丁基-2-(3-甲氧基苯氧基)吡啶-3-甲醯胺(化合物101)，

6-第三丁基-*N*-[(6-側氧基-1*H*-吡啶-2-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物305)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2-氰基-4,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物221)，

*N*-(3-胺基苯基)磺醯基-2-(2,6-二甲基苯氧基)-6-(三氟甲基)吡啶-3-甲醯胺(化合物243)，

*N*-(3-胺基苯基)磺醯基-6-(三氟甲基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物96)，

6-第三丁基-*N*-[(4-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物107)，

*N*-(苯磺醯基)-6-第三丁基-2-(2-吡啶基甲氧基)吡啶-3-甲醯胺(化合物154)，

6-第三丁基-*N*-[(2-側氧基-1*H*-吡啶-4-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物113)，

6-第三丁基-2-(2,4-二甲基苯氧基)-*N*-[(2-羥基-3-吡啶基)磺醯基]吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(三氟甲基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物175)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(三氟甲基)吡啶-3-甲醯胺(化合物246)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環丙基-4-(三氟甲基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物54)，

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-苯氧基-吡啶-3-甲醯胺(化合物272)，

*N*-(3-胺基苯基)磺醯基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物13)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-甲基環戊氧基)吡啶-3-甲醯胺(化合物452)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-苯氧基-吡啶-3-甲醯胺(化合物376)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[1-(3-氟苯基)乙氧基]吡啶-3-甲醯胺(化合物562)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3-乙基氧雜環丁烷-3-基)甲氧基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物618)，

*N*-[[6-(3-胺基丙基胺基)-2-吡啶基]磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物982)，

*N*-[[6-(環丙基胺基)-2-吡啶基]磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物594)，

6-甲基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物646)，

*N*-[[6-(2-胺基乙基胺基)-2-吡啶基]磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物792)，

6-甲基-*N*-[(6-嗎啉基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物883)，

6-甲基-*N*-[[6-(4-甲基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1018)，

*N*-[[6-(二甲基胺基)-2-吡啶基]磺醯基]-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1250)，

2-(2,4-二甲基苯氧基)-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-8,8-二甲基-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1347)，

2-(2,4-二甲基苯氧基)-8,8-二甲基-*N*-(1H-吡唑-3-基磺醯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1246)，

6-第三丁基-*N*-[(2-甲氧基-6-甲基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1153)，

8,8-二甲基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物715)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(氧雜環丁烷-2-基甲氧基)吡啶-3-甲醯胺(化合物640)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(環己氧基)吡啶-3-甲醯胺(化合物649)，

2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物671)，

6-(3-氟-5-異丁氧基-苯基)-2-苯氧基-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物679)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-四氫哌喃-3-基氧基-吡啶-3-甲醯胺(化合物706)，

6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基苯氧基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物738)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基苯氧基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物758)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2-氰基-4,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物767)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,2-二氟環丙基)甲氧基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物769)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[1-(鄰甲苯基)乙氧基]吡啶-3-甲醯胺(化合物782)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3-甲基氧雜環丁烷-3-基)甲氧基]吡啶-3-甲醯胺(化合物824)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4-二氟苯氧基)吡啶-3-甲醯胺(化合物829)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[1-(4-氟苯基)乙氧基]吡啶-3-甲醯胺(化合物867)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(氧雜環丁烷-3-基氧基)吡啶-3-甲醯胺(化合物872)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-苯基乙氧基)吡啶-3-甲醯胺(化合物874)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,2-二甲基環丙基)甲氧基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物894)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(四氫哌喃-4-基甲氧基)吡啶-3-甲醯胺(化合物933)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二氟環己氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物961)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-甲基-2-苯基-乙氧基)吡啶-3-甲醯胺(化合物967)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基環己氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物978)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2-異丙基苯氧基)吡啶-3-甲醯胺(化合物1031)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(1-苯基丙氧基)吡啶-3-甲醯胺(化合物1045)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-苯氧基-吡啶-3-甲醯胺(化合物1046)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3-氟氧雜環丁烷-3-基)甲氧基]吡啶-3-甲醯胺(化合物1053)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-苯基丙氧基)吡啶-3-甲醯胺(化合物1068)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(1-甲基吲哚-7-基)氧基-吡啶-3-甲醯胺(化合物1071)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[[(1R,5S)-3-雙環[3.1.0]己基]氧基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1077)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-氰基-2,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物1089)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-氟-2-甲基-苯氧基)吡啶-3-甲醯胺(化合物1104)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基環己氧基)吡啶-3-甲醯胺(化合物1108)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(環丁氧基)吡啶-3-甲醯胺(化合物1154)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(1-環丙基乙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1165)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(1R,2R,4S)-降冰片烷-2-基]氧基-吡啶-3-甲醯胺(化合物1216)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-降冰片烷-2-基氧基-吡啶-3-甲醯胺(化合物1227)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環丙基甲氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1229)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(1-環丁基乙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1238)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,6-二甲基苯氧基)吡啶-3-甲醯胺(化合物1243)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環庚氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1263)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(1-甲基-2-苯基-乙氧基)吡啶-3-甲醯胺(化合物1314)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2-甲基苯氧基)吡啶-3-甲醯胺(化合物1318)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-四氫哌喃-4-基氧基-吡啶-3-甲醯胺(化合物1324)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-降冰片烷-2-基氧基-吡啶-3-甲醯胺(化合物1349)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-7,7-二甲基-2-(2,4,6-三甲基苯氧基)-6,8-二氫-5*H*-喹啉-3-甲醯胺(化合物665)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基環戊氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物416)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-四氫呋喃-3-基氧基-吡啶-3-甲醯胺(化合物433)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基環己氧基)吡啶-3-甲醯胺(化合物438)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物985)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1461)，

3-[[6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-羰基]胺磺醯基]苯甲酸 (化合物205)，

*N*-(3-胺基苯基)磺醯基-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物231)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-苯乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物268)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-苯甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1)，

*N*-(苯磺醯基)-2-(2,4,6-三甲基苯氧基)喹啉-3-甲醯胺(化合物215)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-8-甲基-2-(2,4,6-三甲基苯氧基)喹啉-3-甲醯胺(化合物70)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)喹啉-3-甲醯胺(化合物91)，

*N*-(3-胺基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)喹啉-3-甲醯胺(化合物260)，

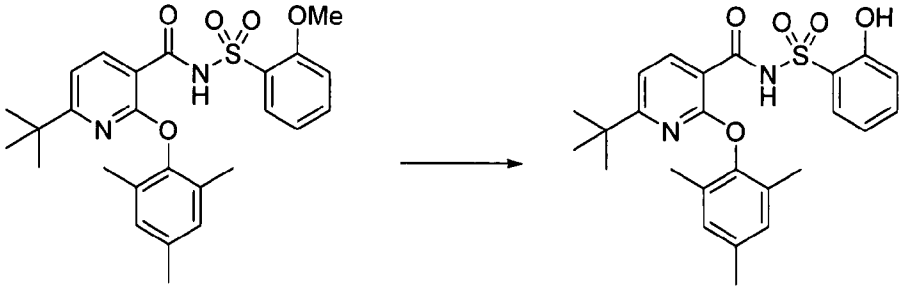
*N*-(4-吡啶基磺醯基)-2-(2,4,6-三甲基苯氧基)喹啉-3-甲醯胺(化合物240)，

6-第三丁基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物214)，

6-第三丁基-*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物262)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物15)。

**製備7：6-第三丁基-*N*-(2-羥基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物131)**



6-第三丁基-*N*-(2-甲氧基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物115) (99 mg，0.21 mmol)溶解於$CH_2Cl_2$ (10 mL)中。混合物冷卻至-78℃，接著緩慢添加$BBr_3$ (1.0 mL，1M，1.0 mmol)。混合物升溫至室溫，隔夜。將反應混合物用飽和$NaHCO_3$ (10 mL)稀釋且用乙酸乙酯(2×5 mL)萃取。有機層經硫酸鈉乾燥且濃縮。殘餘物進行製備型HPLC (20-80%含5 mM HCl之乙腈/水)，得到6-第三丁基-*N*-(2-羥基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物131) (63 mg，66%)。$^1$H NMR (400 MHz, DMSO) δ 11.66 (s, 1H), 11.04 (s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.52 (s, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.02 (s, 2H), 6.93 (s, 2H), 2.26 (s, 3H), 1.98 (s, 6H), 1.04 (s, 9H)。ESI-MS *m/z*計算值468.2, 實驗值469.0 $(M+1)^+$；滯留時間: 2.16 min (3分鐘操作)。

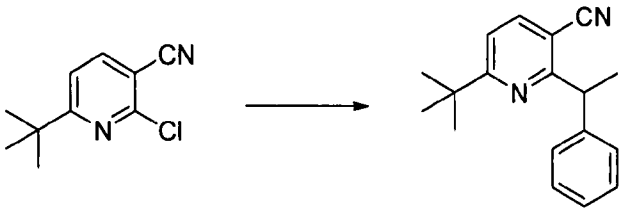
以下化合物可使用本文所述之程序合成：6-第三丁基-*N*-(3-羥基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物47)

及

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-羥基苯基)磺醯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物395)。

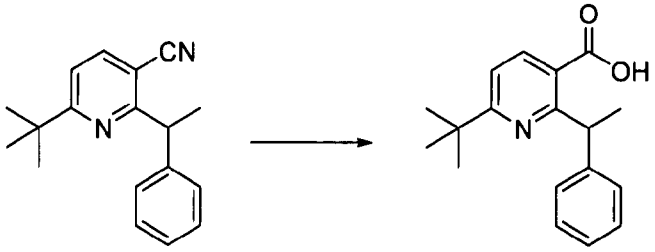
**製備8：6-第三丁基-2-(1-苯基乙基)吡啶-3-甲酸**

**步驟1：6-第三丁基-2-(1-苯基乙基)吡啶-3-甲腈**



將溴(1-苯基乙基)鋅(4.1 mL 0.5 M，2.1 mmol)及二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(38 mg，0.051 mmol)之混合物在室溫下在氮氣下攪拌20分鐘。添加6-第三丁基-2-氯-吡啶-3-甲腈(100 mg，0.51 mmol)且將反應混合物在微波反應器中在150℃下加熱10分鐘。濃縮混合物且殘餘物進行矽膠管柱層析(0-20%乙酸乙酯/己烷)，得到6-第三丁基-2-(1-苯基乙基)吡啶-3-甲腈(120 mg，80.%)。ESI-MS *m/z*計算值264.2，實驗值265.4 $(M+1)^+$；滯留時間: 2.28 min (3分鐘操作)。

**步驟2：6-第三丁基-2-(1-苯基乙基)吡啶-3-甲酸**




將6-第三丁基-2-(1-苯基乙基)吡啶-3-甲腈(120 mg，0.45 mmol)、KOH (1.1 mL 4.0 M，4.4 mmol)及EtOH (1.2 mL)之混合物在90℃下加熱隔夜。濃縮混合物且將濃HCl添加至殘餘物中。收集固體且用水洗滌。固體置於真空烘箱中60℃下隔夜，得到6-第三丁基-2-(1-苯基乙基)吡啶-3-甲酸[ESI-MS *m/z*計算值283.2，實驗值284.3 $(M+1)^+$；滯留時間: 0.78 min (1分鐘操作)]與6-第三丁基-2-(1-苯基乙基)吡啶-3-甲醯胺[ESI-MS *m/z*計算值282.2，實驗值283.4 $(M+1)^+$；滯留時間: 0.69 min (1分鐘操作)]之約1:1混合物。

以下化合物可使用本文所述之程序合成：

6-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡啶-3-甲酸，

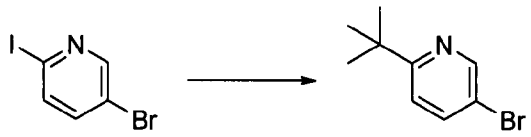
*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(1-苯基乙基)吡啶-3-甲醯胺(化合物271)，及

*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡

啶-3-甲醯胺(化合物346)。

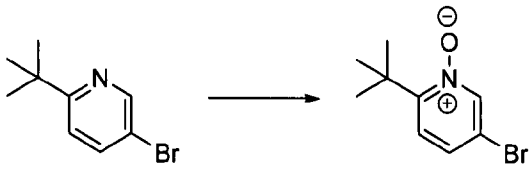
**製備9：6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲酸**

**步驟1：5-溴-2-第三丁基吡啶**



將氯化第三丁基鎂(60 mL 1.0 N於THF中之溶液，60 mmol)緩慢添加至冷卻至-78℃的CuCN (2.7 g，30 mmol)於THF (60 mL)中之微綠色懸浮液且將所得灰色混合物在-78℃下攪拌1小時。接著添加5-溴-2-碘吡啶(4.3 g，15 mmol)於THF (10 mL)中之溶液。將反應混合物在-78℃下攪拌1小時，接著在0℃下攪拌3小時，接著隔夜緩緩升溫至室溫。添加氫氧化銨(80 mL 20%)且過濾所得混合物且用乙酸乙酯(100 mL)洗滌。濾液用鹽水(40 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(0-10%乙酸乙酯/庚烷)來純化，得到呈無色油狀之5-溴-2-第三丁基吡啶(2.2 g，68%；含有20%庚烷)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 7.23 (dd, $J$ = 8.5, 0.9 Hz, 1H), 7.71 (dd, $J$ = 8.5, 2.3 Hz, 1H), 8.60 (d, $J$ = 2.3 Hz, 1H)。$[M+H]^+$ = 214.0。

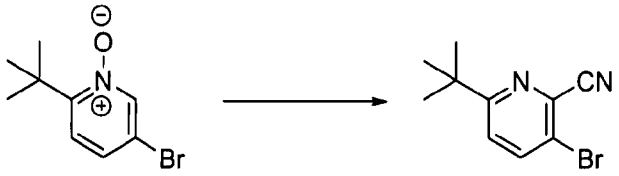
**步驟2：5-溴-2-第三丁基吡啶-*N*-氧化物**



將3-氯過氧苯甲酸(4.40 g 77%級，17.9 mmol)添加至5-溴-2-第三丁基吡啶(3.70 g，13.8 mmol)於二氯甲烷(45 mL)中之溶液中。將反應混合物在室溫下攪拌隔夜。添加$Ca(OH)_2$ (4.1 g，44 mmol)且接著在室溫下攪拌所得混合物30分鐘，接著經矽藻土墊過濾。濾液在減壓下濃縮且殘餘物藉由矽膠層析(0-50%乙酸乙酯/庚烷)來純化，得到呈白色固體狀之5-溴-2-第三丁基吡啶-*N*-氧化物(2.7 g，85%)。$^1$H NMR

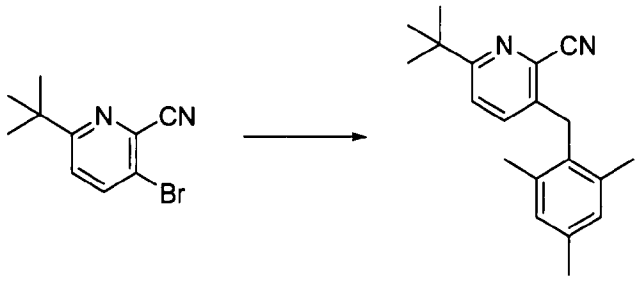
(300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 7.19 (d, $J$ = 8.8 Hz, 1H), 7.31 (dd, $J$ = 8.8, 1.8 Hz, 1H), 8.33 (d, $J$ = 1.8 Hz, 1H)。$[M+H]^+$ = 230.0。

**步驟3：6-第三丁基吡啶-2-甲腈**



在室溫下將三甲基矽烷甲腈(8.8 mL，70 mmol)及$Et_3N$ (7.4 mL，53 mmol)添加至5-溴-2-第三丁基吡啶-*N*-氧化物(2.7 g，12 mmol)於乙腈(20 mL)中之溶液中。接著將反應混合物在100℃下加熱隔夜。添加額外三甲基矽烷甲腈(2.4 mL，19 mmol)及$Et_3N$ (2.1 mL，15 mmol)且將反應混合物在回流下再加熱隔夜。在減壓下移除大部分乙腈且殘餘物溶於乙酸乙酯(100 mL)中。有機層用飽和$NaHCO_3$水溶液(20 mL)、鹽水(20 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(0-15%乙酸乙酯/庚烷)來純化，得到呈無色油狀之3-溴-6-第三丁基吡啶-2-甲腈(2.6 g，93%)。$^1H$ NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 7.42 (d, $J$ = 8.5 Hz, 1H), 7.89 (d, $J$ = 8.5 Hz, 1H)。$[M+H]^+$ = 238.9。

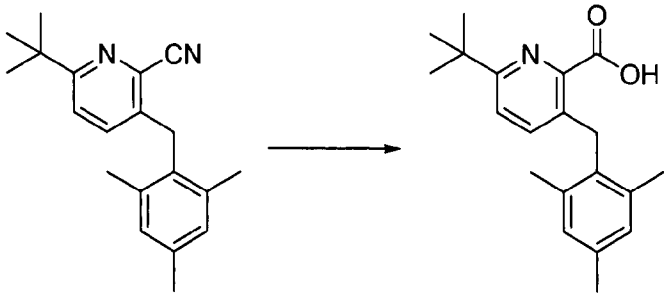
**步驟4：6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲腈**



將肆(三苯基膦)鈀(0) (530 mg，0.46 mmol)添加至密封管中3-溴-6-第三丁基吡啶-2-甲腈(1.1 g，4.6 mmol)於THF (12 mL)中之溶液中。將混合物抽空且用氮氣回填三次，接著在室溫下添加溴化(2,4,6-三甲基苯基)甲基鋅之儲備溶液(9.2 mL 1.0 M於THF中之溶液，9.2

mmol)。將橙色溶液在60℃下攪拌隔夜。將反應混合物用5%檸檬酸(20 mL)淬滅且所得混合物用乙酸乙酯(2×40 mL)萃取。合併之有機層用水(2×15 mL)、鹽水(15 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(5-30%乙酸乙酯/庚烷)來純化，得到呈白色固體狀之6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲腈(1.2 g，89%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.17 (s, 6H), 2.30 (s, 3H), 4.17 (s, 2H), 6.91 (s, 2H), 6.97 (d, $J$ = 8.5 Hz, 1H), 7.32 (d, $J$ = 8.5 Hz, 1H)。$[M+H]^+$ = 293.2。

**步驟5：6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲酸**

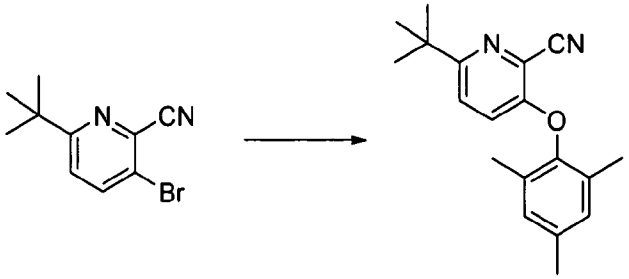



6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲腈(900. mg，3.08 mmol)溶於乙酸(8 mL)中。添加濃HCl (8 mL)且將反應混合物在120℃下攪拌3天。添加額外乙酸(2 mL)及濃HCl (2 mL)且將反應混合物在120℃下再攪拌24小時。在減壓下移除大部分乙酸且將所得不均質混合物用25% NaOH水溶液鹼化至約8-10之pH值。接著添加5%檸檬酸水溶液(20 mL)且水層用甲基第三丁基醚(2×50 mL)萃取。合併之有機層用水(2×20 mL)、鹽水(20 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(0-50%乙酸乙酯/庚烷)來純化，得到呈白色固體狀之6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲酸(660 mg，68.8%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.12 (s, 6H), 2.31 (s, 3H), 4.57 (s, 2H), 6.91 (s, 2H), 7.07 (d, $J$ = 8.2 Hz, 1H), 7.39 (d, $J$ = 8.2 Hz, 1H), 12.25 (br s, 1H)。$[M+H]^+$ = 312.2。

以下化合物可使用本文所述之程序合成：*N*-(苯磺醯基)-6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲醯胺(化合物22)及*N*-(3-胺基苯基)磺醯基-6-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡啶-2-甲醯胺(化合物313)。

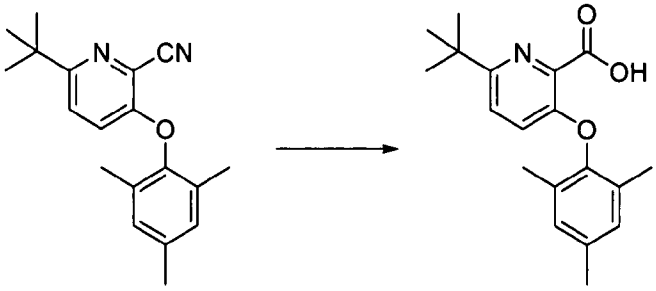
**製備10：6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲酸**

**步驟1：6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲腈**




將3-溴-6-第三丁基吡啶-2-甲腈(1.0 g，4.2 mmol)、2,4,6-三甲基苯酚(0.57 g，4.2 mmol)及$Cs_2CO_3$ (2.0 g，6.3 mmol)於DMSO (8 mL)中之混合物在100℃下加熱隔夜。一旦冷卻至室溫，添加乙酸乙酯(70 mL)且有機層用水(2×20 mL)、鹽水(20 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(0-30%乙酸乙酯/庚烷)來純化，得到呈白色固體狀之6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲腈(1.0 g，81%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.08 (s, 6H), 2.30 (s, 3H), 6.73 (d, *J* = 9.1 Hz, 1H), 6.92 (s, 2H), 7.32 (d, *J* = 8.8 Hz, 1H)。$[M+H]^+$ = 295.1。

**步驟2：6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲酸**



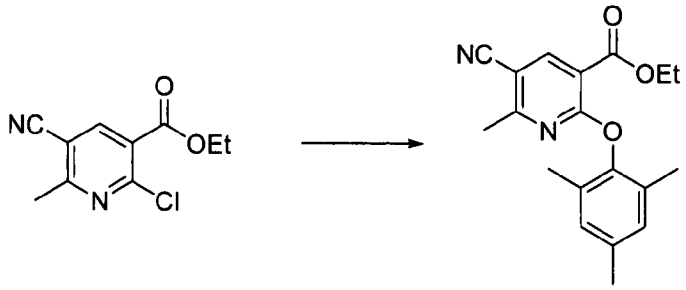

6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲腈(700 mg，2.38 mmol)溶於乙酸(9 mL)中。添加濃HCl (9 mL)且將反應混合物在120℃

下加熱2天。一旦冷卻至室溫，反應混合物在減壓下濃縮至乾。殘餘物懸浮於水(20 mL)中且添加2N NaOH (3 mL)，得到透明水溶液。水層用甲基第三丁基醚(2×10 mL)洗滌，藉由添加5%檸檬酸(20 mL)酸化且所得混合物用乙酸乙酯(2×50 mL)萃取。合併之有機層用水(2×20 mL)、鹽水(20 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。在0℃下殘餘物用庚烷(10 mL)濕磨，得到呈灰白色固體狀之6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲酸(574 mg，77%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.08 (s, 6H), 2.30 (s, 3H), 6.89 - 6.92 (m, 3H), 7.42 (d, $J$ = 8.9 Hz, 1H), 11.68 (br s, 1H)。$[M+H]^+$ = 314.2。

以下化合物可使用本文所述之程序合成：*N*-(3-胺基苯基)磺醯基-6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲醯胺(化合物106)及*N*-(苯磺醯基)-6-第三丁基-3-(2,4,6-三甲基苯氧基)吡啶-2-甲醯胺(化合物350)。

**製備11：*N*-(3-胺基苯基)磺醯基-5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物124)**

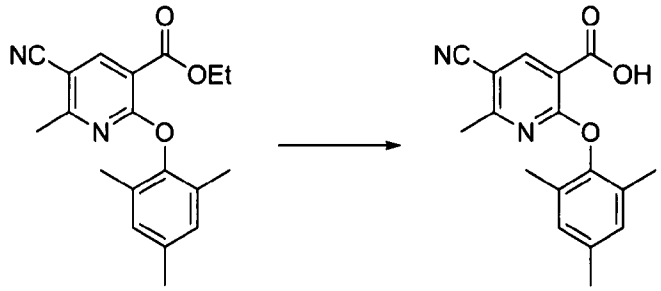
**步驟1：5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯**




將2-氯-5-氰基-6-甲基-吡啶-3-甲酸乙酯(518 mg，2.31 mmol)、2,4,6-三甲基苯酚(377 mg，2.77 mmol)及碳酸銫(1.50 g，4.61 mmol)組合於*N,N*-二甲基甲醯胺(5 mL)中且在90℃下加熱1小時。反應混合物冷卻且分溶於乙酸乙酯與1N HCl之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且蒸發，得到5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯。ESI-MS *m/z* 計算值324.2，實驗值325.2

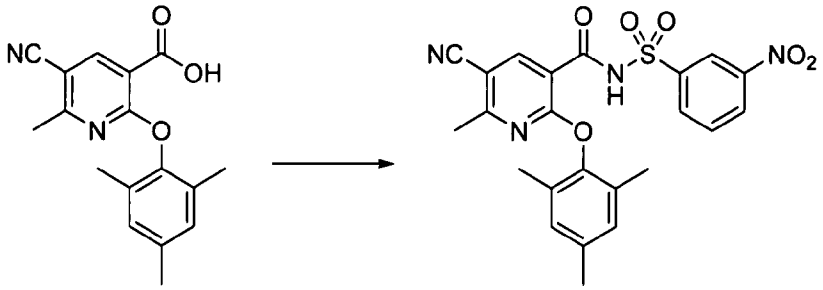
$(M+1)^+$；滯留時間: 0.77 min (1分鐘操作)。

**步驟2：5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸**



粗5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯溶解於甲醇(12 mL)中，接著添加NaOH (12 mL 1.0 M，12 mmol)。將混合物在70℃下加熱3小時。冷卻混合物且藉由添加1 N HCl呈酸性。所得沈澱藉由過濾收集。進一步乾燥固體，得到5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(500 mg，2步73%)。ESI-MS *m/z*計算值296.1，實驗值297.4 $(M+1)^+$；滯留時間: 0.63 min (1分鐘操作)。

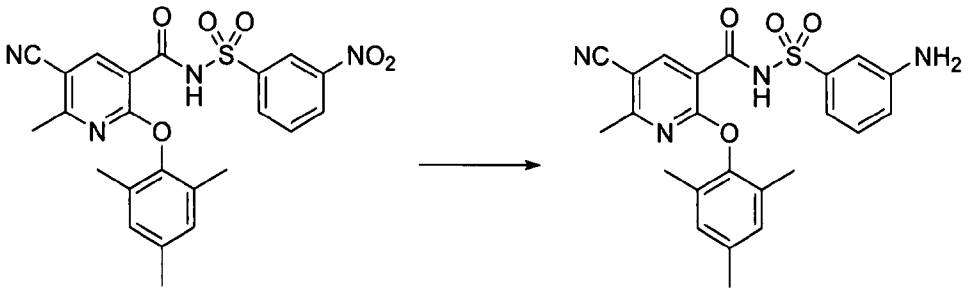
**步驟3：5-氰基-6-甲基-*N*-(3-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



將5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(65 mg，0.22 mmol)、[(3-硝基苯基)磺醯基胺基]鈉(98 mg，0.44 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(170 mg，0.44 mmol)及*N,N*-二甲基甲醯胺(1 mL)組合且將混合物在室溫下攪拌1小時。將反應混合物用水(1 mL)稀釋且用乙酸乙酯(2×5 mL)萃取。有機層經硫酸鈉乾燥，過濾且濃縮。殘餘物進行製備型HPLC (20-80%含5 mM HCl之乙腈/水)，得到5-氰基-6-甲基-*N*-(3-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺。

ESI-MS *m/z*計算值480.1，實驗值481.5 $(M+1)^+$；滯留時間: 0.73 min (1分鐘操作)。

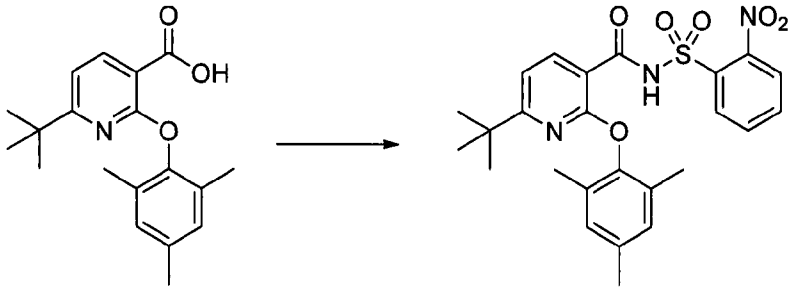
**步驟4：*N*-(3-胺基苯基)磺醯基-5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物124)**



5-氰基-6-甲基-*N*-(3-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(來自步驟3)溶於甲醇(10 mL)中，接著添加10% Pd/C (12 mg，0.011 mmol)。將混合物在氫氣球下在室溫下攪拌2小時。將混合物過濾且濃縮。殘餘物進行製備型HPLC (25-75%含5 mM HCl之乙腈/水)，得到*N*-(3-胺基苯基)磺醯基-5-氰基-6-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物124) (15 mg，2步15%)。ESI-MS *m/z*計算值450.1，實驗值451.0 $(M+1)^+$；滯留時間: 1.68 min (3分鐘操作)。

**製備12：*N*-(2-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物322)**

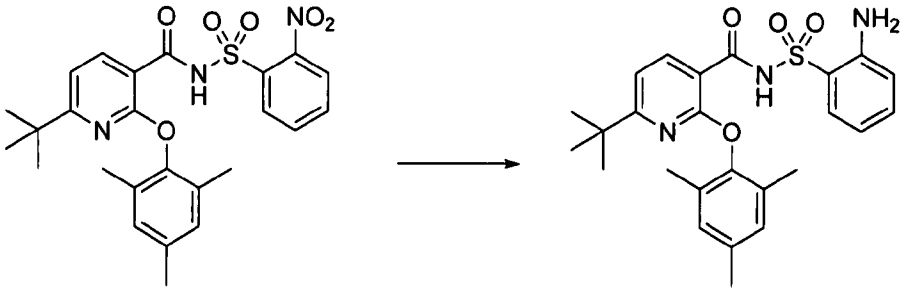
**步驟1：6-第三丁基-*N*-(2-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



將6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(50. mg，0.16 mmol)、2-硝基苯磺醯胺(32 mg，0.16 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(91

mg，0.24 mmol)、乙基二異丙基胺(56 μL，0.32 mmol)及NMP (1 mL)組合。將混合物在75℃下加熱16小時，接著其冷卻至室溫。反應混合物用水(1 mL)稀釋且用乙酸乙酯(2×5 mL)萃取。合併之有機層經硫酸鈉乾燥，過濾且濃縮。殘餘物進行製備型HPLC (含5 mM HCl之30-90%乙腈/水)，得到6-第三丁基-*N*-(2-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺。ESI-MS *m/z*計算值497.2，實驗值498.4 $(M+1)^+$；滯留時間: 0.89 min (1分鐘操作)。

**步驟2：*N*-(2-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物322)**

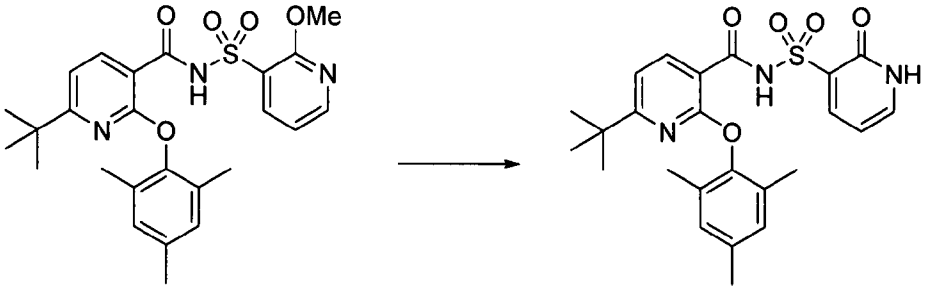


6-第三丁基-*N*-(2-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(23 mg，0.046 mmol)溶於EtOH (5 mL)中，接著添加10% Pd/C (2 mg，0.02 mmol)。將混合物在氫氣球下在室溫下攪拌2小時。將混合物過濾且濃縮濾液。殘餘物進行製備型HPLC (含5 mM HCl之20-80%乙腈/水)，得到*N*-(2-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物322) (4.8 mg，33%)。$^1$H NMR (400 MHz, DMSO) δ 8.06 (s, 1H), 7.74 (s, 1H), 7.36 (s, 1H), 7.20 (s, 1H), 6.99 (s, 2H), 6.87 (s, 1H), 6.72 (s, 1H), 2.34 (s, 3H), 2.04 (s, 6H), 1.33 (s, 2H), 1.13 (s, 9H)。ESI-MS *m/z*計算值467.2，實驗值468.0 $(M+1)^+$；滯留時間: 2.25 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(2,6-二甲基苯氧基)吡啶-3-甲醯胺(化合物286)、*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-環己基-吡啶-3-甲醯胺(化合物537)、*N*-

(3-胺基苯基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物294)及*N*-(3-胺基-1-甲基-吡唑-4-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物41)。

**製備13：6-第三丁基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物51)**



6-第三丁基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物191) (45 mg，0.093 mmol)溶於二噁烷 (1 mL)中，接著添加HCl水溶液(0.5 mL 4.0 M，2.0 mmol)。將反應混合物在90℃下加熱1小時，接著其冷卻且濃縮。殘餘物進行製備型HPLC (含5 μM HCl之20-80%乙腈/水)，得到6-第三丁基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物51) (19 mg，20.%)。$^1$H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 11.83 (s, 1H), 8.27 (dd, *J* = 7.3, 2.1 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 6.3 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.93 (s, 2H), 6.46 (t, *J* = 6.8 Hz, 1H), 2.27 (s, 3H), 1.99 (s, 6H), 1.05 (s, 9H)。ESI-MS *m/z*計算值469.2, 實驗值470.3 $(M+1)^+$；滯留時間: 1.95 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

6-第三丁基-2-(2,4-二甲基苯氧基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物55)，

7,7-二甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)-6,8-二氫-5*H*-喹啉-3-甲醯胺(化合物1199)，

2-(2,4-二甲基苯氧基)-8,8-二甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺

醯基]-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物634)，

8,8-二甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物899)，

6-(1-甲基環丙基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1226)，

6-第三丁基-*N*-[(4-甲基-2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1311)，

6-(4-乙氧基-3-氟-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物901)，

6-(4-甲基環己基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物743)，

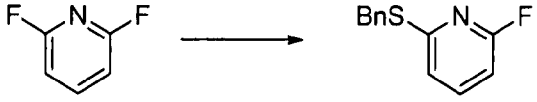
6-(4,4-二甲基環己基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1091)，

6-(4,4-二氟環己基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1329)，及

6-環己基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1357)。

**製備14：6-氟吡啶-2-磺醯胺**

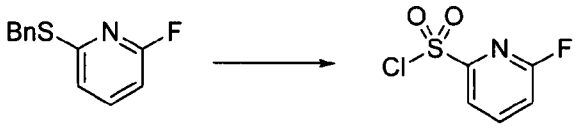
**步驟1：2-(苯甲基硫基)-6-氟吡啶**




經10分鐘向BnSH (18.1 g，146 mmol)於THF (1.12 L)中之溶液中逐份添加60% NaH (6.60 g，165 mmol)。將反應混合物在室溫下攪拌15分鐘，此後經10分鐘逐滴添加2,6-二氟吡啶(13.7 mL，150. mmol)於THF (100 mL)中之溶液。將所得透明溶液在室溫下攪拌2小時。將反應混合物用$H_2O$ (250 mL)淬滅且所得混合物用$Et_2O$ (800 mL)萃取。有

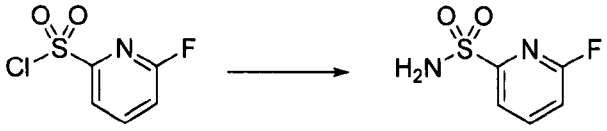
機層用$H_2O$ (400 mL)及鹽水(250 mL)洗滌，經$Na_2SO_4$乾燥且濃縮至乾。殘餘物藉由矽膠管柱層析(100%己烷，接著己烷中1-10%乙酸乙酯之梯度)來純化，得到2-(苯甲基硫基)-6-氟吡啶(32.0 g，100%)。$^1H$ NMR ($CDCl_3$, 250 MHz) δ 7.56 (q, $J$ = 8.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.39-7.21 (m, 3H), 7.03 (dd, $J$ = 7.5, 2.3 Hz, 1H), 6.60 (dd, $J$ = 7.8, 2.5 Hz, 1H), 4.41 (s, 2H)。

**步驟2：6-氟吡啶-2-磺醯氯**



2-(苯甲基硫基)-6-氟吡啶(32.0 g，146 mmol)溶於$CHCl_3$ (500 mL)中且添加$H_2O$ (400 mL)。氯氣緩慢鼓泡穿過反應混合物2小時。(注意：使用30% NaOH水溶液捕集器(1-1.5L)，接著飽和$Na_2S_2O_3$ (1-1.5 L)水溶液捕集器以中和過量$Cl_2$)。反應混合物在添加期間變溫且形成黃色懸浮液。反應用$Na_2S_2O_5$ (200 g)於$H_2O$ (450 mL)中之溶液小心淬滅(放熱及起泡)。分離各層且水層用$CHCl_3$ (200 mL)萃取一次。合併有機層且用$H_2O$ (300 mL)洗滌，經$Na_2SO_4$乾燥且濃縮至乾，得到呈微褐色油狀之不純6-氟吡啶-2-磺醯基氯。此物質原樣用於下一步中。

**步驟3：6-氟吡啶-2-磺醯胺**

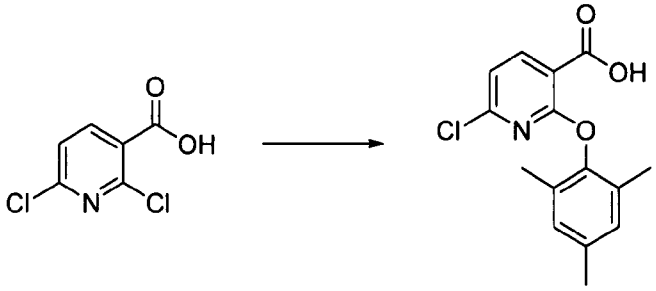


粗6-氟吡啶-2-磺醯基氯(來自步驟2)溶於$CH_2Cl_2$ (1 L)中且溶液冷卻至-78℃。氨氣鼓泡穿過溶液25分鐘。將混合物在室溫下攪拌1小時且沈澱產物藉由過濾移除且用$CH_2Cl_2$ (2次)洗滌。合併濾液及洗滌物且濃縮至約50 mL且過濾；固體用$CH_2Cl_2$/己烷(50/50 mL)洗滌且乾燥，得到呈灰色固體狀之6-氟吡啶-2-磺醯胺(12.0 g，46%產率，純度約90%)。$^1H$ NMR (DMSO, 250 MHz) δ 8.27 (q, $J$=8.0 Hz, 1H), 7.88

(dd, *J*=7.5, 2.1 Hz, 1H), 7.66 (s, 2H), 7.48 (dd, *J*=8.0, 2.4 Hz, 1H)。

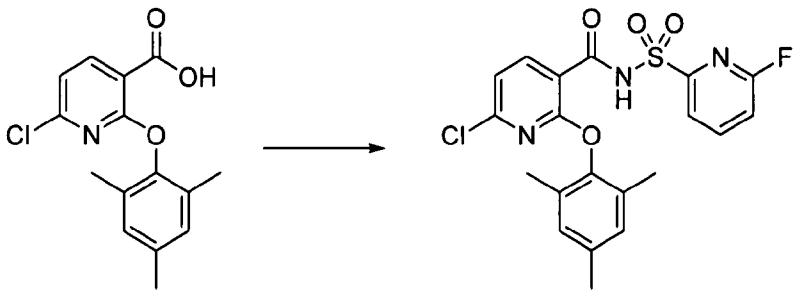
**製備15：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1255)**

**步驟1：6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸**



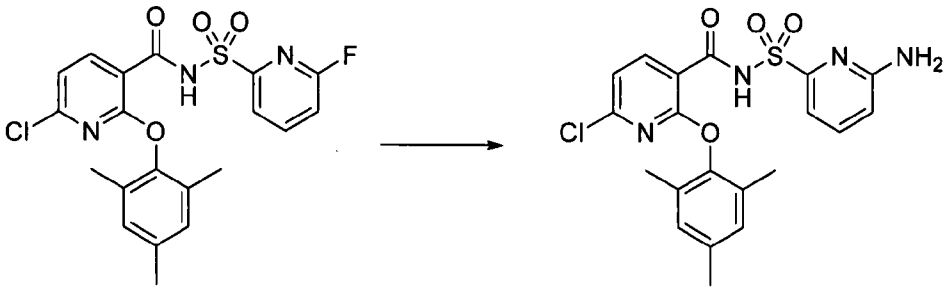
在0-5℃下向2,4,6-三甲基苯酚(13.6 g，100 mmol)於*N,N*-二甲基甲醯胺(300 mL)中之溶液中小心添加NaH固體(60%於礦物油中，8.80 g，220 mmol)。在相同溫度下攪拌所得懸浮液15分鐘後，添加固體2,6-二氯-菸鹼酸(19.2 g，100 mmol)。將反應混合物在室溫下攪拌20分鐘且接著在80℃下攪拌隔夜。冷卻混合物至室溫，接著其傾倒至冷$NaHSO_4$溶液(24.0 g於200 mL水中)。將所得懸浮液在室溫下攪拌30分鐘。沈澱藉由過濾收集，用水、接著$Et_2O$/己烷(200/500 mL)洗滌，且在40℃下在真空下乾燥，得到呈微褐色固體狀之6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(19.2 g，66%)。$^1$H NMR (400 MHz, DMSO) δ 13.38 (s, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 1.1 Hz, 2H), 2.27 (s, 3H), 1.99 (s, 6H)。ESI-MS *m/z*計算值291.1，實驗值292.0 $(M+1)^+$；滯留時間: 2.34 min (3分鐘操作)。

**步驟2：6-氯-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



在5℃下將6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(23.7 g，81.4 mmol)添加至六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(35.0 g，92.1 mmol)、6-氟吡啶-2-磺醯胺(16.5 g，93.8 mmol)及乙基二異丙基胺(36 mL)於*N,N*-二甲基甲醯胺(400 mL)中之混合物中。將所得混合物在室溫下攪拌隔夜，接著其用1 N HCl (150 mL)淬滅。混合物用水(450 mL)稀釋且所得固體藉由過濾收集且用水(500 mL)、甲醇(200 mL)及$Et_2O$ (400 mL)洗滌。固體藉由矽膠管柱層析(0-4%甲醇/$CH_2Cl_2$)來純化，得到呈白色固體狀之6-氯-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(22.2 g，60%)。$^1$H NMR ($CDCl_3$, 250 MHz) δ 8.36 (dd, *J*=15.7, 7.5 Hz, 1H), 8.14 (d, *J*=7.5 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=8.2 Hz, 1H), 7.29 (d, *J*=7.8 Hz, 1H), 6.91 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H)。

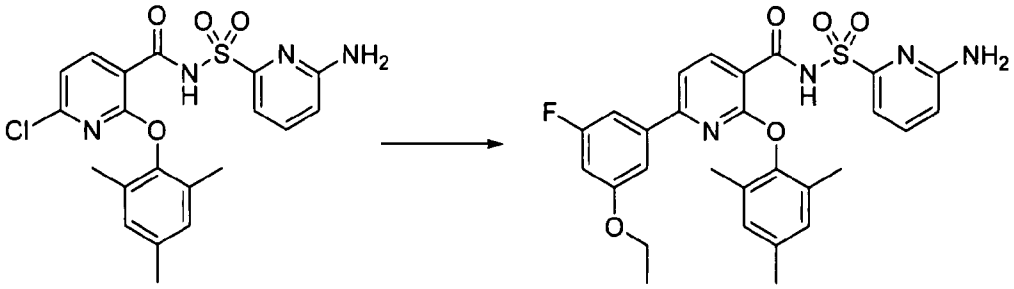
**步驟3：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



在0℃下將6-氯-*N*-[(6-氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(12.0 g，26.7 mmol)與$NH_4OH$ (28-30%，250 mL)及DMSO (200 mL)混合在1L壓力容器中。將容器密封且在92℃(油浴)下加熱2天，且在85℃下再加熱2天。移除溶劑(水及DMSO)且殘餘物懸浮於$CH_2Cl_2$/乙酸乙酯/甲醇(25/25/25 mL)之混合溶劑中。在室溫下對懸浮液進行音波處理15分鐘且過濾。固體用$CH_2Cl_2$/乙酸乙酯/甲醇(10/10/10 mL)洗滌且乾燥，得到呈白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(6.8 g，57%)。$^1$H

NMR ($CDCl_3$, 250 MHz) δ 8.10 (d, *J*=7.8 Hz, 1H), 7.64 (t, *J*=7.8 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 7.21 (d, *J*=7.2 Hz, 1H), 6.92 (s, 2H), 6.71 (d, *J*=8.5 Hz, 1H), 6.60 (br, s, 2H), 2.26 (s, 3H), 1.98 (s, 6H)。

**步驟4：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1255)**



含有*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-2-(均三甲苯基基氧基)-菸鹼醯胺(30. mg，0.067 mmol)、3-乙氧基-5-氟-苯硼酸(25 mg，0.13 mmol)、$Pd(PPh_3)_4$ (5.0 mg)、$K_3PO_4$ (2.0 M, 0.13 mL)及*N,N*-二甲基甲醯胺(0.6 mL)之混合物的小瓶用氮氣沖洗且密封。接著混合物在80℃下加熱隔夜，接著其冷卻且用DMSO (0.3 mL)稀釋。混合物進行製備型HPLC (含5 μM HCl之30-90%乙腈/水)，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1255) (20 mg，54%)。ESI-MS *m/z*計算值550.2, 實驗值551.5 $(M+1)^+$；滯留時間: 3.15 min (5分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-第三丁基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物364)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環丙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1050)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二甲基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物399)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異

丁氧基-苯基)吡啶-3-甲醯胺(化合物639)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)苯甲醯胺(化合物1549)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)-6-乙烯基-吡啶-3-甲醯胺(化合物430)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-羥基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物505)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物513)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-4-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物514)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲基吲唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物451)，

*N*-[[6-(胺基甲基)-2-吡啶基]磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物871)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-甲基-5-(三氟甲基)吡唑-3-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物457)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物463)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氟-5-異丁氧基-苯基)-3-(2,4,6-三甲基苯氧基)吡啶-2-甲醯胺(化合物1456)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-丙基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物469)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4,4-二甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物538)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4,4-二氟環己基)-2-(2,4,6-三甲

基苯氧基)吡啶-3-甲醯胺(化合物783)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-乙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物963)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丙基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1232)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環戊基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1280)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-甲氧基丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物791)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-戊基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物862)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基乙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物929)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環己基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1131)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(1-哌啶基)嘧啶-5-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物475)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-甲氧基-4-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物375)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氟-2-甲氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物387)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,4-二氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物439)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-羥基-3-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物450)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(嗎啉基甲基)苯基]-2-(2,4,6-三

甲基苯氧基)吡啶-3-甲醯胺(化合物465)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲氧基-3-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物477)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-2-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物396)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物436)，

6-(2-氟-4-甲氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物374)，

6-[2-甲基-5-(三氟甲基)吡唑-3-基]-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物391)，

6-(4-氟-2-甲氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物405)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-(1-異丁基吡唑-4-基)吡啶-3-甲醯胺(化合物381)，

6-(4-異丙氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物494)，

6-(1,3-苯并間二氧雜環戊烯-4-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物525)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物93)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-甲基吲哚-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物386)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(氰基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物388)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-甲氧基苯基)-2-(2,4,6-三甲基

苯氧基)吡啶-3-甲醯胺(化合物413)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲氧基嘧啶-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物449)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物531)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-4-(異丙基胺甲醯基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物543)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-乙氧基-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物599)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,6-二甲氧基-4-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物629)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(氰基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物638)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-3-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物661)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(間甲苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物672)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二氫-1,4-苯并二氧雜環己烯-6-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物673)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物682)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(1-哌啶基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物686)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(2,2,2-三氟乙氧基)-3-吡啶基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物697)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氟-2-甲氧基-苯基)-2-(2,4,6-三

甲基苯氧基)吡啶-3-甲醯胺(化合物700)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物725)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-氟-5-(羥基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物727)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-四氫哌喃-4-基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物748)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-羥基-3-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物768)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二甲基胺基)-3-吡啶基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物787)，

6-[3-(胺基甲基)苯基]-*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物801)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,5-二氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物803)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(嗎啉基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物810)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物828)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟-2-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物830)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1272)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物730)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-甲基-2-吡啶基)-2-(2,4,6-三甲

基苯氧基)吡啶-3-甲醯胺(化合物1290)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物602)，

6-(6-甲氧基-5-甲基-3-吡啶基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1044)，

2-(2,4-二甲基苯氧基)-6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)吡啶-3-甲醯胺(化合物610)，

2-(2,4-二甲基苯氧基)-6-(6-甲氧基-5-甲基-3-吡啶基)-*N*-(1H-吡唑-3-基磺醯基)吡啶-3-甲醯胺(化合物892)，

2-(2,4-二甲基苯氧基)-6-(3-氟-5-異丙氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)吡啶-3-甲醯胺(化合物1213)，

2-(2,4-二甲基苯氧基)-6-(4-乙氧基苯基)-*N*-(1H-吡唑-3-基磺醯基)吡啶-3-甲醯胺(化合物813)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物535)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-2-羥基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物866)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-(4-乙氧基苯基)吡啶-3-甲醯胺(化合物641)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-(3-氟-5-異丙氧基-苯基)吡啶-3-甲醯胺(化合物1150)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-(對甲苯基)吡啶-3-甲醯胺(化合物1015)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1118)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丙基苯基)-2-(2,4,6-三甲基

苯氧基)吡啶-3-甲醯胺(化合物1016)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(三氟甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物709)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物900)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物548)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-(6-甲氧基-5-甲基-3-吡啶基)吡啶-3-甲醯胺(化合物533)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氯-2-甲氧基-4-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1284)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲氧基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1034)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1133)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1138)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氟-2-甲氧基-4-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1277)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-4-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物860)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙基吡唑-3-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1317)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-羥基-4-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物793)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-丙氧基苯基)-2-(2,4,6-三甲基

苯氧基)吡啶-3-甲醯胺(化合物996)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基-3-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1268)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1221)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氫-2*H*-哌喃-6-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物937)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-4-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1000)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(環戊烯-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1330)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物897)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-4-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物875)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丙烯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1211)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氯-2-甲氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物993)，

6-(1-異丁基吡唑-4-基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物577)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1278)，

*N*-(1H-吡唑-3-基磺醯基)-6-(2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1353)，

6-(3-乙氧基-5-氟-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基

苯氧基)吡啶-3-甲醯胺(化合物585)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1163)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1173)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1295)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物570)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟-2-羥基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物622)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,6-二氫-2*H*-哌喃-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物976)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1325)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,4-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物950)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-甲基-3-(三氟甲基)吡唑-4-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物812)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氯-6-甲氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1332)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,6-二甲氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物754)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物909)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(三氟甲基)-1*H*-吡唑-4-基]-2-

(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物582)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(二甲基胺基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物962)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氰基-2-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1111)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氟-6-甲氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物612)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基嘧啶-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1130)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲氧基-5-甲基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物705)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲氧基-2-甲基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1212)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物718)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物974)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,3-苯并間二氧雜環戊烯-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1207)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-苯甲氧基-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1113)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氟-2-羥基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1409)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丙基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物808)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-甲氧基-3-吡啶基)-2-(2,4,6-三

甲基苯氧基)吡啶-3-甲醯胺(化合物1115)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-乙基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1312)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,5-二甲基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物584)，

6-苯基-*N*-(1H-吡唑-5-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物784)，

6-(4-甲氧基苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1033)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物939)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1H-吲唑-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物856)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氰基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物886)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟-3-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物919)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-6-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物920)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氰基-3-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物923)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,5-二甲基吡唑-3-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物938)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-4-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物956)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1H-吲哚-4-基)-2-(2,4,6-三甲基

苯氧基)吡啶-3-甲醯胺(化合物977)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,5-二氟-4-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物984)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(對甲苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1035)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二氫苯并呋喃-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1084)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-甲基吲哚-6-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1056)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲基吡唑-3-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1057)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(鄰甲苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1120)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(環丙基胺基)嘧啶-5-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1126)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(二甲基胺基)嘧啶-5-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1139)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-4-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1140)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1146)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(1-羥基-1-甲基-乙基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1147)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丁基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1177)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-甲氧基-苯基)-2-(2,4,6-三

甲基苯氧基)吡啶-3-甲醯胺(化合物1178)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1185)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-羥基-2-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1204)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,5-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1225)，

6-[4-(胺基甲基)苯基]-*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1228)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1244)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-羥基-4-甲氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1251)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1255)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-吡咯啶-1-基嘧啶-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1275)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-甲基吲唑-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1276)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲基吲唑-6-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1299)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲氧基-5-甲基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1320)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,6-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1326)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異戊基吡唑-4-基)-2-(2,4,6-三

甲基苯氧基)吡啶-3-甲醯胺(化合物1336)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1337)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-羥基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1344)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(羥基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物786)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-羥基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物908)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(羥基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1183)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物485)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,4-二甲氧基嘧啶-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物499)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物203)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物17)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物61)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,6-二甲基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物97)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物250)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-呋喃基)-2-(2,4,6-三甲基苯氧

基)吡啶-3-甲醯胺(化合物284)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(三氟甲基)-3-吡啶基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物132)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氰基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物216)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氫-2*H*-1,5-苯并二氧呯-7-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物14)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(甲氧基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物66)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基苯氧基)-6-苯基-吡啶-3-甲醯胺(化合物340)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(甲氧基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物69)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙基嘧啶-5-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物64)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物513)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(羥基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物786)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-羥基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物908)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(羥基甲基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1183)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-乙氧基-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物599)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(二甲基胺甲醯基)苯基]-2-

(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-5-(甲基胺甲醯基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲基吲唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物451)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物828)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,5-二甲氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1225)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異戊基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1336)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-丙基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物469)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-羥基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物505)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丁基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1177)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氟苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物725)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(2-氰基乙基胺甲醯基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-4-(異丙基胺甲醯基)苯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物543)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-甲基-2-四氫哌喃-4-基-乙氧基)吡啶-3-甲醯胺(化合物1361)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(1,1-二甲基-2-苯基-乙氧基)-6-

(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1365)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(1-環戊基乙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1374)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環己基甲氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1395)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基環丁氧基)吡啶-3-甲醯胺(化合物406)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丁基乙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1418)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-苯乙基氧基-吡啶-3-甲醯胺(化合物1426)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[1-(3-吡啶基)乙氧基]吡啶-3-甲醯胺(化合物1434)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環戊基乙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1440)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環丙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1446)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環戊基甲氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1450)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環戊氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1451)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二氟環丁氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1458)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-四氫呋喃-3-基]氧基-吡啶-3-甲醯胺(化合物1464)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環己基乙氧基)-6-(3-氟-5-異丁

氧基-苯基)吡啶-3-甲醯胺(化合物1465)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環己氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1477)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(1-苯甲基環丁氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1479)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(四氫呋喃-3-基甲氧基)吡啶-3-甲醯胺(化合物1499)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丙基環丁氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1530)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲氧基環丁氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1559)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(四氫哌喃-2-基甲氧基)吡啶-3-甲醯胺(化合物1570)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,4-二甲基-3-吡啶基)氧基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1574)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-四氫哌喃-4-基乙氧基)吡啶-3-甲醯胺(化合物1579)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環丁氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1580)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-四氫呋喃-3-基]氧基-吡啶-3-甲醯胺(化合物1592)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-四氫呋喃-2-基乙氧基)吡啶-3-甲醯胺(化合物1604)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(4-吡啶基)乙氧基]吡啶-3-甲醯胺(化合物1605)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲

氧基環己氧基)吡啶-3-甲醯胺(化合物1622)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(2-吡啶基)乙氧基]吡啶-3-甲醯胺(化合物1625)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基環戊氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1629)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-(2,2-二甲基環丙基)丙氧基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1639)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-甲基環丁氧基)吡啶-3-甲醯胺(化合物1644)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(3-吡啶基)乙氧基]吡啶-3-甲醯胺(化合物1654)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(四氫呋喃-2-基甲氧基)吡啶-3-甲醯胺(化合物1661)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(1-甲基環丙基)甲氧基]吡啶-3-甲醯胺(化合物1668)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-四氫哌喃-2-基乙氧基)吡啶-3-甲醯胺(化合物1680)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丙基乙氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1685)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物8)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,6-二甲基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物97)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基-3-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物161)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,4,6-三甲基

苯氧基)吡啶-3-甲醯胺(化合物164)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物196)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-2-氟-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物207)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物234)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物238)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物281)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物320)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(7-氟-1,3-苯并間二氧雜環戊烯-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物345)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物351)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物172)，

6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物300)，

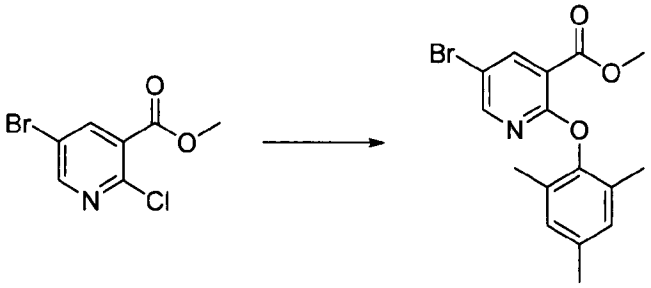
6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物318)，及

6-(4-乙氧基苯基)-*N*-(1H-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物190)。

**製備16：*N*-(3-胺基苯基)磺醯基-5-苯基-2-(2,4,6-三甲基苯氧基)吡啶-**

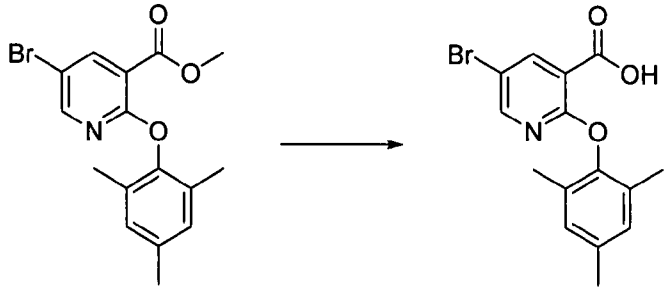
**3-甲醯胺(化合物1321)**

**步驟1：5-溴-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯**



2,4,6-三甲基苯酚(2.68 g，19.7 mmol)及60% NaH (870 mg，22 mmol)組合於*N,N*-二甲基甲醯胺(24 mL)及THF (2.4 mL)之無水混合物中。將反應混合物在氮氣氛圍下在室溫下攪拌15分鐘。添加5-溴-2-氯-吡啶-3-甲酸甲酯(4.93 g，19.7 mmol)且將反應混合物在60℃下加熱1小時。接著使反應混合物冷卻至室溫。反應混合物用水稀釋且用乙酸乙酯萃取。乙酸乙酯層用水洗滌三次且接著在減壓下濃縮。殘餘物進行矽膠管柱層析(0-50%乙酸乙酯/己烷)，得到呈淡黃色固體狀之5-溴-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(5.50 g，73%)。ESI-MS *m/z* 計算值349.0, 實驗值350.3 $(M+1)^+$；滯留時間: 2.09 min (3分鐘操作)。

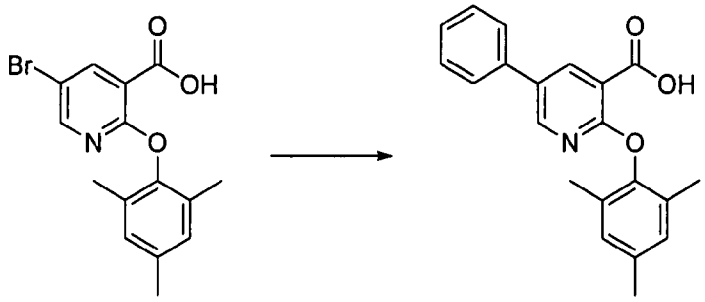
**步驟2：5-溴-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯**



5-溴-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(2.60 g，6.76 mmol)組合於含有氫氧化鈉(810 mg，20.3 mmol)之甲醇(12.95 mL)及水(17.27 mL)之混合物中。將所得懸浮液在60℃下加熱3小時。反應混合物冷卻至室溫且用6 M鹽酸酸化。過濾所得沈澱，用水洗滌且在真空烘箱中在60℃下乾燥隔夜，得到呈白色固體狀之5-溴-2-(2,4,6-三甲

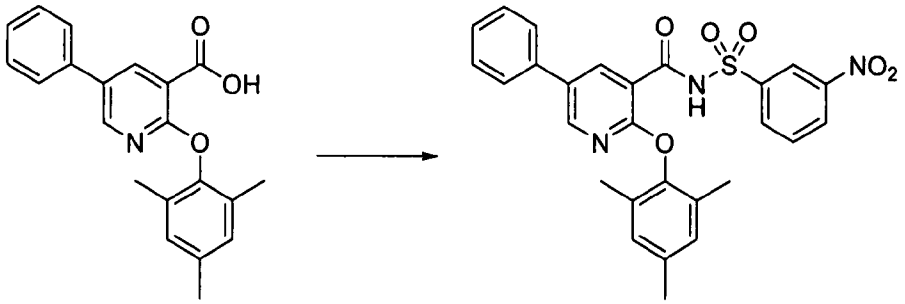
基苯氧基)吡啶-3-甲酸(2.24 g，98%)。ESI-MS *m/z*計算值335.0，實驗值338.2 $(M+1)^+$；滯留時間: 1.75 min (3分鐘操作)。

**步驟3：5-溴-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯**



5-溴-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(89 mg，0.26 mmol)、苯基硼酸(39 mg，0.32 mmol)、$Pd(PPh_3)_4$ (31 mg，0.026 mmol)及$K_2CO_3$ (530 μL 2.0 M，1.1 mmol)組合於DME (2.5 mL)中。反應混合物暫時充氮氣，封蓋，且在80℃下加熱2小時。使反應混合物冷卻至室溫且分離各層。有機層進行製備型HPLC (1-99%含5 μM HCl之乙腈/水)，得到呈白色固體狀之5-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(54 mg，61%)。ESI-MS *m/z*計算值333.1，實驗值334.4 $(M+1)^+$；滯留時間: 0.72 min (1分鐘操作)。

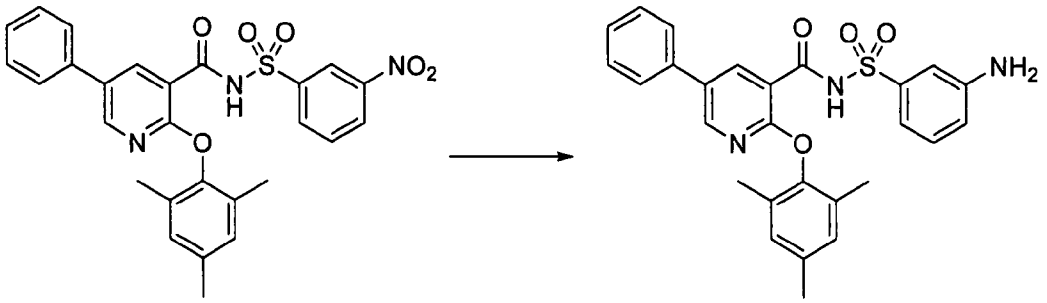
**步驟4：*N*-(3-硝基苯基)磺醯基-5-苯基-2-(2,4,6-三甲基苯氧基)-吡啶-3-甲醯胺**



將5-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(54 mg，0.16 mmol)、(3-硝基苯基)磺醯基胺基鈉(73 mg，0.32 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(62 mg，0.16 mmol)及*N,N*-二甲基甲醯胺(1 mL)組合。將反

應混合物在室溫下攪拌72小時。粗混合物進行製備型HPLC (1-99%含5 μM HCl之乙腈/水)，得到呈白色固體狀之*N*-(3-硝基苯基)磺醯基-5-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(51 mg，61%)。ESI-MS *m/z*計算值517.1，實驗值518.5 $(M+1)^+$；滯留時間: 2.04 min (3分鐘操作)。

**步驟5：*N*-(3-胺基苯基)磺醯基-5-苯基-2-(2,4,6-三甲基苯氧基)-吡啶-3-甲醯胺**



*N*-(3-硝基苯基)磺醯基-5-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(51 mg，0.099 mmol)懸浮於含有鋅(10 mg，0.15 mmol)之乙酸(2 mL)中。將反應混合物在65℃下加熱30分鐘。過濾熱反應混合物且接著冷卻至室溫。濃縮混合物且殘餘物進行製備型HPLC (1-99%含5 mM HCl之乙腈/水)，得到呈白色固體狀之*N*-(3-胺基苯基)磺醯基-5-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1321) (18 mg，38%)。ESI-MS *m/z*計算值487.2，實驗值488.5 $(M+1)^+$；滯留時間: 2.74 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物429)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-異丙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物865)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-第三丁基苯基)-2-(2,4,6-三甲

基苯氧基)吡啶-3-甲醯胺(化合物868)，

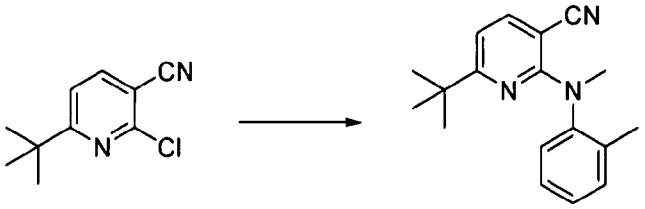
*N*-(3-胺基苯基)磺醯基-6-第三丁基-4-甲氧基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物959)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(鄰甲苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物817)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-乙基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物945)。

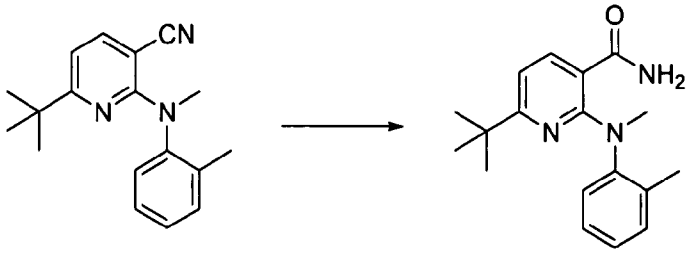
**製備17：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(*N*,2-二甲基苯胺基)吡啶-3-甲醯胺(化合物193)**

**步驟1：6-第三丁基-2-(*N*,2-二甲基苯胺基)吡啶-3-甲腈**



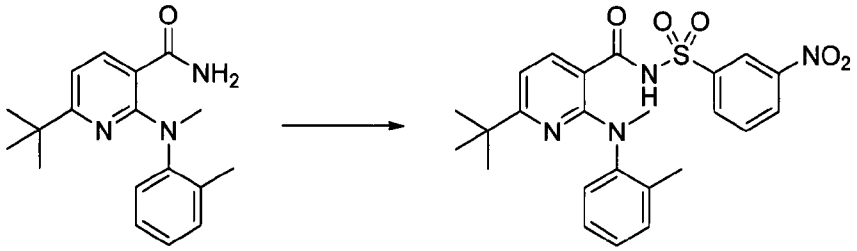

將6-第三丁基-2-氯-吡啶-3-甲腈(100. mg，0.514 mmol)、*N*,2-二甲基苯胺(76 μL，0.62 mmol)、KHMDS (1.2 mL 0.5 M，0.62 mmol)及二噁烷 (1.5 mL)之混合物在100℃下加熱20分鐘。混合物分溶於乙酸乙酯與1N HCl之間。分離各層且水層用乙酸乙酯(3次)萃取。合併之有機物用鹽水洗滌，經硫酸鎂乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-25%乙酸乙酯/己烷)，得到6-第三丁基-2-(N,2-二甲基苯胺基)吡啶-3-甲腈(40 mg，26%)。ESI-MS *m/z*計算值279.2, 實驗值280.4 $(M+1)^+$；滯留時間: 2.28 min (3分鐘操作)。

**步驟2：6-第三丁基-2-(N,2-二甲基苯胺基)吡啶-3-甲醯胺**



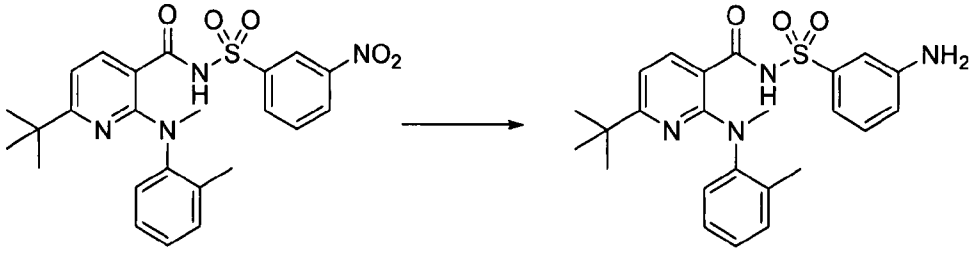
將6-第三丁基-2-(*N*,2-二甲基苯胺基)吡啶-3-甲腈(40 mg，0.14 mmol)及KOH (340 μL 4.0 M，1.4 mmol)於EtOH (1.2 mL)中之混合物在90℃下加熱隔夜。濃縮混合物，用2N HCl酸化且收集固體，得到灰白色固體。固體置於真空烘箱中55℃隔夜，得到呈灰白色固體狀之6-第三丁基-2-(N,2-二甲基苯胺基)吡啶-3-甲醯胺(40 mg，30%)。ESI-MS *m/z*計算值297.2，實驗值298.4 $(M+1)^+$；滯留時間: 0.68 min (1分鐘操作)。

**步驟3：6-第三丁基-2-(*N*,2-二甲基苯胺基)-*N*-(3-硝基苯基)磺醯基-吡啶-3-甲醯胺**



將氫化鈉(16 mg，60%，0.40 mmol)添加至6-第三丁基-2-(*N*,2-二甲基苯胺基)吡啶-3-甲醯胺(40. mg，0.13 mmol)及*N*,*N*-二甲基甲醯胺(1 mL)之混合物中。將混合物攪拌15分鐘，接著添加3-硝基苯磺醯氯(45 mg，0.20 mmol)。將混合物攪拌1小時，接著添加兩滴甲醇。過濾混合物且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到6-第三丁基-2-(*N*,2-二甲基苯胺基)-*N*-(3-硝基苯基)磺醯基-吡啶-3-甲醯胺。ESI-MS *m/z*計算值482.2，實驗值483.3 $(M+1)^+$；滯留時間: 0.82 min (1分鐘操作)。

**步驟4：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(*N*,2-二甲基苯胺基)吡啶-3-甲醯胺(化合物193)**

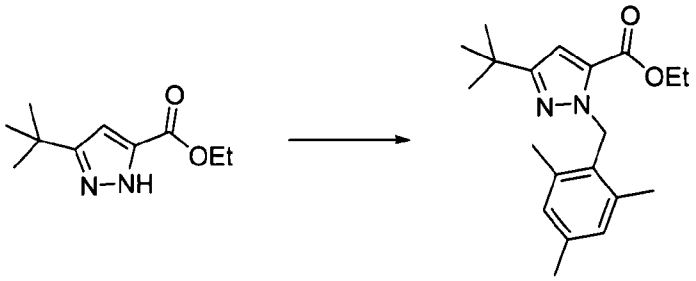


在室溫下將鋅(9.0 mg，0.13 mmol)添加至6-第三丁基-2-(*N*,2-二甲基苯胺基)-*N*-(3-硝基苯基)磺醯基-吡啶-3-甲醯胺及乙酸(1 mL)之混合物中。將混合物攪拌20分鐘，接著過濾且經受製備型HPLC (含0.05 mMHCl之10-99%乙腈/水)，得到*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(*N*,2-二甲基苯胺基)吡啶-3-甲醯胺(化合物193) (1.2 mg，2% 2步)。ESI-MS *m/z*計算值452.2，實驗值453.3 $(M+1)^+$；滯留時間: 1.90分鐘(3分鐘操作)。

以下化合物可使用本文所述之程序合成：*N*-(3-胺基苯基)磺醯基-6-第三丁基-2-(*N*-甲基苯胺基)吡啶-3-甲醯胺(化合物85)。

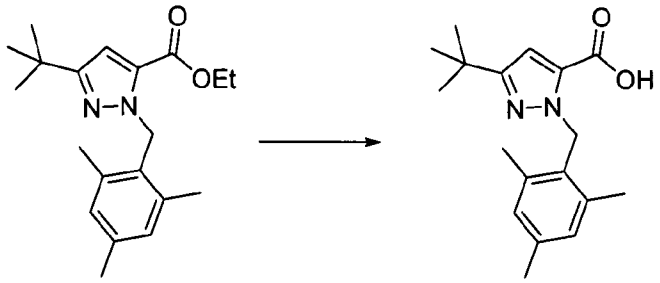
**製備18：*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物110)**

**步驟1：5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸乙酯**



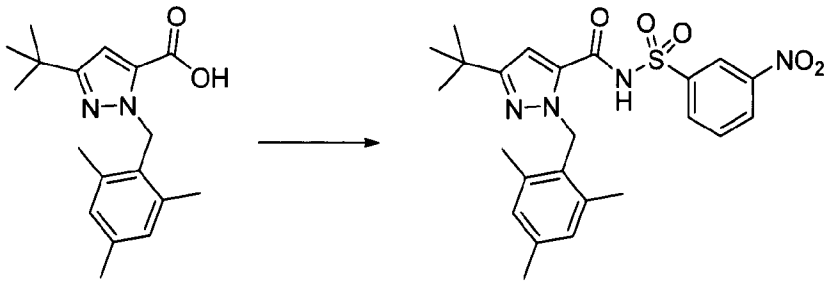

向5-第三丁基-4*H*-吡唑-3-甲酸乙酯(500. mg，2.55 mmol)及*N*,*N*-二甲基甲醯胺(5 mL)之混合物中添加2-(溴甲基)-1,3,5-三甲基-苯(543 mg，2.55 mmol)及$K_2CO_3$ (704 mg，5.10 mmol)。將反應混合物在80℃下加熱隔夜。添加額外2-(溴甲基)-1,3,5-三甲基-苯(200 mg，1.02 mmol)及$K_2CO_3$ (704 mg，5.10 mmol)且混合物在80℃下再加熱18小時。冷卻混合物至室溫，接著添加水(20 mL)。混合物用乙酸乙酯(2×50 mL)萃取。合併之有機層經硫酸鈉乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-50%乙酸乙酯/己烷)，得到5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸乙酯(642 mg，77%)。ESI-MS *m/z*計算值328.2，實驗值329.4 $(M+1)^+$；滯留時間: 0.99 min (1分鐘操作)。

**步驟2：5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸**



5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸乙酯(5.00 g，15.2 mmol)及NaOH (4.87 g，122 mmol)組合於THF (20 mL)及水(20 mL)中。混合物在60℃下加熱3小時。反應混合物藉由添加6 M HCl酸化且用乙酸乙酯萃取。有機物用鹽水洗滌，經硫酸鈉乾燥且蒸發，得到5-第三丁基-2-[(2,4,6-三甲基苯基)-甲基]吡唑-3-甲酸(4.38 g，96%)。$^1$H NMR (400 MHz, DMSO) δ 13.23 (s, 1H), 6.83 (s, 2H), 6.68 (s, 1H), 5.64 (s, 2H), 2.24 (s, 6H), 2.21 (s, 3H), 1.15 (s, 9H)。ESI-MS *m/z*計算值300.2, 實驗值301.4 $(M+1)^+$；滯留時間: 2.21 min (3分鐘操作)。

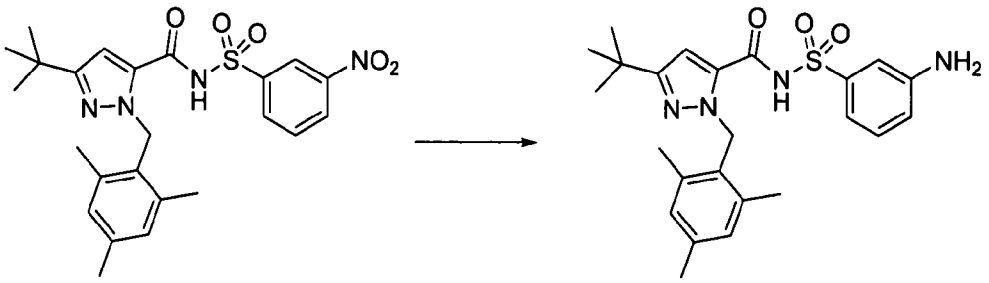
**步驟3：5-第三丁基-*N*-(3-硝基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺**



5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸(108 mg，0.356 mmol)、3-硝基苯磺醯胺(109 mg，0.539 mmol)、*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨六氟磷酸鹽*N*-氧化物(137 mg，0.356 mmol)及三乙胺(100 μL，0.719 mmol)組合於*N,N*-二甲基甲醯胺(2.3 mL)中且在60℃下加熱16小時。過濾反應混合物且經受製備型HPLC (10-99%含0.05 mMHCl之乙腈/水)，得到5-第三

丁基-*N*-(3-硝基苯基)磺醯基-2-[(2,4,6-三甲基苯基)-甲基]吡唑-3-甲醯胺(105 mg，60.9%)。ESI-MS *m/z*計算值484.2，實驗值485.3 $(M+1)^+$；滯留時間: 2.27 min (3分鐘操作)。

**4：*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]-吡唑-3-甲醯胺**




在氫氣球下在Pd/C (38 mg，0.036 mmol)下5-第三丁基-*N*-(3-硝基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]-吡唑-3-甲醯胺(105 mg，0.217 mmol)溶於甲醇(9 mL)中且將混合物攪拌30分鐘。反應混合物過濾，蒸發，且殘餘物藉由LC/MS，利用5 mM HCl水溶液中10-99%乙腈之梯度來純化，得到*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物110) (72 mg，44%)。$^1$H NMR (400 MHz, DMSO) δ 7.26 (t, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 2.0 Hz, 1H), 7.12 - 7.06 (m, 1H), 7.01 (s, 1H), 6.89 - 6.83 (m, 1H), 6.77 (s, 2H), 5.45 (s, 2H), 2.17 (s, 3H), 2.11 (s, 6H), 1.14 (s, 9H)。ESI-MS *m/z*計算值454.2，實驗值455.4 $(M+1)^+$；滯留時間: 2.06 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

3-(第三丁基)-1-(1-均三甲苯基乙基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物201)，

*N*-(3-胺基苯基)磺醯基-3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]吡唑-4-甲醯胺，

3-(第三丁基)-1-(2-氟-5-(三氟甲基)苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物35)，

3-(第三丁基)-*N*-((3-(二甲基胺基)苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物270)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,4,6-tri氯苯甲基)-1*H*-吡唑-5-甲醯胺(化合物303)，

3-(第三丁基)-1-(2,6-二甲基苯甲基)-*N*-((1-甲基-1*H*-吲哚-4-基)磺醯基)-1*H*-吡唑-5-甲醯胺(化合物210)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(4-(第三丁基)-2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物156)，

3-(4-(二氟甲基)苯基)-1-(2,6-二甲基苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物119)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-4-甲氧基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1305)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2-氯-6-(三氟甲基)苯甲基)-1*H*-吡唑-5-甲醯胺(化合物189)，

3-(第三丁基)-*N*-((3-(二甲基胺基)-2-甲基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物104)，

*N*-((3-胺基-2-甲基苯基)磺醯基)-3-(第三丁基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物123)，

3-(第三丁基)-*N*-((1-甲基-1*H*-吲哚-7-基)磺醯基)-1-(2-甲基-3-(三氟甲基)苯甲基)-1*H*-吡唑-5-甲醯胺(化合物276)，

3-(第三丁基)-*N*-(間甲苯基磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物80)，

*N*-((3-胺基-4-氟苯基)磺醯基)-3-(第三丁基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物150)，

3-(第三丁基)-*N*-(喹啉-5-基磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物352)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,3,5,6-四甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物317)，

3-(第三丁基)-1-(2,6-二甲基苯甲基)-*N*-(噻吩-2-基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物77)，

3-(第三丁基)-*N*-(苯基磺醯基)-1-(2,4,6-三氯苯甲基)-1*H*-吡唑-5-甲醯胺(化合物145)，

3-(第三丁基)-1-(2,6-二甲基苯甲基)-*N*-((2-甲氧基-3-甲基苯基)磺醯基)-1*H*-吡唑-5-甲醯胺(化合物59)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[2-(2,4,6-三甲基苯基)乙基]吡唑-3-甲醯胺(化合物7)，

3-(第三丁基)-*N*-(苯基磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-1-(萘-1-基甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物328)，

3-(第三丁基)-*N*-((3-(甲基胺基)苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物249)，

3-(第三丁基)-*N*-((1-(2-羥基乙基)-1*H*-吲哚-4-基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物188)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-4-甲基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物20)，

3-(第三丁基)-1-(2,6-二甲基苯甲基)-*N*-((2-氟苯基)磺醯基)-1*H*-吡唑-5-甲醯胺(化合物57)，

3-(第三丁基)-*N*-((2-氰基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物266)，

3-(第三丁基)-*N*-((3-羥基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物84)，

3-(第三丁基)-1-(2,6-二甲基苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物257)，

*N*-((3-胺基-4-甲基苯基)磺醯基)-3-(第三丁基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物312)，

1-(3-(1*H*-吡咯-1-基)苯甲基)-3-(第三丁基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物108)，

3-(第三丁基)-1-(5-氟-2-(三氟甲基)苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物3)，

*N*-((3-乙醯基苯基)磺醯基)-3-(第三丁基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物332)，

*N*-((1*H*-吲哚-4-基)磺醯基)-3-(第三丁基)-1-(2-甲基-3-(三氟甲基)苯甲基)-1*H*-吡唑-5-甲醯胺(化合物60)，

3-(第三丁基)-*N*-((2,6-二氟苯基)磺醯基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物170)，

*N*-((4-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物81)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2-氟-6-(三氟甲基)苯甲基)-1*H*-吡唑-5-甲醯胺(化合物239)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(1-(鄰甲苯基)乙基)-1*H*-吡唑-5-甲醯胺(化合物342)，

*N*-((6-胺基吡啶-2-基)磺醯基)-3-(第三丁基)-4-甲基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物356)，

*N*-((2-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(1-環己基乙基)-1*H*-吡唑-5-甲醯胺(化合物287)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(1-苯基丙基)-1*H*-吡唑-5-甲醯胺(化合物165)，

3-(第三丁基)-*N*-((4-羥基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物269)，

*N*-((3-胺基苯基)磺醯基)-3-(1-甲基環丙基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物158)，

3-(第三丁基)-1-(2-甲基-3-(三氟甲基)苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物98)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物185)，

*N*-((3-胺基苯基)磺醯基)-3-異丁基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物167)，

3-(第三丁基)-*N*-((2,3-二氫苯并呋喃-7-基)磺醯基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物211)，

*N*-((6-胺基吡啶-2-基)磺醯基)-3-(第三丁基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物173)，

3-(第三丁基)-1-(2-甲氧基苯乙基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物157)，

*N*-((1*H*-吲唑-4-基)磺醯基)-3-(第三丁基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物86)，

*N*-(苯磺醯基)-5-第三丁基-2-[(1-甲基吲哚-4-基)甲基]吡唑-3-甲醯胺(化合物245)，

3-(第三丁基)-*N*-((3-甲氧基吡啶-2-基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(化合物44)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(萘-1-基甲基)-1*H*-吡唑-5-甲醯胺(化合物295)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-((1-甲基-1*H*-吲哚-7-基)甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-1-(2,6-二甲基苯甲基)-*N*-((2-(甲基胺基)吡啶-4-基)磺醯基)-1*H*-吡唑-5-甲醯胺，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(2-甲氧基苯基)磺醯基-吡唑-3-甲醯胺(化合物1551)，

1-((1*H*-吲哚-7-基)甲基)-*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1*H*-吡唑-5-甲醯胺，

*N*-[(2-胺基-3-吡啶基)磺醯基]-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1106)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-((1-甲基環己基)甲基)-1*H*-吡唑-5-甲醯胺，

*N*-(4-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1653)，

3-(第三丁基)-1-(4-(第三丁基)-2,6-二甲基苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-((3-乙基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-((3-氯苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-(1-苯基乙基)吡唑-3-甲醯胺(化合物799)，

*N*-((3-胺基苯基)磺醯基)-3-異丙基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-[3-(2-甲基嘧啶-4-基)苯基]磺醯基-吡唑-3-甲醯胺(化合物1496)，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,4-二氯苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-((3-氟苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-((2-甲氧基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-((3-氰基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

*N*-((4-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

*N*-((2-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-(吡啶-4-基磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

3-(第三丁基)-*N*-((3-甲氧基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

*N*-((3-胺基苯基)磺醯基)-3-(第三丁基)-1-(2,4-二甲基苯甲基)-1*H*-吡唑-5-甲醯胺，

5-第三丁基-*N*-(1H-吲哚-4-基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物180)，

3-(第三丁基)-1-(5-甲基-2-(三氟甲基)苯甲基)-*N*-(苯基磺醯基)-1*H*-吡唑-5-甲醯胺(化合物304)，

*N*-((3-胺基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-苯并[*d*]咪唑-2-甲醯胺(化合物71)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1-甲基吲哚-4-基)甲基]吡唑-3-甲醯胺(化合物927)，

5-第三丁基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物759)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(3-噻吩yl磺醯基)吡唑-3-甲醯胺(化合物603)，

*N*-(2-胺基苯基)磺醯基-5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物88)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(1H-吲哚-7-基磺醯基)吡唑-3-甲醯胺(化合物1358)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-(1H-吲哚-7-基甲基)吡唑-3-甲醯胺(化合物1256)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1-甲基吲哚-7-基)甲基]吡唑-3-甲醯胺(化合物755)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-[[2-(甲基胺基)-4-吡啶基]磺醯基]吡唑-3-甲醯胺(化合物821)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1-甲基環己基)甲基]吡唑-3-甲醯胺(化合物1152)，

*N*-(苯磺醯基)-5-第三丁基-2-[(4-第三丁基-2,6-二甲基-苯基)甲基]吡唑-3-甲醯胺(化合物443)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1R)-1-苯基乙基]吡唑-3-甲醯胺(化合物540)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(3-噻吩yl磺醯基)吡唑-3-甲醯胺(化合物603)，

5-第三丁基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物759)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(2-呋喃基磺醯基)吡唑-3-甲醯胺(化合物1468)，

*N*-[4-(胺基甲基)苯基]磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1670)，

5-第三丁基-*N*-(4-吡啶基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1585)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4-二氯苯基)甲基]吡唑-3-甲醯胺(化合物797)，

5-第三丁基-*N*-(3-乙基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物823)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-(1-苯基乙基)吡唑-3-甲醯胺，

5-第三丁基-*N*-(3-氯苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物472)，

*N*-(2-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1167)，

*N*-(3-胺基苯基)磺醯基-5-異丙基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物566)，

*N*-(1H-吡唑-3-基磺醯基)-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呯-4-甲醯胺(化合物628)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呯-4-甲醯胺(化合物662)，

*N*-[(6-嗎啉基-2-吡啶基)磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呯-4-甲醯胺(化合物669)，

*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呯-4-甲醯胺(化合物747)，

*N*-[[6-(2-羥基乙基胺基)-2-吡啶基]磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呼-4-甲醯胺(化合物838)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呼-4-甲醯胺(化合物876)，

*N*-[(6-甲氧基-2-吡啶基)磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呼-4-甲醯胺(化合物948)，

*N*-(苯磺醯基)-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呼-4-甲醯胺(化合物1039)，

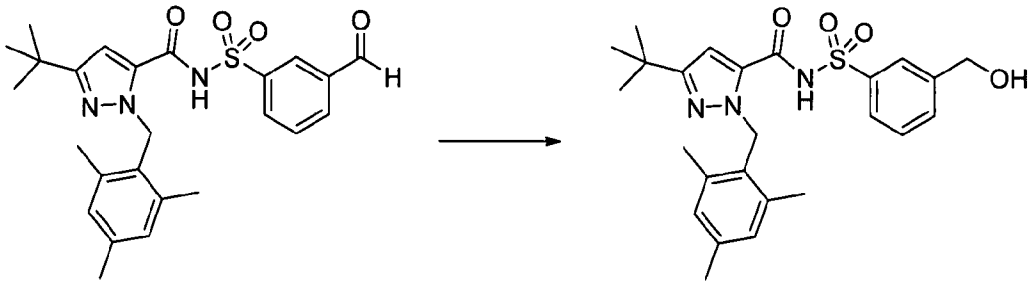
*N*-[(6-胺基-2-吡啶基)磺醯基]-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呼-4-甲醯胺(化合物1055)，

*N*-(2-吡啶基磺醯基)-3-[(2,4,6-三甲基苯基)甲基]-1,2,4,5-四氫-3-苯并氮呼-4-甲醯胺(化合物1093)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1-甲基吲哚-4-基)甲基]吡唑-3-甲醯胺(化合物927)，及

*N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物45)。

**製備19：5-第三丁基-*N*-[3-(羥基甲基)苯基]磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物39)**

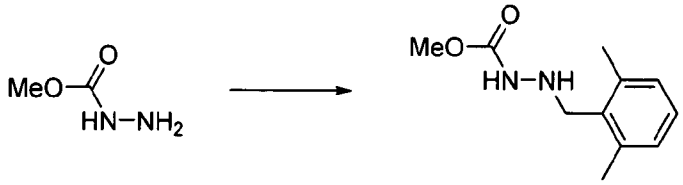


3-(第三丁基)-*N*-((3-甲醯基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(根據本文所述之程序製備，50 mg，0.11 mmol)及無水甲醇(5 mL)之溶液冷卻至0℃。混合物用氮氣淨化，接著添加硼氫化鈉(7.6 mg，0.20 mmol)。使混合物升溫至室溫且攪拌隔夜。反應

混合物再次冷卻至0℃，接著添加額外硼氫化鈉(7.6 mg，0.20 mmol)。混合物升溫至室溫且攪拌4小時。移除溶劑且粗殘餘物溶解於DMSO中且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到5-第三丁基-*N*-[3-(羥基甲基)苯基]磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物39) (28 mg，56%)。$^1$H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 7.99 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.63 (dt, *J* = 15.3, 7.7 Hz, 2H), 7.01 (s, 1H), 6.75 (s, 2H), 5.42 (s, 2H), 4.63 (s, 2H), 2.16 (s, 3H), 2.07 (d, *J* = 6.4 Hz, 6H), 1.14 (s, 9H)。ESI-MS *m/z*計算值469.2，實驗值470.0 $(M+1)^+$；滯留時間: 2.12 min (3分鐘操作)。

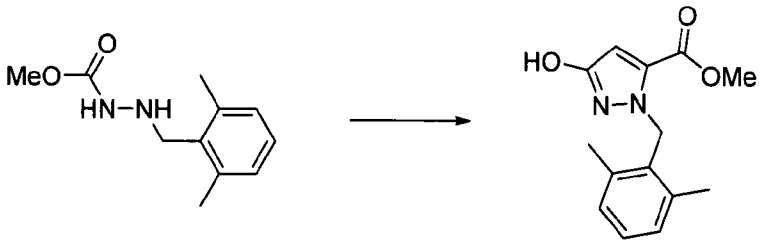
**製備20：*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(2-甲氧基苯基)吡唑-3-甲醯胺(化合物347)**

**步驟1：*N*-[(2,6-二甲基苯基)甲基胺基]胺基甲酸甲酯**



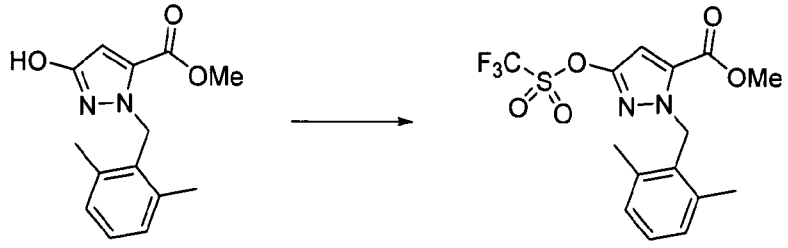

2-(氯甲基)-1,3-二甲基-苯(25.0 g，162 mmol)、*N*-胺基胺基甲酸甲酯(29.1 g，323 mmol)及$K_2CO_3$ (33.5 g，243 mmol)組合於*N,N*-二甲基甲醯胺(150 mL)中且在80℃下加熱2小時。反應混合物濃縮且粗物質分溶於乙酸乙酯與水之間。分離有機物，用鹽水洗滌且經硫酸鈉乾燥。混合物過濾且濃縮濾液。殘餘物進行矽膠管柱層析(0-60%乙酸乙酯/己烷)，得到*N*-[(2,6-二甲基苯基)甲基胺基]胺基甲酸甲酯(18.0 g，53%)。ESI-MS *m/z*計算值208.3，實驗值209.2 $(M+1)^+$；滯留時間: 0.41 min (1分鐘操作)。

**步驟2：2-[(2,6-二甲基苯基)甲基]-5-羥基-吡唑-3-甲酸甲酯**



*N*-[(2,6-二甲基苯基)甲基胺基]胺基甲酸甲酯(18.0 g，86.4 mmol)懸浮於甲醇(126 mL)中且添加丁-2-炔二酸二甲酯(10.6 mL，86.4 mmol)。將反應混合物在回流下攪拌2小時且接著冷卻至室溫。添加甲醇鈉(20.5 mL 25 %w/v，95.1 mmol)且反應混合物再次在回流下加熱。1小時後，冷卻混合物至室溫且逐滴添加至含有1M HCl水溶液(300 mL)於冰水浴中之燒瓶。所得沈澱藉由真空過濾來收集。固體溶解於$CH_2Cl_2$中且分離過量水且有機層經硫酸鈉乾燥且蒸發，得到2-[(2,6-二甲基苯基)甲基]-5-羥基-吡唑-3-甲酸甲酯(21.6 g，96%)。$^1$H NMR (400 MHz, DMSO) δ 10.05 (s, 1H), 7.10 (dd, *J* = 8.4, 6.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 2H), 6.06 (s, 1H), 5.57 (s, 2H), 3.85 (s, 3H), 2.24 (s, 6H)。ESI-MS *m/z*計算值260.1，實驗值261.4 $(M+1)^+$；滯留時間: 0.57 min (1分鐘操作)。

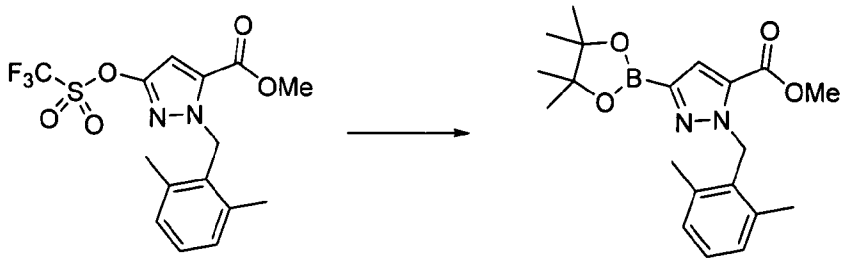
**步驟3：2-[(2,6-二甲基苯基)甲基]-5-(三氟甲基磺醯基氧基)-吡唑-3-甲酸酯**



將2-[(2,6-二甲基苯基)甲基]-5-羥基-吡唑-3-甲酸甲酯(8.40 g，32.3 mmol)及吡啶(3.13 mL，38.7 mmol)組合於甲苯(84.00 mL)中且在鹽水/冰浴中冷卻。逐滴添加三氟甲磺酸(5.98 mL，35.5 mmol)，保持溫度低於0℃。添加結束後，反應混合物升溫至室溫且攪拌1小時。反應混合物用水(30 mL)淬滅且分離各層。水層用甲苯(1×40 mL)萃取。

合併有機物且用水(40 mL)洗滌，經硫酸鈉乾燥，過濾且蒸發，得到2-[(2,6-二甲基苯基)甲基]-5-(三氟甲基磺醯基氧基)-吡唑-3-甲酸甲酯(12.4 g，98%)。ESI-MS *m/z*計算值392.1，實驗值393.2 $(M+1)^+$；滯留時間: 0.82 min (1分鐘操作)。

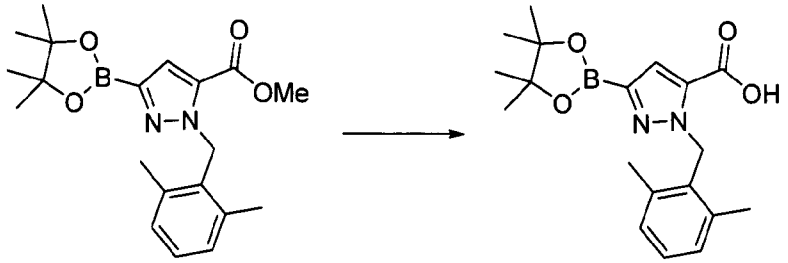
**步驟4：2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲酸酯**



使2-[(2,6-二甲基苯基)甲基]-5-(三氟甲基磺醯基氧基)吡唑-3-甲酸甲酯(12.1 g，30.7 mmol)、4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)-1,3,2-二氧雜硼雜環戊烷(8.59 g，33.8 mmol)及KOAc (9.05 g，92.2 mmol)於二噁烷(240 mL)中之懸浮液脫氣10分鐘。添加二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(1.26 g，1.54 mmol)及1,1'-雙(二苯基膦基)二茂鐵(852 mg，1.54 mmol)且使反應物再脫氣10分鐘。將反應混合物在100℃下加熱4小時。濃縮混合物至約100 mL總體積且用甲苯(250 mL)及水(100 mL)稀釋。混合物經矽藻土墊過濾以移除小的黑色微粒。分離有機物，用水(100 mL)洗滌且經硫酸鈉乾燥。有機物經矽藻土塞過濾(100 g)且二氧化矽再用1 L甲苯洗滌。甲苯蒸發，得到2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲酸甲酯(10.6 g，93%)。$^1$H NMR (400 MHz, 氯仿-d) δ 7.27 (s, 1H), 7.09 (dd, $J$ = 8.2, 6.7 Hz, 1H), 7.00 (d, $J$ = 7.4 Hz, 2H), 5.86 (s, 2H), 3.81 (s, 3H), 2.25 (s, 6H), 1.32 (s, 12H)。

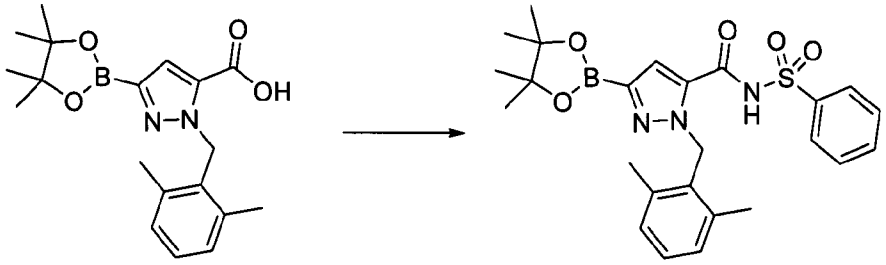
**步驟5：2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜**

環戊-2-基)吡唑-3-甲酸



2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲酸甲酯(7.00 g，14.2 mmol)溶於THF (53 mL)及NaOH (43 mL 1.0 M，43 mmol)中。將反應混合物在60℃下加熱2小時且濃縮。所得固體分溶於乙酸乙酯與1 N HCl溶液之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且蒸發，得到2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲酸(5.5 g，98%)。$^1$H NMR (400 MHz, DMSO) δ 13.44 (s, 1H), 7.13 (dd, *J* = 8.3, 6.6 Hz, 1H), 7.07 - 7.02 (m, 3H), 5.81 (s, 2H), 2.23 (s, 6H), 1.24 (s, 12H)。ESI-MS *m/z*計算值356.2, 實驗值275.4 $(M+1)^+$；滯留時間: 0.42 min (1分鐘操作)。注意：所發現之質量爲[-頻哪醇+H]。

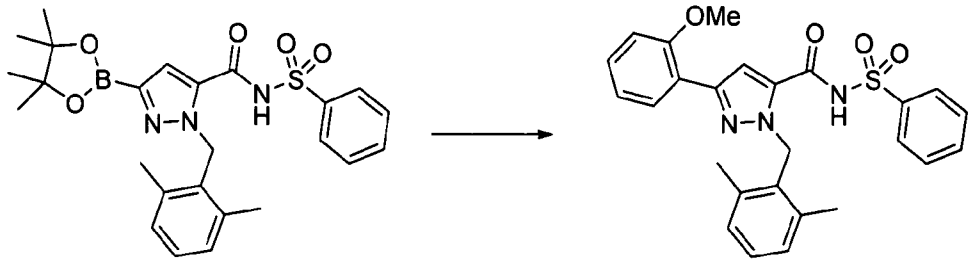
**步驟6：*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲醯胺**



2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲酸(4.14 g，11.6 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(4.42 g，11.6 mmol)及乙基二異丙基胺(6.07 mL，34.9 mmol)組合於$CH_2Cl_2$ (116 mL)中。添加苯磺醯胺(2.19 g，13.9 mmol)且將反應混合物攪拌

16小時，接著其用$CH_2Cl_2$稀釋且用1N HCl洗滌。有機物進一步用鹽水洗滌，經硫酸鈉乾燥，過濾且蒸發。粗物質藉由矽膠層析(0-100%乙酸乙酯/己烷)來純化，得到*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲醯胺(4.14 g，72%)。ESI-MS *m/z*計算值495.2, 實驗值414.4 $(M+1)^+$；滯留時間: 0.68 min (1分鐘操作)。注意：所發現之質量爲減去頻哪醇酯。

**步驟7：*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(2-甲氧基苯基)吡唑-3-甲醯胺(化合物347)**




將*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-3-甲醯胺(50 mg，0.10 mmol)、1-溴-2-甲氧基苯(19 mg，0.10 mmol)、二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(4 mg，0.005 mmol)及2M $K_2CO_3$水溶液(0.20 mL，0.40 mmol)組合於*N,N*-二甲基甲醯胺(0.6 mL)中且在70℃下加熱2小時。反應混合物冷卻，過濾且經受製備型HPLC (10-99%含0.05 mMHCl之乙腈/水)，得到*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(2-甲氧基苯基)吡唑-3-甲醯胺(化合物347)。ESI-MS *m/z*計算值475.2, 實驗值476.3 $(M+1)^+$；滯留時間: 2.08 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[2-(三氟甲氧基)苯基]吡唑-3-甲醯胺(化合物149)，

*N*-(苯磺醯基)-5-(4-氯-3-甲氧基-苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物37)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(3-異丙氧基苯基)吡唑-3-甲醯胺(化合物133)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[3-(三氟甲氧基)苯基]吡唑-3-甲醯胺(化合物225)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[4-(三氟甲基)苯基]吡唑-3-甲醯胺(化合物316)，

*N*-(苯磺醯基)-5-[3-(二氟甲基)苯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物315)，

*N*-(苯磺醯基)-5-(2,4-二甲氧基苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物135)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(1-甲基吲哚-4-基)吡唑-3-甲醯胺(化合物363)，

*N*-(3-胺基苯基)磺醯基-5-(2,6-二甲基苯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物209)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(間甲苯基)吡唑-3-甲醯胺(化合物202)，

*N*-(3-胺基苯基)磺醯基-5-(2-氟-3-甲基-苯基)-2-[(2,4,6-三甲基苯基)甲基] 吡唑-3-甲醯胺，

*N*-(3-胺基苯基)磺醯基-5-苯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物367)，

*N*-(苯磺醯基)-5-[3-(二甲基胺基)苯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物178)，

*N*-(苯磺醯基)-5-[4-(二乙基胺基)苯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物162)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4-氟苯基)吡唑-3-甲醯胺(化合物333)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(3-甲氧基苯基)吡唑-3-甲醯胺(化合物176)，

*N*-(苯磺醯基)-5-(4-二甲基胺基苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物76)，

*N*-(苯磺醯基)-5-(2-氰基苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物99)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(3-氟-4-甲氧基-苯基)吡唑-3-甲醯胺(化合物43)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4-甲氧基苯基)吡唑-3-甲醯胺(化合物49)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[3-(三氟甲基)苯基]吡唑-3-甲醯胺(化合物220)，

*N*-(苯磺醯基)-5-(3-氯苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物83)，

*N*-(苯磺醯基)-5-(2-氯苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物339)，

*N*-(苯磺醯基)-5-(2,5-二甲氧基苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物100)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[4-(三氟甲氧基)苯基]吡唑-3-甲醯胺(化合物159)，

2-[4-[5-(苯磺醯基胺甲醯基)-1-[(2,6-二甲基苯基)甲基]吡唑-3-基]苯基]乙酸乙酯(化合物21)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[5-(5-甲基-1,2,4-噁二唑-3-基)-2-噻吩基]吡唑-3-甲醯胺(化合物151)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(2-乙氧基苯基)吡唑-3-甲醯胺(化合物152)，

*N*-(3-胺基苯基)磺醯基-5-(2-甲氧基-3-甲基-苯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物208)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(2-氟苯基)吡唑-3-甲醯胺(化合物109)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(2-異丙氧基苯基)吡唑-3-甲醯胺(化合物277)，

*N*-(苯磺醯基)-5-(4-氯苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物28)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4-乙氧基苯基)吡唑-3-甲醯胺(化合物29)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(3-乙氧基苯基)吡唑-3-甲醯胺(化合物280)，

*N*-(3-胺基苯基)磺醯基-5-(2-甲氧基苯基)-2-(1-苯基乙基)吡唑-3-甲醯胺(化合物40)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(5-氟-2-甲氧基-苯基)吡唑-3-甲醯胺，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[2-(三氟甲基)苯基]吡唑-3-甲醯胺(化合物369)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(對甲苯基)吡唑-3-甲醯胺(化合物199)，

*N*-(苯磺醯基)-5-[2-(二甲基胺基)苯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物128)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(3-氟苯基)吡唑-3-甲醯胺(化合物166)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(1-甲基吲哚-5-基)吡唑-3-甲醯胺(化合物263)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[6-(1-哌啶基)-3-吡啶基]吡唑-3-甲醯胺(化合物329)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4-氟-2-甲氧基-苯基)吡唑-3-甲醯胺(化合物155)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-[3-(嗎啉基甲基)苯基]吡唑-3-甲醯胺(化合物302)，

*N*-(3-胺基苯基)磺醯基-5-(2-甲氧基-3-吡啶基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物122)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(3-噻吩基)吡唑-3-甲醯胺(化合物357)，

*N*-(3-胺基苯基)磺醯基-5-(4-甲氧基苯基)-2-(1-苯基乙基)吡唑-3-甲醯胺(化合物1024)，

3-[5-(苯磺醯基胺甲醯基)-1-[(2,6-二甲基苯基)甲基]吡唑-3-基]苯甲酸(化合物343)，

*N*-(苯磺醯基)-5-(3-第三丁氧基苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物744)，

*N*-(苯磺醯基)-5-(4*H*-1,3-苯并二氧雜環己烯-7-基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物1621)，

*N*-(苯磺醯基)-5-[2-(二甲基胺基)嘧啶-5-基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物1678)，

*N*-(苯磺醯基)-5-(5-氯-3-氟-2-甲氧基-苯基)-2-[(2,6-二甲基苯基)甲基] 吡唑-3-甲醯胺，

*N*-(苯磺醯基)-5-(5-氯-3-氟-2-甲氧基-苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物379)，

*N*-(苯磺醯基)-5-(3-第三丁氧基苯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物744)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4-異丙氧基苯基)吡唑-3-甲醯胺(化合物1478)，

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(4-側氧基唌烯-3-基)吡唑-3-甲醯胺(化合物1501)，

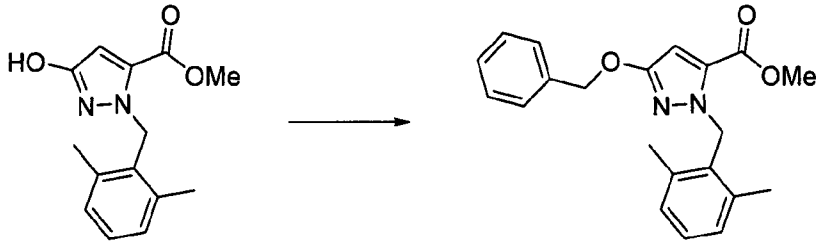
*N*-(3-胺基苯基)磺醯基-5-(4-甲氧基苯基)-2-(1-苯基乙基)吡唑-3-甲醯胺(化合物1024)

*N*-(3-胺基苯基)磺醯基-5-(2-氟-3-甲基-苯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物293)及

*N*-(苯磺醯基)-2-[(2,6-二甲基苯基)甲基]-5-(5-氟-2-甲氧基-苯基)吡唑-3-甲醯胺(化合物27)。

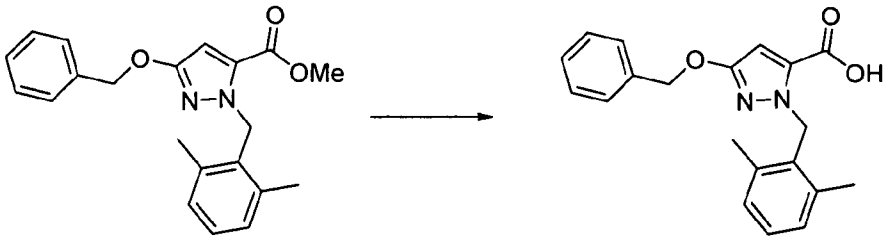
**製備21：5-苯甲氧基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸**

**步驟1：3-(苯甲氧基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲酸甲酯**




向5-羥基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸甲酯(250 mg，0.911 mmol)及$K_2CO_3$ (315 mg，2.28 mmol)於*N,N*-二甲基甲醯胺(5 mL)中之溶液中添加苯甲基溴(130 μL，1.09 mmol)且將反應混合物在室溫下攪拌16小時。濃縮混合物且所得固體分溶於乙酸乙酯與水之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且蒸發，得到3-(苯甲氧基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲酸甲酯。ESI-MS *m/z*計算值364.2，實驗值365.4 $(M+1)^+$；滯留時間: 0.90 min (1分鐘操作)。

**步驟2：5-苯甲氧基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸**



3-(苯甲氧基)-1-(2,6-二甲基苯甲基)-1*H*-吡唑-5-甲酸甲酯(來自步驟1)溶於甲醇(3 mL)中，接著添加1N NaOH (3 mL)。將反應混合物在60℃下加熱2小時且濃縮。粗混合物分溶於乙酸乙酯與1 N HCl之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥，且蒸發，得到5-苯甲氧基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸(295 mg，2步92%)。ESI-MS *m/z*計算值350.2, 實驗值351.4 $(M+1)^+$；滯留時間: 0.79 min (1分鐘操作)。

以下化合物可使用本文所述之程序合成：

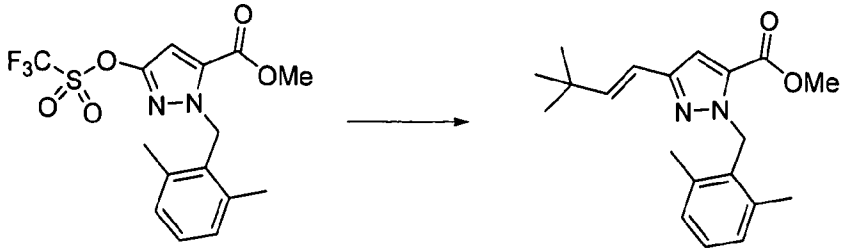
3-(1-苯基乙氧基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸，

*N*-(3-胺基苯基)磺醯基-5-苯甲氧基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物42)，及

*N*-(3-胺基苯基)磺醯基-5-(1-苯基乙氧基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物278)。

**製備22：*N*-(3-胺基苯基)磺醯基-5-(3,3-二甲基丁基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物323)**

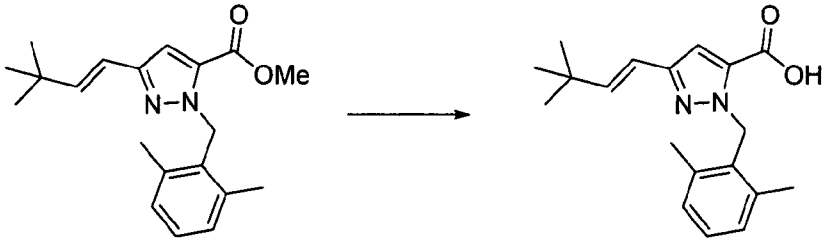
**步驟1：5-[(E)-3,3-二甲基丁-1-烯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸酯**



2-[(2,6-二甲基苯基)甲基]-5-(三氟甲基磺醯基氧基)吡唑-3-甲酸甲酯(500. mg，1.27 mmol)、[(*E*)-3,3-二甲基丁-1-烯基]硼酸(196 mg，

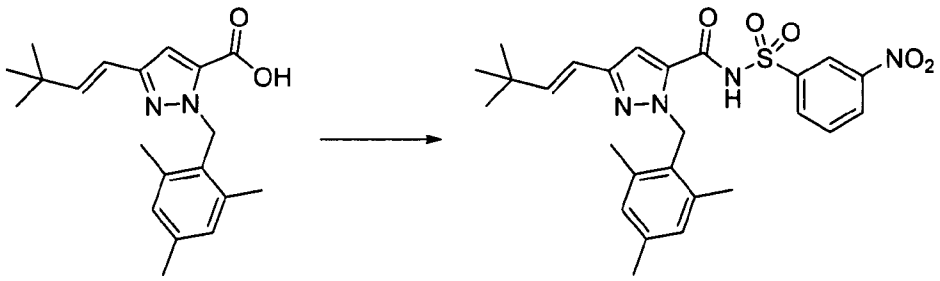
1.53 mmol)、二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷 (52 mg，0.064 mmol)及2M $K_2CO_3$ (1.9 mL 2.0 M，3.8 mmol)組合於二噁烷(10 mL)中且在微波反應器中在120℃下照射30分鐘。反應混合物用乙酸乙酯稀釋且經矽藻土墊過濾。濾液用水、鹽水洗滌，經硫酸鈉乾燥且濃縮。粗物質藉由矽膠管柱層析(0-60%乙酸乙酯/己烷)來純化，得到5-[(*E*)-3,3-二甲基丁-1-烯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸甲酯(300. mg，72%)。ESI-MS *m/z*計算值326.2，實驗值327.5 $(M+1)^+$；滯留時間: 0.94 min (1分鐘操作)。

**步驟2：5-[(*E*)-3,3-二甲基丁-1-烯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸酯**



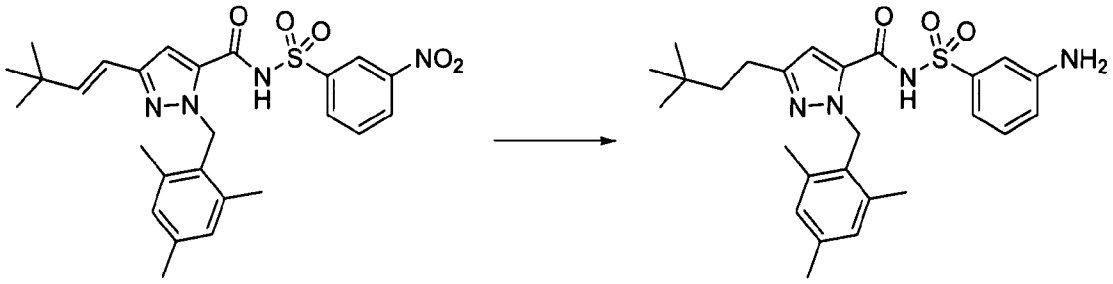

5-[(*E*)-3,3-二甲基丁-1-烯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸甲酯(300. mg，0.919 mmol)溶於THF (3 mL)中，接著添加NaOH (3.0 mL 1.0 M，3.0 mmol)。將反應混合物在60℃下加熱2小時且接著濃縮。所得固體分溶於乙酸乙酯與1 N HCl水溶液之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且濃縮，得到5-[(*E*)-3,3-二甲基丁-1-烯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸(198 mg，69%)。ESI-MS *m/z*計算值312.2，實驗值313.5 $(M+1)^+$；滯留時間: 0.77 min (1分鐘操作)。

**步驟3：(*E*)-3-(3,3-二甲基丁-1-烯-1-基)-*N*-((3-硝基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺**



將5-[(*E*)-3,3-二甲基丁-1-烯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸(50. mg，0.16 mmol)、3-硝基苯磺醯胺(32 mg，0.16 mmol)、六氟磷酸*N*-[(二甲基胺基)-1*H*-1,2,3-三唑并[4,5-*b*]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(61 mg，0.16 mmol)及乙基二異丙基胺(84 μL，0.48 mmol)組合於*N,N*-二甲基甲醯胺(1 mL)中且在室溫下攪拌16小時。反應混合物過濾且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到(*E*)-3-(3,3-二甲基丁-1-烯-1-基)-*N*-((3-硝基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(23 mg，29%)。ESI-MS *m/z* 計算值496.2, 實驗值497.2 $^{+}$；滯留時間: 0.85 min (1分鐘操作)。

**步驟4：*N*-(3-胺基苯基)磺醯基-5-(3,3-二甲基丁基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物323)**



在室溫下(*E*)-3-(3,3-二甲基丁-1-烯-1-基)-*N*-((3-硝基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺(23 mg，0.046 mmol), 甲醇(2 mL)及10% Pd/C (17 mg，0.016 mmol)之混合物置於氫氣球下。將混合物攪拌30分鐘，接著過濾。濾液進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到*N*-(3-胺基苯基)磺醯基-5-(3,3-二甲基丁基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物323) (4.0 mg，17%)。ESI-MS *m/z*計算值468.2, 實驗值469.0 $(M+1)^{+}$；滯留時

間: 2.11 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

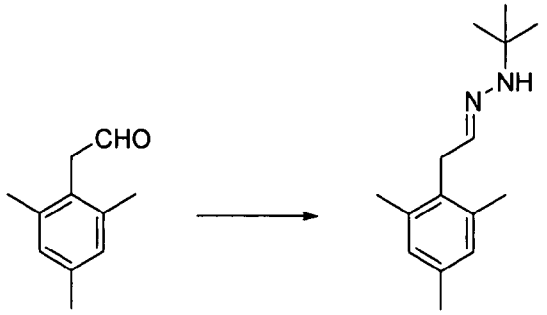
*N*-(3-胺基苯基)磺醯基-2-[(2,6-二甲基苯基)甲基]-5-降冰片烷-2-基-吡唑-3-甲醯胺(化合物370)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-7-乙基-2-[(2,4,6-三甲基苯基)甲基]吲唑-3-甲醯胺(化合物1086)，及

*N*-(3-胺基苯基)磺醯基-5-環戊基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物105)。

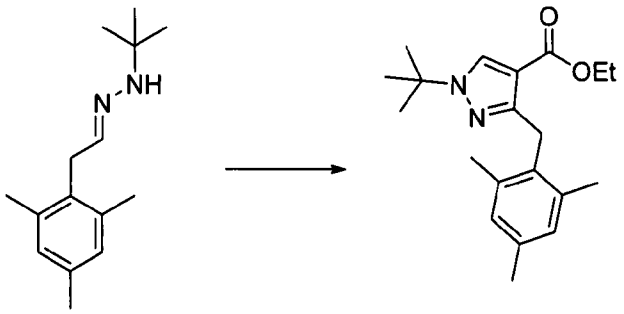
**製備23：1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-4-甲酸**

**步驟1：(*E*)-1-第三丁基-2-[2-(2,4,6-三甲基苯基)亞乙基]肼**



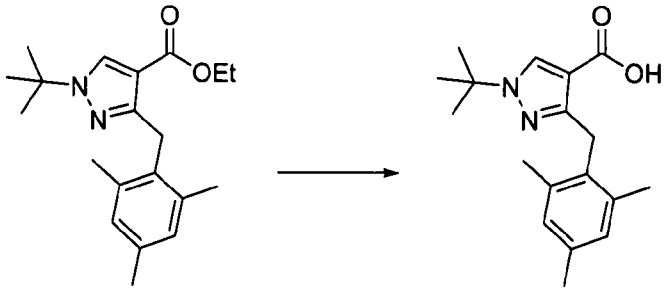

將乙酸(0.2 mL)添加至2-(2,4,6-三甲基苯基)乙醛(0.80 g，4.9 mmol)及第三丁基肼鹽酸鹽(0.73 g，4.9 mmol)於甲醇(10 mL)中之混合物中。將混合物在室溫下攪拌24小時。反應混合物在減壓下濃縮且殘餘物用乙醚(20 mL)處理，得到沈澱，其藉由過濾收集。固體懸浮於乙酸乙酯(150 mL)中，藉由添加飽和$NaHCO_3$將pH值調至>7，有機層用鹽水洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮，得到呈黃色油狀之(*E*)-1-第三丁基-2-[2-(2,4,6-三甲基苯基)亞乙基]肼(0.80 g，70.%)。$^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.22 (s, 9H), 2.18 (s, 3H), 2.23 (s, 6H), 3.68 (d, $J$ = 5.2 Hz, 2H), 6.85 (s, 2H), 8.24 (t, $J$ = 5.2 Hz, 1H), 11.39 (br s, 1H)。ESI-MS *m/z*計算值232.2, 實驗值233.2 $(M+1)^+$；滯留時間: 1.75 min (5分鐘操作)。

**步驟2：1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-4-甲酸乙酯**



將(*E*)-1-第三丁基-2-[2-(2,4,6-三甲基苯基)亞乙基]肼(0.86 g，3.7 mmol)及丙炔酸乙酯(0.44 g，4.5 mmol)於乙腈(3 mL)及乙酸(3 mL)中之混合物在室溫下攪拌2天。反應混合物在減壓下濃縮且殘餘物溶於乙酸乙酯(100 mL)，接著其用飽和$NaHCO_3$、鹽水洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠急驟層析，用庚烷中30%乙酸乙酯溶離來純化，得到呈黃色固體狀之1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-4-甲酸乙酯(0.40 g，33%)。ESI-MS *m/z*計算值328.2, 實驗值329.2 $(M+1)^+$；滯留時間: 2.92 min (5分鐘操作)。

**步驟4：1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-4-甲酸**



將1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-4-甲酸乙酯(0.34 g，1.0 mmol)及$LiOH·H_2O$ (0.22 g，5.2 mmol)於甲醇(4 mL)及水(4 mL)中之混合物在回流下加熱3小時。反應混合物在減壓下濃縮且水層之pH值用5%檸檬酸調至約3。水層用乙酸乙酯(150 mL)萃取，用鹽水洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由$C_{18}$管柱層析，以水中80%甲醇溶離來純化，得到呈黃色固體狀之1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-4-甲酸(0.23 g，74%)。ESI-

MS *m/z*計算值300.2，實驗值301.2 $(M+1)^+$；滯留時間: 2.41 min (5分鐘操作)。

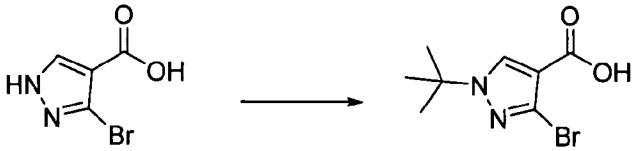
以下化合物可使用本文所述之程序合成：

*N*-(苯磺醯基)-1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡唑-4-甲醯胺(化合物63)及

*N*-(3-胺基苯基)磺醯基-1-第三丁基-3-[(2,4,6-三甲基苯基)甲基]吡唑-4-甲醯胺(化合物324)。

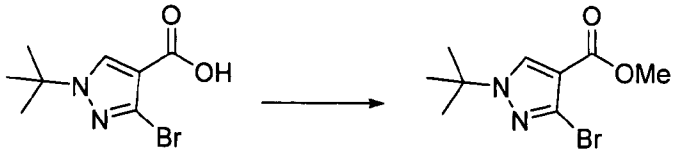
**製備24：1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-3-甲酸**

**步驟1：4-溴-1-第三丁基-1*H*-吡唑-3-甲酸**



將濃硫酸(0.24 mL，4.3 mmol)添加至4-溴-1*H*-吡唑-3-甲酸(860 mg，4.3 mmol)於*t*-BuOH (2.1 mL，22 mmol)中之懸浮液中。將反應混合物在100℃下攪拌2小時。大部分溶劑在加熱期間蒸發且白色固體保留在燒瓶中。冷卻至室溫後，藉由添加飽和$NaHCO_3$水溶液將pH值調至約4。水層用乙酸乙酯(2×40 mL)萃取。合併之有機層用鹽水(20 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮，得到呈白色固體狀之4-溴-1-第三丁基-1*H*-吡唑-3-甲酸(1.0 g，89%)。$^1$H NMR (300 MHz, DMSO) δ 1.52 (s, 9H), 8.23 (s, 1H), 12.92 (br s, 1H)。

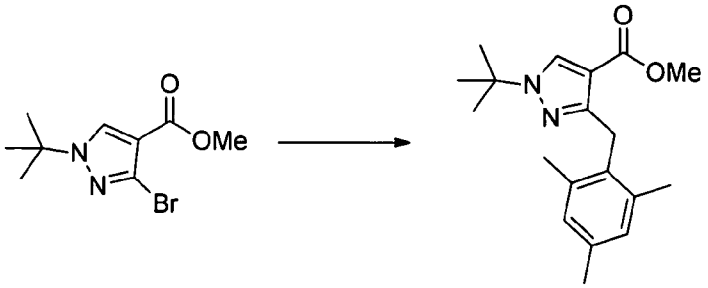
**步驟2：4-溴-1-第三丁基-1*H*-吡唑-3-甲酸甲酯**



碳酸鉀(1.1 g，8.0 mmol)及碘甲烷(0.3 mL，4.8 mmol)添加至4-溴-1-第三丁基-1*H*-吡唑-3-甲酸(980 mg，4.0 mmol)於*N,N*-二甲基甲醯胺(6 mL)中之溶液中。將反應混合物在室溫下攪拌隔夜。添加5%檸檬

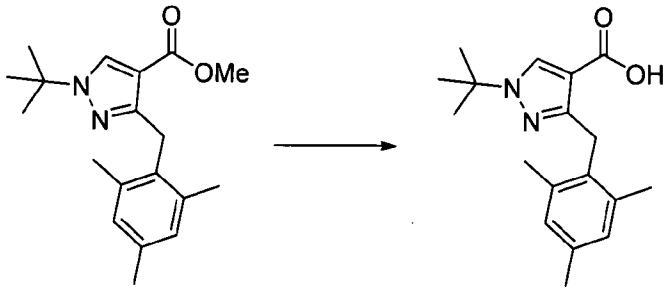
酸溶液(20 mL)且水層用乙酸乙酯(60 mL)萃取。有機層用水(2×15 mL)、鹽水(15 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠管柱層析(0-30%乙酸乙酯/己烷)來純化，得到呈無色油狀之4-溴-1-第三丁基-1*H*-吡唑-3-甲酸甲酯(1.1 g，定量)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H), 3.94 (s, 3H), 7.61 (s, 1H)。

**步驟3：1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-3-甲酸甲酯**




乙酸鈀(45 mg，0.20 mmol)及$^t$Bu$_3$P·HBF$_4$ (120 mg，0.40 mmol)添加至密封管中4-溴-1-第三丁基-1*H*-吡唑-3-甲酸甲酯(1.1 g，4.2 mmol)於四氫呋喃(10 mL)中之溶液中。將反應容器抽空且用氮氣回填三次。在室溫下添加剛剛製備之溴化(2,4,6-三甲基苯基)甲基鋅(8.0 mL 1.0 M於THF中之溶液，8.0 mmol)之溶液。將橙紅色溶液在室溫下攪拌隔夜。將所得黑色反應混合物用5%檸檬酸溶液(20 mL)淬滅且用乙酸乙酯(2×40 mL)萃取。合併之有機層用水(2×15 mL)、鹽水(15 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠管柱層析(5至30%乙酸乙酯/己烷)來純化，得到呈白色固體狀之1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-3-甲酸甲酯(1.1 g，87%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.19 (s, 6H), 2.29 (s, 3H), 3.96 (s, 3H), 4.05 (s, 2H), 6.67 (s, 1H), 6.87 (s, 2H)。

**步驟4：1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-3-甲酸**



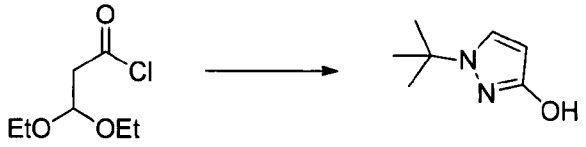
將1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-3-甲酸酯(1.00 g，3.18 mmol)、$LiOH·H_2O$ (667 mg，15.5 mmol)、THF (10 mL)及水(10 mL)之混合物在密封管中在60℃下攪拌4小時。藉由添加5%檸檬酸(30 mL)酸化混合物且用乙酸乙酯(2×30 mL)萃取。合併之有機層用水(2×15 mL)、鹽水(15 mL)洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。殘餘物用甲基第三丁基醚(2 mL)及庚烷(2 mL)之混合物濕磨，得到呈白色固體狀之1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-3-甲酸(769 mg，81%)。$^1H$ NMR (300 MHz, DMSO) δ 1.41 (s, 9H), 2.14 (s, 6H), 2.21 (s, 3H), 3.94 (s, 2H), 6.80 (s, 1H), 6.84 (s, 2H), 12.60 (s, 1H)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-1-第三丁基-4-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物366)。

**製備25：1-第三丁基-3-(2,4,6-三甲基苯氧基)-1*H*-吡唑-4-甲酸**

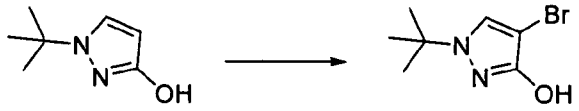
**步驟1：1-第三丁基-1*H*-吡唑-3-醇**



將第三丁基肼鹽酸鹽(3.03 g，24.3 mmol)添加至吡啶(30 mL)中且將混合物在室溫下攪拌1小時。含有不溶物質之混合物冷卻至5℃，接著逐滴添加3,3-二乙氧基丙醯氯(3.27 g，24.3 mmol)。接著將混合物在80℃下加熱48小時，接著其冷卻至室溫。混合物用乙酸乙酯稀釋且有機相用5% $NaHCO_3$水溶液及鹽水洗滌，接著其經無水$Na_2SO_4$乾

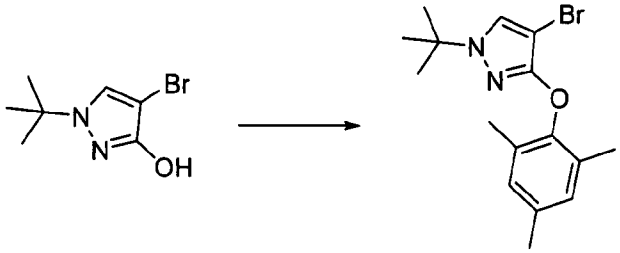
燥。濾去固體且在減壓下移除溶劑。殘餘物藉由矽膠管柱層析(5-50%乙酸乙酯/庚烷)來純化，得到固體，其在庚烷(1×10 mL)中濕磨，過濾且乾燥，得到呈灰白色固體狀之1-第三丁基-1*H*-吡唑-3-醇 (1.38 g，44%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9H), 5.57 (d, $J$ = 2.2 Hz, 1H), 7.24 (d, $J$ = 2.2 Hz, 1H), 12.11 (br. s, 1H)。ESI-MS *m/z*計算值140.1, 實驗值141.2 $(M+1)^+$；滯留時間: 1.12 min (5分鐘操作)。

**步驟2：4-溴-1-第三丁基-1*H*-吡唑-3-醇**




向含1-第三丁基-1*H*-吡唑-3-醇(1.30 g，9.27 mmol)之二氯甲烷(20 mL)添加$NaHCO_3$ (0.97 g，11. mmol)。混合物冷卻至0℃且逐滴添加溴(1.56 g，9.74 mmol)於二氯甲烷(10 mL)中之溶液。將混合物在0-10℃下攪拌60分鐘，接著其用乙酸乙酯稀釋。有機相用5% $NaHCO_3$、1% $Na_2S_2O_3$、5% $NaHCO_3$、鹽水洗滌且經無水$Na_2SO_4$乾燥。濾去固體且在減壓下移除溶劑，得到呈灰白色固體狀之4-溴-1-第三丁基-1*H*-吡唑-3-醇(1.87 g，92%產率)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 7.31 (s, 1H), 11.58 (br. s, 1H)。ESI-MS *m/z*計算值218.0, 實驗值219.1/221.1 $(M+1)^+$；滯留時間: 1.52 min (5分鐘操作)。

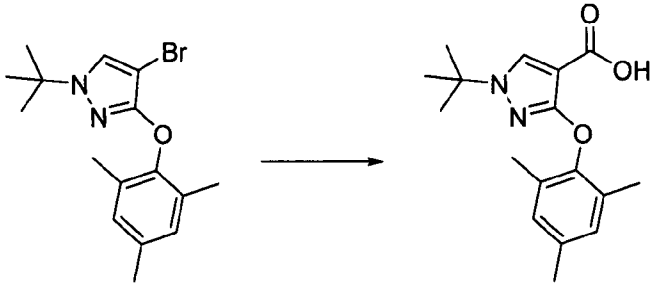
**步驟3：4-溴-1-第三丁基-3-(2,4,6-三甲基苯氧基)-1*H*-吡唑**




將1-2-二氯乙烷(125 mL)添加至直火乾燥之4Å分子篩(4.81 g)中且空氣鼓泡穿過混合物15分鐘。添加4-溴-1-第三丁基-1*H*-吡唑-3-醇(1.75 g，7.99 mmol)，接著2,4,6-三甲基苯基硼酸(3.27 g，20.0 mmol)、吡啶(1.94 mL，24.0 mmol)及乙酸銅(II)(2.18 g，12.0

mmol)。將反應混合物在室溫下在空氣氛圍下攪拌72小時，接著用乙酸乙酯稀釋。有機相用10% $NH_4OH$、鹽水洗滌且經無水$Na_2SO_4$乾燥。濾去固體且在減壓下移除溶劑。殘餘物藉由矽膠管柱層析(5-75%二氯甲烷/庚烷)來純化，得到呈淺黃色固體狀之4-溴-1-第三丁基-3-(2,4,6-三甲基苯氧基)-1*H*-吡唑(1.35 g，50%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.15 (s, 6H), 2.27 (s, 3H), 6.83 (s, 2H), 7.34 (s, 1H)。ESI-MS *m/z*計算值336.1，實驗值337.1/339.1 $(M+1)^+$；滯留時間：2.54 min (5分鐘操作)。

**步驟4：1-第三丁基-3-(2,4,6-三甲基苯氧基)-1*H*-吡唑-4-甲酸**




向冷卻在-78℃下的4-溴-1-第三丁基-3-(2,4,6-三甲基苯氧基)-1*H*-吡唑(1.00 g，2.96 mmol)於THF (8 mL)中之溶液中逐滴添加2.5 M正丁基鋰之己烷溶液(1.36 mL，3.41 mmol)。將混合物在-78℃下攪拌30分鐘且接著$CO_2$鼓泡穿過溶液45分鐘，接著將一大塊乾冰添加至反應混合物中。使反應混合物經3小時自-78℃升溫至-60℃。在0℃下藉由添加水(5 mL)來淬滅反應混合物，接著其用乙酸乙酯(50 mL)稀釋。在攪拌下添加檸檬酸(5%水溶液)以獲得pH 4。混合物用乙酸乙酯萃取。合併之有機萃取物用5%檸檬酸水溶液、3% HCl、$H_2O$及鹽水洗滌且經無水$Na_2SO_4$乾燥。濾去固體且在減壓下移除溶劑。殘餘物在庚烷/甲基第三丁基醚(8 mL/0.5 mL)中濕磨兩次，接著藉由矽膠管柱層析0-20%甲醇/二氯甲烷)純化，得到呈白色固體狀之1-第三丁基-3-(2,4,6-三甲基苯氧基)-1*H*-吡唑-4-甲酸(480 mg，53%產率)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.15 (s, 6H), 2.28 (s, 3H), 6.85 (s, 2H),

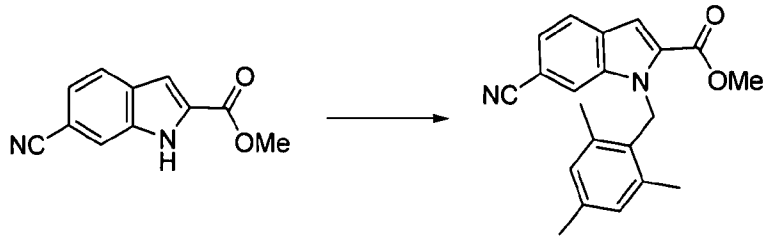
7.91 (s, 1H)。ESI-MS *m/z*計算值302.2, 實驗值303.2 $(M+1)^+$；滯留時間: 3.94 min (5分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-1-第三丁基-3-(2,4,6-三甲基苯氧基)吡唑-4-甲醯胺(化合物256)及*N*-(3-胺基苯基)磺醯基-1-第三丁基-3-(2,4,6-三甲基苯氧基)吡唑-4-甲醯胺(化合物325)。

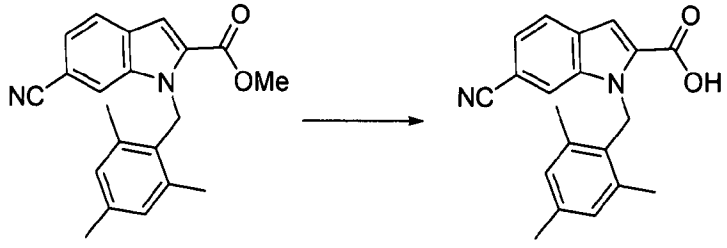
**製備26：*N*-(3-胺基苯基)磺醯基-6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物1082)**

**步驟1：6-氰基-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲酸甲酯**




6-氰基-1*H*-吲哚-2-甲酸甲酯(467 mg，2.33 mmol)溶於*N,N*-二甲基甲醯胺(25 mL)中且在冰浴中冷卻。添加NaH (60%，112 mg，2.80 mmol)且將反應混合物攪拌10分鐘。添加2-(氯甲基)-1,3,5-三甲基-苯(472 mg，2.80 mmol)且使反應混合物升溫至室溫且攪拌12小時。反應混合物傾倒至冰水中且藉由添加1 N HCl酸化。收集所得沈澱，得到6-氰基-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲酸甲酯。ESI-MS *m/z*計算值332.2, 實驗值333.2 $(M+1)^+$；滯留時間: 0.81 min (1分鐘操作)。

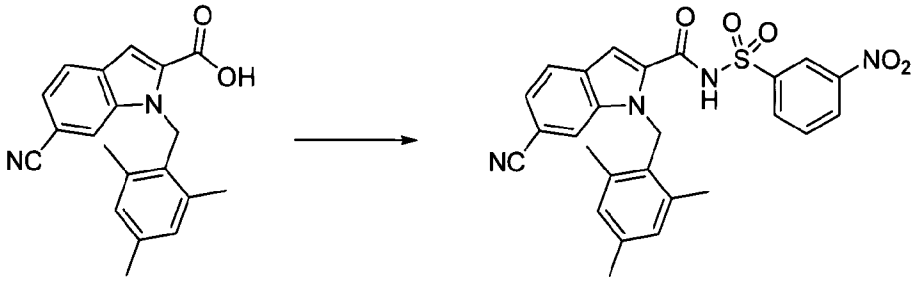
**步驟2：6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲酸**




將6-氰基-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲酸甲酯(來自步驟1)在甲醇(20 mL)、THF (10 mL)及NaOH (9.34 mL 1.0 M，9.34 mmol)

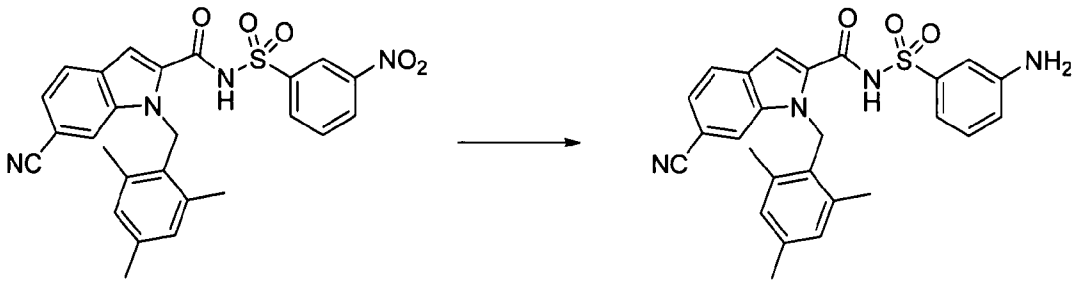
之混合物中攪拌30分鐘。反應混合物在冰浴中冷卻且用6 M HCl酸化至pH 1。混合物用乙酸乙酯萃取。有機物用鹽水洗滌，經硫酸鈉乾燥且蒸發，得到6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲酸(740 mg，2步99%)。ESI-MS *m/z*計算值318.1，實驗值319.2 $(M+1)^+$；滯留時間: 0.68 min (1分鐘操作)。

**步驟3：6-氰基-*N*-((3-硝基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲醯胺**



6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲酸(35 mg，0.11 mmol)、(3-硝基苯基)磺醯基胺基鈉(37 mg，0.16 mmol)、六氟磷酸*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(42 mg，0.11 mmol)及$K_2CO_3$ (46 mg，0.33 mmol)組合於*N,N*-二甲基甲醯胺(1 mL)中。將反應混合物在60℃下加熱2小時且濃縮。粗物質進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到6-氰基-*N*-((3-硝基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲醯胺。ESI-MS *m/z*計算值502.1，實驗值503.2 $(M+1)^+$；滯留時間: 0.75 min (1分鐘操作)。

**步驟4：*N*-(3-胺基苯基)磺醯基-6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物1082)**



在氫氣球下將6-氰基-*N*-((3-硝基苯基)磺醯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲醯胺(來自步驟3)與甲醇(2 mL)及10% Pd/C (12 mg，0.011 mmol)混合。1小時後，反應混合物過濾且濃縮濾液。殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到*N*-(3-胺基苯基)磺醯基-6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物1082) (6.8 mg，2步13%)。ESI-MS *m/z*計算值472.2, 實驗值473.2 $(M+1)^+$；滯留時間: 1.71 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-(苯磺醯基)-6-氯-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物10)，

*N*-(苯磺醯基)-5-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物241)，

*N*-(苯磺醯基)-4-氯-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物127)，

*N*-(苯磺醯基)-4-氟-1-(1-苯基乙基)吲哚-2-甲醯胺(化合物160)，

*N*-(苯磺醯基)-6-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物12)，

*N*-(苯磺醯基)-5-氯-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物137)，

*N*-(苯磺醯基)-4-氟-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物87)，

*N*-(苯磺醯基)-5-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物248)，

*N*-(苯磺醯基)-4-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物143)，

*N*-(苯磺醯基)-7-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺

(化合物354)，

*N*-(苯磺醯基)-5-氟-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物33)，

*N*-(3-胺基苯基)磺醯基-4-氯-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物362)，

*N*-(3-胺基苯基)磺醯基-4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物120)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-乙基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物179)，

*N*-(苯磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物264)，

*N*-(苯磺醯基)-1-[(2,6-二甲基苯基)甲基]-4-甲氧基-吲哚-2-甲醯胺(化合物290)，

*N*-(苯磺醯基)-4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物348)，

*N*-(3-胺基苯基)磺醯基-5-氯-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物344)，

*N*-(3-胺基苯基)磺醯基-5-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物259)，

*N*-(3-胺基苯基)磺醯基-6-氯-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物9)，

*N*-(3-胺基苯基)磺醯基-6-氟-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物142)，

*N*-(苯磺醯基)-6-氟-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物212)，

*N*-(3-胺基苯基)磺醯基-4-氟-1-(1-苯基乙基)吲哚-2-甲醯胺(化合

物186)，

*N*-(3-胺基苯基)磺醯基-4-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物144)，

*N*-(3-胺基苯基)磺醯基-1-[(2,6-二甲基苯基)甲基]-4-甲氧基-吲哚-2-甲醯胺(化合物168)，

*N*-(3-胺基苯基)磺醯基-4-氟-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物181)，

*N*-(3-甲氧基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物335)，

*N*-(3-胺基苯基)磺醯基-7-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物194)，

*N*-(3-胺基苯基)磺醯基-5-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物336)，

*N*-(2-甲氧基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物183)，

*N*-[(6-甲氧基-2-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物253)，

*N*-(3-胺基苯基)磺醯基-5-氟-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物153)，

*N*-(3-胺基苯基)磺醯基-6-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物62)，

*N*-(苯磺醯基)-3-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物232)，

*N*-(3-胺基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物148)，

*N*-(2-羥基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺

(化合物112)，

*N*-(苯磺醯基)-5,6-二甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物198)，

*N*-(4-胺基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物134)，

*N*-(苯磺醯基)-1-[(2,6-二甲基苯基)甲基]吲哚-2-甲醯胺(化合物2)，

*N*-(3-胺基苯基)磺醯基-4-氟基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物306)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-5-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物267)，

4-氟-1-(1-苯基乙基)-*N*-(4-吡啶基磺醯基)吲哚-2-甲醯胺(化合物192)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物18)，

*N*-(3-胺基苯基)磺醯基-1-[(2,6-二甲基苯基)甲基]吲哚-2-甲醯胺(化合物331)，

*N*-(2-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物247)，

*N*-(2-氟基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物358)，

4-氯-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物82)，

6-甲基-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物38)，

4-甲氧基-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-

2-甲醯胺(化合物36)，

4-氟-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物298)，

*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物227)，

5-甲基-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物25)，

*N*-(3-胺基苯基)磺醯基-3-甲基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物118)，

*N*-(3-胺基苯基)磺醯基-1-[(2,6-二甲基苯基)甲基]-6-甲氧基-吲哚-2-甲醯胺(化合物116)，

*N*-[(3-甲氧基-2-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物258)，

5-氯-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物65)，

6-氯-*N*-(4-吡啶基磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物24)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-1-[(4-氰基-2,6-二甲基-苯基)甲基]-5-甲基-吲哚-2-甲醯胺(化合物67)，

*N*-[(4-胺基-2-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物23)，

*N*-(3-胺基苯基)磺醯基-5-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物291)，

*N*-(3-胺基苯基)磺醯基-5,6-二甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物598)，

*N*-(3-胺基苯基)磺醯基-6-氰基-1-[(2,4,6-三甲基苯基)甲基]吲哚-

2-甲醯胺(化合物1082)，

*N*-[(2-胺基-4-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物627)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-異丙基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物404)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-甲基-1-(對甲苯基)吲哚-2-甲醯胺(化合物653)，

*N*-(3-胺基苯基)磺醯基-5,6-二甲氧基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物598)，

*N*-(苯磺醯基)-1-[(2,6-二甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲醯胺(化合物1291)，

*N*-[(2-胺基-4-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物627)，

(2R)-*N*-[(6-胺基-2-吡啶基)磺醯基]-1-[(2,4,6-三甲基苯基)甲基]吲哚啉-2-甲醯胺(化合物462)，

(2R)-*N*-(苯磺醯基)-1-[(2,4,6-三甲基苯基)甲基]吲哚啉-2-甲醯胺(化合物918)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-丙基-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲醯胺(化合物1158)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-乙基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲醯胺(化合物816)，

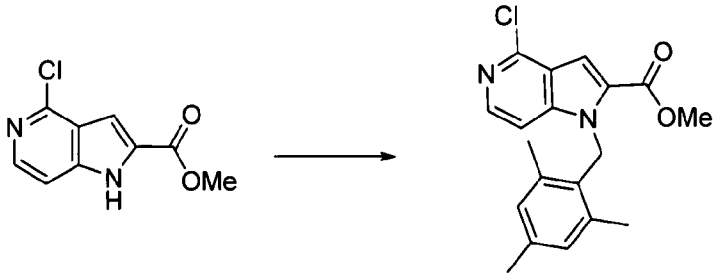
*N*-(3-胺基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲醯胺(化合物184)，及

*N*-(苯磺醯基)-1-[(2,6-二甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲醯胺(化合物1291)。

**製備27：4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲**

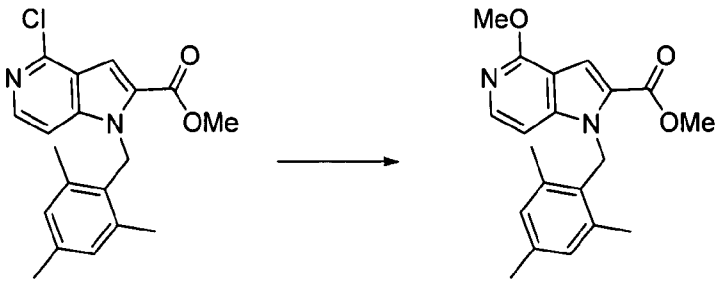
酸

**步驟1：4-氯-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸甲酯**



在0℃下將NaH (60%，62 mg，1.5 mmol)添加至4-氯-1*H*-吡咯并[3,2-*c*]吡啶-2-甲酸甲酯(250. mg，1.19 mmol)及*N,N*-二甲基甲醯胺(5 mL)之混合物中。將混合物在0℃下攪拌15分鐘，接著逐滴添加2-(氯甲基)-1,3,5-三甲基-苯(260. mg，1.54 mmol)於*N,N*-二甲基甲醯胺(1 mL)中之溶液。將混合物在室溫下攪拌1小時，接著在60℃下攪拌4小時。混合物分溶於1N HCl與乙酸乙酯之間。分離各層且水層用乙酸乙酯(3次)萃取。合併之有機層用鹽水(2次)洗滌，經硫酸鎂乾燥，過濾且在減壓下濃縮。透明殘餘物進行矽膠管柱層析(0-20%乙酸乙酯/己烷)，得到4-氯-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸甲酯(370 mg，91%)。ESI-MS *m/z*計算值342.1，實驗值343.4 $(M+1)^+$；滯留時間: 2.09 min (3分鐘操作)。

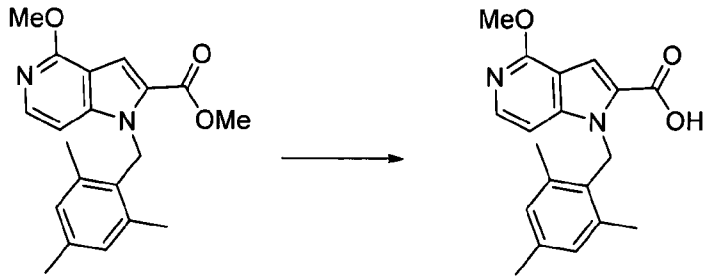
**步驟2：4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸甲酯**



將4-氯-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-c]吡啶-2-甲酸甲酯(130. mg，0.379 mmol)及NaOMe (7.6 mL 0.50 M，3.8 mmol)之混合物

在微波中在110℃下加熱30分鐘。濃縮混合物，得到呈白色固體狀之4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸甲酯(56 mg，15%)。ESI-MS *m/z*計算值338.2，實驗值339.4 $(M+1)^+$；滯留時間: 0.64 min (1分鐘操作)。

**步驟3：4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸**




在室溫下將氫氧化鋰(160 μL 2.0 M，0.32 mmol)添加至4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸甲酯(50. mg，0.15 mmol)及EtOH (1 mL)之混合物中。將混合物在室溫下攪拌隔夜。濃縮混合物且殘餘物分溶於1N HCl與$CH_2Cl_2$之間。分離各層且水層用$CH_2Cl_2$ (3次)萃取。合併之有機物用鹽水洗滌，經硫酸鎂乾燥，過濾且濃縮。殘餘物溶解於*N,N*-二甲基甲醯胺且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)中，得到呈白色固體狀之4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-*c*]吡啶-2-甲酸(39 mg，81%)。ESI-MS *m/z*計算值324.2，實驗值325.4 $(M+1)^+$；滯留時間: 0.52 min (1分鐘操作)。

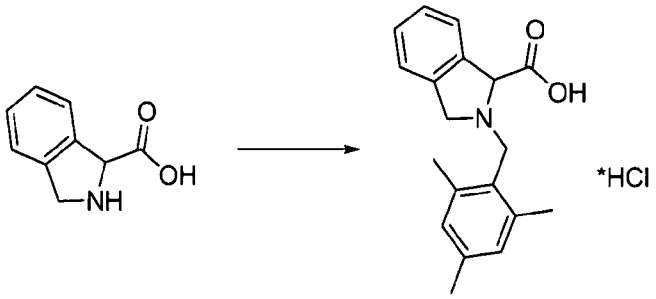
以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[3,2-c]吡啶-2-甲醯胺(化合物943)

及

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-甲氧基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲醯胺(化合物539)

**製備28：2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸鹽**




將異吲哚啉-1-甲酸(100 mg，0.613 mmol)及KOH (103 mg，1.84 mmol)於異丙醇(600 μL)中之懸浮液攪拌直至形成溶液。添加2-(氯甲基)-1,3,5-三甲基-苯(114 mg，0.674 mmol)且將反應混合物攪拌3小時。濃縮混合物且殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸鹽(99 mg，49%)。$^1$H NMR (400 MHz, DMSO) δ 7.39 - 7.33 (m, 1H), 7.34 - 7.25 (m, 3H), 6.87 (s, 2H), 4.97 (s, 1H), 4.34 - 3.94 (m, 4H), 2.40 (s, 6H), 2.23 (s, 3H)。ESI-MS *m/z*計算值295.2, 實驗值296.2 $(M+1)^+$；滯留時間: 0.43 min (1分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物90)，

*N*-(4-吡啶基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物94)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物73)，

*N*-(3-甲氧基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物16)，

*N*-(苯磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物6)，

*N*-(3-羥基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物254)，

*N*-[(6-甲氧基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物174)，

*N*-[(6-側氧基-1*H*-吡啶-2-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物319)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物218)，

*N*-(2-甲氧基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物79)，

*N*-(2-吡啶基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物48)，

*N*-[(6-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物200)，

*N*-(3-胺基苯基)磺醯基-2-(1-苯基乙基)異吲哚啉-1-甲醯胺(化合物187)，

*N*-(4-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物121)，

*N*-[(4-胺基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物32)，

*N*-(2-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物230)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-甲基-2-[(2,4,6-三甲基苯基)甲基]-3,4-二氫-1*H*-異喹啉-3-甲醯胺(化合物95)，

*N*-(3-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]-3,4-二氫-1*H*-異喹啉-3-甲醯胺(化合物213)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-(2,4,6-三甲基苯基)乙基]異吲哚啉-1-甲醯胺(化合物1186)，

*N*-(苯磺醯基)-1-[(2,4,6-三甲基苯基)甲基]-2,3,4,5-四氫-1-苯并氮呯-2-甲醯胺(化合物604)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物895)，

*N*-[(3-羥基-2-吡啶基)磺醯基]-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物377)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-2-[(2-氟-6-甲基-苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1392)，

*N*-(3-胺基-4-丙基-苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1367)，

*N*-(3-胺基-4-異丙基-苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1562)，

*N*-(3-胺基-4-乙基-苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1584)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-(鄰甲苯基甲基)異吲哚啉-1-甲醯胺(化合物1408)

4-乙氧基-*N*-吲哚啉-5-基磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1422)

*N*-(2-胺基苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1457)

*N*-(4-胺基苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1480)

4-乙氧基-1-甲基-*N*-[[6-[(2,2,2-三氟乙醯基)胺基]-2-吡啶基]磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1616)

*N*-[(6-乙醯胺基-2-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1415)

*N*-[(6-胺基-3-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1413)

4-乙氧基-*N*-(2-羥基苯基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1509)

4-乙氧基-*N*-(4-羥基苯基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1453)

4-乙氧基-1-甲基-*N*-(3-吡啶基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1669)

*N*-[(6-胺基-5-氯-2-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1596)

4-乙氧基-*N*-(3-甲氧基苯基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1470)

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-2-[(3-氟-5-異丁氧基-苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1681)

4-乙氧基-1-甲基-*N*-噻唑-5-基磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1606)

4-乙氧基-*N*-(1H-吲哚-6-基磺醯基)-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1393)

*N*-[[6-(二氟甲基)-2-吡啶基]磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1597)

4-乙氧基-*N*-[(3-羥基-2-吡啶基)磺醯基]-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1642) (化合物377)

4-乙氧基-1-甲基-*N*-噻唑-4-基磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1542)

4-乙氧基-1-甲基-*N*-(4-吡啶基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1449)

4-乙氧基-*N*-(1H-吲哚-4-基磺醯基)-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1666)

*N*-(2-乙醯胺基噻唑-5-基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1555)

4-乙氧基-*N*-(3-氟-2-甲氧基-苯基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1403)

4-乙氧基-1-甲基-*N*-(2-吡啶基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1474)

4-乙氧基-1-甲基-*N*-噻唑-2-基磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1546)

4-乙氧基-*N*-(3-氟苯基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1425)

*N*-[(2-胺基-3-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1591)

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-2-[(6-異丙氧基-3-吡啶基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1662)

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,6-二甲基苯基)甲基]-4-乙氧基-1-甲基-異吲哚啉-1-甲醯胺(化合物1498)

2-[(2,6-二甲基苯基)甲基]-4-乙氧基-*N*-[(6-氟-2-吡啶基)磺醯基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1676)

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(6-氯-3-吡啶基)甲基]-4-乙氧基-1-甲基-異吲哚啉-1-甲醯胺(化合物1565)

*N*-(苯磺醯基)-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1539)

*N*-(3-胺基苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1454)

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-2-[(4-異丙基苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1576)

4-乙氧基-*N*-[(6-氟-2-吡啶基)磺醯基]-2-[(4-異丙基苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1655)

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-2-[(4-氟苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1433)

4-乙氧基-2-[(4-氟苯基)甲基]-*N*-[(6-氟-2-吡啶基)磺醯基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1583)

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-2-[(3-氟-5-甲氧基-苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1421)

4-乙氧基-2-[(3-氟-5-甲氧基-苯基)甲基]-*N*-[(6-氟-2-吡啶基)磺醯基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1428)

(1S)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1372) (化合物1346)

(1R)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1582) (化合物1346)

(1S)-4-乙氧基-1-甲基-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1541) (化合物1237) (化合物410)

(1R)-4-乙氧基-1-甲基-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1476) (化合物1237) (化合物410)

*N*-(3-胺基-4-氯-苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1587)

*N*-(3-胺基-4-氟-苯基)磺醯基-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1394)

*N*-(3-胺基吡嗪-2-基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物480)，

1-甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1237)，

*N*-(3-胺基苯基)磺醯基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1273)，

*N*-(苯磺醯基)-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物873)，

1-甲基-*N*-(1H-吡唑-5-基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物378)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-1-甲基-2-(鄰甲苯基甲基)異吲哚啉-1-甲醯胺(化合物666)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物765)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,6-二甲基苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物790)，

*N*-[(3-甲氧基-2-吡啶基)磺醯基]-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物825)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,4-二甲基苯基)甲基]-1-甲基-異吲哚啉-1-甲醯胺(化合物1058)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-3,3-二甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1235)，

4-乙氧基-1-甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1237) (化合物410)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-7-甲氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1075)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物474)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-甲氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1161)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-甲氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物406)，

4-乙氧基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物765) (化合物648)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-乙氧基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1346)，

*N*-(3-胺基-4-甲基-苯基)磺醯基-3,3-二甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物448)，

*N*-(5-胺基-2-甲基-苯基)磺醯基-3,3-二甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物840)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-7-羥基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物394)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-羥基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物885)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-羥基-1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1338)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]-1,3,4,5-四氫-2-苯并氮呯-3-甲醯胺(化合物855)，

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]-1,3,4,5-四氫-2-苯并氮呯-3-甲醯胺(化合物1342)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]-1,3,4,5-四氫-2-苯并氮呯-3-甲醯胺(化合物690)，

3,3-二甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1085)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-3,3-二甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物1101)，

*N*-(苯磺醯基)-2-[(2,4,6-三甲基苯基)甲基]-1,3,4,5-四氫-2-苯并氮呯-1-甲醯胺(化合物674)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]-1,3,4,5-四氫-2-苯并氮呯-1-甲醯胺(化合物696)，

*N*-(3-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]-3,4-二氫-1*H*-異喹啉-1-甲醯胺(化合物309)，及

(2S,4R)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺。

**製備29：4-異丙基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物103)**

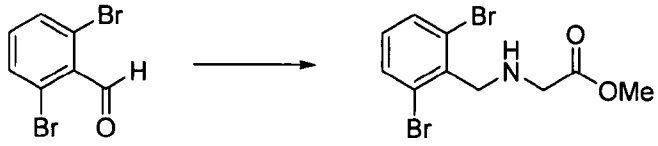
**步驟1：2,6-二溴苯甲醛**




在0℃下向$iPr_2NH$ (21.2 mL，150 mmol)於THF (180 mL)中之溶液中緩慢添加*n*-BuLi (1.6 M，94 mL，150 mmol)。將反應混合物在0℃下攪拌30分鐘且接著冷卻至-78℃。經20分鐘緩慢添加含1,3-二溴苯(17.6 g，74.6 mmol)之THF (80 mL)。將混合物在-78℃下攪拌30分鐘且添加*N,N*-二甲基甲醯胺(11.6 mL，150 mmol)。將混合物攪拌1小時，接著用$H_2SO_4$ (2.5 M，350 mL)處理，且用乙酸乙酯/$Et_2O$ (50/50，3×300 mL)萃取。合併之萃取物經$MgSO_4$乾燥且過濾。濃縮濾

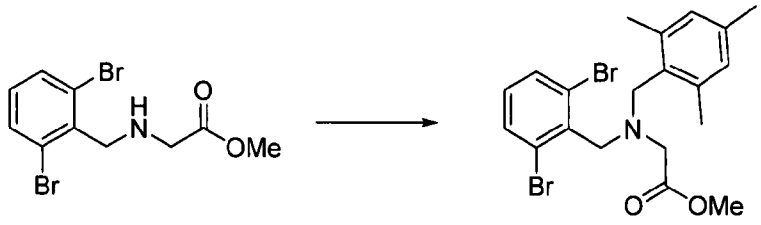
液，得到2,6-二溴苯甲醛(17.6 g，89%)。$^1$H NMR (250 MHz, $CDCl_3$) δ 10.3 (s, 1H), 7.65 (d, *J*=8.0 Hz, 2H), 7.23 (t, *J*= 8.1 Hz, 1H)。

**步驟2：(2,6-二溴苯甲基)甘胺酸甲酯**



向甘胺酸甲酯鹽酸鹽(21.0 g，167 mmol)、2,6-二溴苯甲醛(16.9 g，64.4 mmol)及三乙胺(21.0 mL，142 mmol)於二氯乙烷(380 mL)中之溶液中添加乙酸(8.40 mL，145 mmol)及$NaBH(OAc)_3$ (33.5 g，158 mmol)。將混合物在室溫下在氬氣氛圍下攪拌20小時。添加額外甘胺酸甲酯鹽酸鹽(8.10 g，64.4 mmol)、三乙胺(9.52 g，64.4 mmol)、乙酸(3.73 mL，64.4 mmol)及$NaBH(OAc)_3$ (13.7 g，64.4 mmol)且將反應混合物再攪拌10小時。藉由添加1N NaOH將反應混合物淬滅，且產物用二氯甲烷萃取。有機萃取物用鹽水洗滌，經硫酸鈉乾燥，過濾，且真空移除溶劑。殘餘物藉由經矽藻土墊進行塞過濾(0-50%乙酸乙酯/己烷)純化，得到呈油狀之(2,6-二溴苯甲基)甘胺酸甲酯(13.3g，62%)。$^1$H NMR ($CDCl_3$, 250 MHz) δ 7.52 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J*= 8.0, 1H), 4.20 (s, 2H), 3.70 (s, 3H), 3.50 (s, 2H)。

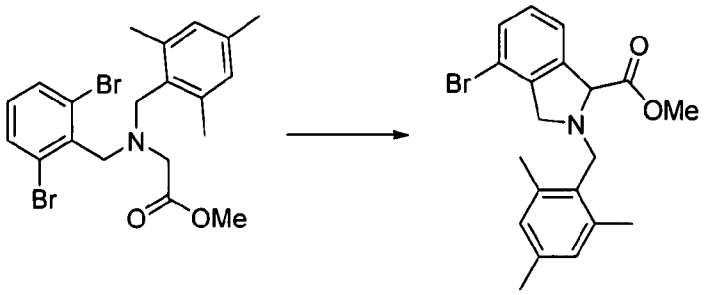
**步驟3：基 *N*-(2,6-二溴苯甲基)-*N*-(2,4,6-三甲基苯甲基)甘胺酸甲酯**



將(2,6-二溴苯甲基)甘胺酸甲酯(13.3 g，39.5 mmol)、2,4,6-三甲基苯甲基溴(7.32 g，43.4 mmol)、$K_2CO_3$ (12.0 g，86.8 mmol)及LiI (300 mg)於乙腈 (300 mL)中之混合物在60℃下攪拌24小時。反應混合物過濾且濃縮濾液。殘餘物藉由矽膠管柱層析(0-20%乙酸乙酯/己烷)來純化，得到呈油狀之*N*-(2,6-二溴苯甲基)-*N*-(2,4,6-三甲基苯甲

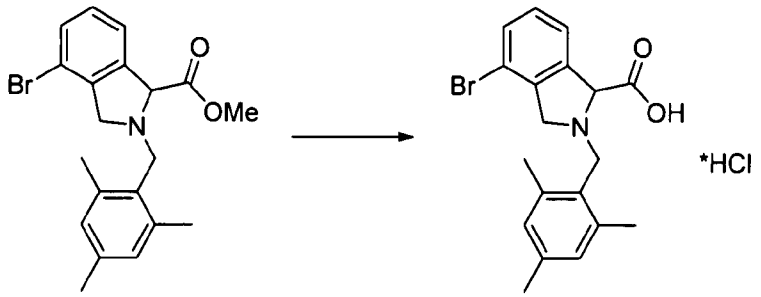
基)甘胺酸甲酯(18.0 g，97%)，其靜置後凝固。$^1$H NMR ($CDCl_3$, 250 MHz) δ 7.54 (d, $J$ = 7.8 Hz, 2H), 7.00 (t, $J$ = 8.0, 1H), 6.79 (s, 2H), 4.34 (s, 2H), 4.04 (s, 2H), 3.71 (s, 3H), 3.50 (s, 2H), 2.23 (s, 3H), 2.18 (s, 6H)。

**步驟4：4-溴-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸甲酯**




將*N*-(2,6-二溴苯甲基)-*N*-(2,4,6-三甲基苯甲基)甘胺酸甲酯(16.0 g，34.1 mmol)、$Cs_2CO_3$ (33.3 g，102 mmol)及$Pd(PPh_3)_4$ (2.0 g，1.7 mmol)於THF (200 mL)中之混合物在110℃下在密封容器中攪拌60小時。藉由用$N_2$沖洗移除一些THF (約50 mL)，接著添加$Cs_2CO_3$ (6.5 g，20 mmol)及$Pd(PPh_3)_4$ (400 mg，0.34 mmol)。將反應混合物在110℃下攪拌24小時。混合物傾倒至水中且用$Et_2O$萃取。有機萃取物用鹽水洗滌，經硫酸鈉乾燥，過濾且濃縮。殘餘物藉由矽膠管柱層析(5-20% $CH_2Cl_2$/己烷)來純化，得到4-溴-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸甲酯(2.9 g，22%)。MS：389 $[M+1]^+$。

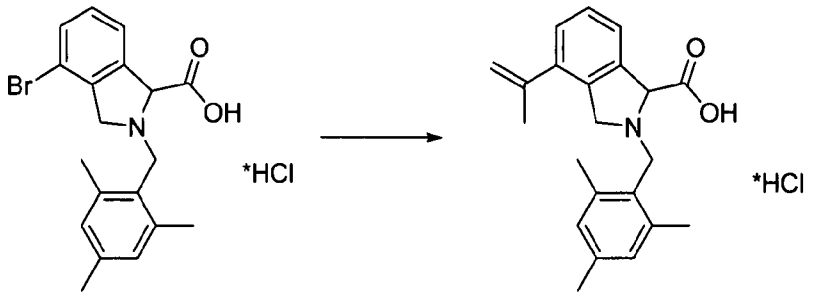
**步驟5：4-溴-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸鹽酸鹽**




將4-溴-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸甲酯(2.9 g，7.4 mmol)組合於含有氫氧化鈉(900. mg，22.5 mmol)之甲醇(45 mL)及水(20 mL)之混合物中。將所得懸浮液在80℃下加熱1小時。濃縮反應混

合物以移除甲醇。添加水(50 mL)且混合物用$Et_2O$萃取。水相用6N HCl調至約pH 2且接著用$CH_2Cl_2$萃取。萃取物經$Na_2SO_4$乾燥，過濾且濃縮。殘餘物藉由矽膠管柱層析(0-5%甲醇/$CH_2Cl_2$)來純化且接著進行製備型HPLC (10-100%含0.05 mM三氟乙酸之乙腈/水)，得到呈三氟乙酸鹽形式之所需產物。該物質溶於甲醇(30 mL)中且用HCl (1M，10 mL)處理。混合物接著濃縮至乾。固體懸浮於$CH_2Cl_2$ (15 mL)中，音波處理10分鐘且過濾。固體用$Et_2O$及己烷洗滌，且乾燥，得到4-溴-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸鹽酸(1.5 g，49%)。$^1H$ NMR (DMSO, 250 MHz) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J*= 7.8, 1H), 7.39 (m, 1H), 6.95 (s, 2H), 5.87 (s, 1H), 4.68 (s, 2H), 4.52 (d, *J*= 10.8 Hz, 1H), 4.30 (d, *J*= 10.8 Hz, 1H), 2.46 (s, 6H), 2.26 (s, 3H)。MS：375 $[M+1]^+$。

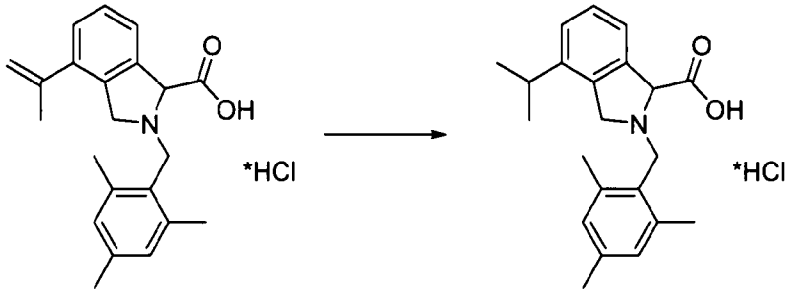
**步驟6：4-異丙烯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸鹽**




將含4-溴-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸鹽(374 mg，0.914 mmol)、2-異丙烯基-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(269 mg，1.60 mmol)及碳酸銫(652 mg，2.00 mmol)之二噁烷(9 mL)及水(900 μL)用氮氣流脫氣1分鐘，接著添加二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(73 mg，0.10 mmol)。反應混合物用氮氣流脫氣1分鐘且將混合物在120℃下攪拌2小時。反應混合物過濾且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到4-異丙烯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸(180 mg，48%)。

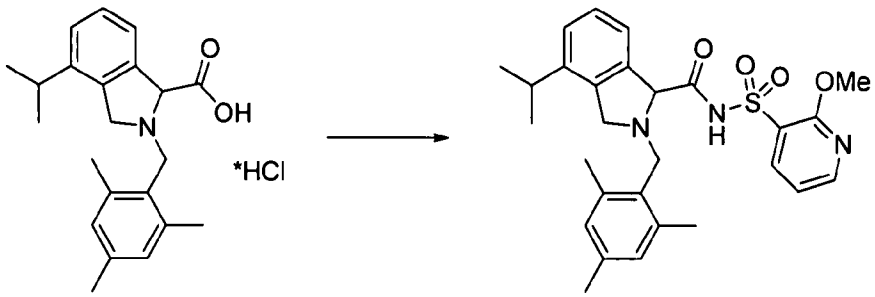
ESI-MS *m/z*計算值335.2, 實驗值336.2 $(M+1)^+$；滯留時間: 0.53 min (1分鐘操作)。

**步驟7：4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸鹽**




將4-(丙-1-烯-2-基)-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸鹽酸鹽(43 mg，0.12 mmol)及10%鈀/碳(5 mg，0.005 mmol)於甲醇(3 mL)中之混合物在氫氣氛圍下攪拌5小時。反應混合物過濾且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到呈無色固體狀之4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸鹽酸鹽(28 mg，65%)。ESI-MS *m/z*計算值337.2, 實驗值338.2 $(M+1)^+$；滯留時間: 0.55 min (1分鐘操作)。

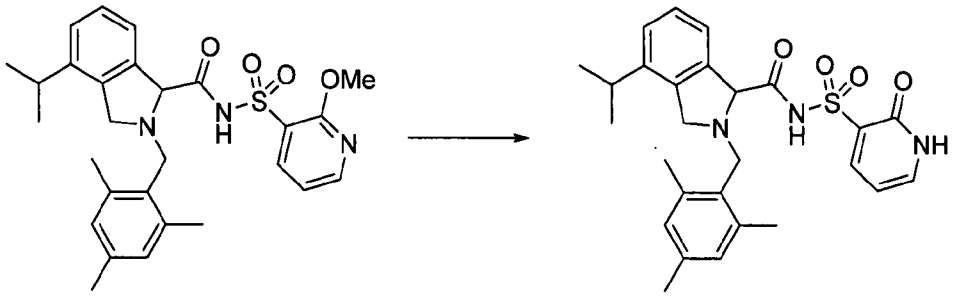
**步驟8：4-異丙基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物218)**




將4-異丙基-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲酸鹽酸鹽(28 mg，0.075 mmol)及碳酸鈉(24 mg，0.22 mmol)於*N,N*-二甲基甲醯胺(1 mL)中之混合物用氮氣流脫氣1分鐘，接著添加六氟磷酸*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(34 mg，0.090 mmol)。混合物脫氣1分鐘且將2-甲氧基吡啶-3-磺醯胺(21 mg，0.11 mmol)添加至反應混合物中。混合物脫氣1分鐘，接著將其

在室溫下攪拌17小時。反應混合物過濾且經受製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到4-異丙基-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物218) (16 mg，42%)。ESI-MS *m/z*計算值507.2, 實驗值508.4 $(M+1)^+$；滯留時間: 0.68 min (1分鐘操作)。

**步驟9：4-異丙基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物103)**




將4-異丙基-*N*-((2-甲氧基吡啶-3-基)磺醯基)-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲醯胺(16 mg，0.032 mmol)於乙酸(1 mL)及HBr (46 μL 33 %w/v，0.19 mmol) (乙酸中)中之混合物在50℃下攪拌1小時。溶劑蒸發且殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到4-異丙基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物103) (12 mg，69%)。ESI-MS *m/z*計算值493.2, 實驗值494.3 $(M+1)^+$；滯留時間: 1.44 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-4-乙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物30)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-4-苯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物508)，

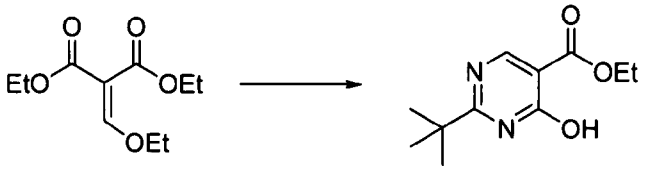
*N*-[(2-甲氧基-3-吡啶基)磺醯基]-4-苯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物427)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物554)，及

*N*-(3-胺基苯基)磺醯基-4-異丙基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物299)。

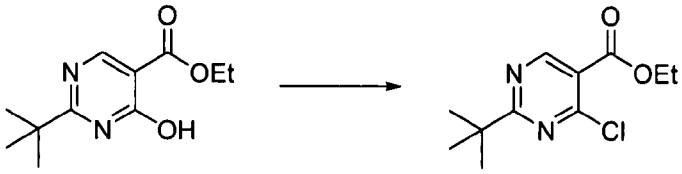
**製備30：2-(第三丁基)-4-(均三甲苯基氧基)嘧啶-5-甲酸**

**步驟1：2-(第三丁基)-4-羥基嘧啶-5-甲酸乙酯**



在EtOH (40 mL)中置放第三丁基胍鹽酸鹽(3.71 g，27.2 mmol)。添加NaOEt溶液(21%於EtOH中，8.80 g，27.2 mmol)且將所得混合物在室溫下攪拌15分鐘。添加乙氧基亞甲基丙二酸二乙酯(5.87 g，27.2 mmol)且將反應混合物在室溫下攪拌隔夜。將反應混合物在回流下加熱1小時且接著移除溶劑。殘餘物溶解於水(100 mL)中且pH值用$NaHSO_4$ (1M)調至3-4。固體藉由過濾收集，用水(50 mL)洗滌且乾燥。合併濾液及洗滌物且用乙酸乙酯(2×150 mL)萃取。合併之萃取物經$Na_2SO_4$乾燥，過濾且濃縮。殘餘物加在過濾期間收集之固體進行矽膠管柱層析，用$CH_2Cl_2$/己烷/甲醇(50/50/0至45/45/10)溶離，得到2-(第三丁基)-4-羥基嘧啶-5-甲酸乙酯(2.85 g，60%)。$^1H$ NMR (250 MHz, $CDCl_3$) δ 8.74 (s, 1H), 4.36 (q, $J$ = 7.3 Hz, 2H), 1.43 (s, 9H), 1.37 (t, $J$ = 7.2 Hz, 3H)。

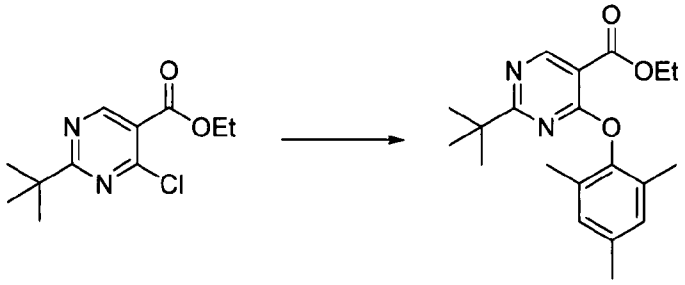
**步驟2：2-(第三丁基)-4-氯嘧啶-5-甲酸乙酯**



在0℃下將$Et_3N$ (1.1 mL)添加至$POCl_3$ (32 mL)中，接著添加2-第三丁基-4-羥基嘧啶-5-甲酸乙酯(3.70 g，16.5 mmol)。將混合物在40℃

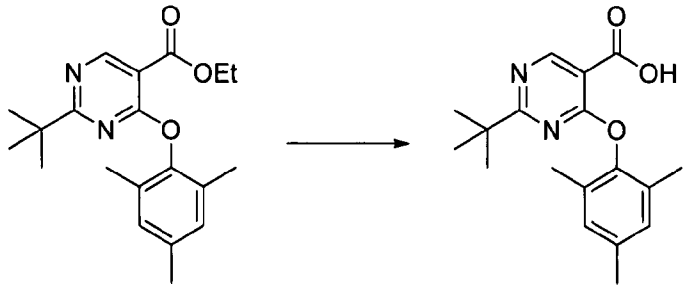
下攪拌1小時且在真空下移除過量$POCl_3$。將殘餘物小心傾倒至冰(400 mL)中且用$CH_2Cl_2$萃取。萃取物用$NaHCO_3$及水洗滌，經$Na_2SO_4$乾燥，過濾且濃縮。粗物質進行矽膠管柱層析(10-90% $CH_2Cl_2$/己烷)，得到呈液體狀之2-(第三丁基)-4-氯嘧啶-5-甲酸乙酯(3.8 g，95%)。$(M+1)^+$ = 243.4。

**步驟3：2-第三丁基-4-(2,4,6-三甲基苯氧基)嘧啶-5-甲酸酯**



2,4,6-三甲基苯酚(2.10 g，15.4 mmol)及氫化鈉(60%，690 mg，17.3 mmol)組合於*N*,*N*-二甲基甲醯胺(20 mL)及四氫呋喃(2 mL)之無水混合物。將反應混合物在氮氣氛圍下在室溫下攪拌15分鐘。添加2-第三丁基-4-氯嘧啶-5-甲酸乙酯(3.80 g，15.7 mmol)且將反應混合物在60℃下加熱1小時。接著使反應混合物冷卻至室溫。反應混合物用水稀釋且用乙酸乙酯萃取。乙酸乙酯層用水洗滌三次，經硫酸鈉乾燥，過濾且濃縮。粗物質藉由矽膠管柱層析(0-30%乙酸乙酯/己烷)來純化，得到呈液體狀之2-第三丁基-4-(2,4,6-三甲基苯氧基)嘧啶-5-甲酸乙酯(3.1 g，58%)。ESI-MS *m/z* 351 $(M+1)^+$；$^1$H NMR (250 MHz, $CDCl_3$) δ 9.07 (s, 1H), 6.88 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 2.21 (s, 6H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 9H)。

**步驟4：2-第三丁基-4-(2,4,6-三甲基苯氧基)嘧啶-5-甲酸**



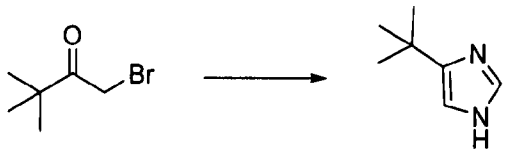
2-第三丁基-4-(2,4,6-三甲基苯氧基)嘧啶-5-甲酸乙酯(3.1 g，9.1 mmol)組合於含有氫氧化鈉(1.2 g，30 mmol)之甲醇(25 mL)及水(30 mL)之混合物中。將所得懸浮液在60℃下加熱3小時。反應混合物冷卻至室溫且用6M鹽酸酸化。所得沈澱過濾，用水洗滌且乾燥，得到呈白色固體狀之2-第三丁基-4-(2,4,6-三甲基苯氧基)嘧啶-5-甲酸(2.2 g，77%)。ESI-MS *m/z* 315 $(M+1)^+$；$^1$H NMR (250 MHz, DMSO) δ 9.01 (s, 1H), 6.95 (s, 2H), 2.27 (s, 3H), 1.98 (s, 6H), 1.11 (s, 9H)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-2-第三丁基-4-(2,4,6-三甲基苯氧基)嘧啶-5-甲醯胺(化合物68)。

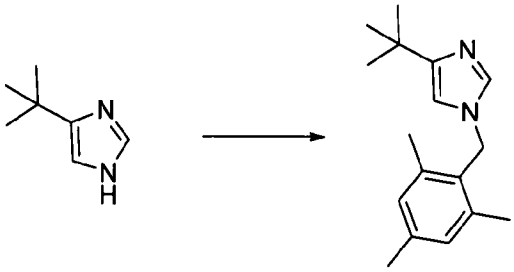
**製備31：4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-咪唑-2-甲酸**

**步驟1：4-第三丁基-1*H*-咪唑**



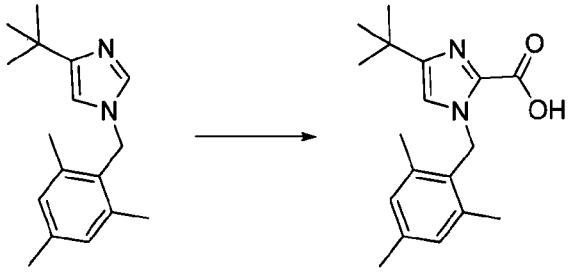

將1-溴-3,3-二甲基丁-2-酮(2.00 g，11.2 mmol)於甲醯胺(10 mL)中之混合物在裝備有安全壓力釋放機構之密封管中在160-180℃之間加熱5小時。混合物冷卻至室溫且傾倒至10%碳酸氫鈉水溶液(30 mL)中。溶液用二氯甲烷(2×30 mL)萃取。合併之有機層用10%碳酸鉀、鹽水洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮，得到呈油狀之4-第三丁基-1*H*-咪唑 (1.37 g，99%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H), 6.76 (s, 1H), 7.56 (s, 1H), 9.63 (br.s., 1H)。

**步驟2：4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-咪唑**



向含4-第三丁基-1*H*-咪唑(1.37 g，11.0 mmol )及碳酸銫(7.20 g，22.0 mmol )之乙腈(24 mL)添加2-(溴甲基)-1,3,5-三甲基苯(1.58 g，9.38 mmol)。將所得懸浮液在室溫下攪拌隔夜。將庚烷(10 mL)添加至反應混合物中，接著經二氧化矽墊過濾且用乙酸乙酯:庚烷之1:1 混合物洗滌。濃縮溶離液，得到呈油狀之4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-咪唑(1.47 g，52%)。$^1$H NMR (300 MHz, DMSO) δ 1.15 (s, 9H), 2.26 (s, 6H), 2.29 (s, 3H), 5.02 (s, 2H), 6.43 (s, 1H), 6.90 (s, 2H), 7.23 (s, 1H)。

**步驟3：4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-咪唑-2-甲酸**



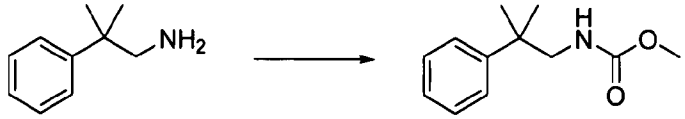

在-78℃下向4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-咪唑(1.40 g，5.46 mmol)於無水THF (40 mL)中之溶液中添加*n*-BuLi (2.5 M，2.62 mL，6.55 mmol)。將反應混合物在-78℃下攪拌1小時。在-78℃下一次性添加一片乾冰。將溶液在-78℃下攪拌20分鐘，且接著使反應混合物達至室溫且在$CO_2$氛圍下攪拌2小時。混合物用水(50 mL)及1N HCl (7 ml)淬滅且接著攪拌10分鐘。混合物用乙酸乙酯(100 mL)萃取。有機層與水相分離且接著在減壓下濃縮。殘餘物用$CH_2Cl_2$濕磨，濃縮，且接著再用甲基第三丁基醚濕磨。固體用甲基第三丁基醚洗滌且在減壓下乾燥，得到呈白色固體狀之4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-咪唑(588 mg，34%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 9H), 2.16 (s, 6H), 2.22 (s, 3H), 5.76 (s, 2H), 6.27 (s, 1H), 6.91 (s, 2H)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]咪唑-2-甲醯胺(化合物255)。

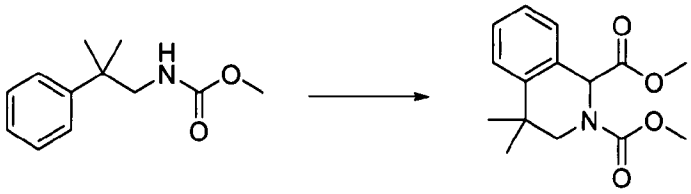
**製備32：4,4-二甲基-2-[(2,4,6-三甲基苯基)甲基]-1,3-二氫異喹啉-1-甲酸**

**步驟1：(2-甲基-2-苯基丙基)胺基甲酸甲酯**



在0℃下將氯甲酸甲酯(518 μL，6.70 mmol)添加至2-甲基-2-苯基-丙-1-胺(1.00 g，6.70 mmol)及吡啶(813 μL，10.1 mmol)於$CH_2Cl_2$ (25 mL)中之溶液中。將混合物在室溫下攪拌1小時，接著其用1N HCl淬滅。混合物用1N HCl (2×25 mL)、鹽水洗滌，經硫酸鈉乾燥，過濾且濃縮，得到(2-甲基-2-苯基丙基)胺基甲酸甲酯(911 mg，66%)。ESI-MS *m/z*計算值207.1，實驗值208.4 $(M+1)^+$；滯留時間: 0.54 min (1分鐘操作)。

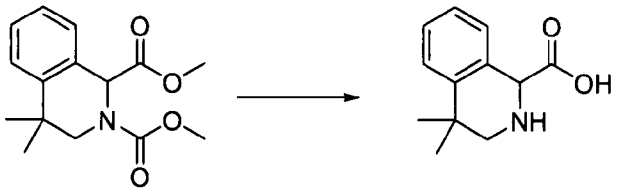
**步驟2：2-甲氧基羰基-4,4-二甲基-1,3-二氫異喹啉-1-甲酸**



(2-甲基-2-苯基丙基)胺基甲酸甲酯(911 mg，4.40 mmol)懸浮於乙酸(15 mL)及$H_2SO_4$ (5 mL)中。冷卻混合物至0℃，接著添加乙醛酸水合物(679 mg，7.37 mmol)。反應混合物經1小時升溫至室溫且在室溫下再攪拌2小時。反應混合物傾倒在冰上且混合物用乙酸乙酯(3×50 mL)萃取。合併之有機層用鹽水洗滌，經硫酸鈉乾燥，過濾且濃縮，得到呈白色固體狀之2-(甲氧基羰基)-4,4-二甲基-1,2,3,4-四氫異喹啉-1-甲酸(1.1 g，79%)。$^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.45 - 7.17 (m, 3H), 5.66 (d, *J* = 35.8 Hz, 1H), 3.90 (d, *J* = 94.9 Hz, 4H), 3.33

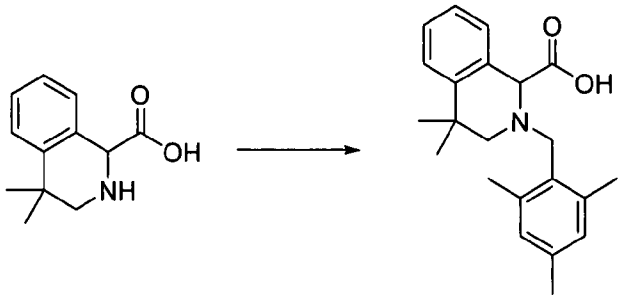
(s, 1H), 1.28 (d, $J$ = 51.5 Hz, 6H)。ESI-MS $m/z$計算值263.1, 實驗值264.0 $(M+1)^+$；滯留時間: 1.27 min (3分鐘操作)。

**步驟3：4,4-二甲基-2,3-二氫-1*H*-異喹啉-1-甲酸**



將碘(三甲基)矽烷(254 μL，1.78 mmol)添加至含2-甲氧基羰基-4,4-二甲基-1,3-二氫異喹啉-1-甲酸(412 mg，1.49 mmol)之氯仿(10 mL)中。混合物在65℃下加熱2小時。添加額外碘(三甲基)矽烷(254 μL，1.78 mmol)且將反應混合物在65℃下加熱2小時。反應混合物濃縮且殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到4,4-二甲基-2,3-二氫-1*H*-異喹啉-1-甲酸(261 mg，85%)。ESI-MS $m/z$計算值205.1, 實驗值206.4 $(M+1)^+$；滯留時間: 0.27 min (1分鐘操作)。

**步驟4：4,4-二甲基-2-[(2,4,6-三甲基苯基)甲基]-1,3-二氫異喹啉-1-甲酸**



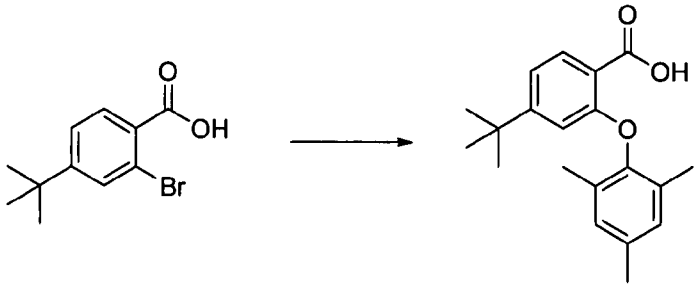
將4,4-二甲基-2,3-二氫-1*H*-異喹啉-1-甲酸(260 mg，1.27 mmol)及KOH (213 mg，3.80 mmol)於異丙醇(1.6 mL)中之懸浮液在室溫下攪拌20分鐘。添加2-(氯甲基)-1,3,5-三甲基苯(235 mg，1.39 mmol)且將反應混合物攪拌3小時。濃縮混合物且殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到4,4-二甲基-2-(2,4,6-三甲基苯甲基)-1,2,3,4-四氫異喹啉-1-甲酸。ESI-MS $m/z$計算值337.2, 實驗值338.0

$(M+1)^+$；滯留時間: 1.42 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-4,4-二甲基-2-[(2,4,6-三甲基苯基)甲基]-1,3-二氫異喹啉-1-甲醯胺(化合物140)。

**製備33：4-第三丁基-2-(2,4,6-三甲基苯氧基)苯甲酸**



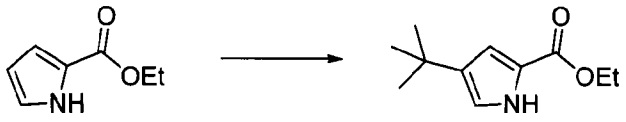

2-溴-4-第三丁基-苯甲酸(500 mg，1.95 mmol)、2,4,6-三甲基苯酚(397 mg，2.92 mmol)、$Cs_2CO_3$ (1.27 g，3.89 mmol)、$Cu(OTf)_2$ (49 mg，0.097 mmol)及甲苯(10 mL)之混合物組合於微波小瓶中，接著密封其且在125℃下加熱4小時。混合物冷卻至室溫且分溶於乙酸乙酯(50 mL)與水(50 mL)之間。分離各層且水層藉由添加1N HCl呈酸性。水層用乙酸乙酯(2×30 mL)萃取。合併之有機物經硫酸鎂乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-3%甲醇/$CH_2Cl_2$)，得到呈白色固體狀之4-第三丁基-2-(2,4,6-三甲基苯氧基)苯甲酸(250 mg，39%)。ESI-MS *m/z*計算值312.2，實驗值313.4 $(M+1)^+$；滯留時間: 2.14 min (3分鐘操作)。$^1$H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 7.73 (d, $J$ = 8.2 Hz, 1H), 7.07 (dd, $J$ = 8.2, 1.8 Hz, 1H), 6.99 (s, 2H), 6.35 (d, $J$ = 1.7 Hz, 1H), 2.28 (s, 3H), 2.01 (s, 6H), 1.10 (s, 9H)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-4-第三丁基-2-(2,4,6-三甲基苯氧基)苯甲醯胺(化合物224)及*N*-[(6-胺基-2-吡啶基)磺醯基]-4-第三丁基-2-(2,4,6-三甲基苯氧基)苯甲醯胺(化合物102)。

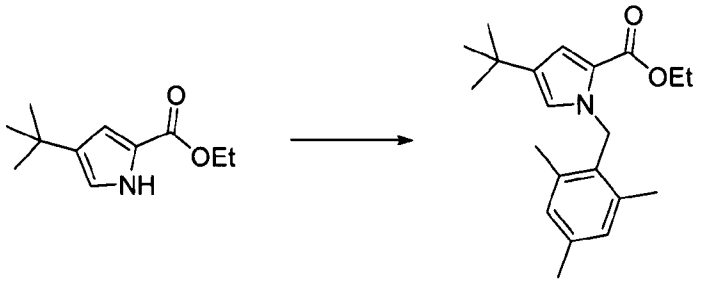
**製備34：4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡咯-2-甲酸**

**步驟1：5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸乙酯**



在室溫下向三氯化鎵(4.00 g，22.7 mmol)於二硫化碳(30 mL)中之溶液中添加吡咯-2-甲酸乙酯(2.87 g，20.6 mmol)及2-氯-2-甲基丙烷(2.50 mL，23.0 mmol)。接著混合物在回流下加熱45分鐘。反應混合物冷卻至室溫且傾倒至冰與1N HCl之混合物中。水層用二氯甲烷萃取。有機層用飽和$NaHCO_3$洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(0-10%乙酸乙酯/庚烷)來純化，得到4-第三丁基-1*H*-吡咯-2-甲酸酯(260 mg，7%)、5-第三丁基-1*H*-吡咯-2-甲酸乙酯(2.1 g，52%)及3,5-二-第三丁基-1*H*-吡咯-2-甲酸乙酯(352 mg，7%)，各呈白色固體狀分離。4-第三丁基-1*H*-吡咯-2-甲酸乙酯：$^1H$ NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H), 4.30 (q, *J* = 7.1 Hz, 2H), 6.76 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.85 (dd, *J* = 2.3, 1.9 Hz, 1H), 8.83 (br. s, 1H)。

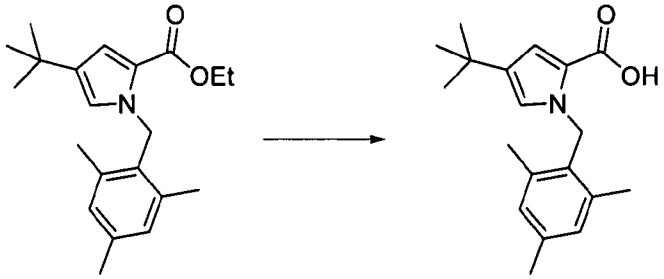
**步驟2：4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡咯-2-甲酸乙酯**



在0℃下將氫化鈉(24 mg呈60%於礦物油中之分散液，0.60 mmol)添加至4-第三丁基-1*H*-吡咯-2-甲酸乙酯(0.10g, 0.51 mmol)於*N,N*-二甲基甲醯胺(3 mL)中之溶液中。將混合物在0℃下攪拌5分鐘，接著將其在室溫下攪拌30分鐘。逐份添加2,4,6-三甲基苯甲基溴(0.12 g，0.55 mmol)且將混合物在室溫下攪拌20小時。在0℃下反應混合物用飽和$NH_4Cl$水溶液(4 mL)淬滅。混合物用乙酸乙酯(80 mL)萃取且有機層用

鹽水(2×30 mL)及水(30 mL)洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析(0-15%乙酸乙酯/庚烷)來純化，得到呈白色固體狀之4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡咯-2-甲酸酯(161 mg，98%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H), 2.20 (s, 6H), 2.31 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 5.47 (s, 2H), 6.11 (d, *J* = 2.1 Hz, 1H), 6.91 (s, 2H), 6.92 (d, *J* = 2.1, 1H)。

**步驟3：4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡咯-2-甲酸**




在室溫下向4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡咯-2-甲酸乙酯(97 mg，0.29 mmol)於甲醇(6.3 mL)中之溶液中添加1.0 N NaOH溶液(5.5 mL)且混合物在回流下加熱4小時。混合物在室溫下冷卻且用水(40 mL)稀釋。pH值使用1.0 N HCl調至4-5且水層用乙酸乙酯(120 mL)萃取。有機層用水(2×40 mL)洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮。固體用二乙醚濕磨，得到呈白色固體狀之4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡咯-2-甲酸(74 mg，84%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 9H), 2.21 (s, 6H), 2.32 (s, 3H), 5.47 (s, 2H), 6.18 (d, *J* = 2.0 Hz, 1H), 6.91 (s, 2H), 7.06 (d, *J* = 2.0 Hz, 1H)。

以下化合物可使用本文所述之程序合成：

*N*-(苯磺醯基)-4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]吡咯-2-甲醯胺(化合物242)及*N*-(3-胺基苯基)磺醯基-4-第三丁基-1-[(2,4,6-三甲基苯基)甲基]吡咯-2-甲醯胺(化合物195)。

**製備35：2-(第三丁基)-5-(2,4,6-三甲基苯甲基)噁唑-4-甲酸**

**步驟1：2-羥基-2-特戊醯胺基乙酸乙酯**



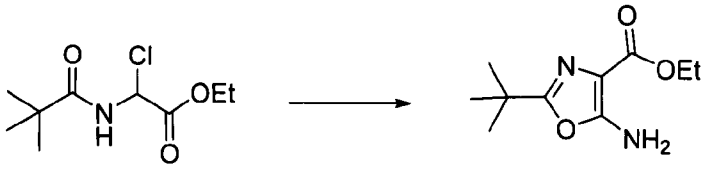
將乙酸(2.61 g，44.5 mmol)添加至三甲基乙醯胺(9.00 g，89.1 mmol)及乙醛酸乙酯(50%於甲苯中，27.6 g，133 mmol)於THF (60 mL)中之懸浮液中。混合物在回流下加熱16小時，接著其冷卻且濃縮至乾。殘餘物用庚烷及二乙基醚(10:1比率，110 mL)處理，得到沈澱，其藉由過濾移除。濃縮濾液，得到呈無色油狀之2-羥基-2-特戊醯胺基乙酸乙酯(16.8 g)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.27 - 1.35 (m, 3H), 3.63 - 3.75 (m, 1H), 4.20 - 4.36 (m, 2H), 5.50 - 5.60 (m, 1H), 6.65 (br s, 1H)。LC-MS分析: $(M+1)^+$ = 204.1。

**步驟2：2-氯-2-特戊醯胺基乙酸乙酯**



在0℃下將硫醯氯(28.6 g，242 mmol)添加至2-羥基-2-特戊醯胺基乙酸乙酯(18.6 g，80.8 mmol)及*N,N*-二甲基甲醯胺(1 mL)於$CH_2Cl_2$ (100 mL)中之溶液中。將混合物在室溫下攪拌16小時，接著其濃縮至乾，得到呈黃色油狀之2-氯-2-特戊醯胺基乙酸乙酯(20 g，64%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.29 - 1.37 (m, 3H), 4.20 - 4.36 (m, 2H), 6.25 (d, *J* = 9.8, 1H), 6.85 (br s, 1H)。

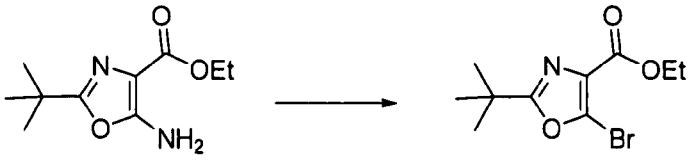
**步驟3：5-胺基-2-(第三丁基)噁唑-4-甲酸乙酯**



在0℃下將氰化二乙基鋁(1N於甲苯中，76.6 mL，76.7 mmol)添加至2-氯-2-(2,2-二甲基丙醯胺基)乙酸乙酯(11.3 g，2.71 mmol)於THF (110 mL)中之溶液中。將混合物在室溫下攪拌16小時，接著將飽和$NH_4Cl$水溶液(4 mL)添加至反應混合物中。混合物經矽藻土過濾且濾

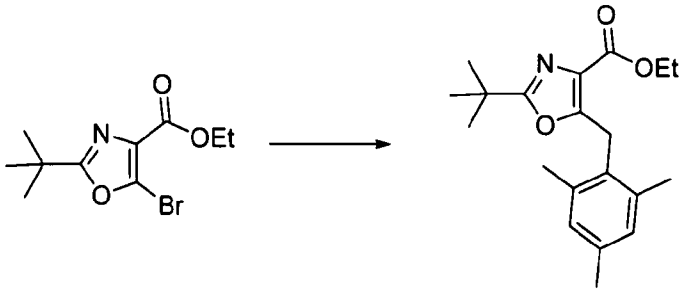
液用乙酸乙酯(200 mL)萃取。有機層用鹽水洗滌，經$Na_2SO_4$乾燥，過濾且濃縮。殘餘物藉由矽膠管柱層析(50%乙酸乙酯/庚烷)來純化，得到呈黃色固體狀之5-胺基-2-第三丁基-1,3-噁唑-4-甲酸乙酯(3.21 g，30%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.33 - 1.38 (m, 3H), 4.28 - 4.38 (m, 2H), 5.42 (br s, 2H)。LC-MS分析: $[M+H]^+$ = 213.1。

**步驟4：5-溴-2-(第三丁基)噁唑-4-甲酸乙酯**



將5-胺基-2-第三丁基-1,3-噁唑-4-甲酸乙酯(1.50 g，7.06 mmol)及$CuBr_2$ (1.59 g，7.12 mmol)於乙腈(25 mL)中之混合物在室溫下攪拌1小時，接著添加亞硝酸第三丁酯(0.94 g，9.2 mmol)。將混合物在室溫下攪拌1小時，且接著在65℃下加熱2.5小時。將鹽水添加至反應混合物中且其用二乙基醚(200 mL)萃取。有機層用加有幾滴1N HCl之鹽水洗滌，經$Na_2SO_4$乾燥，過濾且濃縮。殘餘物藉由矽膠管柱層析(15%乙酸乙酯/己烷)來純化，得到呈黃色油狀之5-溴-2-第三丁基-1,3-噁唑-4-甲酸乙酯(1.31 g，56%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.19 - 1.23 (m, 3H), 1.25 (s, 9H), 4.38 (q, $J$ = 6.8 Hz, 2H)。LC-MS分析: $(M+1)^+$ = 276.0。

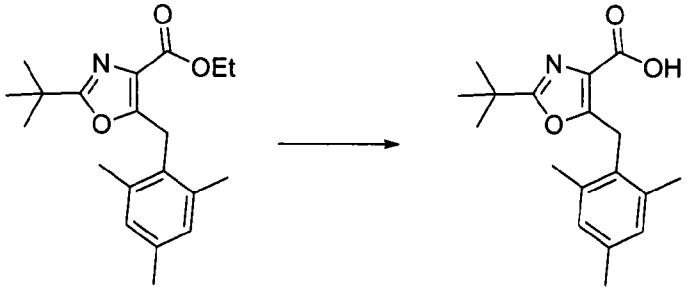
**步驟5：2-(第三丁基)-5-(2,4,6-三甲基苯甲基)噁唑-4-甲酸乙酯**



將5-溴-2-第三丁基-1,3-噁唑-4-甲酸乙酯(1.15 g，4.18 mmol)、$Pd(OAc)_2$ (0.09 g，0.4 mmol)及$^t$BuP-$HBF_4$ (0.24 g，0.83 mmol)於THF

(10 mL)中之混合物抽空且回填$N_2$三次。冷卻混合物至0℃且緩慢添加溴化(2,4,6-三甲基苯甲基)鋅(II) (1M於THF中，8.36 mL，8.36 mmol)。使混合物升溫至室溫且將其攪拌16小時。濃縮混合物且殘餘物進行矽膠管柱層析(15%乙酸乙酯/庚烷)，得到呈黃色油狀之2-第三丁基-5-[(2,4,6-三甲基苯基)甲基]-1,3-噁唑-4-甲酸乙酯(0.48 g，31%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.41 (t, $J$ = 6.9 Hz, 3H), 2.25 (s, 3H), 2.31 (s, 6H), 4.35 (s, 2H), 4.42 (q, $J$ = 7.2 Hz, 2H), 6.85 (s, 2H)。LC-MS分析: $(M+1)^+$ = 300.2。

**步驟6：2-(第三丁基)-5-(2,4,6-三甲基苯甲基)噁唑-4-甲酸**




將2-第三丁基-5-[(2,4,6-三甲基苯基)甲基]-1,3-噁唑-4-甲酸乙酯(0.48 g，1.5 mmol)及$LiOH.H_2O$ (0.30 g，7.3 mmol)於THF (4 mL)及水(4 mL)中之混合物在室溫下攪拌16小時。混合物用乙酸乙酯(150 mL)稀釋，pH值使用5%檸檬酸調至約4。有機層用鹽水洗滌，經$Na_2SO_4$乾燥，過濾且濃縮。殘餘物用二乙醚及己烷(8:1，9 mL)濕磨，得到呈白色固體狀之2-第三丁基-5-[(2,4,6-三甲基苯基)甲基]-1,3-噁唑-4-甲酸(0.33 g，75%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.25 (s, 3H), 2.33 (s, 6H), 4.37 (s, 2H), 6.85 (s, 2H)。LC-MS分析: $(M+1)^+$ = 302.2。

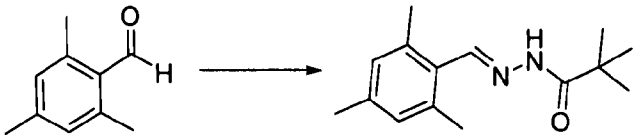
以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-2-第三丁基-5-[(2,4,6-三甲基苯基)甲基]噁唑-4-甲醯胺(化合物360)。

**製備36：3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-1,2,4-三唑-5-甲**

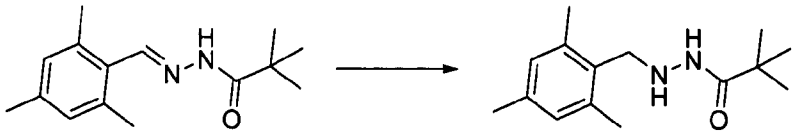
酸鋰

**步驟1：2,2-二甲基-*N*'-[(1*E*)-2,4,6-三甲基苯基)亞甲基]-丙醯肼**



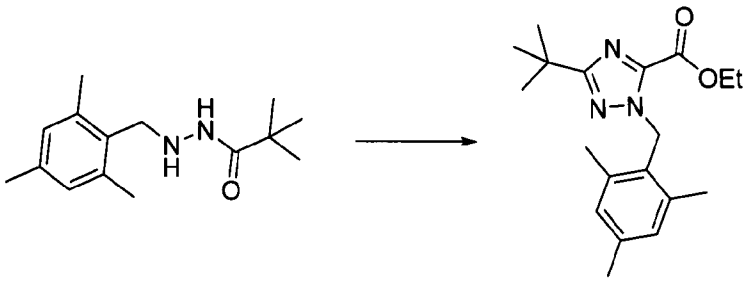
在室溫下向2,4,6-三甲基苯甲醛(2.96 g，20.0 mmol)於1,2-二氯乙烷(16 mL)中之溶液中添加2,2-二甲基丙酸醯肼(2.32 g，20.0 mmol)且將混合物在室溫下攪拌2小時，在此期間形成白色沈澱。添加二乙基醚(30 mL)以促進沈澱且繼續攪拌1小時。經燒結漏斗過濾，接著用二乙基醚(30 mL)洗滌固體且在高真空下乾燥，得到呈白色固體狀之2,2-二甲基-*N*'-[(1*E*)-2,4,6-三甲基苯基)亞甲基]丙醯肼(4.33 g，88%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.28 (s, 3H), 2.45 (s, 6H), 6.87 (s, 2H), 8.52 (br. s, 1H), 8.61 (br. s, 1H)。$(M+1)^+$ = 247.2。

**步驟2：2,2-二甲基-*N*'-[(2,4,6-三甲基苯基)甲基]-丙醯肼**



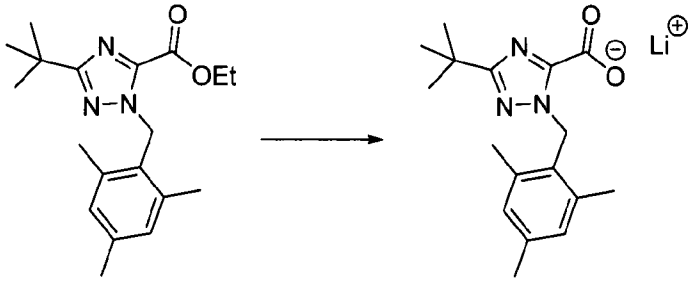
向2,2-二甲基-*N*'-[(1*E*)-2,4,6-三甲基苯基)亞甲基]-丙醯肼(4.33 g，17.6 mmol)於甲醇(90 mL)中之溶液中添加10%鈀/碳(乾基，230 mg，0.21 mmol)。反應混合物用氫氣(3個真空/氫氣循環)淨化，接著在氫氣氛圍下在室溫下攪拌2小時。反應混合物經矽藻土過濾，用甲醇洗滌且在減壓下濃縮。殘餘物藉由矽膠管柱層析(0-35%乙酸乙酯/庚烷)來純化，得到呈白色固體狀之2,2-二甲基-*N*'-[(2,4,6-三甲基苯基)甲基]丙醯肼(3.76 g，86%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 2.26 (s, 3H), 2.43 (s, 6H), 3.97 (s, 2H), 4.59 (br. s, 1H), 6.86 (s, 2H), 7.14 (br. s, 1H)。$(M+1)^+$ = 249.2。

**步驟3：3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-1,2,4-三唑-5-甲酸乙酯**



將四氟硼酸三乙基氧鎓(3.42 g，18.0 mmol)添加逐份至硫基草胺酸乙酯(2.28 g，17.1 mmol)於$CH_2Cl_2$ (35 mL)中之溶液中。將所得混合物在室溫下攪拌20小時。接著混合物冷卻至0℃，且緩慢添加2,2-二甲基-*N'*-[(2,4,6-三甲基苯基)甲基]丙醯肼(4.48 g，18.0 mmol)及三乙胺(2.5 mL，18 mmol)於$CH_2Cl_2$ (20 mL)中之溶液，接著添加額外部分之三乙胺(1.3 mL，9.0 mmol)。接著反應混合物在回流下加熱20小時。粗混合物在減壓下濃縮且所得黃色油狀物藉由矽膠管柱層析(0-40%乙酸乙酯/庚烷)來純化，得到固體。用含有0.1%甲酸之水中40%至95% $CH_3CN$的混合物進行逆相層析分離，得到呈白色固體狀之3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-1,2,4-三唑-5-甲酸乙酯(620 mg，11%)。$^1$H NMR (300 MHz, $CDCl_3$) δ1.29 (s, 9H), 1.43 (t, *J* = 7.1 Hz, 3H), 2.27 (s, 3H), 2.31 (s, 6H), 4.49 (q, *J* = 7.1 Hz, 2H), 5.71 (s, 2H), 6.86 (s, 2H)。$(M+1)^+$= 330.2。

**步驟4：3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-1,2,4-三唑-5-甲酸鋰**



向含有3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-1,2,4-三唑-5-甲酸乙酯(110 mg，0.33 mmol)及LiOH單水合物(17 mg，0.40 mmol)之燒瓶連續添加THF (2 mL)及水(1 mL)，接著一滴甲醇。將混合物在室

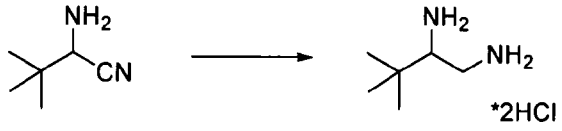
溫下攪拌1小時。在減壓下移除揮發物(大部分THF及甲醇)，接著混合物在乾冰/丙酮浴中冷凍且凍乾，得到呈白色固體狀之3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-1,2,4-三唑-5-甲酸鋰(98 mg，95%)。$^1$H NMR (300 MHz, $CD_3OD$) δ 1.24 (s, 9H), 2.24 (s, 3H), 2.33 (s, 6H), 5.73 (s, 2H), 6.82 (s, 2H)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]-1,2,4-三唑-3-甲醯胺(化合物261)。

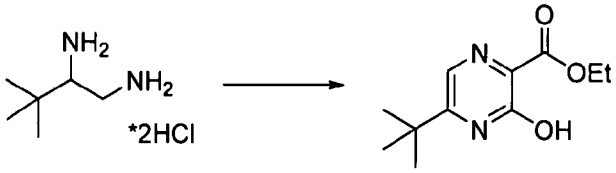
**製備37：5-(第三丁基)-3-(均三甲苯基氧基)吡嗪-2-甲酸**

**步驟1：3,3-二甲基丁-1,2-二胺二鹽酸鹽**




將2-胺基-3,3-二甲基-丁腈鹽酸鹽(2.94 g，20.0 mmol)、HCl (於EtOH中飽和，10 mL)、$PtO_2$ (600 mg)及甲醇(200 mL)之混合物在室溫下用氫氣(50 psi)處理18小時。反應混合物經矽藻土墊過濾且蒸發濾液，得到呈白色固體狀之3,3-二甲基丁-1,2-二胺二鹽酸鹽(3.9 g，79%)。

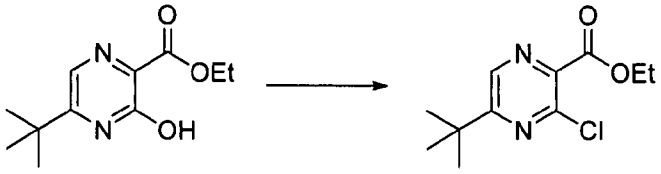
**步驟2：5-(第三丁基)-3-羥基吡嗪-2-甲酸乙酯**




將3,3-二甲基-丁-1,2-二胺二鹽酸鹽(3.9 g，21 mmol)、2-側氧基-丙二酸二乙酯(3.45 mL，22.7 mmol)、$Et_3N$ (5.8 mL，41 mmol)及EtOH (400 mL)之混合物在回流下加熱20小時。移除所有揮發物且殘餘物進行矽膠管柱層析(0-30%乙酸乙酯/己烷) (0/100至30/70)，得到呈黏性油狀之5-(第三丁基)-3-羥基吡嗪-2-甲酸乙酯(0.59 g，13%)，其

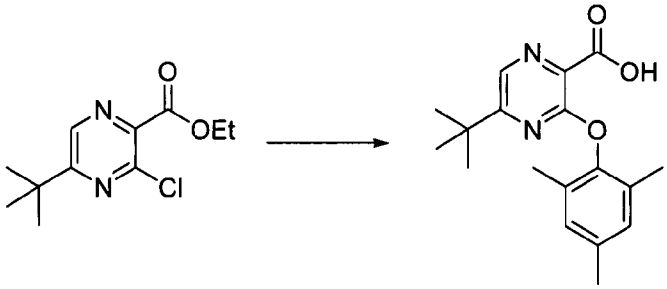
在靜置後凝固。$^1$H NMR (250 MHz, $CDCl_3$) δ 8.36 (s, 1H), 4.55 (q, $J$ = 7.2 Hz, 2H), 1.49 (t, $J$ = 7.2 Hz, 3H), 1.41 (s, 9H)。

**步驟3：5-(第三丁基)-3-氯吡嗪-2-甲酸乙酯**



將5-(第三丁基)-3-羥基吡嗪-2-甲酸乙酯(590. mg，2.63 mmol)及$POCl_3$ (10 mL)之混合物在回流下加熱5小時。在減壓下移除過量$POCl_3$且殘餘物分溶於乙酸乙酯與$NaHCO_3$水溶液(藉由添加碳酸鈉，pH值調至約6)之間。分離有機相，經$Na_2SO_4$乾燥，過濾且濃縮。粗物質藉由矽膠管柱層析(0-30%乙酸乙酯/已烷)來純化，得到5-(第三丁基)-3-氯吡嗪-2-甲酸乙酯(90 mg，14%)。$^1$H NMR (250 MHz, $CDCl_3$) δ 8.59 (s, 1H), 4.49 (q, $J$ = 7.2 Hz, 2H), 1.44 (t, $J$ = 7.2 Hz, 3H), 1.40 (s, 9H)。

**步驟4：5-第三丁基-3-(2,4,6-三甲基苯氧基)吡嗪-2-甲酸**



將2,4,6-三甲基苯酚(51 mg，0.38 mmol)及氫化鈉(18 mg，0.45 mmol)組合於無水*N*,*N*-二甲基甲醯胺(3 mL)中。將反應混合物在氮氣氛圍下在室溫下攪拌15分鐘。接著添加含5-第三丁基-3-氯-吡嗪-2-甲酸乙酯(90. mg，0.37 mmol)之四氫呋喃(1 mL)且將反應混合物在60℃下加熱1小時。向此混合物添加水(1 mL)及NaOH (120 mg)。將所得混合物在70℃下攪拌1小時且冷卻至室溫。混合物用HCl (1 M)處理至pH 3且混合物用乙酸乙酯(3次)萃取。合併之萃取物濃縮至約1 mL (存在

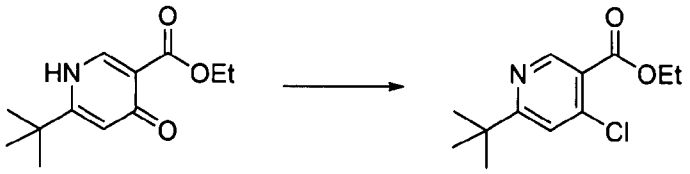
*N,N*-二甲基甲醯胺)。殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到5-第三丁基-3-(2,4,6-三甲基苯氧基)吡嗪-2-甲酸(55 mg，47%)。$^1$HNMR (250 MHz, DMSO) δ 8.41 (s, 1H), 6.94 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H), 1.11 (s, 9H)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-5-第三丁基-3-(2,4,6-三甲基苯氧基)吡嗪-2-甲醯胺(化合物141)。

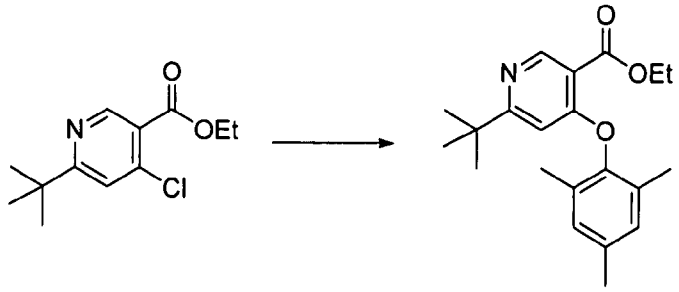
**製備38：5-(第三丁基)-3-(均三甲苯基氧基)吡嗪-2-甲酸**

**步驟1：6-(第三丁基)-4-氯菸鹼酸乙酯**




將6-第三丁基-1,4-二氫-4-側氧基吡啶-3-甲酸乙酯(1.0 g，4.5 mmol)及氧氯化磷(10 mL)之溶液在110℃下加熱1.5小時。反應溶液冷卻至室溫且在減壓下濃縮。殘餘物冷卻至0℃，接著小心添加水(20 mL)及足夠飽和$NaHCO_3$水溶液以使混合物至約pH 8。混合物用乙酸乙酯(3次)萃取。合併之有機物經$MgSO_4$乾燥，過濾，且在真空下濃縮，得到呈褐色油狀之6-(第三丁基)-4-氯菸鹼酸乙酯(0.80 g，73%)。$^1$H NMR ($CDCl_3$, 250 MHz) δ 8.99 (s, 1H), 7.40 (s, 1H), 4.41 (m, 2H), 1.36 (m, 12H)。LC-MS: $(M+1)^+$ = 242.2。

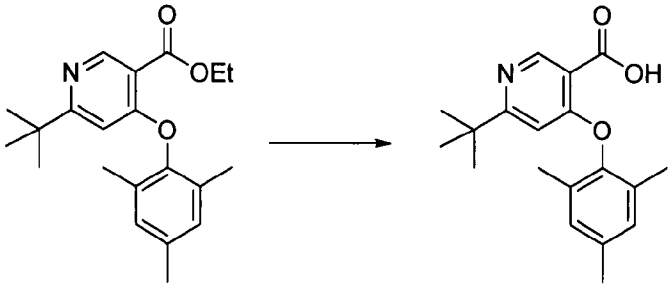
**步驟2：6-第三丁基-4-(2,4,6-三甲基苯氧基)吡啶-3-甲酸酯**




向2,4,6-三甲基苯酚(0.43 g，3.1 mmol)於*N,N*-二甲基甲醯胺(4

mL)及THF (1 mL)中之溶液中緩慢添加60% NaH (0.15 g，3.9 mmol)。將混合物在室溫下攪拌25分鐘，接著添加6-(第三丁基)-4-氯菸鹼酸乙酯(0.74 g，3.1 mmol)。將反應混合物在60℃下攪拌1小時，接著其冷卻至室溫且藉由添加水淬滅。混合物用乙酸乙酯(3次)萃取。合併之有機萃取物濃縮且殘餘物藉由矽膠管柱層析(0-20%乙酸乙酯/己烷)來純化，得到呈淡黃色油狀之6-第三丁基-4-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯(0.45 g，43%)。LC-MS: $(M+1)^+$ = 341.9。

**步驟3：6-第三丁基-4-(2,4,6-三甲基苯氧基)吡啶-3-甲酸**



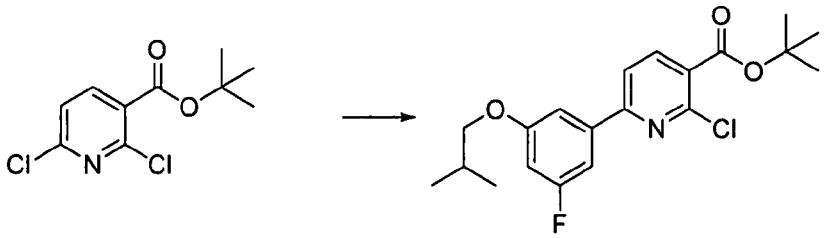
將6-(第三丁基)-4-(均三甲苯基氧基)菸鹼酸酯(0.74 g，2.2 mmol)及氫氧化鈉(0.21 g，5.2 mmol)於EtOH (2 mL)及水(1 mL)中之溶液在室溫下攪拌3小時。反應物濃縮且殘餘物用濃HCl酸化至約pH 3。粗物質藉由矽膠管柱層析(乙酸乙酯)來純化，得到呈白色固體狀之6-第三丁基-4-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(0.38 g，55%)。$^1$H NMR ($CDCl_3$, 250 MHz) δ 9.22 (s, 1H), 6.96 (s, 2H), 6.24 (s, 1H), 2.34 (s, 3H), 2.09 (s, 6H), 1.22 (s, 9H)。LC-MS: $(M+1)^+$ = 314.1。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基苯基)磺醯基-6-第三丁基-4-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物338)。

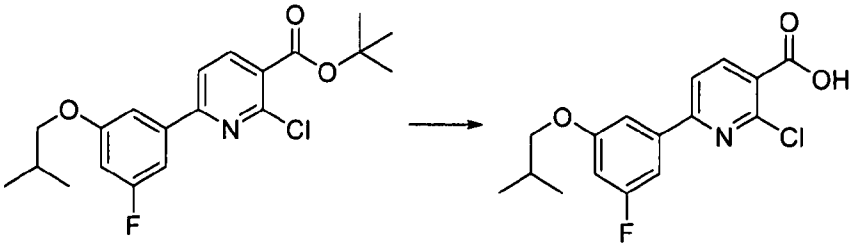
**製備39：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物368)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*R*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1289)**

**步驟1：2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸第三丁酯**



將2,6-二氯吡啶-3-甲酸第三丁酯(15.0 g，60.5 mmol)及(3-氟-5-異丁氧基-苯基)硼酸(13.46 g，63.48 mmol)組合且完全溶解於乙醇(150 mL)及甲苯(150 mL)中。添加碳酸鈉(19.23 g，181.4 mmol)於水(30 mL)中之懸浮液。在氮氣下添加肆(三苯基膦)鈀(0) (2.096 g，1.814 mmol)。將反應混合物在60℃下攪拌16小時。在減壓下移除揮發物。剩餘固體分溶於水(100 mL)與乙酸乙酯(100 mL)之間。有機層用鹽水(1× 100 mL)洗滌，經硫酸鈉乾燥，過濾且在減壓下濃縮。該物質在330公克矽膠管柱上，以己烷中0至20%乙酸乙酯梯度進行矽膠管柱層析。該物質在220公克矽膠管柱上，等度100%己烷10分鐘，接著己烷中0至5%乙酸乙酯梯度再純化，得到呈無色油狀之2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸第三丁酯(18.87 g，49.68 mmol，82.2%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.24 (d, $J$ = 8.0 Hz, 1H), 8.16 (d, $J$ = 8.1 Hz, 1H), 7.48 (dd, $J$ = 9.4, 2.0 Hz, 2H), 6.99 (dt, $J$ = 10.8, 2.2 Hz, 1H), 3.86 (d, $J$ = 6.5 Hz, 2H), 2.05 (dt, $J$ = 13.3, 6.6 Hz, 1H), 1.57 (d, $J$ = 9.3 Hz, 9H), 1.00 (t, $J$ = 5.5 Hz, 6H)。ESI-MS $m/z$計算值379.13504，實驗值380.2 $(M+1)^+$；滯留時間: 2.57分鐘。

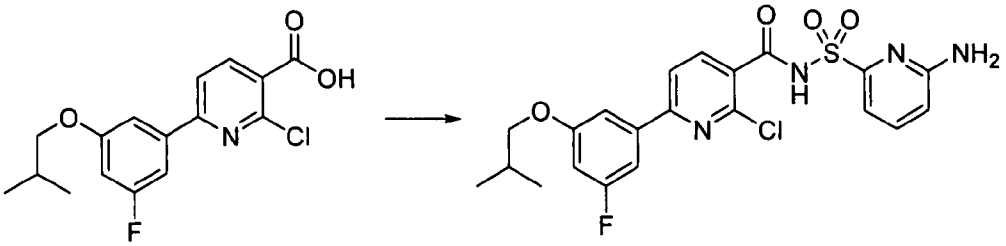
**步驟2：2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸**



2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸第三丁酯(18.57 g，

48.89 mmol)溶於二氯甲烷(200 mL)中。添加三氟乙酸(60 mL，780 mmol)且將反應混合物在室溫下攪拌1小時。將反應混合物在40℃下攪拌2小時。反應混合物在減壓下濃縮且溶於乙酸乙酯(100 mL)中。其用飽和碳酸氫鈉水溶液(1× 100 mL)及鹽水(1× 100 mL)洗滌，經硫酸鈉乾燥，過濾且在減壓下濃縮。粗產物懸浮於乙酸乙酯(75 mL)中且用HCl水溶液(1 N，1× 75 mL)洗滌。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮。在40℃下剩餘固體(17.7 g)在二氯甲烷(35 mL)中攪拌30分鐘呈漿狀物。冷卻至室溫後，過濾剩餘漿料，且接著用冷二氯甲烷沖洗，得到呈白色固體狀之2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(11.35 g，35.06 mmol，72%)。$^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.76 (s, 1H), 8.31 (d, $J$ = 8.0 Hz, 1H), 8.17 (d, $J$ = 8.1 Hz, 1H), 7.54 - 7.47 (m, 2H), 7.00 (dt, $J$ = 10.8, 2.3 Hz, 1H), 3.87 (d, $J$ = 6.5 Hz, 2H), 2.05 (dt, $J$ = 13.3, 6.6 Hz, 1H), 1.01 (d, $J$ = 6.7 Hz, 6H)。ESI-MS $m/z$計算值323.1，實驗值324.1 $(M+1)^+$；滯留時間: 1.96分鐘。

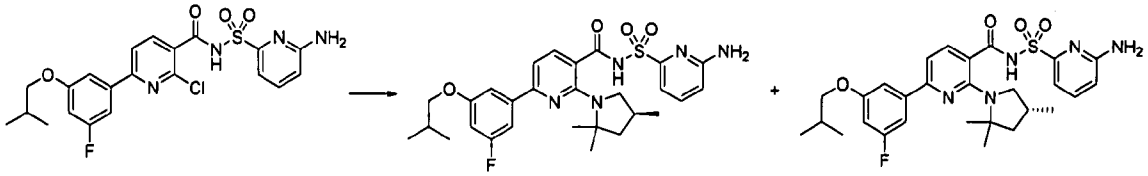
**步驟3：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺**



2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(3.00 g，9.27 mmol)溶於*N,N*-二甲基甲醯胺(30.00 mL)中，且將1,1'-羰基二咪唑(2.254 g，13.90 mmol)添加至溶液中。將溶液在65℃下攪拌1小時。在另一燒瓶中，將氫化鈉(444.8 mg，11.12 mmol)添加至6-胺基吡啶-2-磺醯胺(1.926 g，11.12 mmol)於*N,N*-二甲基甲醯胺(15.00 mL)中之溶液中。將此混合物攪拌一小時，接著添加至先前反應混合物。將最終反應混

合物在65℃下攪拌15分鐘。在減壓下移除揮發物。剩餘油狀物溶於乙酸乙酯中且用HCl水溶液(1 N，1× 75 mL)及鹽水(3× 75 mL)洗滌。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮。剩餘白色固體(4.7 g)完全溶於85℃水浴中異丙醇(120 mL)中。在緩慢攪拌下使無色溶液經16小時緩慢冷卻至室溫。已形成之結晶固體藉由真空過濾收集，且接著用冷異丙醇(50 mL)沖洗。乾燥後，獲得呈白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(3.24 g，6.765 mmol，73%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.78 (s, 1H), 8.15 (d, $J$ = 8.0 Hz, 1H), 8.09 (d, $J$ = 7.9 Hz, 1H), 7.73 - 7.63 (m, 1H), 7.49 (dd, $J$ = 8.6, 1.9 Hz, 2H), 7.21 (d, $J$ = 7.3 Hz, 1H), 6.99 (dt, $J$ = 10.7, 2.2 Hz, 1H), 6.74 (d, $J$ = 8.4 Hz, 1H), 6.64 (s, 2H), 3.86 (d, $J$ = 6.5 Hz, 2H), 2.05 (dp, $J$ = 13.3, 6.5 Hz, 1H), 1.02 (dd, $J$ = 12.7, 6.4 Hz, 6H)。

**步驟4：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*R*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1289)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺**



*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(309 mg，0.645 mmol)溶於二甲亞碸(3.708 mL)中且緩慢添加碳酸鉀(445.9 mg，3.226 mmol)，接著添加2,2,4-三甲基吡咯啶(146.0 mg，1.290 mmol)。將反應混合物密封且在150℃下加熱72小時。反應冷卻，用水(50 mL)稀釋，用50 mL部分之乙酸乙酯萃取3次，用鹽水洗滌，經硫酸鈉乾燥，過濾且蒸發至乾。粗物質溶於2

mL二氯甲烷中且藉由在矽膠上使用0至80%乙酸乙酯之己烷溶液之梯度純化。使用超臨界流體層析，在ChiralPak AD-H (250×4.6 mm) 5 μm管柱上使用$CO_2$中含1.0%二乙胺之25%異丙醇，以3.0 mL/min之流速，分離立體異構體。分開濃縮分離之對映異構體，用乙酸乙酯(3 mL)稀釋且用1N鹽酸水溶液洗滌。有機層經硫酸鈉乾燥，過濾，且蒸發至乾，得到呈淺黃色固體狀之純化合物。

第一化合物，自以上給出之SFC條件溶離得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*R*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1289) (鹽酸(1)) $^1$H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.69 - 7.57 (m, 1H), 7.56 - 7.46 (m, 1H), 7.41 (dt, *J* = 10.1, 1.8 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 6.89 (dt, *J* = 10.7, 2.3 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 3.83 (d, *J* = 6.7 Hz, 2H), 2.61 (dq, *J* = 9.7, 4.9 Hz, 2H), 2.24 (d, *J* = 15.8 Hz, 1H), 2.06 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.93 - 1.82 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H), 1.48 - 1.33 (m, 1H), 1.32 - 1.20 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 6H), 0.88 (d, *J* = 6.2 Hz, 3H)。ESI-MS *m/z*計算值555.2, 實驗值556.4 $(M+1)^+$；滯留時間: 2.76分鐘。

第二化合物，自以上描述之SFC條件溶離得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(鹽酸(1)) $^1$H NMR (400 MHz, 氯仿-d) δ 15.49 (s, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 7.75 - 7.56 (m, 3H), 7.34 (t, *J* = 1.8 Hz, 1H), 7.30 (dt, *J* = 9.4, 1.9 Hz, 1H), 6.75 - 6.66 (m, 2H), 3.95 (s, 1H), 3.78 (d, *J* = 6.5 Hz, 2H), 3.42 (s, 1H), 2.88 - 2.74 (m, 1H), 2.23 (dd, *J* = 12.5, 8.0 Hz, 1H), 2.17 - 2.08 (m, 1H), 1.98 - 1.87 (m, 1H), 1.55 (s, 3H), 1.39 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 6H)。ESI-MS *m/z*計算值555.2, 實驗值556.4 $(M+1)^+$；滯留時間: 2.77分鐘。絕對

立體化學藉由X射線結晶學證實。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物114)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物946)，

*N*-[(6-胺基-4-甲基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1472)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-苯基丁氧基)吡啶-3-甲醯胺(化合物1686)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-(1-萘基)乙基胺基]吡啶-3-甲醯胺(化合物1769)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2-(鄰甲苯基)氮雜環庚烷-1-基]吡啶-3-甲醯胺(化合物1772)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[3-(環丙基甲基)-2,2-二甲基-吡咯啶-1-基]吡啶-3-甲醯胺(化合物1794)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2275)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-[2-(三氟甲基)苯基]乙氧基]吡啶-3-甲醯胺(化合物2501)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2-(1,3-苯并噁唑-2-基)苯氧基]吡啶-3-甲醯胺(化合物2544)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2-環己基環己基)胺基]吡啶-3-甲醯胺(化合物2599)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯基-1-哌啶基)吡啶-3-甲醯胺(化合物2615)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-甲氧基-4-甲基-2-吡啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1482)，

6-(3-氟-5-異丁氧基-苯基)-*N*-四氫呋喃-3-基磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1640)，

*N*-環丙基磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1525)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-4-甲氧基-吡啶-3-甲醯胺(化合物1254)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物171)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3R)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物233)，

2-(2,5-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物321)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[(2,4-二甲基-3-吡啶基)氧基]吡啶-3-甲醯胺(化合物460)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物353)，

6-(3-氟-5-異丁氧基-苯基)-2-(1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物355)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(2R)-

2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1354)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3,3,4-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物435)，

6-(4-乙氧基苯基)-2-(4-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物445)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,3R)-2,3-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物441)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(4-吡啶基)丁氧基]吡啶-3-甲醯胺(化合物1687)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-4-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-3-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(3-吡啶基)丁氧基]吡啶-3-甲醯胺(化合物1690)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(2-吡啶基)丁氧基]吡啶-3-甲醯胺(化合物1688)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-吡唑-1-基丙氧基)吡啶-3-甲醯胺(化合物1692)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-苯基丁氧基)吡啶-3-甲醯胺(化合物1689)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(2-吡啶基)丙氧基]吡啶-3-甲醯胺(化合物1693)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(3-吡啶基)丙氧基]吡啶-3-甲醯胺(化合物1691)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-苯

基丙氧基)吡啶-3-甲醯胺(化合物1694)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,2,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物464)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,4S)-3-氮雜雙環[2.2.1]庚-3-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物476)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[3-(2-吡啶基)-1-哌啶基]吡啶-3-甲醯胺(化合物489)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(三氟甲基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1556)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2,4,4-四甲基吡咯啶-1-基)-6-(三氟甲基)吡啶-3-甲醯胺(化合物1635)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(三氟甲基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1550)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1420)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲氧基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1536)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1607)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]-6,7-二氫-5H-環戊并[b]吡啶-3-甲醯胺(化合物1386)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(丙基)胺基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物500)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-甲基-4-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物502)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-苯基

吡咯啶-1-基)吡啶-3-甲醯胺(化合物509)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3,3,5-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物520)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[2.2.1]庚-3-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物521)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-丙基-1-哌啶基)吡啶-3-甲醯胺(化合物522)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R,4S)-4-氟-2-甲基-吡咯啶-1-基]吡啶-3-甲醯胺(化合物1362)

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3S)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物557)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[3-(3,4-二氟苯基)-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物558)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(1-哌啶基)吡啶-3-甲醯胺(化合物567)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[2-(甲氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物574)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.5]辛-6-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物578)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-吲哚啉-1-基-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物588)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2,4,4-四甲基吡咯啶-1-基)-5-(三氟甲基)吡啶-3-甲醯胺(化合物1638)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2,4,4-四甲基吡咯啶-1-基)-4-(三氟甲基)吡啶-3-甲醯胺(化合物1658)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6,6-二甲基-3-氮雜雙環[3.1.0]己

-3-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物596)，

*N*-[(6-胺基-5-羥基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1563)，

*N*-[(6-胺基-5-羥基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1375)，

*N*-[(6-胺基-5-苯甲氧基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1588)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1593)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1444)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-第三丁基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物597)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基-3-苯基-吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物601)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[4-(甲氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物606)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-乙基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物619)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-甲基-3-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物625)，

*N*-[(6-胺基-5-苯甲氧基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1429)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基吡咯啶-1-基)-6-(6-異丙

氧基-3-吡啶基)吡啶-3-甲醯胺(化合物647)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[3-(2,2,2-三氟乙基)-1-哌啶基]吡啶-3-甲醯胺(化合物656)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基-2-甲基-吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物658)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-甲基-2,3,3a,4,5,6,7,7a-八氫吲哚-1-基)吡啶-3-甲醯胺(化合物675)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[3.1.1]庚-3-基)-6-第三丁基-吡啶-3-甲醯胺(化合物1401)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-甲氧基-2-吡啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1483)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(3-甲基二氮雜環丙烯-3-基)乙基-丙-2-炔基-胺基]吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5S)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物687)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物689)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-甲氧基苯基)磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1452)，

*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1396)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.5]辛-7-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物703)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-異丙基吡咯啶-1-基)吡啶-3-甲醯胺(化合物724)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-氧雜

-7-氮雜螺[3.5]壬-7-基)吡啶-3-甲醯胺(化合物729)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-苯基-1-哌啶基)吡啶-3-甲醯胺(化合物731)，

2-(3,3a,4,5,6,6a-六氫-2*H*-環戊并[b]吡咯-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物732)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[3.5]壬-7-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物733)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物736)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(甲基)胺基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物740)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(4-苯基-1-哌啶基)吡啶-3-甲醯胺(化合物742)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物745)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3R)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物757)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,3S)-2,3-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物764)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(1-苯基乙基胺基)吡啶-3-甲醯胺(化合物766)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-甲氧基苯基)磺醯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1171)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-側氧基-1*H*-吡啶-2-基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1308)，

*N*-(3-胺基苯基)磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基

吡咯啶-1-基)吡啶-3-甲醯胺(化合物1184)，

*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物620)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(2-吡啶基磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1063)，

*N*-(3-胺基苯基)磺醯基-2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1014)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(3-甲氧基苯基)磺醯基-吡啶-3-甲醯胺(化合物510)，

*N*-(苯磺醯基)-2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物583)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-甲氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2430)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-側氧基-1*H*-吡啶-2-基)磺醯基]吡啶-3-甲醯胺(化合物775)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(2-吡啶基磺醯基)吡啶-3-甲醯胺(化合物1069)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-甲氧基-2-吡啶基)磺醯基]吡啶-3-甲醯胺(化合物1090)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物811)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-螺[1H-異苯并呋喃-3,4'-哌啶]-1'-基-吡啶-3-甲醯胺(化合物818)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物834)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3S)-3-

甲基-1-哌啶基]吡啶-3-甲醯胺(化合物836)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[3-(環丙基甲氧基)-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物858)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物864)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[4-(環丙基甲氧基)-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物884)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二氟-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物889)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜雙環[2.2.1]庚-7-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物903)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-氟-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物913)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,2,4,4-四甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物915)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1S,4R)-3-氮雜雙環[2.2.1]庚-3-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物921)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,3,5-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物925)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丙基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物928)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(茚滿-1-基胺基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物935)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(氮雜環庚烷-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物940)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4R)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物949)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙炔基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物954)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙氧基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物960)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二乙基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物971)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物979)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.4]辛-8-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物987)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3R)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物992)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物994)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-苯甲氧基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1012)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1023)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環戊基(甲基)胺基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1025)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(苯甲基胺基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1026)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,2,5-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1040)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[4-(三

氟甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物1043)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-異吲哚啉-2-基-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1072)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(4-苯氧基-1-哌啶基)吡啶-3-甲醯胺(化合物1080)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3S)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1081)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1087)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-苯氧基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1092)，

2-(3,3a,4,5,6,6a-六氫-1*H*-環戊并[c]吡咯-2-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1107)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(3-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1112)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[3-(甲氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物1116)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-環丙基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1132)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1134)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3S,5S)-3,5-二甲基-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1136)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3R,5S)-3,5-二甲基-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1145)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-甲基

-1-哌啶基)吡啶-3-甲醯胺(化合物1182)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1198)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-第三丁基吡咯啶-1-基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1206)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3R)-3-苯基-1-哌啶基]吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-乙氧基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1214)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(2R)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1230)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1247)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(2S)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1248)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2-甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1271)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[3-(三氟甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物1274)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1283)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(3R)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1322)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-(2,3,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1327)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[3-(3-氯苯基)-1-哌啶基]-6-(6-異

丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1339)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基-3-甲基-1-哌啶基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1341)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.4]庚-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1333)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3R,5S)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物371)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-哌啶基)吡啶-3-甲醯胺(化合物380)，

2-(3,3a,4,5,6,6a-六氫-2*H*-環戊并[b]吡咯-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物383)，

(2S)-1-[3-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡啶基]吡咯啶-2-甲酸甲酯(化合物385)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物398)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物408)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(氮雜環庚烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物418)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(甲氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物419)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜雙環[2.2.1]庚-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物420)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物421)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(8-氧

雜-4-氮雜螺[4.4]壬-4-基)吡啶-3-甲醯胺(化合物424)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物425)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-苯基吡咯啶-1-基]吡啶-3-甲醯胺(化合物447)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二氫吡咯-1-基)-6-(3-氟·5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物453)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物458)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物473)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物479)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-4-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物488)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(三氟甲基)-3-氮雜雙環[3.1.0]己-3-基]吡啶-3-甲醯胺(化合物490)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2-(1,1-二甲基丙基)吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物493)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,5-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物496)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-環丙基乙基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物516)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[3.3]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物527)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基-3-甲基-1-哌啶基)-6-(3-

氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物530)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物547)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物555)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物560)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,4-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物575)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,5S)-3-氮雜雙環[3.2.1]辛-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物581)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物587)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡咯啶-1-基-吡啶-3-甲醯胺(化合物592)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物593)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6,6-二甲基-3-氮雜雙環[3.1.0]己-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物609)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-第三丁基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物611)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-第三丁基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物613)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-乙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物615)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-

3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物651)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-環丙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物655)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物657)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(2-吡啶基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物659)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物663)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物678)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[2.2.1]庚-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物680)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丁基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物683)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物684)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物694)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基-3-苯基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物711)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-(甲氧基甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物719)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物720)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-甲

基-1-哌啶基)吡啶-3-甲醯胺(化合物735)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物751)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物772)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2,2-二甲基-3-(三氟甲基)吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物780)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物837)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.4]辛-8-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物845)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物850)，

2-(3,3a,4,5,6,6a-六氫-1*H*-環戊并[c]吡咯-2-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物857)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物859)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(丙基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物881)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物887)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-氮雜雙環[3.1.0]己-4-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物906)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1S,4R)-3-氮雜雙環[2.2.1]庚-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物924)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(9-氮雜螺[4.4]壬-9-基)-6-(3-氟-

5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物926)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物931)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,5S)-8-氮雜雙環[3.2.1]辛-8-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物934)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.5]辛-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物953)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物969)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.5]辛-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物973)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物991)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1004)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[甲基-[(1-甲基環丙基)甲基]胺基]吡啶-3-甲醯胺(化合物1009)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1010)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,5-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1013)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1051)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.4]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1061)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-

2,3,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1065)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-4-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S)-2-第三丁基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1097)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物1098)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1117)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1121)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2,3,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1144)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-(甲氧基甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1149)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,3,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1156)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(異丙基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1157)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-亞甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1162)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(5R)-2,2,5-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1166)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R)-2-第三丁基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1170)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,4S)-3-氮雜雙環[2.2.1]庚-3-

基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1180)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-3-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物1193)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-(3-氯苯基)乙基-甲基-胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1205)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3S,5S)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1210)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1218)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基-5-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1222)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(5S)-2,2,5-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1241)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-異丙基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1258)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-苯基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1260)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.5]壬-8-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1264)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基嗎啉-4-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1267)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1279)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4R)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1289)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[3.5]壬-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1303)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1304)，

2-(2,3,4,4a,5,6,7,7a-八氫環戊并[b]吡啶-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1313)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-3-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物1319) *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.4]庚-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1333)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3R,5S)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物371)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-哌啶基)吡啶-3-甲醯胺(化合物380)，

2-(3,3a,4,5,6,6a-六氫-2*H*-環戊并[b]吡咯-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物383)，

(2S)-1-[3-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡啶基]吡咯啶-2-甲酸甲酯(化合物385)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物398)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物408)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(氮雜環庚烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物418)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(甲

氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物419)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜雙環[2.2.1]庚-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物420)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物421)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(8-氧雜-4-氮雜螺[4.4]壬-4-基)吡啶-3-甲醯胺(化合物424)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物425)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-苯基吡咯啶-1-基]吡啶-3-甲醯胺(化合物447)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二氫吡咯-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物453)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物458)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物473)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物479)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-4-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物488)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(三氟甲基)-3-氮雜雙環[3.1.0]己-3-基]吡啶-3-甲醯胺(化合物490)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2-(1,1-二甲基丙基)吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物493)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,5-

三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物496)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-環丙基乙基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物516)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[3.3]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物527)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基-3-甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物530)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物547)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物555)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物560)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,4-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物575)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,5S)-3-氮雜雙環[3.2.1]辛-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物581)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物587)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡咯啶-1-基-吡啶-3-甲醯胺(化合物592)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物593)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6,6-二甲基-3-氮雜雙環[3.1.0]己-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物609)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-第三丁基吡咯啶-1-基)-6-(3-氟

-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物611)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-第三丁基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物613)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-乙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物615)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物651)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-環丙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物655)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物657)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(2-吡啶基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物659)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物663)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物678)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[2.2.1]庚-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物680)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丁基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物683)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物684)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物694)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基-3-苯基-吡咯啶-1-

基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物711)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-(甲氧基甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物719)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物720)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物735)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物751)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物772)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2,2-二甲基-3-(三氟甲基)吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物780)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物837)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.4]辛-8-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物845)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物850)，

2-(3,3a,4,5,6,6a-六氫-1*H*-環戊并[c]吡咯-2-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物857)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物859)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(丙基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物881)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基-1-哌啶基)-6-(3-氟-5-

異丁氧基-苯基)吡啶-3-甲醯胺(化合物887)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-氮雜雙環[3.1.0]己-4-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物906)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1S,4R)-3-氮雜雙環[2.2.1]庚-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物924)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(9-氮雜螺[4.4]壬-9-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物926)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物931)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,5S)-8-氮雜雙環[3.2.1]辛-8-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物934)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.5]辛-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物953)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物969)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.5]辛-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物973)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物991)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1004)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[甲基-[(1-甲基環丙基)甲基]胺基]吡啶-3-甲醯胺(化合物1009)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1010)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,5-二甲基-1-哌啶基)-6-(3-氟-5-

異丁氧基-苯基)吡啶-3-甲醯胺(化合物1013)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1051)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.4]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1061)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2,3,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1065)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-4-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S)-2-第三丁基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1097)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-異丙基-1-哌啶基)吡啶-3-甲醯胺(化合物1098)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1117)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1121)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2,3,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1144)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-(甲氧基甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1149)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,3,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1156)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(異丙基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1157)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-亞

甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1162)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(5R)-2,2,5-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1166)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R)-2-第三丁基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1170)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,4S)-3-氮雜雙環[2.2.1]庚-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1180)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-3-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物1193)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-(3-氯苯基)乙基-甲基-胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1205)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3S,5S)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1210)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1218)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基-5-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1222)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(5S)-2,2,5-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1241)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-異丙基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1258)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-苯基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1260)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.5]壬-8-基)-6-(3-氟-

5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1264)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基嗎啉-4-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1267)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1279)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1289)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[3.5]壬-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1303)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1304)，

2-(2,3,4,4a,5,6,7,7a-八氫環戊并[b]吡啶-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1313)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-3-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物1319)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-甲基-1-哌啶基)-6-(對甲苯基)吡啶-3-甲醯胺(化合物802)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲氧基-5-甲基-3-吡啶基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物863)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物910)，

6-(3-氟-5-異丙氧基-苯基)-2-(4-甲基-1-哌啶基)-*N*-(1H-吡唑-3-基磺醯基)吡啶-3-甲醯胺(化合物1042)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.4]庚-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1333)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3R,5S)-3,5-二甲基-1-哌啶基]-6-

(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物371)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(1-哌啶基)吡啶-3-甲醯胺(化合物380)，

2-(3,3a,4,5,6,6a-六氫-2*H*-環戊并[b]吡咯-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物383)，

(2S)-1-[3-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡啶基]吡咯啶-2-甲酸甲酯(化合物385)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物398)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物408)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(氮雜環庚烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物418)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(甲氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物419)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜雙環[2.2.1]庚-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物420)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物421)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(8-氧雜-4-氮雜螺[4.4]壬-4-基)吡啶-3-甲醯胺(化合物424)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物425)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-苯基吡咯啶-1-基]吡啶-3-甲醯胺(化合物447)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二氫吡咯-1-基)-6-(3-氟-5-異

丁氧基-苯基)吡啶-3-甲醯胺(化合物453)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物458)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物473)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物479)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-4-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物488)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(三氟甲基)-3-氮雜雙環[3.1.0]己-3-基]吡啶-3-甲醯胺(化合物490)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2-(1,1-二甲基丙基)吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物493)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,5-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物496)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-環丙基乙基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物516)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[3.3]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物527)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基-3-甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物530)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物547)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物555)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5-

三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物560)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,4-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物575)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,5S)-3-氮雜雙環[3.2.1]辛-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物581)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物587)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡咯啶-1-基-吡啶-3-甲醯胺(化合物592)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-環丙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物593)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6,6-二甲基-3-氮雜雙環[3.1.0]己-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物609)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-第三丁基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物611)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-第三丁基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物613)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-乙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物615)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物651)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-環丙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物655)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-2,2,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物657)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-(2-

吡啶基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物659)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物663)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物678)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[2.2.1]庚-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物680)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丁基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物683)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物684)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物694)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基-3-苯基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物711)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-(甲氧基甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物719)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物720)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物735)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物751)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物772)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2,2-二甲基-3-(三氟甲基)吡咯啶-

1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物780)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物837)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.4]辛-8-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物845)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物850)，

2-(3,3a,4,5,6,6a-六氫-1*H*-環戊并[c]吡咯-2-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物857)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物859)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(丙基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物881)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物887)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-氮雜雙環[3.1.0]己-4-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物906)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1S,4R)-3-氮雜雙環[2.2.1]庚-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物924)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(9-氮雜螺[4.4]壬-9-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物926)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物931)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,5S)-8-氮雜雙環[3.2.1]辛-8-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物934)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[2.5]辛-7-基)-6-(3-氟-

5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物953)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物969)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.5]辛-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物973)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物991)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1004)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[甲基-[(1-甲基環丙基)甲基]胺基]吡啶-3-甲醯胺(化合物1009)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1010)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,5-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1013)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1051)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-氮雜螺[2.4]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1061)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2,3,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1065)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-4-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S)-2-第三丁基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1097)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-異

丙基-1-哌啶基)吡啶-3-甲醯胺(化合物1098)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1117)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1121)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2,3,3-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1144)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-(甲氧基甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1149)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,3,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1156)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環丙基甲基(異丙基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1157)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-亞甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1162)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(5R)-2,2,5-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1166)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R)-2-第三丁基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1170)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(1R,4S)-3-氮雜雙環[2.2.1]庚-3-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1180)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-3-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-1,2-二氫吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-甲基-1-哌啶基]吡啶-3-甲醯胺(化合物1193)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[1-(3-氯苯基)乙基-甲基-胺基]-6-

(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1205)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3S,5S)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1210)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1218)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基-5-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1222)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(5S)-2,2,5-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1241)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-異丙基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1258)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-苯基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1260)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(8-氮雜螺[3.5]壬-8-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1264)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基嗎啉-4-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1267)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1279)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1289)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(7-氮雜螺[3.5]壬-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1303)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-(三氟甲基)吡咯啶-1-基]吡啶-3-甲醯胺(化合物1304)，

2-(2,3,4,4a,5,6,7,7a-八氫環戊并[b]吡啶-1-基)-*N*-[(6-胺基-2-吡啶

基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1313)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-3-苯基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物1319)，

2-(2,5-二甲基-3-苯基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1348)，

2-[(3,3-二氟環丁基)甲基胺基]-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物393)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物415)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-[4-(三氟甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物426)，

2-(3-乙炔基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物431)，

6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物442)，

6-(3-氟-5-異丁氧基-苯基)-2-(3-異丙基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物498)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1*H*-吡唑-5-基磺醯基)-2-螺[1*H*-異苯并呋喃-3,4'-哌啶]-1'-基-吡啶-3-甲醯胺(化合物506)，

6-(3-氟-5-異丁氧基-苯基)-2-(2-氧雜-8-氮雜螺[3.5]壬-8-基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物519)，

2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物528)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-異丙基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物553)，

2-[4-(氰基甲基)-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑

-5-基磺醯基)吡啶-3-甲醯胺(化合物556)，

2-(3,3-二氟吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物565)，

2-(2-乙基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物591)，

2-[(3R,5S)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物642)，

6-(3-氟-5-異丁氧基-苯基)-2-[(3R)-3-甲基-1-哌啶基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物668)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-[3-(2-吡啶基)-1-哌啶基]吡啶-3-甲醯胺(化合物677)，

6-(3-氟-5-異丁氧基-苯基)-2-[(2S)-2-苯基吡咯啶-1-基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物716)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-氟-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物728)，

2-(氮雜環庚烷-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物734)，

6-(3-氟-5-異丁氧基-苯基)-2-吲哚啉-1-基-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物739)，

6-(3-氟-5-異丁氧基-苯基)-2-(3-甲氧基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物749)，

6-(3-氟-5-異丁氧基-苯基)-2-(3-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物756)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-甲氧基-4-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物774)，

2-(3-乙氧基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-

基磺醯基)吡啶-3-甲醯胺(化合物843)，

6-(3-氟-5-異丁氧基-苯基)-2-(3-氟-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物878)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物904)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-[3-(三氟甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物907)，

6-(3-氟-5-異丁氧基-苯基)-2-[(3S)-3-苯基-1-哌啶基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物912)，

2-[(3R,5R)-3,5-二甲基-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物942)，

2-(7-氮雜螺[3.5]壬-7-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物944)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-(2,3,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物952)，

6-(3-氟-5-異丁氧基-苯基)-2-[4-(甲氧基甲基)-1-哌啶基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物975)，

6-(3-氟-5-異丁氧基-苯基)-2-異吲哚啉-2-基-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物981)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-(2,2,3-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物997)，

2-(3,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1005)，

2-(4,4-二氟-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1006)，

6-(3-氟-5-異丁氧基-苯基)-2-[3-(甲氧基甲基)-1-哌啶基]-*N*-(1H-吡

唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1028)，

2-(4-乙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1030)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1041)，

6-(3-氟-5-異丁氧基-苯基)-2-[(2R)-2-苯基吡咯啶-1-基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1060)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1083)，

2-[4-(環丙基甲氧基)-1-哌啶基]-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1088)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1110)，

2-(2,6-二甲基嗎啉-4-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1119)，

2-(6-氮雜螺[2.5]辛-6-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1127)，

6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基吡咯啶-1-基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1142)，

2-(4-乙氧基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1155)，

2-(2,3-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1169)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-(3,3,4-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1174)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-[(4R)-2,2,4-

三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1176)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-甲氧基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1245)，

2-(2-苯甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1257)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)-2-[[3-(三氟甲基)環己基]胺基]吡啶-3-甲醯胺(化合物1281)，

2-(8-氮雜螺[3.4]辛-8-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1282)，

6-(6-異丙氧基-3-吡啶基)-*N*-(1H-吡唑-5-基磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1352)，

2-(3-環丙基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1286)，

2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1302)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-苯基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1315)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丙氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物600)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丙氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物972)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丙氧基-苯基)吡啶-3-甲醯胺(化合物1123)，

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-(1-哌啶基)吡啶-3-甲醯胺(化合物753)，

*N*-(4-胺基苯基)磺醯基-2-(苯甲基胺基)-6-第三丁基-吡啶-3-甲醯

胺(化合物1064)，

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-(4-甲氧基-1-哌啶基)吡啶-3-甲醯胺(化合物1298)，

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-[(4-甲基四氫哌嗪-4-基)甲基胺基]吡啶-3-甲醯胺(化合物752)，

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1037)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物794)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3,3-二甲基丁氧基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1008)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[4-(甲氧基甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物986)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3,5-二甲基-1-哌啶基)吡啶-3-甲醯胺(化合物617)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[4-(1-羥基-1-甲基-乙基)-1-哌啶基]吡啶-3-甲醯胺(化合物1038)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-甲氧基-1-哌啶基)吡啶-3-甲醯胺(化合物1164)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(4-乙氧基-1-哌啶基)吡啶-3-甲醯胺(化合物1200)，

2-[(4-甲基四氫哌嗪-4-基)甲基胺基]-6-(對甲苯基)-*N*-(1H-吡唑-3-基磺醯基)吡啶-3-甲醯胺(化合物879)

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4-甲基四氫哌嗪-4-基)甲基胺

基]-6-(對甲苯基)吡啶-3-甲醯胺(化合物1196)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物373)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物1261)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1316)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1240)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1159)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲基-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物532)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[(3R)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物626)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1074)，

6-(6-異丙氧基-3-吡啶基)-2-[(3R)-3-苯基-1-哌啶基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物741)，

6-(6-異丙氧基-3-吡啶基)-2-[(3S)-3-苯基-1-哌啶基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物776)，

2-[(3R,5S)-3,5-二甲基-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物446)，

2-[(3R,5R)-3,5-二甲基-1-哌啶基]-6-(6-異丙氧基-3-吡啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物990)，

6-(6-異丙氧基-3-吡啶基)-2-(4-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基

磺醯基)吡啶-3-甲醯胺(化合物534)，

*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[2.2.2]辛-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1657)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(3S)-2,2-二氘-3,5,5-三甲基-吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1400)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氮雜雙環[3.1.1]庚-3-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1529)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,5,5-三甲基嗎啉-4-基)吡啶-3-甲醯胺(化合物1548)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(5,7-二甲基吲哚啉-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1572)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4R)-4-乙基-2,2-二甲基-吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1611)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4S)-4-乙基-2,2-二甲基-吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1612)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,5,5-四甲基嗎啉-4-基)吡啶-3-甲醯胺(化合物1675)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,5-二異丙基吡唑-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1387)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二氟氮雜環丁烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2155)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2-甲基氮雜環丁烷-1-基)吡啶-3-甲醯胺(化合物1840)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟氮雜環丁烷-1-基)-6-(3-氟-

5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2128)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6,6-二甲基-7-氮雜螺[3.4]辛-7-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2589)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(5-氮雜雙環[4.1.0]庚-5-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2376)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(6-甲基-3-氮雜雙環[3.1.1]庚-3-基)吡啶-3-甲醯胺(化合物2224)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[[1-(2-羥基-2-甲基-丙基)環丙基]甲基胺基]吡啶-3-甲醯胺(化合物1723)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2552)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基氮雜環丁烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1928)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (異構體1) (化合物2178) (異構體2) (化合物2062) (異構體3) (化合物1863) (異構體4)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2451) (異構體1) (化合物1993) (異構體2) (化合物1864) (異構體3) (化合物1855) (異構體4)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-羥基-1-哌啶基)吡啶-3-甲醯胺(化合物2323)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[環己基甲基(甲基)胺基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2289)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,5-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1995)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-異

丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2201)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-BLAH基-吡啶-3-甲醯胺(化合物1821)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(5-甲基-7-氮雜螺[2.4]庚-7-基)吡啶-3-甲醯胺(化合物1754)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-第三丁基-2,2-二甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2538)，

(2R)-1-[3-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡啶基]吡咯啶-2-甲酸第三丁酯(化合物2216)，

(2S)-1-[3-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(3-氟-5-異丁氧基-苯基)-2-吡啶基]吡咯啶-2-甲酸第三丁酯(化合物2204)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基-1-哌啶基)吡啶-3-甲醯胺(化合物2581)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二氟-2,2-二甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2631)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(5,5-二甲基-6-氮雜螺[2.4]庚-6-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1746)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-甲基氮雜環丁烷-1-基)吡啶-3-甲醯胺(化合物2117)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[2,2-二甲基-4-(三氟甲基)吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1788)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[2-甲基-5-(三氟甲基)-1-哌啶基]吡啶-3-甲醯胺(化合物1835)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,5-二甲基氮雜環庚烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2479)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二甲基氮雜環庚烷-1-基)-6-

(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2171)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,3-二甲基氮雜環庚烷-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1901)，

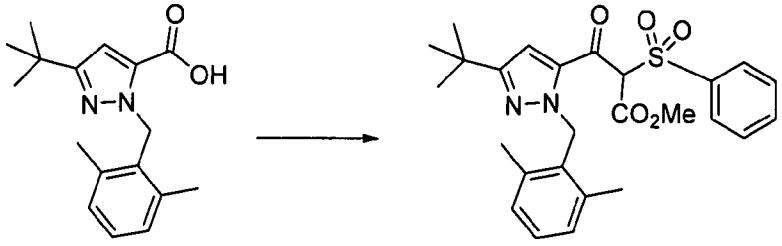
*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(環己基甲基胺基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2375)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(1-哌啶基)吡啶-3-甲醯胺(化合物571)，

及

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物361)。

**製備40：2-(苯磺醯基)-3-[5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-基]-3-側氧基-丙酸酯(化合物4)**

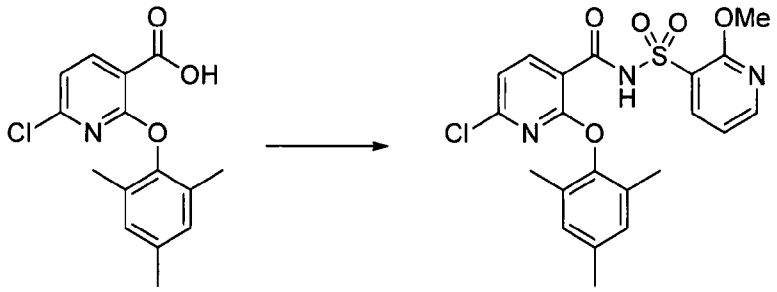



5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸(100 mg，0.35 mmol)溶於硫醯氯(26 μL，0.35 mmol)中且添加一滴*N,N*-二甲基甲醯胺。將混合物攪拌1小時且蒸發，得到酸氯化物。

將酸氯化物(40 mg，0.13 mmol)、2-(苯磺醯基)乙酸甲酯(28 mg，0.13 mmol)及NaH (60%，5.3 mg，0.13 mmol)於*N,N*-二甲基甲醯胺(1 mL)中之混合物在室溫下攪拌15分鐘。混合物過濾且藉由逆相製備型HPLC (10-99% $CH_3CN/H_2O$，HCl改質劑)純化，得到2-(苯磺醯基)-3-[5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-基]-3-側氧基-丙酸酯(化合物4)。ESI-MS *m/z*計算值482.6, 實驗值483.4 $(M+1)^+$；滯留時間: 2.41 min (3分鐘操作)。

**製備41：6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)**

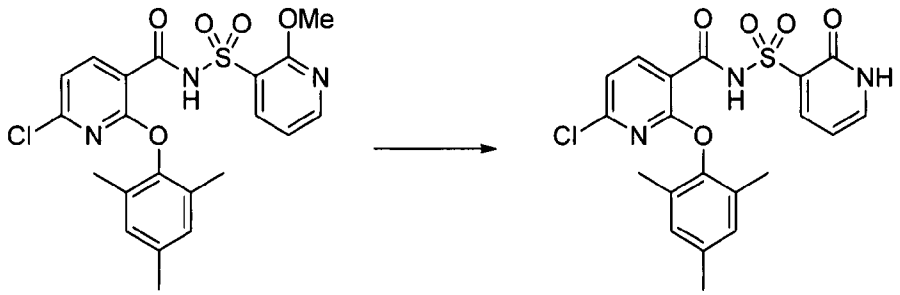
**步驟1：6-氯-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(5.09 g，17.5 mmol)溶於硫醯氯(6.36 mL，87.3 mmol)、$CH_2Cl_2$ (1 mL)及*N,N*-二甲基甲醯胺(一滴)中。將反應混合物攪拌30分鐘，接著濃縮其，得到酸氯化物。

在0℃下酸氯化物溶於$CH_2Cl_2$ (1 mL)中且添加至2-甲氧基吡啶-3-磺醯胺(3.69 g，17.5 mmol)於含有三乙胺(7.30 mL，52.4 mmol)之$CH_2Cl_2$ (1 mL)中的溶液中。將混合物在室溫下攪拌隔夜，接著其用$CH_2Cl_2$稀釋且用1N HCl、飽和$NaHCO_3$且接著鹽水洗滌。有機層經硫酸鈉乾燥且濃縮，得到6-氯-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(6.20 g，77%)。ESI-MS *m/z*計算值461.1，實驗值462.2 $(M+1)^+$；滯留時間: 0.74 min (1分鐘操作)。

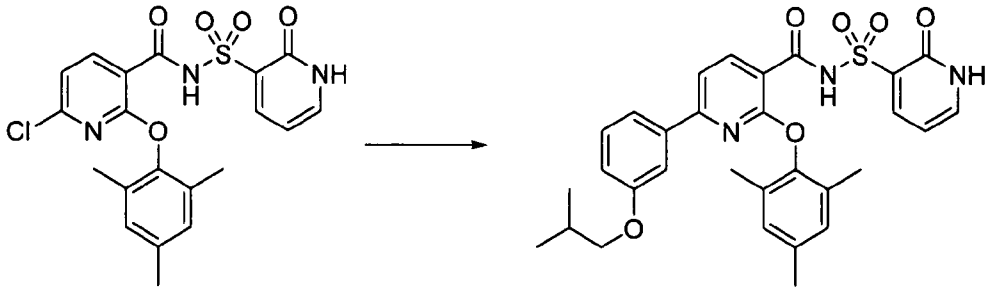
**步驟2：6-氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



將6-氯-*N*-[(2-甲氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(500 mg，1.08 mmol)、1,4-二噁烷(10 mL)及HCl (2.71

mL 4 M，10.8 mmol)之混合物在90℃下加熱3.5小時。移除揮發物，得到6-氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(372 mg，77%)。ESI-MS *m/z*計算值447.1，實驗值448.2 $(M+1)^+$；滯留時間: 0.63 min (1分鐘操作)。

**步驟3：6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)**



將6-氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(56 mmol，0.10 mmol)、3-異丁氧基苯基硼酸(39 mg，0.2 mmol)、$Pd(PPh_3)_4$ (7 mg，0.006 mmol)、$K_2CO_3$ ( 2 M, 200 μL，0.4 mmol)及*N,N*-二甲基甲醯胺(1 mL)之混合物用氮氣沖洗且密封。接著混合物在80℃下攪拌18小時。所得固體用水稀釋且過濾。接著固體溶於乙酸乙酯中，過濾且濃縮，得到6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物125)。ESI-MS *m/z*計算值561.2，實驗值562.2 $(M+1)^+$；滯留時間: 2.23 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

6-(4-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物72)，

2-(2,4-二甲基苯氧基)-6-(4-乙氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物517)，

6-(4-氯-3-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物136)，

6-(2,5-二氟苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物545)，

6-(3,4-二氟苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物546)，

6-(2-氟-5-丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物552)，

6-(4-氟苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物561)，

6-(4,4-二甲基環己烯-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物573)，

6-(4-氯苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物579)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吲哚-4-基磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物549)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(3-羥基苯基)磺醯基-吡啶-3-甲醯胺(化合物1309)，

2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)-*N*-(1H-吲哚-4-基磺醯基)吡啶-3-甲醯胺(化合物1323)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-甲氧基-3-吡啶基)吡啶-3-甲醯胺(化合物726)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1471)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(2,4,6-三甲基苯氧基)-2-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸異丙酯(化合物1366)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙基環己烯-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1370)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-苯甲基-3,6-二氫-2H-吡啶-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1389)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2-二甲基丙-1-烯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1390)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)環己烯-1-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1402)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4,7,7-三甲基-3-雙環[2.2.1]庚-2-烯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1410)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二氫呋喃-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1412)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(2,4,6-三甲基苯氧基)-2-吡啶基]環己-3-烯-1-甲酸乙酯(化合物1432)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,4-二氧雜螺[4.5]癸-8-烯-9-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1437)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6,6-二甲基-2,3-二氫哌喃-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1460)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(環庚en-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1513)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-雙環[2.2.1]庚-2-烯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1518)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5,5-二甲基-3-側氧基-環己烯-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1528)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5,5-二甲基-2-側氧基-環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1427)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環庚yl-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1376)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,2-二甲基四氫哌喃-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1466)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙基環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1475)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2-二甲基丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1486)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,3-二甲基-5-側氧基-環己基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1492)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,6-二氫-2H-硫基哌喃-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1517)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)環己基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1519)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基環己烯-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1630)，

6-(4-乙醯基環己基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1631)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,7,7-三甲基降冰片烷-2-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1650)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(2-甲基丙醯基)-3,6-二氫-2H-吡啶-4-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1540)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,4-二氧雜螺[4.5]癸-8-烯-8-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1558)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,3-二甲基-6-側氧基-環己烯-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1598)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,2,5,5-四甲基-3-呋喃基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1609)，

6-(4-乙醯基環己烯-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1615)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2,3,6-四氫吡啶-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1643)，

6-(1-乙醯基-3,6-二氫-2H-吡啶-4-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1649)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-異丙氧基-5-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1674)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1488)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-乙氧基-5-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1569)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丙氧基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1671)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1646)，

*N*-(2-疊氮基苯基)磺醯基-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺，

*N*-(2-疊氮基苯基)磺醯基-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環己基-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物704)，

6-(4-氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物608)，

6-(4-氟-3-甲氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物624)，

6-(3-氟-5-異丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物645)，

6-(3-氟-5-甲氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物652)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物654)，

6-(2-氟-5-甲氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物762)，

6-(2-氟-3-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物804)，

6-(3,5-二氟苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物815)，

6-(4-乙基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物831)，

6-(3-乙氧基-5-氟-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物835)，

6-(2-氟-4-甲氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物839)，

6-(2-氯苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物877)，

6-(環己烯-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物882)，

6-(2,5-二甲氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物888)，

6-(3-乙氧基-4-氟-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物917)，

6-(6-甲氧基-5-甲基-3-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物930)，

6-(6-乙氧基-3-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物932)，

6-(1-甲基吲哚-6-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物936)，

6-(2-氯-3-丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物955)，

6-(3-丁氧基-2-氯-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物964)，

6-(4-甲氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物980)，

6-(3-氯-4-丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物999)，

6-(4-異丙基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1002)，

6-[4-(環丙基甲氧基)苯基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1007)，

6-(3-氟-4-丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1022)，

6-(4-甲基環己烯-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1052)，

6-(4-異丁氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1079)，

6-(3-氯苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1095)，

6-[3-(環丙基甲氧基)苯基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1105)，

2-(2,4-二甲基苯氧基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-(對甲苯基)吡啶-3-甲醯胺(化合物1129)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-(3-丙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1143)，

6-(5-氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1151)，

6-(4-乙氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1179)，

6-(4-丁氧基-3-氟-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1187)，

6-(3-異丙氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1188)，

6-(2-氯-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1201)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-(4-丙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1202)，

6-(2,3-二氟苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1296)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-(對甲苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1300)，

6-(5-乙氧基-2-氟-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1301)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物169)，

2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-(對甲苯基)吡啶-3-甲醯胺(化合物392)，

6-(6-異丙氧基-3-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物403)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丙氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物487)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物492)，

6-(6-異丙氧基-3-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物497)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物511)，

6-[3-(環丙基甲氧基)-5-氟-苯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物541)，

6-[3-(2,2-二甲基丙氧基)-5-氟-苯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物572)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丙基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物589)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物605)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-苯基-吡啶-3-甲醯胺(化合物660)，

6-[3-(環丙基甲氧基)-5-氟-苯基]-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物664)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異戊基氧基-苯基)-

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物688)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物721)，

6-(3-氟-5-異丙氧基-苯基)-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物737)，

6-(4-氯苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物760)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物770)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-甲氧基-2-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物781)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丁氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物891)，

6-(4-氯-3-異丁氧基-苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物902)，

6-[3-(環丁基甲氧基)-5-氟-苯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物922)，

6-(4-氯-3-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物941)，

6-(3-異丁氧基苯基)-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物958)，

6-(4-氯-3-異丙氧基-苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物1001)，

6-(4-異丁氧基苯基)-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物1017)，

2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-乙氧基-5-氟-苯基)-*N*-

[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物1096)，

8,8-二甲基-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1195)，

6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物1293)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(3S)-3-苯基-1-哌啶基]吡啶-3-甲醯胺(化合物481)，

6-(2-甲氧基-5-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2530)，

6-(3-乙氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2235)，

6-(4-甲氧基-2-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2469)，

6-(4-乙氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2207)，

6-(2-甲氧基-3-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1880)，

6-異丁基-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2467)，

6-(3-甲氧基-4-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2440)，

6-(3-異丙氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2549)，

6-(4-異丙氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1774)，

6-(2-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2629)，

6-(3-氟-4-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2219)，

6-(3-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2267)，

6-(2-氟-6-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2422)，

6-(4-異丁氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2153)，

6-(2-氟-3-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2222)，

6-(5-氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1830)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-[3-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1934)，

6-(2-氟-5-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2606)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-[4-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2234)，

6-(4-氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2356)，

6-(3-氟-5-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2527)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-[3-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2144)，

6-(2-氟-4-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-

[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1858)，

6-(3-氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1779)，

6-(4-氟-3-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1780)，

6-(2-萘基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1803)，

6-(1-萘基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2007)，

6-(2,4-二甲基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2037)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-(2,3,5-三氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1837)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-(2,4,5-三氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1981)，

6-(2,3-二氫-1,4-苯并二氧雜環己烯-6-基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2516)，

6-(2-羥基-3-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2300)，

6-(3-乙氧基-5-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2512)，

6-(2,3-二甲基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2073)，

6-(2-羥基-5-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2174)，

6-(5-氟-2-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2067)，

6-(2-乙氧基-5-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2410)，

6-(4-甲氧基-2,6-二甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2575)，

6-[3-(羥基甲基)-5-甲氧基-苯基]-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2247)，

6-(2,3-二甲氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1786)，

6-(2,5-二甲氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1752)，

6-(2-羥基-4-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2148)，

6-(3,5-二甲氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1878)，

6-(2-乙氧基-5-氟-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2051)，

6-(5-乙氧基-2-氟-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2138)，

6-(3-乙氧基-2-氟-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1802)，

6-(2-乙氧基-4-氟-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1867)，

6-(3,5-二甲基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2626)，

6-(3-乙氧基-5-氟-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2278)，

6-(3-乙氧基-4-氟-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2459)，

6-(3,4-二甲基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2154)，

6-(4-甲基-1-萘基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1811)，

6-(2-異丙基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2635)，

6-(4,5-二氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1904)，

6-(3,5-二氟-2-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2496)，

6-(2,3-二氟-4-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2567)，

6-(3,5-二氟-4-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1801)，

6-(3,4-二氟-5-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1914)，

6-(2,5-二氟-4-甲氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1913)，

6-(4-羥基-3,5-二甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2556)，

6-(1H-吲哚-5-基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1982)，

6-(1H-吲哚-4-基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2636)，

6-(6-乙氧基-4-甲基-2-吡啶基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1745)，

6-(3-氟-4-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2084)，

6-(2-氟-4-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2000)，

6-(3-氟-2-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2491)，

6-(2-氯苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1784)，

6-(3-氟-5-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2348)，

6-(2-氟-5-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1946)，

6-(3-氯苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1791)，

6-(3,4-二氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2284)，

6-(4-氯苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2028)，

6-(2,4-二氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2159)，

6-(2,3-二氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2162)，

6-(3,5-二氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2652)，

6-(2,5-二氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1954)，

6-(2-氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2542)，

6-(2-異丙氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2541)，

6-(3-氰基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2185)，

6-(3-氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1925)，

6-(4-氟苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1807)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-[2-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1960)，

6-(2-甲氧基-3-吡啶基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2454)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-[4-(三氟甲基)環己基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2315)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-[4-(三氟甲基)環己基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1710)，

6-(2,5-二甲基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1990)，

6-(鄰甲苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2176)，

6-(4-氟-3-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2456)，

6-(5-氟-6-甲氧基-3-吡啶基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2444)，

6-(6-甲氧基-2-吡啶基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2101)，

6-(2,6-二甲氧基-3-吡啶基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1853)，

6-(3-異丙基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2498)，

6-(4-異丙基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2483)，

6-(5-氟-2-羥基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2295)，

6-(2-甲氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2485)，

6-(2,3-二氫苯并呋喃-7-基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2583)，

6-(4-甲氧基-3-甲基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2369)，

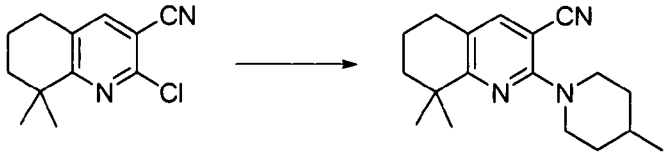
6-(2-乙氧基苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1848)，

6-(3-氟-5-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物422)，及

6-(2-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物279)。

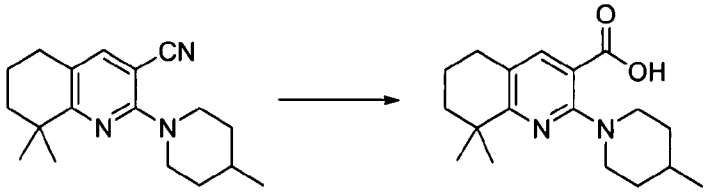
**製備42：*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物197)**

**步驟1**：8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲腈



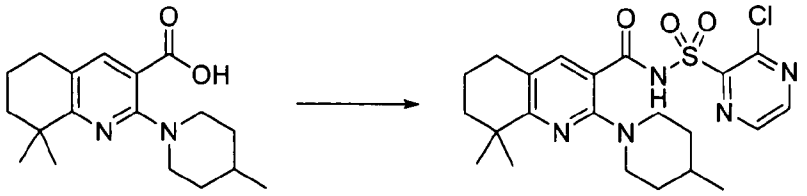
將2-氯-8,8-二甲基-6,7-二氫-5*H*-喹啉-3-甲腈(1.00 g，4.51 mmol)及4-甲基哌啶(4.29 mL，36.3 mmol)之混合物在100℃下攪拌1小時。反應混合物用水稀釋且用乙酸乙酯(3次)萃取。合併之萃取物用水洗滌，經硫酸鈉乾燥，且蒸發。殘餘物藉由矽膠層析，使用己烷中0-5%乙酸乙酯來純化，得到呈無色油狀之8,8-二甲基-2-(4-甲基哌啶-1-基)-5,6,7,8-四氫喹啉-3-甲腈(1.00 g，78%)。ESI-MS *m/z*計算值283.2，實驗值284.3 $(M+1)^+$；滯留時間: 0.94 min (1分鐘操作)。

**步驟2：8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲酸**



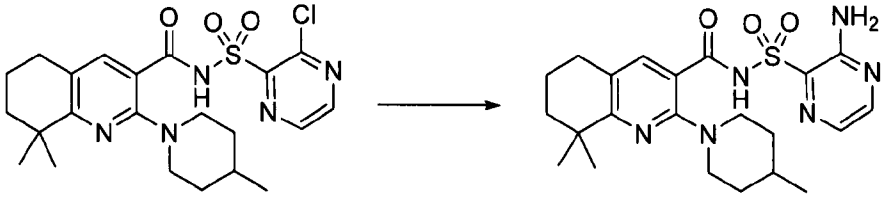
將8,8-二甲基-2-(4-甲基哌啶-1-基)-5,6,7,8-四氫喹啉-3-甲腈(0.80 g，2.8 mmol)及KOH (1.6 g，28 mmol)於乙醇(5.6 mL)中之溶液在回流下加熱4天。反應混合物用1 M HCl中和，且過濾固體，用水洗滌，且在真空下乾燥，得到呈棕褐色固體狀之8,8-二甲基-2-(4-甲基哌啶-1-基)-5,6,7,8-四氫喹啉-3-甲酸(0.71 g，83%)。ESI-MS *m/z*計算值302.2，實驗值303.3 $(M+1)^+$；滯留時間: 0.58 min (1分鐘操作)。

**步驟3：*N*-(3-氯吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺**



將8,8-二甲基-2-(4-甲基哌啶-1-基)-5,6,7,8-四氫喹啉-3-甲酸(0.11 g，0.36 mmol)、六氟磷酸*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(170 mg，0.44 mmol)及 碳酸鈉(77 mg，0.73 mmol)於*N,N*-二甲基甲醯胺(1.8 mL)中之溶液攪拌5分鐘，接著添加3-氯吡嗪-2-磺醯胺(110 mg，0.55 mmol)。將反應混合物攪拌20小時，過濾，且經受製備型HPLC (1-99% $CH_3CN$/水)，得到*N*-(3-氯吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(75mg，43%)。ESI-MS *m/z*計算值477.2, 實驗值478.3 $(M+1)^+$；滯留時間: 0.65 min (1分鐘操作)。

**步驟4：*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺**



將*N*-(3-氯吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(35 mg，0.073 mmol)及氫氧化銨(1 mL，26 mmol)在密封小瓶中在微波反應器中在120℃下加熱20分鐘。反應混合物濃縮，殘餘物溶解於DMSO中且經受製備型HPLC (1-99% $CH_3CN$/水)，得到*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物197) (8.7 mg，26%)。ESI-MS *m/z*計算值458.2, 實驗值459.3 $(M+1)^+$；滯留時間: 1.67 min (3分鐘操作)。

以下化合物可使用本文所述之程序合成：

*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(對甲苯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物707)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(4-乙氧基苯基)-2-(對甲苯基)吡啶-3-甲醯胺(化合物819)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(3-氟-5-異丙氧基-苯基)-2-(對甲苯基)吡啶-3-甲醯胺(化合物1351)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2,6-雙(對甲苯基)吡啶-3-甲醯胺(化合物820)，

*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(對甲苯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物707)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(2,4-二甲基苯氧基)-6-(4-乙氧基苯基)吡啶-3-甲醯胺(化合物434)，

*N*-[(6-胺基-3-吡啶基)磺醯基]-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物702)，

*N*-(6-胺基吡嗪-2-基)磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物586)，

*N*-(3-胺基吡嗪-2-基)磺醯基-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1223)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(2,4-二甲基苯氧基)-8,8-二甲基-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物1239)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1208)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(2,4-二甲基苯氧基)-6-(3-氟-5-異丙氧基-苯基)吡啶-3-甲醯胺(化合物559)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(2,4-二甲基苯氧基)-6-(對甲苯基)吡啶-3-甲醯胺(化合物607)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(2,4-二甲基苯氧基)-6-(1-異丁基吡唑-4-基)吡啶-3-甲醯胺(化合物713)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(2,4-二甲基苯氧基)-6-(6-甲氧基-5-甲基-3-吡啶基)吡啶-3-甲醯胺(化合物893)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(3-氟-5-異丙氧基-苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物989)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(4-乙氧基苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1019)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(對甲苯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1047)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(1-異丁基吡唑-4-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1103)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(6-甲氧基-5-甲基-3-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1249)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-[(4-甲基四氫哌喃-4-基)甲基胺基]-6-(對甲苯基)吡啶-3-甲醯胺(化合物1066)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(4-乙氧基苯基)-2-[(4-甲基四氫哌喃-4-基)甲基胺基]吡啶-3-甲醯胺(化合物1203)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(1-異丁基吡唑-4-基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1288)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(6-甲氧基-5-甲基-3-吡啶基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1191)，

*N*-(3-胺基吡嗪-2-基)磺醯基-2-(4-甲基-1-哌啶基)-6-(對甲苯基)吡啶-3-甲醯胺(化合物1084)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(3-氟-5-異丙氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物699)，

*N*-(3-胺基吡嗪-2-基)磺醯基-6-(4-乙氧基苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物507)，

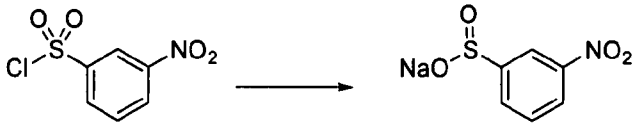
8,8-二甲基-2-(4-甲基-1-哌啶基)-*N*-(1H-吡唑-5-基磺醯基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物800)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(4-甲基-1-哌啶基)-6,7-二氫-5*H*-喹啉-3-甲醯胺(化合物750)，及

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-第三丁基-2-(對甲苯基)吡啶-3-甲醯胺(化合物636)。

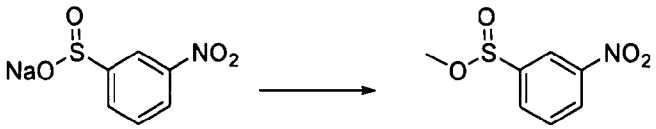
**製備43：*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物292)**

**步驟1：3-硝基苯-1-亞磺酸鈉**



在80℃下向亞硫酸鈉(6.26 g，49.6 mmol)於水(50 mL)中之無色溶液添加3-硝基苯磺醯氯(5.00 g，22.6 mmol)及碳酸鈉(4.30 g，40.6 mmol)。將反應混合物在80℃下攪拌2小時。反應混合物在減壓下濃縮。殘餘物懸浮於乙醇(45 mL)中且在80℃下加熱1小時。反應混合物冷卻至室溫且過濾以移除大部分鹽。濾液在減壓下濃縮，得到3-硝基苯-1-亞磺酸鈉(4.20 g，89%產率，含有一些鹽)。$^1$H NMR (300 MHz, $CDCl_3$) δ 7.68 (t, *J* = 7.8 Hz, 1H), 8.02 (dt, *J* = 7.7, 1.4 Hz, 1H), 8.21 - 8.28 (m, 1H), 8.47 - 8.51 (m, 1H)。$[M+H]^+$ = 188.0。

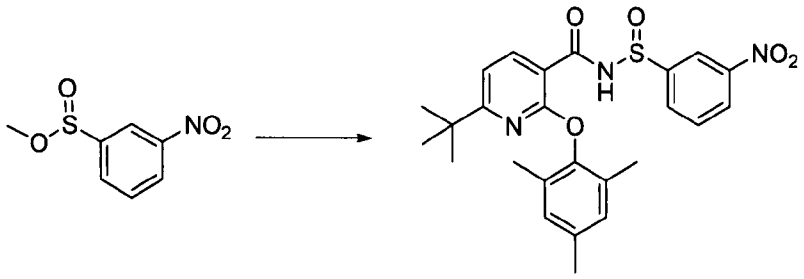
**步驟2：3-硝基苯-1-亞磺酸甲酯**



在0℃下將硫醯氯(3.27 mL，45.0 mmol)添加至3-硝基苯-1-亞磺酸鈉(3.14 g，15.0 mmol)於二氯甲烷(21 mL)中之溶液中。在0℃下20

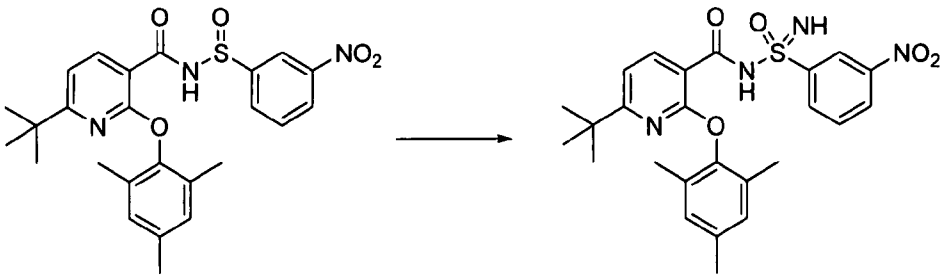
分鐘後，使反應混合物升溫至室溫且攪拌3小時。反應混合物濃縮且在真空下乾燥，得到殘餘物(3.08 g，15 mmol)。在0℃下向殘餘物添加二氯甲烷(5 mL)及甲醇(100 mL)。在此溫度下10分鐘後，添加三乙胺(6.27 mL，45.0 mmol)且將混合物在室溫下攪拌隔夜。在減壓下濃縮混合物。殘餘物溶於二氯甲烷(50 mL)中，用水(25 mL)、鹽水(25 mL)洗滌，經無水硫酸鈉乾燥且濃縮，得到3-硝基苯-1-亞磺酸甲酯(1.40 g，46%產率)。$^1$H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 3H), 7.71 (t, $J$ = 7.8 Hz, 1H), 7.98 (dt, $J$ = 7.7, 1.4 Hz, 1H), 8.21 - 8.28 (m, 1H), 8.47 - 8.51 (m, 1H)。$[M+H]^+$ = 202.0。

**步驟3：6-第三丁基-*N*-(3-硝基苯亞磺醯基)-2-(2,4,6-三甲基苯氧基)-吡啶-3-甲醯胺**



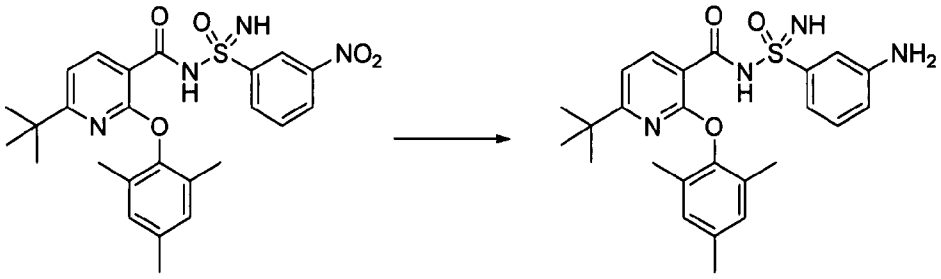
向3-硝基苯-1-亞磺酸甲酯(1.35 g，6.70 mmol)於二甲基甲醯胺(8.0 mL)中之溶液中添加3-硝基苯-1-亞磺酸甲酯(697 mg，2.68 mmol)，接著碳酸銫(2.18 g，6.69 mmol)。將混合物在60℃下攪拌隔夜。混合物用乙酸乙酯(60 mL)稀釋，用水(30 mL)、鹽水(30 mL)洗滌，經無水硫酸鈉乾燥，過濾，且濃縮。粗物質藉由矽膠層析，用庚烷中10-20%乙酸乙酯溶離來純化，得到6-第三丁基-*N*-(3-硝基苯亞磺醯基)-2-(2,4,6-三甲基苯氧基)-吡啶-3-甲醯胺(725 mg，不純)。此物質未經進一步純化即用於下一步。$[M+H]^+$ = 482.1。

**步驟4：6-第三丁基-*N*-[亞胺基(3-硝基苯基)側氧基-λ$^6$-硫基]-2-(2,4,6-三甲基-苯氧基)吡啶-3-甲醯胺**



向6-第三丁基-*N*-(3-硝基苯亞磺醯基)-2-(2,4,6-三甲基苯氧基)-吡啶-3-甲醯胺(724 mg，1.50 mmol)及第三丁醇鉀(337 mg，3.00 mmol)於乙腈(7.5 mL)中之溶液中添加六甲基二矽氮烷(0.94 mL，4.5 mmol)，接著*N*-氯丁二醯亞胺(0.60 g，4.5 mmol)。攪拌15分鐘後，添加額外六甲基二矽氮烷(0.94 mL，4.5 mmol)，接著*N*-氯丁二醯亞胺(0.60 g，4.5 mmol)。攪拌混合物直至TLC指示完成。濃縮混合物且殘餘物藉由急驟層析，用庚烷中20-50%乙酸乙酯溶離來純化，得到6-第三丁基-*N*-[亞胺基(3-硝基苯基)側氧基-$\lambda^6$-硫基]-2-(2,4,6-三甲基-苯氧基)吡啶-3-甲醯胺(95 mg，2步3%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.03 (s, 6H), 2.30 (s, 3H), 6.87 (s, 2H), 6.98 (d, $J$ = 8.0 Hz, 1H), 7.74 (t, $J$ = 8.2 Hz, 1H), 8.30 (d, $J$ = 8.0 Hz, 1H), 8.41 - 8.53 (m, 2H), 8.95 (s, 1H)。$[M+H]^+$ = 497.2。

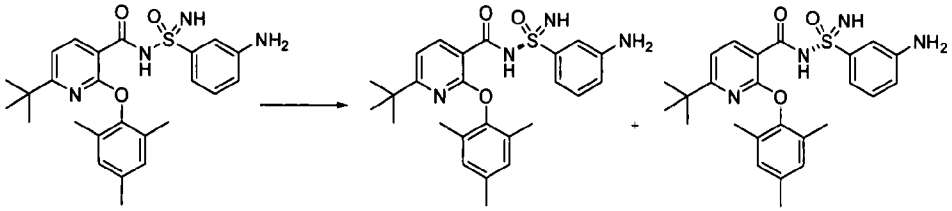
**步驟5：*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



向6-第三丁基-*N*-[亞胺基(3-硝基苯基)側氧基-$\lambda^6$-硫基]-2-(2,4,6-三甲基-苯氧基)吡啶-3-甲醯胺(90 mg，0.18 mmol)於甲醇(2.6 mL)中之溶液中添加10% Pd/C (19 mg，0.018 mmol)且將混合物在室溫下攪拌3小時。在真空下移除溶劑且粗物質藉由急驟層析，用20-50%乙酸乙酯/

庚烷溶離來純化，得到*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(52 mg，62%產率)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9H), 1.92 (s, 6H), 2.22 (s, 3H), 5.57 (br. s, 2H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.85 (s, 2H), 6.97-7.07 (m, 2H), 7.11-7.20 (m, 2H), 7.56 (br. s, 2H), 8.09 (d, *J* = 7.8 Hz, 1H)。$[M+H]^+$ = 467.2。

**步驟6：*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物19及化合物53)**



*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(30 mg，0.064 mmol)溶解於甲醇(1.8 mL)及$CH_2Cl_2$ (0.4 mL)中。溶液進行對掌性SFC (注射30 μL；管柱：Chiralpak AS-H (250×10 mm)，5 μm；移動相：含20 mM $NH_3$之25%甲醇，75% $CO_2$；流速：10 mL/min)，得到*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)-吡啶-3-甲醯胺[峰1，對映異構體1，97.9% ee，$^1$H NMR (400 MHz, 氯仿-d) δ 8.27 (d, *J* = 7.9 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.87 - 6.75 (m, 3H), 3.89 (s, 2H), 2.29 (s, 3H), 2.02 (s, 6H), 1.06 (s, 9H)]及*N*-[(3-胺基苯基)磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺[峰2，對映異構體2，96% ee，$^1$H NMR (400 MHz, 氯仿-d) δ 8.27 (d, *J* = 7.9 Hz, 1H), 7.49 - 7.33 (m, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.88 - 6.74 (m, 3H), 3.89 (s, 2H), 2.29 (s, 3H), 2.02 (s, 6H), 1.06 (s, 9H)]。

以下化合物可使用本文所述之程序製備：

*N*-[*S*-(3-胺基苯基)-*N*-甲基-磺醯亞胺醯基]-6-第三丁基-2-(2,4,6-

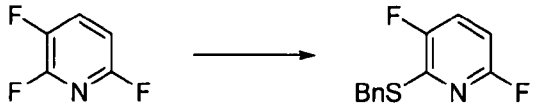
三甲基苯氧基)吡啶-3-甲醯胺(化合物568)，

可使用Chiralcel OJ-H (250×10 mm) 5 μm管柱分離*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[1-苯基乙基]吡唑-3-甲醯胺，得到*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1*S*)-1-苯基乙基]吡唑-3-甲醯胺(化合物138)及*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(1*R*)-1-苯基乙基]吡唑-3-甲醯胺(化合物540)；

可使用Chiralpak AD-H (250×10 mm) 5 μm管柱分離*N*-(3-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺，得到(1*S*)-*N*-(3-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物126) (化合物126)及(1*R*)-*N*-(3-胺基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(化合物310)。

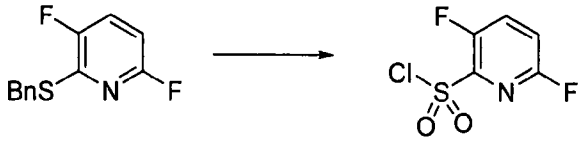
**製備44：*N*-[(6-胺基-3-氟-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物226)**

**步驟1：2-(苯甲基硫基)-3,6-二氟吡啶**



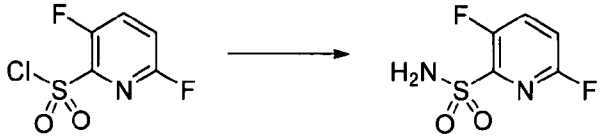

向2,3,6-三氟吡啶(532 mg，4.00 mmol)及苯基甲烷硫醇(470 μL，4.00 mmol)於THF (20 mL)中之溶液中分部分添加NaH (60%，176 mg，4.40 mmol)。1小時後，混合物用飽和氯化銨水溶液淬滅且用乙酸乙酯(3次)萃取。合併之萃取物用水洗滌，經硫酸鈉乾燥，且蒸發。殘餘物藉由矽膠層析，使用己烷中0-20%乙酸乙酯來純化，得到呈無色油狀之2-(苯甲基硫基)-3,6-二氟吡啶(0.63 g，66%)。ESI-MS *m/z*計算值237.0, 實驗值237.9 $(M+1)^+$；滯留時間: 0.72 min (1分鐘操作)。

**步驟2：3,6-二氟吡啶-2-磺醯氯**



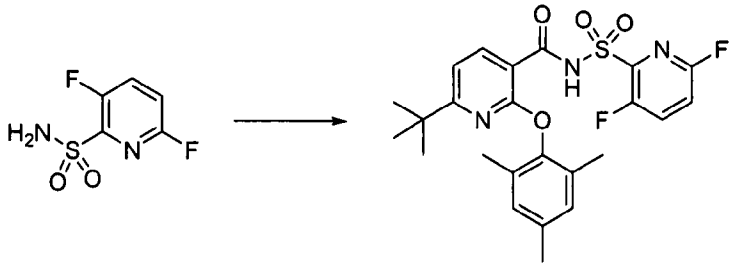
氯氣鼓泡穿過用力攪拌之2-(苯甲基硫基)-3,6-二氟吡啶(0.27 g，1.1 mmol)於氯仿及水中之溶液數分鐘，且將反應混合物攪拌1小時。氯氣再鼓泡穿過混合物15分鐘，且將反應混合物攪拌2小時。將反應混合物用飽和偏亞硫酸氫鈉水溶液淬滅且用二氯甲烷(3次)萃取。合併之萃取物用水洗滌，經硫酸鈉乾燥，且蒸發，得到呈無色油狀之粗3,6-二氟吡啶-2-磺醯基氯(50%純，0.49 g)。ESI-MS *m/z*計算值213.0, 實驗值213.8 $(M+1)^+$；滯留時間: 0.47 min (1分鐘操作)。

**步驟3：3,6-二氟吡啶-2-磺醯胺**



5,6-二氟吡啶-2-磺醯氯(0.35 g，1.6 mmol)於二噁烷(4 mL)中之溶液在冰浴中冷卻，接著添加氨(6.6 mL 0.5 M於二噁烷中，3.3 mmol)。將反應物攪拌3小時且蒸發溶劑。殘餘物藉由矽膠層析，使用己烷中0-50%乙酸乙酯來純化，得到呈無色固體狀之3,6-二氟吡啶-2-磺醯胺(72 mg，23%)。ESI-MS *m/z*計算值194.0, 實驗值194.8 $(M+1)^+$；滯留時間: 0.15 min (1分鐘操作)。

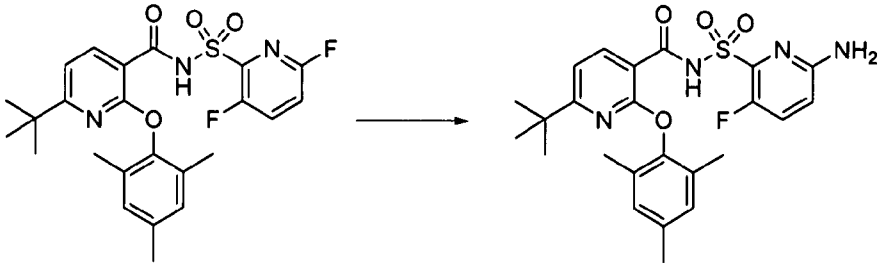
**步驟4：6-第三丁基-*N*-[(3,6-二氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



將6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(107 mg，0.340 mmol)、3,6-二氟吡啶-2-磺醯胺(66 mg，0.34 mmol)、六氟磷酸

*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(194 mg，0.510 mmol)及碳酸鈉(72 mg，0.68 mmol)於*N,N*-二甲基甲醯胺(2 mL)中之溶液在室溫下攪拌18小時。反應物用水稀釋且用乙酸乙酯(3次)萃取。合併之萃取物用水洗滌，經硫酸鈉乾燥，且蒸發。殘餘物藉由矽膠層析，使用0-5%甲醇之二氯甲烷溶液來純化，得到呈無色固體狀之6-(第三丁基)-*N*-((3,6-二氟吡啶-2-基)磺醯基)-2-(均三甲苯基氧基)菸鹼醯胺(33 mg，18%)。ESI-MS *m/z*計算值489.2，實驗值490.2 $(M+1)^+$；滯留時間: 0.85 min (1分鐘操作)。

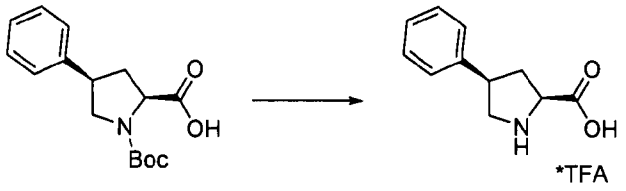
**步驟5：*N*-[(6-胺基-3-氟-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



將6-第三丁基-*N*-[(5,6-二氟-2-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(15 mg，0.028 mmol)及氫氧化銨(1.0 mL 30 %w/v，8.6 mmol)之混合物在密封容器中在微波反應器中在130℃下加熱30分鐘且在150℃下加熱60分鐘。溶劑蒸發且殘餘物進行製備型HPLC (30%-99%乙腈/水(5 mM HCl))，得到*N*-[(6-胺基-3-氟-2-吡啶基)磺醯基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(0.7 mg，5%)。ESI-MS *m/z*計算值486.2，實驗值487.3 $(M+1)^+$；滯留時間: 2.15 min (3分鐘操作)。

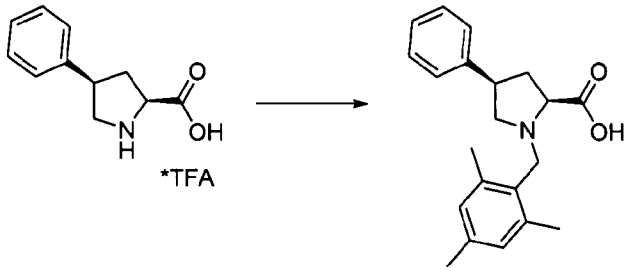
**製備45：(2*S*,4*R*)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺(化合物236)**

**步驟1：(2*S*,4*R*)-4-苯基吡咯啶-2-甲酸三氟乙酸鹽**




在室溫下(2*S*,4*R*)-1-(Boc)-4-苯基吡咯啶-2-甲酸(1.01 g，3.47 mmol)溶於三氟乙酸(20 ml)中且攪拌1小時。反應混合物在減壓下濃縮且所得殘餘物置於高真空下18小時。殘餘物以最少量之二乙醚濕磨且置於超音波浴中1小時，過濾且接著在高真空下乾燥，得到呈固體狀之(2*S*,4*R*)-4-苯基吡咯啶-2-甲酸三氟乙酸鹽(999 mg，99%)。$[M+H]^+$ = 192.2。$^1H$ NMR (300MHz,$CDCl_3$) δ 1.94-2.11 (m, 1H), 2.61-2.75 (m, 1H), 3.09-3.22 (m, 1H), 3.42-3.59 (m, 1H), 3.59-3.73 (m, 1H), 4.35-4.48 (m, 1H), 7.15-7.40 (m, 5H), 8.52 - 10.23 (br. s. 2H)。

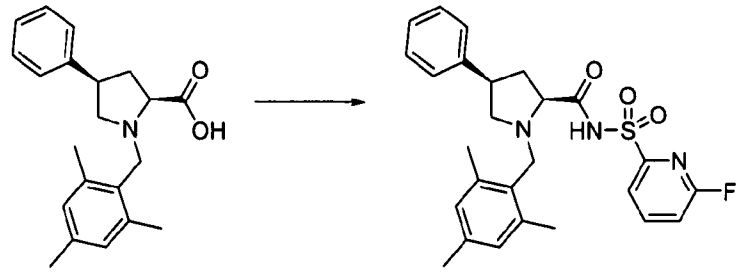
**步驟2：(2*S*,4*R*)-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲酸**




(2*S*-4*R*)-4-苯基吡咯啶-2-甲酸三氟乙酸鹽(999 mg，3.47 mmol)及氫氧化鉀(1.17 g，20.8 mmol)溶於異丙醇(25 mL)中且在40℃下加熱。經由注射器經60分鐘添加2-(溴甲基)-1,3,5-三甲基苯(849 mg，3.99 mmol)於異丙醇(20 mL)中之溶液。在此溫度下將反應物再攪拌2小時。反應混合物用濃HCl處理，直至pH在3與4之間。濾去所得固體且濾液在減壓下濃縮。所得固體溶於二氯甲烷中且在矽膠上(乙酸乙酯中0-10%甲醇)純化。用二氯甲烷稀釋殘餘物後，濾去二氧化矽且濾液在減壓下濃縮，得到呈固體狀之(2*S*-4*R*)-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲酸(1.1 g，98%)。$[M+H]^+$ = 324.2。$^1H$ NMR (300MHz,$CDCl_3$) δ 2.22 (s, 3H), 2.27-2.34 (m, 1H), 2.38(s, 6H), 2.59-

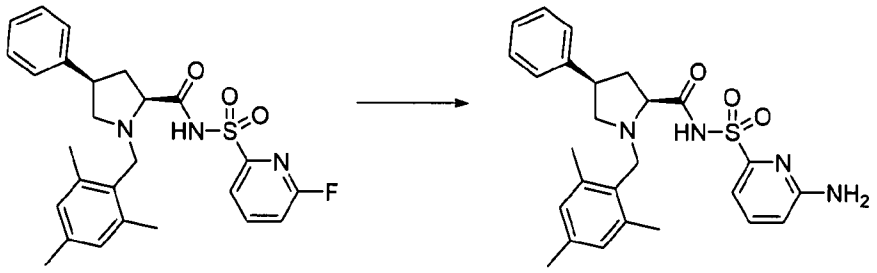
2.94 (m, 1H), 2.96-3.30 (m, 1H) , 3.36 (t, *J*=11.2Hz, 1H), 3.47-3.80 (m, 1H), 4.05 (m, 1H), 4.20 (d, *J*=13.4Hz,1H), 4.35 (d, *J*=13.4Hz,1H), 6.83 (s, 2H), 7.05-7.33(m, 5H)。

**步驟3：(2*S*,4*R*)-*N*-[(6-氟-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺**



將(2*S*,4*R*)-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲酸(75 mg，0.23 mmol)、6-氟吡啶-2-磺醯胺(192 mg，1.09 mmol)、六氟磷酸*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(497 mg，1.31 mmol)及乙基二異丙基胺(380 μL，2.18 mmol)組合於*N,N*-二甲基甲醯胺(1.440 mL)中且在60℃下加熱16小時。反應混合物用水(1 mL)稀釋且用乙酸乙酯(2×5 mL)萃取。有機層經硫酸鈉乾燥，過濾且濃縮。殘餘物進行製備型HPLC，利用5 mM HCl水溶液中30-90%乙腈之梯度，得到(2*S*,4*R*)-*N*-[(6-氟-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺。$^1$H NMR (400 MHz, DMSO) δ 9.18 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 9.1 Hz, 1H), 7.30 (s, 7H), 6.88 (s, 2H), 4.40 (s, 2H), 4.24 (s, 1H), 3.81 (s, 1H), 3.33 - 3.21 (m, 2H), 2.76 (s, 1H), 2.37 (s, 6H), 2.21 (s, 3H), 2.00 (s, 1H)。

**步驟4：(2*S*,4*R*)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺**



(2*S*,4*R*)-*N*-[(6-氟-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺(來自步驟3)懸浮於$NH_4OH$ (2 mL 30 %w/v，17 mmol)中。混合物在微波中在150℃下加熱。反應混合物濃縮，再溶於DMSO中且經受製備型HPLC，利用5 mM HCl水溶液中1-60%乙腈之梯度，得到(2*S*,4*R*)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺(化合物236) (7.5 mg，2步7%)。$^1$H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.33 (s, 7H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.90 (s, 2H), 4.60 (d, *J* = 35.7 Hz, 2H), 4.41 (s, 1H), 3.98 (s, 1H), 3.76 (s, 1H), 3.67 - 3.55 (m, 1H), 2.90 (dt, *J* = 12.8, 6.3 Hz, 1H), 2.41 (d, *J* = 14.1 Hz, 7H), 2.24 (s, 4H)。ESI-MS *m/z*計算值478.2, 實驗值479.0 $(M+1)^+$；滯留時間: 1.41 min (3分鐘操作)。

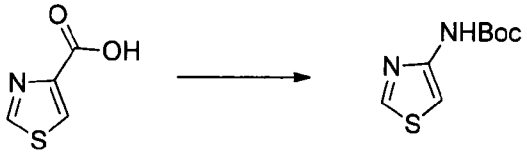
以下化合物可使用本文所述之程序合成：

(2*R*,4*S*)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺(化合物467)及

(2*S*,4*S*)-*N*-[(6-胺基-2-吡啶基)磺醯基]-4-苯基-1-[(2,4,6-三甲基苯基)甲基]吡咯啶-2-甲醯胺(化合物870)

**製備46：*N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)**

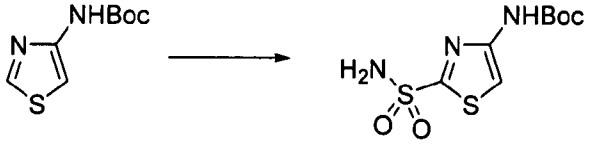
**步驟1：噻唑-4-基胺基甲酸第三丁酯**



將噻唑-4-甲酸(8.16 g，63.2 mmol)及三乙胺(9.7 mL，70 mmol)

於第三丁醇(320 mL)中之混合物用二苯基磷醯基疊氮化物(15 mL，70 mmol)處理且在油浴中緩緩加熱至100℃且攪拌17小時。一旦冷卻，粗反應混合物在減壓下濃縮以移除大部分揮發物。殘餘物轉移至具有乙酸乙酯(300 mL)之1.0 L分液漏斗且有機層用水(2×200 mL)及鹽水(2×100 mL)洗滌。接著有機層經無水硫酸鈉乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析，庚烷中0%至50%乙酸乙酯溶離來純化。所得黏性固體用庚烷濕磨，過濾，用庚烷洗滌且在高真空下乾燥，得到呈白色固體狀之噻唑-4-基胺基甲酸第三丁酯(3.42 g，27%)。$^1$H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9 H), 7.30 (br. s, 1 H), 8.33 (br. s, 1 H), 8.58 (d, $J$ = 2.3 Hz, 1 H)。$[M-C_4H_8+H]^+$ = 145.1。

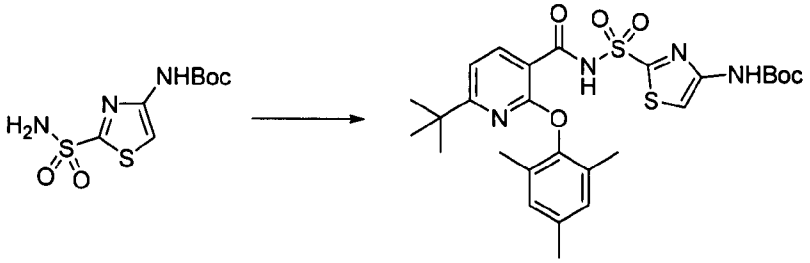
**步驟2：*N*-(2-胺磺醯基-1,3-噻唑-4-基)胺基甲酸第三丁酯**




噻唑-4-基胺基甲酸第三丁酯(1.50 g，7.49 mmol)於甲基第三丁基醚(35 mL)中之溶液在冰浴中冷卻且用氯化異丙基鎂(11 mL 2.0 M於THF中之溶液，22 mmol)緩慢處理。出現大量白色固體。在冰浴中20分鐘後，二氧化硫緩緩鼓泡至反應混合物5分鐘，接著將反應混合物在室溫下攪拌1小時。粗反應混合物在減壓下濃縮以移除大部分揮發物且所得固體懸浮於水(80 mL)中且在冰浴中冷卻。連續添加乙酸鈉(3.40 g，41.5 mmol)及羥基胺-*O*-磺酸(3.39 g，30.0 mmol)。移除冰浴且將反應物在室溫下攪拌45小時。反應混合物轉移至分液漏斗且水層用乙酸乙酯(2×50 mL)萃取。合併之有機層用5%碳酸氫鈉水溶液(30 mL)、鹽水(30 mL)洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠層析，庚烷中0%至75%乙酸乙酯溶離來純化，得到1.2 g經異丙基磺醯胺污染之固體。固體溶於甲醇(3 mL)中且在攪拌下逐滴添加水(2 mL)。過濾沈澱，用水洗滌且在高真空下乾燥，得到呈

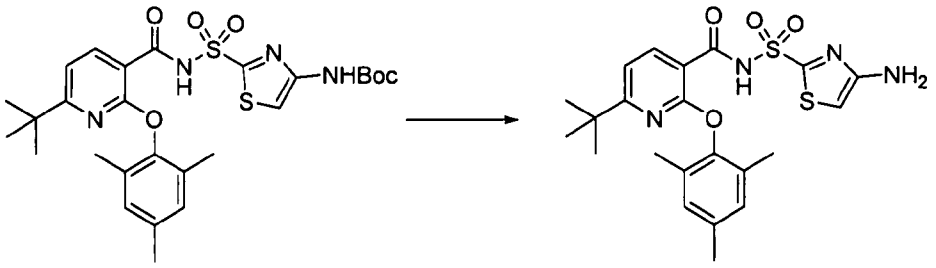
白色固體狀之*N*-(2-胺磺醯基-1,3-噻唑-4-基)胺基甲酸第三丁酯(0.90 g，43%)。$^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.46 (s, 9 H), 7.56 (s, 2 H), 9.12 (s, 1 H), 9.24 (s, 1 H)。$[M-C_4H_8+H]^+$ = 224.0。

**步驟3：*N*-[2-[[6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-羰基]胺磺醯基]噻唑-4-基]胺基甲酸酯**



在室溫下將$K_2CO_3$ (45 mg，0.35 mmol)添加至6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(44 mg，0.14 mmol)、*N*-(2-胺磺醯基噻唑-4-基)胺基甲酸第三丁酯(39 mg，0.14 mmol)、六氟磷酸*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化物(64 mg，0.17 mmol)及*N,N*-二甲基甲醯胺(1 mL)之混合物中。將混合物在60℃下攪拌3小時，接著其冷卻至室溫。混合物分溶於乙酸乙酯與1N HCl之間。分離各層且水層用乙酸乙酯(2次)萃取。合併之有機物用鹽水洗滌，經硫酸鎂乾燥，過濾且濃縮。殘餘物進行矽膠管柱層析(0-50%乙酸乙酯/己烷)，接著進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到呈白色固體狀之*N*-[2-[[6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-羰基]胺磺醯基]噻唑-4-基]胺基甲酸第三丁酯。ESI-MS *m/z*計算值574.2，實驗值575.4 $(M+1)^+$；滯留時間: 2.48 min (3分鐘操作)。

**步驟4：*N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



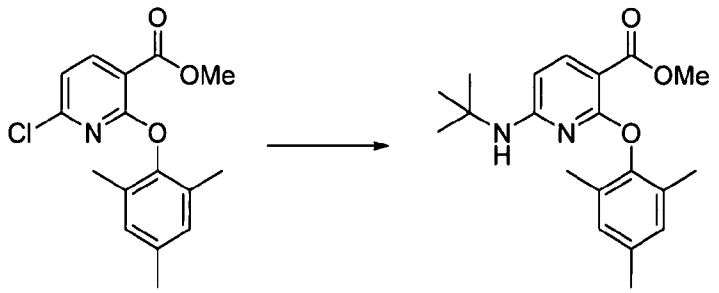
在室溫下將三氟乙酸(11 μL，0.14 mmol)添加至*N*-[2-[[6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-羰基]胺磺醯基]噻唑-4-基]胺基甲酸第三丁酯(來自步驟3)及$CH_2Cl_2$ (5 mL)之混合物中。將混合物攪拌1小時，接著其在減壓下濃縮。殘餘物進行製備型HPLC (10-99%含0.05 mM HCl之乙腈/水)，得到*N*-(4-胺基噻唑-2-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物265)。ESI-MS *m/z*計算值474.1，實驗值475.5 $(M+1)^+$；滯留時間: 2.11 min (3分鐘操作)。$^1$H NMR (400 MHz, DMSO-d6) δ 11.96 (s, 1H), 9.07 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.91 (s, 2H), 6.81 (s, 2H), 2.25 (s, 3H), 1.96 (s, 6H), 1.04 (s, 9H)。

以下化合物可使用本文所述之程序製備：

*N*-(4-胺基噻唑-2-基)磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物842)及*N*-(4-胺基噻唑-2-基)磺醯基-2-(4,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1168)

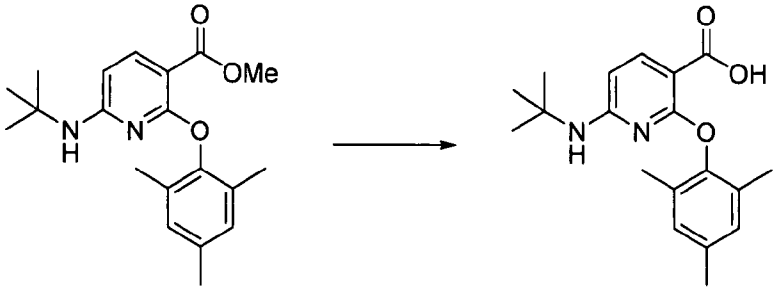
**製備47：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(第三丁基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物273)**

**步驟1：6-(第三丁基胺基)-2-(均三甲苯基氧基)吡啶-3-甲酸甲酯**



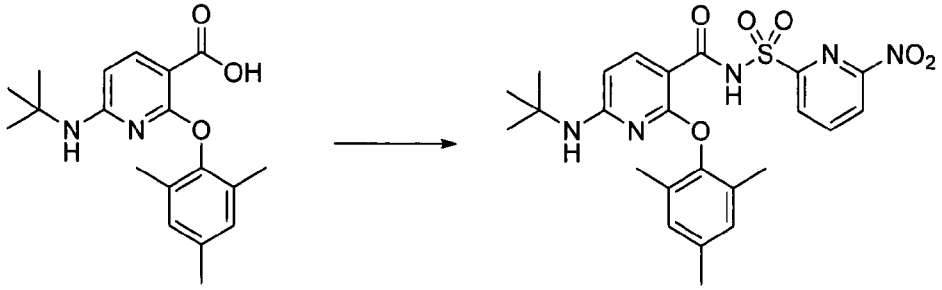
將6-氯-2-(均三甲苯基氧基)吡啶-3-甲酸甲酯(170 mg，0.58 mmol)及第三丁基胺(4.0 mL，38 mmol)於500 mL二甲基乙醯胺中之混合物在微波中在150℃下加熱4小時。粗混合物藉由矽膠管柱層析，用0-40%乙酸乙酯/己烷之梯度溶離來純化，得到呈橙色固體狀之6-(第三丁基胺基)-2-(均三甲苯基氧基)吡啶-3-甲酸甲酯(76 mg，38%產率)。LC-MS: $(M+H)^+$ = 342.5。

**步驟2：6-(第三丁基胺基)-2-(均三甲苯基氧基)吡啶-3-甲酸**



將6-(第三丁基胺基)-2-(均三甲苯基氧基)吡啶-3-甲酸甲酯(76 mg，0.22 mmol)及氫氧化鈉(14 mg，0.34 mmol)於甲醇(1.0 mL)、THF (1.0 mL)及水(0.50 mL)中之混合物在60℃下加熱7小時。添加幾滴濃HCl，形成固體，將所有物質旋轉蒸發，且在真空下乾燥，得到呈白色固體狀之粗6-(第三丁基胺基)-2-(均三甲苯基氧基)吡啶-3-甲酸(98 mg)。LC-MS: $(M+H)^+$ = 329.3。

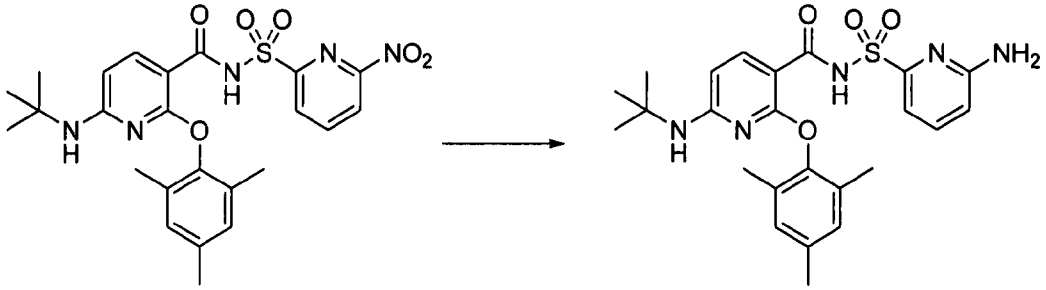
**步驟3：6-(第三丁基胺基)-2-(均三甲苯基氧基)-*N*-((6-硝基吡啶-2-基)磺醯基)菸鹼醯胺**



將粗6-(第三丁基胺基)-2-(均三甲苯基氧基)吡啶-3-甲酸(0.22 mmol)、6-硝基吡啶-2-磺醯胺(58 mg，0.29 mmol)、六氟磷酸*N*-[(二甲基胺基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基亞甲基]-*N*-甲基甲銨*N*-氧化

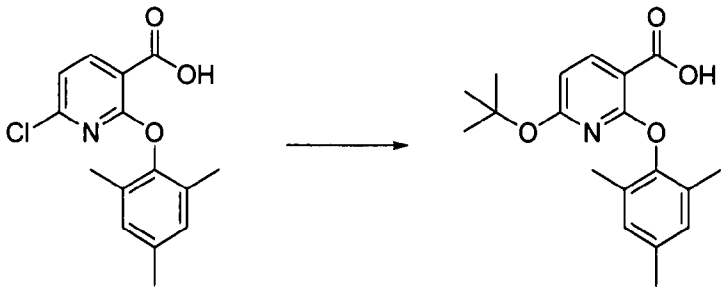
物(0.12 g，0.33 mmol)、乙基二異丙基胺(0.16 mL，0.92 mmol)及*N,N*-二甲基甲醯胺(1 mL)之混合物在封蓋小瓶中在70℃下攪拌6小時且接著在室溫下攪拌18小時。此時LC-MS主要展示活化酸。添加額外70 mg 6-硝基吡啶-2-磺醯胺及0.080 mL乙基二異丙基胺。將混合物在70℃下攪拌4小時且粗物質藉由矽膠管柱層析，用0-20%甲醇/二氯甲烷之梯度溶離來純化兩次，得到呈淡黃色固體狀之6-(第三丁基胺基)-2-(均三甲苯基氧基)-*N*-((6-硝基吡啶-2-基)磺醯基)菸鹼醯胺(34 mg，30%產率)。LC-MS: $(M+H)^+$ = 514.5。

**步驟4：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(第三丁基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



將6-(第三丁基胺基)-2-(均三甲苯基氧基)-*N*-((6-硝基吡啶-2-基)磺醯基)菸鹼醯胺(34 mg，0.064 mmol)及金屬鐵(48 mg，0.86 mmol)於THF (0.7 mL)、EtOH (0.35 mL)、濃HCl (0.06 mL)及水(0.06 mL)中之混合物在60℃下加熱50分鐘。混合物熱過濾且用甲醇洗滌。濾液旋轉蒸發，得到120 mg粗物質，其藉由逆相HPLC來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(第三丁基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物273) (7.2 mg，23%)。LC-MS: $(M+H)^+$ = 484.5。

**製備48：6-(第三丁氧基)-2-(均三甲苯基氧基)菸鹼酸**



向第三丁醇(0.70 mL，7.3 mmol，11當量)於1.0 mL *N,N*-二甲基甲醯胺中之溶液中逐份添加60% NaH (320 mg，8.0 mmol，12當量)。停止鼓泡約10分鐘後，將6-氯-2-(均三甲苯基氧基)吡啶-3-甲酸7 (0.20 g，0.69 mmol，1.0當量)添加至反應混合物中。混合物在封蓋小瓶中在100℃下加熱22小時。冷卻至室溫後，添加幾滴濃鹽酸且反應混合物蒸發至乾。粗物質藉由管柱層析，使用25 g矽膠且用經15分鐘0-30%甲醇之二氯甲烷溶液之梯度溶離來純化。合併含有產物之溶離份且濃縮，得到呈淡黃色固體狀之6-第三丁氧基-2-(均三甲苯基氧基)吡啶-3-甲酸(109 mg，48%產率)。LC-MS: (M+H)+ = 330.1。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(異丙基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物650)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲基吡咯啶-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1553)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-吡咯啶-1-基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物746)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-哌啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物785)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-嗎啉基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物966)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(甲基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物983)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(乙基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1128)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(二甲基胺基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1306)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-乙氧基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物637)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲氧基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物806)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-8,8-二甲基-2-(2,4,6-三甲基苯氧基)-5,7-二氫哌喃o[4,3-*b*]吡啶-3-甲醯胺(化合物714)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[異丁基(甲基)胺基]-5-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1416)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1494)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-甲基-6-(2-甲基吡咯啶-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1516)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-2,6-bis[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1673)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丙氧基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1573)，

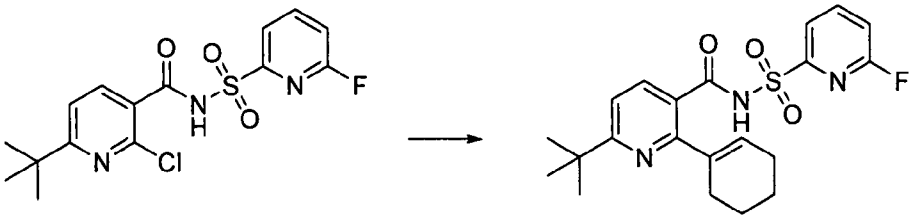
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-5-甲基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1589)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丙氧基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物968)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁氧基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1070)。

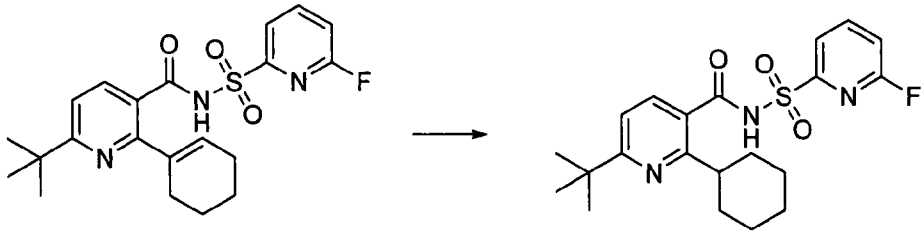
**製備49：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-環戊基-吡啶-3-甲醯胺(化合物1219)**

**步驟1：6-(第三丁基)-2-(環己-1-烯-1-基)-*N*-((6-氟吡啶-2-基)磺醯基)菸鹼醯胺**



含6-第三丁基-2-氯-*N*-[(6-氟-2-吡啶基)磺醯基]吡啶-3-甲醯胺(75 mg，0.20 mmol)、1-環己烯基硼酸(25.41 mg，0.2017 mmol)、碳酸鈉(201.7 μL 2 M，0.4034 mmol)、二氯[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(7.376 mg，0.01008 mmol)之二噁烷(900.0 μL)添加至微波反應小瓶。小瓶用氮氣淨化，封蓋且在微波反應器中加熱至120℃，保持30分鐘。反應混合物用水稀釋且用乙酸乙酯(2×10 mL)萃取。有機層經硫酸鈉乾燥，濃縮，且藉由HPLC，利用5 mM HCl水溶液中0-70%乙腈之梯度純化，得到產物(19.7 mg，23%)。ESI-MS *m/z* 計算值417.5, 實驗值418.4 $(M+1)^+$；滯留時間: 0.64 min (1分鐘操作)。

**步驟2：6-(第三丁基)-2-環己基-*N*-((6-氟吡啶-2-基)磺醯基)菸鹼醯胺**



6-(第三丁基)-2-(環己-1-烯-1-基)-*N*-((6-氟吡啶-2-基)磺醯基)菸鹼醯胺(19.7 mg，0.047 mmol)溶於甲醇(10 mL)中且添加鈀/碳(12.64 mg，0.01188 mmol)。將混合物在氫氣球下在室溫下攪拌16小時。粗物質過濾，濃縮，且藉由HPLC，利用5 mM HCl水溶液中20-80%乙腈之梯度來純化，得到6-(第三丁基)-2-環己基-*N*-((6-氟吡啶-2-基)磺醯基)菸鹼醯胺。

以下化合物可使用本文所述之程序合成：

*N*-(4-胺基苯基)磺醯基-6-第三丁基-2-環戊基-吡啶-3-甲醯胺(化合

物1003)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物1502)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(三氟甲基)環己烯-1-基]吡啶-3-甲醯胺(化合物1667)，

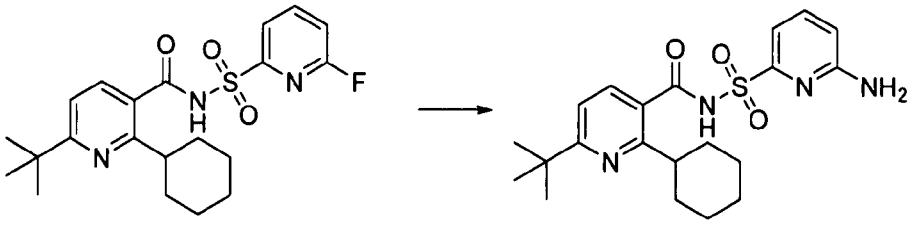
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,6,6-四甲基-3*H*-哌喃-4-基)吡啶-3-甲醯胺(化合物1368)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4,4-二甲基環己烯-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1493)，

及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,5,5-四甲基-3-呋喃基)吡啶-3-甲醯胺(化合物1531)。

**步驟3：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-環己基-吡啶-3-甲醯胺(化合物411)**



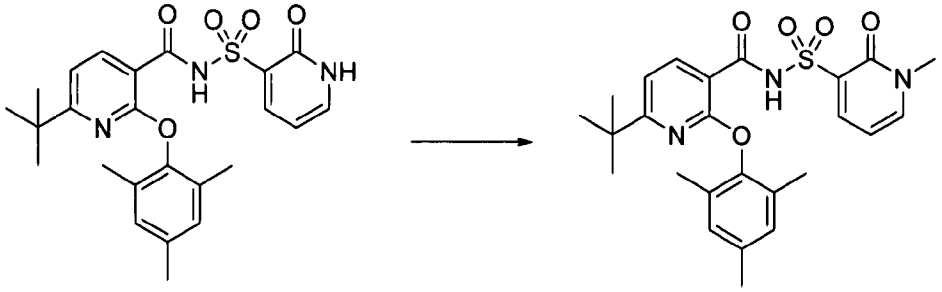
6-(第三丁基)-2-環己基-*N*-((6-氟吡啶-2-基)磺醯基)菸鹼醯胺懸浮於氫氧化銨(1 mL 28 %w/v，8.56 mmol)中。將混合物在微波反應器中在150℃下攪拌0.5小時。反應混合物濃縮，再溶於DMSO中且藉由HPLC，利用5 mM HCl水溶液中10-65%乙腈之梯度純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(環己烯-1-基)吡啶-3-甲醯胺。$^1$H NMR (400 MHz, MeOD) δ 8.56 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.08 (s, 1H), 2.31 (s, 2H), 2.20 (s, 2H), 1.69 (d, *J* = 17.3 Hz, 4H), 1.53 (s, 9H)。ESI-MS *m/z*計算值414.17255, 實驗值415.0 $(M+1)^+$；滯留時

間: 1.48分鐘。

以下化合物可使用本文所述之程序合成：

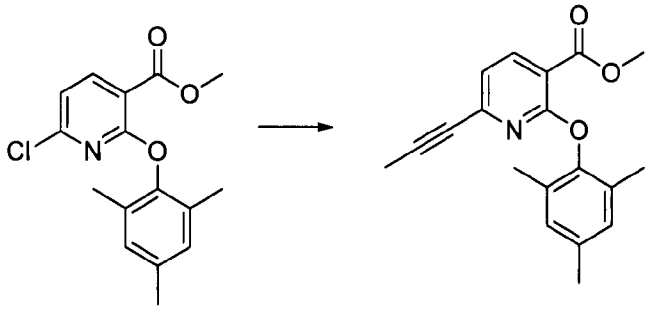
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-環戊基-吡啶-3-甲醯胺(化合物1219)。

**製備50：6-第三丁基-*N*-[(1-甲基-2-側氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物667)**



6-第三丁基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(28 mg，0.060 mmol)溶於含碳酸鉀(24.72 mg，0.1789 mmol)之*N,N*-二甲基甲醯胺中且逐滴添加碘甲烷溶液(8.464 mg，3.712 μL，0.05963 mmol)。將溶液在室溫下攪拌4小時。反應混合物過濾且藉由LC/MS，利用5 mM HCl水溶液中10-99%乙腈之梯度來純化，得到6-第三丁基-*N*-[(1-甲基-2-側氧基-3-吡啶基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物667) (2 mg，0.004 mmol，7%)。ESI-MS *m/z*計算值483.1828, 實驗值484.3 $(M+1)^+$；滯留時間: 2.13分鐘。

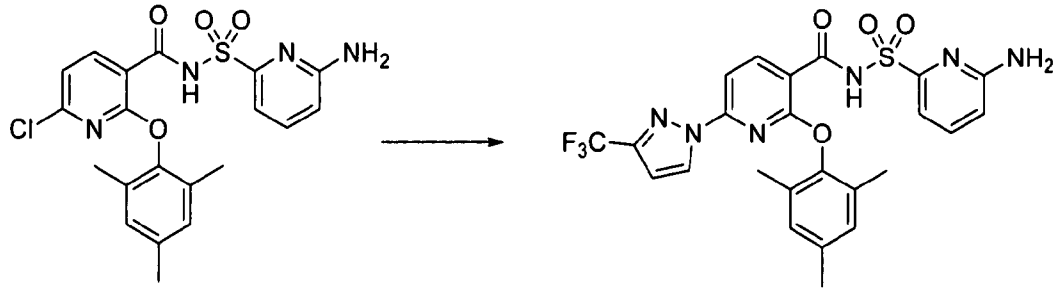
**製備51：2-(均三甲苯基氧基)-6-(丙-1-炔-1-基)菸鹼酸甲酯**



在連續氮氣流下丙-1-炔(25.78 μL，0.4543 mmol)鼓泡穿過*N,N*-二

甲基甲醯胺(2 mL)及三乙胺(409.6 μL，2.939 mmol)之溶液且接著添加至6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(150. mg，0.491 mmol)、三苯基膦二氯鈀(34.44 mg，0.04907 mmol)、碘化銅(I) (14.02 mg，0.07362 mmol)及三苯基膦(17.05 μL，0.07359 mmol)於去氧之*N,N*-二甲基甲醯胺(2 mL)中的混合物中。所得溶液用丙炔淨化且封蓋。接著反應物在105℃下攪拌16小時。冷卻之混合物用乙酸乙酯稀釋且通過矽藻土塞，用乙酸乙酯(10 mL)洗滌。將水(7.5 mL)添加至濾液中且分離各層。水層用乙酸乙酯(2×10 mL)萃取。合併之有機萃取物用飽和氯化鈉水溶液(10 mL)洗滌且經硫酸鈉乾燥。過濾後，在減壓下移除溶劑，得到深褐色殘餘物。殘餘物藉由管柱 矽膠層析，己烷中0-100%乙酸乙酯溶離來純化，得到6-丙-1-炔基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(102.4 mg，0.331 mmol，72.9%)。ESI-MS *m/z*計算值309.1365, 實驗值310.2 $(M+1)^+$；滯留時間: 0.76分鐘。

**製備52：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(三氟甲基)吡唑-1-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物676)**



將*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(30. mg，0.067 mmol)、5-(三氟甲基)-1*H*-吡唑(27.41 mg，0.2014 mmol)、碳酸鉀(19.49 mg，0.1410 mmol)及反-二胺基環己烷(1.534 mg，1.613 μL，0.01343 mmol)組合於*N,N*-二甲基甲醯胺中。此刻，添加碘化銅(I) (0.6393 mg，0.003357 mmol)且將反應物在微波中在150℃下加熱2小時。過濾反應物且藉由LC/MS，利用5 mM HCl水溶液中10-99%乙腈之梯度純化，得到*N*-[(6-胺基-2-吡啶基)磺醯

基]-6-[3-(三氟甲基)吡唑-1-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物676) (8 mg，0.01 mmol，20%)。$^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.54 (s, 1H), 8.32 (d, $J$ = 8.1 Hz, 1H), 7.85 (dd, $J$ = 2.6, 1.1 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.22 (dd, $J$ = 7.4, 0.8 Hz, 1H), 6.99 (d, $J$ = 2.6 Hz, 1H), 6.97 (s, 2H), 6.72 (d, $J$ = 8.4 Hz, 1H), 6.56 (s, 2H), 2.28 (s, 3H), 2.03 (s, 6H)。ESI-MS $m/z$ 計算值 546.1297，實驗值 547.2 $(M+1)^+$；滯留時間: 2.1分鐘。

以下化合物可使用本文所述之程序合成：

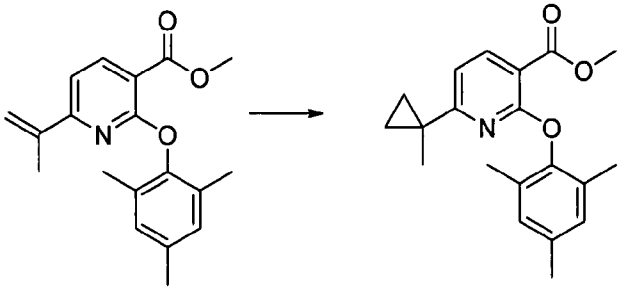
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-吡唑-1-基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物564)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[5-甲基-3-(三氟甲基)吡唑-1-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物633)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)吡唑-1-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物691)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲基吡唑-1-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1220)。

**製備53：2-(均三甲苯基氧基)-6-(1-甲基環丙基)菸鹼酸甲酯**

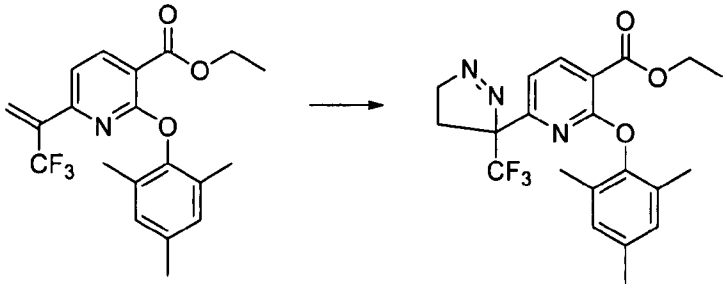


在微波小瓶中，在氮氣下三甲基氧化銻碘(5.2 g，23 mmol)懸浮於無水DMSO (26 mL)中。添加60%於油中之氫化鈉(1.0 g，26 mmol)且在室溫下攪拌所得溶液10分鐘。添加6-(丙-1-烯-2-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(2.6 g，8.4 mmol)，溶於無水THF (8 mL)中且在室溫下攪拌18小時。反應混合物分溶於水(100 mL)與乙酸乙酯

(3×100 mL)之間，分離，接著在減壓下濃縮有機相且所得殘餘物在矽膠上使用庚烷中0至10%乙酸乙酯來純化，得到呈油狀之所需產物6-(1-甲基環丙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(1.59 g，58% )。ESI-MS *m/z*計算值325.2, 實驗值326.2 $(M+1)^+$；$^1$H NMR (300 MHz, $CDCl_3$) ppm：0.60 (m, 2 H), 0.84 (m, 2 H), 1.36 (s, 3 H), 2.01 (s, 6 H), 2.28 (s, 3 H), 3.92 (s, 3 H), 6.83 (s, 2 H), 6.96 (d, *J* = 7.9 Hz, 1 H), 8.16 (d, *J* = 7.9 Hz, 1 H)。

**製備54：2-(均三甲苯基氧基)-6-(1-(三氟甲基)環丙基)菸鹼酸乙酯**

**步驟1：2-(均三甲苯基氧基)-6-(3-(三氟甲基)-4,5-二氫-3*H*-吡唑-3-基)菸鹼酸乙酯**

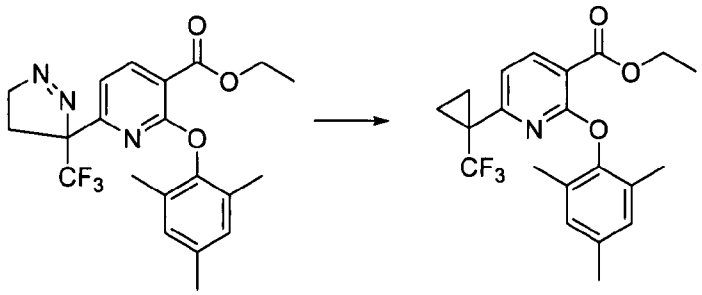


製備重氮甲烷於乙醚中之溶液：將*N*-亞硝基-*N*-甲基脲(1.87 g，15.8 mmol)添加至在冰浴中冷卻的40% KOH水溶液(6.7 mL)及二乙基醚(20 mL)之兩相混合物中。將混合物在冰浴中攪拌20分鐘(變黃)，且接著在乾冰/丙酮浴中冷卻。一旦水層冷凍，則傾析乙醚層且黃色溶液保持在氮氣下直至準備使用。

在0℃下以上重氮甲烷溶液(15.8 mmol)逐滴添加至6-(3,3,3-三氟丙-1-烯-2-基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯(1.5 g，3.95 mmol)於乙醚(20 mL)中之溶液中。重氮甲烷之黃色在添加後自發消失。將反應物在0℃下攪拌30分鐘，且TLC展示起始物質完全消耗。添加乙酸(1 mL)以淬滅過量重氮甲烷，直至其變成無色且停止放出氣泡。接著混合物用乙酸乙酯(50 mL)稀釋，用飽和碳酸氫鈉水溶液(20 mL)、鹽水(20 mL)洗滌，經無水硫酸鈉乾燥且濃縮，得到呈淺黃色油

狀之2-(均三甲苯基氧基)-6-(3-(三氟甲基)-4,5-二氫-3*H*-吡唑-3-基)菸鹼酸乙酯(1.7 g)。$^1$H NMR (300 MHz, $CDCl_3$) ppm, 1.40 (t, *J* = 6.9 Hz, 3 H), 1.68 - 1.92 (m, 2 H), 1.98 (br s, 6 H), 2.31 (s, 3 H), 3.90 - 4.10 (m, 1 H), 4.43 (q, *J* = 6.9 Hz, 2 H), 4.64 (ddd, *J* = 18.1, 9.5, 4.2 Hz, 1 H), 6.87 (s, 2 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 8.31 (d, *J* = 7.8 Hz, 1 H)。LCMS: $[M+H]^+$=422.2。

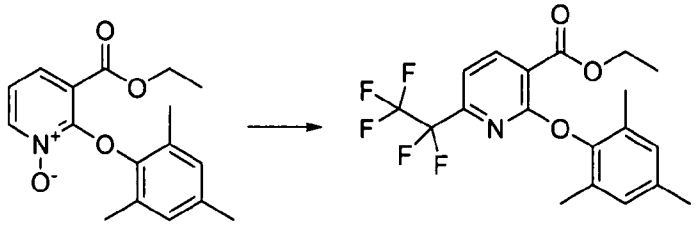
**步驟2：2-(均三甲苯基氧基)-6-(1-(三氟甲基)環丙基)菸鹼酸乙酯**



2-(均三甲苯基氧基)-6-(3-(三氟甲基)-4,5-二氫-3*H*-吡唑-3-基)菸鹼酸乙酯(1.7 g，粗，3.9 mmol)溶於間二甲苯(25 mL)中。溶液緩緩回流2小時。TLC展示反應結束。移除溶劑且殘餘物藉由矽膠層析，用乙酸乙酯及庚烷(0-10%)之混合物溶離來純化，得到1.6 g粗物質(定量產率)，呈6-[1-(三氟甲基)環丙基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯及6-[-1,1,1-三氟丁-2-烯-2-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯之不可分離之混合物(1:1)(烯烴之立體化學未確定)。爲移除烯烴，6-[1-(三氟甲基)環丙基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸酯及6-[(2Z或2E)-1,1,1-三氟丁-2-烯-2-基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯之混合物(1.5 g，3.81 mmol，1:1)溶於第三丁醇(5 mL)中。添加水(3 mL)，接著檸檬酸(549 mg，2.86 mmol)及氧化鉀銨(VI)脫水物(1.4 mg)。最終，添加4-甲基嗎啉*N*-氧化物單水合物(568 mg，4.2 mmol)。將混合物在室溫下攪拌隔夜。LCMS展示50%轉化。添加氧化鉀銨(VI)脫水物(1.4 mg)且繼續攪拌反應物直至HPLC展示反應結束(大

約40小時)。濃縮反應物以移除大部分第三丁醇。所得水性混合物用乙酸乙酯(60 mL)稀釋且用水(10 mL)、鹽水(10 mL)洗滌，經無水硫酸鈉乾燥且在減壓下濃縮。殘餘物藉由矽膠層析，用乙酸乙酯及庚烷(0-10%，接著50%)之混合物溶離來純化，得到呈白色固體狀之6-[1-(三氟甲基)環丙基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯(600 mg，40%)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 0.96 - 1.05 (m, 2 H), 1.15 - 1.23 (m, 2 H), 1.39 (t, $J$ = 7.2 Hz, 3 H), 2.01 (s, 6 H), 2.29 (s, 3 H), 4.41 (q, $J$ = 7.2 Hz, 2 H), 6.85 (s, 2 H), 7.25 (d, $J$ = 8.2 Hz, 1 H), 8.21 (d, $J$ = 8.2 Hz, 1 H)。LCMS: $[M+H]^+$ = 394.0。

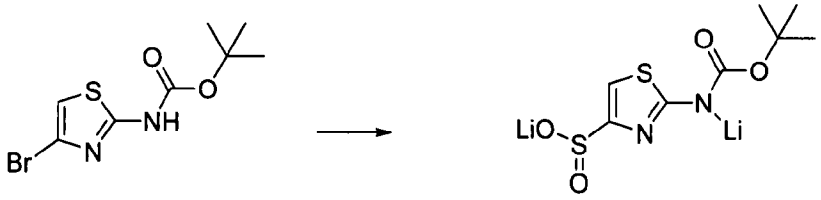
**製備55：2-(均三甲苯基氧基)-6-(全氟乙基)菸鹼酸乙酯**



在0℃下在密封管中，3-(乙氧基羰基)-2-(均三甲苯基氧基)吡啶1-氧化物(1.85 g，6.14 mmol)溶於具有直火乾燥之(在高真空下)氟化銫(93 mg，0.05 mmol)的無水四氫呋喃(18.5 mL)中，接著添加三甲基(五氟乙基)矽烷(3.53 g，18.4 mmol)且將反應混合物在室溫下在氮氣下攪拌5天。蒸餾水(10 mL)及乙酸乙酯(50 mL)添加至粗物質。有機相分離，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。所得殘餘物在矽膠上使用庚烷中0-10%乙酸乙酯來純化，得到呈油狀之6-(五氟乙基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸乙酯(480 mg，25%)。$[M + H]^+$ = 404.1 $^1$H NMR (300 MHz, $CDCl_3$) ppm：1.41 (t, $J$ = 7.1 Hz, 3 H), 2.03 (s, 6 H), 2.29 (s, 3 H), 4.45 (q, $J$ = 7.1 Hz, 2H), 6.87 (s, 2 H), 7.39 (d, $J$ = 7.7 Hz, 1 H), 8.36 (d, $J$ = 7.8Hz, 1 H)。

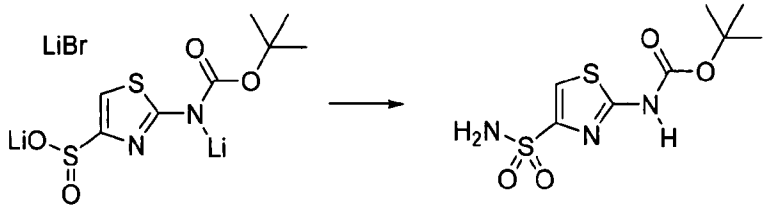
**製備56：(4-胺磺醯基噻唑-2-基)胺基甲酸第三丁酯**

**步驟1：(第三丁氧基羰基)(4-亞磺醯基噻唑-2-基)胺基鋰**



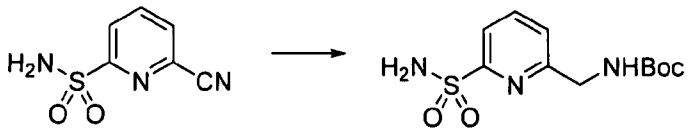
在-78℃下將甲基鋰(0.70 mL，1.6 M於二乙醚中，1.1 mmol)添加至*N*-(4-溴-1,3-噻唑-2-基)胺基甲酸第三丁酯(279 mg，1.00 mmol)於無水四氫呋喃(2 mL)及無水二乙基醚(2 mL)中之溶液中。5分鐘後，在-78℃下添加第三丁基鋰(1.2 mL，1.7 M於戊烷中，2 mmol)。形成淡黃色懸浮液。20分鐘後，在-78℃下二氧化硫(氣體)鼓泡至反應物5分鐘。獲得黃色透明溶液。使反應物緩慢升溫至室溫且攪拌隔夜。反應混合物濃縮至乾且殘餘物用二乙基醚(10 mL)濕磨，得到淡黃色固體(390 mg)，其爲(第三丁氧基羰基)(4-亞磺醯基噻唑-2-基)胺基鋰及溴化鋰之混合物。$[M+Na]^+$ = 287.0。

**步驟2：(4-胺磺醯基噻唑-2-基)胺基甲酸第三丁酯**



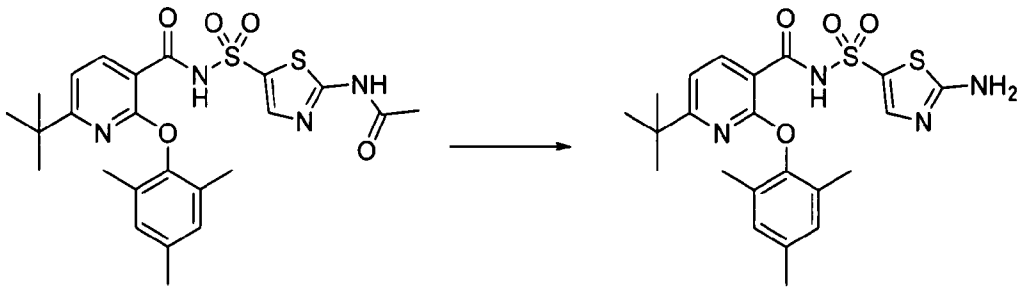
在0℃下將羥基胺-O-磺酸(147 mg，1.2 mmol)添加至2-{[(第三丁氧基)羰基]胺基}-1,3-噻唑-4-亞磺酸鋰(330 mg，含有溴化鋰，0.91 mmol)及乙酸鈉(148 mg，1.8 mmol)於水(4 mL)中之溶液中。將反應物在室溫下攪拌2小時。大量固體沈澱。HPLC展示完全轉化。將混合物在0℃下攪拌5分鐘。濾出固體，用冷水(1 mL)洗滌且在高真空下乾燥，得到呈白色固體狀之*N*-(4-胺甲醯基-1,3-噻唑-2-基)胺基甲酸第三丁酯(130 mg，51%)。$^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.49 (s, 9 H), 7.43 (s, 2 H), 7.67 (s, 1 H), 11.84 (br. s, 1 H)。$[M+Na]^+$ = 302.0。

**製備57：((6-胺磺醯基吡啶-2-基)甲基)胺基甲酸第三丁酯**



6-氰基吡啶-2-磺醯胺(1.00 g，5.46 mmol)於甲醇(25 mL)及氨(5 mL 7.0 N於甲醇中之溶液，35 mmol)中之溶液用一勺Raney鎳(2800，於水中之漿狀物)處理。燒瓶用氫氣淨化三次，接著在室溫下在一大氣壓氫氣下攪拌18小時。粗反應混合物經矽藻土墊過濾，用甲醇洗滌，且在減壓下濃縮。殘餘物溶解於二氯甲烷(25 mL)中且用三乙胺(1.52 mL，10.9 mmol)及二碳酸二第三丁酯(1.55 g，7.10 mmol)連續處理。約1小時後，添加四氫呋喃(10 mL)，試圖幫助溶解反應混合物。又一小時後，在減壓下濃縮反應物，轉移至具有水(50 mL)之250 mL分液漏斗且用乙酸乙酯(3×50 mL)萃取。合併之有機層用鹽水(50 mL)洗滌，經無水硫酸鈉乾燥，過濾，且在減壓下濃縮。殘餘物在40 g矽膠上，利用庚烷中50%至100%乙酸乙酯之梯度來純化，得到呈白色固體狀之((6-胺磺醯基吡啶-2-基)甲基)胺基甲酸第三丁酯(217 mg，14%)。$^1$H NMR (300 MHz, 丙酮-$d_6$) ppm 1.43 (s, 9 H), 4.43 (d, $J$ = 6.0 Hz, 2 H), 6.48 - 6.77 (m, 3 H), 7.58 (d, $J$ = 7.8 Hz, 1 H), 7.83 (d, $J$ = 7.8 Hz, 1 H), 7.97 - 8.10 (m, 1 H)。$[M+Na]^+$ = 310.1。

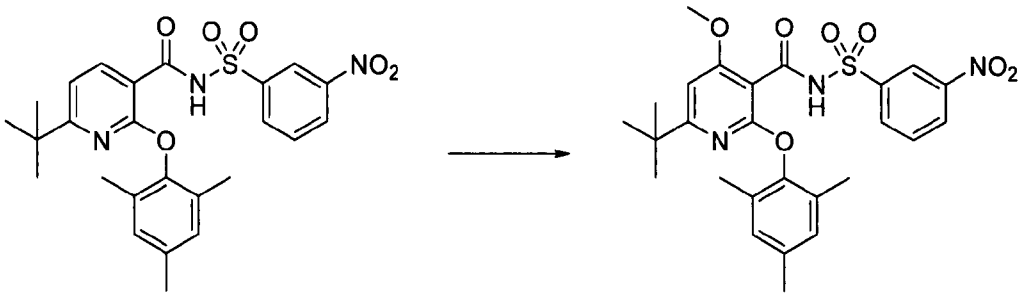
**製備58：*N*-(2-胺基噻唑-5-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1148)**



在4 mL小瓶中將*N*-(2-乙醯胺基噻唑-5-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(14.6 mg，0.0269 mmol)及鹽酸水溶液(268.5 µL 4 M，1.074 mmol)於二噁烷(277.4 µL)中之溶液在90℃

下攪拌1小時。冷卻反應混合物且直接藉由逆相製備型層析，利用C18管柱及含有5 mM鹽酸之水中30-99乙腈之梯度來純化，得到呈白色固體狀之*N*-(2-胺基噻唑-5-基)磺醯基-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1148) (5.9 mg，0.012 mmol，45%)。$^1$H NMR (400 MHz, DMSO) $\delta$ 12.10 (s, 1H), 8.02 (s, 2H), 7.95 (d, $J$ = 7.8 Hz, 1H), 7.67 (s, 1H), 7.12 (d, $J$ = 7.8 Hz, 1H), 6.90 (s, 2H), 2.25 (s, 3H), 1.97 (s, 7H), 1.04 (s, 10H)。ESI-MS *m/z*計算值474.1，實驗值475.2 $(M+1)^+$；滯留時間: 2.11分鐘。

**製備59：6-(第三丁基)-2-(均三甲苯基氧基)-4-甲氧基-*N*-((3-硝基苯基)磺醯基)菸鹼醯胺**

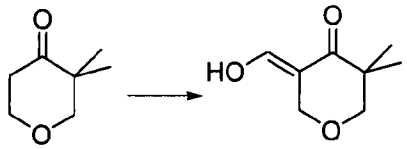


在10 mL微波容器中，添加6-第三丁基-*N*-(3-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(85 mg，0.17 mmol)，溶於無水甲醇(684.1 mg，864.9 μL，21.35 mmol)及二甲苯(850.0 μL)中且向其中添加二乙醯氧基鈀(3.835 mg，0.01708 mmol)、(二乙醯氧基碘)苯(165.0 mg，0.5124 mmol)及4Å分子篩。混合物在油浴中加熱至100℃，歷時18小時。添加第二等分之二乙醯氧基鈀(3.835 mg，0.01708 mmol)且反應混合物在油浴中加熱至100℃，再保持48小時。使混合物冷卻且過濾混合物且所得溶液藉由逆相製備型層析，利用C18管柱及含有5 mM鹽酸之水中30-99乙腈之梯度來純化，得到6-第三丁基-4-甲氧基-*N*-(3-硝基苯基)磺醯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(20.7 mg，0.0388 mmol，23%)。$^1$H NMR (400 MHz, DMSO) $\delta$ 12.89 (s, 1H), 8.61 (t, $J$ = 2.0 Hz, 1H), 8.49 (d, $J$ = 8.2 Hz, 1H), 8.36 (d, $J$ = 8.1 Hz, 1H),

7.92 (t, $J$ = 8.1 Hz, 1H), 6.82 (s, 2H), 6.72 (s, 1H), 3.84 (s, 3H), 2.22 (s, 3H), 1.86 (s, 6H), 1.03 (s, 10H)。ESI-MS $m/z$計算值527.1726, 實驗值528.2 $(M+1)^+$；滯留時間: 2.2分鐘。

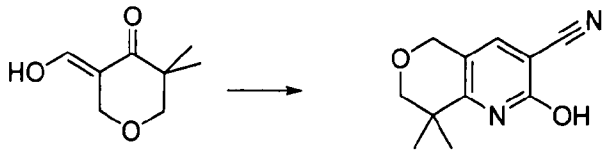
**製備60：2-氯-8,8-二甲基-7,8-二氫-5*H*-哌喃并[4,3-*b*]吡啶-3-甲腈**

**步驟1：5-(羥基亞甲基)-3,3-二甲基四氫-4*H*-哌喃-4-酮**



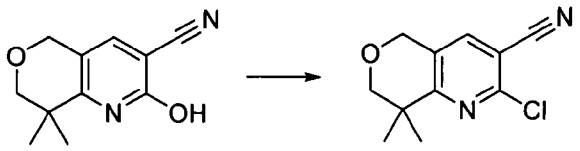
向3,3-二甲基四氫哌喃-4-酮(1.8 g，14 mmol)於乙醚(50 mL)中之溶液中添加甲酸乙酯(1.040 g，1.134 mL，14.04 mmol)。冷卻混合物至0℃。在0℃下添加乙醇鈉(1.051 g，15.44 mmol)。使混合物升溫至室溫，攪拌隔夜且接著蒸發至乾。粗物質未經進一步純化直接用於下一步。

**步驟2：2-羥基-8,8-二甲基-7,8-二氫-5*H*-哌喃并[4,3-*b*]吡啶-3-甲腈**



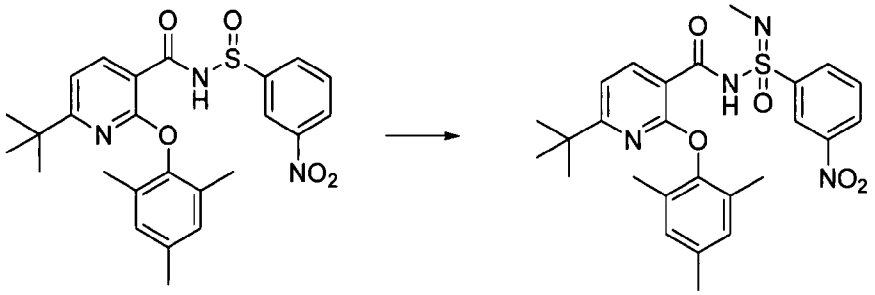
向5-(羥基亞甲基)-3,3-二甲基-四氫哌喃-4-酮(2.2 g，14 mmol)於吡啶(100 mL)中之懸浮液添加2-氰基乙醯胺(1.177 g，14.00 mmol)。混合物在回流下加熱隔夜。反應混合物蒸發至乾且殘餘物分溶於乙酸乙酯與水之間。水層用乙酸乙酯萃取三次，且接著用二氯甲烷與異丙醇之2:1 混合物萃取三次。合併之有機層用鹽水洗滌，經硫酸鎂乾燥，過濾，且蒸發至乾。殘餘物用甲醇洗滌，得到產物(205 mg，1.00 mmol，7.1%)。$^1$H NMR (400 MHz, 氯仿-$d$) $\delta$ 7.55 (s, 1H), 4.54 (s, 2H), 3.61 (s, 2H), 3.49 (s, 1H), 1.42 (s, 6H)。

**步驟3：2-氯-8,8-二甲基-7,8-二氫-5*H*-哌喃并[4,3-*b*]吡啶-3-甲腈**



將2-羥基-8,8-二甲基-7,8-二氫-5*H*-哌喃并[4,3-*b*]吡啶-3-甲腈(240. mg，1.17 mmol)於氧氯化磷(2.5 mL，26.82 mmol)中之混合物加熱至105℃，保持6小時。反應混合物蒸發至乾。殘餘物逐滴添加至水，且接著用乙酸乙酯萃取三次。合併之有機層用鹽水洗滌，經硫酸鎂乾燥，過濾，且濃縮至乾。粗物質藉由矽膠管柱層析(己烷中0-10%乙酸乙酯)來純化，得到呈黃色固體狀之2-氯-8,8-二甲基-7,8-二氫-5*H*-哌喃并[4,3-*b*]吡啶-3-甲腈(240. mg，1.08 mmol，92.3%)。$^1$H NMR (400 MHz, 氯仿-*d*) $\delta$ 7.57 (s, 1H), 4.78 (d, $J$ = 0.9 Hz, 2H), 3.71 (s, 2H), 1.33 (s, 6H)。

**製備61：6-(第三丁基)-2-(均三甲苯基氧基)-*N*-(*N*-甲基-3-硝基苯基磺醯亞胺醯基)菸鹼醯胺**

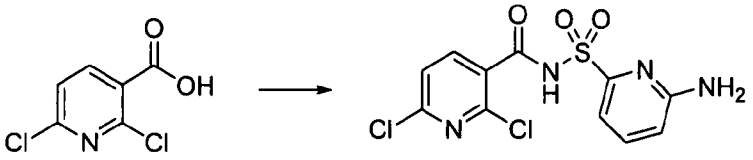


在0℃下向*rac*-6-第三丁基-*N*-(3-硝基苯亞磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(253 mg，0.525 mmol)於乙腈(4.1 mL)中之溶液中添加*N*-氯丁二醯亞胺(217 mg，1.63 mmol)。接著混合物在室溫下攪拌直至不再有起始物質(約1小時)。在0℃下將甲胺 (0.79 mL 2.0 M於THF中之溶液，1.6 mmol)添加至反應物中且將混合物在室溫下攪拌1小時且接著藉由添加水(3 mL)淬滅。混合物用乙酸乙酯(2×10 mL)萃取，合併有機層，經硫酸鈉乾燥，過濾，且在減壓下濃縮。殘餘物在25 g矽膠上，利用庚烷中0%至45%乙酸乙酯之梯度來純化，得到呈白

色固體狀之6-(第三丁基)-2-(均三甲苯基氧基)-*N*-(*N*-甲基-3-硝基苯基磺醯亞胺醯基)菸鹼醯胺(170 mg，63%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.06 (s, 9 H), 2.02 (s, 6 H), 2.28 (s, 3 H), 2.78 (s, 3 H), 6.83 (s, 2 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 7.74 (t, *J* = 8.0 Hz, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 8.38 (d, *J* = 8.3 Hz, 1 H), 8.45 (d, *J* = 7.7 Hz, 1 H), 8.83 - 8.87 (m, 1 H)。$[M+H]^+$ = 511.1。

**製備62：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-甲氧基-2-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物470)**

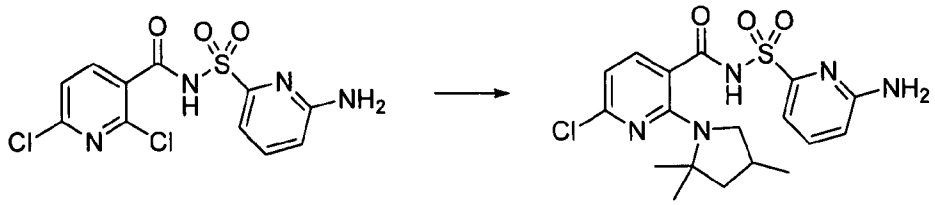
**步驟1：*N*-((6-胺基吡啶-2-基)磺醯基)-2,6-二氯菸鹼醯胺**



2,6-二氯-吡啶-3-甲酸(20.2 g，105 mmol)溶於*N,N*-二甲基甲醯胺(200 mL)中且在氮氣下攪拌且一次性添加CDI (25.5 g，158 mmol)。反應物升溫至65℃且加熱1小時。在另一個容器中，在氮氣下6-胺基吡啶-2-磺醯胺(18.2 g，105 mmol)溶於*N,N*-二甲基甲醯胺(100 mL)中且分部分添加NaH (4.40 g，60%，110 mmol)以減輕氣體放出，且將反應物攪拌1小時。在65℃下兩種反應物一次性合併。將反應物攪拌30分鐘且蒸發以移除大部分*N,N*-二甲基甲醯胺。殘餘物傾倒在冰上且藉由添加6M HCl呈酸性(約pH= 3)。固體藉由過濾收集且用水(100 mL)及甲醇(30 mL)洗滌且在乾燥後與以下粗物質合併。濾液與洗滌物合併且用乙酸乙酯(3×500 mL)萃取。有機物用鹽水(500 mL)洗滌一次，經硫酸鈉乾燥且蒸發。粗物質懸浮於二氯甲烷/乙酸乙酯/甲醇(30/30/30 mL)之混合溶劑中，懸浮液音波處理30分鐘，且過濾。固體用乙醚(2×150 mL)洗滌且乾燥，得到19.8 g白色固體(54%)。濾液進一步濃縮，得到6.0 g (16%)產物。LCMS: 347 [M+H]+；$^1$H NMR

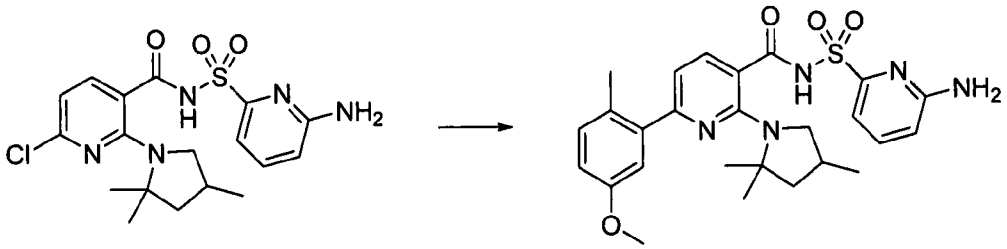
(DMSO-$d_6$, 250 MHz): 8.11 (d, $J$ = 7.5 Hz, 1H), 7.80-7.55 (m, 2H), 7.19 (d, $J$ = 7.2 Hz, 1H), 6.75 (d, $J$ = 8.5 Hz, 1H), 6.71 (s, 2H) ppm

**步驟2：*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯胺**



*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-二氯-吡啶-3-甲醯胺(1.02 g，2.94 mmol)、2,2,4-三甲基吡咯啶(鹽酸(1)) (1.319 g，8.814 mmol)及碳酸鉀(2.030 g，14.69 mmol)組合於二甲亞碸(8.160 mL)中且在100℃下加熱16小時。反應物用水稀釋且pH值調至7。水性混合物用乙酸乙酯(3×100 mL)萃取。合併有機物，用鹽水洗滌，經硫酸鈉乾燥且蒸發。粗物質藉由矽膠層析，用己烷中0-100%乙酸乙酯溶離來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(700. mg，1.65 mmol，56.2%)。ESI-MS *m/z*計算值423.1132，實驗值424.2 $(M+1)^+$；滯留時間: 0.63分鐘。

**步驟3：**



*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(42 mg，0.10 mmol)、(5-甲氧基-2-甲基-苯基)硼酸(25 mg，0.15 mmol)、肆(三苯基膦)鈀(0) (11 mg，0.010 mmol)及2M碳酸鉀水溶液(0.2 mL，4 mmol)組合於*N*,*N*-二甲基甲醯胺(1 mL)中且在微波反應器中在120℃下照射20分鐘。過濾反應物且藉由LC/MS，

利用5 mM HCl水溶液中10-99%乙腈之梯度純化，得到呈鹽酸鹽形式之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-甲氧基-2-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物470)(12 mg，0.022 mmol，22%)。ESI-MS *m/z*計算值509.21，實驗值510.5 $(M+1)^+$；滯留時間：1.42分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(鄰甲苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物761)，

*N*-(苯磺醯基)-6-(3-氟-5-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1538)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-環丙基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1627)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1636)

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物630)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-[(4R)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物890)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物852)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物946)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,4-二甲基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物614)，

5-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-[(4S)-2,2,4-三甲基吡咯啶-1-基]-2-吡啶基]-3,6-二氫-2*H*-吡啶-1-甲酸第三丁酯(化合物

1371)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-3-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-5-(6-異丙氧基-3-吡啶基)吡嗪-2-甲醯胺(化合物1651)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氟-5-異丁氧基-苯基)-3-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺(化合物1526)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-降冰片烷-2-基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1378)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丙烯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1423)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6,6-二甲基-2,3-二氫哌喃-4-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1369)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氫-2H-哌喃-6-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1438)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二氫呋喃-4-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1455)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2-二甲基丙基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1489)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1500)，

*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]-6-四氫哌喃-2-基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1503)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2-二甲基丙-1-烯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1510)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氫-2H-哌喃-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1524)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-四氫呋喃-3-基-2-[(4S)-2,2,4-三甲

基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1534)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-四氫哌喃-3-基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1632)，

6-(1-乙醯基-4-哌啶基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1634) (化合物946)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)環己烯-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1664)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-環丙基乙基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1677)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)環己基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1672)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-羥基-5,5-二甲基-環己基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1439)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,3-二甲基-6-側氧基-環己烯-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1462)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丙基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1505)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-乙基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1507)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,6-二氫-2H-哌喃-4-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1594)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-四氫哌喃-4-基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1595)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-異丁基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1599)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-[(4S)-2,2,4-三甲基吡

咯啶-1-基]-2-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸第三丁酯(化合物1624)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲基丙-1-烯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1683)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-[(4S)-2,2,4-三甲基吡咯啶-1-基]-2-吡啶基]-2,3-二氫吡咯-1-甲酸第三丁酯(化合物1684)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟-2-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物822)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-苯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1334)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物712)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-氟-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1099)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(對甲苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物456)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物695)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1194)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-丙氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物644)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1021)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物440)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物693)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物504)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1020)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1100)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物847)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-5-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1109)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1094)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物1266)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-丙氧基-苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物692)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-(4-甲基-1-哌啶基)吡啶-3-甲醯胺(化合物777)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-苯基-吡啶-3-甲醯胺(化合物805)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-氟苯基)吡啶-3-甲醯胺(化合物1029)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-甲氧基苯基)吡啶-3-甲醯胺(化合物1215)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-乙氧基-5-氟-苯基)吡啶-3-甲醯胺(化合物551)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物459)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丁氧基-苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1197)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丁氧基苯基)吡啶-3-甲醯胺(化合物563)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丙基苯基)吡啶-3-甲醯胺(化合物1343)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-異丙氧基-苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物788)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物773)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(2-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物807)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-異丁氧基苯基)吡啶-3-甲醯胺(化合物957)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-甲氧基-2-吡啶基)吡啶-3-甲醯胺(化合物1141)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(對甲苯基)吡啶-3-甲醯胺(化合物1078)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(4-氟-3-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2472)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2587)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2-氟-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1967)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2199)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(間甲苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2339)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1819)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2-氟-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2016)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2-甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2666)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2240)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3,4-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2229)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(4-甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2327)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2,4-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1947)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2-乙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2050)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2,3-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2110)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-乙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2570)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3,5-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1716)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(4-乙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2525)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2,5-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2489)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2-異丙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1897)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-異丙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2156)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(4-異丙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2120)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-[2-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2070)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-苯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1725)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-[3-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2029)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2-氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2045)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-[4-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1763)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2414)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-[3-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2220)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-[4-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1900)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3,5-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1839)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3,4-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2605)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2,3-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2225)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(2,5-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1736)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(5-氟-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2490)，

2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-乙氧基-5-氟-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物382)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-異丁氧基苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物710)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(2-氟-5-異丁氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物681)，

6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物832)，

6-(4-氯-3-異丁氧基-苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1234)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-甲氧基-2-吡啶基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1236)，

6-(4-氯-3-異丙氧基-苯基)-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物701)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丙氧基-苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1285)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丁氧基苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物1335)，

2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丙基苯基)-*N*-(1H-吡唑-5-基磺醯基)吡啶-3-甲醯胺(化合物414)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-5-甲基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1269)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-5-甲基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物995)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基苯基)-5-甲基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物455)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-甲氧基苯基)-5-甲基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物833)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟苯基)-5-甲基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物763)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-5-甲基-吡啶-3-甲醯胺(化合物483)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)-5-甲基-吡啶-3-甲醯胺(化合物486)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-甲氧基-2-甲基-苯基)-5-甲基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1287)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-4-甲氧基-吡啶-3-甲醯胺(化合物1254)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-吡啶基)-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物643)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物896)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙基-4-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1262)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丙基吡唑-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1067)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丁基吡唑-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物631)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙基吡唑-3-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1242)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-[異丁基(甲基)胺基]-4-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物898)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基吡嗪-2-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1252)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-異丙氧基吡嗪-2-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物965)

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙氧基嘧啶-5-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物844)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-2-甲基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物616)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-5-(2-羥基-2-甲基-丙氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1424)，

*N*-(苯磺醯基)-6-[3-氟-5-(3-羥基-2-甲基-丙氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1515)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-5-(3-羥基-2-甲基-丙氧基)

苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1567)，

*N*-(苯磺醯基)-6-[3-氟-5-(2-羥基-2-甲基-丙氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1581)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(5-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物400)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[5-(環戊氧基)-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物495)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲氧基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物526)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(5-異丁氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1224)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(E)-2-環丙基乙烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1379)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,3-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2291)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-乙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1822)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,5-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2105)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-乙氧基-3-氟-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2403)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,4-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1871)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2205)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-異丙氧基苯基)-2-[(4S)-2,2,4-

三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2623)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(5-乙氧基-2-氟-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2149)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-乙氧基-2-氟-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1847)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-乙氧基-4-氟-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1808)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-乙氧基-5-氟-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2018)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-乙氧基-4-氟-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2665)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氯苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2183)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-甲基-1-萘基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2126)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2539)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2245)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2223)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2040)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4,5-二氟-2-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2334)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(三氟甲基)苯基]-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2593)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,5-二氟-2-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2006)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(鄰甲苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1766)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2048)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,3-二氟-4-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2302)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,5-二氟-4-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2457)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,4-二氟-5-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1998)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-甲氧基-2,3-二甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2450)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,4-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2447)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2164)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1H-吲哚-6-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2054)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-乙氧基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2241)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1-甲基吲哚-6-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2401)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氰基苯基)-2-[(4S)-2,2,4-三甲

基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2437)，

2-[5-[(2-胺基-3-吡啶基)磺醯基胺甲醯基]-6-[(4S)-2,2,4-三甲基吡咯啶-1-基]-2-吡啶基]吲哚-1-甲酸第三丁酯(化合物2657)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1790)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-乙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1945)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1873)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氰基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1824)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2435)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氰基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2096)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-羥基-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1731)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-2-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2446)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1H-吡咯并[2,3-b]吡啶-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1714)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1-異丙基吡唑-4-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2290)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-甲氧基-2,6-二甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2607)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1-異丁基吡唑-4-基)-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2231)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-甲氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2244)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-甲氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1980)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-甲氧基-4-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2646)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-(二甲基胺基)-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2319)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-甲氧基-2-甲基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1866)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(羥基甲基)-5-甲氧基-苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2065)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-甲氧基-5-甲基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2564)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-異喹啉基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2418)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(5-氟-6-甲氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2628)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,4-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1854)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-甲氧基-2-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2268)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,6-二甲氧基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2091)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,5-二氟苯基)-2-[(4S)-2,2,4-三

甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2272)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,3-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1713)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氯苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2367)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,5-二甲基異噁唑-4-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2215)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-羥基-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1999)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(二氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2644)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(間甲苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1829)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(對甲苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2132)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氟-2-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2653)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(5-氟-2-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2046)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-5-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2349)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,5-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1951)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,3-二氫苯并呋喃-7-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2163)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-甲氧基-3-甲基-苯基)-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1747)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-羥基-3-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2592)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-羥基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2426)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-甲氧基-3-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2380)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(羥基甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1738)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-甲氧基-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2379)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(5-氟-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2660)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-羥基-3-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2158)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-甲氧基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2413)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-4-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1851)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-異丁基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2150)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟-6-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2033)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟-3-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2562)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,4-二甲氧基苯基)-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2664)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(5-氟-2-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2189)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氟-3-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2052)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟-5-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2474)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氟-2-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2482)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-5-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1869)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟-4-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1818)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-2-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2355)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(羥基甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2590)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-氟-3-甲氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2124)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2345)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-萘基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2280)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1-萘基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1857)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-苯基-2-[(4S)-2,2,4-三甲基吡咯啶

-1-基]吡啶-3-甲醯胺(化合物1958)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氯苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2066)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,5-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2127)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,4,5-三氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2035)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-氟-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2613)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,3-二氫-1,4-苯并二氧雜環己烯-6-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2522)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-異丙基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2172)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2667)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-乙氧基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1964)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2515)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,4-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2017)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-異丙氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1903)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1944)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-異丁氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2448)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丙基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1991)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,6-二甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1994)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-異丙基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2368)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,3-二甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2436)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-羥基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2257)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,5-二甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2195)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-羥基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1820)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-(羥基甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1706)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-羥基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1712)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,4-二甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1705)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-氟-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2505)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1962)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,5-二甲氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1825)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-甲氧基-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2494)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-(羥基甲基)-4-甲氧基-苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1707)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,4-二甲氧基嘧啶-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2008)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氟-3-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1930)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1922)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基-2,5-二甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2227)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-氟-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1910)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2616)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丙氧基吡唑-1-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2658)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2638)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,2-二氟-1,3-苯并間二氧雜環戊烯-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2104)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-羥基-5-甲基-苯基)-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2232)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,4-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2372)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2236)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-羥基-3-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2203)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-羥基-5-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2034)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2566)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-2-羥基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2386)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-羥基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2555)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-羥基-4-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2043)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,4-二氟苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2559)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1969)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1785)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二氟-4-異丙氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2608)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-4,5-二甲基-苯基)-2-

[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1931)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2392)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3,5-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1771)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-甲基-2-丙氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2085)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(三氟甲基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2296)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,3-二甲基苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2287)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丁基吡唑-3-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2114)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(三氟甲氧基)苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2366)，

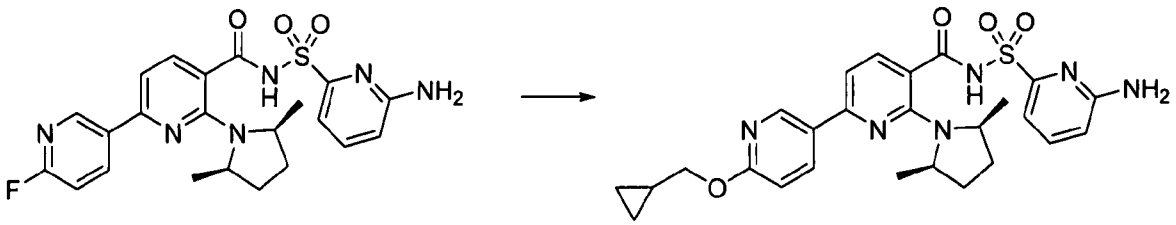
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(二氟甲氧基)-3-甲基-苯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2543)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-氟-2-甲基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2394)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-乙氧基-2-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物536)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-甲氧基-2,5-二甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1259)。

**製備63：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(環丙基甲氧基)-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物789)**



*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-氟-3-吡啶基)吡啶-3-甲醯胺(50. mg，0.11 mmol)及環丙基甲醇(77 mg，1.1 mmol)組合於DMSO (1 mL)中，冷卻至0℃且將NaH (12.75 mg，0.5315 mmol)添加至反應混合物中。混合物加熱至90℃，保持3小時。反應混合物過濾且接著使用逆相HPLC-MS法，使用Phenomenex售出(pn：00B-4252-P0-AX)之Luna C18管柱(50 × 21.2 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度操作來純化。移動相A = $H_2O$ (含有5 mM HCl)。移動相B = $CH_3CN$。流速 = 35 mL/min，注射體積 = 950 μL，及管柱溫度= 25℃。254 nm下UV吸收用於收集溶離份。收集所需溶離份，用20 mL $NaHCO_3$中和，用乙酸乙酯萃取，用鹽水洗滌，經硫酸鈉乾燥，過濾，且濃縮，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(環丙基甲氧基)-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物789) (24 mg，0.046 mmol，42%)。1H NMR (400 MHz, DMSO-$d_6$) δ 8.78 (d, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.60 - 7.42 (m, 2H), 7.01 (bs, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.51 (d, *J* = 8.6 Hz, 1H), 6.23 (bs, 2H), 4.23 (s, 2H), 4.13 (d, *J* = 7.1 Hz, 2H), 1.86 (bs, 2H), 1.56 (bs, 2H), 1.25 (dddd, *J* = 11.9, 7.3, 5.4, 2.6 Hz, 1H), 1.04 (d, *J* = 6.1 Hz, 6H), 0.59 - 0.49 (m, 2H), 0.36 - 0.26 (m, 2H)。ESI-MS *m/z*計算值522.2049, 實驗值523.3 $(M+1)^+$；滯留時間: 1.96分鐘

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-3-吡啶

基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1270)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-4-甲基-2-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1656)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基-4-甲基-2-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1512)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-4-甲基-2-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1637)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二氟甲氧基)-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1679)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(6-異丁氧基-2-甲基-3-吡啶基)吡啶-3-甲醯胺(化合物1537)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-(2-乙氧基乙氧基)乙基-甲基-胺基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2684)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-乙氧基乙基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2685)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-乙氧基乙基胺基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2686)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-2-甲基-3-吡啶基)吡啶-3-甲醯胺(化合物1623)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-4-甲基-3-吡啶基)吡啶-3-甲醯胺(化合物1514)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-[6-(異丁基胺基)-3-吡啶基]吡啶-3-甲醯胺(化合物1398)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[[(1S)-1,3-二甲基丁基]胺基]-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1463)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-[6-[異丁基(甲基)胺基]-3-吡啶基]吡啶-3-甲醯胺(化合物1506)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-6-[6-(1-乙基丙基胺基)-3-吡啶基]吡啶-3-甲醯胺(化合物1397)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[[(1S)-1,2-二甲基丙基]胺基]-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1399)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[異丙基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2687)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丙基胺基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2688)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[乙基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2689)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[[(1R)-1,2-二甲基丙基]胺基]-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1442)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[[(1R)-1,3-二甲基丁基]胺基]-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1527)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(4-異丁氧基-2-吡啶基)吡啶-3-甲醯胺(化合物389)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-2-吡啶基)-2-(2,2,4-

三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物397)，

2-[[5-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-2-吡啶基]-2-吡啶基]氧基]丙酸甲酯(化合物723)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基吡嗪-2-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1523)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[異丁基(甲基)胺基]-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物412)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丁氧基-2-吡啶基)吡啶-3-甲醯胺(化合物432)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丙基胺基)-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物437)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物471)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(6-異丁氧基-3-吡啶基)吡啶-3-甲醯胺(化合物544)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丁基胺基)-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物569)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(1-乙基丙氧基)-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物580)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-2-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物708)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(1,2-二甲基丙氧基)-2-吡啶基]-2-(2,2-二甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物717)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)吡嗪-2-基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物779)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二乙基胺基)-3-吡啶基]-2-

(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物796)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-2-甲基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物814)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[異丁基(甲基)胺基]-2-甲基-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物827)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(1,3-二甲基丁氧基)-2-吡啶基]-2-(2,2-二甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物846)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異戊基氧基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物848)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-4-甲基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物851)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-4-甲基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物905)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丙基胺基)-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物951)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基吡嗪-2-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物988)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基吡咯啶-1-基)-6-(6-異丁氧基-2-吡啶基)吡啶-3-甲醯胺(化合物1011)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丁基胺基)-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1059)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1062)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(1-乙基丙氧基)-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1076)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異戊基氧基-2-吡啶基)-2-

(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1135)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-4-甲基-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1160)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-3-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1181)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-2-吡啶基]-2-(2,2-二甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1328)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二乙基胺基)-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1345)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(1,3-二甲基丁氧基)-4-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物384)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(異丁基胺基)-4-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物523)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-丙氧基-4-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物491)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丁氧基-4-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1192)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙氧基-4-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物402)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丁氧基-4-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1618)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-3-甲基-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1645)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-3-甲基-2-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1659)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-2-吡啶

基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1663)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-5-甲基-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1610)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基-5-甲基-2-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1363)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二乙基胺基)-3-甲基-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1383)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丁基胺基)-3-甲基-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1417)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙氧基)-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1504)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(環丁氧基)-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物428)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-[6-(2-羥基-1-甲基-乙氧基)-3-吡啶基]吡啶-3-甲醯胺(化合物998)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[(1R)-2-苯甲氧基-1-甲基-乙氧基]-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物576)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基-5-甲基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1727)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二乙基胺基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1915)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-[2-(2-疊氮基乙氧基)乙氧基]乙氧基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丁氧基-5-甲基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1741)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[異丁基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2279)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[5-甲基-6-[(1R)-1-甲基丙氧基]-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2576)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-異丙氧基-5-甲基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2170)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-(2-乙氧基乙氧基)乙氧基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1715)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[5-甲基-6-[(1S)-1-甲基丙氧基]-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1728)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-[2-(2-異丙氧基乙氧基)乙氧基]乙氧基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1787)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-(3-丁-3-炔基二氮雜環丙烯-3-基)乙氧基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-乙氧基乙氧基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2404)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-異丙氧基乙氧基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物

1973)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-甲氧基乙氧基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2582)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(2-乙氧基乙氧基)-6-甲基-4-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1948)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(2-異丙氧基乙氧基)-6-甲基-4-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2079)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-(二乙基胺基)-6-甲基-4-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1739)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丁氧基-6-甲基-4-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2010)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[2-[2-(2-乙氧基乙氧基)乙氧基]-6-甲基-4-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1812)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基-6-甲基-4-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2364)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-異丙氧基-6-甲基-4-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2306)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-甲氧基-6-甲基-4-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1748)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-5-甲基-3-吡啶基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1702)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-(2-乙氧基乙氧基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2497)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-乙氧基-5-甲基-3-吡啶基)-2-

[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2651)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-[2-(2-乙氧基乙氧基)乙氧基]-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1783)，

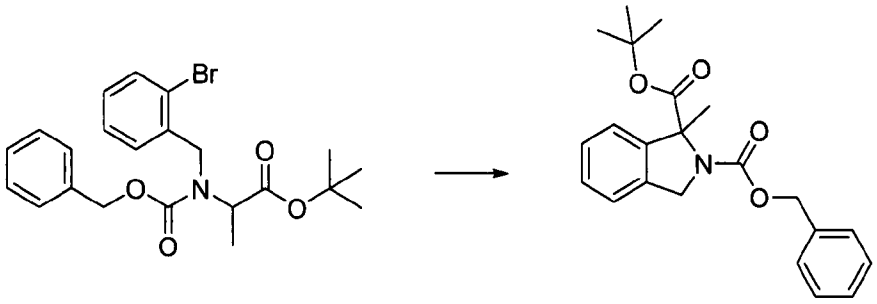
*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-(2-異丙氧基乙氧基)-5-甲基-3-吡啶基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1695)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-[6-[(1-甲基環丙基)甲氧基]-3-吡啶基]吡啶-3-甲醯胺(化合物454)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(環丙氧基)-3-吡啶基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1125)。

**製備64：1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸**

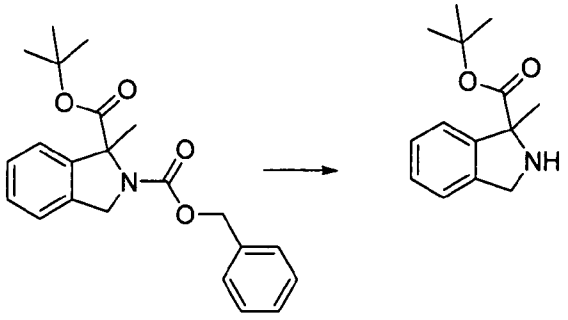
**步驟1：1-甲基異吲哚啉-1,2-二甲酸2-苯甲酯1-(第三丁基)酯**




將2-[苯甲氧基羰基-[(2-溴苯基)甲基]胺基]丙酸第三丁酯(2.69 g，6.00 mmol)於二噁烷(30 mL)中之溶液用氮氣淨化2分鐘。在氮氣下添加2-(2-二苯基磷烷基苯基)-*N*,*N*-二甲基-苯胺(228.9 mg，0.6000 mmol)，接著添加參(二苯亞甲基丙酮)二鈀(0) (274.7 mg，0.3000 mmol)。將第三丁醇鋰(960.7 mg，12.00 mmol)添加至反應混合物中。混合物加熱至90℃，歷時16小時，用乙酸乙酯稀釋且過濾。殘餘物藉由矽膠管柱層析(己烷中0-10% 乙酸乙酯)來純化，得到1-甲基異吲哚

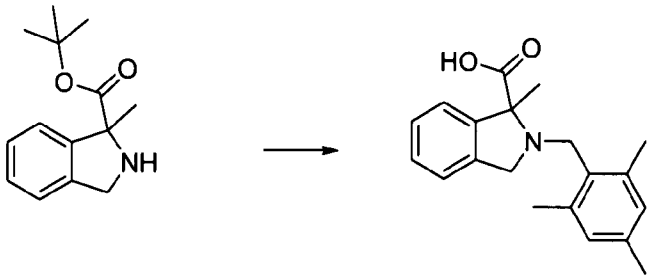
啉-1,2-二甲酸2-苯甲酯1-(第三丁基)酯(1.4 g，3.8 mmol，63%)。ESI-MS *m/z*計算值367.17834，實驗值368.4 $(M+1)^+$；滯留時間: 2.75分鐘。

**步驟2：1-甲基異吲哚啉-1-甲酸第三丁酯**



將1-甲基異吲哚啉-1,2-二甲酸2-苯甲酯1-(第三丁基)酯(718 mg，1.95 mmol)於甲醇(50 mL)中之溶液用氮氣淨化2分鐘。添加鈀/碳(10% w/w，104.0 mg，0.09770 mmol)且混合物置於氫氣氛圍下16小時。催化劑經由矽藻土過濾移除且濾液濃縮至乾，得到1-甲基異吲哚啉-1-甲酸第三丁酯(400. mg，1.71 mmol，87.7%)。粗物質未經進一步純化直接用於下一步。

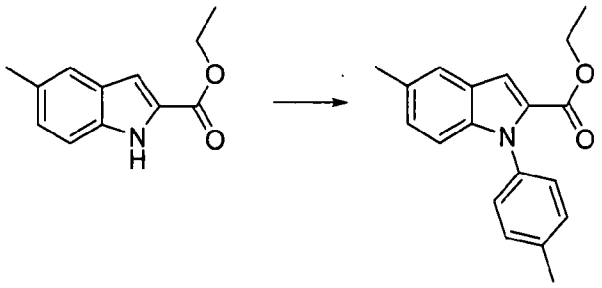
**步驟3：1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸**



向1-甲基異吲哚啉-1-甲酸第三丁酯(1.5 g，6.4 mmol)於乙腈(75.00 mL)中之溶液中添加2-(氯甲基)-1,3,5-三甲基-苯(1.084 g，6.429 mmol)及碳酸銫(4.190 g，12.86 mmol)。將混合物在90℃下加熱隔夜，且接著分溶於乙酸乙酯與水之間。水層用乙酸乙酯萃取。合併之有機層用鹽水洗滌，經硫酸鎂乾燥，過濾，且濃縮至乾。粗物質藉由二氧化矽管柱層析，利用己烷中0-5%乙酸乙酯之梯度純化，得到1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸第三丁酯。接著此物

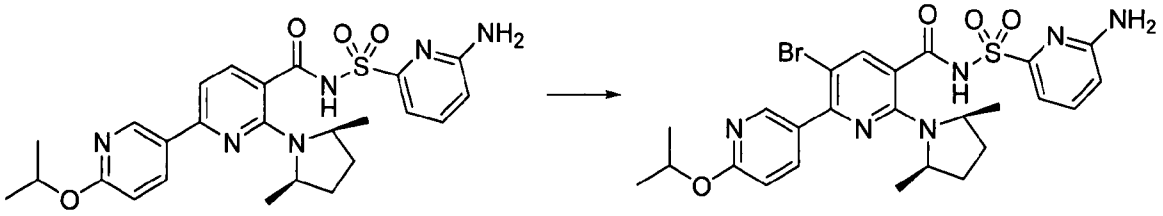
質溶於二噁烷(3.2 mL)中且將鹽酸之二噁烷溶液(5 mL 4 M，20.00 mmol)添加至混合物中。將混合物在室溫下攪拌16小時。接著混合物在70℃下攪拌1小時。反應混合物冷卻至室溫，沈澱過濾且用二噁烷洗滌，得到灰白色固體。1-甲基-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲酸(0.98 g，3.2 mmol，49%)。ESI-MS *m/z*計算值309.17288, 實驗值310.5 $(M+1)^+$；滯留時間: 1.18分鐘 (3分鐘操作)。

**製備65：5-甲基-1-(對甲苯基)-1*H*-吲哚-2-甲酸乙酯**



將5-甲基-1*H*-吲哚-2-甲酸乙酯(2.032 g，10.00 mmol)、1-碘-4-甲基-苯(2.180 g，10.00 mmol)、碘基銅(95.22 mg，0.5000 mmol)、*N*1,*N*2-二甲基環己烷-1,2-二胺(284.5 mg，315.4 μL，2.000 mmol)及磷酸鉀(4.458 g，21.00 mmol)於甲苯(50.00 mL)中之混合物加熱至回流，保持22小時。冷卻之反應物過濾且蒸發。綠色殘餘物藉由矽膠層析，使用己烷中0-15%乙酸乙酯純化，得到呈無色油狀之5-甲基-1-(對甲苯基)-1*H*-吲哚-2-甲酸乙酯(1.43 g，4.875 mmol，48.74%)。ESI-MS *m/z*計算值293.14, 實驗值294.2 $(M+1)^+$；滯留時間: 0.83分鐘(1分鐘操作)。

**製備66：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物390)**

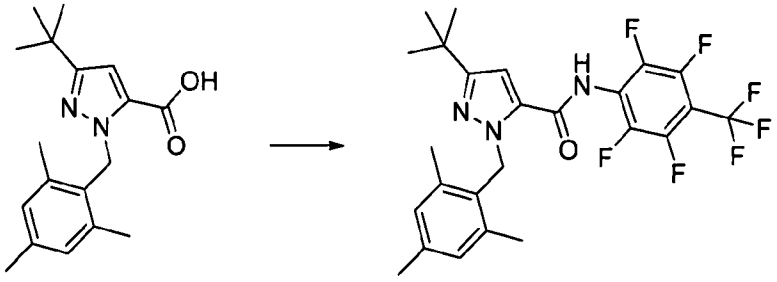


將含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-

1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(147.4 mg，0.2887 mmol)之乙酸(1.5 mL)用溴(69.20 mg，22.31 μL，0.4330 mmol)處理且在室溫下攪拌1小時。所得黃色懸浮液用水(20 mL)稀釋，藉由添加飽和碳酸氫鈉水溶液淬滅至pH 2-3且用二氯甲烷萃取。粗物質藉由矽膠層析(12 g)，使用0至5%甲醇之二氯甲烷溶液之線性梯度來純化，得到呈黃色泡沫狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物390) (90. mg，0.14 mmol，50%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.80 (s, 1H), 8.52 (dd, $J$ = 2.5, 0.7 Hz, 1H), 8.02 (dd, $J$ = 8.7, 2.5 Hz, 1H), 7.85 (s, 1H), 7.64 (t, $J$ = 7.8 Hz, 1H), 7.23 (d, $J$ = 7.2 Hz, 1H), 6.83 (dd, $J$ = 8.6, 0.7 Hz, 1H), 6.72 (d, $J$ = 8.4 Hz, 1H), 6.51 (s, 2H), 5.32 (p, $J$ = 6.2 Hz, 1H), 3.95 (s, 2H), 1.97 - 1.82 (m, 2H), 1.64 (dd, $J$ = 8.9, 5.3 Hz, 2H), 1.33 (d, $J$ = 6.2 Hz, 6H), 1.04 (d, $J$ = 6.1 Hz, 6H)。ESI-MS *m/z* 計算值588.1154, 實驗值589.0 $(M+1)^+$；滯留時間: 2.25分鐘。

**製備67：3-(第三丁基)-4-甲氧基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸**

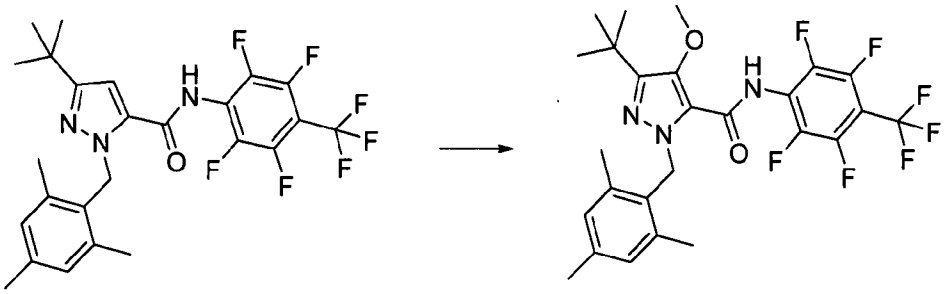
**步驟1：3-(第三丁基)-*N*-(2,3,5,6-四氟-4-(三氟甲基)苯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺**




在含有5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸1 (500. mg，1.66 mmol)之20 mL密封燒瓶中，添加*N*-甲基吡咯啶酮(5.000 mL)及二異丙基胺(537.7 mg，724.7 μL，4.160 mmol)，接著丙基磷酸酐溶液(2.118 mL 50% w/v，3.328 mmol)及2,3,5,6-四氟-4-(三氟

甲基)苯胺(426.5 mg，1.830 mmol)且將所得混合物在80℃下攪拌16小時。該物質用乙酸乙酯(10 mL)稀釋，用水洗滌且萃取有機層。有機層用飽和碳酸氫鈉水溶液，接著鹽水洗滌兩次。該物質 經無水硫酸鈉乾燥，過濾，且在真空下濃縮。所得粗物質吸附至矽藻土且藉由矽膠管柱層析((40 g)，使用0至50%乙酸乙酯之梯度)來純化，得到5-第三丁基-*N*-[2,3,5,6-四氟-4-(三氟甲基)苯基]-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(748 mg，1.44 mmol，86.4%)。ESI-MS *m/z*計算值515.1808, 實驗值516.2 $(M+1)^+$；滯留時間: 2.58分鐘。$^1$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 7.01 (s, 1H), 6.83 (s, 2H), 5.64 (s, 2H), 2.27 (s, 6H), 2.21 (s, 3H), 1.20 (s, 9H)。

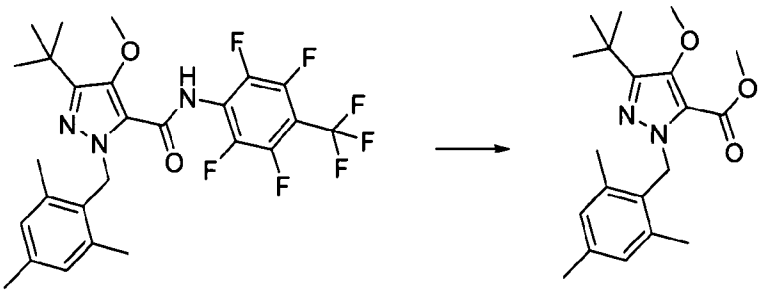
**步驟2：3-(第三丁基)-4-甲氧基-*N*-(2,3,5,6-四氟-4-(三氟甲基)苯基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲醯胺**



將5-第三丁基-*N*-[2,3,5,6-四氟-4-(三氟甲基)苯基]-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(200. mg，0.388 mmol)、無水甲醇(1.554 g，1.965 mL，48.50 mmol)、二甲苯(2.000 mL)、二乙醯氧基鈀(8.711 mg，0.03880 mmol)、(二乙醯氧基碘)苯(374.9 mg，1.164 mmol)及4A分子篩組合於封蓋10 mL小瓶中。混合物在油浴中加熱至100℃，保持40小時。使混合物冷卻，用水稀釋，用二氯甲烷(10 mL)萃取三次，且合併之有機物用飽和碳酸氫鈉水溶液且接著飽和氯化鈉水溶液洗滌。有機層經硫酸鈉乾燥且接著藉由矽膠管柱層析(24 g)，利用己烷中0至50%乙酸乙酯之梯度純化，得到呈灰白色固體狀之5-第三丁基-4-甲氧基-*N*-[2,3,5,6-四氟-4-(三氟甲基)苯基]-2-[(2,4,6-三甲基苯基)

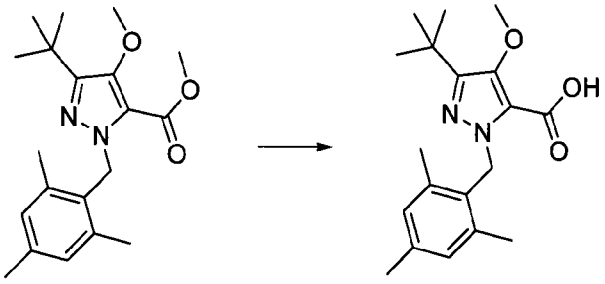
甲基]吡唑-3-甲醯胺(161 mg，0.295 mmol，76.1%)。ESI-MS *m/z*計算值545.19135，實驗值546.2 $(M+1)^+$；滯留時間：2.4分鐘。$^1$H NMR (400 MHz, DMSO) $\delta$ 10.76 (s, 1H), 6.83 (s, 2H), 5.39 (s, 2H), 3.79 (s, 3H), 2.28 (s, 6H), 2.20 (s, 3H), 1.25 (s, 9 H)。

**步驟3：3-(第三丁基)-4-甲氧基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸甲酯**



5-第三丁基-4-甲氧基-*N*-[2,3,5,6-四氟-4-(三氟甲基)苯基]-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(161 mg，0.295 mmol)溶於無水四氫呋喃(3.220 mL)中且在0℃下向混合物添加(雙(三甲基矽烷基)胺基)鋰(442.7 μL 1 M於四氫呋喃中，0.4427 mmol)且將所得混合物攪拌10分鐘。接著添加氯甲酸甲酯(83.66 mg，68.41 μL，0.8853 mmol)且將反應混合物攪拌1小時，且接著在減壓下濃縮。殘餘物再溶於無水四氫呋喃(3.220 mL)中且接著在冰水浴中冷卻混合物至0℃。添加甲醇鈉 (319.0 μL 25% w/v於甲醇中，1.476 mmol)且將反應混合物攪拌10分鐘。混合物用水稀釋，用乙酸乙酯(10 mL)萃取三次且合併之有機物用鹽水洗滌。混合物經硫酸鈉乾燥，且接著藉由逆相製備型層析，利用含有5 mM鹽酸水溶液之水中10至99%乙腈之梯度來純化，得到呈灰白色固體狀之3-(第三丁基)-4-甲氧基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸甲酯(25.8 mg，0.0749 mmol，25.4%)。ESI-MS *m/z*計算值344.21，實驗值345.2 $(M+1)^+$；滯留時間：1.92分鐘。

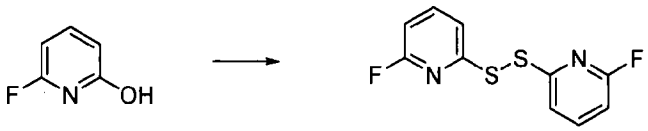
**步驟4：3-(第三丁基)-4-甲氧基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸**



向含3-(第三丁基)-4-甲氧基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸甲酯(30. mg，0.087 mmol)之無水四氫呋喃(600.0 μL)添加氫氧化鈉(108.9 μL 4 M，0.4355 mmol)。混合物加熱至70℃且攪拌3小時。使混合物冷卻且接著其直接藉由逆相製備型層析，利用含有5 mM鹽酸水溶液之水中10至99%乙腈之梯度來純化，得到呈灰白色固體狀之3-(第三丁基)-4-甲氧基-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸(27.3 mg，0.0826 mmol，95%)。ESI-MS *m/z*計算值330.19434, 實驗值331.2 $(M+1)^+$；滯留時間: 2.08分鐘。

**製備68：*N*-[胺基-(6-胺基-2-吡啶基)-側氧基-$l^{6}-亞硫基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1602) (化合物1481) (化合物515)**

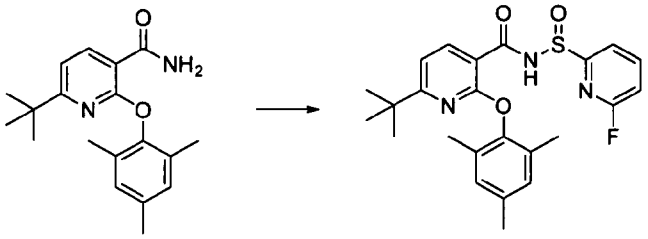
**步驟1：2-氟-6-[(6-氟吡啶-2-基)二硫基]吡啶**



使2-氟-6-羥基吡啶(1.13 g，10.0 mmol)及五硫化磷(4.44 g，20.0 mmol)於甲苯(50 mL)中之混合物回流18小時。一旦冷卻，燒瓶置於冰浴中且用水(50 mL)淬滅且接著用25% NaOH鹼化至約pH 8-9。混合物經矽藻土過濾以移除一些仍然存在之固體且用水(50 mL)及乙酸乙酯(200 mL)洗滌。兩相混合物轉移至1.0 L分液漏斗，萃取且分離各層。水層再次用乙酸乙酯(100 mL)萃取，且接著有機層合併，用鹽水洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。殘餘物藉由矽膠管柱層析，庚烷中0%至10% 乙酸乙酯溶離來純化，得到呈無色油狀之2-

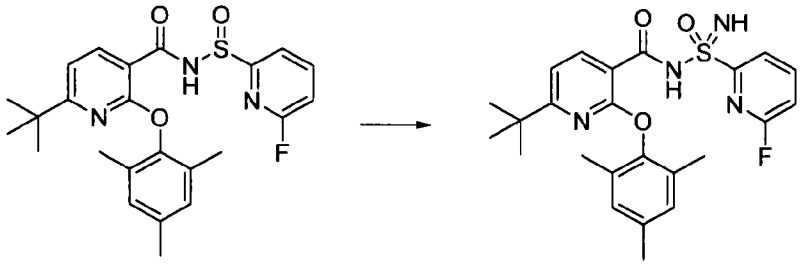
氟-6-[(6-氟吡啶-2-基)二硫基]吡啶(304 mg，23.7%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 6.75 (ddd, $J$ = 8.0, 2.7, 0.5 Hz, 1 H), 7.49 (ddd, $J$ = 7.7, 2.1, 0.6 Hz, 1 H), 7.72 (q, $J$ = 7.9 Hz, 1 H)。$[M+H]^+$ = 257.0。

**步驟2：6-第三丁基-*N*-[(6-氟吡啶-2-基)亞磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



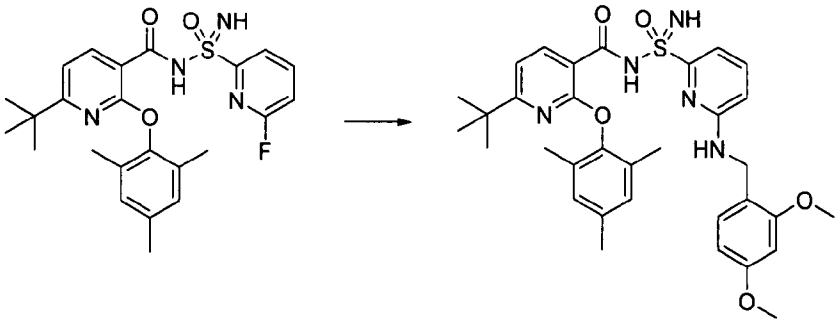
在0℃下向2-氟-6-[(6-氟吡啶-2-基)二硫基]吡啶(744 mg，2.90 mmol)及6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(906 mg，2.90 mmol)於吡啶(10 mL)及乙腈(10 mL)中之溶液中逐滴添加溴(0.172 mL，3.36 mmol)。添加結束後，將混合物在室溫下攪拌隔夜。在室溫下添加額外溴(0.087 mL，1.7 mmol)且將混合物再攪拌1小時。接著在減壓下移除溶劑且在減壓下吡啶進一步與甲苯(10 mL)共蒸發兩次。殘餘物藉由矽膠管柱層析(24g)管柱，庚烷中0%至25%乙酸乙酯溶離來純化，得到呈灰白色固體狀之6-第三丁基-*N*-[(6-氟吡啶-2-基)亞磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(850 mg，64%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 1.08 (s, 9 H), 2.00 (s, 6 H), 2.29 (s, 3 H), 6.86 (s, 2 H), 7.03 - 7.89 (m, 1 H), 7.12 (d, $J$ = 8.0, 1 H), 7.99 - 8.11 (m, 2 H), 8.53 (d, $J$ = 8.0 Hz, 1 H)。$^{19}$F NMR (282 MHz, $CDCl_3$): ppm -64.8 (s, 1 F)。$[M+H]^+$ = 456.1。

**步驟3：6-(第三丁基)-*N*-(6-氟吡啶-2-磺醯亞胺醯基)-2-(均三甲苯基氧基)菸鹼醯胺**



在0℃下向6-第三丁基-*N*-[(6-氟吡啶-2-基)亞磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(419 mg，0.920 mmol)於二氯甲烷(10 mL)中之溶液中添加次氯酸第三丁酯(94.8 μL，0.87 mmol)。將混合物在此溫度下攪拌2天。接著在減壓下在低於21℃下移除溶劑。粗產物未經進一步純化直接用於下一步驟。在0℃下殘餘物溶解於乙腈(11 mL)中，接著添加六甲基二矽氮烷(1.09 mL，5.22 mmol)。將混合物在室溫下攪拌1小時，接著藉由添加水(3 mL)淬滅。混合物用乙酸乙酯(2×20 mL)萃取，經硫酸鈉乾燥，過濾，且在減壓下濃縮。殘餘物藉由矽膠管柱層析管柱(24 g)，0%至5%甲醇之二氯甲烷溶液溶離來純化，得到呈白色固體狀之6-(第三丁基)-*N*-(6-氟吡啶-2-磺醯亞胺醯基)-2-(均三甲苯基氧基)菸鹼醯胺(286 mg，70%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 1.08 (s, 9 H), 2.03 (s, 6 H), 2.29 (s, 3 H), 6.84 (s, 2 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 7.16 (ddd, *J* = 8.0, 2.6, 0.8 Hz, 1 H), 7.94 - 8.11 (m, 2 H), 8.35 (d, *J* = 8.0 Hz, 1 H)。$^{19}$F NMR (282 MHz, $CDCl_3$): ppm -64.1 (s, 1 F)。$[M+H]^+$ = 471.1。

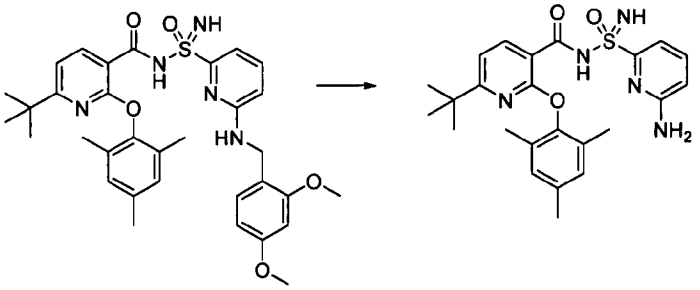
**步驟4：6-(第三丁基)-*N*-(6-((2,4-二甲氧基苯甲基)胺基)吡啶-2-磺醯亞胺醯基)-2-(均三甲苯基氧基)菸鹼醯胺**



將6-(第三丁基)-*N*-(6-((2,4-二甲氧基苯甲基)胺基)吡啶-2-磺醯亞

胺醯基)-2-(均三甲苯基氧基)菸鹼醯胺(400. mg，0.850 mmol)、2,4-二甲氧基苯甲基胺 (0.25 mL，1.7 mmol)及三乙胺(0.24 mL，1.7 mmol)於二甲亞碸(10 mL)中之混合物在100℃下攪拌隔夜。完成後，混合物用乙酸乙酯(20 mL)稀釋，用鹽水(2×10 mL)洗滌，經硫酸鈉乾燥，過濾，且在減壓下濃縮。殘餘物藉由逆相管柱層析，在25 g管柱上，含有0.1%甲酸之水中0%至100%乙腈溶離來純化，得到呈黃色泡沫狀之6-(第三丁基)-*N*-(6-((2,4-二甲氧基苯甲基)胺基)吡啶-2-磺醯亞胺醯基)-2-(均三甲苯基氧基)菸鹼醯胺(426 mg，81.1%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 1.07 (s, 9 H), 2.03 (s, 6 H), 2.27 (s, 3 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 4.42 (s, 2 H), 5.18 - 5.35 (br. s., 1 H), 6.36 (dd, *J* = 8.3, 2.3 Hz, 1 H), 6.45 (d, *J* = 2.3 Hz, 1 H), 6.52 (d, *J* = 8.3 Hz, 1 H), 6.81 (s, 2 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 7.18 (d, *J* = 8.3 Hz, 1 H), 7.28 (d, *J* = 7.4 Hz, 1 H), 7.45 (dd, *J* = 8.5, 7.4 Hz, 1 H), 8.38 (d, *J* = 7.9 Hz, 1 H)。$[M+H]^+$ = 618.2。

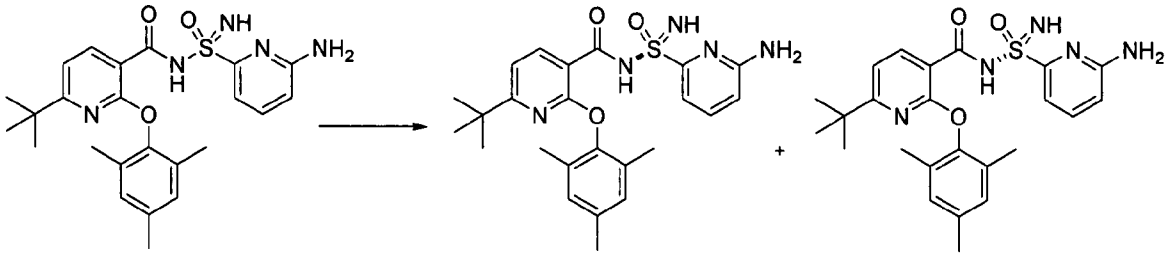
**步驟5：*N*-(6-胺基吡啶-2-磺醯亞胺醯基)-6-(第三丁基)-2-(均三甲苯基氧基)菸鹼醯胺**



向攪拌之*N*-[胺基(6-{[(2,4-二甲氧基苯基)甲基]胺基}吡啶-2-基)側氧基-λ$^6$-亞硫基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(420 mg，0.68 mmol)於二氯甲烷(50 mL)中溶液中添加三氟乙酸(12 mL)且攪拌混合物，直至LCMS指示完成。將反應混合物用二氯甲烷(20 mL)及水(20 mL)稀釋且藉由添加固體$NaHCO_3$，pH值調至超過6。混合物用二氯甲烷(2×20 mL)萃取且合併之有機層經硫酸鈉乾燥，過

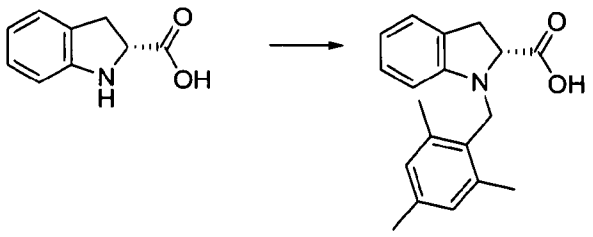
濾且在減壓下濃縮。殘餘物藉由逆相管柱層析，在25 g管柱上，含有0.1%甲酸之水中0%至100%乙腈溶離來純化，得到呈白色固體狀之*N*-(6-胺基吡啶-2-磺醯亞胺醯基)-6-(第三丁基)-2-(均三甲苯基氧基)菸鹼醯胺(90. mg，28%產率)。$^1$H NMR (300 MHz, $CDCl_3$ + 5滴DMSO-$d_6$) ppm 0.96 (s, 9 H), 1.90 (s, 6 H), 2.17 (s, 3 H), 5.78 (br. s., 2 H), 6.59 (d, $J$ = 8.2 Hz, 1 H), 6.71 (s, 2 H), 6.82 (d, $J$ = 7.8 Hz, 1 H), 7.19 - 7.31 (m, 3 H), 7.36 - 7.47 (m, 1 H), 8.15 (d, $J$ = 7.8 Hz, 1 H)。$[M+H]^+$ = 468.1。

**步驟6：*N*-[(*S*)-胺基(6-胺基吡啶-2-基)側氧基-λ$^6$-亞硫基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺及*N*-[(*R*)-胺基(6-胺基吡啶-2-基)側氧基-λ$^6$-亞硫基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺**



*N*-(6-胺基吡啶-2-磺醯亞胺醯基)-6-(第三丁基)-2-(均三甲苯基氧基)菸鹼醯胺溶於甲醇及二甲亞碸混合物(4:1 (v/v))中至約16 mg/mL之濃度。溶液進行對掌性SFC (注射70 µL；管柱：Chiralpak OD-H (250×21.2 mm)，5 µm；移動相：20%甲醇，80% $CO_2$；流速：10.0 mL/min)，得到*N*-[(*S*)-胺基(6-胺基吡啶-2-基)側氧基-λ$^6$-亞硫基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(峰1，對映異構體1，98% ee)及*N*-[(*R*)-胺基(6-胺基吡啶-2-基)側氧基-λ$^6$-亞硫基]-6-第三丁基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(峰2，對映異構體2，97.3% ee)。絕對立體化學未知。

**製備69：(*R*)-1-(2,4,6-三甲基苯甲基)吲哚啉-2-甲酸**



將(*R*)-吲哚啉-2-甲酸(300. mg，1.84 mmol)及氫氧化鉀(309.5 mg，5.517 mmol)之懸浮液在異丙醇(2.010 mL)中攪拌20分鐘。將反應混合物攪拌20分鐘且用2-(氯甲基)-1,3,5-三甲基-苯(341.2 mg，2.023 mmol)處理。將反應混合物攪拌隔夜。反應混合物用乙酸乙酯及水稀釋。混合物用乙酸乙酯萃取且水層酸化至pH 5且再用乙酸乙酯萃取。合併之有機物用水、鹽水洗滌，經硫酸鈉乾燥，過濾且濃縮，得到呈白色固體狀之(*R*)-1-(2,4,6-三甲基苯甲基)吲哚啉-2-甲酸(220. mg，0.745 mmol，40.5%)。ESI-MS *m/z*計算值295.15723，實驗值296.5 $(M+1)^+$；滯留時間: 1.79分鐘。

**製備70：2,3,4,5-四氫-1*H*-1-苯并氮呯-2-甲酸第三丁酯**

**步驟1：3-(2-溴苯基)丙-1-醇**



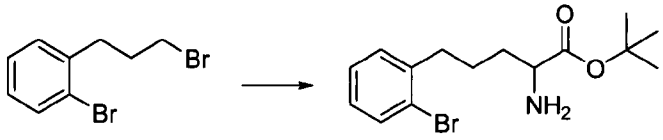
在0℃下將3-(2-溴苯基)丙酸(1.0 g，4.4 mmol)於無水四氫呋喃(5.0 mL)中之溶液用含硼烷-四氫呋喃複合物之四氫呋喃(1.0 M，7.0 mL，7.0 mmol)處理15分鐘之時間。將混合物在0℃下再攪拌1小時。結束後，殘餘硼烷藉由小心添加水(1 mL)淬滅且在真空下移除溶劑。所得殘餘物溶於乙醚(20 mL)中且有機層用水(20 mL)、鹽水(20 mL)洗滌，經硫酸鈉乾燥，過濾，且在壓力下濃縮，得到呈無色油狀之3-(2-溴苯基)丙-1-醇(938 mg，定量產率)。此化合物未經進一步純化即用於以下步驟中。

**步驟2：合成1-溴-2-(3-溴丙基)苯**



在0℃下向3-(2-溴苯基)丙-1-醇(938 mg，4.36 mmol)及三苯基膦(2.29 g，8.72 mmol)於無水二氯甲烷(25 mL)中之溶液中添加*N*-溴丁二醯亞胺(1.63 g，9.16 mmol)且將混合物在室溫下攪拌2小時。結束後，反應藉由添加水(20 mL)來淬滅且分離有機層且經硫酸鈉乾燥，過濾且在壓力下濃縮。殘餘物藉由矽膠層析(40 g)，庚烷中0%至10%乙酸乙酯溶離來純化，得到呈黃色油狀之1-溴-2-(3-溴丙基)苯(830 mg，68.5%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 2.13 - 2.24 (m, 2 H), 2.90 (t, $J$ = 7.7 Hz, 2 H), 3.43 (t, $J$ = 6.5 Hz, 2 H), 7.04 - 7.12 (m, 1H), 7.20 - 7.28 (m, 2 H), 7.54 (d, $J$ = 7.7 Hz, 1 H)。$[M+H]^+$ = 279.1。

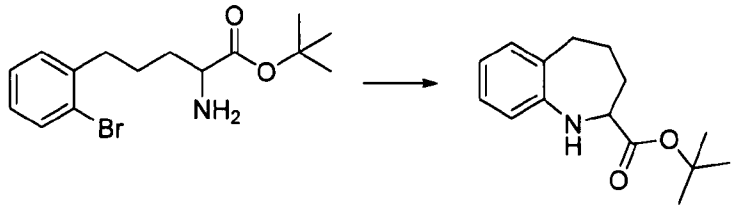
**步驟3：2-胺基-5-(2-溴苯基)戊酸第三丁酯**



向在冷水浴中冷卻的氫氧化鉀(1.27 g，22.6 mmol)於二甲亞碸(10 mL)中之懸浮液中添加*N*-(二苯基亞甲基)甘胺酸第三丁酯(2.23 g，7.55 mmol)。接著逐滴添加1-溴-2-(3-溴丙基)苯(938 mg，4.36 mmol)之二甲亞碸(10 mL)且將混合物在室溫下攪拌1小時。結束後，混合物用乙酸乙酯(100 mL)稀釋且溶液過濾。混合物用水(3×50 mL)、鹽水洗滌，經硫酸鈉乾燥，過濾，且在減壓下濃縮。在高真空下乾燥後，殘餘物溶於四氫呋喃(78 mL)中。在0℃下向此溶液中逐滴添加1 N HCl (75.7 mL，75.7 mmol)且將混合物在此溫度下再攪拌2小時。接著所得混合物藉由添加固體碳酸氫鈉中和且用二氯甲烷(100 mL)萃取。有機層經硫酸鈉乾燥，過濾且在壓力下濃縮。殘餘物藉由矽膠層析(80 g)，庚烷中0%至10% 乙酸乙酯溶離來純化，得到呈黃色油狀之2-胺基-5-(2-溴苯基)戊酸第三丁酯(2.21 g，86.4%產率2步)。$^1$H NMR (300

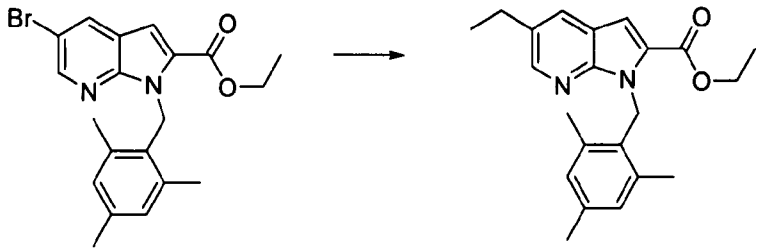
MHz, $CDCl_3$) ppm 1.45 (s, 9 H), 1.60 - 1.81 (m, 2 H), 2.70 - 2.78 (m, 2 H), 3.33 - 3.39 (m, 2 H), 7.00 - 7.09 (m, 1 H), 7.18 - 7.24 (m, 2 H), 7.51 (d, $J$ = 8.1 Hz, 1 H)。$[M+H]^+$ = 328.1。

**步驟4：2,3,4,5-四氫-1*H*-1-苯并氮呯-2-甲酸第三丁酯**



將2-胺基-5-(2-溴苯基)戊酸第三丁酯(1.7 g，5.2 mmol)、乙酸鈀(116 mg，0.518 mmol)、三苯基膦(408 mg，1.55 mmol)及碳酸銫(3.4 g，10. mmol)於甲苯(80 mL)中之混合物在110℃攪拌隔夜。結束後，混合物用乙酸乙酯(100 mL)稀釋且用水(50 mL)、鹽水(50 mL)洗滌，經硫酸鈉乾燥，過濾，且在減壓下濃縮。殘餘物藉由矽膠層析(80 g)，庚烷中0%至20%乙酸乙酯溶離來純化，得到呈黃色油狀之2,3,4,5-四氫-1*H*-1-苯并氮呯-2-甲酸第三丁酯(527 mg，41.0%)。$^1H$ NMR (300 MHz, $CDCl_3$) ppm 1.46-1.57 (m, 10 H), 1.66-1.82 (m, 1 H), 1.94-2.08 (m, 1 H), 2.24-2.36 (m, 1 H), 2.65-2.77 (m, 1 H), 2.78-2.91 (m, 1 H), 3.44 (dd, $J$ = 10.7, 2.3 Hz, 1 H), 4.50 (br. s, 1 H), 6.79-6.88 (m,2 H), 7.01-7.11 (m, 2 H)。$[M+H]^+$ = 248.2

**製備71：5-乙基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲酸酯**

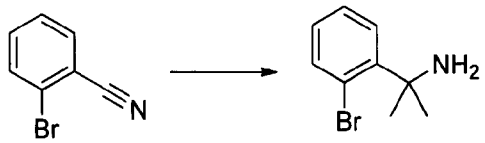


使5-溴-1-[(2,4,6-三甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲酸甲酯(150. mg，0.387 mmol)、1,2-二甲氧基乙烷(1.35 mL)、4,4,5,5-四甲基

-2-乙烯基-1,3,2-二氧雜硼雜環戊烷(119.3 mg，0.7746 mmol)及碳酸鉀(187.4 mg，1.356 mmol)於1,2-二甲氧基乙烷(1.35 mL)及水(0.45 mL)中之溶液脫氣且放在氮氣下。反應混合物用肆(三苯基膦)鈀(0) (44.75 mg，0.03873 mmol)處理且在微波反應器中在120℃下照射30分鐘。混合物用水稀釋且用乙酸乙酯萃取三次。合併之有機物用鹽水洗滌，經硫酸鈉乾燥，過濾，且在減壓下濃縮。所得粗1-[(2,4,6-三甲基苯基)甲基]-5-乙烯基-吡咯并[2,3-b]吡啶-2-甲酸甲酯溶解於甲醇(12.45 mL)中且放在氮氣氛圍下，接著用濕10%鈀/碳(41.22 mg，0.03873 mmol)處理。將混合物抽空且放在氫氣氛圍下16小時。反應混合物放在氮氣氛圍下且經矽藻土過濾，得到粗產物，其在12 g矽膠上，利用己烷中0-40%乙酸乙酯之梯度來純化，得到5-乙基-1-[(2,4,6-三甲基苯基)甲基]吡咯并[2,3-b]吡啶-2-甲酸甲酯。ESI-MS *m/z*計算值336.18378, 實驗值337.5 $(M+1)^+$；滯留時間: 2.24分鐘。

**製備72：**

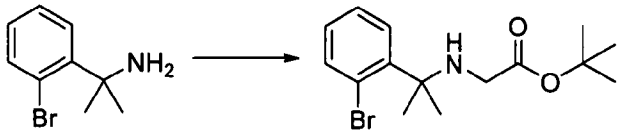
**步驟1：合成2-(2-溴苯基)丙-2-胺**




將溴化甲基鎂(54.9 mL，164.8 mmol，3M於二乙醚中)添加至2-溴苯甲腈(10.0 g，54.9 mmol)於二乙基醚(200 mL)中之溶液中且將反應混合物在室溫下在氮氣下攪拌。30分鐘後，添加異丙醇鈦(16.3 mL，54.9 mmol)且所得混合物回流隔夜。一旦冷卻至0℃，添加2N NaOH (400 mL)且將所得混合物在室溫下攪拌30分鐘。溶液用飽和碳酸氫鈉水溶液(400 mL)稀釋，使用甲基第三丁基醚(3×200 mL)萃取。合併有機層且在減壓下濃縮。殘餘物溶於1N鹽酸(75 mL)中且用甲基第三丁基醚(150 mL)洗滌。水層使用2N氫氧化鈉鹼化至pH 10-11且所得溶液用甲基第三丁基醚(3×200 mL)萃取。合併有機層，經無水硫酸

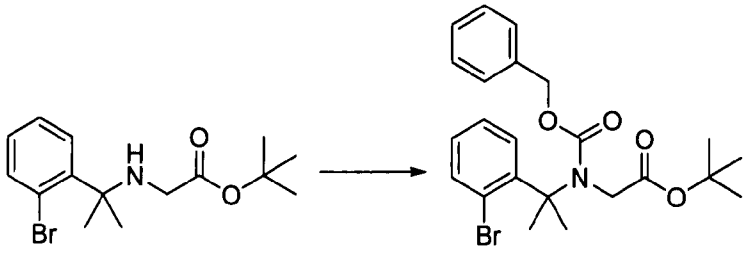
鈉乾燥且在減壓下濃縮，得到呈橙色油狀之2-(2-溴苯基)丙-2-胺(9.0 g，77%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 1.66 (s, 6 H), 7.02 - 7.10 (m, 1 H), 7.13 - 7.43 (m, 1 H), 7.55 - 7.61 (m, 2 H)。$[M+H]^+$ = 214.0。

**步驟2：合成2-{[2-(2-溴苯基)丙-2-基]胺基}乙酸第三丁酯**



在0℃下將2-溴乙酸第三丁酯 (6.24 mL，42.2 mmol)緩慢添加至2-(2-溴苯基)丙-2-胺(9.04 g，42.22 mmol)及碳酸鉀(14.6 g，105.6 mmol)於無水四氫呋喃(100 mL)中之溶液中且將反應混合物在50-55℃下攪拌16小時。一旦冷卻至室溫，反應混合物用鹽水(100 mL)稀釋且使用乙酸乙酯(3×100 mL)萃取。合併有機層，經無水硫酸鎂乾燥，且在減壓下濃縮。殘餘物藉由矽膠層析，庚烷中0% 至20% 乙酸乙酯溶離來純化，得到呈黃色油狀之2-{[2-(2-溴苯基)丙-2-基]胺基}乙酸第三丁酯(4.5 g，32%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.43 (s, 9 H), 1.63 (s, 6 H), 2.94 (s, 2 H), 7.09 (dt, *J* = 7.6, 1.7 Hz, 1 H), 7.22 - 7.31 (m, 1 H), 7.43 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.58 (dd, *J* = 7.9, 1.4 Hz, 1 H)。$[M+H]^+$ = 328.1。

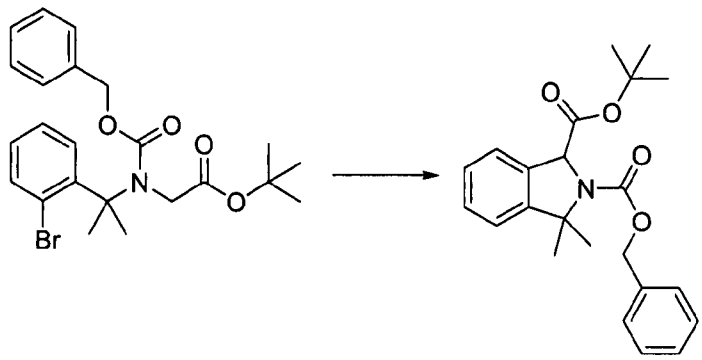
**步驟3：2-{[(苯甲氧基)羰基][2-(2-溴苯基)丙-2-基]胺基}乙酸第三丁酯**



將二異丙基乙胺(5.48 mL，31.4 mmol)添加至2-{[2-(2-溴苯基)丙-2-基]胺基}乙酸第三丁酯(4.48 g，13.7 mmol)於二氯甲烷(50 mL)中之溶液中且溶液冷卻至0℃。在0℃下逐滴添加苯氯甲酸甲酯(3.51 mL，

24.6 mmol)且將反應混合物在室溫下攪拌隔夜。將反應混合物用二氯甲烷(50 mL)稀釋且用5%檸檬酸水溶液(2×50 mL)及鹽水(50 mL)洗滌。有機層經無水硫酸鎂乾燥且在減壓下濃縮。殘餘物藉由矽膠層析，庚烷中0%至10%乙酸乙酯溶離來純化，得到呈黃色油狀之2-{[(苯甲氧基)羰基][2-(2-溴苯基)丙-2-基]胺基}乙酸第三丁酯(4.2 g，67%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 1.41 (s, 6 H), 1.55 (s, 3 H), 1.78 (s, 2 H), 1.84 (s, 4 H), 4.21 (s, 1.3 H), 4.32 (s, 0.7 H), 4.83 (s, 0.7 H), 4.99 (s, 1.3 H), 6.70 - 7.62 (m, 9 H)。$[M+H]^+$ = 484.1。

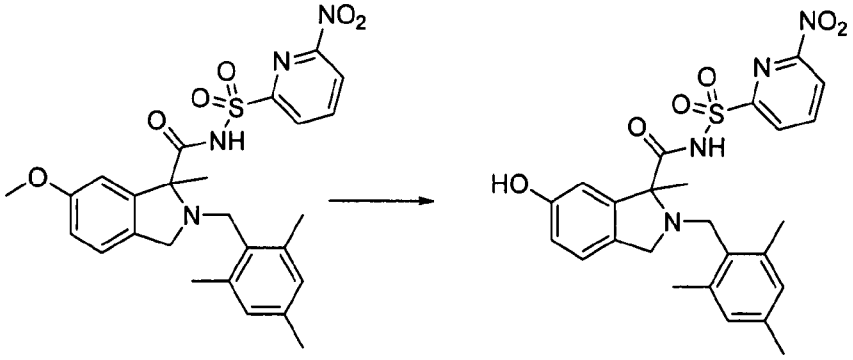
**步驟4：3,3-二甲基-2,3-二氫-1*H*-異吲哚-1,2-二甲酸2-苯甲酯1-第三丁酯**




將參(二苯亞甲基丙酮)二鈀(0) (87 mg，0.10 mmol)、2'-(二苯基膦基)-*N*,*N*'-二甲基-(1,1'-聯苯)-2-胺 (PhDavePhos) (73 mg，0.19 mmol)及第三丁醇鋰(0.31 g，3.81 mmol)依序添加至預先脫氣之2-{[(苯甲氧基)羰基][2-(2-溴苯基)丙-2-基]胺基}乙酸第三丁酯(0.88 g，1.90 mmol)於二噁烷(10 mL)中之溶液中且用氮氣淨化。將反應混合物在90℃下攪拌隔夜。一旦在室溫下冷卻，將反應混合物用乙酸乙酯(20 mL)稀釋，過濾且在減壓下濃縮。殘餘物藉由矽膠層析，庚烷中0%至10%乙酸乙酯溶離來純化，得到呈橙色油狀之3,3-二甲基-2,3-二氫-1*H*-異吲哚-1,2-二甲酸2-苯甲酯1-第三丁酯(0.31 g，43%產率)。$^1$H NMR (300 MHz, $CDCl_3$): ppm 1.31 (s, 6H), 1.45 (s, 3H), 1.65 (s, 1H), 1.73 (s, 1H), 1.76 (s, 2H), 1.81 (s, 2H), 5.11-5.47 (m, 3H), 7.12-7.48 (m,

9H)。$[M+Na]^+ = 404.2$。

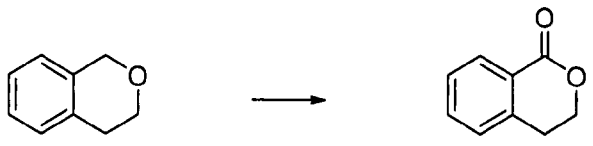
**製備73：6-羥基-1-甲基-*N*-((6-硝基吡啶-2-基)磺醯基)-2-(2,4,6-三甲基苯甲基)異吲哚啉-1-甲醯胺**



在氮氣氛圍下，6-甲氧基-1-甲基-*N*-[(6-硝基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(333 mg，0.635 mmol)溶於二氯甲烷(30 mL)中。冷卻混合物至-78℃，且將三溴硼烷 (5.046 g，1.904 mL 1 M，1.904 mmol)逐滴添加至反應混合物中。混合物緩慢升溫至室溫且攪拌16小時。將反應混合物添加至大約50 mL冰中。分離各層，且水層用二氯甲烷(3×5 mL)萃取。合併之有機層經硫酸鈉乾燥，濃縮，且在矽膠管柱上，利用已烷中0至100%乙酸乙酯之梯度純化，得到6-羥基-1-甲基-*N*-[(6-硝基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]異吲哚啉-1-甲醯胺(90.7 mg，0.178 mmol，28.0%)。ESI-MS *m/z*計算值510.15732, 實驗值511.5 $(M+1)^+$；滯留時間: 0.56分鐘

**製備74：2,3,4,5-四氫-1*H*-苯并[*c*]氮呼-3-甲酸第三丁酯**

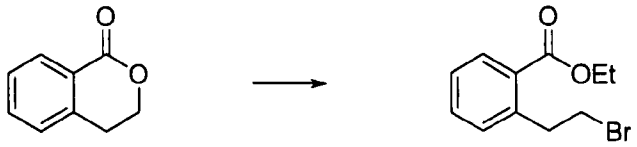
**步驟1：3, 4-二氫-1*H*-2-苯并哌喃-1-酮**



在室溫下經15分鐘向攪拌的異烷(15.0 g，112 mmol)於二氯甲烷(1.4 L)中之溶液中添加過錳酸鉀(106 g，672 mmol)及二氧化錳(58.0 g，672 mmol)之均勻混合物(藉由研磨過錳酸鉀且接著使用研杵及研

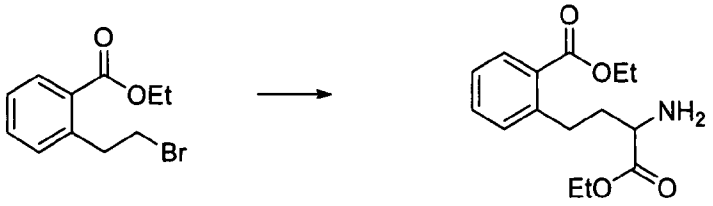
砵與二氧化錳混合來製備)。在室溫下懸浮液用力攪拌4天，且接著經矽藻土墊過濾。濃縮濾液且殘餘物藉由二氧化矽層析，用庚烷及乙酸乙酯(0至20%)之混合物溶離來純化，得到呈無色油狀之3,4-二氫-1*H*-2-苯并哌喃-1-酮(8.2 g，49%產率)。$^1$H NMR ($CDCl_3$, 300 MHz) ppm 3.06 (t, *J* = 6.0 Hz, 2 H), 4.52 (t, *J* = 6.0 Hz, 2 H), 7.20 - 7.30 (m, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J*= 7.6 Hz, 1 H), 8.06 (d, *J* = 7.6 Hz, 1 H)。

**步驟2：2-(2-溴乙基)苯甲酸乙酯**




將三溴化磷(1.05 mL，11.0 mmol)及溴(0.62 mL，12 mmol)緩慢添加至在冰水浴中冷卻之3,4-二氫-1*H*-2-苯并哌喃-1-酮(1.5 g，10. mmol)於四氯化碳(15 mL)中之溶液中。接著混合物在室溫下攪拌16小時。將所得橙色懸浮液在60℃下攪拌3小時。接著紅色混合物冷卻且在0℃下緩慢添加乙醇(10 mL)(放熱!)。將反應混合物(橙色溶液)攪拌一小時。反應混合物分溶於二氯甲烷(50 mL)與水(20 mL)之間。分離有機相且用鹽水(10 mL)洗滌，經硫酸鈉乾燥且在減壓下濃縮。殘餘物藉由二氧化矽層析，用乙酸乙酯及庚烷(0至10%)之混合物溶離純化，得到呈淺黃色油狀之2-(2-溴乙基)苯甲酸乙酯(2.0 g，78%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.41 (t, *J* = 6.9 Hz, 3 H), 3.50 (t, *J* = 6.9 Hz, 2 H), 3.64 (t, *J* = 6.9 Hz, 2 H), 4.38 (q, *J* = 6.9 Hz, 2 H), 7.27 - 7.39 (m, 2 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.96 (d, *J*=7.5 Hz, 1 H)。

**步驟3：2-(3-胺基-4-乙氧基-4-側氧基丁基)苯甲酸乙酯**

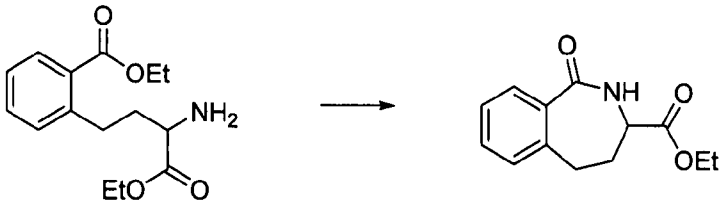


反應分開兩批進行。

將*N*-(二苯基亞甲基)甘胺酸乙酯 (4.17 g，15.6 mmol)添加至用冰水浴冷卻之細粉狀氫氧化鉀(2.63 g，46.8 mmol)於 二甲亞碸(20 ml)中之懸浮液中(獲得橙色混合物)。接著逐滴添加2-(2-溴乙基)苯甲酸乙酯(4.0 g，15.6 mmol)。將反應物在室溫下攪拌60分鐘且接著用乙酸乙酯(150 mL)稀釋。溶液傾析至分液漏斗中且棄去固體(KOH)。有機相用水(3×50 mL)、鹽水洗滌，經無水$Na_2SO_4$乾燥且在減壓下濃縮。第二批以類似方式操作：2-(2-溴乙基)苯甲酸乙酯(9.3 g，36.1 mmol)、*N*-(二苯基亞甲基)甘胺酸乙酯(9.65 g，36.1 mmol)、氫氧化鉀(6.08 g，108.3 mmol)及二甲亞碸(50 mL)。

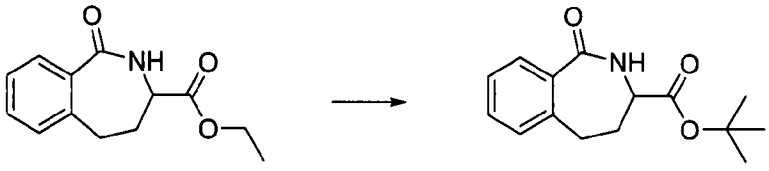
合併兩批粗產物(19 g)且溶於四氫呋喃(50 mL)中。溶液用冰水浴冷卻且添加1 N HCl水溶液(60 mL)。將混合物在室溫下攪拌30分鐘。添加水(50 mL)及乙酸乙酯(50 mL)，萃取兩相混合物且分離兩相。接著在0℃下水相用2 N NaOH水溶液(30 mL)鹼化且所得水溶液用乙酸乙酯(2×50 mL)萃取。合併有機層，用鹽水(20 mL)洗滌，經無水$Na_2SO_4$乾燥且在減壓下濃縮。殘餘物用二氧化矽層析，用甲醇及二氯甲烷(0-7%)之混合物溶離來純化，得到呈黃色油狀之2-(3-胺基-4-乙氧基-4-側氧基丁基)苯甲酸乙酯(6.6 g，46%產率)。$^1$H NMR (300 MHz, $CDCl_3$) 1.27 (t, *J* = 7.1 Hz, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.75 - 1.93 (m, 1 H), 1.97 - 2.14 (m, 1 H), 2.95 - 3.15 (m, 2 H), 3.42 - 3.54 (m, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 7.20 - 7.30 (m, 2 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 7.88 (d, *J* = 7.5 Hz, 1 H)。LCMS: $[M+H]^+$ = 280.2。

**步驟4：合成1-側氧基-2,3,4,5-四氫-1*H*-2-苯并氮呼-3-甲酸乙酯**



在室溫下將金屬鈉(823 mg，35.8 mmol)添加至燒瓶中無水乙醇(270 mL，經3Å分子篩乾燥)中。將混合物在室溫下攪拌直至所有鈉均消失。接著在室溫下添加2-(3-胺基-4-乙氧基-4-側氧基丁基)苯甲酸乙酯(5.0 g，18 mmol)於無水乙醇(30 mL)中之溶液。將反應物在室溫下攪拌2天且接著用冰水浴冷卻。緩慢添加硫醯氯(10 mL) (反應猛烈)且反應回流2小時。在減壓下移除溶劑且殘餘物溶於乙酸乙酯(100 mL)中，用飽和碳酸氫鈉水溶液(30 mL)、鹽水洗滌，經$Na_2SO_4$乾燥且在減壓下濃縮。殘餘物藉由二氧化矽層析，用乙酸乙酯及庚烷(10至100%)之混合物溶離來純化，得到呈黃色油狀之1-側氧基-2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲酸乙酯(2.9 g，69%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.24 (t, *J* = 6.7 Hz, 3 H), 2.07 - 2.25 (m, 1 H), 2.26 - 2.43 (m, 1 H), 2.70 - 2.84 (m, 1 H), 2.89 - 3.08 (m, 1 H), 3.80 - 3.95 (m, 1 H), 4.20 (q, *J* = 6.7 Hz, 2 H), 6.69 (s, 1 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.70 (d, *J* = 7.2 Hz, 1 H)。LCMS: $[M+H]^+$ = 234.1。

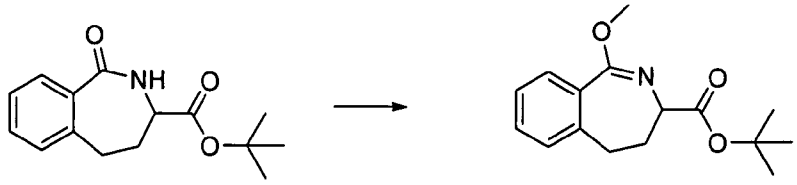
**步驟5：1-側氧基-2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲酸第三丁酯**



在壓力管中在氮氣下在-78℃下將丁基鋰(17.4 mL 2.5 M於已烷中，43.4 mmol)添加至無水第三丁醇(4.7 mL，50. mmol，蒸餾且接著經碳酸鉀乾燥)於無水四氫呋喃(40 mL)中之溶液中。將混合物在室溫下攪拌10分鐘，接著添加1-側氧基-2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲

酸乙酯(2.9 g，12 mmol)於無水四氫呋喃(10 mL)中之溶液且將混合物在30℃下攪拌隔夜。在減壓下移除揮發物且殘餘物溶於水(40 mL)及二氯甲烷(100 mL)之混合物中。分離兩相且有機相經無水$Na_2SO_4$乾燥且在減壓下濃縮。殘餘物藉由二氧化矽層析，用乙酸乙酯及庚烷(0至30%)之混合物溶離來純化，得到呈白色固體狀之1-側氧基-2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲酸第三丁酯(1.4 g，43%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.44 (s, 9 H), 1.99 - 2.23 (m, 1 H), 2.32 (tt, *J* = 12.7, 6.3 Hz, 1 H), 2.77 (dd, *J* = 13.7, 6.3 Hz, 1 H), 2.89 - 3.11 (m, 1 H), 3.68 - 3.88 (m, 1 H), 6.64 (br. s., 1 H), 7.21 (d, *J* = 7.3 Hz, 1 H), 7.29 - 7.49 (m, 2 H), 7.71 (d, *J* = 7.5 Hz, 1 H)。$[M+H]^+$ = 262.1。

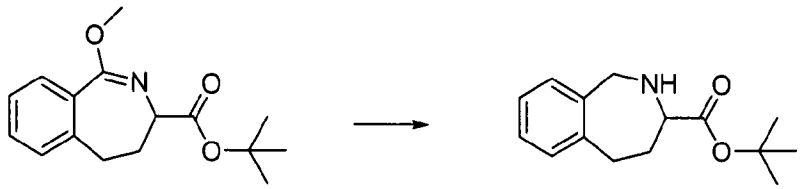
**步驟6：1-甲氧基-4,5-二氫-*H*-2-苯并氮呯-3-甲酸第三丁酯**



反應以相同兩批操作。將4 Å分子篩添加至密封管。管在真空下直火乾燥且接著用氮氣沖洗。管冷卻至室溫後，添加1-側氧基-2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲酸第三丁酯(522 mg，2.00 mmol)，接著無水二氯甲烷(9 mL)及四氟硼酸三甲基氧鎓(296 mg，2.00 mmol)。將混合物在30℃下攪拌16小時。混合物用飽和碳酸氫鈉水溶液(30 mL)淬滅。所得混合物用乙酸乙酯(2×40 mL)萃取。合併有機相且用鹽水(20 mL)洗滌，經無水$Na_2SO_4$乾燥且在減壓下濃縮。兩批殘餘物合併且藉由二氧化矽層析，用乙酸乙酯及庚烷(0至30%)之混合物溶離來純化，得到呈無色油狀之1-甲氧基-4,5-二氫-3*H*-2-苯并氮呯-3-甲酸第三丁酯(900. mg，3.27 mmol，81.7%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.43 (s, 9 H), 2.33-2.49 (m, 2 H), 2.58 - 2.70 (m, 2 H), 3.50 (dd, *J* = 11.0, 7.2 Hz, 1 H), 3.96 (s, 3 H), 7.20 - 7.28 (m, 1 H),

7.30 - 7.40 (m, 2 H), 7.41 - 7.47 (m, 1 H)。LCMS: $[M+H]^+$=276.1。

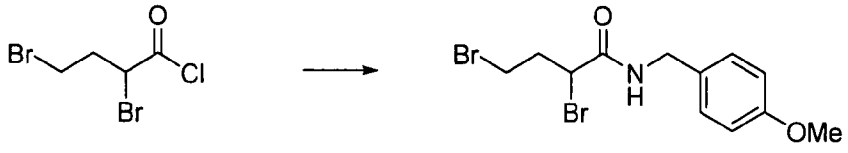
**步驟7：2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲酸第三丁酯**



在0℃下將氰基硼氫化鈉(821 mg，13.1 mmol)添加至1-甲氧基-4,5-二氫-3*H*-2-苯并氮呯-3-甲酸第三丁酯(900. mg，3.27 mmol)於乙酸(3 mL)中之溶液中。將混合物在室溫下攪拌2小時。混合物用乙酸乙酯(40 mL)稀釋且用冰水浴冷卻。緩慢添加NaOH水溶液(25% w/v)以調整pH值至約8。分離兩相且水相用乙酸乙酯(40 mL)萃取。有機相合併，用鹽水洗滌(10 mL)，經無水$Na_2SO_4$乾燥且在減壓下濃縮。殘餘物藉由二氧化矽層析，用乙酸乙酯及二氯甲烷(0至50%)之混合物溶離來純化，得到呈黃色油狀之2,3,4,5-四氫-1*H*-2-苯并氮呯-3-甲酸第三丁酯(610. mg，2.47 mmol，75.5%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.46 (s, 9 H), 1.53 - 1.66 (m, 1 H), 2.17 - 2.37 (m, 1 H), 2.79 - 2.99 (m, 1 H), 2.99 - 3.18 (m, 1 H), 3.65 (dd, *J* = 10.6, 2.9 Hz, 1 H), 3.93 (d, *J* = 15.1 Hz, 1 H), 3.97 (d, *J* = 15.1 Hz, 1 H), 7.06 - 7.21 (m, 4 H)。$[M+H]^+$ = 248.1。

**製備75：1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-磺醯胺**

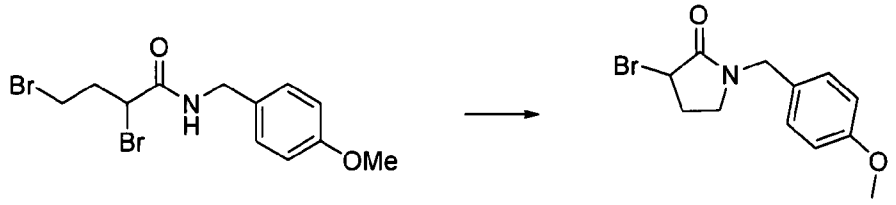
**步驟1：2,4-二溴-*N*-[(4-甲氧基苯基)甲基]丁醯胺**



在0℃下向2,4-二溴丁醯氯(5.00 g，18.9 mmol)於二氯甲烷(250 mL)中之溶液中添加三乙胺(2.38 g，23.6 mmol)，接著4-甲氧基苯甲基胺(2.59 g，18.9 mmol)且將混合物在0℃下攪拌2小時。接著在0℃

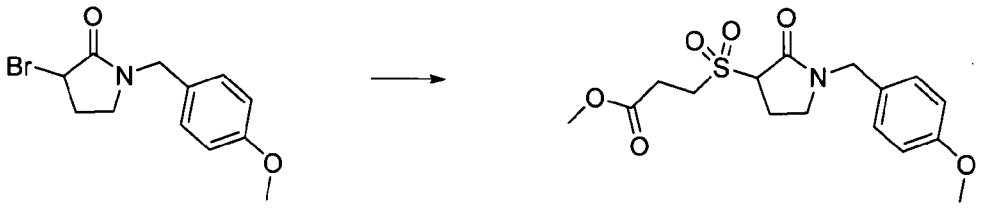
下反應物傾倒至pH = 3-4之5%檸檬酸溶液(80 mL)中且用二氯甲烷(100 mL)及水(50 mL)稀釋。分離有機層且水層再用二氯甲烷(50 mL)萃取。合併之有機層經$Na_2SO_4$乾燥，過濾且在減壓下濃縮，得到呈褐色固體狀之粗2,4-二溴-*N*-[(4-甲氧基苯基)甲基]丁醯胺(7.09 g，103%)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 2.41 - 2.55 (m, 1 H), 2.64 - 2.84 (m, 1 H), 3.52 - 3.61 (m, 2 H), 3.80 (s, 3 H), 4.36 - 4.44 (m, 2 H), 4.55 (dd, *J* = 9.0, 4.8 Hz, 1 H), 6.54 (br. s, 1 H), 6.85 - 6.91 (m, 2 H), 7.19 - 7.23 (m, 2 H)。$[M+H]^+$ = 366.0。

**步驟2：3-溴-1-[(4-甲氧基苯基)甲基]吡咯啶-2-酮**



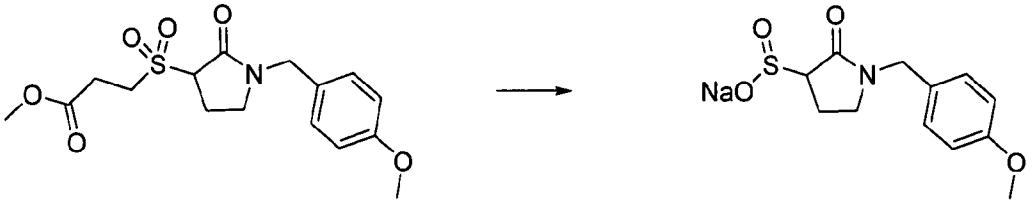

在0℃下向2,4-二溴-*N*-[(4-甲氧基苯基)甲基]丁醯胺(3.25 g，8.90 mmol)於四氫呋喃(120 mL)及*N*,*N*-二甲基甲醯胺(12 mL)中之溶液中逐份添加氫化鈉(427 mg 60%於礦物油中之分散液，17.8 mmol)且將混合物在室溫下攪拌2.5小時。反應混合物再次冷卻至0℃且小心用5%檸檬酸水溶液(10 mL)淬滅。接著在減壓下移除揮發物。反應混合物用水及二氯甲烷稀釋且水層用二氯甲烷萃取兩次。合併之有機層經$Na_2SO_4$乾燥，過濾，在減壓下濃縮且與作爲共溶劑之庚烷共蒸發(兩次)，得到呈淺黃色油狀之粗3-溴-1-[(4-甲氧基苯基)甲基]吡咯啶-2-酮(2.5 g，99%)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 2.22 - 2.32 (m, 1 H), 2.47 - 2.60 (m, 1 H), 3.14 - 3.21 (m, 1 H), 3.35 - 3.44 (m, 1 H), 3.80 (s, 3 H), 4.33 - 4.52 (m, 3 H), 6.84 - 6.87 (m, 2 H), 7.15 - 7.20 (m, 2 H)。$[M+H]^+$ = 284.0。

**步驟3：3-({1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-基}磺醯基)丙酸甲酯**



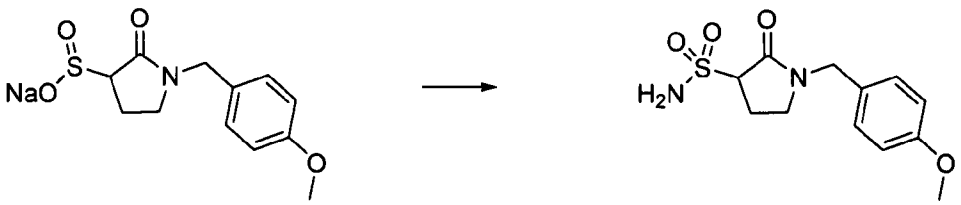
向3-溴-1-[(4-甲氧基苯基)甲基]吡咯啶-2-酮(2.50 g，8.80 mmol)於二甲亞碸(50 mL)中之溶液中添加3-亞磺醯基丙酸1-甲酯鈉(1.53 g，8.80 mmol)且將反應物在室溫下攪拌3天。溶液用水(400 mL)稀釋且用二氯甲烷(2×250 mL)萃取。合併之有機層用水(150 mL)、鹽水(100 mL)洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮，得到粗3-({1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-基}磺醯基)丙酸甲酯(2.5 g，80.%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 2.31 - 2.45 (m, 1 H), 2.65 - 2.75 (m, 1 H), 2.85 - 3.05 (m, 2 H), 3.26 (dt, *J* = 9.4, 3.8 Hz, 1 H), 3.41 - 3.50 (m, 1 H), 3.74 (s, 3 H), 3.79 (s, 3 H), 3.77 - 3.92 (m, 2 H), 4.01 (dd, *J* = 10.2, 4.6 Hz, 1 H), 4.44 (s, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H)。$[M+H]^+$ = 356.1。

**步驟4：1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-亞磺酸鈉**



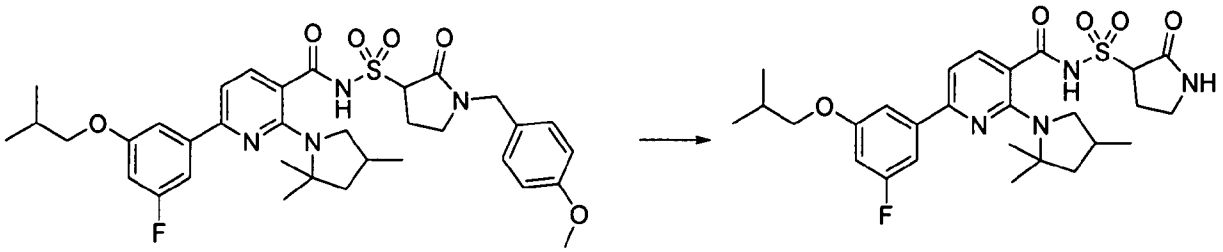
向3-({1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-基}磺醯基)丙酸甲酯(2.50 g，7.03 mmol)於四氫呋喃及甲醇之1:1 (v/v)混合物(40 mL)中之溶液中添加甲醇鈉(3.39 mL 25 wt.%於甲醇中，14.8 mmol)且將反應物在室溫下攪拌4小時。接著反應混合物在減壓下濃縮以移除丙烯酸甲酯且保持在減壓下，得到粗1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-亞磺酸鈉，其未經進一步純化直接用於下一步中。$[M+H]^+$ = 270.0 (亞磺酸)。

**步驟5：合成1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-磺醯胺**



在0℃下向粗1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-亞磺酸鈉(2.05 g，7.03 mmol)於二甲亞碸(20 ml)中之溶液中添加羥基胺-*O*-磺酸(3.98 g，35.2 mmol)及乙酸鈉(2.19 g，26.7 mmol)於水(7 mL)中之溶液。將反應物在室溫下攪拌16小時，接著用乙酸乙酯及水稀釋。水層用乙酸乙酯(2×100 mL)萃取。合併之有機層用鹽水(75 mL)洗滌，經$Na_2SO_4$乾燥，過濾且在減壓下濃縮。粗物質藉由矽膠層析，使用0%至10%甲醇之二氯甲烷溶液(含有1% $NH_4OH$)來純化，得到呈淺褐色固體狀之1-[(4-甲氧基苯基)甲基]-2-側氧基吡咯啶-3-磺醯胺(1.3 g，63%產率)。$^1$H NMR (300MHz, $CDCl_3$) ppm 2.29 - 2.73 (m, 2 H), 3.14 - 3.34 (m, 1 H), 3.34 - 3.51 (m, 1 H), 3.80 (s, 3 H), 3.89 - 4.11 (m, 1 H), 4.30 - 4.61 (m, 2 H), 5.25 (br. s., 2 H), 6.75 - 6.98 (m, 2 H), 7.10 - 7.22 (m, 2 H)。$[M+H]^+$ = 285.1。

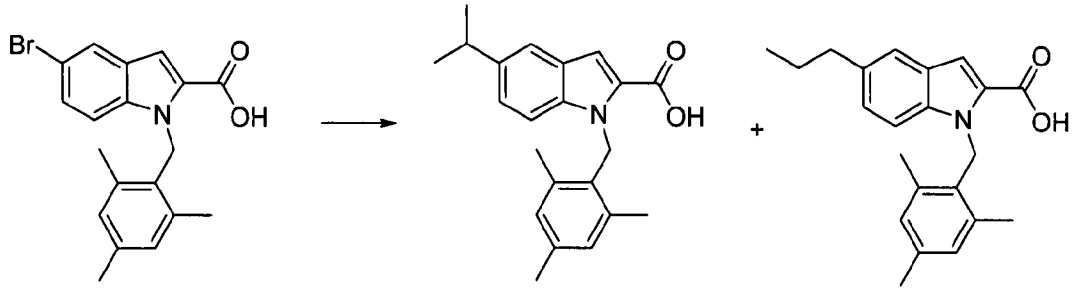
**製備76：6-(3-氟-5-異丁氧基-苯基)-*N*-(2-側氧基吡咯啶-3-基)磺醯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物466)**



6-(3-氟-5-異丁氧基-苯基)-*N*-[1-[(4-甲氧基苯基)甲基]-2-側氧基-吡咯啶-3-基]磺醯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(32.7 mg，0.0490 mmol)溶於三氟乙酸(0.9319 mL)及二氯甲烷(0.9319 mL)之混合物中。接著添加三氟甲烷磺酸(25.75 mg，15.18 μL，0.1716 mmol)且混合物在周圍溫度下攪拌20小時。濃縮反應混合物，接著用

二甲亞碸稀釋且藉由逆相層析，利用C18管柱及含於5 mM HCl水溶液中之1-99%乙腈之梯度來純化，得到6-(3-氟-5-異丁氧基-苯基)-*N*-(2-側氧基吡咯啶-3-基)磺醯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物466)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.27 (d, $J$ = 19.3 Hz, 1H), 7.94 (d, $J$ = 8.0 Hz, 1H), 7.72 (d, $J$ = 8.0 Hz, 1H), 7.51 (s, 1H), 7.43 (d, $J$ = 10.1 Hz, 1H), 7.28 (dd, $J$ = 14.4, 8.0 Hz, 1H), 6.90 (dt, $J$ = 10.6, 2.3 Hz, 1H), 4.61 - 4.44 (m, 1H), 3.84 (d, $J$ = 6.7 Hz, 2H), 3.40 - 2.86 (m, 4H), 2.16 - 1.91 (m, 2H), 1.71 - 1.60 (m, 7H), 1.60 - 1.49 (m, 1H), 1.16 (s, 1H), 1.06 - 0.96 (m, 10H)。ESI-MS *m/z*計算值546.2312，實驗值547.3 $(M+1)^+$；滯留時間: 1.87分鐘

**製備77：5-異丙基-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲酸及5-丙基-1-(2,4,6-三甲基苯甲基)-1*H*-吲哚-2-甲酸**

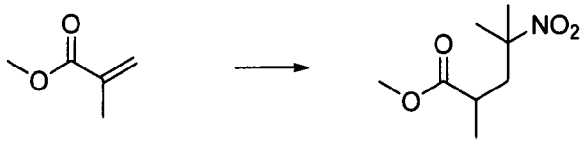



步驟1：將含5-溴-1-[(2,4,6-三甲基苯基)甲基]吲哚-2-甲酸(0.7000 g，1.880 mmol)、[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(68.78 mg，0.09400 mmol)、碳酸鈉水溶液(1.880 mL 2 M，3.760 mmol)及2-異丙烯基-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(315.9 mg，1.880 mmol)之二噁烷(5 mL)添加至微波反應小瓶。小瓶用氮氣淨化，封蓋且在微波反應器中加熱至120℃，保持45分鐘。反應混合物用水稀釋且用乙酸乙酯(2×10 mL)萃取。有機層經硫酸鈉乾燥，濃縮，且藉由逆相層析，利用C18管柱及5 mM HCl水溶液中30-90%乙腈之梯度來純化，得到產物混合物，其在此等特定條件下無法分離。此物質溶於甲醇(10 mL)中且將鈀/碳(20.01 mg，0.01880 mmol)

添加至反應混合物中。將混合物在氫氣氛圍下攪拌4小時。粗產物之混合物經矽膠墊過濾，使用100 mL含15%甲醇之二氯甲烷且未經進一步操作即用於下一步。ESI-MS *m/z*計算值335.19，實驗值336.5 $(M+1)^+$；滯留時間: 0.84分鐘。

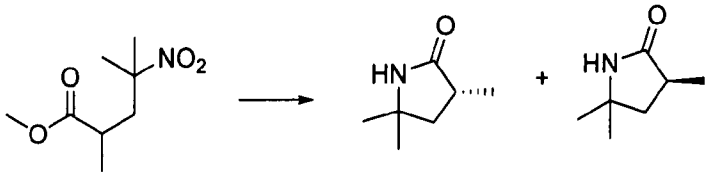
**製備78：(4*R*)-2,2,4-三甲基吡咯啶**

**步驟1：2,4-二甲基-4-硝基戊酸甲酯**



1 L三頸燒瓶裝配有滴液漏斗及溫度計。2-硝基丙烷(178 g，2.00 mol)於二噁烷(100 mL)中之溶液及40%氫氧化苯甲基三甲基銨水溶液(Triton B，20.0 mL，420. mmol)添加至燒瓶。將燒瓶在油浴中加熱至70℃且甲基丙烯酸甲酯(200. g，212.3 mL，2.00 mol)經由滴液漏斗經45分鐘添加。在添加期間溫度上升至約100℃，接著降至約90℃。接著混合物在100℃下加熱4小時。反應混合物冷卻至室溫且添加1 N鹽酸(80 mL)。水(500 mL)及二乙基醚(1000 mL)添加至反應燒瓶。混合物傾倒至分液漏斗中且有機層用水(2×400 mL)、鹽水(400 mL)洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮，得到黃色液體。產物經由短程蒸餾設備蒸餾，得到淺黃色液體(356 g，94%) (油浴溫度150℃，油泵，收集溫度100至108℃)。$^1$H NMR ($CDCl_3$, 250 MHz): $\delta$ 3.67 (s, 3H), 2.55-2.35 (m, 2H), 2.10 - 1.90 (m, 1H), 1.58 (s, 3H), 1.53 (s, 3H), 1.18 (d, *J*=6.5 Hz, 3H)。

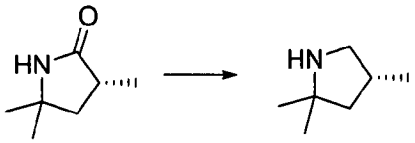
**步驟2：(*R*)-3,5,5-三甲基吡咯啶-2-酮及(*S*)-3,5,5-三甲基吡咯啶-2-酮**



2,4-二甲基-4-硝基-戊酸甲酯(100. g，528.5 mmol)、氯化鎳(II)六

水合物(25.12 g，105.7 mmol)、水(28.57 g，28.57 mL，1.586 mol)及甲醇(1.200 L)之溶液冷卻至0至5℃。硼氫化鈉(49.98 g，1.321 mol)緩慢添加至反應混合物，同時維持反應溫度低於20℃。添加爲放熱的，穩定且長期產生氣體。反應混合物靜置14天。碳酸鉀(146.1 g，1.057 mol)於水(1.000 L)中之溶液緩慢添加至反應混合物。接著反應混合物經矽藻土墊過濾。接著墊用三個100 mL部分之甲醇洗滌。接著反應混合物在減壓下濃縮以移除甲醇。添加甲基第三丁基醚(1 L)。分離各層且水層用400 mL部分甲基第三丁基醚萃取兩次。合併之有機層經硫酸鈉乾燥，過濾，且蒸發至乾。接著此物質分溶於甲基第三丁基醚與氯化鈉水溶液之間。有機層分離，經硫酸鎂乾燥，過濾，且接著蒸發至乾，得到41.5 g (61.7%)灰白色固體。使用超臨界流體層析，在ChiralPak AS-H (250×4.6 mm) 5 μm管柱上，使用$CO_2$中10%甲醇，以3.0 mL/min之流速，分離立體異構體。

**步驟3：(4*R*)-2,2,4-三甲基吡咯啶**




(3*R*)-3,5,5-三甲基吡咯啶-2-酮(20.0 g，157 mmol)於四氫呋喃(200.0 mL)中之溶液冷卻至0至5℃。氫化鋰鋁(8.006 g，236.0 mmol)經10分鐘分部分添加，同時維持反應混合物溫度低於20℃。添加有點放熱且觀測到脫氣。將懸浮液加熱至回流，保持9.5小時。冷卻至室溫後，將額外部分氫化鋰鋁(1.601 g，1.746 mL，47.19 mmol)添加至反應混合物中。接著混合物加熱至回流，保持2.5小時。反應混合物冷卻至7℃且硫酸鈉水溶液(27.93 mL 20 % w/v，39.32 mmol)緩慢添加至反應混合物。接著反應混合物用200 mL甲基第三丁基醚稀釋且經矽藻土墊過濾。濾液經硫酸鈉乾燥，過濾，且在周圍壓力下濃縮以移除醚。粗物質藉由蒸餾(28℃/50托)純化，得到10. g (56%)無色液體。

1H NMR (400 MHz, 氯仿-*d*) $\delta$ 3.11 (dd, *J* = 10.8, 7.3 Hz, 1H), 2.51 (dd, *J* = 10.9, 8.1 Hz, 1H), 2.32 - 2.15 (m, 1H), 1.80 (dd, *J* = 12.4, 8.1 Hz, 1H), 1.65 (s, 1H), 1.19 (s, 3H), 1.17 - 1.08 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H)。絕對立體化學藉由(2*R*)-2-(2-氯苯基)-2-羥基-乙酸鹽之X射線結晶學確定。

以下化合物可使用本文所述之程序合成：

(*S*)-4-乙基-2,2-二甲基吡咯啶，及

(*R*)-4-乙基-2,2-二甲基吡咯啶

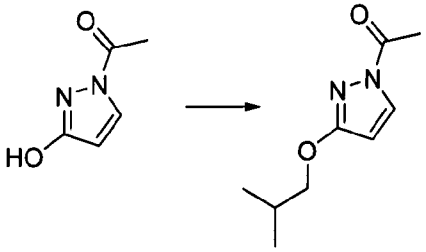
以下化合物可使用本文所述之程序，使用氘化鋰鋁合成：

(*S*)-2,2,4-三甲基吡咯啶-5,5-$d_2$及，

(*R*)-2,2,4-三甲基吡咯啶-5,5-$d_2$

**製備79：3-異丁氧基-1*H*-吡唑**

**步驟1：1-(3-異丁氧基-1*H*-吡唑-1-基)乙-1-酮**

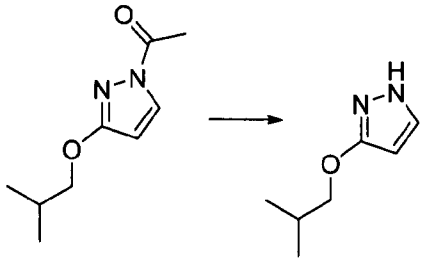


向4 mL小瓶饋入1-(3-羥基吡唑-1-基)乙酮(100. mg，0.793 mmol)、碳酸鉀(164.3 mg，1.189 mmol)及無水DMF (1.000 mL)。添加1-溴-2-甲基-丙烷(119.5 mg，94.84 μL，0.8722 mmol)，將小瓶封蓋且將混合物在室溫下攪拌16小時。將反應物在80℃下攪拌一小時。混合物用乙酸乙酯(50 ml)及水(25 mL)稀釋且分離兩相。水相(pH = 9-10)進一步用乙酸乙酯(20 mL)萃取。合併之萃取物經硫酸鈉乾燥且蒸發溶劑，得到100 mg粗油狀物。產物溶於二氯甲烷中且藉由矽膠急驟層析(4 g管柱)，使用已烷中乙酸乙酯(經15分鐘0至50%)之梯度純化。合併純溶離份且在減壓下移除溶劑，得到呈無色油狀之1-(3-異丁氧基吡

唑-1-基)乙酮(78 mg，0.43 mmol，54%)。

ESI-MS *m/z*計算值182.10553，實驗值183.2 $(M+1)^+$；滯留時間：1.34分鐘。$^1$H NMR (400 MHz，氯仿-d) δ 8.05 (d, *J* = 3.0 Hz, 1H), 5.96 (d, *J* = 3.0 Hz, 1H), 3.99 (d, *J* = 6.6 Hz, 2H), 2.58 (s, 3H), 2.09 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 6H)。

**步驟2：3-異丁氧基-1*H*-吡唑**



在室溫下1-(3-異丁氧基-1*H*-吡唑-1-基)乙-1-酮(72 mg，0.40 mmol)用甲醇(1 mL)及NaOH (65.85 μL 6 M，0.3951 mmol)處理1小時。在減壓下移除揮發物。殘餘物溶解於乙酸乙酯(25 mL)及鹽水(20 mL)中且分離兩相。水相進一步用乙酸乙酯(20 mL)萃取且合併之萃取物經硫酸鈉乾燥。蒸發溶劑後，分離呈無色黏稠油狀之3-異丁氧基-1*H*-吡唑(55 mg，0.39 mmol，99%)。ESI-MS *m/z*計算值140.09496，實驗值141.2 $(M+1)^+$；滯留時間：0.86分鐘。$^1$H NMR (400 MHz，氯仿-d) *δ* 7.34 (d, *J* = 2.4 Hz, 1H), 5.71 (d, *J* = 2.5 Hz, 1H), 3.90 (d, *J* = 6.6 Hz, 2H), 2.08 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 6H)。

以下化合物可使用本文所述之程序合成：

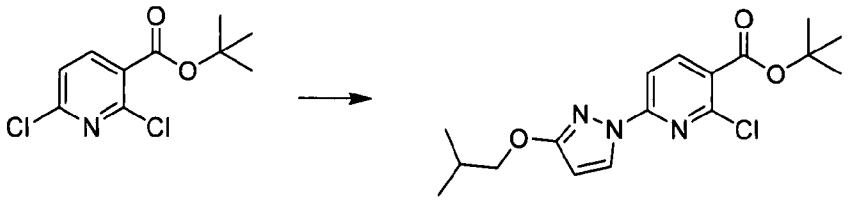
3-異丁氧基-5-甲基-1*H*-吡唑，

4-異丁氧基-1*H*-吡唑，及

3-異丁氧基-4-甲基-1*H*-吡唑

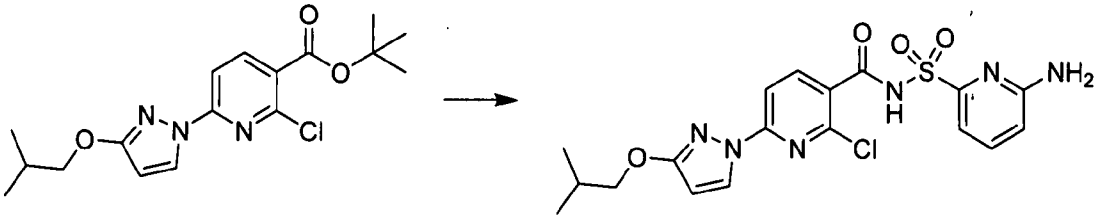
**製備80：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1620)**

**步驟1：2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸第三丁酯**



在氮氣下向4 mL小瓶饋入3-異丁氧基-1*H*-吡唑(131.5 mg，0.9383 mmol)及無水DMF (1 mL)。添加氫化鈉(37.48 mg，0.9370 mmol，60%於礦物油中)且將混合物攪拌直至氣體停止放出。添加2,6-二氯吡啶-3-甲酸第三丁酯(155 mg，0.625 mmol)。將小瓶封蓋且將混合物在100℃下攪拌4小時。LCMS展示存在兩種單加成異構體(比率約60:40)及作爲雙加成產物之主要產物。反應混合物用乙酸乙酯(30 mL)及水(20 mL)稀釋且分離兩相。水相進一步用乙酸乙酯(25 mL)萃取。合併之萃取物經硫酸鈉乾燥且在減壓下移除溶劑，得到247 mg粗固體。殘餘物溶於二氯甲烷中且進行矽膠急驟層析(40 g管柱)，使用己烷中乙酸乙酯(經20分鐘0至20%)之梯度，得到2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸第三丁酯(58 mg，0.1649 mmol，26.39%) (灰白色固體)。ESI-MS *m/z*計算值351.13498, 實驗值352.4 $(M+1)^+$；滯留時間: 2.25分鐘。

**步驟2：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺**

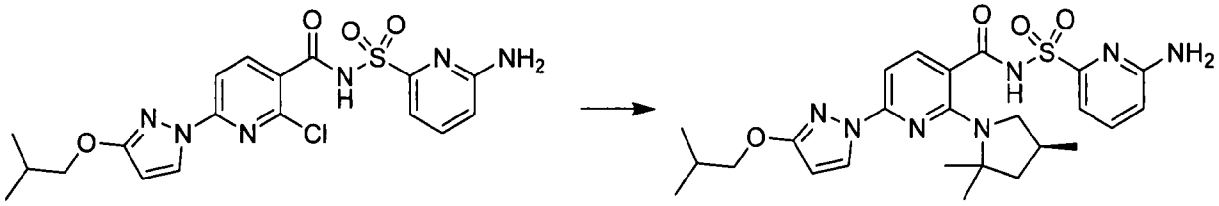


含有2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸第三丁酯(58 mg，0.16 mmol)之100 mL圓底燒瓶用二氯甲烷(600 μL)及三氟乙酸(180μL，2.336 mmol)處理。將混合物在45℃下攪拌1.5小時。在減壓下移除揮發物，得到白色固體。接著在氮氣氛圍下無水DMF (500 μL)添加至含有酸之100 mL燒瓶且在40℃下攪拌混合物。添加1,1'-羰基二

咪唑(32.09 mg，0.1979 mmol)且混合物在40℃下攪拌1小時。在氮氣下向另一4 mL小瓶饋入6-胺基吡啶-2-磺醯胺(34.27 mg，0.1979 mmol)及無水DMF (500 μL)。

添加NaH (7.915 mg，0.1979 mmol，60%油分散液)。氣體停止放出後，將小瓶封蓋且將其在40℃下攪拌1小時。將此混合物添加至第一燒瓶中且將混合物在室溫下攪拌2小時。將反應用冰及水淬滅且用乙酸(148.6 mg，140.7 μL，2.474 mmol，最終pH = 4)酸化。所得白色固體過濾，用水洗滌且在減壓下乾燥。分離呈白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺(57 mg，0.13 mmol，77%)。ESI-MS *m/z*計算值450.0877, 實驗值451.3 $(M+1)^+$；滯留時間: 1.54分鐘

**步驟3：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1620)**



在氮氣下向4 mL小瓶饋入*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺(57 mg，0.13 mmol)、CsF (96.00 mg，0.6320 mmol)、碳酸鉀(87.35 mg，0.6320 mmol)、(4*S*)-2,2,4-三甲基吡咯啶(47.64 mg，0.3792 mmol)及無水二甲亞碸(200 μL)。將小瓶封蓋且將內含物在150℃下攪拌4小時。混合物用水(200 μL)、*N*-甲基吡咯啶酮(600 μL)稀釋且過濾混合物。該化合物藉由逆相製備型HPLC，使用5 mM甲酸銨水溶液中水中乙腈(經15分鐘1至99%)之梯度來純化。合併純溶離份，添加幾滴鹽水且在減壓下移除有機溶劑。沉出之固體用二氯甲烷(3×20 mL)萃取。合併之萃取物經硫酸鈉乾燥，過濾，且在減壓下移除溶劑，得到28 mg仍然含有雜質之物質。該物

質藉由製備型HPLC使用5 mM鹽酸水溶液中水中乙腈(經15分鐘1至99%)之梯度第二次純化。使用相同萃取程序分離產物。濃縮二氯甲烷後藉由添加己烷，獲得固體。蒸發溶劑得到呈灰白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1620) (18 mg，0.03394 mmol，26.86%)。ESI-MS *m/z* 計算值527.23145，實驗值528.5 $(M+1)^+$；滯留時間：1.77分鐘。$^1$H NMR (400 MHz, 氯仿-d) $\delta$ 13.87 (寬單峰, 1H), 8.29 (d, $J$ = 8.0 Hz, 1H) 8.21 (d, $J$ = 2.9 Hz, 1H), 7.65 - 7.58 (m, 2H), 7.52 (d, $J$ = 8.5 Hz, 1H), 6.65 (p, $J$ = 3.8 Hz, 1H), 5.95 (d, $J$ = 2.8 Hz, 1H), 4.80 (寬單峰, 2H), 4.02 (d, $J$ = 6.6 Hz, 2H), 3.52 - 3.41 (m, 1H), 3.15 (dd, $J$ = 10.5, 8.1 Hz, 1H), 2.69 - 2.50 (m, 1H), 2.18 - 2.02 (m, 2H), 1.72 (dd, $J$ = 12.3, 9.7 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.19 (d, $J$ = 6.6 Hz, 3H), 1.02 (d, $J$ = 6.7 Hz, 6H)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基-5-甲基-吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1407)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(環丁基甲氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2694)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(環丙基甲氧基)吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2695)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)-4-甲基-吡唑-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2699)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1411)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(5-異丁基吡唑-1-基)-2-[(4*S*)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1431)，

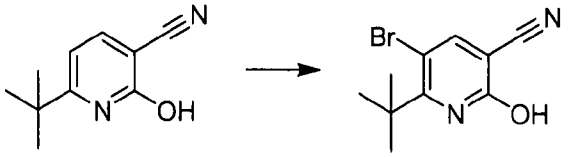
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1443)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-乙氧基-5-甲基-吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1473)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丁氧基-4-甲基-吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1532)

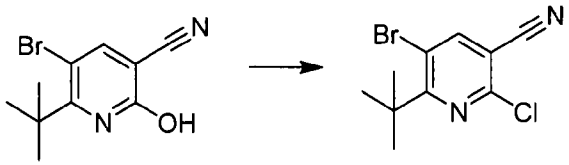
**製備81：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(3,4-二氫-2*H*-哌喃-5-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1487)**

**步驟1：5-溴-6-第三丁基-2-羥基吡啶-3-甲腈**



將*N*-溴丁二醯亞胺(10.3 g，57.9 mmol)添加至含6-第三丁基-2-羥基吡啶-3-甲腈(6.8 g，38.6 mmol)之1,2-二氯乙烷(50 mL)中且反應混合物回流3小時。添加水且用二氯甲烷(2×50 mL)萃取兩次。有機相用水洗滌，經無水硫酸鈉乾燥且在減壓下濃縮。殘餘物藉由急驟層析(100%二氯甲烷至10%甲醇/90%二氯甲烷)來純化，得到呈白色固體狀之5-溴-6-第三丁基-2-羥基吡啶-3-甲腈，65%產率(6.4 g)。$^1$H NMR (300 MHz, DMSO-$d_6$) ppm 1.43 (s, 9H), 8.36 (s, 1H)。$[M+H]^+$ = 255.0, 257.0。

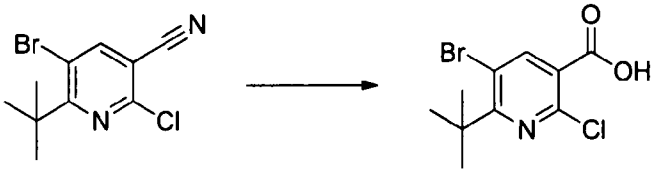
**步驟2：5-溴-6-第三丁基-2-氯吡啶-3-甲腈**



將氧氯化磷(30.3 mL，325 mmol)及五氯化磷(20.3 g，97.6 mmol)添加至5-溴-6-第三丁基-2-羥基吡啶-3-甲腈(8.30 g，32.5 mmol)且反應

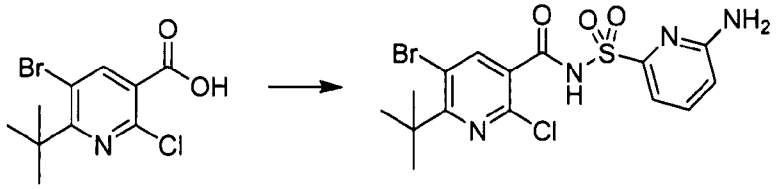
混合物回流2天。反應混合物冷卻至室溫且在減壓下濃縮。水添加至殘餘物，用乙酸乙酯(75 mL部分)萃取3次，用鹽水(75 mL)洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。殘餘物藉由急驟層析(100%庚烷至50%乙酸乙酯/50%庚烷)純化，得到呈灰白色固體狀之5-溴-6-第三丁基-2-氯吡啶-3-甲腈，39%產率(3.5 g)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.52 (s, 9H), 8.08 (s, 1H)。$[M+H]^+$ = 273.0, 275.0。

**步驟3：5-溴-6-第三丁基-2-氯吡啶-3-甲酸**



將含氫氧化鉀(4.3 g，77 mmol)之水(15 mL)添加至含5-溴-6-第三丁基-2-氯吡啶-3-甲腈之2-丙醇(15 mL)中且將反應混合物在90℃下加熱16小時。添加乙酸乙酯(50 mL)且用1N 氫氧化鈉(3×50 mL)萃取3次。水相用10%鹽酸酸化至約pH 4且水相用乙酸乙酯(3×75 mL)萃取3次，且用鹽水(100 mL)洗滌。所需化合物存在於所有有機相中，因此將其合併，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。粗化合物藉由逆相層析(甲醇/水，0至100%)純化，得到呈灰白色固體狀之5-溴-6-第三丁基-2-氯吡啶-3-甲酸(2.3 g，61%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.53 (s, 9H), 8.46 (s, 1H)。$[M+H]^+$ = 292.0, 294.0。

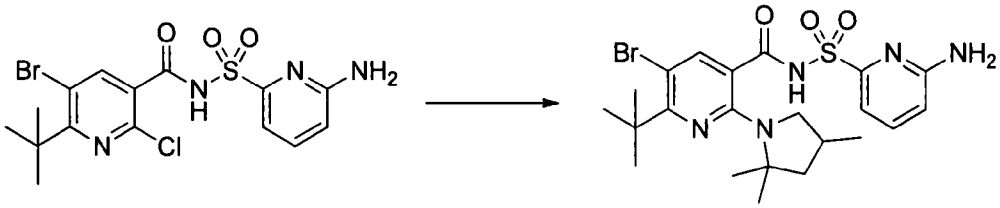
**步驟4：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-氯-吡啶-3-甲醯胺**



在周圍溫度下在氮氣下向50 mL圓底燒瓶中攪拌的5-溴-6-第三丁基-2-氯-吡啶-3-甲酸(500.0 mg，1.709 mmol)於無水DMF (3.5 mL)中之溶液中一次性添加1,1'-羰基二咪唑(346.3 mg，2.136 mmol)。反應升

溫至45℃且攪拌1.5小時。在另一50 mL圓底燒瓶中，在氮氣下6-胺基吡啶-2-磺醯胺(369.9 mg，2.136 mmol)溶於無水DMF (2.5 mL)中且在周圍溫度下分部分添加氫化鈉(60%於礦物油中) (85.43 mg，2.136 mmol)以減輕氣體放出。不均質混合物升溫至40℃且攪拌1小時。在45℃下將此混合物一次性添加至攪拌的活化酸混合物中。停止加熱且將反應物再攪拌一小時。反應混合物緩慢(經2分鐘)添加至100 mL圓底燒瓶中冰冷水(50 mL)中，且置於冰浴中。接著添加乙酸(528.5 mg，500.5 μL，8.801 mmol)且混合物用力攪拌10分鐘且過濾固體且用水(3×20 mL)洗滌。固體在己烷(20 mL)中成漿狀物且過濾。固體進一步且乾燥，得到呈白色固體狀之所需偶合產物。*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-氯-吡啶-3-甲醯胺(585 mg，1.31 mmol，76.5%)。$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.87 (s, 1H), 8.15 (s, 1H), 7.60 (d, $J$ = 1.5 Hz, 1H), 7.54 (t, $J$ = 7.8 Hz, 1H), 7.09 (d, $J$ = 7.3 Hz, 1H), 6.58 (d, $J$ = 8.3 Hz, 1H), 6.35 (s, 2H), 1.46 (s, 9H)。ESI-MS *m/z*計算值445.9815, 實驗值449.2 $(M+1)^+$；滯留時間: 1.52分鐘

**步驟5：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1628)**

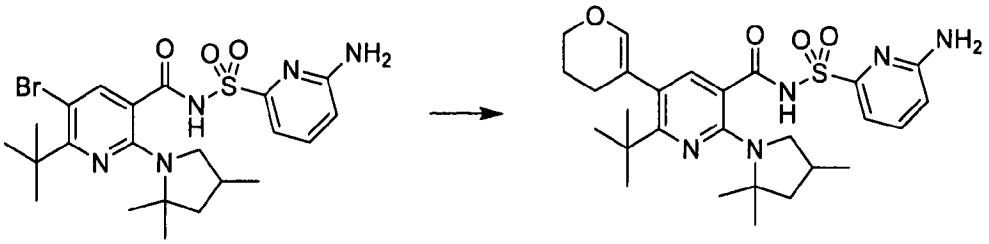


2,2,4-三甲基吡咯啶(252.9 mg，2.234 mmol)及碳酸鉀(617.5 mg，4.468 mmol)添加至20 mL反應小瓶中*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-氯-吡啶-3-甲醯胺(500.0 mg，1.117 mmol)於無水DMSO (4.0 mL)中之溶液中。將小瓶在氮氣氛圍下封蓋且在預加熱油浴中在145℃下加熱24小時。反應容器移除且使其冷卻至周圍溫度。在攪拌下反應混合物傾倒至冰及水(50 mL)之混合物上。接著所得反

應混合物用1 M HCl水溶液調至約6.0之pH值。混合物用力攪拌15分鐘。將固體過濾，用水(4×20 mL)洗滌，且在真空下乾燥，得到呈白色固體狀之所需產物。

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1628) (495 mg，0.944 mmol，84.5%) $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.49 (s, 1H), 8.52 (s, 1H), 7.70 (s, 1H), 7.49 (s, 1H), 7.07 (d, $J$ = 7.2 Hz, 1H), 6.53 (s, 1H), 6.20 (s, 2H), 3.37 (dd, $J$ = 11.6, 8.2 Hz, 1H), 2.77 (dd, $J$ = 11.6, 8.9 Hz, 1H), 2.16 (dt, $J$ = 12.5, 6.4 Hz, 1H), 1.99 (dd, $J$ = 12.9, 7.6 Hz, 1H), 1.81 (dd, $J$ = 11.8, 5.5 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.44 (s, 9H), 0.87 (d, $J$ = 6.3 Hz, 3H)。ESI-MS *m/z*計算值523.12524, 實驗值526.1 $(M+1)^+$；滯留時間: 1.43分鐘

**步驟6：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(3,4-二氫-2*H*-哌喃-5-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1487)**



向4 mL小瓶饋入攪拌棒、*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1628) (29 mg，0.055 mmol)及乙烯基硼酸(34.85 mg，0.1659 mmol)。接著添加DMF (0.5 mL)及水(0.1 mL)，接著碳酸鉀(30.57 mg，0.2212 mmol)。氮氣鼓泡穿過小瓶1分鐘。接著添加肆(三苯基膦)鈀(0) (6.389 mg，0.005529 mmol)且氮氣鼓泡再穿過溶液1分鐘。在氮氣下用密封蓋密封且在130℃下(外部溫度)加熱13小時。反應混合物經由注射器濾盤過濾，且藉由逆相HPLC，利用含有5 mM HCl之水中10至99%乙腈之

梯度來純化，得到呈鹽酸鹽形式之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(3,4-二氫-2*H*-哌喃-5-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1487) (3.3 mg，0.0058 mmol，11%)。ESI-MS *m/z*計算值527.26，實驗值528.3 $(M+1)^+$；滯留時間: 1.21分鐘

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[4-(三氟甲基)環己烯-1-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1380)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-3,3-二甲基丁-1-烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1613)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-環己基乙烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1484)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-己-1-烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1377)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-5-甲基己-1-烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1682)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-環戊基乙烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1633)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-[4-(三氟甲基)苯基]乙烯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1566)，

(E)-3-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-[(4S)-2,2,4-三甲基吡咯啶-1-基]-3-吡啶基]丙-2-烯酸(化合物1547)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-雙環[2.2.1]庚-2-烯基)-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-苯基-2-(2,2,4-三甲基

吡咯啶-1-基)吡啶-3-甲醯胺(化合物1364)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-苯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1384)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4,7,7-三甲基-3-雙環[2.2.1]庚-2-烯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1544)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[(E)-2-環丙基乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1571)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(1,2-二甲基丙-1-烯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1590)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-(4-甲氧基苯基)乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-戊-1-烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-雙環[2.2.1]庚-2-烯基)-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

(E)-3-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]丙-2-烯乙酯，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-乙氧基乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)-5-乙烯基-吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-環丙基乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-戊-1-烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-(4-甲氧基苯

基)乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-環丙基乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)-5-乙烯基-吡啶-3-甲醯胺，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-乙氧基乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺，

(E)-3-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]丙-2-烯酸乙酯，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-甲基丙-1-烯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1561)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸苯甲酯(化合物1404)，

3-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]-8-氮雜雙環[3.2.1]辛-3-烯-8-甲酸第三丁酯(化合物1388)，

5-(4-乙醯基環己烯-1-基)-*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1461)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(1,4-二氧雜螺[4.5]癸-8-烯-8-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1459)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-溴-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1628)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2,2,6,6-四甲基-3H-哌喃-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1647)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(4,7,7-三甲基-3-雙環[2.2.1]庚-2-烯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1578)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(3,4-二氫-2H-哌喃-6-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1485)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(5,5-二甲基-3-側氧基-環己烯-1-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1405)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(1,4-二氧雜螺[4.5]癸-8-烯-9-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1469)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸第三丁酯(化合物1522)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(1-甲基-3,6-二氫-2H-吡啶-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1382)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]環己-3-烯-1-甲酸(化合物1381)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-氰基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1419)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(3,6-二氫-2H-哌喃-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1495)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-甲氧基-5-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2499)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[(E)-己-1-烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1916)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-異丁氧基-5-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2558)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[2-(三氟甲基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1921)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氯苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2429)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氰基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1849)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-甲氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1792)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-第三丁基-5-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2322)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-[1-(羥基甲基)環丙基]苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2112)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-第三丁基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2463)，

3-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]-4-甲氧基-苯甲酸乙酯(化合物2134)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-氯苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2399)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氯-5-甲氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2545)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-甲氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1735)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-氰基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2304)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-異丙基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1809)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-異丙氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2283)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[3-(2-甲氧基乙氧基甲基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1943)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-異丁氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2089)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-異丁基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2395)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(1H-吲唑-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2157)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-(1-羥基-1-甲基-乙基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2547)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[(E)-2-[4-(三氟甲基)苯基]乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2014)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[3-(環戊氧基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1918)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(6-乙氧基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2384)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(鄰甲苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1701)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-(1-氰基-1-甲基-乙基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2521)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(6-甲氧基-3-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1886)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[3-(環戊氧基)-5-甲基-苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2313)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-二甲基胺基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2288)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(1-異丁基吡唑-3-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2303)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-甲氧基環己烯-1-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1920)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-氰基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2584)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氯-5-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1963)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-(三氟甲氧基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2649)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-乙氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2557)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3,5-二甲基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2093)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-(2,2,4-三甲基吡咯啶-1-基)-3-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸第三丁酯(化合物2129)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(4-甲基環己烯-1-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2361)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-異戊基氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1894)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[3-(三氟甲基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1950)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[(E)-5-甲基己-1-烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2647)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(6-甲氧基-2-吡啶基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1861)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[3-異丙氧基-5-(三氟甲基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1815)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-氟-5-甲氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2431)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(1,1,4,4,7-五甲基萘滿-6-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1759)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-異丙氧基-5-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1889)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3,5-二氯苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1721)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-異丁氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1979)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(5-苯甲氧基-2-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2588)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-異丙氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1804)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3,5-二氟苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2259)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-(羥基甲基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2088)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-(三氟甲基)環己烯-1-基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2510)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(間甲苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2184)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-氯苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2312)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[4-(三氟甲基)苯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2337)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(2-氯-5-異丙氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2210)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-甲氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2031)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-第三丁基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2180)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[(E)-2-(4-甲氧基苯基)乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1726)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-雙環[2.2.1]庚-2-烯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1888)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-乙氧基-5-甲基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1843)，

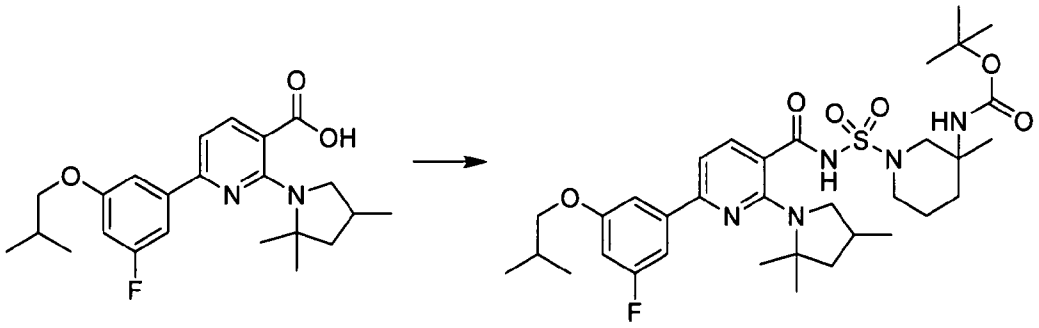
*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-甲基-4-丙氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2095)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-[(E)-2-環己基乙烯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2063)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(環己烯-1-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1601)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(1-甲基吡唑-4-基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1441)

**製備82：*N*-[1-[[6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-3-甲基-3-哌啶基]胺基甲酸第三丁酯(化合物1520)**



將6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲酸(40.45 mg，0.1000 mmol)及異氰酸氯磺醯酯(16.98 mg，10.44 μL，0.1200 mmol)於二氯甲烷(1.000 mL)中之溶液攪拌45分鐘。添加三乙胺(15.18 mg，20.91 μL，0.1500 mmol)及第三丁基-*N*-(3-甲基-3-哌啶基)胺基甲酸酯(32.15 mg，0.1500 mmol)，且將反應物攪拌3天。反應藉由矽膠層析，用0-5%甲醇之二氯甲烷溶液來純化，得到呈無色固體狀之(1-(*N*-(6-(3-氟-5-異丁氧基苯基)-2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯基)胺磺醯基)-3-甲基哌啶-3-基)胺基甲酸第三丁酯(34 mg，0.050 mmol，50.%)。

以下化合物可使用本文所述之程序合成：

*N*-[(3R)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1360)，

*N*-(3-乙醯胺基吡咯啶-1-基)磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1391)，

*N*-[[3-(二甲基胺基)-1-哌啶基]磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1414)，

*N*-[[(3S)-3-胺基-1-哌啶基]磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1435)，

*N*-[(3-胺基-3-甲基-1-哌啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1445)，

*N*-[(3-胺基-1-哌啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1447)

*N*-(3-胺基吡咯啶-1-基)磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1467)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[3-(甲基胺基)-1-哌啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1508)，

*N*-[(5-胺基-3-氮雜雙環[3.1.0]己-3-基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1521)，

*N*-[3-[乙醯基(甲基)胺基]吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1533)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(3-甲氧基-1-哌啶基)磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1545)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[3-(甲基胺基)吡咯啶-1-基]磺醯基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1554)，

*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1557)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-甲基磺醯基吡咯啶-1-基)磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1560)，

*N*-[(3-乙醯胺基-1-哌啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1586)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[3-(甲烷磺醯胺基)-1-哌啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1600)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(3-羥基-1-哌啶基)磺醯基]-2-[(4S)-

2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1608)，

*N*-[[(3R)-3-胺基-1-哌啶基]磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1614)，

6-(3-氟-5-異丁氧基-苯基)-*N*-吡咯啶-1-基磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1619)，及

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-羥基吡咯啶-1-基)磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1648)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-羥基-3-甲基-氮雜環丁烷-1-基)磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2398)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(2-吡啶基胺磺醯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(4S)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基]磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1789)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(3R)-3-哌啶基]胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2677)，

*N*-[(6-胺基-2-吡啶基)胺磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-吡啶基胺磺醯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1448)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-甲氧基-3-吡啶基)胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1359)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(1R,4R)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基]磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2347)，

*N*-(3,3-二氟吡咯啶-1-基)磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-

[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1956)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(3,3,3-三氟-2-羥基-2-甲基-丙基)胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

*N*-(3,8-二氮雜雙環[3.2.1]辛-3-基磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2237)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(3R)-3-羥基吡咯啶-1-基]磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2427)，

*N*-[(3R,4R)-3,4-二羥基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2534)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(3S)-吡咯啶-3-基]胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1935)，

*N*-[(5-胺基-3,3-二氟-1-哌啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2209)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-甲氧基-2-吡啶基)胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(3R)-吡咯啶-3-基]胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(3S)-3-氟吡咯啶-1-基]磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2228)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[(3R)-3-甲氧基吡咯啶-1-基]磺醯基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1893)，

*N*-[(3,3-二氟-5-羥基-1-哌啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2508)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(3S)-3-哌啶基]胺磺醯基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺，

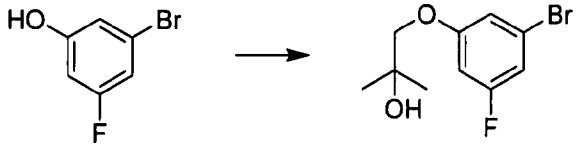
*N*-[(3R)-3-胺基吡咯啶-1-基]磺醯基-2-(2-苯甲基-2-甲基-吡咯啶-

1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2325) (異構體1，*R*或*S*立體異構體)

*N*-[(3R)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2477) (異構體2，*R*或*S*立體異構體)

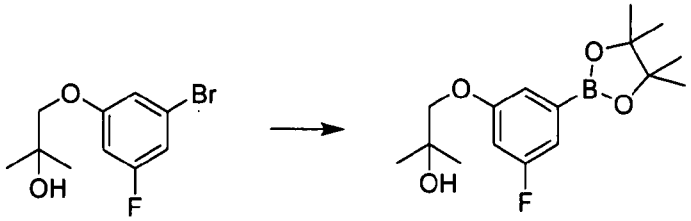
**製備83：1-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-2-醇**

**步驟1：1-(3-溴-5-氟-苯氧基)-2-甲基-丙-2-醇**




向3-溴-5-氟-苯酚(9.0 g，47 mmol)及1-氯-2-甲基-丙-2-醇(5.116 g，47.12 mmol)中添加氫氧化鈉水溶液(37.69 g，94.24 mmol)且在壓力容器中將反應混合物在120℃下加熱5天。反應物冷卻且接著用乙酸乙酯萃取三次。合併之有機層經硫酸鈉乾燥，過濾，且溶劑在減壓下蒸發。粗產物在220 g矽膠上，利用0至10%乙酸乙酯之二氯甲烷溶液之梯度來純化。不純產物在220 g gold矽膠上，利用0至10%乙酸乙酯之二氯甲烷溶液之梯度再純化，得到1-(3-溴-5-氟-苯氧基)-2-甲基-丙-2-醇(4.75 g，18.0 mmol，38%)。ESI-MS *m/z*計算值262.00046, 實驗值263.0 $(M+1)^+$；滯留時間: 1.57分鐘(3分鐘操作)。

**步驟2：1-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-2-醇**

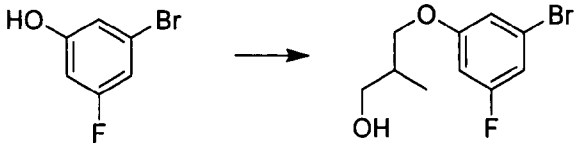



向燒瓶中1-(3-溴-5-氟-苯氧基)-2-甲基-丙-2-醇(5.250 g，19.95

mmol)及4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)-1,3,2-二氧雜硼雜環戊烷(7.598 g，29.92 mmol)中添加乙酸鉀(4.894 g，49.87 mmol)及二氯化[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(729.9 mg，0.9975 mmol)，接著二噁烷(32.58 mL)。藉由充以氮氣使懸浮液脫氣10分鐘且接著將反應物在油浴中在85℃下加熱3小時。反應物用乙酸乙酯稀釋，過濾，且濃縮。粗產物在330 g矽膠上，利用己烷中0至50% 乙酸乙酯之梯度來純化，得到1-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-2-醇(5.23 g，16.86 mmol，84.52%)。產物不純且其未經進一步純化即用於下一步中。ESI-MS *m/z*計算值310.17517, 實驗值311.5 $(M+1)^+$；滯留時間: 1.895分鐘 (3分鐘操作)。

**製備84：3-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-1-醇**

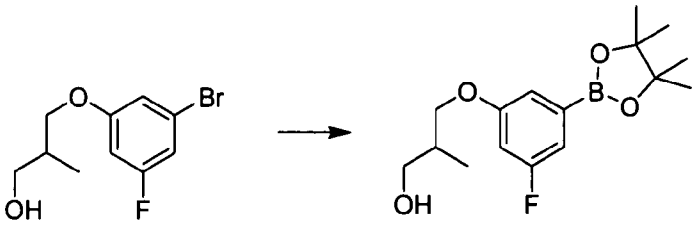
**步驟1：3-(3-溴-5-氟-苯氧基)-2-甲基-丙-1-醇**




在0℃下向攪拌的3-溴-5-氟-苯酚(2.270 g，11.88 mmol)、2-甲基丙-1,3-二醇(1.071 g，11.88 mmol)及三苯基膦(3.428 g，3.028 mL，13.07 mmol)於四氫呋喃(71.82 mL)中之溶液中添加偶氮二甲酸二異丙酯(2.643 g，2.532 mL，13.07 mmol)。移除冰浴且將反應物在55℃下攪拌18小時。反應物用乙酸乙酯稀釋且用碳酸氫鈉洗滌兩次及用鹽水洗滌兩次。有機層經硫酸鈉乾燥，過濾且溶劑在減壓下蒸發。粗產物在220 g矽膠上，利用甲烷中0至15%乙酸乙酯二氯之梯度來純化，得到呈無色液體狀之3-(3-溴-5-氟-苯氧基)-2-甲基-丙-1-醇(1.73 g，6.57 mmol，55.3%)。$^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.09 - 7.03 (m, 1H),

7.03 - 6.98 (m, 1H), 6.87 (dt, *J* = 11.2, 2.3 Hz, 1H), 4.57 (t, *J* = 5.3 Hz, 1H), 3.97 (dd, *J* = 9.5, 5.9 Hz, 1H), 3.85 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.48 - 3.34 (m, 2H), 2.05 - 1.84 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H)。ESI-MS *m/z*計算值262.00046, 實驗值265.0 (M+1)+；滯留時間: 1.58分鐘 (3分鐘操作)。

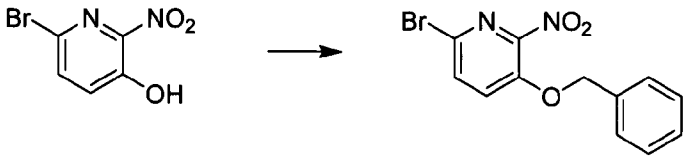
**步驟2：3-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-1-醇**




向燒瓶中3-(3-溴-5-氟-苯氧基)-2-甲基-丙-1-醇(1.7 g，6.5 mmol)及4,4,5,5-四甲基-2-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)-1,3,2-二氧雜硼雜環戊烷(2.461 g，9.692 mmol)中添加乙酸鉀(1.585 g，16.15 mmol)及二氯化[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)二氯甲烷加合物(236.3 mg，0.3230 mmol)，接著二噁烷(10.55 mL)。經由氮氣鼓泡穿過反應混合物使懸浮液脫氣10分鐘且接著將反應物在油浴中在85℃下加熱2.5小時。反應物用乙酸乙酯稀釋，過濾，且濃縮。粗產物在220 g矽膠上，利用己烷中0至50% 乙酸乙酯之梯度來純化，得到呈橙色黏稠液體狀之3-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-1-醇(1.77 g，5.71 mmol，88%)。產物含有一些雜質。其未經進一步純化即用於下一步中。ESI-MS *m/z*計算值310.17517, 實驗值311.2 $(M+1)^+$；滯留時間: 1.81分鐘 (3分鐘操作)。

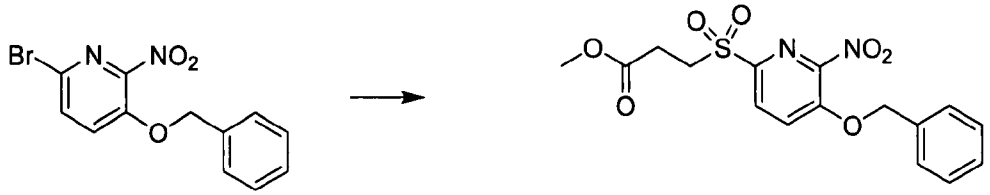
**製備85：5-(苯甲氧基)-6-硝基吡啶-2-磺醯胺**

**步驟1：3-苯甲氧基-6-溴-2-硝基-吡啶**



向6-溴-2-硝基-吡啶-3-醇(1.36 g，6.21 mmol)於*N,N*-二甲基甲醯胺(15 mL)中之溶液中添加碳酸鉀(1.717 g，12.42 mmol)，接著添加溴甲基苯(1.115 g，775.4 μL，6.520 mmol)。混合物在60℃下加熱隔夜，且分溶於乙酸乙酯與水之間。水層用乙酸乙酯萃取三次。合併之有機層用水、鹽水洗滌三次，經硫酸鎂乾燥，過濾，且濃縮至乾。粗物質懸浮於己烷中，經由過濾收集且空氣乾燥，得到呈黃色固體狀之3-苯甲氧基-6-溴-2-硝基-吡啶(1.61 g，5.21 mmol，83.8%)。$^1$H NMR (400 MHz, 氯仿-d) δ 7.60 (d, *J* = 8.7 Hz, 1H), 7.45 - 7.29 (m, 6H), 5.25 (s, 2H)。

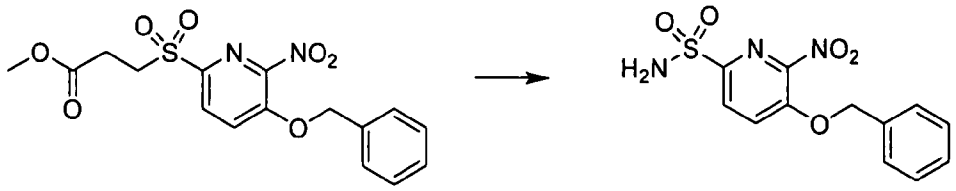
**步驟2：3-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]丙酸甲酯**



將3-苯甲氧基-6-溴-2-硝基-吡啶(585 mg，1.89 mmol)及(3-甲氧基-3-側氧基-丙基)亞磺醯基氧基鈉(329.5 mg，1.892 mmol)於二甲亞碸(5 mL)中之混合物用氮氣淨化2分鐘。將碘基銅(720.7 mg，3.784 mmol)添加至反應混合物中。混合物在80℃下加熱隔夜，分溶於乙酸乙酯與飽和氯化銨水溶液之間。所得沈澱藉由過濾移除且用乙酸乙酯洗滌。水層用乙酸乙酯萃取三次。合併之有機層用水、鹽水洗滌三次，經硫酸鎂乾燥，過濾且濃縮至乾。粗物質藉由管柱層析(己烷中40-60%乙酸乙酯)來純化，得到呈淺黃色固體狀之3-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]丙酸甲酯(210. mg，0.552 mmol，29.2%)。$^1$H NMR (400 MHz, 氯仿-*d*) δ 8.20 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.50 - 7.31 (m, 5H), 5.35 (s, 2H), 3.75 - 3.63 (m, 5H), 2.87 (t, *J*

= 7.5 Hz, 2H)。

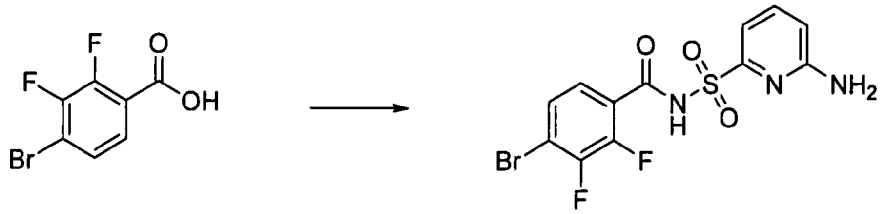
**步驟3：5-(苯甲氧基)-6-硝基吡啶-2-磺醯胺**



將四氫呋喃(10 mL)添加至3-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]丙酸甲酯(1.141 g，3.000 mmol)於甲醇(20 mL)中之懸浮液中。所得溶液冷卻至0℃。以逐滴方式添加甲醇鈉(6.000 mL 0.5 M於甲醇中，3.000 mmol)。將混合物在室溫下攪拌15分鐘。混合物蒸發至乾，得到淡褐色固體。接著此固體懸浮於二氯甲烷(30 mL)中且將*N*-氯丁二醯亞胺(400.6 mg，3.000 mmol)添加至反應混合物中。將混合物在室溫下攪拌10分鐘。向反應物再饋入*N*-氯丁二醯亞胺(80.12 mg，0.6000 mmol)。混合物變透明。將混合物在室溫下攪拌5分鐘。在0℃下將所得溶液添加至氨(36 mL 0.5 M，18.00 mmol)中。將混合物在室溫下攪拌30分鐘，且接著分溶於二氯甲烷與水之間。水層用二氯甲烷萃取三次。合併之有機層用鹽水洗滌，經硫酸鎂乾燥，過濾，且濃縮至乾，得到黃色固體(342 mg)。粗物質未經進一步純化直接用於下一步中。ESI-MS *m/z*計算值309.04，實驗值310.3 $(M+1)^+$；滯留時間: 1.10分鐘 (3分鐘操作)。

**製備86：*N*-[(6-胺基-2-吡啶基)磺醯基]-3-氟-4-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)苯甲醯胺(化合物1497)**

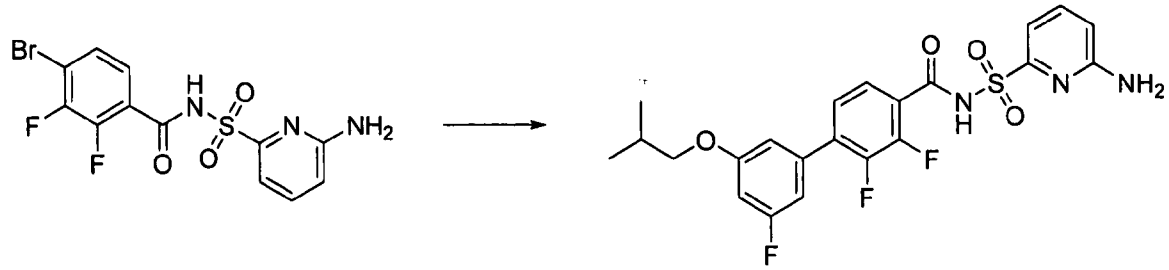
**步驟1：*N*-[(6-胺基-2-吡啶基)磺醯基]-4-溴-2,3-二氟-苯甲醯胺**



在室溫下向含4-溴-2,3-二氟-苯甲酸(2.66 g，11.2 mmol)之*N*, *N*-

二甲基甲醯胺(2.3 mL)中添加二(咪唑-1-基)甲酮(2.7 g，17 mmol)且將反應物在65℃下加熱1小時。分開地，在0℃下向含6-胺基吡啶-2-磺醯胺(2.4 g，14.0 mmol)之*N*, *N*-二甲基甲醯胺(2 mL)中添加氫化鈉(561 mg，14.0 mmol)且攪拌1小時10分鐘。反應冷卻回0℃且添加來自以上之加合物且將反應物在65℃下加熱1.5小時。反應物冷卻至室溫且用乙酸乙酯稀釋且用鹽水溶液洗滌。分離有機物，乾燥且濃縮，得到殘餘物，其用矽膠，用己烷中0至100%乙酸乙酯溶離來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-4-溴-2,3-二氟-苯甲醯胺(3.8 g，9.7 mmol，86%)作爲產物。ESI-MS *m/z*計算值390.94，實驗值392.0 $(M+1)^+$；滯留時間: 1.1分鐘 (3分鐘操作)

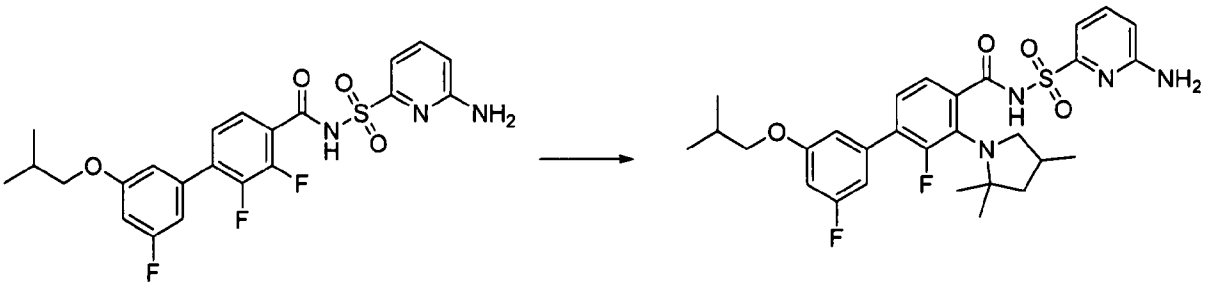
**步驟2：*N*-[(6-胺基-2-吡啶基)磺醯基]-2,3-二氟-4-(3-氟-5-異丁氧基-苯基)苯甲醯胺**



向小瓶中*N*-[(6-胺基-2-吡啶基)磺醯基]-4-溴-2,3-二氟-苯甲醯胺(700. mg，1.79 mmol)、(3-氟-5-異丁氧基-苯基)硼酸(568 mg，2.68 mmol)及碳酸鉀(740 mg，5.4 mmol)之混合物中添加二氯化[1,1'-雙(二苯基膦基)二茂鐵]鈀(II)(130.6 mg，0.1785 mmol)及*N*, *N*-二甲基甲醯胺(4.8 mL)及水(1.2 mL)且將反應混合物在氮氣下在100℃下攪拌16小時。反應混合物冷卻，經矽藻土墊過濾且濾液用乙酸乙酯及鹽水溶液稀釋。有機物分離，經硫酸鈉乾燥，且濃縮，得到殘餘物，其用矽膠，使用5至100%乙酸乙酯之二氯甲烷溶液來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2,3-二氟-4-(3-氟-5-異丁氧基-苯基)苯甲醯胺(174 mg，0.363 mmol，20.3%)。$^1$H NMR (400 MHz,甲醇-$d_4$) δ 7.64 - 7.53

(m, 2H), 7.29 (d, $J$ = 7.4 Hz, 1H), 7.25 - 7.18 (m, 1H), 6.90 (d, $J$ = 2.7 Hz, 1H), 6.88 - 6.81 (m, 1H), 6.73 (dt, $J$ = 10.8, 2.3 Hz, 1H), 6.64 (d, $J$ = 8.3 Hz, 1H), 3.79 (d, $J$ = 6.4 Hz, 2H), 2.07 (hept, $J$ = 6.7 Hz, 1H), 1.04 (d, $J$ = 6.7 Hz, 6H)。ESI-MS $m/z$ 計算值479.11, 實驗值480.2 $(M+1)^+$；LCMS 滯留時間: 1.8分鐘 (3分鐘操作)。

**步驟3：*N*-[(6-胺基-2-吡啶基)磺醯基]-3-氟-4-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)苯甲醯胺(化合物1497)**

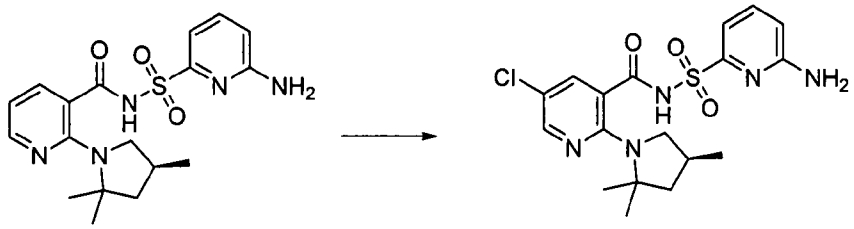


向2,2,4-三甲基吡咯啶(35.41 mg，0.3128 mmol)及*N*-[(6-胺基-2-吡啶基)磺醯基]-2,3-二氟-4-(3-氟-5-異丁氧基-苯基)苯甲醯胺(30.00 mg，0.06257 mmol)之混合物中添加1-甲基吡咯啶-2-酮(0.3 mL)且將反應混合物加熱至190℃，保持2小時。反應混合物冷卻且藉由逆相HPLC，利用含有5 mM甲酸銨之水中10至99%乙腈之梯度純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-3-氟-4-(3-氟-5-異丁氧基-苯基)-2-(2,2,4-三甲基吡咯啶-1-基)苯甲醯胺(化合物1497) (7.6 mg，0.013 mmol，4.2%)。$^1$H NMR (400 MHz,甲醇-$d_4$) $\delta$ 8.03 (dd, $J$ = 8.3, 1.2 Hz, 1H), 7.68 (dd, $J$ = 8.5, 7.3 Hz, 1H), 7.59 (dd, $J$ = 8.3, 7.1 Hz, 1H), 7.38 (dd, $J$ = 7.4, 0.8 Hz, 1H), 6.93 - 6.82 (m, 2H), 6.82 - 6.74 (m, 2H), 3.92 (t, $J$ = 9.4 Hz, 1H), 3.79 (d, $J$ = 6.4 Hz, 2H), 2.84 - 2.72 (m, 1H), 2.23 (dd, $J$ = 12.6, 7.3 Hz, 1H), 2.12 - 2.02 (m, 1H), 1.87 (t, $J$ = 11.7 Hz, 1H), 1.38 (s, 3H), 1.24 (d, $J$ = 6.6 Hz, 6H), 1.04 (d, $J$ = 6.7 Hz, 6H)。ESI-MS $m/z$計算值572.23, 實驗值573.1 $(M+1)^+$；LCMS 滯留時間: 1.77分鐘(3分鐘操作)。

**製備87：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1641)**

將含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(56.79 mg，0.1022 mmol)及*N*-氯丁二醯亞胺(13.65 mg，0.1022 mmol)之二氯甲烷(400 μL)在回流下攪拌隔夜。二氯甲烷在氮氣流下蒸發，且殘餘物溶於二甲亞碸中且藉由製備型HPLC 層析，利用水中10至99%乙腈之梯度來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-6-(3-氟-5-異丁氧基-苯基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1641) (18 mg，0.030 mmol，29.5%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.59 (s, 1H), 7.80 (s, 1H), 7.64 (dd, $J$ = 8.4, 7.3 Hz, 1H), 7.27 - 7.18 (m, 1H), 7.10 - 6.99 (m, 2H), 6.93 (dt, $J$ = 11.0, 2.3 Hz, 1H), 6.70 (dd, $J$ = 8.4, 0.8 Hz, 1H), 6.54 (s, 2H), 3.80 (d, $J$ = 6.6 Hz, 2H), 2.65 - 2.53 (m, 2H), 2.22 (dt, $J$ = 11.5, 5.9 Hz, 1H), 2.08 - 1.96 (m, 1H), 1.84 (dd, $J$ = 12. 0 , 5.6 Hz, 1H), 1.57 - 1.33 (m, 7H), 0.97 (d, $J$ = 6.7 Hz, 6H), 0.86 (d, $J$ = 6.3 Hz, 3H)。ESI-MS *m/z*計算值589.19257, 實驗值590.0 $(M+1)^+$；滯留時間: 3.06分鐘。

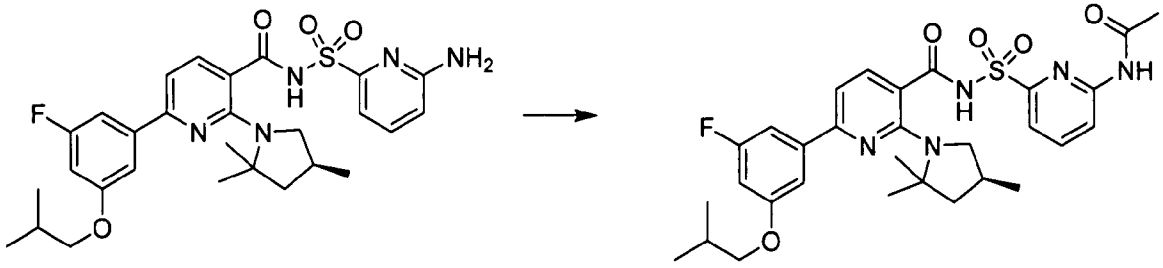
**製備88：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1603)**



將含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物946) (40.0 mg，0.102 mmol)及*N*-氯丁二醯亞胺(13.65 mg，0.1022 mmol)之二氯甲烷(400 μL)在回流下攪拌3天。反

應混合物直接藉由矽膠(4g)層析，用0至5%甲醇之二氯甲烷溶液之線性梯度來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1603) (25 mg，0.058 mmol，57%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.54 (s, 1H), 8.27 - 8.00 (m, 1H), 7.72 - 7.54 (m, 2H), 7.18 (d, $J$ = 7.2 Hz, 1H), 6.66 (d, $J$ = 8.4 Hz, 1H), 6.50 (s, 2H), 2.55 (s, 2H), 2.17 (dq, $J$ = 13.0, 7.1, 6.7 Hz, 1H), 1.83 (dd, $J$ = 11.8, 5.6 Hz, 1H), 1.47 (d, $J$ = 7.1 Hz, 6H), 1.37 (t, $J$ = 12.1 Hz, 1H), 0.85 (d, $J$ = 6.3 Hz, 3H)。ESI-MS *m/z*計算值423.1132，實驗值424.0 $(M+1)^+$；滯留時間: 1.75分鐘。

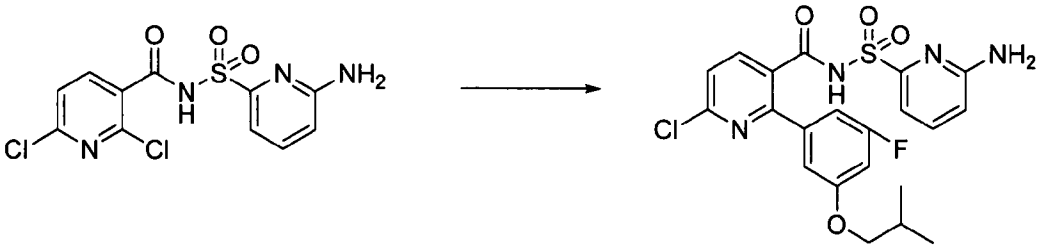
**製備89：*N*-[(6-乙醯胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1652)**



含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(56.78 mg，0.1022 mmol)之吡啶(161.7 mg，165.3 µL，2.044 mmol)用乙酸酐(104.3 mg，96.40µL，1.022 mmol)處理且加熱至45℃，保持2.5小時。將反應混合物用二甲亞碸於水中之9:1 (v/v)混合物稀釋且藉由製備型HPLC層析來純化，得到*N*-[(6-乙醯胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1652) (22 mg，0.036 mmol，35%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.68 (s, 1H), 10.87 (s, 1H), 8.35 (d, $J$ = 8.4 Hz, 1H), 8.17 - 8.05 (m, 1H), 7.88 - 7.80 (m, 2H), 7.51 - 7.45 (m, 1H), 7.42 (ddd, $J$ = 10.2, 2.4, 1.3 Hz, 1H), 7.30 (d, $J$ = 8.0 Hz, 1H), 6.90 (dt, $J$ = 10.7, 2.3 Hz, 1H), 3.83 (d, $J$ = 6.6

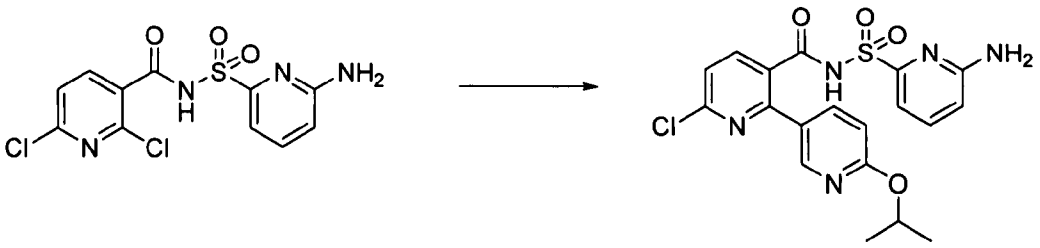
Hz, 2H), 2.60 (dd, $J$ = 10.2, 7.2 Hz, 1H), 2.52 (d, $J$ = 5.3 Hz, 1H), 2.14 (s, 4H), 2.07 - 2.00 (m, 1H), 1.87 (dd, $J$ = 11.8, 5.6 Hz, 1H), 1.59 (d, $J$ = 6.0 Hz, 6H), 1.41 (t, $J$ = 12.1 Hz, 1H), 0.99 (d, $J$ = 6.7 Hz, 6H), 0.77 (d, $J$ = 6.3 Hz, 3H)。ESI-MS $m/z$計算值597.2421，實驗值598.0 $(M+1)^+$；滯留時間: 2.83分鐘。

**製備90：*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-2-(3-氟-5-異丁氧基苯基)菸鹼醯胺**



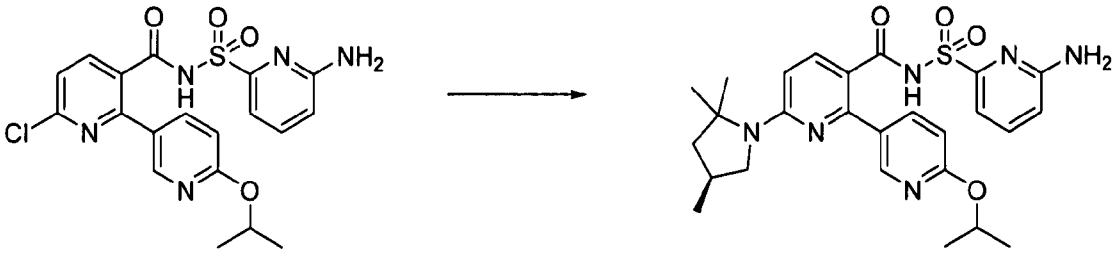
*N*-((6-胺基吡啶-2-基)磺醯基)-2,6-二氯菸鹼醯胺(2.6 g，7.4 mmol)及2-(3-氟-5-異丁氧基苯基)-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(2.3 g，7.7 mmol)於12 mL *N,N*-二甲基甲醯胺及3 mL水中之混合物在氮氣下加熱至70℃，保持30分鐘且接著肆(三苯基膦)鈀(0) (0.20 g，0.17 mmol)及碳酸鈉(4.8 g，45 mmol)添加至反應混合物。將混合物在70℃下攪拌18小時且接著藉由矽膠層析，用己烷中40至100%乙酸乙酯之梯度溶離來純化。產物在逆相HPLC上進一步純化且分離呈白色固體狀之*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-2-(3-氟-5-異丁氧基苯基)菸鹼醯胺(0.37 g，0.77 mmol，14%)。$^1$H NMR (DMSO-$d_6$, 250 MHz): δ 8.03 (d, $J$ = 8.3 Hz, 1H), 7.62 (m, 2H), 7.11 (d, J = 7.3 Hz, 1H), 6.93 (m, 2H), 6.81 (d, $J$ = 9.3 Hz, 1H), 6.73 (d, $J$ = 8.5 Hz, 1H), 3.87 (d, $J$ = 6.5 Hz, 2H), 2.02 (m, 1H), 1.00 (d, $J$ = 6.5 Hz, 6H) ppm。LC-MS: $(M+H)^+$ = 479.1

**製備91：*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-6'-異丙氧基-[2,3'-bi吡啶]-3-甲醯胺**



將磺醯胺*N*-((6-胺基吡啶-2-基)磺醯基)-2,6-二氯菸鹼醯胺(2.1 g，6.0 mmol)及2-異丙氧基-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡啶(1.7 g，6.6 mmol)於12 mL *N,N*-二甲基甲醯胺及3 mL水中之混合物在氮氣下在70℃下加熱20分鐘且添加肆(三苯基膦)鈀(0) (0.15 g，0.13 mmol)及碳酸鈉(1.9 g，18 mmol)。將混合物在70℃下攪拌19小時。反應混合物蒸發至乾，且粗產物藉由矽膠層析，利用己烷中40至100%乙酸乙酯之梯度來純化。產物在逆相HPLC上進一步純化且分離呈白色固體狀之*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-6'-異丙氧基-[2,3'-聯吡啶]-3-甲醯胺(0.72 g，1.6 mmol，27%)。$^1$H NMR (DMSO-$d_6$, 250 MHz): δ 8.33 (s, 1H), 8.06 (d, $J$ = 8.0 Hz, 1H), 7.64 (m, 3H), 7.15 (d, J = 7.3 Hz, 1H), 6.93 (m, 2H), 6.80 (d, $J$ = 7.3 Hz, 1H), 6.69 (d, $J$ = 8.8 Hz, 1H), 5.27 (m, 1H), 1.32 (d, $J$ = 6.3 Hz, 6H) ppm。

**製備92：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-異丙氧基-3-吡啶基)-6-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1436)**



*N*-((6-胺基吡啶-2-基)磺醯基)-6-氯-6'-異丙氧基-[2,3'-聯吡啶]-3-甲醯胺(0.050 g，0.11mmol)及氟化銫(0.085 g，0.56 mmol)組合於二甲亞碸(0.5 mL)中。將反應混合物在150℃下攪拌16小時。將(4S)-2,2,4-三甲基吡咯啶(0.0379 g，0.335 mmol)添加至反應混合物中且在150℃下攪拌混合物10小時。粗產物藉由逆相HPLC，利用水中10至99%乙

腈之梯度來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-異丙氧基-3-吡啶基)-6-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1436) (0.0026 g，0.0050 mmol，4.5%)。ESI-MS *m/z*計算值424.2，實驗值525.3 $(M+1)^+$；滯留時間: 1.89分鐘。

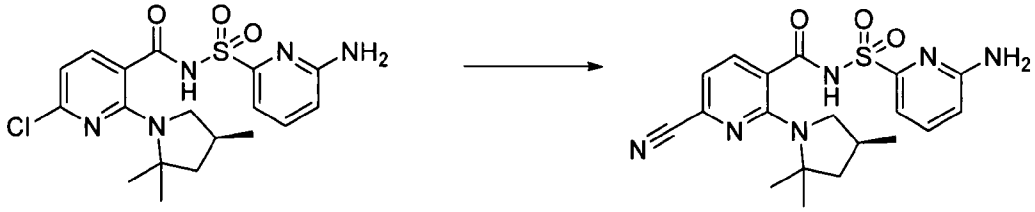
以下化合物可使用本文所述之程序合成:

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟-5-異丁氧基-苯基)-6-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1409)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟-5-異丁氧基-苯基)-6-[(4*R*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1385)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(6-異丙氧基-3-吡啶基)-6-[(4*R*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1491)。

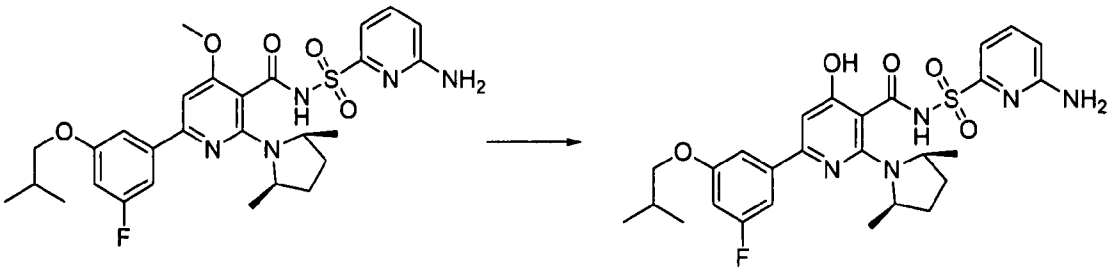
**製備93：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氰基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1564)**



甲烷磺酸[(2-二-第三丁基膦基-2',4',6'-三異丙基-1,1'-聯苯)-2-(2'-胺基-1,1'-聯苯)]鈀(II)(4.186 mg，0.005270 mmol)、二-第三丁基-[2-(2,4,6-三異丙基苯基)苯基]膦(2.238 mg，0.005270 mmol、六氰基亞鐵酸鉀(II)三水合物(22.26 mg，0.05270 mmol)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物852) (44.7 mg，0.1054 mmol)添加至小瓶且小瓶用氮氣淨化。將去氧二噁烷(500 μL)及碳酸鉀溶液(263.6 μL 0.05 M，0.01318 mmol)添加至反應混合物中，頂部空間用氮氣淨化且將密封小瓶在100℃下攪拌1小時。粗產物藉由逆相HPLC，利用水中10至99%乙腈之梯度來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氰基-2-[(4S)-2,2,4-三甲基吡咯啶

-1-基]吡啶-3-甲醯胺(化合物1564) (1.8 mg，0.0043 mmol，4.1%)。ESI-MS *m/z*計算值414.1474，實驗值415.2 $(M+1)^+$；滯留時間：1.49分鐘。

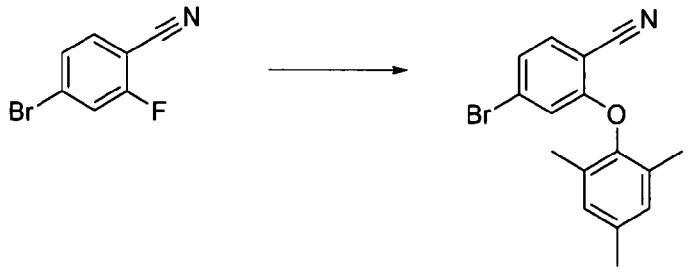
**製備94：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-4-羥基-吡啶-3-甲醯胺(化合物1430)**



在氮氣淨化之燒瓶中，*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-4-甲氧基-吡啶-3-甲醯胺(化合物1254) (17.5 mg，0.0306 mmol)溶於二氯甲烷(1.577 mL)中。冷卻混合物至-78℃，且將三溴硼烷(811.2 mg，306.1 μL 1 M，0.3061 mmol)以逐滴方式添加至反應混合物中。混合物緩慢升溫至室溫。將混合物在周圍溫度下攪拌隔夜。將反應混合物添加至冰(約5 mL)中。分離各層，且水層用二氯甲烷萃取。合併之有機層經硫酸鈉乾燥，濃縮，且藉由逆相HPLC，利用5 mM鹽酸水溶液中1-99%乙腈之梯度來純化。該化合物在矽膠上，使用二氯甲烷作爲溶離劑進一步純化，得到呈灰白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-4-羥基-吡啶-3-甲醯胺(化合物1430) (3.2 mg，0.0057 mmol，19%)。ESI-MS *m/z*計算值557.2108，實驗值558.3 $(M+1)^+$，滯留時間：1.84 分鐘。

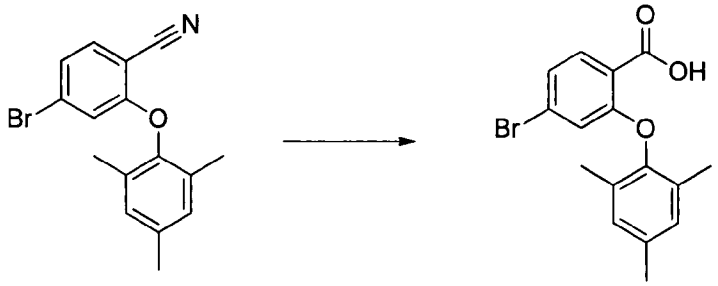
**製備95：4-溴-2-(均三甲苯基氧基)苯甲酸**

**步驟1：4-溴-2-(均三甲苯基氧基)苯甲腈**



將4-溴-2-氟-苯甲腈(1.2 g，6.0 mmol)、2,4,6-三甲基苯酚(780 mg，6.1 mmol)、碳酸鉀(2.50 g，18.1 mmol)及二甲亞碸(9.0 mL)之混合物在140℃下微波照射2小時。添加水(20 mL)且將所得混合物攪拌5分鐘。過濾所得懸浮液且固體用水洗滌且在真空下50℃下乾燥16小時，得到呈褐色固體狀之4-溴-2-(均三甲苯基氧基)苯甲腈(1.8 g，95%)。$^1$H NMR ($CDCl_3$, 250 MHz): 7.50 (d, $J$ = 8.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 6.94 (s, 2H), 6.61 (s, 1H), 2.33 (s, 3H), 2.10 (s, 6H) ppm。

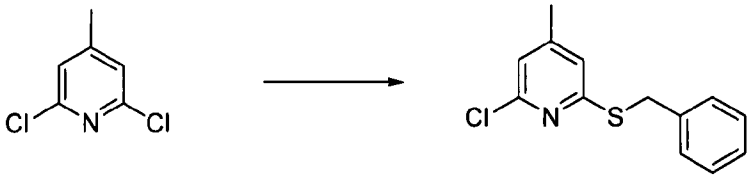
**步驟2：4-溴-2-(均三甲苯基氧基)苯甲酸**



4-溴-2-(均三甲苯基氧基)苯甲腈(1.8 g，9.0 mmol)懸浮於含有氫氧化鈉(3.0 g，75 mmol)之乙醇(6 mL)及水(12 mL)中。將混合物在90℃下攪拌16小時。將鹽酸(6M，13 mL)添加至反應混合物中，接著添加水(20 mL)且將懸浮液攪拌10分鐘，過濾，且用水及接著己烷洗滌，得到呈灰白色固體狀之4-溴-2-(均三甲苯基氧基)苯甲酸(1.7 g，5.1 mmol，57%)。$^1$H NMR (DMSO-$d_6$, 250 MHz): 7.74 (d, $J$ = 8.2 Hz, 1H), 7.28 (d, $J$ = 8.2 Hz, 1H), 7.01 (s, 2H), 6.41 (s, 1H), 2.28 (s, 3H), 2.02 (s, 6H) ppm。

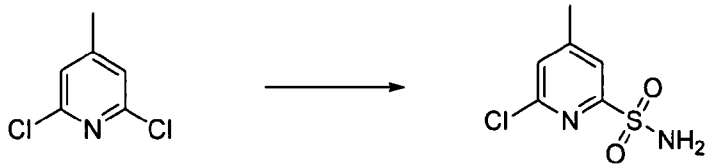
**製備96：6-甲氧基-4-甲基吡啶-2-磺醯胺**

**步驟1：2-苯甲基硫基-6-氯-4-甲基吡啶**



將2,6-二氯-4-甲基-吡啶(4.74 g，29.3 mmol)溶於含苯基甲烷硫醇(3.634 g，3.435 mL，29.26 mmol)之四氫呋喃(47.40 mL)中且2-甲基丙-2-醇鹽(鈉鐵(1)) (29.26 mL 2 M，58.52 mmol)添加至反應混合物中。將反應物攪拌16小時且分溶於水與乙酸乙酯之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且蒸發。粗物質未經進一步純化即使用。2-苯甲基硫基-6-氯-4-甲基-吡啶(6.91 g，27.7 mmol，94.5%)。ESI-MS *m/z* 計算值249.0379, 實驗值250.0 $(M+1)^+$；滯留時間: 0.78分鐘。

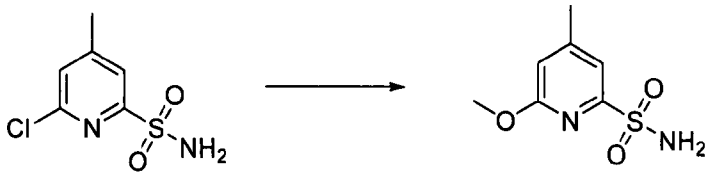
**步驟2：6-氯-4-甲基吡啶-2-磺醯胺**



2-苯甲基硫基-6-氯-4-甲基-吡啶(6.87 g，27.5 mmol)於二氯甲烷(41.22 mL)、水(13.74 mL)及鹽酸水溶液(2.751 mL 1 M，2.751 mmol)中之兩相混合物在鹽水冰浴中冷卻。(注意：添加鹽酸水溶液以避免在添加氯氣後另外延遲放熱)。氯氣(7.800 g，110.0 mmol)鼓泡穿過溶液(3次，時間間隔爲2分鐘)一個小時。將反應物在0℃下攪拌。1.5小時 (反應藉由UPLC監測)後，反應物逐滴添加至氫氧化銨冰浴冷卻溶液(41.32 mL 28 %w/v，330.1 mmol)。反應升溫至室溫且攪拌15分鐘。反應混合物分溶於乙酸乙酯(60 mL)與水(20 mL)之間。有機物分離，且水層用乙酸乙酯( 60 mL部分)萃取兩次。合併有機物，用鹽水洗滌，經硫酸鈉乾燥且蒸發。所得固體用二氯甲烷(30 mL)濕磨且過濾。固體用最少二氯甲烷洗滌，得到呈灰白色固體狀之6-氯-4-甲基-吡啶-2-磺醯胺(3.18 g，15.4 mmol，56.0%)。$^1$H NMR (400 MHz,

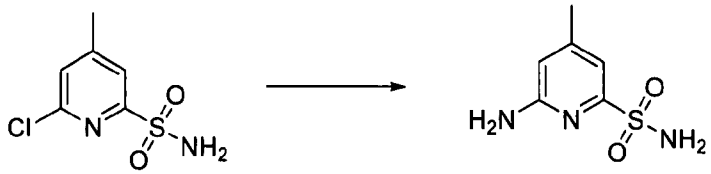
DMSO-$d_6$) δ 7.78 (dd, $J$ = 1.3, 0.7 Hz, 1H), 7.66 - 7.63 (m, 1H), 7.59 (s, 2H), 2.45 (s, 3H)。ESI-MS $m/z$計算值205.99167, 實驗值206.9 $(M+1)^+$；滯留時間: 0.3分鐘。

**步驟3：6-甲氧基-4-甲基吡啶-2-磺醯胺**



6-氯-4-甲基吡啶-2-磺醯胺(500. mg，2.42 mmol)溶於含甲醇鈉之甲醇(2.537 g，2.615 mL 25 % w/v，12.10 mmol)中且在65℃下加熱。1小時後，所有起始物質消失且已形成兩種產物。反應混合物分溶於乙酸乙酯與飽和氯化銨水溶液之間。分離有機物，用水、鹽水洗滌，經硫酸鈉乾燥且蒸發至乾。粗產物藉由矽膠層析，用己烷中0至100%乙酸乙酯溶離來純化，得到6-甲氧基-4-甲基吡啶-2-磺醯胺(126 mg，0.623 mmol，25.7%)。ESI-MS $m/z$計算值202.04121, 實驗值203.0 $(M+1)^+$；滯留時間: 0.32分鐘。

**製備97：6-胺基-4-甲基吡啶-2-磺醯胺**

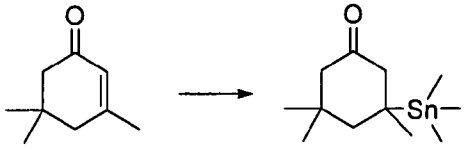


6-氯-4-甲基吡啶-2-磺醯胺(500. mg，2.42 mmol)溶於氫氧化銨水溶液(3.029 mL 28 %w/v，24.20 mmol)中且在微波反應器中在150℃下照射1小時。反應物蒸發且固體用水及甲醇洗滌以移除過量氫氧化銨。所得固體爲產物與起始物質之混合物。混合物未經進一步純化即用於下一步中。6-胺基-4-甲基吡啶-2-磺醯胺(200. mg，1.07 mmol，44.2%)。ESI-MS $m/z$計算值187.04155, 實驗值188.0 $(M+1)^+$；滯留時間: 0.21分鐘。

**製備98：4,4,5,5-四甲基-2-(3,3,5,5-四甲基環戊烯-1-基)-1,3,2-二氧雜**

**硼雜環戊烷**

**步驟1：3,3,5-三甲基-5-三甲基錫烷基-環己酮**



在-20℃下向攪拌的三甲基(三甲基錫烷基)錫烷(3.555 g，2.250 mL，10.85 mmol)於四氫呋喃(50 mL)中之溶液中添加甲基鋰(4.964 g，6.781 mL 1.6 M，10.85 mmol)且在-20℃下攪拌混合物15分鐘。接著緩慢添加3,5,5-三甲基環己-2-烯-1-酮(1.00 g，7.24 mmol)且反應混合物升溫至0℃，攪拌30分鐘，且接著用甲醇(695.6 mg，879.4 μL，21.71 mmol)淬滅。反應混合物升溫至室溫且用水稀釋，接著用二乙醚萃取兩次。合併之有機層乾燥(硫酸鈉)，過濾且濃縮成黃色油狀物，其藉由矽膠層析，使用100%己烷作爲溶離劑，接著100%二氯甲烷作爲溶離劑來純化，得到呈透明油狀之3,3,5-三甲基-5-三甲基錫烷基-環己酮(2.01 g，6.63 mmol，91.7%)。$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.59 - 2.45 (m, 1H), 2.21 - 2.12 (m, 3H), 1.92 (d, $J$ = 14.2 Hz, 1H), 1.59 (d, $J$ = 14.2 Hz, 1H), 1.28 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 0.13 (d, $J$ = 1.1 Hz, 1H), 0.07 (s, 9H), 0.01 (d, $J$ = 1.1 Hz, 1H)。

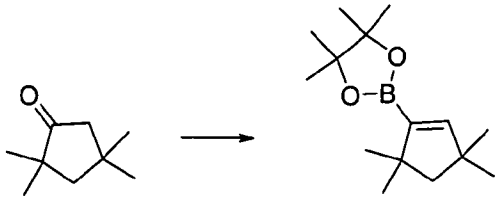
**步驟2：2,2,4,4-四甲基環戊酮**



在0℃下在氮氣氛圍下向攪拌的3,3,5-三甲基-5-三甲基錫烷基-環己酮(4.17 g，13.8 mmol)於二氯甲烷(79.23 mL)中之溶液中添加(逐滴)四氯鈦(2.610 g，2.183 mL，13.76 mmol)，添加後得到深褐色。添加結束後，反應混合物爲褐色懸浮液，將其在0℃下攪拌20分鐘且接著藉由添加飽和碳酸氫鈉水溶液(注意：氣體放出，反應物變成兩相，

其中紫色懸浮液爲水層)淬滅。所得混合物用二氯甲烷萃取兩次，乾燥(硫酸鎂)，過濾且小心濃縮成透明油狀物。藉由矽膠層析，用100%溶離來純化，得到呈透明油狀之2,2,4,4-四甲基環戊酮 (1.67 g，11.9 mmol，86.6%)。

**步驟3：4,4,5,5-四甲基-2-(3,3,5,5-四甲基環戊烯-1-基)-1,3,2-二氧雜硼雜環戊烷**

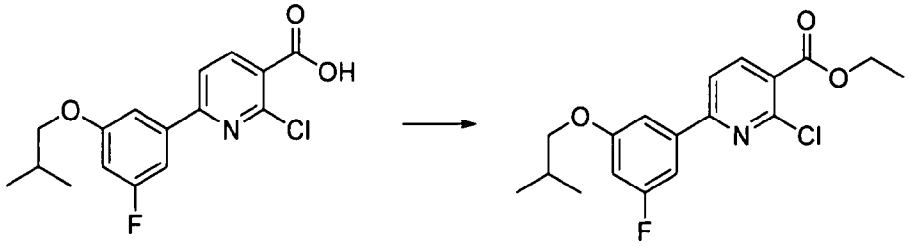


向2,2,4,4-四甲基環戊酮(1.67 g，11.9 mmol)中添加四氫呋喃(16.70 mL)且反應冷卻至-78℃。將反應物攪拌10分鐘且逐滴添加雙(三甲基矽烷基)胺基鋰(14.29 mL 1 M，14.29 mmol)且將反應物在-78℃下攪拌1小時。逐滴添加溶於四氫呋喃(12.5 mL)中之1,1,1-三氟-*N*-苯基-*N*-(三氟甲基磺醯基)甲烷磺醯胺(5.105 g，14.29 mmol)且使反應升溫至室溫且攪拌16小時。將反應用飽和氯化鈉水溶液淬滅且用乙酸乙酯萃取。有機層經硫酸鈉乾燥且蒸發成色糖漿狀物。將粗橙色糖漿狀物添加至雙(頻哪醇)二硼(4.535 g，17.86 mmol)、[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(871.5 mg，1.191 mmol)及乙酸鉀(3.507 g，35.73 mmol)於二甲基甲醯胺(16.70 mL)中之混合物中。反應物用氮氣淨化且加熱至65℃，保持16小時。將反應用飽和氯化鈉水溶液淬滅且用乙酸乙酯萃取。有機層經硫酸鈉乾燥且蒸發至乾。粗產物藉由矽膠層析，使用己烷中100%己烷至40%乙酸乙酯之梯度來純化，得到呈白色固體狀之4,4,5,5-四甲基-2-(3,3,5,5-四甲基環戊烯-1-基)-1,3,2-二氧雜硼雜環戊烷(651 mg，2.60 mmol，21.8%)。

**製備99：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (異構體1) (化合**

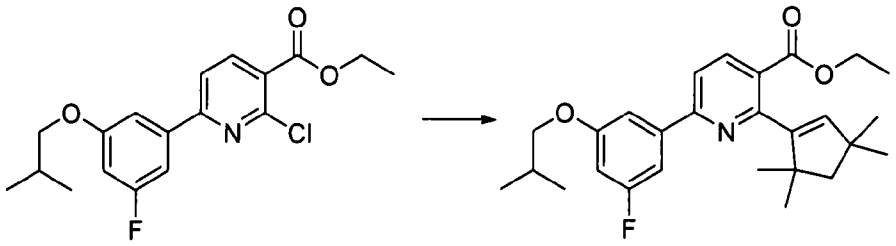
**物2374) (異構體2)**

**步驟1：2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸乙酯**



逐滴添加溶於乙醇(50.26 mL)及硫醯氯(2.218 g，1.360 mL，18.64 mmol)中之2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(5.077 g，15.53 mmol)。所得溶液緩慢加熱至76℃(回流)且在76℃下攪拌5小時。濃縮微褐色溶液以移除溶劑。粗殘餘物再溶於乙酸乙酯中且用飽和碳酸氫鈉水溶液萃取。水相用乙酸乙酯萃取兩次。合併之有機層用飽和鹽水水溶液萃取，經硫酸鈉乾燥，濃縮且藉由矽膠層析，使用100%已烷至100%乙酸乙酯之梯度來純化，得到呈白色固體狀之2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸乙酯(3.64 g，10.3 mmol，66.6%)。

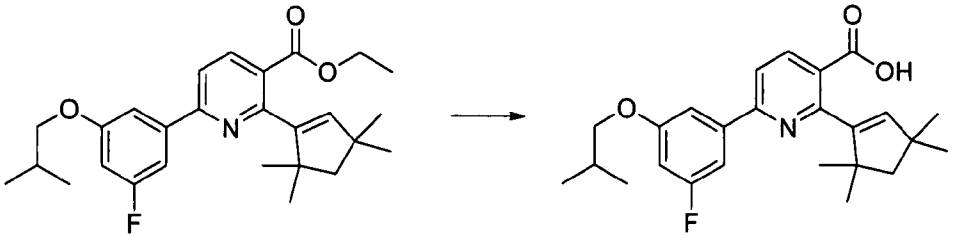
**步驟2：6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸乙酯**



將2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸乙酯(841.8 mg，2.393 mmol)、4,4,5,5-四甲基-2-(3,3,5,5-四甲基環戊烯-1-基)-1,3,2-二氧雜硼雜環戊烷(598.7 mg，2.393 mmol)、[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(525.3 mg，0.7179 mmol)及碳酸鈉(760.9 mg，7.179 mmol)於二噁烷(10.77 mL)及水(1.196 mL)中之混合物在密封容器中在150℃下加熱16小時。過濾反應物且固體用乙酸乙

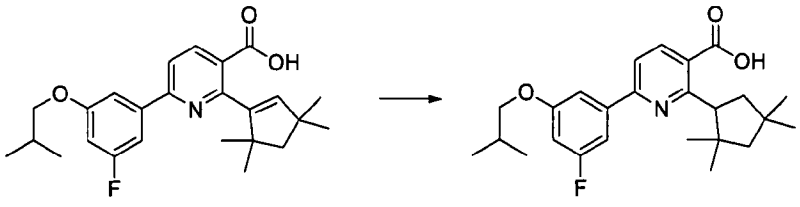
酯洗滌。蒸發萃取物且殘餘物藉由矽膠層析，使用己烷中100%己烷至25%乙酸乙酯之梯度來純化，得到呈淡黃色固體狀之6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸乙酯(460.3 mg，1.047 mmol，43.75%)。

**步驟3：6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸**



將6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸乙酯(460.3 mg，1.047 mmol)及氫氧化鈉(2.617 mL 1 M，2.617 mmol)於四氫呋喃(2.606 mL)及水(2.606 mL)中之溶液在50℃下攪拌6.5小時。反應冷卻至室溫且接著用1M鹽酸中和且用乙酸乙酯萃取兩次。合併之萃取物經硫酸鈉乾燥且蒸發，得到呈黃色針狀之6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸(389.1 mg，0.9455 mmol，90.32%)。

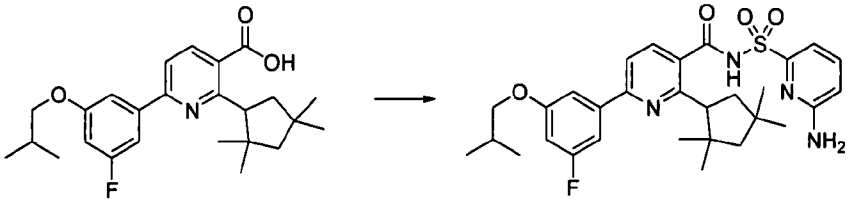
**步驟4：6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲酸**



6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸(389.1 mg，0.9455 mmol)、氫氧化鈀(79.67 mg，0.5673 mmol)及甲酸銨(1.192 g，18.91 mmol)於乙醇(10 mL)中之混合物組合於微波小瓶中且加熱至85℃，保持3小時。反應混合物冷卻至室溫，不封蓋，

添加甲酸銨(1.192 g，18.91 mmol)及氫氧化鈀(79.67 mg，0.5673 mmol)，氮氣鼓泡穿過溶液，保持2分鐘，且將小瓶封蓋且回至微波反應器85℃下又4 小時。反應經矽藻土過濾，用甲醇溶離且在減壓下濃縮。接著混合物用1N鹽酸水溶液稀釋且用乙酸乙酯洗滌兩次。合併有機層，乾燥(硫酸鈉)，過濾且濃縮成透明油狀物，存在一些白色固體。粗物質藉由矽膠層析，使用100%二氯甲烷至20%甲醇之二氯甲烷溶液，接著乙酸乙酯中20%甲醇之梯度來純化，得到呈白色固體狀之6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲酸(52.3 mg，0.126 mmol，13.4%)。

**步驟5：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (異構體1) (化合物2374) (異構體2)**

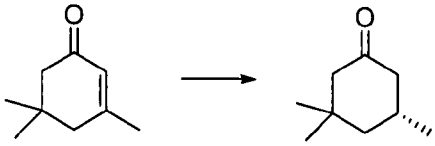


將6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲酸(52.0 mg，0.126 mmol)及羰基二咪唑(30.58 mg，0.1886 mmol)於二甲基甲醯胺(0.5 mL)中之溶液在45℃下攪拌90分鐘。接著添加在45℃下攪拌45分鐘的6-胺基吡啶-2-磺醯胺(43.54 mg，0.2514 mmol)及氫化鈉(10.06 mg，0.2514 mmol)於二甲基甲醯胺(0.5 mL)中之另一溶液且將所得混合物攪拌在45℃下2小時。過濾反應物且使用逆相HPLC-MS法，使用Phenomenex售出之Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)(pn：00C-4252-U0-AX)及經15.0分鐘1至99%移動相B (移動相A = $H_2O$ (5 mM HCl)，移動相B =乙腈，流速 = 50 mL/min，注射體積 = 950 μL及管柱溫度= 25℃)的雙重梯度操作來純化，得到呈灰白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-

(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (異構體1) (化合物2374) (異構體2)鹽酸鹽(51 mg，0.084 mmol，67%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.63 (s, 1H), 7.91 (dd, $J$ = 20.4, 8.2 Hz, 2H), 7.66 (t, $J$ = 7.9 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J = 9.8 Hz, 1H), 7.25 (d, $J$ = 7.3 Hz, 1H), 6.93 (d, $J$ = 10.7 Hz, 1H), 6.73 (d, $J$ = 8.4 Hz, 1H), 6.51 (s, 2H), 3.86 (d, $J$ = 6.6 Hz, 2H), 3.58 (dd, $J$ = 12.2, 6.5 Hz, 1H), 2.55 (d, $J$ = 12.3 Hz, 1H), 2.06 (dt, $J$ = 13.2, 6.6 Hz, 1H), 1.63 (dd, $J$ = 12.4, 6.4 Hz, 1H), 1.50 (d, $J$ = 13.0 Hz, 1H), 1.39 (d, $J$ = 12.9 Hz, 1H), 1.15 (s, 3H), 1.08 - 0.93 (m, 9H), 0.80 (s, 3H), 0.69 (s, 3H)。ESI-MS $m/z$計算值568.25195，實驗值569.3 $(M+1)^+$；滯留時間: 2.4分鐘。

**製備100：4,4,5,5-四甲基-2-[(5*S*)-3,3,5-三甲基環己烯-1-基]-1,3,2-二氧雜硼雜環戊烷**

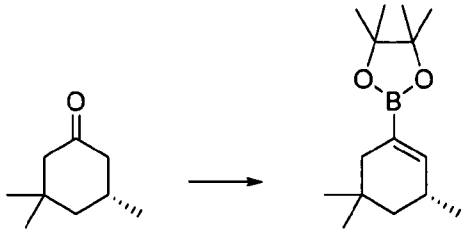
**步驟1：(5*R*)-3,3,5-三甲基環己酮**



向用氮氣淨化之圓底燒瓶中添加乙酸銅(II) (14.53 mg，0.08000 mmol)、[(4*S*)-4-[5-雙(3,5-二第三丁基-4-甲氧基-苯基)磷烷基-1,3-苯并間二氧雜環戊烯-4-基]-4,5,6,7-四氫-1,3-苯并間二氧雜環戊烯-5-基]-雙(3,5-二第三丁基-4-甲氧基-苯基)膦(47.34 mg，0.04000 mmol)及甲苯(27.64 mL)。將反應物在室溫下攪拌90分鐘。添加聚甲基氫矽氧烷(4.8 mL)且將反應物在室溫下攪拌30分鐘。接著逐滴添加3,5,5-三甲基環己-2-烯-1-酮(5.528 g，6.009 mL，40.00 mmol)且將反應物在室溫下攪拌90分鐘。反應物傾倒至3M 氫氧化鈉溶液中且用力攪拌2小時。粗反應物用乙酸乙酯萃取且經硫酸鈉乾燥。移除溶劑且粗產物未經進一步純化即用於下一步，得到呈淺色油狀之(5*R*)-3,3,5-三甲基環己酮

(5.1 g，36 mmol，91%)。ESI-MS *m/z*計算值140.12012，實驗值141.2 $(M+1)^+$；滯留時間: 1.44分鐘。

**步驟2：4,4,5,5-四甲基-2-[(5*S*)-3,3,5-三甲基環己烯-1-基]-1,3,2-二氧雜硼雜環戊烷**

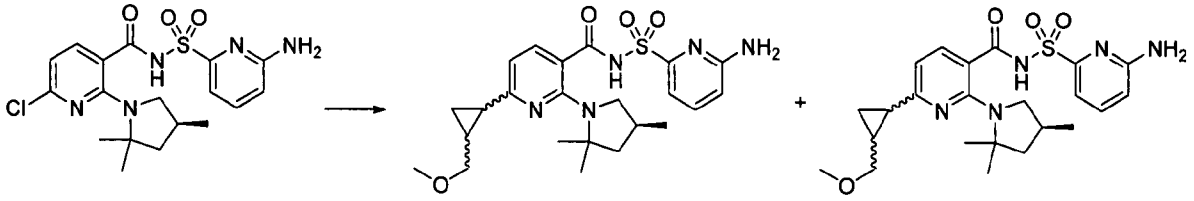


向粗(5*R*)-3,3,5-三甲基環己酮(2.85 g，20.3 mmol)中添加四氫呋喃(28.50 mL)且反應冷卻至-78℃。將反應物攪拌10分鐘且逐滴添加雙(三甲基矽烷基)胺基鋰(24.38 mL 1 M，24.38 mmol)且將反應物在-78℃下攪拌1小時。逐滴添加溶於四氫呋喃(20 mL)中之1,1,1-三氟-*N*-苯基-*N*-(三氟甲基磺醯基)甲烷磺醯胺(8.710 g，24.38 mmol)且使反應升溫至室溫且攪拌16小時。反應用鹽水淬滅且用乙酸乙酯萃取。有機層經硫酸鈉乾燥且蒸發成黃色油狀物。粗三氟甲磺酸乙烯酯未經進一步純化即用於下一步。將粗三氟甲磺酸乙烯酯添加至雙(頻哪醇)二硼(7.740 g，30.48 mmol)、雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(1.487 g，2.032 mmol)、乙酸鉀(5.983 g，60.96 mmol)於*N*.*N*-二甲基甲醯胺(28.50 mL)中之混合物中。反應物用氮氣淨化且加熱至65℃，保持16小時。將反應物用鹽水淬滅且用乙酸乙酯萃取。有機層經硫酸鈉乾燥且蒸發。粗產物藉由矽膠層析，利用己烷中0至40%乙酸乙酯之梯度來純化，得到呈區位異構體之混合物形式的4,4,5,5-四甲基-2-[(5*S*)-3,3,5-三甲基環己烯-1-基]-1,3,2-二氧雜硼雜環戊烷(2.2 g，8.8 mmol，43%)。ESI-MS *m/z*計算值250.2104，實驗值251.6 $(M+1)^+$；滯留時間: 2.17分鐘

**製備101：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(1*S*,2*S*)-2-(甲氧基甲基)環**

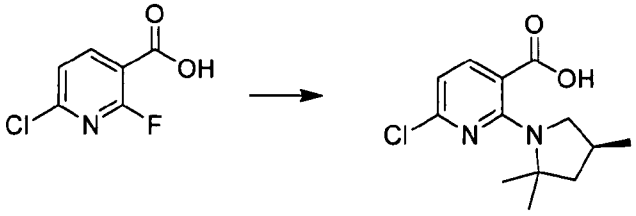
**丙基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1575)**

**步驟1：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(1*S*,2*S*)-2-(甲氧基甲基)環丙基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1575)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(1*R*,2*R*)-2-(甲氧基甲基)環丙基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺**



向微波小瓶中添加*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物852)三氟乙酸鹽(100 mg，0.186 mmol)、二氯化[1,3-雙(2,6-二異丙基苯基)咪唑-2-亞基](3-氯吡啶基)鈀(II) (6.3 mg，0.0093 mmol)及二噁烷(600 μL)。反應物用氮氣淨化2分鐘且添加反式2-[(1*S*,2*S*)-2-(甲氧基甲基)環丙基]-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(68.99 mg，0.325 mmol)，接著2M碳酸鉀水溶液(279 μL 2 M，0.558 mmol)。接著反應物在微波反應器中經16小時照射至120℃。使反應混合物冷卻，過濾且接著直接藉由逆相製備型層析，利用C18管柱及HPLC-MS法，含有5 mM鹽酸之水中1至99乙腈來純化，得到兩種化合物。化合物1 (2.26 mg，0.0044 mmol，2.39%) ESI-MS *m/z*計算值473.2097, 實驗值474.2 $(M+1)^+$；滯留時間: 1.13分鐘。化合物2 (0.86 mg，0.0018 mmol，0.97%) ESI-MS *m/z*計算值473.2097, 實驗值474.2 $(M+1)^+$；滯留時間: 1.26分鐘，呈淡黃色固體狀。

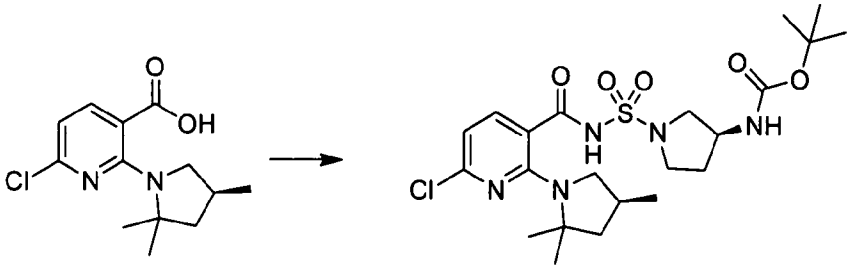
**製備102：*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺**



**步驟1：6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲酸**

6-氯-2-氟-吡啶-3-甲酸(1.50 g，8.545 mmol)及(4S)-2,2,4-三甲基吡咯啶(鹽酸) (1.534 g，10.25 mmol)組合於DMSO (4.500 mL)中。添加碳酸鉀(2.362 g，17.09 mmol)。注意：在混合後觀測到實質鼓泡。反應混合物密封且在90℃下加熱隔夜。將反應混合物用EtOAc (50 mL)稀釋且用0.5 N HCl水溶液洗滌。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮成黃色油狀物。爲移除任何殘餘溶劑，油狀物進行氮氣流1小時，得到結晶固體。產物未經進一步純化即用於下一步。ESI-MS *m/z*計算值268.09787, 實驗值269.2 $(M+1)^+$；滯留時間: 1.49分鐘

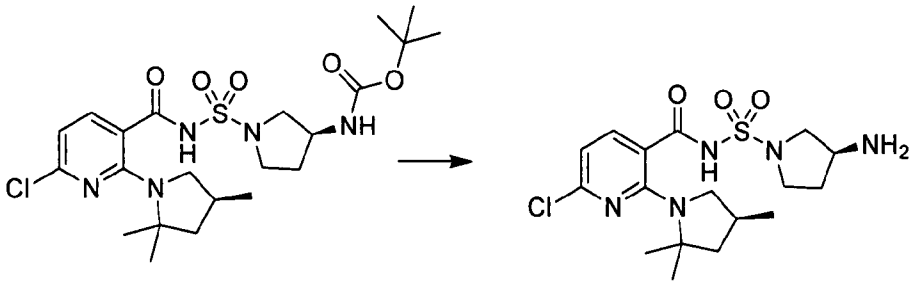
**步驟2：*N*-[(3S)-1-[[6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-羰基]胺磺醯基]吡咯啶-3-基]胺基甲酸第三丁酯**



6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲酸(1.61 g，5.99 mmol)溶於二氯甲烷(8 mL)中，升溫至40℃且添加*N*-(側氧基亞甲基)胺磺醯氯(1.017 g，625.5 μL，7.189 mmol)。注意：在添加期間觀測到實質鼓泡。在40℃下攪拌3分鐘後，添加額外二氯甲烷(10 mL)，接著*N*-[(3*S*)-吡咯啶-3-基]胺基甲酸第三丁酯(2.80 g，15.0 mmol)。觀測到鼓泡。在40℃下攪拌隔夜後，將反應混合物用EtOAc (75 mL)稀釋且用水及鹽水洗滌。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮。產物藉由矽膠管柱層析分離：在80公克矽膠管柱上，0至40% EtOAc/己

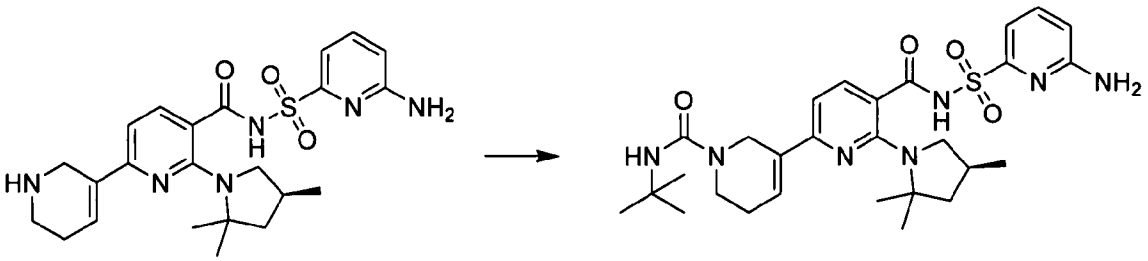
烷梯度。獲得呈淡褐色泡沫固體狀之*N*-[(3S)-1-[[6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-羰基]胺磺醯基]吡咯啶-3-基]胺基甲酸第三丁酯(965 mg，1.87 mmol，31.2%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.92 (s, 1H), 7.62 (d, $J$ = 7.9 Hz, 1H), 7.18 (s, 1H), 6.61 (d, $J$ = 7.9 Hz, 1H), 3.96 (s, 1H), 3.65 - 3.45 (m, 3H), 3.14 (dd, $J$ = 9.7, 5.9 Hz, 1H), 3.03 (t, $J$ = 10.3 Hz, 1H), 2.97 - 2.85 (m, 1H), 2.33 (s, 1H), 2.04 (dd, $J$ = 12.7, 5.7 Hz, 1H), 1.92 (dd, $J$ = 11.4, 5.1 Hz, 1H), 1.78 (dd, $J$ = 12.6, 6.9 Hz, 1H), 1.54 (d, $J$ = 6.1 Hz, 6H), 1.38 (s, 9H), 1.01 (d, $J$ = 6.3 Hz, 3H), 0.83 (s, 1H)。ESI-MS m/z計算值515.1969，實驗值516.4 $(M+1)^+$；滯留時間: 0.77分鐘。

**步驟3：*N*-[(3S)-3-胺基吡咯啶-1-基]磺醯基-6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺**



*N*-[(3S)-1-[[6-氯-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-羰基]胺磺醯基]吡咯啶-3-基]胺基甲酸第三丁酯(100 mg，0.1938 mmol)溶於CH2Cl2 (1 mL)中，且添加TFA (1 mL，12.98 mmol)。將溶液在室溫下攪拌30分鐘。在減壓下移除揮發物。粗產物未經進一步純化即用於下一步中。

**製備103：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(第三丁基胺甲醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2568)**

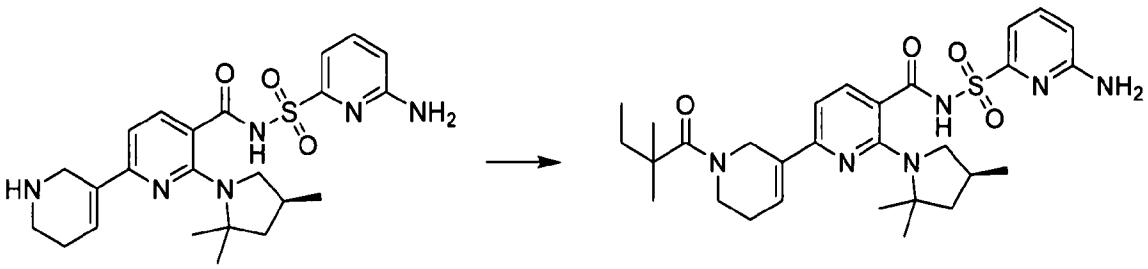


在0℃下在氮氣下向攪拌的*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2,3,6-四氫吡啶-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(鹽酸(2)) (27 mg，0.037mmol)於無水二氯甲烷(1.0 mL)中之溶液中添加三乙胺(50μL，0.3587 mmol)及2-異氰酸酯基-2-甲基-丙烷(8.0 mg，0.081 mmol)。將黃色溶液在周圍溫度下攪拌2小時。在減壓下移除揮發物且殘餘物藉由逆相HPLC來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(第三丁基胺甲醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2568) (鹽酸(1)) (9.2 mg，0.015 mmol，41%)。ESI-MS m/z計算值569.27844, 實驗值570.4 $(M+1)^+$；滯留時間: 1.3分鐘

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[1-(環己基胺甲醯基)-3,6-二氫-2H-吡啶-4-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2520)

**製備104：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(2,2-二甲基丁醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2612)**



在0℃下在氮氣下向攪拌的*N*-[(6-胺基-2-吡啶基)磺醯基]-6-

(1,2,3,6-四氫吡啶-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(鹽酸(2)) (27 mg，0.037 mmol)於無水二氯甲烷(1.0 mL)中之溶液中添加三乙胺(50.μL，0.36 mmol)及2,2-二甲基丁醯氯(11 mg，0.082 mmol)。將黃色溶液在周圍溫度下攪拌2小時。在減壓下移除揮發物且殘餘物由逆相HPLC來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(2,2-二甲基丁醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2612) (鹽酸(1)) (6.7 mg，0.011 mmol，27%)。ESI-MS m/z計算值568.2832，實驗值569.7 (M+1)+；滯留時間: 1.44分鐘

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(3-氯苯并基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1984)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(1-哌啶基磺醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1942)，

*N*-[[6-[(2-苯基乙醯基)胺基]-2-吡啶基]磺醯基]-6-[1-(2-苯基乙醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2243)，

*N*-[6-[[6-(1,2,3,6-四氫吡啶-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基甲酸異丙酯(化合物2624)，

5-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-6-[(4S)-2,2,4-三甲基吡咯啶-1-基]-2-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸異丙酯(化合物2622)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(3,3-二甲基丁醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2650)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[1-(2-環己基乙醯基)-3,6-二氫-2H-吡啶-4-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2596)，

4-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-[(4S)-2,2,4-三甲基吡咯啶-1-基]-3-吡啶基]-3,6-二氫-2H-吡啶-1-甲酸異丙酯(化合物2027)，

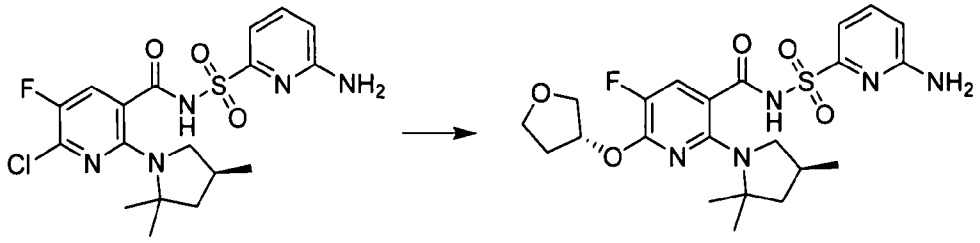
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[1-(2-苯基乙醯基)-3,6-二氫-2H-吡啶-4-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2417)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[1-(3,3-二甲基丁醯基)-3,6-二氫-2H-吡啶-4-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2344)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[1-(2-環己基乙醯基)-3,6-二氫-2H-吡啶-5-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2633)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-異丁基磺醯基-3,6-二氫-2H-吡啶-5-基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1882)

**製備105：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-[(3R)-四氫呋喃-3-基]氧基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2281)**



向4 mL小瓶中添加NaH (10. mg，0.25 mmol)、(3*R*)-四氫呋喃-3-醇(27.63 mg，25.19 μL，0.3136 mmol)及DMSO (800 μL)。將混合物

在周圍溫度下攪拌2分鐘。接著*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-5-氟-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(鹽酸(1)) (30. mg，0.063 mmol)添加至小瓶且將反應物在150℃下攪拌2小時。反應混合物過濾且藉由製備型HPLC (經30分鐘1-99%乙腈，含5 mM HCl之改質劑)純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-[(3R)-四氫呋喃-3-基]氧基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2281) (鹽酸(1)) (9 mg，0.02 mmol，30%)。$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.29 (s, 1H), 7.66 - 7.57 (m, 2H), 7.17 (d, $J$ = 7.3 Hz, 1H), 6.66 (d, $J$ = 8.3 Hz, 1H), 6.41 (s, 2H), 5.55 - 5.48 (m, 1H), 3.94 - 3.83 (m, 2H), 3.83 - 3.76 (m, 2H), 2.56 (d, $J$ = 10.6 Hz, 1H), 2.44 (t, $J$ = 8.7 Hz, 1H), 2.32 - 2.16 (m, 1H), 2.10 - 2.02 (m, 1H), 1.84 (dd, $J$ = 11.8, 5.6 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.37 (t, $J$ = 12.0 Hz, 1H), 0.85 (d, $J$ = 6.3 Hz, 3H)。ESI-MS *m/z*計算值493.1795，實驗值494.3 $(M+1)^+$；滯留時間: 1.08分鐘

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[(1R)-1,2-二甲基丙氧基]-5-氟-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2020)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-環己基乙氧基)-5-氟-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1730)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-[(3S)-四氫呋喃-3-基]氧基-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2056)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-環戊基乙氧基)-5-氟-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1966)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-(1-四氫哌喃-4-基乙氧基)-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1891)，

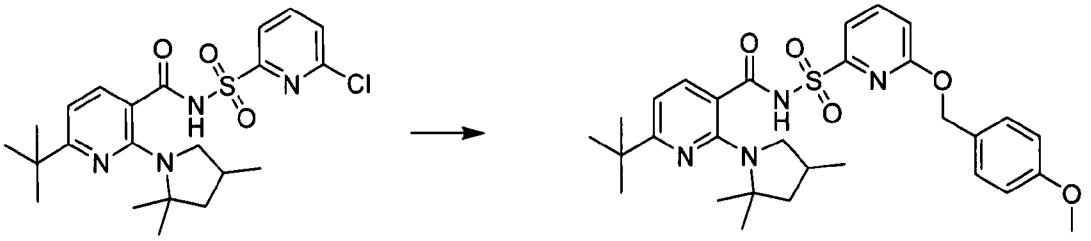
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(環戊氧基)-5-氟-2-[(4S)-2,2,4-三

甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2100)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2,2-二甲基嗎啉-4-基)-5-氟-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2586)，及

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-[1-(4-吡啶基)乙氧基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2212)

**製備106：6-第三丁基-*N*-[[6-[(4-甲氧基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2724) (異構體1) (化合物2428) (異構體2)**



6-(第三丁基)-*N*-((6-氯吡啶-2-基)磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯胺(100. mg，0.215 mmol)及(4-甲氧基苯基)甲醇(59.6 mg，0.431 mmol)溶解於無水二甲亞碸(1 mL)中，且接著將碳酸銫(210 mg，0.645 mmol)添加至反應混合物中。將所得混合物在130℃下加熱24小時且冷卻至室溫。添加水(10 mL)及鹽酸水溶液(1N)直至溶液之pH值爲約2。反應溶液用乙酸乙酯萃取，且萃取物用鹽水洗滌，經硫酸鈉乾燥且過濾。溶劑在減壓下移除。所得殘餘物藉由逆相HPLC，利用含0.1%三氟乙酸之水及含0.1%三氟乙酸之乙腈之梯度來純化。溶離份凍乾，得到6-第三丁基-*N*-[[6-[(4-甲氧基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2724) (異構體1) (化合物2428) (異構體2) (35.2 mg，0.0621 mmol，28.9%)。MS (ESI, m/z)：$[M+H]^+$ 567.3。

以下化合物可使用本文所述之程序合成：

*N*-[[6-[2-(4-氟苯基)乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡

咯啶-1-基)吡啶-3-甲醯胺(化合物1704)，

*N*-[[6-(3-苯基吡咯啶-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1708)，

*N*-[[6-[甲基(丙基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1711)，

*N*-[[6-[(4-甲氧基苯基)甲基-甲基-胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1717)，

*N*-[(6-第三丁氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1718)，

*N*-[[6-(3-甲氧基-5-甲基-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1719)，

*N*-[[6-(2-氰基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1720)，

*N*-[[6-(4-異丙基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1722)，

*N*-[[6-(4-環戊基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1733)，

*N*-[[6-(吡咯啶-3-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1734)，

*N*-[[6-(4-乙醯基-2-甲氧基-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1744)，

*N*-[[6-(3,5-二甲基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1749)，

*N*-[[6-(1-萘氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1751)，

*N*-[(6-丙-2-炔氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-

基)吡啶-3-甲醯胺(化合物1753)，

*N*-[[6-(3-苯基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1755)，

*N*-[[6-(4-第三丁基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1756)，

*N*-[[6-[4-(二甲基胺基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1757)，

*N*-[[6-(3,4-二甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1761)，

*N*-[[6-(四氫呋喃-2-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1764)，

*N*-[[6-(環己基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1767)，

*N*-[[6-[(2,5-二氟苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1770)，

4-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]哌嗪-1-甲酸第三丁酯(化合物1773)，

*N*-[[6-(1,3-苯并噻唑-6-基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1775)，

*N*-[[6-(3,4,4a,5,6,7,8,8a-八氫-2H-喹啉-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1776)，

*N*-[[6-[(5-苯基異噁唑-3-基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1777)，

*N*-[[6-[(3-氯-4-甲氧基-苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1778)，

*N*-[[6-(3-乙炔基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物1782)，

*N*-[[6-(2,4,5-三氟苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1796)，

*N*-[[6-[(2-氟苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1798)，

*N*-[[6-(2-環己基乙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1800)，

*N*-[[6-[3-(甲氧基甲基)-1-哌啶基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1805)，

*N*-[[6-(2,4-二氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1806)，

*N*-[[6-(4-氟苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1813)，

*N*-[[6-(1,3-苯并間二氧雜環戊烯-5-基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1814)，

*N*-[[6-[4-(2-吡啶基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1816)，

*N*-[[6-(1H-吲哚-5-基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1823)，

*N*-[[6-(8-喹啉基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1826)，

*N*-[[6-[苯甲基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1827)，

*N*-[[6-(3-乙氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1828)，

*N*-[[6-(3-氯-4-氟-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物1831)，

*N*-[[6-(1,3,4,9-四氫吡啶并[3,4-b]吲哚-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1833)，

*N*-[[6-(環戊氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1834)，

*N*-[(6-異吲哚啉-2-基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1838)，

*N*-[[6-(3-氯苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1841)，

*N*-[[6-[(1R)-1-苯基乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1842)，

*N*-[[6-[(4-乙基-2-吡啶基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1862)，

*N*-[[6-(噻唑-2-基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1865)，

*N*-[[6-[乙基(2-甲氧基乙基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1870)，

*N*-[[6-(2-氯苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1872)，

*N*-[[6-(3,4-二氫-2H-哌喃-2-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1874)，

*N*-[[6-(7-喹啉基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1875)，

*N*-[[6-[(1-乙醯基吲哚啉-5-基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1877)，

*N*-[[6-[3-(*N*-甲基苯胺基)丙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三

甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1879)，

*N*-[[6-[(E)-丁-2-烯氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1881)，

*N*-[[6-(3-甲基環戊氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1884)，

*N*-[[6-(對甲苯基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1892)，

*N*-[[6-(2-甲基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1898)，

*N*-[[6-[(2-氯-4-氟-苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1899)，

*N*-[[6-(4-異丙基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1902)，

*N*-[[6-(1-苯基乙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1905)，

*N*-[[6-(2,3-二氯苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1906)，

*N*-[[6-(環己氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1908)，

*N*-[[6-(茚滿-5-基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1909)，

*N*-[[6-(1-苯基乙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1917)，

*N*-[[6-(1-環己基乙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1919)，

*N*-[[6-(4-乙氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物1924)，

*N*-[[6-(3-第三丁基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1926)，

*N*-[[6-[(2,4-二氯苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1929)，

*N*-[[6-(氮雜環庚烷-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1932)，

*N*-[[6-(3-異喹啉基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1933)，

*N*-[[6-(1-甲基環戊氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1936)，

*N*-[[6-[4-(1,3-間二氧雜環戊烷-2-基甲基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1937)，

*N*-[[6-(苯甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1938)，

*N*-[[6-(四氫哌喃-2-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1939)，

*N*-[[6-[(3-甲氧基苯基)甲基-甲基-胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1940)，

*N*-[[6-(2-氯-5-氟-苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1941)，

*N*-[[6-(3-乙醯基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1949)，

*N*-[[6-[[3-(三氟甲基)苯基]甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1953)，

*N*-[(6-萘滿-5-基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-

基)吡啶-3-甲醯胺(化合物1955)，

*N*-[[6-[(5-氯-3-吡啶基)氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1957)，

*N*-[[6-(2-甲氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1959)，

*N*-[[6-[(2-甲氧基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1965)，

*N*-[[6-[(2,4-二氯苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1968)，

*N*-[[6-[(4-第三丁基環己基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1971)，

*N*-[[6-[(3-甲氧基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1972)，

*N*-[[6-[4-(三氟甲氧基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1977)，

*N*-[[6-[甲基(苯乙基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1978)，

*N*-[[6-[(2-氯苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1983)，

*N*-[[6-(4-戊基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1985)，

*N*-[[6-(1,3-二氫苯并[de]異喹啉-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1986)，

*N*-[[6-(4-苯基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1987)，

*N*-[[6-(3-甲基環己氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物1988)，

*N*-[[6-(2-喹啉基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1989)，

*N*-[[6-(3-噻吩基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1992)，

*N*-[[6-[[(1R)-1-環己基乙基]胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1996)，

*N*-[[6-[(6-甲基環己-3-烯-1-基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2001)，

*N*-[[6-(1H-吲哚-5-基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2003)，

*N*-[[6-(2-噻吩基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2004)，

*N*-[[6-[甲基-[2-(3-吡啶基)乙基]胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2005)，

*N*-[[6-(3,4,4a,5,6,7,8,8a-八氫-1H-異喹啉-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2011)，

*N*-[[6-[[3-(二甲基胺基)苯基]甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2012)，

*N*-[[6-(1,3-苯并間二氧雜環戊烯-5-基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2013)，

*N*-[[6-(2-氟苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2015)，

*N*-[[6-(2-環己基丙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2019)，

*N*-[[6-(4-苯基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-

1-基)吡啶-3-甲醯胺(化合物2023)，

*N*-[[6-[(2S)-2-(甲氧基甲基)吡咯啶-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2024)，

*N*-[[6-(3,3-二甲基丁氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2025)，

*N*-[[6-(環戊基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2026)，

*N*-[[6-(3-甲基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2030)，

*N*-[[6-(四氫哌喃-4-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2032)，

*N*-[[6-(3,3-二甲基環己氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2038)，

*N*-[[6-(3,4-二甲氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2041)，

*N*-[[6-[環丙基甲基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2044)，

*N*-[[6-[1-(1-萘基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2049)，

*N*-[[6-(環戊基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2053)，

*N*-[[6-[2-(三氟甲基)吡咯啶-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2055)，

*N*-[[6-(1-甲基環庚氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2057)，

*N*-[[6-(1,7,7-三甲基降冰片烷-2-基)氧基-2-吡啶基]磺醯基]-2-

(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2059)，

3-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]苯甲酸乙酯(化合物2060)，

*N*-[[6-(3,4-二氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2061)，

*N*-[[6-[(3-氯苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2064)，

*N*-[[6-(2-吡啶基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2068)，

*N*-[[6-[2-(4-甲氧基苯基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2072)，

*N*-[[6-(5-喹啉基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2074)，

*N*-[(6-異戊基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2075)，

*N*-[[6-(4-氰基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2076)，

*N*-[[6-[(3S)-1-苯甲基吡咯啶-3-基]氧基-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2078)，

*N*-[[6-[(4-甲基-2-吡啶基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2082)，

*N*-[[6-(2-第三丁基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2083)，

*N*-[[6-[4-(1-哌啶基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2087)，

*N*-[[6-[(2-甲氧基苯基)甲基-甲基-胺基]-2-吡啶基]磺醯基]-2-

(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2090)，

*N*-[[6-(2-苯基吡咯啶-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2094)，

*N*-[[6-(3,4-二氫-1H-異喹啉-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2098)，

*N*-[[6-[(2,4-二氟苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2099)，

*N*-[[6-(4-氟苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2102)，

*N*-[[6-(2,4,6-三氟苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2106)，

*N*-[[6-(4-苯甲基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2107)，

*N*-[[6-(3-異丙基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2108)，

*N*-[[6-[(1S,2S)-2-甲基環戊氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2109)，

*N*-[[6-[(1-苯基吡唑-4-基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2111)，

*N*-[[6-(2,3-二氫-1,4-苯并二氧雜環己烯-3-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2115)，

*N*-[[6-(3-甲基吡咯啶-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2116)，

*N*-[[6-[(4-吡唑-1-基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2118)，

*N*-[[6-(4-苯基丁基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物2119)，

4-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]苯甲酸乙酯(化合物2122)，

*N*-[[6-(3-苯甲基吡咯啶-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2123)，

*N*-[[6-(1,1-二甲基丁氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2130)，

*N*-[[6-(四氫呋喃-2-基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2131)，

*N*-[[6-(3-甲氧基丙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2135)，

*N*-[[6-(1-萘基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2136)，

*N*-[[6-(2-甲基-2-吡咯-1-基-丙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2137)，

6-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]吡啶-3-甲酸甲酯(化合物2140)，

*N*-[[6-(3-第三丁基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2142)，

*N*-[[6-[3-(三氟甲氧基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2143)，

*N*-[[6-(4-氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2145)，

*N*-[[6-[2-(2-噻吩基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2146)，

*N*-[(6-環己-2-烯-1-基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物2147)，

*N*-[[6-(2-萘基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2151)，

*N*-[[6-(3-甲氧基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2152)，

*N*-[[6-[(4,6-二甲基-2-吡啶基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2160)，

*N*-[[6-[2-(3-噻吩基)乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2161)，

*N*-[[6-(3-氯-2-氟-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2165)，

*N*-[[6-(3,3-二氟吡咯啶-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2166)，

*N*-[(6-丁氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2167)，

*N*-[[6-[(3-甲氧基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2168)，

*N*-[[6-(1,3-苯并間二氧雜環戊烯-5-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2169)，

*N*-[[6-(4-異丙基環己氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2173)，

*N*-[[6-[4-(4-吡啶基甲基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2175)，

*N*-[[6-(3-氯-5-氰基-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2177)，

*N*-[[6-(2,5-二甲氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡

咯啶-1-基)吡啶-3-甲醯胺(化合物2179)，

*N*-[[6-(2-噻吩基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2181)，

*N*-[[6-[(4-氯-2-氟-苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2182)，

*N*-[[6-[(1S)-1-苯基乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2186)，

*N*-[[6-[(4-異丙基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2187)，

*N*-[[6-(環丁基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2188)，

*N*-[[6-(2,3-二氫-1,4-苯并二氧雜環己烯-6-基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2190)，

*N*-[[6-[(1-甲基吲哚-5-基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2193)，

*N*-[[6-(1-甲基丁基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2197)，

*N*-[[6-[(2-甲基-1,3-苯并噻唑-5-基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2198)，

*N*-[[6-(異丙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2200)，

*N*-[[6-(環辛基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2202)，

*N*-[[6-(2-苯氧基乙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2206)，

*N*-[[6-(4-苯基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物2208)，

*N*-[(6-十氫萘-2-基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2211)，

*N*-[[6-(4-乙氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2214)，

*N*-[[6-(2,4-二氯苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2217)，

*N*-[[6-[(2-甲基環己基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2218)，

*N*-[[6-[1-(甲氧基甲基)丙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2221)，

*N*-[[6-[4-(1-甲基丁基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2226)，

*N*-[[6-(2,3-二甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2233)，

*N*-[[6-(4-甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2239)，

*N*-[[6-(1,3-苯并間二氧雜環戊烯-4-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2249)，

*N*-[[6-(環己基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2250)，

2-[甲基-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]乙酸第三丁酯(化合物2251)，

*N*-[[6-(環庚氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2252)，

4-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡

啶基]胺基]哌啶-1-甲酸乙酯(化合物2253)，

*N*-[[6-(4-吡嗪-2-基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2254)，

*N*-[(6-吲哚啉-1-基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2255)，

*N*-[[6-(6-甲氧基-3,4-二氫-1H-異喹啉-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2260)，

*N*-[[6-[[2-(三氟甲基)苯基]甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2261)，

*N*-[[6-[2-(4-氯苯基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2262)，

*N*-[[6-[3-(5-甲基-1,2,4-噁二唑-3-基)苯氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2263)，

*N*-[[6-[(3-氯苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2264)，

*N*-[[6-(1-萘基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2270)，

*N*-[[6-[(2-氯苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2273)，

*N*-[[6-(5-異喹啉基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2274)，

*N*-[[6-(3,5-二氟苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2282)，

*N*-[[6-[4-(6-甲基-2-吡啶基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2285)，

*N*-[[6-[(4-第三丁基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲

基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2286)，

*N*-[[6-[4-(三氟甲基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2292)，

*N*-[[6-(3,5-二甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2293)，

*N*-[[6-[(6-甲基-2-吡啶基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2294)，

*N*-[[6-(3-苯甲基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2297)，

*N*-[[6-(2-氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2298)，

*N*-[[6-[(3-氰基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2299)，

*N*-[[6-(2-乙基丁基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2305)，

*N*-[[6-[丁基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2307)，

*N*-[[6-(2-呋喃基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2308)，

*N*-[[6-(2,6-二甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2309)，

*N*-[[6-[(2-甲氧基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2310)，

*N*-[[6-(4-胺基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2314)，

*N*-[[6-(3-氰基-4-氟-苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡

咯啶-1-基)吡啶-3-甲醯胺(化合物2316)，

*N*-[(6-環戊-3-烯-1-基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2317)，

*N*-[[6-[[(1R)-1,2-二甲基丙基]胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2318)，

*N*-[[6-(3-甲基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2320)，

(3S)-2-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]-3,4-二氫-1H-異喹啉-3-甲酸(化合物2321)，

*N*-[[6-(2-甲基嗎啉-4-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2324)，

*N*-[[6-(4-乙醯基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2328)，

*N*-[[6-(2-四氫哌喃-4-基乙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2329)，

*N*-[[6-(4-甲基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2330)，

*N*-[[6-(3-氟苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2332)，

*N*-[[6-(8-喹啉基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2333)，

*N*-[4-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]丁基]胺基甲酸第三丁酯(化合物2335)，

*N*-[[6-(4-甲基環己氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2336)，

*N*-[[6-(1H-吲哚-4-基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物2338)，

*N*-[[6-(3,3a,4,5,6,6a-六氫-1H-環戊并[c]吡咯-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2340)，

*N*-[[6-(3,4-二氟苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2341)，

*N*-[[6-(環丙基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2342)，

*N*-[[6-[2-甲氧基乙基(丙基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2343)，

*N*-[[6-[異戊基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2346)，

*N*-[[6-(2,2-二氟乙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2350)，

*N*-[[6-(3-異丙氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2353)，

*N*-[[6-(2-乙氧基乙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2354)，

*N*-[[6-(3,5-二甲氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2357)，

*N*-[[6-[2-(2-吡啶基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2359)，

*N*-[[6-[[6-(三氟甲基)-2-吡啶基]甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2365)，

*N*-[[6-(環丁氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2371)，

*N*-[[6-[(3-氯苯基)甲基-甲基-胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三

甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2378)，

*N*-[[6-[3-(三氟甲基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2381)，

*N*-[[6-(3,4-二氫-2H-喹啉-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2382)，

*N*-[[6-[4-(2-二甲基胺基乙基)-1-哌啶基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2383)，

*N*-[[6-(5-氯吲哚啉-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2385)，

*N*-[[6-(3-乙醯胺基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2387)，

*N*-[[6-(1H-吲唑-5-基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2389)，

*N*-[[6-[(2,6-二氯苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2390)，

*N*-[[6-(間甲苯基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2391)，

*N*-[[6-[(3S)-3-氟吡咯啶-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2393)，

*N*-[[6-(四氫呋喃-3-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2396)，

*N*-[[6-[2-(三氟甲基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2397)，

*N*-甲基-*N*-[2-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]乙基]胺基甲酸第三丁酯(化合物2400)，

*N*-[[6-[(3,4-二氯苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基

吡咯啶-1-基)吡啶-3-甲醯胺(化合物2402)，

*N*-[[6-[(1-苯甲基吡咯啶-3-基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2407)，

*N*-[[6-[1-(2-氟苯基)乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2408)，

*N*-[[6-[(3-氟苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2409)，

*N*-[[6-(2,2-二甲基丙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2412)，

*N*-[[6-[(4-異丙基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2415)，

*N*-[[6-[(6-甲氧基-2-吡啶基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2420)，

*N*-[[6-[(3,5-二氟苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2421)，

*N*-[[6-(4-己基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2423)，

*N*-[[6-[(4-甲氧基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2428)，

*N*-[(6-甲氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2430)，

*N*-[[6-(3-乙醯胺基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2433)，

*N*-[[6-[(1-甲基環丙基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2434)，

*N*-[4-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-

吡啶基]胺基]環己基]胺基甲酸第三丁酯(化合物2439)，

*N*-[[6-(4-咪唑-1-基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2441)，

1-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]哌啶-4-甲酸甲酯(化合物2442)，

*N*-[[6-[3-(二甲基胺基)苯氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2443)，

*N*-[[6-(3-喹啉基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2449)，

*N*-[[6-[2-(4-哌啶基)乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2452)，

*N*-[[6-(4-氟-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2453)，

*N*-[[6-(4-甲基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2460)，

*N*-[[6-(3-氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2461)，

*N*-[[6-[(3,5-二氟苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2462)，

*N*-[(6-嗎啉基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2464)，

*N*-[[6-[2-(3-甲氧基苯基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2465)，

*N*-[[6-[[6-(三氟甲基)-3-吡啶基]胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2466)，

*N*-[[6-[(1R)-1-甲基-2-苯基-乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三

甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2470)，

*N*-[[6-[[6-(三氟甲基)-3-吡啶基]甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2476)，

*N*-[[6-(3-氰基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2484)，

*N*-[[6-(2-異丙基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2486)，

1-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]哌啶-4-甲酸乙酯(化合物2488)，

3-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]苯甲酸甲酯(化合物2493)，

3-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]丙酸第三丁酯(化合物2495)，

*N*-[[6-[2-(對甲苯基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2502)，

*N*-[[6-(5-氯-2-甲氧基-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2503)，

*N*-[[6-[4-(2-吡啶基甲基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2504)，

4-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]哌嗪-1-甲酸甲酯(化合物2506)，

*N*-[[6-(3-呋喃基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2507)，

*N*-[(6-苯氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2509)，

*N*-[[6-(2,6-二氟苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶

-1-基)吡啶-3-甲醯胺(化合物2513)，

*N*-[[6-[3-(二甲基胺基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2517)，

*N*-[[6-(7-氟-3,4-二氫-1H-異喹啉-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2518)，

*N*-[[6-(1-側氧基萘滿-6-基)氧基-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2523)，

*N*-[[6-[(4-氟苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2524)，

*N*-[[6-(3-乙氧基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2526)，

*N*-[(6-丙氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2528)，

*N*-[[6-(3-丁氧基丙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2529)，

*N*-[[6-[4-(二乙基胺基)苯胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2531)，

*N*-[[6-[(3,4-二氟苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2533)，

*N*-[[6-(甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2535)，

(2R)-1-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]吡咯啶-2-甲酸第三丁酯(化合物2536)，

*N*-[(3R)-1-[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]吡咯啶-3-基]胺基甲酸第三丁酯(化合物2537)，

*N*-[[6-(4-噁唑-5-基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡

咯啶-1-基)吡啶-3-甲醯胺(化合物2546)，

*N*-[[6-[3-(3-甲基吡唑-1-基)丙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2550)，

*N*-[[6-(3-甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2551)，

*N*-[(6-吡咯啶-1-基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2561)，

*N*-[[6-(4-吡咯-1-基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2563)，

*N*-[[6-[4-(1-乙基丙基)哌嗪-1-基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2565)，

*N*-[[6-(3-乙醯基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2569)，

*N*-[[6-(3-氯-4-甲氧基-苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2571)，

*N*-[[6-(3-甲基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2572)，

*N*-[[6-(環丙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2574)，

*N*-[[6-[(4-甲氧基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2579)，

*N*-[[6-(5-氟異吲哚啉-2-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2580)，

*N*-[[6-[(4-氯苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2585)，

*N*-[[6-(2-氨-5-氟-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯

啶-1-基)吡啶-3-甲醯胺(化合物2591)，

*N*-[[6-(唍烷-3-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2595)，

*N*-[[6-(2-呋喃基甲基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2597)，

*N*-[[6-(5-氯-2-氟-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2598)，

*N*-[[6-[(3-吡咯-1-基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2600)，

*N*-[[6-(4-環己基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2601)，

*N*-[[6-(2-丙氧基乙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2602)，

*N*-[[6-(2-甲基吡咯啶-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2609)，

*N*-[[6-[(4-乙炔基苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2610)，

*N*-[[6-(2-萘氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2611)，

*N*-[(6-乙氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2617)，

*N*-[[6-[[4-(三氟甲基)苯基]甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2618)，

*N*-[(6-苯甲氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2619)，

*N*-[[6-(4-丁基-1,4-二氮雜環庚烷-1-基)-2-吡啶基]磺醯基]-2-

(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2620)，

*N*-[[6-(4-嘧啶-2-基哌嗪-1-基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2621)，

*N*-[[6-[2-(2-氟苯基)乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2625)，

*N*-[[6-(4H-1,3-苯并二氧雜環己烯-2-基甲氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2627)，

*N*-[[6-(2-環戊基乙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2630)，

*N*-[[6-[2-(2-氯苯基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2632)，

*N*-[[6-(2-甲氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2637)，

*N*-[(6-苯胺基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2639)，

*N*-[[6-[(2,3-二氟苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2640)，

*N*-[[6-[4-(三氟甲基)-1-哌啶基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2641)，

*N*-[[6-[2-(4-乙氧基苯基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2642)，

*N*-[[6-[(2-甲基-8-喹啉基)氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2643)，

*N*-[[6-[(5-氯-2-甲氧基-苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2645)，

*N*-[[6-(3-甲基丁-2-烯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡

咯啶-1-基)吡啶-3-甲醯胺(化合物2648)，

*N*-[[6-(2,4,6-三氟苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2654)，

*N*-[[6-[(5-氯-2-吡啶基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2656)，

*N*-[[6-(2-氰基苯胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2659)，

*N*-[[6-[(5-氯-2-吡啶基)氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2747)，

*N*-[[6-[2-(4-吡啶基)乙基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2746)，

*N*-[[6-(2-胺基乙氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2754)，

*N*-[(6-丁-2-炔氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2753)，

*N*-[[6-[3-甲氧基丙基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2745)，

*N*-[[6-(4-甲氧基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2743)，

*N*-[[6-(1-側氧基茚滿-5-基)氧基-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2744)，

*N*-[[6-[(6-甲基-2-吡啶基)氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2742)，

*N*-[[6-(4-乙醯基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2741)，

*N*-[[6-[(2-甲基-1,3-苯并噻唑-5-基)氧基]-2-吡啶基]磺醯基]-2-

(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2740)，

*N*-[[6-[[(1R)-1,2,2-三甲基丙基]胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2757)，

甲基 4-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]氧基]苯甲酸酯(化合物2739)，

*N*-[[6-(2,1,3-苯并噁二唑-5-基氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2738)，

*N*-[[6-(4-第三丁氧基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2751)，

*N*-[[6-[異丁基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2758)，

*N*-[[6-(二乙基胺基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2737)，

*N*-[[6-(3-氰基苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2736)，

*N*-[[6-[異丙基(甲基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2735)，

*N*-[4-[[6-[[2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-羰基]胺磺醯基]-2-吡啶基]胺基]苯基]胺基甲酸第三丁酯(化合物2755)，

*N*-[[6-[2-(3-氟苯基)乙氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2752)，

*N*-[[6-[2-(1-哌啶基)苯氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2750)，

*N*-[[6-(2-甲基-1-哌啶基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2759)，

*N*-[[6-[環丙基甲基(丙基)胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基

吡咯啶-1-基)吡啶-3-甲醯胺(化合物2734)，

*N*-[[6-[(2,5-二甲氧基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2733)，

*N*-[(6-苯乙基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2732)，

*N*-[[6-(2,3-二氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2731)，

*N*-[[6-(3-氯-5-氟-苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2730)，

*N*-[[6-[(2-氯苯基)甲基-甲基-胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2756)，

*N*-[(6-吭烷-4-基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2749)，

*N*-[[6-[3-(三氟甲基)苯氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2729)，

*N*-[[6-[(2-氯-6-氟-苯基)甲氧基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2728)，

6-第三丁基-*N*-[(6-異戊基氧基-2-吡啶基)磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2727)，

*N*-[[6-(1,3-苯并間二氧雜環戊烯-5-基甲氧基)-2-吡啶基]磺醯基]-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2725)，

*N*-[[6-[(E)-丁-2-烯氧基]-2-吡啶基]磺醯基]-6-第三丁基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2726)，

6-第三丁基-*N*-[[6-[(4-甲氧基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2723)，

*N*-[[6-[(3,4-二甲氧基苯基)甲基胺基]-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2662)，及

*N*-[[6-(3,5-二氯苯氧基)-2-吡啶基]磺醯基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2663)

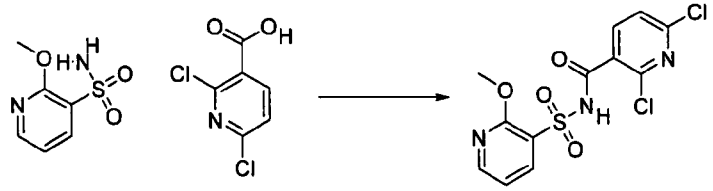
**製備107**：*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-苯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2445)

**步驟1**：2-甲氧基吡啶-3-磺醯胺



2-氯吡啶-3-磺醯氯(5.00 g，23.6 mmol)溶於氨之甲醇溶液(16.8 mL 7 M，117.9 mmol)中且將反應混合物攪拌30分鐘。反應混合物在減壓下濃縮且溶於甲醇鈉(24.9 mL 25 %w/v，115.1 mmol)中且經2天加熱至60℃。反應混合物蒸發且殘餘物分溶於乙酸乙酯與1N HCl之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且在減壓下濃縮。粗物質藉由矽膠管柱層析，用己烷中0-100%乙酸乙酯溶離來純化，得到2-甲氧基吡啶-3-磺醯胺(3.12 g，70%)。ESI-MS m/z計算值188.02556，實驗值189.0 $(M+1)^+$；滯留時間: 0.23分鐘

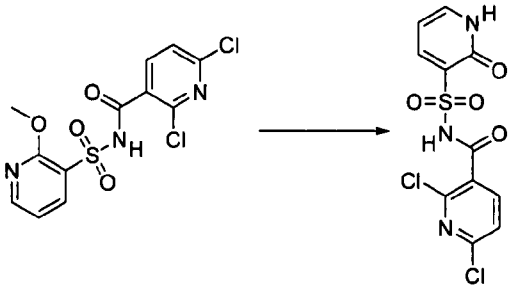
**步驟2**：2,6-二氯-*N*-[(2-甲氧基-3-吡啶基)磺醯基]吡啶-3-甲醯胺



將2,6-二氯吡啶-3-甲酸(2.00 g，10.4 mmol)、硫醯氯(7.45 g，4.56 mL，62.5 mmol)及DMF (0.1 mL)之混合物在45℃下攪拌5小時。反應在減壓下濃縮，溶於二氯甲烷(5.30 mL)中且緩慢添加至冷卻在冰浴中的2-甲氧基吡啶-3-磺醯胺(1.96 g，10.4 mmol)及三乙胺(3.16 g，4.36 mL，31.3 mmol)於二氯甲烷(5.30 mL)中之溶液中。將反應混合

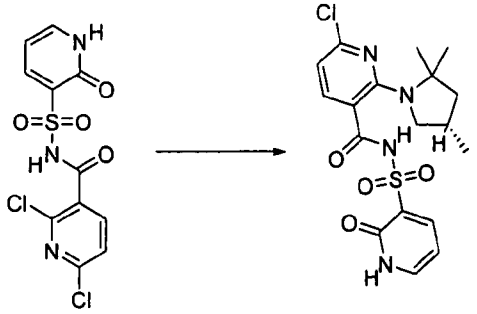
物攪拌隔夜，接著用二氯甲烷稀釋且用1 M HCl (20 mL×1)、水(20 mL)洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物藉由矽膠管柱層析(0-5%甲醇之二氯甲烷溶液)來純化。所得固體溶於二氯甲烷中且用碳酸氫鈉(約pH 5)洗滌，有機層經硫酸鈉乾燥且在減壓下蒸發，得到2,6-二氯-*N*-[(2-甲氧基-3-吡啶基)磺醯基]吡啶-3-甲醯胺(3.50 g，93%)。ESI-MS m/z計算值360.9691，實驗值362.0 $(M+1)^+$；滯留時間:0.46分鐘。

**步驟3**：2,6-二氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺



將2,6-二氯-*N*-[(2-甲氧基-3-吡啶基)磺醯基]吡啶-3-甲醯胺(0.76 g，2.10 mmol)及HCl (5.25 mL 4 M於二噁烷中，21.0 mmol)於二噁烷(5 mL)中之混合物在90℃下攪拌90分鐘。在減壓下蒸發溶劑，得到呈棕褐色固體狀之2,6-二氯-*N*-((2-側氧基-1,2-二氫吡啶-3-基)磺醯基)菸鹼醯胺(0.72 g，99%)。

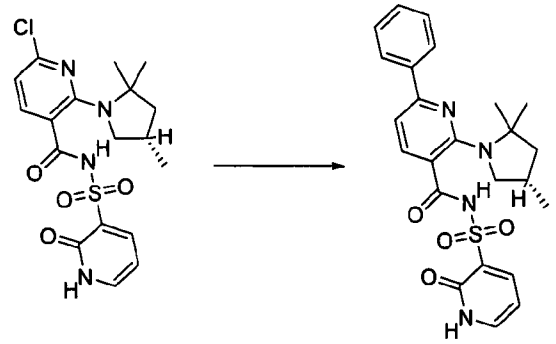
**步驟4**：6-氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



向2,6-二氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(HCl 鹽) (4.04 g，10.5 mmol)、(4*S*)-2,2,4-三甲基吡咯啶(HCl鹽) (2.36

g，15.8 mmol)及 $K_2CO_3$ (7.26 g，52.5 mmol)中添加DMSO (8.86 mL)且將反應混合物在120℃下加熱24小時。反應混合物用乙酸乙酯稀釋且過濾殘餘碳酸鉀。有機物用0.1 M HCl水溶液(150 mL)洗滌。水層之pH值藉由添加HCl水溶液達至5，且接著用乙酸乙酯洗滌。合併之有機層用鹽水洗滌，經硫酸鈉乾燥且在減壓下濃縮，得到6-氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(4.15 g，94%)。

**步驟5**：*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-苯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2445)



將6-氯-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(30.0 mg，0.07 mmol)、苯基硼酸(10.3 mg，0.08 mmol)、[1,3-雙(2,6-二異丙基苯基)-2H-咪唑-2-基]-二氯-(3-氯-1-吡啶基)鈀(4.80 mg，0.01 mmol)及2M $K_2CO_3$ (177 μL，0.35 mmol)組合於DMF (1.0 mL)中且在120℃下加熱16小時。反應混合物過濾且藉由LC/MS，利用5 mM HCl水溶液中10-99%乙腈之梯度純化，得到*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-苯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2445)。ESI-MS m/z 467.4 $(M+1)^+$；滯留時間: 1.13分鐘；1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (d, J = 6.3 Hz, 1H), 8.24 (dd, J = 7.2, 2.2 Hz, 1H), 8.08 - 8.02 (m, 2H), 7.83 (dt, J = 6.6, 3.3 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.54 - 7.46 (m, 2H), 7.46 - 7.40 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.45

(t, J = 6.8 Hz, 1H), 2.82 - 2.63 (m, 2H), 2.30 - 2.18 (m , 1H), 1.89 (dd, J = 11.8, 5.5 Hz, 1H), 1.62 (s, 6H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H)。

以下化合物可使用本文所述之程序合成：

6-(間甲苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2424)，6-(2-羥基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2480)，

*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-[4-(三氟甲基)苯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1799)，*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-(對甲苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2438)，

6-(3-甲氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1927)，*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-6-[2-(三氟甲氧基)苯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2514)，

6-[3-(羥基甲基)苯基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1997)，

6-(4-甲氧基苯基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2080)，

*N*-(苯磺醯基)-6-(6-甲氧基-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2411)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-羥基苯基)磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1885)，

*N*-(苯磺醯基)-6-(2-羥基-3-甲基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2133)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(4-羥基苯基)磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1750)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(2-羥基苯基)磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1836)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(4-甲氧基苯基)磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1876)，

*N*-(苯磺醯基)-6-苯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2092)，

*N*-(苯磺醯基)-2-[(3S)-2,2-二氘-3,5,5-三甲基-吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2560)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-乙氧基-3-甲基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1860)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[1-甲基-3-(三氟甲基)吡唑-4-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1740)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1*H*-吲哚-5-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2125)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-(二甲基胺基)嘧啶-5-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2021)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1*H*-吲哚-4-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2478)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-羥基-3,5-二甲基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1923)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-甲基-5-(三氟甲基)吡唑-3-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2416)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-乙氧基-6-氟-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2103)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-乙氧基-5-氟-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2071)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-甲基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2363)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1-甲基吲哚-5-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2352)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1,3,5-三甲基吡唑-4-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2668)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2,5-二氟-4-甲氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2388)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-羥基-2-萘基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2468)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-羥基-3-甲氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2614)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-甲氧基-5-甲基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2086)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-吡啶基磺醯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2377)，

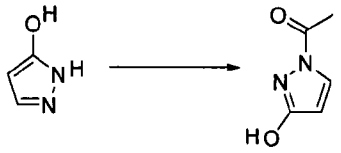
6-(3-氟-5-異丁氧基-苯基)-*N*-(2-吡啶基磺醯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1832)，

6-(3,5-二甲基苯基)-*N*-[(6-異戊基氧基-2-吡啶基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2707)，及

2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-1-基]-6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-側氧基-1H-吡啶-3-基)磺醯基]吡啶-3-甲醯胺(化合物307)。

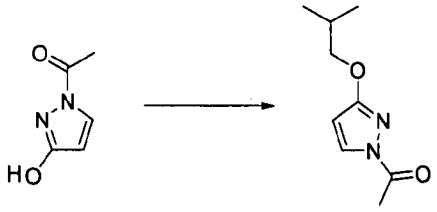
**製備108**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)

**步驟1**：1-(3-羥基吡唑-1-基)乙酮



將1*H*-吡唑-5-醇(1.02 g，12.1 mmol)及吡啶(5.0 mL，61.8 mmol)在95℃下攪拌且經3分鐘之時間逐滴添加乙酸酐(1.24 g，1.14 mL，12.1 mmol)於吡啶(2.0 mL，24.7 mmol)中之溶液。接著反應混合物在95℃下再攪拌1.5小時。在減壓下移除溶劑且固體殘餘物用二乙基醚(30 mL)濕磨，過濾，用二乙醚洗滌且在高真空下乾燥，得到呈黃色固體狀之1-(3-羥基吡唑-1-基)乙酮(1.34 g，88%)。ESI-MS m/z計算值126.04293，實驗值127.1 $(M+1)^+$；滯留時間: 0.3分鐘；1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1H), 8.12 (d, J = 2.9 Hz, 1H), 6.00 (d, J = 3.0 Hz, 1H), 2.48 (s, 3H)。

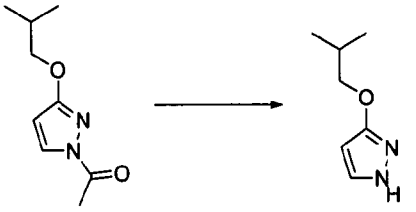
**步驟2**：1-(3-異丁氧基吡唑-1-基)乙酮



在氮氣氛圍下向1-(3-羥基吡唑-1-基)乙酮(1.25 g，9.91 mmol)、碳酸鉀(2.06 g，14.9 mmol)及無水DMF (10 mL)添加1-溴-2-甲基-丙烷(1.49 g，1.19 mL，10.9 mmol)。將反應物在80℃下攪拌2小時。將反應混合物用EtOAc (50 ml)及水(25 mL)稀釋且分離兩相。水相(pH = 9-10)進一步用EtOAc (20 mL)萃取。合併之萃取物經硫酸鈉乾燥且溶劑蒸發。所得油狀物藉由矽膠管柱層析，使用己烷中EtOAc (0至30%)之梯度來純化，得到呈無色油狀之1-(3-異丁氧基吡唑-1-基)乙酮(1.24 g，69%)。ESI-MS m/z計算值182.10553，實驗值183.3 $(M+1)^+$；滯留時間: 1.35分鐘；1H NMR (400 MHz, 氯仿-d) δ 8.05 (d, J = 3.0 Hz, 1H), 5.96 (d, J = 3.0 Hz, 1H), 3.99 (d, J = 6.6 Hz, 2H), 2.58 (s, 3H),

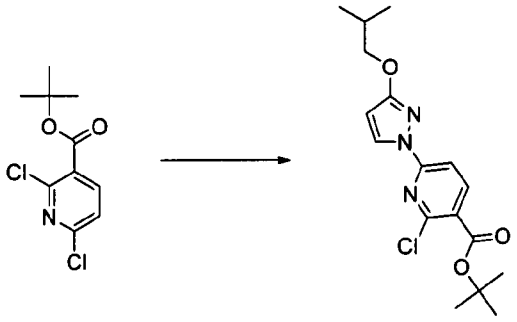
2.08 (dq, J = 12.9, 6.4 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H)。

**步驟3**：3-異丁氧基-1*H*-吡唑



在室溫下將1-(3-異丁氧基吡唑-1-基)乙酮(1.24 g，6.82 mmol)用MeOH (20 mL)及NaOH (1.14 mL 6 M，6.82 mmol) (6N水溶液)處理2小時。在減壓下移除揮發物。殘餘物溶於EtOAc (25 mL)及鹽水(20 ml)中且分離兩相。水相進一步用EtOAc (2×25 mL)萃取且合併之萃取物經硫酸鈉乾燥且在減壓下濃縮，得到呈略帶顏色之黏稠油狀之3-異丁氧基-1*H*-吡唑(955 mg，99%)。ESI-MS m/z計算值140.09496, 實驗值141.2 $(M+1)^+$；滯留時間: 0.86分鐘；1H NMR (400 MHz, 氯仿-d) δ 9.25 (極寬單峰, 1H), 7.35 (d, J = 2.5 Hz, 1H), 5.73 (d, J = 2.5 Hz, 1H), 3.91 (d, J = 6.7 Hz, 2H), 2.15 - 2.02 (m, 1H), 1.06 - 0.98 (m, 6H)。

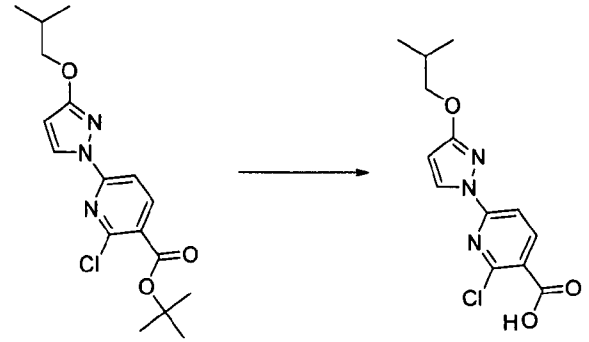
**步驟4**：2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸第三丁酯



將NaH (64 mg，1.6 mmol) (60 %油狀懸浮液)添加至含3-異丁氧基-1*H*-吡唑(224 mg，1.60 mmol)之無水DMF (2 mL)中。將反應混合物攪拌直至氣體停止放出。添加2,6-二氯吡啶-3-甲酸第三丁酯(330 mg，1.33 mmol)且將反應混合物在100℃下在氮氣下攪拌30分鐘。將反應混合物用EtOAc (50 mL)及水+ 鹽水(40 mL)稀釋且分離兩相。水相進一步用EtOAc (2×30 mL)萃取。合併之萃取物經硫酸鈉乾燥且在

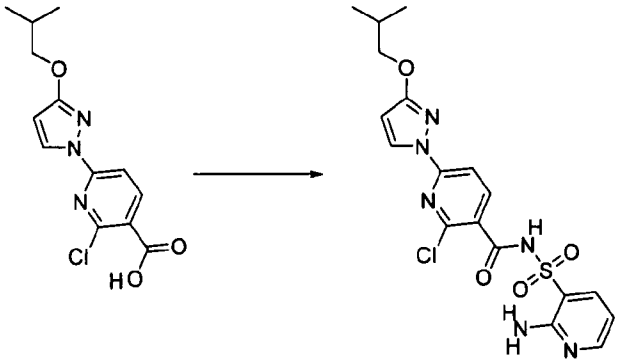
減壓下移除溶劑，得到殘餘物，其藉由矽膠管柱層析，使用己烷中AcOEt (0至20%)之梯度來純化，得到呈灰白色固體狀之2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸第三丁酯(235 mg，50%)。ESI-MS m/z計算值351.13498，實驗值352.2 $(M+1)^+$；滯留時間：2.34分鐘，1H NMR (400 MHz，氯仿-d) δ 8.35 (d, J = 2.8 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 5.97 (d, J = 2.9 Hz, 1H), 4.02 (d, J = 6.6 Hz, 2H), 2.12 (dp, J = 13.4, 6.7 Hz, 1H), 1.62 (s, 9H), 1.03 (d, J = 6.7 Hz, 6H)。

**步驟5**：2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸



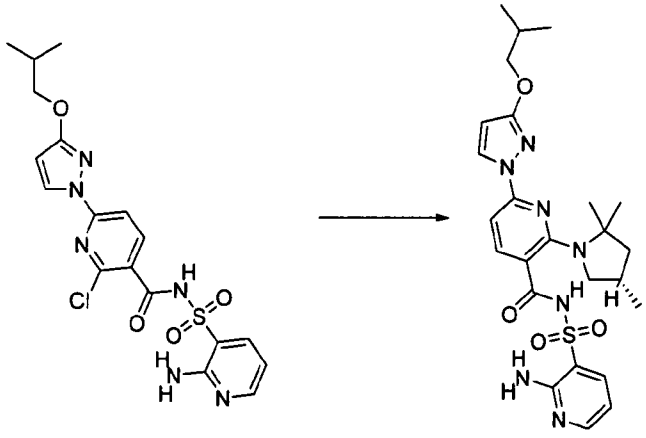
將2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸第三丁酯(203 mg，0.57 mmol)、DCM (2 mL)及TFA (615 μL，7.98 mmol)在40-45℃下攪拌3小時。在減壓下移除揮發物，得到呈白色固體狀之2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸(170 mg，100%)。ESI-MS m/z計算值295.07236，實驗值296.3 $(M+1)^+$；滯留時間：1.64分鐘；1H NMR (400 MHz, DMSO-d6) δ 13.58 (s, 1H), 8.41 (d, J = 2.9 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 6.20 (d, J = 2.9 Hz, 1H), 4.02 (d, J = 6.6 Hz, 2H), 2.06 (七重峰, J = 6.6 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H)。

**步驟6**：*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺



在氮氣氛圍下將DMF (1.2 mL)添加至2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲酸(128 mg，0.43 mmol)及CDI (87 mg，0.54 mmol)中。將反應混合物在40℃下在氮氣下攪拌1小時。在氮氣下2-胺基吡啶-3-磺醯胺(91 mg，0.53 mmol)溶解於無水DMF (1.2 mL)中且添加NaH (21 mg，0.53 mmol) (60%油狀懸浮液)且將反應混合物在氮氣下攪拌直至氣體停止放出且接著在40℃下攪拌45分鐘。合併兩種反應混合物且在室溫下攪拌1.5小時。添加水及冰，接著乙酸(400 μL，7.03 mmol)。過濾所得固體，用水洗滌且乾燥，得到呈白色固體狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺(189 mg，97%)。ESI-MS m/z計算值450.0877, 實驗值451.4 (M+1)+；滯留時間: 1.42分鐘。

**步驟7**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191)

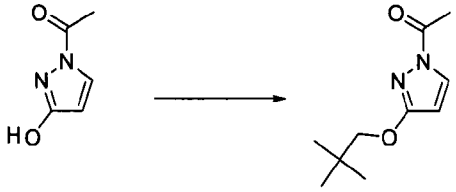


在氮氣氛圍下將*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺(177 mg，0.39 mmol)、(4*S*)-2,2,4-三甲基

吡咯啶(HCl 鹽) (237 mg，1.58 mmol)、$K_2CO_3$ (327 mg，2.37 mmol)及無水DMSO (550 μL)在150℃下加熱6小時。接著冷卻反應混合物且逐滴添加攪拌的水(40 mL)及乙酸(400 μL，7.034 mmol)之混合物。過濾所得黃色固體且用水洗滌。固體溶於二氯甲烷中且有機相經硫酸鈉乾燥且在減壓下濃縮。所得固體藉由矽膠管柱層析，使用DCM中MeOH (0至10%)之梯度來純化，接著藉由逆相製備型HPLC，使用水及作爲改質劑之HCl中MeCN (經15分鐘1至99%)之梯度來純化，得到呈淺黃色固體狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2191) (77 mg，36%)。ESI-MS m/z計算值527.23145, 實驗值528.3 $(M+1)^+$；滯留時間: 1.55分鐘；1H NMR (400 MHz, DMSO-d6) δ 12.45 (寬單峰, 1H), 8.28 - 8.22 (m, 1H), 8.20 (d, J = 2.7 Hz, 1H), 8.06 - 7.99 (m, 1H), 7.84 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.77 (dd, J = 7.7, 4.9 Hz, 1H), 6.69 (br s, 2H), 6.12 (d, J = 2.6 Hz, 1H), 3.98 (d, J = 6.6 Hz, 2H), 2.45 (d, J = 8.6 Hz, 2H), 2.13-2.01 (m , 2H), 1.90 - 1.79 (m, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.38 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.8 Hz, 6H), 0.74 (d, J = 6.2 Hz, 3H)。

**製備109**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)

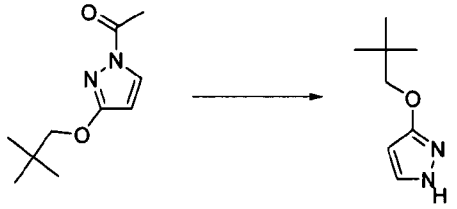
**步驟1**：1-[3-(2,2-二甲基丙氧基)吡唑-1-基]乙酮



向1-(3-羥基吡唑-1-基)乙酮(1.21 g，9.60 mmol)於無水THF (20 mL)中之懸浮液中添加三苯基膦(2.78 g，10.6 mmol)及2,2-二甲基丙-1-醇(846 mg，9.60 mmol)。反應混合物在冰浴中在氮氣下冷卻。經由

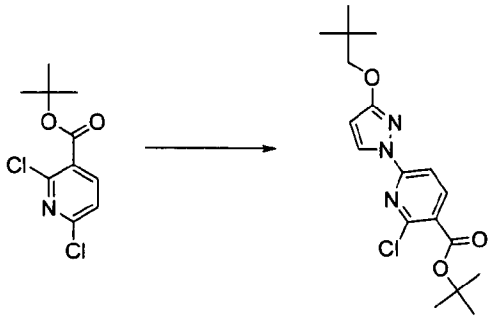
注射器經3分鐘逐滴添加DIAD (2.1 mL，10.7 mmol)。接著反應混合物在氮氣下攪拌，升溫至室溫隔夜。將反應混合物用乙酸乙酯(100 mL)稀釋且合併之有機相用飽和碳酸氫鈉水溶液(2×50 mL)、鹽水(50 mL)洗滌且經硫酸鈉乾燥且在減壓下濃縮。殘餘物藉由矽膠管柱層析，使用己烷中乙酸乙酯(0至30%)之梯度來純化，得到呈黃色固體狀之1-[3-(2,2-二甲基丙氧基)吡唑-1-基]乙酮(967 mg，51%)。ESI-MS m/z計算值196.12119, 實驗值197.3 $(M+1)^+$；滯留時間: 1.62分鐘；1H NMR (400 MHz, 氯仿-d) δ 8.05 (d, J = 3.0 Hz, 1H), 5.97 (d, J = 3.0 Hz, 1H), 3.89 (s, 2H), 2.58 (s, 3H), 1.03 (s, 9H)。

**步驟2**：3-(2,2-二甲基丙氧基)-1*H*-吡唑



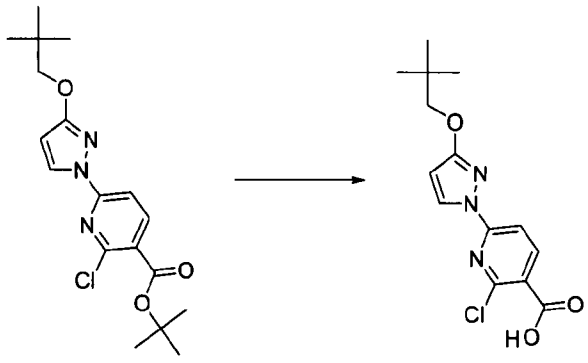
將1-[3-(2,2-二甲基丙氧基)吡唑-1-基]乙酮(960 mg，4.89 mmol)、MeOH (15 mL)及NaOH (815 μL 6 M，4.89 mmol) (6N水溶液)在室溫下攪拌21小時。在減壓下移除揮發物。殘餘物溶於EtOAc (25 mL)及鹽水(20 ml)中且分離兩相。水相進一步用EtOAc (2×25 mL)萃取且合併之有機萃取物經硫酸鈉乾燥且在減壓下蒸發，得到呈灰白色固體狀之3-(2,2-二甲基丙氧基)-1*H*-吡唑(719 mg，95%)。ESI-MS m/z計算值154.11061, 實驗值155.3 $(M+1)^+$；滯留時間: 1.13分鐘；1H NMR (400 MHz, 氯仿-d) δ 7.36 (d, J = 2.4 Hz, 1H), 5.74 (d, J = 2.5 Hz, 1H), 3.81 (s, 2H), 1.02 (s, 9H)。

**步驟3**：2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸第三丁酯



將NaH (95 mg，2.375 mmol) (60 %油狀懸浮液) (注意到略微放熱)添加至含3-(2,2-二甲基丙氧基)-1*H*-吡唑(363 mg，2.35 mmol)之無水DMF (3 mL)中且將反應混合物攪拌直至氣體停止放出。逐份添加2,6-二氯吡啶-3-甲酸第三丁酯(530 mg，2.14 mmol)且將反應混合物在100℃下在氮氣下攪拌1小時。反應混合物用EtOAc (60 mL)及水+ 鹽水(60 mL)稀釋且分離兩相。水相進一步用EtOAc (2×30 mL)萃取。合併之萃取物經硫酸鈉乾燥且在減壓下移除溶劑。殘餘物藉由矽膠管柱層析，使用己烷中EtOAc (經40分鐘0至20%)之梯度來純化，得到呈黃色固體狀之2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸第三丁酯(497 mg，64%)。ESI-MS m/z計算值365.1506, 實驗值366.2 $(M+1)^+$；滯留時間: 2.44分鐘。

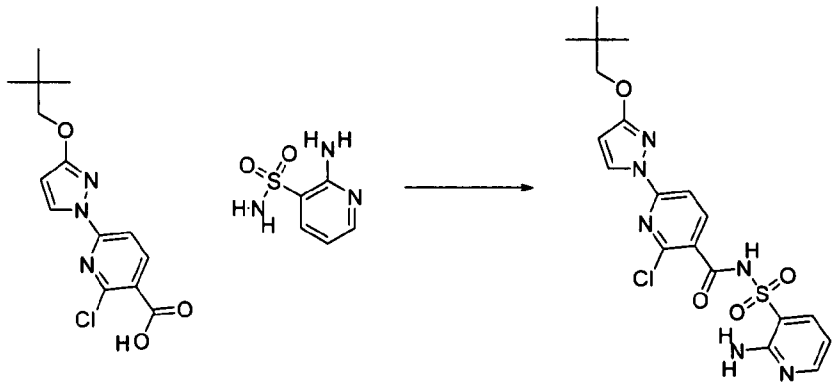
**步驟4**：2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸



將2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸第三丁酯(497 mg，1.36 mmol)、DCM (5 mL)及TFA (1.5 mL，19.5 mmol)在40℃下攪拌4小時。藉由在減壓下蒸發移除揮發物，得到呈白色固體狀之2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸(413 mg，98%)。

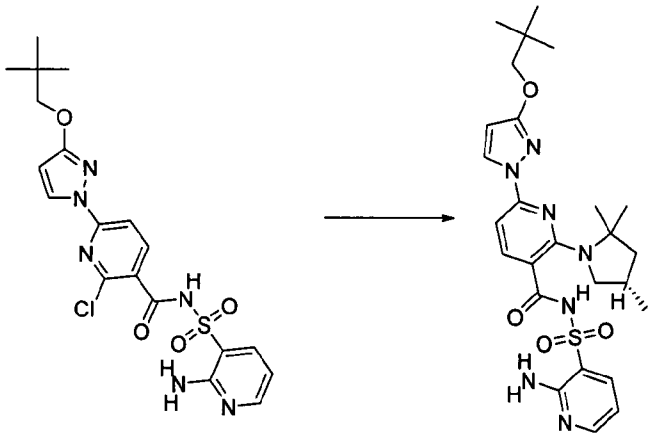
ESI-MS m/z計算值309.088, 實驗值310.1 $(M+1)^+$；滯留時間: 1.8分鐘；1H NMR (400 MHz, DMSO-d6) δ 13.58 (s, 1H), 8.42 (dd, J = 2.8, 0.8 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 6.22 (dd, J = 2.8, 0.8 Hz, 1H), 3.93 (s, 2H), 1.01 (s, 9H)。

**步驟5**：*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲醯胺



將DMF (1 mL)添加至2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸(105 mg，0.34 mmol)及CDI (69 mg，0.43 mmol)中且將反應混合物在40℃下在氮氣下攪拌1小時。在另一4 mL小瓶中，在氮氣下2-胺基吡啶-3-磺醯胺(73 mg，0.42mmol)溶解於無水DMF (1 mL)中。添加NaH (22 mg，0.55 mmol) (60%油狀懸浮液)且將反應混合物在氮氣下攪拌直至氣體停止放出，接著在40℃下攪拌一小時。合併兩種反應混合物且在室溫下攪拌4小時。添加水及冰，接著乙酸(400 μL，7.034 mmol)。過濾所得固體，用水洗滌且乾燥，得到呈白色固體狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲醯胺(150 mg，95%)。產物未經任何進一步純化即用於下一步。ESI-MS m/z計算值464.10336, 實驗值465.2 $(M+1)^+$；滯留時間: 1.5分鐘。

**步驟6**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975)



在氮氣氛圍下將*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲醯胺(150 mg，0.32 mmol)、(4*S*)-2,2,4-三甲基吡咯啶(HCl 鹽) (195 mg，1.30 mmol)、$K_2CO_3$ (274 mg，1.98 mmol)及無水DMSO (480 μL)在150℃下攪拌7.5小時。反應混合物傾倒至水(25 mL)及乙酸(400 μL，7.034 mmol)之混合物中且所得黃色固體藉由過濾分離。濕固體溶於DCM中，有機相經硫酸鈉乾燥且蒸發溶劑，得到粗玻璃狀物，其藉由矽膠管柱層析，使用DCM中MeOH (0至10%)之梯度來純化。蒸發溶劑得到灰白色固體，其溶於MeOH (3 mL)中且藉由逆相製備型HPLC，使用水中MeCN (經15分鐘1至99%)及HCl作爲改質劑(3×950 μL注射液)之梯度來純化，得到呈棕褐色固體狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1975) (75 mg，42%)。ESI-MS m/z計算值541.24713，實驗值542.3 $(M+1)^+$；滯留時間: 1.65分鐘；1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.24 (dd, J = 4.7, 1.9 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 7.8, 1.9 Hz, 1H), 7.84 (d, J= 8.3 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.69 (寬單峰, 2H), 6.14 (d, J = 2.7 Hz, 1H), 3.89 (s, 2H), 2.45 (d, J = 8.9 Hz, 2H), 2.12 (br s, 1H), 1.85 (dd, J = 11.9, 5.4 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.43 - 1.33 (m, 1H), 1.00 (s, 9H), 0.74 (d, J = 6.2 Hz, 3H)。

以下化合物可使用本文所述之程序合成：

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2036)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2406)，

6-(3-異丙氧基吡唑-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2360)，

*N*-(苯磺醯基)-6-(4-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1912)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-乙氧基-4-甲基-吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2248)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2-乙氧基乙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1742)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[4-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2603)，

6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2578)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(4-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1895)，

6-(3-異丁氧基-4-甲基-吡唑-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1743)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丙氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1844)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-[(2S)-2-甲基丁氧基]吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2458)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-第二丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1970)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(3-羥基-2-甲基-丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2192)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-異丙氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1709)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基-4-甲基-吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1758)，

*N*-環丙基磺醯基-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2554)，

6-(4-異丁氧基吡唑-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1760)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基-5-甲基-吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2238)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-[2-(2-乙氧基乙氧基)乙氧基]吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2326)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2604) (異構體1) (化合物2481) (異構體2) (化合物2194) (異構體3) (化合物2615) (異構體4)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1887)，

6-(3-乙氧基-4-甲基-吡唑-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1856)，

6-(3-異丁氧基吡唑-1-基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-

[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1896)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1952)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-[3,3,3-三氘-2,2-雙(三氘甲基)丙氧基]吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2703)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(1-甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2704)，

*N*-(苯磺醯基)-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1114)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-環丙基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2701)，

*N*-環丙基磺醯基-2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-1-基]-6-(3-苯基吡唑-1-基)吡啶-3-甲醯胺(化合物2676)，

*N*-環丙基磺醯基-6-(3-苯基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2674)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-苯基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2702)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-2-[(2*S*,5*R*)-2,5-二甲基吡咯啶-1-基]-6-(3-異丁氧基吡唑-1-基)吡啶-3-甲醯胺(化合物1732)，

*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-6-(3-異丁氧基吡唑-1-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2716)，

*N*-環丙基磺醯基-6-[3-(2-吡啶基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2718)，

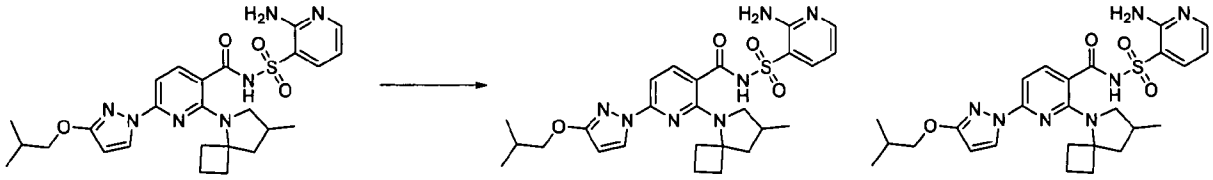
*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)-4-甲基-吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物

2699)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(環丁基甲氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2694)及

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(環丙基甲氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2695)。

**製備110**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2604) (異構體1，*R*或*S*立體異構體)及*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2481) (異構體2，*R*或*S*立體異構體)



使用超臨界流體層析，在ChiralPak AD-H (250×10 mm) 5 μm管柱上，使用$CO_2$中30%甲醇，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮，用乙酸乙酯(3 mL)稀釋且用1N鹽酸水溶液洗滌。有機層經硫酸鈉乾燥，過濾，且蒸發至乾，得到純化合物。SFC峰1：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2604) (化合物2481) ESI-MS *m/z*計算值539.23145, 實驗值540.2 $(M+1)^+$；滯留時間: 1.67分鐘。SFC峰2：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3-異丁氧基吡唑-1-基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2604) (異構體1，*R*或*S*立體異構體) (化合物2481) (異構體2，*R*或*S*立體異構體) ESI-MS *m/z*計算值539.23145, 實驗值540.2 $(M+1)^+$；滯留時間: 1.67分鐘。

以下化合物可使用本文所述之程序合成：

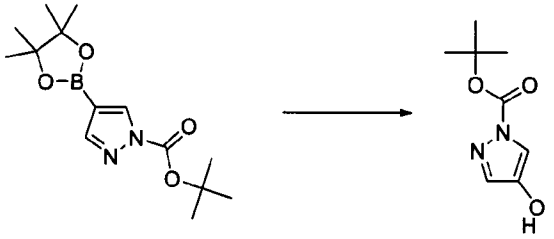
*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-(2,2-二甲基丙氧基)吡唑-1-

基]-2-[6-甲基-8-氮雜螺[3.4]辛-8-基]吡啶-3-甲醯胺(化合物2358) (異構體1，*R*或*S*立體異構體)，接著SFC管柱層析，使用ChiralPak AS-H (250×10 mm) 5 μm，使用$CO_2$中38% MeOH (無改質劑)作爲溶離劑。

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[3-[(1-甲基丙氧基)吡唑-1-基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2594) (異構體2，*R*或*S*立體異構體)，使用ChiralPak IA (250×4.6 mm)，5 μm；移動相：$CO_2$中25 % MeOH:EtOH (50:50；0.1% TFA)。

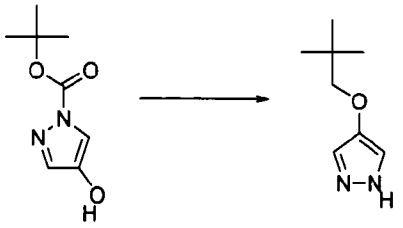
**製備111**：4-(2,2-二甲基丙氧基)-1*H*-吡唑

**步驟1**：4-羥基吡唑-1-甲酸第三丁酯



在0℃下向含4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)吡唑-1-甲酸第三丁酯(25 g，85 mmol)之THF (170 mL)中添加氫氧化鈉(85 mL 2 M，170 mmol)，接著過氧化氫(19.27 mL 30 %w/v，170.0 mmol)且將反應混合物在0℃下攪拌10分鐘且室溫下攪拌45分鐘。反應混合物冷卻至0℃且用DCM稀釋且添加2 M HCl直至達到pH 2。分離有機物，乾燥且在減壓下濃縮，得到呈黃色固體狀之4-羥基吡唑-1-甲酸第三丁酯(15 g 100%)。ESI-MS m/z 計算值 184.19, 實驗值 185.0 $(M+1)^+$；LCMS滯留時間(3分鐘操作) 0.63 min。

**步驟2**：4-(2,2-二甲基丙氧基)-1*H*-吡唑



在0℃下向含4-羥基吡唑-1-甲酸第三丁酯(1000 mg，5.429 mmol)

及$Ph_3P$ (2.136 g，8.144 mmol)之THF (2.500 mL)中添加2,2-二甲基丙-1-醇(717.9 mg，8.144 mmol)。向反應混合物中添加含DIAD (1.647 g，1.578 mL，8.144 mmol)之THF (2 mL)。將反應混合物在60℃下攪拌16小時，接著冷卻且用DCM稀釋且用6 M HCl溶液洗滌。分離有機物，乾燥且濃縮，得到殘餘物，其藉由矽膠管柱層析，使用5-100% EA-已烷，接著5-40% EA-DCM來純化，得到4-(2,2-二甲基丙氧基)吡唑-1-甲酸第三丁酯(435.5 mg) ESI-MS m/z 計算值 254.16, 實驗值255.4 $(M+1)^+$；LCMS滯留時間(3分鐘操作) = 1.82 min；1H NMR (400 MHz, 氯仿-d) δ 7.57 (d, J = 1.0 Hz, 1H), 7.51 (d, J = 1.0 Hz, 1H), 3.52 (s, 2H), 1.64 (s, 9H), 1.00 (s, 9H)。向含4-(2,2-二甲基丙氧基)吡唑-1-甲酸第三丁酯(435.5 mg，1.712 mmol)之DCM (0.2 mL)中添加4M HCl-二噁烷(2 mL)。在室溫下5小時後，在減壓下移除溶劑且殘餘物用二乙醚濕磨，得到4-(2,2-二甲基丙氧基)-1*H*-吡唑(HCl鹽) (210 mg，20%) ESI-MS m/z 計算值 154.11，實驗值155.4 $(M+1)^+$；LCMS滯留時間(3分鐘操作) 1.13 min。

**製備112**：3-異丁氧基-4-甲基-1*H*-吡唑

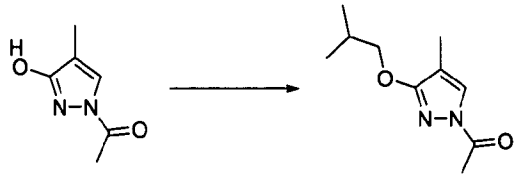
**步驟1**：1-(3-羥基-4-甲基-吡唑-1-基)乙酮



將4-甲基-1*H*-吡唑-3-醇(1.0 g，10.2 mmol)及吡啶(4.0 mL，49.5 mmol)在95℃下加熱。經2分鐘之時間逐滴添加乙酸酐(1.0 g，961.2 μL，10.2 mmol)於吡啶(1.5 mL，18.6 mmol)中之溶液。接著反應混合物在95℃下再攪拌2小時。在減壓下移除溶劑且固體殘餘物用二乙醚(30 mL)濕磨，過濾，用二乙醚洗滌且乾燥，得到呈白色固體狀之1-(3-羥基-4-甲基-吡唑-1-基)乙酮(1.2 g，86%)。ESI-MS m/z計算值140.05858, 實驗值141.1 $(M+1)^+$；滯留時間0.39分鐘；1H NMR (400

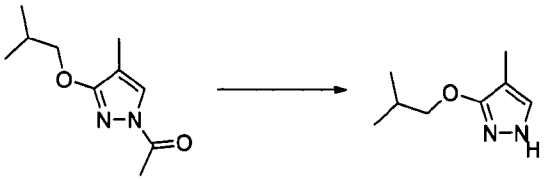
MHz, DMSO-d6) δ 10.99 (s, 1H), 7.92 (q, J = 1.1 Hz, 1H), 2.43 (s, 3H), 1.88 (d, J = 1.2 Hz, 3H)。

步驟2：1-(3-異丁氧基-4-甲基-吡唑-1-基)乙酮



在氮氣氛圍下將1-溴-2-甲基-丙烷(658 mg，522 μL，4.80 mmol)添加至1-(3-羥基-4-甲基-吡唑-1-基)乙酮(612 mg，4.37 mmol)、碳酸鉀(905 mg，6.55 mmol)及無水DMF (5 mL)中。將反應混合物在80℃下攪拌2.5小時，接著用EtOAc (50 ml)及水(25 mL)稀釋且分離兩相。水相(pH = 9-10)進一步用EtOAc (20 mL)萃取。合併之萃取物經硫酸鈉乾燥且溶劑蒸發，得到粗油狀物。油狀物藉由矽膠管柱層析，使用己烷中AcOEt (0至30%)之梯度來純化，得到呈無色液體狀之1-(3-異丁氧基-4-甲基-吡唑-1-基)乙酮(726 mg，85%)。ESI-MS m/z計算值196.12119, 實驗值197.3 $(M+1)^+$；滯留時間: 1.57分鐘；1H NMR (400 MHz, 氯仿-d) δ 7.82 (s, 1H), 4.01 (d, J = 6.6 Hz, 2H), 2.53 (s, 3H), 2.10 (sep, J = 6.7 Hz, 1H), 1.95 (d, J = 1.0 Hz, 3H), 1.01 (d, J = 6.7 Hz, 6H)。

**步驟3**：3-異丁氧基-4-甲基-1*H*-吡唑



在室溫下將1-(3-異丁氧基-4-甲基-吡唑-1-基)乙酮(726 mg，3.70 mmol)用MeOH (10 mL)及NaOH (617 μL 6 M，3.70 mmol) (6N水溶液)處理2小時。在減壓下移除揮發物。殘餘物溶於EtOAc (25 mL)及鹽水(20 ml)中且分離兩相。水相進一步用EtOAc (2×25 mL)萃取且合併之萃取物經硫酸鈉乾燥。蒸發溶劑後，分離呈略帶顏色之黏稠油狀之3-

異丁氧基-4-甲基-1*H*-吡唑(564 mg，99%)。ESI-MS m/z計算值154.11061，實驗值155.0 $(M+1)^+$；滯留時間：1.17分鐘；1H NMR (400 MHz，氯仿-d) δ 8.83 (寬單峰，1H)，7.16 - 7.09 (m，1H)，3.95 (d，J = 6.7 Hz，2H)，2.09 (m，1H)，1.95 (d，J = 0.9 Hz，3H)，1.01 (d，J = 6.7 Hz，6H)。

以下化合物可根據以下所述之程序製備：

3-(2-乙氧基乙氧基)-1*H*-吡唑，

(*S*)-3-(2-甲基丁氧基)-1*H*-吡唑，

3-(*第二丁氧基*)-1*H*-吡唑，

3-((1*H*-吡唑-5-基)氧基)-2-甲基丙-1-醇，

5-異丙氧基-1*H*-吡唑，

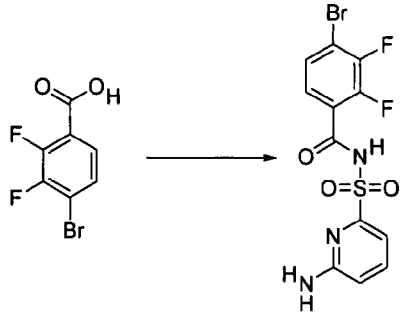
5-異丁氧基-3-甲基-1*H*-吡唑，

3-(2-(2-乙氧基乙氧基)乙氧基)-1*H*-吡唑及

3-(2-(甲基-d3)丙氧基-2,3,3,3-d4)-1*H*-吡唑

**製備113**：*N*-[(6-胺基-2-吡啶基)磺醯基]-3-氟-4-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]苯甲醯胺(化合物2634)

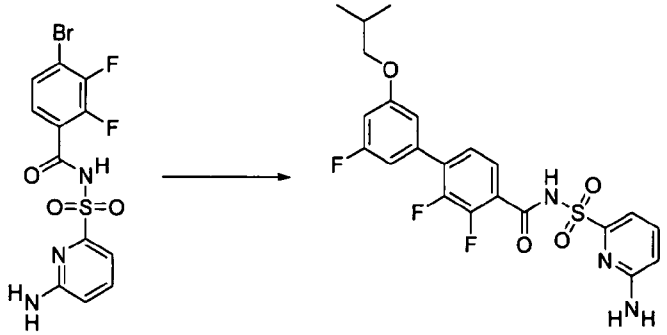
**步驟1**：*N*-[(6-胺基-2-吡啶基)磺醯基]-4-溴-2,3-二氟-苯甲醯胺



在室溫下向含4-溴-2,3-二氟-苯甲酸(2.66 g，11.2 mmol)之DMF (2.30 mL)中添加二(咪唑-1-基)甲酮(2.73 g，16.8 mmol)且將反應混合物在65℃下加熱1小時。分開地，在0℃下向含6-胺基吡啶-2-磺醯胺(2.43 g，14.0 mmol)之DMF (2 mL)添加氫化鈉(561 mg，14.0 mmol)，

且攪拌10分鐘且室溫下攪拌1小時。反應混合物冷卻回0℃且添加CDI加合物且將反應混合物在65℃下加熱1.5小時，接著冷卻至室溫且用乙酸乙酯稀釋且用鹽水洗滌溶液。分離有機物，乾燥且在減壓下濃縮，得到殘餘物，其藉由矽膠管柱層析，用0-100%乙酸乙酯-己烷溶離來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-4-溴-2,3-二氟-苯甲醯胺(3.80 g，986%)。ESI-MS m/z 計算值 390.94，實驗值394.2 $(M+4)^+$；LCMS滯留時間(3分鐘操作) 1.13 min。

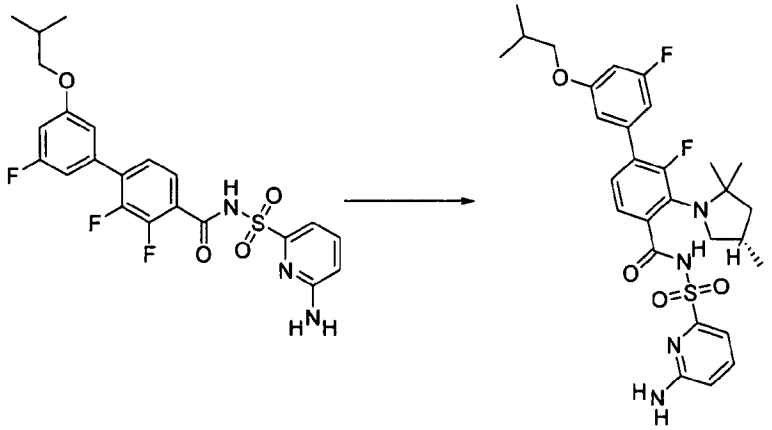
**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2,3-二氟-4-(3-氟-5-異丁氧基-苯基)苯甲醯胺



向*N*-[(6-胺基-2-吡啶基)磺醯基]-4-溴-2,3-二氟-苯甲醯胺(1.3 g，3.3 mmol)及(3-氟-5-異丁氧基-苯基)硼酸(1.1 g，5.0 mmol)及$K_2CO_3$(1.4 g，9.9 mmol)之混合物中添加環戊基(二苯基)膦二氯鈀鐵(243 mg，0.33 mmol)及DMF (8.8 mL)及水(2.2 mL)且將反應混合物在氮氣下在100℃下攪拌16小時。反應混合物冷卻，經矽藻土墊過濾且濾液用乙酸乙酯及鹽水溶液稀釋。分離有機物，乾燥且濃縮，得到殘餘物，其藉由矽膠管柱層析，使用5-100%乙酸乙酯-DCM 作爲溶離劑來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2,3-二氟-4-(3-氟-5-異丁氧基-苯基)苯甲醯胺(356 mg，22%)。1H NMR (400 MHz,甲醇-d4) δ 7.64 - 7.53 (m, 2H), 7.29 (d, J = 7.4 Hz, 1H), 7.25 - 7.18 (m, 1H), 6.90 (d, J = 2.7 Hz, 1H), 6.88 - 6.81 (m, 1H), 6.73 (dt, J = 10.8, 2.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 3.79 (d, J = 6.4 Hz, 2H), 2.07 (七重峰, J = 6.7 Hz,

1H), 1.04 (d, J = 6.7 Hz, 6H); ESI-MS m/z 計算值 479.11, 實驗值 480.2 $(M+1)^+$；LCMS滯留時間(3分鐘操作) 1.78 min。

步驟3：*N*-[(6-胺基-2-吡啶基)磺醯基]-3-氟-4-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]苯甲醯胺(化合物2634)

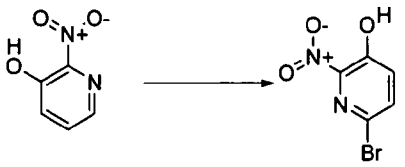


向含*N*-[(6-胺基-2-吡啶基)磺醯基]-2,3-二氟-4-(3-氟-5-異丁氧基-苯基)苯甲醯胺(356 mg，0.74 mmol)及$K_2CO_3$ (277 mg，2.00 mmol)之NMP (650 µl)添加(4*S*)-2,2,4-三甲基吡咯啶(HCl鹽) (150 mg，1.00 mmol)且將反應混合物在195℃下攪拌5小時，接著冷卻且過濾且用EtOAc及鹽水溶液稀釋。分離有機物，乾燥且在減壓下濃縮，得到殘餘物，其使用矽膠管柱層析，使用0-15% MeOH-DCM來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-3-氟-4-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]苯甲醯胺(化合物2634) (42 mg，2%) 1H NMR (400 MHz,甲醇-d4) δ 7.69 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.26 (s, 1H), 7.08 (dd, J = 7.3, 0.8 Hz, 1H), 6.62 - 6.51 (m, 2H), 6.44 (dd, J = 19.3, 9.7 Hz, 2H), 3.58 (s, 1H), 3.49 (d, J = 6.4 Hz, 2H), 2.52 (t, J = 0.8 Hz, 1H), 2.45 (s, 1H), 1.90 (s, 1H), 1.82 - 1.69 (m, 2H), 1.53 (s, 1H), 1.04 (s, 3H), 0.92 (s, 6H), 0.74 (d, J = 6.7 Hz, 6H)。ESI-MS m/z 計算值572.2，實驗值 573.3 $(M+1)^+$；LCMS滯留時間(3分鐘操作) 1.91 min。

**製備114**：*N*-[(6-胺基-5-羥基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-

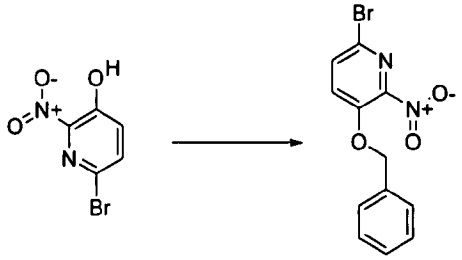
6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2331)

**步驟1**：6-溴-2-硝基-吡啶-3-醇



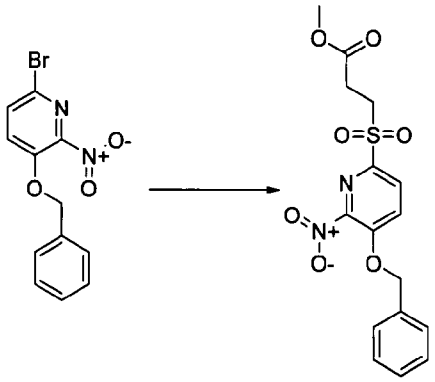
在-40℃下將三溴化苯基三甲基銨(8.45 g，22.3 mmol)於THF (68 mL)中之溶液逐滴添加至攪拌的2-硝基吡啶-3-醇(3.00 g，21.4 mmol)及三乙胺(4.33 g，5.97 mL，42.8 mmol)於THF (91 mL)中之溶液中。添加進行5分鐘之時間且反應混合物保持在-40℃下1小時。添加1N HCl及$Na_2S_2O_3$水溶液且水相用二氯甲烷萃取。合併之有機相用鹽水洗滌，經$MgSO_4$乾燥，過濾且濾液在減壓下蒸發。殘餘物藉由矽膠管柱層析，用30至100%EtOAc/己烷溶離來純化，得到呈黃色固體狀之標題化合物。

**步驟2**：3-苯甲氧基-6-溴-2-硝基-吡啶



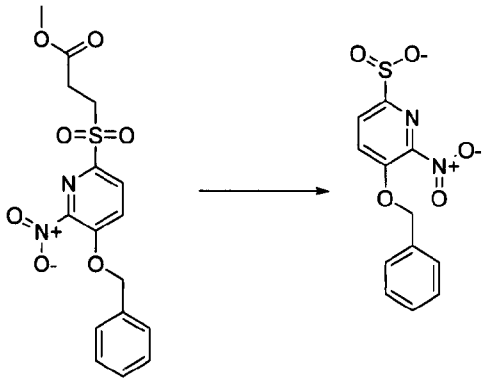
向 6-溴-2-硝基-吡啶-3-醇(5.04 g，23.0 mmol)於DMF (40 mL)中之溶液中添加碳酸鉀(6.36 g，46.0 mmol)，接著添加溴甲基苯(4.13 g，2.87 mL，24.2 mmol)。將反應混合物在60℃下加熱隔夜，接著分溶於EtOAc與水之間。水層用EtOAc (3次)萃取。合併之有機層用水(3次)、鹽水洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。粗物質懸浮於己烷中，經由過濾收集且空氣乾燥，得到呈黃色固體狀之3-苯甲氧基-6-溴-2-硝基-吡啶(6.22 g，87%)。

**步驟3**：3-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]丙酸甲酯



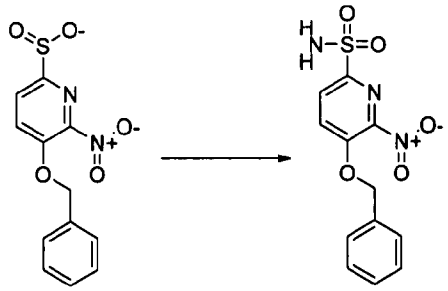
將3-苯甲氧基-6-溴-2-硝基-吡啶(6.21 g，20.1 mmol)及(3-甲氧基-3-側氧基-丙基)亞磺醯基氧基鈉(3.50 g，20.1 mmol)於DMSO (50 mL)中之混合物用氮氣淨化2分鐘。添加碘基銅(7.66 g，40.2 mmol)。將反應混合物在80℃下加熱24小時，接著分溶於EtOAc與飽和$NH_4Cl$之間。所得沈澱經由過濾移除且用EtOAc洗滌。水層用EtOAc (3次)萃取。合併之有機層用水(3次)、鹽水洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。粗物質藉由矽膠管柱層析(40-60% EtOAc-Hex)來純化，得到呈褐色固體狀之3-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]丙酸甲酯(2.50 g，33%) 。

**步驟4**：5-苯甲氧基-6-硝基-吡啶-2-亞磺酸酯



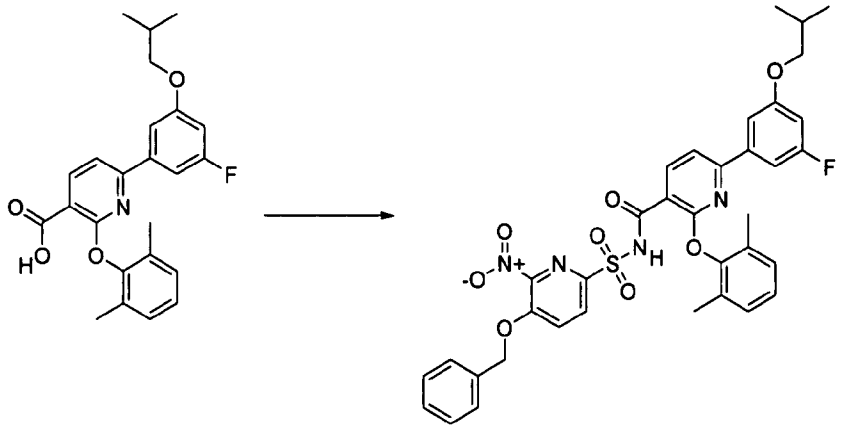
將THF (1 mL)添加至3-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]丙酸甲酯(76 mg，0.2 mmol)於MeOH (2 mL)中之懸浮液中。逐滴添加甲醇鈉(400 μL 0.5 M，0.2 mmol) (MeOH中)。將反應混合物在室溫下攪拌30分鐘，接著在減壓下蒸發，得到淡褐色固體。粗物質未經進一步純化直接用於下一步。

**步驟5**：5-苯甲氧基-6-硝基-吡啶-2-磺醯胺



向胺基硫酸氫鹽(3.68 g，32.5 mmol)及乙酸鈉(5.32 g，65.0 mmol)於水(40 mL)中之溶液中添加含5-苯甲氧基-6-硝基-吡啶-2-亞磺酸鹽(鈉鹽) (2.06 g，6.5 mmol)之MeOH (25 mL)。將反應混合物在室溫下攪拌隔夜，接著分溶於水與EtOAc之間。水層用EtOAc (3次)萃取。合併之有機層用鹽水洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮，得到呈粗物質形式之5-苯甲氧基-6-硝基-吡啶-2-磺醯胺(1.10 g，55%)。粗物質(淡黃色固體)未經進一步純化直接用於下一步中。

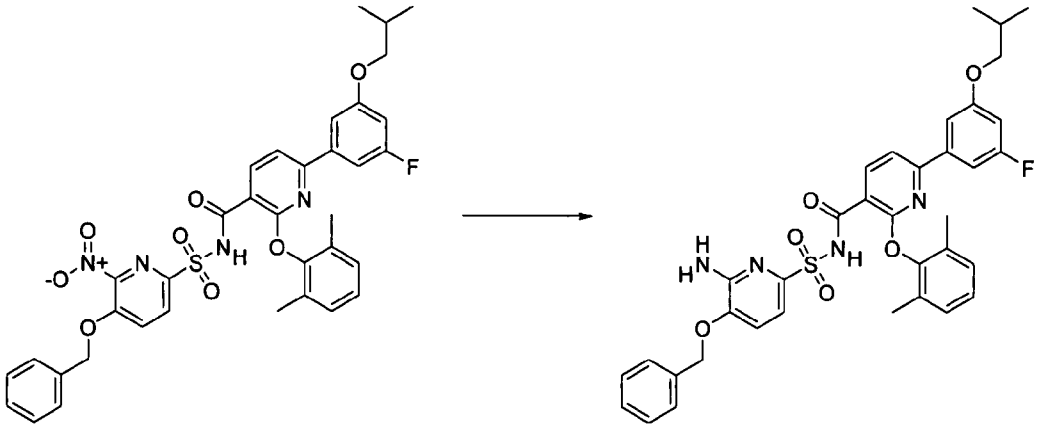
**步驟6**：*N*-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺



向5-苯甲氧基-6-硝基-吡啶-2-磺醯胺(155 mg，0.50 mmol)、2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(248 mg，0.60 mmol)及HATU (228 mg，0.60 mmol)於DMF (10 mL)之混合物中添加碳酸鉀(207 mg，1.50 mmol)。將反應混合物在60℃下加熱7小時，分溶於EtOAc與水之間。水層用EtOAc (3次)萃取。合併之有機層用水(3次)、鹽水洗滌，經$MgSO_4$乾燥，過濾且在減壓下濃縮。粗物

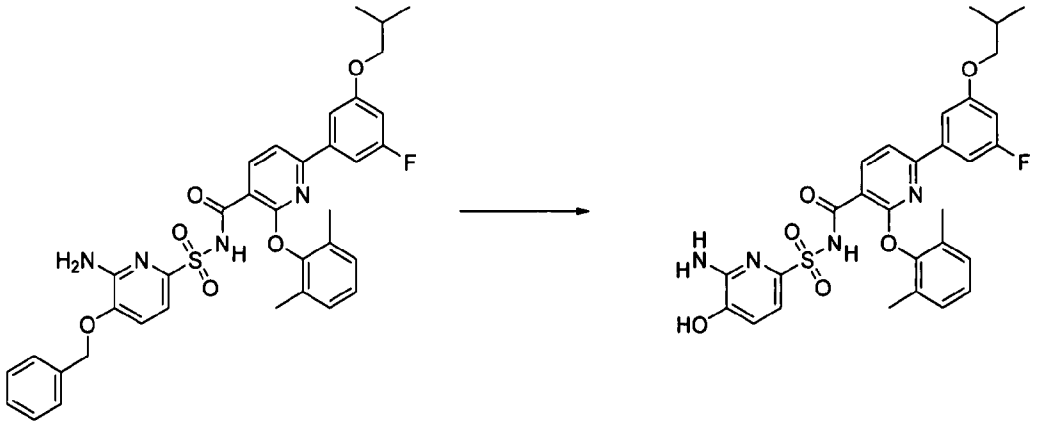
質藉由矽膠管柱層析(20-40% EtOAc-Hex)來純化，得到呈黃色固體狀之*N*-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(220 mg，63%)。

**步驟7**：*N*-[(6-胺基-5-苯甲氧基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1762)



向*N*-[(5-苯甲氧基-6-硝基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(215 mg，0.31 mmol)於二噁烷(4 mL)及乙醇(2 mL)中之溶液中添加Fe (171 mg，3.07 mmol)及HCl (511 μL 6 M，3.07 mmol)。將反應混合物在65℃下加熱30分鐘。移除鐵且沈澱經由過濾收集。濃縮濾液至乾，溶於DMSO中，過濾且藉由製備型HPLC來純化，得到*N*-[(6-胺基-5-苯甲氧基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1762) (25 mg，12%)　1H NMR (400 MHz, DMSO-d6) δ 12.23 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.57 - 7.46 (m, 2H), 7.45 - 7.23 (m, 5H), 7.23 - 7.04 (m, 5H), 6.83 (dt, J = 10.9, 2.3 Hz, 1H), 6.33 (s, 2H), 5.24 (s, 2H), 3.61 (d, J = 6.6 Hz, 2H), 2.05 (s, 6H), 1.98 (dt, J = 13.4, 6.7 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H)。ESI-MS m/z計算值670.22614, 實驗值670.0 $(M+1)^+$；滯留時間: 3.6分鐘。

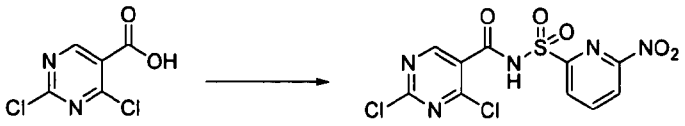
**步驟8**：*N*-[(6-胺基-5-羥基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2331)



向*N*-[(6-胺基-5-苯甲氧基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1762) (21 mg，0.03 mmol)於MeOH (20 mL)中之懸浮液添加EtOAc (1 mL)。溶液用氮氣淨化2分鐘。添加Pd (3. mg，0.003 mmol)。將反應混合物在氫氣氛圍下在室溫下攪拌隔夜。Pd催化劑經由過濾移除。濃縮濾液至乾。殘餘物再溶於DMSO中且藉由製備型HPLC來純化，得到*N*-[(6-胺基-5-羥基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2331) (5.0 mg，24%)。ESI-MS m/z計算值580.1792, 實驗值580.0 $(M+1)^+$；滯留時間: 3.15分鐘。

**製備115**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟-5-異丁氧基-苯基)-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]嘧啶-5-甲醯胺(化合物2121)

**步驟1**：2,4-二氯-*N*-((6-硝基吡啶-2-基)磺醯基)嘧啶-5-甲醯胺



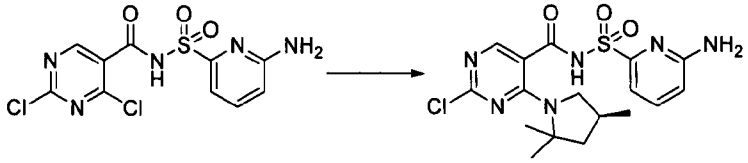
2,4-二氯嘧啶-5-甲酸(4.56 g，23.8 mmol)於亞硫醯氯(30 mL)中之溶液回流1小時，且蒸發以移除亞硫醯氯。殘餘物溶於二氯甲烷(50 mL)中，且小心添加6-硝基吡啶-2-磺醯胺(5.14 g，23.7 mmol)，接著三甲基胺(10 mL)。將反應混合物在室溫下攪拌30分鐘且濃縮。粗物質藉由矽膠層析，用己烷中30-100%乙酸乙酯溶離來純化，得到所需產物(9.1 g，100%)。

**步驟2**：*N*-((6-胺基吡啶-2-基)磺醯基)-2,4-二氯嘧啶-5-甲醯胺



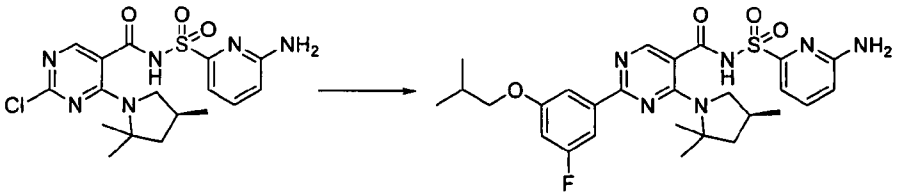
將2,4-二氯-*N*-((6-硝基吡啶-2-基)磺醯基)嘧啶-5-甲醯胺(1.7 g，4.5 mmol，1.0當量)及鐵(2.6 g，47 mmol，10當量)於HCl (1.9 mL 23 mmol，5.1當量)、乙醇(6 mL)、四氫呋喃(6 mL)及水(0.90 mL)中之混合物在60℃下加熱1小時。反應混合物經矽藻土過濾且用甲醇及乙酸乙酯洗滌。濾液在減壓下濃縮，得到所需化合物(1.7 g，100%) LC-MS: $(M+H)^+$ = 348.0。

**步驟3**：(*S*)-*N*-((6-胺基吡啶-2-基)磺醯基)-2-氯-4-(2,2,4-三甲基吡咯啶-1-基)嘧啶-5-甲醯胺



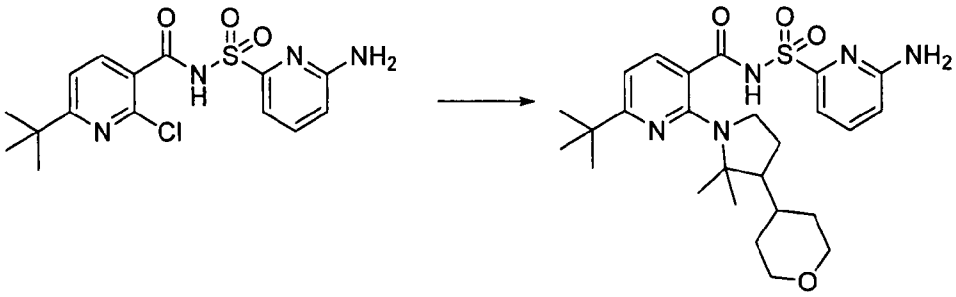
將*N*-((6-胺基吡啶-2-基)磺醯基)-2,4-二氯嘧啶-5-甲醯胺(0.60 g，1.7 mmol，1.0當量)、(*S*)-2,2,4-三甲基吡咯啶鹽酸鹽(0.26 g，1.8 mmol，1.0當量)及碳酸鉀(0.96 g，7.0 mmol，4.0當量)於4.0 mL二甲亞碸中之混合物在封蓋小瓶中在125℃下加熱20小時。反應混合物藉由矽膠層析且用乙酸乙酯中0-80%甲醇之梯度溶離來純化，得到呈褐色固體狀之(*S*)-*N*-((6-胺基吡啶-2-基)磺醯基)-2-氯-4-(2,2,4-三甲基吡咯啶-1-基)嘧啶-5-甲醯胺(0.22 g，30%產率)。$^1$H NMR (DMSO-$d_6$, 250 MHz): δ 8.04 (m, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.25 (s, br, 2H), 2.99 (m, 1H), 2.84 (m, 1H), 2.14 (m, 1H), 1.84 (m, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.38 (m, 1H), 0.85 (d, *J* = 6.3 Hz, 3H) ppm。LC-MS: $(M+H)^+$ = 424.9。

**步驟4**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟-5-異丁氧基-苯基)-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]嘧啶-5-甲醯胺(化合物2121)



在氮氣氛圍下向*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]嘧啶-5-甲醯胺(70 mg，0.1647 mmol)、環戊基(二苯基)膦二氯鈀鐵(12.05 mg，0.01647 mmol)及二噁烷(840.0 μL)添加(3-氟-5-異丁氧基-苯基)硼酸(69.84 mg，0.3294 mmol)，接著碳酸鈉(247.0 μL 2 M，0.4941 mmol)。反應混合物在微波中在120℃下照射1小時。反應混合物過濾且接著直接藉由逆相製備型層析，利用C18管柱及HPLC-MS法，10-99 A1B1 (乙腈-水+ 5 mM HCl，30分鐘時間)來純化，得到呈棕褐色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-氟-5-異丁氧基-苯基)-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]嘧啶-5-甲醯胺(化合物2121) (14 mg，15%) ESI-MS m/z計算值556.2268, 實驗值557.2 $(M+1)^+$；滯留時間: 1.71分鐘。1H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 7.73 (s, 3H), 7.70 - 7.63 (m, 1H), 7.59 (d, J = 9.7 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.07 (d, J = 10.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.86 (d, J = 6.6 Hz, 2H), 2.86 - 2.74 (m, 1H), 2.69 (t, J = 10.9 Hz, 1H), 2.34 - 2.18 (m, 1H), 2.13 - 1.99 (m, 1H), 1.95 (dd, J = 11.9, 5.5 Hz, 1H), 1.63 (d, J = 23.9 Hz, 6H), 1.50 (t, J = 12.2 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.90 (d, J = 6.3 Hz, 3H)。

**製備116**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (化合物2266) (外消旋混合物)



在5 mL微波小瓶中*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-氯-吡啶-3-甲醯胺(85 mg，0.2305 mmol)及氟基銫(175.0 mg，42.53μL，1.152 mmol)組合於DMSO (510.0 μL)中，接著$K_2CO_3$ (318.6 mg，2.305 mmol)及2,2-二甲基-3-四氫哌喃-4-基-吡咯啶(169.0 mg，0.9220 mmol)。將小瓶封蓋且在油浴中加熱至150℃，保持16小時。添加額外氟基銫(175.0 mg，42.53 μL，1.152 mmol)、$K_2CO_3$ (318.6 mg，2.305 mmol)及2,2-二甲基-3-四氫哌喃-4-基-吡咯啶(169.0 mg，0.9220 mmol)且加熱至165℃，再保持16小時。反應混合物過濾且接著直接藉由逆相製備型層析，利用C18管柱及HPLC-MS法，10-99%乙腈-水+ 5 mM HCl來純化，得到呈淡黃色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (化合物2266) (80 mg，66%)。ESI-MS m/z計算值515.25665，實驗值516.2 $(M+1)^+$；滯留時間：1.31分鐘。1H NMR (400 MHz, DMSO) δ 12.47 (s, 1H), 7.70 - 7.52 (m, 2H), 7.17 (dd, J = 7.3, 0.5 Hz, 1H), 6.78 - 6.59 (m, 2H), 5.14 (s, 2H), 3.84 (d, J = 3.5 Hz, 2H), 3.30 (d, J = 10.7 Hz, 2H), 2.84 (t, J = 10.0 Hz, 1H), 2.68 - 2.55 (m, 1H), 2.07 (s, 4H), 1.87 - 1.73 (m, 1H), 1.65 (dd, J = 30.6, 10.5 Hz, 2H), 1.55 (d, J = 8.6 Hz, 6H), 1.49 (s, 3H), 1.28 (d, J = 6.6 Hz, 10H)。使用超臨界流體層析，在ChiralPak AS-H (250×10 mm) 5 μm管柱上，使用$CO_2$中12% MeOH，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮至乾，得到純化合物。

以下化合物可以本文所述之方式製備：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3-環丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2577) (異構體1，*R*或*S*立體異構體) (化合物2022) (異構體2，*R*或*S*立體異構體)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[3-(環丙基甲基)-2,2-二甲基-吡咯啶-1-基]吡啶-3-甲醯胺(化合物2242)，

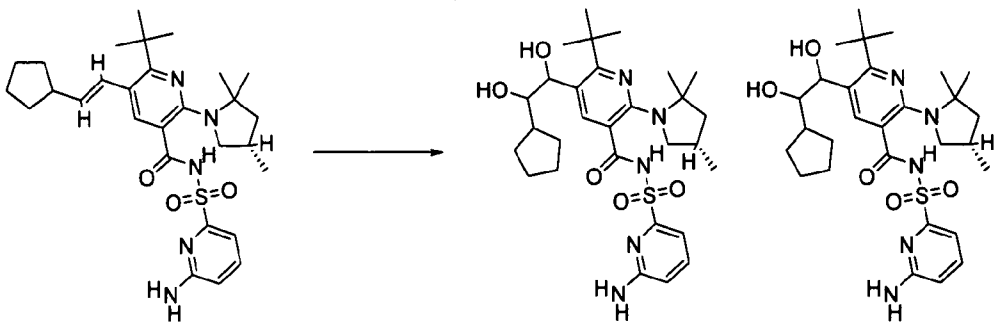
*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3-苯甲基-2,2-二甲基-吡咯啶-1-基)-6-第三丁基-吡啶-3-甲醯胺(化合物1852)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3-環丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2577) (異構體1，*R*或*S*立體異構體) (化合物2022) (異構體2，*R*或*S*立體異構體)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (異構體1，*R*或*S*立體異構體) (化合物2266) (異構體2，*R*或*S*立體異構體)，

6-第三丁基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1765)

**製備117**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環戊基-1,2-二羥基乙基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(異構體1，*R*或*S*立體異構體)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環戊基-1,2-二羥基乙基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(異構體2，*R*或*S*立體異構體)



向*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(E)-2-環戊基乙烯

基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1633) (8 mg，0.01 mmol)於丙酮(1.0 mL)及水(0.5 mL)中之溶液中依序添加4-甲基嗎啉*N*-氧化物(16 mg，0.14 mmol)及四氧化鋨(15 μL 2.5 %w/v，0.001 mmol)，且將反應混合物在空氣下在周圍溫度下攪拌。2小時後，反應混合物變成透明溶液，且濃縮成淡黃色糊狀物。糊狀物溶於DMSO (1 mL)中且藉由逆相HPLC-MS法來純化，得到呈白色固體狀之兩種非對映異構體二醇。異構體1：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環戊基-1,2-二羥基-乙基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(HCl鹽) (2 mg，23%) ESI-MS m/z計算值573.29846, 實驗值574.4 $(M+1)^+$；滯留時間: 1.51分鐘；異構體2：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環戊基-1,2-二羥基-乙基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(HCl 鹽) (4 mg，47%) ESI-MS m/z計算值573.29846, 實驗值574.4 $(M+1)^+$；滯留時間: 1.55分鐘

以下化合物可以如本文所述之方式製備：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環戊基-1,2-二羥基乙基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2661) (異構體1)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(1,2-二羥基-3,3-二甲基丁基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2069) (異構體2)，

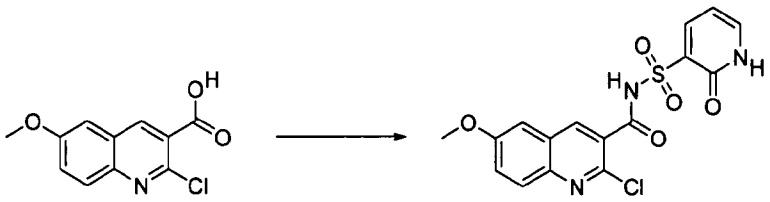
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環己基-1,2-二羥基乙基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(異構體1)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-(2-環己基-1,2-二羥基乙基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(異構體2)，

**製備118**：6-甲氧基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-

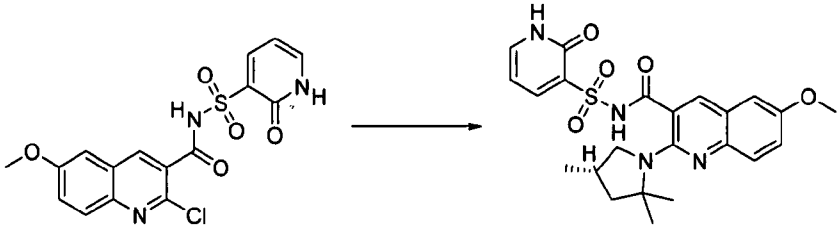
三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2419)

**步驟1**：2-氯-6-甲氧基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]喹啉-3-甲醯胺



將2-氯喹啉-3-甲酸(62 mg，0.3 mmol)及CDI (73 mg，0.5mmol)組合於DMF (2 mL)中且在40℃下攪拌2小時。在另一小瓶中，將NaH (15 mg，0.4 mmol)添加至含2-甲氧基吡啶-3-磺醯胺(71 mg，0.4 mmol)之DMF (1 mL)中。合併溶液且在周圍溫度下攪拌隔夜。反應混合物溶解於EtOAc中且用HCl (1 N，1 × 5 mL)洗滌。水層用EtOAc (2×10 mL)反洗滌，合併之有機層用鹽水(1× 10 mL)洗滌且經硫酸鈉乾燥，過濾且在減壓下濃縮。固體溶於含4M HCl (750 μL，4.0 mmol)之1,4-二噁烷(2 mL)中，且加熱至90℃，保持2小時。反應混合物冷卻，在減壓下移除溶劑，得到固體，其用乙酸乙酯濕磨，得到所需化合物(89 mg，79%)。ESI-MS m/z 394.2 $(M+1)^+$, 滯留時間0.39分鐘。

**步驟2**：6-甲氧基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2419) (化合物2405)



2-氯-*N*-甲基磺醯基-喹啉-3-甲醯胺(40 mg，0.1 mmol)、碳酸鉀(69 mg，0.5 mmol)及(4*S*)-2,2,4-三甲基吡咯啶(HCl 鹽) (30 mg，0.2 mmol)懸浮於DMSO (1 mL)中。將反應物在120℃下加熱2天，接著冷卻，用DMSO-甲醇稀釋，過濾，且接著經由逆相HPLC-MS法，使用經15.0分鐘1-99%移動相B之雙重梯度操作(移動相A = $H_2O$ (5 mM

TFA)，移動相B =乙腈)來純化，得到所需化合物(8 mg，17%)。ESI-MS m/z 471.3 $(M+1)^+$, 滯留時間1.19分鐘。

以下化合物可使用本文所述之程序合成：

6-甲基-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2471)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-7-甲基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2519)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲氧基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2196)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-甲基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2548)，

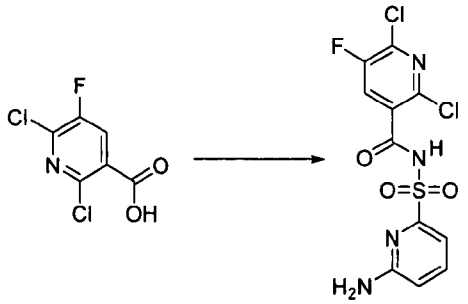
*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2405)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物2265)及

*N*-[(2-甲氧基-3-吡啶基)磺醯基]-7-甲基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]喹啉-3-甲醯胺(化合物1859)

**製備119**：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-異丙氧基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2230)

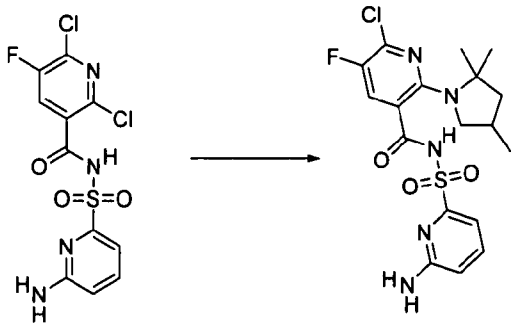
**步驟1**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-二氯-5-氟-吡啶-3-甲醯胺




將2,6-二氯-5-氟-吡啶-3-甲酸(5.0 g，23.8 mmol)、CDI (6.8 g，

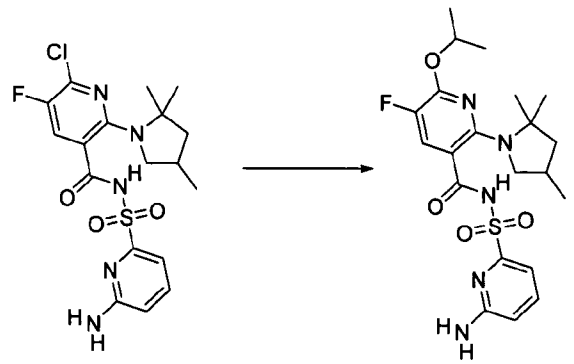
41.9 mmol)及DMF (30 mL)在60℃下攪拌50分鐘。在另一燒瓶中，6-胺基吡啶-2-磺醯胺(5.2 g，29.8 mmol)、NaH (1.2 g，29.8 mmol)及DMF (25 mL)。將反應混合物在60℃下攪拌1小時。在室溫下含有6-胺基吡啶-2-磺醯胺之內含物逐滴添加至活化酸。將反應混合物在室溫下攪拌16小時。接著反應混合物置於冰浴中，用水(300 mL)稀釋，且調整pH至2。所得漿狀物用力攪拌30分鐘。過濾沈澱，用水(50 ML×3)及己烷(50 mL×3)洗滌，且真空乾燥，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-二氯-5-氟-吡啶-3-甲醯胺(6.9 g，79%)。

**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-5-氟-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺



向*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-二氯-5-氟-吡啶-3-甲醯胺(1.0 g，2.7 mmol)於DMSO (8 mL)中之溶液中添加2,2,4-三甲基吡咯啶(HCl鹽) (820 mg，5.5 mmol)及$K_2CO_3$ (2.3 g，16.4 mmol)。將反應物在150℃下攪拌16小時。反應混合物過濾且經由製備型HPLC (1-99% ACN，15 min，HCl改質劑)純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-5-氟-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(HCl 鹽) (200 mg，30%)。

**步驟3**：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-異丙氧基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2230)



*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-5-氟-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(HCl鹽) (50 mg，0.10 mmol)、異丙醇(31mg，40μL，0.52 mmol)、NaH (10 mg，0.24 mmol)及DMSO (1mL)。將反應混合物在150℃下攪拌2小時。接著反應混合物過濾且經由製備型HPLC (1-99% ACN，15分鐘，HCL改質劑)純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-異丙氧基-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2230) (HCl 鹽) (13 mg，23%) 1H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 7.66 - 7.55 (m, 2H), 7.17 (dd, J = 7.3, 0.7 Hz, 1H), 6.66 (dd, J = 8.4, 0.8 Hz, 1H), 6.41 (s, 2H), 5.26 (p, J = 6.1 Hz, 1H), 2.60 - 2.51 (m, 1H), 2.49 - 2.40 (m, 1H), 2.33 (p, J = 1.8 Hz, 0H), 2.20 (s, 1H), 1.84 (dd, J = 11.8, 5.6 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.43 - 1.30 (m, 4H), 1.29 (d, J = 6.2 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H)。ESI-MS m/z計算值465.1846, 實驗值466.3 $(M+1)^+$；滯留時間: 1.38分鐘。

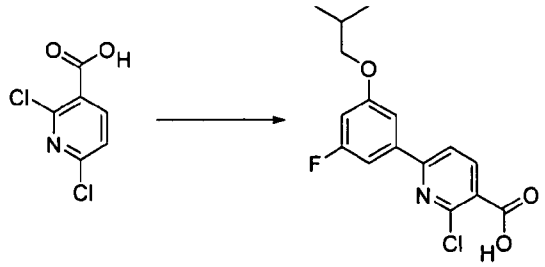
以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1-環丙基乙氧基)-5-氟-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2373)及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(1,2-二甲基丙氧基)-5-氟-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1810)

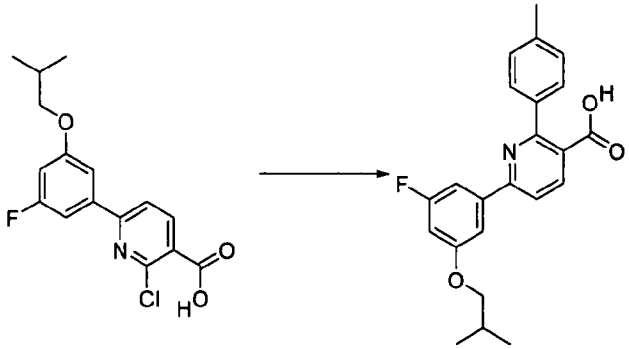
**製備120**：*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(對甲苯基)吡啶-3-甲醯胺(化合物2276)

**步驟1**：2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸



添加含2,6-二氯吡啶-3-甲酸(1.000 g，4.861 mmol)之IPA (30 mL)、$K_2CO_3$ (6.075 mL 2 M，12.15 mmol)及三苯基膦二氯鈀(341.2 mg，0.4861 mmol)。在氮氣氛圍下將反應混合物加熱至80℃且含(3-氟-5-異丁氧基-苯基)硼酸(1.082 g，5.104 mmol)之IPA (30 mL)經1小時緩慢添加。將反應混合物再加熱4小時。反應混合物冷卻，添加6 M HCl (2 mL)且接著用額外6 M HCl將pH調至2-3。有機相收集，經硫酸鈉乾燥且在減壓下濃縮。殘餘物藉由逆相管柱層析，使用水中10-80% ACN (含TFA改質劑)純化，得到所需化合物。ESI-MS m/z 324.0 $(M+1)^+$；滯留時間: 1.0分鐘。

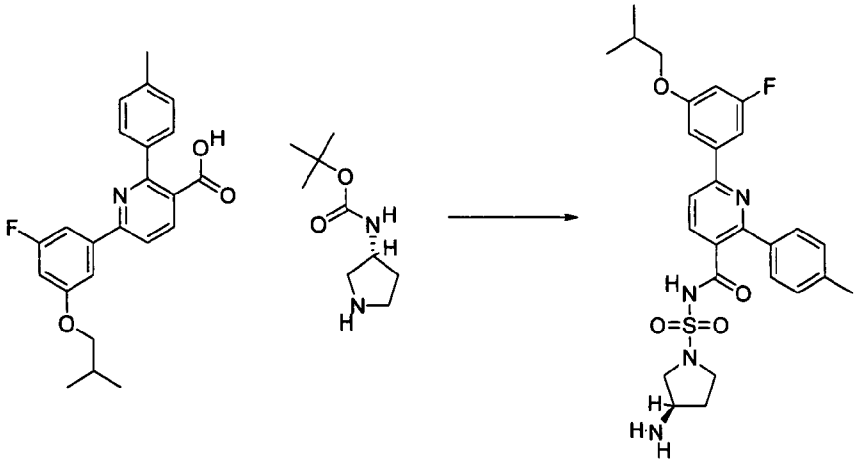
**步驟2**：6-(3-氟-5-異丁氧基-苯基)-2-(對甲苯基)吡啶-3-甲酸



2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(324 mg，1.00 mmol)、對甲苯基硼酸(272 mg，2.00 mmol)、$K_2CO_3$ (415 mg，3.00 mmol)及肆(三苯基膦)鈀(0) (116 mg，0.10 mmol)於DMF (10 mL)中之混合物在氮氣流下脫氣且在120℃下攪拌16小時。添加肆(三苯基膦)鈀(0)之另一等分試樣(116 mg，0.10 mmol)，且將反應混合物在150℃下攪拌17小時。反應混合物用水稀釋，用1 M HCl調至pH 5，且用乙

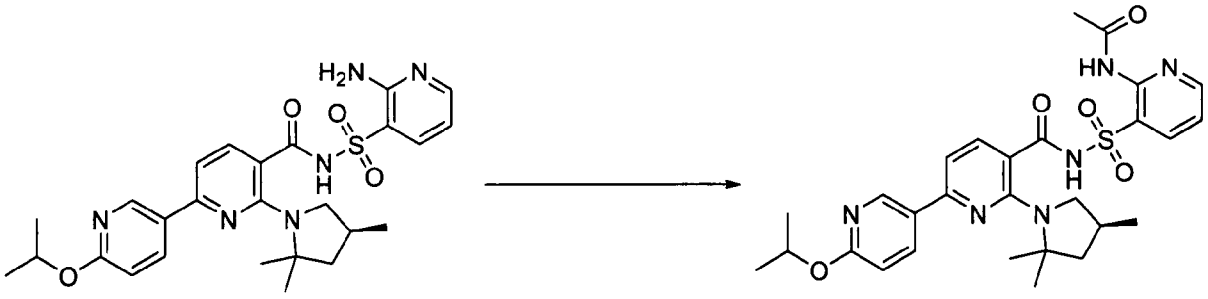
酸乙酯萃取。合併之萃取物用鹽水洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物藉由矽膠層析，使用0-5%甲醇之二氯甲烷溶液作爲溶離劑來純化，得到6-(3-氟-5-異丁氧基-苯基)-2-(對甲苯基)吡啶-3-甲酸(314 mg，83%)。

**步驟3**：*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(對甲苯基)吡啶-3-甲醯胺(化合物2276)



將6-(3-氟-5-異丁氧基苯基)-2-(對甲苯基)菸鹼酸(38 mg，0.1 mmol)及*N*-(側氧基亞甲基)胺磺醯氯(17 mg，10 μL，0.1 mmol)於二氯甲烷(1 mL)中之溶液攪拌一小時，接著添加*N*-[(3R)-吡咯啶-3-基]胺基甲酸第三丁酯(28 mg，0.2 mmol)及三乙胺(15 mg，21μL，0.2 mmol)。17小時後，添加HCl (200 μL 4 M，0.8 mmol) (二噁烷中)，且將反應混合物攪拌兩小時。反應混合物過濾且使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度 (移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$，流速 = 50 mL/min，及管柱溫度= 25℃)來純化，得到所需化合物。ESI-MS m/z 527.4 $(M+1)^+$；滯留時間: 1.62分鐘。

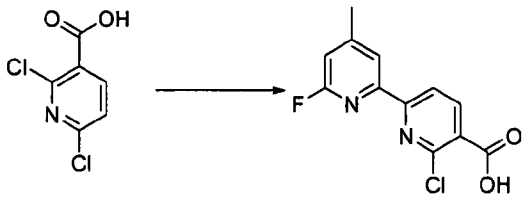
**製備121**：*N*-[(2-乙醯胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1976)



將含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(80 mg，0.1525 mmol)之吡啶(800 μL，9.891 mmol)用乙酸酐(400μL，4.239 mmol)處理且在室溫下攪拌隔夜。藉由製備型HPLC分離產物，得到*N*-[(2-乙醯胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1976) (HCl 鹽) (20 mg，21%) 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.67 (d, J = 4.7 Hz, 1H), 8.43 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.53 - 7.42 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.31 (p, J = 6.3 Hz, 1H), 2.41 (s, 2H), 2.25 (s, 3H), 2.18 (dt, J = 16.2, 7.6 Hz, 1H), 1.88 (dd, J = 12.1, 5.8 Hz, 1H), 1.55 (d, J = 4.4 Hz, 6H), 1.42 (t, J = 12.0 Hz, 1H), 1.31 (d, J = 6.1 Hz, 6H), 0.74 (d, J = 6.3 Hz, 3H)。ESI-MS m/z計算值566.23114，實驗值567.0 $(M+1)^+$；滯留時間：2.19分鐘。

**製備122**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-乙氧基-4-甲基-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2256)

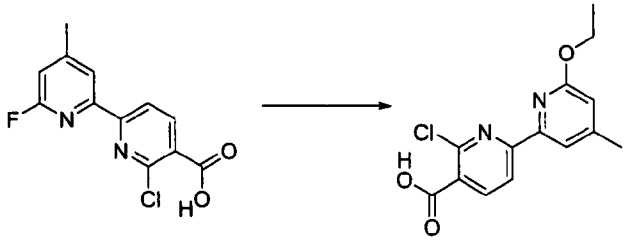
**步驟1**：2-氯-6-(6-氟-4-甲基-2-吡啶基)吡啶-3-甲酸



向含2,6-二氯菸鹼酸(661 mg，3.44 mmol)、(6-氟-4-甲基-2-吡啶基)硼酸(560 mg，3.62 mmol)、$K_2CO_3$ (4.13 mL 2 M，8.26 mmol)之

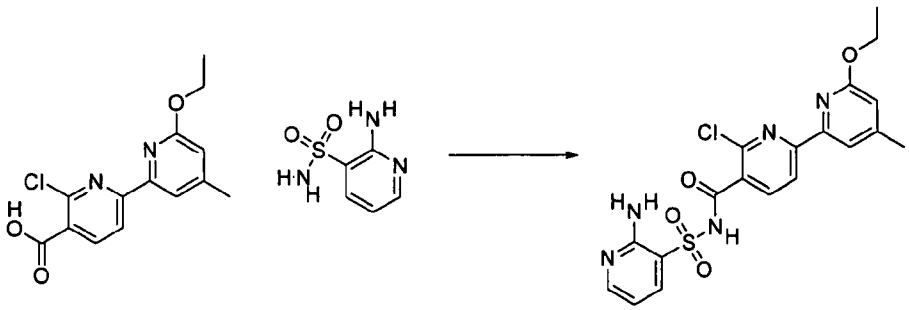
IPA (20 mL)中添加$Pd(PPh_3)_2Cl_2$ (48.3 mg，0.07 mmol)。反應混合物置於氮氣氛圍下且加熱至80℃，保持10小時。反應混合物過濾，在減壓下蒸發溶劑且粗混合物藉由逆相管柱層析，使用水中10-80%乙腈(TFA改質劑)來純化，得到所需化合物。ESI-MS m/z 267.0 $(M+1)^+$；滯留時間: 0.82分鐘。

**步驟2**：2-氯-6-(6-乙氧基-4-甲基-2-吡啶基)吡啶-3-甲酸



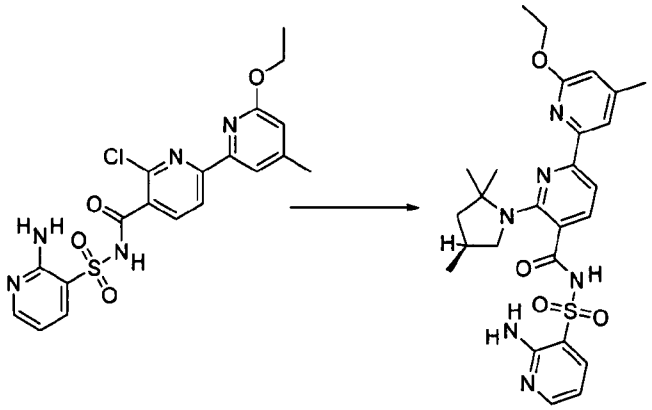
2-氯-6-(6-氟-4-甲基-2-吡啶基)吡啶-3-甲酸(4.2 g，15 mmol)溶於乙醇鈉(25 mL 21 %w/v，79 mmol)於乙醇中之溶液中。將反應混合物加熱至75℃且攪拌3小時。反應混合物用EtOAc (75 mL)稀釋且用含一些鹽水(20 mL)之水(1×75 mL)洗滌。水層用EtOAc (1×75 mL)萃取。合併有機層，經硫酸鈉乾燥，過濾且在減壓下濃縮，得到橙色固體。固體溶於EtOAc (75 mL)及NaOH水溶液(1 M，75 mL)中。水層分離且酸化至pH 2，用EtOAc (2×75 mL)萃取。最終有機層經硫酸鈉乾燥，過濾且在減壓下濃縮。所得固體藉由矽膠管柱層析管柱，使用0-10% MeOH/DCM作爲溶離劑來純化，得到呈白色固體狀之2-氯-6-(6-乙氧基-4-甲基-2-吡啶基)吡啶-3-甲酸(1.17 g，25%)。ESI-MS m/z計算值292.06146, 實驗值293.1 $(M+1)^+$；滯留時間: 1.72分鐘。

**步驟3**：*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(6-乙氧基-4-甲基-2-吡啶基)吡啶-3-甲醯胺



2-氯-6-(6-乙氧基-4-甲基-2-吡啶基)吡啶-3-甲酸(200 mg，0.68 mg)溶於DMF (2.5 mL)中。添加CDI (123 mg，0.75 mmol)，且將反應混合物在60℃下攪拌1小時。在另一燒瓶中，磺醯胺溶於DMF (600 μL)中，且添加NaH (34 mg，0.85 mmol)且將反應混合物在室溫下攪拌45分鐘。接著活化甲酸混合物添加至去質子化之磺醯胺。將最終反應混合物在60℃下攪拌隔夜。冷卻至室溫後，將反應混合物用EtOAc (50 mL)稀釋且用水(1× 50 mL)及鹽水(2× 75 mL)洗滌。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮，得到所需化合物(297 mg，97%)。ESI-MS m/z 448.0 $(M+1)^+$；滯留時間: 0.53分鐘。

**步驟4**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-乙氧基-4-甲基-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2256)

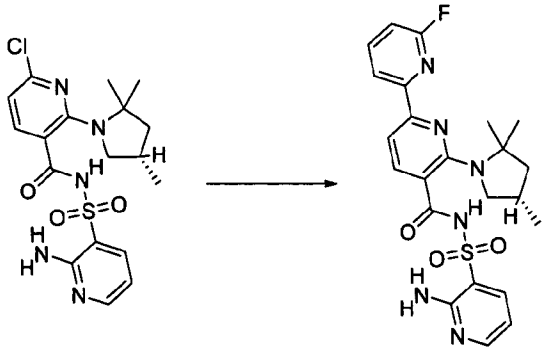


2-氯-6-(6-乙氧基-4-甲基-2-吡啶基)-*N*-甲基磺醯基-吡啶-3-甲醯胺(60 mg，0.13 mmol)及(4*S*)-2,2,4-三甲基吡咯啶(游離鹼，45 mg，0.4 mmol)組合於DMSO (100 μL)中。添加碳酸鉀(55 mg，0.4 mmol)且將反應混合物在140℃下加熱隔夜，接著在165℃下加熱3小時。反應混合物，使用逆相HPLC法，使用Luna C18 (2)管柱(50 × 21.2 mm，5 μm

粒徑)及經15.0分鐘10-99%移動相B之雙重梯度(移動相A =水(去離子化，無酸改質劑)，移動相B =乙腈)來純化，得到所需化合物。ESI-MS m/z 525.3 $(M+1)^+$；滯留時間: 1.57分鐘。

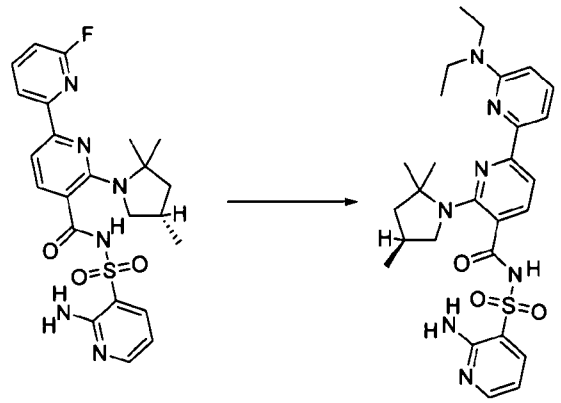
**製備123**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-(二乙基胺基)-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1845)

**步驟1**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-氟-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



*N*-[(2-胺基-3-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(0.12 g，0.28 mmol)、(6-氟-2-吡啶基)硼酸(0.06 g，0.42 mmol)、[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(0.02 g，0.02 mmol)及$Na_2CO_3$ (0.09 g，0.85 mmol)於DMF (2.2 mL)及水(566 μL)中之混合物在氮氣流下脫氣且在100℃下攪拌20小時。反應混合物用水稀釋且用乙酸乙酯萃取。合併之萃取物用鹽水洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物藉由矽膠管柱層析，使用0-5%甲醇之二氯甲烷溶液作爲溶離劑來純化，得到呈黃色固體狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-氟-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(0.11 g，80%)。

**步驟2**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-(二乙基胺基)-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1845)



將*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-氟-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(30 mg，0.06 mmol)及二乙基胺(1 mL，9.67 mmol)之溶液在密封容器中在120℃下攪拌17小時，接著在150℃下攪拌22小時。二乙基胺在真空下移除，且殘餘物使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘25-75%移動相B之雙重梯度 (移動相 A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到所需化合物。ESI-MS m/z 483.5 $(M+1)^+$；滯留時間: 0.88分鐘

以下化合物可使用本文所述之程序合成

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[6-(2,2-二甲基丙基胺基)-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2500)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二乙基胺基)-5-甲基-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物1907)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丁基胺基)-5-甲基-2-吡啶基]-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2362)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(二乙基胺基)-4-甲基-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2002)，

6-(6-乙氧基-4-甲基-2-吡啶基)-*N*-(1*H*-吡唑-3-基磺醯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2487)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-(2-乙氧基乙氧基)乙氧基]-

4-甲基-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1696)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-異丙氧基乙氧基)-4-甲基-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1703)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-乙氧基乙氧基)-4-甲基-2-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1700)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[異丙基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2687)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(異丙基胺基)-5-甲基-3-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2688)

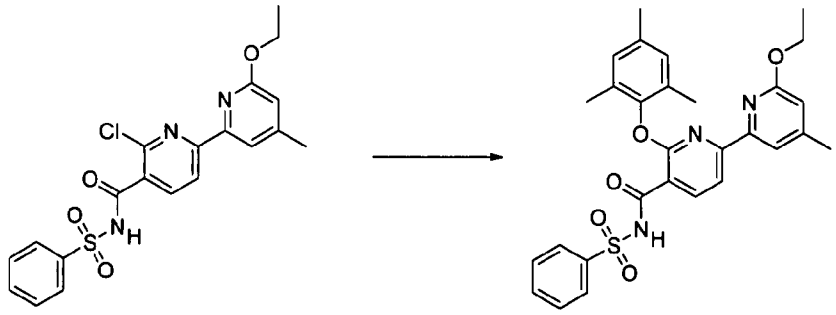
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[乙基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2689)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-乙氧基乙基(甲基)胺基]-5-甲基-3-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2685)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-[2-(2-乙氧基乙氧基)乙基-甲基-胺基]-5-甲基-3-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2684)及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[6-(2-乙氧基乙基胺基)-5-甲基-3-吡啶基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2686)。

**製備124**：*N*-(苯磺醯基)-6-(6-乙氧基-4-甲基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物2455)



*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(6-乙氧基-4-甲基-2-吡啶基)吡啶-3-甲醯胺(50 mg，0.1 mmol)及2,4,6-三甲基-苯酚(45 mg，0.3 mmol)溶解於DMSO (175 μL)及二噁烷(175 μL)中。添加氫化鈉(13mg，0.3 mmol)且將反應混合物在微波照射下在150℃下加熱20分鐘。反應混合物使用逆相HPLC法，使用Luna C18 (2)管柱(50 × 21.2 mm，5 μm粒徑)及經15.0分鐘10-99%移動相B之雙重梯度(移動相A = 水(去離子化，無酸改質劑)，移動相B =乙腈)來純化，得到*N*-(苯磺醯基)-6-(6-乙氧基-4-甲基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物2455)。ESI-MS m/z 532.5 $(M+1)^+$；滯留時間: 2.52分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(6-乙氧基-4-甲基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物2511)，

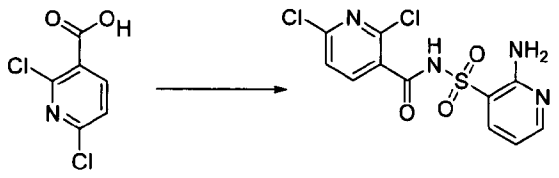
*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-乙氧基-4-甲基-2-吡啶基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1795)，

6-(6-乙氧基-4-甲基-2-吡啶基)-*N*-(1*H*-吡唑-3-基磺醯基)-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物2301)及

6-(6-乙氧基-4-甲基-2-吡啶基)-*N*-[(2-側氧基-1*H*-吡啶-3-基)磺醯基]-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物1768)。

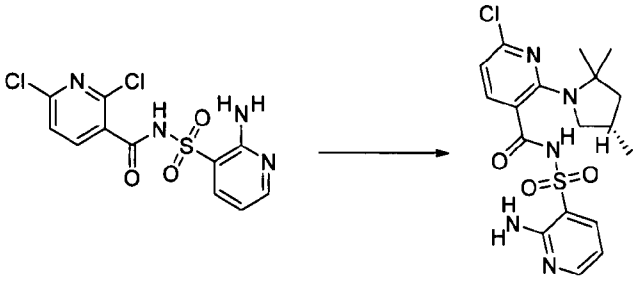
**製備125**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1697)

**步驟1**：*N*-[(2-胺基-3-吡啶基)磺醯基]-2,6-二氯-吡啶-3-甲醯胺



將含2,6-二氯吡啶-3-甲酸(1.5 g，7.8 mmol)及CDI (1.9 g，11.7 mmol)之DMF (17 mL)在60℃下攪拌。在另一小瓶中，將含2-胺基吡啶-3-磺醯胺(1.7 g，9.8 mmol)及NaH (0.4 g，9.8 mmol)之DMF (8 mL)在周圍溫度下攪拌。合併兩種反應混合物且在室溫下攪拌隔夜。反應混合物溶解於EtOAc中且用HCl (1 N，1 × 25 mL)洗滌且水層用EtOAc (4×20 mL)洗滌。合併之有機層用鹽水(1× 15 mL)洗滌且經硫酸鈉乾燥，過濾，且在減壓下濃縮。沉出之所得固體用乙酸乙酯洗滌且母液濃縮，殘餘物用乙酸乙酯及己烷洗滌，得到呈白色固體狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-2,6-二氯-吡啶-3-甲醯胺(2.5 g，94%)。1H NMR (400 MHz, DMSO-d6) δ 8.28 - 8.12 (m, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 7.7, 5.4 Hz, 1H)。

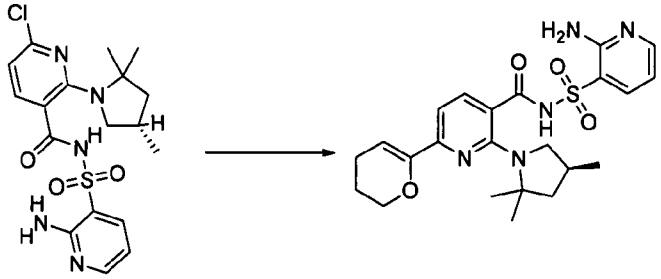
**步驟2**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



將DMSO (17 mL)添加至*N*-[(2-胺基-3-吡啶基)磺醯基]-2,6-二氯-吡啶-3-甲醯胺(2.1 g，6.0 mmol)、(4*S*)-2,2,4-三甲基吡咯啶(HCl 鹽)(1.1 g，7.3 mmol)及碳酸鉀(3.3 g，24 mmol)中。反應混合物密封且在120℃下攪拌2天。使反應混合物冷卻且接著用乙酸乙酯(40 mL)及水(60 mL)稀釋。向水層添加HCl水溶液至pH 7且接著用乙酸乙酯(5×50 mL)洗滌。合併之有機層濃縮至一半體積，接著用鹽水洗滌且經硫酸

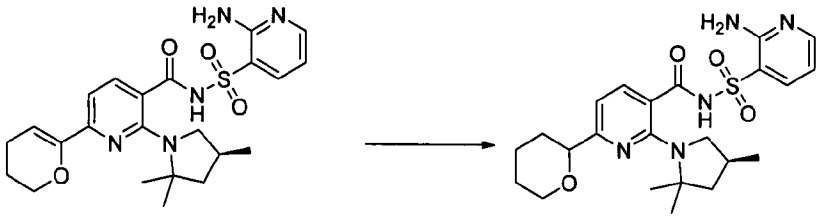
鈉乾燥，過濾且在減壓下蒸發，得到呈黃色粉末狀之*N*-[(2-胺基-3-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(2.5 g，100%)。1H NMR (400 MHz, DMSO-d6) δ 8.26 (dd, J = 4.8, 1.8 Hz, 1H), 8.06 (dd, J = 7.9, 1.8 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 6.79 (dd, J = 7.9, 4.8 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.19 - 2.03 (m, 1H), 1.82 (dd, J = 12.1, 5.6 Hz, 1H), 1.47 (d, J = 3.3 Hz, 6H), 1.36 (t, J = 12.2 Hz, 1H), 0.74 (d, J = 6.3 Hz, 3H)。

**步驟3**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,4-二氫-2H-哌喃-6-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1699)



*N*-[(2-胺基-3-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(32 mg，0.08 mmol)、2-(3,4-二氫-2H-哌喃-6-基)-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(19 mg，0.09 mmol)及1,3-雙(2,6-二異丙基苯基)-4,5-二氫咪唑3-氯吡啶二氯鈀(3 mg，0.005 mmol，5 mol%)溶於EtOH (600 μL)中且添加碳酸鉀溶液(150 μL，2M)。將反應混合物在氮氣氛圍下在120℃下加熱16小時。反應混合物冷卻，過濾且經由LC/MS，利用5 mM HCl水溶液中25-75%乙腈之梯度來純化。將碳酸鈉添加至所收集之溶離份(pH 7-8)且溶劑移除至乾，得到所需化合物。ESI-MS m/z 472.3 $(M+1)^+$；滯留時間: 1.18分鐘

**步驟4**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2351)



向含*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(3,4-二氫-2H-哌喃-6-基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1699) (37 mg，0.08 mmol)之EtOH (3 mL)添加鈀/碳(8 mg，0.008 mmol，10w/w%)。將反應混合物在氫氣氛圍下在周圍溫度下攪拌16小時。反應混合物過濾且蒸發至乾，溶於DMSO-甲醇中且經由逆相HPLC-MS法，使用經15.0分鐘1-99%移動相B之雙重梯度來純化。移動相A = $H_2O$ (5 mM TFA)，移動相B =乙腈，得到*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2351)。ESI-MS m/z 474.4$(M+1)^+$；滯留時間: 1.15分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(1,2-二甲基丙基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1911)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(5,5-二甲基-2-側氧基-環己基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1793)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-降冰片烷-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2097)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-4-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1850)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-環丙基乙基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2553)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-羥基-5,5-二甲基-環己基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2047)

*N*-(苯磺醯基)-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]

吡啶-3-甲醯胺(化合物1868)

*N*-(苯磺醯基)-6-異丁基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2246)

*N*-(苯磺醯基)-6-四氫呋喃-3-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2277)

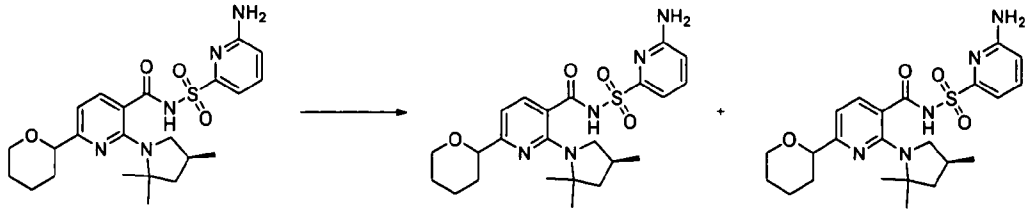
*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-3-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2311)

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-雙環[2.2.1]庚-2-烯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2709)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(三氟甲基)環己基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2077) (異構體1，順式或反式立體異構體)

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[4-(三氟甲基)環己基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2432) (異構體2，順式或反式立體異構體)。

**製備126**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2351) (異構體1，*RS*或*SS*立體異構體)及*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2351) (異構體2，*RS*或*SS*立體異構體)



使用超臨界流體層析，在Phenomenex LUX-4 (250×10 mm) 5 μm管柱上，使用$CO_2$中48% EtOH/IPA (50/50)，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮至乾，得到純化合物。

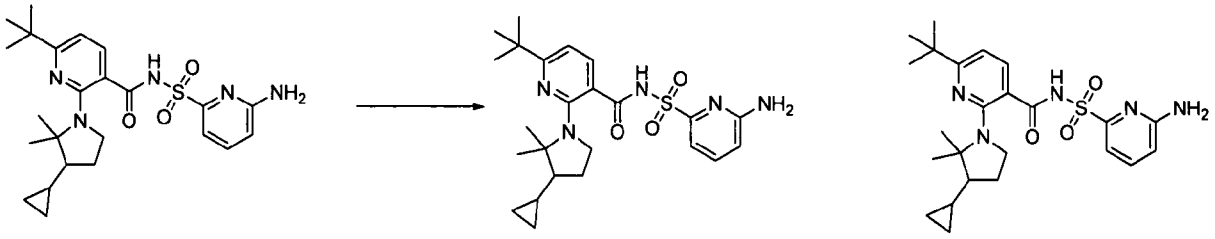
SFC峰1：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2351) ESI-MS m/z 474.4(M+1)$^+$；滯留時間: 1.15分鐘。SFC峰2：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-四氫哌喃-2-基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2351) ESI-MS m/z 474.4(M+1)$^+$；滯留時間: 1.15分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-四氫哌喃-2-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2672) (異構體1，*RS*或*SS*立體異構體)及

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-四氫哌喃-2-基]-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2675) (異構體2，*RS*或*SS*立體異構體)。

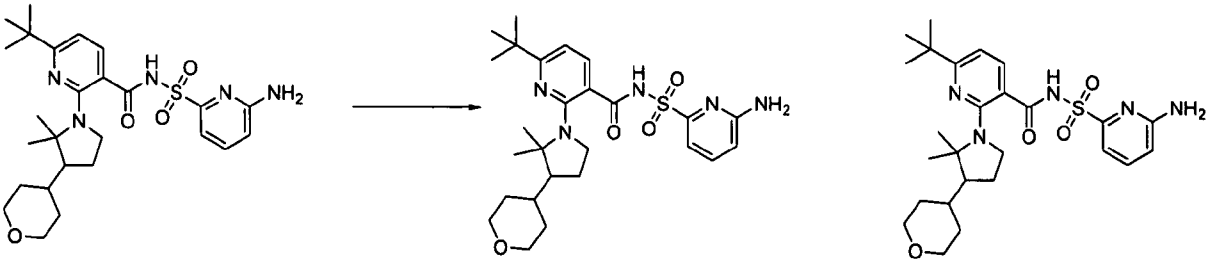
**製備127**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3-環丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2577) (化合物2022) (異構體1，*R*或*S*立體異構體)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3-環丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2577) (化合物2022) (異構體2，*R*或*S*立體異構體)



使用超臨界流體層析，在ChiralPak AD-H (250×10 mm) 5 μm管柱上，使用$CO_2$中22% EtOH/MeOH (90:10，20 mM $NH_3$)，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮，用乙酸乙酯(3 mL)稀釋且用1N鹽酸水溶液洗滌。有機層經硫酸鈉乾燥，過濾，且蒸發至乾，得到純化合物。SFC峰1：*N*-[(6-胺基-2-吡啶基)磺

醯基]-6-第三丁基-2-(3-環丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2577) (化合物2022) 1H NMR (400 MHz, DMSO) δ 12.35 (s, 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.14 (d, J = 6.7 Hz, 1H), 6.73 - 6.58 (m, 2H), 6.43 (s, 2H), 2.79 (s, 1H), 2.62 (s, 1H), 1.80 - 1.59 (m, 2H), 1.56 (s, 3H), 1.51 (s, 3H), 1.27 (s, 9H), 1.13 - 1.03 (m, 1H), 0.71 - 0.58 (m, 1H), 0.56 - 0.46 (m, 1H), 0.46 - 0.33 (m, 1H), 0.24 (td, J = 9.2, 5.0 Hz, 1H), 0.12 - 0.01 (m, 1H)。SFC峰2：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(3-環丙基-2,2-二甲基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2577) (化合物2022) 1H NMR (400 MHz, DMSO) δ 12.35 (s, 1H), 7.58 (d, J = 7.1 Hz, 2H), 7.14 (d, J = 7.1 Hz, 1H), 6.77 - 6.56 (m, 2H), 6.42 (s, 2H), 2.79 (s, 1H), 2.66 (dd, J = 12.3, 10.5 Hz, 1H), 1.69 (d, J = 20.9 Hz, 2H), 1.56 (s, 3H), 1.51 (s, 3H), 1.27 (s, 9H), 1.17 - 1.05 (m, 1H), 0.73 - 0.63 (m, 1H), 0.58 - 0.47 (m, 1H), 0.40 (dd, J = 8.2, 3.9 Hz, 1H), 0.24 (dd, J = 9.0, 4.1 Hz, 1H), 0.07 (dd, J = 9.0, 4.0 Hz, 1H)。

**製備128**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (化合物2266) (異構體1，*R*或*S*立體異構體)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (化合物2266) (異構體2，*R*或*S*立體異構體)

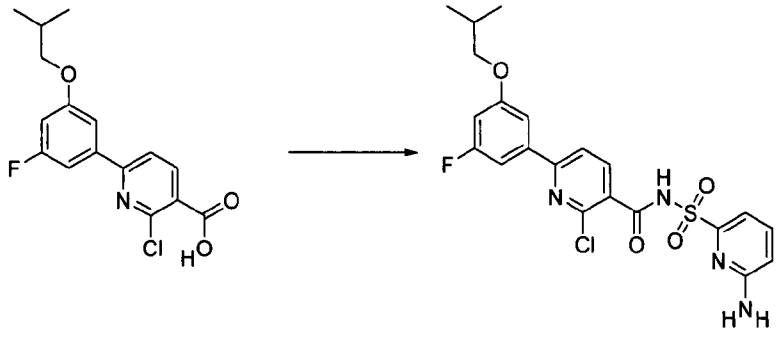


使用超臨界流體層析，在ChiralPak AD-H (250×10 mm) 5 μm管柱上，使用$CO_2$中12% MeOH，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮，用乙酸乙酯(3 mL)稀釋且用1N鹽酸水

溶液洗滌。有機層經硫酸鈉乾燥，過濾，且蒸發至乾，得到純化合物。SFC峰1：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (化合物2266) ESI-MS *m/z*計算值515.25665, 實驗值516.2 $(M+1)^+$；滯留時間: 1.31分鐘。SFC峰2：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-(2,2-二甲基-3-四氫哌喃-4-基-吡咯啶-1-基)吡啶-3-甲醯胺(化合物2425) (化合物2266) ESI-MS *m/z*計算值515.25665, 實驗值516.2 $(M+1)^+$；滯留時間: 1.31分鐘。1H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 7.70 - 7.52 (m, 2H), 7.17 (dd, J = 7.3, 0.5 Hz, 1H), 6.70 (dd, J = 9.7, 8.5 Hz, 2H), 5.19 (s, 2H), 3.84 (td, J = 11.1, 3.7 Hz, 2H), 3.38 - 3.18 (m, 2H), 2.84 (t, J = 10.0 Hz, 1H), 2.68 - 2.55 (m, 1H), 2.07 (s, 4H), 1.81 (t, J = 6.4 Hz, 1H), 1.65 (dd, J = 30.6, 10.5 Hz, 2H), 1.55 (d, J = 8.6 Hz, 6H), 1.49 (s, 3H), 1.28 (d, J = 6.6 Hz, 10H)。

**製備129**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (異構體1) (化合物2178) (異構體2) (化合物2062) (異構體3) (化合物1863) (異構體4)

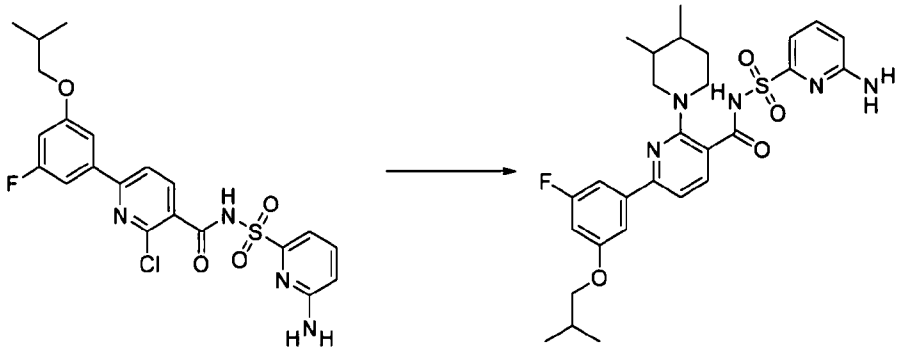
**步驟1**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺



將溶於DMF (31mL)中之2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(3.91 g，9.66 mmol)在氮氣下攪拌且一次性添加CDI (2.35 g，14.5 mmol)。反應混合物升溫至65℃且加熱1小時。同時在另一個容器

中，在氮氣下6-胺基吡啶-2-磺醯胺(2.09 g，12.1 mmol)在DMF (15 mL)中形成漿狀物且逐份添加NaH (483 mg，12.1 mmol)以減輕氣體放出且將反應物攪拌1小時。在65℃下兩種反應物一次性組合。將反應物攪拌15分鐘且蒸發。反應混合物傾倒在冰上且藉由添加6M HCl酸化(ph=4)。所得混合物用乙酸乙酯(1 L)萃取。有機物用鹽水(2×500 mL)洗滌，經硫酸鈉乾燥且在減壓下蒸發。粗物質藉由矽膠管柱層析，用己烷中0-100%乙酸乙酯溶離來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(4.02 g，887%) ESI-MS m/z計算值478.08777, 實驗值479.1 $(M+1)^+$；滯留時間: 0.7分鐘。

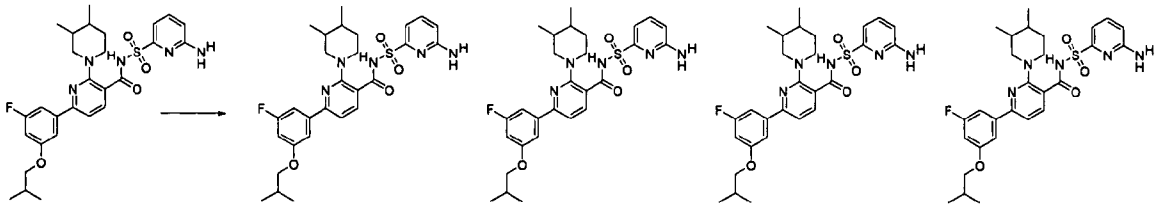
**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (化合物2178) (化合物2062) (化合物1863)



*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(100 mg，0.21 mmol)及氟基銫(156 mg，38.5 μL，1.04 mmol)之DMSO (600 μL)，接著$K_2CO_3$ (289 mg，2.09 mmol)及3,4-二甲基哌啶(118 mg，1.04 mmol)。反應混合物密封且加熱至150℃，隔夜，接著165℃，保持6小時。反應混合物過濾且接著直接藉由逆相HPLC-MS，使用10-99%乙腈-水+ 5 mM HCl作爲溶離劑純化，得到呈淡黃色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (化合物

2178) (化合物2062) (化合物1863) (86 mg，74%) ESI-MS m/z計算值555.23157, 實驗值556.2 $(M+1)^+$；滯留時間: 2.0分鐘。1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.50 - 7.41 (m, 3H), 7.22 (d, J = 7.3 Hz, 1H), 6.91 (d, J = 10.9 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.47 (s, 1H), 3.85 (d, J = 6.5 Hz, 2H), 3.51 (d, J = 8.5 Hz, 1H), 3.40 (d, J = 12.8 Hz, 1H), 3.13 (d, J = 11.8 Hz, 1H), 2.97 (d, J = 6.0 Hz, 1H), 2.06 (d, J = 9.3 Hz, 1H), 1.89 - 1.72 (m, 2H), 1.42 (s, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H

**步驟3**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (化合物2178) (化合物2062) (化合物1863) (異構體1-4，*RR*, *RS*, *SS*,或*SR*立體異構體)



使用超臨界流體層析，在ChiralCel OZ-H (250×10 mm) 5 μm管柱上，使用$CO_2$中25% MeOH:EtOH 50:50，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮，得到純化合物。SFC峰1：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (化合物2178) (化合物2062) (化合物1863) ESI-MS m/z計算值555.23157, 實驗值556.2 $(M+1)^+$；滯留時間: 2.02分鐘。SFC峰2 (*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2532) (化合物2178) (化合物2062) (化合物1863) ESI-MS m/z計算值555.23157, 實驗值556.2 $(M+1)^+$；滯留時間: 2.01分鐘。SFC峰3 *N*-[(6-胺基-2-吡啶基)磺醯基]-2-(3,4-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧

基-苯基)吡啶-3-甲醯胺(化合物2532) (化合物2178) (化合物2062) (化合物1863) ESI-MS m/z計算值555.23157, 實驗值556.2 $(M+1)^+$；滯留時間: 1.96分鐘。SFC 峰4 ESI-MS m/z計算值555.23157, 實驗值556.2 $(M+1)^+$；滯留時間: 1.96分鐘。1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 10.7 Hz, 1H), 7.45 (d, J = 11.6 Hz, 3H), 7.20 (d, J = 6.5 Hz, 1H), 6.90 (d, J = 10.7 Hz, 1H), 6.70 (d, J = 7.1 Hz, 1H), 6.44 (s, 2H), 3.84 (d, J = 6.5 Hz, 2H), 3.50 (s, 1H), 3.38 (s, 1H), 3.12 (d, J = 13.0 Hz, 1H), 2.96 (s, 1H), 2.08 - 1.98 (m, 1H), 1.80 (s, 2H), 1.41 - 1.37 (m, 1H), 1.30 - 1.22 (m, 1H), 1.00 (d, J = 6.7 Hz, 7H), 0.86 (d, J = 6.5 Hz, 4H), 0.76 (d, J = 6.6 Hz, 3H)。

以下化合物可使用本文所述之程序合成：

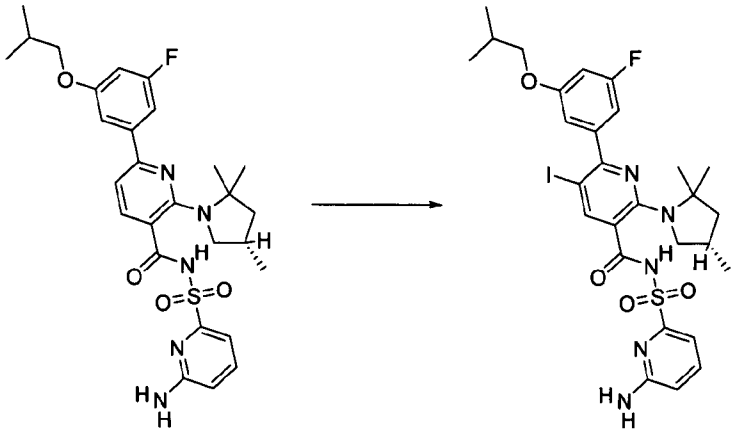
*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,5-二甲基-1-哌啶基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2451) (化合物1993) (化合物1864) (化合物1855) (異構體1-4，立體異構體*RR*, *RS*, *SS*, *SR*)，使用SFC ChiralCel OZ-H (250×10 mm)，5 μm管柱及溶離劑$CO_2$中25% MeOH (20 mM $NH_3$)

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(6-甲基-8-氮雜螺[3.4]辛-8-基)吡啶-3-甲醯胺(化合物2552) (異構體1，*R*或*S*立體異構體) (化合物2269) (異構體2，*R*或*S*立體異構體)，使用SFC ChiralPak IA (250×10 mm)，5 μm管柱及溶離劑$CO_2$中22% EtOH (0.1% TFA)

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2-乙基-2,4-二甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2213) (化合物2058) (化合物1817) (化合物1729) (異構體1-4,立體異構體s *RR*, *RS*, *SS*, *SR*)，使用SFC ChiralCel OZ-H (250×10 mm)，5 μm管柱及溶離劑$CO_2$中22% IPA:EtOH 50:50

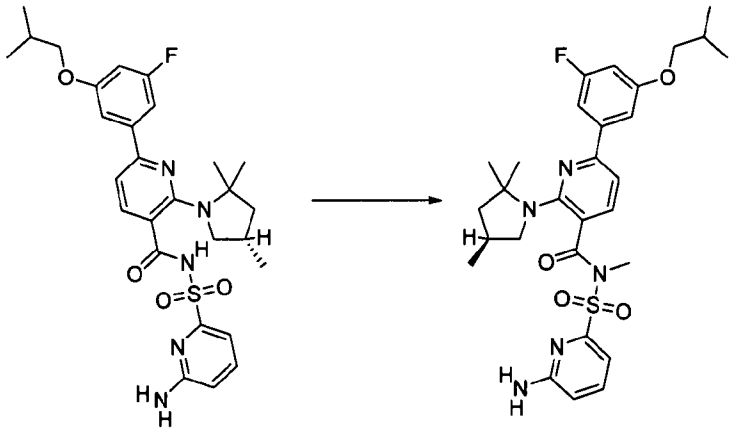
*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-4-(三氟甲基)吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2271) (異構體1，*R*或*S*立體異構體)，使用SFC ChiralCel OZ-H (250×10 mm)，5 μm管柱及溶離劑$CO_2$中25% MeOH:EtOH (50:50) 。

**製備130**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-5-碘-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2009)



*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(100 mg，0.18 mmol)溶於$CH_2Cl_2$ (700 μL)中且用1-碘吡咯啶-2,5-二酮(44 mg，0.19 mmol)處理。將反應混合物在40℃下攪拌30分鐘。揮發物在緩慢氮氣流下蒸發。剩餘殘餘物再溶於DMSO中，過濾且藉由逆相HPLC，使用Luna C18 (2)管柱(50 × 21.2 mm，5 μm粒徑)及經15.0分鐘30-99%移動相B之雙重梯度(移動相A =水(去離子化，無酸改質劑)，移動相B =乙腈)來純化，得到所需化合物。ESI-MS m/z計算值681.1282, 實驗值682.2 $(M+1)^+$；滯留時間: 2.26分鐘。

**製備131**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-*N*-甲基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2258)

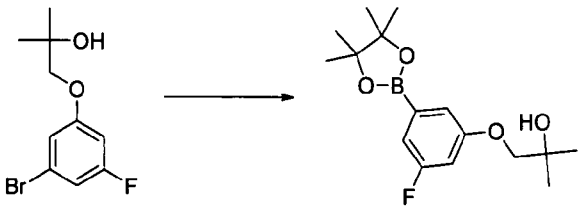


將含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(500 mg，0.90 mmol)之DMF (5 mL)用$Cs_2CO_3$ (352 mg，1.1 mmol)處理且將反應混合物在室溫下攪拌0.5小時，接著在冰浴中冷卻且用MeI (141 mg，61μL，1.0 mmol)處理。將反應混合物在室溫下攪拌隔夜。將懸浮液添加至水(25 ml)中，在室溫下攪拌1小時且懸浮液過濾且用水洗滌。固體藉由矽膠管柱層析，使用二氯甲烷作爲溶離劑來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-*N*-甲基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2258) (315 mg，61%)。ESI-MS m/z 570.0 $(M+1)^+$；滯留時間: 3.4分鐘；1H NMR (400 MHz, DMSO-d6) δ 7.67 - 7.54 (m, 2H), 7.49 (t, J = 1.8 Hz, 1H), 7.40 (dt, J = 10.2, 1.8 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.64 (s, 2H), 3.84 (d, J = 6.7 Hz, 2H), 3.43 (s, 3H), 2.82 (s, 1H), 2.64 (s, 1H), 2.34 - 2.22 (m, 1H), 2.05 (七重峰, J = 6.6 Hz, 1H), 1.91 (dd, J = 11.9, 5.7 Hz, 1H), 1.62 (d, J = 4.4 Hz, 6H), 1.46 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 6.3 Hz, 3H)

**製備132**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-[3-氟-5-(2-羥基-2-甲基-丙氧基)苯基]吡啶-3-甲醯胺(化合物1890)

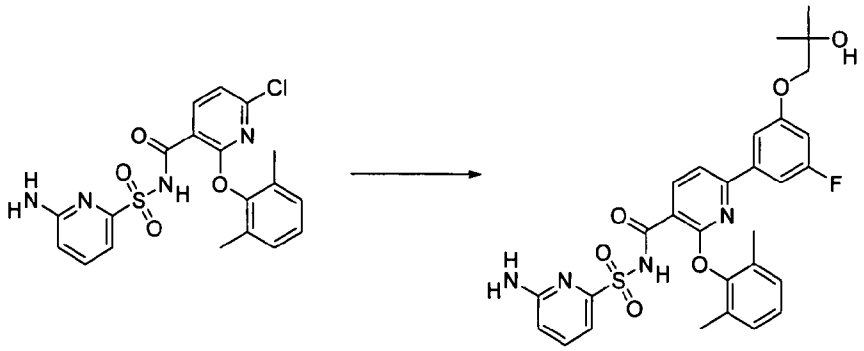
**步驟1**：1-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧

基]-2-甲基-丙-2-醇



在氮氣氛圍下向1-(3-溴-5-氟-苯氧基)-2-甲基-丙-2-醇(25.0 g，95 mmol)、雙(頻哪醇根基)二硼(26.5 g，105 mmol)及KOAc (18.7 g，190 mmol)於二噁烷(375 mL)中之懸浮液添加$Pd(dppf)Cl_2$.DCM (768 mg，1.0 mmol)且將反應混合物加熱至103℃，保持2小時，冷卻且在室溫下攪拌隔夜。反應混合物經Florisil過濾且在減壓下濃縮濾液，得到黃色油狀物。油狀物藉由矽膠管柱層析，用EtOAc/庚烷(10-20% EtOAc)溶離來純化，得到呈淺黃色液體狀之1-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-2-醇(12.6 g (86%))。

**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-[3-氟-5-(2-羥基-2-甲基-丙氧基)苯基]吡啶-3-甲醯胺(化合物1890)



*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-(2,6-二甲基苯氧基)吡啶-3-甲醯胺(140 mg，0.32 mmol)、1-[3-氟-5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊-2-基)苯氧基]-2-甲基-丙-2-醇(215 mg，0.69 mmol)、碳酸鉀(647 μL 2 M，1.29 mmol)及1,3-雙(2,6-二異丙基苯基)-4,5-二氫咪唑3-氯吡啶二氯鈀(PEPPSI-IPr) (11 mg，0.02 mmol)組合於乙醇(3 mL)中且將反應混合物在80℃下加熱21小時。反應混合物冷卻至40℃，添加冰AcOH (0.20 mL)，過濾且濾液在減壓下蒸發。殘餘物溶於DMSO (3

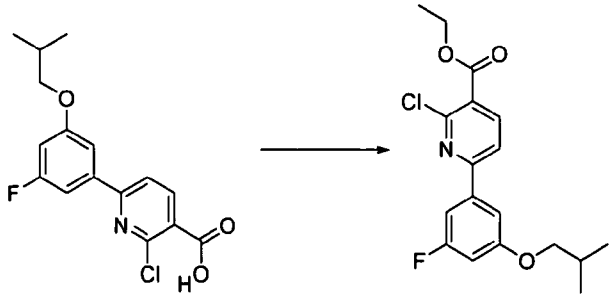
mL)中，過濾且使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經30.0分鐘10-99%移動相B之雙重梯度(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-[3-氟-5-(2-羥基-2-甲基-丙氧基)苯基]吡啶-3-甲醯胺(化合物1890) (HCl鹽) (80 mg，40 %) 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.21 - 7.14 (m, 4H), 7.14 - 7.07 (m, 1H), 6.84 (dt, J = 10.6, 2.3 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 4.61 (s, 1H), 3.61 (s, 2H), 2.07 (s, 1H), 2.06 (s, 6H), 1.19 (s, 6H)。ESI-MS m/z計算值580.1792, 實驗值581.2 $(M+1)^+$；滯留時間: 1.76分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,6-二甲基苯氧基)-6-[3-氟-5-(3-羥基-2-甲基-丙氧基)苯基]吡啶-3-甲醯胺(化合物1797)

**製備133**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物2081) (異構體1，*R*或*S*立體異構體) (化合物2039) (異構體2，*R*或*S*立體異構體)

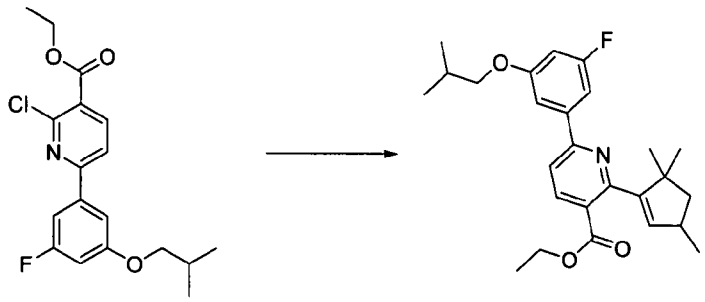
**步驟1**：2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸乙酯



向2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(1.3 g，4.0 mmol)於乙醇(40 mL)中之溶液中緩慢添加硫醯氯(1.0 g，584 μL，8.0 mmol)且將反應混合物在回流下攪拌六小時。在減壓下蒸發溶劑，得到呈無色固體狀之2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸乙酯(1.3 g，

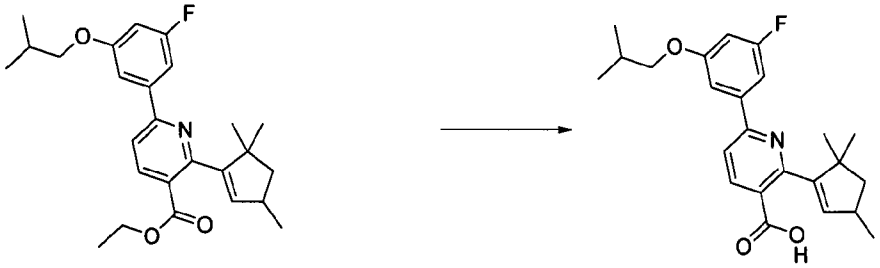
95%)。

**步驟2**：6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲酸乙酯



將2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸乙酯(700 mg，1.99 mmol)、4,4,5,5-四甲基-2-(3,5,5-三甲基環戊烯-1-基)-1,3,2-二氧雜硼雜環戊烷(517 mg，2.19 mmol)、二氯化1,1'-雙(二苯基膦基)二茂鐵-鈀(437 mg，0.60 mmol)及$Na_2CO_3$ (633 mg，5.97 mmol)於二噁烷(9 mL)及水(1 mL)中之混合物在密封容器中在150℃下加熱16小時。反應混合物過濾，且固體用EtOAc洗滌。合併之有機物蒸發，且殘餘物藉由矽膠管柱層析，使用100%己烷至己烷中20% EtOAc之梯度來純化，得到呈白色固體狀之6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲酸乙酯(97 mg，11%)。ESI-MS m/z計算值425.23663，實驗值426.2 $(M+1)^+$；滯留時間: 2.4分鐘。

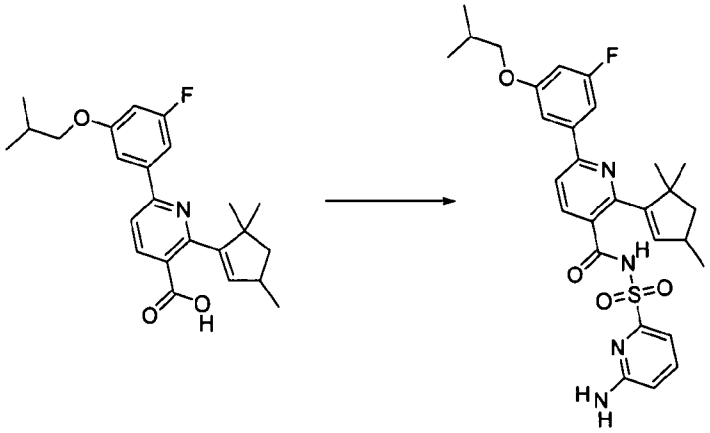
**步驟3**：6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲酸



向6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲酸乙酯(92 mg，0.2 mmol)於THF (520 μL)中之溶液中添加NaOH (650 μL 1 M，0.6 mmol)且接著MeOH (520 μL)且將反應混合物加熱至

50℃，保持4小時。反應混合物用1 M HCl (3.0 mL)中和且用EtOAc (10 mL×2)萃取。合併之萃取物經$Na_2SO_4$乾燥且在減壓下蒸發，得到呈淡黃色固體之6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲酸(77 mg，90%)。ESI-MS m/z計算值397.20532, 實驗值398.2 $(M+1)^+$；滯留時間: 1.92分鐘；1H NMR (400 MHz, DMSO) δ 13.11 (s, 1H), 7.98 (s, 2H), 7.56 (s, 1H), 7.49 (d, J = 9.9 Hz, 1H), 6.93 (d, J = 10.7 Hz, 1H), 5.67 (s, 1H), 3.85 (d, J = 6.6 Hz, 2H), 2.87 (dd, J = 14.1, 7.0 Hz, 1H), 2.13 - 1.98 (m, 2H), 1.46 - 1.38 (m, 4H), 1.24 (s, 4H), 1.08 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H)。

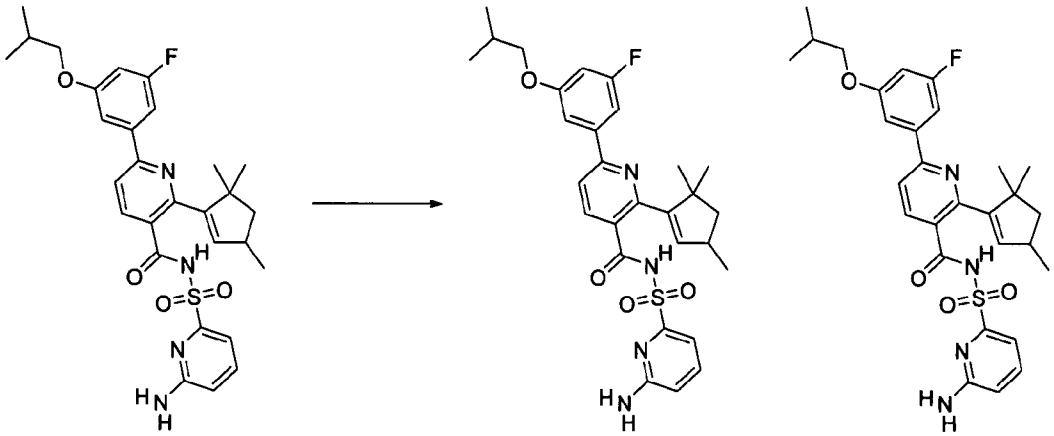
**步驟4**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物2081) (化合物2039)



在氮氣氛圍下6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲酸(74 mg，0.19 mmol)及CDI (45 mg，0.28 mmol)混合於DMF (740 μL)中且將反應混合物加熱至45℃，保持45分鐘。在另一小瓶中，6-胺基吡啶-2-磺醯胺(80.62 mg，0.4655 mmol)及NaH (18 mg，0.46 mmol)緩慢混合於DMF (370.0 μL)中且將混合物加熱至45℃，保持45分鐘。將6-胺基吡啶-2-磺醯胺反應混合物添加至活化酸中且將反應混合物在50℃下加熱16小時。反應混合物過濾且接著直接藉由逆相製備型層析，利用C18管柱及HPLC-MS法，10-99% 移動相B (移動相A =水(去離子化，無酸改質劑)，移動相B =乙腈)來純化，得到呈灰

白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物2081) (化合物2039) (64 mg，62%)，ESI-MS m/z計算值552.22064，實驗值553.4 $(M+1)^+$；滯留時間: 2.25分鐘；1H NMR (400 MHz, DMSO) δ 12.55 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.68 - 7.60 (m, 1H), 7.56 (s, 1H), 7.49 (d, J = 9.6 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.01 - 6.84 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.55 (s, 2H), 5.62 (d, J = 1.7 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 2.66 (ddd, J = 14.3, 7.4, 1.8 Hz, 1H), 2.03 (dd, J = 13.2, 6.6 Hz, 1H), 1.95 (dd, J = 12.1, 7.5 Hz, 1H), 1.38 - 1.28 (m, 4H), 1.25 (s, 3H), 0.99 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.9 Hz, 3H)。

**步驟5**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物2081) (異構體1，*R*或*S*立體異構體)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物2039) (異構體2，*R*或*S*立體異構體)

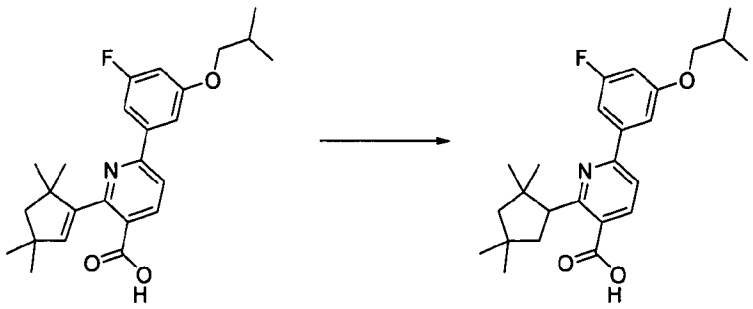


使用超臨界流體層析，在ChiralCel AD-H (250×10 mm) 5 μm管柱上，使用$CO_2$中20% EtOH (0.1% TFA)，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮，得到純化合物。SFC峰1：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲

基環戊烯-1-基)吡啶-3-甲醯胺(化合物2081) (異構體1，*R*或*S*立體異構體) ESI-MS m/z計算值552.22064, 實驗值553.2 $(M+1)^+$；滯留時間: 2.26分鐘。SFC峰2 *N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3,5,5-三甲基環戊烯-1-基)吡啶-3-甲醯胺(化合物2039) (異構體2，*R*或*S*立體異構體) ESI-MS m/z計算值552.22064, 實驗值553.2 $(M+1)^+$；滯留時間: 2.26分鐘。

**製備134**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (異構體1，*R*或*S*立體異構體) (化合物2374) (異構體2，*R*或*S*立體異構體)

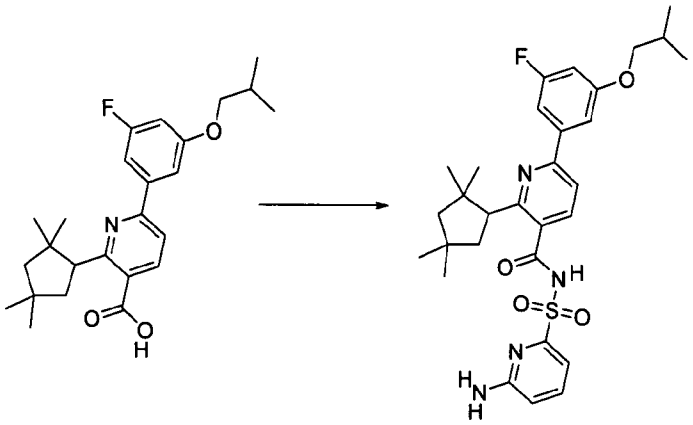
**步驟1**：6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲酸




將6-(3-氟-5-異丁氧基-苯基)-2-(3,3,5,5-四甲基環戊烯-1-基)吡啶-3-甲酸(389 mg，0.94 mmol) (以類似於製備133中所述之方式製備)、氫氧化鈀(80 mg，0.57 mmol)及甲酸銨(1.19 g，18.91 mmol)於乙醇(10 mL)中之混合物組合於微波小瓶中且加熱至85℃，保持3小時。反應混合物冷卻至室溫且添加另一等分試樣甲酸銨(1.19 g，18.91 mmol)及氫氧化鈀(80 mg，0.57 mmol)，且在微波條件下在85℃下照射4小時。反應混合物經矽藻土過濾，用甲醇洗滌且濾液在減壓下濃縮，接著用1N HCl稀釋且用乙酸乙酯(2次)洗滌。合併之有機層經硫酸鈉乾燥，過濾且在減壓下濃縮成透明油狀物。油狀物藉由矽膠管柱層析，使用100%二氯甲烷至20%甲醇之二氯甲烷溶液，接著乙酸乙酯中20%

甲醇之梯度來純化，得到呈白色固體狀之6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲酸(52 mg，13%)。

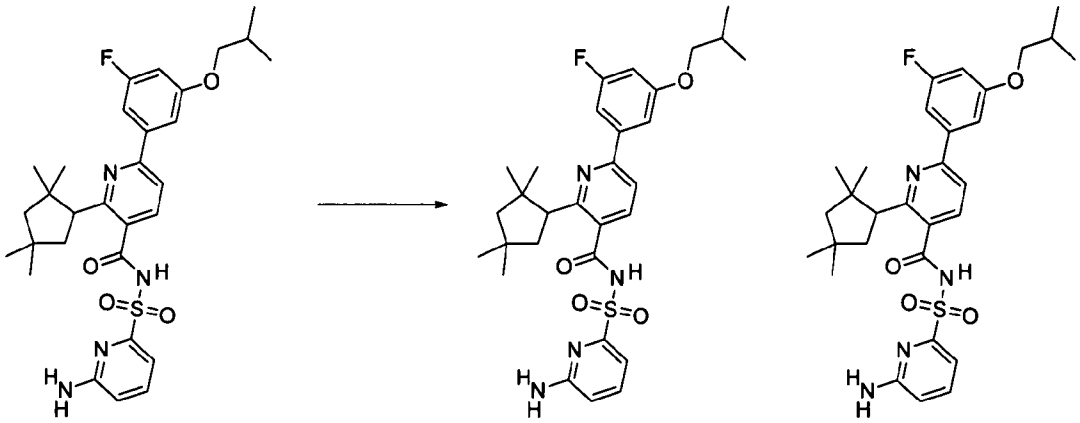
**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (化合物2374)



將6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲酸(52 mg，0.13 mmol)及羰基二咪唑(31 mg，0.19 mmol)於二甲基甲醯胺(0.5 mL)中之溶液在45℃下攪拌90分鐘。將6-胺基吡啶-2-磺醯胺(44 mg，0.25 mmol)及氫化鈉(10 mg，0.25 mmol)於二甲基甲醯胺(0.5 mL)中之另一溶液在45℃下攪拌45分鐘，接著添加至活化酸且將所得混合物在45℃下攪拌2小時。反應混合物過濾且使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度 (移動相A = $H_2O$ (5 mM HCl)，移動相B = 乙腈)純化，得到呈灰白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (化合物2374) (HCl鹽) (51 mg，67%)。1H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 7.91 (dd, J = 20.4, 8.2 Hz, 2H), 7.66 (t, J = 7.9 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J = 9.8 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 6.93 (d, J = 10.7 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 3.86 (d, J = 6.6 Hz, 2H), 3.58 (dd, J = 12.2, 6.5 Hz, 1H), 2.55 (d, J = 12.3 Hz, 1H), 2.06 (dt, J = 13.2, 6.6 Hz, 1H), 1.63 (dd, J = 12.4, 6.4 Hz, 1H),

1.50 (d, J = 13.0 Hz, 1H), 1.39 (d, J = 12.9 Hz, 1H), 1.15 (s, 3H), 1.08 - 0.93 (m, 9H), 0.80 (s, 3H), 0.69 (s, 3H)。ESI-MS m/z計算值568.25195, 實驗值569.3 $(M+1)^+$；滯留時間: 2.4分鐘。

**步驟3**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (異構體1，*R*或*S*立體異構體)及*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2374) (異構體2，*R*或*S*立體異構體)

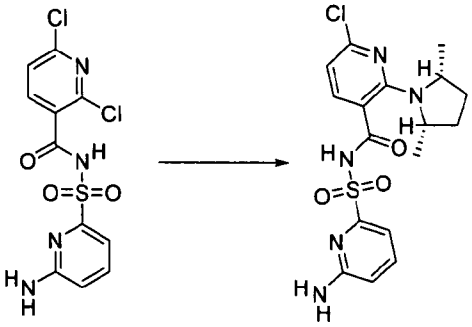


使用超臨界流體層析，在Chiralpak IC (250×10 mm) 5 μm管柱上，使用$CO_2$中17% EtOH (DeNat) + 0.1% TFA，以10.0 mL/min之流速，分離立體異構體。分開對映異構體分開濃縮，得到純化合物。SFC峰1：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (化合物2374) ESI-MS m/z計算值568.25195, 實驗值569.3 $(M+1)^+$；滯留時間: 2.4分鐘。1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 8.3, 7.4 Hz, 1H), 7.54 (s, 1H), 7.46 - 7.38 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.75 (dt, J = 10.5, 2.3 Hz, 1H), 3.82 (d, J = 6.5 Hz, 2H), 3.67 (dd, J = 12.3, 6.4 Hz, 1H), 2.66 (t, J = 12.5 Hz, 1H), 2.11 (dt, J = 13.3, 6.7 Hz, 1H), 1.69 (dd, J = 12.6, 6.3 Hz, 1H), 1.49 (dd, J = 38.8, 13.1 Hz, 2H), 1.18 (d, J = 5.6 Hz, 3H), 1.10 - 1.00 (m, 9H),

0.81 (s, 3H), 0.75 (s, 3H)。SFC峰2：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(2,2,4,4-四甲基環戊烯基)吡啶-3-甲醯胺(化合物2492) (化合物2374)。ESI-MS m/z計算值568.25195, 實驗值569.3 $(M+1)^+$；滯留時間: 2.4分鐘。1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 8.3, 7.4 Hz, 1H), 7.54 (s, 1H), 7.46 - 7.38 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.75 (dt, J = 10.5, 2.3 Hz, 1H), 3.82 (d, J = 6.5 Hz, 2H), 3.67 (dd, J = 12.3, 6.4 Hz, 1H), 2.66 (t, J = 12.5 Hz, 1H), 2.11 (dt, J = 13.3, 6.7 Hz, 1H), 1.69 (dd, J = 12.6, 6.3 Hz, 1H), 1.49 (dd, J = 38.8, 13.1 Hz, 2H), 1.18 (d, J = 5.6 Hz, 3H), 1.10 - 1.00 (m, 9H), 0.81 (s, 3H), 0.75 (s, 3H)。

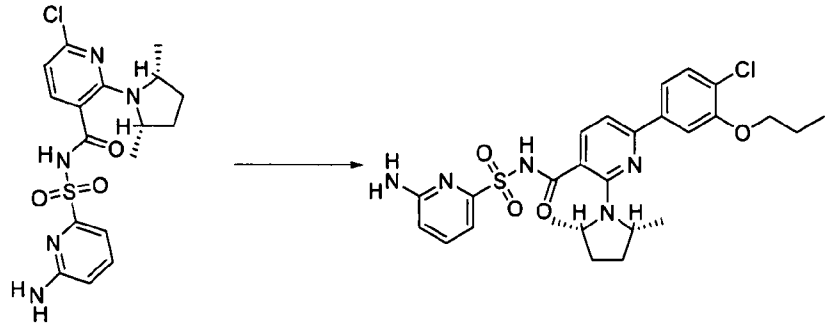
**製備135**：6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-*N*-[[6-(戊-4-炔醯基胺基)-2-吡啶基]磺醯基]吡啶-3-甲醯胺(化合物2540)

**步驟1**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺



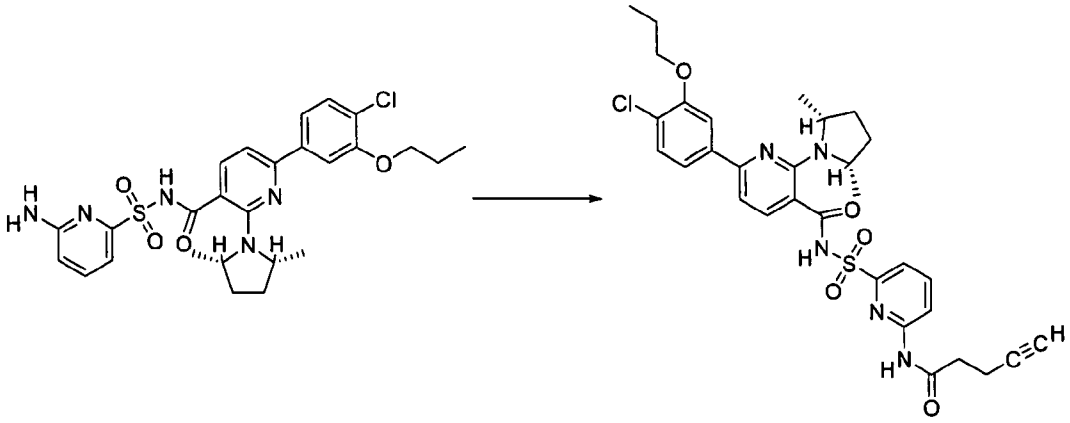
將含*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-二氯-吡啶-3-甲醯胺(2.0 g，5.8 mmol)及(2R,5S)-2,5-二甲基吡咯啶(0.7 g，7.2 mmol)之DMSO (10 mL)用$K_2CO_3$ (2.4 g，17 mmol)處理且在120℃下在攪拌下加熱3小時。反應混合物冷卻且小心添加至HCl (2.881 mL 12 M，35 mmol)與水(50 mL)之冷混合物，形成白色泡沫。將反應混合物在室溫下攪拌30分鐘，過濾且白色固體用IPA (100 mL)濕磨，得到所需化合物。

**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物773)



*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(2S,5R)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(62 mg，0.15 mmol)、(4-氯-3-丙氧基-苯基)硼酸(48 mg，0.23 mmol)、肆(三苯基膦)鈀(0) (10 mg，0.009 mmol)、碳酸鉀(300 μL，2 M, 0.40 mmol)及DMF (1.7 mL)在100℃下加熱隔夜。反應混合物過濾且藉由逆相HPLC，利用含於5 mM HCl水溶液中之1-99%乙腈之梯度來純化。ESI-MS m/z 544.3 $(M+1)^+$；滯留時間: 1.7分鐘；1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 7.83 (d, J = 1.9 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70 - 7.61 (m, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.23 (dd, J = 7.3, 0.8 Hz, 1H), 6.72 (d, 1H), 6.48 (s, 2H), 4.13 (t, J = 6.5 Hz, 2H), 4.09 - 3.97 (m, 2H), 2.05 - 1.91 (m, 2H), 1.81 (h, J = 7.2 Hz, 2H), 1.74 - 1.61 (m, 2H), 1.10 (d, J = 6.2 Hz, 6H), 1.03 (t, J = 7.4 Hz, 3H)。

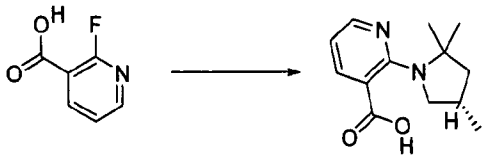
**步驟3**：6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]-*N*-[[6-(戊-4-炔醯基胺基)-2-吡啶基]磺醯基]吡啶-3-甲醯胺(化合物2540)



在0℃下向含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(4-氯-3-丙氧基-苯基)-2-[(2R,5S)-2,5-二甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物773) (10 mg，0.02 mmol)之DCM (2 mL)中添加三乙胺(11 mg，15 μL，0.11 mmol)及戊-4-炔醯氯(4 mg，0.04 mmol)。接著反應混合物在0℃下攪拌5分鐘，接著在室溫下攪拌2小時。反應混合物在減壓下蒸發且粗混合物藉由逆相HPLC，使用水中10-100% ACN (TFA改質劑)來純化。鹽用SPE-$CO_3H$濾筒中和，用MeOH/DCM溶離，得到所需化合物。ESI-MS m/z 624.3 $(M+1)^+$；滯留時間: 0.9分鐘；1H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.04 (t, J = 7.9 Hz, 1H), 7.98 - 7.89 (m, 2H), 7.56 (dd, J = 8.2, 1.9 Hz, 1H), 7.51 (d, J = 2.4 Hz, 2H), 4.21 (d, J = 6.1 Hz, 2H), 4.10 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 6.9 Hz, 2H), 2.64 - 2.47 (m, 4H), 2.11 (d, J = 2.8 Hz, 2H), 2.00 - 1.85 (m, 4H), 1.34 (d, J = 6.6 Hz, 6H), 1.25 (s, 6H), 1.11 (t, J = 7.4 Hz, 5H), 0.93 - 0.79 (m, 3H)。

**製備136**：*N*-[4-[3-(4-氯苯基)丙基]哌嗪-1-基]磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2141)

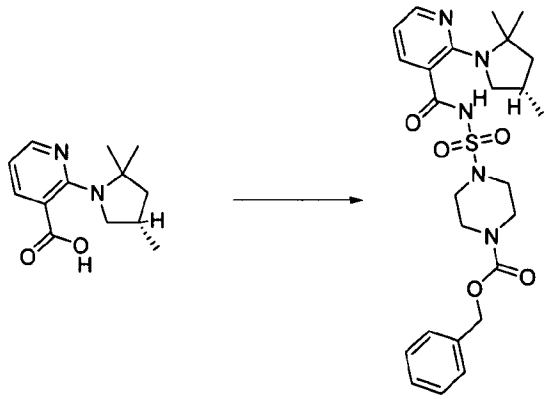
**步驟1**：2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲酸



將2-氟吡啶-3-甲酸(71 mg，0.5 mmol)、(4*S*)-2,2,4-三甲基吡咯啶

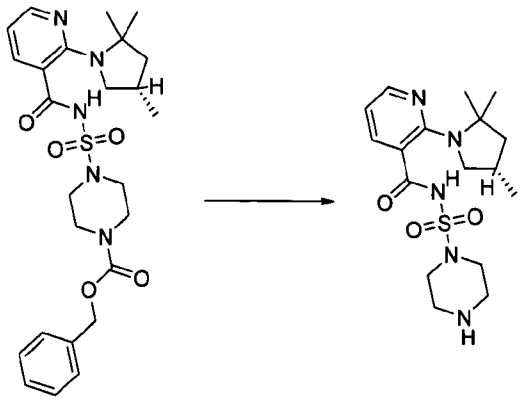
(HCl 鹽) (150 mg，1.0 mmol)、碳酸鉀(207 mg，1.5 mmol)及氟化銫(152 mg，1.0 mmol)於DMSO (500 μL)中之混合物在130℃下攪拌六小時。反應混合物用水稀釋，用1 M HCl調至pH 4，且用乙酸乙酯萃取。合併之萃取物用鹽水洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物使用逆相HPLC-MS，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-70%移動相B之雙重梯度(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到所需化合物。

**步驟2**：4-[[2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-羰基]胺磺醯基]哌嗪-1-甲酸苯甲酯



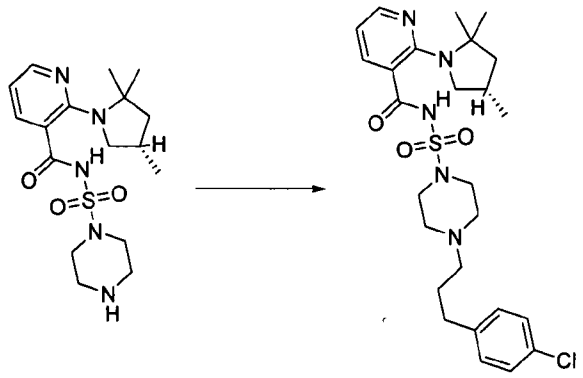
將(S)-2-(2,2,4-三甲基吡咯啶-1-基)菸鹼酸(117 mg，0.5 mmol)及異氰酸氯磺醯酯(85 mg，52 μL，0.6 mmol)於二氯甲烷(3 mL)中之溶液攪拌30分鐘，且緩慢添加至哌嗪-1-甲酸苯甲酯(110 mg，96μL，0.5 mmol)及吡啶(59 mg，60 μL，0.8 mmol)於二氯甲烷(2 mL)中之溶液中。將反應混合物攪拌2小時，在減壓下蒸發且藉由矽膠管柱層析，用0-5%甲醇之二氯甲烷溶液作爲溶離劑來純化，得到呈無色油狀之(S)-4-(*N*-(2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯基)胺磺醯基)哌嗪-1-甲酸苯甲酯(35 mg，13%)。ESI-MS m/z 516.6 $(M+1)^+$；滯留時間: 1.65分鐘。

**步驟3**：*N*-哌嗪-1-基磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



將(S)-4-(*N*-(2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯基)胺磺醯基)哌嗪-1-甲酸苯甲酯(0.22 g，0.43 mmol)及鈀/碳(20 mg，0.02 mmol)於甲醇(2 mL)中之混合物在氫氣氛圍下攪拌16小時。反應混合物過濾且蒸發，得到呈無色固體狀之(S)-*N*-(哌嗪-1-基磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯胺(0.13 g，80%)。

**步驟4**：*N*-[4-[3-(4-氯苯基)丙基]哌嗪-1-基]磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2141)



將(S)-*N*-(哌嗪-1-基磺醯基)-2-(2,2,4-三甲基吡咯啶-1-基)菸鹼醯胺(30 mg，0.08 mmol)及3-(4-氯苯基)丙醛(14 mg，0.08 mmol)於1,2-二氯乙烷(800 μL)中之溶液攪拌五分鐘，且添加三乙醯氧基硼氫化鈉(33 mg，0.16 mmol)。將反應混合物攪拌16小時，用甲醇稀釋，過濾，且使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到所需化合物。ESI-MS m/z 534.6 $(M+1)^+$；滯留時間: 1.23分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(3*R*)-3-[(4-第三丁氧基苯基)甲基胺基]吡咯啶-1-基]磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2698)，

*N*-[[3-[(4-第三丁氧基苯基)甲基胺基]-1-哌啶基]磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2697)，

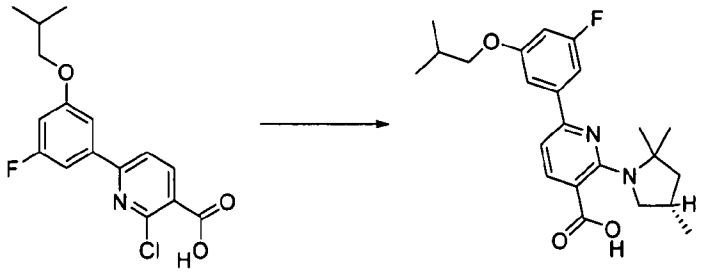
*N*-[(3*R*)-3-[[4-氟-3-(三氟甲氧基)苯基]甲基胺基]吡咯啶-1-基]磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2681)，

*N*-[(3*R*)-3-[3-(4-氯苯基)丙基胺基]吡咯啶-1-基]磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2717)及

*N*-[(3*R*)-3-[(2,4-二氯苯基)甲基胺基]吡咯啶-1-基]磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2693)

**製備137**：6-(3-氟-5-異丁氧基-苯基)-*N*-(3-哌啶基磺醯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2655)

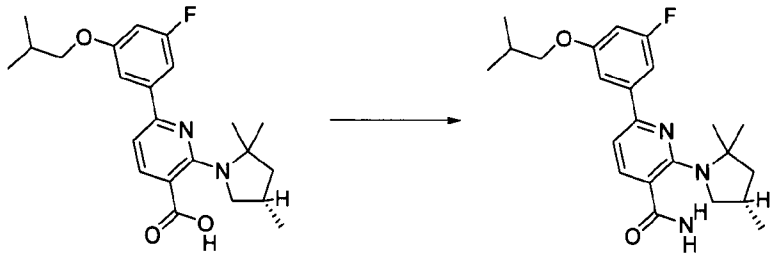
**步驟1**：6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲酸



將2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(1.5 g，3.6 mmol)、(4*S*)-2,2,4-三甲基吡咯啶(HCl鹽) (0.8 g，5.8 mmol)、$K_2CO_3$ (1.6 g，11.6 mmol)及CsF (1.1 g，7.5 mmol)於DMSO (5 mL)中之混合物在130℃下攪拌2天。反應混合物用水稀釋，用 1 M HCl調至pH 4，且用乙酸乙酯萃取。合併之萃取物用鹽水洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物藉由矽膠層析，用0-6%甲醇之二氯甲烷溶液純化，得到呈棕褐色泡沫狀之6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三

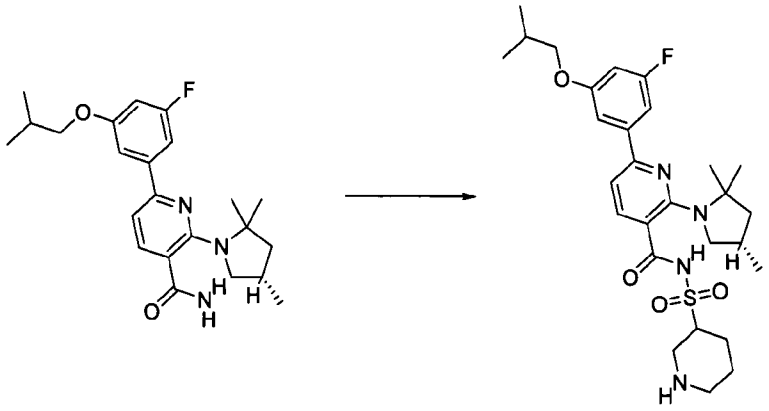
甲基吡咯啶-1-基]吡啶-3-甲酸(1.2 g，82%)。ESI-MS m/z計算值400.21622，實驗值401.0 $(M+1)^+$；滯留時間: 1.92分鐘 (3 min)。

**步驟2**：6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



將6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲酸(120 mg，0.3 mmol)及CDI (73 mg，0.5 mmol)於DMF (1.5 mL)中之溶液在45℃下攪拌30分鐘，且添加氫氧化銨(525 μL 30 %w/v，4.5 mmol)。將反應混合物在45℃下攪拌3天，用水稀釋，且用乙酸乙酯萃取。合併之萃取物用鹽水洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物藉由矽膠管柱層析，用0-5%甲醇之二氯甲烷溶液來純化，得到6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(82 mg，68%)。ESI-MS m/z 400.5 $(M+1)^+$；滯留時間: 1.78分鐘 (3 min)。

**步驟3**：6-(3-氟-5-異丁氧基-苯基)-*N*-(3-哌啶基磺醯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2655)



將6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(32 mg，0.1 mmol)及NaH (5 mg，0.1 mmol)於DMF (800

μL)中之溶液攪拌30分鐘，且添加3-氯磺醯基哌啶-1-甲酸苯甲酯(51 mg，0.2 mmol)。將反應混合物攪拌16小時。過濾反應物且使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99% 移動相B之雙重梯度(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化。將含中間物及鈀(10 mg，0.01 mmol) (10%於碳上)之MeOH在氫氣氛圍下攪拌17小時。過濾反應物且使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到所需化合物。ESI-MS m/z 547.6 $(M+1)^+$；滯留時間: 1.65分鐘 (3 min)

以下化合物可使用本文所述之程序合成：

6-(3-氟-5-異丁氧基-苯基)-*N*-吡咯啶-3-基磺醯基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2042)，

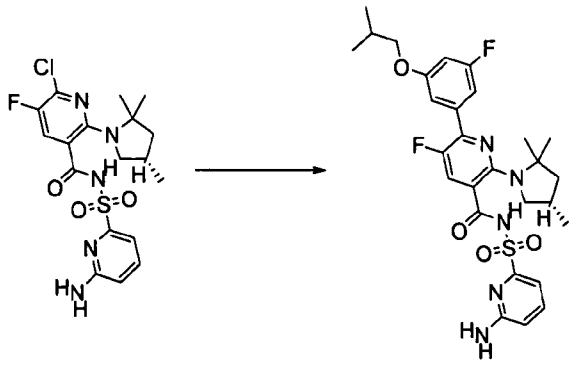
*N*-環戊基磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2113)，

6-(3-氟-5-異丁氧基-苯基)-*N*-[[(3*R*)-3-哌啶基]胺磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2677)，

6-(3-氟-5-異丁氧基-苯基)-*N*-(3-吡啶基胺磺醯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1448)及

6-(3-氟-5-異丁氧基-苯基)-*N*-[(2-甲氧基-3-吡啶基)胺磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1359)。

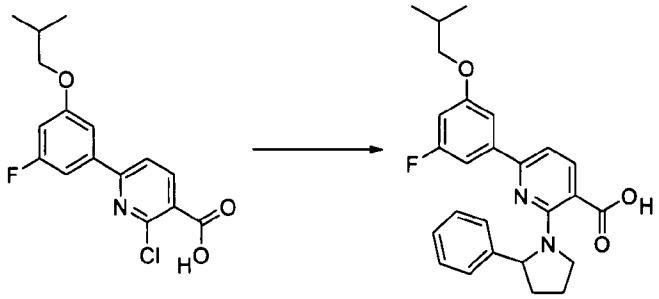
**製備138**：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氟-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2473)



(3-氟-5-異丁氧基-苯基)硼酸(5 mg，0.02 mmol), *N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-5-氟-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(10 mg，0.02 mmol)、1,3-雙(2,6-二異丙基苯基)-4,5-二氫咪唑3-氯吡啶二氯鈀(3 mg，0.005 mmol)及$K_2CO_3$ (3 mg，0.02 mmol)組合於*N*-丙醇(0.5 mL)中。在氮氣氛圍下將反應混合物加熱至90℃，保持16小時。過濾反應混合物且藉由逆相HPLC，使用經15分鐘水中1-99% ACN (0.05% HCl改質劑)來純化，得到呈淺色固體狀之所需化合物。1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 7.73 (d, J = 11.2 Hz, 1H), 7.36 (s, 1H), 7.24 (dd, J = 15.0, 8.6 Hz, 2H), 6.96 (dt, J = 10.9, 2.5 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.53 (s, 1H), 3.82 (d, J = 6.6 Hz, 2H), 2.59 (p, J = 10.2 Hz, 2H), 2.22 (s, 1H), 2.07 - 1.98 (m, 1H), 1.87 (dd, J = 12.0, 5.7 Hz, 1H), 1.54 (d, J = 6.6 Hz, 6H), 1.41 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H)。1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 7.73 (d, J = 11.2 Hz, 1H), 7.36 (s, 1H), 7.24 (dd, J = 15.0, 8.6 Hz, 2H), 6.96 (dt, J = 10.9, 2.5 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.53 (s, 1H), 3.82 (d, J = 6.6 Hz, 2H), 2.59 (p, J = 10.2 Hz, 2H), 2.22 (s, 1H), 2.07 - 1.98 (m, 1H), 1.87 (dd, J = 12.0, 5.7 Hz, 1H), 1.54 (d, J = 6.6 Hz, 6H), 1.41 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H)。

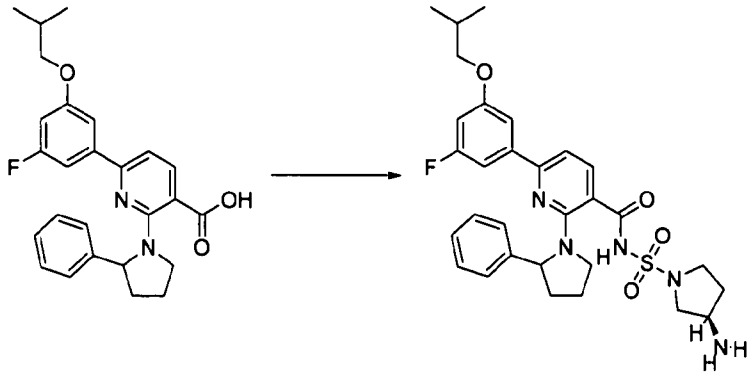
**製備139**：*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2477)

**步驟1**：6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲酸



將2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(227 mg，0.7 mmol)、2-苯基吡咯啶(206 mg，1.4 mmol)、CsF (213 mg，1.4 mmol)及$K_2CO_3$ (194 mg，1.4 mmol)於DMSO ( 3.5 mL)中之混合物在120℃下攪拌16小時。反應混合物用水稀釋，用 1 M HCl調至pH 4，且用乙酸乙酯(2次)萃取。合併之萃取物用鹽水洗滌，經硫酸鈉乾燥，且在減壓下蒸發。殘餘物藉由矽膠管柱層析，用0-5%甲醇之二氯甲烷溶液來純化，得到6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲酸(190 mg，62%)。ESI-MS m/z 435.5 $(M+1)^+$；滯留時間: 0.9分鐘(3 min)。

**步驟2**：*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2477)



將6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲酸(43 mg，0.1 mmol)及異氰酸氯磺醯酯(11 μL，0.1 mmol)於二氯甲烷中之溶液攪拌30分鐘，且添加*N*-[(3*R*)-吡咯啶-3-基]胺基甲酸第三丁酯(27 mg，0.2 mmol)及三乙胺(21 μL，0.2 mmol)。將反應混合物攪拌16

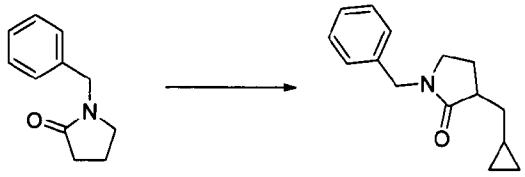
小時，且添加HCl (4M於二噁烷中之溶液) ( 200 μL，0.8 mmol)。攪拌4小時後，在減壓下移除溶劑，且殘餘物使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-6-(3-氟-5-異丁氧基-苯基)-2-(2-苯基吡咯啶-1-基)吡啶-3-甲醯胺(化合物2477) (9 mg，16%)。ESI-MS m/z 582.6 $(M+1)^+$；滯留時間: 1.82分鐘 (3 min)。

以下化合物 可使用本文所述之程序合成：

*N*-[(3*R*)-3-胺基吡咯啶-1-基]磺醯基-2-(2-苯甲基-2-甲基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2325)

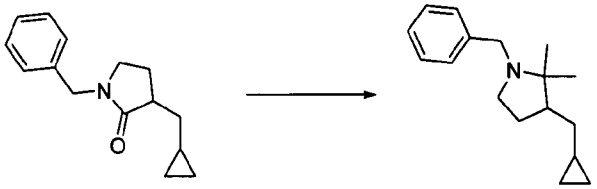
**製備140**：3-(環丙基甲基)-2,2-二甲基-吡咯啶

**步驟1**：1-苯甲基-3-(環丙基甲基)吡咯啶-2-酮



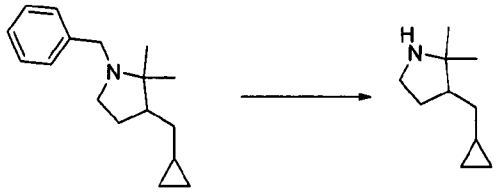
1-苯甲基吡咯啶-2-酮(5.0 g，28.6 mmol)溶於THF (100 mL)中且冷卻至-78℃。在-78℃下逐滴添加n-BuLi (2.5M，13.7 mL，34.3 mmol)且將反應混合物在-78℃下攪拌30分鐘。添加(溴-甲基)環丙烷(4.6 g，34.3 mmol)且在-78℃下繼續攪拌30分鐘。使反應混合物緩慢達至室溫，隔夜。混合物用飽和$NH_4Cl$水溶液淬滅且用EtOAc (2×)萃取。合併之有機層用鹽水洗滌，經$Na_2SO_4$乾燥且在減壓下濃縮。殘餘物藉由矽膠管柱層析(庚烷/EtOAc 2:1)來純化，得到呈無色油狀之1-苯甲基-3-(環丙基甲基)-吡咯啶-2-酮(3.9 g，60%)。1H NMR ($CDCl_3$, 300 MHz): 0.05 (m, 2H); 0.43 (m, 2H); 0.74 (m,1H); 1.22 (m, 1H); 1.68 (m, 1H); 1.76 (m, 1H); 2.21 (m, 1H); 2.55 (m, 1H); 3.08 (m, 2H); 4.43 (q, 2H); 7.24 (m, 5H)。

**步驟2**：1-苯甲基-3-(環丙基甲基)-2,2-二甲基-吡咯啶



在-10℃中將$ZrCl_4$ (3.96 g，17.0 mmol)添加至THF (100 mL)中且將反應混合物攪拌30分鐘。添加1-苯甲基-3-(環丙基甲基)吡咯啶-2-酮(3.95 g，17.0 mmol)於THF (10 mL)中之溶液。將反應混合物攪拌10分鐘，接著在0℃下逐滴添加MeMgBr (3.0 M，34 mL，102 mmol)。使反應混合物達至室溫，隔夜。在0℃下其用30% NaOH水溶液(20 mL)淬滅且攪拌10分鐘。添加水(100 mL)且反應混合物用$CH_2Cl_2$ (2×)萃取。合併之有機層用鹽水洗滌，經$Na_2SO_4$乾燥且在減壓下濃縮。殘餘物藉由矽膠管柱層析(庚烷/EtOAc 4:1)來純化，得到呈無色油狀之1-苯甲基-3-(環丙基甲基)-2,2-二甲基吡咯啶(2.0 g，48%)。1H NMR ($CDCl_3$, 300 MHz): -0.03 (m, 1H); 0.07 (m, 1H); 0.42 (m, 2H); 0.66 (m, 1H); 0.76 (s, 3H); 1.12 (s, 3H); 1.19 (m, 2H); 1.39 (m, 1H); 1.90 (m, 1H); 2.03 (m, 1H); 2.32 (m, 1H); 2.85 (m, 1H); 3.20 (d, 1H); 3.87 (d, 1H); 7.25 (m, 5H)。

**步驟3**：3-(環丙基甲基)-2,2-二甲基-吡咯啶

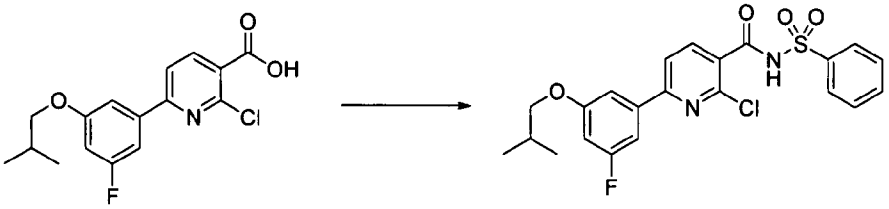


添加溶於MeOH (100 mL)及濃HCl (5 mL)中之1-苯甲基-3-(環丙基甲基)-2,2-二甲基吡咯啶(2.0 g，8.2 mmol)。添加Pd/C (400 mg)且將反應混合物在5巴$H_2$下攪拌週末。反應混合物經矽藻土過濾且在減壓下濃縮，得到呈灰白色固體狀之3-(環丙基甲基)-2,2-二甲基-吡咯啶鹽酸鹽(1.3 g，84%)。1H NMR ($CD_3OD$, 300 MHz): 0.07 (m, 1H); 0.13 (m,

1H); 0.47 (m, 2H); 0.72 (m, 1H); 1.17 (s, 3H); 1.19 (m, 1H); 1.34 (m, 1H); 1.43 (s, 3H); 1.83 (m, 1H); 2.01 (m, 1H); 2.38 (m, 1H); 3.26 (m, 2H)。ESI-MS m/z計算值153.15175, 實驗值154.0 $(M+1)^+$。

**製備141**：*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺

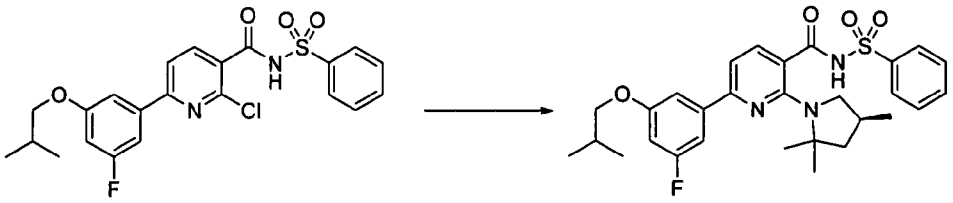
**步驟1**：*N*-(苯磺醯基)-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺



在周圍溫度下向圓底燒瓶中2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(10.0 g，30.89 mmol)於DMF (30.0 mL)中之溶液中緩慢逐份添加羰基二咪唑(5.510 g，33.98 mmol)且混合物攪拌100分鐘。同時經由注射器經30-45分鐘向另一圓底燒瓶中含苯磺醯胺(6.069 g，38.61 mmol)之DMF (30.0 mL) (均質溶液)中逐份添加含NaHMDS之THF (38.61 mL 1.0 M，38.61 mmol)且在添加結束後，將混合物再攪拌30分鐘。接著含有活化酸之混合物添加至含有去質子化之磺醯胺的混合物且將組合之混合物攪拌1小時。反應用0℃浴冷卻且藉由經2-3分鐘分部分添加12N HCl水溶液(11.58 mL)淬滅，使得固體沈澱。轉移反應混合物至分液漏斗且添加乙酸乙酯(100.0 mL)。添加1N HCl水溶液(20.0 mL)，得到pH = 2-3，接著分離各層且用5:1水/飽和鹽水水溶液(120.0 mL)、飽和鹽水水溶液(1×50 mL，1×30 mL)洗滌有機層，乾燥(硫酸鈉)，過濾且在減壓下濃縮成透明淡黃色油狀物，其再自異丙醇濃縮若干次，使固體沈澱。固體在異丙醇中隔夜形成漿狀物，接著過濾且用庚烷(50 mL)洗滌固體且真空乾燥，得到呈白色固體狀之*N*-(苯磺醯基)-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(10.22 g，22.08 mmol，71.47%)。$^1$H NMR (400 MHz, DMSO) δ 12.85 (s, 1H), 8.15 (d,

J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.02 (dd, J = 5.3, 3.3 Hz, 2H), 7.76 (d, J = 7.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 2H), 7.51 - 7.43 (m, 2H), 6.99 (dd, J = 10.8, 2.3 Hz, 1H), 3.85 (d, J = 6.5 Hz, 2H), 2.04 (dt, J = 13.3, 6.6 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H)。ESI-MS m/z計算值462.08163, 實驗值463.19 $(M+1)^+$；滯留時間: 2.93分鐘[5分鐘法]。

**步驟2**：*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺

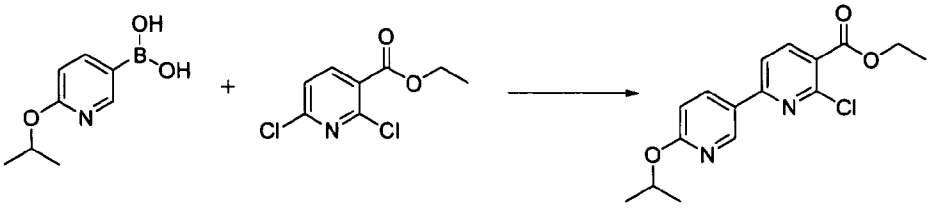


向裝備回流冷凝器之圓底燒瓶中添加*N*-(苯磺醯基)-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(10.0 g，21.60 mmol)及NMP (40 mL)且開始攪拌。升溫至50℃且開始逐份添加碳酸鉀(5.970 g，43.20 mmol)，接著一次性添加(4*S*)-2,2,4-三甲基吡咯啶(4.890 g，43.20 mmol)。攪拌10分鐘後，加熱混合物至125℃，保持65小時，接著冷卻至10℃且分部分添加1N HCl水溶液(50.0 mL，50.00 mmol)，得到pH 1-2及沈澱固體。添加乙酸乙酯(100.0 mL)以溶解固體且用水(50.0 mL)稀釋水層且攪拌10分鐘。混合物轉移至分液漏斗且分離各層。逐滴添加1N HCl水溶液，直至所有固體均溶解。分離各層且水層用乙酸乙酯(50.00 mL)反萃取，接著合併有機層。向合併之有機層添加水(50.00 mL)，得到乳液，其藉由添加1N HCl水溶液(25.00 mL)澄清。分離各層，接著有機層用飽和鹽水水溶液(50.00 mL)洗滌，經$Na_2SO_4$乾燥，經矽藻土過濾且用乙酸乙酯(30.00 mL)沖洗。濾液在減壓下濃縮且殘餘物藉由矽膠層析，使用100%己烷至50% EtOAc之梯度來純化，得到淡琥珀色油狀物，其在減壓下自異丙醇蒸發若干次，得到呈黃色固體狀之*N*-(苯磺醯基)-6-(3-氟-5-異丁氧基-苯基)-2-[(4*S*)-2,2,4-三

甲基吡咯啶-1-基]吡啶-3-甲醯胺(9.73 g，18.03 mmol，83.5%)。$^1$H NMR (400 MHz, DMSO-d6) δ 12.57 (s, 1H), 8.16 - 7.88 (m, 2H), 7.82 - 7.57 (m, 4H), 7.47 (t, J = 1.8 Hz, 1H), 7.40 (dt, J = 9.9, 2.0 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 6.89 (dt, J = 10.8, 2.3 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.48 - 2.28 (m, 2H), 2.07 (dtt, J = 26.6, 13.4, 6.4 Hz, 2H), 1.83 (dd, J = 11.9, 5.5 Hz, 1H), 1.57 (d, J = 17.3 Hz, 6H), 1.38 (t, J = 12.1 Hz, 1H), 1.04 (d, J = 6.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.66 (d, J = 6.3 Hz, 3H)。ESI-MS m/z計算值539.2254，實驗值540.0 $(M+1)^+$；滯留時間: 3.25分鐘[5分鐘法]。

**製備142**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺

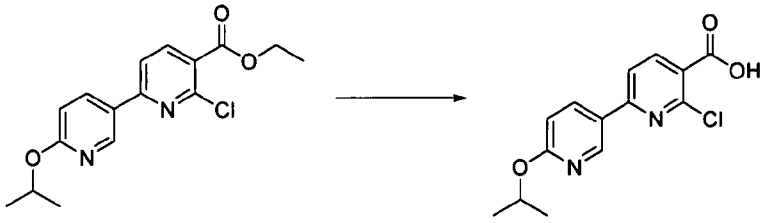
**步驟1**：2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲酸乙酯



2,6-二氯吡啶-3-甲酸乙酯(7.00 g，31.81 mmol)及(6-異丙氧基-3-吡啶基)硼酸(5.04 g，27.85 mmol)組合且溶於乙醇(50.40 mL)及甲苯(50.40 mL)中。添加碳酸鈉(10.12 g，95.47 mmol)於水(10.08 mL)中之懸浮液。在氮氣下，添加肆(三苯基膦)鈀(1.103 g，0.9547 mmol)。使反應混合物升溫至80℃且攪拌2小時。在減壓下移除揮發物。剩餘固體分溶於水(75 mL)與乙酸乙酯(75 mL)之間。有機層用飽和氯化鈉水溶液(1× 75 mL)洗滌，經硫酸鈉乾燥，過濾且在減壓下濃縮。該物質進行矽膠管柱層析，使用己烷中100%己烷至5%乙酸乙酯之梯度。獲得呈透明無色油狀之2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲酸乙酯(3.95 g，12.07 mmol，43.33%)。$^1$H NMR (400 MHz, DMSO) δ 8.91 (s, 1H), 8.37 (dd, J = 8.7, 2.3 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H), 8.10 (d, J =

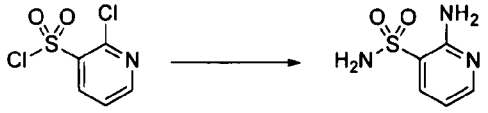
8.1 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 5.34 (dt, J = 12.3, 6.1 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.51 (d, J = 1.7 Hz, 1H), 1.42 - 1.30 (m, 9H)。ESI-MS m/z計算值320.09277, 實驗值321.2 $(M+1)^+$；滯留時間: 0.72分鐘。

**步驟2**：2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲酸



將氫氧化鈉(2.594 g，64.85 mmol)於水(20.80 mL)中之溶液添加至在90℃下攪拌的2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲酸乙酯(4.16 g，12.97 mmol)於異丙醇(20.8 mL)中之溶液中。將反應混合物在90℃下攪拌30分鐘。冷卻至室溫後，將反應混合物用乙酸乙酯(75 mL)稀釋且用飽和碳酸氫鈉水溶液(1× 75 mL)及NaOH水溶液(1 N, 5 × 50 mL)萃取。合併水層且藉由添加6 N HCl水溶液酸化至pH = 1。形成之白色沈澱藉由真空過濾收集且用1 N HCl水溶液沖洗，得到呈白色固體狀之2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲酸(4.2446 g，12.89 mmol，99.43%)。ESI-MS m/z計算值292.06146, 實驗值293.1 $(M+1)^+$；滯留時間: 0.59分鐘。

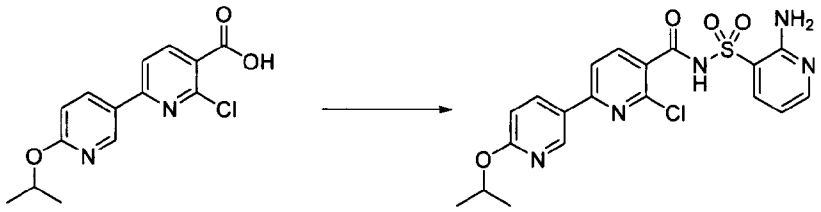
**步驟3**：2-胺基吡啶-3-磺醯胺



攪拌氫氧化銨(590.3 mL 28 %w/v，4.716 mol)且在冰浴中冷卻。2-氯吡啶-3-磺醯氯(50 g，235.8 mmol)溶於二氯甲烷(150 mL)中且逐滴添加至攪拌的氨溶液中以維持溫度在5-12℃之間。添加結束後，將混合物攪拌1小時。停止攪拌且分離所得各層。在真空下濃縮水層以移除氨，產生白色固體沈澱，其藉由過濾收集且用水洗滌。該物質溶

於氫氧化銨(236.1 mL 28 %w/v，1.886 mol)中且在壓力容器中在100℃下加熱隔夜，接著反應溫度增加至150℃且攪拌隔夜。冷卻混合物至室溫，產生沈澱，接著在真空下濃縮以移除氨，產生白色固體沈澱，其藉由過濾收集且用甲基第三丁基醚(100 mL)洗滌，得到2-胺基吡啶-3-磺醯胺(25.73 g，148.6 mmol，63.00%) ESI-MS m/z計算值173.0259，實驗值174.0 $(M+1)^+$。

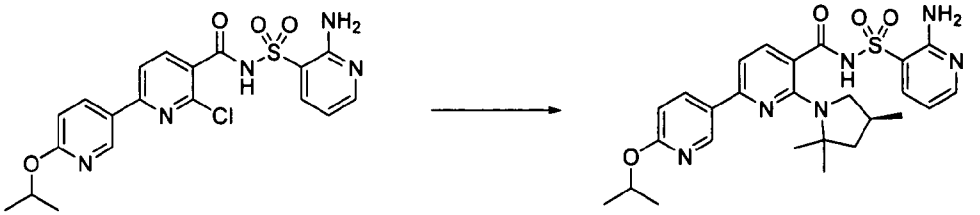
**步驟4**：*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺



向圓底燒瓶中2-胺基吡啶-3-磺醯胺(4.068 g，23.49 mmol)於DMF (38.50 mL) (均質溶液)中之溶液中逐份添加NaH (939.5 mg，23.49 mmol)，得到灰白色稠漿狀物且在添加期間自20℃輕微放熱至32℃。將混合物在周圍溫度下攪拌30分鐘。同時，在周圍溫度下向另一個圓底燒瓶中2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲酸(5.5 g，18.79 mmol)於DMF (38.50 mL)中之溶液中逐份緩慢添加羰基二咪唑(3.352 g，20.67 mmol)且混合物攪拌20分鐘，在此期間，其變成淡黃色均質溶液，其接著添加至含有去質子化之磺醯胺的反應混合物。在添加期間，混合物保持均質，其中輕微放熱至31℃。將組合之混合物在周圍溫度下攪拌，得到深橙色均質混合物且5分鐘後，緩慢添加至冷HCl (93.95 mL 1 M，93.95 mmol) (輕微放熱)，得到約pH 1。混合物得到沈澱且將漿狀物在周圍溫度下攪拌60分鐘。接著混合物過濾且固體用50 mL水洗滌三次。接著固體用50 mL異丙醇洗滌三次，得到灰白色固體，其空氣乾燥1小時。固體接著在50 mL異丙醇中形成漿狀物且沈澱過濾且用5 mL異丙醇洗滌三次。所得灰白色固體空氣乾燥2小

時，接著在45℃下真空乾燥48小時，得到*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(8.0 g，17.86 mmol，95.06%) $^1$H NMR (400 MHz, DMSO-d6) δ 8.87 (d, J = 2.5 Hz, 1H), 8.33 (dd, J = 8.7, 2.6 Hz, 1H), 8.24 (dd, J = 5.1, 1.8 Hz, 1H), 8.13 - 8.00 (m, 3H), 6.96 (s, 2H), 6.88 (d, J = 8.7 Hz, 1H), 6.83 (dd, J = 7.8, 5.0 Hz, 1H), 5.33 (七重峰, J = 6.3 Hz, 1H), 1.32 (d, J = 6.2 Hz, 6H)。ESI-MS m/z計算值447.0768, 實驗值448.18 $(M+1)^+$；滯留時間: 1.55分鐘。

**步驟5**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



向裝備有磁性攪拌棒之小瓶中饋入含*N*-[(2-胺基-3-吡啶基)磺醯基]-2-氯-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(147.8 mg，0.330 mmol)、(4*S*)-2,2,4-三甲基吡咯啶(74.71 mg，0.660 mmol)及碳酸鉀(228.0 mg，1.65 mmol)之DMSO (739 μL)。小瓶密封且在120℃下攪拌16小時，接著在140℃下攪拌30小時。反應混合物冷卻，用最少DMSO及甲醇稀釋且過濾。濾液直接使用逆相HPLC-MS法，使用Phenomenex售出(pn：00C-4252-U0-AX)之Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度操作(移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$，流速 = 50 mL/min，注射體積 = 950 μL及管柱溫度= 25℃)來純化，得到*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(25.2 mg，0.048 mmol，14.6%)。$^1$H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.31 - 8.27 (m, 1H), 8.25 (dd, J = 7.4, 4.4 Hz, 1H), 8.03 (dd, J = 7.9, 1.7 Hz, 1H), 7.75 (d, J

= 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.69 (s, 2H), 5.37 - 5.26 (m, 1H), 2.52 (s, 1H), 2.14 (s, 1H), 1.85 (dd, J = 11.9, 5.5 Hz, 1H), 1.58 (d, J = 10.7 Hz, 6H), 1.39 (t, J = 12.1 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 1.26 (d, J = 13.3 Hz, 1H), 0.86 (t, J = 6.9 Hz, 1H), 0.76 (d, J = 6.3 Hz, 3H)。ESI-MS m/z計算值524.2206, 實驗值525.3 $(M+1)^+$；滯留時間: 1.38分鐘。

以下化合物可使用本文所述之程序合成：

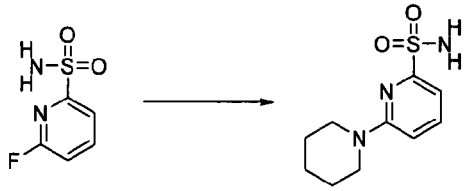
*N*-[(2-胺基-6-甲氧基-3-吡啶基)磺醯基]-6-(6-異丙氧基-3-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2692)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-2-[(4*S*)-3,3-二氘-2,2-二甲基-4-(三氘甲基)吡咯啶-1-基]-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物1543)及

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-[(2*R*,5*S*)-2,5-二甲基吡咯啶-1-基]-6-[6-[1,2,2,2-四氘-1-(三氘甲基)乙氧基]-3-吡啶基]吡啶-3-甲醯胺(化合物2714)

**製備143**：6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[[6-(1-哌啶基)-2-吡啶基]磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物484)

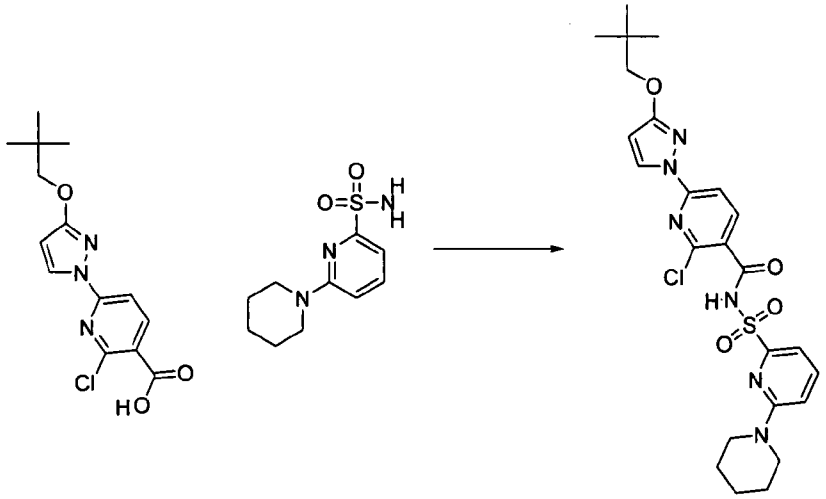
**步驟1**：6-(1-哌啶基)吡啶-2-磺醯胺



向6-氟-2-吡啶磺醯胺(215 mg，1.220 mmol)添加哌啶(312 mg，362μL，3.66 mmol)且將反應混合物在90℃下加熱2.5小時。反應混合物冷卻且所得固體乾燥。1 H NMR (400 MHz, DMSO-d6) δ 7.66 (dd, J = 8.8, 7.2 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H),

2.75 (d, J = 5.5 Hz, 3H), 1.61 (p, J = 3.4, 2.9 Hz, 2H), 1.54 (dd, J = 7.0, 3.9 Hz, 3H), 1.49 (s, 4H)。ESI-MS m/z 實驗值242.2 $(M+1)^+$；滯留時間: 0.45分鐘。

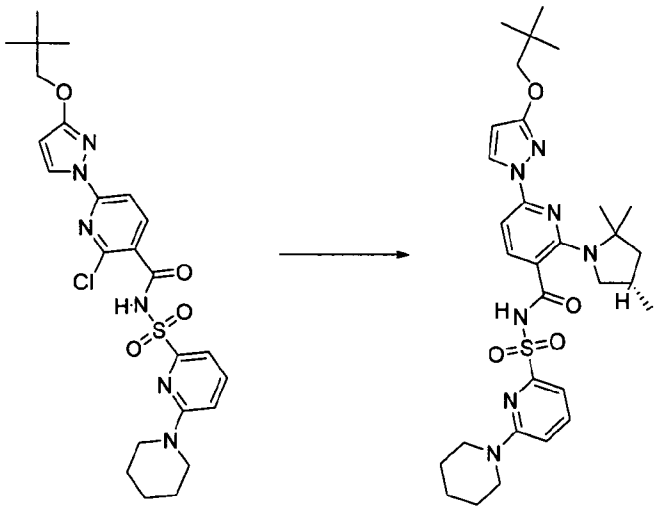
**步驟2**：2-氯-6-(3-(新戊基氧基)-1*H*-吡唑-1-基)-*N*-((6-(哌啶-1-基)吡啶-2-基)磺醯基)菸鹼醯胺



在室溫下向含2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]吡啶-3-甲酸(100 mg，0.323 mmol)之DMF (0.6 mL)中添加羰基二咪唑(78.5 mg，0.484 mmol)且將反應混合物攪拌40分鐘。分開地，含6-(1-哌啶基)吡啶-2-磺醯胺(93.5 mg，0.387 mmol)之DMF (0.6 mL)冷卻至0℃且用氫化鈉(15.5 mg，0.387 mmol)處理且攪拌10分鐘且接著在室溫下30分鐘。接著組合反應混合物且在室溫下攪拌30分鐘。反應混合物冷卻至0℃且添加乙酸(194 mg，184μL，3.23 mmol)，接著HCL (269 μL 6 M，1.61 mmol)且將反應混合物用EtOAc (5 mL)稀釋且分離各層。有機物乾燥且在減壓下濃縮，得到殘餘物，其藉由矽膠管柱層析純化且用0-14% MeOH-DCM溶離，得到2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[[6-(1-哌啶基)-2-吡啶基]磺醯基]吡啶-3-甲醯胺(158 mg，82%) ESI-MS m/z 實驗值533.2 $(M+1)^+$；滯留時間: 0.89分鐘 (1 min)；1H NMR (400 MHz, DMSO-d6) δ 8.44 - 8.38 (m, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.95 (s, 1H), 7.79 - 7.70 (m, 2H), 7.23 (d, J = 7.2 Hz, 1H), 7.12 (d,

J = 8.7 Hz, 1H), 6.22 (t, J = 2.5 Hz, 1H), 3.93 (d, J = 1.2 Hz, 2H), 3.59 (t, J = 5.4 Hz, 3H), 1.66 - 1.58 (m, 2H), 1.53 (td, J = 10.2, 4.8 Hz, 3H), 1.00 (s, 9H)。

**步驟3**：6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[[6-(1-哌啶基)-2-吡啶基]磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物484)



將2-氯-6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[[6-(1-哌啶基)-2-吡啶基]磺醯基]吡啶-3-甲醯胺(140 mg，0.223 mmol)、碳酸鉀(185 mg，1.34 mmol)及(4*S*)-2,2,4-三甲基吡咯啶(HCl鹽) (75 mg，0.501 mmol)於DMSO (744 μL)中之混合物在150℃下加熱5小時。反應混合物冷卻，用EtOAc稀釋且分離水層與有機層。有機物用鹽水洗滌，乾燥，在減壓下濃縮且所得殘餘物藉由矽膠管柱層析，用0-15% MeOH-DCM溶離來純化，得到6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[[6-(1-哌啶基)-2-吡啶基]磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物484) (38 mg，28%)。ESI-MS m/z 計算值 609.31, 實驗值 610.1 $(M+1)^+$；滯留時間2.1 min (3分鐘操作)；1H NMR (400 MHz,甲醇-d4) δ 8.25 (d, J = 2.8 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 8.7, 7.2 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 6.98 (dd, J = 8.5, 6.5 Hz, 2H), 5.99 (d, J = 2.8 Hz, 1H), 3.90 (s, 2H), 3.63 (q, J = 6.1, 5.3 Hz, 4H), 2.80

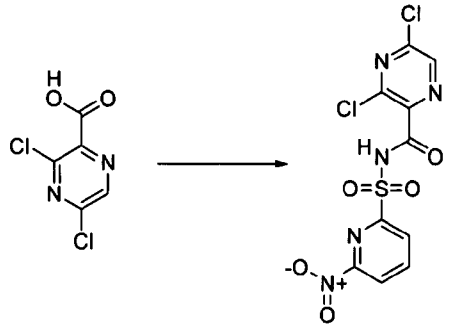
- 2.66 (m, 2H), 2.26 (d, J = 10.4 Hz, 1H), 1.90 (dd, J = 11.9, 5.6 Hz, 1H), 1.68 (q, J = 5.1, 4.7 Hz, 2H), 1.61 (d, J = 5.3 Hz, 10H), 1.47 (t, J = 12.2 Hz, 1H), 1.04 (s, 9H), 0.88 (d, J = 6.3 Hz, 3H)。

以下化合物可使用本文所述之程序合成：

6-[3-(2,2-二甲基丙氧基)吡唑-1-基]-*N*-[[2-(1-哌啶基)-3-吡啶基]磺醯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2670)

**製備144**：*N*-[(6-胺基-2-吡啶基)磺醯基]-3-(3-氟-5-異丁氧基-苯基)-5-[(*4S*)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺(化合物2673)

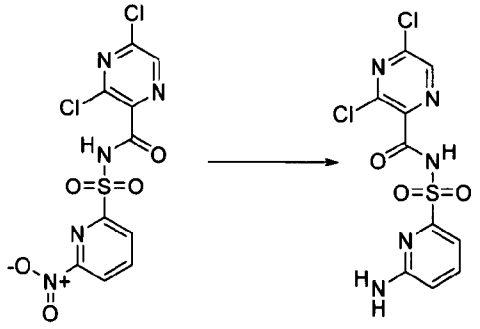
**步驟1**：3,5-二氯-*N*-[(6-硝基-2-吡啶基)磺醯基]吡嗪-2-甲醯胺



在氮氣氛圍下向攪拌的3,5-二氯吡嗪-2-甲酸(2.21 g，11.5 mmol)於無水$CH_2Cl_2$ (20 mL)中之不均質混合物中添加硫醯氯(7.5 mL，103 mmol)，接著無水DMF (30 mg，0.41 mmol)且將反應混合物在室溫下攪拌1小時。反應混合物蒸發，溶於$CH_2Cl_2$ (40 mL)中且在0℃下逐滴添加至6-硝基吡啶-2-磺醯胺(2.32 g，11.5 mmol)與三乙胺(8.5 mL，61.0 mmol)之溶液中，攪拌隔夜(24小時)，同時升溫至周圍溫度。反應混合物在減壓下濃縮。殘餘物分溶於$CH_2Cl_2$ (10 mL)與冰水(200 mL)之間且用2 M HCl酸化至約pH 4.0。所得固體過濾，分離各層且水層用$CH_2Cl_2$ (3×50 mL)萃取。合併之有機物依序用1N HCl、飽和氯化鈉溶液洗滌，接著經硫酸鈉乾燥，過濾且在減壓下蒸發。粗物質藉由用二氯甲烷(10 mL)濕磨來純化，過濾及乾燥，得到呈白色固體狀之3,5-二氯-*N*-[(6-硝基-2-吡啶基)磺醯基]吡嗪-2-甲醯胺(2.90 g，67%)。

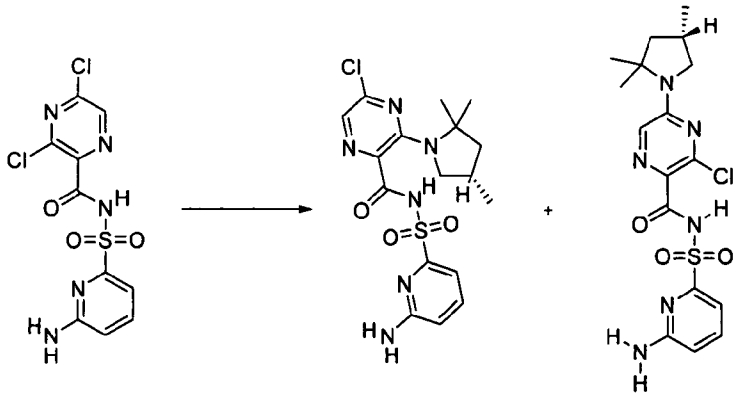
ESI-MS m/z計算值376.93884, 實驗值378.0 $(M+1)^+$；滯留時間: 0.6分鐘。

**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-3,5-二氯-吡嗪-2-甲醯胺



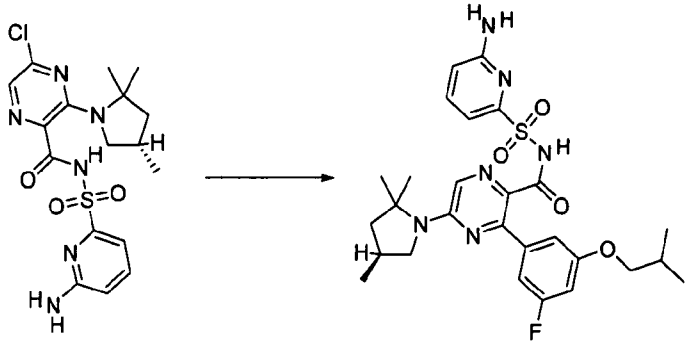
向3,5-二氯-*N*-[(6-硝基-2-吡啶基)磺醯基]吡嗪-2-甲醯胺(830 mg，2.20 mmol)於THF (8 mL)及EtOH (4 mL)中之溶液中添加鐵(Fe)粉(613 mg，11.0 mmol)，接著HCl (6 N) (1.8 mL 6.0 M，10.80 mmol)。將反應混合物在60℃下加熱15分鐘。冷卻至室溫後，反應混合物過濾且濾液在減壓下濃縮。殘餘物用EtOAc (50 mL)稀釋且用NaOH (4 mL，1 N)洗滌。再次過濾各層且藉由添加1 N HCl (水溶液)將水層酸化至pH 2且用EtOAc (2 × 50 mL)萃取。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮。粗物質藉由矽膠管柱層析，使用$CH_2Cl_2$中0-20 % MeOH作爲溶離劑來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-3,5-二氯-吡嗪-2-甲醯胺(404 mg，53%) ESI-MS m/z計算值346.96466, 實驗值348.0 $(M+1)^+$；滯留時間: 0.53分鐘。

**步驟3**：*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-3-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺及(*S*)-*N*-((6-胺基吡啶-2-基)磺醯基)-3-氯-5-(2,2,4-三甲基吡咯啶-1-基)吡嗪-2-甲醯胺



向*N*-[(6-胺基-2-吡啶基)磺醯基]-3,5-二氯-吡嗪-2-甲醯胺(36 mg，0.10 mmol)於DMSO (142 μL)中之溶液中添加DIEA (90 μL，0.52 mmol)及(4*S*)-2,2,4-三甲基吡咯啶(32 mg，0.26 mmol)。將反應混合物在85℃下攪拌6小時。冷卻之反應經由逆相HPLC-MS法，使用經15.0分鐘15-99%移動相B之雙重梯度 (移動相A = $H_2O$ (5 mM HCl)，移動相B =乙腈)來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-3-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺與(*S*)-*N*-((6-胺基吡啶-2-基)磺醯基)-3-氯-5-(2,2,4-三甲基吡咯啶-1-基)吡嗪-2-甲醯胺之混合物(28 mg，64%)　ESI-MS m/z計算值424.10843，實驗值425.2 $(M+1)^+$。

**步驟4**：*N*-[(6-胺基-2-吡啶基)磺醯基]-3-(3-氟-5-異丁氧基-苯基)-5-[(*4S*)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺(化合物2673)

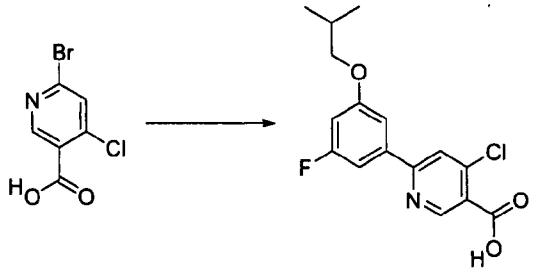


向*N*-[(6-胺基-2-吡啶基)磺醯基]-5-氯-3-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺(*S*)-*N*-((6-胺基吡啶-2-基)磺醯基)-3-氯-5-(2,2,4-三甲基吡咯啶-1-基)吡嗪-2-甲醯胺(60 mg，0.14 mmol)及(3-氟-5-異丁氧基-苯基)硼酸(60 mg，0.28 mmol)於二噁烷(3.0 mL)中之溶液中添加

$H_2O$ (1.0 mL)、$K_2CO_3$ (78 mg，0.56 mmol)及雙(2-二苯基磷烷基環戊并-2,4-二烯-1-基)鐵二氯鈀 [$Cl_2Pd(dppf).CH_2Cl_2$] (8 mg，0.011 mmol)。氮氣鼓泡5分鐘且反應混合物密封且在微波照射下在120℃下攪拌30分鐘。使反應混合物冷卻至周圍溫度，過濾且經由逆相HPLC-MS (使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經30.0分鐘30-99%移動相B之雙重梯度；移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)來純化，得到呈灰白色固體之*N*-[(6-胺基-2-吡啶基)磺醯基]-3-(3-氟-5-異丁氧基-苯基)-5-[(*4S*)-2,2,4-三甲基吡咯啶-1-基]吡嗪-2-甲醯胺(化合物2673) (5.7 mg，6%)。1H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 7.89 (s, 1H), 7.62 - 7.53 (m, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.88 - 6.79 (m, 2H), 6.75 - 6.69 (m, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.52 (s, 2H), 3.83 (t, J = 9.1 Hz, 1H), 3.74 (d, J = 6.5 Hz, 2H), 3.12 (t, J = 10.4 Hz, 1H), 2.47 - 2.35 (m, 1H), 2.02 (dd, J = 12.8, 6.3 Hz, 2H), 1.61 (d, J = 12.2 Hz, 1H), 1.56 (s, 3H), 1.45 (s, 3H), 1.10 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H)。ESI-MS m/z計算值556.2268, 實驗值557.4 $(M+1)^+$；滯留時間: 2.15分鐘。

**製備145**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2679)

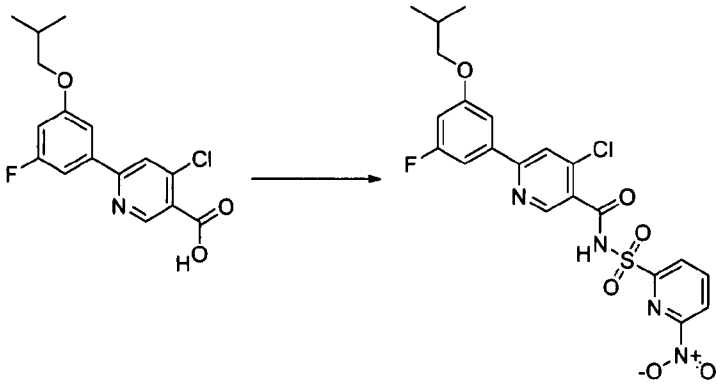
**步驟1**：4-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸




在氮氣氛圍下向含6-溴-4-氯-吡啶-3-甲酸(205 mg，0.865 mmol)、(3-氟-5-異丁氧基-苯基)硼酸(184 mg，0.865 mmol)及三苯基膦鈀(30.0 mg，0.0260 mmol)之二噁烷(4 mL)中添加碳酸鉀溶液

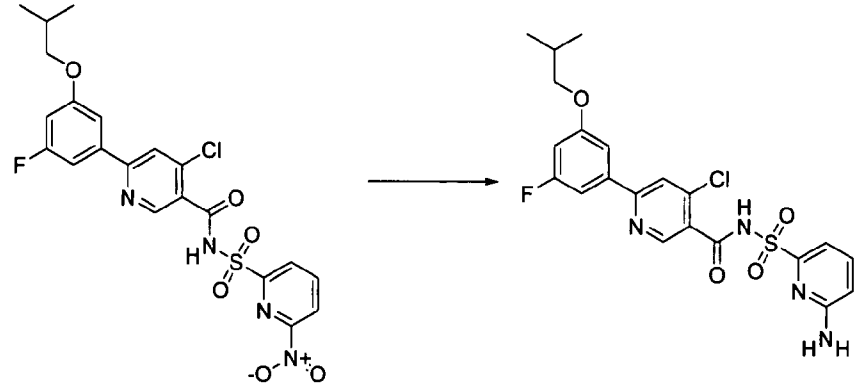
(1.73 mL 2 M，3.46 mmol)且將反應混合物在80℃下攪拌10小時。反應混合物在減壓下濃縮，分溶於水(15 mL)與EtOAc (15 mL)之間。水層用HCl酸化且用 EtOAc (3×15 mL)洗滌。合併之有機層用鹽水(1×25 mL)洗滌，經硫酸鈉乾燥，過濾且在減壓下濃縮。所得固體用己烷洗滌，得到呈棕褐色固體狀之4-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(232 mg，83%)。ESI-MS m/z計算值323.07245，實驗值324.1 $(M+1)^+$；滯留時間: 0.74分鐘。

**步驟2**：4-氯-6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-硝基-2-吡啶基)磺醯基]吡啶-3-甲醯胺



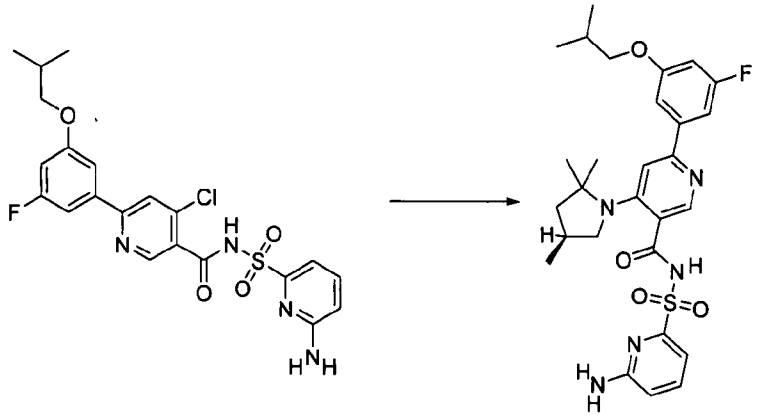
將具有一滴DMF的4-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲酸(104 mg，0.32 mmol)及$SOCl_2$ (190 mg，116μL，1.60 mmol)在周圍溫度下攪拌30分鐘。在減壓下移除揮發物。在另一個燒瓶中含6-硝基吡啶-2-磺醯胺(65 mg，0.32 mmol)及TEA (97 mg，134 μL，0.96 mmol)之DCM (1.2 mL)在冰水浴中冷卻。緩慢添加所產生之酸氯化物於DCM中之溶液。將反應混合物在冰水浴中攪拌且達至室溫。將反應混合物用DCM稀釋，用1N HCl、飽和NaHCO3及鹽水洗滌。有機物分離且經硫酸鈉乾燥且在減壓下蒸發，得到4-氯-6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-硝基-2-吡啶基)磺醯基]吡啶-3-甲醯胺(157 mg，97%) ESI-MS m/z計算值508.06195，實驗值509.1 $(M+1)^+$；滯留時間: 0.74分鐘。

**步驟3**：*N*-[(6-胺基-2-吡啶基)磺醯基]-4-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺



4-氯-6-(3-氟-5-異丁氧基-苯基)-*N*-[(6-硝基-2-吡啶基)磺醯基]吡啶-3-甲醯胺(123 mg，0.242 mmol)溶於THF (615 μL)及EtOH (615 μL)中。添加粉末狀Fe (135 mg，2.42 mmol)與HCl (80.6 μL 6 M，0.483 mmol)。將反應混合物在65℃下加熱10分鐘。冷卻至室溫後，反應混合物過濾，濾液用EtOAc稀釋且用NaOH (4 mL，1 N)洗滌。再次過濾各層且水層藉由HCl水溶液酸化至pH 2且用EtOAc (1× 8 mL)萃取。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮，得到呈黃色粉末狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-4-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(61 mg，53%)。ESI-MS m/z計算值478.08777，實驗值479.1 $(M+1)^+$；滯留時間: 0.69分鐘。

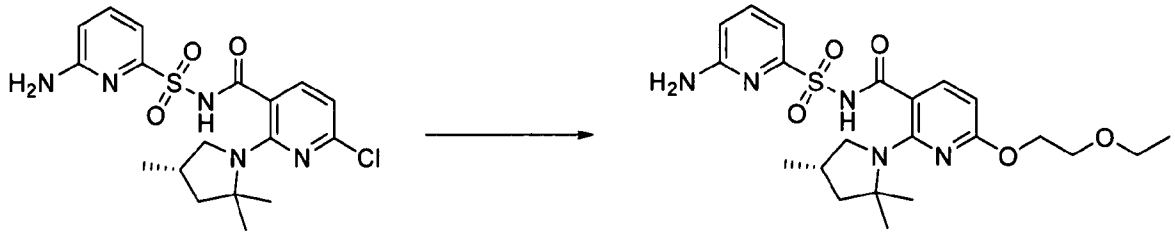
**步驟4**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2679)



向*N*-[(6-胺基-2-吡啶基)磺醯基]-4-氯-6-(3-氟-5-異丁氧基-苯基)

吡啶-3-甲醯胺(24 mg，0.050 mmol)於DMSO (0.1 mL)中之溶液中添加CsF (23 mg，0.15 mmol)及(4*S*)-2,2,4-三甲基吡咯啶(27 mg，0.15 mmol)。反應混合物密封且在120℃下攪拌隔夜。反應混合物冷卻，用DMSO稀釋且經由HPLC/MS，利用含於5 mM HCl水溶液中之1-99%乙腈之梯度純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-4-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2679) (5 mg，19%)。ESI-MS m/z計算值555.23157，實驗值556.4 $(M+1)^+$；滯留時間: 1.47分鐘。

**製備146**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基乙氧基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2678)



*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物852) (25 mg，0.059 mmol)、2-乙氧基乙醇(53 mg，57μL，0.59 mmol)、NaH (7.0 mg，0.29 mmol)及三氟甲烷磺酸鈧(3+)(2.9 mg，0.0058 mmol)溶解於DMSO (0.5 mL)中且在120℃下加熱8小時。反應混合物分溶於乙酸乙酯與1N HCl水溶液之間。分離有機物，用鹽水洗滌，經硫酸鈉乾燥且在減壓下蒸發。粗物質藉由矽膠層析，用己烷中0-100% 乙酸乙酯溶離來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(2-乙氧基乙氧基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2678) (7 mg，25%) ESI-MS *m/z*計算值477.2046，實驗值478.4 $(M+1)^+$；滯留時間: 1.25分鐘。

以下化合物可使用本文所述之程序合成：

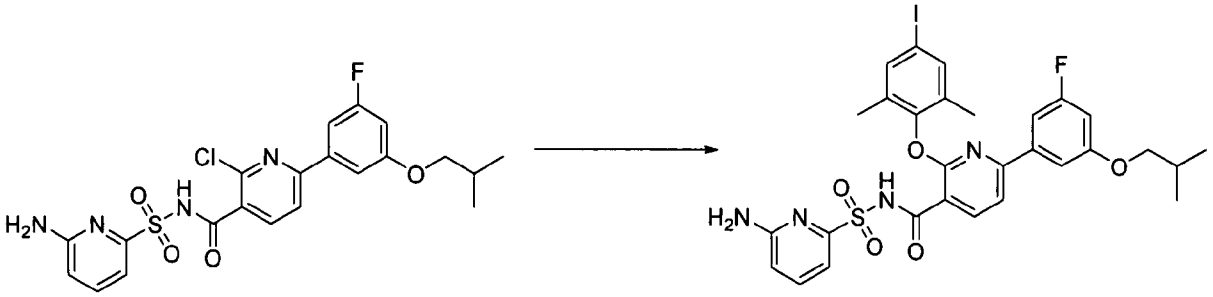
*N*-[(2-胺基-3-吡啶基)磺醯基]-6-甲氧基-2-[(4*S*)-2,2,4-三甲基吡咯

啶-1-基]吡啶-3-甲醯胺(化合物2704)，

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(2-乙氧基乙氧基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2705)及

*N*-[(2-胺基-3-吡啶基)磺醯基]-6-[2-(2-乙氧基乙氧基)乙氧基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2706)。

**製備147**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-碘-2,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物2671)



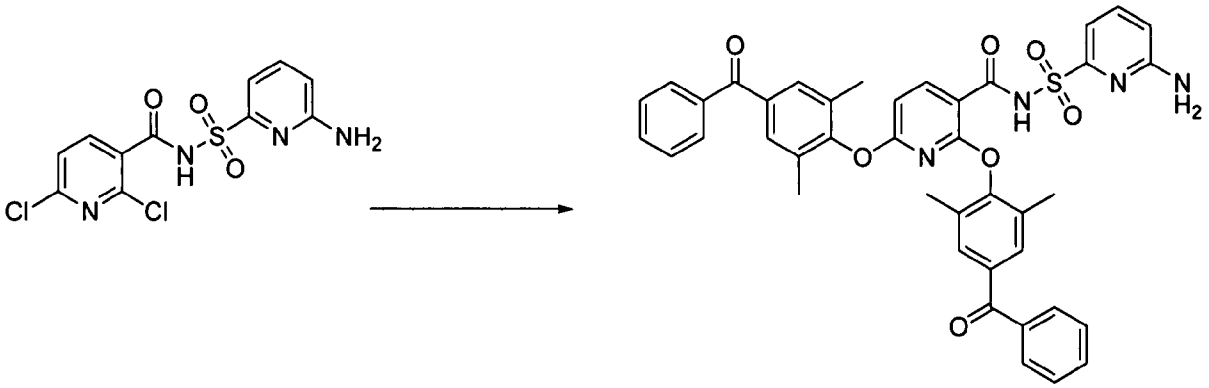
向含*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(69 mg，0.14 mmol)及4-碘-2,6-二甲基-苯酚(71 mg，0.29 mmol)之NMP (4 mL)中添加NaH (17 mg，0.43 mmol)。將反應混合物在室溫下攪拌5分鐘，接著在150℃下攪拌2小時。將反應混合物用$NH_4Cl$溶液淬滅，粗混合物藉由逆相矽膠管柱層析，使用水中10-100% ACN (TFA改質劑)作爲溶離劑來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-碘-2,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物2671) (8 mg，7%)。1H NMR (300 MHz, CDCl3) δ 8.47 (d, J = 8.1 Hz, 1H), 7.76 - 7.68 (m, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.47 (s, 2H), 7.04 - 6.95 (m, 3H), 6.76 (d, J = 8.2 Hz, 1H), 6.63 (dt, J = 10.3, 2.2 Hz, 1H), 3.56 (t, J = 7.0 Hz, 2H), 2.13 - 2.06 (m, 6H), 1.01 (t, J = 6.6 Hz, 6H), 0.85 (t, J = 6.7 Hz, 3H), 0.47 (s, 1H)。ESI-MS m/z 實驗值691.4 $(M+1)^+$；滯留時間: 0.83分鐘

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-苯甲醯基-2,6-二甲基-苯氧基)-6-(6-異丙氧基-3-吡啶基)吡啶-3-甲醯胺(化合物2715)及

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(4-苯甲醯基-2,6-二甲基-苯氧基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物2669)。

**製備148**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-雙(4-苯甲醯基-2,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物970)

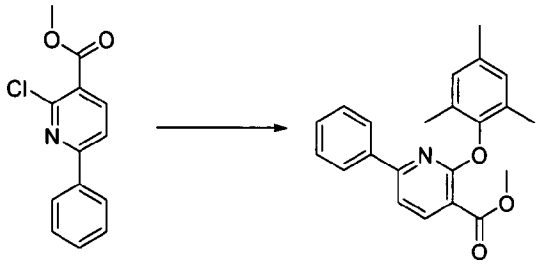


向含*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-二氯-吡啶-3-甲醯胺(487 mg，1.40 mmol)之DMF (4 mL)中添加(4-羥基-3,5-二甲基-苯基)-苯基-甲酮(390 mg，1.57 mmol)及NaH (140.3 mg，3.508 mmol)。將反應混合物在室溫下攪拌20分鐘，接著在150℃下攪拌1小時。粗混合物藉由逆相矽膠管柱層析，使用水中0-80% ACN (TFA改質劑)作爲溶離劑來純化，接著藉由矽膠管柱層析，用庚烷中30-100% EtOAc溶離進一步純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-2,6-雙(4-苯甲醯基-2,6-二甲基-苯氧基)吡啶-3-甲醯胺(化合物970) (51 mg，4%)。1H NMR (300 MHz, DMSO) δ 8.24 (dd, J = 15.6, 8.2 Hz, 1H), 7.80 - 7.66 (m, 1H), 7.66 - 7.39 (m, 10H), 7.31 - 7.22 (m, 4H), 7.11 (d, J = 7.2 Hz, 1H), 6.74 (t, J = 10.3 Hz, 1H), 6.55 (d, J = 7.9 Hz, 1H), 6.27 (s, 2H), 1.92 (d, J = 1.9 Hz, 12H)；ESI-MS m/z 實驗值727.5 $(M+1)^+$；滯留時間: 0.68分鐘(4分鐘操作)。

**製備149**：*N*-[(6-氟-2-吡啶基)磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)

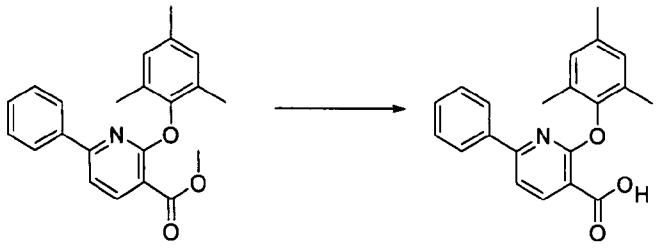
吡啶-3-甲醯胺(化合物698)

**步驟1**：6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯



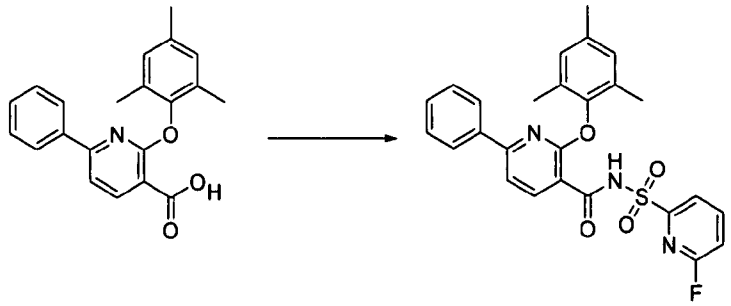
將2-氯-6-苯基-吡啶-3-甲酸甲酯(224 mg，0.904 mmol)、2,4,6-三甲基苯酚(123 mg，0.904 mmol)、碳酸銫(295 mg，0.904 mmol)及DMF (3.14 mL)之混合物在80℃下加熱隔夜。反應混合物冷卻至室溫，接著分溶於乙酸乙酯與1N HCl之間。分離各層且水層用乙酸乙酯(2次)萃取。合併之有機物用鹽水洗滌，經硫酸鎂乾燥，過濾且在減壓下濃縮。殘餘物進行管柱層析(0-25%乙酸乙酯/己烷)，得到6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(250 mg，71%)。ESI-MS m/z計算值347.15213, 實驗值348.4 $(M+1)^+$；滯留時間: 2.28分鐘 (3分鐘操作)。

**步驟2**：6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸



6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸甲酯(562 mg，1.62 mmol)溶於甲醇(8 mL)中：添加THF (3 mL)及NaOH (8.09 mL 1 M，8.09 mmol)。將反應混合物在65℃下加熱3小時。反應混合物傾倒在冰上且用6M HCl酸化。所得白色固體收集且接著溶於甲醇中且在減壓下蒸發，得到6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(466 mg，86%) ESI-MS m/z計算值333.1365, 實驗值334.2 $(M+1)^+$；滯留時間: 0.74分鐘。

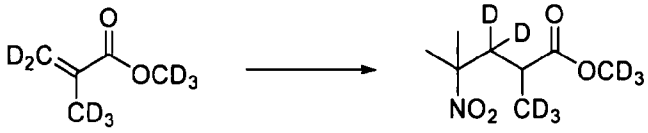
**步驟3**：*N*-[(6-氟-2-吡啶基)磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物698)



向6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲酸(150 mg，0.450 mmol)、HATU (171 mg，0.450 mmol)、DMF (1.5 mL)及三乙胺(137 mg，188 μL，1.35 mmol)中添加6-氟吡啶-2-磺醯胺(79.3 mg，0.450 mmol)且將反應混合物在65℃下攪拌1小時。反應混合物過濾且經由HPLC (1%-99%)，含0.1% HCl改質劑之ACN:$H_2O$純化，得到*N*-[(6-氟-2-吡啶基)磺醯基]-6-苯基-2-(2,4,6-三甲基苯氧基)吡啶-3-甲醯胺(化合物698) (79 mg，36%)。1H NMR (400 MHz, DMSO-d6) δ 8.37 (q, J = 7.8 Hz, 1H), 8.16 (dd, J = 7.5, 2.1 Hz, 1H), 8.12 (d, J =7.8 Hz, 1H), 7.80 - 7.73 (m, 3H), 7.59 (dd, J = 8.3, 2.2 Hz, 1H), 7.41 (ddt, J = 5.5, 3.8, 2.2 Hz, 3H), 6.94 (s, 2H), 2.28 (s, 3H), 2.01 (s, 6H)。ESI-MS m/z計算值491.1315, 實驗值492.4 $(M+1)^+$；滯留時間: 2.19分鐘。

**製備150**：(*S*)-2,2-二甲基-4-(甲基-$d_3$)吡咯啶-3,3-$d_2$

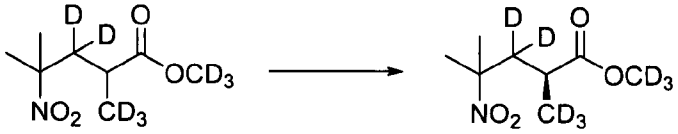
**步驟1**：甲基-$d_3$ 4-甲基-2-(甲基-$d_3$)-4-硝基戊酸酯-3,3-$d_2$



向裝備有磁性攪拌棒、氮氣管線及具有加熱套之J-Kem熱電偶之500 mL三頸圓底燒瓶中饋入2-硝基丙烷(34.3 g，385 mmol)及甲基丙烯酸$d_8$-甲酯(50 g，462 mmol)，在周圍溫度下攪拌，此時一次性添加1,8-二氮雜雙環[5.4.0]十一-7-烯(1.47 g，9.63 mmol)。反應溶液自20℃放熱至約40℃且在無加熱或冷卻下攪拌16小時。將反應混合物在80℃

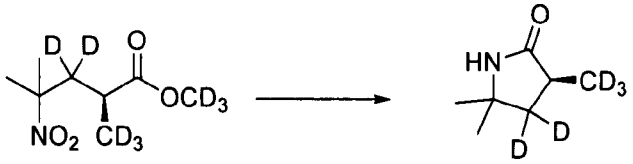
下加熱4小時。將反應混合物用MTBE (170 mL)稀釋，用1 M HCl (15 mL)洗滌，乾燥($MgSO_4$)，過濾且在減壓下濃縮，得到呈淡黃色油狀之甲基-$d_3$ 4-甲基-2-(甲基-$d_3$)-4-硝基戊酸酯-3,3-$d_2$(75 g，99%)，其未經進一步純化即用於下一步。

**步驟2**：甲基-$d_3$ (*S*)-4-甲基-2-(甲基-$d_3$)-4-硝基戊酸酯-3,3-$d_2$



向裝備有頂置式機械攪拌器、氮氣管線及具有加熱套之J-Kem熱電偶的5L三頸圓底燒瓶饋入甲基-$d_3$ 4-甲基-2-(甲基-$d_3$)-4-硝基戊酸酯-3,3-$d_2$ (75 g，380 mmol)及pH 7.5 0.8 M磷酸鈉緩衝液(2000 mL)。向其中添加來自Rhizomucor miehei之脂肪酶(sigma L4277，來自Novozymes之palatase) (37.5 mL)且在30℃下攪拌25小時。反應混合物用MTBE (每次1 L)萃取兩次。合併之有機物用$NaHCO_3$ (5體積)、鹽水(5體積)洗滌兩次，經硫酸鈉乾燥且真空濃縮，得到呈淺黃色油狀之甲基-$d_3$ (*S*)-4-甲基-2-(甲基-$d_3$)-4-硝基戊酸酯-3,3-$d_2$(32.5 g，43%產率)。

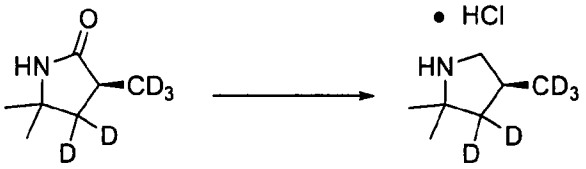
**步驟3**：(*S*)-5,5-二甲基-3-(甲基-$d_3$)吡咯啶-2-酮-4,4-$d_2$



高壓容器(帕爾震盪瓶(Parr shaker bottle)，500 mL)用$N_2$淨化且維持於$N_2$下。容器依序饋入DI水清洗(3次)的潮濕Raney®2800 Ni (6.1 g)、甲基-d3 (*S*)-4-甲基-2-(甲基-d3)-4-硝基戊酸酯-3,3-d2 (32.5 g，165 mmol)及EtOH (290 mL)。容器密封且抽空/回填$N_2$ (3次)。在無攪拌下，接著容器抽空且回填$H_2$ (30 psi)。震盪帕爾瓶，同時在60℃下加熱混合物，且$H_2$壓力維持在30 psi下8小時。將容器抽空/回填$N_2$ (3次)

且催化劑/矽藻土藉由真空過濾(矽藻土墊；$N_2$層)移除。燒瓶/濾墊用EtOH (3×50 mL)洗滌。濾液及洗滌物合併且真空濃縮，得到呈白色固體狀之(*S*)-5,5-二甲基-3-(甲基-$d_3$)吡咯啶-2-酮-4,4-$d_2$ (20 g，92%)。

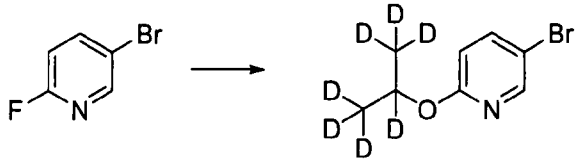
**步驟4**：(*S*)-2,2-二甲基-4-(甲基-$d_3$)吡咯啶-3,3-$d_2$



向裝備有頂置式機械攪拌器、氮氣管線及J-Kem熱電偶之1L三頸圓底燒瓶饋入含LAH小球(7.6 g，202 mmol)之THF (80 mL)。經30分鐘將(*S*)-5,5-二甲基-3-(甲基-$d_3$)吡咯啶-2-酮-4,4-$d_2$ (20 g，151 mmol)於THF (120 mL)中之溶液添加至懸浮液中，同時使反應溫度升至約60℃。反應溫度增加至接近回流 (約68℃)且維持16小時。反應混合物冷卻至40℃以下且用MTBE (200 mL)稀釋。藉由經2小時逐滴添加飽和$Na_2SO_4$水溶液(1體積)，小心淬滅反應混合物。添加結束後，反應混合物冷卻至室溫。固體藉由過濾移除(矽藻土墊)且用EtOAc (4體積)洗滌。在外部冷卻及$N_2$層下，濾液及洗滌物合併且藉由逐滴添加無水4 M HCl之二噁烷溶液(1當量)處理，同時維持溫度低於20℃。添加結束後(20分鐘)，所得懸浮液在45℃下在減壓下濃縮。在濃縮期間懸浮液回填庚烷(4體積)兩次。懸浮液冷卻至30℃以下，此時固體藉由在$N_2$層下過濾收集。固體在高真空下在45℃下乾燥，得到呈白色結晶固體狀之(*S*)-2,2-二甲基-4-(甲基-$d_3$)吡咯啶-3,3-$d_2$ (17.5 g，75%)。

**製備151**：(6-((丙-2-基-d7)氧基)吡啶-3-基)硼酸

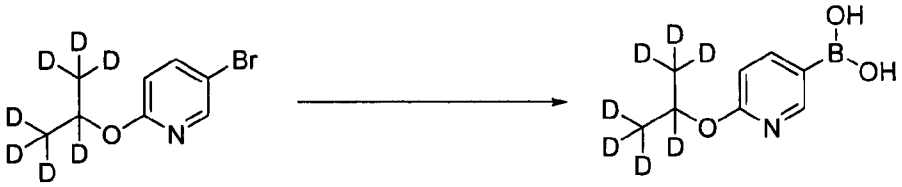
**步驟1**：5-溴-2-((丙-2-基-d7)氧基)吡啶



向於DMF (7 mL)中形成漿狀物之NaH (245 g，10.2 mmol)中添加

d7-IPA (610 mg，9.09 mmol)且將反應混合物在室溫下攪拌30分鐘。添加5-溴-2-氟吡啶(1.00g, 5.68 mmol)且將反應混合物加熱至120℃，保持2.5小時，接著添加其他等分試樣NaH (40 mg)及d7-IPA (0.07 mL)。再加熱2小時後，使反應混合物冷卻至室溫。添加水(21 mL)，接著MTBE (14 mL)，且攪拌後，分離各層。有機層用水(14 mL)洗滌，經硫酸鈉乾燥，過濾且濃縮，得到5-溴-2-((丙-2-基-d7)氧基)吡啶。1H NMR (400 mHz) δ 8.17 (m, 1H), 7.60 (dd, J= 8.8, 2.6 Hz, 1H), 6.58 (dd, J= 8.8, 0.7 Hz, 1H)。

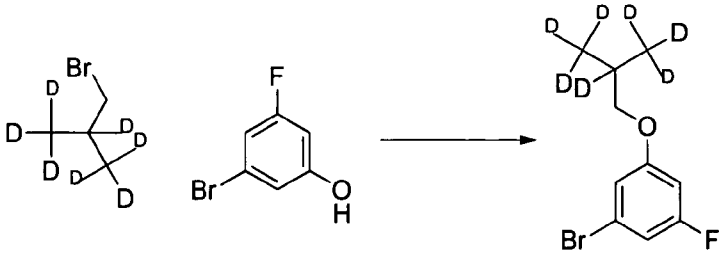
**步驟2**：(6-((丙-2-基-d7)氧基)吡啶-3-基)硼酸



在氮氣氛圍下將5-溴-2-[1,2,2,2-四氘-1-(三氘甲基)乙氧基]吡啶(1.24 g，5.00 mmol)、雙(頻哪醇根基)二硼(1.52 g，6.00 mmol)、KOAc (1.47 g，15.0 mmol)、$Pd(OAc)_2$ (44.9 mg，0.20 mmol)、X-Phos (119 mg，0.25 mmol)於2-MeTHF (11 mL)中之混合物加熱至80℃，保持2.5小時。使反應混合物冷卻，接著添加水(8 mL)且反應混合物經矽藻土墊過濾，用2-MeTHF (2×5 mL)洗滌。分離各層且有機層經硫酸鈉乾燥，過濾，且在減壓下濃縮。粗物質溶於2-MeTHF (12 mL)中，添加10% w/v NaOH水溶液且攪拌反應混合物。分離各層，用濃HCl將水層酸化至pH 5且與2-MeTHF (12 mL)一起攪拌，接著分離，有機層經硫酸鈉乾燥，過濾且在減壓下濃縮，得到(6-((丙-2-基-d7)氧基)吡啶-3-基)硼酸。

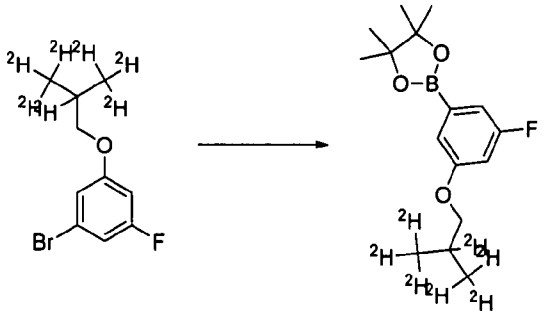
**製備152**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2708)

**步驟1**：1-溴-3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯



向含3-溴-5-氟-苯酚(6.00 g，31.41 mmol)之DMF (60 mL)中緩慢添加NaH (1.38 g，34.55 mmol)且將反應混合物在周圍溫度下攪拌15分鐘。向混合物添加NaI (1.18 g，7.85 mmol)，接著2-(溴甲基)-1,1,1,2,3,3,3-七氘-丙烷(5.05 g，34.55 mmol)。將反應混合物在80℃下攪拌6小時。反應混合物冷卻至周圍溫度且用水(120 mL)緩慢淬滅。反應混合物用EtOAc (240 mL)萃取且分離有機相。有機相用鹽水洗滌，經$MgSO_4$乾燥，過濾且真空濃縮。粗淡黃色油狀物藉由矽膠管柱層析，用0-100% EtOAc/己烷溶離來純化，得到1-溴-3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯(6.8 g，85%)。1H NMR (400 MHz, 氯仿-d) δ 6.90 - 6.77 (m, 2H), 6.55 (dt, J = 10.7, 2.2 Hz, 1H), 3.75 - 3.61 (m, 2H)。

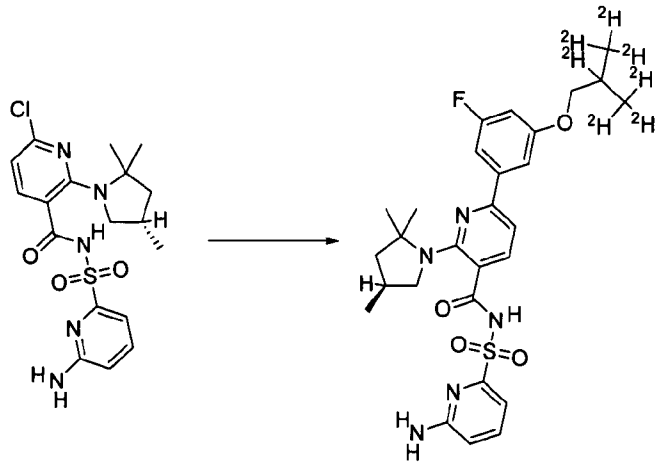
**步驟2**：2-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷



向含1-溴-3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯(10.8 g，42.50 mmol)之二噁烷(162 mL)添加雙(二頻哪醇根基)二硼(16.2 g，63.75 mmol)及KOAc (12.5 g，127.5 mmol)且反應混合物用$N_2$淨化20分鐘。向反應混合物中添加$PdCl_2(dppf)_2.CH_2Cl_2$ (1.74 g，2.13 mmol)

且將反應混合物加熱至100℃，保持3小時。反應混合物冷卻至周圍溫度且經矽藻土過濾且真空濃縮，得到深色油狀物。該物質使用矽膠管柱層析，用0-100% EtOAc/己烷溶離來純化，得到2-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(8.92 g，70%). 1H NMR (400 MHz, DMSO-d6) δ 6.99 (dd, J = 2.4, 0.8 Hz, 1H), 6.96 - 6.87 (m, 2H), 3.76 (s, 2H), 1.29 (s, 12H)。

**步驟3**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2708)



向含*N*-[(6-胺基-2-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物852) (1.4 g，3.3 mmol)之1-丙醇(14 mL)及水(4.2 mL)緩慢添加$K_2CO_3$ (1.4 g，9.9 mmol)，接著1,3-雙(2,6-二異丙基苯基)咪唑啶-2-化物;3-氯吡啶;二氯化鈀(2+)(45 mg，0.06 mmol)且將反應混合物加熱至80℃。向反應混合物緩慢添加含2-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷(1.2 g，4.1 mmol)之1-丙醇(2.8 mL)。將反應混合物在80℃下攪拌19小時。反應混合物冷卻至周圍溫度且緩慢添加至含有HCl (20 mL 1 M，19.8 mmol)之水(80 mL)。將反應混合物用EtOAc (100 mL)稀釋且有機相分離。有機相用鹽水洗滌，經$MgSO_4$乾燥，經矽藻

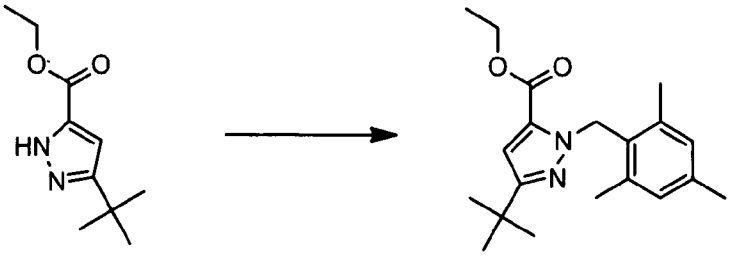
土過濾且真空濃縮。粗產物藉由矽膠管柱層析，用0-10% MeOH/DCM溶離，接著藉由逆相管柱層析，用5-100% ACN/水溶離來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2708) (495 mg，27%)。1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.40 (dt, J = 10.0, 2.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 3.83 (s, 2H), 2.76 - 2.54 (m, 3H), 2.22 (s, 1H), 1.88 (dd, J = 11.9, 5.7 Hz, 1H), 1.60 (d, J = 5.7 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 0.88 (d, J = 6.2 Hz, 3H)。ESI-MS m/z計算值562.2755, 實驗值563.36 (M+1)+；滯留時間: 2.73分鐘。

以下化合物可使用本文所述之程序合成：

*N*-(苯磺醯基)-6-[3-氟-5-[2,3,3,3-四氘-2-(三氘甲基)丙氧基]苯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物2713)。

**製備153**：5-第三丁基-*N*-(2-氰基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物266)

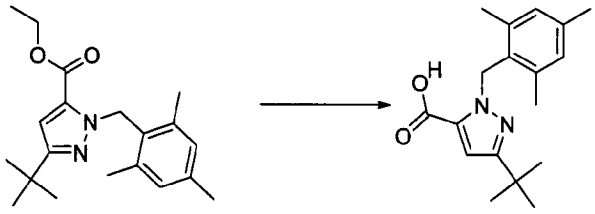
**步驟1**：3-(第三丁基)-1-(2,4,6-三甲基苯甲基)-1*H*-吡唑-5-甲酸乙酯



將5-第三丁基-4*H*-吡唑-3-甲酸乙酯(0.5 g，2.5 mmol)、2-(溴甲基)-1,3,5-三甲基-苯(0.5 g，2.5 mmol)及$K_2CO_3$ (0.7 g，5.1 mmol)於DMF (5 mL)中之混合物加熱至80℃，隔夜。添加2-(溴甲基)-1,3,5-三甲基-苯(200 mg)及$K_2CO_3$ (0.7 g，5.1 mmol)之另一等分試樣且溫度增

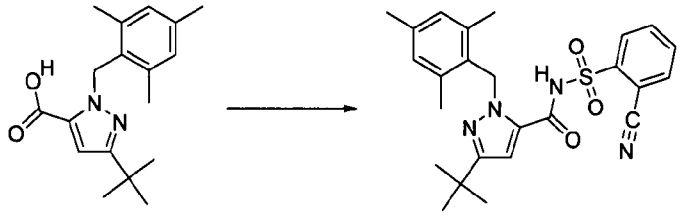
加至85℃。將反應混合物加熱隔夜。反應混合物冷卻，添加水(20 ml)且用乙酸乙酯(2×50 ml)萃取。有機層經$Na_2SO_4$乾燥，真空濃縮，且藉由矽膠管柱層析來純化。

**步驟2**：5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸



將5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸乙酯(2.0 g，6.0 mmol)及氫氧化鈉(1.9 g，48 mmol)於THF (10 mL)及水(10 mL)中之溶液在60℃下攪拌17小時。反應混合物冷卻至室溫且用1 M鹽酸酸化。白色沈澱過濾，用水洗滌，且在真空下乾燥，得到呈白色粉末狀之5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸(1.7 g，96%)。1H NMR (400 MHz, DMSO) δ 6.92 - 6.77 (m, 2H), 6.67 (s, 1H), 5.63 (s, 2H), 2.25 (dd, J = 23.8, 13.5 Hz, 9H), 1.13 (d, J = 10.4 Hz, 9H)。ESI-MS m/z計算值300.18378, 實驗值301.0 $(M+1)^+$；滯留時間: 2.06分鐘。

**步驟3**：5-第三丁基-*N*-(2-氰基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物266)



5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲酸(30mg，0.1 mmol)、2-氰基苯磺醯胺(18 mg，0.1 mmol)、HATU (38 mg，0.1 mmol)及DIEA (39 mg，52 μL，0.3 mmol)組合於DMF (1.5 mL)中且在60℃下加熱16小時。反應混合物過濾且藉由HPLC/MS，利用含於5 mM HCl水溶液中之1-99%乙腈之梯度來純化，得到5-第三丁基-*N*-(2-

氰基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物266) (11 mg，24%)。1H NMR (400 MHz, DMSO-d6) δ 8.22 (dd, J = 7.9, 1.3 Hz, 1H), 8.12 (dd, J = 7.6, 1.4 Hz, 1H), 7.97 (td, J = 7.8, 1.5 Hz, 1H), 7.90 (td, J = 7.6, 1.3 Hz, 1H), 7.00 (s, 1H), 6.74 (s, 2H), 5.43 (s, 2H), 2.17 (s, 3H), 2.06 (s, 6H), 1.16 (s, 9H)。ESI-MS m/z計算值464.1882, 實驗值465.4 $(M+1)^+$；滯留時間: 2.29分鐘。

以下化合物可使用本文所述之程序合成：

*N*-(苯磺醯基)-5-第三丁基-2-[1-(2,4,6-三甲基苯基)乙基]吡唑-3-甲醯胺(化合物201)，

*N*-(苯磺醯基)-5-第三丁基-2-[[2-氟-5-(三氟甲基)苯基]甲基]吡唑-3-甲醯胺(化合物35)，

5-第三丁基-*N*-[3-(二甲基胺基)苯基]磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物270)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三氯苯基)甲基]吡唑-3-甲醯胺(化合物303)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(4-第三丁基-2,6-二甲基-苯基)甲基]吡唑-3-甲醯胺(化合物156)，

*N*-(苯磺醯基)-5-[4-(二氟甲基)苯基]-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物119)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[[2-氯-6-(三氟甲基)苯基]甲基]吡唑-3-甲醯胺(化合物189)，

5-第三丁基-*N*-[3-(二甲基胺基)-2-甲基-苯基]磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物104)，

*N*-(3-胺基-2-甲基-苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物123)，

5-第三丁基-*N*-(1-甲基吲哚-7-基)磺醯基-2-[[2-甲基-3-(三氟甲基)

苯基]甲基]吡唑-3-甲醯胺(化合物276)，

5-第三丁基-*N*-(間甲苯基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物80)，

5-第三丁基-*N*-(5-喹啉基磺醯基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物352)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,3,5,6-四甲基苯基)甲基]吡唑-3-甲醯胺(化合物317)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(2-噻吩基磺醯基)吡唑-3-甲醯胺(化合物77)，

*N*-(苯磺醯基)-5-第三丁基-2-[(2,4,6-三氯苯基)甲基]吡唑-3-甲醯胺(化合物145)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(2-甲氧基-3-甲基-苯基)磺醯基-吡唑-3-甲醯胺(化合物59)，

*N*-(苯磺醯基)-5-第三丁基-2-(1-萘基甲基)吡唑-3-甲醯胺(化合物328)，

5-第三丁基-*N*-[3-(甲基胺基)苯基]磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物249)，

5-第三丁基-*N*-[1-(2-羥基乙基)吲哚-4-基]磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物188)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-4-甲基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物20)，

5-第三丁基-*N*-(3-羥基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物84)，

5-第三丁基-*N*-(1-甲基咪唑-4-基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物1568)，

*N*-(苯磺醯基)-5-第三丁基-2-[(3-吡咯-1-基苯基)甲基]吡唑-3-甲醯

胺(化合物108)，

5-第三丁基-*N*-(1H-吲哚-4-基磺醯基)-2-[[2-甲基-3-(三氟甲基)苯基]甲基]吡唑-3-甲醯胺(化合物60)，

*N*-(3-乙醯基苯基)磺醯基-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物332)，

*N*-(苯磺醯基)-5-第三丁基-2-[[5-甲基-2-(三氟甲基)苯基]甲基]吡唑-3-甲醯胺(化合物304)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[[2-氟-6-(三氟甲基)苯基]甲基]吡唑-3-甲醯胺(化合物239)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[1-(鄰甲苯基)乙基]吡唑-3-甲醯胺(化合物342)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-第三丁基-4-甲基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物356)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-(1-環己基乙基)吡唑-3-甲醯胺(化合物287)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-(1-苯基丙基)吡唑-3-甲醯胺(化合物165)，

5-第三丁基-*N*-(4-羥基苯基)磺醯基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物269)，

*N*-(3-胺基苯基)磺醯基-5-(1-甲基環丙基)-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物158)，

*N*-(苯磺醯基)-5-第三丁基-2-[[2-甲基-3-(三氟甲基)苯基]甲基]吡唑-3-甲醯胺(化合物98)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物185)，

*N*-(3-胺基苯基)磺醯基-5-異丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑

-3-甲醯胺(化合物167)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物173)，

*N*-(苯磺醯基)-5-第三丁基-2-[2-(2-甲氧基苯基)乙基]吡唑-3-甲醯胺(化合物157)，

5-第三丁基-*N*-[(3-甲氧基-2-吡啶基)磺醯基]-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-甲醯胺(化合物44)，

*N*-(3-胺基苯基)磺醯基-5-第三丁基-2-(1-萘基甲基)吡唑-3-甲醯胺(化合物295)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(2-氟苯基)磺醯基-吡唑-3-甲醯胺(化合物57)，

*N*-(4-胺基苯基)磺醯基-5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物81)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(1H-吲唑-4-基磺醯基)吡唑-3-甲醯胺(化合物86)，

*N*-(3-胺基-4-氟-苯基)磺醯基-5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物150)，

5-第三丁基-*N*-(2,6-二氟苯基)磺醯基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物170)，

5-第三丁基-2-[(2,6-二甲基苯基)甲基]-*N*-(1-甲基吲哚-4-基)磺醯基-吡唑-3-甲醯胺(化合物210)，

5-第三丁基-*N*-(2,3-二氫苯并呋喃-7-基磺醯基)-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物211)，

*N*-(苯磺醯基)-5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲醯胺(化合物257)，

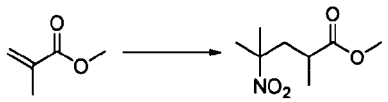
*N*-(3-胺基-4-甲基-苯基)磺醯基-5-第三丁基-2-[(2,6-二甲基苯基)

甲基]吡唑-3-甲醯胺(化合物312)及

*N*-(3-胺基苯基)磺醯基-1-[(2,4,6-三甲基苯基)甲基]苯并咪唑-2-甲醯胺(化合物71)。

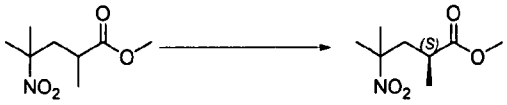
**製備154**：(3*S*)-3,5,5-三甲基吡咯啶-2-酮

**步驟1**：甲基-2,4-二甲基-4-硝基-戊酸酯



將THF (4.5 L)添加至20 L玻璃反應器中且在氮氣氛圍下在室溫下攪拌。接著2-硝基丙烷(1.5 kg)及DBU (1.282 kg，0.5當量)饋入反應器(觀測到中間物黃色)且夾套溫度增加至50℃。一旦反應內含物接近50℃，經100分鐘緩慢添加甲基丙烯酸甲酯(1.854 kg，1.1當量)。反應溫度維持在或接近50℃，其中反應在21小時結束。在反應過程期間，觀測到自黃色至深綠色之顏色改變。反應混合物真空濃縮，接著轉移回反應器且用MTBE (14 L)稀釋。添加2 M HCl (7.5 L)且將此攪拌5分鐘，接著靜置。可見兩個透明層-下層黃色水相及上層綠色有機相。移除水溶液且將有機物再與2 M HCl (3 L)攪拌。分離後，重組HCl洗滌物且與MTBE (3 L)一起攪拌5分鐘。移除水溶液且所有有機物組合於反應器中且與水(3 L)一起攪拌5分鐘。分離後，有機物真空濃縮，得到混濁綠色移動油狀物，其經$MgSO_4$乾燥且過濾，得到呈透明綠色移動油狀的外消旋甲基-2,4-二甲基-4-硝基-戊酸酯(3.16 kg) (99%產率)。$^1$H NMR (400 MHz, 氯仿-*d*) δ 3.68 (s, 3H), 2.56 - 2.35 (m, 2H), 2.11 - 2.00 (m, 1H), 1.56 (d, *J* = 20.2 Hz, 6H), 1.19 (d, *J* = 6.8 Hz, 3H)。

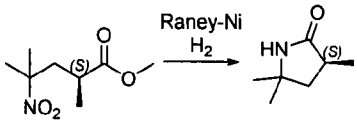
**步驟2**：(2*S*)-2,4-二甲基-4-硝基-戊酸甲酯



反應容器提供有2,4-二甲基-4-硝基-戊酸甲酯(7 kg，105.7 mmol)且與70 L pH 6.5 0.1 M磷酸鉀緩衝液一起攪拌。

向其中添加3.5 L脂肪酶(來自Novozymes之palatase)且在34℃下攪拌約43小時。反應pH值藉由pH恆定法給與$K_2CO_3$ (水溶液)維持於pH 6.5。反應混合物用MTBE (2×5體積，1×2體積)萃取。接著合併之MTBE層用2 M $Na_2CO_3$ (4×2.5體積)、水(3體積)及鹽水(3體積)洗滌。藉由蒸發MTBE將產物在反應器中濃縮至約10 L且轉移至大的旋轉蒸發儀以進行最終濃縮，得到呈移動黃色油狀之(2*S*)-2,4-二甲基-4-硝基-戊酸甲酯(3072.2 g，44%產率)。

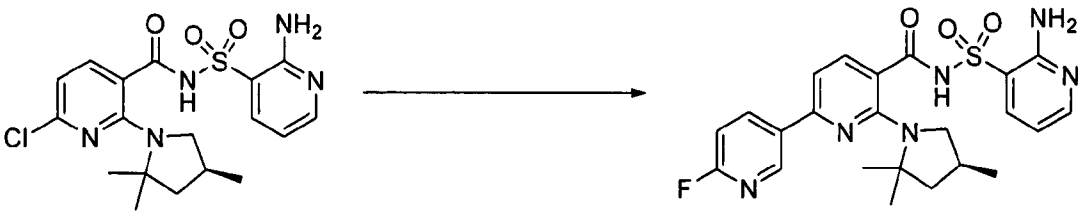
**步驟3**：(3*S*)-3,5,5-三甲基吡咯啶-2-酮




20 L Hastelloy反應容器用$N_2$淨化且維持在$N_2$下。容器依序饋入DI水清洗之潮濕Raney® Ni (2800級，250 g)、(2*S*)-2,4-二甲基-4-硝基-戊酸甲酯(1741 g，9.2 mol)及乙醇(13.9 L，8體積)。在900 rpm下開始攪拌且反應器用$H_2$沖洗且維持在約2.5巴下。5小時後，反應混合物過濾以移除Raney鎳且固體餅狀物用乙醇(3.5 L，2體積)沖洗。產物之乙醇溶液真空濃縮以減少至最少體積的乙醇(約1.5體積)，接著添加庚烷(2.5 L)且懸浮液再濃縮至約1.5體積。此再重複3次，接著所得懸浮液冷卻至0-5℃且抽吸過濾且用庚烷(2.5 L)洗滌。產物在過濾器上在真空下乾燥20分鐘，接著轉移至乾燥盤且在真空烘箱中在40℃下乾燥隔夜(N2放出)。此得到呈白色結晶固體狀之(3*S*)-3,5,5-三甲基吡咯啶-2-酮(2.042 kg，87 %)。$^1$H NMR (400 MHz, 氯仿-*d*) δ 6.39 (s, 1H), 2.62 (ddq, J = 9.9, 8.6, 7.1 Hz, 1H), 2.17 (ddd, J = 12.4, 8.6, 0.8 Hz, 1H), 1.56 (dd, J = 12.5, 9.9 Hz, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.20 (d, J = 7.1 Hz, 3H)。

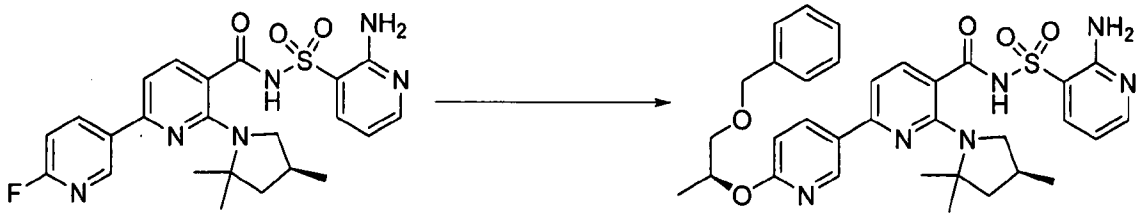
**製備155**：*N*-((2-胺基吡啶-3-基)磺醯基)-6'-(((*S*)-1-羥基丙-2-基)氧基)-6-((*S*)-2,2,4-三甲基吡咯啶-1-基)-[2,3'-聯吡啶]-5-甲醯胺(化合物2690)

**步驟1**：*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-氟-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



*N*-[(2-胺基-3-吡啶基)磺醯基]-6-氯-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(3.8 g，8.96 mmol)、(6-氟-2-吡啶基)硼酸(2.00 g，14.2 mmol)、[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(1.40 g，2.32 mmol)及$Na_2CO_3$ (4.00 g，37.7 mmol)於二甲基甲醯胺(80 mL)及水(20 mL)中之混合物在氮氣流下脫氣且在100℃下攪拌18小時。添加(6-氟-2-吡啶基)硼酸(0.90 g，6.4 mmol)、[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)與二氯甲烷之複合物(0.40 g，0.55 mmol)，且將反應混合物在100℃下再攪拌一天。反應混合物經矽藻土墊過濾且濾液用水(300 mL)稀釋，調至約pH 7且用乙酸乙酯(5×300 mL)萃取。萃取物用鹽水(2×200 mL)洗滌，經$Na_2SO_4$乾燥，且濃縮。殘餘物藉由矽膠層析，用己烷中0-100%乙酸乙酯溶離純化，得到黃色泡沫產物(2.2 g，約85%純度)及起始物質 (**3**) (560 mg)。

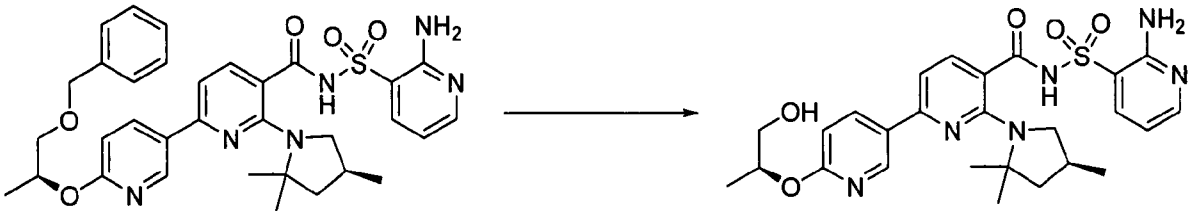
**步驟2**：*N*-((2-胺基吡啶-3-基)磺醯基)-6'-(((*S*)-1-(苯甲氧基)丙-2-基)氧基)-6-((*S*)-2,2,4-三甲基-吡咯啶-1-基)-[2,3'-聯吡啶]-5-甲醯胺



將氫化鈉(44 mg，1.1 mmol) (60 wt%於礦物油中)添加至(*R*)-1-苯甲氧基-丙-2-醇(117 mg，0.7 mmol)於二甲基甲醯胺(2.0 mL)中之溶液中。在室溫下攪拌5分鐘後，添加*N*-[(2-胺基-3-吡啶基)磺醯基]-6-(6-氟-2-吡啶基)-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(108

mg，0.18 mmol)。將反應混合物在微波照射下在75℃下加熱30分鐘。反應混合物用水(10 mL)淬滅，調至pH 3-4，且用乙酸乙酯(2×10 mL)萃取。合併之萃取物用鹽水(2×5 mL)洗滌，經$Na_2SO_4$乾燥且在減壓下濃縮，得到*N*-((2-胺基吡啶-3-基)磺醯基)-6'-(((*S*)-1-(苯甲氧基)丙-2-基)氧基)-6-((*S*)-2,2,4-三甲基-吡咯啶-1-基)-[2,3'-聯吡啶]-5-甲醯胺。ESI-MS m/z 631 $(M+1)^+$。

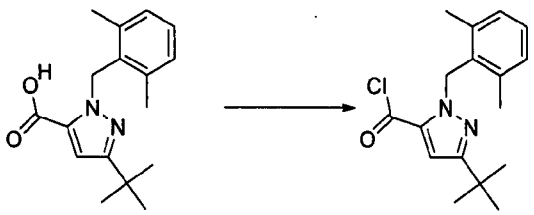
**步驟3**：*N*-((2-胺基吡啶-3-基)磺醯基)-6'-(((*S*)-1-羥基丙-2-基)氧基)-6-((*S*)-2,2,4-三甲基吡咯啶-1-基)-[2,3'-聯吡啶]-5-甲醯胺(化合物2690)



在室溫下在1大氣壓氫氣下在Pd/C (10%，260 mg)下在甲醇(25 mL)中將*N*-((2-胺基吡啶-3-基)磺醯基)-6'-(((*S*)-1-(苯甲氧基)丙-2-基)氧基)-6-((*S*)-2,2,4-三甲基-吡咯啶-1-基)-[2,3'-聯吡啶]-5-甲醯胺氫化。4小時後，催化劑藉由過濾移除，在減壓下蒸發且藉由矽膠管柱層析(甲烷中0-10%二氯甲醇)來純化，接著藉由矽膠管柱層析，用乙酸乙酯及己烷比率50/50之混合溶劑中0-8%甲醇溶離來進一步純化，得到*N*-((2-胺基吡啶-3-基)磺醯基)-6'-(((*S*)-1-羥基丙-2-基)氧基)-6-((*S*)-2,2,4-三甲基吡咯啶-1-基)-[2,3'-聯吡啶]-5-甲醯胺(化合物2690) (9 mg)。ESI-MS m/z 541 $(M+1)^+$。

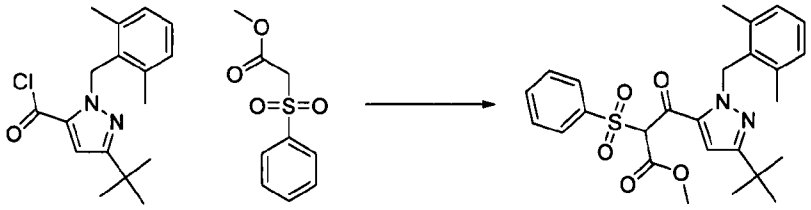
**製備156**：2-(苯磺醯基)-3-[5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-基]-3-側氧基-丙酸甲酯(化合物4)

**步驟1**：5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-羰基氯



5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-甲酸(100 mg，0.3492 mmol)溶於硫醯氯(41.54 mg，25.47 μL，0.3492 mmol)中且添加一滴DMF。將反應物攪拌1小時且蒸發，得到酸氯化物，其未經進一步純化即使用。

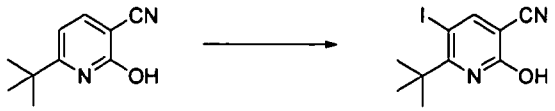
**步驟2**：2-(苯磺醯基)-3-[5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-基]-3-側氧基-丙酸甲酯(化合物4)



將含5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-羰基氯(40 mg，0.13 mmol)、2-(苯磺醯基)乙酸甲酯(28 mg，22 μL，0.13 mmol)及NaH (5 mg，0.13 mmol)之DMF在室溫下攪拌15分鐘。反應物過濾且藉由逆相LC-MS (10-99% $CH_3CN/H_2O$，HCl改質劑)來純化，得到2-(苯磺醯基)-3-[5-第三丁基-2-[(2,6-二甲基苯基)甲基]吡唑-3-基]-3-側氧基-丙酸甲酯(化合物4) (18 mg，28%)。ESI-MS m/z 483.4 $(M+1)^+$；滯留時間: 2.41分鐘。

**製備157**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(*E*)-2-(4-甲氧基苯基)乙烯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1535)

**步驟1**：5-碘-6-第三丁基-2-羥基吡啶-3-甲腈



將*N*-碘丁二醯亞胺(31.9 g，142 mmol)添加至6-第三丁基-2-羥基吡啶-3-甲腈(10.0 g，56.8 mmol)於1,2-二氯乙烷(120 mL)及三氟乙酸(40 mL)之混合物中之溶液中且將反應混合物在50℃下加熱隔夜。溶液在減壓下濃縮且添加乙酸乙酯(300 mL)。有機層用10%硫代硫酸鈉

溶液(300 mL)、水(2×200 mL)及鹽水(150 mL)洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。殘餘物藉由急驟層析，庚烷中30% EtOAc至庚烷中60% EtOAc溶離純化，得到呈白色固體狀之5-碘-6-第三丁基-2-羥基吡啶-3-甲腈(15.85 g，92%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.57 (s, 9 H), 8.17 (s, 1 H)。$[M+H]^+$ = 303.0。

**步驟2**：5-碘-6-第三丁基-2-氯吡啶-3-甲腈



氧氯化磷(67.0 mL，718 mmol)及五氯化磷(44.9 g，216 mmol)添加至5-碘-6-第三丁基-2-羥基吡啶-3-甲腈(21.7 g，71.8 mmol)且反應混合物回流隔夜。反應混合物冷卻至室溫且在減壓下濃縮以移除大部分剩餘氧氯化磷。添加水(*注意*：放熱)，接著50% NaOH溶液，直至達至約pH 9且水層用乙酸乙酯(3×100 mL)萃取。合併之有機層用鹽水(100 mL)洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮，得到呈黃色固體狀之5-碘-6-第三丁基-2-氯吡啶-3-甲腈(17.35 g，75%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.55 (s, 9 H), 8.38 (s, 1 H)。$[M+H]^+$ = 320.9。

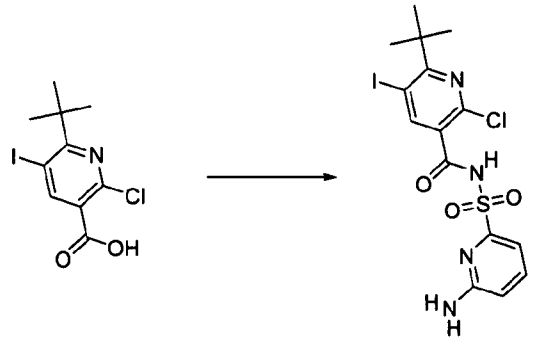
**步驟3**：5-碘-6-第三丁基-2-氯吡啶-3-甲酸



將含氫氧化鉀(18.2 g，325 mmol)之水(60 mL)添加至含5-碘-6-第三丁基-2-氯吡啶-3-甲腈(17.35 g，54.1 mmol)之2-丙醇(60 mL)中且將反應混合物在90℃下加熱隔夜。添加乙酸乙酯(50 mL)且將有機層用1 N NaOH (3×50 mL)萃取。合併鹼性水層且在減壓下濃縮以移除大部分2-丙醇。剩餘水層用濃HCl酸化至pH 1-2且用乙酸乙酯(3×100 mL)萃取。合併有機層，用鹽水(100 mL)洗滌，經無水硫酸鈉乾燥，過濾且在減壓下濃縮。殘餘物藉由逆相層析(甲醇/水，0%至100%)來純

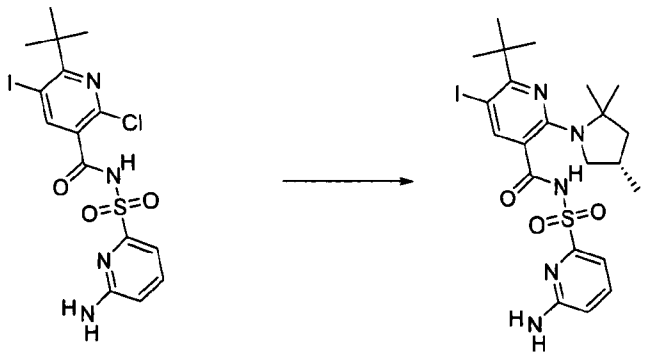
化，得到呈灰白色固體狀之5-碘-6-第三丁基-2-氯吡啶-3-甲酸(8.2 g，45%產率)。$^1$H NMR (300 MHz, $CDCl_3$) ppm 1.57 (s, 9 H), 8.77 (s, 1 H)。$[M+H]^+$ = 339.9。

**步驟4**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-氯-5-碘-吡啶-3-甲醯胺



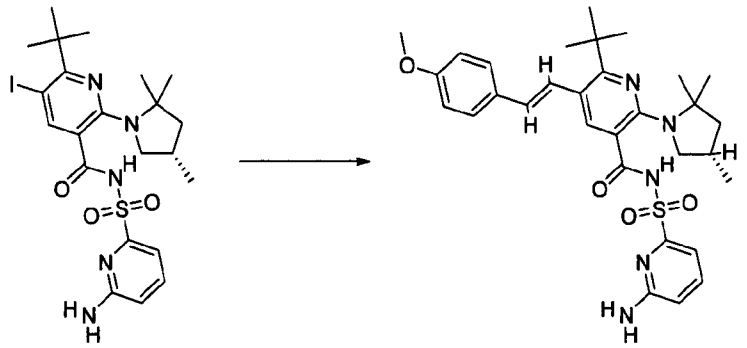
在氮氣下在周圍溫度下向攪拌的6-第三丁基-2-氯-5-碘-吡啶-3-甲酸(1.57 g，4.62 mmol)於無水DMF (11.0 mL)中之溶液中一次性添加CDI (0.94 g，5.78 mmol)。反應升溫至45℃且攪拌1.5小時。在另一燒瓶中，在氮氣下6-胺基吡啶-2-磺醯胺(1.00 g，5.78 mmol)溶於無水DMF (9.0 mL)中且在周圍溫度下分部分添加氫化鈉(60%於礦物油中)(231 mg，5.78 mmol)以減輕氣體放出。不均質混合物升溫至40℃且攪拌1小時。在45℃下將此反應混合物一次性添加至攪拌的活化酸混合物中。移除熱且將反應物再攪拌。反應混合物緩慢添加至冰冷水(160 mL)，接著添加AcOH (1.43 g，1.35 mL，23.81 mmol)且將反應混合物用力攪拌10分鐘且過濾固體且用水(3×20 mL)洗滌。固體在己烷(50 mL)中形成漿狀物且過濾。進一步乾燥固體，得到呈白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-氯-5-碘-吡啶-3-甲醯胺(2.11 g，92%)。

**步驟5**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-碘-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺



向*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-氯-5-碘-吡啶-3-甲醯胺(2.11 g，4.27 mmol)於無水DMSO (10 mL)中之溶液中依序添加(4S)-2,2,4-三甲基吡咯啶(1.01 g，8.96 mmol)及$K_2CO_3$ (2.95 g，21.32 mmol)。將反應混合物在氮氣氛圍下在150℃下加熱18小時。在攪拌下使反應混合物冷卻至周圍溫度，接著傾倒至冰水(125 mL)上。藉由添加1 M HCl，pH值調至約6.0至7.0，固體過濾，用水(4×20 mL)洗滌且在真空下乾燥，得到呈灰白色固體狀之*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-碘-2-[(4S)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(2.15 g，88%)。

**步驟6**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(*E*)-2-(4-甲氧基苯基)乙烯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1535)



在氮氣氛圍下將DMF (0.5 mL)及$H_2O$ (0.1 mL)添加至*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-碘-2-(2,2,4-三甲基吡咯啶-1-基)吡啶-3-甲醯胺(30 mg，0.05 mmol)及[(*E*)-2-(4-甲氧基苯基)乙烯基]硼酸(19 mg，0.11 mmol)，接著$K_2CO_3$ (29 mg，0.21 mmol)。接著添加肆

(三苯基膦)鈀(0) (6 mg，0.005 mmol)，反應混合物在氮氣氛圍下密封且在130℃下加熱13小時。使反應混合物冷卻至周圍溫度且產物使用逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經30.0分鐘10-99%移動相B (移動相A = $H_2O$ (5 mM HCl)，移動相B = $CH_3CN$)之雙重梯度來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(*E*)-2-(4-甲氧基苯基)乙烯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1535) (5 mg，16%)。ESI-MS m/z 578.6 $(M+1)^+$；滯留時間: 1.78分鐘；1H NMR (400 MHz,甲醇-d4) δ 8.26 (s, 1H), 7.68 (dd, J = 8.5, 3.4 Hz 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 15.9 Hz 1H), 7.37 (d, J = 7.3 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 15.9 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.48 (dd, J = 10.9, 8.2 Hz, 1H), 3.17 (dd, J = 11.1, 9.3 Hz, 1H), 2.69 - 2.52 (m, 1H), 2.11 (dd, J = 12.4, 6.8 Hz, 1H), 1.74 (t, J = 11.8 Hz, 1H), 1.54 (s, 3H), 1.49 (s, 9H), 1.46 (s, 3H), 1.13 (d, J = 6.5 Hz, 3H)。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-5-(3-雙環[2.2.1]庚-2-烯基)-6-第三丁基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1577)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(*E*)-戊-1-烯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1617)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(*E*)-2-環丙基乙烯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1665)，

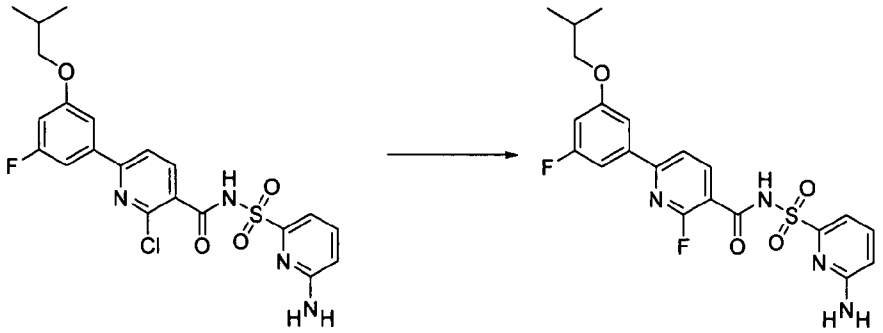
(*E*)-3-[5-[(6-胺基-2-吡啶基)磺醯基胺甲醯基]-2-第三丁基-6-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]-3-吡啶基]丙-2-烯酸乙酯(化合物1490)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]-5-乙烯基-吡啶-3-甲醯胺(化合物1373)及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-第三丁基-5-[(*E*)-2-乙氧基乙烯基]-2-[(4*S*)-2,2,4-三甲基吡咯啶-1-基]吡啶-3-甲醯胺(化合物1626)

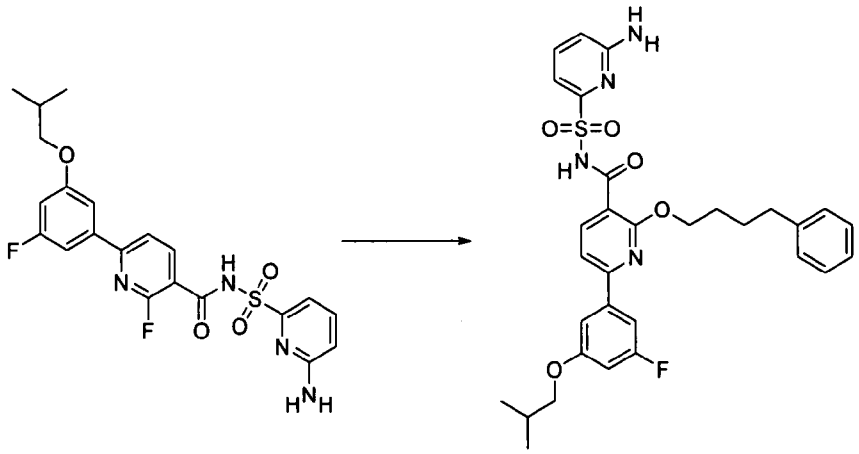
**製備158**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-苯基丁氧基)吡啶-3-甲醯胺(化合物1686)

**步驟1**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氟-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺



*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氯-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(300 mg，0.63 mmol)溶於DMSO (1.2 mL)中。添加氟化銫(476 mg，3.13 mmol)。將反應混合物密封且在150℃下攪拌隔夜。添加額外氟化銫(100 mg)，且將反應混合物在150℃下攪拌隔夜。冷卻至室溫後，混合物用EtOAc (75 mL)稀釋且用稀HCl水溶液(0.1 N，1×75 mL)洗滌。有機層經硫酸鈉乾燥，過濾且在減壓下濃縮。產物未經進一步純化即用於下一步。ESI-MS m/z 463.2 $(M+1)^+$；滯留時間:1.83分鐘。

**步驟2**：*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-苯基丁氧基)吡啶-3-甲醯胺(化合物1686)



4-苯基丁-1-醇(23 mg，0.15 mmol)溶於二噁烷(250 μL)中。添加氫化鈉(6 mg，0.15 mmol)，且將反應混合物在室溫下攪拌5分鐘。添加*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氟-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(35 mg，0.08 mmol)於DMSO (250 μL)中之溶液。再攪拌5分鐘後，將反應混合物在微波照射下在100℃下加熱30分鐘，接著在減壓下濃縮且藉由逆相HPLC-MS法，使用Luna C18 (2)管柱(75 × 30 mm，5 μm粒徑)及經15.0分鐘1-99%移動相B之雙重梯度(移動相A =水(5 mM HCl)，移動相B =乙腈)來純化，得到*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(4-苯基丁氧基)吡啶-3-甲醯胺(化合物1686) (30 mg，64%)。ESI-MS m/z 593.4 $(M+1)^+$；滯留時間: 2.47分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-苯基丁氧基)吡啶-3-甲醯胺(化合物1689)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-苯基丙氧基)吡啶-3-甲醯胺(化合物1694)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(3-吡啶基)丁氧基]吡啶-3-甲醯胺(化合物1690)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(4-

吡啶基)丁氧基]吡啶-3-甲醯胺(化合物1687)，

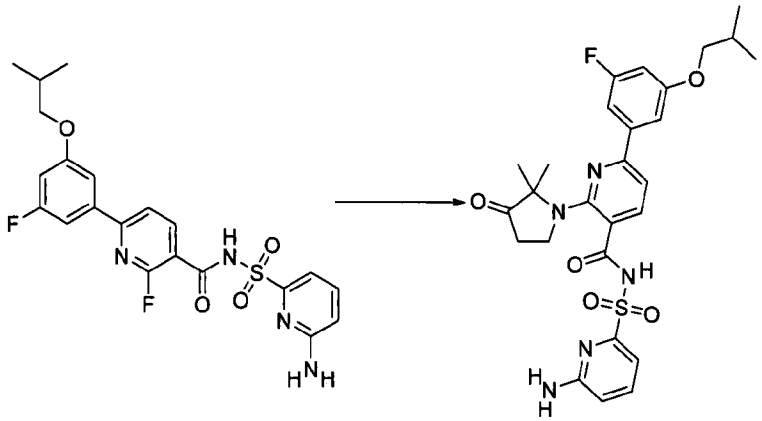
*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[4-(2-吡啶基)丁氧基]吡啶-3-甲醯胺(化合物1688)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(2-吡啶基)丙氧基]吡啶-3-甲醯胺(化合物1693)，

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-[3-(3-吡啶基)丙氧基]吡啶-3-甲醯胺(化合物1691)及

*N*-[(6-胺基-2-吡啶基)磺醯基]-6-(3-氟-5-異丁氧基-苯基)-2-(3-吡唑-1-基丙氧基)吡啶-3-甲醯胺(化合物1692)。

**製備159**：*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-3-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1189)

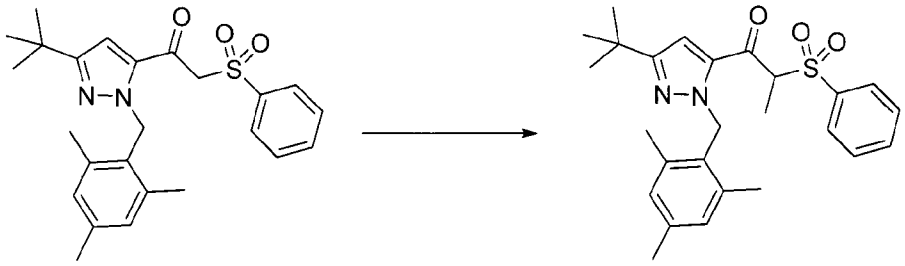


將固體碳酸鉀(90 mg，0.65 mmol)添加至2,2-二甲基吡咯啶-3-酮(49 mg，0.32 mmol)於DMSO (250 μL)中之懸浮液中，接著添加*N*-[(6-胺基-2-吡啶基)磺醯基]-2-氟-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(HCl鹽) (50 mg，0.11 mmol)。將反應混合物在150℃下攪拌3小時。反應混合物使用逆相HPLC法，使用Luna C18 (2)管柱(50 × 21.2 mm，5 μm粒徑)及經15.0分鐘10-99%移動相B (移動相 A =水(5 mM HCl)，移動相B =乙腈)之雙重梯度來純化。ESI-MS m/z 556.4 $(M+1)^+$；滯留時間: 2.01分鐘。

以下化合物可使用本文所述之程序合成：

*N*-[(6-胺基-2-吡啶基)磺醯基]-2-(2,2-二甲基-4-側氧基-吡咯啶-1-基)-6-(3-氟-5-異丁氧基-苯基)吡啶-3-甲醯胺(化合物1073)。

**製備160**：2-(苯磺醯基)-1-[5-第三丁基-2-[(2,4,6-三甲基苯基)甲基]吡唑-3-基]丙-1-酮(化合物139)



向2-(苯磺醯基)-1-{3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-5-基}乙-1-酮(50 mg，0.11 mmol)於THF (3.0 mL)及DMF (1.0 mL)中之溶液中添加DBU (52 mg，0.34 mmol)且將混合物在室溫下攪拌30分鐘。接著添加碘甲烷(40 mg，0.28 mmol)且將反應物在室溫下攪拌隔夜。藉由LCMS分析等分試樣，指示僅僅發生單甲基化(非雙甲基化)。粗反應混合物轉移至具有水之分液漏斗，且用二乙醚萃取兩次。合併有機層，經硫酸鈉乾燥，過濾且在減壓下濃縮，得到粗產物。在另一個實驗中，向2-(苯磺醯基)-1-{3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-5-基}乙-1-酮(50 mg，0.11 mmol)於THF (3.0 mL)及DMF (1.0 mL)中之溶液添加DBU (52 mg，0.34 mmol)且混合物在油浴中在80℃下加熱10分鐘。接著添加碘甲烷(40 mg，0.28 mmol)，將小瓶封蓋且將反應物在油浴中在80℃下加熱隔夜。藉由LCMS分析等分試樣，指示僅僅發生單甲基化(非雙甲基化)。粗反應混合物轉移至具有水之分液漏斗且用二乙醚萃取兩次。合併有機層，經硫酸鈉乾燥，過濾且在減壓下濃縮，得到粗產物。兩種粗反應混合物合併在一起且藉由矽膠管柱層析，用庚烷中5%至20% EtOAc溶離來純化，得到呈白色固體狀之*rac* 2-(苯磺醯基)-1-{3-第三丁基-1-[(2,4,6-三甲基苯基)甲基]-1*H*-吡唑-5-基丙-1-酮(64 mg，60%產率)。$^1$H NMR

(300 MHz, DMSO-$d_6$) ppm 1.10 (s, 9 H), 1.46 (d, $J$ = 6.8 Hz, 3 H), 2.16 (s, 6 H), 2.21 (s, 3 H), 5.40 - 5.53 (m, 3 H), 6.83 (s, 2 H), 7.15 (s, 1 H), 7.55 - 7.62 (m, 2 H), 7.68 - 7.76 (m, 3 H)。ESI-MS m/z 453.2 $(M+1)^+$。

下表2敍述表1化合物之分析資料。

**表2.**

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1 | 503.00 | 1.96 | |
| 2 | 419.00 | 2.04 | |
| 3 | 484.05 | 2.00 | |
| 4 | 483.40 | 2.41 | |
| 5 | 438.40 | 1.74 | |
| 6 | 435.20 | 1.50 | |
| 7 | 469.40 | 2.06 | 1H NMR (400 MHz, DMSO-d6) δ 12.19 (s, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.17 (t, J = 2.1 Hz, 1H), 7.09 - 7.03 (m, 2H), 6.83 (ddd, J = 8.1, 2.3, 1.0 Hz, 1H), 6.72 (s, 2H), 5.68 (s, 2H), 4.42 - 4.35 (m, 2H), 2.84 - 2.76 (m, 2H), 2.15 (s, 3H), 2.08 (s, 6H), 1.23 (s, 9H). |
| 8 | 561.40 | 2.30 | |
| 9 | 482.10 | 1.98 | |
| 10 | 467.10 | 2.18 | |
| 11 | 468.00 | 2.14 | 1H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 7.92 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 7.8 Hz, 1H), 6.91 (s, 2H), 6.62 (d, J = 11.3 Hz, 2H), 6.17 (s, 2H), 2.26 (s, 3H), 1.95 (s, 6H), 1.04 (s, 9H). |
| 12 | 447.20 | 2.14 | |
| 13 | 426.40 | 1.80 | |
| 14 | 561.14 | 2.91 | |
| 15 | 481.00 | 2.15 | 1H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.69 (s, 1H), 7.62 (s, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 26.9 Hz, 3H), 6.69 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.69 (s, 2H), 2.29 (s, 3H), 2.04 (d, J = 25.4 Hz, 3H), 1.67 (d, J = 28.9 Hz, 4H), 0.98 (s, 6H). |
| 16 | 465.30 | 1.52 | |
| 17 | 519.00 | 1.93 | 1H NMR (400 MHz, DMSO) δ 8.10 (d, J = 7.9 Hz, 1H), 7.33 (s, 2H), 7.20 (s, 3H), 7.07 (s, 2H), 6.94 (s, 4H), 6.71 (d, J = 8.3 Hz, 1H), 6.52 (s, 2H). |
| 18 | 464.00 | 1.97 | 1H NMR (400 MHz, DMSO) δ 12.71 (s, 1H), 8.47 (d, J = 6.8 Hz, 1H), 8.28 (d, J = 9.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H), 7.25 (s, 1H), 7.15 (s, 1H), 7.07 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.62 (s, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3.92 (s, 3H), 2.18 (s, 3H), 1.84 (s, 6H). |
| 19 | 467.20 | 2.83 | 1H NMR (400 MHz, 氯仿-d) δ 8.27 (d, J = 7.9 Hz, 1H), 7.49 - 7.33 (m, 2H), 7.23 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.88 - 6.74 (m, 3H), 3.89 (s, 2H), 2.29 (s, 3H), 2.02 (s, 6H), 1.06 (s, 9H). |
| 20 | 469.40 | 2.04 | |
| 21 | 532.30 | 2.08 | |
| 22 | 451.00 | 2.44 | |
| 23 | 449.00 | 1.54 | 1H NMR (400 MHz, DMSO) δ 8.02 (s, 1H), 7.60 (s, 1H), 7.25 (s, 1H), 7.18 (s, 1H), 6.98 (s, 2H), 6.78 (s, 4H), 2.17 (s, 3H), 1.97 (s, 6H). |
| 24 | 468.20 | 1.92 | |
| 25 | 448.20 | 1.91 | |
| 26 | 452.50 | 1.81 | |
| 27 | 494.07 | 2.08 | |
| 28 | 480.30 | 2.20 | |
| 29 | 490.00 | 2.16 | |
| 30 | 478.34 | 1.45 | |
| 31 | 425.40 | 1.64 | |
| 32 | 451.00 | 0.90 | 1H NMR (400 MHz, MeOD) δ 7.99 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 6.2 Hz, 1H), 7.44 - 7.26 (m, 4H), 6.92 (s, 2H), 6.86 (d, J = 9.5 Hz, 1H), 5.36 (s, 1H), 4.69 (d, J = 20.6 Hz, 3H), 2.44 (s, 6H), 2.25 (s, 3H). |
| 33 | 451.20 | 2.07 | |
| 34 | 484.00 | 2.30 | 1H NMR (400 MHz, DMSO) δ 12.52 (s, 1H), 8.04 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.3 Hz, 1H), 7.15 (dd, J = 12.9, 8.1 Hz, 2H), 6.90 (s, 2H), 3.85 (s, 3H), 2.25 (s, 3H), 1.94 (s, 6H), 1.05 (s, 9H). |
| 35 | 484.05 | 1.97 | |
| 36 | 464.20 | 1.82 | |
| 37 | 510.00 | 2.13 | |
| 38 | 448.30 | 1.90 | |
| 39 | 470.00 | 2.12 | 1H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 7.99 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.63 (dt, J = 15.3, 7.7 Hz, 2H), 7.01 (s, 1H), 6.75 (s, 2H), 5.42 (s, 2H), 4.63 (s, 2H), 2.16 (s, 3H), 2.07 (d, J = 6.4 Hz, 6H), 1.14 (s, 9H). |
| 40 | 477.25 | 1.86 | |
| 41 | 472.28 | 2.06 | |
| 42 | 505.40 | 1.92 | |
| 43 | 494.07 | 2.02 | |
| 44 | 471.30 | 2.28 | |
| 45 | 440.40 | 2.25 | 1H NMR (400 MHz, 氯仿-d) δ 8.33 (s, 1H), 8.17 - 8.11 (m, 2H), 7.72 - 7.65 (m, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.58 (dd, J = 8.5, 7.1 Hz, 2H), 6.74 (s, 2H), 6.45 (s, 1H), 5.51 (s, 2H), 2.22 (s, 3H), 2.12 (s, 6H), 1.17 (s, 9H). |
| 46 | 428.17 | 1.77 | |
| 47 | 469.00 | 2.16 | 1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 10.19 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 4.7 Hz, 3H), 7.14 - 7.04 (m, 2H), 6.89 (s, 2H), 2.25 (s, 3H), 1.93 (s, 6H), 1.04 (s, 9H). |
| 48 | 436.00 | 1.20 | 1H NMR (400 MHz, DMSO) δ 10.14 (s, 1H), 8.59 (s, 1H), 7.97 (s, 2H), 7.56 (d, J = 23.1 Hz, 2H), 7.32 (d, J = 21.5 Hz, 3H), 6.89 (s, 2H), 5.27 (s, 1H), 4.49 (d, J = 13.2 Hz, 1H), 4.31 (s, 3H), 2.35 (s, 6H), 2.23 (s, 3H). |
| 49 | 476.30 | 2.05 | |
| 50 | 437.40 | 2.11 | |
| 51 | 470.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 11.83 (s, 1H), 8.28 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.16 (s, 1H), 6.92 (s, 1H), 6.46 (s, 1H), 2.26 (s, 3H), 1.98 (s, 6H), 1.04 (s, 9H). |
| 52 | 438.22 | 1.88 | |
| 53 | 467.30 | 2.84 | 1H NMR (400 MHz, 氯仿-d) δ 8.27 (d, J = 7.9 Hz, 1H), 7.49 - 7.36 (m, 2H), 7.22 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.87 - 6.75 (m, 3H), 3.89 (s, 2H), 2.29 (s, 3H), 2.02 (s, 6H), 1.06 (s, 9H). |
| 54 | 521.00 | 1.81 | |
| 55 | 456.40 | 1.91 | 1H NMR (400 MHz, DMSO-d6) δ 12.55 (s, 1H), 12.03 (s, 1H), 8.25 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.83 (s, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.10 (s, 1H), 7.04 (s, 2H), 6.45 (t, J = 6.8 Hz, 1H), 2.30 (s, 3H), 2.02 (s, 3H), 1.09 (s, 9H). |
| 56 | 483.00 | 2.34 | 1H NMR (400 MHz, DMSO) δ 12.23 (s, 1H), 7.95 (s, 1H), 7.54 (d, J = 36.2 Hz, 3H), 7.30 (s, 1H), 7.12 (s, 1H), 6.90 (s, 2H), 3.80 (s, 3H), 2.25 (s, 3H), 1.92 (s, 6H), 1.04 (s, 9H). |
| 57 | 444.38 | 3.14 | |
| 58 | 425.40 | 1.63 | |
| 59 | 470.30 | 2.27 | |
| 60 | 519.00 | 1.98 | 1H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 11.67 (s, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.28 (d, J = 21.0 Hz, 3H), 6.86 (s, 1H), 6.55 (s, 1H), 5.51 (s, 2H), 2.20 (s, 3H), 2.07 (s, 2H), 1.24 (s, 9H). |
| 61 | 533.22 | 3.09 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 62 | 462.40 | 1.91 | |
| 63 | 440.00 | 2.11 | 1H NMR (400 MHz, DMSO-d6) δ 11.90 (s, 1H), 8.57 (s, 1H), 8.05 - 7.96 (m, 2H), 7.77 - 7.70 (m, 1H), 7.70 - 7.61 (m, 2H), 6.73 (s, 2H), 3.98 (s, 2H), 2.17 (s, 3H), 2.07 (s, 6H), 1.38 (s, 9H). |
| 64 | 533.22 | 2.85 | 1H NMR (400 MHz, DMSO) δ 12.52 (s, 1H), 9.02 (s, 2H), 8.22 - 8.19 (d, 1H), 7.89 - 7.86 (d, 1H), 7.66 (t, J = 7.91, 1H), 7.25 - 7.22 (d, 1H), 6.96 (s, 2H), 6.74 - 7.61 (d, 1H), 6.59 (s, 2H), 3.22 - 3.08 (m, 1H), 2.2 9 (s, 3H), 2.03 (s, 6H), 1.27 - 1.24 (d, 6H) |
| 65 | 468.20 | 1.93 | |
| 66 | 533.22 | 2.90 | |
| 67 | 474.50 | 1.70 | 1H NMR (400 MHz, DMSO-d6) δ 7.61 (dd, J = 8.4, 7.3 Hz, 1H), 7.48 (s, 2H), 7.38 (s, 2H), 7.11 (d, J = 7.3 Hz, 1H), 7.02 (dd, J = 8.9, 1.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.46 (s, 2H),, 3.18 (s, 1H), 2.34 (s, 3H), 1.97 (d, J = 15.9 Hz, 6H). |
| 68 | 469.40 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 8.78 (s, 1H), 7.30 - 7.21 (m, 2H), 7.12 (dd, J = 7.4, 1.8 Hz, 1H), 6.93 (s, 2H), 6.86 (dd, J = 7.9, 2.2 Hz, 1H), 2.26 (s, 3H), 1.94 (s, 6H), 1.11 (s, 9H)；NH2未觀測到。 |
| 69 | 533.22 | 2.89 | |
| 70 | 477.40 | 2.03 | |
| 71 | 449.20 | 1.41 | |
| 72 | 582.20 | 2.26 | |
| 73 | 451.00 | 1.07 | 1H NMR (400 MHz, CD3CN) δ 7.70 (s, 1H), 7.37 (d, J = 26.5 Hz, 4H), 7.18 (d, J = 7.3 Hz, 1H), 6.94 (s, 2H), 6.84 (d, J = 8.6 Hz, 1H), 5.06 (s, 1H), 4.62 (d, J = 14.0 Hz, 1H), 4.45 (s, 2H), 4.37 (d, J = 14.0 Hz, 1H), 2.43 (s, 6H), 2.27 (s, 3H). |
| 74 | 409.30 | 1.93 | |
| 75 | 440.40 | 1.91 | |
| 76 | 489.40 | 1.58 | |
| 77 | 432.04 | 2.04 | |
| 78 | 478.00 | 2.26 | 1H NMR (400 MHz, DMSO) δ 8.27 (d, J = 7.9 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 8.00 (s, 2H), 7.91 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.89 (s, 2H), 2.25 (s, 3H), 1.92 (s, 6H), 1.04 (s, 9H). |
| 79 | 465.00 | 1.57 | 1H NMR (400 MHz, DMSO) δ 7.84 (d, J = 7.9 Hz, 1H), 7.60 (s, 1H), 7.33 (s, 4H), 7.16 (d, J = 8.4 Hz, 1H), 7.07 (s, 1H), 6.87 (s, 2H), 5.14 (s, 1H), 4.25 (d, J = 39.6 Hz, 4H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3.86 (s, 3H), 2.31 (s, 6H), 2.22 (s, 3H). |
| 80 | 454.00 | 2.31 | 1H NMR (400 MHz, DMSO) δ 7.69 (s, 1H), 7.43 (s, 1H), 7.30 (s, 1H), 7.17 (s, 1H), 7.04 (s, 1H), 6.68 (s, 2H), 5.40 (s, 2H), 2.35 (s, 3H), 2.10 (s, 3H), 2.02 (s, 6H), 1.07 (s, 9H). |
| 81 | 441.38 | 2.84 | 1H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 7.63 - 7.60 (d, 2H), 7.07 - 6.92 (m, 4H), 6.64 - 6.61 (d, 2H), 6.21 (s, 2H), 5.48 (s, 2H), 2.13 (s, 6H), 1.12 (s, 9H) |
| 82 | 468.20 | 1.91 | |
| 83 | 480.30 | 2.19 | |
| 84 | 456.40 | 2.06 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 10.23 (s, 1H), 7.50 - 7.39 (m, 3H), 7.12 (dt, J = 8.0, 1.8 Hz, 1H), 7.01 (s, 1H), 6.77 (s, 2H), 5.46 (s, 2H), 2.19 (s, 3H), 2.10 (s, 6H), 1.16 (s, 9H). |
| 85 | 439.30 | 1.85 | |
| 86 | 466.30 | 2.93 | 1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 7.99 - 7.96 (d, 1H), 7.87 - 7.84 (d, 1H), 7.60 (t, J = 7.8, 1H), 7.04 - 6.94 (m, 2H), 6.86 - 6.83 (m, 2H), 5.35 (s, 2H), 1.92 (s, 6H), 1.14 (s, 9H) |
| 87 | 451.20 | 2.09 | |
| 88 | 441.08 | 3.03 | |
| 89 | 470.40 | 2.27 | |
| 90 | 450.20 | 1.19 | |
| 91 | 463.00 | 1.76 | 1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 8.63 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 20.4 Hz, 2H), 7.54 (d, J = 14.6 Hz, 2H), 7.23 (d, J = 7.3 Hz, 1H), 6.94 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.59 (s, 2H), 2.28 (s, 3H), 2.01 (s, 6H). |
| 92 | 484.00 | 2.12 | 1H NMR (400 MHz, DMSO) δ 12.15 (s, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.73 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.92 (s, 2H), 3.95 (s, 3H), 2.26 (s, 3H), 1.99 (s, 6H), 1.06 (s, 9H). |
| 93 | 507.00 | 1.98 | 1H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.82 (s, 2H), 7.73 (d, J = 7.9 Hz, 1H), 7.65 (s, 1H), 7.25 (s, 3H), 6.95 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.53 (s, 2H), 2.28 (s, 3H), 2.03 (s, 6H). |
| 94 | 436.20 | 1.06 | |
| 95 | 479.50 | 1.20 | |
| 96 | 480.30 | 1.88 | 1H NMR (400 MHz, DMSO-d6) δ 12.64 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.25 - 7.16 (m, 2H), 7.10 - 7.05 (m, 1H), 6.91 (s, 2H), 6.81 (ddd, J = 8.1, 2.3, 1.0 Hz, 1H), 5.68 (s, 2H), 2.26 (s, 3H), 1.94 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (s, 6H). |
| 97 | 517.00 | 2.03 | 1H NMR (400 MHz, DMSO) δ 12.42 (s, 1H), 8.11 (d, J = 6.8 Hz, 1H), 7.64 (s, 1H), 7.16 (dd, J = 53.1, 23.0 Hz, 6H), 6.83 (s, 2H), 6.71 (d, J = 8.5 Hz, 1H), 6.54 (s, 2H), 2.18 (s, 3H), 1.98 (s, 6H), 1.88 (s, 6H). |
| 98 | 480.09 | 2.06 | 1H NMR (400 MHz, DMSO) δ 7.91 (s, 2H), 7.69 (s, 1H), 7.58 (s, 2H), 7.45 (s, 1H), 7.37 (s, 1H), 7.21 (s, 1H), 6.60 (s, 1H), 5.60 (s, 2H), 2.31 (s, 3H), 1.25 (s, 9H). |
| 99 | 471.30 | 1.95 | |
| 100 | 506.09 | 2.02 | |
| 101 | 441.40 | 2.07 | |
| 102 | 468.40 | 2.11 | 1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 7.69 - 7.54 (m, 2H), 7.21 (d, J = 7.3 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.00 (s, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 6.38 - 6.30 (m, 1H), 2.28 (s, 3H), 2.02 (s, 6H), 1.10 (s, 9H). |
| 103 | 494.30 | 1.44 | |
| 104 | 497.00 | 2.15 | 1H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.43 (s, 2H), 7.06 (s, 1H), 6.75 (s, 2H), 5.40 (s, 2H), 2.66 (s, 6H), 2.56 (s, 3H), 2.17 (s, 3H), 2.06 (s, 6H), 1.15 (s, 9H). |
| 105 | 453.00 | 1.95 | 1H NMR (400 MHz, DMSO-d6) δ 12.34 (s, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.21 (t, J = 2.1 Hz, 1H), 7.11 - 7.03 (m, 2H), 7.01 - 6.94 (m, 3H), 6.85 (dd, J = 7.8, 2.2 Hz, 1H), 5.49 (s, 2H), 2.90 (p, J = 7.6 Hz, 1H), 2.13 (s, 6H), 1.92 - 1.80 (m, 2H), 1.68 - 1.44 (m, 6H). |
| 106 | 468.20 | 2.07 | |
| 107 | 470.00 | 1.87 | 1H NMR (400 MHz, DMSO) δ 12.19 (s, 1H), 11.76 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.80 (s, 1H), 7.16 (s, 1H), 6.92 (s, 2H), 6.34 (s, 1H), 2.26 (s, 3H), 1.98 (s, 6H), 1.04 (s, 9H). |
| 108 | 463.00 | 2.19 | |
| 109 | 464.30 | 2.08 | |
| 110 | 455.40 | 4.15 | 1H NMR (400 MHz, DMSO-d6) δ 7.26 (t, J = 7.9 Hz, 1H), 7.21 (t, J = 2.0 Hz, 1H), 7.12 - 7.06 (m, 1H), 7.01 (s, 1H), 6.89 - 6.83 (m, 1H), 6.77 (s, 2H), 5.45 (s, 2H), 2.17 (s, 3H), 2.11 (s, 6H), 1.14 (s, 9H). |
| 111 | 479.40 | 1.91 | 1H NMR (400 MHz, CDCl3) δ 10.13 (s, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.45 (s, 2H), 7.34 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.00 (s, 1H), 2.11 (d, J = 8.2 Hz, 7H), 1.05 (s, 9H). |
| 112 | 449.00 | 1.92 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 113 | 470.00 | 1.95 | 1H NMR (400 MHz, DMSO) δ 12.23 (s, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.63 (d, J = 6.2 Hz, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.90 (s, 3H), 6.85 (s, 1H), 6.57 (s, 1H), 2.25 (s, 3H), 1.95 (s, 6H), 1.04 (s, 10H). |
| 114 | 539.30 | 1.83 | |
| 115 | 483.00 | 2.27 | 1H NMR (400 MHz, DMSO) δ 12.11 (s, 1H), 8.03 (s, 2H), 7.78 (s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.30 - 7.19 (m, 2H), 7.00 (s, 2H), 3.95 (s, 3H), 2.35 (s, 3H), 2.04 (s, 6H), 1.13 (s, 9H). |
| 116 | 464.09 | 1.69 | |
| 117 | 454.00 | 2.15 | 1H NMR (400 MHz, DMSO) δ 8.90 (d, J = 5.9 Hz, 2H), 7.99 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 6.0 Hz, 2H), 7.11 (d, J = 7.8 Hz, 1H), 6.89 (s, 2H), 2.25 (s, 3H), 1.92 (s, 6H), 1.04 (s, 9H). |
| 118 | 462.20 | 1.85 | |
| 119 | 496.21 | 2.08 | |
| 120 | 478.20 | 1.85 | |
| 121 | 450.00 | 1.36 | 1H NMR (400 MHz, DMSO) δ 7.55 (d, J = 8.6 Hz, 2H), 7.33 (s, 3H), 7.21 (d, J = 7.1 Hz, 1H), 6.83 (s, 2H), 6.61 (d, J = 8.8 Hz, 2H), 5.21 (s, 1H), 4.40 (s, 2H), 4.22 (s, 2H), 2.30 (s, 6H), 2.22 (s, 3H). |
| 122 | 506.30 | 1.92 | 1H NMR (400 MHz, DMSO) δ 8.14 (dd, J = 4.9, 1.9 Hz, 1H), 7.98 (dd, J = 7.5, 1.9 Hz, 1H), 7.68 (s, 1H), 7.47 - 7.38 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.13 - 7.01 (m, 2H), 6.80 (s, 3H), 5.60 (s, 2H), 4.01 (s, 3H), 2.18 (s, 3H), 2.14 (d, J = 2.9 Hz, 6H). |
| 123 | 469.30 | 2.39 | |
| 124 | 451.00 | 1.68 | 1H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 8.44 (s, 1H), 7.19 (s, 3H), 7.08 (s, 1H), 6.90 (s, 2H), 6.82 (s, 1H), 5.69 (s, 2H), 2.42 (s, 3H), 2.24 (s, 3H), 1.92 (s, 9H). |
| 125 | 562.20 | 2.23 | |
| 126 | 450.40 | 1.20 | |
| 127 | 467.30 | 2.15 | |
| 128 | 489.00 | 1.45 | |
| 129 | 478.40 | 1.90 | |
| 130 | 425.40 | 2.23 | |
| 131 | 469.00 | 2.16 | 1H NMR (400 MHz, DMSO) δ 11.66 (s, 1H), 11.04 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.02 (s, 2H), 6.93 (s, 2H), 2.26 (s, 3H), 1.98 (s, 6H), 1.04 (s, 9H). |
| 132 | 558.14 | 2.91 | |
| 133 | 504.23 | 2.17 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 134 | 448.00 | 1.82 | 1H NMR (400 MHz, DMSO) δ 7.63 (dd, J = 19.9, 8.3 Hz, 3H), 7.38 (s, 1H), 7.07 (d, J = 25.7 Hz, 2H), 6.91 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.15 (s, 2H), 5.66 (s, 2H), 2.16 (s, 3H), 1.90 (s, 6H). |
| 135 | 506.09 | 2.04 | |
| 136 | 596.20 | 2.37 | |
| 137 | 467.10 | 2.19 | |
| 138 | 427.50 | 1.84 | |
| 139 | 453.20 | 6.23 | 1H NMR (400 MHz, DMSO) δ 1.10 (s, 9 H), 1.46 (d, J = 6.8 Hz, 3 H), 2.16 (s, 6 H), 2.21 (s, 3 H), 5.40 - 5.53 (m, 3 H), 6.83 (s, 2 H), 7.15 (s, 1 H), 7.55 - 7.62 (m, 2 H), 7.68 - 7.76 (m, 3 H) |
| 140 | 493.00 | 1.49 | 1H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 7.59 (s, 1H), 7.32 (s, 1H), 7.19 (s, 3H), 7.14 (d, J = 7.2 Hz, 1H), 6.80 (s, 2H), 6.67 (d, J = 8.4 Hz, 1H), 6.43 (s, 1H), 4.64 (s, 1H), 2.95 (d, J = 11.1 Hz, 1H), 2.20 (s, 9H), 2.00 (d, J = 11.2 Hz, 1H), 1.05 (s, 3H), 0.91 (s, 3H). |
| 141 | 469.40 | 2.02 | |
| 142 | 466.40 | 1.87 | |
| 143 | 447.20 | 2.14 | |
| 144 | 462.40 | 1.93 | |
| 145 | 502.20 | 2.34 | |
| 146 | 506.00 | 2.31 | 1H NMR (400 MHz, DMSO) δ 12.22 (s, 1H), 7.84 (s, 2H), 7.76 (s, 1H), 7.53 (s, 1H), 7.35 (s, 1H), 7.09 (s, 1H), 6.87 (s, 3H), 3.84 (s, 3H), 2.24 (s, 3H), 1.84 (s, 6H), 1.02 (s, 9H). |
| 147 | 453.40 | 2.34 | |
| 148 | 448.90 | 1.85 | 1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.46 (s, 1H), 7.25 - 7.18 (m, 2H), 7.13 - 7.09 (m, 1H), 7.08 - 7.02 (m, 2H), 6.91 - 6.87 (m, 1H), 6.84 - 6.80 (m, 1H), 6.74 (s, 2H), 5.68 (s, 2H), 2.17 (s, 3H), 1.92 (s, 6H). |
| 149 | 530.30 | 2.18 | 1H NMR (400 MHz, DMSO-d6) δ 8.07 - 8.01 (m, 2H), 7.81 - 7.74 (m, 1H), 7.73 - 7.65 (m, 3H), 7.49 (s, 1H), 7.48 - 7.39 (m, 3H), 7.10 - 7.03 (m, 1H), 6.99 - 6.95 (m, 2H), 5.63 (s, 2H), 2.13 (s, 6H). |
| 150 | 459.39 | 3.00 | |
| 151 | 534.19 | 2.03 | |
| 152 | 490.00 | 2.17 | |
| 153 | 466.20 | 1.88 | |
| 154 | 426.40 | 1.66 | |
| 155 | 494.07 | 2.09 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 156 | 497.00 | 2.23 | 1H NMR (400 MHz, DMSO) δ 7.25 (s, 1H), 7.21 (s, 1H), 7.09 (s, 1H), 7.01 (s, 1H), 6.97 (s, 2H), 6.86 (s, 1H), 5.46 (s, 2H), 2.16 (s, 6H), 2.08 (s, 1H), 1.23 (s, 9H), 1.15 (s, 9H). |
| 157 | 442.06 | 1.81 | |
| 158 | 453.50 | 2.06 | 1H NMR (400 MHz, DMSO-d6) δ 7.26 - 7.16 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 6.88 - 6.78 (m, 2H), 6.76 (s, 2H), 5.44 (s, 2H), 2.17 (s, 3H), 2.10 (s, 6H), 1.27 (s, 3H), 0.75 - 0.69 (m, 2H), 0.67 - 0.62 (m, 2H). |
| 159 | 530.30 | 2.27 | |
| 160 | 423.15 | 1.93 | |
| 161 | 551.20 | 2.11 | |
| 162 | 517.39 | 1.70 | |
| 163 | 469.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 8.27 (s, 1H), 8.16 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.90 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H), 1.04 (s, 9H). |
| 164 | 531.20 | 2.34 | 1H NMR (400 MHz, DMSO-d6) δ 12.24 (s, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.73 - 7.60 (m, 4H), 7.31 - 7.19 (m, 3H), 6.95 (s, 2H), 6.71 (d, J = 8.2 Hz, 1H), 6.52 (s, 2H), 2.88 (p, J = 6.9 Hz, 1H), 2.28 (s, 3H), 2.03 (s, 6H), 1.18 (d, J = 6.9 Hz, 6H). |
| 165 | 441.40 | 2.04 | |
| 166 | 464.30 | 2.10 | |
| 167 | 455.00 | 1.92 | 1H NMR (400 MHz, DMSO) δ 7.26 (d, J = 12.4 Hz, 2H), 7.13 (s, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.77 (s, 2H), 5.44 (s, 2H), 3.18 (s, 1H), 2.30 (s, 2H), 2.18 (s, 3H), 2.07 (s, 6H), 1.75 (s, 1H), 0.83 (d, J = 6.6 Hz, 6H). |
| 168 | 464.09 | 1.73 | |
| 169 | 580.30 | 2.24 | |
| 170 | 462.39 | 3.09 | |
| 171 | 542.60 | 1.70 | |
| 172 | 509.20 | 2.32 | |
| 173 | 456.50 | 1.92 | |
| 174 | 466.00 | 1.41 | 1H NMR (400 MHz, DMSO) δ 10.10 (s, 1H), 7.83 (s, 1H), 7.60 (s, 2H), 7.31 (d, J = 12.3 Hz, 3H), 7.00 - 6.85 (m, 3H), 5.22 (s, 1H), 4.46 (d, J = 13.2 Hz, 1H), 4.38 - 4.17 (m, 3H), 3.78 (s, 3H), 2.36 (s, 6H), 2.23 (s, 3H). |
| 175 | 481.00 | 1.76 | 1H NMR (400 MHz, DMSO) δ 12.76 (s, 1H), 8.28 (s, 1H), 7.66 (s, 2H), 7.20 (s, 1H), 6.92 (s, 2H), 6.65 (d, J = 46.8 Hz, 3H), 2.25 (s, 3H), 1.97 (s, 6H). |
| 176 | 476.30 | 2.05 | |
| 177 | 442.17 | 1.85 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 178 | 489.50 | 1.72 | |
| 179 | 477.20 | 2.01 | 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.52 - 7.44 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.97 (dd, J = 8.8, 1.7 Hz, 1H), 6.74 (d, J = 6.0 Hz, 3H), 6.69 (d, J = 8.4 Hz, 1H), 6.46 (s, 2H), 5.66 (s, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.18 (s, 3H), 1.95 (s, 6H), 1.17 (t, J = 7.5 Hz, 3H). |
| 180 | 479.30 | 2.09 | |
| 181 | 466.40 | 1.88 | |
| 182 | 495.00 | 2.18 | 1H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 7.74 (s, 1H), 7.63 (s, 1H), 7.21 (d, J = 7.3 Hz, 1H), 6.90 (s, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 2.68 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H), 1.66 (d, J = 27.0 Hz, 4H), 0.92 (s, 6H). |
| 183 | 463.00 | 2.02 | 1H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 7.90 (s, 1H), 7.67 (s, 2H), 7.57 (s, 1H), 7.13 (d, J = 48.8 Hz, 4H), 6.90 (s, 1H), 6.72 (s, 2H), 5.64 (s, 2H), 3.84 (s, 3H), 2.17 (s, 3H), 1.88 (s, 6H). |
| 184 | 449.20 | 1.64 | 1H NMR (400 MHz, DMSO-d6) δ 8.39 (dd, J = 4.6, 1.6 Hz, 1H), 8.15 (dd, J = 8.0, 1.6 Hz, 1H), 7.30 (s, 1H), 7.28 - 7.21 (m, 2H), 7.18 (dd, J = 8.0, 4.6 Hz, 1H), 7.06 - 7.01 (m, 1H), 6.96 - 6.90 (m, 1H), 6.58 (s, 2H), 5.65 (s, 2H), 2.10 (s, 3H), 1.88 (s, 6H). |
| 185 | 441.00 | 1.91 | 1H NMR (400 MHz, DMSO) δ 7.34 (s, 2H), 7.23 (s, 1H), 7.03 (s, 2H), 7.00 (s, 1H), 6.96 (s, 2H), 5.50 (s, 2H), 2.14 (s, 6H), 1.14 (s, 9H). |
| 186 | 438.17 | 1.72 | |
| 187 | 422.17 | 0.93 | |
| 188 | 523.00 | 2.02 | 1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.84 (s, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 6.99 (s, 1H), 6.75 (s, 1H), 6.66 (s, 2H), 5.36 (s, 2H), 4.38 (s, 2H), 3.90 (s, 2H), 2.15 (s, 3H), 1.93 (s, 6H), 1.17 (s, 10H). |
| 189 | 515.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 7.80 (s, 2H), 7.61 (s, 1H), 7.25 (s, 2H), 7.14 (s, 1H), 7.10 (s, 1H), 6.85 (s, 1H), 5.68 (s, 2H), 2.08 (s, 1H), 1.06 (s, 9H). |
| 190 | 507.00 | 1.97 | 1H NMR (400 MHz, DMSO) δ 13.75 (s, 1H), 12.32 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.96 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.64 (s, 1H), 6.94 (s, 4H), 6.86 (s, 1H), 4.03 (s, 2H), 2.28 (s, 3H), 2.02 (s, 6H), 1.31 (s, 3H). |
| 191 | 484.00 | 2.28 | 1H NMR (400 MHz, DMSO) δ 12.43 (s, 1H), 8.49 (d, J = 6.5 Hz, 1H), 8.34 (d, J = 9.3 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.27 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.90 (s, 2H), 3.94 (s, 3H), 2.25 (s, 3H), 1.93 (s, 6H), 1.05 (s, 9H). |
| 192 | 424.17 | 1.65 | |
| 193 | 453.30 | 1.90 | |
| 194 | 462.30 | 1.88 | |
| 195 | 454.00 | 2.07 | |
| 196 | 579.30 | 2.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.37 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.27 - 7.14 (m, 3H), 6.95 (s, 2H), 6.85 (dt, J = 10.7, 2.3 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.53 (s, 2H), 3.65 (d, J = 6.6 Hz, 2H), 2.27 (s, 3H), 2.02 (s, 6H), 1.97 (dt, J = 13.3, 6.6 Hz, 1H), 0.97 (d, J = 6.8 Hz, 6H). |
| 197 | 459.32 | 1.67 | |
| 198 | 493.20 | 1.91 | |
| 199 | 460.20 | 2.12 | |
| 200 | 466.60 | 1.40 | |
| 201 | 454.14 | 2.22 | |
| 202 | 460.50 | 2.23 | |
| 203 | 489.40 | 2.82 | 1H NMR (400 MHz, DMSO-d6) δ 12.30 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.81 - 7.70 (m, 3H), 7.64 (s, 1H), 7.44 - 7.38 (m, 3H), 7.23 (d, J = 7.3 Hz, 1H), 6.95 (s, 2H), 6.69 (s, 1H), 6.52 (s, 2H), 2.28 (s, 3H), 2.04 (s, 6H). |
| 204 | 455.40 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 12.14 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 7.08 - 7.00 (m, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.30 (s, 3H), 2.01 (s, 3H), 1.09 (s, 9H). |
| 205 | 497.00 | 2.13 | 1H NMR (400 MHz, DMSO) δ 8.13 (s, 1H), 7.92 (s, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 7.62 (s, 1H), 7.26 (s, 1H), 6.63 (d, J = 28.8 Hz, 3H), 1.98 (s, 3H), 1.68 (s, 6H), 0.76 (s, 9H). |
| 206 | 439.30 | 1.95 | |
| 207 | 541.10 | 2.20 | |
| 208 | 519.30 | 2.08 | |
| 209 | 503.30 | 2.07 | 1H NMR (400 MHz, DMSO) δ 7.26 (dd, J = 14.6, 6.7 Hz, 2H), 7.12 (dd, J = 14.0, 7.3 Hz, 3H), 7.04 (d, J = 7.5 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 6.77 (s, 2H), 5.74 (s, 1H), 5.56 (s, 2H), 2.17 (s, 3H), 2.08 (d, J = 2.2 Hz, 6H), 1.97 (s, 6H). |
| 210 | 479.20 | 3.14 | |
| 211 | 468.39 | 3.11 | 1H NMR (400 MHz, DMSO) δ 7.65 - 7.62 (d, 1H), 7.59 - 7.56 (d, 1H), 7.06 - 6.94 (m, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 5H), 5.47 (s, 2H), 4.68 (t, J = 8.68, 2H), 3.29 (t, J = 9.01, 2H), 2.13 - 2.09 (m, 6H), 1.16 (s, 9H) |
| 212 | 451.20 | 2.08 | |
| 213 | 464.30 | 1.20 | |
| 214 | 443.50 | 2.86 | |
| 215 | 447.30 | 2.07 | |
| 216 | 514.31 | 2.79 | |
| 217 | 484.00 | 2.33 | 1H NMR (400 MHz, DMSO) δ 8.46 (d, J = 5.3 Hz, 1H), 8.00 (d, J = 7.8 Hz. 1H), 7.49 (d, J = 5.3 Hz, 1H), 7.29 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.90 (s, 2H), 3.91 (s, 3H), 2.25 (s, 4H), 1.93 (s, 6H), 1.05 (s, 9H). |
| 218 | 466.00 | 1.38 | 1H NMR (400 MHz, DMSO) δ 10.21 (s, 1H), 8.28 (s, 1H), 8.18 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.34 (s, 2H), 7.28 (s, 1H), 7.10 (s, 1H), 6.89 (s, 2H), 5.21 (s, 1H), 4.42 (s, 1H), 4.22 (s, 5H), 3.89 (s, 3H), 2.36 (s, 6H), 2.23 (s, 3H). |
| 219 | 454.00 | 2.07 | 1H NMR (400 MHz, MeOD) δ 8.07 (s, 1H), 7.40 (s, 2H), 7.33 (s, 3H), 7.27 (s, 3H), 7.06 (s, 1H), 6.94 (s, 1H), 6.34 (s, 1H), 1.73 (s, 3H), 1.22 (s, 9H). |
| 220 | 514.03 | 2.17 | |
| 221 | 479.40 | 1.93 | |
| 222 | 454.00 | 2.19 | 1H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 8.73 (s, 1H), 8.18 (s, 2H), 7.96 (s, 1H), 7.74 (s, 1H), 7.13 (s, 1H), 6.90 (s, 2H), 2.25 (s, 3H), 1.95 (s, 6H), 1.05 (s, 9H). |
| 223 | 444.10 | 1.81 | |
| 224 | 467.40 | 2.20 | |
| 225 | 530.20 | 2.22 | |
| 226 | 487.27 | 2.15 | |
| 227 | 434.20 | 1.80 | |
| 228 | 469.00 | 2.07 | 1H NMR (400 MHz, DMSO) δ 8.02 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.91 (s, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H), 1.05 (s, 9H). |
| 229 | 466.25 | 2.06 | |
| 230 | 450.00 | 1.40 | 1H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 7.1 Hz, 1H), 7.23 (d, J = 22.0 Hz, 4H), 6.85 (s, 2H), 6.74 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 4.97 (s, 1H), 4.19 (d, J = 35.8 Hz, 5H), 2.31 (s, 6H), 2.22 (s, 3H). |
| 231 | 488.40 | 2.08 | |
| 232 | 447.20 | 2.06 | |
| 233 | 573.30 | 1.97 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 234 | 523.20 | 2.15 | |
| 235 | 469.00 | 2.05 | 1H NMR (400 MHz, DMSO) δ 8.23 (d, J = 5.8 Hz, 1H), 8.05 (dd, J = 7.9, 1.0 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.90 (s, 2H), 6.82 (s, 1H), 6.75 (s, 1H), 2.25 (s, 3H), 1.95 (s, 6H), 1.04 (s, 10H). |
| 236 | 479.00 | 1.41 | 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.33 (s, 7H), 6.99 (d, J = 8.7 Hz, 1H), 6.90 (s, 2H), 4.60 (d, J = 35.7 Hz, 2H), 4.41 (s, 1H), 3.98 (s, 1H), 3.76 (s, 1H), 3.67 - 3.55 (m, 1H), 2.90 (dt, J = 12.8, 6.3 Hz, 1H), 2.41 (d, J = 14.1 Hz, 7H), 2.24 (s, 4H). |
| 237 | 442.21 | 1.87 | |
| 238 | 595.20 | 2.43 | 1H NMR (400 MHz, DMSO-d6) δ 8.09 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.50 - 7.32 (m, 4H), 7.07 (d, J = 7.4 Hz, 1H), 6.90 (s, 2H), 6.45 (d, J = 8.2 Hz, 1H), 6.09 (s, 2H), 3.60 (d, J = 6.5 Hz, 2H), 2.26 (s, 3H), 2.02 (s, 7H), 1.01 (d, J = 6.7 Hz, 6H). |
| 239 | 499.00 | 1.89 | 1H NMR (400 MHz, DMSO) δ 7.57 (d, J = 19.8 Hz, 3H), 7.28 (s, 2H), 7.16 (d, J = 18.2 Hz, 2H), 6.94 (s, 1H), 5.67 (s, 2H), 1.09 (s, 9H). |
| 240 | 448.30 | 1.82 | |
| 241 | 463.20 | 2.04 | |
| 242 | 439.00 | 2.28 | 1H NMR (400 MHz, DMSO-d6) δ 11.87 (s, 1H), 8.03 - 7.97 (m, 2H), 7.75 - 7.69 (m, 1H), 7.68 - 7.62 (m, 2H), 7.24 (d, J = 2.0 Hz, 1H), 6.88 (s, 2H), 6.15 (d, J = 1.9 Hz, 1H), 5.27 (s, 2H), 2.23 (s, 3H), 2.05 (s, 6H), 1.07 (s, 9H). |
| 243 | 466.00 | 1.70 | 1H NMR (400 MHz, DMSO) δ 8.23 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 11.1 Hz, 2H), 7.12 (s, 4H), 6.85 (d, J = 9.9 Hz, 1H), 1.98 (s, 6H). |
| 244 | 465.30 | 2.06 | |
| 245 | 451.40 | 1.94 | 1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 7.98 - 7.89 (m, 2H), 7.75 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.7 Hz, 2H), 7.27 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.05 (s, 1H), 6.87 (dd, J = 8.2, 7.2 Hz, 1H), 6.44 - 6.36 (m, 2H), 5.72 (s, 2H), 3.73 (s, 3H), 1.23 (s, 9H). |
| 246 | 467.00 | 1.64 | 1H NMR (400 MHz, DMSO) δ 8.28 (d, J = 7.6 Hz, 1H), 7.64 (s, 2H), 7.21 (d, J = 7.3 Hz, 1H), 7.10 (s, 4H), 6.71 (d, J = 8.4 Hz, 1H), 6.59 (s, 2H), 2.01 (s, 6H). |
| 247 | 434.00 | 1.88 | 1H NMR (400 MHz, DMSO) δ 8.60 (s, 1H), 8.03 (s, 2H), 7.61 (s, 2H), 7.01 (s, 3H), 6.83 (s, 1H), 6.72 (s, 2H), 5.79 (s, 2H), 2.17 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3H), 1.92 (s, 6H). |
| 248 | 447.20 | 2.15 | |
| 249 | 469.40 | 2.19 | |
| 250 | 533.22 | 3.09 | |
| 251 | 454.00 | 2.04 | 1H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.21 (s, 2H), 7.14 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 14.6 Hz, 4H), 6.81 (s, 1H), 5.66 (s, 2H), 2.30 (s, 3H), 1.99 (s, 3H), 1.09 (s, 9H). |
| 252 | 466.50 | 2.04 | |
| 253 | 464.00 | 2.02 | 1H NMR (400 MHz, DMSO) δ 12.78 (s, 1H), 8.01 (s, 1H), 7.70 (s, 2H), 7.57 (s, 1H), 7.15 (s, 2H), 7.07 (s, 1H), 7.00 (s, 1H), 6.69 (s, 2H), 5.63 (s, 2H), 3.79 (s, 3H), 2.16 (s, 3H), 1.85 (s, 6H). |
| 254 | 451.30 | 1.32 | 1H NMR (400 MHz, DMSO-d6) δ 10.51 (s, 1H), 9.87 (s, 1H), 7.39 - 7.34 (m, 1H), 7.32 - 7.21 (m, 6H), 6.91 (ddd, J = 7.7, 2.5, 1.5 Hz, 1H), 6.85 (s, 2H), 4.98 (s, 1H), 4.33 - 4.08 (m, 4H), 2.33 (s, 6H), 2.22 (s, 3H). |
| 255 | 455.00 | 1.49 | |
| 256 | 458.00 | 1.77 | 1H NMR (400 MHz, DMSO) δ 11.45 (s, 1H), 8.52 (s, 1H), 7.63 (s, 1H), 7.18 (d, J = 7.3 Hz, 1H), 6.86 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.47 (s, 2H), 2.22 (s, 3H), 1.99 (s, 6H), 1.35 (s, 9H). |
| 257 | 426.07 | 3.16 | |
| 258 | 464.00 | 1.80 | 1H NMR (400 MHz, DMSO) δ 12.46 (s, 1H), 8.17 (s, 1H), 7.79 (s, 1H), 7.70 (s, 2H), 7.60 (s, 1H), 7.09 (d, J = 15.2 Hz, 2H), 6.90 (s, 1H), 6.76 (s, 2H), 5.69 (s, 2H), 3.91 (s, 3H), 2.19 (s, 3H), 1.96 (s, 6H). |
| 259 | 462.20 | 1.95 | |
| 260 | 462.30 | 1.87 | |
| 261 | 456.09 | 1.84 | |
| 262 | 483.40 | 3.30 | |
| 263 | 499.04 | 2.06 | |
| 264 | 433.20 | 2.06 | |
| 265 | 475.50 | 2.11 | 1H NMR (400 MHz, DMSO-d6) δ 11.96 (s, 1H), 9.07 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.91 (s, 2H), 6.81 (s, 2H), 2.25 (s, 3H), 1.96 (s, 6H), 1.04 (s, 9H). |
| 266 | 465.40 | 2.29 | 1H NMR (400 MHz, DMSO-d6) δ 8.22 (dd, J = 7.9, 1.3 Hz, 1H), 8.12 (dd, J = 7.6, 1.4 Hz, 1H), 7.97 (td, J = 7.8, 1.5 Hz, 1H), 7.90 (td, J = 7.6, 1.3 Hz, 1H), 7.00 (s, 1H), 6.74 (s, 2H), 5.43 (s, 2H), 2.17 (s, 3H), 2.06 (s, 6H), 1.16 (s, 9H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 267 | 478.30 | 2.09 | |
| 268 | 517.00 | 2.08 | 1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 7.18 (s, 3H), 7.11 (d, J = 7.1 Hz, 1H), 6.96 (dd, J = 17.7, 9.9 Hz, 5H), 6.69 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.85 (s, 2H), 2.75 (s, 2H), 2.26 (s, 3H), 1.97 (s, 6H). |
| 269 | 456.40 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 12.28 (s, 1H), 10.62 (s, 1H), 7.85 - 7.80 (m, 2H), 6.99 - 6.93 (m, 3H), 6.75 (s, 2H), 5.43 (s, 2H), 2.17 (s, 3H), 2.07 (s, 6H), 1.14 (s, 9H). |
| 270 | 483.40 | 2.28 | 1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 7.46 - 7.39 (m, 1H), 7.27 - 7.20 (m, 2H), 7.07 - 7.01 (m, 1H), 6.98 (d, J = 1.2 Hz, 1H), 6.75 (s, 2H), 5.44 (s, 2H), 2.98 (s, 6H), 2.17 (s, 3H), 2.08 (s, 6H), 1.14 (s, 9H). |
| 271 | 438.30 | 1.95 | |
| 272 | 426.00 | 1.84 | 1H NMR (400 MHz, DMSO) δ 7.92 (d, J = 7.8 Hz, 1H), 7.43 (s, 2H), 7.24 (d, J = 37.6 Hz, 7H), 6.93 (s, 1H), 3.17 (s, 2H), 1.12 (s, 9H). |
| 273 | 484.30 | 2.95 | |
| 274 | 438.22 | 1.86 | |
| 275 | 492.00 | 2.36 | 1H NMR (400 MHz, DMSO) δ 12.28 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.32 (s, 1H), 7.24 (s, 1H), 7.13 (s, 2H), 6.89 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H), 1.04 (s, 9H). |
| 276 | 533.00 | 2.07 | |
| 277 | 504.40 | 2.28 | |
| 278 | 519.30 | 1.98 | |
| 279 | 580.20 | 2.25 | |
| 280 | 490.16 | 2.12 | |
| 281 | 581.30 | 2.29 | |
| 282 | 424.40 | 1.74 | |
| 283 | 469.00 | 1.79 | 1H NMR (400 MHz, DMSO) δ 8.10 (s, 1H), 7.99 (s, 1H), 7.21 (s, 1H), 7.10 (s, 1H), 7.00 (s, 1H), 6.89 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H), 1.04 (s, 9H). |
| 284 | 478.90 | 2.81 | |
| 285 | 467.00 | 1.89 | |
| 286 | 454.00 | 2.02 | 1H NMR (400 MHz, DMSO) δ 12.04 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.22 (s, 2H), 7.09 (s, 5H), 6.82 (d, J = 9.3 Hz, 1H), 5.66 (s, 2H), 1.99 (s, 6H), 1.03 (s, 9H). |
| 287 | 433.30 | 2.08 | |
| 288 | 434.60 | 1.86 | |
| 289 | 482.00 | 2.26 | 1H NMR (400 MHz, DMSO) δ 12.04 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.30 (s, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 7.13 (s, 3H), 6.90 (s, 2H), 6.81 (d, J = 10.4 Hz, 1H), 6.28 (s, 1H), 2.68 (s, 3H), 2.25 (s, 3H), 1.94 (s, 6H), 1.04 (s, 9H). |
| 290 | 449.00 | 2.03 | |
| 291 | 473.20 | 1.74 | 1H NMR (400 MHz, DMSO-d6) δ 8.31 - 8.30 (m, 1H), 7.52 (d, J = 0.8 Hz, 1H), 7.49 (dd, J = 8.8, 1.6 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.19 (t, J = 2.0 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 7.05 - 7.01 (m, 1H), 6.84 (ddd, J = 8.0, 2.3, 1.0 Hz, 1H), 6.73 (s, 2H), 5.69 (s, 2H), 2.16 (s, 3H), 1.89 (s, 6H). |
| 292 | 467.20 | 5.47 | 1H NMR (300 MHz, DMSO) δ 1.01 (s, 9H), 1.92 (s, 6H), 2.22 (s, 3H), 5.57 (br. s, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.85 (s, 2H), 6.97-7.07 (m, 2H), 7.11-7.20 (m, 2H), 7.56 (br. s, 2H), 8.09 (d, J=7.8 Hz, 1H) |
| 293 | 507.30 | 2.11 | |
| 294 | 468.20 | 2.16 | 1H NMR (400 MHz, DMSO-d6) δ 12.00 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.25 - 7.19 (m, 2H), 7.12 (d, J = 7.8 Hz, 1H), 7.09 (dd, J = 1.8, 0.9 Hz, 1H), 6.90 (s, 2H), 6.83 (s, 1H), 5.66 (s, 2H), 2.26 (s, 3H), 1.95 (s, 6H), 1.04 (s, 9H). |
| 295 | 463.40 | 1.90 | |
| 296 | 440.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 12.07 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.27 - 7.12 (m, 6H), 7.08 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 11.0 Hz, 1H), 5.68 (s, 2H), 2.03 (s, 3H), 1.08 (s, 9H). |
| 297 | 424.30 | 1.73 | |
| 298 | 452.20 | 1.82 | |
| 299 | 492.38 | 1.55 | |
| 300 | 477.00 | 1.99 | |
| 301 | 424.40 | 1.74 | |
| 302 | 545.50 | 1.66 | |
| 303 | 517.20 | 2.13 | |
| 304 | 480.22 | 2.09 | |
| 305 | 470.00 | 2.05 | 1H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 11.71 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.61 (s, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.05 - 6.85 (m, 3H), 2.25 (s, 3H), 1.96 (s, 6H), 1.05 (s, 9H). |
| 306 | 473.29 | 1.84 | |
| 307 | 543.36 | 1.74 | 1H NMR (400 MHz, DMSO) δ 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.90 - 7.81 (m, J = 6.1 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.50 (s, 1H), 7.45 (d, J = 10.1 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 6.98 - 6.84 (m, J = 10.7 Hz, 1H), 6.54 - 6.40 (m, J = 6.7 Hz, 1H), 4.17 - 4.01 (m, 2H), 3.84 (d, J = 6.5 Hz, 2H), 2.15 - |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.01 (m, 1H), 2.01 - 1.90 (m, J = 22.2 Hz, 2H), 1.80 - 1.61 (m, 2H), 1.13 (d, J = 6.2 Hz, 6H), 0.99 (d, J = 6.7 Hz, 6H). |
| 308 | 450.40 | 1.87 | |
| 309 | 464.30 | 1.26 | |
| 310 | 450.40 | 1.20 | |
| 311 | 496.00 | 2.38 | 1H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 7.95 (s, 1H), 7.39 (s, 1H), 7.22 (s, 2H), 7.12 (s, 1H), 7.00 (s, 1H), 6.90 (s, 2H), 2.92 (s, 6H), 2.25 (s, 3H), 1.93 (s, 6H), 1.04 (s, 9H). |
| 312 | 455.18 | 2.91 | |
| 313 | 466.20 | 2.22 | |
| 314 | 452.40 | 1.95 | |
| 315 | 496.08 | 2.07 | |
| 316 | 514.09 | 2.20 | |
| 317 | 469.00 | 2.09 | 1H NMR (400 MHz, DMSO) δ 7.26 (s, 1H), 7.21 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 6.85 (d, J = 10.3 Hz, 1H), 2.14 (s, 6H), 2.04 (s, 6H), 1.13 (s, 9H). |
| 318 | 553.00 | 2.24 | 1H NMR (400 MHz, DMSO) δ 13.80 (s, 1H), 12.51 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 9.8 Hz, 1H), 7.18 (s, 1H), 6.95 (s, 2H), 6.89 (s, 1H), 6.84 (d, J = 12.9 Hz, 1H), 3.65 (d, J = 6.5 Hz, 2H), 2.27 (s, 3H), 2.07 (s, 1H), 2.01 (s, 7H), 0.97 (d, J = 6.7 Hz, 6H). |
| 319 | 452.00 | 1.11 | 1H NMR (400 MHz, DMSO) δ 9.99 (s, 1H), 7.64 (d, J = 28.4 Hz, 3H), 7.33 (d, J = 17.6 Hz, 4H), 6.89 (s, 2H), 6.65 (s, 1H), 5.30 (s, 1H), 4.50 (s, 1H), 4.30 (s, 3H), 2.38 (s, 6H), 2.22 (s, 3H). |
| 320 | 561.30 | 2.31 | 1H NMR (400 MHz, DMSO-d6) δ 12.15 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.75 - 7.61 (m, 4H), 7.23 (d, J = 7.2 Hz, 1H), 6.99 - 6.88 (m, 4H), 6.71 (d, J = 8.4 Hz, 1H), 6.56 - 6.46 (m, 2H), 3.77 (d, J = 6.6 Hz, 2H), 2.28 (s, 3H), 2.03 (s, 7H), 0.95 (d, J = 6.7 Hz, 6H). |
| 321 | 511.30 | 1.58 | |
| 322 | 468.00 | 2.25 | 1H NMR (400 MHz, DMSO) δ 8.06 (s, 1H), 7.74 (s, 1H), 7.36 (s, 1H), 7.20 (s, 1H), 6.99 (s, 2H), 6.87 (s, 1H), 6.72 (s, 1H), 2.34 (s, 3H), 2.04 (s, 6H), 1.33 (s, 2H), 1.13 (s, 9H). |
| 323 | 469.00 | 2.11 | |
| 324 | 455.00 | 1.88 | |
| 325 | 457.30 | 1.87 | |
| 326 | 464.40 | 2.14 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 327 | 439.30 | 1.98 | |
| 328 | 448.10 | 2.17 | |
| 329 | 530.34 | 1.70 | |
| 330 | 454.00 | 2.16 | 1H NMR (400 MHz, DMSO) δ 12.52 (s, 1H), 9.15 (s, 1H), 8.90 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.70 (s, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.89 (s, 2H), 2.25 (s, 3H), 1.91 (s, 6H), 1.04 (s, 9H). |
| 331 | 434.05 | 1.71 | |
| 332 | 482.00 | 2.18 | 1H NMR (400 MHz, DMSO) δ 8.40 (s, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 7.76 (s, 1H), 6.89 (s, 1H), 6.64 (s, 2H), 5.34 (s, 2H), 2.60 (s, 3H), 2.08 (s, 3H), 1.95 (s, 6H), 1.07 (s, 9H). |
| 333 | 464.30 | 3.03 | |
| 334 | 411.30 | 1.54 | |
| 335 | 463.00 | 2.07 | 1H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.53 (s, 2H), 7.44 (s, 2H), 7.30 (d, J = 7.7 Hz, 1H), 7.14 (s, 1H), 7.06 (s, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.68 (s, 2H), 5.64 (s, 2H), 3.84 (s, 3H), 2.14 (s, 3H), 1.87 (s, 6H). |
| 336 | 478.20 | 1.83 | |
| 337 | 511.30 | 1.41 | |
| 338 | 468.40 | 1.58 | |
| 339 | 480.30 | 2.11 | |
| 340 | 475.40 | 2.70 | 1H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.82 (dd, J = 6.8, 2.9 Hz, 2H), 7.75 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.46 - 7.39 (m, 3H), 7.22 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 4.2 Hz, 2H), 7.12 - 7.05 (m, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.52 (s, 2H), 2.33 (s, 3H), 2.07 (s, 3H). |
| 341 | 453.00 | 2.38 | |
| 342 | 441.00 | 1.95 | 1H NMR (400 MHz, DMSO) δ 7.19 (s, 1H), 7.13 (s, 1H), 7.06 (d, J = 8.0 Hz, 4H), 6.96 (s, 2H), 6.83 (s, 1H), 6.39 (s, 1H), 5.67 (s, 1H), 2.17 (s, 3H), 1.67 (s, 3H), 1.28 (s, 9H). |
| 343 | 489.50 | 1.76 | |
| 344 | 482.10 | 1.99 | |
| 345 | 551.20 | 2.06 | |
| 346 | 466.00 | 2.00 | |
| 347 | 476.30 | 2.08 | |
| 348 | 463.20 | 2.06 | |
| 349 | 442.17 | 1.88 | |
| 350 | 453.00 | 2.28 | |
| 351 | 579.30 | 2.33 | |
| 352 | 491.30 | 2.06 | 1H NMR (400 MHz, DMSO-d6) δ 9.12 - 9.10 (m, 1H), 9.10 - 9.08 (m, 1H), 8.49 (dd, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | J = 7.4, 1.2 Hz, 1H), 8.44 - 8.40 (m, 1H), 8.02 (dd, J = 8.5, 7.4 Hz, 1H), 7.81 - 7.76 (m, 1H), 6.97 (s, 1H), 6.59 (s, 2H), 5.26 (s, 2H), 2.10 (s, 3H), 1.78 (s, 6H), 1.15 (s, 9H). |
| 353 | 525.50 | 1.49 | |
| 354 | 447.20 | 2.08 | 1H NMR (400 MHz, DMSO-d6) δ 7.72 - 7.67 (m, 2H), 7.41 - 7.30 (m, 4H), 6.94 (s, 1H), 6.84 (dd, J = 7.8, 7.0 Hz, 1H), 6.76 (dt, J = 7.0, 1.2 Hz, 1H), 6.68 (s, 2H), 6.11 (s, 2H), 2.28 (s, 3H), 2.16 (s, 3H), 1.70 (s, 6H). |
| 355 | 502.15 | 1.71 | |
| 356 | 470.60 | 1.91 | |
| 357 | 452.18 | 2.00 | |
| 358 | 458.00 | 192.00 | 1H NMR (400 MHz, DMSO) δ 8.49 (s, 1H), 8.14 (s, 1H), 7.91 (s, 2H), 7.74 (s, 1H), 7.61 (s, 1H), 7.16 (d, J = 38.6 Hz, 3H), 6.81 (s, 2H), 5.80 (s, 2H), 2.10 (d, J = 38.6 Hz, 9H). |
| 359 | 438.22 | 1.93 | |
| 360 | 456.09 | 1.94 | |
| 361 | 542.40 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.50 - 7.47 (m, 1H), 7.41 (dt, J = 10.0, 1.8 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.8, 2.3 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.46 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 2.81 - 2.72 (m, 2H), 2.05 (dt, J = 13.4, 6.7 Hz, 1H), 1.82 - 1.71 (m, 4H), 1.59 (s, 6H), 0.99 (d, J = 6.7 Hz, 6H). |
| 362 | 482.40 | 1.97 | |
| 363 | 499.10 | 2.04 | |
| 364 | 545.00 | 2.13 | 1H NMR (400 MHz, DMSO) δ 12.42 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.26 - 7.16 (m, 2H), 7.11 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.81 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 2.17 (s, 3H), 1.98 (s, 6H), 0.97 (s, 10H). |
| 365 | 482.00 | 2.18 | 1H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.92 (s, 1H), 7.27 (s, 1H), 7.09 (s, 1H), 6.89 (s, 2H), 3.93 (s, 3H), 2.24 (s, 3H), 1.90 (s, 6H), 1.32 (s, 3H), 0.67 (d, J = 15.3 Hz, 4H). |
| 366 | 475.20 | 4.99 | 1H NMR (300 MHz, DMSO-d6) : δ 2.16 (s, 6 H), 2.17 (s, 3 H), 5.55 (s, 2 H), 6.80 (s, 2 H), 6.83 - 6.90 (m, 1 H), 7.08 - 7.15 (m, 1 H), 7.21 - 7.34 (m, 3 H), 7.35 - 7.44 (m, 2 H), 7.54 (s, 1 H), 7.60 - 7.67 (m, 2 H). |
| 367 | 455.00 | 2.00 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 368 | 556.40 | 2.77 | 1H NMR (400 MHz, 氯仿-d) δ 15.49 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.75 - 7.56 (m, 3H), 7.34 (t, J = 1.8 Hz, 1H), 7.30 (dt, J = 9.4, 1.9 Hz, 1H), 6.75 - 6.66 (m, 2H), 3.95 (s, 1H), 3.78 (d, J = 6.5 Hz, 2H), 3.42 (s, 1H), 2.88 - 2.74 (m, 1H), 2.23 (dd, J = 12.5, 8.0 Hz, 1H), 2.17 - 2.08 (m, 1H), 1.98 - 1.87 (m, 1H), 1.55 (s, 3H), 1.39 (s, 3H), 1.31 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 6H). |
| 369 | 514.03 | 2.07 | |
| 370 | 479.00 | 2.05 | |
| 371 | 556.40 | 2.87 | 1H NMR (400 MHz, 氯仿-d) δ 13.89 (s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 7.72 - 7.59 (m, 3H), 7.39 - 7.32 (m, 2H), 6.75 - 6.65 (m, 2H), 3.78 (d, J = 6.5 Hz, 2H), 3.50 - 3.43 (m, 2H), 2.91 (s, 2H), 2.44 (dq, J = 10.0, 6.3 Hz, 2H), 2.13 (七重峰, J = 6.6 Hz, 1H), 1.20 (d, J = 6.8 Hz, 6H), 1.06 (d, J = 6.7 Hz, 6H). |
| 372 | 485.30 | 1.89 | |
| 373 | 432.70 | 1.29 | |
| 374 | 511.00 | 1.89 | 1H NMR (400 MHz, DMSO) δ 13.81 (s, 1H), 12.45 (s, 1H), 8.03 (s, 2H), 7.66 (s, 1H), 7.36 (s, 1H), 6.91 (s, 5H), 3.84 (s, 3H), 2.24 (s, 3H), 2.01 (s, 6H). |
| 375 | 533.20 | 2.20 | |
| 376 | 537.30 | 3.07 | |
| 377 | 466.00 | 1.38 | 1H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 9.72 (s, 1H), 8.03 (s, 1H), 7.53 (s, 1H), 7.31 (t, J = 20.3 Hz, 6H), 6.91 (s, 2H), 4.41 (d, J = 13.3 Hz, 1H), 4.26 (d, J = 15.8 Hz, 2H), 4.14 (d, J = 13.2 Hz, 1H), 2.39 (s, 7H), 2.24 (s, 3H), 1.82 (s, 3H). |
| 378 | 439.00 | 1.27 | 1H NMR (400 MHz, DMSO) δ 10.20 (s, 1H), 7.73 (s, 1H), 7.42 (s, 1H), 7.26 (d, J = 18.8 Hz, 3H), 6.90 (s, 2H), 6.60 (s, 1H), 4.13 (s, 4H), 2.40 (s, 7H), 2.24 (s, 3H), 1.73 (s, 3H). |
| 379 | 528.30 | 2.28 | |
| 380 | 528.29 | 1.90 | |
| 381 | 521.50 | 1.78 | 1H NMR (400 MHz, DMSO-d6) δ 12.08 (s, 1H), 8.07 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.68 (s, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.06 (dd, J = 8.3, 2.1 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.65 - 6.34 (m, 2H), 3.90 (d, J = 7.1 Hz, 2H), 2.31 (s, 3H), 2.07 (d, J = 4.0 Hz, 4H), 0.81 (d, J = 6.7 Hz, 6H). |
| 382 | 488.30 | 1.47 | 1H NMR (400 MHz, DMSO-d6) δ 13.77 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 13.34 (s, 1H), 7.97 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.66 - 7.27 (m, 3H), 7.01 - 6.76 (m, 2H), 4.13 (q, J = 6.9 Hz, 2H), 4.02 (s, 2H), 2.00 (s, 2H), 1.74 - 1.61 (m, 2H), 1.36 (t, J = 6.9 Hz, 3H), 1.07 (d, J = 6.2 Hz, 6H). |
| 383 | 554.40 | 3.03 | |
| 384 | 567.40 | 2.73 | 1H NMR (400 MHz, DMSO-d6) δ 12.50 (s, 1H), 8.24 (d, J = 5.4 Hz, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.51 (dd, J = 5.4, 1.5 Hz, 1H), 7.28 (s, 2H), 7.16 (s, 1H), 6.62 (s, 1H), 6.42 (s, 1H), 5.30 (p, J = 6.2 Hz, 1H), 2.19 (td, J = 12.8, 11.1, 6.8 Hz, 1H), 1.86 (dd, J = 11.8, 5.6 Hz, 1H), 1.78 - 1.62 (m, 2H), 1.61 (s, 3H), 1.58 (s, 3H), 1.45 - 1.35 (m, 2H), 1.27 (d, J = 6.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 1H), 0.89 (dd, J = 12.8, 6.3 Hz, 9H). |
| 385 | 572.25 | 1.99 | |
| 386 | 542.23 | 2.97 | |
| 387 | 538.20 | 2.03 | |
| 388 | 528.12 | 2.75 | |
| 389 | 525.33 | 1.12 | |
| 390 | 589.00 | 2.25 | 1H NMR (400 MHz, DMSO-d6) δ 12.80 (s, 1H), 8.52 (dd, J = 2.5, 0.7 Hz, 1H), 8.02 (dd, J = 8.7, 2.5 Hz, 1H), 7.85 (s, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 6.83 (dd, J = 8.6, 0.7 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 5.32 (p, J = 6.2 Hz, 1H), 3.95 (s, 2H), 1.97 - 1.82 (m, 2H), 1.64 (dd, J = 8.9, 5.3 Hz, 2H), 1.33 (d, J = 6.2 Hz, 6H), 1.04 (d, J = 6.1 Hz, 6H). |
| 391 | 534.00 | 2.00 | 1H NMR (400 MHz, DMSO) δ 13.80 (s, 1H), 12.63 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.97 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.45 (s, 1H), 6.94 (s, 2H), 6.88 (s, 1H), 3.48 (s, 3H), 2.26 (s, 3H), 1.99 (s, 6H). |
| 392 | 467.20 | 1.28 | 1H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 12.55 (s, 1H), 8.25 (dd, J = 7.2, 2.2 Hz, 1H), 8.02 - 7.96 (m, 2H), 7.82 (d, J = 7.9 Hz, 2H), 7.30 (dd, J = 8.1, 6.6 Hz, 3H), 6.44 (t, J = 6.8 Hz, 1H), 4.13 - 4.02 (m, 2H), 2.36 (s, 3H), 2.03 - 1.92 (m, 2H), 1.76 - 1.61 (m, 2H), 1.14 (d, J = 6.2 Hz, 6H). |
| 393 | 538.25 | 2.14 | |
| 394 | 481.00 | 1.20 | 1H NMR (400 MHz, DMSO) δ 9.77 (s, 1H), 7.64 (s, 1H), 7.14 (s, 2H), 6.90 (s, 2H), 6.69 (s, 3H), 4.37 (d, J = 12.8 Hz, 1H), 4.25 (s, 2H), 3.96 (d, J = 12.9 Hz, 1H), 2.39 (s, 6H), 2.24 (s, 3H), 1.85 (s, 3H). |
| 395 | 556.34 | 2.90 | |
| 396 | 537.50 | 1.93 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 397 | 539.50 | 1.72 | |
| 398 | 582.28 | 2.12 | |
| 399 | 517.20 | 2.18 | |
| 400 | 511.32 | 1.04 | |
| 401 | 443.40 | 2.08 | 1H NMR (400 MHz, DMSO-d6) δ 13.72 (s, 1H), 12.02 (s, 1H), 8.51 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 7.8 Hz, 1H), 6.90 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H), 1.04 (s, 9H). |
| 402 | 525.30 | 2.16 | 1H NMR (400 MHz, DMSO-d6) δ 8.21 (d, J = 5.4 Hz, 1H), 7.71 - 7.57 (m, 1H), 7.55 - 7.43 (m, 2H), 7.29 - 7.23 (m, 1H), 7.17 (s, 1H), 7.00 (s, 1H). 6.54 (s, 1H), 6.32 (s, 2H), 5.27 (p, J = 6.1 Hz, 1H), 2.87 (s, 2H), 2.16 - 2.07 (m, 1H), 1.82 (dd, J = 11.7, 5.6 Hz, 1H), 1.62 (s, 3H), 1.55 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 0.79 (d, J = 6.3 Hz, 3H). |
| 403 | 526.20 | 1.56 | |
| 404 | 491.00 | 2.06 | 1H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 7.63 (s, 1H), 7.49 (d, J = 6.2 Hz, 2H), 7.18 (d, J = 7.3 Hz, 1H), 7.02 (d, J = 10.4 Hz, 1H), 6.75 (d, J = 9.0 Hz, 3H), 6.69 (d, J = 8.4 Hz, 1H), 6.46 (s, 2H), 5.66 (s, 2H), 2.90 (s, 1H), 2.18 (s, 3H), 1.96 (s, 6H), 1.19 (d, J = 6.9 Hz, 6H). |
| 405 | 511.00 | 2.00 | |
| 406 | 495.00 | 1.27 | 1H NMR (400 MHz, DMSO) δ 9.74 (s, 1H), 7.77 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 6.91 (s, 6H), 4.39 - 4.21 (m, 3H), 4.08 (d, J = 13.2 Hz, 1H), 3.71 (s, 5H), 3.17 (s, 1H), 2.40 (s, 6H), 2.24 (s, 3H), 1.81 (s, 3H). |
| 407 | 410.30 | 1.76 | |
| 408 | 542.40 | 1.98 | |
| 409 | 489.00 | 1.67 | 1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.95 (dd, J = 22.2, 8.2 Hz, 2H), 7.64 (s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 3.9 Hz, 3H), 7.06 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.4 Hz, 1H), 4.11 (d, J = 7.0 Hz, 2H), 2.33 (s, 3H), 1.38 (s, 3H). |
| 410 | 510.00 | 1.37 | 1H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 10.44 (s, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.17 (s, 1H), 6.89 (s, 2H), 6.81 (s, 2H), 6.35 (s, 1H), 4.01 (d, J = 16.8 Hz, 4H), 3.76 (s, 2H), 3.17 (s, 4H), 2.39 (s, 6H), 2.24 (s, 3H), 2.07 (s, 1H), 1.62 (s, 3H), 1.24 (s, 3H). |
| 411 | 417.00 | 1.90 | 1H NMR (400 MHz, MeOD) δ 8.21 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 7.48 (d, J = 7.2 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | Hz, 1H), 7.07 (d, J = 8.8 Hz, 1H), 3.16 (s, 1H), 1.74 (d, J = 21.2 Hz, 7H), 1.46 (s, 9H), 1.26 (s, 3H). |
| 412 | 552.60 | 1.08 | |
| 413 | 519.42 | 2.97 | |
| 414 | 468.30 | 1.62 | |
| 415 | 516.22 | 1.63 | 1H NMR (400 MHz, DMSO) δ 13.77 (s, 1H), 13.32 (s, 1H), 7.97 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.53 - 7.40 (m, 3H), 6.90 (dt, J = 10.8, 2.3 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 4.01 (d, J = 5.0 Hz, 2H), 3.84 (d, J = 6.6 Hz, 2H), 3.31 (s, 3H), 2.51 (dq, J = 7.3, 1.8 Hz, 1H), 2.07 - 1.94 (m, 4H), 1.67 (d, J = 3.6 Hz, 2H), 1.06 (d, J = 6.2 Hz, 6H), 0.99 (d, J = 6.7 Hz, 7H). |
| 416 | 557.36 | 2.41 | |
| 417 | 429.40 | 1.61 | |
| 418 | 542.40 | 2.80 | |
| 419 | 572.32 | 2.03 | |
| 420 | 540.40 | 2.17 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 7.76 - 7.59 (m, 2H), 7.50 - 7.40 (m, 3H), 7.24 (d, J = 7.1 Hz, 1H), 6.91 (dt, J = 10.7, 2.3 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 6.48 (s, 2H), 4.23 (p, J = 2.3 Hz, 2H), 3.85 (d, J = 6.5 Hz, 2H), 2.12 - 1.97 (m, 1H), 1.68 - 1.57 (m, 4H), 1.47 - 1.36 (m, 4H), 1.00 (d, J = 6.7 Hz, 6H). |
| 421 | 528.50 | 1.90 | |
| 422 | 543.36 | 1.95 | |
| 423 | 510.00 | 2.38 | 1H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.47 (s, 1H), 8.33 (d, J = 7.6 Hz, 1H), 7.69 (s, 1H), 7.26 (s, 1H), 6.89 (s, 2H), 3.94 (s, 3H), 2.66 (s, 2H), 2.25 (s, 3H), 1.92 (s, 6H), 1.65 (d, J = 35.1 Hz, 4H), 0.91 (s, 6H). |
| 424 | 570.40 | 2.66 | |
| 425 | 542.30 | 2.54 | |
| 426 | 570.12 | 1.98 | |
| 427 | 542.00 | 1.74 | 1H NMR (400 MHz, MeOD) δ 8.27 (s, 1H), 8.21 (d, J = 9.4 Hz, 1H), 7.40 (s, 9H), 7.05 (s, 1H), 6.89 (s, 2H), 5.12 (s, 1H), 4.52 (s, 4H), 3.81 (s, 3H), 2.39 (s, 6H), 2.25 (s, 4H). |
| 428 | 523.30 | 2.01 | 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 2.4 Hz, 1H), 8.27 (dd, J = 8.7, 2.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 7.0 Hz, 2H), 6.82 (d, J = 8.7 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.15 (s, 2H), 5.24 - 5.11 (m, 1H), 4.25 (s, 2H), 2.42 (dddd, J = 10.5, 9.4, 5.2, 2.4 Hz, 2H), 2.07 (qdd, J = 9.8, 7.8, 2.7 Hz, 2H), 1.96 - 1.74 (m, 3H), 1.62 (dddd, J = 29.1, 15.5, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 11.3, 8.4 Hz, 3H), 1.06 (d, J = 6.1 Hz, 6H). |
| 429 | 531.00 | 2.09 | 1H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 8.10 (s, 1H), 7.90 (s, 1H), 7.63 (s, 1H), 7.37 - 7.20 (m, 5H), 6.91 (s, 2II), 6.69 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 2.52 (s, 2H), 2.25 (s, 3H), 2.00 (s, 6H), 1.39 (s, 2H), 0.73 (s, 3H). |
| 430 | 439.20 | 1.85 | |
| 431 | 526.13 | 1.91 | |
| 432 | 525.33 | 1.70 | |
| 433 | 531.18 | 1.95 | |
| 434 | 520.50 | 2.00 | 1H NMR (400 MHz, DMSO-d6) δ 8.31 (d, J = 2.1 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.78 - 7.73 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.16 - 7.04 (m, 4H), 6.97 - 6.91 (m, 2H), 4.05 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.04 (s, 3H), 1.31 (t, J = 6.9 Hz, 3H). |
| 435 | 539.30 | 1.81 | |
| 436 | 547.30 | 2.20 | |
| 437 | 524.50 | 0.90 | |
| 438 | 557.26 | 2.42 | |
| 439 | 525.20 | 2.04 | |
| 440 | 538.24 | 1.97 | |
| 441 | 511.40 | 1.59 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.85 (d, J = 2.4 Hz, 1H), 8.31 (dd, J = 8.8, 2.5 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.19 (dd, J = 9.7, 7.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 5.31 (p, J = 6.2 Hz, 1H), 4.41 (t, J = 6.6 Hz, 1H), 3.12 - 2.97 (m, 1H), 2.86 - 2.72 (m, 1H), 2.26 - 2.11 (m, 1H), 1.89 (s, 1H), 1.70 - 1.52 (m, 1H), 1.32 (d, J = 6.1 Hz, 6H), 1.04 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H). |
| 442 | 516.21 | 1.67 | |
| 443 | 482.00 | 2.41 | 1H NMR (400 MHz, DMSO) δ 8.01 (s, 2H), 7.70 (d, J = 34.2 Hz, 3H), 6.96 (d, J = 10.2 Hz, 3H), 5.43 (s, 2H), 2.09 (s, 6H), 1.21 (s, 9H), 1.15 (s, 9H). |
| 444 | 451.40 | 1.63 | |
| 445 | 470.35 | 1.60 | 1H NMR (400 MHz, DMSO) δ 8.11 - 8.02 (m, J = 8.9 Hz, 2H), 7.97 (d, J = 2.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.07 - 6.99 (m, J = 8.9 Hz, 2H), 6.85 (d, J = 2.4 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.70 - 3.55 (m, J = 12.7 Hz, 2H), 2.97 - 2.81 (m, J = 11.6 Hz, 2H), 1.72 - 1.62 (m, J = 13.0 Hz, 2H), 1.62 - 1.50 (m, 1H), 1.35 (t, J = 7.0 Hz, 3H), 1.32 - 1.16 (m, 2H), 0.94 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (d, J = 6.4 Hz, 3H). |
| 446 | 499.60 | 1.76 | |
| 447 | 590.33 | 2.18 | |
| 448 | 492.00 | 1.59 | 1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 7.64 (s, 1H), 7.33 (s, 4H), 7.20 (s, 1H), 7.11 (s, 1H), 6.72 (s, 2H), 4.58 (s, 1H), 4.16 (s, 2H), 3.91 (s, 2H), 2.22 (s, 3H), 2.19 (s, 3H), 2.12 (s, 6H), 1.60 (s, 3H), 1.48 (s, 3H). |
| 449 | 521.22 | 2.59 | |
| 450 | 519.30 | 2.01 | |
| 451 | 543.43 | 2.65 | |
| 452 | 543.29 | 2.35 | |
| 453 | 512.40 | 2.02 | |
| 454 | 537.30 | 2.16 | 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 8.6, 2.5 Hz, 1H), 7.60 - 7.42 (m, 2H), 7.00 (t, J = 6.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 1H), 6.56 - 6.46 (m, 1H), 6.25 (s, 2H), 4.23 (bs, 2H), 4.10 (s, 2H), 1.86 (s, 2H), 1.56 (bs, 2H), 1.17 (bs, 3H), 1.03 (d, J = 6.1 Hz, 6H), 0.58 - 0.49 (m, 2H), 0.43 - 0.34 (m, 2H). |
| 455 | 524.30 | 1.51 | |
| 456 | 480.24 | 1.75 | |
| 457 | 561.14 | 2.97 | |
| 458 | 542.30 | 1.92 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69 - 7.60 (m, 1H), 7.52 - 7.45 (m, 1H), 7.42 (d, J = 10.0 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 6.93 - 6.84 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 4.13 (s, 2H), 3.84 (d, J = 6.5 Hz, 2H), 2.11 - 1.99 (m, 3H), 1.52 - 1.45 (m, 2H), 1.04 - 0.95 (m, 12H). |
| 459 | 486.20 | 1.43 | |
| 460 | 456.21 | 1.17 | |
| 461 | 608.00 | 2.23 | 1H NMR (400 MHz, DMSO) δ 13.78 (s, 1H), 13.05 (s, 1H), 8.36 (d, J = 28.4 Hz, 3H), 8.16 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.28 - 7.16 (m, 2H), 6.93 (s, 2H), 6.84 (d, J = 10.7 Hz, 1H), 3.65 (d, J = 6.5 Hz, 2H), 2.26 (s, 3H), 2.02 (d, J = 42.5 Hz, 9H), 0.97 (d, J = 6.7 Hz, 6H). |
| 462 | 451.50 | 1.72 | |
| 463 | 507.41 | 3.02 | |
| 464 | 525.30 | 1.57 | |
| 465 | 588.50 | 1.31 | 1H NMR (400 MHz, DMSO-d6) δ 8.10 (d, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.54 (s, 1H), 7.45 - 7.40 (m, 1H), 7.35 - 7.22 (m, 2H), 7.11 - 7.05 (m, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.91 (s, 2H), 6.48 - 6.43 (m, 1H), 6.08 (s, 2H), 3.55 (t, J = 4.6 Hz, 4H), 3.42 (s, 2H), 2.55 (s, 1H), 2.32 - 2.27 (m, 5H), 2.27 (s, 3H), 2.03 (s, 6H). |
| 466 | 547.30 | 1.87 | 1H NMR (400 MHz, DMSO-d6) δ 8.27 (d, J = 19.3 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.43 (d, J = 10.1 Hz, 1H), 7.28 (dd, J = 14.4, 8.0 Hz, 1H), 6.90 (dt, J = 10.6, 2.3 Hz, 1H), 4.61 - 4.44 (m, 1H), 3.84 (d, J = 6.7 Hz, 2H), 3.40 - 2.86 (m, 4H), 2.16 - 1.91 (m, 2H), 1.71 - 1.60 (m, 7H), 1.60 - 1.49 (m, 1H), 1.16 (s, 1H), 1.06 - 0.96 (m, 10H). |
| 467 | 479.32 | 1.20 | |
| 468 | 497.51 | 3.50 | |
| 469 | 521.52 | 2.73 | |
| 470 | 510.50 | 1.42 | |
| 471 | 539.50 | 1.66 | |
| 472 | 474.00 | 2.36 | 1H NMR (400 MHz, DMSO) δ 7.88 (dd, J = 10.8, 4.8 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 6.88 (s, 1H), 6.67 (s, 2H), 5.37 (s, 2H), 3.11 (s, 1H), 2.09 (s, 3H), 2.00 (d, J = 6.5 Hz, 6H), 1.08 (s, 9H). |
| 473 | 604.40 | 3.25 | |
| 474 | 495.00 | 1.18 | 1H NMR (400 MHz, DMSO) δ 9.96 (s, 1H), 9.61 (s, 1H), 7.90 (s, 1H), 7.44 - 6.61 (m, 7H), 4.39 (s, 3H), 4.16 (s, 2H), 3.74 (s, 3H), 2.41 (s, 5H), 2.24 (s, 3H), 1.97 (d, J = 80.3 Hz, 3H). |
| 475 | 574.34 | 3.13 | |
| 476 | 509.60 | 1.54 | 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 8.85 (d, J = 2.5 Hz, 1H), 8.31 (dd, J = 8.7, 2.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.2 Hz, 1H), 7.19 (dd, J = 14.2, 7.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.45 (s, 1H), 5.30 (h, J = 6.2 Hz, 1H), 4.56 (s, 1H), 2.98 (d, J = 9.7 Hz, 1H), 2.44 (s, 1H), 2.35 - 2.26 (m, 1H), 1.71 - 1.13 (m, 7H) 1.32 (d, J = 96.2 Hz, 6H). |
| 477 | 533.20 | 2.06 | |
| 478 | 415.00 | 1.48 | 1H NMR (400 MHz, MeOD) δ 8.56 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 6.08 (s, 1H), 2.31 (s, 2H), 2.20 (s, 2H), 1.69 (d, J = 17.3 Hz, 4H), 1.53 (s, 9H). |
| 479 | 528.31 | 1.99 | |
| 480 | 466.00 | 1.26 | |
| 481 | 605.40 | 2.21 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 482 | 469.27 | 2.05 | |
| 483 | 556.30 | 1.76 | 1H NMR (400 MHz, DMSO-d6) δ 13.97 (s, 1H), 7.84 (s, 1H), 7.65 - 7.60 (m, 1H), 7.23 - 7.18 (m, 1H), 6.99 - 6.94 (m, 2H), 6.89 (d, J = 11.3 Hz, 1H), 6.72 - 6.67 (m, 1H), 6.42 (s, 2H), 3.92 - 3.87 (m, 2H), 3.81 (d, J = 6.5 Hz, 2H), 2.30 (s, 3H), 2.09 - 1.98 (m, 1H), 1.65 - 1.60 (m, 2H), 1.07 (d, J = 6.2 Hz, 6H), 0.98 (d, J = 6.7 Hz, 6H). |
| 484 | 610.40 | 2.10 | 1H NMR (400 MHz,甲醇-d4) δ 8.25 (d, J = 2.8 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 8.7, 7.2 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 6.98 (dd, J = 8.5, 6.5 Hz, 2H), 5.99 (d, J = 2.8 Hz, 1H), 3.90 (s, 2H), 3.63 (q, J = 6.1, 5.3 Hz, 4H), 2.80 - 2.66 (m, 2H), 2.26 (d, J = 10.4 Hz, 1H), 1.90 (dd, J = 11.9, 5.6 Hz, 1H), 1.68 (q, J = 5.1, 4.7 Hz, 2H), 1.61 (d, J = 5.3 Hz, 10H), 1.47 (t, J = 12.2 Hz, 1H), 1.04 (s, 9H), 0.88 (d, J = 6.3 Hz, 3H). |
| 485 | 549.43 | 2.85 | |
| 486 | 525.30 | 1.41 | 1H NMR (400 MHz, DMSO-d6) δ 14.19 (s, 1H), 8.46 (d, J = 2.5 Hz, 1H), 7.98 (dd, J = 8.6, 2.5 Hz, 1H), 7.88 (s, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.40 (s, 2H), 5.32 (p, J = 6.2 Hz, 1H), 3.97 - 3.85 (m, 2H), 2.36 (s, 3H), 2.11 - 2.00 (m, 2H), 1.71 - 1.57 (m, 2H), 1.33 (d, J = 6.2 Hz, 6H), 1.08 (d, J = 6.3 Hz, 6H). |
| 487 | 529.18 | 1.44 | |
| 488 | 604.40 | 323.20 | |
| 489 | 574.33 | 1.33 | |
| 490 | 594.30 | 3.20 | 1H NMR (400 MHz,甲醇-d4) δ 8.16 (d, J = 8.1 Hz, 1H), 7.74 - 7.62 (m, 2H), 7.49 (t, J = 1.9 Hz, 1H), 7.45 - 7.36 (m, 2H), 6.79 (ddd, J = 8.5, 4.5, 1.9 Hz, 2H), 5.45 (p, J = 6.1 Hz, 1H), 3.89 - 3.77 (m, 2H), 3.62 (d, J = 9.3 Hz, 1H), 3.16 (dd, J = 9.2, 4.8 Hz, 1H), 2.16 - 1.95 (m, 2H), 1.89 (tt, J = 8.1, 4.3 Hz, 1H), 1.15 (s, 1H), 1.06 (dd, J = 6.8, 2.3 Hz, 6H), 0.85 (td, J = 8.1, 5.8 Hz, 1H). |
| 491 | 525.30 | 2.23 | 1H NMR (400 MHz, DMSO-d6) δ 8.20 (d, J = 5.4 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.32 (d, J = 1.4 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 6.32 (s, 2H), 4.24 (t, J = 6.7 Hz, 2H), 2.89 (dd, J = 15.6, 8.8 Hz, 2H), 2.09 (d, J = 13.2 Hz, 1H), 1.87 - 1.67 (m, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.36 (t, J = 11.9 Hz, 1H), 0.97 (t, J = 7.4 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3H), 0.78 (d, J = 6.3 Hz, 3H). |
| 492 | 557.50 | 1.89 | |
| 493 | 584.40 | 3.12 | 1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.53 (t, J = 1.8 Hz, 1H), 7.45 (dt, J = 10.0, 2.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.88 (dt, J = 10.6, 2.3 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.44 (s, 2H), 5.12 (dd, J = 8.5, 3.7 Hz, 1H), 3.83 (qd, J = 9.2, 6.6 Hz, 2H), 2.81 (dt, J = 14.0, 7.2 Hz, 1H), 2.67 (t, J = 9.3 Hz, 1H), 2.10 - 1.97 (m, 1H), 1.87 - 1.63 (m, 4H), 1.26 (dp, J = 21.5, 7.3 Hz, 2H), 0.99 (dd, J = 6.6, 1.3 Hz, 6H), 0.83 (t, J = 7.5 Hz, 3H), 0.74 (d, J = 12.5 Hz, 6H). |
| 494 | 548.20 | 2.08 | |
| 495 | 537.34 | 1.23 | |
| 496 | 556.40 | 2.54 | 1H NMR (400 MHz,甲醇-d4) δ 8.60 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.70 (dd, J = 8.6, 7.3 Hz, 1H), 7.50 (t, J = 1.9 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.36 (dd, J = 7.4, 0.8 Hz, 1H), 6.85 (dt, J = 10.5, 2.3 Hz, 1H), 6.80 (dd, J = 8.5, 0.8 Hz, 1H), 4.59 (h, J = 7.2 Hz, 1H), 3.84 (d, J = 6.4 Hz, 2H), 2.61 - 2.47 (m, 1H), 2.30 - 2.19 (m, 2H), 2.17 - 1.92 (m, 2H), 1.53 (s, 3H), 1.37 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 6.7 Hz, 6H). |
| 497 | 526.50 | 1.50 | |
| 498 | 544.22 | 1.94 | |
| 499 | 551.53 | 2.74 | |
| 500 | 525.25 | 1.49 | |
| 501 | 504.20 | 2.33 | 1H NMR (400 MHz, DMSO) δ 12.83 (s, 1H), 8.44 - 8.28 (m, 2H), 8.04 (d, J = 6.5 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 31.1, 23.3 Hz, 2H), 6.89 (d, J = 3.4 Hz, 2H), 2.24 (s, 3H), 1.92 (s, 6H), 1.04 (s, 9H). |
| 502 | 573.30 | 1.97 | |
| 503 | 557.26 | 2.39 | |
| 504 | 558.07 | 2.02 | |
| 505 | 523.32 | 2.65 | 1H NMR (400 MHz, DMSO) δ 12.43 (s, 1H), 10.17 (s, 1H), 8.14 - 8.11 (d, 1H), 7.70 - 7.63 (m, 2H), 7.25 - 7.22 (d, 1H), 7.02 - 6.96 (m, 4H), 6.73 - 7.60 (d, 1H), 6.64 - 6.58 (m, 2H), 2.28 (s, 3H), 2.03 (s, 6H) |
| 506 | 606.15 | 2.02 | |
| 507 | 497.31 | 1.64 | 1H NMR (400 MHz, DMSO) δ 8.31 (d, J = 2.2 Hz, 1H), 8.12 - 8.04 (m, J = 8.9 Hz, 2H), 7.94 - 7.86 (m, J = 5.1, 2.9 Hz, 2H), 7.51 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 4.10 (q, J = 7.0 Hz, 2H), 3.67 - 3.61 (m, J = 12.5 Hz, 2H), 3.03 - 2.89 (m, J = 11.6 Hz, 2H), 1.73 - 1.51 (m, J = 22.5, 9.5 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H), 1.33 - 1.18 (m, 2H), 0.94 (d, J = 6.4 Hz, 3H). |
| 508 | 528.00 | 1.45 | |
| 509 | 559.20 | 1.87 | |
| 510 | 570.44 | 3.43 | 1H NMR (400 MHz, DMSO) δ 7.82 - 7.79 (d, 1H), 7.63 - 7.57 (m, 2H), 7.52 - 7.46 (m, 3H), 7.35 - 7.32 (d, 1H), 6.95 - 6.91 (d, 1H), 3.85 (s, 3H), 3.85 - 3.83 (d, 2H), 3.17 (m, 4H), 2.10 - 2.00 (m, 1H), 1.30 (m, 4H), 1.01 - 0.98 (d, 6H), 0.94 (s, 6H). |
| 511 | 525.40 | 1.62 | |
| 512 | 440.40 | 1.93 | |
| 513 | 504.41 | 1.87 | |
| 514 | 508.31 | 2.51 | |
| 515 | 468.10 | 5.33 | 0.96 (s, 9H), 1.90 (s, 6H), 2.17 (s, 3H), 5.78 (br. s., 2H), 6.59 (d, J=8.2 Hz, 1H), 6.71 (s, 2H), 6.82 (d, J=7.8 Hz, 1H), 7.19-7.31 (m, 3H), 7.36-7.47 (m, 1H),8.15 (d, J=7.8 Hz, 1H). |
| 516 | 542.30 | 2.58 | |
| 517 | 520.40 | 1.83 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 12.06 (s, 1H), 8.26 (d, J = 7.3 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 5.6 Hz, 1H), 7.79 - 7.73 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.16 - 7.04 (m, 3H), 6.97 - 6.91 (m, 2H), 6.46 (t, J = 6.7 Hz, 1H), 4.05 (q, J = 6.9 Hz, 2H), 2.32 (s, 3H), 2.07 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H). |
| 518 | 481.00 | 1.90 | 1H NMR (400 MHz, DMSO) δ 13.82 (s, 1H), 12.52 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 7.81 (s, 2H), 7.74 (d, J = 7.9 Hz, 1H), 7.26 (s, 2H), 6.95 (s, 2H), 6.89 (s, 1H), 2.28 (s, 3H), 2.01 (s, 6H). |
| 519 | 544.19 | 1.75 | |
| 520 | 539.30 | 1.85 | |
| 521 | 509.18 | 1.34 | |
| 522 | 539.23 | 1.77 | |
| 523 | 538.30 | 1.58 | 1H NMR (400 MHz, DMSO-d6) δ 8.00 (d, J = 5.3 Hz, 1H), 7.72 - 7.57 (m, 1H), 7.54 - 7.36 (m, 1H), 7.13 - 6.91 (m, 4H), 6.60 (s, 1H), 6.49 (s, 1H), 6.15 (s, 1H), 3.06 (t, J = 6.4 Hz, 2H), 3.00 - 2.86 (m, 1H), 2.25 - 2.07 (m, 0H), 1.85 (ddd, J = 16.9, 12.2, 6.0 Hz, 2H), 1.61 (s, 3H), 1.57 (s, 3H), 1.39 (t, J = 11.8 Hz, 1H), 1.26 - 1.12 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H), 0.86 (d, J = 6.2 Hz, 3H). |
| 524 | 474.00 | 1.85 | 1H NMR (400 MHz, DMSO) δ 13.10 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 8.56 (d, J = 4.9 Hz, 1H), 8.25 (d, J = 9.4 Hz, 1H), 8.08 (d, J = 8.2 Hz, 2H), 8.00 - 7.92 (m, 2H), 7.35 (d, J = 4.4 Hz, 4H), 7.24 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 4.04 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H). |
| 525 | 534.20 | 1.90 | |
| 526 | 497.50 | 1.25 | |
| 527 | 540.30 | 2.99 | |
| 528 | 530.22 | 1.86 | |
| 529 | 401.00 | 1.40 | 1H NMR (400 MIIz, MeOD) δ 8.48 (d, J = 8.4 Hz, 1H), 7.99 - 7.82 (m, 2H), 7.44 (d, J = 7.3 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.30 (s, 1H), 2.71 (s, 2H), 2.54 (s, 2H), 2.01 (s, 2H). |
| 530 | 570.50 | 2.12 | 1H NMR (400 MHz, DMSO-d6) δ 7.78 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.48 (t, J = 1.8 Hz, 1H), 7.43 (dt, J = 10.0, 1.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.90 (dt, J = 10.6, 2.3 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.46 (s, 1H), 3.84 (d, J = 6.6 Hz, 2H), 3.29 - 3.15 (m, 2H), 3.15 - 2.96 (m, 2H), 2.05 (七重峰, J = 6.7 Hz, 1H), 1.43 (s, 2H), 1.38 - 1.16 (m, 4H), 0.99 (d, J = 6.7 Hz, 6H), 0.80 (s, 3H), 0.76 (t, J = 7.4 Hz, 3H). |
| 531 | 520.32 | 2.85 | |
| 532 | 452.20 | 2.05 | |
| 533 | 520.50 | 1.89 | 1H NMR (400 MHz, DMSO-d6) δ 8.32 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.92 (dd, J = 2.3, 1.0 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.43 (dd, J = 8.2, 7.3 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 7.08 - 7.00 (m, 2H), 6.94 (d, J = 8.1 Hz, 1H), 6.46 (dd, J = 8.3, 0.9 Hz, 1H), 6.12 (s, 2H), 3.87 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H), 2.04 (s, 3H). |
| 534 | 485.60 | 1.63 | |
| 535 | 581.30 | 2.34 | 1H NMR (400 MHz, DMSO-d6) δ 12.32 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.52 - 7.41 (m, 2H), 7.40 (d, J = 1.7 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 6.95 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.53 (s, 2H), 3.80 (t, J = 6.4 Hz, 2H), 2.27 (s, 3H), 2.02 (s, 6H), 1.73 (h, J = 7.1 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H). |
| 536 | 524.50 | 1.50 | |
| 537 | 416.00 | 1.96 | 1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.8 Hz, 3H), 7.49 (s, 1H), 6.93 (d, J = 8.7 Hz, 2H), 2.82 (s, 1H), 1.62 (s, 8H), 1.39 (s, 9H), 1.18 (s, 3H). |
| 538 | 523.30 | 2.38 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 539 | 480.19 | 1.46 | |
| 540 | 427.50 | 1.84 | |
| 541 | 541.36 | 1.58 | |
| 542 | 410.40 | 1.64 | |
| 543 | 592.35 | 2.77 | |
| 544 | 525.40 | 1.57 | |
| 545 | 526.10 | 1.89 | |
| 546 | 526.20 | 1.92 | |
| 547 | 556.40 | 2.66 | 1H NMR (400 MHz, DMSO-d6) δ 7.53 - 7.41 (m, 3H), 7.35 (ddd, J = 10.4, 2.3, 1.2 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.79 (dt, J = 10.8, 2.3 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.14 (s, 2H), 3.82 (d, J = 6.6 Hz, 2H), 3.29 - 3.21 (m, 1H), 2.88 (t, J = 9.5 Hz, 1H), 2.05 (七重峰, J = 6.6 Hz, 1H), 1.80 (dp, J = 13.3, 6.8 Hz, 1H), 1.66 (q, J = 6.5, 5.3 Hz, 1H), 1.59 (s, 3H), 1.48 - 1.36 (m, 1H), 1.33 (s, 3H), 0.99 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 6.8 Hz, 3H). |
| 548 | 557.10 | 2.21 | 1H NMR (400 MHz, DMSO-d6) δ 8.10 (d, J = 7.7 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.3 Hz, 1H), 6.91 (s, 2H), 6.46 (d, J = 8.2 Hz, 1H), 6.06 (s, 2H), 3.42 (s, 13H), 2.27 (s, 3H), 2.03 (s, 6H). |
| 549 | 579.45 | 3.38 | 1H NMR (400 MHz, DMSO-d6) δ 12.74 (s, 1H), 12.19 (s, 1H), 7.77 - 7.69 (m, 2H), 7.56 - 7.53 (d, 1H), 7.48 (s, 1H), 7.43 - 7.39 (d, 1H), 7.34 - 7.23 (m, 3H), 7.12 (t, J = 7.47, 1H), 6.92 - 6.88 (d, 1H), 3.84 - 3.81 (d, 2H), 2.09 - 1.98 (m, 2H), 1.81 - 1.73 (m, 1H), 1.58 (s, 3H), 1.53 (s, 3H), 1.30 (t, J = 12.41, 1H), 1.00 - 0.97 (d, 6H), 0.30 - 0.27 (d, 3H) |
| 550 | 440.40 | 1.63 | |
| 551 | 514.30 | 1.48 | |
| 552 | 566.20 | 2.15 | |
| 553 | 544.34 | 2.20 | |
| 554 | 527.00 | 1.41 | |
| 555 | 556.50 | 1.95 | 1H NMR (400 MHz,甲醇-d4) δ 7.93 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 1.8 Hz, 1H), 7.42 - 7.30 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 6.79 - 6.66 (m, 2H), 3.81 (d, J = 6.5 Hz, 2H), 2.91 (d, J = 7.5 Hz, 1H), 2.85 (d, J = 10.1 Hz, 1H), 2.37 (s, 1H), 1.64 (s, 6H), 1.58 (d, J = 12.0 Hz, 1H), 1.05 (d, J = 6.7 Hz, 6H), 1.00 (d, J = 6.4 Hz, 3H). |
| 556 | 541.18 | 1.73 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 557 | 525.30 | 1.50 | |
| 558 | 609.20 | 2.06 | |
| 559 | 552.50 | 2.11 | |
| 560 | 570.30 | 3.05 | |
| 561 | 508.20 | 1.88 | |
| 562 | 583.22 | 2.25 | |
| 563 | 524.40 | 1.67 | |
| 564 | 479.20 | 0.69 | |
| 565 | 524.17 | 1.83 | |
| 566 | 441.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 7.28 (d, J = 9.7 Hz, 2H), 7.15 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 6.77 (s, 2H), 5.45 (s, 2H), 2.75 (s, 1H), 2.18 (s, 3H), 2.09 (s, 6H), 1.10 (d, J = 6.9 Hz, 6H). |
| 567 | 497.26 | 1.45 | |
| 568 | 481.20 | 5.67 | 1H NMR (300 MHz, CDCl3) δ 1.06 (s, 9H), 2.04 (s, 6H), 2.29 (s, 3H), 2.71 (s, 3H), 6.80-6.86 (m, 3H), 6.90 (d, J=7.8 Hz, 1H), 7.23-7.31 (m, 1H), 7.32-7.41 (m, 3H), 8.25 (d, J=7.8 Hz, 1H). |
| 569 | 538.60 | 0.99 | |
| 570 | 507.20 | 2.01 | |
| 571 | 418.50 | 1.26 | |
| 572 | 557.40 | 1.86 | |
| 573 | 522.30 | 2.25 | |
| 574 | 541.29 | 1.45 | |
| 575 | 570.40 | 3.00 | |
| 576 | 617.20 | 1.69 | |
| 577 | 509.00 | 1.87 | |
| 578 | 523.30 | 1.65 | 1H NMR (400 MHz, DMSO) δ 8.90 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 8.7, 2.4 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.73 - 7.63 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 5.32 (dt, J = 12.3, 6.1 Hz, 1H), 3.43 - 3.28 (m, 4H), 2.60 - 2.44 (m, 7H), 1.44 (d, J = 4.5 Hz, 4H), 1.32 (d, J = 6.2 Hz, 6H). |
| 579 | 524.10 | 2.03 | 1H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 8.10 (d, J = 7.7 Hz, 1H), 8.05 - 7.93 (m, 2H), 7.76 - 7.68 (m, 2H), 7.68 - 7.53 (m, 2H), 7.47 - 7.39 (m, 2H), 6.91 (s, 2H), 6.23 (s, 1H), 2.27 (s, 3H), 2.01 (s, 6H). |
| 580 | 553.50 | 1.82 | |
| 581 | 554.30 | 2.69 | |
| 582 | 547.20 | 1.65 | |
| 583 | 540.43 | 3.43 | 1H NMR (400 MHz, DMSO-d6) δ 12.89 (s, 1H), 8.02 - 7.99 (d, 2H), 7.80 - 7.64 (m, 4H), 7.51 - 7.44 (m, 3H), 6.94 - 6.90 (d, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 3.85 - 3.82 (d, 2H), 3.16 (m, 4H), 2.09 - 1.99 (m, 1H), 1.29 (m, 4H), 1.01 - 0.98 (d, 6H), 0.93 (s, 6H) |
| 584 | 507.20 | 1.64 | |
| 585 | 525.00 | 2.03 | 1H NMR (400 MHz, DMSO) δ 13.81 (s, 1H), 12.52 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.24 - 7.14 (m, 2H), 6.96 (s, 2H), 6.92 - 6.80 (m, 2H), 5.75 (s, 1H), 3.93 (d, J = 7.0 Hz, 2H), 2.27 (s, 3H), 2.00 (s, 6H), 1.29 (s, 3H). |
| 586 | 580.00 | 2.23 | 1H NMR (400 MHz, DMSO) δ 12.65 (s, 1H), 8.31 (s, 1H), 8.13 (d, J = 7.9 Hz, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.18 (dd, J = 29.3, 16.8 Hz, 4H), 6.94 (s, 2H), 6.84 (d, J = 10.7 Hz, 1H), 3.65 (d, J = 6.5 Hz, 2H), 2.27 (s, 3H), 2.00 (s, 7H), 0.96 (s, 7H). |
| 587 | 542.31 | 2.09 | |
| 588 | 531.20 | 1.82 | |
| 589 | 495.18 | 1.46 | |
| 590 | 565.40 | 3.28 | |
| 591 | 516.27 | 2.05 | |
| 592 | 514.30 | 2.78 | |
| 593 | 554.40 | 2.70 | |
| 594 | 467.27 | 2.00 | |
| 595 | 533.50 | 1.90 | |
| 596 | 523.23 | 1.80 | |
| 597 | 539.30 | 1.76 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.33 (dd, J = 8.8, 2.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.45 (s, 2H), 5.32 (p, J = 6.2 Hz, 1H), 5.06 - 4.95 (m, 1H), 2.89 - 2.76 (m, 1H), 2.75 - 2.60 (m, 1H), 1.88 - 1.63 (m, 4H), 1.32 (d, J = 6.2 Hz, 6H), 0.82 (s, 9H). |
| 598 | 508.20 | 1.68 | |
| 599 | 551.53 | 3.14 | |
| 600 | 528.37 | 1.82 | 1H NMR (400 MHz, DMSO) δ 7.83 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.47 - 7.40 (m, J = 11.0, 1.7 Hz, 2H), 7.21 (d, J = 6.8 Hz, 1H), 6.91 (dt, J = 10.9, 2.2 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 4.73 (七重峰, 1H), 3.78 - 3.63 (m, J = 13.0 Hz, 2H), 2.94 - 2.78 (m, J = 11.6 Hz, 2H), 1.69 - 1.59 (m, J = 12.8 Hz, 2H), 1.58 - 1.49 (m, 1H), 1.30 (d, J = 6.0 Hz, 6H), 1.24 - 1.07 (m, 2H), 0.91 (d, J = 6.4 Hz, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 601 | 587.50 | 1.78 | |
| 602 | 551.50 | 2.05 | |
| 603 | 432.04 | 2.02 | |
| 604 | 463.50 | 2.09 | |
| 605 | 557.50 | 1.89 | |
| 606 | 541.36 | 1.49 | |
| 607 | 490.50 | 2.01 | 1H NMR (400 MHz, DMSO-d6) δ 8.33 (d, J = 2.2 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.71 (dd, J = 8.1, 1.8 Hz, 3H), 7.22 (d, J = 8.1 Hz, 2H), 7.17 - 7.04 (m, 5H), 2.31 (d, J = 5.4 Hz, 6H), 2.04 (s, 3H). |
| 608 | 538.20 | 1.88 | |
| 609 | 554.50 | 2.23 | |
| 610 | 463.50 | 1.92 | 1H NMR (400 MHz, DMSO-d6) δ 13.79 (s, 1H), 12.40 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.98 (s, 1H), 7.74 - 7.68 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 5.2, 3.0 Hz, 2H), 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 2.05 (s, 3H). |
| 611 | 570.40 | 3.23 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.51 - 7.41 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.0 Hz, 1H), 6.89 (d, J = 10.9 Hz, 1H), 6.69 (dd, J = 8.3, 4.0 Hz, 1H), 6.48 (s, 2H), 3.84 (d, J = 6.2 Hz, 2H), 3.25 - 3.06 (m, 5H), 2.10 - 1.90 (m, 2H), 1.88 - 1.75 (m, 1H), 1.68 - 1.52 (m, 1H), 0.99 (d, J = 7.1 Hz, 6H), 0.88 (s, 9H). |
| 612 | 538.50 | 1.90 | 1H NMR (400 MHz, DMSO-d6) δ 8.30 (d, J = 1.9 Hz, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.93 (dd, J = 11.9, 2.0 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 7.3, 0.8 Hz, 1H), 6.93 (s, 2H), 6.44 (d, J = 8.3 Hz, 1H), 6.08 (s, 2H), 3.94 (s, 3H), 2.39 (s, 1H), 2.28 (s, 3H), 2.01 (s, 6H). |
| 613 | 570.38 | 2.17 | |
| 614 | 494.30 | 1.58 | |
| 615 | 556.60 | 2.02 | |
| 616 | 553.40 | 2.39 | 1H NMR (400 MHz, DMSO-d6) δ 7.67 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.22 (s, 2H), 4.04 (d, J = 6.7 Hz, 2H), 3.03 - 2.84 (m, 2H), 2.42 (s, 3H), 2.04 (tq, J = 12.4, 5.7 Hz, 2H), 1.76 (dd, J = 11.8, 5.7 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.33 (t, J = 12.0 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.80 (d, J = 6.3 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3H). |
| 617 | 446.50 | 1.57 | |
| 618 | 559.28 | 2.08 | |
| 619 | 525.30 | 1.70 | |
| 620 | 540.43 | 2.73 | 1H NMR (400 MHz, DMSO-d6) δ 12.60 (s, 1H), 8.03 - 8.00 (d, 2H), 7.75 - 7.34 (m, 4H), 7.48 (s, 1H), 7.43 - 7.39 (d, 1H), 7.29 - 7.26 (d, 1H), 6.92 - 6.89 (d, 1H), 3.84 - 3.81 (d, 2H), 2.51 - 2.29 (m, 2H), 2.11 - 1.99 ( m, 2H), 1.87 - 1.80 (m, 1H), 1.59 (s, 3H), 1.55 (s, 3H), 1.38 (t, J = 11.76, 1H), 1.00 - 0.97 (d, 6H), 0.67 - 0.64 (d, 3H) |
| 621 | 521.30 | 2.06 | 1H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 8.3, 7.4 Hz, 1H), 7.26 (d, J = 7.1 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 6.90 (s, 2H), 6.70 (d, J = 8.3 Hz, 1H), 6.53 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H), 1.29 (q, J = 4.5 Hz, 2H), 0.97 (s, 2H). |
| 622 | 523.20 | 1.91 | |
| 623 | 434.30 | 1.79 | |
| 624 | 538.20 | 1.92 | |
| 625 | 573.32 | 1.90 | |
| 626 | 494.50 | 1.85 | |
| 627 | 449.00 | 1.45 | 1H NMR (400 MHz, DMSO) δ 8.27 (s, 1H), 8.10 (d, J = 6.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 32.1 Hz, 2H), 7.12 (d, J = 29.1 Hz, 3H), 6.97 (d, J = 6.4 Hz, 1H), 6.68 (s, 2H), 5.71 (s, 2H), 2.16 (s, 3H), 1.89 (s, 6H). |
| 628 | 453.30 | 1.25 | 1H NMR (400 MHz,甲醇-d4) δ 7.78 (d, J = 2.7 Hz, 1H), 7.29 - 7.10 (m, 4H), 6.99 (s, 2H), 6.84 (s, 1H), 4.37 (s, 2H), 4.26 - 4.12 (m, 1H), 3.65 (s, 1H), 3.51 - 3.33 (m, 3H), 3.27 - 3.09 (m, 2H), 2.32 (s, 6H), 2.28 (s, 3H). |
| 629 | 563.24 | 2.89 | |
| 630 | 508.00 | 2.49 | 1H NMR (400 MHz, DMSO) δ 12.41 (s, 11H), 7.97 (d, J = 8.3 Hz, 23H), 7.77 (d, J = 8.0 Hz, 11H), 7.63 (dd, J = 8.2, 7.5 Hz, 12H), 7.36 (d, J = 8.3 Hz, 23H), 7.18 (dd, J = 16.2, 7.6 Hz, 23H), 6.68 (d, J = 8.3 Hz, 11H), 6.48 (s, 22H), 2.92 (dd, J = 13.8, 6.9 Hz, 11H), 2.61 (d, J = 8.8 Hz, 23H), 2.30 (d, J = 22.9 Hz, 1H), 2.27 - 2.09 (m, 11H), 1.87 (dd, J = 11.8, 5.6 Hz, 11H), 1.61 (d, J = 3.5 Hz, 67H), 1.42 (t, J = 12.1 Hz, 13H), 1.23 (d, J = 6.9 Hz, 70H), 0.88 (d, J = 6.3 Hz, 36H). |
| 631 | 512.30 | 1.85 | 1H NMR (400 MHz, DMSO-d6) δ 8.05 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.84 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.46 (d, J = 8.3 Hz, 1H), 6.15 (d, J = 4.6 Hz, 2H), 3.93 (d, J = 7.1 Hz, 2H), 2.95 (t, J = 10.6 Hz, 1H), 2.85 (dd, J = 10.8, 7.4 Hz, 1H), 2.18 - 2.02 (m, 2H), 1.78 (dd, J = 11.7, 5.7 Hz, 1H), 1.59 (s, 3H), 1.54 (s, 3H), 1.34 (t, J = 12.0 Hz, 1H), 0.85 (d, J = 6.7 Hz, 6H), 0.81 (d, J = 6.3 Hz, 3H). |
| 632 | 399.40 | 1.63 | 1H NMR (400 MHz, DMSO-d6) δ 13.90 (s, 1H), 12.73 (s, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.42 - 7.34 (m, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 2.5 Hz, 1H), 2.34 (s, 3H), 1.35 (s, 9H). |
| 633 | 561.20 | 0.81 | |
| 634 | 482.00 | 1.95 | 1H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 11.91 (s, 1H), 8.24 (d, J = 9.4 Hz, 1H), 7.83 (s, 1H), 7.74 (s, 1H), 7.09 (s, 1H), 7.01 (s, 2H), 6.45 (s, 1H), 2.67 (s, 2H), 2.29 (s, 3H), 2.02 (s, 3H), 1.70 (s, 2H), 1.61 (s, 2H), 0.97 (s, 6H). |
| 635 | 451.40 | 1.29 | |
| 636 | 425.40 | 1.29 | |
| 637 | 457.30 | 2.84 | |
| 638 | 528.12 | 2.71 | |
| 639 | 565.60 | 2.28 | 1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.66 (dd, J = 8.4, 7.3 Hz, 1H), 7.29 - 7.06 (m, 6H), 6.84 (dt, J = 10.8, 2.3 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 3.61 (d, J = 6.7 Hz, 2H), 2.06 (s, 6H), 1.98 (dt, J = 13.4, 6.7 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H). |
| 640 | 531.18 | 1.97 | |
| 641 | 519.50 | 1.96 | 1H NMR (400 MHz, DMSO-d6) δ 12.19 (s, 1H), 8.11 - 8.01 (m, 1H), 7.83 - 7.73 (m, 2H), 7.66 (p, J = 8.3 Hz, 2H), 7.28 - 7.04 (m, 4H), 7.00 - 6.90 (m, 2H), 6.71 (d, J = 8.7 Hz, 1H), 6.51 (s, 2H), 4.05 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.06 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H). |
| 642 | 530.23 | 1.88 | |
| 643 | 467.30 | 1.16 | 1H NMR (400 MHz, DMSO-d6) δ 12.63 (s, 1H), 9.00 - 8.86 (m, 2H), 8.42 (d, J = 5.8 Hz, 2H), 7.91 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.54 (dd, J = 8.1, 1.5 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.51 (s, 1H), 2.71 - 2.53 (m, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2H), 2.23 (dt, J = 12.5, 5.7 Hz, 1H), 1.91 (dd, J = 11.9, 5.5 Hz, 1H), 1.63 (s, 3H), 1.59 (s, 3H), 1.45 (t, J = 12.1 Hz, 1H), 0.88 (d, J = 6.3 Hz, 3H). |
| 644 | 558.07 | 2.09 | |
| 645 | 566.30 | 2.10 | 1H NMR (400 MHz, DMSO-d6) δ 8.10 (d, J = 7.7 Hz, 1H), 7.98 (dd, J = 7.3, 1.9 Hz, 1H), 7.96 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.46 (s, 1H), 7.16 (d, J = 10.0 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 6.92 (s, 2H), 6.70 (dd, J = 10.8, 2.4 Hz, 1H), 6.20 (s, 1H), 4.39 (p, J = 6.1 Hz, 1H), 2.90 (s, 1H), 2.27 (s, 3H), 2.01 (s, 6H), 1.22 (d, J = 6.0 Hz, 6H). |
| 646 | 441.26 | 1.88 | |
| 647 | 573.32 | 1.90 | |
| 648 | 524.00 | 1.64 | 1H NMR (400 MHz, DMSO) δ 10.00 (s, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 7.29 (s, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.92 (s, 3H), 4.28 - 3.92 (m, 7H), 3.81 (s, 3H), 2.40 (s, 6H), 2.24 (s, 3H), 2.07 (s, 1H), 1.74 (s, 3H), 1.24 (s, 3H). |
| 649 | 433.25 | 2.10 | |
| 650 | 470.50 | 2.71 | |
| 651 | 604.38 | 2.31 | |
| 652 | 538.20 | 1.91 | |
| 653 | 421.26 | 1.73 | |
| 654 | 490.30 | 1.87 | |
| 655 | 568.40 | 2.98 | |
| 656 | 579.24 | 1.81 | |
| 657 | 556.30 | 2.67 | 1H NMR (400 MHz, DMSO-d6) δ 7.51 (d, J = 7.6 Hz, 1H), 7.47 - 7.42 (m, 2H), 7.37 - 7.33 (m, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.79 (dt, J = 10.8, 2.3 Hz, 1H), 6.48 (d, J = 8.3 Hz, 1H), 6.11 (s, 2H), 3.82 (d, J = 6.6 Hz, 2H), 3.27 (d, J = 10.2 Hz, 1H), 2.95 - 2.84 (m, 1H), 2.09 - 1.99 (m, 1H), 1.79 (dq, J = 13.2, 6.6 Hz, 1H), 1.68 (t, J = 6.3 Hz, 1H), 1.59 (s, 3H), 1.45 - 1.38 (m, 1H), 1.33 (s, 3H), 0.99 (d, J = 6.7 Hz, 6H), 0.95 (d, J = 6.7 Hz, 3H). |
| 658 | 587.30 | 1.91 | |
| 659 | 591.29 | 1.53 | |
| 660 | 453.23 | 1.17 | |
| 661 | 537.43 | 2.87 | 1H NMR (400 MHz, DMSO-d6) δ 8.16 - 8.13 (d, 1H), 7.65 - 7.46 (m, 2H), 7.22 - 7.10 (m, 3H), 7.04 - 6.91 (m, 3H), 6.69 - 6.66 (d, 1H), 6.51 (s, 2H), 3.85 (s, 3H), 2.25 (s, 3H), 2.02 (s, 6H) |
| 662 | 480.30 | 1.25 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 663 | 618.36 | 2.27 | |
| 664 | 541.33 | 1.78 | |
| 665 | 495.50 | 2.06 | |
| 666 | 437.00 | 1.04 | 1H NMR (400 MHz, DMSO) δ 7.83 (s, 1H), 7.61 (s, 2H), 7.26 (dd, J = 41.7, 19.3 Hz, 7H), 6.96 (d, J = 8.7 Hz, 1H), 4.68 (d, J = 12.3 Hz, 1H), 4.46 (d, J = 12.6 Hz, 1H), 4.23 (d, J = 12.9 Hz, 2H), 2.43 (s, 3H), 1.81 (s, 3H). |
| 667 | 484.30 | 2.13 | |
| 668 | 516.21 | 1.81 | |
| 669 | 549.40 | 1.73 | 1H NMR (400 MHz, DMSO-d6) δ 7.80 - 7.70 (m, 1H), 7.24 (d, J = 7.0 Hz, 1H), 7.08 (dt, J = 14.8, 6.6 Hz, 5H), 6.85 (s, 2H), 3.95 - 3.72 (m, 3H), 3.47 - 3.34 (m, 7H), 3.24 (dd, J = 14.0, 7.4 Hz, 3H), 3.16 - 3.01 (m, 1H), 2.99 - 2.66 (m, 3H), 2.22 (s, 3H), 2.16 (s, 6H). |
| 670 | 401.30 | 1.67 | |
| 671 | 539.20 | 2.26 | |
| 672 | 503.21 | 3.11 | |
| 673 | 547.33 | 2.94 | |
| 674 | 463.30 | 1.59 | |
| 675 | 551.27 | 1.53 | |
| 676 | 547.20 | 2.10 | 1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 7.85 (dd, J = 2.6, 1.1 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.22 (dd, J = 7.4, 0.8 Hz, 1H), 6.99 (d, J = 2.6 Hz, 1H), 6.97 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.56 (s, 2H), 2.28 (s, 3H), 2.03 (s, 6H). |
| 677 | 579.30 | 1.65 | |
| 678 | 528.30 | 2.93 | |
| 679 | 511.20 | 2.09 | |
| 680 | 540.30 | 2.86 | |
| 681 | 516.30 | 1.71 | 1H NMR (400 MHz, DMSO-d6) δ 13.78 (s, 1H), 13.22 (s, 1H), 7.98 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 6.4, 3.3 Hz, 1H), 7.28 - 7.17 (m, 2H), 7.03 (dt, J = 9.0, 3.6 Hz, 1H), 6.87 (s, 1H), 4.00 (s, 2H), 3.78 (d, J = 6.6 Hz, 2H), 2.11 - 1.96 (m, 1H), 1.98 (s, 2H), 1.66 (s, 2H), 1.06 (d, J = 6.2 Hz, 6H), 0.98 (d, J = 6.7 Hz, 6H). |
| 682 | 537.43 | 3.01 | |
| 683 | 528.30 | 2.64 | |
| 684 | 604.32 | 2.30 | |
| 685 | 436.40 | 1.72 | |
| 686 | 586.35 | 2.21 | |
| 687 | 511.30 | 1.53 | |
| 688 | 557.40 | 1.85 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 689 | 511.40 | 1.66 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.31 (dd, J = 8.7, 2.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.31 - 7.16 (m, 2H), 6.84 (d, J = 8.7 Hz, 1H), 6.70 (t, J = 8.6 Hz, 1H), 6.48 (s, 2H), 5.31 (p, J = 6.1 Hz, 1H), 4.36 - 4.20 (m, 1H), 2.57 (m, 遮蔽多重峰), 2.29 - 2.14 (m, 1H), 1.31 (d, J = 6.2 Hz, 6H), 1.27 (d, J = 5.9 Hz, 2H), 1.14 (q, J = 11.5 Hz, 1H), 0.92 (d, J = 6.3 Hz, 2H). |
| 690 | 479.00 | 1.25 | 1H NMR (400 MHz, DMSO) δ 10.18 (s, 1H), 7.68 (s, 1H), 7.30 - 7.09 (m, 4H), 6.90 (d, J = 30.5 Hz, 3H), 6.77 (d, J = 8.4 Hz, 1H), 4.40 (s, 1H), 4.15 (s, 3H), 3.96 (s, 2H), 2.96 (s, 2H), 2.23 (s, 3H), 2.15 (s, 6H). |
| 691 | 547.20 | 0.77 | |
| 692 | 544.30 | 1.91 | |
| 693 | 508.26 | 1.94 | |
| 694 | 528.50 | 1.89 | |
| 695 | 538.26 | 2.00 | |
| 696 | 479.30 | 1.25 | |
| 697 | 588.15 | 3.05 | |
| 698 | 492.40 | 2.19 | |
| 699 | 529.39 | 1.85 | 1H NMR (400 MHz, DMSO) δ 8.33 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.48 - 7.40 (m, J = 8.7, 1.8 Hz, 2H), 6.92 (dt, J = 11.0, 2.3 Hz, 1H), 4.74 (七重峰, J = 6.0 Hz, 1H), 3.73 - 3.60 (m, J = 12.9 Hz, 2H), 2.98 - 2.82 (m, J = 11.7 Hz, 2H), 1.69 - 1.49 (m, J = 11.6 Hz, 3H), 1.30 (d, J = 6.0 Hz, 6H), 1.27 - 1.11 (m, J = 23.3, 11.6 Hz, 2H), 0.92 (d, J = 6.1 Hz, 3H). |
| 700 | 537.43 | 2.95 | |
| 701 | 518.50 | 1.65 | 1H NMR (400 MHz, DMSO-d6) δ 13.78 (s, 1H), 13.21 (s, 1H), 7.98 (s, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 1.9 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 6.86 (s, 1H), 4.77 (p, J = 6.1 Hz, 1H), 4.02 (s, 2H), 2.06 - 1.94 (m, 3H), 1.75 - 1.63 (m, 2H), 1.35 (d, J = 6.1 Hz, 6H), 1.07 (d, J = 6.2 Hz, 6H). |
| 702 | 425.40 | 1.31 | |
| 703 | 523.23 | 1.51 | |
| 704 | 458.30 | 1.47 | |
| 705 | 534.50 | 1.99 | 1H NMR (400 MHz, DMSO-d6) δ 8.26 (s, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.89 (s, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.7 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.08 (d, J = 7.3 Hz, 1H), 6.92 (s, 2H), 6.44 (d, J = 8.2 Hz, 1H), 6.05 (s, 2H), 3.87 (s, 3H), 2.90 (s, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 2.02 (s, 6H). |
| 706 | 545.21 | 2.10 | |
| 707 | 452.00 | 1.48 | 1H NMR (400 MHz, DMSO) δ 12.94 (s, 1H), 8.40 (s, 1H), 8.04 (s, 1H), 7.59 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 14.8 Hz, 4H), 2.81 (s, 2H), 2.31 (s, 3H), 1.77 (s, 4H), 1.29 (s, 6H). |
| 708 | 525.50 | 1.60 | |
| 709 | 557.20 | 2.18 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.04 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.79 - 7.72 (m, 1H), 7.70 - 7.61 (m, 2H), 7.24 (d, J = 7.0 Hz, 1H), 6.95 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 2.27 (s, 3H), 2.02 (s, 6H). |
| 710 | 498.40 | 1.67 | |
| 711 | 618.36 | 2.11 | |
| 712 | 484.20 | 1.47 | |
| 713 | 522.50 | 1.83 | |
| 714 | 497.20 | 2.75 | 1H NMR (400 MHz, 氯仿-d) δ 10.71 - 10.46 (m, 1H), 8.04 (s, 1H), 7.64 (d, J = 3.6 Hz, 2H), 6.90 (s, 2H), 6.65 (s, 1H), 4.70 (s, 2H), 3.60 (s, 2H), 2.33 (s, 3H), 2.08 (s, 6H), 0.99 (s, 6H). |
| 715 | 468.00 | 2.20 | 1H NMR (400 MHz, DMSO) δ 13.78 (s, 1H), 12.16 (s, 1H), 7.97 (s, 1H), 7.69 (s, 1H), 6.90 (s, 2H), 6.86 (s, 1H), 2.67 (s, 2H), 2.25 (s, 3H), 1.95 (s, 6H), 1.68 (s, 2H), 1.60 (s, 2H), 0.92 (s, 6H). |
| 716 | 564.29 | 2.14 | 1H NMR (400 MHz, DMSO) δ 13.81 (s, 1H), 12.70 (s, 1H), 8.01 (s, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.29 - 7.19 (m, 5H), 7.17 - 7.06 (m, 3H), 6.93 (s, 1H), 6.77 (dt, J = 10.7, 2.3 Hz, 1H), 5.31 (t, J = 7.6 Hz, 1H), 3.72 (ddd, J = 31.5, 9.2, 6.4 Hz, 2H), 3.17 (dd, J = 16.6, 9.7 Hz, 1H), 2.81 (t, J = 7.5 Hz, 1H), 2.38 (dd, J = 10.9, 5.0 Hz, 1H), 2.07 - 1.98 (m, 1H), 1.93 - 1.72 (m, 2H), 1.64 (dd, J = 18.4, 8.3 Hz, 1H), 1.01 (dd, J = 6.7, 2.1 Hz, 6H). |
| 717 | 539.60 | 1.71 | |
| 718 | 534.20 | 2.01 | |
| 719 | 558.30 | 2.00 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.51 (dt, J = 7.0, 1.8 Hz, 2H), 7.48 - 7.42 (m, 2H), 7.35 (dd, J = 7.9, 5.5 Hz, 2H), 7.21 (d, J = 7.2 Hz, 1H), 6.89 (dt, J = 10.6, 2.3 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2H), 6.71 (d, J = 8.4 Hz, 1H), 4.59 (dd, J = 7.2, 3.3 Hz, 1H), 4.55 - 4.46 (m, 1H), 3.85 (d, J = 3.2 Hz, 2H), 3.83 (d, J = 3.1 Hz, 2H), 3.81 (dd, J = 9.1, 3.3 Hz, 1H), 3.74 (dd, J = 9.1, 3.3 Hz, 1H), 3.59 - 3.52 (m, 2H), 3.35 (dd, J = 9.1, 7.5 Hz, 2H), 3.32 (s, 3H), 3.27 (s, 3H), 2.94 (dd, J = 9.7, 6.7 Hz, 1H), 2.89 - 2.78 (m, 1H), 2.14 - 1.94 (m, 5H), 1.86 - 1.68 (m, 5H), 1.00 (d, J = 2.3 Hz, 6H), 0.99 (d, J = 2.2 Hz, 6H)。兩種旋轉異構體約1:1比率。因此兩組峰。 |
| 720 | 542.34 | 2.02 | |
| 721 | 543.30 | 1.66 | |
| 722 | 521.00 | 1.85 | 1H NMR (400 MHz, DMSO) δ 12.95 (s, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.64 (s, 1H), 7.56 (s, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 8.2 Hz, 3H), 6.96 (d, J = 10.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.76 (s, 1H), 2.33 (s, 3H), 1.32 (s, 6H). |
| 723 | 555.10 | 1.25 | |
| 724 | 525.25 | 1.76 | |
| 725 | 525.42 | 3.01 | |
| 726 | 483.20 | 1.17 | 1H NMR (400 MHz, DMSO-d6) δ 13.13 (s, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.36 (dd, J = 8.7, 2.5 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.76 - 6.69 (m, 1H), 4.06 - 4.00 (m, 2H), 3.92 (s, 3H), 2.05 - 1.93 (m, 2H), 1.73 - 1.60 (m, 2H), 1.09 (d, J = 6.3 Hz, 6H). |
| 727 | 537.43 | 2.51 | |
| 728 | 520.21 | 1.83 | |
| 729 | 539.30 | 1.68 | |
| 730 | 504.30 | 1.65 | |
| 731 | 573.25 | 1.70 | |
| 732 | 523.23 | 1.69 | |
| 733 | 537.30 | 1.75 | |
| 734 | 516.21 | 1.82 | |
| 735 | 542.31 | 2.00 | |
| 736 | 511.30 | 1.56 | |
| 737 | 529.32 | 1.77 | 1H NMR (400 MHz, DMSO) δ 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.91 - 7.80 (m, J = 7.9 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 9.9, 1.7 Hz, 2H), 6.91 (dt, J = 10.9, 2.2 Hz, 1H), 6.46 (dd, J = 7.1, 6.5 Hz, 1H), 4.73 (七重峰, J = 6.0 Hz, 1H), 3.78 - 3.66 (m, J = 12.8 Hz, 2H), 2.95 - 2.80 (m, J = 11.6 Hz, 2H), 1.69 - 1.49 (m, J = 20.3, 9.3 Hz, 3H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.30 (d, J = 6.0 Hz, 6H), 1.27 - 1.12 (m, J = 12.0 Hz, 2H), 0.92 (d, J = 6.3 Hz, 3H). |
| 738 | 525.20 | 2.16 | |
| 739 | 536.16 | 1.92 | |
| 740 | 497.21 | 1.37 | |
| 741 | 547.60 | 1.97 | |
| 742 | 573.32 | 1.90 | 1H NMR (400 MHz, DMSO) δ 8.92 (d, J = 2.4 Hz, 1H), 8.38 (dd, J = 8.7, 2.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.26 (tt, J = 12.8, 6.5 Hz, 6H), 6.87 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.33 (dd, J = 12.3, 6.2 Hz, 1H), 3.87 (d, J = 12.4 Hz, 2H), 3.02 (t, J = 11.9 Hz, 2H), 2.75 (s, 1H), 2.59 - 2.46 (m, 3H), 1.93 - 1.63 (m, 4H), 1.32 (d, J = 6.2 Hz, 6H). |
| 743 | 510.30 | 2.20 | |
| 744 | 518.12 | 2.21 | |
| 745 | 515.25 | 1.65 | |
| 746 | 482.50 | 2.86 | 10.67 (s, 1H), 7.92 - 7.89 (d, 1H), 7.63 (t, J = 7.80, 1H), 7.23 - 7.20 (d, 1H), 6.94 (s, 2H), 6.70 - 6.67 (d, 1H), 6.49 (s, 2H), 6.22 - 6.19 (d, 1H), 2.27 (s, 3H), 2.06 (s, 6H), 1.81 (s, 4H) |
| 747 | 493.20 | 1.72 | |
| 748 | 497.51 | 2.65 | 1H NMR (400 MHz, DMSO) δ 7.95 - 7.92 (d, 1H), 7.46 (t, J = 7.03, 1H), 7.09 - 7.06 (d, 1H), 6.89 - 6.87 (m, 3H), 6.52 - 6.49 (d, 1H), 6.20 (s, 2H), 3.80 - 3.76 (m, 2H), 2.67-2.59 (m, 1H), 2.25 (s, 3H), 1.96 (s, 6H) , 1.56 - 1.34 (m, 4H) |
| 749 | 532.20 | 1.80 | |
| 750 | 458.38 | 1.59 | |
| 751 | 542.40 | 1.95 | 1H NMR (400 MHz, DMSO-d6) δ 12.58 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.42 (dt, J = 10.2, 1.8 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.8, 2.3 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.13 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 2.12 - 1.98 (m, 3H), 1.49 (dd, J = 9.8, 7.4 Hz, 2H), 0.99 (dd, J = 6.7, 3.9 Hz, 12H). |
| 752 | 461.40 | 1.73 | |
| 753 | 417.30 | 1.75 | |
| 754 | 550.20 | 2.11 | |
| 755 | 466.50 | 1.79 | |
| 756 | 516.22 | 1.82 | |
| 757 | 511.30 | 1.66 | |
| 758 | 525.20 | 2.17 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 759 | 471.50 | 3.24 | 1H NMR (400 MHz, DMSO-d6) δ 12.77 (s, 1H), 8.50 (dd, J = 4.9, 1.9 Hz, 1H), 8.33 (dd, J = 7.7, 1.9 Hz, 1H), 7.27 (dd, J = 7.7, 4.9 Hz, 1H), 7.06 (s, 1H), 6.74 (s, 2H), 5.40 (s, 2H), 3.96 (s, 3H), 2.17 (s, 3H), 2.05 (s, 6H), 1.16 (s, 9H). |
| 760 | 487.11 | 1.32 | |
| 761 | 480.30 | 1.47 | |
| 762 | 538.20 | 1.91 | |
| 763 | 498.30 | 1.45 | |
| 764 | 511.40 | 1.64 | 1H NMR (400 MHz, 乙醇-d6) δ 8.85 (d, J = 2.4 Hz, 1H), 8.31 (dd, J = 8.7, 2.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.22 (dd, J = 13.7, 7.5 Hz, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 5.31 (p, J = 6.2 Hz, 2H), 3.70 (dd, J = 8.1, 5.9 Hz, 1H), 2.93 - 2.77 (m, 1H), 2.72 - 2.61 (m, 1H), 1.96 - 1.67 (m, 2H), 1.32 (s, 6H) 1.32 (遮蔽多重峰, 1H), 1.26 (d, J = 5.9 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H). |
| 765 | 480.00 | 1.51 | 1H NMR (400 MHz, DMSO) δ 9.89 (s, 1H), 8.20 (d, J = 24.9 Hz, 2H), 7.55 (s, 1H), 7.29 (d, J = 41.2 Hz, 3H), 7.08 (s, 1H), 6.91 (s, 2H), 4.37 - 4.01 (m, 4H), 3.82 (s, 3H), 2.41 (s, 6H), 2.24 (s, 3H), 1.78 (s, 3H). |
| 766 | 533.31 | 1.88 | |
| 767 | 480.30 | 1.86 | |
| 768 | 535.32 | 2.59 | |
| 769 | 551.13 | 2.13 | |
| 770 | 512.20 | 1.25 | |
| 771 | 589.00 | 2.38 | 1H NMR (400 MHz, DMSO) δ 8.49 (d, J = 7.9 Hz, 1H), 8.44 (s, 1H), 8.36 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 11.5 Hz, 1H), 7.18 (s, 1H), 6.94 (s, 2H), 6.84 (d, J = 10.7 Hz, 1H), 3.65 (d, J = 6.5 Hz, 2H), 2.26 (s, 3H), 2.07 (s, 3H), 1.99 (s, 7H), 0.97 (d, J = 6.7 Hz, 6H). |
| 772 | 604.50 | 2.25 | |
| 773 | 544.30 | 1.70 | 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 7.83 (d, J = 1.9 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70 - 7.61 (m, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.23 (dd, J = 7.3, 0.8 Hz, 1H), 6.72 (d, 1H), 6.48 (s, 2H), 4.13 (t, J = 6.5 Hz, 2H), 4.09 - 3.97 (m, 2H), 2.05 - 1.91 (m, 2H), 1.81 (h, J = 7.2 Hz, 2H), 1.74 - 1.61 (m, 2H), 1.10 (d, J = 6.2 Hz, 6H), 1.03 (t, J = 7.4 Hz, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 774 | 546.21 | 1.75 | |
| 775 | 557.24 | 2.72 | 1H NMR (400 MHz, DMSO-d6) δ 7.95 (t, J = 7.80, 1H), 8.86 - 8.83 (d, 1H), 7.62 - 7.59 (d, 1H), 7.52 - 7.48 (m, 3H), 6.99 - 6.90 (m, 2H), 3.86 - 3.83 (d, 2H), 3.26 (m, 4H), 2.10 - 1.97 (m, 1H), 1.33 (m, 4H), 1.01 - 0.98 (d, 6H), 0.94 (s, 6H) |
| 776 | 547.60 | 1.97 | 1H NMR (400 MHz, DMSO) δ 13.74 (s, 1H), 12.85 (s, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.32 (dd, J = 8.7, 2.5 Hz, 1H), 7.94 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.38 - 7.30 (m, 4H), 7.27 - 7.20 (m, 1H), 6.84 (d, J = 8.8 Hz, 2H), 5.37 - 5.23 (m, 1H), 3.93 (d, J = 11.4 Hz, 1H), 3.59 (d, J = 12.7 Hz, 1H), 3.02 - 2.83 (m, 3H), 1.91 (d, J = 8.9 Hz, 1H), 1.70 (t, J = 11.4 Hz, 3H), 1.31 (d, J = 6.2 Hz, 6H). |
| 777 | 524.30 | 1.89 | |
| 778 | 551.40 | 2.22 | |
| 779 | 554.60 | 1.79 | |
| 780 | 610.38 | 2.24 | |
| 781 | 484.30 | 1.20 | |
| 782 | 579.27 | 2.29 | |
| 783 | 531.30 | 1.98 | |
| 784 | 463.30 | 1.96 | 1H NMR (400 MHz, DMSO-d6) δ 13.80 (s, 1H), 12.46 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.82 - 7.71 (m, 3H), 7.41 (dp, J = 3.5, 1.9 Hz, 3H), 6.95 (s, 2H), 6.88 (s, 1H), 2.28 (s, 3H), 2.03 (s, 6H). |
| 785 | 496.60 | 2.96 | |
| 786 | 519.42 | 2.53 | 1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 8.17 - 8.14 (d, 1H), 7.76 - 7.56 (m, 4H), 7.37 - 7.35 (m, 2H), 7.26 - 7.23 (d, 1H), 6.95 (s, 2H), 6.74 - 7.61 (d, 1H), 6.56 (s, 2H), 4.48 (s, 2H), 2.28 (s, 3H), 2.04 (s, 6H) |
| 787 | 533.22 | 2.05 | |
| 788 | 544.30 | 1.65 | |
| 789 | 523.30 | 1.96 | 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 2.4 Hz, 1H), 8.28 (dd, J = 8.7, 2.5 Hz, 1H), 7.60 - 7.42 (m, 2H), 7.01 (bs, 2H), 6.87 (d, J = 8.7 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.23 (bs, 2H), 4.23 (s, 2H), 4.13 (d, J = 7.1 Hz, 2H), 1.86 (bs, 2H), 1.56 (bs, 2H), 1.25 (dddd, J = 11.9, 7.3, 5.4, 2.6 Hz, 1H), 1.04 (d, J = 6.1 Hz, 6H), 0.59 - 0.49 (m, 2H), 0.36 - 0.26 (m, 2H). |
| 790 | 451.00 | 1.10 | 1H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 7.74 (s, 1H), 7.49 (s, 1H), 7.42 - 7.07 (m, 7H), 6.82 (s, 1H), 4.36 - 4.09 (m, 5H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.44 (s, 5H), 1.82 (s, 3H). |
| 791 | 485.50 | 2.71 | |
| 792 | 470.32 | 1.38 | |
| 793 | 519.20 | 1.87 | |
| 794 | 432.40 | 1.50 | |
| 795 | 571.34 | 3.04 | 1H NMR (400 MHz, DMSO) δ 12.89 (s, 1H), 8.04 (t, J = 8.04, 1H), 7.83 - 7.75 (m, 2H), 7.49 (s, 1H), 7.44 - 7.40 (d, 1H), 7.32 - 7.29 (d, 1H), 7.18 - 7.15 (d, 1H), 6.93 - 6.89 (d, 1H), 3.91 (s, 3H), 3.85 - 3.82 (d, 2 H), 2.10 (m, 1H), 2.07 - 1.99 (m, 1H), 1.88 - 1.83 (m, 1H), 1.59 (s, 6H), 1.39 (t, J = 12.41, 1H), 1.00 - 0.97 (d, 6H), 0.78 - 0.75 (d, 3H) |
| 796 | 538.60 | 0.97 | |
| 797 | 481.00 | 2.01 | 1H NMR (400 MHz, DMSO) δ 7.60 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 14.5 Hz, 2H), 7.13 (s, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.81 (d, J = 10.1 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.59 (s, 2H), 1.25 (s, 9H). |
| 798 | 536.00 | 201.00 | 1H NMR (400 MHz, DMSO) δ 13.12 (s, 1H), 8.56 (d, J = 6.0 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 10.1 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.24 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 13.1 Hz, 1H), 4.75 (s, 1H), 4.03 (s, 3H), 2.32 (s, 3H), 1.30 (d, J = 6.0 Hz, 6H). |
| 799 | 427.30 | 1.90 | |
| 800 | 432.36 | 1.60 | |
| 801 | 518.22 | 2.05 | |
| 802 | 466.33 | 1.61 | |
| 803 | 525.42 | 2.97 | |
| 804 | 580.20 | 2.19 | |
| 805 | 452.30 | 1.24 | |
| 806 | 443.18 | 2.74 | |
| 807 | 542.30 | 1.70 | |
| 808 | 521.20 | 1.81 | |
| 809 | 425.30 | 1.72 | |
| 810 | 588.15 | 2.07 | |
| 811 | 525.30 | 1.57 | 1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.82 (d, J = 2.4 IIz, 1H), 8.27 (dd, J = 8.8, 2.6 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.63 (s, 1H), 6.41 (s, 2H), 5.32 (h, J = 6.3 Hz, 1H), 2.83 - 2.56 (m, 2H), 2.27 - 2.13 (m, 1H), 1.86 (dd, J = 11.9, 5.7 Hz, 1H), 1.59 (d, J = 4.8 Hz, 6H), 1.41 (t, J = 12.0 Hz, 1H), 1.31 (d, J = 6.2 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6H), 0.88 (d, J = 6.3 Hz, 3H). |
| 812 | 561.50 | 1.75 | |
| 813 | 493.20 | 1.96 | 1H NMR (400 MHz, DMSO-d6) δ 13.78 (s, 1H), 12.33 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.79 - 7.73 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.13 (dd, J = 5.0, 3.0 Hz, 2H), 7.10 - 7.04 (m, 1H), 6.97 - 6.91 (m, 2H), 6.86 (s, 1H), 4.05 (q, J = 6.9 Hz, 2H), 2.32 (s, 3H), 2.05 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H). |
| 814 | 539.50 | 1.44 | |
| 815 | 526.10 | 1.98 | |
| 816 | 478.50 | 1.78 | 1H NMR (400 MHz, DMSO) δ 8.25 (d, J = 2.1 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.61 (dd, J = 8.3, 7.4 Hz, 1H), 7.32 (s, 1H), 7.08 (d, J = 6.9 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.60 (s, 2H), 5.63 (s, 2H), 4.81 (br s, 2H), 2.68 (q, J = 7.5 Hz, 2H), 2.12 (s, 3H), 1.91 (s, 6H), 1.21 (t, J = 7.6 Hz, 3H). |
| 817 | 503.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 12.47 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 7.31 (d, J = 11.3 Hz, 4H), 7.22 (d, J = 7.3 Hz, 1H), 6.91 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.24 (d, J = 4.4 Hz, 6H), 2.00 (s, 6H). |
| 818 | 601.31 | 1.90 | |
| 819 | 490.00 | 1.68 | 1H NMR (400 MHz, DMSO) δ 13.14 (s, 1H), 8.42 (s, 1H), 8.14 (d, J = 8.7 Hz, 2H), 8.06 (s, 1H), 7.96 (s, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.09 (dd, J = 21.2, 8.3 Hz, 4H), 4.10 (s, 2H), 2.34 (s, 3H), 1.36 (s, 3H). |
| 820 | 460.00 | 1.68 | 1H NMR (400 MHz, DMSO) δ 13.12 (s, 1H), 8.42 (d, J = 2.2 Hz, 1H), 8.07 (dd, J = 12.6, 5.2 Hz, 3H), 7.99 (s, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.10 (t, J = 15.8 Hz, 4H), 2.36 (d, J = 14.8 Hz, 6H). |
| 821 | 456.10 | 2.19 | 1H NMR (400 MHz, DMSO) δ 8.01 - 7.99 (d, 1H), 7.46 (s, 2H), 7.06 - 6.77 (m, 6H), 6.41 (s, 1H), 5.67 (s, 2H), 2.80 (s, 3H), 2.23 (s, 6H), 1.12 (s, 9H) |
| 822 | 498.50 | 1.46 | |
| 823 | 468.40 | 2.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 7.85 - 7.80 (m, 2H), 7.63 - 7.54 (m, 2H), 6.99 (s, 1H), 6.74 (s, 2H), 5.43 (s, 2H), 2.75 (q, J = 7.6 Hz, 2H), 2.16 (s, 3H), 2.05 (s, 6H), 1.23 (t, J = 7.6 Hz, 3H), 1.14 (s, 9H). |
| 824 | 545.28 | 2.00 | |
| 825 | 480.00 | 1.33 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 826 | 466.00 | 2.04 | 1H NMR (400 MHz, DMSO) δ 11.95 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.23 (s, 2H), 7.10 (s, 2H), 6.94 - 6.81 (m, 3H), 3.51 (s, 2H), 2.25 (s, 3H), 1.92 (s, 6H), 1.31 (s, 3H), 0.67 (d, J = 14.3 Hz, 4H). |
| 827 | 566.30 | 1.11 | |
| 828 | 549.43 | 2.97 | |
| 829 | 463.17 | 1.86 | |
| 830 | 537.43 | 2.98 | |
| 831 | 518.20 | 2.12 | |
| 832 | 518.20 | 1.71 | |
| 833 | 510.30 | 1.41 | |
| 834 | 511.20 | 1.48 | 1H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.28 (dd, J = 8.8, 2.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.69 - 7.60 (m, 1H), 7.18 (t, J = 7.2 Hz, 2H), 6.86 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 5.32 (dt, J = 12.1, 6.1 Hz, 1H), 2.76 (s, 2H), 1.76 (s, 4H), 1.56 (d, J = 14.3 Hz, 6H), 1.32 (d, J = 6.2 Hz, 6H). |
| 835 | 552.20 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 11.83 (s, 1H), 8.10 (d, J = 7.7 Hz, 1H), 8.01 (dd, J = 7.0, 2.0 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.20 - 7.08 (m, 2H), 6.92 (s, 2H), 6.75 (dt, J = 10.7, 2.3 Hz, 1H), 6.27 (s, 1H), 3.91 (q, J = 7.0 Hz, 2H), 2.26 (s, 3H), 2.00 (s, 6H), 1.29 (t, J = 7.0 Hz, 3H). |
| 836 | 511.30 | 1.66 | |
| 837 | 556.50 | 1.90 | |
| 838 | 523.40 | 1.50 | |
| 839 | 538.20 | 1.89 | |
| 840 | 492.00 | 1.29 | 1H NMR (400 MHz, DMSO) δ 11.11 (s, 1H), 7.64 (s, 1H), 7.31 (s, 4H), 7.19 (s, 1H), 7.10 (s, 1H), 6.72 (s, 2H), 4.58 (s, 1H), 4.15 (d, J = 7.4 Hz, 1H), 3.90 (d, J = 12.5 Hz, 1H), 2.22 (s, 3H), 2.19 (s, 3H), 2.12 (s, 6H), 1.60 (s, 3H), 1.48 (s, 3H). |
| 841 | 441.40 | 1.82 | |
| 842 | 562.34 | 3.06 | 1H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 9.10 (s, 1H), 7.72 - 7.69 (d, 1H), 7.49 (s, 1H), 7.44 - 7.40 (d, 1H), 7.30 - 7.27 (d, 1H), 6.92 - 6.88 (d, 1H), 3.85 - 3.82 (d, 2H), 2.67 - 2.59 (m, 2H), 2.20 (m, 1H), 2.10 - 2.00 (m, 1H), 1.92 - 1.85 (m, 1H), 1.64 (s, 3H), 1.59 (s, 3H), 1.45 (t, J = 12.09, 1H), 1.00 - 0.97 (d, 6H), 0.84 - 0.81 (d, 3H) |
| 843 | 546.20 | 1.86 | |
| 844 | 526.30 | 2.00 | 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 2H), 7.65 (s, 1H), 7.53 (s, 1H), 7.09 (d, J = 31.1 Hz, 2H), 6.57 (s, 1H), 6.34 (s, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 5.26 (h, J = 6.2 Hz, 1H), 2.80 (s, 1H), 2.13 (s, 1H), 1.84 (dd, J = 11.7, 5.6 Hz, 1H), 1.59 (s, 3H), 1.55 (s, 3H), 1.34 (d, J = 6.2 Hz, 6H), 0.82 (d, J = 6.2 Hz, 3H). |
| 845 | 554.50 | 1.94 | |
| 846 | 553.60 | 1.81 | |
| 847 | 494.30 | 1.81 | |
| 848 | 553.50 | 1.79 | |
| 849 | 495.00 | 1.81 | 1H NMR (400 MHz, DMSO) δ 13.93 (s, 1H), 12.89 (s, 1H), 8.02 (d, J = 24.9 Hz, 3H), 7.57 (s, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 12.7 Hz, 1H), 6.81 (s, 1H), 4.76 (s, 1H), 2.36 (s, 3H), 1.32 (s, 6H). |
| 850 | 570.30 | 2.05 | 1H NMR (400 MHz, DMSO) δ 12.52 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.46 (s, 1H), 7.38 (d, J = 9.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 3.83 (d, J = 6.6 Hz, 2H), 2.59 (s, 2H), 2.05 (dd, J = 11.6, 5.0 Hz, 1H), 1.76 (s, 2H), 1.65 (s, 6H), 1.03 - 0.95 (m, 12H). |
| 851 | 553.60 | 1.64 | |
| 852 | 424.19 | 2.24 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.62 (dd, J = 8.4, 7.3 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 6.51 (s, 2H), 2.60 - 2.52 (m, 2H), 2.20 (dq, J = 16.9, 6.4 Hz, 1H), 1.85 (dd, J = 12.0, 5.6 Hz, 1H), 1.48 (d, J = 9.8 Hz, 6H), 1.39 (t, J = 12.2 Hz, 1H), 0.86 (d, J = 6.2 Hz, 3H). |
| 853 | 531.30 | 1.96 | 1H NMR (400 MHz, DMSO) δ 12.72 (s, 1H), 8.29 (d, J = 7.6 Hz, 1H), 7.68 - 7.59 (m, 2H), 7.20 (d, J = 7.2 Hz, 1H), 6.90 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.59 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H). |
| 854 | 467.00 | 1.92 | 1H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.03 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.87 (s, 2H), 6.71 (d, J = 8.3 Hz, 1H), 6.50 (s, 2H), 2.24 (s, 3H), 1.94 (s, 6H), 1.37 (s, 3H), 0.89 (s, 2H), 0.75 (s, 2H). |
| 855 | 480.00 | 1.32 | 1H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.20 (d, J = 9.3 Hz, 1H), 7.82 (s, 1H), 7.12 (d, J = 28.2 Hz, 3H), 6.93 (s, 1H), 6.82 (s, 2H), 6.43 (s, 1H), 4.41 (s, 1H), 2.83 (s, 2H), 2.21 (s, 3H), 2.14 (s, 6H), 2.07 (s, 2H). |
| 856 | 529.02 | 2.55 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 857 | 554.50 | 2.13 | |
| 858 | 567.27 | 1.72 | |
| 859 | 590.30 | 2.21 | |
| 860 | 563.30 | 1.99 | |
| 861 | 505.00 | 1.80 | 1H NMR (400 MHz, DMSO) δ 13.12 (s, 1H), 8.81 (s, 1H), 8.56 (d, J = 6.8 Hz, 1H), 8.31 (s, 1H), 8.25 (d, J = 7.6 Hz, 1H), 7.97 (s, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.25 (s, 1H), 7.04 (d, J = 7.9 Hz, 2H), 4.04 (s, 3H), 3.96 (s, 3H), 2.28 (d, J = 30.8 Hz, 6H). |
| 862 | 483.40 | 3.22 | |
| 863 | 497.31 | 1.53 | |
| 864 | 573.28 | 1.92 | |
| 865 | 531.00 | 2.10 | 1H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 7.42 (d, J = 17.4 Hz, 2H), 7.21 (s, 3H), 6.91 (s, 2H), 6.68 (s, 1H), 6.47 (s, 2H), 2.90 (s, 1H), 2.25 (s, 3H), 2.00 (s, 6H), 1.12 (d, J = 6.8 Hz, 6H). |
| 866 | 523.20 | 1.83 | |
| 867 | 583.22 | 2.27 | |
| 868 | 545.00 | 2.13 | 1H NMR (400 MHz, DMSO) δ 12.52 (s, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.71 - 7.55 (m, 2H), 7.37 (s, 1H), 7.23 (d, J = 6.7 Hz, 2H), 7.00 (d, J = 6.1 Hz, 1H), 6.90 (s, 2H), 6.69 (d, J = 11.3 Hz, 1H), 6.48 (s, 1H), 2.24 (s, 3H), 2.00 (s, 6H), 1.12 (s, 9H). |
| 869 | 517.50 | 2.19 | |
| 870 | 479.32 | 1.22 | |
| 871 | 593.00 | 1.81 | 1H NMR (400 MHz, DMSO) δ 12.76 (s, 1H), 8.49 (s, 2H), 8.25 - 8.09 (m, 3H), 7.76 (s, 2H), 7.25 - 7.13 (m, 2H), 6.94 (s, 2H), 6.82 (d, J = 10.4 Hz, 1H), 4.25 (s, 2H), 3.64 (d, J = 6.5 Hz, 2H), 2.27 (s, 3H), 2.02 (s, 7H), 0.97 (d, J = 6.7 Hz, 6H). |
| 872 | 517.18 | 1.89 | |
| 873 | 449.50 | 1.57 | |
| 874 | 565.20 | 2.24 | |
| 875 | 521.20 | 2.14 | |
| 876 | 494.30 | 1.53 | |
| 877 | 524.10 | 2.66 | |
| 878 | 520.21 | 1.84 | |
| 879 | 470.50 | 1.46 | 1H NMR (400 MHz, DMSO-d6) δ 13.72 (s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.95 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 3.63 (dt, J = 11.9, 4.6 Hz, 2H), 3.55 (s, 2H), 3.49 (ddd, J = 11.8, 9.1, 3.0 Hz, 2H), 2.36 (s, 3H), 1.45 (ddd, J = 13.4, 9.1, 4.1 Hz, 2H), 1.27 - 1.19 (m, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 0.97 (s, 3H). |
| 880 | 414.00 | 1.65 | 1H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 7.61 (s, 3H), 7.31 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.7 Hz, 2H), 5.77 (s, 10H), 5.57 (s, 1H), 2.33 (s, 2H), 1.79 (s, 2H), 1.57 (s, 2H), 1.48 (s, 2H), 1.28 (s, 9H). |
| 881 | 556.50 | 1.87 | |
| 882 | 494.30 | 2.08 | |
| 883 | 497.31 | 1.93 | |
| 884 | 567.33 | 1.72 | |
| 885 | 481.00 | 1.07 | 1H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 7.81 (s, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.05 (s, 2H), 6.91 (s, 3H), 6.72 (d, J = 10.1 Hz, 1H), 4.39 - 4.01 (m, 4H), 2.39 (s, 6H), 2.24 (s, 3H), 1.82 (s, 3H). |
| 886 | 514.31 | 2.83 | |
| 887 | 556.50 | 2.03 | |
| 888 | 550.30 | 1.84 | |
| 889 | 533.28 | 1.82 | |
| 890 | 508.00 | 2.50 | 1H NMR (400 MHz, DMSO) δ 12.40 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.3, 7.4 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.24 - 7.11 (m, 2H), 6.68 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 2.93 (dd, J = 13.7, 6.9 Hz, 1H), 2.61 (d, J = 8.9 Hz, 2H), 2.28 - 2.12 (m, 1H), 1.95 - 1.76 (m, 1H), 1.61 (d, J = 3.2 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H), 0.88 (d, J = 6.3 Hz, 3H). |
| 891 | 525.23 | 1.52 | |
| 892 | 494.50 | 1.85 | 1H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 12.91 (s, 1H), 8.36 - 8.29 (m, 1H), 8.06 (dd, J = 21.6, 7.8 Hz, 1H), 7.92 (d, J = 1.9 Hz, 1H), 7.66 (s, 0.5H), 7.40 (s, 0.5H), 7.54 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.1, 2.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.51 (s, 1H), 3.87 (s, 3H), 2.31 (s, 3H), 2.15 - 2.09 (m, 3H), 2.04 (s, 3H). |
| 893 | 521.50 | 1.95 | 1H NMR (400 MHz, DMSO-d6) δ 8.40 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.98 (dd, J = 2.3, 1.0 Hz, 1H), 7.92 - 7.89 (m, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.18 - 7.05 (m, 4H), 3.89 (s, 3H), 2.33 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H). |
| 894 | 543.22 | 2.35 | |
| 895 | 465.30 | 1.23 | |
| 896 | 509.30 | 1.50 | 1H NMR (400 MHz, DMSO-d6) δ 9.11 (d, J = 2.3 Hz, 1H), 8.23 (dd, J = 8.3, 2.4 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.49 (t, J = 6.9 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.04 (dd, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 25.8, 6.0 Hz, 2H), 6.50 (d, J = 7.1 Hz, 1H), 6.23 (s, 2H), 3.05 (p, J = 6.9 Hz, 1H), 2.99 - 2.82 (m, 2H), 2.19 - 2.05 (m, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H), 0.82 (d, J = 6.2 Hz, 3H). |
| 897 | 553.20 | 2.16 | |
| 898 | 552.30 | 1.68 | 1H NMR (400 MHz, DMSO-d6) δ 8.10 (d, J = 5.3 Hz, 1H), 7.61 (s, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 7.13 - 6.95 (m, 3H), 6.47 (s, 1H), 3.35 (d, J = 7.5 Hz, 2H), 3.06 (s, 3H), 2.98 (s, 1H), 2.22 - 2.01 (m, 2H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.63 (s, 3H), 1.58 (s, 3H), 1.38 (t, J = 12.0 Hz, 1H), 0.86 (dd, J = 11.1, 6.7 Hz, 9H). |
| 899 | 496.00 | 2.06 | 1H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 11.71 (s, 1H), 8.25 (s, 1H), 7.83 (s, 2H), 6.92 (s, 2H), 6.45 (s, 1H), 2.67 (s, 2H), 2.26 (s, 3H), 1.98 (s, 6H), 1.65 (d, J = 27.5 Hz, 4H), 0.92 (s, 6H). |
| 900 | 517.20 | 2.25 | |
| 901 | 552.20 | 1.97 | |
| 902 | 559.08 | 1.65 | |
| 903 | 509.40 | 1.78 | |
| 904 | 530.40 | 1.97 | |
| 905 | 539.60 | 1.47 | |
| 906 | 526.30 | 2.85 | |
| 907 | 570.11 | 2.03 | |
| 908 | 505.31 | 2.55 | |
| 909 | 548.30 | 2.13 | |
| 910 | 496.30 | 1.60 | |
| 911 | 457.40 | 2.29 | 1H NMR (400 MHz, DMSO-d6) δ 7.98 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.99 - 6.94 (m, 1H), 6.90 (s, 2H), 4.07 (s, 3H), 2.25 (s, 3H), 1.93 (s, 6H), 1.05 (s, 9H). |
| 912 | 578.16 | 2.04 | |
| 913 | 515.25 | 1.64 | |
| 914 | 539.50 | 2.11 | 1H NMR (400 MHz, DMSO-d6) δ 13.80 (s, 1H), 12.51 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.13 (t, J = 1.8 Hz, 1H), 6.96 (s, 2H), 6.88 (s, 1H), 6.79 (dt, J = 10.9, 2.4 Hz, 1H), 4.41 (p, J = 6.0 Hz, 1H), 2.27 (s, 3H), 2.00 (s, 6H), 1.21 (d, J = 6.0 Hz, 6H). |
| 915 | 539.30 | 1.71 | |
| 916 | 513.41 | 3.01 | |
| 917 | 552.30 | 1.99 | |
| 918 | 435.50 | 1.96 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 919 | 537.43 | 2.98 | |
| 920 | 537.43 | 2.79 | |
| 921 | 509.60 | 1.54 | 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 2.5 Hz, 1H), 8.31 (dd, J = 8.7, 2.5 Hz, 1H), 7.84 (s, 0H), 7.71 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4 Hz, 1H), 7.19 (dd, J = 15.2, 7.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.31 (七重峰, J = 6.1 Hz, 1H), 4.56 (s, 1H), 2.98 (d, J = 9.9 Hz, 1H), 2.44 (s, 1H), 2.31 (d, J = 9.8 Hz, 1H), 1.68 - 1.19 (m, 7H), 1.32 (d, J = 6.2 Hz, 6H). |
| 922 | 555.37 | 1.78 | |
| 923 | 544.33 | 2.84 | |
| 924 | 540.30 | 1.98 | 1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.47 - 7.39 (m, 2H), 7.30 - 7.17 (m, 2H), 6.89 (dt, J = 10.8, 2.3 Hz, 1H), 6.72 (dd, J = 8.4, 0.8 Hz, 1H), 6.49 (s, 2H), 4.54 (s, 1H), 3.84 (d, J = 6.5 Hz, 2H), 2.99 (d, J = 9.4 Hz, 1H), 2.44 (s, 1H), 2.37 - 2.27 (m, 1H), 2.09 - 2.00 (m, 1H), 1.70 - 1.48 (m, 4H), 1.45 - 1.35 (m, 1H), 1.32 - 1.21 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H). |
| 925 | 525.30 | 1.45 | 1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.32 (dd, J = 8.7, 2.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 7.3, 0.8 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.30 (h, J = 6.1 Hz, 1H), 4.24 - 3.70 (m, 2H), 2.27 - 2.16 (m, 1H), 2.16 - 2.04 (m, 1H), 1.48 - 1.34 (m, 1H), 1.32 (d, J = 6.2 Hz, 6H), 1.08 (d, J = 6.1 Hz, 3H), 0.97 (d, J = 6.5 Hz, 6H). |
| 926 | 568.40 | 2.68 | 1H NMR (400 MHz, DMSO-d6) δ 12.51 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.38 (t, J = 1.8 Hz, 1H), 7.35 - 7.29 (m, 1H), 7.20 (dd, J = 7.6, 4.1 Hz, 2H), 6.89 (dt, J = 10.9, 2.3 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.47 (s, 1H), 3.83 (d, J = 6.5 Hz, 2H), 2.83 (t, J = 13.4 Hz, 2H), 2.74 (t, J = 6.1 Hz, 2H), 2.04 (dt, J = 13.3, 7.0 Hz, 1H), 1.96 - 1.85 (m, 2H), 1.76 (dq, J = 12.5, 6.2 Hz, 4H), 1.69 - 1.57 (m, 2H), 1.34 - 1.23 (m, 2H), 1.17 - 1.13 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H). |
| 927 | 466.40 | 1.75 | |
| 928 | 523.23 | 1.56 | |
| 929 | 485.50 | 2.73 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 930 | 535.20 | 1.97 | 1H NMR (400 MHz, DMSO-d6) δ 8.25 (d, J = 2.2 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.85 (dd, J = 2.4, 1.1 Hz, 1H), 7.72 (dd, J = 4.8, 2.4 Hz, 1H), 7.65 (dd, J = 7.1, 2.5 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 6.91 (s, 2H), 5.88 (dd, J = 7.1, 4.8 Hz, 1H), 3.86 (s, 3H), 2.27 (s, 3H), 2.11 (s, 3H), 2.02 (s, 6H). |
| 931 | 542.30 | 3.60 | |
| 932 | 535.20 | 1.88 | 1H NMR (400 MHz, DMSO-d6) δ 11.81 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 8.00 - 7.93 (m, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.52 (s, 1H), 7.19 - 7.02 (m, 3H), 6.89 (s, 2H), 6.21 (s, 1H), 3.80 (s, 3H), 2.74 (s, 2H), 2.24 (s, 3H), 2.01 (s, 6H). |
| 933 | 559.21 | 2.09 | |
| 934 | 554.30 | 1.96 | 1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 7.72 - 7.61 (m, 2H), 7.48 - 7.38 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.8, 2.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.46 (s, 2H), 4.23 (d, J = 3.9 Hz, 2H), 3.84 (d, J = 6.5 Hz, 2H), 2.03 (dt, J = 13.4, 6.6 Hz, 1H), 1.78 (dd, J = 8.3, 4.2 Hz, 2H), 1.69 (q, J = 9.9, 7.2 Hz, 5H), 1.41 (s, 1H), 1.33 (d, J = 8.6 Hz, 2H), 0.99 (d, J = 6.7 Hz, 6H). |
| 935 | 545.28 | 1.97 | |
| 936 | 543.20 | 1.93 | |
| 937 | 495.20 | 1.97 | |
| 938 | 507.11 | 2.63 | |
| 939 | 504.30 | 2.21 | |
| 940 | 511.20 | 1.62 | |
| 941 | 559.30 | 2.00 | 1H NMR (400 MHz, DMSO-d6) δ 13.25 (s, 1H), 12.51 (s, 1H), 8.25 (dd, J = 7.2, 2.1 Hz, 1H), 7.90 - 7.81 (m, 2H), 7.77 (d, J = 2.0 Hz, 1H), 7.69 (dd, J = 8.3, 1.9 Hz, 1H), 7.53 (dd, J = 8.1, 4.6 Hz, 2H), 6.46 (t, J = 6.8 Hz, 1H), 3.96 (d, J = 6.5 Hz, 2H), 3.72 (d, J = 12.7 Hz, 2H), 2.88 (t, J = 12.1 Hz, 2H), 2.17 - 2.02 (m, 1H), 1.70 - 1.47 (m, 3H), 1.30 - 1.13 (m, 2H), 1.03 (d, J = 6.7 Hz, 6H), 0.92 (d, J = 6.2 Hz, 3H). |
| 942 | 530.22 | 1.93 | |
| 943 | 479.40 | 1.94 | 1H NMR (400 MHz, DMSO-d6) δ 12.36 (s, 1H), 7.67 (d, J = 6.2 Hz, 1H), 7.53 (s, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.20 - 7.16 (m, 1H), 7.06 - 7.00 (m, 1H), 6.82 (dd, J = 7.8, 2.4 Hz, 1H), 6.76 (s, 2H), 6.41 (d, J = 6.2 Hz, 1H), 5.79 - 5.52 (m, 4H), 3.97 (s, 3H), 2.18 (s, 3H), 1.93 (s, 6H). |
| 944 | 542.13 | 1.92 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 945 | 517.00 | 2.02 | 1H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.72 (s, 1H), 7.39 (d, J = 50.3 Hz, 5H), 7.00 (s, 2H), 6.79 (d, J = 8.3 Hz, 1H), 6.59 (s, 2H), 2.65 (s, 2H), 2.34 (s, 3H), 2.10 (s, 6H), 1.13 (s, 3H). |
| 946 | 390.00 | 1.15 | 1H NMR (400 MHz, DMSO) δ 12.41 (s, 1H), 8.22 - 8.03 (m, 1H), 7.74 - 7.54 (m, 2H), 7.18 (d, J = 7.3 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.57 (dd, J = 7.5, 4.6 Hz, 1H), 6.46 (s, 2H), 2.57 (d, J = 7.3 Hz, 2H), 2.18 (s, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.50 (d, J = 9.2 Hz, 6H), 1.38 (t, J = 12.0 Hz, 1H), 0.86 (d, J = 6.3 Hz, 3H). |
| 947 | 540.43 | 2.73 | |
| 948 | 494.30 | 1.56 | |
| 949 | 525.30 | 1.56 | 1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.83 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 8.8, 2.5 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.17 (dd, J = 12.3, 7.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.45 (s, 2H), 5.31 (七重峰, J = 6.3 Hz, 1H), 2.63 (s, 2H), 2.22 (dd, J = 13.1, 7.4 Hz, 1H), 1.87 (dd, J = 11.9, 5.7 Hz, 1H), 1.59 (d, J = 3.4 Hz, 6H), 1.41 (t, J = 12.0 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 0.88 (d, J = 6.2 Hz, 3H). |
| 950 | 549.20 | 1.98 | |
| 951 | 524.50 | 1.09 | |
| 952 | 530.30 | 2.05 | |
| 953 | 554.40 | 1.93 | |
| 954 | 521.40 | 1.81 | |
| 955 | 582.29 | 2.05 | |
| 956 | 537.43 | 2.97 | 1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 8.09 - 8.06 (d, 1H), 7.62 - 7.56 (d, 2H), 7.33 (t, J = 7.91, 1H), 7.20 - 7.17 (d, 1H), 7.06 - 7.01 (d, 1H), 6.91 (s, 2H), 6.83 - 6.76 (m, 1H), 6.66 - 6.63 (d, 1H), 6.45 (s, 2 H), 3.84 (s, 3H), 2.25 (s, 3H), 2.02 (s, 6H) |
| 957 | 524.30 | 1.67 | |
| 958 | 525.40 | 1.82 | 1H NMR (400 MHz, DMSO-d6) δ 13.42 (s, 1H), 12.50 (s, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.92 - 7.80 (m, 2H), 7.70 - 7.58 (m, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.07 - 6.99 (m, 1H), 6.46 (dd, J = 7.3, 6.3 Hz, 1H), 3.83 (d, J = 6.5 Hz, 2H), 3.70 (d, J = 12.1 Hz, 2H), 2.96 - 2.85 (m, 2H), 2.13 - 1.99 (m, 2H), 1.69 - 1.60 (m, 2H), 1.33 - 1.18 (m, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.2 Hz, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 959 | 498.30 | 2.03 | 1H NMR (400 MHz, DMSO) δ 12.23 (s, 1H), 7.20 (dd, J = 9.7, 6.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 1H), 6.88 - 6.80 (m, 3H), 6.71 (s, 1H), 3.84 (s, 3H), 2.23 (s, 3H), 1.93 (s, 6H), 1.04 (s, 9H). |
| 960 | 541.50 | 1.60 | |
| 961 | 579.23 | 2.23 | |
| 962 | 546.50 | 1.27 | |
| 963 | 441.20 | 1.89 | |
| 964 | 596.34 | 2.15 | |
| 965 | 526.30 | 2.13 | 1H NMR (400 MHz, DMSO-d6) δ 8.90 (d, J = 1.3 Hz, 1H), 8.25 (d, J = 1.3 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.50 (d, J = 8.2 Hz, 1H), 6.25 (s, 2H), 5.28 (h, J = 6.2 Hz, 1H), 2.93 (d, J = 23.0 Hz, 2H), 2.07 (s, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.63 (s, 3H), 1.58 (s, 3H), 1.35 (d, J = 1.6 Hz, 3H), 1.34 (d, J = 1.7 Hz, 3H), 0.80 (d, J = 6.3 Hz, 3H). |
| 966 | 498.40 | 2.55 | |
| 967 | 579.20 | 2.38 | |
| 968 | 471.69 | 3.25 | |
| 969 | 618.40 | 3.26 | |
| 970 | 727.50 | 0.68 | 1H NMR (300 MHz, DMSO) δ 8.24 (dd, J = 15.6, 8.2 Hz, 1H), 7.80 - 7.66 (m, 1H), 7.66 - 7.39 (m, 10H), 7.31 - 7.22 (m, 4H), 7.11 (d, J = 7.2 Hz, 1H), 6.74 (t, J = 10.3 Hz, 1H), 6.55 (d, J = 7.9 Hz, 1H), 6.27 (s, 2H), 1.92 (d, J = 1.9 Hz, 12H). |
| 971 | 553.28 | 1.80 | |
| 972 | 542.30 | 1.77 | |
| 973 | 554.50 | 2.03 | |
| 974 | 533.20 | 1.99 | |
| 975 | 546.20 | 1.72 | |
| 976 | 495.30 | 1.76 | 1H NMR (400 MHz, DMSO-d6) δ 7.98 (d, J = 7.7 Hz, 1H), 7.41 (dd, J = 8.2, 7.4 Hz, 1H), 7.09 - 7.01 (m, 2H), 6.88 - 6.81 (m, 2H), 6.44 (dd, J = 8.2, 0.9 Hz, 1H), 6.35 (dt, J = 3.2, 1.6 Hz, 1H), 6.07 (s, 2H), 4.12 (q, J = 2.8 Hz, 2H), 3.68 (t, J = 5.5 Hz, 2H), 2.23 (d, J = 5.4 Hz, 5H), 1.98 (s, 6H). |
| 977 | 528.12 | 2.75 | 1H NMR (400 MHz, DMSO-d6) δ 12.23 (s, 1H), 11.19 (s, 1H), 8.17 - 8.14 (d, 1H), 7.79 - 7.76 (d, 1H), 7.65 (t, J = 8.02, 1H) 7.53 - 7.50 (d, 1H), 7.47 - 7.44 (d, 1H), 7.26 - 7.23 (d, 1H), 7.15 - 7.09 (m, 2H), 6.97 (s, 2 H), 6.72 - 6.69 (d, 1H), 6.54 (s, 2H), 6.22 (s, 1H), 2.31 (s, 3H), 2.04 (s, 6H) |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 978 | 571.32 | 2.42 | |
| 979 | 525.25 | 1.66 | |
| 980 | 520.20 | 1.85 | |
| 981 | 536.17 | 1.94 | |
| 982 | 484.29 | 1.41 | |
| 983 | 442.58 | 2.86 | |
| 984 | 555.13 | 2.98 | |
| 985 | 446.00 | 1.35 | |
| 986 | 462.50 | 1.32 | |
| 987 | 523.30 | 1.58 | 1H NMR (400 MHz, DMSO-d6) δ 12.50 (s, 1H), 8.87 (d, J = 2.5 Hz, 1H), 8.33 (dd, J = 8.8, 2.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 5.32 (p, J = 6.2 Hz, 1H), 3.50 (q, J = 10.2, 9.6 Hz, 2H), 2.69 (t, J = 6.6 Hz, 2H), 2.02 (t, J = 6.5 Hz, 2H), 1.98 - 1.86 (m, 1H), 1.86 - 1.75 (m, 1H), 1.68 (q, J = 7.9, 6.0 Hz, 4H), 1.32 (d, J = 6.2 Hz, 6H)(NH2在H2O峰下). |
| 988 | 540.50 | 1.69 | |
| 989 | 566.50 | 2.20 | 1H NMR (400 MHz, DMSO-d6) δ 8.32 (d, J = 2.2 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.23 (dt, J = 9.8, 2.0 Hz, 1H), 7.13 (t, J = 1.8 Hz, 3H), 6.95 (s, 2H), 6.79 (dt, J = 10.7, 2.3 Hz, 1H), 4.41 (p, J = 6.1 Hz, 1H), 2.27 (s, 3H), 2.00 (s, 6H), 1.21 (d, J = 6.0 Hz, 6H). |
| 990 | 499.70 | 1.83 | |
| 991 | 542.40 | 1.96 | 1H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.6, 2.2 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 6.92 (dd, J = 10.8, 2.3 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.44 (s, 2H), 3.85 (d, J = 6.5 Hz, 2H), 3.71 (d, J = 12.8 Hz, 2H), 2.85 (t, J = 12.1 Hz, 2H), 2.05 (dt, J = 13.3, 6.7 Hz, 1H), 1.62 (d, J = 13.3 Hz, 2H), 1.58 - 1.48 (m, 1H), 1.15 (q, J = 10.8, 10.2 Hz, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.3 Hz, 3H). |
| 992 | 525.40 | 1.50 | |
| 993 | 554.10 | 2.16 | |
| 994 | 573.30 | 1.93 | |
| 995 | 539.30 | 1.53 | |
| 996 | 547.20 | 2.25 | 1H NMR (400 MHz, DMSO-d6) δ 8.05 (s, 1H), 7.64 (s, 2H), 7.44 (s, 2H), 7.07 (s, 1H), 6.90 (s, 4H), 6.45 (s, 1H), 6.07 (s, 2H), 3.93 (s, 2H), 2.27 (s, 2H), 2.02 (s, 5H), 1.71 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2H). |
| 997 | 530.27 | 2.03 | |
| 998 | 527.20 | 1.42 | 1H NMR (400 MHz, DMSO) δ 13.12 (s, 1H), 8.86 (s, 1H), 8.32 (dd, J = 8.8, 2.3 Hz, 1H), 7.79 (s, 1H), 7.62 (s, 1H), 7.31 (s, 1H), 7.21 (d, J = 6.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.70 (s, 1H), 6.47 (d, J = 22.7 Hz, 2H), 5.21 (dd, J = 11.2, 5.9 Hz, 1H), 4.82 (t, J = 5.7 Hz, 1H), 4.02 (s, 2H), 3.59 (dt, J = 11.3, 5.7 Hz, 1H), 3.56 - 3.46 (m, 1H), 1.96 (s, 2H), 1.65 (s, 2H), 1.26 (d, J = 6.3 Hz, 3H), 1.08 (t, J = 8.4 Hz, 6H). |
| 999 | 582.20 | 2.20 | |
| 1000 | 521.20 | 2.16 | |
| 1001 | 545.11 | 1.50 | |
| 1002 | 532.20 | 2.21 | |
| 1003 | 401.00 | 1.90 | 1H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 7.59 (s, 3H), 7.24 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 1.6 Hz, 2H), 3.02 (s, 1H), 1.68 (s, 6H), 1.48 (s, 2H), 1.28 (s, 9H). |
| 1004 | 556.35 | 1.83 | |
| 1005 | 530.23 | 1.86 | |
| 1006 | 538.19 | 1.91 | |
| 1007 | 560.20 | 2.07 | |
| 1008 | 432.50 | 1.41 | |
| 1009 | 542.30 | 2.75 | |
| 1010 | 528.40 | 1.78 | |
| 1011 | 525.60 | 1.62 | |
| 1012 | 603.34 | 1.87 | |
| 1013 | 556.40 | 2.10 | 1H NMR (400 MHz, DMSO-d6) δ 12.76 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.52 - 7.43 (m, 3H), 7.22 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.48 (s, 2H), 3.85 (d, J = 6.6 Hz, 2H), 3.69 (d, J = 12.5 Hz, 2H), 3.36 - 3.34 (m, 2H), 2.56 - 2.53 (m, 1H), 2.42 (t, J = 11.8 Hz, 1H), 2.05 (dt, J = 13.3, 6.7 Hz, 1H), 1.79 - 1.69 (m, 2H), 1.00 (d, J = 6.8 Hz, 6H), 0.83 (d, J = 6.5 Hz, 6H). |
| 1014 | 555.43 | 3.03 | 1H NMR (400 MHz, DMSO-d6) δ 7.78 - 7.75 (d, 1H), 7.50 - 7.47 (m, 3H), 7.30 - 7.22 (m, 2H), 7.10 - 7.07 (d, 1H), 6.95 - 6.85 (m, 2H), 3.86 - 3.83 (d, 2H), 3.20 (m, 4H), 2.10 - 2.00 (m, 1H), 1.33 (m, 4H), 1.01 - 0.98 (d , 6H), 0.95 (s, 6H) |
| 1015 | 489.50 | 1.95 | 1H NMR (400 MHz, DMSO-d6) δ 12.25 (s, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 3H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.25 - 7.19 (m, 3H), 7.16 - 7.11 (m, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 6.71 (dd, J = 8.5, 0.8 Hz, 1H), 6.52 (s, 2H), 2.32 (s, 3H), 2.31 (s, 3H), 2.06 (s, 3H). |
| 1016 | 531.30 | 2.32 | |
| 1017 | 525.30 | 1.82 | |
| 1018 | 510.34 | 1.42 | |
| 1019 | 534.50 | 2.07 | |
| 1020 | 524.24 | 1.82 | |
| 1021 | 572.16 | 2.16 | |
| 1022 | 566.20 | 2.10 | |
| 1023 | 525.18 | 1.65 | |
| 1024 | 477.25 | 1.81 | |
| 1025 | 511.30 | 1.49 | |
| 1026 | 519.28 | 1.82 | |
| 1027 | 532.50 | 1.54 | |
| 1028 | 546.22 | 1.79 | |
| 1029 | 470.30 | 1.28 | |
| 1030 | 530.22 | 1.91 | |
| 1031 | 469.23 | 2.08 | |
| 1032 | 503.50 | 2.07 | |
| 1033 | 493.00 | 1.86 | 1H NMR (400 MHz, DMSO) δ 13.80 (s, 1H), 12.38 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.98 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 3.76 (s, 3H), 2.28 (s, 3H), 2.02 (s, 6H). |
| 1034 | 520.20 | 2.08 | |
| 1035 | 503.21 | 3.11 | |
| 1036 | 424.20 | 1.63 | |
| 1037 | 431.40 | 1.90 | |
| 1038 | 476.50 | 1.21 | 1H NMR (400 MHz, DMSO-d6) δ 7.82 (d, J = 8.0 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.19 (d, J = 6.9 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.70 - 3.60 (m, 3H), 2.81 (t, J = 12.0 Hz, 2H), 1.74 (d, J =2 Hz, 2H), 1.41 - 1.30 (m, 2H), 1.28 (s, 9H), 1.04 (s, 6H). 三個質子埋在水峰中，因此整體歪斜 |
| 1039 | 463.30 | 1.60 | |
| 1040 | 525.40 | 1.42 | 1H NMR (400 MHz, DMSO-d6) δ 8.88 (d, J = 2.5 Hz, 1H), 8.34 (dd, J = 8.8, 2.5 Hz, 1H), 8.24 - 8.14 (m, 1H), 7.84 - 7.71 (m, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.28 (p, J = 6.1 Hz, 1H), 4.20 - 4.03 (m, 1H), 2.29 - 2.16 (m, 1H), 2.00 - 1.88 (m, 2H), 1.80 - 1.65 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H), 1.29 (s, 3H), 1.09 (d, J = 6.2 Hz, 3H). |
| 1041 | 530.30 | 2.00 | 1H NMR (400 MHz, DMSO) δ 13.75 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 12.59 (s, 1H), 7.97 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.48 (s, 1H), 7.40 (d, J = 9.9 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.93 - 6.84 (m, 2H), 3.83 (d, J = 6.6 Hz, 2H), 3.17 (s, 0H), 2.58 (d, J = 9.4 Hz, 2H), 2.22 (s, 1H), 2.05 (dt, J = 13.3, 6.7 Hz, 1H), 1.88 (dd, J = 11.8, 5.5 Hz, 1H), 1.60 (d, J = 12.9 Hz, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H). |
| 1042 | 502.36 | 1.81 | 1H NMR (400 MHz, DMSO) δ 7.98 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.47 - 7.40 (m, J = 10.2, 1.5 Hz, 2H), 6.91 (dt, J = 10.9, 2.3 Hz, 1H), 6.88 - 6.84 (m, 1H), 4.82 - 4.66 (m, 1H), 3.72 - 3.59 (m, J = 12.9 Hz, 2H), 2.93 - 2.78 (m, J = 11.9 Hz, 2H), 1.70 - 1.50 (m, J = 20.8, 9.2 Hz, 3H), 1.30 (d, J = 6.0 Hz, 6H), 1.27 - 1.09 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H). |
| 1043 | 565.27 | 1.87 | |
| 1044 | 508.50 | 1.94 | 1H NMR (400 MHz, DMSO-d6) δ 13.81 (d, J = 6.2 Hz, 1H), 12.50 - 12.35 (m, 1H), 8.33 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 8.03 - 7.93 (m, 2H), 7.70 (d, J = 7.8 Hz, 1H), 6.96 (s, 2H), 6.92 - 6.84 (m, 1H), 3.88 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.01 (s, 6H). |
| 1045 | 469.26 | 2.08 | |
| 1046 | 427.19 | 1.83 | |
| 1047 | 504.50 | 2.10 | |
| 1048 | 531.42 | 2.96 | |
| 1049 | 523.20 | 1.87 | |
| 1050 | 453.30 | 1.93 | |
| 1051 | 528.30 | 2.93 | |
| 1052 | 508.30 | 2.19 | |
| 1053 | 549.17 | 2.00 | |
| 1054 | 512.51 | 2.61 | |
| 1055 | 479.30 | 1.17 | 1H NMR (500 MHz, DMSO-d6) δ 9.38 (s, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.18 - 7.07 (m, 4H), 7.04 (d, J = 7.3 Hz, 1H), 6.91 (s, 2H), 6.80 (d, J = 8.5 Hz, 1H), 4.31 (d, J = 13.7 Hz, 1H), 4.16 (dd, J = 17.7, 10.2 Hz, 2H), 3.54 (d, J = 13.0 Hz, 1H), 3.39 - 3.25 (m, 2H), 3.22 - 3.08 (m, 2H), 3.02 (d, J = 16.8 Hz, 1H), 2.22 (d, J = 8.3 Hz, 9H). |
| 1056 | 542.23 | 3.03 | |
| 1057 | 493.30 | 2.57 | |
| 1058 | 450.00 | 1.17 | |
| 1059 | 538.60 | 1.19 | |
| 1060 | 564.29 | 2.14 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1061 | 540.40 | 2.98 | |
| 1062 | 553.50 | 1.82 | |
| 1063 | 541.33 | 3.03 | 1H NMR (500 MHz, DMSO-d6) δ 12.90 (s, 1H), 8.80 - 8.78 (d, 1H), 8.19 - 8.17 (d, 2H), 7.81 - 7.73 (m, 2H), 7.49 (s, 1H), 7.43 - 7.39 (d, 1H), 7.31 - 7.28 (d, 1H), 6.92 - 6.88 (d, 1H), 3.84 - 3.81 (d, 2H), 2.51 - 2.36 ( m, 1H), 2.21 (m, 1H), 2.10 - 1.99 (m, 1H), 1.89 - 1.82 (m, 1H), 1.58 (s, 6H), 1.34 (t, J = 11.87, 1H), 1.00 - 0.97 (d, 6H), 0.82 - 0.79 (d, 3H) |
| 1064 | 439.40 | 1.94 | |
| 1065 | 556.60 | 1.96 | |
| 1066 | 497.50 | 1.38 | 1H NMR (400 MHz, DMSO-d6) δ 8.30 (d, J = 2.2 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 8.01 - 7.98 (m, 1H), 7.94 - 7.91 (m, 0H), 7.88 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.1 Hz, 0H), 3.63 (ddd, J = 16.6, 10.6, 5.6 Hz, 2H), 3.54 (s, 2H), 3.53 - 3.46 (m, 2H), 2.37 (s, (3+1.5)H), 1.51 (ddt, J = 13.5, 9.3, 4.7 Hz, 1H), 1.41 (ddd, J = 13.4, 9.2, 4.2 Hz, 2H), 1.33 - 1.25 (m, 1H), 1.24 - 1.16 (m, 2H), 1.02 (s, 1.5H), 0.93 (s, 3H)。旋轉異構體2:1比率 |
| 1067 | 498.30 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 7.76 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.47 (dd, J = 8.3, 7.3 Hz, 1H), 7.03 - 6.91 (m, 2H), 6.61 (d, J = 2.3 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 6.25 (s, 2H), 4.52 (七重峰, J = 6.7 Hz, 1H), 2.92 (t, J = 10.6 Hz, 1H), 2.81 (dd, J = 10.7, 7.4 Hz, 1H), 2.07 (q, J = 6.7, 6.1 Hz, 1H), 1.78 (dd, J = 11.6, 5.6 Hz, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.45 (d, J = 6.7 Hz, 6H), 1.34 (t, J = 12.0 Hz, 1H), 0.78 (d, J = 6.2 Hz, 3H). |
| 1068 | 579.24 | 2.30 | |
| 1069 | 541.33 | 3.16 | 1H NMR (400 MHz, DMSO-d6) δ 8.76 - 8.74 (d, 1H), 8.19 (m, 2H), 7.84 - 7.74 (m, 2H), 7.52 - 7.45 (m, 3H), 6.95 - 6.91 (d, 1H), 3.86 - 3.83 (d, 2H), 3.23 (m, 4H), 2.10 - 1.99 (m, 1H), 1.33 (m, 4H), 1.01 - 0.98 (d, 6H), 0.94 (s, 6H) |
| 1070 | 485.50 | 3.11 | |
| 1071 | 480.30 | 1.84 | |
| 1072 | 531.30 | 1.83 | |
| 1073 | 556.31 | 2.06 | |
| 1074 | 485.40 | 1.42 | |
| 1075 | 495.00 | 1.30 | 1H NMR (400 MHz, DMSO) δ 10.31 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 9.76 (s, 1H), 7.76 (s, 1H), 7.21 (d, J = 27.9 Hz, 2H), 6.91 (d, J = 51.5 Hz, 6H), 3.99 (d, J = 59.4 Hz, 4H), 3.61 (s, 3H), 2.29 (s, 6H), 2.22 (s, 3H), 1.55 (s, 3H). |
| 1076 | 553.50 | 1.76 | |
| 1077 | 541.19 | 2.27 | |
| 1078 | 466.30 | 1.37 | |
| 1079 | 562.20 | 2.25 | 1H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 11.92 (s, 1H), 8.27 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.84 (s, 1H), 7.71 (d, J = 8.8 Hz, 3H), 6.96 (s, 4H), 6.47 (s, 1H), 3.77 (d, J = 6.5 Hz, 2H), 2.29 (s, 3H), 2.01 (d, J = 25.1 Hz, 7H), 0.95 (d, J = 6.7 Hz, 6H). |
| 1080 | 589.31 | 1.91 | |
| 1081 | 497.21 | 1.62 | |
| 1082 | 473.20 | 1.71 | |
| 1083 | 516.20 | 2.01 | 1H NMR (400 MHz, DMSO-d6) δ 13.75 (s, 1H), 12.97 (s, 1H), 8.05 - 7.93 (m, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.55 - 7.42 (m, 3H), 6.92 (dd, J = 10.8, 2.3 Hz, 1H), 6.85 (t, J = 2.2 Hz, 1H), 3.85 (d, J = 6.5 Hz, 2H), 3.67 (d, J = 12.7 Hz, 2H), 2.89 - 2.79 (m, 2H), 2.05 (dt, J = 13.3, 6.6 Hz, 1H), 1.67 - 1.57 (m, 2H), 1.27 - 1.22 (m, 1H), 1.21 - 1.13 (m, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.2 Hz, 3H). |
| 1084 | 467.31 | 1.65 | |
| 1085 | 480.00 | 1.43 | 1H NMR (400 MHz, DMSO) δ 12.40 (s, 1H), 11.29 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.74 (s, 1H), 7.26 (d, J = 3.7 Hz, 2H), 7.15 (t, J = 12.4 Hz, 2H), 6.71 (s, 2H), 6.32 (s, 1H), 4.57 (s, 1H), 4.02 (d, J = 12.6 Hz, 1H), 3.83 (d, J = 12.6 Hz, 1H), 2.20 (d, J = 15.0 Hz, 9H), 1.56 (s, 3H), 1.37 (s, 3H). |
| 1086 | 478.30 | 1.96 | |
| 1087 | 511.26 | 1.62 | |
| 1088 | 572.19 | 1.89 | |
| 1089 | 480.30 | 1.89 | |
| 1090 | 571.34 | 3.21 | 1H NMR (400 MHz, DMSO) δ 8.05 (t, J = 7.91, 1H), 8.88 - 8.85 (d, 1H), 7.78 - 7.75 (d, 1H), 7.54 - 7.47 (m, 3H), 7.21 - 7.18 (d, 1H), 6.95 - 6.91 (d, 1H), 3.86 - 3.83 (m, 5H), 3.23 (m, 4H), 2.10 - 1.99 (m, 1H), 1.31 (m, 4H), 1.01 - 0.98 (d, 6H), 0.94 (s, 6H) |
| 1091 | 524.30 | 2.32 | |
| 1092 | 575.31 | 1.84 | |
| 1093 | 464.30 | 1.36 | |
| 1094 | 524.40 | 1.86 | 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.09 - 8.00 (m, 2H), 7.85 (d, J = 8.0 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.04 (d, J = 8.9 Hz, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.42 (s, 2H), 3.81 (d, J = 6.5 Hz, 2H), 3.67 (d, J = 12.7 Hz, 2H), 2.88 (t, J = 12.4 Hz, 2H), 2.03 (td, J = 14.0, 13.5, 6.9 Hz, 1H), 1.74 - 1.47 (m, 3H), 1.21 (q, J = 13.7, 12.8 Hz, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.92 (d, J = 6.4 Hz, 3H). |
| 1095 | 524.10 | 2.00 | |
| 1096 | 515.30 | 1.42 | |
| 1097 | 570.60 | 2.04 | |
| 1098 | 570.50 | 2.13 | |
| 1099 | 528.19 | 1.87 | |
| 1100 | 500.20 | 1.63 | |
| 1101 | 479.00 | 1.22 | 1H NMR (400 MHz, DMSO) δ 7.56 (s, 1H), 7.26 (d, J = 29.4 Hz, 4H), 6.89 (d, J = 7.3 Hz, 1H), 6.80 - 6.68 (m, 3H), 4.69 (s, 1H), 4.16 (d, J = 12.9 Hz, 1H), 2.20 (d, J = 25.7 Hz, 9H), 1.63 (s, 3H), 1.45 (s, 3H). |
| 1102 | 503.00 | 1.86 | 1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 7.75 (s, 2H), 7.65 (s, 1H), 7.57 (s, 1H), 7.46 - 7.36 (m, 3H), 7.24 (d, J = 7.2 Hz, 1H), 6.93 (s, 2H), 6.73 (d, J = 8.4 Hz, 1H), 6.48 (s, 2H), 2.29 (d, J = 13.2 Hz, 6H), 2.05 (s, 6H). |
| 1103 | 536.50 | 1.91 | |
| 1104 | 459.18 | 1.96 | |
| 1105 | 560.50 | 2.08 | |
| 1106 | 456.50 | 2.78 | |
| 1107 | 523.20 | 1.79 | |
| 1108 | 557.25 | 2.41 | |
| 1109 | 542.30 | 1.92 | |
| 1110 | 530.20 | 2.09 | |
| 1111 | 544.50 | 1.77 | |
| 1112 | 559.32 | 1.87 | |
| 1113 | 613.50 | 2.15 | |
| 1114 | 526.20 | 2.19 | 1H NMR (400 MHz,甲醇-d4) δ 8.23 (d, J = 2.7 Hz, 1H), 8.08 (dd, J = 7.2, 1.7 Hz, 2H), 7.76 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.59 (dd, J = 8.4, 6.7 Hz, 2H), 6.97 (d, J = 8.3 Hz, 1H), 5.98 (d, J = 2.8 Hz, 1H), 3.89 (s, 2H), 2.65 (d, J = 10.4 Hz, 1H), 2.52 (s, 1H), 2.17 (s, 1H), 1.85 (dd, J = 11.7, 5.7 Hz, 1H), 1.59 (d, J = 12.2 Hz, 6H), 1.45 (t, J = 12.1 Hz, 1H), 1.03 (s, 9H), 0.76 (d, J = 6.3 Hz, 3H). |
| 1115 | 520.20 | 1.47 | |
| 1116 | 541.33 | 1.58 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1117 | 514.30 | 2.86 | |
| 1118 | 517.20 | 2.23 | |
| 1119 | 532.20 | 1.87 | |
| 1120 | 503.21 | 3.01 | |
| 1121 | 556.50 | 1.91 | |
| 1122 | 560.50 | 1.60 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 10.03 (s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.80 - 7.68 (m, 4H), 7.57 (s, 1H), 7.44 - 7.37 (m, 3H), 7.32 (d, J = 7.2 Hz, 1H), 6.95 (s, 2H), 6.84 (d, J = 8.5 Hz, 1H), 3.62 - 3.53 (m, 2H), 3.23 (q, J = 5.7 Hz, 2H), 2.78 (d, J = 4.6 Hz, 6H), 2.28 (s, 3H), 2.01 (s, 6H). |
| 1123 | 528.30 | 1.57 | 1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 7.81 (dd, J = 7.8, 1.6 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.46 - 7.35 (m, 2H), 7.23 (dd, J = 7.3, 0.7 Hz, 1H), 6.88 (dt, J = 10.9, 2.3 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.73 (h, J = 6.1 Hz, 1H), 4.08 - 3.95 (m, 2H), 2.06 - 1.91 (m, 2H), 1.73 - 1.61 (m, 2H), 1.31 (d, J = 6.0 Hz, 6H), 1.09 (d, J = 6.2 Hz, 6H). |
| 1124 | 439.30 | 1.90 | |
| 1125 | 509.30 | 1.66 | 1H NMR (400 MHz, DMSO-d6) δ 8.89 - 8.78 (m, 1H), 8.30 (dd, J = 8.8, 2.5 Hz, 1H), 7.56 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.03 (s, 2H), 6.92 (d, J = 8.6 Hz, 1H), 6.16 (s, 2H), 4.25 (tt, J = 7.1, 3.7 Hz, 3H), 1.87 (s, 2H), 1.57 (q, J = 8.6, 8.2 Hz, 2H), 1.07 (d, J = 6.1 Hz, 6H), 0.82 - 0.74 (m, 2H), 0.74 - 0.64 (m, 2H). |
| 1126 | 546.13 | 2.47 | |
| 1127 | 528.20 | 1.86 | |
| 1128 | 456.38 | 2.97 | |
| 1129 | 490.40 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 12.16 (s, 1H), 8.27 (dd, J = 7.3, 2.1 Hz, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.84 (s, 1H), 7.75 - 7.68 (m, 3H), 7.22 (d, J = 8.1 Hz, 2H), 7.16 - 7.10 (m, 2H), 7.07 (dd, J = 8.2, 2.1 Hz, 1H), 6.46 (dd, J = 7.3, 6.3 Hz, 1H), 2.34 - 2.29 (m, 6H), 2.07 (s, 3H). |
| 1130 | 535.20 | 1.82 | |
| 1131 | 495.40 | 3.25 | |
| 1132 | 537.50 | 1.76 | |
| 1133 | 534.20 | 2.19 | |
| 1134 | 525.33 | 1.67 | 1H NMR (400 MHz, DMSO) δ 12.97 (s, 1H), 8.90 (s, 1H), 8.37 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.32 (s, 1H), 3.29 (s, 4H), 1.40 (s, 4H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.32 (d, J = 6.2 Hz, 6H), 0.96 (s, 6H). |
| 1135 | 553.50 | 1.83 | |
| 1136 | 525.40 | 1.73 | |
| 1137 | 427.27 | 2.61 | |
| 1138 | 565.20 | 2.26 | 1H NMR (400 MHz, DMSO-d6) δ 8.08 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.42 (dd, J = 8.2, 7.3 Hz, 1H), 7.15 (ddd, J = 10.1, 2.4, 1.3 Hz, 1H), 7.11 - 7.04 (m, 2H), 6.91 (s, 2H), 6.69 (dt, J = 10.8, 2.3 Hz, 1H), 6.45 (dd, J = 8.2, 0.9 Hz, 1H), 6.08 (s, 2H), 4.38 (p, J = 6.0 Hz, 1H), 2.26 (s, 3H), 2.00 (s, 6H), 1.21 (d, J = 6.0 Hz, 6H). |
| 1139 | 534.12 | 2.71 | |
| 1140 | 537.43 | 2.95 | |
| 1141 | 483.20 | 1.28 | |
| 1142 | 502.14 | 1.78 | |
| 1143 | 548.20 | 2.12 | |
| 1144 | 556.60 | 1.96 | |
| 1145 | 525.33 | 1.64 | |
| 1146 | 549.43 | 2.81 | 1H NMR (400 MHz, DMSO-d6) δ 12.19 (s, 1H), 8.13 - 8.10 (d, 1H), 7.74 - 7.63 (m, 2H), 7.49 - 7.46 (d, 1H), 7.29 - 7.23 (m, 2H), 7.00 - 6.96 (m, 3H), 6.74 - 6.71 (d, 1H), 6.56 (s, 2H), 3.77 (s, 3H), 3.61 (s, 3H), 2.26 ( s, 3H), 2.04 (s, 6H) |
| 1147 | 547.33 | 2.68 | |
| 1148 | 475.20 | 2.11 | 1H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 8.02 (s, 2H), 7.95 (d, J = 7.8 Hz, 1H), 7.67 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.90 (s, 2H), 2.25 (s, 3H), 1.97 (s, 7H), 1.04 (s, 10H). |
| 1149 | 558.30 | 2.00 | |
| 1150 | 551.50 | 2.09 | 1H NMR (400 MHz, DMSO-d6) δ 12.37 (s, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.81 (dd, J = 7.1, 2.4 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.29 - 7.20 (m, 2H), 7.19 - 7.06 (m, 4H), 6.81 (dt, J = 10.8, 2.3 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.58 - 6.46 (m, 2H), 4.45 (h, J = 6.0 Hz, 1H), 2.32 (d, J = 3.2 Hz, 3H), 2.04 (s, 3H), 1.22 (d, J = 5.9 Hz, 6H). |
| 1151 | 538.20 | 1.87 | |
| 1152 | 433.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 12.24 (s, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.97 (s, 1H), 6.81 (d, J = 9.6 Hz, 1H), 5.68 (s, 1H), 4.21 (s, 2H), 1.30 (d, J = 48.6 Hz, 14H), 1.11 - 0.97 (m, 5H), 0.60 (s, 3H). |
| 1153 | 498.00 | 2.34 | 1H NMR (400 MHz, DMSO) δ 12.24 (s, 1H), 8.26 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 7.11 (dd, J = 25.3, 6.4 Hz, 2H), 6.91 (s, 2H), 3.89 (s, 3H), 2.70 (s, 3H), 2.26 (s, 3H), 1.94 (s, 6H), 1.05 (s, 9H). |
| 1154 | 405.21 | 1.94 | |
| 1155 | 546.20 | 1.81 | |
| 1156 | 556.50 | 2.03 | |
| 1157 | 556.50 | 1.82 | |
| 1158 | 491.00 | 2.08 | 1H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 7.63 (s, 1H), 7.47 (d, J = 17.9 Hz, 2H), 7.17 (d, J = 7.0 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 8.4 Hz, 3H), 6.69 (d, J = 8.1 Hz, 1H), 6.47 (s, 2H), 5.66 (s, 2H), 2.56 (s, 2H), 2.18 (s, 3H), 1.92 (s, 6H), 1.56 (s, 2H), 0.87 (s, 3H). |
| 1159 | 542.20 | 1.58 | 1H NMR (400 MHz, DMSO-d6) δ 13.47 (s, 1H), 8.26 (dd, J = 5.1, 1.8 Hz, 1H), 8.16 (dd, J = 7.8, 1.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.56 - 7.46 (m, 2H), 7.04 (s, 1H), 6.93 (dt, J = 10.7, 2.3 Hz, 1H), 6.84 (dd, J = 7.8, 5.1 Hz, 1H), 4.04 (q, J = 6.0 Hz, 2H), 3.85 (d, J = 6.5 Hz, 2H), 2.06 - 1.98 (m, 2H), 1.77 - 1.62 (m, 2H), 1.05 (d, J = 6.3 Hz, 6H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1160 | 567.60 | 1.74 | |
| 1161 | 495.00 | 1.38 | 1H NMR (400 MHz, MeOD) δ 7.94 (s, 1H), 7.36 (s, 2H), 7.01 (s, 5H), 4.38 (d, J = 100.8 Hz, 4H), 3.81 (s, 3H), 2.48 (s, 6H), 2.30 (s, 3H), 1.96 (s, 3H). |
| 1162 | 540.30 | 3.03 | 1H NMR (400 MHz, DMSO-d6) δ 12.70 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.66 (dd, J = 8.4, 7.3 Hz, 1H), 7.52 - 7.37 (m, 3H), 7.22 (d, J = 7.1 Hz, 1H), 6.92 (dt, J = 10.8, 2.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.48 (s, 1H), 4.74 (s, 2H), 3.85 (d, J = 6.5 Hz, 2H), 3.32 (dd, J = 6.9, 4.5 Hz, 4H), 2.21 (t, J = 5.6 Hz, 4H), 2.09 - 1.90 (m, 1H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1163 | 548.30 | 2.13 | |
| 1164 | 448.50 | 1.41 | 1H NMR (400 MHz, CDCl3) δ 14.47 (s, 1H), 8.43 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.58 - 7.41 (m, 2H), 6.94 (s, 1H), 3.87 (s, 2H), 3.70 (s, 3H), 3.42 (d, J = 6.3 Hz, 3H), 2.48 (s, 2H), 2.26 (d, J = 13.3 Hz, 2H), 1.36 (s, 9H). |
| 1165 | 529.20 | 2.31 | |
| 1166 | 556.30 | 2.49 | 1H NMR (400 MHz, DMSO-d6) δ 7.64 (d, J = 7.8 Hz, 1H), 7.53 - 7.43 (m, 2H), 7.37 (dt, J = 10.1, 2.0 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.80 (dt, J = |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 10.8, 2.3 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 6.19 (s, 2H), 4.01 - 3.86 (m, 1H), 3.82 (d, J = 6.6 Hz, 2H), 2.10 - 1.98 (m, 1H), 1.94 - 1.77 (m, 1H), 1.73 - 1.62 (m, 2H), 1.60 (s, 3H), 1.49 (s, 3H), 1.43 (dd, J = 18.5, 9.9 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.77 (d, J = 6.0 Hz, 3H). |
| 1167 | 455.40 | 2.18 | 1H NMR (400 MHz, DMSO-d6) δ 7.68 (dd, J = 8.2, 1.6 Hz, 1H), 7.34 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 6.95 (s, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.75 (s, 2H), 6.67 (t, J = 7.6 Hz, 1H), 5.41 (s, 2H), 2.17 (s, 3H), 2.09 (s, 6H), 1.15 (s, 9H). |
| 1168 | 562.04 | 3.03 | 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 7.83 - 7.80 (d, 1H), 7.52 - 7.48 (m, 3H), 6.95 - 6.91 (d, 1H), 3.86 - 3.83 (d, 2H), 3.26 (m, 4H), 2.10 - 2.00 (m, 1H), 1.36 (m, 4H), 1.01 - 0.98 (d, 6H), 0.96 (s, 6H) |
| 1169 | 530.22 | 1.76 | |
| 1170 | 570.60 | 2.04 | |
| 1171 | 570.44 | 3.29 | 1H NMR (400 MHz, DMSO-d6) δ 12.58 (s, 1H), 7.77 - 7.74 (d, 1H), 7.61 - 7.59 (m, 2H), 7.49 (s, 2H), 7.44 - 7.40 (d, 1H), 7.33 - 7.28 (m, 2H), 6.93 - 6.89 (d, 1H), 3.85 - 3.82 (m, 5H), 2.47 - 2.37 (m, 2H), 2.11 - 2.03 ( m, 2H), 1.89 - 1.82 (m, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.41 (t, J = 12.52, 1H), 1.01 - 0.98 (d, 6H), 0.71 - 0.68 (d, 3H) |
| 1172 | 451.30 | 1.74 | |
| 1173 | 519.20 | 1.97 | |
| 1174 | 544.23 | 1.92 | |
| 1175 | 425.30 | 1.82 | |
| 1176 | 530.30 | 1.99 | 1H NMR (400 MHz, DMSO) δ 13.76 (s, 1H), 12.59 (s, 1H), 7.97 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.40 (d, J = 9.4 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.93 - 6.84 (m, 2H), 3.83 (d, J = 6.6 Hz, 2H), 3.17 (s, 0H), 2.58 (d, J = 9.7 Hz, 2H), 2.21 (s, 1H), 2.05 (dt, J = 13.3, 6.7 Hz, 1H), 1.88 (dd, J = 11.7, 5.6 Hz, 1H), 1.60 (d, J = 12.8 Hz, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H). |
| 1177 | 535.32 | 2.85 | |
| 1178 | 537.43 | 3.07 | |
| 1179 | 534.20 | 1.99 | |
| 1180 | 540.40 | 1.98 | 1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.47 - 7.40 (m, 2H), 7.23 (dd, J = 16.7, 7.6 Hz, 2H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.49 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (s, 2H), 4.54 (s, 1H), 3.84 (d, J = 6.5 Hz, 2H), 2.99 (d, J = 9.9 Hz, 1H), 2.44 (s, 1H), 2.33 (d, J = 9.5 Hz, 1H), 2.10 - 1.98 (m, 1H), 1.69 - 1.48 (m, 4H), 1.44 - 1.37 (m, 1H), 1.33 - 1.22 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1181 | 553.50 | 1.77 | |
| 1182 | 511.20 | 1.47 | |
| 1183 | 519.12 | 2.47 | |
| 1184 | 555.43 | 2.90 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 7.71 - 7.68 (d, 1H), 7.49 (s, 1H), 7.43 - 7.39 (d, 1H), 7.29 - 7.24 (m, 3H), 7.12 - 7.09 (d, 1H), 6.93 - 9.85 (m, 2H), 3.85 - 3.82 (d, 2H), 2.14 - 2.00 (m, 1H), 1.90 - 1.83 ( m, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.41 (t, J = 12.42, 1H), 1.00 - 0.97 (d, 6H), 0.78 - 0.75 (d, 3H) |
| 1185 | 534.12 | 2.95 | 1H NMR (400 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.12 - 8.09 (d, 1H), 8.04 - 8.01 (d, 1H), 7.64 - 7.53 (m, 2H), 7.15 - 7.12 (d, 1H), 6.94 (s, 2H), 6.83 - 6.80 (d, 1H), 6.58 - 6.56 (d, 1H), 6.32 (s, 2H), 3.30 (q, J = 7.25, 2H ), 2.28 (s, 3H), 2.02 (s, 6H), 1.30 (t, J = 7.02, 3H) |
| 1186 | 465.50 | 3.00 | |
| 1187 | 580.20 | 2.21 | |
| 1188 | 548.20 | 2.08 | |
| 1189 | 556.35 | 2.01 | |
| 1190 | 436.30 | 1.73 | |
| 1191 | 498.30 | 1.56 | |
| 1192 | 539.40 | 2.42 | 1H NMR (400 MHz, DMSO-d6) δ 8.20 (d, J = 5.5 Hz, 1H), 7.62 (s, 1H), 7.57 - 7.45 (m, 2H), 7.38 - 7.25 (m, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 6.51 (s, 1H), 6.23 (s, 2H), 4.06 (d, J = 6.6 Hz, 2H), 3.00 - 2.86 (m, 2H), 2.19 - 2.00 (m, 2H), 1.83 (dd, J = 11.7, 5.6 Hz, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 1.37 (t, J = 11.9 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H), 0.81 (d, J = 6.3 Hz, 3H). |
| 1193 | 542.40 | 2.00 | |
| 1194 | 556.19 | 2.05 | |
| 1195 | 459.36 | 1.54 | 1H NMR (400 MHz, DMSO) δ 8.20 (dd, J = 7.2, 2.2 Hz, 1H), 7.76 (dd, J = 6.3, 2.0 Hz, 1H), 7.74 (s, 1H), 6.41 (dd, J = 7.2, 6.4 Hz, 1H), 3.44 - 3.33 (m, J = 12.4 Hz, 2H), 3.05 - 2.91 (m, J = 12.1, 9.9 Hz, 2H), 2.76 - 2.64 (m, J = 5.6 Hz, 2H), 1.79 - 1.66 (m, J = 12.8 Hz, 6H), 1.66 - 1.54 (m, 1H), 1.54 - 1.39 (m, 2H), 1.25 (s, 6H), 0.95 (d, J = 6.3 Hz, 3H). |
| 1196 | 496.50 | 1.44 | 1H NMR (400 MHz, DMSO-d6) δ 8.28 (d, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 8.2 Hz, 1H), 8.02 (d, J = 8.1 Hz, 2H), 7.67 (dd, J = 8.4, 7.3 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.62 (dt, J = 11.7, 4.6 Hz, 2H), 3.54 (s, 2H), 3.48 (ddd, J = 11.9, 9.2, 3.0 Hz, 3H), 2.36 (s, 3H), 1.42 (ddd, J = 13.4, 9.2, 4.3 Hz, 2H), 1.21 (dt, J = 11.3, 2.9 Hz, 2H), 0.94 (s, 3H). |
| 1197 | 558.30 | 1.82 | 1H NMR (400 MHz, DMSO-d6) δ 12.97 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.70 - 7.60 (m, 2H), 7.52 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.48 (s, 2H), 4.12 - 3.99 (m, 2H), 3.94 (d, J = 6.6 Hz, 2H), 2.16 - 2.06 (m, 1H), 2.04 - 1.90 (m, 2H), 1.73 - 1.58 (m, 2H), 1.10 (d, J = 6.2 Hz, 6H), 1.03 (d, J = 6.7 Hz, 7H). |
| 1198 | 511.30 | 1.55 | 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 2.4 Hz, 1H), 8.30 (dd, J = 8.8, 2.5 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.23 (dd, J = 7.6, 3.3 Hz, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 5.30 (p, J = 6.2 Hz, 1H), 4.30 - 3.96 (m, 2H), 2.22 - 1.94 (m, 2H), 1.62 - 1.36 (m, 2H), 1.31 (d, J = 6.2 Hz, 6H), 0.97 (d, J = 6.2 Hz, 6H). |
| 1199 | 496.50 | 1.94 | 1H NMR (400 MHz, DMSO) δ 12.76 - 12.41 (m, 1H), 11.80 (bs, 1H), 8.26 (dd, J = 7.3, 2.1 Hz, 1H), 7.86 - 7.72 (m, 2H), 6.89 (s, 2H), 6.49 - 6.38 (m, J = 6.8 Hz, 1H), 2.78 - 2.60 (m, 3H), 2.33 - 2.13 (m, 5H), 1.97 (s, 6H), 1.56 - 1.31 (m, 2H), 0.89 (s, 6H). |
| 1200 | 462.60 | 1.55 | |
| 1201 | 596.34 | 2.23 | |
| 1202 | 548.20 | 2.13 | |
| 1203 | 527.50 | 1.40 | 1H NMR (400 MHz, DMSO-d6) δ 8.61 (dd, J = 4.4, 1.5 Hz, 0H), 8.35 (dd, J = 8.3, 1.5 Hz, 0H), 8.05 (d, J = 7.7 Hz, 0H), 8.02 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.8 Hz, 1H), 7.37 (dd, J = 8.3, 4.4 Hz, 0H), 7.06 (d, J = 7.8 Hz, 1H), 7.03 - 6.96 (m, 2H), 6.48 (t, J = 6.2 Hz, 1H), 4.08 (q, J = 6.9 Hz, 2H), 3.66 (dt, J = 11.6, 4.5 Hz, 2H), 3.55 - 3.50 (m, 2H), 3.49 (d, J = 6.2 Hz, 2H), 1.51 (ddd, J = 13.6, 9.3, 4.2 Hz, 2H), 1.35 (t, J = 6.9 Hz, 3H), 1.29 - 1.22 (m, 2H), 1.02 (s, 3H)。旋轉異構體比率約5:1 |
| 1204 | 519.12 | 2.56 | |
| 1205 | 612.32 | 2.29 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1206 | 539.23 | 1.89 | |
| 1207 | 533.20 | 1.91 | |
| 1208 | 470.28 | 2.20 | |
| 1209 | 573.30 | 1.97 | 1H NMR (400 MHz, CDCl3) δ 14.58 (s, 1H), 8.87 (s, 1H), 8.57 (s, 1H), 8.23 (s, 1H), 7.80 (s, 2H), 7.38 (dd, J = 64.6, 37.5 Hz, 7H), 6.89 (d, J = 40.0 Hz, 2H), 5.39 (s, 1H), 4.09 (s, 2H), 3.63 (s, 3H), 2.56 (s, 1H), 2.26 (s, 2H), 1.88 (s, 1H), 1.39 (s, 7H). |
| 1210 | 556.40 | 2.99 | 1H NMR (400 MHz, 氯仿-d) δ 14.73 (s, 1H), 8.49 (d, J = 8.1 Hz, 1H), 7.75 - 7.67 (m, 2H), 7.63 (d, J = 7.3 Hz, 1H), 7.35 (dd, J = 9.0, 2.1 Hz, 2H), 6.76 - 6.68 (m, 2H), 3.79 (d, J = 6.5 Hz, 2H), 3.50 (s, 2H), 2.88 (t, J = 11.7 Hz, 2H), 2.34 (s, 2H), 2.13 (dq, J = 13.4, 6.7 Hz, 1H), 2.00 (t, J = 6.7 Hz, 1H), 1.05 (dd, J = 6.7, 4.7 Hz, 12H), 0.89 (t, J = 12.3 Hz, 1H). |
| 1211 | 453.30 | 1.97 | |
| 1212 | 534.20 | 1.87 | |
| 1213 | 525.50 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 13.80 (s, 1H), 12.50 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.27 - 7.21 (m, 1H), 7.19 - 7.06 (m, 4H), 6.87 (d, J = 2.3 Hz, 1H), 6.81 (dt, J = 10.8, 2.3 Hz, 1H), 4.46 (h, J = 6.0 Hz, 1H), 2.32 (s, 3H), 2.03 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H). |
| 1214 | 541.33 | 1.59 | |
| 1215 | 482.30 | 1.24 | |
| 1216 | 555.29 | 2.40 | |
| 1217 | 446.30 | 1.77 | |
| 1218 | 542.40 | 2.93 | |
| 1219 | 403.00 | 1.70 | 1H NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.88 (s, 1H), 7.60 (s, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 3.47 (s, 1H), 1.91 (s, 4H), 1.77 (s, 2H), 1.64 (s, 2H), 1.43 (s, 9H). |
| 1220 | 493.20 | 0.72 | |
| 1221 | 523.10 | 2.01 | |
| 1222 | 556.40 | 1.85 | |
| 1223 | 496.00 | 2.23 | 1H NMR (400 MHz, DMSO) δ 12.42 (s, 1H), 8.32 (s, 1H), 7.90 (s, 1H), 7.72 (s, 1H), 7.10 (s, 2H), 6.89 (s, 2H), 2.69 (s, 2H), 2.25 (s, 3H), 1.95 (s, 6H), 1.65 (d, J = 36.4 Hz, 4H), 0.92 (s, 6H). |
| 1224 | 525.36 | 1.23 | |
| 1225 | 549.43 | 2.95 | |
| 1226 | 468.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 11.69 (s, 1H), 8.26 (d, J = 7.2 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 8.04 (d, J = 7.9 Hz, 1H), 7.83 (s, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.91 (s, 2H), 6.46 (s, 1H), 2.26 (s, 3H), 1.96 (s, 6H), 1.32 (s, 3H), 0.68 (d, J = 12.5 Hz, 4H). |
| 1227 | 555.26 | 2.37 | |
| 1228 | 518.22 | 1.99 | |
| 1229 | 515.10 | 2.25 | |
| 1230 | 551.20 | 1.82 | |
| 1231 | 450.30 | 1.78 | |
| 1232 | 455.30 | 2.04 | |
| 1233 | 503.00 | 1.88 | 1H NMR (400 MHz, DMSO) δ 12.36 (s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.61 (s, 1H), 7.28 (s, 4H), 7.20 (s, 2H), 6.87 (s, 2H), 6.69 (d, J = 8.7 Hz, 1H), 6.48 (s, 2H), 3.93 (s, 2H), 2.23 (s, 3H), 1.94 (s, 6H). |
| 1234 | 532.20 | 1.84 | |
| 1235 | 493.00 | 1.74 | 1H NMR (400 MHz, MeOD) δ 8.32 (s, 1H), 8.06 (s, 1H), 7.12 (dd, J = 130.1, 74.1 Hz, 7H), 4.30 (d, J = 79.9 Hz, 2H), 3.58 (s, 3H), 2.43 (s, 6H), 2.26 (s, 3H), 1.98 (s, 3H), 1.56 (s, 3H). |
| 1236 | 457.30 | 1.26 | 1H NMR (400 MHz, DMSO-d6) δ 13.17 (s, 1H), 12.90 (s, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.76 - 7.35 (m, 3H), 6.79 (d, J = 8.0 Hz, 1H), 6.51 (s, 1H), 4.29 (s, 3H), 3.96 (d, J = 1.2 Hz, 2H), 1.89 (s, 2H), 1.61 (s, 2H), 1.13 (d, J = 6.1 Hz, 6H). |
| 1237 | 466.00 | 1.20 | 1H NMR (400 MHz, DMSO) δ 12.29 (s, 1H), 10.30 (s, 1H), 8.13 (s, 1H), 7.68 (s, 1H), 7.38 (s, 1H), 7.24 (s, 3H), 6.90 (s, 2H), 6.34 (s, 1H), 4.12 (s, 2H), 3.96 (s, 2H), 3.17 (s, 1H), 2.41 (s, 6H), 2.24 (s, 3H), 1.73 (s, 3H). |
| 1238 | 543.22 | 2.35 | |
| 1239 | 482.00 | 2.13 | 1H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.68 (s, 1H), 7.04 (d, J = 30.5 Hz, 5H), 2.67 (s, 3H), 2.29 (s, 3H), 1.99 (s, 3H), 1.66 (d, J = 20.8 Hz, 4H), 0.98 (s, 6H). |
| 1240 | 525.40 | 1.38 | 1H NMR (400 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.33 - 8.19 (m, 2H), 8.13 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.93 - 6.79 (m, 2H), 5.34 - 5.19 (m, 1H), 2.71 - 2.58 (m, 1H), 2.58 - 2.53 (m, 1H, 由溶劑峰遮蔽), 2.26 - 2.12 (m, 1H), 1.88 (dd, J = 12.1, 5.8 Hz, 1H), 1.53 (d, J = 4.5 Hz, 6H), 1.41 (t, J = 12.0 Hz, 1H), 1.29 (d, J = 6.1 Hz, 6H), 0.77 (d, J = 6.2 Hz, 3H). |
| 1241 | 556.30 | 2.50 | 1H NMR (400 MHz, DMSO-d6) δ 7.64 (d, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 7.6 Hz, 1H), 7.48 (d, J = 6.9 Hz, 2H), 7.41 - 7.30 (m, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.85 - 6.75 (m, 1H), 6.50 (d, J = 8.4 Hz, 1H), 6.20 (s, 2H), 3.99 - 3.90 (m, 1H), 3.82 (d, J = 6.7 Hz, 2H), 2.05 (tt, J = 11.5, 5.9 Hz, 1H), 1.93 - 1.79 (m, 1H), 1.74 - 1.62 (m, 2H), 1.63 - 1.56 (m, 3H), 1.49 (s, 3H), 1.44 (t, J = 8.3 Hz, 1H), 0.98 (d, J = 6.8 Hz, 6H), 0.76 (d, J = 6.1 Hz, 3H). |
| 1242 | 498.30 | 1.77 | 1H NMR (400 MHz, DMSO-d6) δ 7.58 (d, J = 7.6 Hz, 1H), 7.48 - 7.42 (m, 2H), 6.99 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.47 (d, J = 8.3 Hz, 1H), 6.40 (d, J = 1.8 Hz, 1H), 6.15 (s, 2H), 5.30 (p, J = 6.6 Hz, 1H), 3.08 - 2.92 (m, 2H), 2.18 - 2.03 (m, 1H), 1.80 (dd, J = 11.7, 5.6 Hz, 1H), 1.49 (d, J = 8.4 Hz, 6H), 1.38 (d, J = 6.4 Hz, 3H), 1.36 - 1.33 (m, 1H), 1.31 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.3 Hz, 3H). |
| 1243 | 455.23 | 2.02 | |
| 1244 | 525.42 | 2.95 | |
| 1245 | 532.20 | 1.90 | |
| 1246 | 455.00 | 2.02 | 1H NMR (400 MHz, DMSO) δ 13.78 (s, 1H), 12.23 (s, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 7.08 (s, 1H), 7.01 (s, 2H), 6.83 (s, 1H), 2.67 (s, 2H), 2.29 (s, 3H), 2.00 (s, 3H), 1.66 (d, J = 22.4 Hz, 4H), 0.98 (s, 6H). |
| 1247 | 525.30 | 1.61 | 1H NMR (400 MHz, DMSO) δ 12.43 (s, 1H), 8.84 (d, J = 2.1 Hz, 1H), 8.28 (dd, J = 8.7, 2.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.19 (dd, J = 10.1, 7.4 Hz, 2H), 6.86 (d, J = 8.7 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.38 - 5.27 (m, 1H), 2.59 (d, J = 9.1 Hz, 2H), 2.22 (s, 1H), 1.87 (dd, J = 11.9, 5.6 Hz, 1H), 1.59 (d, J = 1.7 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1248 | 551.40 | 1.81 | |
| 1249 | 535.50 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 8.33 (dd, J = 3.3, 2.2 Hz, 2H), 8.11 (d, J = 7.9 Hz, 1H), 7.96 (dd, J = 2.4, 1.1 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.20 - 7.05 (m, 2H), 6.96 (s, 2H), 3.88 (s, 3H), 2.28 (s, 3H), 2.12 (s, 3H), 2.01 (s, 6H). |
| 1250 | 455.30 | 2.04 | |
| 1251 | 535.32 | 2.59 | |
| 1252 | 512.30 | 2.05 | 1H NMR (400 MHz, DMSO-d6) δ 8.92 (s, 1H), 8.27 (d, J = 5.7 Hz, 1H), 7.67 (bs, 1H), 7.45 (bs, 2H), 7.04 (bs, 1H), 6.50 (bs, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.16 (bs, 1H), 4.48 (q, J = 7.0 Hz, 2H), 2.99 (bs, 1H), 2.15 (bs, 1H), 1.85 (dd, J = 10.7, 5.0 Hz, 1H), 1.64 (s, 3H), 1.59 (s, 3H), 1.40 (t, J = 7.0 Hz, 4H), 0.85 (d, J = 6.2 Hz, 3H). |
| 1253 | 517.00 | 1.95 | 1H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 7.95 (d, J = 2.3 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.64 (s, 1H), 7.23 (s, 6H), 6.87 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 2.86 (s, 4H), 2.23 (s, 3H), 1.94 (s, 6H). |
| 1254 | 572.40 | 1.94 | 1H NMR (400 MHz, DMSO-d6) δ 12.24 (s, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.50 - 7.44 (m, 1H), 7.29 - 7.19 (m, 1H), 6.99 (s, 1H), 6.90 - 6.84 (m, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.51 (s, 2H), 4.10 (s, 2H), 3.88 (s, 3H), 3.82 (d, J = 6.6 Hz, 2H), 2.10 - 2.00 (m, 1H), 1.97 - 1.85 (m, 2H), 1.69 - 1.55 (m, 2H), 1.08 (d, J = 6.2 Hz, 6H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1255 | 551.53 | 3.15 | |
| 1256 | 452.40 | 1.77 | |
| 1257 | 578.15 | 2.02 | |
| 1258 | 556.40 | 2.20 | |
| 1259 | 524.60 | 1.51 | |
| 1260 | 590.33 | 2.18 | |
| 1261 | 494.50 | 1.86 | |
| 1262 | 509.30 | 1.51 | 1H NMR (400 MHz, DMSO-d6) δ 8.54 (d, J = 5.2 Hz, 1H), 7.97 - 7.82 (m, 1H), 7.74 (dd, J = 5.2, 1.7 Hz, 1H), 7.64 (s, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 (s, 1H), 6.57 - 6.43 (m, 1H), 6.24 (s, 2H), 3.06 (h, J = 6.9 Hz, 1H), 2.91 (d, J = 11.8 Hz, 2H), 2.16 - 2.09 (m, 1H), 1.84 (dd, J = 11.8, 5.7 Hz, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.38 (t, J = 12.0 Hz, 1H), 1.28 (d, J = 6.8 Hz, 6H), 0.82 (d, J = 6.3 Hz, 3H). |
| 1263 | 557.22 | 2.39 | |
| 1264 | 568.90 | 2.98 | |
| 1265 | 425.30 | 1.76 | |
| 1266 | 558.30 | 2.04 | |
| 1267 | 558.30 | 2.75 | |
| 1268 | 563.30 | 2.00 | |
| 1269 | 570.30 | 1.86 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 7.68 - 7.59 (m, 2H), 7.21 (d, J = 7.3 Hz, 1H), 6.96 - 6.82 (m, 3H), 6.68 (d, J = 8.3 Hz, 1H), 6.51 (s, 2H), 3.80 (d, J = 6.5 Hz, 2H), 2.71 - 2.53 (m, 2H), 2.27-2.15 (遮蔽多重峰1H), 2.22 (s, 3H), 2.09 - 1.97 (m, 1H), 1.82 (dd, J = 11.9, 5.7 Hz, 1H), 1.47 (d, J = 11.2 Hz, 6H), 1.38 (t, J = 12.0 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 0.97 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.2 Hz, 3H). |
| 1270 | 539.37 | 1.68 | 1H NMR (400 MHz, 氯仿-d) δ 14.94 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.82 (d, J = 8.3 Hz, 1H), 8.34 (d, J = 8.9 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.9, 7.0 Hz, 1H), 7.42 (dd, J = 18.0, 8.0 Hz, 2H), 6.95 (d, J = 8.8 Hz, 1H), 4.27 (s, 2H), 4.10 (s, 2H), 2.55 - 2.47 (m, 2H), 2.38 - 2.32 (m, 2H), 1.44 (d, 6H), 1.33 - 1.22 (m, 2H), 1.07 (d, J = 5.4 Hz, 9H). |
| 1271 | 497.26 | 1.52 | |
| 1272 | 504.50 | 1.47 | |
| 1273 | 464.50 | 1.25 | |
| 1274 | 565.20 | 1.98 | |
| 1275 | 560.24 | 2.67 | |
| 1276 | 543.43 | 2.75 | |
| 1277 | 538.20 | 1.94 | |
| 1278 | 490.00 | 1.57 | 1H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 8.67 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.65 (s, 2H), 7.43 (s, 1H), 7.23 (d, J = 7.2 Hz, 1H), 6.97 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.58 (s, 1H), 2.29 (s, 3H), 2.04 (s, 6H). |
| 1279 | 556.40 | 2.92 | |
| 1280 | 481.50 | 2.07 | 1H NMR (400 MHz, DMSO-d6) δ 7.95 (d, J = 7.7 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.89 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.45 (s, 2H), 3.03 - 2.93 (m, 1H), 2.24 (s, 3H), 1.96 (s, 6H), 1.83 - 1.66 (m, 2H), 1.52 - 1.33 (m, 6H). |
| 1281 | 584.20 | 2.29 | |
| 1282 | 528.27 | 1.94 | |
| 1283 | 525.30 | 1.70 | |
| 1284 | 554.20 | 1.94 | |
| 1285 | 502.30 | 157.00 | |
| 1286 | 542.16 | 1.90 | |
| 1287 | 524.30 | 1.47 | |
| 1288 | 499.35 | 1.42 | |
| 1289 | 556.40 | 2.76 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.69 - 7.57 (m, 1H), 7.56 - 7.46 (m, 1H), 7.41 (dt, J = 10.1, 1.8 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 3.83 (d, J = 6.7 Hz, 2H), 2.61 (dq, J = 9.7, 4.9 Hz, 2H), 2.24 (d, J = 15.8 Hz, 1H), 2.06 (dq, J = 13.3, 6.7 Hz, 1H), 1.93 - 1.82 (m, 1H), 1.61 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (s, 3H), 1.59 (s, 3H), 1.48 - 1.33 (m, 1H), 1.32 - 1.20 (m, 2H), 0.99 (d, J = 6.6 Hz, 6H), 0.88 (d, J = 6.2 Hz, 3H). |
| 1290 | 504.20 | 1.70 | |
| 1291 | 420.40 | 1.77 | |
| 1292 | 425.00 | 1.60 | 1H NMR (400 MHz, DMSO) δ 13.87 (s, 1H), 12.65 (s, 1H), 8.00 (s, 1H), 7.54 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.78 (s, 1H), 2.80 (s, 2H), 2.32 (s, 3H), 1.76 (s, 4H), 1.29 (s, 6H). |
| 1293 | 545.13 | 1.54 | 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 12.57 (s, 1H), 8.26 (dd, J = 7.3, 2.1 Hz, 1H), 7.85 (dd, J = 6.7, 2.1 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.66 (dd, J = 8.3, 1.9 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 4.17 - 4.05 (m, 4H), 2.02 - 1.90 (m, 2H), 1.87 - 1.74 (m, 2H), 1.74 - 1.63 (m, 2H), 1.14 (d, J = 6.2 Hz, 6H), 1.03 (t, J = 7.4 Hz, 3H). |
| 1294 | 475.20 | 4.69 | 1H NMR (300 MHz, CDCl3) δ 1.07 (s, 9H), 2.05 (s, 6H), 2.32 (s, 3H), 5.34 (s, 2H), 6.89 (s, 2H), 7.09 (d, J=8.1 Hz, 1H), 7.68 (s, 1H), 8.39 (d, J=7.9 Hz, 1H), 10.50 (s, 1H). |
| 1295 | 523.20 | 2.12 | |
| 1296 | 526.20 | 1.89 | |
| 1297 | 466.00 | 2.03 | 1H NMR (400 MHz, DMSO) δ 11.55 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 7.8 Hz, 1H), 6.89 (s, 2H), 6.61 (d, J = 8.6 Hz, 2H), 6.14 (s, 2H), 2.25 (s, 3H), 1.92 (s, 6H), 1.31 (s, 3H), 0.66 (d, J = 16.9 Hz, 4H). |
| 1298 | 447.40 | 1.73 | |
| 1299 | 543.13 | 2.65 | |
| 1300 | 504.20 | 2.01 | |
| 1301 | 552.20 | 2.01 | |
| 1302 | 516.25 | 1.67 | |
| 1303 | 568.35 | 2.14 | |
| 1304 | 582.28 | 2.12 | 1H NMR (400 MHz, DMSO-d6) δ 12.68 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.66 (dd, J = 8.4, 7.3 Hz, 1H), 7.59 - 7.36 (m, 3H), 7.22 (d, J = 7.2 Hz, 1H), 6.91 (dt, J = 10.7, 2.3 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.50 (s, 2H), 5.62 (qd, J = 8.1, 3.9 Hz, 1H), 3.93 - 3.73 (m, 2H), 2.98 (dt, J = 10.0, 6.8 Hz, 1H), 2.84 - 2.73 (m, 1H), 2.21 - 1.79 (m, 5H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1305 | 485.20 | 2.18 | 1H NMR (400 MHz, CDCl3) δ 9.71 (s, 1H), 8.11 - 7.78 (m, 2H), 7.44 (s, 2H), 6.76 (s, 2H), 5.45 (s, 2H), 3.85 (s, 3H), 2.21 (s, 3H), 2.14 (s, 6H), 1.20 (d, J = 8.8 Hz, 10H). 1H |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | NMR (400 MHz, DMSO) ? 7.30 (dd, J = 9.0, 6.8 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.73 (s, 2H), 5.14 (s, 2H), 4.09 (s, 3H), 3.67 (s, 3H), 2.15 (s, 3H), 2.07 (s, 6H), 1.19 (s, 9H). |
| 1306 | 456.08 | 2.91 | |
| 1307 | 450.30 | 1.79 | |
| 1308 | 557.24 | 2.64 | 1H NMR (400 MHz, CDCl3) δ 8.78 - 8.75 (d, 1H), 7.90 - 7.87 (d, 1H), 7.49 - 7.43 (m, 1H), 7.30 (s, 2H), 6.96 - 6.93 (d, 1H), 6.77 - 6.67 (m, 2H), 4.05 (t, J = 9.23, 1H), 3.80 - 3.77 (d, 2H), 3.48 (t, J = 9.45, 1H), 2.9 6 - 2.86 (m, 1H), 2.39 - 2.30 (m, 1H), 2.21 - 2.01 (m, 2H), 1.65 (s, 3H), 1.36 - 1.34 (m, 6H), 1.07 - 1.04 (d, 6H) |
| 1309 | 556.34 | 3.03 | 1H NMR (400 MHz, CDCl3) δ 8.47 - 8.44 (d, 1H), 7.75 (s, 1H), 7.67 - 7.62 (m, 2H), 7.41 - 7.34 (m, 3H), 7.11 - 7.08 (d, 1H), 6.74 - 6.70 (d, 1H), 3.79 - 3.76 (d, 2H), 3.27 (m, 4H), 2.18 - 2.08 (m, 1H), 1.79 (m, 4H), 1.1 3 (s, 6H), 1.07 - 1.04 (d, 6H) |
| 1310 | 467.00 | 2.08 | 1H NMR (400 MHz, DMSO) δ 11.99 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.10 (d, J = 7.1 Hz, 1H), 6.89 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 2.25 (s, 3H), 1.94 (s, 6H), 1.32 (s, 3H), 0.67 (d, J = 17.0 Hz, 4H). |
| 1311 | 484.00 | 1.99 | 1H NMR (400 MHz, DMSO) δ 12.34 (s, 1H), 11.45 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 6.5 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.94 (s, 2H), 6.30 (d, J = 6.5 Hz, 1H), 2.60 (s, 3H), 2.27 (s, 3H), 2.00 (s, 6H), 1.04 (s, 9H).1H NMR (400 MHz, DMSO) ? 12.34 (s, 1H), 11.45 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 6.5 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.94 (s, 2H), 6.30 (d, J = 6.5 Hz, 1H), 2.60 (s, 3H), 2.27 (s, 3H), 2.00 (s, 6H), 1.04 (s, 9H). |
| 1312 | 507.50 | 1.66 | |
| 1313 | 568.40 | 2.73 | |
| 1314 | 469.26 | 2.08 | |
| 1315 | 578.16 | 2.04 | |
| 1316 | 511.20 | 1.24 | 1H NMR (400 MHz, DMSO-d6) δ 13.74 (s, 1H), 8.94 (d, J = 2.5 Hz, 1H), 8.39 (dt, J = 8.7, 2.2 Hz, 1H), 8.30 - 8.18 (m, 2H), 8.05 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.25 (s, 2H), 6.98 - 6.82 (m, 2II), 5.41 - 5.26 (m, 1H), 4.21 - 4.04 (m, 2H), 2.23 - 2.06 (m, 2H), 1.83 - 1.67 (m, 2H), 1.32 (d, J = 6.2 Hz, 6H), 1.08 (d, J = 6.4 Hz, 6H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1317 | 521.30 | 1.88 | |
| 1318 | 441.19 | 1.93 | |
| 1319 | 604.30 | 3.24 | |
| 1320 | 533.22 | 3.07 | |
| 1321 | 488.50 | 2.74 | |
| 1322 | 497.15 | 1.62 | |
| 1323 | 579.45 | 3.40 | 1H NMR (400 MHz, DMSO-d6) δ 12.20 (s, 1H), 7.86 - 7.83 (d, 1H), 7.73 - 7.70 (d, 1H), 7.56 - 7.46 (m, 4H), 7.33 (t, J = 8.13, 1H), 7.21 - 7.11 (m, 2H), 6.94 - 6.90 (d, 1H), 3.85 - 3.82 (d, 2H), 3.13 (m, 4H), 2.06 - 1.98 (m, 1H), 1.15 (m, 4H), 1.00 - 0.97 (d, 6H), 0.81 (s, 6H) |
| 1324 | 545.21 | 2.05 | |
| 1325 | 525.50 | 2.00 | |
| 1326 | 549.43 | 2.77 | |
| 1327 | 525.30 | 1.74 | |
| 1328 | 539.60 | 1.73 | |
| 1329 | 532.20 | 1.85 | |
| 1330 | 479.30 | 2.16 | |
| 1331 | 442.21 | 1.80 | |
| 1332 | 554.10 | 2.14 | |
| 1333 | 540.31 | 1.96 | |
| 1334 | 466.23 | 1.66 | |
| 1335 | 498.40 | 1.68 | |
| 1336 | 549.43 | 3.01 | |
| 1337 | 533.22 | 3.10 | 1H NMR (400 MHz, DMSO-d6) δ 8.10 - 8.07 (d, 1H), 7.71 - 7.52 (m, 4H), 7.18 - 7.15 (d, 1H), 7.93 - 7.90 (m, 4H), 6.60 - 6.57 (d, 1H), 6.36 (s, 2H), 4.04 (q, J = 6.92, 2H), 2.28 (s, 3H), 2.03 (s, 6H), 1.31 (t, J = 6.92, 3H) |
| 1338 | 481.00 | 1.10 | 1H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 7.52 (s, 1H), 7.13 (s, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.90 (s, 2H), 6.86 (d, J = 7.5 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 6.56 (d, J = 8.3 Hz, 1H), 6.23 (s, 2H), 4.14 (d, J = 12.7 Hz, 1H), 4.01 (d, J = 12.7 Hz, 1H), 3.92 (s, 2H), 2.38 (s, 6H), 2.24 (s, 3H), 1.69 (s, 3H). |
| 1339 | 607.21 | 2.04 | |
| 1340 | 557.00 | 1.91 | 1H NMR (400 MHz, DMSO) δ 13.27 (s, 1H), 8.18 (s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.83 (dd, J = 12.8, 7.9 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 6.94 (s, 1H), 4.58 (s, 2H), 3.84 (s, 2H), 3.64 (d, J = 12.8 Hz, 2H), 2.87 (t, J = 12.1 Hz, 2H), 2.11 - 1.98 (m, 3H), 1.57 (d, J = 10.1 Hz, 3H), 1.18 (t, J = 10.6 Hz, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.0 Hz, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1341 | 539.20 | 1.83 | |
| 1342 | 494.00 | 1.64 | 1H NMR (400 MHz, DMSO) δ 8.45 (d, J = 6.7 Hz, 1H), 8.26 (d, J = 9.4 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.24 (s, 1H), 7.13 (s, 2H), 7.05 (s, 1H), 6.88 (s, 1H), 6.81 (s, 2H), 4.33 (d, J = 15.1 Hz, 1H), 3.90 (s, 3H), 3.73 (s, 2H), 3.58 (d, J = 13.6 Hz, 2H), 2.79 (s, 2H), 2.20 (s, 3H), 2.11 (s, 6H), 2.00 (s, 2H). |
| 1343 | 494.40 | 1.60 | |
| 1344 | 505.31 | 2.55 | |
| 1345 | 538.60 | 1.23 | |
| 1346 | 509.00 | 1.44 | 1H NMR (400 MHz, DMSO) δ 9.91 (s, 1H), 7.73 (s, 1H), 7.31 (s, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.92 (s, 3H), 6.82 (s, 1H), 4.15 (s, 3H), 4.03 (s, 4H), 2.38 (s, 6H), 2.25 (s, 3H), 1.78 (s, 3H), 1.25 (s, 3H). |
| 1347 | 496.00 | 2.28 | |
| 1348 | 592.19 | 1.91 | |
| 1349 | 445.22 | 2.12 | |
| 1350 | 442.21 | 1.80 | |
| 1351 | 522.00 | 1.87 | 1H NMR (400 MHz, DMSO) δ 13.07 (s, 1H), 8.43 (s, 1H), 8.05 (d, J = 15.1 Hz, 3H), 7.56 (s, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 67.1, 10.4 Hz, 5H), 4.78 (s, 1H), 2.34 (s, 3H), 1.31 (d, J = 5.9 Hz, 6H). |
| 1352 | 499.30 | 1.61 | 1H NMR (400 MHz, DMSO) δ 14.22 - 13.30 (m, 1H), 12.56 (s, 1H), 8.83 (d, J = 2.3 Hz, 1H), 8.28 (dd, J = 8.7, 2.5 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 5.5, 3.1 Hz, 2H), 5.31 (dt, J = 12.3, 6.2 Hz, 1H), 2.58 (dd, J = 17.5, 7.2 Hz, 2H), 2.21 (s, 1H), 1.88 (dd, J = 11.8, 5.7 Hz, 1H), 1.59 (d, J = 8.8 Hz, 6H), 1.43 (t, J = 12.1 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H). |
| 1353 | 464.00 | 1.53 | 1H NMR (400 MHz, DMSO) δ 13.86 (s, 1H), 12.60 (s, 1H), 8.66 (s, 1H), 8.12 (d, J = 4.6 Hz, 2H), 7.99 (s, 1H), 7.85 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.42 (s, 1H), 6.96 (s, 2H), 6.89 (s, 1H), 2.29 (s, 3H), 2.03 (s, 6H). |
| 1354 | 497.21 | 1.50 | |
| 1355 | 424.30 | 1.84 | |
| 1356 | 540.00 | 3.27 | 1H NMR (400 MHz, DMSO) δ 12.36 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.28 - 7.19 (m, 2H), 7.17 (s, 1H), 6.95 (s, 2H), 6.84 (d, J = 10.8 Hz, 1H), 6.70 (d, J = 6.5 Hz, 1H), 6.51 (s, 2H), 3.65 (d, J = 6.5 Hz, 2H), 2.27 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3H), 2.11 - 1.92 (m, 7H), 0.97 (d, J = 6.7 Hz, 6H). |
| 1357 | 496.20 | 2.09 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 11.86 (s, 1H), 8.26 (dd, J = 7.2, 2.1 Hz, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.83 (s, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.95 - 6.91 (m, 2H), 6.46 (dd, J = 7.3, 6.3 Hz, 1H), 2.47 - 2.36 (m, 1H), 2.26 (s, 3H), 1.98 (s, 6H), 1.78 - 1.50 (m, 6H), 1.21 (h, J = 10.9, 10.4 Hz, 4H). |
| 1358 | 465.39 | 3.36 | 1H NMR (400 MHz, DMSO-d6) δ 11.0 (s, 1H), 7.98 - 7.95 (d, 1H), 7.75 - 7.72 (d, 1H), 7.56 (s, 1H), 7.24 (t, J = 7.8, 1H), 7.01 - 6.95 (m, 2H), 6.87 - 6.84 (m, 2H), 6.68 (s, 1H), 5.36 (s, 2H), 1.94 (s, 6H), 1.14 (s, 9H) |
| 1359 | 586.60 | 2.24 | |
| 1360 | 548.60 | 1.60 | |
| 1361 | 587.30 | 2.22 | |
| 1362 | 546.20 | 2.01 | 1H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.69 - 7.57 (m, 1H), 7.52 - 7.40 (m, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.90 (d, J = 10.8 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.52 (s, 2H), 5.32 (d, J = 54.8 Hz, 1H), 4.64 (t, J = 6.6 Hz, 1H), 3.84 (d, J = 6.6 Hz, 2H), 3.34 - 3.15 (m, 2H), 2.36 - 2.15 (m, 1H), 2.05 (dt, J = 13.2, 5.3 Hz, 1H), 1.99 - 1.83 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1363 | 525.50 | 1.65 | |
| 1364 | 522.30 | 1.85 | 1H NMR (400 MHz, DMSO-d6) δ 12.25 (s, 1H), 7.62 (dd, J = 8.4, 7.3 Hz, 1H), 7.45 - 7.32 (m, 3H), 7.36 - 7.24 (m, 3H), 7.18 (dd, J = 7.3, 0.7 Hz, 1H), 6.67 (dd, J = 8.4, 0.8 Hz, 1H), 6.45 (s, 2H), 2.60 - 2.51 (m, 2H), 2.21 (ddt, J = 17.6, 11.9, 6.4 Hz, 1H), 1.86 (dd, J = 11.8, 5.6 Hz, 1H), 1.58 (d, J = 8.4 Hz, 6H), 1.46 - 1.35 (m, 1H), 1.13 (s, 9H), 0.90 - 0.79 (m, 3H). |
| 1365 | 593.20 | 2.40 | |
| 1366 | 580.50 | 1.89 | |
| 1367 | 550.40 | 2.69 | 1H NMR (400 MHz, DMSO-d6) δ 10.55 (s, 1H), 7.26 (s, 1H), 7.20 (t, J = 7.9 Hz, 1H), 7.05 (q, J = 7.9 Hz, 2H), 6.85 (d, J = 8.2 Hz, 3H), 4.01 (dd, J = 15.5, 9.3 Hz, 3H), 3.79 (q, J = 14.0, 13.4 Hz, 4H), 2.45 (t, J = 7.7 Hz, 2H), 2.31 (s, 6H), 2.23 (s, 3H), 1.61 (s, 3H), 1.52 (p, J = 7.4 Hz, 2H), 1.24 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). |
| 1368 | 583.20 | 2.10 | 1H NMR (400 MHz, DMSO) δ 12.61 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.64 (dd, J = 8.3, 7.4 Hz, 1H), 7.58 - 7.49 (m, 2H), 7.21 (d, J = 6.9 Hz, 1H), 6.95 (dt, J = 10.8, 2.3 Hz, 1H), 6.79 - 6.68 (m, 1H), 6.54 (s, 2H), 5.90 (s, 1H), 3.86 (d, J = 6.6 Hz, 2H), 3.32 (s, 1H), 2.42 (s, 2H), 1.22 (s, 6H), 1.15 (s, 6H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1369 | 500.30 | 1.27 | |
| 1370 | 521.50 | 2.27 | |
| 1371 | 571.40 | 1.57 | |
| 1372 | 509.00 | 1.34 | 1H NMR (400 MHz, MeOD) δ 8.10 (s, 1H), 7.52 (s, 1H), 7.25 (s, 2H), 6.97 (s, 3H), 6.87 (d, J = 7.9 Hz, 1H), 6.61 (s, 1H), 4.40 (s, 1H), 4.17 (s, 2H), 4.04 (s, 2H), 2.44 (s, 6H), 2.29 (s, 3H), 1.85 (s, 2H), 1.32 (s, 3H), 1.15 (d, J = 6.1 Hz, 1H). |
| 1373 | 472.50 | 1.50 | |
| 1374 | 557.08 | 2.48 | |
| 1375 | 527.20 | 1.99 | 1H NMR (400 MHz, 氯仿-d) δ 8.87 (d, J = 2.5 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.22 (dd, J = 8.7, 2.6 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 6.78 (dd, J = 8.6, 4.5 Hz, 2H), 5.38 (七重峰, J = 6.2 Hz, 1H), 3.94 (q, J = 6.4 Hz, 2H), 2.34 (ddt, J = 9.8, 7.1, 3.7 Hz, 2H), 2.11 - 1.89 (m, 2H), 1.38 (d, J = 6.1 Hz, 6H), 1.34 - 1.22 (m, 6H). |
| 1376 | 509.30 | 2.27 | |
| 1377 | 528.60 | 1.89 | |
| 1378 | 484.30 | 1.57 | 1H NMR (400 MHz, DMSO-d6) δ 12.31 (s, 1H), 7.61 (d, J = 7.6 Hz, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.58 - 6.37 (m, 3H), 3.23 - 3.11 (m, 1H), 2.62 - 2.53 (m, 2H, 由溶劑峰遮蔽), 2.28 (s, 1H), 2.25 - 2.12 (m, 1H), 1.88 - 1.69 (m, 3H), 1.54 (dd, J = 7.9, 4.6 Hz, 7H), 1.47 - 1.03 (m, 7H), 0.87 (d, J = 6.2 Hz, 3H). |
| 1379 | 456.20 | 1.38 | |
| 1380 | 594.50 | 1.84 | |
| 1381 | 570.45 | 1.21 | |
| 1382 | 541.40 | 0.80 | |
| 1383 | 552.50 | 1.18 | |
| 1384 | 466.30 | 1.45 | |
| 1385 | 556.30 | 2.20 | |
| 1386 | 430.30 | 1.14 | |
| 1387 | 595.30 | 2.32 | 1H NMR (400 MHz, DMSO) δ 12.41 (s, 1H), 8.09 (s, 2H), 7.60 (s, 1H), 7.55 - 7.47 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 6.97 (d, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 10.3 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 6.54 (s, 2H), 6.20 (s, 1H), 3.86 (d, J = 6.5 Hz, 2H), 3.62 (s, 1H), 2.82 - 2.71 (m, 1H), 2.09 - 2.00 (m, 1H), 1.25 (d, J = 6.9 Hz, 6H), 1.16 (d, J = 6.9 Hz, 6H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1388 | 653.40 | 1.88 | 1H NMR (400 MHz,甲醇-d4) δ 7.81 (d, J = 13.5 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.35 (d, J = 7.3 Hz, 1H), 6.88 (dd, J = 8.6, 5.6 Hz, 1H), 5.93 (dd, J = 12.2, 5.1 Hz, 1H), 4.45 (s, 1H), 4.39 (t, J = 6.3 Hz, 1H), 3.77 - 3.51 (m, 1H), 3.27 - 3.16 (m, 1H), 3.00 (dd, J = 20.5, 12.5 Hz, 1H), 2.67 (s, 1H), 2.28 (s, 1H), 2.17 (td, J = 13.3, 7.0 Hz, 1H), 2.04 (s, 2H), 1.92 (s, 1H), 1.85 - 1.69 (m, 1H), 1.52 (d, J = 5.2 Hz, 3H), 1.49 (s, 9H), 1.45 - 1.35 (m, 12H), 1.23 - 1.12 (m, 3H). |
| 1389 | 584.40 | 1.34 | |
| 1390 | 481.30 | 2.02 | |
| 1391 | 590.60 | 2.05 | |
| 1392 | 499.00 | 1.23 | 1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.43 (d, J = 6.1 Hz, 1H), 7.32 (d, J = 16.0 Hz, 2H), 7.21 - 7.09 (m, 3H), 7.05 (d, J = 8.9 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 4.52 (s, 4H), 4.09 (s, 2H), 2.55 (s, 3H), 1.92 (s, 3H), 1.33 (s, 3H). |
| 1393 | 532.00 | 1.84 | 1H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 10.77 (s, 1H), 8.04 (s, 1H), 7.64 (s, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.15 (s, 1H), 6.83 (s, 3H), 6.67 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 3.97 (d, J = 7.0 Hz, 3H), 3.73 (s, 1H), 3.57 (s, 3H), 2.23 (d, J = 15.3 Hz, 9H), 2.07 (s, 1H), 1.56 (s, 3H), 1.23 (s, 3H). |
| 1394 | 526.00 | 1.67 | 1H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.23 (s, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 6.87 (d, J = 8.4 Hz, 3H), 6.81 (d, J = 7.7 Hz, 1H), 5.52 (s, 1H), 4.08 (d, J = 12.3 Hz, 1H), 4.01 (s, 2H), 3.83 (d, J = 19.7 Hz, 3H), 2.34 (s, 6H), 2.24 (s, 3H), 2.08 (s, 1H), 1.64 (s, 3H), 1.25 (s, 3H). |
| 1395 | 557.36 | 2.50 | |
| 1396 | 540.00 | 3.26 | 1H NMR (400 MHz, DMSO-d6) δ 8.09 - 7.95 (m, 2H), 7.79 - 7.70 (m, 2H), 7.70 - 7.61 (m, 2H), 7.48 (dd, J = 2.3, 1.4 Hz, 1H), 7.40 (ddd, J = 10.2, 2.4, 1.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 3.92 - 3.67 (m, 3H), 2.43 (t, J = 10.3 Hz, 1H), 2.36 (dd, J = 10.1, 7.0 Hz, 1H), 2.08 (ddt, J = 32.6, 13.3, 6.3 Hz, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.83 (dd, J = 11.9, 5.5 Hz, 1H), 1.57 (d, J = 17.5 Hz, 6H), 1.38 (t, J = 12.1 Hz, 1H), 1.04 (d, J = 6.1 Hz, 5H), 0.98 (d, J = 6.7 Hz, 6H), 0.66 (d, J = 6.3 Hz, 3H). |
| 1397 | 538.30 | 1.25 | |
| 1398 | 524.30 | 1.17 | |
| 1399 | 538.30 | 1.25 | |
| 1400 | 558.34 | 2.73 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.51 - 7.46 (m, 1H), 7.40 (dt, J = 9.9, 1.9 Hz, 1H), 7.22 (dd, J = 22.1, 7.6 Hz, 2H), 6.89 (dt, J = 10.9, 2.3 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.48 (s, 2H), 3.83 (d, J = 6.6 Hz, 2H), 2.26 - 2.13 (m, 1H), 2.05 (dt, J = 13.3, 6.7 Hz, 1H), 1.94 - 1.83 (m, 1H), 1.60 (d, J = 6.8 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1401 | 430.00 | 1.49 | 1H NMR (400 MHz, DMSO) δ 12.40 (s, 1H), 7.69 - 7.49 (m, 2H), 7.24 - 7.07 (m, 1H), 6.82 - 6.61 (m, 2H), 4.84 (s, 2H), 3.46 (s, 4H), 2.42 (t, J = 5.8 Hz, 2H), 2.12 - 2.00 (m, 2H), 1.27 (s, 9H), 1.23 (dd, J = 6.7, 2.7 Hz, 2H). |
| 1402 | 561.40 | 2.07 | |
| 1403 | 541.00 | 1.79 | 1H NMR (400 MHz, DMSO) δ 7.64 (d, J = 7.9 Hz, 1H), 7.42 (s, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.92 (s, 3H), 4.24 - 3.99 (m, 6H), 3.84 (s, 3H), 2.40 (s, 6H), 2.25 (s, 4H), 2.07 (s, 1H), 1.75 (s, 3H), 1.24 (s, 3H). |
| 1404 | 661.40 | 1.84 | 1H NMR (400 MHz,甲醇-d4) δ 7.73 (s, 1H), 7.67 (t, J = 8.1 Hz, 1H), 7.43 - 7.27 (m, 6H), 6.77 (d, J = 8.5 Hz, 1H), 5.59 (s, 1H), 5.18 (s, 2H), 4.11 (s, 2H), 3.72 (s, 2H), 3.39 (q, J = 16.4, 13.3 Hz, 1H), 3.12 (t, J = 10.2 Hz, 1H), 2.57 (s, 1H), 2.40 (s, 2H), 2.09 (dd, J = 12.5, 6.8 Hz, 1H), 1.72 (t, J = 11.8 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.39 (s, 9H), 1.11 (d, J = 6.5 Hz, 3H). |
| 1405 | 568.39 | 1.26 | 1H NMR (400 MHz,甲醇-d4) δ 7.70 (dd, J = 8.5, 7.3 Hz, 1H), 7.63 (s, 1H), 7.36 (dd, J = 7.3, 0.8 Hz, 1H), 6.81 (dd, J = 8.6, 0.8 Hz, 1H), 5.93 (d, J = 1.7 Hz, 1H), 3.10 (t, J = 9.1 Hz, 1H), 2.95 (t, J = 10.3 Hz, 1H), 2.71 - 2.57 (m, 2H), 2.46 (dd, J = 11.1, 6.4 Hz, 1H), 2.36 (d, J = 2.1 Hz, 2H), 2.02 (dd, J = 12.2, 6.2 Hz, 1H), 1.62 (t, J = 12.0 Hz, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 1.40 (s, 9H), 1.17 (d, J = 1.3 Hz, 6H), 1.04 (d, J = 6.5 Hz, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1406 | 529.20 | 2.32 | 1H NMR (400 MHz, DMSO) δ 7.90 - 7.84 (m, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.51 - 7.40 (m, 3H), 7.07 (dt, J = 7.3, 2.6 Hz, 1H), 6.85 (dt, J = 10.7, 2.2 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 6.13 (s, 2H), 5.07 (dq, J = 119.9, 7.4 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 2.46 - 2.18 (m, 2H), 2.14 - 2.01 (m, 3H), 2.01 - 1.76 (m, 2H), 1.36 - 1.21 (m, 1H), 1.16 (d, J = 6.7 Hz, 2H), 1.05 - 0.91 (m, 7H). |
| 1407 | 542.50 | 1.65 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 7.82 (寬單峰, 1H), 7.59 (br s, 1H), 7.16 (br s, 1H), 6.89 (br s, 1H), 6.64 (br s, 1H), 6.45 (br s, 2H), 5.80 (s, 1H), 3.89 (d, J = 6.6 Hz, 2H), 2.67 (br s, 2H), 2.20 (br s, 1H), 2.02 (dt, J = 13.3, 6.7 Hz, 1H), 1.86 (dd, J = 12.0, 5.6 Hz, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.39 (t, J = 12.0 Hz, 1H), 0.95 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H). |
| 1408 | 481.00 | 1.15 | 1H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 7.62 (s, 1H), 7.34 (s, 5H), 7.14 (d, J = 42.4 Hz, 2H), 6.96 (s, 1H), 4.65 (s, 2H), 4.37 (s, 2H), 4.08 (s, 2H), 2.53 (s, 3H), 2.07 (s, 3H), 1.90 (s, 3H), 1.35 (s, 3H). |
| 1409 | 556.50 | 2.19 | |
| 1410 | 547.50 | 2.33 | |
| 1411 | 512.50 | 1.78 | 1H NMR (400 MHz, 氯仿-d) δ13.85 (br s, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.31 (d, J = 2.6 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.70 - 7.59 (m, 2H), 6.68 (d, J = 7.7 Hz, 1H), 6.28 (d, J = 2.7 Hz, 1H), 3.61 (bra s, 1H), 3.24 (br t, 1H), 2.67 (m, 1H), 2.58 (d, J = 7.1 Hz, 2H), 2.14 (dd, J = 12.4, 7.7 Hz, 1H), 1.97-2.04 (m, 1H), 1.78 (br t, J = 11.0 Hz, 1H), 1.42 (s, 3H), 1.29 - 1.19 (m, 6H), 0.98 (d, J = 6.6 Hz, 6H). |
| 1412 | 481.40 | 1.77 | 1H NMR (400 MHz, DMSO-d6) δ 11.86 (s, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 1.8 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.90 (s, 2H), 6.70 (d, J = 8.3 Hz, 1H), 6.53 - 6.45 (m, 2H), 4.43 (t, J = 9.6 Hz, 2H), 2.69 - 2.62 (m, 2H), 2.25 (s, 3H), 2.00 (s, 6H). |
| 1413 | 509.00 | 1.17 | 1H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 8.34 (s, 2H), 8.12 (d, J = 9.2 Hz, 1H), 7.29 (s, 1H), 7.04 - 6.86 (m, 4H), 4.14 (d, J = 84.4 Hz, 7H), 2.40 (s, 6H), 2.25 (s, 3H), 1.77 (s, 3H), 1.25 (s, 3H). |
| 1414 | 590.60 | 1.63 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1415 | 551.00 | 1.46 | 1H NMR (400 MHz, MeOD) δ 8.17 (d, J = 8.3 Hz, 1H), 7.92 (s, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.34 (s, 1H), 7.12 (d, J = 7.4 Hz, 1H), 6.99 (s, 2H), 6.94 (d, J = 8.3 Hz, 1H), 4.49 (s, 2H), 4.35 (s, 2H), 4.06 (s, 2H), 2.42 (s, 6H), 2.29 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H), 1.32 (s, 3H). |
| 1416 | 512.30 | 3.06 | |
| 1417 | 552.60 | 1.19 | |
| 1418 | 543.20 | 2.40 | |
| 1419 | 471.50 | 1.79 | |
| 1420 | 404.30 | 1.03 | 1H NMR (400 MHz, DMSO-d6) δ 12.33 (s, 1H), 7.66 - 7.55 (m, 2H), 7.18 (dd, J = 7.3, 0.7 Hz, 1H), 6.67 (dd, J = 8.4, 0.8 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 2.55 - 2.50 (m, 2H, 由溶劑峰遮蔽), 2.31 (s, 3H), 2.21 - 2.13 (m, 1H), 1.82 (dd, J = 11.9, 5.7 Hz, 1H), 1.51 (d, J = 9.4 Hz, 6H), 1.37 (t, J = 12.0 Hz, 1H), 0.86 (d, J = 6.3 Hz, 3H). |
| 1421 | 515.00 | 1.27 | H NMR (400 MHz, DMSO) δ 10.72 (s, 1H), 7.67 (s, 1H), 7.27 (s, 1H), 7.11 (d, J = 7.3 Hz, 1H), 7.05 (s, 1H), 6.95 (dd, J = 18.9, 8.7 Hz, 2H), 6.84 (dd, J = 19.9, 9.2 Hz, 2H), 6.75 (d, J = 8.4 Hz, 1H), 4.14 (dd, J = 49.8, 18.9 Hz, 7H), 3.80 (s, 3H), 1.53 (s, 3H), 1.28 (s, 3H). |
| 1422 | 534.00 | 1.72 | 1H NMR (400 MHz, MeOD) δ 7.67 - 7.54 (m, 2H), 7.23 (s, 1H), 6.96 (s, 2H), 6.88 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 4.30 (d, J = 12.8 Hz, 1H), 4.07 (d, J = 26.0 Hz, 5H), 3.60 (s, 2H), 3.00 (s, 2H), 2.42 (s, 6H), 2.29 (s, 3H), 2.03 (s, 1H), 1.79 (s, 3H), 1.31 (s, 3H). |
| 1423 | 430.30 | 1.27 | 1H NMR (400 MHz, DMSO-d6) δ 7.73 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.89 (s, 1H), 5.35 (s, 1H), 2.66 - 2.56 (m, 2H), 2.25 - 2.20 (m, 1H), 2.11 (s, 3H), 1.87 (dd, J = 12.1, 5.7 Hz, 1H), 1.53 (d, J = 2.5 Hz, 6H), 1.45 - 1.34 (m, 1H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1424 | 572.30 | 1.50 | 1H NMR (400 MHz, DMSO-d6) δ 12.57 - 12.38 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.45 - 7.34 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.90 (dt, J = 10.6, 2.3 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.64 - 6.10 (s, 1H), 3.80 (s, 2H), 2.67 - 2.56 (m, 2H), 2.33 - 2.15 (m, 1H), 1.94 - 1.82 (m, 1H), 1.61 (s, 3H), 1.60 (s, 3H), 1.50 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | - 1.34 (m, 1H), 1.21 (s, 6H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1425 | 511.00 | 1.71 | 1H NMR (400 MHz, DMSO) δ 9.77 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.9 Hz, 1H), 7.51 (s, 1H), 7.30 (d, J = 23.3 Hz, 2H), 7.02 - 6.90 (m, 4H), 4.28 - 4.12 (m, 4H), 4.07 - 4.01 (m, 2H), 2.39 (s, 6H), 2.25 (s, 3H), 1.76 (s, 3H), 1.24 (s, 3H). |
| 1426 | 565.34 | 2.30 | |
| 1427 | 537.30 | 2.11 | |
| 1428 | 518.00 | 1.43 | |
| 1429 | 662.20 | 2.07 | |
| 1430 | 558.30 | 1.84 | |
| 1431 | 512.50 | 1.56 | |
| 1432 | 565.50 | 1.94 | |
| 1433 | 485.00 | 1.12 | 1H NMR (400 MHz, DMSO) δ 10.35 (s, 1H), 7.74 (s, 1H), 7.60 (s, 2H), 7.28 (s, 4H), 7.16 (s, 1H), 7.03 (s, 1H), 6.93 (s, 1H), 6.83 (s, 1H), 4.32 (s, 3H), 4.15 - 4.02 (m, 5H), 1.63 (s, 3H), 1.27 (t, J = 6.9 Hz, 3H). |
| 1434 | 566.06 | 1.77 | |
| 1435 | 562.50 | 1.62 | |
| 1436 | 525.30 | 1.89 | |
| 1437 | 551.20 | 1.81 | |
| 1438 | 472.50 | 1.31 | |
| 1439 | 516.30 | 1.40 | |
| 1440 | 557.30 | 2.44 | |
| 1441 | 526.60 | 1.33 | |
| 1442 | 538.30 | 1.25 | 1H NMR (400 MHz, DMSO-d6) δ 8.49 (d, J = 9.8 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.24 (dd, J = 13.1, 7.6 Hz, 3H), 6.72 (d, J = 8.3 Hz, 1H), 4.09 - 3.95 (m, 2H), 3.87 (bs, 1H), 1.95 (p, J = 8.0 Hz, 2H), 1.83 (h, J = 6.8 Hz, 1H), 1.67 (dd, J = 9.4, 5.6 Hz, 2H), 1.18 (d, J = 6.4 Hz, 3H), 1.07 (dd, J = 6.3, 2.3 Hz, 6H), 0.95 (dd, J = 12.0, 6.7 Hz, 6H). |
| 1443 | 528.40 | 1.83 | 1H NMR (400 MHz, 氯仿-d) δ 13.43 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 0.9 Hz, 1H), 7.67 - 7.59 (m, 3H), 7.53 (d, J = 0.9 Hz, 1H), 6.65 (p, J = 3.8 Hz, 1H), 4.66 (s, 2H), 3.72 (d, J = 6.5 Hz, 2H), 3.50 - 3.37 (m, 1H), 3.15 (dd, J = 10.4, 8.1 Hz, 1H), 2.61 (d, J = 6.5 Hz, 1H), 2.16 - 2.02 (m, 2H), 1.73 (dd, J = 12.3, 9.9 Hz, 1H), 1.47 (s, 3H), 1.42 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.7 Hz, 6H). |
| 1444 | 556.30 | 1.69 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 8.26 (dd, J = 4.8, 1.9 Hz, 1H), 8.05 (dd, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | J = 7.9, 1.9 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.46 - 7.37 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.90 (dt, J = 10.7, 2.3 Hz, 1H), 6.78 (dd, J = 7.9, 4.7 Hz, 1H), 6.72 (s, 2H), 3.84 (d, J = 6.7 Hz, 2H), 3.39 (s, 6H), 2.15 (s, 1H), 2.05 (dt, J = 13.4, 6.7 Hz, 1H), 1.87 (dd, J = 11.9, 5.5 Hz, 1H), 1.59 (d, J = 14.2 Hz, 6H), 1.40 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.76 (d, J = 6.3 Hz, 3H). |
| 1445 | 576.60 | 1.63 | |
| 1446 | 501.20 | 2.12 | |
| 1447 | 562.60 | 1.61 | |
| 1448 | 556.60 | 1.68 | |
| 1449 | 494.00 | 1.33 | 1H NMR (400 MHz, DMSO) δ 9.48 (s, 1H), 8.83 (d, J = 6.0 Hz, 2H), 7.99 (d, J = 6.0 Hz, 2H), 7.32 (s, 1H), 7.09 (d, J = 7.7 Hz, 1H), 6.93 (s, 3H), 4.34 (s, 10H), 4.04 (s, 4H), 2.40 (s, 6H), 2.25 (s, 3H), 1.82 (s, 3H), 1.25 (s, 3H). |
| 1450 | 542.81 | 2.48 | |
| 1451 | 529.10 | 2.41 | |
| 1452 | 570.00 | 2.19 | |
| 1453 | 509.00 | 1.64 | |
| 1454 | 508.00 | 1.44 | 1H NMR (400 MHz, DMSO) δ 10.03 (s, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 7.20 (s, 1H), 6.91 (s, 4H), 4.10 (d, J = 78.6 Hz, 6H), 2.37 (s, 6H), 2.24 (s, 3H), 1.73 (s, 3H), 1.25 (s, 3H). |
| 1455 | 458.50 | 1.10 | |
| 1456 | 579.45 | 3.55 | 1H NMR (400 MHz, DMSO) δ 8.43 (s, 1H), 7.48 (s, 1H), 7.18-7.15 (d, 1H), 6.98 (s, 2H), 6.89-6.85 (m, 3H), 6.71 (s, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 3.80-3.77 (d, 2H), 2.26 (s, 3H), 2.05 (s, 6H), 0.97-0.94 (d, 3H) |
| 1457 | 508.00 | 1.66 | |
| 1458 | 551.20 | 2.14 | |
| 1459 | 584.60 | 1.54 | |
| 1460 | 523.20 | 1.89 | |
| 1461 | 568.60 | 1.54 | |
| 1462 | 512.30 | 1.36 | |
| 1463 | 552.30 | 1.42 | |
| 1464 | 531.08 | 2.14 | |
| 1465 | 571.30 | 2.55 | |
| 1466 | 525.30 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 12.14 (s, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.20 (dd, J = 7.3, 0.7 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 6.91 (s, 2H), 6.70 (dd, J = 8.4, 0.8 Hz, 1H), 6.51 (s, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3.59 - 3.52 (m, 2H), 2.94 - 2.83 (m, 1H), 2.25 (s, 3H), 1.97 (s, 6H), 1.56 - 1.43 (m, 2H), 1.34 - 1.20 (m, 2H), 1.14 (s, 3H), 1.06 (s, 3H). |
| 1467 | 548.60 | 1.59 | |
| 1468 | 416.16 | 2.91 | |
| 1469 | 584.60 | 1.57 | |
| 1470 | 523.00 | 1.73 | 1H NMR (400 MHz, MeOD) δ 7.46 (s, 2H), 7.37 (s, 1H), 7.27 (s, 1H), 7.09 (d, J = 6.2 Hz, 1H), 6.99 (s, 2H), 6.92 (dd, J = 11.5, 8.0 Hz, 2H), 4.41 (s, 2H), 4.27 (d, J = 13.0 Hz, 2H), 4.04 (s, 2H), 3.80 (s, 3H), 2.45 (s, 6H), 2.30 (s, 3H), 2.03 (s, 1H), 1.90 (s, 3H), 1.32 (s, 3H |
| 1471 | 526.28 | 1.08 | |
| 1472 | 570.30 | 1.88 | |
| 1473 | 514.50 | 1.40 | 1H NMR (400 MHz, 氯仿-d) δ 15.64 (s, 1H), 8.45 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.69 - 7.58 (m, 2H), 6.64 (dd, J = 7.0, 2.1 Hz, 1H), 5.71 (d, J = 1.0 Hz, 1H), 4.67 (br s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.76 (t, J = 9.3 Hz, 1H), 3.21 (dd, J = 10.1, 7.3 Hz, 1H), 2.68 (s, 3H)與2.65-2.72 (m, 1H)重疊, 2.21 (dd, J = 12.5, 8.2 Hz, 1H), 1.79 (dd, J = 12.5, 9.0 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.32 (s, 3H), 1.26 (s, 6H)。偵測到一些大的信號。 |
| 1474 | 494.00 | 1.48 | 1H NMR (400 MHz, DMSO) δ 9.99 (s, 1H), 8.56 (s, 1H), 7.98 (s, 2H), 7.51 (s, 1H), 7.29 (s, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.91 (s, 3H), 4.21 (s, 1H), 4.13 (s, 2H), 4.01 (s, 3H), 2.38 (s, 6H), 2.24 (s, 3H), 1.75 (s, 3H), 1.25 (s, 3H). |
| 1475 | 523.20 | 2.37 | |
| 1476 | 510.00 | 1.37 | 1H NMR (400 MHz, MeOD) δ 8.26 (d, J = 6.5 Hz, 1H), 8.10 (s, 1H), 7.57 (d, J = 4.9 Hz, 1H), 7.21 (s, 1H), 6.99 (s, 2H), 6.88 (dd, J = 19.2, 7.9 Hz, 2H), 6.44 (s, 1H), 4.54 (d, J = 12.3 Hz, 1H), 4.33 (dd, J = 33.8, 9.1 Hz, 1H), 4.13 (s, 2H), 4.08 - 3.99 (m, 2H), 2.50 (s, 6H), 2.30 (s, 3H), 1.82 (s, 3H), 1.32 (s, 3H). |
| 1477 | 542.96 | 2.48 | |
| 1478 | 504.50 | 2.19 | |
| 1479 | 605.20 | 2.43 | |
| 1480 | 508.00 | 1.65 | 1H NMR (400 MHz, DMSO) δ 10.63 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.18 (s, 1H), 6.84 (d, J = 11.3 Hz, 3H), 6.64 (d, J = 7.6 Hz, 1H), 6.58 (d, J = 8.7 Hz, 2H), 3.99 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 4H), 3.73 (s, 3H), 2.29 (s, 6H), 2.23 (s, 3H), 2.07 (s, 1H), 1.76 (s, 1H), 1.55 (s, 3H), 1.24 (s, 3H). |
| 1481 | 468.20 | 2.80 | |
| 1482 | 585.30 | 2.29 | |
| 1483 | 571.00 | 3.17 | 1H NMR (400 MHz, DMSO) δ 12.85 (s, 1H), 8.04 (dd, J = 8.4, 7.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 7.3, 0.5 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.42 (dd, J = 9.8, 1.7 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.16 (dd, J = 8.4, 0.5 Hz, 1H), 6.90 (dt, J = 10.7, 2.3 Hz, 1H), 3.91 (s, 3H), 3.83 (d, J = 6.6 Hz, 2H), 2.50 - 2.36 (m, 2H), 2.30 - 2.15 (m, 1H), 2.05 (dt, J = 13.3, 6.7 Hz, 1H), 1.87 (dd, J = 11.8, 5.5 Hz, 1H), 1.59 (d, J = 1.3 IIz, 6H), 1.40 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.77 (d, J = 6.3 Hz, 3II). |
| 1484 | 554.60 | 2.01 | |
| 1485 | 528.34 | 1.30 | 1H NMR (400 MHz,甲醇-d4) δ 7.94 (s, 1H), 7.91 (s, 1H), 7.77 - 7.70 (m, 1H), 7.69 - 7.62 (m, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.34 (s, 1H), 6.85 (d, J = 8.5 Hz, 1II), 6.76 (d, J = 8.4 Hz, 1H), 4.20 - 4.09 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.37 (t, J = 10.0 Hz, 1H), 3.15 - 3.02 (m, 2H), 2.90 (dt, J = 17.7, 7.3 Hz, 1H), 2.73 (d, J = 7.6 Hz, 2H), 2.56 (s, 1H), 2.19 (td, J = 6.4, 4.0 Hz, 2H), 2.09 (dd, J = 12.5, 6.6 Hz, 1H), 2.03 (s, 3H), 1.92 (dq, J = 12.4, 6.3 Hz, 3H), 1.77 (ddd, J = 14.3, 8.9, 5.4 Hz, 2H), 1.72 - 1.64 (m, 2H), 1.63 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H), 1.43 (s, 8H), 1.35 (s, 9H), 1.10 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H)。(兩組峰，歸因於烯烴與半縮醛之1:1混合物) |
| 1486 | 483.20 | 2.14 | |
| 1487 | 528.34 | 1.21 | |
| 1488 | 524.28 | 1.21 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.42 (d, J = 2.0 Hz, 2H), 7.19 (t, J = 7.4 Hz, 2H), 6.82 (t, J = 1.9 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 4.07 (q, J = 6.9 Hz, 2H), 2.63 - 2.55 (m, 2H), 2.34 (s, 3H), 2.23 (td, J = 13.6, 13.1, 6.9 Hz, 1H), 1.87 (dd, J = 11.9, 5.7 Hz, 1H), 1.61 (d, J = 4.4 Hz, 6H), 1.42 (t, J = 12.1 IIz, 1H), 1.34 (t, J = 6.9 Hz, 3H), 0.88 (d, J = 6.2 Hz, 3H). |
| 1489 | 460.30 | 1.56 | |
| 1490 | 544.60 | 1.79 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1491 | 525.30 | 1.90 | |
| 1492 | 537.30 | 1.84 | |
| 1493 | 553.50 | 2.20 | |
| 1494 | 510.30 | 2.11 | 1H NMR (400 MHz, DMSO-d6) δ 10.59 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.94 (s, 2H), 6.69 (d, J = 8.2 Hz, 1H), 6.45 (s, 2H), 6.26 (d, J = 8.8 Hz, 1H), 3.69 (s, 2H), 2.26 (s, 3H), 2.05 (s, 6H), 1.96 - 1.85 (m, 2H), 1.57 (q, J = 9.5, 8.6 Hz, 2H), 0.92 (s, 6H). |
| 1495 | 528.50 | 1.43 | |
| 1496 | 518.22 | 2.99 | DMSO(d6) δ 8.86 - 8.84 (d, 1H), 8.80 (s, 1H), 8.54 - 8.51 (d, 1H), 8.17 - 8.14 (d, 1H), 8.01 - 7.99 (d, 1H), 7.84 (t, J = 7.81, 1H), 7.01 - 6.84 (m, 4H), 5.44 (s, 2H), 2.72 (s, 3H), 2.03 (s, 6H), 1.13 (s, 9H) |
| 1497 | 573.10 | 1.77 | 1H NMR (400 MHz,甲醇-d4) δ 8.03 (dd, J = 8.3, 1.2 Hz, 1H), 7.68 (dd, J = 8.5, 7.3 Hz, 1H), 7.59 (dd, J = 8.3, 7.1 Hz, 1H), 7.38 (dd, J = 7.4, 0.8 Hz, 1H), 6.93 - 6.82 (m, 2H), 6.82 - 6.74 (m, 2H), 3.92 (t, J = 9.4 Hz, 1H), 3.79 (d, J = 6.4 Hz, 2H), 2.84 - 2.72 (m, 1H), 2.23 (dd, J = 12.6, 7.3 Hz, 1H), 2.12 - 2.02 (m, 1H), 1.87 (t, J = 11.7 Hz, 1H), 1.38 (s, 3H), 1.24 (d, J = 6.6 Hz, 6H), 1.04 (d, J = 6.7 Hz, 6H). |
| 1498 | 495.00 | 1.23 | |
| 1499 | 545.03 | 2.16 | 1H NMR (400 MHz, DMSO) δ 11.84 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.70 - 7.62 (m, 1H), 7.52 (t, J = 5.6 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 6.96 (dd, J = 10.8, 2.1 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 4.48 (dd, J = 10.4, 6.5 Hz, 1H), 4.38 (dd, J = 10.4, 7.8 Hz, 1H), 3.86 (d, J = 6.5 Hz, 2H), 3.85 - 3.76 (m, 2H), 3.74 - 3.66 (m, 1H), 3.66 - 3.58 (m, 1H), 2.71 (dt, J = 14.5, 7.4 Hz, 1H), 2.04 (qd, J = 13.5, 7.5 Hz, 2H), 1.76 (dt, J = 14.3, 6.8 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1500 | 474.30 | 1.34 | |
| 1501 | 514.24 | 2.00 | |
| 1502 | 567.40 | 2.39 | 1H NMR (400 MHz, MeOD) δ 7.86 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.66 - 7.59 (m, 1H), 7.53 (s, 1H), 7.39 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 6.78 - 6.72 (m, 2H), 5.64 (s, 1H), 3.82 (d, J = 6.5 Hz, 2H), 2.15 - 2.05 (m, 1H), 1.75 (s, 2H), 1.38 (s, 6H), 1.09 - 1.00 (m, 12H). |
| 1503 | 475.30 | 1.27 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1504 | 553.00 | 1.76 | 1H NMR (400 MHz, DMSO) δ 12.43 (s, 1H), 8.83 (s, 1H), 8.31 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.20 (s, 2H), 6.96 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 4.02 (s, 2H), 2.60 (d, J = 9.6 Hz, 2H), 2.22 (s, 1H), 1.87 (s, 1H), 1.60 (s, 6H), 1.42 (s, 1H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1505 | 432.30 | 1.31 | |
| 1506 | 538.30 | 1.29 | 1H NMR (400 MHz, DMSO-d6) δ 8.61 - 8.48 (m, 2H), 7.81 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.4, 7.3 Hz, 1H), 7.38 (d, J = 9.5 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 4.01 (h, J = 5.6 Hz, 2H), 3.56 (d, J = 7.5 Hz, 2H), 3.28 (s, 3H), 2.15 - 2.02 (m, 1H), 1.96 (qq, J = 6.6, 3.2 Hz, 2H), 1.68 (tq, J = 8.5, 5.2, 4.7 Hz, 2H), 1.08 (d, J = 6.2 Hz, 6H), 0.93 (d, J = 6.6 Hz, 6H). |
| 1507 | 418.30 | 1.17 | |
| 1508 | 576.60 | 1.61 | |
| 1509 | 509.00 | 1.70 | |
| 1510 | 458.30 | 1.48 | |
| 1511 | 446.20 | 1.49 | |
| 1512 | 525.30 | 2.31 | 1H NMR (400 MHz, DMSO-d6) δ 7.64 - 7.58 (m, 2H), 7.51 - 7.44 (m, 1H), 7.42 (d, J = 7.7 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.60 (t, J = 1.1 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 6.24 (s, 2H), 4.40 (q, J = 7.0 Hz, 2H), 2.93 (dt, J = 21.0, 10.6 Hz, 2H), 2.31 (s, 3H), 2.09 (bs, 1H), 1.81 (dd, J = 11.6, 5.6 Hz, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.35 (t, J = 6.9 Hz, 4H), 0.79 (d, J = 6.3 Hz, 3H). |
| 1513 | 507.50 | 2.16 | |
| 1514 | 525.30 | 1.92 | 1H NMR (400 MHz, DMSO-d6) δ 8.23 (s, 1H), 7.89 (dd, J = 7.8, 2.1 Hz, 1H), 7.70 - 7.55 (m, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.04 (dd, J = 8.0, 2.7 Hz, 1H), 6.71 (d, J = 10.0 Hz, 2H), 5.28 (h, J = 6.2 Hz, 1H), 3.94 (q, J = 6.0 Hz, 2H), 2.36 (s, 3H), 1.99 (p, J = 7.4 Hz, 2H), 1.70 - 1.55 (m, 2H), 1.30 (d, J = 6.1 Hz, 6H), 1.07 (d, J = 6.2 Hz, 6H). |
| 1515 | 556.50 | 1.83 | |
| 1516 | 510.30 | 2.11 | 1H NMR (400 MHz, DMSO-d6) δ 10.56 (s, 1H), 7.72 - 7.57 (m, 2H), 7.21 (d, J = 7.0 Hz, 1H), 6.93 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.45 (s, 2H), 3.76 - 3.60 (m, 2H), 3.53 (dt, J = 10.1, 6.8 Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.82 (ddd, J = 11.4, 6.6, 3.2 Hz, 2H), 1.74 - 1.59 (m, 1H), 1.37 (td, J = 9.9, 4.0 Hz, 1H), 0.62 (d, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 6.1 Hz, 3H). |
| 1517 | 511.20 | 1.92 | |
| 1518 | 505.20 | 2.18 | |
| 1519 | 563.20 | 2.13 | |
| 1520 | 676.60 | 2.46 | |
| 1521 | 560.50 | 1.61 | |
| 1522 | 627.44 | 1.34 | |
| 1523 | 540.00 | 1.67 | 1H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 8.94 (s, 1H), 8.36 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.64 (s, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.23 (d, J = 6.4 Hz, 2H), 2.64 (s, 2H), 2.19 (d, J = 38.0 Hz, 2H), 1.89 (s, 1H), 1.62 (s, 6H), 1.44 (s, 1H), 1.03 (d, J = 6.7 Hz, 6H), 0.89 (d, J = 6.2 Hz, 3H). |
| 1524 | 472.30 | 1.23 | |
| 1525 | 504.30 | 2.22 | |
| 1526 | 557.30 | 2.22 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 8.51 (s, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.56 - 7.45 (m, 2H), 7.22 (d, J = 7.2 Hz, 1H), 6.98 (dt, J = 10.9, 2.3 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.55 (s, 2H), 3.85 (d, J = 6.7 Hz, 2H), 2.72 - 2.63 (m, 1H), 2.59 (t, J = 10.6 Hz, 1H), 2.23 (s, 1H), 2.06 (dt, J = 13.3, 6.6 Hz, 1H), 1.92 (dd, J = 12.0, 5.6 Hz, 1H), 1.62 (s, 3H), 1.55 (s, 3H), 1.47 (t, J = 12.2 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.89 (d, J = 6.3 Hz, 3H). |
| 1527 | 552.30 | 1.42 | |
| 1528 | 535.50 | 1.76 | |
| 1529 | 540.30 | 2.11 | 1H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.45 (dd, J = 8.7, 2.3 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 7.0 Hz, 1H), 6.89 (dt, J = 10.8, 2.3 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.49 (s, 2H), 3.84 (d, J = 6.5 Hz, 2H), 3.54 (s, 4H), 2.46 (t, J = 5.8 Hz, 2H), 2.06 (ddd, J = 19.9, 9.8, 4.6 Hz, 3H), 1.26 (dd, J = 6.6, 2.6 Hz, 2H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1530 | 555.20 | 2.34 | |
| 1531 | 569.50 | 2.01 | |
| 1532 | 542.60 | 1.89 | 1H NMR (400 MHz, 氯仿-d) δ 14.55 (br s, 1H), 8.31 (br s, 1H), 7.93 (br s, 1H), 7.57 (br m, 3H), 6.59 (br s, 1H), 4.75及5.49 (br m, 2H), 4.04 (d, J = 6.7 Hz, 2H), 3.55 (br s, 1H), 3.17 (br s, 1H), 2.66 (br s, 1H), 2.11 (dq, J = 13.4, 6.7 Hz, 2H), 2.00 (s, 3H), 1.82 (br s, 1H), 1.42-1.36 (br m, 6H), 1.21 (br s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3H), 1.02 (d, J = 6.7 Hz, 6H). |
| 1533 | 604.60 | 2.10 | |
| 1534 | 460.30 | 1.03 | |
| 1535 | 578.60 | 1.78 | |
| 1536 | 420.20 | 1.09 | |
| 1537 | 539.30 | 2.17 | 1H NMR (400 MHz, DMSO-d6) δ 7.92 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.66 (dd, J = 8.4, 7.3 Hz, 1H), 7.22 (d, J = 7.0 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.76 (dd, J = 17.4, 8.5 Hz, 2H), 4.08 (d, J = 6.6 Hz, 2H), 3.96 (q, J = 5.9 Hz, 2H), 2.08 - 1.93 (m, 3H), 1.73 - 1.56 (m, 2H), 1.08 (d, J = 6.2 Hz, 6H), 0.98 (d, J = 6.7 Hz, 6H). |
| 1538 | 484.30 | 1.65 | 1H NMR (400 MHz, DMSO-d6) δ 12.58 - 12.52 (s, 1H), 10.09 (s, 1H), 8.38 - 7.93 (m, 2H), 7.78 - 7.69 (m, 2H), 7.69 - 7.62 (m, 2H), 7.29 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 10.2 Hz, 1H), 7.14 (d, J = 7.9 Hz, 1H), 6.90 - 6.36 (m, 1H), 2.48 - 2.26 (m, 2H), 2.18 - 2.08 (m, 1H), 1.91 - 1.70 (m, 1H), 1.58 (s, 3H), 1.55 (s, 3H), 1.38 (t, J = 12.1 Hz, 1H), 0.66 (d, J = 6.2 Hz, 3H). |
| 1539 | 493.00 | 1.72 | 1H NMR (400 MHz, MeOD) δ 7.93 (s, 2H), 7.50 (d, J = 32.1 Hz, 3H), 7.26 (s, 1H), 6.98 (s, 2H), 6.91 (s, 2H), 4.31 (d, J = 65.9 Hz, 4H), 4.05 (s, 2H), 2.44 (s, 6H), 2.29 (s, 3H), 2.03 (s, 1H), 1.87 (s, 3H), 1.32 (s, 3H). |
| 1540 | 564.50 | 1.69 | |
| 1541 | 510.00 | 1.37 | 1H NMR (400 MHz, MeOD) δ 8.26 (d, J = 6.4 Hz, 1H), 8.10 (s, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.21 (s, 1H), 6.99 (s, 2H), 6.88 (dd, J = 19.4, 7.9 Hz, 2H), 6.44 (s, 1H), 4.54 (d, J = 12.7 Hz, 1H), 4.33 (dd, J = 34.0, 9.6 Hz, 1H), 4.13 (s, 2H), 4.08 - 3.99 (m, 2H), 2.50 (s, 6H), 2.31 (s, 3H), 1.82 (s, 3H), 1.32 (s, 3H). |
| 1542 | 500.00 | 1.45 | 1H NMR (400 MHz, DMSO) δ 9.88 (s, 1H), 9.06 (s, 1H), 8.24 (s, 1H), 7.28 (s, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.92 (s, 3H), 4.27 - 4.12 (m, 3H), 4.05 - 3.97 (m, 3H), 2.40 (s, 7H), 2.25 (s, 3H), 1.76 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H). |
| 1543 | | | |
| 1544 | 524.40 | 1.89 | |
| 1545 | 577.60 | 2.29 | |
| 1546 | 500.00 | 1.49 | 1H NMR (400 MHz, DMSO) δ 9.50 (s, 1H), 7.86 (d, J = 3.1 Hz, 1H), 7.82 (d, J = 3.1 Hz, 1H), 7.34 (s, 1H), 7.19 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 12.8 Hz, 3H), 4.34 (s, 2H), 4.06 (s, 2H), 2.42 (s, 6H), 2.25 (s, 3H), 1.84 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 3H), 1.23 (s, 3H). |
| 1547 | 516.50 | 1.47 | |
| 1548 | 572.20 | 1.99 | 1H NMR (400 MHz, DMSO) δ 15.07 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.65 (dd, J = 8.4, 7.4 Hz, 1H), 7.59 - 7.50 (m, 2H), 7.31 - 7.19 (m, 1H), 6.99 (dt, J = 10.8, 2.3 Hz, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.38 (s, 2H), 3.93 (ddd, J = 13.4, 6.0, 2.9 Hz, 1H), 3.87 (d, J = 6.6 Hz, 2H), 3.76 (d, J = 11.4 Hz, 1H), 3.63 (d, J = 11.4 Hz, 1H), 3.39 - 3.27 (m, 1H), 3.02 (dd, J = 12.5, 2.6 Hz, 1H), 2.06 (dq, J = 13.3, 6.6 Hz, 1H), 1.52 (s, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.07 - 0.95 (m, 9H). |
| 1549 | 578.55 | 3.75 | 7.61-7.58 (d, 1H), 7.46 (t, J=7.15, 1H), 7.21-7.18 (d, 1H), 7.04-7.01 (d, 1H), 6.94 (s, 1H), 6.80-6.68 (m, 2H), 6.51-6.47 (d, 1H),6.32-6.28 (d,3H), 3.76-3.74 (d, 2H), 2.24 (s, 3H), 2.03 (s, 6H), 0.96 -0.93 (d, 6H) |
| 1550 | 458.30 | 1.75 | 1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 8.47 (d, J = 2.5 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.52 (s, 2H), 2.65 - 2.52 (m, 2H), 2.22 - 2.17 (m, 1H), 1.92 - 1.82 (m, 1H), 1.52 (s, 6H), 1.42 (t, J = 12.1 Hz, 1H), 0.86 (d, J = 6.3 Hz, 3H). |
| 1551 | 456.38 | 3.05 | |
| 1552 | 569.30 | 2.40 | 1H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 7.91 (dd, J = 20.4, 8.2 Hz, 2H), 7.66 (t, J = 7.9 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J = 9.8 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 6.93 (d, J = 10.7 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.51 (s, 2H), 3.86 (d, J = 6.6 Hz, 2H), 3.58 (dd, J = 12.2, 6.5 Hz, 1H), 2.55 (d, J = 12.3 Hz, 1H), 2.06 (dt, J = 13.2, 6.6 Hz, 1H), 1.63 (dd, J = 12.4, 6.4 Hz, 1H), 1.50 (d, J = 13.0 Hz, 1H), 1.39 (d, J = 12.9 Hz, 1H), 1.15 (s, 3H), 1.08 - 0.93 (m, 9H), 0.80 (s, 3H), 0.69 (s, 3H). |
| 1553 | 496.50 | 1.95 | |
| 1554 | 562.60 | 1.59 | |
| 1555 | 557.00 | 1.46 | 1H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 9.74 (s, 1H), 7.78 (s, 1H), 7.28 (s, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.93 (s, 3H), 4.22 (dd, J = 26.1, 10.6 Hz, 4H), 4.03 (d, J = 7.4 Hz, 3H), 2.43 (s, 6H), 2.25 (s, 4H), 2.14 (s, 3H), 1.77 (s, 3H), 1.23 (s, 3H). |
| 1556 | 458.30 | 1.72 | |
| 1557 | 548.50 | 1.60 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1558 | 551.50 | 1.75 | |
| 1559 | 621.30 | 2.35 | |
| 1560 | 611.50 | 2.06 | |
| 1561 | 500.30 | 1.73 | |
| 1562 | 550.40 | 2.60 | 1H NMR (400 MHz, DMSO-d6) δ 10.48 (s, 1H), 7.30 (s, 1H), 7.26 - 7.07 (m, 3H), 6.86 (d, J = 6.7 Hz, 3H), 6.78 (d, J = 7.6 Hz, 1H), 4.09 - 3.94 (m, 3H), 3.79 (d, J = 16.5 Hz, 4H), 3.00 (p, J = 6.8 Hz, 1H), 2.31 (s, 6H), 2.23 (s, 3H), 1.63 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.14 (dd, J = 6.8, 3.0 Hz, 6H). |
| 1563 | 571.20 | 2.73 | 1H NMR (400 MHz,甲醇-d4) δ 7.74 (d, J = 7.9 Hz, 1H), 7.46 (t, J = 1.8 Hz, 1H), 7.35 - 7.20 (m, 2H), 7.01 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.65 (dt, J = 10.4, 2.3 Hz, 1H), 3.79 (d, J = 6.5 Hz, 2H), 3.02 - 2.90 (m, 1H), 2.18 (dtd, J = 12.0, 9.2, 7.9, 4.3 Hz, 1H), 2.08 (dh, J = 13.4, 6.7 Hz, 1H), 1.83 (dd, J = 11.7, 5.6 Hz, 1H), 1.65 (m, 1H), 1.50 - 1.38 (m, 1H), 1.39 - 1.23 (m, 6H), 1.04 (d, J = 6.7 Hz, 6H), |
| 1564 | 415.20 | 1.49 | |
| 1565 | 502.00 | 1.13 | |
| 1566 | 616.50 | 1.99 | |
| 1567 | 572.40 | 1.48 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.57 - 7.45 (m, 1H), 7.45 - 7.34 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 6.93 - 6.80 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.46 (s, 1H), 4.03 (dd, J = 9.4, 6.0 Hz, 1H), 3.90 (dd, J = 9.6, 6.3 Hz, 1H), 3.46 - 3.39 (m, 2H), 2.64 - 2.55 (m, 2H), 2.28 - 2.14 (m, 1H), 2.06 - 1.95 (m, 1H), 1.95 - 1.80 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H), 1.42 (t, J = 12.1 Hz, 1H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1568 | 444.00 | 1.94 | 1H NMR (400 MHz, DMSO) δ 8.04 (s, 1H), 7.82 (s, 1H), 7.03 (s, 1H), 6.78 (s, 2H), 5.48 (s, 2H), 3.75 (s, 3H), 2.16 (d, J = 21.1 Hz, 9H), 1.14 (s, 9H). |
| 1569 | 578.30 | 2.63 | |
| 1570 | 558.98 | 2.36 | |
| 1571 | 456.40 | 1.44 | 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 8.12 (s, 1H), 7.61 (d, J = 13.8 Hz, 2H), 7.19 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 6.36 (d, J = 15.9 Hz, 1H), 5.68 (dd, J = 15.9, 9.0 Hz, 1H), 2.17 (s, 1H), 1.82 (dd, J = 11.9, 5.7 Hz, 1H), 1.55 (dq, J = 8.8, 4.7, 4.2 Hz, 1H), 1.48 (d, J = 5.3 Hz, 6H), 1.36 (t, J = 12.1 Hz, 1H), 0.85 (d, J = |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.3 Hz, 3H), 0.81 - 0.71 (m, 2H), 0.50 (dq, J = 8.8, 5.5, 3.7 Hz, 2H). |
| 1572 | 590.20 | 2.24 | 1H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.74 - 7.61 (m, 2H), 7.41 - 7.33 (m, 2H), 7.27 - 7.20 (m, 1H), 6.90 (s, 1H), 6.86 (dt, J = 10.6, 2.3 Hz, 1H), 6.82 (s, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.52 (s, 2H), 3.70 (d, J = 6.6 Hz, 2H), 3.42 (s, 2H), 3.33 (s, 2H), 2.25 (s, 3H), 2.08 - 1.96 (m, 1H), 1.91 (s, 3H), 0.98 (d, J = 6.7 Hz, 7H). |
| 1573 | 448.20 | 1.32 | |
| 1574 | 566.20 | 1.43 | |
| 1575 | 474.20 | 1.13 | |
| 1576 | 509.00 | 1.41 | 1H NMR (400 MHz, DMSO) δ 10.47 (s, 1H), 7.58 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.9 Hz, 3H), 7.09 (d, J = 7.3 Hz, 1H), 6.93 (dd, J = 19.4, 7.9 Hz, 2H), 6.64 (d, J = 8.2 Hz, 1H), 6.40 (s, 1H), 4.20 (d, J = 12.5 Hz, 1H), 4.05 (d, J = 24.9 Hz, 4H), 2.93 (s, 1H), 2.07 (s, 1H), 1.57 (s, 3H), 1.26 (s, 9H). |
| 1577 | 538.40 | 1.91 | |
| 1578 | 579.52 | 1.50 | |
| 1579 | 573.35 | 2.17 | |
| 1580 | 515.02 | 2.35 | |
| 1581 | 556.50 | 1.83 | 1H NMR (400 MHz, DMSO-d6) δ 12.62 - 12.53 (s,1H), 8.17 - 7.93 (m, 2H), 7.78 - 7.71 (m, 2H), 7.71 - 7.61 (m, 2H), 7.52 - 7.44 (m, 1H), 7.43 - 7.35 (m, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.90 (dt, J = 10.6, 2.4 Hz, 1H), 3.80 (s, 2H), 2.48 - 2.26 (m, 2H), 2.26 - 2.10 (m, 1H), 1.84 (dd, J = 11.9, 5.5 Hz, 1H), 1.60 (s, 3H), 1.55 (s, 3H), 1.38 (t, J = 12.0 Hz, 1H), 1.21 (s, 6H), 0.66 (d, J = 6.3 Hz, 3H). |
| 1582 | 509.00 | 1.34 | 1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.24 (s, 2H), 6.97 (s, 3H), 6.87 (d, J = 7.9 Hz, 1H), 6.61 (s, 1H), 4.39 (s, 1H), 4.16 (s, 2H), 4.03 (s, 2H), 2.44 (s, 6H), 2.29 (s, 3H), 1.85 (s, 3H), 1.32 (s, 4H), 1.15 (d, J = 6.1 Hz, 1H). |
| 1583 | 488.00 | 1.31 | |
| 1584 | 536.40 | 2.49 | 1H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 7.19 (dt, J = 30.9, 7.9 Hz, 3H), 6.85 (d, J = 22.6 Hz, 4H), 4.16 - 3.92 (m, 4H), 3.82 (d, J = 14.9 Hz, 4H), 2.33 (s, 6H), 2.23 (s, 3H), 1.64 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.13 (td, J = 7.5, 2.5 Hz, 3H). |
| 1585 | 441.50 | 2.01 | 1H NMR (400 MHz, DMSO-d6) δ 8.96 - |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 8.85 (m, 2H), 7.96 - 7.87 (m, 2H), 6.94 (s, 1H), 6.73 (s, 2H), 5.44 (s, 2H), 2.16 (s, 3H), 2.05 (s, 6H), 1.15 (s, 9H). |
| 1586 | 604.60 | 2.09 | |
| 1587 | 542.00 | 1.75 | 1H NMR (400 MHz, DMSO) δ 10.28 (s, 1H), 7.35 (d, J = 2.1 IIz, 1H), 7.29 - 7.22 (m, 2H), 6.96 (dd, J = 8.3, 2.2 Hz, 1H), 6.89 (d, J = 7.2 Hz, 4H), 5.70 (s, 2H), 4.13 (d, J = 12.7 Hz, 1H), 3.97 (dd, J = 33.5, 9.7 Hz, 5H), 2.36 (s, 6H), 2.24 (s, 3H), 2.08 (s, 3H), 1.68 (s, 3H), 1.25 (s, 3H). |
| 1588 | 617.30 | 2.64 | 1H NMR (400 MHz, 氯仿-d) δ 8.87 (d, J = 2.5 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.22 (dd, J = 8.7, 2.5 Hz, 1H), 7.68 (dd, J = 8.2, 4.0 Hz, 2H), 7.47 - 7.33 (m, 5H), 7.08 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 5.39 (七重峰, J = 6.2 Hz, 1H), 5.12 (s, 2H), 3.96 - 3.68 (m, 2H), 2.29 (ddt, J = 9.6, 6.7, 3.6 Hz, 2H), 2.03 (d, J = 13.7 Hz, 2H), 1.38 (d, J = 6.2 Hz, 6H), 1.27 (dd, J = 6.8, 2.8 Hz, 6H). |
| 1589 | 524.30 | 2.17 | 1H NMR (400 MHz, DMSO-d6) δ 10.54 (s, 1H), 7.70 (s, 1H), 7.67 - 7.59 (m, 1H), 7.21 (d, J = 7.4 Hz, 1H), 6.93 (s, 2H), 6.69 (d, J = 8.6 Hz, 1H), 3.99 (p, J = 6.1, 5.7 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 3H), 2.04 (s, 6H), 1.84 (pt, J = 6.6, 3.0 Hz, 2H), 1.61 - 1.48 (m, 2H), 0.88 (d, J = 6.2 Hz, 6H). |
| 1590 | 458.20 | 1.54 | |
| 1591 | 509.00 | 1.20 | 1H NMR (400 MHz, MeOD) δ 8.52 (s, 1H), 8.00 (s, 1H), 7.31 (s, 1H), 7.05 (d, J = 27.3 Hz, 4H), 6.93 (d, J = 8.2 Hz, 1H), 4.50 (s, 2H), 4.33 (d, J = 45.1 Hz, 2H), 4.06 (s, 2H), 2.49 (s, 6H), 2.31 (s, 3H), 1.93 (s, 3H), 1.33 (s, 3H). |
| 1592 | 531.09 | 2.15 | |
| 1593 | 556.30 | 1.69 | |
| 1594 | 472.30 | 1.10 | 1H NMR (400 MHz, DMSO-d6) δ 12.36 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.4, 7.3 Hz, 1H), 7.22 - 7.15 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.75 - 6.69 (m, 1H), 6.67 (d, J = 8.5, 0.8 Hz, 1H), 6.47 (s, 2H), 4.26 (q, J = 2.8 Hz, 2H), 3.81 (dq, J = 14.5, 5.6 Hz, 2H), 2.59 - 2.54 (m, 2H, 由溶劑遮蔽), 2.21 - 2.16 (m, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.52 (s, 6H), 1.38 (t, J = 12.1 Hz, 1H), 1.22 - 1.11 (m, 1H), 0.86 (d, J = 6.3 Hz, 3H). |
| 1595 | 474.40 | 1.12 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1596 | 543.00 | 1.48 | |
| 1597 | 544.00 | 1.64 | |
| 1598 | 535.20 | 1.92 | |
| 1599 | 446.40 | 1.44 | 1H NMR (400 MHz, DMSO-d6) δ 7.47 - 7.32 (m, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.42 (d, J = 8.1 Hz, 1H), 6.21 (d, J = 7.7 Hz, 1H), 6.01 (s, 2H), 3.04 - 2.90 (m, 2H), 2.44 - 2.28 (m, 2H), 2.17 - 2.00 (m, 2H), 1.76 (dd, J = 11.6, 5.7 Hz, 1H), 1.50 (d, J = 5.4 Hz, 6H), 1.34 (t, J = 5.9 Hz, 1H), 0.92 - 0.79 (m, 9H). |
| 1600 | 640.60 | 2.11 | |
| 1601 | 526.60 | 1.78 | 1H NMR (400 MHz,甲醇-d4) δ 7.79 (s, 1H), 7.60 (dd, J = 8.4, 7.3 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 5.56 (tt, J = 3.6, 1.7 Hz, 1H), 3.60 (dd, J = 11.2, 8.3 Hz, 1H), 3.21 (dd, J = 11.2, 9.0 Hz, 1H), 2.66 (dt, J = 13.8, 8.4 Hz, 1H), 2.30 - 2.22 (m, 2H), 2.20 - 2.15 (m, 2H), 2.15 - 2.10 (m, 1H), 1.83 - 1.75 (m, 3H), 1.75 - 1.67 (m, 2H), 1.52 (s, 3H), 1.42 (s, 9H), 1.40 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H). |
| 1602 | 468.20 | 2.80 | |
| 1603 | 424.00 | 1.75 | 1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 8.27 - 8.00 (m, 1H), 7.72 - 7.54 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.55 (s, 2H), 2.17 (dq, J = 13.0, 7.1, 6.7 Hz, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.47 (d, J = 7.1 Hz, 6H), 1.37 (t, J = 12.1 Hz, 1H), 0.85 (d, J = 6.3 Hz, 3H). |
| 1604 | 559.30 | 2.18 | |
| 1605 | 566.32 | 1.68 | |
| 1606 | 500.00 | 1.47 | 1H NMR (400 MHz, DMSO) δ 9.64 (s, 1H), 8.12 (s, 2H), 7.77 (d, J = 7.3 Hz, 1H), 7.30 (s, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.92 (s, 3H), 4.27 (s, 3H), 4.04 (s, 3H), 2.39 (s, 6H), 2.24 (s, 3H), 1.79 (s, 3H), 1.24 (s, 3H). |
| 1607 | 408.20 | 0.98 | |
| 1608 | 563.60 | 2.13 | |
| 1609 | 537.20 | 1.97 | |
| 1610 | 567.50 | 1.91 | |
| 1611 | 570.30 | 2.02 | |
| 1612 | 570.30 | 2.02 | |
| 1613 | 528.60 | 1.85 | |
| 1614 | 562.60 | 1.61 | |
| 1615 | 535.50 | 1.75 | |
| 1616 | 605.00 | 1.67 | 1H NMR (400 MHz, MeOD) δ 8.16 (d, J = 8.2 Hz, 1H), 8.00 (s, 1H), 7.88 (s, 1H), 7.27 (s, 1H), 7.12 (d, J = 6.8 Hz, 1H), 6.99 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2H), 6.89 (d, J = 8.2 Hz, 1H), 4.47 (s, 2H), 4.26 (d, J = 33.1 Hz, 2H), 4.05 (s, 2H), 2.43 (s, 6H), 2.30 (s, 3H), 1.93 (s, 3H), 1.31 (s, 3H). |
| 1617 | 514.30 | 1.89 | |
| 1618 | 539.00 | 1.66 | 1H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 8.27 (d, J = 5.4 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.64 (s, 1H), 7.58 (d, J = 6.7 Hz, 1H), 7.41 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 4.09 (d, J = 6.7 Hz, 2H), 2.61 (s, 2H), 2.23 (s, 1H), 2.07 (s, 1H), 1.88 (s, 1H), 1.60 (d, J = 7.4 Hz, 6H), 1.43 (s, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1619 | 533.30 | 2.40 | |
| 1620 | 528.50 | 1.77 | 1H NMR (400 MHz, 氯仿-d) δ 13.87 (寬單峰, 1H), 8.29 (d, J = 8.0 Hz, 1H) 8.21 (d, J = 2.9 Hz, 1H), 7.65 - 7.58 (m, 2H), 7.52 (d, J = 8.5 Hz, 1H), 6.65 (p, J = 3.8 Hz, 1H), 5.95 (d, J = 2.8 Hz, 1H), 4.80 (寬單峰, 2H), 4.02 (d, J = 6.6 Hz, 2H), 3.52 - 3.41 (m, 1H), 3.15 (dd, J = 10.5, 8.1 Hz, 1H), 2.69 - 2.50 (m, 1H), 2.18 - 2.02 (m, 2H), 1.72 (dd, J = 12.3, 9.7 Hz, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.7 Hz, 6H). |
| 1621 | 504.23 | 1.97 | |
| 1622 | 573.14 | 2.40 | |
| 1623 | 525.30 | 1.89 | 1H NMR (400 MHz, DMSO-d6) δ 7.90 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H), 6.70 (t, J = 8.6 Hz, 2H), 5.31 (p, J = 6.2 Hz, 1H), 3.95 (q, J = 5.9 Hz, 2H), 2.04 - 1.93 (m, 5H), 1.71 - 1.57 (m, 3H), 1.31 (d, J = 6.2 Hz, 6H), 1.07 (d, J = 6.2 Hz, 6H). |
| 1624 | 571.40 | 1.55 | |
| 1625 | 566.32 | 1.67 | |
| 1626 | 516.60 | 1.58 | |
| 1627 | 430.30 | 1.19 | |
| 1628 | 524.40 | 1.65 | |
| 1629 | 557.03 | 2.48 | |
| 1630 | 535.30 | 2.43 | 1H NMR (400 MHz, DMSO-d6) δ 12.08 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.24 - 7.16 (m, 2H), 6.91 (s, 2H), 6.70 (d, J = 8.3 Hz, 1H), 6.57 - 6.44 (m, 3H), 2.38 - 2.30 (m, 1H), 2.25 (s, 3H), 2.19 - 2.05 (m, 2H), 1.99 (s, 6H), 1.88 - 1.76 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (m, 2H), 1.44 (h, J = 6.9 Hz, 1H), 1.25 - 1.09 (m, 2H), 0.85 (dd, J = 6.8, 4.7 Hz, 6H). |
| 1631 | 537.30 | 1.80 | |
| 1632 | 474.30 | 1.18 | |
| 1633 | 540.60 | 1.91 | |
| 1634 | 515.30 | 0.95 | |
| 1635 | 472.30 | 1.79 | 1H NMR (400 MHz, DMSO-d6) δ 12.70 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.21 (dd, J = 7.3, 0.7 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.70 (dd, J = 8.5, 0.8 Hz, 1H), 6.56 (s, 2H), 2.60 (s, 2H), 1.75 (s, 2H), 1.55 (s, 6H), 0.97 (s, 6H). |
| 1636 | 500.20 | 1.27 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 10.50 - 9.90 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.26 - 7.17 (m, 2H), 7.14 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 10.5 Hz, 1H), 2.65 - 2.53 (m, 2H), 2.29 - 2.11 (m, 1H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.42 (t, J = 12.0 Hz, 1H), 0.88 (d, J = 6.2 Hz, 3H). |
| 1637 | 539.40 | 2.47 | 1H NMR (400 MHz, DMSO-d6) δ 7.65 - 7.56 (m, 2H), 7.48 (dd, J = 8.2, 7.3 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 6.98 (dd, J = 7.4, 0.8 Hz, 1H), 6.60 - 6.46 (m, 2H), 6.28 (s, 2H), 5.38 (p, J = 6.2 Hz, 1H), 3.00 - 2.83 (m, 2H), 2.30 (s, 3H), 2.09 (dq, J = 11.6, 6.0 Hz, 1H), 1.81 (dd, J = 12.0, 5.7 Hz, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.41 - 1.29 (m, 8H), 0.78 (d, J = 6.3 Hz, 3H). |
| 1638 | 472.30 | 1.82 | |
| 1639 | 571.36 | 2.49 | |
| 1640 | 534.30 | 2.08 | 1H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.43 (dd, J = 9.9, 1.9 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.91 (dt, J = 10.7, 2.3 Hz, 1H), 4.47 (s, 1H), 4.18 - 3.97 (m, 2H), 3.92 - 3.82 (m, 3H), 3.77 - 3.68 (m, 1H), 3.09 (q, J = 10.6 Hz, 1H), 2.94 - 2.82 (m, 1H), 2.40 - 2.18 (m, 3H), 2.06 (dt, J = 13.3, 6.7 Hz, 1H), 2.01 - 1.93 (m, 1H), 1.68 (d, J = 1.8 Hz, 3H), 1.63 (s, 3H), 1.56 (td, J = 12.3, 3.7 Hz, 1H), 1.05 (dd, J = 6.4, 3.2 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1641 | 590.00 | 3.06 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 7.80 (s, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.27 - 7.18 (m, 1H), 7.10 - 6.99 (m, 2H), 6.93 (dt, J = 11.0, 2.3 Hz, 1H), 6.70 (dd, J = 8.4, 0.8 Hz, 1H), 6.54 (s, 2H), 3.80 (d, J = 6.6 Hz, 2H), 2.65 - 2.53 (m, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.22 (dt, J = 11.5, 5.9 Hz, 1H), 2.08 - 1.96 (m, 1H), 1.84 (dd, J = 12.0, 5.6 Hz, 1H), 1.57 - 1.33 (m, 7H), 0.97 (d, J = 6.7 Hz, 6H), 0.86 (d, J = 6.3 Hz, 3H). |
| 1642 | 510.00 | 1.52 | 1H NMR (400 MHz, DMSO) δ 10.48 (s, 1H), 7.37 (d, J = 4.2 Hz, 1H), 7.35 (s, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 7.8 Hz, 3H), 4.24 (s, 3H), 4.02 (s, 3H), 2.39 (s, 6H), 2.24 (s, 3H), 1.78 (s, 3H), 1.24 (s, 3H). |
| 1643 | 494.60 | 1.06 | |
| 1644 | 529.20 | 2.30 | 1H NMR (400 MHz, DMSO) δ 7.84 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 5.7 Hz, 1H), 7.47 - 7.36 (m, 3H), 7.06 (dd, J = 7.3, 0.7 Hz, 1H), 6.84 (dt, J = 10.7, 2.2 Hz, 1H), 6.45 (dd, J = 8.2, 0.7 Hz, 1H), 6.07 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 2.44 - 2.31 (m, 2H), 2.24 (dd, J = 10.0, 6.9 Hz, 2H), 2.06 (dt, J = 13.3, 6.6 Hz, 1H), 1.83 - 1.71 (m, 2H), 1.68 (s, 3H), 1.01 (t, J = 8.3 Hz, 6H). |
| 1645 | 567.50 | 1.78 | |
| 1646 | 552.32 | 1.39 | |
| 1647 | 584.42 | 1.36 | |
| 1648 | 549.60 | 2.10 | |
| 1649 | 536.50 | 1.49 | |
| 1650 | 549.30 | 2.44 | |
| 1651 | 512.30 | 1.86 | |
| 1652 | 598.00 | 2.83 | 1H NMR (400 MHz, DMSO-d6) δ 12.68 (s, 1H), 10.87 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.17 - 8.05 (m, 1H), 7.88 - 7.80 (m, 2H), 7.51 - 7.45 (m, 1H), 7.42 (ddd, J = 10.2, 2.4, 1.3 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.90 (dt, J = 10.7, 2.3 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.60 (dd, J = 10.2, 7.2 Hz, 1H), 2.52 (d, J = 5.3 Hz, 1H), 2.14 (s, 4H), 2.07 - 2.00 (m, 1H), 1.87 (dd, J = 11.8, 5.6 Hz, 1H), 1.59 (d, J = 6.0 Hz, 6H), 1.41 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.77 (d, J = 6.3 Hz, 3H). |
| 1653 | 455.40 | 2.05 | 1H NMR (400 MHz, DMSO-d6) δ 12.04 (s, 1H), 7.65 - 7.59 (m, 2H), 6.95 (s, 1H), 6.76 (s, 2H), 6.67 - 6.61 (m, 2H), 6.19 (s, 2H), 5.45 (s, 2H), 2.17 (s, 3H), 2.10 (s, 6H), 1.13 (s, 9H). |
| 1654 | 566.32 | 1.68 | |
| 1655 | 512.00 | 1.60 | |
| 1656 | 553.40 | 2.62 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.69 - 7.59 (m, 2H), 7.54 (d, J = 7.9 Hz, 1H), 7.20 (d, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 7.1 Hz, 1H), 6.78 - 6.62 (m, 2H), 4.15 (dd, J = 6.6, 1.7 Hz, 2H), 2.70 - 2.56 (m, 2H), 2.34 (s, 3H), 2.29 - 2.16 (m, 1H), 2.07 (七重峰, J = 6.7 Hz, 1H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.62 (d, J = 5.9 Hz, 6H), 1.43 (t, J = 12.0 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H), 0.89 (d, J = 6.2 Hz, 3H). |
| 1657 | 554.20 | 2.05 | 1H NMR (400 MHz, DMSO) δ 12.47 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 12.0 Hz, 2H), 7.27 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.89 (d, J = 10.8 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.46 (s, 2H), 4.29 (s, 1H), 3.84 (d, J = 6.5 Hz, 2H), 2.86 (s, 2H), 2.03 (dd, J = 13.5, 6.8 Hz, 1H), 1.86 - 1.75 (m, 3H), 1.54 (ddd, J = 36.2, 22.1, 10.7 Hz, 6H), 0.99 (d, J = 6.7 Hz, 6H). |
| 1658 | 472.20 | 1.71 | |
| 1659 | 553.50 | 1.69 | |
| 1660 | 525.30 | 1.38 | |
| 1661 | 545.09 | 2.22 | 1H NMR (400 MHz, DMSO) δ 11.70 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.69 - 7.61 (m, 1H), 7.53 (t, J = 5.3 Hz, 2H), 7.22 (d, J = 7.3 Hz, 1H), 7.02 - 6.93 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.53 (s, 2H), 4.50 (qd, J = 11.1, 4.8 Hz, 2H), 4.26 (d, J = 5.2 Hz, 1H), 3.93 - 3.78 (m, 3H), 3.68 (dd, J = 13.9, 7.0 Hz, 1H), 2.13 - 1.98 (m, 2H), 1.98 - 1.74 (m, 3H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1662 | 526.00 | 1.21 | 1H NMR (400 MHz, MeOD) δ 8.53 (s, 1H), 8.30 (s, 1H), 7.96 (s, 1H), 7.15 (dd, J = 97.7, 47.9 Hz, 7H), 5.31 (s, 1H), 4.50 (d, J = 44.1 Hz, 3H), 4.11 (s, 2H), 1.83 (s, 3H), 1.40 (d, J = 29.2 Hz, 10H). |
| 1663 | 553.00 | 1.81 | 1H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 7.91 - 7.78 (m, 3H), 7.64 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 4.10 (s, 2H), 2.62 (s, 2H), 2.23 (s, 1H), 1.88 (s, 1H), 1.62 (d, J = 6.0 Hz, 6H), 1.43 (s, 1H), 1.04 (s, 9H), 0.89 (d, J = 6.3 Hz, 3H). |
| 1664 | 538.30 | 1.62 | |
| 1665 | 512.60 | 1.67 | |
| 1666 | 532.00 | 1.72 | |
| 1667 | 593.20 | 2.15 | 1H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.66 (dd, J = 8.4, 7.3 Hz, 1H), 7.54 - 7.47 (m, 2H), 7.26 - 7.16 (m, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.95 (dt, J = 10.8, 2.3 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.56 (s, 2H), 5.81 (s, 1H), 3.86 (d, J = 6.5 Hz, 2H), 3.35 (s, 1H), 2.73 - 2.60 (m, 1H), 2.47 - 2.37 (m, 1H), 2.25 (dt, J = 9.1, 4.0 Hz, 1H), 2.08 - 1.98 (m, 3H), 1.49 (qd, J = 12.2, 5.5 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1668 | 529.00 | 2.40 | |
| 1669 | 494.00 | 1.38 | |
| 1670 | 469.40 | 1.60 | |
| 1671 | 538.29 | 1.27 | |
| 1672 | 540.30 | 1.58 | |
| 1673 | 519.30 | 1.59 | 1H NMR (400 MHz, DMSO-d6) δ 14.11 (s, 1H), 7.73 - 7.46 (m, 2H), 7.16 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 8.5, 2.4 Hz, 1H), 3.79 (dt, J = 11.0, 6.2 Hz, 1H), 3.31 (td, J = 10.8, 3.7 Hz, 2H), 2.96 (t, J = 9.6 Hz, 1H), 2.41 - 2.27 (m, 2H), 1.99 (ddd, J = 23.1, 12.1, 6.4 Hz, 2H), 1.58 - 1.50 (m, 2H), 1.49 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 1.04 (dd, J = 6.5, 1.9 Hz, 6H). |
| 1674 | 592.30 | 1.42 | |
| 1675 | 586.20 | 1.95 | 1H NMR (400 MHz, DMSO) δ 13.79 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.64 (dd, J = 8.4, 7.4 Hz, 1H), 7.58 - 7.46 (m, 2H), 7.24 (d, J = 7.0 Hz, 1H), 6.98 (dt, J = 10.7, 2.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.44 (s, 2H), 3.87 (d, J = 6.6 Hz, 2H), 3.56 (s, 2H), 3.14 (s, 2H), 2.06 (dq, J = 13.3, 6.6 Hz, 1H), 1.26 (d, J = 19.1 Hz, 12H), 1.00 (d, J = 6.7 Hz, 6H). |
| 1676 | 498.00 | 1.43 | 1H NMR (400 MHz, DMSO) δ 9.60 (d, J = 113.0 Hz, 1H), 8.13 (s, 1H), 7.89 (s, 1H), 7.39 - 7.07 (m, 7H), 6.94 (s, 1H), 4.29 (d, J = 27.5 Hz, 3H), 4.04 (s, 3H), 2.44 (s, 6H), 1.81 (s, 3H), 1.26 (s, 3H). |
| 1677 | 458.30 | 1.49 | 1H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 7.80 - 7.55 (m, 2H), 7.18 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 6.34 - 5.83 (m, 2H), 2.75 - 2.58 (m, 2H), 2.53 (d, J = 8.9 Hz, 2H), 2.17 (dd, J = 13.5, 7.1 Hz, 1H), 1.82 (dd, J = 11.9, 5.7 Hz, 1H), 1.59 - 1.49 (m, 8H), 1.39 (dd, J = 26.5, 14.4 Hz, 1H), 0.86 (d, J = 6.3 Hz, 3H), 0.69 (ddd, J = 12.8, 7.9, 4.9 Hz, 1H), 0.43 - 0.32 (m, 2H), 0.07 - 0.00 (m, 2H). |
| 1678 | 491.50 | 1.74 | |
| 1679 | 519.20 | 1.78 | |
| 1680 | 573.30 | 2.25 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1681 | 557.00 | 1.66 | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 7.62 (s, 1H), 7.26 (s, 1H), 7.13 - 7.01 (m, 2H), 6.92 (s, 2H), 6.80 (s, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.43 (s, 1H), 4.08 (d, J = 30.9 Hz, 4H), 3.89 (s, 2H), 3.79 (s, 2H), 2.01 (s, 1H), 1.50 (s, 3H), 1.28 (s, 3H), 0.96 (d, J = 6.6 Hz, 6H). |
| 1682 | 542.60 | 1.97 | |
| 1683 | 444.30 | 1.32 | |
| 1684 | 557.40 | 1.56 | |
| 1685 | 529.29 | 2.29 | |
| 1686 | 593.37 | 2.47 | |
| 1687 | 594.20 | 1.66 | |
| 1688 | 594.20 | 1.64 | |
| 1689 | 593.33 | 2.44 | |
| 1690 | 594.20 | 1.67 | |
| 1691 | 580.35 | 1.74 | |
| 1692 | 569.33 | 2.06 | |
| 1693 | 580.32 | 1.71 | |
| 1694 | 579.34 | 2.39 | |
| 1695 | 583.30 | 1.48 | |
| 1696 | 613.50 | 1.62 | |
| 1697 | 474.40 | 1.35 | |
| 1698 | 474.40 | 1.35 | |
| 1699 | 472.30 | 1.21 | |
| 1700 | 569.40 | 1.65 | |
| 1701 | 480.21 | 1.62 | |
| 1702 | 539.30 | 1.56 | |
| 1703 | 583.50 | 1.74 | |
| 1704 | 513.41 | 2.61 | |
| 1705 | 526.16 | 1.40 | |
| 1706 | 496.31 | 1.14 | |
| 1707 | 526.18 | 1.24 | |
| 1708 | 520.32 | 2.43 | |
| 1709 | 514.30 | 1.65 | 1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 8.19 (d, J = 2.7 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.49 (寬單峰, 2H), 6.07 (d, J = 2.8 Hz, 1H), 4.86 (七重峰, J = 6.0 Hz, 1H), 2.57 (br m, 2H), 2.21 (br s, 1H), 1.87 (dd, J = 11.9, 5.7 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.44 - 1.35 (m, 1H), 1.33 (dd, J = 6.1, 3.1 Hz, 6H), 0.87 (d, J = 6.1 Hz, 3H) |
| 1710 | 541.30 | 1.64 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (d, J = 23.3 Hz, 2H), 8.22 (dd, J = 7.2, 2.1 Hz, 1H), 7.81 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 6.44 (dd, J = 13.0, 7.1 Hz, 2H), 2.65 (d, J = |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 9.1 Hz, 2H), 2.58 (d, J = 12.3 Hz, 1H), 2.35 - 2.12 (m, 2H), 1.97 (d, J = 11.7 Hz, 3H), 1.92 - 1.78 (m, 2H), 1.64 - 1.47 (m, 8H), 1.46 - 1.32 (m, 3H), 0.89 (d, J = 6.2 Hz, 3H). |
| 1711 | 446.18 | 2.53 | |
| 1712 | 482.24 | 0.73 | |
| 1713 | 494.57 | 1.08 | |
| 1714 | 506.20 | 1.15 | |
| 1715 | 613.50 | 1.58 | 1H NMR (400 MHz, DMSO) δ 8.63 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 6.99 (dd, J = 10.5, 7.4 Hz, 2H), 6.45 (d, J = 8.1 Hz, 1H), 6.09 (d, J = 4.6 Hz, 2H), 4.44 (dd, J = 5.7, 3.9 Hz, 2H), 3.77 (dd, J = 5.8, 4.0 Hz, 2H), 3.59 (dd, J = 5.8, 3.8 Hz, 2H), 3.49 (dd, J = 5.9, 3.7 Hz, 2H), 3.42 (q, J = 7.0 Hz, 2H), 3.06 - 2.93 (m, 2H), 2.20 (s, 3H), 2.16 - 2.04 (m, 2H), 1.81 (dd, J = 11.5, 5.6 Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.37 (t, J = 11.9 Hz, 1H), 1.08 (t, J = 6.9 Hz, 3H), 0.85 (d, J = 6.3 Hz, 4H). |
| 1716 | 494.31 | 1.52 | |
| 1717 | 524.52 | 2.49 | |
| 1718 | 447.08 | 2.71 | |
| 1719 | 511.31 | 2.49 | 1H NMR (400 MHz, DMSO) δ 12.91 (s, 1H), 8.20 - 8.14 (m, 2H), 7.92 - 7.89 (d, 1H), 7.53 - 7.50 (dd, 1H), 7.33 - 7.30 (d, 1H), 6.68 (s, 1H), 6.59 - 6.55 (m, 3H), 3.70(s, 3H), 2.26 (s, 3H), 2.26 - 2.17 (m, 1H), 1.89 - 1.82 (m, 1 H), 1.50 (s, 3H), 1.47 (s, 3H), 1.45 - 1.35 (m, 1H), 0.88 - 0.86 (d, 3H) |
| 1720 | 492.10 | 2.12 | |
| 1721 | 534.18 | 1.98 | |
| 1722 | 508.31 | 2.64 | |
| 1723 | 586.30 | 2.00 | 1H NMR (400 MHz, DMSO) δ 13.01 - 11.30 (m, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.56 - 7.42 (m, 2H), 7.22 (t, J = 8.2 Hz, 2H), 6.91 (d, J = 10.6 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.58 (s, 2H), 3.84 (d, J = 6.4 Hz, 2H), 3.65 (s, 2H), 2.13 - 1.99 (m, 1H), 1.37 (s, 2H), 1.13 (s, 6H), 1.00 (d, J = 6.6 Hz, 6H), 0.46 (s, 2H), 0.28 (s, 2H). |
| 1724 | 556.20 | 2.02 | |
| 1725 | 458.30 | 1.36 | |
| 1726 | 522.35 | 1.65 | |
| 1727 | 525.30 | 2.35 | 1H NMR (400 MHz, DMSO) δ 8.63 (s, 3H), 8.09 (s, 3H), 7.61 - 7.53 (m, 4H), 7.48 - 7.37 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (m, 4H), 6.99 (dq, J = 13.5, 6.1 Hz, 7H), 6.52 - 6.38 (m, 4H), 6.17 - 6.02 (m, 6H), 4.37 (q, J = 7.1 Hz, 6H), 3.07 - 2.88 (m, 7H), 2.19 (s, 8H), 2.17 - 2.04 (m, 1H), 1.81 (q, J = 8.4, 7.7 Hz, 3H), 1.61 (s, 8H), 1.57 (s, 8H), 1.41 - 1.30 (m, 11H), 0.84 (d, J = 6.0 Hz, 9H). |
| 1728 | | | 1H NMR (400 MHz, DMSO) δ 8.61 (d, J = 2.3 Hz, 1H), 8.11 - 8.01 (m, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 6.97 (t, J = 6.9 Hz, 2H), 6.48 (d, J = 8.3 Hz, 1H), 6.20 (s, 2H), 5.16 (h, J = 6.2 Hz, 1H), 2.98 (t, J = 10.6 Hz, 1H), 2.92 - 2.82 (m, 1H), 2.17 (s, 3H), 2.10 (t, J = 8.0 Hz, 1H), 1.81 (dd, J = 11.4, 5.6 Hz, 1H), 1.75 - 1.64 (m, 2H), 1.61 (s, 3H), 1.56 (s, 3H), 1.36 (t, J = 11.9 Hz, 1H), 1.28 (d, J = 6.1 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 0.81 (d, J = 6.3 Hz, 3H). |
| 1729 | 570.20 | 2.07 | |
| 1730 | 534.30 | 1.91 | |
| 1731 | 496.30 | 1.29 | 1H NMR (400 MHz, DMSO-d6) δ 11.79 (s, 1H), 8.26 (dd, J = 4.9, 1.8 Hz, 1H), 8.08 (dd, J = 7.8, 1.8 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 7.8, 4.8 Hz, 1H), 6.73 (d, J = 7.4 Hz, 2H), 2.70 - 2.53 (m, 2H), 2.27 (s, 3H), 2.23 - 2.12 (m, 1H), 1.89 (dd, J = 12.1, 5.5 Hz, 1H), 1.51 (d, J = 2.0 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 0.77 (d, J = 6.3 Hz, 3H). |
| 1732 | 513.00 | 1.12 | 1H NMR (400 MHz, DMSO-d6) δ 12.80 (s, 1H), 8.30 (d, J = 2.8 Hz, 1H), 8.26 (dd, J = 4.7, 1.9 Hz, 1H), 8.03 (dd, J = 7.9, 1.9 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.76 (dd, J = 7.8, 4.8 Hz, 2H), 6.10 (d, J = 2.7 Hz, 1H), 3.98 (d, J = 6.6 Hz, 2H), 3.92 (d, J = 5.4 Hz, 2H), 2.05 (dq, J = 13.4, 6.8 Hz, 1H), 1.94 - 1.84 (m, 2H), 1.65 - 1.55 (m, 2H), 0.97 (dd, J = 7.9, 6.4 Hz, 12H). |
| 1733 | 527.22 | 1.46 | |
| 1734 | 474.09 | 2.57 | |
| 1735 | 496.20 | 1.53 | |
| 1736 | 486.33 | 1.49 | |
| 1737 | 568.20 | 2.00 | |
| 1738 | 496.31 | 1.14 | |
| 1739 | 552.40 | 1.70 | 1H NMR (400 MHz, DMSO) δ 12.57 - 12.26 (m, 2H), 7.69 (s, 0H), 7.57 - 7.36 (m, 3H), 7.19 - 7.02 (m, 7H), 6.93 (s, 3H), 6.74 - 5.97 (m, 4H), 3.52 (q, J = 6.9 Hz, 12H), 2.35 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (s, 9H), 2.18 (s, 4H), 1.85 (dd, J = 11.6, 5.7 Hz, 3H), 1.62 (s, 9H), 1.59 (s, 8H), 1.40 (t, J = 12.1 Hz, 3H), 1.13 (t, J = 6.9 Hz, 18H), 0.87 (d, J = 6.2 Hz, 9H), 3.05 - 2.58 (m, 6H). |
| 1740 | 538.22 | 1.37 | |
| 1741 | 553.40 | 2.75 | 1H NMR (400 MHz, DMSO-d6) δ 8.63 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.02 (s, 2H), 6.51 (d, J = 8.7 Hz, 1H), 6.23 (s, 2H), 4.10 (d, J = 6.6 Hz, 2H), 2.87 (s, 2H), 2.21 (s, 3H), 2.19 - 1.98 (m, 2H), 1.82 (dd, J = 11.7, 5.6 Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.83 (d, J = 6.4 Hz, 3H). |
| 1742 | 544.30 | 1.32 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 1H), 8.37 (d, J = 2.8 Hz, 0H), 8.26 (dd, J = 4.8, 1.9 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 8.06 (dd, J = 7.8, 1.8 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.79 (dd, J = 7.8, 4.9 Hz, 1H), 6.14 (d, J = 2.8 Hz, 1H), 4.35 - 4.28 (m, 2H), 3.74 - 3.67 (m, 2H), 3.50 (q, J = 7.0 Hz, 2H), 2.46 (d, J = 8.8 Hz, 2H), 2.22 - 2.03 (m, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.44 - 1.33 (m, 1H), 1.13 (t, J = 7.0 Hz, 3H), 0.74 (d, J = 6.3 Hz, 3H). |
| 1743 | 543.30 | 1.95 | 1H NMR (400 MHz, DMSO-d6) δ 12.51 (寬雙峰, 1H), 12.47 (s, 1H), 8.22 (d, J = 7.2 Hz, 1H), 8.00 (s, 1H), 7.81 (br t, J = 6.3 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.44 (t, J = 6.8 Hz, 1H), 4.01 (d, J = 6.7 Hz, 2H), 2.69 (d, J = 9.2 Hz, 2H), 2.21 (br m, 1H), 2.07 (七重峰, J = 6.6 Hz, 1H), 1.95 (s, 3H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.42 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 5H), 0.89 (d, J = 6.3 Hz, 3H). |
| 1744 | 539.53 | 2.10 | |
| 1745 | 526.21 | 1.18 | |
| 1746 | 568.50 | 1.99 | 1H NMR (400 MHz, DMSO) δ 12.43 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 9.7, 1.7 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.19 (dd, J = 7.3, 0.6 Hz, 1H), 6.90 (dt, J = 10.7, 2.3 Hz, 1H), 6.71 (dd, J = 8.4, 0.6 Hz, 1H), 6.49 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 2.69 (s, 2H), 2.12 - 1.98 (m, 1H), 1.77 (s, 2H), 1.69 (s, 6H), 0.99 (d, J = 6.7 Hz, 6H), 0.49 (d, J = 12.5 Hz, 4H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1747 | 510.16 | 1.47 | |
| 1748 | 511.20 | 1.34 | 1H NMR (400 MHz, DMSO) δ 7.59 (d, J = 7.6 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.40 (s, 1H), 7.16 (s, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.13 (s, 2H), 3.86 (s, 3H), 3.01 (t, J = 9.2 Hz, 2H), 2.44 (s, 3H), 2.12 (s, 1H), 1.82 (dd, J = 11.6, 5.6 Hz, 1H), 1.61 (s, 3H), 1.55 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 0.84 (d, J = 6.3 Hz, 3H). |
| 1749 | 486.40 | 2.76 | |
| 1750 | 556.00 | 2.08 | 1H NMR (400 MHz, DMSO) δ 12.30 (s, 1H), 10.56 (s, 1H), 7.83 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 7.9 Hz, 1H), 7.47 (s, 1H), 7.39 (d, J = 10.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 10.7 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.45 (d, J = 10.4 Hz, 1H), 2.36 (s, 1H), 2.07 (s, 3H), 1.83 (s, 1H), 1.57 (d, J = 18.9 Hz, 6H), 1.41 (d, J = 12.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.71 (d, J = 6.3 Hz, 3H). |
| 1751 | 517.32 | 2.45 | |
| 1752 | 527.30 | 1.38 | |
| 1753 | 429.07 | 1.97 | |
| 1754 | 554.20 | 1.98 | 1H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.64 (dt, J = 12.1, 6.0 Hz, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.35 (t, J = 9.1 Hz, 2H), 7.22 (d, J = 6.9 Hz, 1H), 6.92 - 6.85 (m, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.50 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 2.94 (dd, J = 10.2, 6.9 Hz, 1H), 2.60 (dd, J = 10.3, 7.3 Hz, 1H), 2.26 (dd, J = 14.1, 7.0 Hz, 1H), 2.00 (ddd, J = 14.6, 11.5, 6.1 Hz, 3H), 1.87 (dd, J = 11.9, 6.4 Hz, 1H), 1.66 (dd, J = 11.8, 8.2 Hz, 1H), 0.99 (t, J = 5.2 Hz, 10H), 0.68 - 0.38 (m, 2H). |
| 1755 | 534.42 | 2.82 | |
| 1756 | 522.42 | 2.92 | |
| 1757 | 509.21 | 1.36 | 1H NMR (DMSO(d6)) δ12.85 (s, 1H), 10.07 (s, 1H), 8.16 - 8.14 (dd, 1H), 8.00 - 7.97 (d, 2H), 7.89 (t, J = 7.80, 1H), 7.75 - 7.72 (dd, 1H), 7.69 - 7.66 (d, 2H), 7.54 - 7.51 (d, 1H), 7.17 - 7.14 (d, 1H), 6.60 - 6.57 (dd, 1H), 2.44 - 2.40 (m, 1H), 1.92 - 1.84 (m, 1H), 1.77 - 1.70 (m, 1H), 1.47 (s, 3H), 1.43 (s, 3H), 1.29 (t, J = 11.86, 1H), 0.70 - 0.68 (d, 3H) |
| 1758 | 542.60 | 1.63 | |
| 1759 | 590.40 | 2.09 | |
| 1760 | 529.40 | 1.68 | 1H NMR (400 MHz,甲醇-d4) δ 8.38 (dd, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 7.2, 2.3 Hz, 1H), 7.99 (d, J = 1.1 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.71 (s, 1H), 7.67 (d, J = 4.8 Hz, 1H), 7.50 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.55 - 6.47 (m, 1H), 4.54 (s, 1H), 3.74 - 3.70 (m, 2H), 2.92 (s, 2H), 2.31 (s, 1H), 2.04 (dd, J = 13.2, 6.7 Hz, 1H), 1.92 (dd, J = 11.8, 6.0 Hz, 1H), 1.64 (s, 6H), 1.01 (dd, J = 6.8, 2.0 Hz, 6H), 0.97 (d, J = 6.3 Hz, 3H). |
| 1761 | 527.22 | 2.10 | |
| 1762 | 670.00 | 3.60 | 1H NMR (400 MHz, DMSO-d6) δ 12.23 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.57 - 7.46 (m, 2H), 7.45 - 7.23 (m, 5H), 7.23 - 7.04 (m, 5H), 6.83 (dt, J = 10.9, 2.3 Hz, 1H), 6.33 (s, 2H), 5.24 (s, 2H), 3.61 (d, J = 6.6 Hz, 2H), 2.05 (s, 6H), 1.98 (dt, J = 13.4, 6.7 Hz, 1H), 0.96 (d, J = 6.6 Hz, 6H). |
| 1763 | 542.29 | 1.64 | |
| 1764 | 475.29 | 1.95 | |
| 1765 | 447.30 | 1.37 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 2H), 8.22 (dd, J = 7.3, 2.3 Hz, 1H), 7.81 (s, 1H), 7.62 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.43 (t, J = 6.8 Hz, 1H), 2.67 (d, J = 9.6 Hz, 2H), 2.22 (s, 1H), 1.86 (d, J = 5.8 Hz, 1H), 1.54 (d, J = 11.1 Hz, 6H), 1.27 (d, J = 5.0 Hz, 10H), 0.89 (d, J = 6.2 Hz, 3H). |
| 1766 | 480.28 | 1.36 | |
| 1767 | 487.30 | 2.90 | |
| 1768 | 549.50 | 2.14 | |
| 1769 | 447.98 | 1.58 | |
| 1770 | 516.41 | 2.28 | |
| 1771 | 494.50 | 1.71 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.69 - 7.57 (m, 3H), 7.20 (dd, J = 7.3, 0.7 Hz, 1H), 7.16 (d, J = 8.1 IIz, 1H), 7.09 - 7.04 (m, 1H), 6.68 (dd, J = 8.4, 0.8 Hz, 3H), 2.60 (d, J = 9.0 Hz, 2H), 2.33 (s, 6H), 2.22 (s, 1H), 1.87 (dd, J = 11.8, 5.6 Hz, 1H), 1.60 (d, J = 3.6 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1772 | 466.29 | 1.96 | |
| 1773 | 559.34 | 2.56 | |
| 1774 | 525.50 | 1.68 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (d, J = 8.6 Hz, 2H), 8.24 (d, J = 7.3 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.82 (t, J = 5.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.44 (t, J = 6.8 Hz, 1H), 4.69 (p, J = 6.0 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.72 (d, J = 9.2 Hz, 2H), 2.23 (s, 1H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.61 (s, 6H), 1.44 (t, J = 12.2 Hz, 1H), 1.29 (d, J = 6.0 Hz, 6H), 0.91 (d, J = 6.3 Hz, 3H). |
| 1775 | 523.32 | 1.90 | |
| 1776 | 512.51 | 3.00 | |
| 1777 | 548.23 | 2.54 | |
| 1778 | 545.23 | 2.58 | 1H NMR DMSO(d6) δ12.76 (s, 1H), 8.18 - 8.16 (dd, 1H), 8.06 (t, J = 7.80, 1H), 7.81 - 7.75 (m, 2H), 7.58 - 7.56 (m, 2H), 7.16 - 7.13 (d, 1H), 6.94 - 6.91 (d, 1H), 6.64 - 6.61 (dd, 1H), 5.30 (q, J = 11.76, 2H ), 3.64 (s, 3H), 1.89 - 1.81 (m, 2H), 1.75 - 1.69 (m, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.24 (t, J = 11.86, 1H), 0.58 - 0.56 (d, 3H) |
| 1779 | 515.15 | 1.72 | |
| 1780 | 515.21 | 1.61 | |
| 1781 | 556.00 | 1.85 | |
| 1782 | 491.20 | 2.41 | |
| 1783 | 613.30 | 1.36 | 1H NMR (400 MHz, DMSO) δ 8.62 (s, 1H), 8.10 (s, 1H), 7.94 (dd, J = 4.8, 1.8 Hz, 1H), 7.84 (dd, J = 7.5, 1.8 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.55 (dd, J = 7.5, 4.8 Hz, 1H), 6.29 (s, 2H), 4.48 - 4.39 (m, 2H), 3.81 - 3.74 (m, 2H), 3.63 - 3.57 (m, 2H), 3.51 - 3.46 (m, 2H), 3.42 (q, J = 7.0 Hz, 2H), 2.94 (p, J = 10.5 Hz, 2H), 2.20 (s, 3H), 2.08 (d, J = 10.6 Hz, 1H), 1.80 (dd, J = 11.4, 5.7 Hz, 1H), 1.58 (d, J = 12.5 Hz, 6H), 1.35 (t, J = 12.0 Hz, 1H), 1.08 (t, J = 7.0 Hz, 3H), 0.78 (d, J = 6.3 Hz, 3H). |
| 1784 | 501.30 | 1.48 | |
| 1785 | 550.30 | 1.71 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.19 - 8.11 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.22 (t, J = 7.5 Hz, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.65 - 2.56 (m, 2H), 2.23 (d, J = 9.1 Hz, 1H), 1.88 (dd, J = 12.0, 5.6 Hz, 1H), 1.60 (d, J = 4.6 Hz, 6H), 1.43 (t, J = 12.0 Hz, 1H), 0.88 (d, J = 6.2 Hz, 3H). |
| 1786 | 527.36 | 0.99 | |
| 1787 | 671.60 | 1.94 | 1H NMR (400 MHz, DMSO) δ 8.63 (d, J = 2.3 Hz, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.48 - 7.39 (m, 1H), 6.98 (dd, J = 7.5, 3.9 Hz, 2H), 6.47 (d, J = 8.3 Hz, 1H), 6.16 (s, 2H), 4.48 - 4.42 (m, 2H), 3.80 - 3.74 (m, 2H), 3.62 - 3.58 (m, 2H), 3.53 (ddd, J = 7.5, 5.3, 2.7 Hz, 3H), 3.48 (dd, J = 5.7, 3.7 Hz, 2H), 3.45 - 3.42 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (m, 2H), 3.04 - 2.88 (m, 2H), 2.20 (s, 3H), 2.11 (dd, J = 11.6, 5.8 Hz, 1H), 1.81 (dd, J = 11.5, 5.7 Hz, 1H), 1.61 (s, 3H), 1.56 (s, 3H), 1.36 (t, J = 11.9 Hz, 1H), 1.04 (d, J = 6.1 Hz, 6H), 0.82 (d, J = 6.3 Hz, 3H). |
| 1788 | 610.30 | 2.23 | |
| 1789 | 561.60 | 2.32 | |
| 1790 | 484.27 | 0.92 | |
| 1791 | 501.40 | 1.61 | 1H NMR (400 MHz, DMSO-d6) δ 12.63 (s, 1H), 12.54 (d, J = 6.0 Hz, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 8.08 (t, J = 1.9 Hz, 1H), 8.01 (dt, J = 7.4, 1.7 Hz, 1H), 7.83 (dd, J = 6.7, 4.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.57 - 7.47 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.82 - 2.64 (m, 2H), 2.31 - 2.17 (m, 0H), 1.89 (dd, J = 11.9, 5.6 Hz, 1H), 1.61 (d, J = 1.7 Hz, 6H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 1792 | 496.27 | 1.48 | |
| 1793 | 514.30 | 1.25 | |
| 1794 | 430.27 | 1.70 | 1H NMR (400 MHz, DMSO-d6) δ 8.18 - 8.16 (dd, 1H), 7.73 - 7.70 (dd, 1H), 7.865 (t, J = 7.80, 1H), 7.20 - 7.17 (d, 1H), 6.74 - 6.71 (d, 1H), 6.69 - 6.69 (dd, 1H), 2.94 - 2.84 (m, 21H), 2.72 - 2.65 (m, 1H), 1.99 - 1.92 ( m, 1H), 1.82 - 1.75 (m, 1H), 1.67 - 1.54 (m, 1H), 1.46 (s, 3H), 1.26 (s, 3H), 1.21 - 1.06 (m, 2H), 0.74 - 0.65 (m, 1H), 0.51 - 0.34 (m, 2H), 0.09 - 0.03 (m, 2H) |
| 1795 | 548.20 | 2.27 | |
| 1796 | 520.32 | 2.35 | |
| 1797 | 581.20 | 1.77 | 1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.21 - 7.13 (m, 4H), 7.13 - 7.07 (m, 1H), 6.83 (dt, J = 10.6, 2.3 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 4.56 (s, 1H), 3.83 (dd, J = 9.4, 6.2 Hz, 1H), 3.69 (dd, J = 9.5, 6.2 Hz, 1H), 3.46 - 3.35 (m, 3H), 2.06 (s, 6H), 1.95 (dp, J = 12.7, 6.3 Hz, 1H), 0.95 (d, J = 6.7 Hz, 3H). |
| 1798 | 499.31 | 2.48 | 1H NMR (400 MHz, DMSO-d6) δ 12.81 (s, 1H), 8.19 - 8.17 (dd, 1H), 8.06 (t, J = 7.91, 1H), 7.81 - 7.73 (m, 3H), 7.53 - 7.50 (dd, 1H), 7.38 - 7.21 (m, 3H), 6.64 - 6.61 (dd, 1H), 5.41 (s, 2H), 2.30 - 2.15 (m, 2H), 2.02 - 1.93 (m, 1H), 1.80 - 1.73 (m, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.30 (t, J = 11.86, 1H), 0.65 - 0.63 (d, 3H) |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1799 | 535.30 | 1.72 | 1H NMR (400 MHz, DMSO-d6) δ 12.66 (s, 1H), 12.54 (d, J = 6.2 Hz, 1H), 8.29 - 8.19 (m, 3H), 7.91 - 7.74 (m, 4H), 7.27 (d, J = 8.0 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.83 - 2.64 (m, 2H), 2.31 - 2.18 (m, 1H), 1.90 (dd, J = 12.0, 5.5 Hz, 1H), 1.61 (d, J = 3.9 Hz, 6H), 1.46 (t, J = 12.1 Hz, 1H), 0.92 (d, J = 6.3 Hz, 3H). |
| 1800 | 501.41 | 3.06 | |
| 1801 | 533.31 | 1.16 | |
| 1802 | 529.20 | 1.58 | |
| 1803 | 517.40 | 1.64 | |
| 1804 | 524.30 | 1.69 | |
| 1805 | 502.31 | 2.38 | |
| 1806 | 535.02 | 2.67 | |
| 1807 | 485.50 | 1.53 | |
| 1808 | 528.19 | 1.48 | |
| 1809 | 508.28 | 1.78 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.63 (t, J = 8.3 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.49 (s, 2H), 2.92 (p, J = 6.9 Hz, 1H), 2.56 (d, J = 8.7 Hz, 2H), 2.28 - 2.12 (m, 1H), 1.85 (dd, J = 11.8, 5.6 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.40 (t, J = 12.0 Hz, 1H), 1.24 (d, J = 7.0 Hz, 6H), 0.87 (d, J = 6.2 Hz, 3H). |
| 1810 | 494.60 | 1.63 | 1H NMR (400 MHz, DMSO-d6) δ 12.24 (s, 1H), 7.66 - 7.55 (m, 2H), 7.17 (d, J = 7.2 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.40 (s, 2H), 5.02 (td, J = 6.1, 3.1 Hz, 1H), 2.56 (d, J = 10.6 Hz, 1H), 2.20 (dt, J = 11.7, 6.0 Hz, 1H), 1.88 (ddt, J = 30.9, 11.8, 6.0 Hz, 2H), 1.51 (d, J = 2.8 Hz, 3H), 1.45 (d, J = 5.1 Hz, 3H), 1.37 (t, J = 12.0 Hz, 1H), 1.22 (dd, J = 19.8, 6.3 Hz, 3H), 0.97 - 0.82 (m, 9H). |
| 1811 | 531.35 | 1.24 | 1H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 12.55 (s, 1H), 8.27 (dd, J = 7.3, 2.1 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.45 (s, 2H), 6.77 (d, J = 7.8 Hz, 1H), 6.46 (t, J = 6.8 Hz, 1H), 2.84 - 2.73 (m, 2H), 2.70 (s, 3H), 2.24 (s, 1H), 1.81 (dd, J = 11.7, 5.6 Hz, 1H), 1.53 - 1.37 (m, 7H), 0.92 (d, J = 6.3 Hz, 3H). |
| 1812 | 613.30 | 1.47 | |
| 1813 | 485.20 | 2.18 | |
| 1814 | 524.22 | 1.97 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1815 | 592.30 | 2.02 | |
| 1816 | 536.22 | 1.85 | |
| 1817 | 570.20 | 2.07 | 1H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.38 (d, J = 9.7 Hz, 1H), 7.22 (dd, J = 19.7, 7.6 Hz, 2H), 6.88 (d, J = 10.7 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 3.82 (d, J = 6.6 Hz, 2H), 2.63 - 2.53 (m, 2H), 2.31 (dt, J = 17.2, 8.5 Hz, 1H), 2.25 - 2.12 (m, 1H), 2.05 (dt, J = 13.3, 6.6 Hz, 1H), 1.86 (td, J = 14.2, 7.1 Hz, 1H), 1.67 (dd, J = 11.7, 6.1 Hz, 1H), 1.61 (s, 3H), 1.52 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.2 Hz, 3H), 0.69 (t, J = 7.4 Hz, 3H). |
| 1818 | 514.21 | 1.42 | |
| 1819 | 490.29 | 1.52 | |
| 1820 | 482.24 | 0.76 | 1H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 9.57 (s, 1H), 8.25 (dd, J = 4.8, 1.8 Hz, 1H), 8.05 (dd, J = 7.8, 1.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.48 - 7.39 (m, 2H), 7.27 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.86 - 6.81 (m, 1H), 6.78 (dd, J = 7.8, 4.8 Hz, 1H), 2.14 (s, 1H), 1.85 (dd, J = 11.6, 5.6 Hz, 1H), 1.59 (d, J = 12.1 Hz, 6H), 1.40 (t, J = 12.2 Hz, 1H), 0.76 (d, J = 6.2 Hz, 3H). |
| 1821 | 566.40 | 2.24 | 1H NMR (400 MHz, DMSO) δ 12.40 (s, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.48 (d, J = 1.4 Hz, 1H), 7.43 (d, J = 10.1 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.7, 2.1 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.46 (s, 2H), 4.14 (d, J = 5.7 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 3.66 (t, J = 8.8 Hz, 1H), 3.35 (d, J = 9.9 Hz, 1H), 2.30 (s, 2H), 2.11 (s, 1H), 2.08 - 1.99 (m, 1H), 1.54 (d, J = 10.1 Hz, 1H), 1.39 (d, J = 7.9 Hz, 2H), 1.12 (d, J = 10.1 Hz, 1H), 1.04 (s, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.80 (d, J = 10.2 Hz, 1H). |
| 1822 | 510.53 | 1.06 | |
| 1823 | 505.31 | 1.34 | |
| 1824 | 491.30 | 1.16 | |
| 1825 | 526.13 | 1.42 | |
| 1826 | 517.32 | 2.03 | |
| 1827 | 494.20 | 2.49 | |
| 1828 | 511.31 | 2.52 | 1H NMR (400 MHz, DMSO) δ12.89 (s, 1H), 8.22 - 8.15 (m, 2H), 7.92 - 7.89 (d, 1H), 7.51 - 7.48 (dd, 1H), 7.37 - 7.30 (m, 2H), 6.85 - 6.82 (dd, 1H), 6.74 - 6.70 (m, 2H), 6.60 - 6.57 (dd, 1H), 3.94 (q, J = 7.04, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2H), 2.26 - 2.17 (m, 1H), 1.89 - 1.82 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.44 - 1.35 (m, 1H), 1.25 (t, J = 6.92, 3H), 0.88 - 0.86 (d, 3H) |
| 1829 | 480.28 | 0.99 | |
| 1830 | 515.20 | 1.58 | |
| 1831 | 519.12 | 2.38 | |
| 1832 | 541.30 | 1.72 | 1H NMR (400 MHz,甲醇-d4) δ 8.65 (d, J = 4.9 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.04 (t, J = 7.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.32 (d, J = 10.4 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 6.72 - 6.65 (m, 1H), 3.80 (d, J = 6.6 Hz, 2H), 3.09 (dd, J = 16.7, 7.0 Hz, 1H), 2.93 (t, J = 10.3 Hz, 1H), 2.36 (s, 1H), 2.16 - 2.01 (m, 1H), 1.92 (d, J = 6.3 Hz, 1H), 1.63 (s, 6H), 1.55 (t, J = 12.0 Hz, 1H), 1.03 (dd, J = 6.7, 1.9 Hz, 6H), 0.96 (d, J = 6.3 Hz, 3H). |
| 1833 | 545.23 | 2.34 | |
| 1834 | 459.39 | 2.54 | |
| 1835 | 610.20 | 2.22 | 1H NMR (400 MHz, DMSO) δ 12.53 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.46 (d, J = 10.0 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.46 (s, 2H), 4.19 (d, J = 13.8 Hz, 1H), 3.83 (d, J = 6.5 Hz, 2H), 3.62 (s, 1H), 3.04 (t, J = 12.4 Hz, 1H), 2.66 (s, 1H), 2.12 - 1.95 (m, 1H), 1.76 (s, 1H), 1.72 - 1.62 (m, 1H), 1.56 (d, J = 17.7 Hz, 2H), 0.97 (dd, J = 13.9, 6.7 Hz, 10H). |
| 1836 | 556.00 | 2.13 | 1H NMR (400 MHz, DMSO) δ 12.47 (s, 1H), 10.90 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.49 (s, 2H), 7.41 (d, J = 9.9 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 10.5 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.70 (s, 1H), 2.60 (s, 1H), 2.22 (s, 1H), 2.05 (s, 1H), 1.87 (s, 1H), 1.59 (s, 6H), 1.41 (s, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.84 (d, J = 6.2 Hz, 3H). |
| 1837 | 521.30 | 1.64 | |
| 1838 | 492.40 | 2.52 | |
| 1839 | 486.33 | 1.53 | |
| 1840 | 514.40 | 2.00 | 1H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.50 - 7.47 (m, 1H), 7.47 - 7.40 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 7.3, 0.6 Hz, 1H), 6.90 (dt, J = 10.8, 2.3 Hz, 1H), 6.69 (dd, J = 8.4, 0.6 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.46 (s, 2H), 4.45 (d, J = 8.0 Hz, 1H), 3.84 (d, J = 6.6 Hz, 2H), 3.61 - 3.53 (m, 1H), 3.32 (d, J = 6.8 Hz, 1H), 2.38 - 2.26 (m, 1H), 2.05 - 1.95 (m, 1H), 1.87 - 1.80 (m, 1H), 1.38 (d, J = 6.2 Hz, 3H), 1.00 - 0.95 (m, 6H). |
| 1841 | 500.21 | 2.37 | 1H NMR (400 MHz, DMSO) δ12.81 (s, 1H), 9.83 (s, 1H), 8.15 - 8.13 (dd, 1H), 7.93 - 7.86 (m, 2H), 7.75 - 7.72 (m, 2H), 7.55 - 7.52 (d, 1H), 7.26 (t, J = 8.13, 1H), 7.12 - 7.09 (d, 1H), 6.99 - 6.96 (dd, 1H), 6.55 - 6 .52 (dd, 1H), 1.91 (m, 1H), 1.79 - 1.72 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.31 (t, J = 12.09, 1H), 0.72 - 0.70 (d, 3H) |
| 1842 | 495.40 | 2.60 | |
| 1843 | 524.29 | 1.74 | |
| 1844 | 514.30 | 1.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 8.24 (dd, J = 4.8, 1.9 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 7.8, 2.0 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.68 (寬單峰, 2H), 6.08 (d, J = 2.8 Hz, 1H), 4.95 - 4.77 (m, 1H), 2.44 (m, 2H部分與溶劑峰重疊), 2.12 (br s, 1H), 1.85 (dd, J = 11.8, 5.6 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.41-1.38 (m, 1H與以下信號重疊), 1.34-1.31 (m, 6H), 0.74 (d, J = 6.2 Hz, 3H). |
| 1845 | 538.60 | 1.32 | |
| 1846 | 588.50 | 1.65 | |
| 1847 | 528.26 | 1.45 | |
| 1848 | 511.50 | 1.53 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 12.53 (d, J = 6.3 Hz, 1H), 8.24 (dd, J = 7.2, 2.2 Hz, 1H), 7.86 - 7.79 (m, 1H), 7.73 - 7.65 (m, 2H), 7.40 - 7.31 (m, 1H), 7.13 (dd, J = 11.0, 8.1 Hz, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.45 (t, J = 6.9 Hz, 1H), 4.10 (q, J = 6.9 Hz, 2H), 2.77 - 2.71 (m, 2H), 2.24 (s, 1H), 1.86 (dd, J = 11.8, 5.6 Hz, 1H), 1.55 (s, 7H), 1.43 (t, J = 12.2 Hz, 1H), 1.34 (t, J = 6.9 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). |
| 1849 | 491.23 | 1.63 | |
| 1850 | 474.30 | 0.94 | 1H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 8.24 (dd, J = 4.8, 1.9 Hz, 1H), 8.03 (dd, J = 7.9, 2.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 6.94-6.58 (m, 2H), 6.77 (dd, J = 7.9, 4.8 Hz, 1H, 由先前信號遮蔽), 6.54 (d, J = 7.8 Hz, 1H), 4.00 - 3.85 (m, 2H), 3.53 - 3.30 (m, 2H), 2.89 - 2.73 (m, 1H), 2.49 - 2.37 (m, 2H), 2.17 - 2.04 (m, 1H), 1.86 - 1.61 (m, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 5H), 1.52 (s, 6H), 1.36 (t, J = 12.0 Hz, 1H), 0.74 (d, J = 6.3 Hz, 3H). |
| 1851 | 514.22 | 1.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 1H), 8.24 (dd, J = 4.9, 1.8 Hz, 1H), 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 7.91 - 7.81 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.9 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 3.89 (s, 3H), 2.53 (d, J = 10.6 Hz, 1H), 2.14 (s, 1H), 2.06 (s, 1H), 1.85 (dd, J = 11.9, 5.7 Hz, 1H), 1.58 (d, J = 12.2 Hz, 7H), 1.39 (t, J = 12.1 Hz, 1H), 0.75 (d, J = 6.3 Hz, 3H). |
| 1852 | 522.20 | 1.64 | 1H NMR (400 MHz, DMSO) δ 12.38 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.61 - 7.53 (m, 1H), 7.34 - 7.26 (m, 2H), 7.21 (dd, J = 7.1, 5.5 Hz, 3H), 7.13 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.36 (s, 1H), 2.80 (d, J = 11.1 Hz, 2H), 2.62 (dd, J = 17.8, 11.4 Hz, 1H), 2.54 (s, 1H), 2.37 (dd, J = 27.9, 9.4 Hz, 1H), 2.00 (dd, J = 27.6, 18.9 Hz, 1H), 1.57 (s, 5H), 1.48 (s, 3H), 1.28 (s, 9H). |
| 1853 | 528.14 | 1.59 | |
| 1854 | 502.52 | 1.03 | |
| 1855 | 556.20 | 1.85 | 1H NMR (400 MHz, DMSO) δ 8.40 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.82 - 7.54 (m, 3H), 7.52 - 7.41 (m, 1H), 7.25 - 7.16 (m, 1H), 6.96 (dd, J = 42.8, 10.7 Hz, 1H), 6.70 (t, J = 8.3 Hz, 1H), 6.37 (s, 1H), 3.86 (dd, J = 12.1, 6.6 Hz, 2H), 3.58 (d, J = 9.5 Hz, 2H), 3.26 (d, J = 11.5 Hz, 1H), 2.82 (dt, J = 24.3, 11.1 Hz, 1H), 2.06 - 1.99 (m, 3H), 1.93 - 1.74 (m, 1H), 1.73 - 1.48 (m, 2H), 1.41 - 1.27 (m, 2H), 1.01 - 0.81 (m, 14H). |
| 1856 | 515.40 | 1.69 | |
| 1857 | 516.23 | 1.51 | |
| 1858 | 515.17 | 1.58 | |
| 1859 | 469.40 | 1.55 | 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.45 (s, 1H), 8.31 (d, J = 7.3 Hz, 1H), 8.15 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.32 (s, 1H), 7.25 (s, 1H), 7.05 (d, J = 8.2 Hz, 1H), 4.02 (s, 3H), 2.83 - 2.64 (m, 1H), 2.59 - 2.53 (m, 1H, 由溶劑峰遮蔽), 2.43 (s, 3H), 2.28 - 2.13 (m, 1H), 1.84 (dd, J = 11.8, 5.8 Hz, 1H), 1.60 (d, J = 3.7 Hz, 6H), 1.37 (t, J = 12.0 Hz, 1H), 0.78 (d, J = 6.2 Hz, 3H). |
| 1860 | 524.25 | 1.63 | |
| 1861 | 497.27 | 1.58 | |
| 1862 | 495.40 | 1.68 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1863 | 556.20 | 2.01 | |
| 1864 | 556.00 | 1.85 | |
| 1865 | 487.30 | 1.88 | |
| 1866 | 511.15 | 1.33 | |
| 1867 | 529.36 | 1.13 | |
| 1868 | 458.40 | 1.69 | |
| 1869 | 514.15 | 1.45 | |
| 1870 | 476.19 | 2.17 | |
| 1871 | 494.60 | 1.45 | |
| 1872 | 500.21 | 2.64 | 1H NMR (400 MHz, DMSO-d6) δ12.70 (s, 1H), 8.93 (s, 1H), 8.25 - 8.22 (d, 1H), 8.15 - 8.13 (dd, 1H), 7.88 (t, J = 7.91, 1H), 7.62 - 7.59 (dd, 1H), 7.53 - 7.48 (m, 2H), 7.35 - 7.32 (d, 1H), 7.27 (t, J = 7.91, 1H), 7.08 (t, J = 7.91, 1H), 6.53 - 6.50 (dd, 1H), 2.03 - 1.94 (m, 1H), 1.82 - 1.75 (m, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.33 (t, J = 11.91, 1H), 0.79 - 0.77 (d, 3H) |
| 1873 | 484.27 | 0.94 | |
| 1874 | 487.30 | 2.59 | |
| 1875 | 518.22 | 1.47 | 1H NMR (400 MHz, DMSO-d6) δ9.28 - 9.26 (dd, 1H), 9.17 - 9.14 (d, 1H), 8.44 - 8.41 (d, 1H), 8.33 (t, J = 7.80, 1H), 8.23 - 8.22 (d, 1H), 8.14 - 8.12 (dd, 1H), 8.06 - 8.00 (m, 2H), 7.82 - 7.78 (dd, 1H), 6.75 - 6.72 (d, 1H), 7.50 - 7.47 (dd, 1H), 6.53 - 6.50 (dd, 1H), 2.33 - 2.22 (m, 1H), 1.88 - 1.81 (m, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.39- 1.34 (m, 1H), 0.89 - 0.87 (d, 3H) |
| 1876 | 570.00 | 2.23 | 1H NMR (400 MHz, DMSO) δ 12.39 (s, 1H), 7.94 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.40 (d, J = 10.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 10.7 Hz, 1H), 3.83 (d, J = 6.7 Hz, 2H), 3.31 (s, 3H), 2.41 (s, 1H), 2.32 (s, 1H), 2.04 (s, 2H), 1.84 (d, J = 11.9 Hz, 1H), 1.57 (d, J = 18.4 Hz, 6H), 1.38 (s, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.65 (d, J = 6.2 Hz, 3H). |
| 1877 | 549.43 | 1.81 | |
| 1878 | 527.20 | 1.47 | |
| 1879 | 537.43 | 1.63 | |
| 1880 | 511.14 | 1.59 | |
| 1881 | 445.28 | 2.38 | |
| 1882 | 591.60 | 1.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 7.74 - 7.66 (m, 1H), 7.66 - 7.59 (m, 1H), 7.18 (dd, J = 7.2, 2.5 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.82 (s, 1H), 6.69 (dd, J = 10.1, 8.0 Hz, 1H), 4.19 (q, J = 18.4, 17.6 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2H), 3.35 (t, J = 5.7 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.54 (d, J = 8.8 Hz, 1H), 2.41 (s, 2H), 2.12 (dq, J = 13.4, 6.7 Hz, 1H), 1.85 (dd, J = 11.7, 5.7 Hz, 1H), 1.53 (d, J = 7.3 Hz, 1H), 1.51 (s, 3H), 1.39 - 1.33 (m, 1H), 1.17 (t, J = 7.3 Hz, 1H), 1.05 (s, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.99 - 0.92 (m, 1H), 0.89 (t, J = 3.1 Hz, 1H), 0.86 (d, J = 6.3 Hz, 3H). |
| 1883 | 562.40 | 1.54 | |
| 1884 | 473.19 | 2.73 | |
| 1885 | 556.00 | 2.04 | 1H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 10.18 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 25.5 Hz, 5H), 7.26 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 6.89 (d, J = 10.6 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.39 (s, 1H), 2.08 (d, J = 42.4 Hz, 2H), 1.84 (s, 1H), 1.58 (d, J = 17.2 Hz, 6H), 1.39 (s, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.72 (d, J = 6.2 Hz, 3H). |
| 1886 | 497.27 | 1.36 | |
| 1887 | 535.40 | 1.59 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.23 (d, J = 3.7 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 8.02 (dd, J = 7.8, 1.9 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.76 (dd, J = 7.8, 4.8 Hz, 1H), 6.68 (寬單峰, 2H), 6.12 (d, J = 2.8 Hz, 1H), 3.97 (s, 2H), 2.46 (d, J = 7.8 Hz, 2H), 2.20 - 2.02 (br m, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.38 (t, J = 12.2 Hz, 1H), 0.74 (d, J = 6.3 Hz, 3H). |
| 1888 | 482.30 | 1.59 | 1H NMR (400 MHz, DMSO-d6) δ 8.03 (t, J = 2.5 Hz, 1H), 7.47 (dd, J = 4.0, 2.5 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.42 (d, J = 8.1 Hz, 1H), 6.08 (d, J = 3.1 Hz, 1H), 6.01 (s, 2H), 2.97 (ddd, J = 31.6, 19.5, 11.1 Hz, 3H), 2.09 (d, J = 15.9 Hz, 1H), 1.85 - 1.63 (m, 3H), 1.48 (dt, J = 4.5, 2.5 Hz, 7H), 1.43 - 1.25 (m, 2H), 1.25 - 0.91 (m, 3H), 0.85 (d, J = 6.3 Hz, 3H). |
| 1889 | 538.34 | 1.78 | 1H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 8.50 (d, J = 2.4 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 17.8 Hz, 2H), 6.87 - 6.58 (m, 2H), 6.48 (s, 2H), 4.69 (p, J = 6.1 Hz, 1H), 2.33 (s, 3H), 2.20 (s, 1H), 1.85 (dd, J = 11.9, 5.7 Hz, 1H), 1.54 (d, J = 7.2 Hz, 6H), 1.40 (t, J = 12.0 Hz, 1H), 1.28 (d, J = 6.0 Hz, 6H), 0.86 (d, J = 6.3 Hz, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1890 | 581.20 | 1.76 | 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.21 - 7.14 (m, 4H), 7.14 - 7.07 (m, 1H), 6.84 (dt, J = 10.6, 2.3 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 4.61 (s, 1H), 3.61 (s, 2H), 2.07 (s, 1H), 2.06 (s, 6H), 1.19 (s, 6H). |
| 1891 | 536.50 | 1.35 | 1H NMR (400 MHz, DMSO-d6) δ 12.24 (s, 1H), 7.66 - 7.55 (m, 2H), 7.17 (dd, J = 7.3, 0.7 Hz, 1H), 6.66 (dd, J = 8.4, 0.8 Hz, 1H), 6.44 (s, 2H), 5.03 (dt, J = 10.8, 6.2 Hz, 1H), 3.86 (s, 2H), 3.28 (dd, J = 12.8, 10.6 Hz, 2H), 2.63 - 2.51 (m, 1H), 2.43 (t, J = 8.8 Hz, 1H), 2.19 (dq, J = 11.9, 6.2 Hz, 1H), 1.83 (dd, J = 12.0, 5.9 Hz, 2H), 1.72 - 1.51 (m, 2H), 1.51 (s, 3H), 1.47 - 1.19 (m, 9H), 0.85 (d, J = 6.3 Hz, 3H). |
| 1892 | 494.20 | 2.42 | |
| 1893 | 563.60 | 2.26 | |
| 1894 | 552.39 | 1.98 | |
| 1895 | 528.20 | 1.52 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 8.24 (d, J = 4.8 Hz, 1H), 8.02 (dd, J = 7.9, 1.9 Hz, 1H), 7.92 (d, J = 1.0 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 0.9 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 7.8, 4.8 Hz, 1H), 6.67 (dd, J = 7.7, 4.8 Hz, 1H), 3.74 (d, J = 6.4 Hz, 2H), 2.14 (s, 1H), 2.01 (dt, J = 13.3, 6.6 Hz, 1H), 1.86 (dd, J = 11.9, 5.6 Hz, 1H), 1.56 (d, J = 5.3 Hz, 6H), 1.39 (t, J = 12.1 Hz, 1H), 0.96 (d, J = 6.7 Hz, 6H), 0.75 (d, J = 6.3 Hz, 3H). |
| 1896 | 529.30 | 1.80 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 2H), 8.23 (d, J = 7.2 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.87 - 7.72 (m, 2H), 6.88 (d, J = 8.3 Hz, 1H), 6.44 (寬三重峰, 1H), 6.11 (d, J = 2.6 Hz, 1H), 3.98 (d, J = 6.6 Hz, 2H), 2.72-2.70 (m , 2H), 2.22 (br s, 1H), 2.05 (sep, J = 8.0 1H), 1.88 (dd, J = 11.8, 5.5 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.43 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.89 (d, J = 6.3 Hz, 3H). |
| 1897 | 516.36 | 1.50 | |
| 1898 | 480.10 | 2.33 | |
| 1899 | 533.22 | 2.84 | |
| 1900 | 526.30 | 1.59 | |
| 1901 | 570.50 | 2.10 | 1H NMR (400 MHz, DMSO) δ 12.55 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.3, 7.4 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.47 - 7.38 (m, 1H), 7.30 (d, J = 7.9 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.24 - 7.17 (m, 1H), 6.88 (dt, J = 10.7, 2.3 Hz, 1H), 6.73 - 6.67 (m, 1H), 6.48 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 3.60 (s, 2H), 3.16 (t, J = 5.9 Hz, 2H), 2.09 - 1.99 (m, 1H), 1.55 (d, J = 4.7 Hz, 2H), 1.45 (s, 2H), 1.35 - 1.25 (m, 2H), 0.99 (d, J = 6.7 Hz, 6H), 0.83 (s, 6H). |
| 1902 | 509.21 | 2.59 | |
| 1903 | 524.34 | 1.50 | 1H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 8.25 (dd, J = 4.8, 1.8 Hz, 1H), 8.05 (dd, J = 7.8, 1.7 Hz, 1H), 7.98 (d, J = 8.9 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.78 (dd, J = 7.8, 4.8 Hz, 1H), 4.69 (dt, J = 12.0, 6.0 Hz, 1H), 2.57 - 2.51 (m, 2H), 2.15 (s, 1H), 1.85 (dd, J = 11.8, 5.6 Hz, 1H), 1.60 (s, 3H), 1.58 (s, 3H), 1.40 (t, J = 12.1 Hz, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 0.76 (d, J = 6.3 Hz, 3H). |
| 1904 | 533.31 | 1.12 | |
| 1905 | 494.20 | 2.32 | 1H NMR (400 MHz, DMSO) δ 12.41 (s, 1H), 8.19 - 8.15 (m, 1H), 7.80 - 7.77 (d, 1H), 7.63 - 7.54 (m, 1H), 7.45 - 7.42 (d, 2H), 7.33 - 7.06 (m, 4H), 6.75 - 6.53 (m, 2H), 5.14 - 5.12 (d, 1H), 2.21 (t, J = 10.66, 1H), 1. 88 - 1.81 (m, 1H), 1.72 - 1.65 (m, 1H), 1.52 - 1.43 (m, 9H), 1.22 (t, J = 11.65, 1H), 0.85 - 0.83 (d, 1H), 0.56 - 0.54 (d, 2H) |
| 1906 | 534.12 | 2.82 | |
| 1907 | 552.50 | 1.08 | |
| 1908 | 473.19 | 2.70 | |
| 1909 | 506.21 | 2.75 | 1H NMR (400 MHz, DMSO) δ 12.71 (s, 1H), 9.45 (s, 1H), 8.15 - 8.13 (dd, 1H), 7.83 - 7.70 (m, 3H), 7.47 - 7.44 (dd, 1H), 7.42 - 7.39 (d, 1H), 7.10 - 7.07 (d, 1H), 7.05 - 7.02 (d, 1H), 6.52 - 6.49 (dd, 1H), 2.80 - 2.6 1 (m, 3H), 1.96 - 1.90 (m, 2H), 1.75 - 1.69 (m, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.29 (t, J = 11.91, 1H), 0.72 - 0.70 (d, 3H) |
| 1910 | 498.23 | 1.63 | |
| 1911 | 460.40 | 1.34 | |
| 1912 | 512.40 | 1.82 | 1H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 8.02 - 7.97 (m, 2H), 7.92 (d, J = 1.0 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.76 - 7.71 (m, 1H), 7.70 - 7.63 (m, 3H), 7.04 (d, J = 8.3 Hz, 1H), 3.73 (d, J = 6.4 Hz, 2H), 2.43 (t, J = 10.4 Hz, 1H), 2.34 - 2.25 (m, 1H), 2.10 (dq, J = 12.0, 6.1 Hz, 1H), 2.01 (dq, J = 13.3, 6.7 Hz, 1H), 1.88 - 1.79 (m, 1H), 1.54 (d, J = 8.1 Hz, 6H), 1.38 (t, J = 12.1 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 0.96 (d, J = 6.7 Hz, 6H), 0.66 (d, J = 6.3 Hz, 3H). |
| 1913 | 533.31 | 1.09 | 1H NMR (400 MHz, DMSO) δ 12.67 (s, 1H), 12.54 (s, 1H), 8.88 (d, J = 1.7 Hz, 1H), 8.42 (d, J = 2.8 Hz, 1H), 8.25 (dd, J = 7.3, 2.2 Hz, 1H), 8.04 (d, J = 1.7 Hz, 1H), 7.83 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.49 - 6.42 (m, 1H), 3.93 (s, 3H), 2.73 (tt, J = 16.6, 8.3 Hz, 2H), 2.25 (d, J = 4.1 Hz, 1H), 1.90 (dd, J = 12.0, 5.5 Hz, 1H), 1.61 (d, J = 2.4 Hz, 6H), 1.46 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 1914 | 533.31 | 1.18 | |
| 1915 | 552.30 | 1.63 | 1H NMR (400 MHz, DMSO) δ 8.72 (d, J = 2.5 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 6.98 (dd, J = 13.6, 7.5 Hz, 2H), 6.45 (d, J = 8.1 Hz, 1H), 6.11 (s, 2H), 3.23 (q, J = 6.8 Hz, 4H), 3.04 - 2.88 (m, 2H), 2.27 (d, J = 5.1 Hz, 3H), 2.12 (qd, J = 12.2, 11.5, 5.2 Hz, 1H), 1.83 - 1.75 (m, 1H), 1.62 (s, 2H), 1.57 (s, 2H), 1.35 (d, J = 11.9 Hz, 1H), 1.05 (t, J = 6.9 Hz, 6H), 0.84 (d, J = 6.3 Hz, 4H). |
| 1916 | 472.30 | 1.70 | |
| 1917 | 495.40 | 2.60 | |
| 1918 | 550.38 | 1.88 | |
| 1919 | 501.41 | 3.02 | |
| 1920 | 500.50 | 1.44 | |
| 1921 | 534.25 | 1.75 | |
| 1922 | 498.50 | 1.67 | |
| 1923 | 510.16 | 1.36 | |
| 1924 | 511.31 | 2.48 | |
| 1925 | 485.50 | 1.56 | |
| 1926 | 523.32 | 2.90 | |
| 1927 | 497.40 | 1.40 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (s, 1H), 8.25 (dd, J = 7.3, 2.2 Hz, 1H), 7.83 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.66 - 7.57 (m, 2H), 7.40 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.05 - 6.96 (m, 1H), 6.45 (t, J = 6.8 Hz, 1H), 3.82 (s, 3H), 2.79 - 2.65 (m, 2H), 2.30 - 2.17 (m, 1H), 1.89 (dd, J = 11.9, 5.5 Hz, 1H), 1.62 (d, J = 1.7 Hz, 6H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 1928 | 528.40 | 2.25 | |
| 1929 | 549.13 | 2.85 | |
| 1930 | 498.23 | 1.65 | |
| 1931 | 538.40 | 2.65 | |
| 1932 | 472.29 | 2.49 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 1933 | 517.32 | 1.70 | |
| 1934 | 551.50 | 1.82 | 1H NMR (400 MHz, DMSO-d6) δ 12.64 (s, 1H), 12.56 - 12.50 (m, 1H), 8.28 - 8.21 (m, 1H), 8.10 - 8.02 (m, 2H), 7.83 (t, J = 6.3 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.45 (t, J = 6.7 Hz, 1H), 2.81 - 2.65 (m, 2H), 2.25 (s, 1H), 1.90 (dd, J = 12.2, 5.5 Hz, 1H), 1.60 (d, J = 3.6 Hz, 6H), 1.45 (t, J = 12.2 Hz, 1H), 0.91 (d, J = 6.2 Hz, 3H). |
| 1935 | 548.60 | 1.72 | |
| 1936 | 473.19 | 2.85 | |
| 1937 | 545.23 | 1.42 | |
| 1938 | 480.10 | 2.21 | |
| 1939 | 489.10 | 2.19 | |
| 1940 | 524.52 | 2.48 | |
| 1941 | 518.22 | 2.63 | |
| 1942 | 618.70 | 1.47 | |
| 1943 | 554.34 | 1.46 | |
| 1944 | 498.53 | 1.05 | |
| 1945 | 510.31 | 1.42 | |
| 1946 | 499.50 | 1.60 | |
| 1947 | 494.28 | 1.44 | |
| 1948 | 569.30 | 1.49 | |
| 1949 | 508.31 | 2.00 | |
| 1950 | 534.28 | 1.80 | |
| 1951 | 494.57 | 1.10 | |
| 1952 | 542.60 | 1.99 | 1H NMR (400 MHz, DMSO-d6) δ 12.35 (s, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.62 (寬單峰, 1H), 7.18 (d, J = 7.0 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.50 (br s, 2H), 6.13 (s, 1H), 3.89 (s, 2H), 2.59 (br s, 2H), 2.20 (br s, 1H), 1.93 - 1.82 (m, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.41 (t, J = 12.1 Hz, 1H), 1.00 (s, 9H), 0.88 (d, J = 6.3 Hz, 3H). |
| 1953 | 549.43 | 2.72 | |
| 1954 | 503.30 | 1.52 | |
| 1955 | 521.22 | 2.49 | |
| 1956 | 569.50 | 2.27 | |
| 1957 | 502.31 | 2.10 | |
| 1958 | 466.28 | 1.33 | |
| 1959 | 496.60 | 2.30 | |
| 1960 | 535.30 | 1.53 | 1H NMR (400 MHz, DMSO-d6) δ 12.63 (s, 1H), 12.55 (d, J = 4.9 Hz, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.88 - 7.78 (m, 2H), 7.76 - 7.71 (m, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.45 (t, J = 6.8 Hz, 1H), 2.78 - 2.65 (m, 2H), 2.28 - 2.14 (m, 1H), 1.82 (dd, J = 11.8, 5.6 Hz, 1H), 1.48 - 1.35 (m, 7H), 0.90 (d, J = 6.3 Hz, 3H). |
| 1961 | 553.20 | 2.26 | |
| 1962 | 496.28 | 0.92 | |
| 1963 | 514.21 | 1.82 | |
| 1964 | 524.25 | 1.54 | |
| 1965 | 511.31 | 2.52 | |
| 1966 | 520.40 | 1.80 | 1H NMR (400 MHz, DMSO-d6) δ 12.23 (s, 1H), 7.66 - 7.54 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.44 (s, 1H), 5.09 (td, J = 6.4, 3.8 Hz, 1H), 2.59 - 2.51 (m, 1H), 2.43 (dd, J = 10.7, 5.8 Hz, 1H), 2.15 (dt, J = 16.6, 8.6 Hz, 3H), 1.83 (dd, J = 11.9, 5.5 Hz, 1H), 1.70 (d, J = 11.9 Hz, 2H), 1.52 (d, J = 17.4 Hz, 7H), 1.44 (d, J = 4.6 Hz, 3H), 1.38 (d, J = 12.1 Hz, 1H), 1.28 (d, J = 6.1 Hz, 2H), 1.23 (d, J = 6.2 Hz, 2H), 0.85 (d, J = 6.3 Hz, 3H). |
| 1967 | 490.32 | 1.50 | |
| 1968 | 548.23 | 2.62 | |
| 1969 | 538.40 | 2.66 | 1H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.62 (q, J = 7.4, 6.9 Hz, 3H), 7.38 (t, J = 7.9 Hz, 1H), 7.21 (dd, J = 7.6, 5.4 Hz, 2H), 7.00 (dd, J = 8.2, 2.3 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.48 (s, 1H), 3.81 (d, J = 6.6 Hz, 2H), 2.64 - 2.57 (m, 2H), 2.22 (dt, J = 13.4, 7.1 Hz, 1H), 2.04 (dq, J = 13.4, 6.7 Hz, 1H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.42 (t, J = 12.0 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.2 Hz, 3H). |
| 1970 | 528.40 | 1.62 | |
| 1971 | 528.42 | 2.68 | |
| 1972 | 511.31 | 2.45 | |
| 1973 | 583.70 | 1.68 | |
| 1974 | 472.50 | 1.58 | 1H NMR (400 MHz, DMSO) δ 12.35 (s, 1H), 7.58 (d, J = 7.1 Hz, 2H), 7.14 (d, J = 7.1 Hz, 1H), 6.77 - 6.56 (m, 2H), 6.42 (s, 2H), 2.79 (s, 1H), 2.66 (dd, J = 12.3, 10.5 Hz, 1H), 1.69 (d, J = 20.9 Hz, 2H), 1.56 (s, 3H), 1.51 (s, 3H), 1.27 (s, 9H), 1.17 - 1.05 (m, 1H), 0.73 - 0.63 (m, 1H), 0.58 - 0.47 (m, 1H), 0.40 (dd, J = 8.2, 3.9 Hz, 1H), 0.24 (dd, J = 9.0, 4.1 Hz, 1H), 0.07 (dd, J = 9.0, 4.0 Hz, 1H). |
| 1975 | 542.30 | 1.65 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.24 (dd, J = 4.7, 1.9 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 7.8, 1.9 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.69 (寬單峰, 2H), 6.14 (d, J = 2.7 Hz, 1H), 3.89 (s, 2H), 2.45 (d, J = 8.9 Hz, 2H), 2.12 (br s, 1H), 1.85 (dd, J = 11.9, 5.4 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.43 - 1.33 (m, 1H), 1.00 (s, 9H), 0.74 (d, J = 6.2 Hz, 3H). |
| 1976 | 567.00 | 2.19 | 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.67 (d, J = 4.7 Hz, 1H), 8.43 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.53 - 7.42 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.31 (p, J = 6.3 Hz, 1H), 2.41 (s, 2H), 2.25 (s, 3H), 2.18 (dt, J = 16.2, 7.6 Hz, 1H), 1.88 (dd, J = 12.1, 5.8 Hz, 1H), 1.55 (d, J = 4.4 Hz, 6H), 1.42 (t, J = 12.0 Hz, 1H), 1.31 (d, J = 6.1 Hz, 6H), 0.74 (d, J = 6.3 Hz, 3H). |
| 1977 | 550.33 | 2.61 | |
| 1978 | 508.31 | 2.63 | |
| 1979 | 538.30 | 1.77 | |
| 1980 | 497.20 | 1.30 | |
| 1981 | 521.61 | 1.73 | |
| 1982 | 506.25 | 1.26 | |
| 1983 | 514.31 | 2.67 | |
| 1984 | 609.60 | 1.41 | |
| 1985 | 529.32 | 1.98 | |
| 1986 | 542.23 | 2.86 | |
| 1987 | 534.12 | 2.79 | |
| 1988 | 487.30 | 2.88 | |
| 1989 | 518.22 | 2.19 | |
| 1990 | 495.40 | 1.54 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (d, J = 6.3 Hz, 1H), 8.25 (dd, J = 7.3, 2.2 Hz, 1H), 7.82 (dt, J = 6.5, 3.4 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.19 - 7.06 (m, 3H), 6.64 (d, J = 7.8 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.79 - 2.69 (m, 2H), 2.29 (s, 3H), 2.24 (s, 4H), 1.84 (dd, J = 11.9, 5.7 Hz, 1H), 1.49 (d, J = 6.2 Hz, 6H), 1.41 (t, J = 12.0 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 1991 | 508.32 | 1.12 | |
| 1992 | 487.30 | 2.39 | |
| 1993 | 556.00 | 1.85 | |
| 1994 | 526.18 | 1.38 | |
| 1995 | 570.20 | 1.86 | |
| 1996 | 500.51 | 2.65 | |
| 1997 | 497.50 | 1.07 | 1H NMR (400 MHz, DMSO-d6) δ 7.94 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.84 - 7.74 (m, 1H), 7.66 - 7.53 (m, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.97 (d, J |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | = 7.7 Hz, 1H), 6.19 - 5.99 (m, 1H), 5.26 - 5.08 (m, 1H), 4.54 (s, 2H), 3.18 - 3.09 (m, 1H), 3.05 (t, J = 10.8 Hz, 1H), 2.20 - 2.08 (m, 1H), 1.81 (dd, J = 11.2, 5.6 Hz, 1H), 1.60 (d, J = 16.0 Hz, 6H), 1.37 (t, J = 11.9 Hz, 1H), 0.86 (d, J = 6.2 Hz, 3H). |
| 1998 | 532.16 | 1.49 | 1H NMR (400 MHz, DMSO-d6) δ 12.51 (s, 1H), 8.26 (dd, J = 4.8, 1.9 Hz, 1H), 8.07 (dd, J = 7.9, 1.8 Hz, 1H), 7.80 (dd, J = 8.0, 1.7 Hz, 1H), 7.76 - 7.59 (m, 2H), 7.34 (dd, J = 8.0, 1.7 Hz, 1H), 6.90 - 6.65 (m, 3H), 3.96 (d, J = 1.6 Hz, 3H), 2.16 (s, 1H), 1.86 (dd, J = 11.9, 5.6 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.41 (t, J = 12.2 Hz, 1H), 0.76 (d, J = 6.4 Hz, 3H). |
| 1999 | 496.19 | 1.21 | |
| 2000 | 499.40 | 1.55 | |
| 2001 | 499.31 | 2.89 | |
| 2002 | 552.40 | 1.87 | 1H NMR (400 MHz, DMSO-d6) δ 7.58 (s, 1H), 7.52 - 7.33 (m, 2H), 7.25 (s, 1H), 7.02 (s, 1H), 6.43 (d, J = 22.8 Hz, 2H), 6.11 (s, 2H), 3.55 (q, J = 7.0 Hz, 4H), 3.09 - 2.90 (m, 2H), 2.26 (s, 3H), 2.19 - 2.05 (m, 2H), 1.82 (dd, J = 12.1, 5.7 Hz, 1H), 1.63 (s, 3H), 1.59 (s, 3H), 1.38 (t, J = 12.0 Hz, 1H), 1.15 (t, J = 6.9 Hz, 6H), 0.85 (d, J = 6.4 Hz, 3H). |
| 2003 | 506.21 | 2.00 | |
| 2004 | 486.40 | 2.18 | |
| 2005 | 509.21 | 1.46 | |
| 2006 | 532.16 | 1.46 | |
| 2007 | 517.15 | 1.70 | |
| 2008 | 528.21 | 1.28 | |
| 2009 | 682.20 | 2.26 | |
| 2010 | 553.40 | 2.43 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.16 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 4.05 (d, J = 6.7 Hz, 2H), 2.60 (q, J = 10.6, 8.9 Hz, 2H), 2.44 (s, 3H), 2.28 - 2.12 (m, 1H), 2.05 (dp, J = 13.3, 6.6 Hz, 1H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.61 (s, 3H), 1.59 (s, 3H), 1.42 (t, J = 12.1 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.2 Hz, 3H). |
| 2011 | 512.51 | 2.69 | |
| 2012 | 524.52 | 2.10 | |
| 2013 | 511.31 | 2.08 | |
| 2014 | 560.25 | 1.88 | 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.70 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (d, J = 8.3 Hz, 2H), 7.67 - 7.61 (m, 1H), 7.37 (d, J = 16.5 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 7.19 (d, J = 16.5 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.54 (s, 2H), 2.69 - 2.59 (m, 1H), 2.59 - 2.52 (m, 1H), 2.29 - 2.11 (m, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.53 (s, 6H), 1.38 (d, J = 12.1 Hz, 1H), 0.86 (d, J = 6.3 Hz, 3H). |
| 2015 | 485.20 | 2.31 | |
| 2016 | 490.32 | 1.47 | |
| 2017 | 494.31 | 1.52 | |
| 2018 | 528.19 | 1.54 | |
| 2019 | 515.51 | 3.21 | |
| 2020 | 494.30 | 1.64 | 1H NMR (400 MHz, DMSO-d6) δ 12.25 (s, 1H), 7.66 - 7.55 (m, 2H), 7.17 (dd, J = 7.3, 0.7 Hz, 1H), 6.66 (dd, J = 8.4, 0.7 Hz, 1H), 6.44 (s, 2H), 5.02 (p, J = 6.2 Hz, 1H), 2.56 (d, J = 10.6 Hz, 1H), 2.44 (t, J = 8.7 Hz, 1H), 2.25 - 2.15 (m, 1H), 1.88 (ddq, J = 24.1, 11.8, 6.1, 5.5 Hz, 2H), 1.51 (s, 3H), 1.44 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 1.24 (d, J = 6.4 Hz, 3H), 0.89 (dd, J = 6.8, 4.5 Hz, 6H), 0.85 (d, J = 6.3 Hz, 3H). |
| 2021 | 511.18 | 1.33 | |
| 2022 | 472.50 | 1.55 | 1H NMR (400 MHz, CDCl3) δ 15.20 (s, 1H), 8.47 (d, J = 8.2 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.41 (dd, J = 12.8, 7.7 Hz, 2H), 7.12 (d, J = 8.6 Hz, 1H), 4.23 (s, 1H), 3.83 (d, J = 6.6 Hz, 1H), 2.53 - 2.37 (m, 1H), 2.22 - 2.03 (m, 1H), 1.80 (dd, J = 18.4, 9.3 Hz, 1H), 1.56 (s, 3H), 1.27 (d, J = 13.6 Hz, 9H), 1.25 - 1.16 (m, 3H), 0.70 (d, J = 4.1 Hz, 1H), 0.53 (d, J = 7.6 Hz, 2H), 0.15 (s, 2H). |
| 2023 | 542.23 | 2.65 | |
| 2024 | 488.20 | 2.49 | |
| 2025 | 474.99 | 2.98 | |
| 2026 | 472.29 | 1.98 | |
| 2027 | 613.50 | 1.72 | 1H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 7.66 - 7.57 (m, 1H), 7.29 (s, 1H), 7.18 (d, J = 7.2 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 6.46 (s, 2H), 5.54 (s, 1H), 4.82 (h, J = 6.1 Hz, 1H), 4.12 - 3.84 (m, 2H), 3.67 - 3.51 (m, 2H), 2.56 (d, J = 10.5 Hz, 1H), 2.41 - 2.24 (m, 2H), 2.24 - 2.11 (m, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.41 - 1.32 (m, 2H), 1.31 (s, 9H), 1.23 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H). |
| 2028 | 501.30 | 1.62 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2029 | 542.29 | 1.62 | |
| 2030 | 472.29 | 2.57 | |
| 2031 | 496.24 | 1.57 | |
| 2032 | 489.40 | 2.07 | |
| 2033 | 514.21 | 1.40 | |
| 2034 | 496.60 | 1.57 | |
| 2035 | 520.17 | 1.49 | |
| 2036 | 512.50 | 1.56 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (寬單峰, 1H), 8.27 (d, J = 2.5 Hz, 1H), 8.25 (dd, J = 4.8, 1.9 Hz, 1H), 8.03 (dd, J = 7.8, 1.9 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.69 (br s, 2H), 6.41 (d, J = 2.6 Hz, 1H), 2.52 (可能雙峰 , 2H, 部分與DMSO重疊), 2.46 (d, J = 8.8 Hz, 2H), 2.13 (br m, 1H), 1.95 (dt, J = 13.5, 6.8 Hz, 1H), 1.85 (dd, J = 12.0, 5.6 Hz, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 1.39 (t, J = 12.1 Hz, 1H), 0.93 (d, J = 2.2 Hz, 3H), 0.92 (d, J = 2.1 Hz, 3H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2037 | 495.40 | 1.55 | |
| 2038 | 501.41 | 2.98 | |
| 2039 | 553.40 | 2.25 | 1H NMR (400 MHz, DMSO) δ 12.55 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.68 - 7.60 (m, 1H), 7.56 (s, 1H), 7.49 (d, J = 9.6 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.01 - 6.84 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.55 (s, 2H), 5.62 (d, J = 1.7 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 2.66 (ddd, J = 14.3, 7.4, 1.8 Hz, 1H), 2.03 (dd, J = 13.2, 6.6 Hz, 1H), 1.95 (dd, J = 12.1, 7.5 Hz, 1H), 1.38 - 1.28 (m, 4H), 1.25 (s, 3H), 0.99 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.9 Hz, 3H). |
| 2040 | 534.22 | 1.01 | |
| 2041 | 526.02 | 2.29 | 1H NMR (400 MHz, DMSO) δ12.56 (s, 1H), 9.42 (s, 1H), 8.15 - 8.13 (dd, 1H), 7.78 (t, J = 7.80, 1H), 7.67 - 7.64 (d, 1H), 7.42 - 7.37 (m, 2H), 7.33 - 7.30 (dd, 1H), 7.0 - 6.97 (d, 1H), 6.83 - 6.80 (d, 1H), 6.53 - 6. 50 (dd, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 1.99 - 1.94 (m, 1H), 1.80 - 1.73 (m, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.32 (t, J = 11.91, 1H), 0.77 - 0.74 (d, 3H) |
| 2042 | 533.50 | 1.47 | |
| 2043 | 496.30 | 1.53 | 1H NMR (400 MHz, DMSO-d6) δ 12.51 (s, 1H), 11.99 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 6.76 - 6.65 (m, 3H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.68 (d, J = 8.7 Hz, 2H), 2.27 (s, 3H), 2.32 - 2.14 (m, 1H), 2.07 (s, 2H), 1.90 (dd, J = 11.9, 5.6 Hz, 1H), 1.52 (d, J = 3.1 Hz, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.88 (d, J = 6.3 Hz, 3H). |
| 2044 | 458.18 | 2.35 | |
| 2045 | 476.25 | 1.38 | |
| 2046 | 500.18 | 1.40 | |
| 2047 | 516.40 | 1.23 | 1H NMR (400 MHz,甲醇-d4) δ 8.26 - 8.11 (m, 2H), 7.89 (dd, J = 12.7, 7.8 Hz, 1H), 6.90 - 6.73 (m, 2H), 3.28 - 3.13 (m, 1H), 3.07 - 2.93 (m, 1H), 2.92 - 2.75 (m, 1H), 2.57 - 2.40 (m, 1H), 2.09 - 1.96 (m, 1H), 1.94 - 1.81 (m, 1H), 1.77 - 1.35 (m, 12H), 1.17 - 0.89 (m, 9H). |
| 2048 | 534.22 | 1.08 | |
| 2049 | 544.33 | 2.68 | |
| 2050 | 502.33 | 1.44 | 1H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 8.15 (s, 3H), 7.73 (dd, J = 7.7, 1.8 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.09 - 7.03 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.88 - 3.79 (m, 1H), 3.76 (dd, J = 10.2, 6.6 Hz, 1H), 3.72 - 3.62 (m, 1H), 3.58 (dd, J = 15.0, 8.8 Hz, 1H), 3.41 (dd, J = 10.2, 4.8 Hz, 1H), 3.09 (t, J = 10.1 Hz, 1H), 2.98 - 2.89 (m, 1H), 2.35 (dd, J = 10.9, 5.8 Hz, 1H), 2.28 - 2.16 (m, 1H), 1.96 (ddd, J = 17.2, 12.6, 6.5 Hz, 2H), 1.61 (s, 3H), 1.58 (s, 3H), 1.52 (d, J = 12.1 Hz, 1H), 1.34 (t, J = 6.9 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H). |
| 2051 | 529.36 | 1.13 | 1H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 12.53 (s, 1H), 8.25 (dd, J = 7.3, 2.2 Hz, 1H), 7.82 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 9.9, 3.2 Hz, 1H), 7.25 - 7.17 (m, 2H), 7.14 (dd, J = 9.1, 4.7 Hz, 1H), 6.49 - 6.42 (m, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.81 - 2.68 (m, 2H), 2.23 (s, 1H), 1.87 (dd, J = 11.8, 5.5 Hz, 1H), 1.55 (s, 6H), 1.43 (t, J = 12.1 Hz, 1H), 1.34 (t, J = 6.9 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2052 | 498.53 | 1.08 | |
| 2053 | 458.49 | 2.14 | |
| 2054 | 505.20 | 1.37 | |
| 2055 | 512.51 | 2.62 | 1H NMR (400 MHz, DMSO) δ12.69 (s, 1H), 8.16 - 8.14 (dd, 1H), 7.88 (t, J = 8.02, 1H), 7.68 - 7.65 (d, 1H), 7.50 - 7.47 (dd, 1H), 7.06 - 7.03 (dd, 1H), 6.61 - 6.58 (dd, 1H), 4.95 (m, 1H), 3.60 (m, 1H), 3.46 - 3.39 ( m, 1H), 2.11 (m, 5H), 1.87 - 1.77 (m, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.51 - 1.29 (m, 7H), 0.78 - 0.75 (d, 1.5H), 0.71 - 0.68 (d, 1.5H) |
| 2056 | 494.30 | 1.06 | |
| 2057 | 501.11 | 3.27 | |
| 2058 | 570.20 | 1.99 | |
| 2059 | 527.22 | 3.17 | |
| 2060 | 538.33 | 2.62 | |
| 2061 | 535.02 | 2.71 | |
| 2062 | 556.20 | 1.96 | 1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 10.7 Hz, 1H), 7.45 (d, J = 11.6 Hz, 3H), 7.20 (d, J = 6.5 Hz, 1H), 6.90 (d, J = 10.7 Hz, 1H), 6.70 (d, J = 7.1 Hz, 1H), 6.44 (s, 2H), 3.84 (d, J = 6.5 Hz, 2H), 3.50 (s, 1H), 3.38 (s, 1H), 3.12 (d, J = 13.0 Hz, 1H), 2.96 (s, 1H), 2.08 - 1.98 (m, 1H), 1.80 (s, 2H), 1.41 - 1.37 (m, 1H), 1.30 - 1.22 (m, 1H), 1.00 (d, J = 6.7 Hz, 7H), 0.86 (d, J = 6.5 Hz, 4H), 0.76 (d, J = 6.6 Hz, 3H). |
| 2063 | 498.34 | 1.82 | |
| 2064 | 514.31 | 2.39 | |
| 2065 | 526.18 | 1.43 | |
| 2066 | 500.23 | 1.42 | |
| 2067 | 499.40 | 1.50 | |
| 2068 | 467.19 | 1.43 | 1H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 8.32 - 8.30 (dd, 1H), 8.18 - 8.16 (dd, 1H), 8.11 - 8.08 (d, 1H), 8.01 (t, J = 7.91, 1H), 7.84 - 7.75 (m, 2H), 7.66 - 7.63 (dd, 2H), 7.06 (t, J = 6.26, 1H), 6.62 - 6.59 (dd, 1 H), 2.46 - 2.43(d, 1H), 1.93 - 1.89 (m, 1H), 1.78 - 1.72 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.27 (t, J = 11.91, 1H), 0.68 - 0.66 (d, 3H) |
| 2069 | 574.40 | 1.51 | |
| 2070 | 542.29 | 1.53 | |
| 2071 | 528.22 | 1.53 | |
| 2072 | 524.22 | 2.30 | 1H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 8.15 - 8.13 (dd, 1H), 7.69 - 7.66 (dd, 1H), 7.60 (t, J = 7.80, 1H), 7.25 - 7.15 (m, 4H), 6.85 - 6.82 (d, 2H), 6.74 - 6.71 (d, 1H), 6.53 - 6.50 (dd, 1H), 3.71 (s, 3H), 3.45 - 3.36 (m, 2H), 2.79 (t, J = 7.47, 2H), 2.12 - 2.08 (m, 1H), 1.85 - 1.78 (m, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.36 (t, J = 11.65, 1H), 0.82 - 0.80 (d, 3H) |
| 2073 | 495.30 | 1.53 | |
| 2074 | 517.32 | 1.36 | |
| 2075 | 461.19 | 2.68 | |
| 2076 | 492.40 | 2.00 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2077 | 540.40 | 1.46 | 1H NMR (400 MHz,甲醇-d4) δ 8.50 (dd, J = 7.7, 1.8 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.13 (dd, J = 5.9, 1.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.00 (dd, J = 7.7, 5.8 Hz, 1H), 3.74 (t, J = 10.0 Hz, 1H), 3.33 - 3.25 (m, 1H, 由溶劑峰遮蔽), 2.88 - 2.68 (m, 2H), 2.28 - 2.18 (m, 2H), 2.14 - 2.06 (m, 4H), 1.92 - 1.82 (m, 1H), 1.75 - 1.60 (m, 2H), 1.57 - 1.45 (m, 6H), 1.36 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H). |
| 2078 | 550.33 | 2.02 | |
| 2079 | 583.30 | 1.59 | |
| 2080 | 497.40 | 1.36 | 1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 8.24 (dd, J = 7.2, 2.1 Hz, 1H), 8.05 - 7.97 (m, 2H), 7.82 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 7.09 - 7.00 (m, 2H), 6.44 (t, J = 6.8 Hz, 1H), 3.81 (s, 2H), 2.76 - 2.66 (m, 2H), 2.22 (s, 1H), 1.88 (dd, J = 11.9, 5.6 Hz, 1H), 1.61 (s, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.2 Hz, 3H). |
| 2081 | 553.20 | 2.26 | |
| 2082 | 481.30 | 1.56 | 1H NMR (400 MHz, DMSO-d6) δ10.99 (s, 1H), 8.22 - 8.18 (m, 2H), 8.06 (t, J = 8.13, 1H), 7.81 - 7.62 (m, 4H), 7.00 - 6.98 (d, 1H), 6.65 - 6.62 (dd, 1H), 2.30 (s, 3H), 1.87 - 1.72 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1. 26 (t, J = 11.87, 1H), 0.65 - 0.63 (d, 3H) |
| 2083 | 523.32 | 2.14 | |
| 2084 | 499.40 | 1.59 | |
| 2085 | 538.29 | 1.23 | |
| 2086 | 511.30 | 2.13 | 1H NMR (400 MHz, DMSO) δ 8.65 (d, J = 2.2 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.49 - 7.36 (m, 1H), 6.98 (dd, J = 7.5, 2.8 Hz, 2H), 6.47 (d, J = 8.2 Hz, 1H), 6.17 (s, 2H), 3.92 (s, 3H), 3.04 - 2.85 (m, 2H), 2.20 (s, 3H), 2.09 (d, J = 17.6 Hz, 1H), 1.81 (dd, J = 11.6, 5.5 Hz, 1H), 1.61 (s, 3H), 1.56 (s, 3H), 1.36 (t, J = 12.0 Hz, 1H), 0.82 (d, J = 6.3 Hz, 3H). |
| 2087 | 549.43 | 2.09 | |
| 2088 | 496.24 | 1.27 | |
| 2089 | 538.34 | 1.88 | |
| 2090 | 524.52 | 2.54 | |
| 2091 | 527.16 | 1.45 | |
| 2092 | 450.50 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 12.55 (s, 1H), 8.02 (ddt, J = 9.9, 7.2, 1.6 Hz, 4H), 7.77 - 7.70 (m, 2H), 7.70 - 7.62 (m, 2H), 7.53 - 7.46 (m, 2H), 7.46 - 7.40 (m, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 7.21 (d, J = 8.0 Hz, 1H), 2.45 (t, J = 10.3 Hz, 1H), 2.36 (dd, J = 10.2, 7.1 Hz, 1H), 2.19 - 2.08 (m, 1H), 1.83 (dd, J = 12.0, 5.6 Hz, 1H), 1.58 (d, J = 15.4 Hz, 6H), 1.38 (t, J = 12.1 Hz, 1H), 0.67 (d, J = 6.3 Hz, 3H). |
| 2093 | 494.31 | 1.69 | |
| 2094 | 520.32 | 2.62 | |
| 2095 | 538.34 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 8.46 (s, 1H), 7.84 (d, J = 2.5 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.43 (d, J = 12.2 Hz, 2H), 7.22 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 6.48 (s, 2H), 3.97 (t, J = 6.4 Hz, 2H), 3.35 (d, J = 7.2 Hz, 1H), 2.55 (d, J = 8.4 Hz, 2H), 2.23 (s, 3H), 1.84 (dd, J = 11.8, 5.7 Hz, 1H), 1.76 (p, J = 7.0 Hz, 2H), 1.54 (s, 3H), 1.52 (s, 3H), 1.39 (t, J = 12.0 Hz, 1H), 1.02 (t, J = 7.4 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H). |
| 2096 | 491.40 | 1.17 | |
| 2097 | 484.30 | 1.41 | 1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.60 (dd, J = 7.9, 3.2 Hz, 1H), 6.76 (dd, J = 7.8, 4.8 Hz, 1H), 6.55 (dd, J = 7.9, 5.9 Hz, 1H), 3.24 - 3.14 (m, 1H), 2.46 - 2.39 (m, 2H, 由溶劑峰遮蔽), 2.31 - 2.24 (m, 1H), 2.20 - 2.04 (m, 1H), 1.89 - 1.67 (m, 3H), 1.59 - 1.54 (m, 1H), 1.52 (d, J = 5.1 Hz, 6H), 1.49 - 0.95 (m, 7H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2098 | 506.21 | 2.66 | |
| 2099 | 517.32 | 2.55 | |
| 2100 | 492.30 | 1.57 | 1H NMR (400 MHz, DMSO) δ 12.28 (s, 1H), 7.66 - 7.50 (m, 2H), 7.17 (d, J = 7.2 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 5.45 - 5.31 (m, 1H), 2.58 - 2.53 (m, 1H), 2.47 - 2.40 (m, 1H), 2.20 (dp, J = 18.4, 6.1 Hz, 1H), 1.99 - 1.79 (m, 4H), 1.78 - 1.65 (m, 4H), 1.65 - 1.55 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 0.85 (d, J = 6.2 Hz, 3H). |
| 2101 | 498.30 | 1.37 | |
| 2102 | 484.30 | 2.09 | |
| 2103 | 528.17 | 1.51 | |
| 2104 | 546.23 | 1.23 | 1H NMR (400 MHz, DMSO) δ 12.45 (s, 1H), 7.99 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.22 (t, J = 8.0 Hz, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.50 (s, 2H), 2.63 - 2.56 (m, 2H), 2.21 (q, J = 9.7, 7.7 Hz, 2H), 1.88 (dd, J = 11.8, 5.5 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.60 (d, J = 5.4 Hz, 6H), 1.42 (t, J = 12.0 Hz, 1H), 0.88 (d, J = 6.1 Hz, 3H). |
| 2105 | 502.26 | 1.41 | |
| 2106 | 520.32 | 2.21 | |
| 2107 | 548.23 | 2.68 | |
| 2108 | 509.21 | 2.57 | |
| 2109 | 473.19 | 2.72 | |
| 2110 | 494.31 | 1.45 | |
| 2111 | 547.33 | 2.45 | |
| 2112 | 536.50 | 1.40 | |
| 2113 | 532.50 | 2.29 | |
| 2114 | 512.30 | 1.18 | 1H NMR (400 MHz,甲醇-d4) δ 7.94 (d, J = 8.0 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.99 (d, J = 7.3 Hz, 2H), 3.03 (t, J = 9.3 Hz, 1H), 2.91 (t, J = 10.3 Hz, 1H), 2.41 (s, 1H), 2.29 - 2.16 (m, 1H), 1.97 (dd, J = 13.3, 7.1 Hz, 1H), 1.63 - 1.53 (m, 7H), 1.34 (d, J = 9.5 Hz, 1H), 1.03 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H). |
| 2115 | 539.23 | 2.51 | |
| 2116 | 458.18 | 2.27 | |
| 2117 | 514.40 | 2.02 | 1H NMR (400 MHz, DMSO) δ 7.77 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.3, 7.4 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.23 - 7.15 (m, 1H), 6.90 (d, J = 10.8 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.48 (s, 2H), 3.85 (dd, J = 14.4, 7.6 Hz, 4H), 3.30 (dd, J = 8.9, 5.8 Hz, 2H), 2.72 - 2.59 (m, 1H), 2.03 (d, J = 6.7 Hz, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.7 Hz, 6H). |
| 2118 | 547.33 | 2.32 | |
| 2119 | 522.42 | 2.59 | |
| 2120 | 516.36 | 1.53 | |
| 2121 | 557.20 | 1.71 | 1H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 7.73 (s, 3H), 7.70 - 7.63 (m, 1H), 7.59 (d, J = 9.7 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.07 (d, J = 10.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.86 (d, J = 6.6 Hz, 2H), 2.86 - 2.74 (m, 1H), 2.69 (t, J = 10.9 Hz, 1H), 2.34 - 2.18 (m, 1H), 2.13 - 1.99 (m, 1H), 1.95 (dd, J = 11.9, 5.5 Hz, 1H), 1.63 (d, J = 23.9 Hz, 6H), 1.50 (t, J = 12.2 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.90 (d, J = 6.3 Hz, 3H). |
| 2122 | 538.33 | 2.56 | |
| 2123 | 534.42 | 2.52 | |
| 2124 | 514.15 | 1.42 | |
| 2125 | 505.22 | 1.38 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2126 | 530.24 | 1.57 | |
| 2127 | 494.31 | 1.53 | |
| 2128 | 518.30 | 1.93 | 1H NMR (400 MHz, DMSO) δ 12.55 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 15.7, 7.4 Hz, 1H), 7.57 - 7.33 (m, 3H), 7.21 (d, J = 7.2 Hz, 1H), 6.92 (dt, J = 10.7, 2.2 Hz, 1H), 6.76 - 6.66 (m, 1H), 6.51 (s, 2H), 5.38 (ddd, J = 61.0, 5.7, 2.8 Hz, 1H), 4.12 (ddd, J = 17.3, 11.5, 5.4 Hz, 2H), 3.85 (d, J = 6.5 Hz, 4H), 2.04 (dt, J = 13.3, 6.6 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H). |
| 2129 | 571.38 | 1.58 | |
| 2130 | 475.29 | 2.83 | |
| 2131 | 474.09 | 1.63 | |
| 2132 | 480.28 | 0.99 | |
| 2133 | 480.50 | 2.09 | 1H NMR (400 MHz, DMSO-d6) δ 13.25 (s, 1H), 12.66 (s, 1H), 8.04 - 7.99 (m, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.77 - 7.70 (m, 2H), 7.70 - 7.63 (m, 2H), 7.36 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 6.84 - 6.78 (m, 1H), 2.62 - 2.51 (m, 2H), 2.19 (s, 3H), 2.14 (q, J = 5.8 Hz, 1H), 1.89 (dd, J = 11.9, 5.5 Hz, 1H), 1.50 (d, J = 3.3 Hz, 6H), 1.41 (t, J = 12.1 Hz, 1H), 0.66 (d, J = 6.3 Hz, 3H). |
| 2134 | 568.33 | 1.62 | |
| 2135 | 462.39 | 1.74 | |
| 2136 | 516.41 | 2.64 | 1H NMR (400 MHz, DMSO-d6) δ 12.67 (s, 1H), 9.43 (s, 1H), 8.24 - 8.09 (m, 3H), 7.96 - 7.94 (dd, 1H), 7.86 (t, J = 8.02, 1H), 7.70 - 7.67 (d, 1H), 7.60 - 7.43 (m, 5H), 7.27 - 7.24 (d, 1H), 6.45 - 6.42 (dd, 1H), 2.07 - 1 .91 (m, 1H), 1.77 - 1.73 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.33 (t, J = 11.91, 1H), 0.79 - 0.77 (d, 3H) |
| 2137 | 512.51 | 2.56 | |
| 2138 | 529.20 | 1.64 | |
| 2139 | 516.20 | 1.31 | 1H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 7.70 - 7.52 (m, 2H), 7.17 (dd, J = 7.3, 0.5 Hz, 1H), 6.70 (dd, J = 9.7, 8.5 Hz, 2H), 5.19 (s, 2H), 3.84 (td, J = 11.1, 3.7 Hz, 2H), 3.38 - 3.18 (m, 2H), 2.84 (t, J = 10.0 Hz, 1H), 2.68 - 2.55 (m, 1H), 2.07 (s, 4H), 1.81 (t, J = 6.4 Hz, 1H), 1.65 (dd, J = 30.6, 10.5 Hz, 2H), 1.55 (d, J = 8.6 Hz, 6H), 1.49 (s, 3H), 1.28 (d, J = 6.6 Hz, 10H). |
| 2140 | 525.42 | 1.65 | |
| 2141 | 534.60 | 1.23 | |
| 2142 | 522.42 | 2.85 | 1H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 9.52 (s, 1H), 8.13 - 8.11 (dd, 1H), 8.01 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | - 7.98 (d, 1H), 7.81 (t, J = 7.80, 1H), 7.71 - 7.68 (dd, 1H), 7.45 - 7.42 (d, 1H), 7.36 (s, 1H), 7.17 (t, J = 7.92, 1H), 7.06 - 6.97 (m, 2H), 6.52 - 6.49 (dd, 1H), 1.86 - 1.70 (m, 2H), 1.45 (s, 3H), 1.41 (s, 3H), 1.28 (m, 10H), 0.74 - 0.72 (d, 3H) |
| 2143 | 550.33 | 2.55 | |
| 2144 | 535.50 | 1.76 | 1H NMR (400 MHz, DMSO-d6) δ 12.65 (d, J = 4.1 Hz, 1H), 12.53 (s, 1H), 8.40 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.25 (dd, J = 7.3, 2.2 Hz, 1H), 7.78 (ddt, J = 24.0, 15.6, 7.9 Hz, 4H), 7.35 - 7.30 (m, 1H), 6.54 - 6.35 (m, 1H), 2.82 - 2.63 (m, 2H), 2.24 (s, 1H), 1.90 (dd, J = 12.0, 5.7 Hz, 1H), 1.61 (d, J = 3.3 Hz, 6H), 1.46 (t, J = 12.3 Hz, 1H), 0.91 (t, J = 7.0 Hz, 3H). |
| 2145 | 501.11 | 2.34 | |
| 2146 | 500.21 | 2.30 | |
| 2147 | 471.39 | 2.56 | |
| 2148 | 497.30 | 1.49 | |
| 2149 | 528.19 | 1.49 | 1H NMR (400 MHz, DMSO-d6) δ 12.58 (s, 1H), 8.26 (dd, J = 4.8, 1.8 Hz, 1H), 8.07 (dd, J = 7.8, 1.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.44 (dd, J = 6.3, 3.2 Hz, 1H), 7.24 (dd, J = 11.1, 9.0 Hz, 1H), 7.09 (dd, J = 7.9, 2.2 Hz, 1H), 7.01 (dt, J = 9.0, 3.5 Hz, 1H), 6.80 (dd, J = 7.9, 4.8 Hz, 3H), 4.04 (q, J = 6.9 Hz, 2H), 2.55 (dd, J = 10.1, 7.3 Hz, 2H), 2.15 (td, J = 11.6, 10.3, 5.8 Hz, 1H), 1.84 (dd, J = 11.8, 5.6 Hz, 1H), 1.57 (s, 3H), 1.54 (s, 3H), 1.40 (t, J = 12.0 Hz, 1H), 1.33 (t, J = 6.9 Hz, 3H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2150 | 446.40 | 1.27 | 1H NMR (400 MHz,乙腈-d3) δ 8.27 (d, J = 8.0 Hz, 1H), 8.24 (dd, J = 7.7, 1.8 Hz, 1H), 8.09 (dd, J = 5.3, 1.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.81 (dd, J = 7.7, 5.3 Hz, 1H), 3.76 (dd, J = 11.5, 8.8 Hz, 1H), 3.24 (dd, J = 11.5, 8.2 Hz, 1H), 2.81 - 2.71 (m, 1H), 2.69 (d, J = 7.2 Hz, 2H), 2.23 - 2.11 (m, 3H), 1.86 (dd, J = 12.7, 10.2 Hz, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.20 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 6H). |
| 2151 | 531.12 | 2.71 | |
| 2152 | 488.50 | 2.10 | |
| 2153 | 539.50 | 1.87 | |
| 2154 | 495.40 | 1.59 | 1H NMR (400 MHz, DMSO-d6) δ 12.55 (s, 1H), 12.52 (d, J = 6.4 Hz, 1H), 8.24 (dd, J = 7.3, 2.1 Hz, 1H), 7.83 (s, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.44 (t, J = 6.9 Hz, 1H), 2.77 - 2.64 (m, 2H), 2.38 - 2.13 (m, 8H), 1.88 (dd, J = 12.1, 5.7 Hz, 1H), 1.61 (s, 6H), 1.44 (t, J = 12.4 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2155 | 536.30 | 2.01 | 1H NMR (400 MHz, DMSO) δ 12.65 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 8.4, 7.3 Hz, 1H), 7.59 - 7.46 (m, 3H), 7.22 (dd, J = 7.3, 0.6 Hz, 1H), 6.93 (dt, J = 10.8, 2.3 Hz, 1H), 6.76 - 6.68 (m, 1H), 6.54 (s, 2H), 4.15 (t, J = 12.5 Hz, 4H), 3.85 (d, J = 6.5 Hz, 2H), 2.05 (dt, J = 13.3, 4.4 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H). |
| 2156 | 516.36 | 1.55 | |
| 2157 | 506.21 | 1.34 | |
| 2158 | 512.16 | 1.32 | |
| 2159 | 503.30 | 1.51 | 1H NMR (400 MHz, DMSO-d6) δ 12.64 (s, 1H), 12.54 (d, J = 6.0 Hz, 1H), 8.25 (dd, J = 7.2, 2.3 Hz, 1H), 7.91 (td, J = 8.9, 6.7 Hz, 1H), 7.83 (dd, J = 7.1, 4.6 Hz, 1H), 7.77 - 7.71 (m, 1H), 7.37 (ddd, J = 11.9, 9.3, 2.6 Hz, 1H), 7.25 (td, J = 8.5, 2.6 Hz, 1H), 6.96 (dd, J = 7.8, 2.5 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.81 - 2.63 (m, 2H), 2.30 - 2.14 (m, 1H), 1.91 - 1.81 (m, 1H), 1.54 (d, J = 1.9 Hz, 6H), 1.43 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.4 Hz, 3H). |
| 2160 | 495.40 | 2.16 | |
| 2161 | 501.11 | 2.53 | |
| 2162 | 503.40 | 1.52 | 1H NMR (400 MHz, DMSO-d6) δ 12.67 (s, 1H), 12.55 (s, 1H), 8.25 (dd, J = 7.3, 2.2 Hz, 1H), 7.84 (dt, J = 7.5, 3.7 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.65 (ddt, J = 8.2, 6.7, 1.6 Hz, 1H), 7.55 - 7.45 (m, 1H), 7.35 (tdd, J = 8.1, 5.1, 1.5 Hz, 1H), 7.00 (dd, J = 7.9, 2.3 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.81 - 2.68 (m, 2H), 2.25 (tt, J = 11.7, 6.4 Hz, 1H), 1.87 (dd, J = 11.9, 5.6 Hz, 1H), 1.54 (s, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2163 | 508.16 | 1.42 | |
| 2164 | 496.28 | 0.93 | |
| 2165 | 519.12 | 2.58 | |
| 2166 | 480.10 | 2.02 | |
| 2167 | 447.08 | 2.52 | |
| 2168 | 510.41 | 2.20 | 1H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 8.16 - 8.14 (dd, 1H), 7.68 - 7.60 (m, 3H), 7.23 - 7.20 (d, 1H), 7.16 - 7.13 (d, 1H), 6.97 - 6.93 (m, 2H), 6.79 - 6.73 (m 2H), 6.57 - 6.54 (dd, 1H), 4.47 (s, 2H), 3.66 (s, 3H) , 2.44 - 2.33 (m, 1H), 2.05 - 1.98 (m, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.82 - 1.75 (m, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.33 (t, J = 12.09, 1H), 0.76 - 0.74 (d, 3H) |
| 2169 | 525.42 | 2.44 | 1H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 8.19 - 8.17 (dd, 1H), 8.03 (t, J = 7.80, 1H), 7.77 - 7.74 (d, 2H), 7.16 - 7.13 (d, 1H), 7.09 (s, 1H), 7.05 - 7.02 (dd, 1H), 6.83 - 6.80 (d, 1H), 6.64 - 6.61 (dd, 1H), 5.99 (s , 1H), 5.94 (s, 1H), 5.26, (s, 1H), 5.25 (s, 1H), 2.27 (s, 1H), 2.24 (s, 1H), 2.09 - 2.01 (m, 1H), 1.82 - 1.75 (m, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.35 (t, J = 11.86, 1H), 0.67 - 0.65 (d, 3H) |
| 2170 | 539.40 | 2.55 | 1H NMR (400 MHz, DMSO-d6) δ 8.63 (d, J = 2.4 Hz, 1H), 8.09 (d, J = 2.6 Hz, 1H), 7.60 (bs, 1H), 7.49 (bs, 1H), 7.01 (bs, 2H), 6.52 (bs, 1H), 6.24 (bs, 2H), 5.32 (p, J = 6.1 Hz, 1H), 3.01 - 2.73 (m, 2H), 2.17 (s, 3H), 2.15 - 2.05 (m, 1H), 1.82 (dd, J = 11.8, 5.6 Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.42 - 1.33 (m, 1H), 1.32 (d, J = 6.2 Hz, 6H), 0.82 (d, J = 6.3 Hz, 3H). |
| 2171 | 570.50 | 2.19 | 1H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.44 (ddd, J = 10.1, 2.2, 1.4 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.22 (dd, J = 7.3, 0.6 Hz, 1H), 6.93 - 6.83 (m, 1H), 6.72 (dd, J = 8.4, 0.6 Hz, 1H), 6.48 (s, 2H), 3.84 (d, J = 6.6 Hz, 2H), 3.23 (t, J = 5.4 Hz, 2H), 3.14 - 3.04 (m, 2H), 2.05 (dd, J = 11.8, 5.1 Hz, 1H), 1.72 (s, 2H), 1.57 - 1.49 (m, 2H), 1.30 - 1.20 (m, 2H), 0.99 (d, J = 6.7 Hz, 6H), 0.83 (s, 6H). |
| 2172 | 508.31 | 1.55 | |
| 2173 | 515.51 | 3.19 | |
| 2174 | 497.30 | 1.48 | |
| 2175 | 550.33 | 1.25 | |
| 2176 | 481.50 | 1.52 | |
| 2177 | 526.02 | 2.42 | |
| 2178 | 556.20 | 1.96 | |
| 2179 | 526.32 | 2.25 | |
| 2180 | 522.40 | 1.86 | |
| 2181 | 487.30 | 2.37 | |
| 2182 | 533.22 | 2.72 | |
| 2183 | 500.23 | 1.49 | |
| 2184 | 480.50 | 1.57 | |
| 2185 | 492.18 | 1.47 | |
| 2186 | 495.40 | 2.60 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2187 | 522.42 | 2.86 | |
| 2188 | 459.39 | 2.57 | |
| 2189 | 514.17 | 1.42 | |
| 2190 | 524.52 | 2.32 | |
| 2191 | 528.50 | 1.50 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (寬單峰, 1H), 8.25 (dd, J = 4.8, 1.8 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 7.9, 1.8 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.70 (寬單峰與先前信號重疊, 2H), 6.12 (d, J = 2.7 Hz, 1H), 3.98 (d, J = 6.6 Hz, 2H), 2.45 (d, J = 8.7 Hz, 2H), 2.20-2.01 (m, 2H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.38 (t, J = 12.2 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2192 | 544.40 | 1.15 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.23 (dd, J = 4.8, 1.9 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 8.02 (dd, J = 7.8, 1.9 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.76 (dd, J = 7.8, 4.7 Hz, 1H), 6.67 (寬單峰, 2H), 6.11 (d, J = 2.8 Hz, 1H), 4.57 (br s, 1H), 4.19 (ddd, J = 9.9, 5.9, 2.4 Hz, 1H), 4.03 (ddd, J = 9.8, 6.5, 3.2 Hz, 1H), 3.41 (br s, 2H), 2.47 (d, J = 8.4 Hz, 2H), 2.19 - 2.06 (m, 1H), 2.06 - 1.92 (m, 1H), 1.85 (dd, J = 11.9, 5.5 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.38 (t, J = 12.1 Hz, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2193 | 519.42 | 2.24 | |
| 2194 | 540.20 | 1.67 | |
| 2195 | 526.13 | 1.39 | |
| 2196 | 470.30 | 1.25 | 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.69 (dd, J = 8.5, 7.3 Hz, 1H), 7.62 - 7.54 (m, 1H), 7.38 - 7.30 (m, 2H), 7.26 (d, J = 7.3 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 3.84 (s, 3H), 3.09 - 2.98 (m, 1H), 2.77 (t, J = 9.9 Hz, 1H), 2.34 - 2.29 (m, 1H), 1.93 (dd, J = 11.9, 6.0 Hz, 1H), 1.57 (d, J = 13.2 Hz, 6H), 1.47 (t, J = 12.1 Hz, 1H), 0.93 (d, J = 6.3 Hz, 3H). |
| 2197 | 460.29 | 2.34 | |
| 2198 | 537.43 | 1.62 | |
| 2199 | 490.32 | 1.45 | |
| 2200 | 432.37 | 2.23 | |
| 2201 | 584.40 | 2.16 | 1H NMR (400 MHz, DMSO) δ 7.55 (d, J = 7.7 Hz, 1H), 7.46 (s, 1H), 7.38 (dd, J = 18.8, 10.8 Hz, 2H), 7.06 (d, J = 7.7 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.79 (d, J = 10.7 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 6.42 (d, J = 8.2 Hz, 1H), 6.01 (s, 2H), 3.82 (d, J = 6.6 Hz, 2H), 3.39 (t, J = 10.7 Hz, 1H), 3.23 - 3.14 (m, 1H), 2.05 (dt, J = 13.4, 6.8 Hz, 1H), 1.86 (d, J = 11.5 Hz, 1H), 1.79 (s, 1H), 1.61 (d, J = 22.2 Hz, 6H), 1.45 (t, J = 11.4 Hz, 1H), 1.36 (d, J = 6.8 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.86 (dd, J = 16.6, 6.5 Hz, 6H). |
| 2202 | 500.21 | 2.74 | |
| 2203 | 496.60 | 1.72 | |
| 2204 | 614.20 | 2.11 | 1H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 9.2 Hz, 2H), 7.37 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 6.89 (d, J = 10.7 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.48 (s, 2H), 4.51 (dd, J = 7.7, 3.8 Hz, 1H), 3.84 (d, J = 6.4 Hz, 2H), 2.96 - 2.72 (m, 2H), 2.27 - 2.10 (m, 1H), 2.09 - 1.98 (m, 1H), 1.97 - 1.86 (m, 1H), 1.80 (qd, J = 10.5, 5.7 Hz, 2H), 1.29 (s, 9H), 1.00 (d, J = 6.7 Hz, 6H). |
| 2205 | 498.53 | 1.05 | |
| 2206 | 510.41 | 2.30 | |
| 2207 | 511.30 | 1.48 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (d, J = 10.1 Hz, 2H), 8.24 (dd, J = 7.2, 2.1 Hz, 1H), 8.02 - 7.93 (m, 2H), 7.82 (t, J = 6.6 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.06 - 6.95 (m, 2H), 6.44 (t, J = 7.0 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.71 (dd, J = 12.1, 8.5 Hz, 2H), 2.23 (s, 1H), 1.88 (dd, J = 11.8, 5.6 Hz, 1H), 1.61 (s, 6H), 1.44 (t, J = 12.1 Hz, 1H), 1.34 (t, J = 6.9 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2208 | 535.32 | 2.08 | |
| 2209 | 598.30 | 1.63 | |
| 2210 | 558.25 | 1.85 | |
| 2211 | 527.22 | 3.22 | |
| 2212 | 529.20 | 0.81 | 1H NMR (400 MHz, DMSO-d6) δ 12.31 (s, 1H), 8.87 - 8.78 (m, 2H), 7.92 (dd, J = 19.3, 6.1 Hz, 2H), 7.69 (dd, J = 10.6, 1.5 Hz, 1H), 7.60 (ddd, J = 8.4, 7.3, 3.4 Hz, 1H), 7.20 - 7.12 (m, 1H), 6.66 (dt, J = 8.4, 0.9 Hz, 1H), 6.44 (s, 1H), 6.14 (q, J = 6.7 Hz, 1H), 2.50 - 2.33 (m, 2H), 2.20 - 2.03 (m, 1H), 1.80 - 1.62 (m, 4H), 1.43 (d, J = 19.0 Hz, 3H), 1.35 - 1.12 (m, 1H), 0.86 - 0.73 (m, 6H). |
| 2213 | 570.20 | 1.97 | |
| 2214 | 510.41 | 2.57 | |
| 2215 | 485.20 | 1.23 | 1H NMR (400 MHz, DMSO-d6) δ 8.25 (dd, J = 4.8, 1.8 Hz, 1H), 8.05 (dd, J = 7.8, 1.8 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.01 - 6.55 (m, 4H), 2.16 (s, 1H), 1.83 (dd, J = 12.1, 5.7 Hz, 1H), 1.48 (d, J = 4.1 Hz, 6H), 1.36 (t, J = 12.1 Hz, 1H), 0.75 (d, J = 6.3 Hz, 3H). |
| 2216 | 614.20 | 2.11 | 1H NMR (400 MHz, DMSO) δ 12.60 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 10.8 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 4.63 - 4.34 (m, 1H), 3.84 (d, J = 6.5 Hz, 2H), 2.83 (t, J = 5.9 Hz, 2H), 2.27 - 2.11 (m, 1H), 2.10 - 1.98 (m, 1H), 1.93 (tt, J = 10.8, 5.6 Hz, 1H), 1.86 - 1.69 (m, 2H), 1.29 (s, 9H), 1.00 (d, J = 6.7 Hz, 6H). |
| 2217 | 534.12 | 2.88 | |
| 2218 | 486.40 | 2.53 | |
| 2219 | 515.20 | 1.65 | |
| 2220 | 526.34 | 1.63 | |
| 2221 | 476.19 | 2.36 | |
| 2222 | 515.20 | 1.57 | |
| 2223 | 550.22 | 1.10 | |
| 2224 | 554.20 | 2.12 | 1H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 6.7 IIz, 1H), 7.46 (s, 2H), 7.33 (d, J = 7.7 Hz, 1H), 7.22 (d, J = 7.1 Hz, 1H), 6.89 (d, J = 10.8 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.48 (s, 2H), 3.84 (d, J = 6.3 Hz, 2H), 3.52 (d, J = 11.3 Hz, 2H), 3.40 (d, J = 11.3 Hz, 3H), 2.30 (d, J = 4.4 Hz, 2H), 2.24 (dd, J = 12.3, 5.3 Hz, 1H), 1.92 (d, J = 4.5 Hz, 1H), 1.25 (d, J = 9.3 Hz, 1H), 1.04 - 0.94 (m, 6H), 0.74 (d, J = 6.2 Hz, 3H). |
| 2225 | 486.33 | 1.45 | |
| 2226 | 529.32 | 1.56 | |
| 2227 | 538.32 | 1.22 | |
| 2228 | 551.60 | 2.40 | |
| 2229 | 494.28 | 1.50 | |
| 2230 | 466.30 | 1.38 | 1H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 7.66 - 7.55 (m, 2H), 7.17 (dd, J = 7.3, 0.7 Hz, 1H), 6.66 (dd, J = 8.4, 0.8 Hz, 1H), 6.41 (s, 2H), 5.26 (p, J = 6.1 Hz, 1H), 2.60 - 2.51 (m, 1H), 2.49 - 2.40 (m, 1H), 2.33 (p, J = 1.8 Hz, 0H), 2.20 (s, 1H), 1.84 (dd, J = 11.8, 5.6 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.43 - 1.30 (m, 4H), 1.29 (d, J = 6.2 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H). |
| 2231 | 512.20 | 1.35 | |
| 2232 | 496.40 | 1.20 | 1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.25 (dd, J = 5.1, 2.9 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.84 - 6.19 (m, 5H), 2.60 (d, J = 8.8 Hz, 2H), 2.29 (s, 3H), 2.26 - 2.14 (m, 1H), 1.87 (dd, J = 11.9, 5.6 Hz, 1H), 1.65 - 1.53 (m, 6H), 1.42 (t, J = 12.0 Hz, 1H), 0.88 (d, J = 6.2 Hz, 3H). |
| 2233 | 527.22 | 2.22 | |
| 2234 | 551.50 | 1.82 | 1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 12.54 (s, 1H), 8.28 - 8.22 (m, 1H), 8.16 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 6.9 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.1 Hz, 1H), 6.45 (t, J = 6.7 Hz, 1H), 2.75 (q, J = 10.2 Hz, 2H), 2.24 (d, J = 12.0 Hz, 1H), 1.89 (dd, J = 12.2, 5.5 Hz, 1H), 1.61 (s, 6H), 1.45 (t, J = 11.9 Hz, 1H), 0.91 (d, J = 6.2 Hz, 3H). |
| 2235 | 511.30 | 1.52 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (d, J = 6.2 Hz, 1H), 8.24 (dd, J = 7.2, 2.1 Hz, 1H), 7.83 (td, J = 6.2, 2.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 7.3, 1.4 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.01 - 6.96 (m, 1H), 6.45 (t, J = 6.8 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.74 (dd, J = 16.1, 9.7 Hz, 2H), 2.24 (s, 1H), 1.93 - 1.85 (m, 1H), 1.62 (d, J = 1.4 Hz, 6H), 1.45 (t, J = 12.1 Hz, 1H), 1.36 (t, J = 7.0 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2236 | 502.50 | 1.66 | |
| 2237 | 574.60 | 1.59 | |
| 2238 | 542.50 | 1.44 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 1H), 8.24 (dd, J = 4.8, 1.8 Hz, 1H), 8.03 (dd, J = 7.9, 1.8 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 1H), 6.69 (寬單峰, 2H), 5.83 (s, 1H), 3.90 (d, J = 6.6 Hz, 2H), 2.52 (s, 3H), 2.14 (br s, 1H), 2.02 (七重峰, J = 6.6 Hz, 1H), 1.85 (dd, J = 12.0, 5.6 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 1.36 (t, J = 11.9 Hz, 1H), 1.24 (br s, 1H), 0.95 (d, J = 6.7 Hz, 6H), 0.88-0.82 (m, 1H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2239 | 497.51 | 2.12 | 1H NMR (400 MHz, DMSO-d6) δ12.83 (s, 1H), 8.18 - 8.12 (m, 2H), 7.88 - 7.85 (d, 1H), 7.50 - 7.47 (d, 1H), 7.31 - 7.28 (d, 1H), 7.14 - 6.99 (m, 4H), 6.63 - 6.60 (dd, 1H), 3.78 (s, 3H), 2.30 - 2.21 (m, 1H), 1.89 - 1.82 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.46 - 1.35 (m, 1H), 0.89 - 0.87 (d, 3H) |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2240 | 488.33 | 1.38 | |
| 2241 | 524.24 | 1.55 | |
| 2242 | 486.20 | 1.58 | |
| 2243 | 707.50 | 1.57 | |
| 2244 | 497.20 | 1.30 | |
| 2245 | 550.22 | 1.10 | |
| 2246 | 430.40 | 1.80 | |
| 2247 | 527.30 | 1.47 | |
| 2248 | 514.40 | 1.44 | 1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 8.23 (dd, J = 4.8, 1.8 Hz, 1H), 8.02 (dd, J = 7.8, 1.9 Hz, 1H), 8.00 (d, J = 1.2 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 7.8, 4.7 Hz, 1H), 6.68 (寬單峰, 2H), 4.29 (q, J = 7.0 Hz, 2H), 2.45 (d, J = 8.7 Hz, 2H), 2.12 (br s, 1H), 1.94 (d, J = 0.9 Hz, 3H), 1.84 (dd, J = 12.0, 5.6 Hz, 1H), 1.55 (s, 3H), 1.54 (s, 3H), 1.40-1.33 (m, 4H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2249 | 525.42 | 2.42 | |
| 2250 | 472.29 | 2.32 | |
| 2251 | 518.22 | 2.48 | |
| 2252 | 487.30 | 2.84 | |
| 2253 | 545.23 | 2.34 | |
| 2254 | 537.43 | 2.28 | |
| 2255 | 492.40 | 2.73 | |
| 2256 | 525.30 | 1.57 | |
| 2257 | 482.24 | 0.90 | |
| 2258 | 570.00 | 3.40 | 1H NMR (400 MHz, DMSO-d6) δ 7.67 - 7.54 (m, 2H), 7.49 (t, J = 1.8 Hz, 1H), 7.40 (dt, J = 10.2, 1.8 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 6.64 (s, 2H), 3.84 (d, J = 6.7 Hz, 2H), 3.43 (s, 3H), 2.82 (s, 1H), 2.64 (s, 1H), 2.34 - 2.22 (m, 1H), 2.05 (七重峰, J = 6.6 Hz, 1H), 1.91 (dd, J = 11.9, 5.7 Hz, 1H), 1.62 (d, J = 4.4 Hz, 6H), 1.46 (t, J = 12.1 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 6.3 Hz, 3H). |
| 2259 | 502.24 | 1.76 | |
| 2260 | 536.22 | 2.32 | |
| 2261 | 549.43 | 2.69 | |
| 2262 | 528.12 | 2.54 | |
| 2263 | 549.43 | 2.30 | |
| 2264 | 515.21 | 2.70 | |
| 2265 | 440.40 | 1.17 | |
| 2266 | 516.20 | 1.31 | 1H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 7.70 - 7.52 (m, 2H), 7.17 (dd, J = 7.3, 0.5 Hz, 1H), 6.70 (dd, J = 9.7, 8.5 Hz, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 5.19 (s, 2H), 3.84 (td, J = 11.1, 3.7 Hz, 2H), 3.38 - 3.18 (m, 2H), 2.84 (t, J = 10.0 Hz, 1H), 2.68 - 2.55 (m, 1H), 2.07 (s, 4H), 1.81 (t, J = 6.4 Hz, 1H), 1.65 (dd, J = 30.6, 10.5 Hz, 2H), 1.55 (d, J = 8.6 Hz, 6H), 1.49 (s, 3H), 1.28 (d, J = 6.6 Hz, 10H). |
| 2267 | 539.60 | 1.90 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (d, J = 6.4 Hz, 1H), 8.24 (dd, J = 7.3, 2.1 Hz, 1H), 7.82 (dt, J = 6.5, 3.5 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.65 - 7.58 (m, 2H), 7.37 (td, J = 8.4, 3.1 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.02 - 6.96 (m, 1H), 6.45 (t, J = 6.8 Hz, 1H), 3.81 (d, J = 6.6 Hz, 2H), 2.79 - 2.69 (m, 2H), 2.24 (s, 1H), 2.05 (dt, J = 13.2, 6.6 Hz, 1H), 1.89 (dd, J = 11.8, 5.6 Hz, 1H), 1.62 (d, J = 1.9 Hz, 6H), 1.45 (t, J = 12.0 Hz, 1H), 0.99 (dd, J = 6.8, 2.9 Hz, 6H), 0.91 (d, J = 6.4 Hz, 3H). |
| 2268 | 497.13 | 1.40 | |
| 2269 | 568.20 | 2.00 | 1H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.53 (s, 1H), 7.47 (d, J = 9.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 6.92 (d, J = 10.7 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 3.84 (d, J = 6.5 Hz, 2H), 3.61 (d, J = 9.7 Hz, 1H), 3.49 (q, J = 9.8 Hz, 1H), 2.71 - 2.51 (m, 2H), 2.38 - 2.19 (m, 1H), 2.03 (dd, J = 13.2, 6.7 Hz, 2H), 1.98 - 1.86 (m, 1H), 1.86 - 1.73 (m, 2H), 1.61 (dt, J = 22.9, 10.5 Hz, 2H), 0.98 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.4 Hz, 3H). |
| 2270 | 531.12 | 2.72 | |
| 2271 | 610.30 | 2.23 | |
| 2272 | 502.52 | 1.05 | |
| 2273 | 515.21 | 2.62 | 1H NMR (400 MHz, DMSO) δ12.81 (s, 1H), 8.19 - 8.17 (dd, 1H), 8.06 (t, J = 7.91, 1H), 7.81 - 7.66 (m, 3H), 7.43 - 7.34 (m, 1H), 7.29 - 7.09 (m, 3H), 6.64 - 6.61 (dd, 1H), 5.44 (s, 2H), 2.37 - 2.14 (m, 2H), 2.00 - 1 .94 (m, 1H), 1.80 - 1.73 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3II), 1.30 (t, J = 11.86, 1H), 0.67 - 0.65 (d, 3H) |
| 2274 | 517.32 | 1.37 | |
| 2275 | 466.29 | 1.87 | |
| 2276 | 527.40 | 1.62 | |
| 2277 | 444.60 | 1.40 | |
| 2278 | 529.20 | 1.71 | 1H NMR (400 MHz, DMSO) δ 12.62 (s, 1H), 12.53 (d, J = 5.8 Hz, 1H), 8.24 (dd, J = 7.3, 2.2 Hz, 1H), 7.83 (dd, J = 6.4, 4.3 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.47 (d, J = |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.9 Hz, 1H), 7.41 (d, J = 10.2 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.88 (dt, J = 10.8, 2.3 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.74 (dd, J = 17.6, 10.2 Hz, 2H), 2.25 (s, 1H), 1.89 (dd, J = 11.9, 5.7 Hz, 1H), 1.60 (d, J = 1.9 Hz, 6H), 1.45 (t, J = 12.1 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2279 | 566.30 | 1.82 | 1H NMR (400 MHz, DMSO) δ 8.70 (s, 1H), 7.99 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 6.97 (dd, J = 17.9, 7.5 Hz, 2H), 6.45 (d, J = 8.2 Hz, 1H), 6.12 (s, 2H), 3.11 - 2.91 (m, 4H), 2.83 (s, 3H), 2.30 (s, 3H), 2.13 (dq, J = 17.3, 9.3, 8.4 Hz, 1H), 1.90 (t, J = 6.8 Hz, 1H), 1.81 (dd, J = 11.6, 5.5 Hz, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.37 (t, J = 11.9 Hz, 1H), 0.88 - 0.81 (m, 10H). |
| 2280 | 516.23 | 1.54 | |
| 2281 | 494.30 | 1.08 | 1H NMR (400 MHz, DMSO-d6) δ 12.29 (s, 1H), 7.66 - 7.57 (m, 2H), 7.17 (d, J = 7.3 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.41 (s, 2H), 5.55 - 5.48 (m, 1H), 3.94 - 3.83 (m, 2H), 3.83 - 3.76 (m, 2H), 2.56 (d, J = 10.6 Hz, 1H), 2.44 (t, J = 8.7 Hz, 1H), 2.32 - 2.16 (m, 1H), 2.10 - 2.02 (m, 1H), 1.84 (dd, J = 11.8, 5.6 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.37 (t, J = 12.0 Hz, 1H), 0.85 (d, J = 6.3 Hz, 3H). |
| 2282 | 502.31 | 2.63 | 1H NMR (400 MHz, DMSO-d6) δ12.93 (s, 1H), 10.03 (s, 1H), 8.16 - 8.14 (dd, 1H), 7.93 (t, J = 7.80, 1H), 7.74 - 7.71 (dd, 1H), 7.61 - 7.58 (d, 1H), 7.54 - 7.49 (m, 2H), 7.13 - 7.10 (d, 1H), 6.80 - 6.72 (m, 1H), 6.56 - 6.53 (dd, 1H), 2.04 - 1.93 (m, 1H), 1.81 - 1.74 (m, 1H), 1.45 (s, 6H), 1.32 (t, J = 11.87, 1H), 0.73 - 0.71 (d, 3H) |
| 2283 | 524.22 | 1.65 | |
| 2284 | 503.30 | 1.56 | 1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 12.53 (d, J = 6.1 Hz, 1H), 8.24 (dd, J = 7.3, 2.2 Hz, 1H), 8.04 (ddd, J = 12.0, 8.3, 2.2 Hz, 1H), 7.92 (dt, J = 8.8, 3.1 Hz, 1H), 7.83 (dt, J = 7.0, 3.5 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.57 (dt, J = 10.5, 8.6 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.73 (dd, J = 9.6, 7.8 Hz, 2H), 2.30 - 2.16 (m, 1H), 1.89 (dd, J = 12.0, 5.5 Hz, 1H), 1.60 (d, J = 2.0 Hz, 6H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2285 | 550.33 | 1.49 | |
| 2286 | 537.43 | 3.02 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2287 | 494.50 | 1.63 | |
| 2288 | 509.22 | 1.23 | |
| 2289 | 570.30 | 2.21 | 1H NMR (400 MHz, DMSO) δ 12.52 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.43 (dd, J = 9.7, 1.7 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 7.3, 0.6 Hz, 1H), 6.88 (dt, J = 10.7, 2.3 Hz, 1H), 6.69 (dd, J = 8.4, 0.6 Hz, 1H), 6.46 (s, 2H), 3.83 (d, J = 6.5 Hz, 2H), 3.47 (d, J = 7.2 Hz, 2H), 2.68 (d, J = 7.2 Hz, 3H), 2.05 (dt, J = 13.3, 4.3 Hz, 1H), 1.76 (s, 1H), 1.61 (d, J = 11.7 Hz, 5H), 1.12 (t, J = 9.5 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H), 0.95 - 0.80 (m, 2H). |
| 2290 | 498.23 | 1.27 | |
| 2291 | 502.26 | 1.39 | |
| 2292 | 534.12 | 2.70 | |
| 2293 | 527.22 | 2.36 | |
| 2294 | 496.30 | 1.44 | |
| 2295 | 501.30 | 1.46 | 1H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 11.69 (s, 1H), 8.00 - 7.88 (m, 1H), 7.78 - 7.61 (m, 2H), 7.55 - 7.40 (m, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.09 - 7.00 (m, 1H), 6.85 (dd, J = 8.9, 5.1 Hz, 1H), 6.27 - 6.13 (m, 1H), 3.23 - 3.07 (m, 2H), 2.22 - 2.11 (m, 1H), 1.87 (dd, J = 11.8, 5.7 Hz, 1H), 1.50 (d, J = 3.4 Hz, 6H), 1.41 (t, J = 12.1 Hz, 1H), 0.88 (d, J = 6.1 Hz, 3H). |
| 2296 | 534.20 | 1.70 | |
| 2297 | 548.23 | 2.70 | |
| 2298 | 501.11 | 2.43 | |
| 2299 | 506.21 | 2.30 | |
| 2300 | 497.30 | 1.62 | |
| 2301 | 522.30 | 2.22 | |
| 2302 | 532.22 | 1.41 | |
| 2303 | 512.23 | 1.56 | |
| 2304 | 491.23 | 1.61 | |
| 2305 | 474.39 | 2.52 | |
| 2306 | 539.40 | 2.16 | 1H NMR (400 MHz, DMSO-d6) δ 7.63 (s, 1H), 7.49 (s, 1H), 7.36 (s, 1H), 7.13 (d, J = 6.9 Hz, 1H), 7.06 (s, 2H), 6.52 (s, 1H), 6.23 (s, 2H), 5.26 (p, J = 6.2 Hz, 1H), 2.91 (s, 1H), 2.42 (s, 3H), 2.18 (t, J = 7.4 Hz, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.61 (s, 3H), 1.56 (s, 3H), 1.47 (q, J = 6.6, 6.1 Hz, 1H), 1.38 (t, J = 11.9 Hz, 1H), 1.30 (d, J = 6.2 Hz, 6H), 0.83 (d, J = 5.9 Hz, 3H). |
| 2307 | 460.29 | 2.51 | |
| 2308 | 471.39 | 2.51 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2309 | 527.22 | 2.12 | |
| 2310 | 510.41 | 2.25 | |
| 2311 | 474.40 | 1.00 | |
| 2312 | 500.30 | 1.62 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.30 (d, J = 2.2 Hz, 1H), 7.72 (d, J = 2.3 Hz, 1H), 7.68 - 7.53 (m, 2H), 7.51 - 7.43 (m, 1H), 7.46 - 7.34 (m, 2H), 7.21 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.48 (s, 2H), 2.22 (s, 1H), 1.86 (dd, J = 11.9, 5.6 Hz, 1H), 1.55 (d, J = 10.4 Hz, 6H), 1.41 (t, J = 12.0 Hz, 1H), 0.87 (d, J = 6.3 Hz, 3H). |
| 2313 | 564.42 | 1.95 | |
| 2314 | 482.20 | 1.34 | |
| 2315 | 541.30 | 1.54 | 1H NMR (400 MHz, DMSO-d6) δ 12.64 - 12.32 (m, 2H), 8.22 (dd, J = 7.2, 2.2 Hz, 1H), 7.85 - 7.77 (m, 1H), 7.60 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 6.43 (t, J = 6.8 Hz, 1H), 2.81 - 2.72 (m, 1H), 2.67 (d, J = 8.7 Hz, 2H), 2.48 - 2.39 (m, 由溶劑峰遮蔽),2.21 (s, 1H), 2.07 (s, 1H), 1.84 (dd, J = 11.8, 5.6 Hz, 1H), 1.78 - 1.60 (m, 6H), 1.51 (d, J = 10.8 Hz, 6H), 1.39 (t, J = 12.1 Hz, 1H), 0.89 (d, J = 6.2 Hz, 3H). |
| 2316 | 509.21 | 2.17 | |
| 2317 | 457.28 | 2.40 | |
| 2318 | 460.29 | 2.31 | |
| 2319 | 510.19 | 1.02 | |
| 2320 | 481.30 | 2.30 | |
| 2321 | 550.33 | 2.40 | |
| 2322 | 536.50 | 2.01 | |
| 2323 | 544.27 | 1.17 | |
| 2324 | 474.09 | 2.01 | |
| 2325 | 610.70 | 1.93 | |
| 2326 | 588.30 | 1.32 | 1H NMR (400 MHz, DMSO-d6) δ 12.50 (s, 1H), 8.29 - 8.18 (m, 2H), 8.07 (dd, J = 7.8, 1.8 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.90 - 6.63 (m, 0H), 6.79 (dd, J = 7.8, 4.8 Hz, 1H), 6.14 (d, J = 2.8 Hz, 1H), 4.36 - 4.29 (m, 2H), 3.79 - 3.71 (m, 2H), 3.62 - 3.54 (m, 2H), 3.52 - 3.47 (m, 2H), 3.43 (q, J = 7.0 Hz, 2H), 2.46 (d, J = 8.8 Hz, 2H), 2.13 (m, J = 5.8 IIz, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.44 - 1.33 (m, 1H), 1.09 (t, J = 7.0 Hz, 3H), 0.74 (d, J = 6.3 Hz, 3H). |
| 2327 | 488.29 | 1.36 | |
| 2328 | 508.31 | 1.79 | |
| 2329 | 503.21 | 2.21 | |
| 2330 | 472.29 | 2.57 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2331 | 580.00 | 3.15 | |
| 2332 | 485.20 | 2.20 | |
| 2333 | 518.22 | 1.47 | |
| 2334 | 532.16 | 1.44 | |
| 2335 | 561.14 | 2.31 | |
| 2336 | 487.30 | 2.89 | |
| 2337 | 534.25 | 1.83 | |
| 2338 | 506.21 | 2.08 | |
| 2339 | 472.30 | 1.46 | |
| 2340 | 484.30 | 2.52 | |
| 2341 | 502.31 | 1.84 | |
| 2342 | 445.28 | 2.29 | |
| 2343 | 490.30 | 2.55 | |
| 2344 | 625.60 | 1.71 | 1H NMR (400 MHz, DMSO-d6) δ 12.29 (s, 1H), 7.65 - 7.59 (m, 1H), 7.33 - 7.24 (m, 1H), 7.22 - 7.14 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.53 (s, 1H), 4.19 - 4.02 (m, 2H), 2.54 (s, 1H), 2.31 (s, 2H), 2.28 (d, J = 5.3 Hz, 1H), 2.19 (d, J = 6.7 Hz, 1H), 1.83 (dd, J = 11.9, 5.7 Hz, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.40 - 1.32 (m, 2H), 1.31 (s, 9H), 1.18 (s, 2H), 1.02 (s, 9H), 0.98 (s, 1H), 0.85 (d, J = 6.2 Hz, 3H). (醯胺旋轉異構體) |
| 2345 | 498.53 | 1.09 | |
| 2346 | 474.09 | 2.70 | |
| 2347 | 561.60 | 2.32 | |
| 2348 | 499.40 | 1.59 | |
| 2349 | 500.17 | 1.29 | |
| 2350 | 453.98 | 1.90 | |
| 2351 | 474.30 | 1.15 | 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.24 (dd, J = 5.0, 1.9 Hz, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 6.77 (dd, J = 7.8, 4.8 Hz, 2H), 6.68 (d, J = 7.8 Hz, 2H), 4.21 (dd, J = 38.7, 11.0 Hz, 1H), 4.02 (d, J = 11.4 Hz, 1H), 3.63 - 3.44 (m, 1H), 2.47 - 2.36 (m, 2H), 2.18 - 2.04 (m, 1H), 2.04 - 1.91 (m, 1H), 1.91 - 1.73 (m, 2H), 1.72 - 1.58 (m, 1H), 1.53 (s, 2H), 1.51 - 1.42 (m, 6H), 1.43 - 1.24 (m, 2H), 0.73 (d, J = 6.1 Hz, 3H). |
| 2352 | 519.04 | 1.49 | |
| 2353 | 524.52 | 2.49 | |
| 2354 | 462.39 | 1.84 | |
| 2355 | 514.17 | 1.43 | |
| 2356 | 515.22 | 1.77 | |
| 2357 | 526.32 | 2.22 | |
| 2358 | 554.70 | 1.81 | 1H NMR (400 MHz, DMSO-d6) δ 12.51 (s, 1H), 8.24 (d, J = 2.8 Hz, 1H), 8.22 (寬單峰, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.85 (d, J = |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 8.2 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.78 - 6.70 (m, 1H), 6.65 (br s, 2H), 6.16 (d, J = 2.7 Hz, 1H), 3.90 (s, 2H), 3.50 (br d, J = 9.9 Hz, 1H), 3.39 (br d, J = 8.8 Hz, 1H), 2.48-2.38 (br m, 2H), 2.26 (dd, J = 11.8, 5.2 Hz, 1H), 1.92-1.90 (br m, 2H), 1.80-1.75 (br m, 2H), 1.61 (br s, 1H), 1.51 (t, J = 11.5 Hz, 1H), 1.01 (s, 9H), 0.78 (d, J = 6.4 Hz, 3H). |
| 2359 | 495.40 | 1.34 | |
| 2360 | 515.40 | 1.63 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 2H), 8.23 (d, J = 7.1 Hz, 1H), 8.18 (d, J = 2.8 Hz, 1H), 7.87 - 7.71 (m, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.44 (寬單峰, 1H), 6.07 (d, J = 2.7 Hz, 1H), 4.85 (sep, J = 6.2 Hz, 1H), 2.71 (br s, 2H), 2.22 (br s, 1H), 1.88 (dd, J = 12.0, 5.6 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.43 (t, J = 12.0 Hz, 1H), 1.33 (d, J = 2.9 Hz, 3H), 1.32 (d, J = 2.9 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H). |
| 2361 | 484.30 | 1.74 | 1H NMR (400 MHz, DMSO-d6) δ 7.96 (s, 1H), 7.51 (s, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 5.98 (s, 3H), 5.88 (s, 1H), 3.05 - 2.96 (m, 2H), 2.24 (d, J = 19.4 Hz, 2H), 2.11 (s, 3H), 1.64 (s, 2H), 1.48 (d, J = 5.0 Hz, 7H), 0.97 (d, J = 6.4 Hz, 4H), 0.86 (d, J = 6.3 Hz, 4H). |
| 2362 | 552.60 | 1.24 | |
| 2363 | 481.23 | 1.10 | |
| 2364 | 525.30 | 2.04 | 1H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.14 (s, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.49 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 2.71 - 2.58 (m, 2H), 2.45 (s, 3H), 2.29 - 2.13 (m, 1H), 1.87 (dd, J = 11.9, 5.7 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 2H), 1.42 (t, J = 12.1 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H). |
| 2365 | 549.43 | 2.57 | |
| 2366 | 550.30 | 1.72 | |
| 2367 | 500.20 | 1.04 | |
| 2368 | 508.32 | 1.13 | |
| 2369 | 511.15 | 1.63 | |
| 2370 | 562.40 | 1.58 | |
| 2371 | 445.28 | 2.37 | |
| 2372 | 502.50 | 1.59 | |
| 2373 | 492.30 | 1.51 | 1H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 7.65 - 7.55 (m, 2H), 7.17 (dd, J = 7.3, 0.7 Hz, 1H), 6.66 (dd, J = 8.5, 0.8 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 6.45 (s, 2H), 4.88 - 4.57 (m, 1H), 2.63 - 2.51 (m, 1H), 2.43 (t, J = 8.8 Hz, 1H), 2.17 (s, 1H), 1.82 (dd, J = 11.9, 5.6 Hz, 1H), 1.49 - 1.26 (m, 10H), 1.19 (dtd, J = 13.5, 9.0, 8.5, 5.1 Hz, 1H), 0.85 (d, J = 6.3 Hz, 3H), 0.62 - 0.44 (m, 2H), 0.32 - 0.21 (m, 2H). |
| 2374 | 569.30 | 2.39 | 1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.54 (s, 1H), 7.42 (t, J = 7.8 Hz, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 10.5 Hz, 1H), 3.82 (d, J = 6.5 Hz, 2H), 3.67 (dd, J = 12.3, 6.3 Hz, 1H), 2.66 (t, J = 12.5 Hz, 1H), 2.11 (dt, J = 13.2, 6.6 Hz, 1H), 1.69 (dd, J = 12.5, 6.3 Hz, 1H), 1.57 - 1.40 (m, 2H), 1.18 (s, 3H), 1.05 (d, J = 6.9 Hz, 9H), 0.81 (s, 3H), 0.75 (s, 3H). |
| 2375 | 556.30 | 2.43 | 1H NMR (400 MHz, DMSO) δ 12.84 - 11.49 (m, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.26 - 8.05 (m, 0H), 7.66 (t, J = 7.9 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 9.8 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 10.7 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.59 (s, 2H), 3.84 (d, J = 6.5 Hz, 2H), 3.35 (d, J = 6.4 Hz, 2H), 2.10 - 1.97 (m, 1H), 1.64 (d, J = 21.5 Hz, 6H), 1.24 - 1.04 (m, 3H), 1.00 (d, J = 6.7 Hz, 6H), 0.94 (d, J = 10.5 Hz, 2H). |
| 2376 | 540.20 | 2.11 | 1H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.63 (dd, J = 8.3, 7.4 Hz, 1H), 7.46 - 7.38 (m, 2H), 7.34 (d, J = 7.9 Hz, 1H), 7.26 - 7.20 (m, 1H), 6.88 (dt, J = 10.8, 2.3 Hz, 1H), 6.71 - 6.67 (m, 1H), 6.45 (s, 2H), 4.21 (d, J = 12.9 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.60 (t, J = 11.5 Hz, 1H), 2.47 - 2.39 (m, 1H), 2.10 - 1.95 (m, 1H), 1.86 (dd, J = 12.8, 6.3 Hz, 1H), 1.73 (d, J = 12.8 Hz, 1H), 1.58 (d, J = 10.8 Hz, 1H), 1.17 (dd, J = 15.0, 8.4 Hz, 2H), 0.99 (d, J = 6.7 Hz, 6H), 0.69 (dt, J = 9.3, 5.7 Hz, 1H), -0.11 (t, J = 7.8 Hz, 1H). |
| 2377 | 541.20 | 1.63 | 1H NMR (400 MHz,甲醇-d4) δ 9.19 (s, 1H), 8.80 (d, J = 5.0 Hz, 1H), 8.48 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 8.1, 4.9 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 10.2 Hz, 1H), 6.75 (d, J = 10.9 Hz, 1H), 3.81 (d, J = 6.5 Hz, 2H), 2.98 (t, J = 9.1 Hz, 1H), 2.86 (t, J = 10.0 Hz, 1H), 2.42 (s, 1H), 2.05 (ddd, J = 19.8, 13.3, 7.1 Hz, 3H), 1.58 (d, J = 17.4 Hz, 6H), 1.03 (dd, J = 7.5, 3.4 Hz, 6H), 0.94 (d, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | J = 6.4 Hz, 3H). |
| 2378 | 528.12 | 2.64 | |
| 2379 | 510.17 | 1.51 | |
| 2380 | 510.15 | 1.46 | |
| 2381 | 534.12 | 2.50 | |
| 2382 | 506.21 | 2.34 | |
| 2383 | 529.32 | 1.55 | 1H NMR (400 MHz, DMSO) δ12.56 (s, 1H), 10.51 (s, 1H), 8.18 - 8.16 (dd, 1H), 7.79 - 7.69 (m, 2H), 7.26 - 7.23 (d, 1H), 7.13 - 7.10 (d, 1H), 6.63 - 6.60 (dd, 1H), 4.44 - 4.35 (m, 1H), 3.05 (m, 2H), 2.83 - 2.80 (m, 2 H), 2.72 (s, 3H), 2.70 (s, 3H), 2.23 - 2.12 (m, 1H), 1.83 - 1.73 (m, 3H), 1.60 (m, 3H), 1.52 (s, 3H), 1.49 (s, 3H), 1.37 (t, J = 11.98, 1H), 1.09 (m, 2H), 0.79 - 0.77 (d, 3H) |
| 2384 | 511.25 | 1.47 | |
| 2385 | 526.02 | 2.69 | |
| 2386 | 500.60 | 1.53 | |
| 2387 | 523.32 | 1.90 | |
| 2388 | 532.21 | 1.49 | |
| 2389 | 506.21 | 1.37 | 1H NMR (400 MHz, DMSO) δ 9.03 - 9.00 (d, 1H), 8.68 (s, 1H), 8.40 - 8.30 (m, 2H), 8.18 - 8.16 (dd, 1H), 8.08 - 8.05 (dd, 1H), 8.01 (s, 1H), 7.87 - 7.84 (dd, 1H), 7.63 - 7.60 (dd, 1H), 6.66 - 6.63 (dd, 1H), 2.28 - 2. 24 (d, 2H), 1.65 - 1.47 (m, 2H), 1.47 (s, 3H), 1.40 (s, 3H), 1.17 (t, J = 11.09, 1H), 0.15 - 0.13 (d, 3H) |
| 2390 | 549.13 | 2.70 | |
| 2391 | 494.20 | 2.42 | |
| 2392 | 534.30 | 1.67 | |
| 2393 | 462.39 | 1.80 | |
| 2394 | 498.50 | 1.58 | |
| 2395 | 522.30 | 1.86 | |
| 2396 | 475.29 | 1.93 | |
| 2397 | 534.12 | 2.50 | |
| 2398 | 549.50 | 2.03 | |
| 2399 | 500.19 | 1.68 | |
| 2400 | 547.33 | 2.26 | |
| 2401 | 519.27 | 1.44 | |
| 2402 | 549.13 | 2.81 | |
| 2403 | 528.19 | 1.46 | |
| 2404 | 569.50 | 1.59 | |
| 2405 | 441.40 | 1.13 | 1H NMR (400 MHz, DMSO-d6) δ 12.90 (s, 1H), 12.57 (s, 1H), 8.27 (dd, J = 7.3, 2.2 Hz, 1H), 8.17 (s, 1H), 7.85 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.62 - 7.48 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 6.46 (t, J = 6.8 Hz, 1H), 3.01 (t, J = 8.5 Hz, 1H), 2.76 (t, J = 10.1 Hz, 1H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.30 - 2.17 (m, 1H), 1.88 (dd, J = 11.8, 5.7 Hz, 1H), 1.63 (s, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.92 (d, J = 6.3 Hz, 3H). |
| 2406 | 542.20 | 1.66 | 1H NMR (400 MHz, DMSO-d6) δ 8.25 (dd, J = 4.8, 1.8 Hz, 1H), 8.05 (dd, J = 7.8, 1.8 Hz, 1H), 7.92 (d, J = 1.0 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.71 (s, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.78 (dd, J = 7.8, 4.8 Hz, 2H), 2.46 (s, 1H), 2.13 (s, 1H), 1.86 (dd, J = 12.0, 5.7 Hz, 1H), 1.56 (d, J = 4.4 Hz, 6H), 1.39 (t, J = 12.2 Hz, 1H), 0.98 (s, 9H), 0.75 (d, J = 6.2 Hz, 3H). |
| 2407 | 549.43 | 2.09 | |
| 2408 | 513.41 | 2.62 | |
| 2409 | 499.31 | 2.49 | |
| 2410 | 525.30 | 1.62 | |
| 2411 | 481.50 | 1.83 | |
| 2412 | 461.19 | 2.69 | |
| 2413 | 510.17 | 1.46 | |
| 2414 | 476.29 | 1.42 | 1H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 8.14 (s, 3H), 7.92 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 10.4, 2.0 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.56 (td, J = 8.0, 6.2 Hz, 1H), 7.33 - 7.25 (m, 2H), 3.78 (ddd, J = 16.8, 10.7, 6.2 Hz, 2H), 3.71 - 3.62 (m, 1H), 3.62 - 3.53 (m, 1H), 3.41 (dd, J = 10.0, 4.7 Hz, 1H), 3.10 (t, J = 10.2 Hz, 1H), 2.99 - 2.91 (m, 1H), 2.36 (dd, J = 13.6, 9.2 Hz, 1H), 2.28 - 2.16 (m, 1H), 1.97 (dd, J = 12.2, 5.8 Hz, 2H), 1.68 (s, 3H), 1.64 (s, 3H), 1.56 (dd, J = 15.4, 8.1 Hz, 1H), 1.05 (d, J = 6.3 Hz, 3H). |
| 2415 | 523.32 | 2.92 | |
| 2416 | 538.17 | 1.49 | |
| 2417 | 645.50 | 1.63 | 1H NMR (400 MHz, DMSO-d6) δ 12.28 (s, 1H), 7.65 - 7.57 (m, 1H), 7.25 (ddd, J = 34.6, 18.8, 7.3 Hz, 7H), 6.67 (d, J = 8.3 Hz, 1H), 5.50 (d, J = 19.3 Hz, 1H), 4.26 - 3.97 (m, 2H), 3.81 (s, 1H), 3.77 (d, J = 7.4 Hz, 1H), 3.73 - 3.51 (m, 3H), 2.30 - 2.04 (m, 2H), 1.82 (dd, J = 12.0, 5.7 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.37 (d, J = 10.9 Hz, 2H), 1.27 (s, 9H), 1.17 (s, 1H), 0.84 (d, J = 6.3 Hz, 3H). (旋轉異構體) |
| 2418 | 517.14 | 1.14 | |
| 2419 | 471.30 | 1.19 | |
| 2420 | 497.51 | 2.15 | |
| 2421 | 516.41 | 2.36 | |
| 2422 | 515.20 | 1.60 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2423 | 543.43 | 1.87 | |
| 2424 | 481.40 | 1.50 | |
| 2425 | 516.20 | 1.31 | 1H NMR (400 MHz, DMSO) δ 12.47 (s, 1H), 7.70 - 7.52 (m, 2H), 7.17 (dd, J = 7.3, 0.5 Hz, 1H), 6.78 - 6.59 (m, 2H), 5.14 (s, 2H), 3.84 (d, J = 3.5 Hz, 2H), 3.30 (d, J = 10.7 Hz, 2H), 2.84 (t, J = 10.0 Hz, 1H), 2.68 - 2.55 (m, 1H), 2.07 (s, 4H), 1.87 - 1.73 (m, 1H), 1.65 (dd, J = 30.6, 10.5 Hz, 2H), 1.55 (d, J = 8.6 Hz, 6H), 1.49 (s, 3H), 1.28 (d, J = 6.6 Hz, 10H). |
| 2426 | 496.60 | 1.33 | |
| 2427 | 549.60 | 2.10 | |
| 2428 | 511.31 | 2.44 | 1H NMR (400 MHz, DMSO) δ12.79 (s, 1H), 8.19 - 8.17 (dd, 1H), 8.01 (t, J = 7.80, 1H), 7.80 - 7.74 (m, 2H), 7.50 - 7.47 (d, 2H), 7.14 - 7.11 (d, 1H), 6.82 - 6.79 (d, 2H), 6.64 - 6.61 (dd, 1H), 5.35 - 5.22 (m, 2H), 3 .60 (s, 3H), 2.18 - 1.87 (m, 3H), 1.77 - 1.70 (m, 1H), 1.49 (s, 3II), 1.44 (s, 3H), 1.31- 1.21 (m, 1H), 0.60 - 0.58 (d, 3H) |
| 2429 | 500.20 | 1.70 | |
| 2430 | 405.36 | 1.83 | |
| 2431 | 514.21 | 1.67 | |
| 2432 | 540.40 | 1.36 | 1H NMR (400 MHz,甲醇-d4) δ 8.55 (dd, J = 7.6, 1.7 Hz, 1H), 8.38 (dd, J = 7.2, 2.1 Hz, 1H), 8.11 (dd, J = 6.0, 1.7 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.08 - 6.99 (m, 1H), 3.91 (dd, J = 11.5, 8.5 Hz, 1H), 3.47 - 3.34 (m, 1H), 3.14 - 3.05 (m, 1H), 2.91 - 2.75 (m, 1H), 2.48 - 2.32 (m, 0H), 2.33 - 2.17 (m, 3H), 1.98 - 1.76 (m, 7H), 1.55 (s, 3H), 1.33 (s, 3H), 1.24 (d, J = 6.6 Hz, 3H). |
| 2433 | 524.52 | 1.75 | |
| 2434 | 459.39 | 2.51 | |
| 2435 | 484.24 | 0.94 | |
| 2436 | 526.40 | 1.22 | 1H NMR (400 MHz, DMSO-d6) δ 12.53 (s, 1H), 8.25 (dd, J = 4.8, 1.9 Hz, 1H), 8.05 (dd, J = 7.7, 1.9 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.24 (dd, J = 7.7, 1.8 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.13 - 7.06 (m, 2H), 6.78 (dd, J = 7.8, 4.8 Hz, 3H), 3.85 (s, 3H), 2.53 (s, 2H), 2.15 (s, 1H), 1.82 (dd, J = 11.9, 5.6 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.38 (t, J = 12.1 Hz, 1H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2437 | 491.40 | 1.17 | 1H NMR (400 MHz, DMSO-d6) δ 12.58 (s, 1H), 8.26 (dd, J = 4.8, 1.9 Hz, 1H), 8.24 - 8.15 (m, 2H), 8.05 (dd, J = 7.9, 1.8 Hz, 1H), 8.01 - 7.93 (m, 2H), 7.83 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.90 - 6.52 |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | (m, 3H), 2.60 - 2.40 (m, 24H), 2.22 - 2.05 (m, 1H), 1.86 (dd, J = 11.9, 5.6 Hz, 1H), 1.60 (s, 3H), 1.56 (s, 3H), 1.40 (t, J = 12.1 Hz, 1H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2438 | 481.30 | 1.50 | |
| 2439 | 587.25 | 2.39 | |
| 2440 | 511.16 | 1.69 | 1H NMR (400 MHz, DMSO-d6) δ 12.73 - 12.37 (m, 1H), 8.25 (dd, J = 7.2, 2.2 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.57 - 7.51 (m, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.46 (t, J = 6.8 Hz, 1H), 3.85 (s, 3H), 2.79 - 2.66 (m, 2H), 2.29 - 2.16 (m, 4H), 1.89 (dd, J = 11.7, 5.5 Hz, 1H), 1.63 (d, J = 2.7 Hz, 6H), 1.49 - 1.41 (m, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2441 | 533.22 | 1.45 | |
| 2442 | 516.41 | 2.47 | |
| 2443 | 510.41 | 1.84 | |
| 2444 | 516.19 | 1.61 | |
| 2445 | 467.40 | 1.13 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (d, J = 6.3 Hz, 1H), 8.24 (dd, J = 7.2, 2.2 Hz, 1H), 8.08 - 8.02 (m, 2H), 7.83 (dt, J = 6.6, 3.3 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.54 - 7.46 (m, 2H), 7.46 - 7.40 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.82 - 2.63 (m, 2H), 2.30 - 2.18 (m , 1H), 1.89 (dd, J = 11.8, 5.5 Hz, 1H), 1.62 (s, 6H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2446 | 500.50 | 1.27 | |
| 2447 | 502.48 | 1.03 | |
| 2448 | 538.38 | 1.61 | |
| 2449 | 517.32 | 1.62 | 1H NMR (400 MHz, DMSO-d6) δ12.92 (s, 1H), 10.37 (s, 1H), 9.22 - 9.21 (d, 1H), 9.08 - 9.07 (d, 1H), 8.13 - 8.11 (dd, 1H), 8.02 - 7.93 (m, 2H), 7.87 - 7.84 (d, 1H), 7.81 - 7.78 (dd, 1H), 7.63 - 7.44 (m, 3H), 7.28 - 7.2 5 (d, 1H), 6.49 - 6.46 (dd, 1H), 2.46 - 2.42 (m, 2H), 1.63 - 1.57 (m, 1H), 1.50 - 1.43 (m, 1H), 1.38 (s, 3H), 1.23 - 1.13 (m, 1H), 1.12 (s, 3H), 0.61 - 0.59 (d, 3H) |
| 2450 | 524.26 | 1.52 | |
| 2451 | 556.00 | 1.85 | |
| 2452 | 502.31 | 2.82 | |
| 2453 | 476.19 | 2.13 | |
| 2454 | 498.15 | 1.43 | |
| 2455 | 532.50 | 2.52 | |
| 2456 | 499.30 | 1.56 | 1H NMR (400 MHz, DMSO-d6) δ 12.58 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 12.53 (d, J = 6.2 Hz, 1H), 8.25 (dd, J = 7.2, 2.2 Hz, 1H), 8.02 - 7.94 (m, 1H), 7.91 (td, J = 5.5, 2.7 Hz, 1H), 7.88 - 7.80 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.32 - 7.21 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.76 - 2.65 (m, 2H), 2.31 (d, J = 1.8 Hz, 3H), 1.89 (dd, J = 11.9, 5.6 Hz, 1H), 1.61 (s, 6H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2457 | 532.16 | 1.46 | 1H NMR (400 MHz, DMSO-d6) δ 12.55 (s, 1H), 8.26 (dd, J = 4.9, 1.8 Hz, 1H), 8.07 (dd, J = 7.9, 1.8 Hz, 1H), 7.90 - 7.69 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 7.8, 4.9 Hz, 3H), 3.99 (d, J = 1.0 Hz, 3H), 2.17 (dq, J = 15.9, 6.5 Hz, 1H), 1.86 (dd, J = 12.0, 5.6 Hz, 1H), 1.60 (s, 3H), 1.56 (s, 3H), 1.41 (t, J = 12.1 Hz, 1H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2458 | 542.40 | 1.77 | |
| 2459 | 529.20 | 1.62 | |
| 2460 | 481.30 | 2.30 | |
| 2461 | 501.41 | 2.35 | |
| 2462 | 517.32 | 2.56 | |
| 2463 | 522.35 | 1.85 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.49 (s, 2H), 2.56 (d, J = 8.8 Hz, 2H), 2.28 - 2.10 (m, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.55 (s, 3H), 1.53 (s, 3H), 1.40 (t, J = 12.1 Hz, 1H), 1.32 (s, 9H), 0.87 (d, J = 6.1 Hz, 3H). |
| 2464 | 460.29 | 1.76 | |
| 2465 | 524.52 | 2.33 | |
| 2466 | 535.32 | 2.20 | |
| 2467 | 447.30 | 1.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.50 (s, 1H), 12.44 (s, 1H), 8.22 (dd, J = 7.2, 2.1 Hz, 1H), 7.81 (d, J = 5.8 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 6.47 - 6.37 (m, 2H), 2.66 (d, J = 8.8 Hz, 2H), 2.48 - 2.38 (m, 2H), 2.25 - 2.14 (m, 1H), 2.14 (s, 1H), 2.13 - 2.03 (m, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.52 (d, J = 11.0 Hz, 6H), 1.39 (t, J = 12.0 Hz, 1H), 0.93 - 0.83 (m, 9H). |
| 2468 | 532.41 | 1.35 | |
| 2469 | 511.16 | 1.64 | |
| 2470 | 509.21 | 2.73 | |
| 2471 | 455.40 | 1.22 | 1H NMR (400 MHz, DMSO-d6) δ 12.89 (s, 1H), 12.57 (s, 1H), 8.27 (dd, J = 7.2, 2.1 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 8.09 (s, 1H), 7.85 (dd, J = 6.4, 2.2 Hz, 1H), 7.49 (s, 1H), 7.48 - 7.39 (m, 2H), 6.46 (dd, J = 7.2, 6.4 Hz, 1H), 3.04 - 2.95 (m, 1H), 2.76 (t, J = 10.1 Hz, 1H), 2.40 (s, 3H), 2.31 - 2.18 (m, 1H), 1.87 (dd, J = 11.9, 5.7 Hz, 1H), 1.61 (d, J = 3.8 Hz, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2472 | 490.32 | 1.50 | |
| 2473 | | | 1H NMR (400 MHz, DMSO-d6) δ 12.62 (s, 1H), 7.73 (d, J = 11.4 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.35 (s, 1H), 7.23 (dd, J = 15.3, 8.6 Hz, 2H), 6.96 (dt, J = 10.8, 2.4 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.53 (s, 1H), 3.82 (d, J = 6.6 Hz, 2H), 2.69 - 2.52 (m, 2H), 2.22 (s, 1H), 2.05 (七重峰, J = 6.6 Hz, 1H), 1.87 (dd, J = 11.9, 5.6 Hz, 1H), 1.54 (d, J = 6.7 Hz, 6H), 1.41 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.6 Hz, 6H), 0.87 (d, J = 6.3 Hz, 3H). |
| 2474 | 514.21 | 1.42 | |
| 2475 | 588.50 | 1.62 | |
| 2476 | 550.33 | 2.40 | |
| 2477 | 582.60 | 1.82 | |
| 2478 | 505.22 | 1.36 | |
| 2479 | 570.40 | 2.14 | 1H NMR (400 MHz, DMSO) δ 12.46 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 8.4, 7.3 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.47 - 7.40 (m, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.22 (dd, J = 7.3, 0.6 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.71 (dd, J = 8.4, 0.6 Hz, 1H), 6.50 (s, 2H), 3.89 - 3.75 (m, 3H), 3.15 (dd, J = 9.8, 4.4 Hz, 1H), 2.75 (ddd, J = 18.0, 13.7, 7.5 Hz, 2H), 2.03 (td, J = 13.3, 6.6 Hz, 2H), 1.68 - 1.47 (m, 3H), 1.34 (d, J = 7.5 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.88 (dt, J = 23.3, 11.7 Hz, 7H). |
| 2480 | 483.40 | 1.38 | 1H NMR (400 MHz, DMSO-d6) δ 12.67 (s, 1H), 12.53 (s, 1H), 11.94 (s, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.89 - 7.81 (m, 2H), 7.78 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.26 (ddd, J = 8.5, 7.2, 1.7 Hz, 1H), 6.95 - 6.86 (m, 2H), 6.50 - 6.41 (m, 1H), 2.85 - 2.74 (m, 2H), 2.32 - 2.18 (m, 1H), 1.91 (dd, J = 11.9, 5.6 Hz, 1H), 1.54 (d, J = 5.3 Hz, 6H), 1.46 (t, J = 12.0 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2481 | 540.20 | 1.67 | |
| 2482 | 514.21 | 1.43 | |
| 2483 | 509.50 | 1.84 | 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 12.55 - 12.49 (m, 1H), 8.24 (dd, J = 7.2, 2.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 7.83 (d, J = 6.5 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.44 (t, J = 6.8 Hz, 1H), 2.93 (p, J = 6.9 Hz, 1H), 2.78 - 2.69 (m, 2H), 2.24 (s, 1H), 1.88 (dd, J = 11.9, 5.5 Hz, 1H), 1.61 (s, 6H), 1.44 (t, J = 12.0 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H), 0.91 (d, J = 6.2 Hz, 3H). |
| 2484 | 491.20 | 2.10 | |
| 2485 | 497.30 | 1.33 | 1II NMR (400 MHz, DMSO-d6) δ 12.58 (s, 2H), 8.24 (dd, J = 7.2, 2.2 Hz, 1H), 7.83 (s, 1H), 7.72 - 7.64 (m, 2H), 7.38 (td, J = 7.9, 1.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.2, 6.5 Hz, 2H), 6.45 (t, J = 6.7 Hz, 1H), 3.82 (s, 3H), 2.78 - 2.66 (m, 2H), 2.22 (d, J = 12.7 Hz, 1H), 1.85 (dd, J = 12.0, 5.7 Hz, 1H), 1.54 (s, 6H), 1.42 (t, J = 12.0 Hz, 1H), 0.91 (d, J = 6.2 Hz, 3H). |
| 2486 | 509.21 | 2.53 | 1H NMR (400 MHz, DMSO-d6) δ12.85 (s, 1H), 8.21 - 8.15 (m, 2H), 7.91 - 7.88 (d, 1H), 7.44 - 7.26 (m, 5H), 7.03 - 7.01 (dd, 1H), 6.61 - 6.58 (dd, 1H), 3.05 - 2.94 (m, 1H), 2.63 - 2.59 (m, 1H), 2.26 - 2.19 (m, 1H), 1.90 - 1.83 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.47 - 1.36 (m, 1H), 1.12 - 1.09 (d, 3H), 1.10 - 1.07 (d, 3H), 0.89 - 0.87 (d, 3H) |
| 2487 | 499.20 | 0.64 | |
| 2488 | 530.22 | 2.14 | |
| 2489 | 494.28 | 1.47 | |
| 2490 | 490.32 | 1.45 | |
| 2491 | 499.40 | 1.51 | |
| 2492 | 569.30 | 2.41 | 1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 8.3, 7.4 Hz, 1H), 7.54 (s, 1H), 7.46 - 7.38 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.75 (dt, J = 10.5, 2.3 Hz, 1H), 3.82 (d, J = 6.5 Hz, 2H), 3.67 (dd, J = 12.3, 6.4 Hz, 1H), 2.66 (t, J = 12.5 Hz, 1H), 2.11 (dt, J = 13.3, 6.7 Hz, 1H), 1.69 (dd, J = 12.6, 6.3 Hz, 1H), 1.49 (dd, J = 38.8, 13.1 Hz, 2H), 1.18 (d, J = 5.6 Hz, 3H), 1.10 - 1.00 (m, 9H), 0.81 (s, 3H), 0.75 (s, 3H). |
| 2493 | 524.52 | 2.39 | |
| 2494 | 510.16 | 1.42 | |
| 2495 | 518.22 | 2.30 | |
| 2496 | 533.31 | 1.15 | 1H NMR (400 MHz, DMSO) δ 12.62 (s, 1H), 12.54 (s, 1H), 11.31 (s, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.83 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.54 - 7.49 (m, 1H), 7.47 (t, J = 5.8 Hz, 2H), 7.23 - 7.18 (m, 1H), 7.11 (d, J = |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 7.9 Hz, 1H), 6.70 (s, 1H), 6.45 (t, J = 6.9 Hz, 1H), 2.84 - 2.70 (m, 2H), 2.25 (s, 1H), 1.87 (dd, J = 11.5, 5.3 Hz, 1H), 1.59 (d, J = 3.9 Hz, 6H), 1.45 (t, J = 11.7 Hz, 1H), 0.92 (d, J = 6.3 Hz, 3H).. |
| 2497 | 569.30 | 1.39 | |
| 2498 | 509.50 | 1.84 | |
| 2499 | 510.31 | 1.62 | |
| 2500 | 552.60 | 1.33 | |
| 2501 | 467.19 | 2.63 | 1H NMR (400 MHz, DMSO) δ 12.23 (s, 1H), 8.23 - 8.21 (dd, 1H), 7.90 - 7.87 (dd, 1H), 7.74 - 7.62 (m, 4H), 7.48 (t, J = 7.47, 1H), 7.25 - 7.22 (d, 1H), 7.06 - 7.03 (dd, 1H), 6.74 - 6.71 (d, 1H), 6.55 - 6.49 (m, 3H), 1.56 - 1.53 (d, 3H) |
| 2502 | 508.31 | 2.50 | |
| 2503 | 531.12 | 2.53 | |
| 2504 | 550.33 | 1.74 | |
| 2505 | 498.53 | 1.09 | |
| 2506 | 517.32 | 1.87 | |
| 2507 | 471.39 | 2.22 | |
| 2508 | 599.60 | 2.25 | |
| 2509 | 467.19 | 2.14 | |
| 2510 | 538.31 | 1.68 | |
| 2511 | 548.30 | 2.27 | |
| 2512 | 523.36 | 1.74 | |
| 2513 | 502.31 | 2.51 | |
| 2514 | 551.30 | 1.60 | 1H NMR (400 MHz, DMSO-d6) δ 12.63 (s, 1H), 12.55 (s, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.83 (dd, J = 6.4, 2.2 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.71 (dd, J = 7.2, 2.3 Hz, 1H), 7.60 - 7.43 (m, 3H), 6.84 (d, J = 7.8 Hz, 1H), 6.45 (t, J = 6.8 Hz, 1H), 2.81 - 2.65 (m, 2H), 2.30 - 2.14 (m, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.51 (d, J = 8.1 Hz, 6H), 1.43 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2515 | 524.34 | 1.50 | |
| 2516 | 525.30 | 1.30 | 1H NMR (400 MHz, DMSO-d6) δ 12.62 - 12.42 (m, 2H), 8.24 (dd, J = 7.2, 2.1 Hz, 1H), 7.87 - 7.78 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.61 - 7.51 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.44 (t, J = 6.8 Hz, 1H), 4.28 (s, 4H), 2.79 - 2.68 (m, 2H), 1.88 (dd, J = 11.5, 5.4 Hz, 1H), 1.60 (s, 6H), 1.44 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.2 Hz, 3H). |
| 2517 | 509.21 | 1.51 | |
| 2518 | 524.22 | 2.59 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2519 | 454.30 | 1.27 | |
| 2520 | 652.60 | 1.67 | |
| 2521 | 533.22 | 1.61 | |
| 2522 | 524.19 | 1.36 | |
| 2523 | 535.32 | 2.19 | |
| 2524 | 499.31 | 2.49 | |
| 2525 | 502.33 | 1.46 | |
| 2526 | 510.41 | 2.54 | |
| 2527 | 515.30 | 1.53 | |
| 2528 | 433.27 | 2.30 | |
| 2529 | 504.11 | 2.45 | |
| 2530 | 511.15 | 1.59 | |
| 2531 | 537.43 | 1.46 | |
| 2532 | 556.20 | 2.00 | 1H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.50 - 7.41 (m, 3H), 7.22 (d, J = 7.3 Hz, 1H), 6.91 (d, J = 10.9 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.47 (s, 1H), 3.85 (d, J = 6.5 Hz, 2H), 3.51 (d, J = 8.5 Hz, 1H), 3.40 (d, J = 12.8 Hz, 1H), 3.13 (d, J = 11.8 Hz, 1H), 2.97 (d, J = 6.0 Hz, 1H), 2.06 (d, J = 9.3 Hz, 1H), 1.89 - 1.72 (m, 2H), 1.42 (s, 2H), 1.00 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H). |
| 2533 | 517.32 | 2.55 | |
| 2534 | 565.50 | 1.97 | |
| 2535 | 404.46 | 1.96 | |
| 2536 | 544.33 | 2.76 | |
| 2537 | 559.04 | 2.32 | |
| 2538 | 598.50 | 2.21 | 1H NMR (400 MHz, DMSO) δ 7.54 (d, J = 7.6 Hz, 1H), 7.46 (s, 1H), 7.38 (dd, J = 17.3, 9.4 Hz, 2H), 7.05 (dd, J = 14.0, 7.6 Hz, 2H), 6.79 (d, J = 10.6 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H), 3.82 (d, J = 6.7 Hz, 2H), 3.59 (t, J = 10.8 Hz, 1H), 3.08 - 2.98 (m, 1H), 2.05 (dt, J = 13.7, 6.8 Hz, 2H), 1.58 (dd, J = 26.1, 16.0 Hz, 8H), 0.99 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 24.3 Hz, 9H). |
| 2539 | 550.26 | 1.03 | |
| 2540 | 624.30 | 0.89 | 1H NMR (300 MHz, CDCl3) δ 8.73 (d, J = 8.2 Hz, 1H), 8.28 (d, J = 8.1 Hz, 1H), 8.04 (t, J = 7.9 Hz, 1H), 7.98 - 7.89 (m, 2H), 7.56 (dd, J = 8.2, 1.9 Hz, 1H), 7.51 (d, J = 2.4 Hz, 2H), 4.21 (d, J = 6.1 Hz, 2H), 4.10 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 6.9 Hz, 2H), 2.64 - 2.47 (m, 4H), 2.11 (d, J = 2.8 Hz, 2H), 2.00 - 1.85 (m, 4H), 1.34 (d, J = 6.6 Hz, 6H), 1.25 (s, 6H), 1.11 (t, J = 7.4 Hz, 5H), 0.93 - 0.79 (m, 3H). |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2541 | 525.40 | 1.55 | |
| 2542 | 485.50 | 1.52 | |
| 2543 | 546.27 | 1.16 | |
| 2544 | 488.20 | 2.47 | |
| 2545 | 530.14 | 1.78 | |
| 2546 | 533.22 | 1.98 | |
| 2547 | 524.30 | 1.28 | |
| 2548 | 454.30 | 1.27 | |
| 2549 | 525.60 | 1.72 | 1H NMR (400 MHz, DMSO-d6) δ 12.59 (s, 1H), 12.53 (s, 1H), 8.24 (d, J = 7.4 Hz, 1H), 7.83 (d, J = 6.0 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.62 (s, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.00 - 6.93 (m, 1H), 6.45 (t, J = 7.0 Hz, 1H), 4.66 (p, J = 6.1 Hz, 1H), 2.75 (q, J = 9.8, 9.0 Hz, 2H), 2.24 (s, 1H), 1.89 (dd, J = 11.9, 5.5 Hz, 1H), 1.62 (s, 6H), 1.45 (t, J = 12.1 Hz, 1H), 1.31 (d, J = 6.0 Hz, 6H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2550 | 512.51 | 1.80 | |
| 2551 | 497.51 | 2.16 | 1H NMR (400 MHz, DMSO-d6) δ12.90 (s, 1H), 8.21 - 8.15 (m, 2H), 7.92 - 7.89 (d, 1H), 7.50 - 7.47 (dd, 1H) 7.39 - 7.33 (m, 2H), 6.87 - 6.84 (dd, 1H), 6.75 (s, 1H), 6.75 - 6.72 (d, 1H), 6.61 - 6.58 (dd, 1H), 3.73 (s, 3H ), 2.27 - 2.18 (m, 1H), 1.89 - 1.82 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.47 - 1.35 (m, 1H), 0.89 - 0.87 (d, 3H) |
| 2552 | 568.20 | 2.00 | |
| 2553 | 458.40 | 1.26 | |
| 2554 | 490.30 | 1.86 | 1H NMR (400 MHz,甲醇-d4) δ 8.27 (d, J = 2.8 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.00 (d, J = 2.8 Hz, 1H), 3.90 (s, 2H), 3.15 - 3.04 (m, 2H), 2.41 (dd, J = 11.2, 5.6 Hz, 1H), 1.98 (dd, J = 11.9, 5.8 Hz, 1H), 1.67 (d, J = 13.8 Hz, 6H), 1.61 (d, J = 12.2 Hz, 1H), 1.36 (ddd, J = 9.5, 7.0, 4.7 Hz, 1H), 1.28 - 1.13 (m, 2H), 1.09 (d, J = 6.4 Hz, 4H), 1.04 (s, 9H). |
| 2555 | 482.60 | 1.46 | |
| 2556 | 511.33 | 0.90 | |
| 2557 | 510.30 | 1.54 | |
| 2558 | 552.39 | 1.97 | |
| 2559 | 502.50 | 1.61 | |
| 2560 | 542.32 | 3.22 | 1H NMR (400 MHz, DMSO-d6) δ 12.57 (s, 1H), 8.06 - 7.96 (m, 2H), 7.78 - 7.70 (m, 2H), 7.67 (dd, J = 8.4, 6.8 Hz, 2H), 7.51 - 7.45 (m, 1H), 7.40 (dt, J = 10.1, 1.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.89 (dt, J = 10.8, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 2.2 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.07 (ddt, J = 23.2, 13.3, 6.4 Hz, 2H), 1.83 (dd, J = 11.9, 5.7 Hz, 1H), 1.57 (d, J = 18.0 Hz, 6H), 1.38 (t, J = 12.1 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.66 (d, J = 6.3 Hz, 3H). |
| 2561 | 444.38 | 2.06 | |
| 2562 | 514.20 | 1.38 | |
| 2563 | 532.32 | 2.58 | 1H NMR (400 MHz, DMSO-d6) δ12.86 (s, 1H), 8.23 - 8.13 (m, 2H), 7.92 - 7.89 (d, 1H), 7.69 - 7.65 (d, 2H), 7.49 - 7.38 (m, 4H), 7.28 - 7.24 (d, 2H), 6.57 - 6.54 (dd, 1H), 6.28 (t, J = 2.20, 2H), 2.28 - 2.18 (m, 1H), 1. 89 - 1.82 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.46 - 1.34 (m, 1H), 0.90 - 0.87 (d, 3H) |
| 2564 | 511.09 | 1.41 | |
| 2565 | 529.32 | 1.96 | |
| 2566 | 484.50 | 1.52 | |
| 2567 | 533.30 | 1.52 | |
| 2568 | 570.40 | 1.30 | 1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.5, 7.3 Hz, 1H), 7.19 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.80 (dq, J = 4.3, 1.8 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.70 (s, 1H), 4.20 (q, J = 2.4 Hz, 2H), 3.39 - 3.32 (m, 2H), 2.55 (d, J = 8.7 Hz, 2H), 2.27 (s, 2H), 2.18 (dd, J = 12.7, 6.4 Hz, 1H), 1.84 (dd, J = 11.8, 5.6 Hz, 1H), 1.53 (s, 6H), 1.40 (d, J = 12.2 Hz, 1H), 1.26 (s, 9H), 0.86 (d, J = 6.3 Hz, 3H). |
| 2569 | 509.21 | 1.98 | |
| 2570 | 502.29 | 1.47 | |
| 2571 | 530.22 | 2.49 | |
| 2572 | 480.10 | 2.68 | |
| 2573 | 610.20 | 2.23 | |
| 2574 | 430.27 | 1.81 | |
| 2575 | 525.37 | 1.08 | |
| 2576 | 553.40 | 2.74 | 1H NMR (400 MHz, DMSO) δ 8.61 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 2.5 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 6.97 (dd, J = 7.4, 3.2 Hz, 2H), 6.49 (d, J = 8.3 Hz, 1H), 6.23 (s, 2H), 5.16 (h, J = 6.3 Hz, 1H), 2.97 (t, J = 10.6 Hz, 1H), 2.91 - 2.81 (m, 1H), 2.17 (s, 3H), 2.09 (qt, J = 11.8, 7.9, 6.2 Hz, 1H), 1.81 (dd, J = 11.5, 5.6 Hz, 1H), 1.75 - 1.64 (m, 2H), 1.61 (s, 3H), 1.56 (s, 3H), 1.36 (t, J = 12.0 Hz, 1H), 1.28 (d, J = 6.1 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.80 (d, J = 6.2 Hz, 3H). |
| 2577 | 472.50 | 1.57 | 1H NMR (400 MHz, DMSO) δ 12.35 (s, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.14 (d, J = 6.7 Hz, 1H), 6.73 - 6.58 (m, 2H), 6.43 (s, 2H), 2.79 (s, 1H), 2.62 (s, 1H), 1.80 - 1.59 (m, 2H), 1.56 (s, 3H), 1.51 (s, 3H), 1.27 (s, 9H), 1.13 - 1.03 (m, 1H), 0.71 - 0.58 (m, 1H), 0.56 - 0.46 (m, 1H), 0.46 - 0.33 (m, 1H), 0.24 (td, J = 9.2, 5.0 Hz, 1H), 0.12 - 0.01 (m, 1H). |
| 2578 | 543.40 | 1.92 | 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 2H), 8.23 (d, J = 7.4 Hz, 1H), 8.20 (d, J = 2.7 Hz, 1H), 7.87 - 7.74 (m, 2H), 6.88 (d, J = 8.2 Hz, 1H), 6.51 - 6.38 (m, 1H), 6.13 (d, J = 2.7 Hz, 1H), 3.89 (s, 2H), 2.71 (寬雙峰 , J = 8.6 Hz, 2H), 2.22 (br s, 1H), 1.88 (dd, J = 12.0, 5.6 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.43 (t, J = 12.1 Hz, 1H), 1.00 (s, 9H), 0.89 (d, J = 6.3 Hz, 3H). |
| 2579 | 510.41 | 2.16 | |
| 2580 | 510.11 | 2.33 | |
| 2581 | 570.20 | 1.88 | 1H NMR (400 MHz, DMSO) δ 8.41 (d, J = 8.2 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 7.65 - 7.49 (m, 3H), 7.19 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 10.9 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.30 (s, 1H), 3.87 (d, J = 6.5 Hz, 2H), 3.82 - 3.74 (m, 1H), 3.18 (d, J = 10.9 Hz, 1H), 2.06 (dt, J = 13.2, 6.6 Hz, 2H), 2.01 - 1.59 (m, 4H), 1.58 (s, 3H), 1.13 (s, 3H), 0.99 (t, J = 6.9 Hz, 9H). |
| 2582 | 555.10 | 1.47 | 1H NMR (400 MHz, DMSO) δ 12.41 (s, 0H), 3.32 - 3.32 (m, 6H), 8.66 (d, J = 2.4 Hz, 2H), 8.14 (d, J = 2.4 Hz, 2H), 7.68 (s, 2H), 7.55 (s, 1H), 7.12 (s, 4H), 6.60 (s, 1H), 6.33 (s, 0H), 4.52 - 4.39 (m, 5H), 3.74 - 3.65 (m, 5H), 2.86 - 2.61 (m, 1H), 2.21 (s, 7H), 2.19 - 2.10 (m, 5H), 1.85 (dd, J = 11.7, 5.6 Hz, 2H), 1.61 (s, 7H), 1.58 (s, 7H), 1.40 (t, J = 11.9 Hz, 2H), 0.86 (d, J = 6.3 Hz, 8H). |
| 2583 | 509.20 | 1.57 | |
| 2584 | 491.30 | 1.51 | |
| 2585 | 515.21 | 2.65 | |
| 2586 | 521.30 | 1.72 | 1H NMR (400 MHz, DMSO) δ 7.62 (t, J = 7.9 Hz, 1H), 7.51 (d, J = 14.0 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 3.73 (t, J = 4.9 Hz, 2H), 3.48 - 3.42 (m, 2H), 3.33 (s, 2H), 2.70 - 2.54 (m, 2H), 2.27 - 2.15 (m, 1H), 1.85 (dd, J = 11.9, 5.9 Hz, 1H), 1.51 - 1.32 (m, 8H), 1.18 (d, J = 10.2 Hz, 7H), 0.88 (d, J = 6.2 Hz, 3H). |
| 2587 | 490.32 | 1.52 | |
| 2588 | 586.35 | 1.88 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2589 | 582.20 | 2.05 | |
| 2590 | 496.27 | 1.11 | |
| 2591 | 519.12 | 2.49 | |
| 2592 | 496.60 | 1.45 | |
| 2593 | 534.22 | 1.07 | |
| 2594 | 554.50 | 1.78 | 1H NMR (400 MHz, DMSO-d6) 讠 12.51 (寬單峰, 1H), 8.25-8.23 (m, 2H), 8.02 (dd, J = 7.8, 1.9 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.76 (dd, J = 7.8, 4.7 Hz, 1H), 6.67 (br s, 2H), 6.16 (d, J = 2.7 Hz, 1H), 3.90 (s, 2H), 3.49 (br d, J = 9.9 Hz, 1H), 3.39 (br d, J = 8.9 Hz, 1H), 2.47 - 2.30 (m, 2H), 2.26 (dd, J = 11.8, 5.2 Hz, 1H), 1.92-1.90 (m, 2H), 1.85 - 1.72 (m, 2H), 1.61 (br s, 1H), 1.51 (t, J = 11.5 Hz, 1H), 1.01 (s, 9H), 0.78 (d, J = 6.4 Hz, 3H). |
| 2595 | 537.43 | 2.64 | |
| 2596 | 651.50 | 1.82 | |
| 2597 | 470.49 | 1.34 | |
| 2598 | 519.12 | 2.54 | 1H NMR (400 MHz, DMSO-d6) δ12.92 (s, 1H), 8.27 - 8.17 (m, 2H), 7.97 - 7.94 (d, 1H), 7.59 - 7.38 (m, 5H), 6.65 - 6.62 (dd, 1H), 2.63 - 2.54 (m, 1H), 2.28 - 2.20 (m, 1H), 1.89 - 1.82 (m, 1H), 1.50 (s, 3H), 1.46 (s, 3H) , 1.40- 1.35 (m, 1H), 0.89 - 0.87 (d, 3H) |
| 2599 | 458.18 | 1.80 | |
| 2600 | 546.13 | 2.70 | |
| 2601 | 541.33 | 1.65 | |
| 2602 | 476.19 | 2.38 | |
| 2603 | 542.20 | 1.85 | |
| 2604 | 540.20 | 1.67 | 1H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 8.25 (dd, J = 4.8, 2.1 Hz, 2H), 8.03 (dd, J = 7.8, 1.8 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.75 (dt, J = 26.8, 13.4 Hz, 3H), 6.15 (d, J = 2.7 Hz, 1H), 3.99 (d, J = 6.6 Hz, 2H), 3.49 (d, J = 9.5 Hz, 1H), 3.38 (d, J = 8.7 Hz, 1H), 2.40 (dt, J = 27.2, 9.9 Hz, 2H), 2.26 (dd, J = 11.8, 4.8 Hz, 1H), 2.10 - 2.01 (m, 1H), 1.91 (dd, J = 15.4, 8.5 Hz, 2H), 1.78 (dd, J = 12.4, 7.5 Hz, 2H), 1.67 - 1.56 (m, 1H), 1.52 (t, J = 11.5 Hz, 1H), 0.98 (d, J = 6.7 Hz, 6H), 0.78 (d, J = 6.3 Hz, 3H). |
| 2605 | 486.33 | 1.53 | |
| 2606 | 515.40 | 1.46 | |
| 2607 | 524.23 | 1.48 | |
| 2608 | 560.27 | 1.30 | |
| 2609 | 458.18 | 2.31 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2610 | 505.01 | 2.51 | 1H NMR (400 MHz, DMSO) δ12.82 (s, 1H), 8.19 - 8.17 (dd, 1H), 8.05 (t, J = 7.91, 1H), 7.79 - 7.72 (m, 2H), 7.56 - 7.53 (d, 2H), 7.42 - 7.39 (d, 2H), 7.21 - 7.18 (d, 1H), 6.64 - 6.61 (dd, 1H), 5.38 (s, 2H), 4.18 (s, 1H), 2.26 - 2.10 (m, 2H), 2.00 - 1.89 (m, 1H), 1.79 - 1.72 (m, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.28 (t, J = 11.86, 1H), 0.61 - 0.59 (d, 3H) |
| 2611 | 517.32 | 2.42 | |
| 2612 | 569.70 | 1.44 | |
| 2613 | 498.53 | 1.07 | |
| 2614 | 512.18 | 1.25 | |
| 2615 | 438.07 | 1.77 | |
| 2616 | 498.50 | 1.58 | |
| 2617 | 419.16 | 2.05 | |
| 2618 | 549.43 | 2.73 | |
| 2619 | 481.30 | 2.47 | |
| 2620 | 529.32 | 1.56 | |
| 2621 | 537.43 | 1.79 | |
| 2622 | 557.40 | 1.39 | 1H NMR (400 MHz, DMSO-d6) δ 12.39 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 7.1 Hz, 1H), 7.19 (d, J = 7.1 Hz, 1H), 6.91 (s, 1H), 6.76 (s, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.80 (h, J = 6.1 Hz, 1H), 4.35 (d, J = 16.5 Hz, 2H), 3.49 (t, J = 5.9 Hz, 2H), 2.55 (d, J = 8.9 Hz, 1H), 2.35 - 2.27 (m, 2H), 2.26 - 2.08 (m, 1H), 1.85 (dd, J = 11.9, 5.6 Hz, 1H), 1.53 (d, J = 2.6 Hz, 6H), 1.39 (t, J = 12.1 Hz, 1H), 1.21 (d, J = 1.8 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 0.87 (d, J = 6.3 Hz, 3H). |
| 2623 | 524.57 | 1.04 | |
| 2624 | 557.40 | 1.82 | |
| 2625 | 513.41 | 2.78 | |
| 2626 | 495.40 | 1.62 | 1H NMR (400 MHz, DMSO-d6) δ 12.57 (s, 1H), 12.52 (s, 1H), 8.24 (dd, J = 7.3, 2.2 Hz, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.44 (t, J = 6.9 Hz, 1H), 2.77 - 2.63 (m, 2H), 2.33 (s, 6H), 2.29 - 2.15 (m, 1H), 1.88 (dd, J = 11.7, 5.5 Hz, 1H), 1.61 (s, 6H), 1.51 - 1.37 (m, 2H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2627 | 539.23 | 2.51 | |
| 2628 | 515.21 | 1.38 | |
| 2629 | 539.50 | 1.78 | 1H NMR (400 MHz, DMSO-d6) δ 12.55 (d, J = 13.7 Hz, 2H), 8.24 (dd, J = 7.3, 2.1 Hz, 1H), 7.85 - 7.78 (m, 1H), 7.73 (dd, J = 7.7, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1.8 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.35 (ddd, J = 8.6, 7.3, 1.8 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.4, 1.1 Hz, 1H), 7.08 - 7.01 (m, 1H), 6.44 (t, J = 6.8 Hz, 1H), 3.84 (dd, J = 6.4, 2.2 Hz, 2H), 2.76 - 2.65 (m, 2H), 2.23 (s, 1H), 2.10 - 1.98 (m, 1H), 1.86 (dd, J = 11.8, 5.6 Hz, 1H), 1.55 (d, J = 4.8 Hz, 6H), 1.48 - 1.38 (m, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2630 | 487.30 | 2.91 | |
| 2631 | 578.20 | 2.10 | |
| 2632 | 528.12 | 2.32 | |
| 2633 | 595.70 | 1.57 | 1H NMR (400 MHz, DMSO-d6) δ 12.40 (s, 1H), 7.69 (dd, J = 8.1, 2.7 Hz, 1H), 7.62 (t, 1H), 7.19 (d, J = 7.4 Hz, 1H), 6.95 (d, J = 8.1 Hz, 0.5 H), 6.86 (d, J = 8.1 Hz, 0.5 H), 6.83 - 6.74 (m, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.43 (d, J = 11.6 Hz, 2H), 2.55 (d, J = 8.9 Hz, 1H), 2.34 (d, J = 6.2 Hz, 1H), 2.25 (d, J = 6.7 Hz, 3H), 2.20 (s, 1H), 1.85 (ddd, J = 11.9, 8.8, 5.6 Hz, 1H), 1.70 - 1.58 (m, 6H), 1.55 (兩個單峰, 3H), 1.53 ((兩個單峰, 3H), 1.39 (td, J = 12.2, 3.8 Hz, 2H), 1.30 - 1.05 (m, 4H), 1.05 - 0.88 (m, 3H), 0.87 (d, J = 6.3 Hz, 3H). |
| 2634 | 573.20 | 1.73 | 1H NMR (400 MHz,甲醇-d4) δ 7.69 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.26 (s, 1H), 7.08 (dd, J = 7.3, 0.8 Hz, 1H), 6.62 - 6.51 (m, 2H), 6.44 (dd, J = 19.3, 9.7 Hz, 2H), 3.58 (s, 1H), 3.49 (d, J = 6.4 Hz, 2H), 2.52 (t, J = 0.8 Hz, 1H), 2.45 (s, 1H), 1.90 (s, 1H), 1.82 - 1.69 (m, 2H), 1.53 (s, 1H), 1.04 (s, 3H), 0.92 (s, 6H), 0.74 (d, J = 6.7 Hz, 6H). |
| 2635 | 509.30 | 1.63 | |
| 2636 | 506.19 | 1.26 | |
| 2637 | 497.51 | 2.10 | |
| 2638 | 498.50 | 1.65 | |
| 2639 | 466.29 | 2.26 | 1H NMR (400 MHz, DMSO-d6) δ12.75 (s, 1H), 9.62 (s, 1H), 8.14 - 8.12 (dd, 1H), 7.87 - 7.70 (m, 4H), 7.47 - 7.44 (d, 1H), 7.26 (t, J = 7.91, 2H), 7.09 - 7.06 (d, 1H), 6.94 (t, J = 7.36, 1H), 6.53 - 6.50 (dd, 1H), 2.47 - 2.43 (m, 1H), 1.87 - 1.70 (m, 2H), 1.45 (s, 3H), 1.41 (s, 3H), 1.29 (t, J = 11.86, 1H), 0.73 - 0.71 (d, 3H) |
| 2640 | 516.41 | 2.36 | |
| 2641 | 526.32 | 2.54 | |
| 2642 | 538.33 | 2.48 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2643 | 532.32 | 1.45 | |
| 2644 | 516.30 | 1.29 | |
| 2645 | 545.23 | 2.66 | |
| 2646 | 497.22 | 1.31 | 1H NMR (400 MHz, DMSO-d6) δ 8.27 (ddd, J = 11.0, 5.1, 2.6 Hz, 2H), 8.06 (dt, J = 7.8, 2.3 Hz, 1H), 7.82 (dd, J = 7.9, 2.9 Hz, 1H), 7.58 (s, 1H), 7.39 (s, 1H), 7.34 (dd, J = 7.8, 2.9 Hz, 1H), 6.97 - 6.56 (m, 4H), 3.97 - 3.85 (m, 3H), 2.59 (s, 2H), 2.16 (s, 1H), 1.85 (s, 1H), 1.58 (dd, J = 15.1, 2.8 Hz, 6H), 1.40 (t, J = 12.3 Hz, 1H), 0.76 (dd, J = 6.3, 3.0 Hz, 3H). |
| 2647 | 486.33 | 1.80 | 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 8.16 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 8.4, 7.3 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.50 (s, 2H), 6.35 - 6.27 (m, 1H), 6.16 - 6.07 (m, 1H), 2.56 (td, J = 10.3, 7.0 Hz, 2H), 2.17 (q, J = 7.1 Hz, 3H), 1.82 (dd, J = 11.9, 5.7 Hz, 1H), 1.60 (dh, J = 13.4, 6.8, 6.4 Hz, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.39 - 1.29 (m, 3H), 0.90 (d, J = 6.6 Hz, 6H), 0.85 (d, J = 6.3 Hz, 3H). |
| 2648 | 459.09 | 2.52 | |
| 2649 | 550.24 | 1.80 | |
| 2650 | 569.50 | 1.41 | |
| 2651 | 525.20 | 1.44 | |
| 2652 | 503.40 | 1.60 | 1H NMR (400 MHz, DMSO-d6) δ 12.66 (s, 1H), 12.54 (d, J = 6.2 Hz, 1H), 8.25 (dd, J = 7.3, 2.1 Hz, 1H), 7.83 (td, J = 6.4, 2.2 Hz, 1H), 7.79 - 7.70 (m, 3H), 7.36 - 7.28 (m, 2H), 6.45 (t, J = 6.8 Hz, 1H), 2.81 - 2.68 (m, 2H), 2.24 (dq, J = 11.6, 6.2 Hz, 1H), 1.90 (dd, J = 11.9, 5.6 Hz, 1H), 1.45 (t, J = 12.1 Hz, 1H), 0.91 (d, J = 6.3 Hz, 3H). |
| 2653 | 500.12 | 1.43 | |
| 2654 | 521.22 | 2.44 | |
| 2655 | 547.60 | 1.65 | |
| 2656 | 501.11 | 1.72 | |
| 2657 | 605.32 | 1.71 | |
| 2658 | 513.20 | 0.64 | |
| 2659 | 491.20 | 2.48 | |
| 2660 | 498.53 | 1.05 | |
| 2661 | 574.40 | 1.55 | |
| 2662 | 540.43 | 2.40 | |
| 2663 | 535.02 | 2.76 | |
| 2664 | 526.18 | 1.32 | |
| 2665 | 528.19 | 1.48 | 1H NMR (400 MHz, DMSO-d6) δ 12.53 (s, 1H), 8.25 (dd, J = 4.8, 1.8 Hz, 1H), 8.06 (dd, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | J = 7.8, 1.8 Hz, 1H), 7.92 - 7.69 (m, 2H), 7.62 (ddd, J = 8.5, 4.3, 2.1 Hz, 1H), 7.37 - 7.17 (m, 2H), 6.78 (dd, J = 7.8, 4.8 Hz, 3H), 4.19 (q, J = 7.0 Hz, 2H), 2.54 (d, J = 10.2 Hz, 2H), 2.15 (s, 1H), 1.85 (dd, J = 11.7, 5.6 Hz, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.38 (t, J = 6.9 Hz, 4H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2666 | 488.33 | 1.33 | |
| 2667 | 496.27 | 1.33 | 1H NMR (400 MHz, DMSO) δ 12.51 (s, 1H), 8.25 (dd, J = 4.8, 1.9 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 8.04 - 7.98 (m, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 9.5, 2.5 Hz, 2H), 6.78 (dd, J = 7.8, 4.8 Hz, 1H), 3.81 (s, 3H), 2.56 - 2.51 (m, 2H), 2.15 (s, 1H), 1.85 (dd, J = 11.9, 5.7 Hz, 1H), 1.60 (s, 3H), 1.58 (s, 3H), 1.40 (t, J = 12.1 Hz, 1H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2668 | 498.24 | 1.23 | |
| 2669 | 669.52 | 0.76 | 1H NMR (300 MHz, CDCl3) δ 10.43 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 4.1 Hz, 1H), 7.66 (s, 1H), 7.62 (s, 1H), 7.58 (d, J = 4.4 Hz, 1H), 7.56 - 7.56 (m, 1H), 7.55 (s, 1H), 7.09 (s, 1H), 7.01 (d, J = 9.1 Hz, 1H), 6.77 - 6.70 (m, 1H), 6.66 (d, J = 10.3 Hz, 1H), 4.74 (s, 2H), 3.60 (d, J = 6.4 Hz, 2H), 2.28 (s, 6H), 2.10 - 1.96 (m, 1H), 0.98 (d, J = 6.7 Hz, 6H). |
| 2670 | 610.20 | 0.83 | 1H NMR (400 MHz,甲醇-d4) δ 8.67 (dd, J = 4.8, 1.9 Hz, 1H), 8.48 (dd, J = 8.0, 1.8 Hz, 1H), 8.32 (d, J = 2.8 Hz, 1H), 8.09 (dd, J = 8.5, 1.6 Hz, 1H), 7.66 (dd, J = 8.3, 1.5 Hz, 1H), 7.61 (dd, J = 8.0, 4.7 Hz, 1H), 6.01 (d, J = 2.8 Hz, 1H), 3.92 (d, J = 1.8 Hz, 2H), 3.76 - 3.65 (m, 4H), 3.34 (d, J = 1.9 Hz, 5H), 2.04 (p, J = 5.9 Hz, 4H), 1.85 - 1.70 (m, 2H), 1.03 (d, J = 1.9 Hz, 9H). |
| 2671 | 691.40 | 0.83 | 1H NMR (300 MHz, CDCl3) δ 8.47 (d, J = 8.1 Hz, 1H), 7.76 - 7.68 (m, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.47 (s, 2H), 7.04 - 6.95 (m, 3H), 6.76 (d, J = 8.2 Hz, 1H), 6.63 (dt, J = 10.3, 2.2 Hz, 1H), 3.56 (t, J = 7.0 Hz, 2H), 2.13 - 2.06 (m, 6H), 1.01 (t, J = 6.6 Hz, 6H), 0.85 (t, J = 6.7 Hz, 3H), 0.47 (s, 1H). |
| 2672 | 474.50 | 1.18 | |
| 2673 | 557.40 | 2.15 | 1H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 7.89 (s, 1H), 7.62 - 7.53 (m, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.88 - 6.79 (m, 2H), 6.75 - 6.69 (m, 1H), 6.66 (d, J = 8.3 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 6.52 (s, 2H), 3.83 (t, J = 9.1 Hz, 1H), 3.74 (d, J = 6.5 Hz, 2H), 3.12 (t, J = 10.4 Hz, 1H), 2.47 - 2.35 (m, 1H), 2.02 (dd, J = 12.8, 6.3 Hz, 2H), 1.61 (d, J = 12.2 Hz, 1H), 1.56 (s, 3H), 1.45 (s, 3H), 1.10 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H). |
| 2674 | 480.20 | 1.97 | 1H NMR (400 MHz,甲醇-d4) δ 8.50 (d, J = 2.8 Hz, 1H), 7.95 - 7.87 (m, 2H), 7.84 (dd, J = 8.1, 1.2 Hz, 1H), 7.46 - 7.38 (m, 2H), 7.36 (dd, J = 7.8, 1.8 Hz, 1H), 7.30 (dd, J = 8.2, 1.2 Hz, 1H), 6.94 - 6.88 (m, 1H), 3.18 - 3.01 (m, 2H), 2.51 - 2.35 (m, 1H), 2.01 (dd, J = 11.8, 5.8 Hz, 1H), 1.76 - 1.66 (m, 6H), 1.63 (d, J = 12.0 Hz, 1H), 1.39 (dt, J = 8.7, 5.3 Hz, 1H), 1.26 - 1.14 (m, 2H), 1.10 (dd, J = 8.7, 5.4 Hz, 4H). |
| 2675 | 474.50 | 1.17 | |
| 2676 | 466.20 | 1.78 | 1H NMR (400 MHz,甲醇-d4) δ 8.60 (d, J = 2.7 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.97 - 7.90 (m, 2H), 7.66 (d, J = 8.3 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.39 - 7.33 (m, 1H), 6.94 (d, J = 2.7 Hz, 1H), 4.20 (q, J = 6.1 Hz, 2H), 3.09 (tt, J = 8.1, 4.7 Hz, 1H), 2.30 - 2.19 (m, 2H), 1.90 - 1.79 (m, 2H), 1.33 - 1.25 (m, 8H), 1.18 - 1.10 (m, 2H). |
| 2677 | 562.60 | 1.75 | |
| 2678 | 478.40 | 1.25 | |
| 2679 | 556.40 | 1.47 | |
| 2680 | 574.40 | 1.27 | |
| 2681 | 626.20 | 1.12 | |
| 2682 | 582.30 | 1.12 | |
| 2683 | 568.40 | 1.00 | |
| 2684 | 552.40 | 1.14 | |
| 2685 | 538.30 | 0.97 | |
| 2686 | 539.30 | 1.04 | |
| 2687 | 541.30 | 1.04 | |
| 2688 | 555.00 | 2.01 | 1H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 8.85 (d, J = 2.4 Hz, 1H), 8.33 - 8.26 (m, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.77 (s, 1H), 6.14 (d, J = 8.6 Hz, 1H), 5.39 - 5.25 (m, 1H), 3.82 (s, 3H), 2.15 (s, 1H), 1.85 (dd, J = 11.8, 5.6 Hz, 1H), 1.59 (d, J = 11.4 Hz, 6H), 1.41 (t, J = 12.2 Hz, 1H), 1.32 (d, J = 6.2 Hz, 6H), 0.76 (d, J = 6.3 Hz, 3H). |
| 2689 | 540.40 | 1.18 | |
| 2690 | 540.40 | 1.62 | |
| 2691 | 526.40 | 1.47 | |
| 2692 | 558.50 | 1.30 | |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2693 | 544.50 | 1.26 | |
| 2694 | 556.50 | 1.83 | |
| 2695 | 496.30 | 0.64 | 1H NMR (400 MHz,甲醇-d4) δ 8.66 (dd, J = 7.8, 1.8 Hz, 1H), 8.35 (d, J = 2.8 Hz, 1H), 8.24 - 8.13 (m, 2H), 7.49 (d, J = 8.5 Hz, 1H), 7.16 - 7.07 (m, 1H), 6.31 - 6.23 (m, 1H), 3.24 (d, J = 9.6 Hz, 1H), 3.10 (t, J = 10.1 Hz, 1H), 2.56 (d, J = 11.8 Hz, 1H), 2.13 (dd, J = 12.4, 6.6 Hz, 1H), 2.01 (dq, J = 11.6, 3.6 Hz, 1H), 1.72 (t, J = 11.9 Hz, 1H), 1.56 (dd, J = 27.3, 5.2 Hz, 6H), 1.38 - 1.22 (m, 1H), 1.08 (d, J = 6.4 Hz, 3H), 1.00 (ddt, J = 8.4, 4.5, 2.2 Hz, 3H), 0.82 (ddd, J = 7.2, 4.9, 2.8 Hz, 3H). |
| 2696 | 532.20 | 0.69 | 1H NMR (400 MHz,甲醇-d4) δ 8.59 - 8.49 (m, 2H), 8.28 - 8.20 (m, 1H), 8.09 (dd, J = 10.7, 5.2 Hz, 1H), 8.02 - 7.91 (m, 2H), 7.61 - 7.36 (m, 5H), 7.11 - 6.94 (m, 2H), 3.11 - 2.89 (m, 2H), 2.48 (d, J = 15.9 Hz, 1H), 2.06 (dd, J = 11.8, 6.4 Hz, 1H), 1.63 (dd, J = 14.0, 5.6 Hz, 6H), 1.00 (d, J = 6.9 Hz, 3H). |
| 2697 | 551.50 | 1.74 | 1H NMR (400 MHz, DMSO-d6) δ 12.48 (寬單峰, 1H), 8.24 (dd, J = 4.8, 1.9 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 8.02 (dd, J = 7.8, 1.8 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 7.8, 4.8 Hz, 1H), 6.70 (br s, 2H), 6.14 (d, J = 2.7 Hz, 1H), 3.88 (s, 2H), 2.43 (d, J = 8.8 Hz, 2H), 2.13 (br s, 1H), 1.84 (dd, J = 11.9, 5.5 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.37 (t, J = 12.2 Hz, 1H), 0.73 (d, J = 6.2 Hz, 3H). |
| 2698 | 420.30 | 0.94 | 1H NMR (400 MHz, DMSO) δ 7.92 (dd, J = 4.8, 1.9 Hz, 1H), 7.80 (dd, J = 7.5, 1.9 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 6.52 (dd, J = 7.5, 4.8 Hz, 1H), 6.27 (s, 2H), 5.80 (d, J = 8.0 Hz, 1H), 3.74 (s, 3H), 2.90 (t, J = 10.8 Hz, 1H), 2.79 (dd, J = 10.7, 7.2 Hz, 1H), 2.14 - 2.00 (m, 1H), 1.76 (dd, J = 11.4, 5.7 Hz, 1H), 1.51 (d, J = 2.7 Hz, 6H), 1.31 (t, J = 12.0 Hz, 1H), 0.76 (d, J = 6.4 Hz, 3H). |
| 2699 | 478.30 | 1.06 | |
| 2700 | 522.30 | 1.07 | |
| 2701 | 565.30 | 2.34 | |
| 2702 | 563.36 | 2.73 | 1H NMR (400 MHz, DMSO-d6) δ 12.46 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.4, 7.3 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.40 (dt, J = 10.0, 2.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 6.68 (d, J = 8.4 Hz, |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| | | | 1H), 6.49 (s, 2H), 3.83 (s, 2H), 2.76 - 2.54 (m, 3H), 2.22 (s, 1H), 1.88 (dd, J = 11.9, 5.7 Hz, 1H), 1.60 (d, J = 5.7 Hz, 6H), 1.42 (t, J = 12.1 Hz, 1H), 0.88 (d, J = 6.2 Hz, 3H). |
| 2703 | 482.30 | 1.56 | |
| 2704 | 528.50 | 1.60 | |
| 2705 | 528.50 | 1.59 | |
| 2706 | 547.00 | 3.25 | 1H NMR (400 MHz, DMSO-d6) δ 12.57 (s, 1H), 8.07 - 7.95 (m, 2H), 7.78 - 7.70 (m, 2H), 7.70 - 7.62 (m, 2H), 7.50 - 7.45 (m, 1H), 7.40 (ddd, J = 10.2, 2.4, 1.3 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.89 (dt, J = 10.7, 2.3 Hz, 1H), 3.82 (s, 2H), 2.43 (t, J = 10.3 Hz, 1H), 2.36 (dd, J = 10.2, 7.1 Hz, 1H), 2.11 (ddt, J = 17.5, 11.9, 6.2 Hz, 1H), 1.83 (dd, J = 11.8, 5.6 Hz, 1H), 1.59 (s, 3H), 1.55 (s, 3H), 1.38 (t, J = 12.1 Hz, 1H), 0.66 (d, J = 6.3 Hz, 3H). |
| 2707 | | | |
| 2708 | | | 1H NMR (300 MHz, DMSO) δ 8.55 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 7.9 Hz, 1H), 8.02 (dd, J = 8.8, 2.5 Hz, 1H), 7.76 (dd, J = 8.4, 1.6 Hz, 3H), 7.72 - 7.65 (m, 2H), 7.64 - 7.57 (m, 2H), 7.56 (s, 2H), 7.24 (d, J = 6.9 Hz, 1H), 6.75 (dd, J = 18.5, 8.4 Hz, 2H), 5.26 (dt, J = 12.3, 6.2 Hz, 2H), 2.14 (s, 6H), 1.27 (d, J = 6.2 Hz, 6H). |
| 2709 | 520.50 | 1.59 | |
| 2710 | 534.40 | 1.28 | |
| 2711 | 480.00 | 0.53 | 1H NMR (400 MHz,甲醇-d4) δ 8.84 - 8.78 (m, 1H), 8.74 - 8.67 (m, 2H), 8.62 - 8.57 (m, 1H), 8.04 (ddd, J = 7.4, 5.9, 1.3 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.45 - 7.39 (m, 2H), 3.34 (s, 1H), 3.18 - 3.06 (m, 2H), 2.51 - 2.39 (m, 1H), 2.07 - 1.99 (m, 1H), 1.72 (d, J = 14.8 Hz, 6H), 1.65 (d, J = 12.2 Hz, 1H), 1.45 - 1.38 (m, 1H), 1.27 - 1.15 (m, 2H), 1.12 (d, J = 6.4 Hz, 3H). |
| 2712 | 566.54 | 2.88 | |
| 2713 | 567.44 | 3.07 | |
| 2714 | 581.25 | 2.98 | |
| 2715 | 501.41 | 3.05 | |
| 2716 | 517.32 | 3.33 | 1H NMR (400 MHz, DMSO) δ 12.70 (s, 1H), 8.01 (t, J = 8.02, 1H), 7.74 - 7.67 (m, 2H), 7.13 - 7.10 (d, 1H), 6.67 - 6.64 (d, 1H), 4.34 - 4.20 (m, 2H), 2.43 - 2.40 (m, 2H), 2.14 (m, 1H), 1.85 - 1.69 (m, 2H), 1.62 (q, J = 6.48, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.35 (t, J = 11.97, 1H), 1.26 (s, 9H), 0.92 - 0.90 (d, 6H), 0.77 - 0.75 (d, 3H) |

| 化合物編號 | LC/MS M+1 | LC/RT min | NMR |
|---|---|---|---|
| 2717 | 533.22 | 2.62 | |
| 2718 | 535.02 | 2.64 | |
| 2719 | 519.12 | 2.66 | |
| 2720 | 535.02 | 2.62 | 1H NMR (400 MHz, DMSO) δ 8.03 - 7.95 (m, 2H), 7.77 - 7.74 (d, 1H), 7.59 - 7.56 (d, 1H), 7.42 (t, J = 8.13, 1H), 7.34 - 7.31 (dd, 1H), 7.27 - 7.24 (d, 1H), 7.08 (m, 1H), 6.46 - 6.43 (dd, 1H), 2.89 (m, 2H), 2.21 - 2. 15 (m, 1H), 1.84 - 1.77 (m, 1H), 1.50 (s, 3H), 1.48 (s, 3H), 1.36 (t, J = 12.08, 1H), 0.90 - 0.88 (d, 3H) |
| 2721 | 495.10 | 2.62 | |
| 2722 | 540.43 | 2.26 | |
| 2723 | 486.40 | 2.71 | |
| 2724 | 446.18 | 2.32 | |
| 2725 | 492.10 | 2.18 | |
| 2726 | 446.18 | 2.32 | |
| 2727 | 509.21 | 2.29 | |
| 2728 | 525.42 | 2.34 | |
| 2729 | 538.33 | 2.22 | |
| 2730 | 509.21 | 2.01 | |
| 2731 | 482.20 | 1.92 | |
| 2732 | 488.20 | 2.10 | |
| 2733 | 521.22 | 2.00 | |
| 2734 | 476.19 | 2.10 | |
| 2735 | 495.40 | 1.35 | |
| 2736 | 502.31 | 1.84 | |
| 2737 | 523.32 | 2.55 | |
| 2738 | 550.33 | 1.73 | |
| 2739 | 539.23 | 2.70 | |
| 2740 | 513.41 | 2.63 | |
| 2741 | 443.18 | 2.20 | |
| 2742 | 434.17 | 2.31 | |
| 2743 | 581.25 | 2.23 | |
| 2744 | 528.12 | 2.51 | |
| 2745 | 474.09 | 2.26 | |
| 2746 | 460.29 | 2.33 | |
| 2747 | 472.29 | 2.31 | |

分析

方案**1**

偵測及量測化合物之**F508del**增強特性的分析

用於分析化合物之**F508del**調節特性的膜電位光學方法

該分析利用螢光電壓感測染料，使用螢光盤式讀取器(例如

FLIPR III，Molecular Devices, Inc.)量測膜電位之改變作爲NIH 3T3細胞中功能F508del增加的讀數。該反應之驅動力爲在細胞預先用化合物處理且隨後負載電壓感測染料之後藉由單一液體添加步驟，產生氯離子梯度以及通道活化。

**增效劑化合物之鑑別**

爲鑑別F508del之增效劑，研發一種雙重添加HTS分析格式。此HTS分析利用螢光電壓感測染料在FLIPR III上量測膜電位之改變作爲溫度校正之F508del NIH 3T3細胞中F508del閘控(傳導)之增加的量度。該反應之驅動力爲在細胞預先用增效劑化合物(或DMSO媒劑對照)處理且隨後負載再分佈染料之後使用螢光盤式讀取器，諸如FLIPR III，在單一液體添加步驟中使用弗斯可林(forskolin)下的$Cl^-$離子梯度以及通道活化。

***溶液***

**電解液#1**：(mM) NaCl 160，KCl 4.5，$CaCl_2$ 2，$MgCl_2$ 1，HEPES 10，pH 7.4，與NaOH。

**無氯離子之浴液**：浴液#1 (以上)中之氯鹽經葡糖酸鹽取代。

***細胞培養***

穩定表現F508del之NIH3T3小鼠纖維母細胞用於膜電位之光學量測。將細胞維持在37℃下5% $CO_2$及90%濕度中175 $cm^2$培養燒瓶中補充有2 mM麩醯胺酸、10%胎牛血清、1 X NEAA、β-ME、1 X青黴素/鏈黴素及25 mM HEPES之達爾伯克改良伊格爾培養基(Dulbecco's modified Eagle's medium)中。對於所有光學分析，細胞以約20,000個/孔接種於384孔經基質膠塗佈之培養盤中且在37℃下培養2小時，接著在27℃下培養24小時用於增效劑分析。對於校正分析，細胞在27℃或37℃下在有及無化合物下培養16-24小時。

用於分析化合物之F508del調節特性的電生理學分析

*尤斯室分析(Ussing Chamber Assay)*

在表現F508del之極化呼吸道上皮細胞上進行尤斯室實驗以進一步表徵在光學分析中鑑別之F508del增效劑或誘導劑。非CF及CF呼吸道上皮自支氣管組織分離，如先前所描述進行培養(Galietta, L.J.V., Lantero, S., Gazzolo, A., Sacco, O., Romano, L., Rossi, G.A., 及 Zegarra-Moran, O. (1998) *In Vitro Cell. Dev. Biol.* **34**, 478-481)，且塗鋪至預塗NIH3T3條件培養基之Costar® Snapwell™過濾器上。四天後，移除頂部培養基且在使用前細胞在空氣液體界面生長>14天。此產生有纖毛之單層完全分化柱狀細胞(表徵呼吸道上皮之特徵)。自無任何已知肺病之非吸菸者分離非CF HBE。自F508del同種接合之患者分離CF-HBE。

在Costar® Snapwell™細胞培養插入物上生長之HBE安裝在尤斯室(Physiologic Instruments, Inc., San Diego, CA)中，且使用電壓鉗系統(Department of Bioengineering, University of Iowa, IA)量測在底外側至頂部$Cl^-$梯度($I_{SC}$)存在下的經上皮電阻及短路電流。簡言之，在電壓鉗記錄條件($V_{保持}$=0 mV)下在37℃下檢驗HBE。底外側溶液含有(mM) 145 NaCl、0.83 $K_2HPO_4$、3.3 $KH_2PO_4$、1.2 $MgCl_2$、1.2 $CaCl_2$、10葡萄糖、10 HEPES (pH值用NaOH調整至7.35)且頂部溶液含有(mM) 145 葡糖酸鈉、1.2 $MgCl_2$、1.2 $CaCl_2$、10葡萄糖、10 HEPES (pH值用NaOH調整至7.35)。

*增效劑化合物之鑑別*

典型方案利用底外側至頂端膜$Cl^-$濃度梯度。爲設定此梯度，在底外側膜上使用正常林格氏，而頂部NaCl經等莫耳葡糖酸鈉(用NaOH滴定至pH 7.4)置換，得到跨越上皮細胞的大$Cl^-$濃度梯度。弗斯可林(10 μM)及所有測試化合物添加至細胞培養插入物之頂部側。推定F508del增效劑之功效與已知增效劑金雀異黃酮之功效相比。

*膜片鉗記錄*

使用如先前所描述之穿孔膜片記錄組態，監測F508del-NIH3T3細胞中全部$Cl^-$流(Rae, J., Cooper, K., Gates, P., 及Watsky, M. (1991) *J. Neurosci. Methods* **37**, 15-26)。在22℃下使用Axopatch 200B膜片鉗放大器(Axon Instruments Inc., Foster City, CA)進行電壓鉗記錄。移液管溶液含有(mM) 150 *N*-甲基-D-還原葡糖胺(NMDG)-Cl、2 $MgCl_2$、2 $CaCl_2$、10 EGTA、10 HEPES及240 μg/mL兩性黴素-B (pH值用HCl調至7.35)。細胞外培養基含有(mM) 150 NMDG-Cl、2 $MgCl_2$、2 $CaCl_2$、10 HEPES (pH值用HCl調至7.35)。使用裝備有Digidata 1320 A/D介面以及Clampex 8 (Axon Instruments Inc.)的PC執行脈衝產生、資料獲取及分析。爲活化F508del，10 μM弗斯可林及20 μM金雀異黃酮添加至浴槽中且每30秒監測電流-電壓關係。

**增效劑化合物之鑑別**

亦使用穿孔膜片記錄技術研究穩定表現F508del之NIH3T3細胞中F508del增效劑增加宏觀F508del $Cl^-$流($I_{F508del}$)之能力。由光學分析鑑別之增效劑引起$I_{F508del}$之劑量依賴性增加，具有在光學分析中觀測到之類似效能及功效。在所有檢驗之細胞中，在增效劑施加之前及期間的逆轉電位爲約-30 mV，其爲計算$E_{Cl}$ (-28 mV)。

*細胞培養*

穩定表現F508del之NIH3T3小鼠纖維母細胞用於全細胞記錄。將細胞維持在37℃下5% $CO_2$及90%濕度中175 $cm^2$培養燒瓶中補充有2 mM麩醯胺酸、10%胎牛血清、1 X NEAA、β-ME、1 X青黴素/鏈黴素及25 mM HEPES之達爾伯克改良伊格爾培養基中。對於全細胞記錄，2,500-5,000個細胞接種於經聚-L-離胺酸塗佈之玻璃蓋玻片上且在用於測試增效劑之活性之前在27℃下培養24-48小時；且與或不與校正化合物一起在37℃下培育以量測校正劑之活性。

*單一通道記錄*

使用如先前所描述之切除之由內而外膜片記錄(Dalemans, W., Barbry, P., Champigny, G., Jallat, S., Dott, K., Dreyer, D., Crystal, R.G., Pavirani, A., Lecocq, J-P., Lazdunski, M. (1991) *Nature* 354, 526 - 528)，使用Axopatch 200B膜片鉗放大器(Axon Instruments Inc.)，觀測在NIH3T3細胞中表現之wt-CFTR及溫度校正之F508del的閘控活性。移液管含有(mM)：150 NMDG、150天冬胺酸、5 $CaCl_2$、2 $MgCl_2$及10 HEPES (pH值用Tris鹼調至7.35)。浴槽含有(mM)：150 NMDG-Cl、2 $MgCl_2$、5 EGTA、10 TES及14 Tris鹼(pH值用HCl調至7.35)。在切除之後，wt-及F508del均藉由添加1 mM Mg-ATP、75 nM cAMP依賴性蛋白激酶催化次單元(PKA；Promega Corp. Madison, WI)及10 mM NaF活化以抑制阻止電流衰減之蛋白質磷酸酶。移液管電位維持在80 mV下。自含有≤2個活性通道之膜片分析通道活性。在實驗過程期間同時打開之最大數目決定活性通道之數目。爲測定單一通道電流幅度，自F508del活性之120秒記錄的資料在100 Hz下「離線」過濾且接著用於構築所有點幅度直方圖，其使用Bio-Patch分析軟體(Bio-Logic Comp. France)與多高斯函數擬合。自通道活性之120秒測定全部顯微電流及打開概率($P_o$)。使用Bio-Patch軟體或由關係式$P_o$ = I/i(N)確定$P_o$，其中I = 平均電流，i = 單一通道電流幅度，且N = 膜片中活性通道數目。

*細胞培養*

穩定表現F508del之NIH3T3小鼠纖維母細胞用於切除之膜片鉗記錄。將細胞維持在37℃下5% $CO_2$及90%濕度中175 $cm^2$培養燒瓶中補充有2 mM麩醯胺酸、10%胎牛血清、1 X NEAA、β-ME、1 X青黴素/鏈黴素及25 mM HEPES之達爾伯克改良伊格爾培養基中。對於單一通道記錄，2,500-5,000個細胞接種於經聚-L-離胺酸塗佈之玻璃蓋玻

片上且在使用之前在27℃下培養24-48小時。

**方案2**

**偵測及量測化合物之F508del校正特性的分析**

用於分析化合物之F508del調節特性的膜電位光學方法

光學膜電位分析利用Gonzalez及Tsien描述之電壓敏感性FRET感測器(*參見*Gonzalez, J. E.及R. Y. Tsien (1995) 「Voltage sensing by fluorescence resonance energy transfer in single cells」 **Biophys J** 69(4): 1272-80, 及Gonzalez, J. E.及R. Y. Tsien (1997) 「Improved indicators of cell membrane potential that use fluorescence resonance energy transfer」 **Chem Biol** 4(4): 269-77)以及用於量測螢光改變之測試設備，諸如電壓/離子探針讀取器(VIPR)(**參見**Gonzalez, J. E., K. Oades等人, (1999) 「Cell-based assays and instrumentation for screening ion-channel targets」 **Drug Discov Today** 4(9): 431-439)。

此等電壓敏感性分析係基於膜可溶性、電壓敏感性染料$DiSBAC_2(3)$與螢光磷脂CC2-DMPE之間的螢光共振能量傳遞(FRET)之改變，螢光磷脂CC2-DMPE附接於質膜外層且充當FRET供體。膜電位($V_m$)之改變引起帶負電之$DiSBAC_2(3)$跨越質膜再分佈且來自CC2-DMPE之能量傳遞的量因此改變。使用VIPR™ II監測螢光發射之改變，其爲經設計以在96或384孔微量滴定盤中進行基於細胞之篩選的整合式液體處置器及螢光偵測器。

**校正化合物之鑑別**

爲鑑別校正與F508del相關之輸送缺陷的小分子，研發出單一添加HTS分析格式。細胞在無血清培養基中在37℃下在測試化合物存在或不存在(陰性對照)下培育16小時。作爲陽性對照，塗鋪在384孔盤中之細胞在27℃下針對「溫度校正」F508del培育16小時。隨後細胞用Krebs林格氏溶液沖洗3次且負載電壓敏感性染料。爲活化

F508del，添加10 μM弗斯可林及CFTR增效劑金雀異黃酮(20 μM)以及無$Cl^-$之培養基至各孔。無$Cl^-$之培養基的添加促進回應於F508del活化之$Cl^-$流出，且使用基於FRET之電壓敏感性染料光學監測所得膜去極化。

**增效劑化合物之鑑別**

爲鑑別F508del之增效劑，研發一種雙重添加HTS分析格式。在第一次添加期間，有或無測試化合物之無$Cl^-$之培養基添加至各孔。在22秒之後，添加含有2-10 μM弗斯可林之無$Cl^-$之培養基的第二次添加以活化F508del。兩次添加後細胞外$Cl^-$濃度爲28 mM，其促進回應於F508del活化之$Cl^-$流出，且使用基於FRET之電壓敏感性染料光學監測所得膜去極化。

**溶液**

浴液#1：(mM) NaCl 160、KCl 4.5、$CaCl_2$ 2、$MgCl_2$ 1、HEPES 10，pH 7.4，與NaOH。

無氯離子之浴液：浴液#1(以上)中之氯鹽經葡糖酸鹽取代。

CC2-DMPE：製備爲於DMSO中之10 mM儲備溶液且儲存在-20℃下。

$DiSBAC_2(3)$：製備爲於DMSO中之10 mM儲備液且儲存在-20℃下。

**細胞培養**

穩定表現F508del之NIH3T3小鼠纖維母細胞用於膜電位之光學量測。將細胞維持在37℃下5% $CO_2$及90%濕度中175 $cm^2$培養燒瓶中補充有2 mM麩醯胺酸、10%胎牛血清、1 X NEAA、β-ME、1 X青黴素/鏈黴素及25 mM HEPES之達爾伯克改良伊格爾培養基中。對於所有光學分析，細胞以約30,000個/孔接種於384孔經基質膠塗佈之培養盤中且在37℃下培養2小時，接著在27℃下培養24小時用於增效劑分

析。對於校正分析，細胞在27℃或37℃下在有及無化合物下培養16-24小時。

用於分析化合物之F508del調節特性的電生理學分析

**尤斯室分析**

在表現F508del之極化呼吸道上皮細胞上進行尤斯室實驗以進一步表徵在光學分析中鑑別之F508del增效劑或誘導劑。在Costar Snapwell細胞培養插入物上生長之$FRT^{F508del}$上皮細胞安裝在尤斯室(Physiologic Instruments, Inc., San Diego, CA)中，且使用電壓鉗系統(Department of Bioengineering, University of Iowa, IA)使單層連續短路。藉由施加2 mV脈衝量測經上皮抗性。在此等條件下，FRT上皮證實4 $K\Omega/cm^2$或更大電阻。溶液維持在27℃下且用空氣鼓泡。使用無細胞插入物，校正電極偏移電位及流體電阻。在此等條件下，電流反映$Cl^-$穿過在頂端膜中表現之F508del的流動。$I_{SC}$使用MP100A-CE介面及AcqKnowledge軟體(v3.2.6；BIOPAC Systems, Santa Barbara, CA)用數位方式獲得。

**校正化合物之鑑別**

典型方案利用底外側至頂端膜$Cl^-$濃度梯度。爲設定此梯度，在底外側膜上使用正常林格氏，而頂部NaCl經等莫耳葡糖酸鈉(用NaOH滴定至pH 7.4)置換，得到跨越上皮細胞的大$Cl^-$濃度梯度。所有實驗均用完整單層進行。爲完全活化F508del，施加弗斯可林(10 μM)及PDE抑制劑IBMX (100 μM)，接著添加CFTR增效劑金雀異黃酮(50 μM)。

如在其他細胞類型中所觀測，在低溫下培育穩定表現F508del之FRT細胞增加質膜中CFTR之功能密度。爲確定校正化合物之活性，在記錄前將細胞與10 μM測試化合物一起在37℃下培育24小時且隨後洗滌3次。在經化合物處理之細胞中cAMP及金雀異黃酮介導之$I_{SC}$相

對於27℃及37℃對照標準化且表現爲活性百分比。與37℃對照相比，細胞與校正化合物一起預培育顯著增加cAMP及金雀異黃酮介導之$I_{SC}$。

**增效劑化合物之鑑別**

典型方案利用底外側至頂端膜$Cl^-$濃度梯度。爲設定此梯度，在底外側膜上使用正常林格氏且滲透耐絲他汀(nystatin)(360 μg/ml)，而頂部NaCl經等莫耳葡糖酸鈉(用NaOH滴定至pH 7.4)置換，得到跨越上皮細胞的大$Cl^-$濃度梯度。所有實驗在耐絲他汀滲透之後30分鐘進行。弗斯可林(10 μM)及所有測試化合物添加至細胞培養插入物之兩側。推定F508del增效劑之功效與已知增效劑金雀異黃酮之功效相比。

**溶液**

底外側溶液(mM)：NaCl (135)、$CaCl_2$ (1.2)、$MgCl_2$ (1.2)、$K_2HPO_4$ (2.4)、$KHPO_4$ (0.6)、N-2-羥基乙基哌嗪-N'-2-乙烷磺酸(HEPES) (10)及右旋糖(10)。溶液用NaOH滴定至pH 7.4。

頂部溶液(mM)：與底外側溶液相同，其中NaCl經葡糖酸鈉置換(135)。

**細胞培養**

表現F508del之費舍爾大鼠上皮($FRT^{F508del}$)細胞用於針對自光學分析鑑別之推定F508del增效劑或誘導劑的尤斯室實驗。細胞在Costar Snapwell細胞培養插入物上培養且在37℃及5% $CO_2$下在補充有5%胎牛血清、100 U/ml青黴素及100 μg/ml鏈黴素之庫恩改良漢姆氏F-12培養基中培養五天。在用於表徵化合物之增效劑活性前，細胞在27℃下培育16-48小時以校正F508del。爲確定校正化合物之活性，將細胞與及不與化合物一起在27℃或37℃下培育24小時。

**全細胞記錄**

使用穿孔膜片全細胞記錄，監測穩定表現F508del之溫度及測試化合物校正之NIH3T3細胞中宏觀F508del電流($I_{F508del}$)。簡言之，在室溫下使用Axopatch 200B膜片鉗放大器(Axon Instruments Inc., Foster City, CA)進行$I_{F508del}$之電壓鉗記錄。所有記錄均在10 kHz之取樣頻率下獲得，且在1 kHz下低通過濾。當填充胞內溶液時，吸液管具有5-6 MΩ之電阻。在此等記錄條件下，在室溫下$Cl^-$之計算逆轉電位($E_{Cl}$)爲-28 mV。所有記錄之密封電阻>20 GΩ且串聯電阻<15 MΩ。使用裝備有Digidata 1320 A/D介面以及Clampex 8 (Axon Instruments Inc.)的PC執行脈衝產生、資料獲取及分析。浴槽含有<250 μl生理食鹽水且使用重力驅動之灌注系統，以2 ml/min之速率連續灌注。

**校正化合物之鑑別**

爲確定校正化合物增加質膜中功能F508del之密度的活性，在用校正化合物處理24小時後使用上述穿孔膜片記錄技術量測電流密度。爲完全活化F508del，10 μM弗斯可林及20 μM金雀異黃酮添加至細胞。在記錄條件下，在27℃下培育24小時後電流密度高於在37℃下培育24小時後觀測到之電流密度。此等結果與已知之低溫培育對質膜中F508del之密度的作用一致。爲確定校正化合物對CFTR電流密度之作用，將細胞與10 μM測試化合物一起在37℃下培育24小時且電流密度與27℃及37℃對照相比(活性%)。在記錄前，細胞用細胞外記錄培養基洗滌3次以移除任何剩餘測試化合物。與37℃對照相比，與10 μM校正化合物一起預培育顯著增加cAMP及金雀異黃酮依賴性電流。

**增效劑化合物之鑑別**

亦使用穿孔膜片記錄技術研究穩定表現F508del之NIH3T3細胞中F508del增效劑增加宏觀F508del $Cl^-$電流($I_{F508del}$)之能力。由光學分析鑑別之增效劑引起$I_{F508del}$之劑量依賴性增加，具有在光學分析中觀測到之類似效能及功效。在所有檢驗之細胞中，在增效劑施加之前及期

間的逆轉電位爲約-30 mV，其爲計算$E_{Cl}$ (-28 mV)。

**溶液**

胞內溶液(mM)：天冬胺酸銫(90)、CsCl (50)、$MgCl_2$ (1)、HEPES (10)及240 μg/ml兩性黴素-B (pH值用CsOH調至7.35)。

細胞外溶液(mM)：N-甲基-D-還原葡糖胺(NMDG)-Cl (150)、$MgCl_2$ (2)、$CaCl_2$ (2)、HEPES (10) (pH值用HCl調至7.35)。

**細胞培養**

穩定表現F508del之NIH3T3小鼠纖維母細胞用於全細胞記錄。將細胞維持在37℃下5% $CO_2$及90%濕度中175 $cm^2$培養燒瓶中補充有2 mM麩醯胺酸、10%胎牛血清、1 X NEAA、β-ME、1 X青黴素/鏈黴素及25 mM HEPES之達爾伯克改良伊格爾培養基中。對於全細胞記錄，2,500-5,000個細胞接種於經聚-L-離胺酸塗佈之玻璃蓋玻片上且在用於測試增效劑之活性之前在27℃下培養24-48小時；且與或不與校正化合物一起在37℃下培育以量測校正劑之活性。

**單一通道記錄**

使用切除之由內而外膜片觀測在NIH3T3細胞中穩定表現之溫度校正之F508del的單一通道活性及增效劑化合物之活性。簡言之，在室溫下使用Axopatch 200B膜片鉗放大器(Axon Instruments Inc.)進行單一通道活性之電壓鉗記錄。所有記錄均在10 kHz之取樣頻率下獲得，且在400 Hz下低通過濾。膜片吸液管由Corning Kovar Sealing #7052玻璃(World Precision Instruments, Inc., Sarasota, FL)構造且當填充有細胞外溶液時具有5-8 MΩ之電阻。在切除之後，藉由添加1 mM Mg-ATP及75 nM cAMP依賴性蛋白激酶催化次單元(PKA；Promega Corp. Madison, WI)活化F508del。在穩定通道活性之後，使用重力驅動的微灌注系統灌注膜片。內流與膜片相鄰置放，使得在1-2秒內完成溶液交換。爲在快速灌注期間維持F508del活性，非特異性磷酸酶

抑制劑$F^-$ (10 mM NaF)添加至浴液。在此等記錄條件，通道活性在整個膜片記錄持續時間(長達60分鐘)中保持恆定。藉由自細胞內移動至細胞外溶液之正電荷產生的電流(以相反方向移動之陰離子)展示爲正電流。移液管電位($V_p$)維持在80 mV下。

自含有≤2個活性通道之膜片分析通道活性。在實驗過程期間同時打開之最大數目決定活性通道之數目。爲測定單一通道電流幅度，自F508del活性之120秒記錄的資料在100 Hz下「離線」過濾且接著用於構築所有點幅度直方圖，其使用Bio-Patch分析軟體 (Bio-Logic Comp. France)與多高斯函數擬合。自通道活性之120秒測定全部顯微電流及打開概率($P_o$)。使用Bio-Patch軟體或由關係式$P_o = I/i(N)$確定$P_o$，其中I = 平均電流，i = 單一通道電流幅度，且N = 膜片中活性通道數目。

**溶液**

細胞外溶液(mM)：NMDG (150)、天冬胺酸(150)、$CaCl_2$ (5)、$MgCl_2$ (2)及HEPES (10) (pH值用Tris鹼調至7.35)。

胞內溶液(mM)：NMDG-Cl (150)、$MgCl_2$ (2)、EGTA (5)、TES (10)及Tris鹼(14) (pH值用HCl調至7.35)。

**細胞培養**

穩定表現F508del之NIH3T3小鼠纖維母細胞用於切除之膜片鉗記錄。將細胞維持在37℃下5% $CO_2$及90%濕度中175 $cm^2$培養燒瓶中補充有2 mM麩醯胺酸、10%胎牛血清、1 X NEAA、β-ME、1 X青黴素/鏈黴素及25 mM HEPES之達爾伯克改良伊格爾培養基中。對於單一通道記錄，2,500-5,000個細胞接種於經聚-L-離胺酸塗佈之玻璃蓋玻片上且在使用之前在27℃下培養24-48小時。

式I化合物適用作CFTR活性之調節劑。以下表3說明表1化合物之EC30及相對功效。在以下表3中，以下含義適用。EC30：「+++」意

謂<3 μM；「++」意謂3 μM與10 μM之間；「+」意謂超過10 μM。

表3.

| 化合物編號 | EC30 (μM) |
|---|---|
| 1 | +++ |
| 2 | +++ |
| 3 | +++ |
| 4 | + |
| 5 | ++ |
| 6 | +++ |
| 7 | +++ |
| 8 | +++ |
| 9 | +++ |
| 10 | +++ |
| 11 | +++ |
| 12 | +++ |
| 13 | ++ |
| 14 | +++ |
| 15 | +++ |
| 16 | +++ |
| 17 | +++ |
| 18 | +++ |
| 19 | +++ |
| 20 | +++ |
| 21 | +++ |
| 22 | +++ |
| 23 | ++ |
| 24 | ++ |
| 25 | ++ |
| 26 | ++ |
| 27 | +++ |
| 28 | +++ |
| 29 | +++ |
| 30 | +++ |
| 31 | ++ |
| 32 | ++ |
| 33 | +++ |
| 34 | +++ |
| 35 | +++ |
| 36 | +++ |
| 37 | +++ |
| 38 | +++ |
| 39 | ++ |
| 40 | +++ |
| 41 | +++ |
| 42 | ++ |
| 43 | +++ |
| 44 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 45 | +++ |
| 46 | ++ |
| 47 | +++ |
| 48 | ++ |
| 49 | +++ |
| 50 | +++ |
| 51 | +++ |
| 52 | +++ |
| 53 | +++ |
| 54 | ++ |
| 55 | ++ |
| 56 | +++ |
| 57 | +++ |
| 58 | ++ |
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| 79 | ++ |
| 80 | +++ |
| 81 | +++ |
| 82 | +++ |
| 83 | +++ |
| 84 | +++ |
| 85 | ++ |
| 86 | ++ |
| 87 | +++ |
| 88 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 89 | +++ |
| 90 | +++ |
| 91 | ++ |
| 92 | +++ |
| 93 | +++ |
| 94 | +++ |
| 95 | +++ |
| 96 | +++ |
| 97 | +++ |
| 98 | +++ |
| 99 | +++ |
| 100 | +++ |
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| 126 | +++ |
| 127 | +++ |
| 128 | +++ |
| 129 | ++ |
| 130 | +++ |
| 131 | +++ |
| 132 | +++ |
| 133 | +++ |
| 134 | +++ |
| 135 | +++ |
| 136 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 137 | +++ |
| 138 | ++ |
| 139 | +++ |
| 140 | +++ |
| 141 | +++ |
| 142 | +++ |
| 143 | +++ |
| 144 | +++ |
| 145 | +++ |
| 146 | +++ |
| 147 | +++ |
| 148 | +++ |
| 149 | +++ |
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| 175 | ++ |
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| 180 | +++ |
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| 182 | +++ |
| 183 | +++ |
| 184 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 185 | +++ |
| 186 | +++ |
| 187 | ++ |
| 188 | +++ |
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| 190 | +++ |
| 191 | +++ |
| 192 | +++ |
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| 224 | +++ |
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| 226 | +++ |
| 227 | ++ |
| 228 | +++ |
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| 230 | ++ |
| 231 | +++ |
| 232 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 233 | +++ |
| 234 | +++ |
| 235 | +++ |
| 236 | ++ |
| 237 | ++ |
| 238 | +++ |
| 239 | +++ |
| 240 | ++ |
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| 254 | ++ |
| 255 | +++ |
| 256 | +++ |
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| 258 | ++ |
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| 266 | +++ |
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| 268 | +++ |
| 269 | +++ |
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| 272 | ++ |
| 273 | +++ |
| 274 | +++ |
| 275 | +++ |
| 276 | +++ |
| 277 | +++ |
| 278 | ++ |
| 279 | +++ |
| 280 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 281 | +++ |
| 282 | ++ |
| 283 | +++ |
| 284 | +++ |
| 285 | +++ |
| 286 | +++ |
| 287 | +++ |
| 288 | +++ |
| 289 | +++ |
| 290 | +++ |
| 291 | ++ |
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| 324 | ++ |
| 325 | +++ |
| 326 | +++ |
| 327 | +++ |
| 328 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 329 | +++ |
| 330 | +++ |
| 331 | +++ |
| 332 | +++ |
| 333 | +++ |
| 334 | ++ |
| 335 | +++ |
| 336 | +++ |
| 337 | +++ |
| 338 | +++ |
| 339 | +++ |
| 340 | +++ |
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| 347 | +++ |
| 348 | +++ |
| 349 | ++ |
| 350 | +++ |
| 351 | +++ |
| 352 | +++ |
| 353 | +++ |
| 354 | +++ |
| 355 | +++ |
| 356 | +++ |
| 357 | ++ |
| 358 | +++ |
| 359 | +++ |
| 360 | +++ |
| 361 | +++ |
| 362 | +++ |
| 363 | +++ |
| 364 | +++ |
| 365 | +++ |
| 366 | +++ |
| 367 | +++ |
| 368 | +++ |
| 369 | +++ |
| 370 | +++ |
| 371 | +++ |
| 372 | ++ |
| 373 | ++ |
| 374 | +++ |
| 375 | +++ |
| 376 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 377 | +++ |
| 378 | +++ |
| 379 | +++ |
| 380 | +++ |
| 381 | ++ |
| 382 | +++ |
| 383 | +++ |
| 384 | +++ |
| 385 | +++ |
| 386 | +++ |
| 387 | +++ |
| 388 | ++ |
| 389 | +++ |
| 390 | +++ |
| 391 | + |
| 392 | ++ |
| 393 | ++ |
| 394 | +++ |
| 395 | +++ |
| 396 | +++ |
| 397 | +++ |
| 398 | +++ |
| 399 | +++ |
| 400 | ++ |
| 401 | +++ |
| 402 | +++ |
| 403 | ++ |
| 404 | +++ |
| 405 | +++ |
| 406 | +++ |
| 407 | ++ |
| 408 | +++ |
| 409 | + |
| 410 | +++ |
| 411 | +++ |
| 412 | +++ |
| 413 | +++ |
| 414 | +++ |
| 415 | +++ |
| 416 | +++ |
| 417 | ++ |
| 418 | +++ |
| 419 | +++ |
| 420 | +++ |
| 421 | +++ |
| 422 | +++ |
| 423 | +++ |
| 424 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 425 | +++ |
| 426 | +++ |
| 427 | +++ |
| 428 | +++ |
| 429 | +++ |
| 430 | +++ |
| 431 | ++ |
| 432 | +++ |
| 433 | +++ |
| 434 | +++ |
| 435 | +++ |
| 436 | +++ |
| 437 | +++ |
| 438 | +++ |
| 439 | +++ |
| 440 | +++ |
| 441 | +++ |
| 442 | +++ |
| 443 | + |
| 444 | ++ |
| 445 | + |
| 446 | +++ |
| 447 | +++ |
| 448 | +++ |
| 449 | + |
| 450 | +++ |
| 451 | ++ |
| 452 | +++ |
| 453 | +++ |
| 454 | +++ |
| 455 | +++ |
| 456 | +++ |
| 457 | +++ |
| 458 | +++ |
| 459 | +++ |
| 460 | ++ |
| 461 | ++ |
| 462 | +++ |
| 463 | ++ |
| 464 | +++ |
| 465 | ++ |
| 466 | +++ |
| 467 | ++ |
| 468 | +++ |
| 469 | ++ |
| 470 | +++ |
| 471 | +++ |
| 472 | + |

| 化合物編號 | EC30 (μM) |
|---|---|
| 473 | +++ |
| 474 | +++ |
| 475 | +++ |
| 476 | ++ |
| 477 | +++ |
| 478 | ++ |
| 479 | +++ |
| 480 | +++ |
| 481 | +++ |
| 482 | +++ |
| 483 | +++ |
| 484 | |
| 485 | +++ |
| 486 | ++ |
| 487 | ++ |
| 488 | +++ |
| 489 | +++ |
| 490 | +++ |
| 491 | +++ |
| 492 | +++ |
| 493 | +++ |
| 494 | +++ |
| 495 | ++ |
| 496 | +++ |
| 497 | +++ |
| 498 | +++ |
| 499 | ++ |
| 500 | +++ |
| 501 | +++ |
| 502 | +++ |
| 503 | +++ |
| 504 | +++ |
| 505 | ++ |
| 506 | +++ |
| 507 | +++ |
| 508 | ++ |
| 509 | +++ |
| 510 | +++ |
| 511 | +++ |
| 512 | ++ |
| 513 | ++ |
| 514 | + |
| 515 | +++ |
| 516 | +++ |
| 517 | ++ |
| 518 | +++ |
| 519 | ++ |
| 520 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 521 | ++ |
| 522 | +++ |
| 523 | +++ |
| 524 | ++ |
| 525 | ++ |
| 526 | +++ |
| 527 | +++ |
| 528 | +++ |
| 529 | ++ |
| 530 | +++ |
| 531 | +++ |
| 532 | ++ |
| 533 | +++ |
| 534 | ++ |
| 535 | +++ |
| 536 | +++ |
| 537 | +++ |
| 538 | +++ |
| 539 | + |
| 540 | + |
| 541 | +++ |
| 542 | +++ |
| 543 | ++ |
| 544 | +++ |
| 545 | ++ |
| 546 | ++ |
| 547 | +++ |
| 548 | +++ |
| 549 | +++ |
| 550 | ++ |
| 551 | +++ |
| 552 | ++ |
| 553 | +++ |
| 554 | +++ |
| 555 | +++ |
| 556 | + |
| 557 | +++ |
| 558 | +++ |
| 559 | +++ |
| 560 | +++ |
| 561 | +++ |
| 562 | +++ |
| 563 | +++ |
| 564 | ++ |
| 565 | + |
| 566 | + |
| 567 | ++ |
| 568 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 569 | +++ |
| 570 | +++ |
| 571 | ++ |
| 572 | +++ |
| 573 | +++ |
| 574 | ++ |
| 575 | +++ |
| 576 | +++ |
| 577 | ++ |
| 578 | +++ |
| 579 | +++ |
| 580 | +++ |
| 581 | +++ |
| 582 | ++ |
| 583 | +++ |
| 584 | ++ |
| 585 | +++ |
| 586 | +++ |
| 587 | +++ |
| 588 | ++ |
| 589 | +++ |
| 590 | +++ |
| 591 | +++ |
| 592 | +++ |
| 593 | +++ |
| 594 | ++ |
| 595 | +++ |
| 596 | ++ |
| 597 | +++ |
| 598 | ++ |
| 599 | +++ |
| 600 | +++ |
| 601 | +++ |
| 602 | +++ |
| 603 | +++ |
| 604 | +++ |
| 605 | +++ |
| 606 | ++ |
| 607 | +++ |
| 608 | ++ |
| 609 | +++ |
| 610 | +++ |
| 611 | +++ |
| 612 | +++ |
| 613 | +++ |
| 614 | +++ |
| 615 | +++ |
| 616 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 617 | +++ |
| 618 | ++ |
| 619 | +++ |
| 620 | +++ |
| 621 | +++ |
| 622 | +++ |
| 623 | ++ |
| 624 | ++ |
| 625 | +++ |
| 626 | +++ |
| 627 | + |
| 628 | +++ |
| 629 | +++ |
| 630 | +++ |
| 631 | +++ |
| 632 | ++ |
| 633 | +++ |
| 634 | +++ |
| 635 | + |
| 636 | ++ |
| 637 | ++ |
| 638 | ++ |
| 639 | +++ |
| 640 | ++ |
| 641 | +++ |
| 642 | +++ |
| 643 | ++ |
| 644 | +++ |
| 645 | ++ |
| 646 | ++ |
| 647 | +++ |
| 648 | +++ |
| 649 | ++ |
| 650 | ++ |
| 651 | +++ |
| 652 | ++ |
| 653 | + |
| 654 | +++ |
| 655 | +++ |
| 656 | +++ |
| 657 | +++ |
| 658 | +++ |
| 659 | ++ |
| 660 | + |
| 661 | +++ |
| 662 | + |
| 663 | +++ |
| 664 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 665 | +++ |
| 666 | ++ |
| 667 | +++ |
| 668 | +++ |
| 669 | +++ |
| 670 | ++ |
| 671 | +++ |
| 672 | +++ |
| 673 | +++ |
| 674 | +++ |
| 675 | +++ |
| 676 | +++ |
| 677 | ++ |
| 678 | +++ |
| 679 | +++ |
| 680 | +++ |
| 681 | +++ |
| 682 | +++ |
| 683 | +++ |
| 684 | +++ |
| 685 | +++ |
| 686 | +++ |
| 687 | ++ |
| 688 | +++ |
| 689 | +++ |
| 690 | ++ |
| 691 | +++ |
| 692 | +++ |
| 693 | +++ |
| 694 | +++ |
| 695 | +++ |
| 696 | +++ |
| 697 | +++ |
| 698 | |
| 699 | +++ |
| 700 | +++ |
| 701 | +++ |
| 702 | ++ |
| 703 | +++ |
| 704 | ++ |
| 705 | +++ |
| 706 | +++ |
| 707 | + |
| 708 | +++ |
| 709 | +++ |
| 710 | +++ |
| 711 | +++ |
| 712 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 713 | ++ |
| 714 | +++ |
| 715 | +++ |
| 716 | +++ |
| 717 | +++ |
| 718 | +++ |
| 719 | +++ |
| 720 | +++ |
| 721 | ++ |
| 722 | + |
| 723 | ++ |
| 724 | +++ |
| 725 | +++ |
| 726 | ++ |
| 727 | + |
| 728 | ++ |
| 729 | ++ |
| 730 | +++ |
| 731 | +++ |
| 732 | +++ |
| 733 | +++ |
| 734 | +++ |
| 735 | +++ |
| 736 | +++ |
| 737 | +++ |
| 738 | +++ |
| 739 | ++ |
| 740 | ++ |
| 741 | +++ |
| 742 | +++ |
| 743 | +++ |
| 744 | +++ |
| 745 | ++ |
| 746 | +++ |
| 747 | +++ |
| 748 | ++ |
| 749 | +++ |
| 750 | +++ |
| 751 | +++ |
| 752 | ++ |
| 753 | ++ |
| 754 | +++ |
| 755 | ++ |
| 756 | +++ |
| 757 | +++ |
| 758 | ++ |
| 759 | +++ |
| 760 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 761 | +++ |
| 762 | ++ |
| 763 | +++ |
| 764 | +++ |
| 765 | ++ |
| 766 | ++ |
| 767 | +++ |
| 768 | ++ |
| 769 | +++ |
| 770 | ++ |
| 771 | +++ |
| 772 | +++ |
| 773 | +++ |
| 774 | +++ |
| 775 | +++ |
| 776 | +++ |
| 777 | +++ |
| 778 | +++ |
| 779 | +++ |
| 780 | +++ |
| 781 | + |
| 782 | +++ |
| 783 | +++ |
| 784 | +++ |
| 785 | +++ |
| 786 | + |
| 787 | +++ |
| 788 | +++ |
| 789 | +++ |
| 790 | +++ |
| 791 | ++ |
| 792 | ++ |
| 793 | +++ |
| 794 | +++ |
| 795 | +++ |
| 796 | +++ |
| 797 | + |
| 798 | +++ |
| 799 | + |
| 800 | ++ |
| 801 | + |
| 802 | +++ |
| 803 | +++ |
| 804 | +++ |
| 805 | +++ |
| 806 | ++ |
| 807 | +++ |
| 808 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 809 | ++ |
| 810 | ++ |
| 811 | +++ |
| 812 | ++ |
| 813 | +++ |
| 814 | +++ |
| 815 | ++ |
| 816 | ++ |
| 817 | +++ |
| 818 | +++ |
| 819 | + |
| 820 | + |
| 821 | ++ |
| 822 | +++ |
| 823 | + |
| 824 | ++ |
| 825 | ++ |
| 826 | +++ |
| 827 | +++ |
| 828 | +++ |
| 829 | +++ |
| 830 | +++ |
| 831 | +++ |
| 832 | +++ |
| 833 | +++ |
| 834 | +++ |
| 835 | ++ |
| 836 | ++ |
| 837 | +++ |
| 838 | ++ |
| 839 | ++ |
| 840 | +++ |
| 841 | +++ |
| 842 | +++ |
| 843 | ++ |
| 844 | ++ |
| 845 | +++ |
| 846 | +++ |
| 847 | +++ |
| 848 | +++ |
| 849 | + |
| 850 | +++ |
| 851 | +++ |
| 852 | ++ |
| 853 | +++ |
| 854 | ++ |
| 855 | + |
| 856 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 857 | +++ |
| 858 | ++ |
| 859 | +++ |
| 860 | ++ |
| 861 | ++ |
| 862 | +++ |
| 863 | ++ |
| 864 | +++ |
| 865 | +++ |
| 866 | +++ |
| 867 | +++ |
| 868 | +++ |
| 869 | +++ |
| 870 | ++ |
| 871 | +++ |
| 872 | ++ |
| 873 | +++ |
| 874 | +++ |
| 875 | +++ |
| 876 | +++ |
| 877 | +++ |
| 878 | ++ |
| 879 | + |
| 880 | ++ |
| 881 | +++ |
| 882 | +++ |
| 883 | ++ |
| 884 | ++ |
| 885 | ++ |
| 886 | +++ |
| 887 | +++ |
| 888 | ++ |
| 889 | ++ |
| 890 | +++ |
| 891 | +++ |
| 892 | ++ |
| 893 | +++ |
| 894 | +++ |
| 895 | +++ |
| 896 | +++ |
| 897 | +++ |
| 898 | +++ |
| 899 | +++ |
| 900 | +++ |
| 901 | ++ |
| 902 | +++ |
| 903 | ++ |
| 904 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 905 | +++ |
| 906 | +++ |
| 907 | +++ |
| 908 | + |
| 909 | +++ |
| 910 | +++ |
| 911 | +++ |
| 912 | +++ |
| 913 | ++ |
| 914 | +++ |
| 915 | +++ |
| 916 | +++ |
| 917 | ++ |
| 918 | +++ |
| 919 | +++ |
| 920 | +++ |
| 921 | ++ |
| 922 | +++ |
| 923 | +++ |
| 924 | +++ |
| 925 | +++ |
| 926 | +++ |
| 927 | ++ |
| 928 | +++ |
| 929 | ++ |
| 930 | ++ |
| 931 | +++ |
| 932 | + |
| 933 | +++ |
| 934 | +++ |
| 935 | ++ |
| 936 | ++ |
| 937 | +++ |
| 938 | ++ |
| 939 | +++ |
| 940 | +++ |
| 941 | +++ |
| 942 | +++ |
| 943 | + |
| 944 | +++ |
| 945 | +++ |
| 946 | ++ |
| 947 | +++ |
| 948 | +++ |
| 949 | +++ |
| 950 | +++ |
| 951 | +++ |
| 952 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 953 | +++ |
| 954 | +++ |
| 955 | ++ |
| 956 | +++ |
| 957 | +++ |
| 958 | +++ |
| 959 | +++ |
| 960 | ++ |
| 961 | +++ |
| 962 | ++ |
| 963 | ++ |
| 964 | +++ |
| 965 | +++ |
| 966 | + |
| 967 | +++ |
| 968 | +++ |
| 969 | +++ |
| 970 | |
| 971 | +++ |
| 972 | +++ |
| 973 | +++ |
| 974 | +++ |
| 975 | ++ |
| 976 | ++ |
| 977 | ++ |
| 978 | +++ |
| 979 | +++ |
| 980 | ++ |
| 981 | ++ |
| 982 | ++ |
| 983 | ++ |
| 984 | +++ |
| 985 | +++ |
| 986 | ++ |
| 987 | +++ |
| 988 | +++ |
| 989 | +++ |
| 990 | +++ |
| 991 | +++ |
| 992 | +++ |
| 993 | +++ |
| 994 | +++ |
| 995 | +++ |
| 996 | +++ |
| 997 | ++ |
| 998 | ++ |
| 999 | ++ |
| 1000 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1001 | ++ |
| 1002 | +++ |
| 1003 | + |
| 1004 | +++ |
| 1005 | +++ |
| 1006 | +++ |
| 1007 | +++ |
| 1008 | +++ |
| 1009 | +++ |
| 1010 | +++ |
| 1011 | +++ |
| 1012 | +++ |
| 1013 | +++ |
| 1014 | +++ |
| 1015 | +++ |
| 1016 | +++ |
| 1017 | ++ |
| 1018 | ++ |
| 1019 | +++ |
| 1020 | +++ |
| 1021 | +++ |
| 1022 | ++ |
| 1023 | +++ |
| 1024 | ++ |
| 1025 | +++ |
| 1026 | ++ |
| 1027 | ++ |
| 1028 | ++ |
| 1029 | ++ |
| 1030 | +++ |
| 1031 | +++ |
| 1032 | +++ |
| 1033 | +++ |
| 1034 | +++ |
| 1035 | +++ |
| 1036 | + |
| 1037 | ++ |
| 1038 | ++ |
| 1039 | +++ |
| 1040 | +++ |
| 1041 | +++ |
| 1042 | +++ |
| 1043 | +++ |
| 1044 | +++ |
| 1045 | ++ |
| 1046 | ++ |
| 1047 | +++ |
| 1048 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1049 | +++ |
| 1050 | ++ |
| 1051 | +++ |
| 1052 | +++ |
| 1053 | ++ |
| 1054 | +++ |
| 1055 | ++ |
| 1056 | +++ |
| 1057 | + |
| 1058 | +++ |
| 1059 | +++ |
| 1060 | +++ |
| 1061 | +++ |
| 1062 | +++ |
| 1063 | +++ |
| 1064 | +++ |
| 1065 | +++ |
| 1066 | ++ |
| 1067 | +++ |
| 1068 | +++ |
| 1069 | +++ |
| 1070 | +++ |
| 1071 | +++ |
| 1072 | ++ |
| 1073 | + |
| 1074 | ++ |
| 1075 | +++ |
| 1076 | +++ |
| 1077 | +++ |
| 1078 | ++ |
| 1079 | +++ |
| 1080 | +++ |
| 1081 | ++ |
| 1082 | + |
| 1083 | +++ |
| 1084 | ++ |
| 1085 | +++ |
| 1086 | ++ |
| 1087 | +++ |
| 1088 | +++ |
| 1089 | +++ |
| 1090 | +++ |
| 1091 | +++ |
| 1092 | ++ |
| 1093 | ++ |
| 1094 | +++ |
| 1095 | ++ |
| 1096 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1097 | +++ |
| 1098 | +++ |
| 1099 | +++ |
| 1100 | +++ |
| 1101 | +++ |
| 1102 | +++ |
| 1103 | +++ |
| 1104 | +++ |
| 1105 | + |
| 1106 | + |
| 1107 | +++ |
| 1108 | +++ |
| 1109 | ++ |
| 1110 | +++ |
| 1111 | +++ |
| 1112 | ++ |
| 1113 | +++ |
| 1114 | |
| 1115 | + |
| 1116 | ++ |
| 1117 | +++ |
| 1118 | +++ |
| 1119 | ++ |
| 1120 | +++ |
| 1121 | +++ |
| 1122 | ++ |
| 1123 | +++ |
| 1124 | +++ |
| 1125 | ++ |
| 1126 | + |
| 1127 | +++ |
| 1128 | ++ |
| 1129 | ++ |
| 1130 | ++ |
| 1131 | +++ |
| 1132 | +++ |
| 1133 | +++ |
| 1134 | +++ |
| 1135 | +++ |
| 1136 | +++ |
| 1137 | ++ |
| 1138 | +++ |
| 1139 | +++ |
| 1140 | +++ |
| 1141 | ++ |
| 1142 | ++ |
| 1143 | ++ |
| 1144 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1145 | +++ |
| 1146 | ++ |
| 1147 | ++ |
| 1148 | +++ |
| 1149 | +++ |
| 1150 | +++ |
| 1151 | ++ |
| 1152 | + |
| 1153 | +++ |
| 1154 | ++ |
| 1155 | ++ |
| 1156 | +++ |
| 1157 | +++ |
| 1158 | +++ |
| 1159 | +++ |
| 1160 | +++ |
| 1161 | +++ |
| 1162 | +++ |
| 1163 | +++ |
| 1164 | ++ |
| 1165 | ++ |
| 1166 | +++ |
| 1167 | +++ |
| 1168 | +++ |
| 1169 | ++ |
| 1170 | +++ |
| 1171 | +++ |
| 1172 | ++ |
| 1173 | +++ |
| 1174 | +++ |
| 1175 | +++ |
| 1176 | +++ |
| 1177 | ++ |
| 1178 | +++ |
| 1179 | ++ |
| 1180 | +++ |
| 1181 | +++ |
| 1182 | ++ |
| 1183 | + |
| 1184 | +++ |
| 1185 | +++ |
| 1186 | +++ |
| 1187 | +++ |
| 1188 | +++ |
| 1189 | +++ |
| 1190 | +++ |
| 1191 | ++ |
| 1192 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1193 | +++ |
| 1194 | +++ |
| 1195 | + |
| 1196 | ++ |
| 1197 | +++ |
| 1198 | +++ |
| 1199 | ++ |
| 1200 | ++ |
| 1201 | +++ |
| 1202 | +++ |
| 1203 | + |
| 1204 | + |
| 1205 | +++ |
| 1206 | ++ |
| 1207 | +++ |
| 1208 | +++ |
| 1209 | +++ |
| 1210 | +++ |
| 1211 | ++ |
| 1212 | +++ |
| 1213 | ++ |
| 1214 | ++ |
| 1215 | ++ |
| 1216 | +++ |
| 1217 | + |
| 1218 | +++ |
| 1219 | ++ |
| 1220 | +++ |
| 1221 | +++ |
| 1222 | +++ |
| 1223 | +++ |
| 1224 | ++ |
| 1225 | +++ |
| 1226 | +++ |
| 1227 | +++ |
| 1228 | ++ |
| 1229 | +++ |
| 1230 | ++ |
| 1231 | +++ |
| 1232 | +++ |
| 1233 | ++ |
| 1234 | +++ |
| 1235 | +++ |
| 1236 | ++ |
| 1237 | ++ |
| 1238 | +++ |
| 1239 | +++ |
| 1240 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1241 | +++ |
| 1242 | +++ |
| 1243 | +++ |
| 1244 | +++ |
| 1245 | + |
| 1246 | +++ |
| 1247 | +++ |
| 1248 | +++ |
| 1249 | +++ |
| 1250 | +++ |
| 1251 | ++ |
| 1252 | +++ |
| 1253 | ++ |
| 1254 | +++ |
| 1255 | +++ |
| 1256 | ++ |
| 1257 | ++ |
| 1258 | +++ |
| 1259 | +++ |
| 1260 | +++ |
| 1261 | +++ |
| 1262 | ++ |
| 1263 | +++ |
| 1264 | +++ |
| 1265 | ++ |
| 1266 | +++ |
| 1267 | +++ |
| 1268 | +++ |
| 1269 | +++ |
| 1270 | +++ |
| 1271 | +++ |
| 1272 | +++ |
| 1273 | +++ |
| 1274 | +++ |
| 1275 | +++ |
| 1276 | ++ |
| 1277 | +++ |
| 1278 | + |
| 1279 | +++ |
| 1280 | +++ |
| 1281 | ++ |
| 1282 | +++ |
| 1283 | +++ |
| 1284 | +++ |
| 1285 | +++ |
| 1286 | +++ |
| 1287 | +++ |
| 1288 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1289 | +++ |
| 1290 | +++ |
| 1291 | ++ |
| 1292 | + |
| 1293 | ++ |
| 1294 | +++ |
| 1295 | +++ |
| 1296 | + |
| 1297 | +++ |
| 1298 | ++ |
| 1299 | ++ |
| 1300 | +++ |
| 1301 | ++ |
| 1302 | ++ |
| 1303 | +++ |
| 1304 | +++ |
| 1305 | +++ |
| 1306 | +++ |
| 1307 | ++ |
| 1308 | +++ |
| 1309 | +++ |
| 1310 | +++ |
| 1311 | +++ |
| 1312 | ++ |
| 1313 | +++ |
| 1314 | +++ |
| 1315 | +++ |
| 1316 | +++ |
| 1317 | +++ |
| 1318 | +++ |
| 1319 | +++ |
| 1320 | +++ |
| 1321 | ++ |
| 1322 | ++ |
| 1323 | + |
| 1324 | +++ |
| 1325 | +++ |
| 1326 | ++ |
| 1327 | +++ |
| 1328 | +++ |
| 1329 | ++ |
| 1330 | +++ |
| 1331 | + |
| 1332 | +++ |
| 1333 | +++ |
| 1334 | +++ |
| 1335 | +++ |
| 1336 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1337 | +++ |
| 1338 | ++ |
| 1339 | +++ |
| 1340 | +++ |
| 1341 | +++ |
| 1342 | +++ |
| 1343 | +++ |
| 1344 | ++ |
| 1345 | +++ |
| 1346 | +++ |
| 1347 | +++ |
| 1348 | +++ |
| 1349 | +++ |
| 1350 | + |
| 1351 | ++ |
| 1352 | +++ |
| 1353 | + |
| 1354 | +++ |
| 1355 | ++ |
| 1356 | +++ |
| 1357 | +++ |
| 1358 | +++ |
| 1359 | |
| 1360 | +++ |
| 1361 | +++ |
| 1362 | +++ |
| 1363 | +++ |
| 1364 | +++ |
| 1365 | +++ |
| 1366 | +++ |
| 1367 | +++ |
| 1368 | +++ |
| 1369 | +++ |
| 1370 | +++ |
| 1371 | +++ |
| 1372 | +++ |
| 1373 | +++ |
| 1374 | +++ |
| 1375 | ++ |
| 1376 | +++ |
| 1377 | +++ |
| 1378 | +++ |
| 1379 | +++ |
| 1380 | +++ |
| 1381 | ++ |
| 1382 | + |
| 1383 | +++ |
| 1384 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1385 | +++ |
| 1386 | ++ |
| 1387 | +++ |
| 1388 | +++ |
| 1389 | +++ |
| 1390 | +++ |
| 1391 | +++ |
| 1392 | +++ |
| 1393 | +++ |
| 1394 | +++ |
| 1395 | +++ |
| 1396 | +++ |
| 1397 | +++ |
| 1398 | ++ |
| 1399 | +++ |
| 1400 | +++ |
| 1401 | +++ |
| 1402 | +++ |
| 1403 | +++ |
| 1404 | +++ |
| 1405 | +++ |
| 1406 | +++ |
| 1407 | +++ |
| 1408 | +++ |
| 1409 | +++ |
| 1410 | +++ |
| 1411 | +++ |
| 1412 | +++ |
| 1413 | +++ |
| 1414 | +++ |
| 1415 | +++ |
| 1416 | +++ |
| 1417 | ++ |
| 1418 | +++ |
| 1419 | +++ |
| 1420 | ++ |
| 1421 | +++ |
| 1422 | +++ |
| 1423 | +++ |
| 1424 | +++ |
| 1425 | +++ |
| 1426 | +++ |
| 1427 | +++ |
| 1428 | +++ |
| 1429 | +++ |
| 1430 | +++ |
| 1431 | +++ |
| 1432 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1433 | ++ |
| 1434 | +++ |
| 1435 | +++ |
| 1436 | ++ |
| 1437 | ++ |
| 1438 | +++ |
| 1439 | ++ |
| 1440 | +++ |
| 1441 | ++ |
| 1442 | +++ |
| 1443 | +++ |
| 1444 | +++ |
| 1445 | +++ |
| 1446 | +++ |
| 1447 | +++ |
| 1448 | |
| 1449 | +++ |
| 1450 | +++ |
| 1451 | +++ |
| 1452 | +++ |
| 1453 | +++ |
| 1454 | +++ |
| 1455 | +++ |
| 1456 | +++ |
| 1457 | +++ |
| 1458 | +++ |
| 1459 | +++ |
| 1460 | +++ |
| 1461 | +++ |
| 1462 | +++ |
| 1463 | +++ |
| 1464 | +++ |
| 1465 | +++ |
| 1466 | ++ |
| 1467 | +++ |
| 1468 | +++ |
| 1469 | ++ |
| 1470 | +++ |
| 1471 | +++ |
| 1472 | +++ |
| 1473 | +++ |
| 1474 | +++ |
| 1475 | +++ |
| 1476 | +++ |
| 1477 | +++ |
| 1478 | +++ |
| 1479 | +++ |
| 1480 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1481 | +++ |
| 1482 | +++ |
| 1483 | +++ |
| 1484 | +++ |
| 1485 | +++ |
| 1486 | +++ |
| 1487 | +++ |
| 1488 | +++ |
| 1489 | +++ |
| 1490 | +++ |
| 1491 | ++ |
| 1492 | ++ |
| 1493 | +++ |
| 1494 | +++ |
| 1495 | +++ |
| 1496 | +++ |
| 1497 | +++ |
| 1498 | +++ |
| 1499 | ++ |
| 1500 | +++ |
| 1501 | +++ |
| 1502 | +++ |
| 1503 | ++ |
| 1504 | +++ |
| 1505 | +++ |
| 1506 | +++ |
| 1507 | ++ |
| 1508 | +++ |
| 1509 | +++ |
| 1510 | +++ |
| 1511 | +++ |
| 1512 | +++ |
| 1513 | +++ |
| 1514 | +++ |
| 1515 | +++ |
| 1516 | +++ |
| 1517 | +++ |
| 1518 | +++ |
| 1519 | +++ |
| 1520 | +++ |
| 1521 | +++ |
| 1522 | +++ |
| 1523 | +++ |
| 1524 | +++ |
| 1525 | +++ |
| 1526 | +++ |
| 1527 | +++ |
| 1528 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1529 | +++ |
| 1530 | +++ |
| 1531 | ++ |
| 1532 | +++ |
| 1533 | +++ |
| 1534 | ++ |
| 1535 | +++ |
| 1536 | ++ |
| 1537 | +++ |
| 1538 | + |
| 1539 | +++ |
| 1540 | + |
| 1541 | +++ |
| 1542 | +++ |
| 1543 | |
| 1544 | +++ |
| 1545 | +++ |
| 1546 | +++ |
| 1547 | ++ |
| 1548 | +++ |
| 1549 | +++ |
| 1550 | ++ |
| 1551 | +++ |
| 1552 | +++ |
| 1553 | +++ |
| 1554 | +++ |
| 1555 | +++ |
| 1556 | +++ |
| 1557 | +++ |
| 1558 | ++ |
| 1559 | +++ |
| 1560 | +++ |
| 1561 | +++ |
| 1562 | +++ |
| 1563 | +++ |
| 1564 | ++ |
| 1565 | + |
| 1566 | +++ |
| 1567 | +++ |
| 1568 | +++ |
| 1569 | +++ |
| 1570 | +++ |
| 1571 | +++ |
| 1572 | +++ |
| 1573 | +++ |
| 1574 | ++ |
| 1575 | ++ |
| 1576 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1577 | +++ |
| 1578 | +++ |
| 1579 | +++ |
| 1580 | +++ |
| 1581 | +++ |
| 1582 | +++ |
| 1583 | ++ |
| 1584 | +++ |
| 1585 | +++ |
| 1586 | +++ |
| 1587 | +++ |
| 1588 | +++ |
| 1589 | +++ |
| 1590 | +++ |
| 1591 | +++ |
| 1592 | +++ |
| 1593 | +++ |
| 1594 | +++ |
| 1595 | +++ |
| 1596 | +++ |
| 1597 | +++ |
| 1598 | +++ |
| 1599 | +++ |
| 1600 | +++ |
| 1601 | +++ |
| 1602 | +++ |
| 1603 | ++ |
| 1604 | +++ |
| 1605 | +++ |
| 1606 | +++ |
| 1607 | ++ |
| 1608 | +++ |
| 1609 | +++ |
| 1610 | +++ |
| 1611 | +++ |
| 1612 | +++ |
| 1613 | +++ |
| 1614 | +++ |
| 1615 | +++ |
| 1616 | +++ |
| 1617 | +++ |
| 1618 | +++ |
| 1619 | +++ |
| 1620 | +++ |
| 1621 | +++ |
| 1622 | +++ |
| 1623 | +++ |
| 1624 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1625 | ++ |
| 1626 | +++ |
| 1627 | +++ |
| 1628 | +++ |
| 1629 | +++ |
| 1630 | +++ |
| 1631 | ++ |
| 1632 | ++ |
| 1633 | +++ |
| 1634 | ++ |
| 1635 | +++ |
| 1636 | ++ |
| 1637 | +++ |
| 1638 | +++ |
| 1639 | +++ |
| 1640 | +++ |
| 1641 | +++ |
| 1642 | +++ |
| 1643 | ++ |
| 1644 | +++ |
| 1645 | +++ |
| 1646 | +++ |
| 1647 | +++ |
| 1648 | +++ |
| 1649 | ++ |
| 1650 | +++ |
| 1651 | ++ |
| 1652 | +++ |
| 1653 | +++ |
| 1654 | +++ |
| 1655 | +++ |
| 1656 | +++ |
| 1657 | +++ |
| 1658 | ++ |
| 1659 | +++ |
| 1660 | +++ |
| 1661 | +++ |
| 1662 | ++ |
| 1663 | +++ |
| 1664 | +++ |
| 1665 | +++ |
| 1666 | +++ |
| 1667 | ++ |
| 1668 | +++ |
| 1669 | +++ |
| 1670 | ++ |
| 1671 | +++ |
| 1672 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1673 | +++ |
| 1674 | +++ |
| 1675 | ++ |
| 1676 | +++ |
| 1677 | +++ |
| 1678 | + |
| 1679 | +++ |
| 1680 | +++ |
| 1681 | +++ |
| 1682 | +++ |
| 1683 | +++ |
| 1684 | +++ |
| 1685 | +++ |
| 1686 | +++ |
| 1687 | +++ |
| 1688 | +++ |
| 1689 | +++ |
| 1690 | +++ |
| 1691 | ++ |
| 1692 | ++ |
| 1693 | +++ |
| 1694 | +++ |
| 1695 | +++ |
| 1696 | +++ |
| 1697 | +++ |
| 1698 | +++ |
| 1699 | +++ |
| 1700 | +++ |
| 1701 | +++ |
| 1702 | +++ |
| 1703 | +++ |
| 1704 | +++ |
| 1705 | +++ |
| 1706 | ++ |
| 1707 | ++ |
| 1708 | +++ |
| 1709 | +++ |
| 1710 | +++ |
| 1711 | +++ |
| 1712 | +++ |
| 1713 | +++ |
| 1714 | ++ |
| 1715 | +++ |
| 1716 | ++ |
| 1717 | +++ |
| 1718 | +++ |
| 1719 | +++ |
| 1720 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1721 | +++ |
| 1722 | +++ |
| 1723 | +++ |
| 1724 | +++ |
| 1725 | ++ |
| 1726 | +++ |
| 1727 | +++ |
| 1728 | +++ |
| 1729 | +++ |
| 1730 | +++ |
| 1731 | +++ |
| 1732 | |
| 1733 | ++ |
| 1734 | +++ |
| 1735 | +++ |
| 1736 | ++ |
| 1737 | +++ |
| 1738 | +++ |
| 1739 | +++ |
| 1740 | +++ |
| 1741 | +++ |
| 1742 | +++ |
| 1743 | +++ |
| 1744 | ++ |
| 1745 | +++ |
| 1746 | +++ |
| 1747 | +++ |
| 1748 | +++ |
| 1749 | +++ |
| 1750 | +++ |
| 1751 | +++ |
| 1752 | ++ |
| 1753 | ++ |
| 1754 | +++ |
| 1755 | ++ |
| 1756 | +++ |
| 1757 | +++ |
| 1758 | +++ |
| 1759 | +++ |
| 1760 | ++ |
| 1761 | ++ |
| 1762 | +++ |
| 1763 | +++ |
| 1764 | ++ |
| 1765 | +++ |
| 1766 | +++ |
| 1767 | +++ |
| 1768 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1769 | ++ |
| 1770 | +++ |
| 1771 | +++ |
| 1772 | ++ |
| 1773 | +++ |
| 1774 | +++ |
| 1775 | +++ |
| 1776 | +++ |
| 1777 | +++ |
| 1778 | +++ |
| 1779 | +++ |
| 1780 | ++ |
| 1781 | +++ |
| 1782 | +++ |
| 1783 | +++ |
| 1784 | +++ |
| 1785 | +++ |
| 1786 | ++ |
| 1787 | ++ |
| 1788 | +++ |
| 1789 | +++ |
| 1790 | +++ |
| 1791 | +++ |
| 1792 | +++ |
| 1793 | +++ |
| 1794 | ++ |
| 1795 | +++ |
| 1796 | +++ |
| 1797 | +++ |
| 1798 | +++ |
| 1799 | +++ |
| 1800 | +++ |
| 1801 | +++ |
| 1802 | +++ |
| 1803 | +++ |
| 1804 | +++ |
| 1805 | ++ |
| 1806 | +++ |
| 1807 | +++ |
| 1808 | +++ |
| 1809 | +++ |
| 1810 | +++ |
| 1811 | +++ |
| 1812 | ++ |
| 1813 | +++ |
| 1814 | +++ |
| 1815 | +++ |
| 1816 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1817 | +++ |
| 1818 | +++ |
| 1819 | ++ |
| 1820 | ++ |
| 1821 | +++ |
| 1822 | +++ |
| 1823 | +++ |
| 1824 | +++ |
| 1825 | +++ |
| 1826 | +++ |
| 1827 | +++ |
| 1828 | +++ |
| 1829 | +++ |
| 1830 | +++ |
| 1831 | +++ |
| 1832 | +++ |
| 1833 | +++ |
| 1834 | +++ |
| 1835 | +++ |
| 1836 | +++ |
| 1837 | +++ |
| 1838 | +++ |
| 1839 | +++ |
| 1840 | +++ |
| 1841 | +++ |
| 1842 | +++ |
| 1843 | +++ |
| 1844 | +++ |
| 1845 | +++ |
| 1846 | +++ |
| 1847 | +++ |
| 1848 | +++ |
| 1849 | ++ |
| 1850 | +++ |
| 1851 | +++ |
| 1852 | +++ |
| 1853 | ++ |
| 1854 | +++ |
| 1855 | +++ |
| 1856 | +++ |
| 1857 | +++ |
| 1858 | ++ |
| 1859 | +++ |
| 1860 | +++ |
| 1861 | +++ |
| 1862 | +++ |
| 1863 | +++ |
| 1864 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1865 | ++ |
| 1866 | +++ |
| 1867 | +++ |
| 1868 | +++ |
| 1869 | +++ |
| 1870 | ++ |
| 1871 | +++ |
| 1872 | +++ |
| 1873 | +++ |
| 1874 | +++ |
| 1875 | ++ |
| 1876 | +++ |
| 1877 | ++ |
| 1878 | ++ |
| 1879 | +++ |
| 1880 | ++ |
| 1881 | +++ |
| 1882 | + |
| 1883 | +++ |
| 1884 | +++ |
| 1885 | +++ |
| 1886 | ++ |
| 1887 | +++ |
| 1888 | ++ |
| 1889 | +++ |
| 1890 | ++ |
| 1891 | +++ |
| 1892 | +++ |
| 1893 | +++ |
| 1894 | +++ |
| 1895 | +++ |
| 1896 | +++ |
| 1897 | +++ |
| 1898 | ++ |
| 1899 | +++ |
| 1900 | ++ |
| 1901 | +++ |
| 1902 | +++ |
| 1903 | +++ |
| 1904 | +++ |
| 1905 | +++ |
| 1906 | +++ |
| 1907 | +++ |
| 1908 | +++ |
| 1909 | +++ |
| 1910 | +++ |
| 1911 | +++ |
| 1912 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1913 | +++ |
| 1914 | +++ |
| 1915 | +++ |
| 1916 | +++ |
| 1917 | +++ |
| 1918 | +++ |
| 1919 | +++ |
| 1920 | ++ |
| 1921 | +++ |
| 1922 | +++ |
| 1923 | ++ |
| 1924 | +++ |
| 1925 | +++ |
| 1926 | +++ |
| 1927 | +++ |
| 1928 | ++ |
| 1929 | +++ |
| 1930 | +++ |
| 1931 | +++ |
| 1932 | +++ |
| 1933 | +++ |
| 1934 | +++ |
| 1935 | +++ |
| 1936 | +++ |
| 1937 | ++ |
| 1938 | +++ |
| 1939 | ++ |
| 1940 | +++ |
| 1941 | +++ |
| 1942 | ++ |
| 1943 | ++ |
| 1944 | +++ |
| 1945 | +++ |
| 1946 | +++ |
| 1947 | ++ |
| 1948 | +++ |
| 1949 | +++ |
| 1950 | +++ |
| 1951 | +++ |
| 1952 | +++ |
| 1953 | +++ |
| 1954 | +++ |
| 1955 | +++ |
| 1956 | +++ |
| 1957 | ++ |
| 1958 | +++ |
| 1959 | +++ |
| 1960 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 1961 | +++ |
| 1962 | +++ |
| 1963 | +++ |
| 1964 | +++ |
| 1965 | +++ |
| 1966 | +++ |
| 1967 | ++ |
| 1968 | +++ |
| 1969 | +++ |
| 1970 | +++ |
| 1971 | +++ |
| 1972 | +++ |
| 1973 | +++ |
| 1974 | +++ |
| 1975 | +++ |
| 1976 | +++ |
| 1977 | +++ |
| 1978 | +++ |
| 1979 | +++ |
| 1980 | +++ |
| 1981 | +++ |
| 1982 | ++ |
| 1983 | +++ |
| 1984 | ++ |
| 1985 | ++ |
| 1986 | +++ |
| 1987 | +++ |
| 1988 | +++ |
| 1989 | +++ |
| 1990 | +++ |
| 1991 | +++ |
| 1992 | +++ |
| 1993 | +++ |
| 1994 | +++ |
| 1995 | +++ |
| 1996 | +++ |
| 1997 | ++ |
| 1998 | +++ |
| 1999 | ++ |
| 2000 | +++ |
| 2001 | +++ |
| 2002 | +++ |
| 2003 | +++ |
| 2004 | +++ |
| 2005 | ++ |
| 2006 | +++ |
| 2007 | +++ |
| 2008 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2009 | +++ |
| 2010 | +++ |
| 2011 | +++ |
| 2012 | +++ |
| 2013 | +++ |
| 2014 | +++ |
| 2015 | +++ |
| 2016 | ++ |
| 2017 | +++ |
| 2018 | +++ |
| 2019 | +++ |
| 2020 | +++ |
| 2021 | ++ |
| 2022 | +++ |
| 2023 | +++ |
| 2024 | ++ |
| 2025 | +++ |
| 2026 | +++ |
| 2027 | +++ |
| 2028 | +++ |
| 2029 | +++ |
| 2030 | +++ |
| 2031 | +++ |
| 2032 | ++ |
| 2033 | +++ |
| 2034 | +++ |
| 2035 | +++ |
| 2036 | +++ |
| 2037 | +++ |
| 2038 | +++ |
| 2039 | +++ |
| 2040 | +++ |
| 2041 | +++ |
| 2042 | +++ |
| 2043 | +++ |
| 2044 | +++ |
| 2045 | ++ |
| 2046 | +++ |
| 2047 | ++ |
| 2048 | +++ |
| 2049 | +++ |
| 2050 | +++ |
| 2051 | +++ |
| 2052 | +++ |
| 2053 | +++ |
| 2054 | +++ |
| 2055 | +++ |
| 2056 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2057 | +++ |
| 2058 | +++ |
| 2059 | +++ |
| 2060 | +++ |
| 2061 | +++ |
| 2062 | +++ |
| 2063 | +++ |
| 2064 | +++ |
| 2065 | +++ |
| 2066 | +++ |
| 2067 | +++ |
| 2068 | +++ |
| 2069 | +++ |
| 2070 | +++ |
| 2071 | +++ |
| 2072 | ++ |
| 2073 | +++ |
| 2074 | ++ |
| 2075 | +++ |
| 2076 | +++ |
| 2077 | +++ |
| 2078 | ++ |
| 2079 | +++ |
| 2080 | ++ |
| 2081 | +++ |
| 2082 | ++ |
| 2083 | +++ |
| 2084 | +++ |
| 2085 | +++ |
| 2086 | +++ |
| 2087 | +++ |
| 2088 | ++ |
| 2089 | +++ |
| 2090 | +++ |
| 2091 | +++ |
| 2092 | +++ |
| 2093 | +++ |
| 2094 | +++ |
| 2095 | +++ |
| 2096 | +++ |
| 2097 | +++ |
| 2098 | +++ |
| 2099 | +++ |
| 2100 | +++ |
| 2101 | +++ |
| 2102 | +++ |
| 2103 | +++ |
| 2104 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2105 | +++ |
| 2106 | +++ |
| 2107 | +++ |
| 2108 | +++ |
| 2109 | +++ |
| 2110 | + |
| 2111 | +++ |
| 2112 | ++ |
| 2113 | +++ |
| 2114 | +++ |
| 2115 | +++ |
| 2116 | +++ |
| 2117 | +++ |
| 2118 | +++ |
| 2119 | +++ |
| 2120 | +++ |
| 2121 | +++ |
| 2122 | +++ |
| 2123 | +++ |
| 2124 | +++ |
| 2125 | +++ |
| 2126 | +++ |
| 2127 | +++ |
| 2128 | ++ |
| 2129 | +++ |
| 2130 | +++ |
| 2131 | + |
| 2132 | +++ |
| 2133 | +++ |
| 2134 | +++ |
| 2135 | ++ |
| 2136 | +++ |
| 2137 | +++ |
| 2138 | +++ |
| 2139 | +++ |
| 2140 | ++ |
| 2141 | +++ |
| 2142 | +++ |
| 2143 | +++ |
| 2144 | +++ |
| 2145 | +++ |
| 2146 | +++ |
| 2147 | +++ |
| 2148 | ++ |
| 2149 | +++ |
| 2150 | +++ |
| 2151 | +++ |
| 2152 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2153 | +++ |
| 2154 | +++ |
| 2155 | ++ |
| 2156 | +++ |
| 2157 | + |
| 2158 | ++ |
| 2159 | +++ |
| 2160 | ++ |
| 2161 | +++ |
| 2162 | +++ |
| 2163 | +++ |
| 2164 | +++ |
| 2165 | +++ |
| 2166 | ++ |
| 2167 | +++ |
| 2168 | +++ |
| 2169 | +++ |
| 2170 | +++ |
| 2171 | +++ |
| 2172 | +++ |
| 2173 | +++ |
| 2174 | ++ |
| 2175 | ++ |
| 2176 | +++ |
| 2177 | +++ |
| 2178 | +++ |
| 2179 | +++ |
| 2180 | +++ |
| 2181 | +++ |
| 2182 | +++ |
| 2183 | +++ |
| 2184 | +++ |
| 2185 | ++ |
| 2186 | +++ |
| 2187 | +++ |
| 2188 | +++ |
| 2189 | +++ |
| 2190 | +++ |
| 2191 | +++ |
| 2192 | +++ |
| 2193 | +++ |
| 2194 | +++ |
| 2195 | +++ |
| 2196 | +++ |
| 2197 | +++ |
| 2198 | +++ |
| 2199 | ++ |
| 2200 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2201 | +++ |
| 2202 | +++ |
| 2203 | +++ |
| 2204 | +++ |
| 2205 | +++ |
| 2206 | +++ |
| 2207 | +++ |
| 2208 | +++ |
| 2209 | +++ |
| 2210 | +++ |
| 2211 | +++ |
| 2212 | ++ |
| 2213 | +++ |
| 2214 | +++ |
| 2215 | ++ |
| 2216 | +++ |
| 2217 | +++ |
| 2218 | +++ |
| 2219 | ++ |
| 2220 | ++ |
| 2221 | ++ |
| 2222 | ++ |
| 2223 | +++ |
| 2224 | +++ |
| 2225 | ++ |
| 2226 | ++ |
| 2227 | +++ |
| 2228 | +++ |
| 2229 | ++ |
| 2230 | +++ |
| 2231 | +++ |
| 2232 | ++ |
| 2233 | +++ |
| 2234 | +++ |
| 2235 | +++ |
| 2236 | +++ |
| 2237 | +++ |
| 2238 | +++ |
| 2239 | +++ |
| 2240 | ++ |
| 2241 | +++ |
| 2242 | +++ |
| 2243 | +++ |
| 2244 | +++ |
| 2245 | +++ |
| 2246 | +++ |
| 2247 | ++ |
| 2248 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2249 | +++ |
| 2250 | +++ |
| 2251 | +++ |
| 2252 | +++ |
| 2253 | ++ |
| 2254 | ++ |
| 2255 | +++ |
| 2256 | +++ |
| 2257 | +++ |
| 2258 | +++ |
| 2259 | +++ |
| 2260 | +++ |
| 2261 | +++ |
| 2262 | +++ |
| 2263 | +++ |
| 2264 | +++ |
| 2265 | +++ |
| 2266 | +++ |
| 2267 | +++ |
| 2268 | +++ |
| 2269 | +++ |
| 2270 | +++ |
| 2271 | +++ |
| 2272 | +++ |
| 2273 | +++ |
| 2274 | ++ |
| 2275 | ++ |
| 2276 | +++ |
| 2277 | +++ |
| 2278 | +++ |
| 2279 | +++ |
| 2280 | +++ |
| 2281 | ++ |
| 2282 | +++ |
| 2283 | +++ |
| 2284 | +++ |
| 2285 | +++ |
| 2286 | +++ |
| 2287 | +++ |
| 2288 | +++ |
| 2289 | +++ |
| 2290 | ++ |
| 2291 | +++ |
| 2292 | +++ |
| 2293 | +++ |
| 2294 | ++ |
| 2295 | ++ |
| 2296 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2297 | +++ |
| 2298 | +++ |
| 2299 | +++ |
| 2300 | ++ |
| 2301 | +++ |
| 2302 | +++ |
| 2303 | ++ |
| 2304 | +++ |
| 2305 | +++ |
| 2306 | +++ |
| 2307 | +++ |
| 2308 | +++ |
| 2309 | +++ |
| 2310 | +++ |
| 2311 | +++ |
| 2312 | +++ |
| 2313 | +++ |
| 2314 | ++ |
| 2315 | +++ |
| 2316 | +++ |
| 2317 | +++ |
| 2318 | +++ |
| 2319 | ++ |
| 2320 | +++ |
| 2321 | ++ |
| 2322 | +++ |
| 2323 | ++ |
| 2324 | ++ |
| 2325 | +++ |
| 2326 | +++ |
| 2327 | ++ |
| 2328 | ++ |
| 2329 | +++ |
| 2330 | +++ |
| 2331 | +++ |
| 2332 | +++ |
| 2333 | ++ |
| 2334 | +++ |
| 2335 | ++ |
| 2336 | +++ |
| 2337 | +++ |
| 2338 | +++ |
| 2339 | +++ |
| 2340 | +++ |
| 2341 | +++ |
| 2342 | +++ |
| 2343 | +++ |
| 2344 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2345 | +++ |
| 2346 | +++ |
| 2347 | +++ |
| 2348 | +++ |
| 2349 | ++ |
| 2350 | ++ |
| 2351 | +++ |
| 2352 | +++ |
| 2353 | +++ |
| 2354 | ++ |
| 2355 | +++ |
| 2356 | +++ |
| 2357 | +++ |
| 2358 | +++ |
| 2359 | ++ |
| 2360 | ++ |
| 2361 | +++ |
| 2362 | +++ |
| 2363 | ++ |
| 2364 | +++ |
| 2365 | +++ |
| 2366 | +++ |
| 2367 | +++ |
| 2368 | +++ |
| 2369 | +++ |
| 2370 | +++ |
| 2371 | +++ |
| 2372 | +++ |
| 2373 | +++ |
| 2374 | +++ |
| 2375 | ++ |
| 2376 | +++ |
| 2377 | +++ |
| 2378 | +++ |
| 2379 | +++ |
| 2380 | +++ |
| 2381 | +++ |
| 2382 | +++ |
| 2383 | ++ |
| 2384 | +++ |
| 2385 | +++ |
| 2386 | +++ |
| 2387 | ++ |
| 2388 | +++ |
| 2389 | ++ |
| 2390 | +++ |
| 2391 | +++ |
| 2392 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2393 | ++ |
| 2394 | +++ |
| 2395 | +++ |
| 2396 | ++ |
| 2397 | +++ |
| 2398 | +++ |
| 2399 | +++ |
| 2400 | ++ |
| 2401 | +++ |
| 2402 | +++ |
| 2403 | +++ |
| 2404 | +++ |
| 2405 | +++ |
| 2406 | +++ |
| 2407 | ++ |
| 2408 | +++ |
| 2409 | +++ |
| 2410 | +++ |
| 2411 | +++ |
| 2412 | +++ |
| 2413 | +++ |
| 2414 | ++ |
| 2415 | +++ |
| 2416 | +++ |
| 2417 | +++ |
| 2418 | +++ |
| 2419 | ++ |
| 2420 | ++ |
| 2421 | +++ |
| 2422 | ++ |
| 2423 | +++ |
| 2424 | +++ |
| 2425 | +++ |
| 2426 | +++ |
| 2427 | +++ |
| 2428 | +++ |
| 2429 | +++ |
| 2430 | ++ |
| 2431 | +++ |
| 2432 | +++ |
| 2433 | ++ |
| 2434 | +++ |
| 2435 | +++ |
| 2436 | +++ |
| 2437 | +++ |
| 2438 | +++ |
| 2439 | +++ |
| 2440 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2441 | ++ |
| 2442 | ++ |
| 2443 | +++ |
| 2444 | ++ |
| 2445 | +++ |
| 2446 | +++ |
| 2447 | +++ |
| 2448 | +++ |
| 2449 | +++ |
| 2450 | +++ |
| 2451 | +++ |
| 2452 | +++ |
| 2453 | +++ |
| 2454 | ++ |
| 2455 | +++ |
| 2456 | +++ |
| 2457 | +++ |
| 2458 | +++ |
| 2459 | +++ |
| 2460 | +++ |
| 2461 | +++ |
| 2462 | +++ |
| 2463 | +++ |
| 2464 | ++ |
| 2465 | +++ |
| 2466 | +++ |
| 2467 | +++ |
| 2468 | +++ |
| 2469 | ++ |
| 2470 | +++ |
| 2471 | ++ |
| 2472 | ++ |
| 2473 | +++ |
| 2474 | +++ |
| 2475 | +++ |
| 2476 | +++ |
| 2477 | +++ |
| 2478 | +++ |
| 2479 | +++ |
| 2480 | ++ |
| 2481 | +++ |
| 2482 | +++ |
| 2483 | +++ |
| 2484 | +++ |
| 2485 | +++ |
| 2486 | +++ |
| 2487 | +++ |
| 2488 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2489 | ++ |
| 2490 | +++ |
| 2491 | +++ |
| 2492 | +++ |
| 2493 | +++ |
| 2494 | +++ |
| 2495 | +++ |
| 2496 | +++ |
| 2497 | +++ |
| 2498 | +++ |
| 2499 | +++ |
| 2500 | +++ |
| 2501 | ++ |
| 2502 | +++ |
| 2503 | +++ |
| 2504 | ++ |
| 2505 | +++ |
| 2506 | ++ |
| 2507 | +++ |
| 2508 | +++ |
| 2509 | +++ |
| 2510 | +++ |
| 2511 | +++ |
| 2512 | +++ |
| 2513 | ++ |
| 2514 | +++ |
| 2515 | +++ |
| 2516 | ++ |
| 2517 | +++ |
| 2518 | +++ |
| 2519 | +++ |
| 2520 | ++ |
| 2521 | +++ |
| 2522 | +++ |
| 2523 | ++ |
| 2524 | +++ |
| 2525 | ++ |
| 2526 | +++ |
| 2527 | +++ |
| 2528 | +++ |
| 2529 | +++ |
| 2530 | +++ |
| 2531 | +++ |
| 2532 | +++ |
| 2533 | +++ |
| 2534 | +++ |
| 2535 | ++ |
| 2536 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2537 | ++ |
| 2538 | +++ |
| 2539 | +++ |
| 2540 | +++ |
| 2541 | +++ |
| 2542 | +++ |
| 2543 | +++ |
| 2544 | + |
| 2545 | +++ |
| 2546 | +++ |
| 2547 | +++ |
| 2548 | +++ |
| 2549 | +++ |
| 2550 | ++ |
| 2551 | +++ |
| 2552 | +++ |
| 2553 | +++ |
| 2554 | +++ |
| 2555 | +++ |
| 2556 | ++ |
| 2557 | +++ |
| 2558 | +++ |
| 2559 | +++ |
| 2560 | +++ |
| 2561 | +++ |
| 2562 | +++ |
| 2563 | +++ |
| 2564 | +++ |
| 2565 | ++ |
| 2566 | +++ |
| 2567 | +++ |
| 2568 | ++ |
| 2569 | +++ |
| 2570 | ++ |
| 2571 | +++ |
| 2572 | +++ |
| 2573 | +++ |
| 2574 | ++ |
| 2575 | +++ |
| 2576 | +++ |
| 2577 | +++ |
| 2578 | +++ |
| 2579 | +++ |
| 2580 | +++ |
| 2581 | +++ |
| 2582 | +++ |
| 2583 | ++ |
| 2584 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2585 | +++ |
| 2586 | ++ |
| 2587 | ++ |
| 2588 | +++ |
| 2589 | +++ |
| 2590 | +++ |
| 2591 | +++ |
| 2592 | +++ |
| 2593 | +++ |
| 2594 | +++ |
| 2595 | +++ |
| 2596 | +++ |
| 2597 | ++ |
| 2598 | +++ |
| 2599 | ++ |
| 2600 | +++ |
| 2601 | ++ |
| 2602 | ++ |
| 2603 | +++ |
| 2604 | +++ |
| 2605 | ++ |
| 2606 | +++ |
| 2607 | +++ |
| 2608 | +++ |
| 2609 | +++ |
| 2610 | +++ |
| 2611 | +++ |
| 2612 | ++ |
| 2613 | +++ |
| 2614 | ++ |
| 2615 | ++ |
| 2616 | +++ |
| 2617 | ++ |
| 2618 | +++ |
| 2619 | +++ |
| 2620 | ++ |
| 2621 | ++ |
| 2622 | +++ |
| 2623 | ++ |
| 2624 | ++ |
| 2625 | +++ |
| 2626 | +++ |
| 2627 | +++ |
| 2628 | +++ |
| 2629 | +++ |
| 2630 | +++ |
| 2631 | +++ |
| 2632 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2633 | ++ |
| 2634 | +++ |
| 2635 | +++ |
| 2636 | + |
| 2637 | +++ |
| 2638 | +++ |
| 2639 | +++ |
| 2640 | +++ |
| 2641 | +++ |
| 2642 | +++ |
| 2643 | +++ |
| 2644 | +++ |
| 2645 | +++ |
| 2646 | +++ |
| 2647 | +++ |
| 2648 | +++ |
| 2649 | +++ |
| 2650 | ++ |
| 2651 | +++ |
| 2652 | +++ |
| 2653 | +++ |
| 2654 | +++ |
| 2655 | +++ |
| 2656 | +++ |
| 2657 | ++ |
| 2658 | ++ |
| 2659 | ++ |
| 2660 | +++ |
| 2661 | +++ |
| 2662 | ++ |
| 2663 | +++ |
| 2664 | +++ |
| 2665 | +++ |
| 2666 | ++ |
| 2667 | +++ |
| 2668 | ++ |
| 2669 | +++ |
| 2670 | +++ |
| 2671 | +++ |
| 2672 | +++ |
| 2673 | +++ |
| 2674 | +++ |
| 2675 | +++ |
| 2676 | +++ |
| 2677 | +++ |
| 2678 | ++ |
| 2679 | ++ |
| 2680 | ++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2681 | +++ |
| 2682 | +++ |
| 2683 | +++ |
| 2684 | +++ |
| 2685 | +++ |
| 2686 | +++ |
| 2687 | ++ |
| 2688 | +++ |
| 2689 | ++ |
| 2690 | +++ |
| 2691 | +++ |
| 2692 | ++ |
| 2693 | ++ |
| 2694 | +++ |
| 2695 | +++ |
| 2696 | +++ |
| 2697 | +++ |
| 2698 | +++ |
| 2699 | +++ |
| 2700 | +++ |
| 2701 | +++ |
| 2702 | +++ |
| 2703 | +++ |
| 2704 | +++ |
| 2705 | +++ |
| 2706 | +++ |
| 2707 | +++ |
| 2708 | +++ |
| 2709 | +++ |
| 2710 | ++ |
| 2711 | ++ |
| 2712 | +++ |
| 2713 | +++ |
| 2714 | +++ |

| 化合物編號 | EC30 (μM) |
|---|---|
| 2715 | +++ |
| 2716 | +++ |
| 2717 | +++ |
| 2718 | +++ |
| 2719 | +++ |
| 2720 | +++ |
| 2721 | +++ |
| 2722 | +++ |
| 2723 | +++ |
| 2724 | +++ |
| 2725 | +++ |
| 2726 | +++ |
| 2727 | +++ |
| 2728 | +++ |
| 2729 | +++ |
| 2730 | ++ |
| 2731 | ++ |
| 2732 | ++ |
| 2733 | ++ |
| 2734 | ++ |
| 2735 | ++ |
| 2736 | ++ |
| 2737 | +++ |
| 2738 | +++ |
| 2739 | +++ |
| 2740 | +++ |
| 2741 | ++ |
| 2742 | ++ |
| 2743 | +++ |
| 2744 | +++ |
| 2745 | +++ |
| 2746 | +++ |
| 2747 | +++ |

## 其他實施例

本說明書中所提及之所有公開案及專利均以引用的方式併入本文中，其引用的程度如同各個別公開案或專利申請案經特定且個別地指示以引入的方式併入一般。若以引用的方式併入之任一專利或公開案中術語之含義與用於本發明之術語的含義矛盾，則本發明中術語之含義欲爲準。此外，以上論述僅僅揭示及描述本發明之示例性實施例。熟習此項技術者將自此類論述及附圖及申請專利範圍容易認識

到，可在不背離如以下申請專利範圍中所定義的本發明之精神及範疇下在其中進行各種改變、修改及變化。

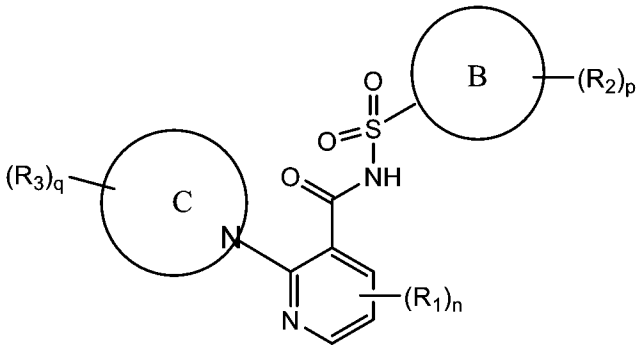
**【符號說明】**

(無)

第104132917號專利申請案申請專利範圍替換本
日期：110年3月22日

# 申請專利範圍

1. 一種式Ib-iii化合物：




**Ib-iii**

、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中：

環B為C6-C10芳基環或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；

環C為其中1至4個環原子中任一個獨立地為N、O或S的C3-C14雜芳基或雜環，且其中環C上之一個氮為與吡啶環之附接點；

以及其中每次出現時獨立地：

$R_1$為鹵基；CN；$F_5S$；SiRRR；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-

$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C2-C6烯基；C2-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；-C≡CH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n為0、1、2或3；

p為0、1、2或3；且

q為0、1、2、3、4或5；

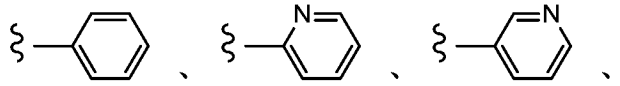
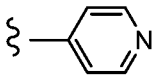
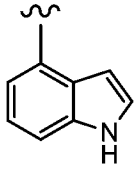
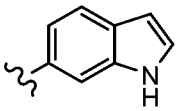
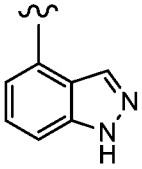
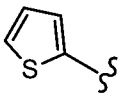
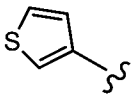
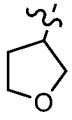
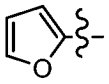
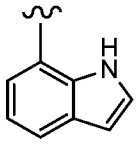
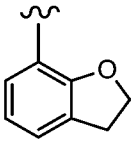
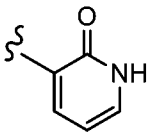
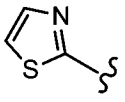
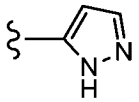
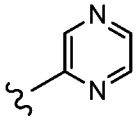
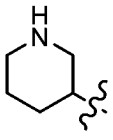
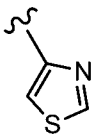
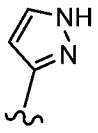
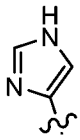
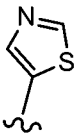
其中變數$R_1$-$R_4$之每一特定基團可視情況經一或多個選自以下各者之基團取代：鹵基、磷醯基、OH、環烷基、雜環烷基、芳基、雜芳基、氟烷基、烷基、烯基、炔基、硝基、CN、羥基及其中至多4個$CH_2$單元獨立地經O、S、$SO_2$、SO、CO、NH、*N*-烷基、*N*-烯基或*N*-炔基置換的(C1-C9伸烷基)-E，且E為H、芳基、

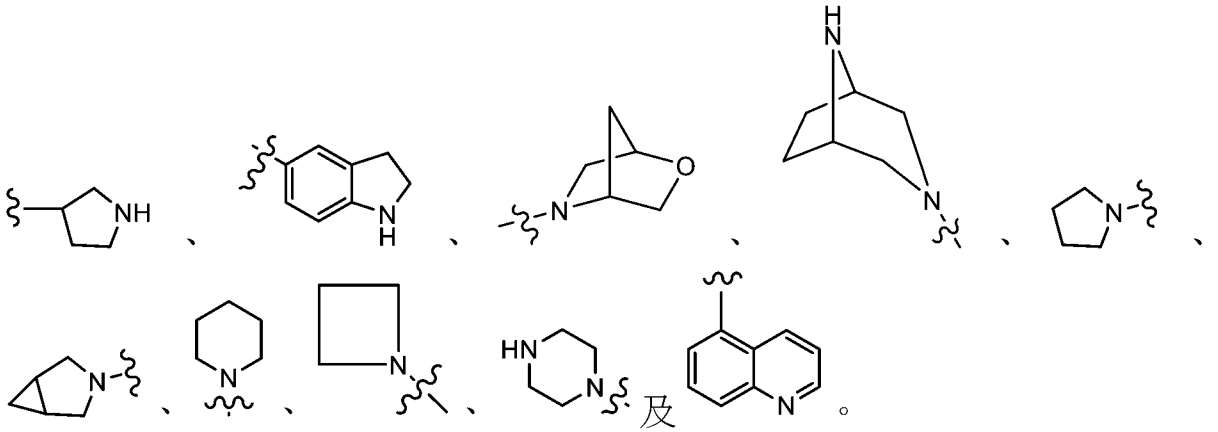
環烷基、雜環烷基、雜芳基、烷氧基、CN或$CF_3$，進一步其中芳基、環烷基、雜環烷基及雜芳基每一者視情況經一或多個選自鹵基、烷基、胺基、CN、烯基、炔基及烷氧基之基團取代；及

當兩個烷氧基結合於同一原子或相鄰原子時，兩個烷氧基可與其結合之原子一起形成環；及

其中術語「胺基」係指$NH_2$，其視情況經一或兩個獨立地選自烷基、環烷基及雜環烷基之基團取代。

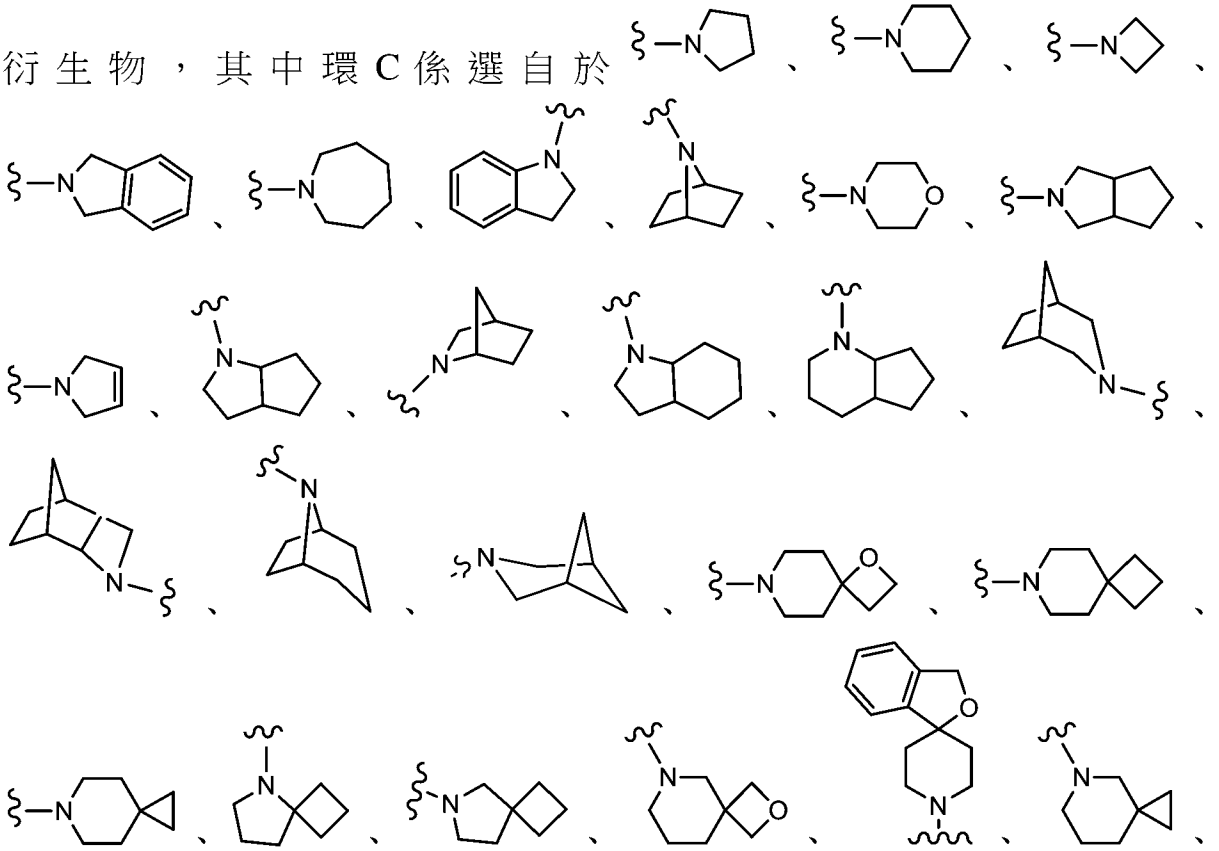
2. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中環B為苯基、吡啶基、吡啶-2(1*H*)-酮、吡唑、吲哚、氮雜吲哚、噻吩、二氫苯并呋喃或喹啉。

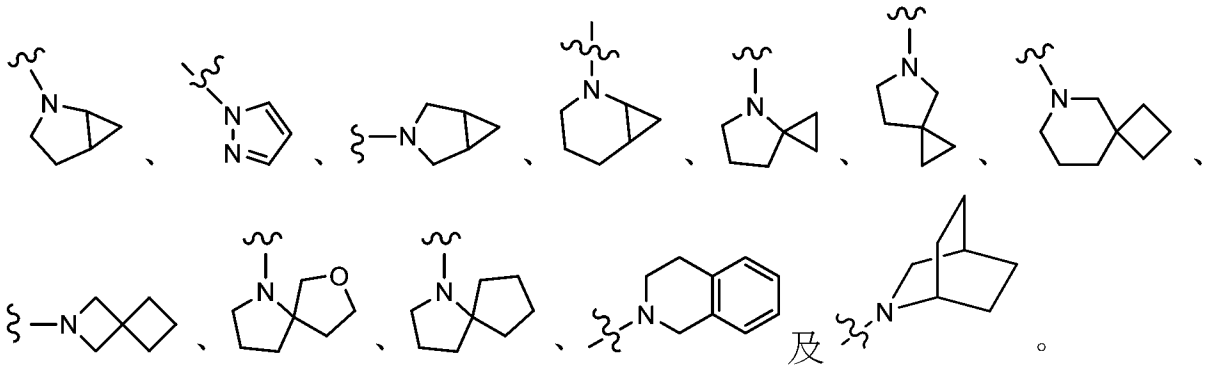
3. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中環B係選自於  、、、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、



4. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中環C係選自於吲哚、哌啶、氧雜環庚烷、氮雜環丁烷、吲哚啉、異吲哚啉及吡咯啶。

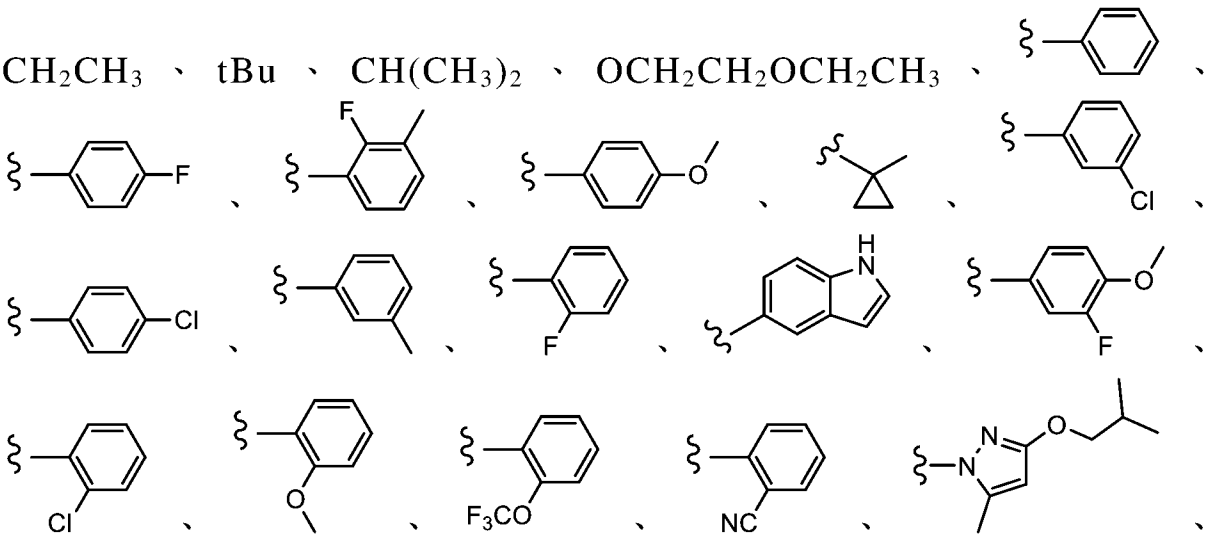
5. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中環C係選自於

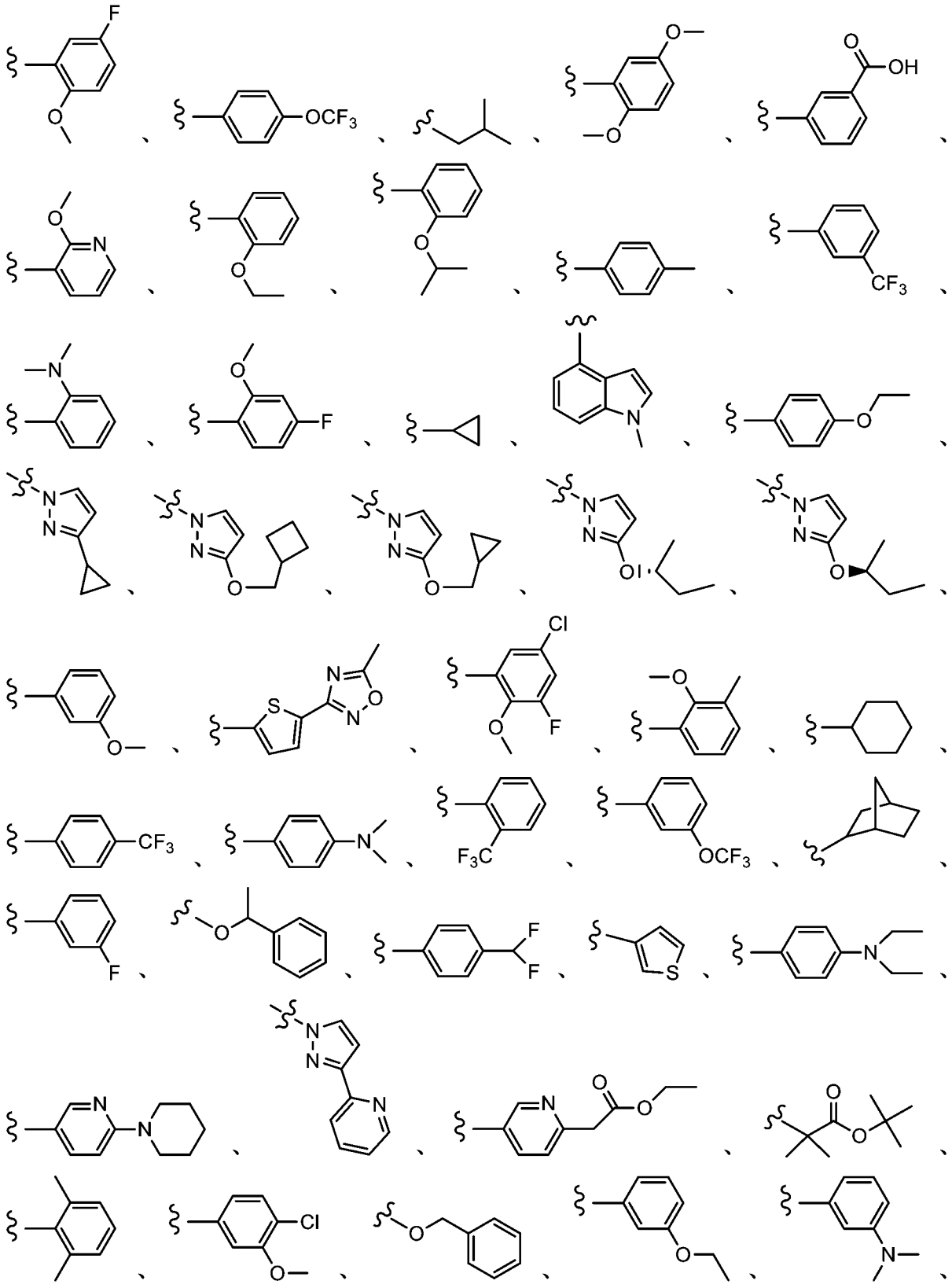


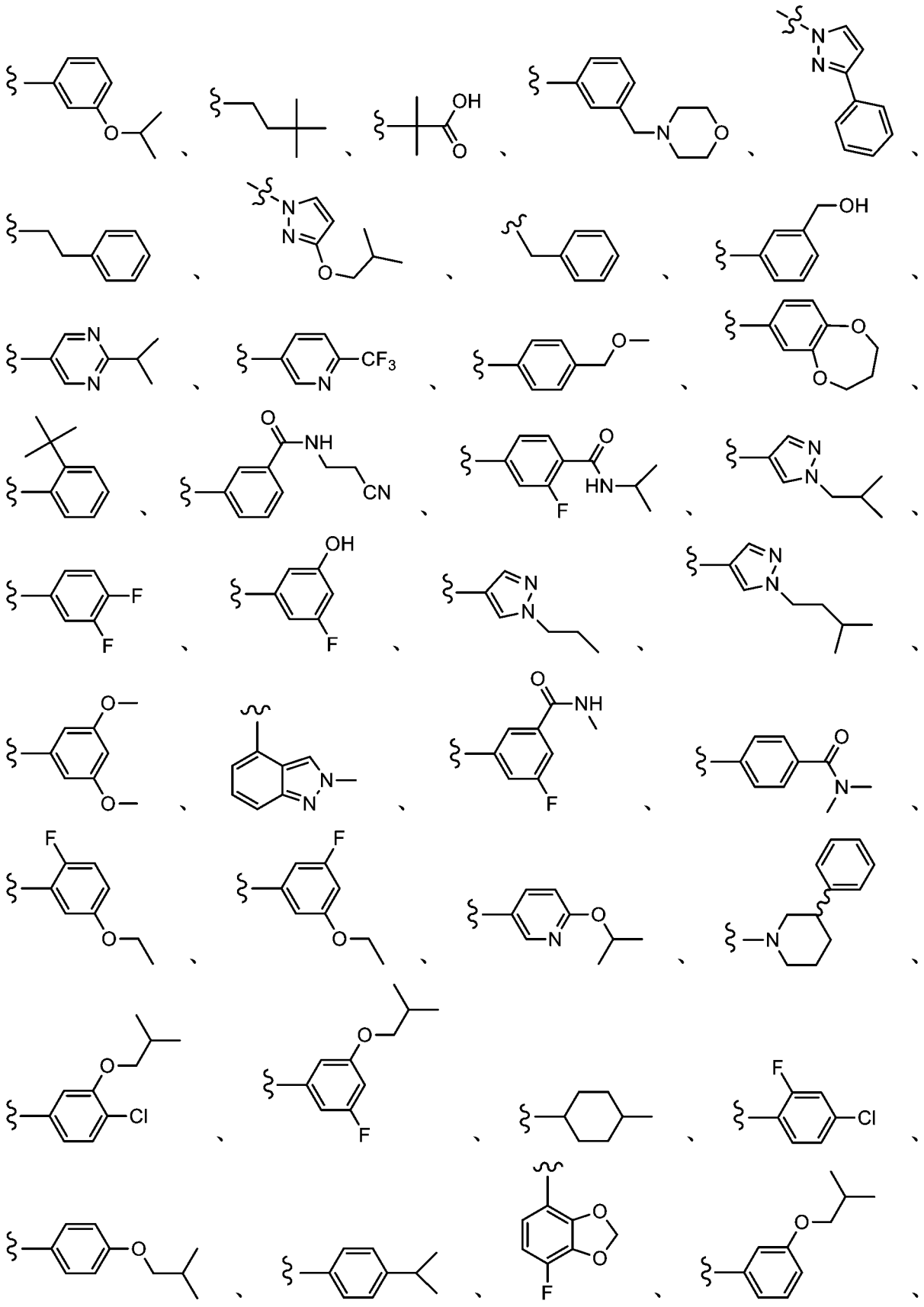


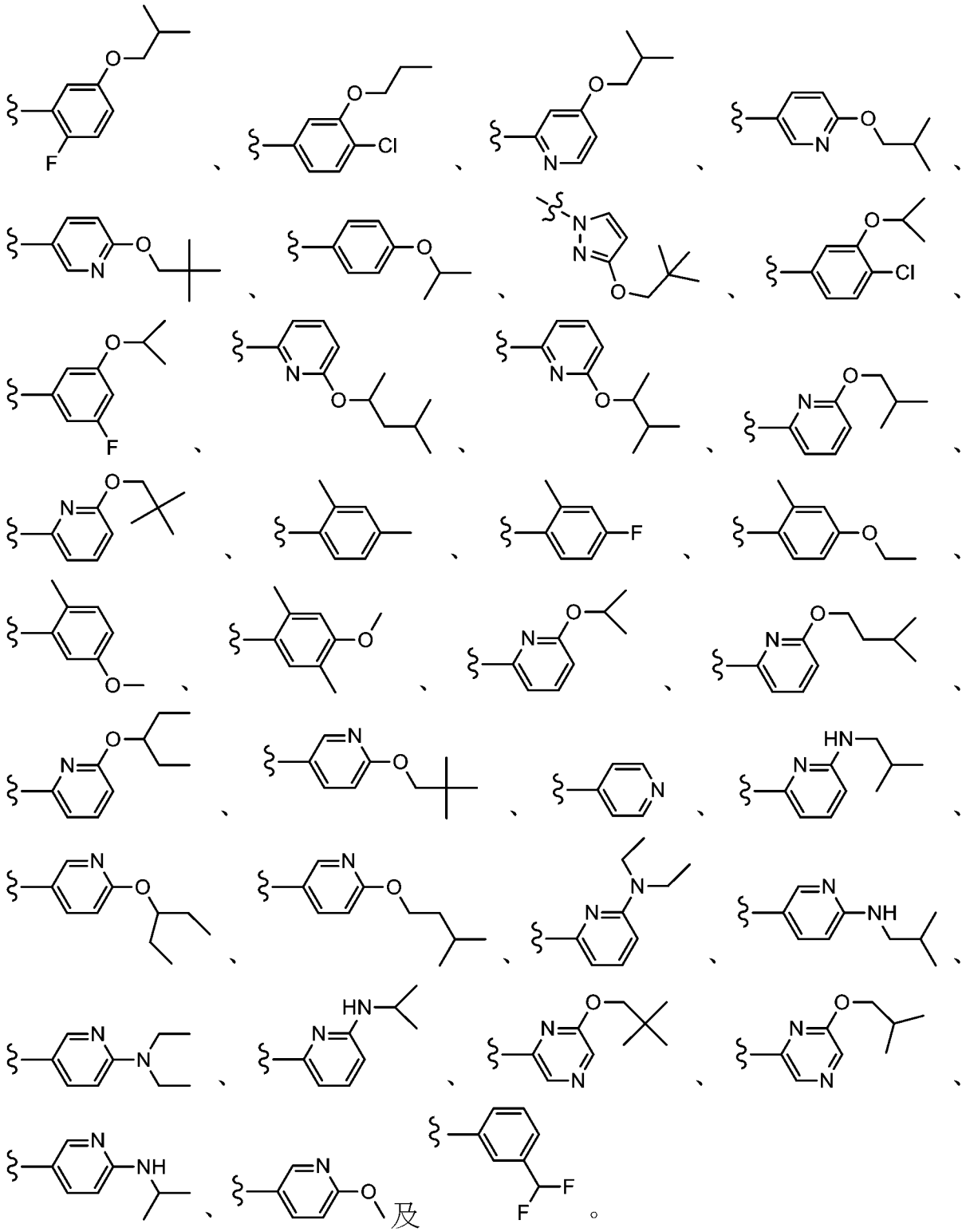
6. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_1$為鹵基、CN、C1-C6烷基、C1-C6烷氧基、C3-C8環烷基或苯基、吡啶基、嘧啶、吲哚、氮雜吲哚、吡唑或噻吩環，或是其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；其中所有環任擇地經一或多個選自於下列之基團取代：鹵基、C1-C6烷基、C1-C6烷氧基、C1-C6氟烷基、C1-C6氟烷氧基、OH、$CH_2OH$、$CH_2OCH_3$、CN、$CO_2H$、胺基、醯胺基、C3-C10雜芳基及C3-C10雜環烷基。

7. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_1$係選自於$CH_3$、Cl、F、CN、$OCH_3$、$CF_3$、$CH_2CH_3$、tBu、$CH(CH_3)_2$、$OCH_2CH_2OCH_2CH_3$、





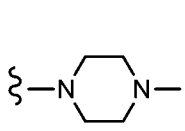
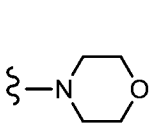
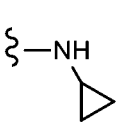
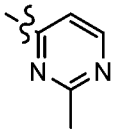
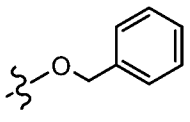
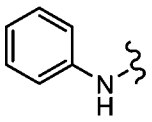


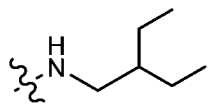
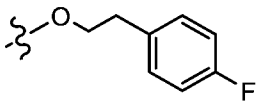
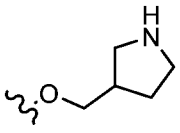
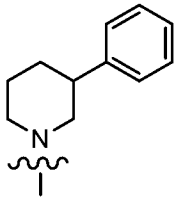
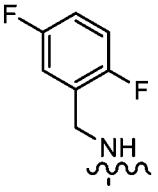


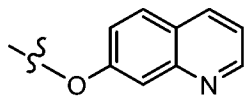
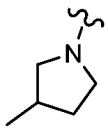
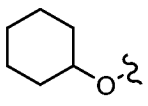
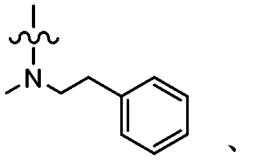
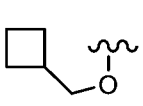
8. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_2$係選自於鹵基、OH、CN、疊氮化物、胺基、C1-C6烷基或氟烷基、C1-C6烷氧基或氟烷氧基、其中至多4個環原子

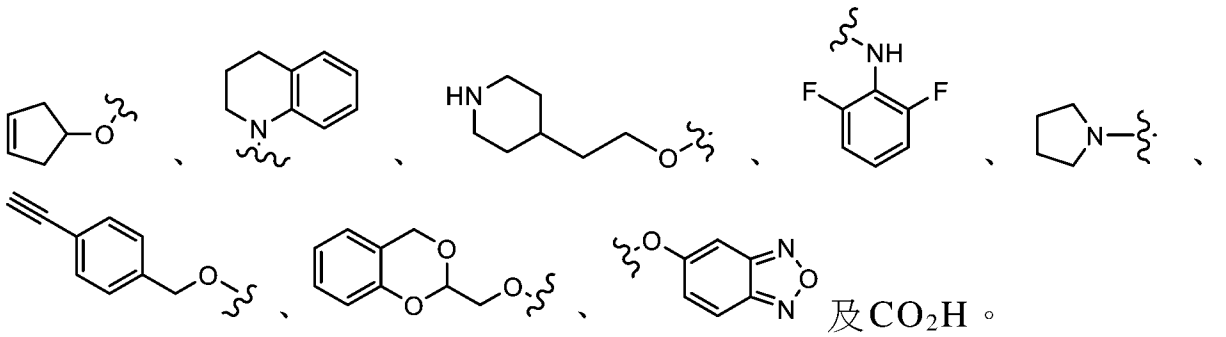
獨立地為O、S、N或NR的C3-C10雜環，以及其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$。

9. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_2$係選自於$_2$為Cl、F、OH、CN、$N_3$、$NH_2$、$NH(CH_3)$、$N(CH_3)_2$、$N(CH_3)CH_2CH_2CH_3$、$N(CH_3)CH_2CH_2CH_2CH_3$、$CH_3$、$CH_2OH$、$CH_2CH_3$、$CH_2CH_2CH_3$、=O、$CH_3SO_2$、$CH_3SO_2NH$、$CF_3CONH$、$CH_3CONH$、$CH_3CON(CH_3)$、tBuOCONH、$(CH_3)_2CHOCONH$、$CH(CH_3)_2$、$CHF_2$、$OCH_3$、$OCH_2CH_3$、$OCH_2CH_2CH_3$、$OCH_2CH_2CH(CH_3)_2$、$OCF_3$、$OCHF_2$、$OC(CH_3)_3$、$OCH_2CH_2tBu$、$NHCH(CH_3)(CH_2CH_2CH_3)$、$OCH(CH_3)_2$、$NH(CH_2)_2O(CH_2)_2CH_3$、$C(O)CH_3$、$CH_2CH_2OH$、$CH_2NH_2$、$NH(CH_2)_2OH$、$N(CH_3)CH_2CH_2CH_2OCH_3$、$NHCH_2CH_2COOH$、$NH(CH_2)_2N(CH_3)_2$、$NH(CH_2)_2NH_2$、$NH(CH_2)_3NH_2$、$NH(CH_2)_2OCH_3$、$NHCH(CH_3)_2$、

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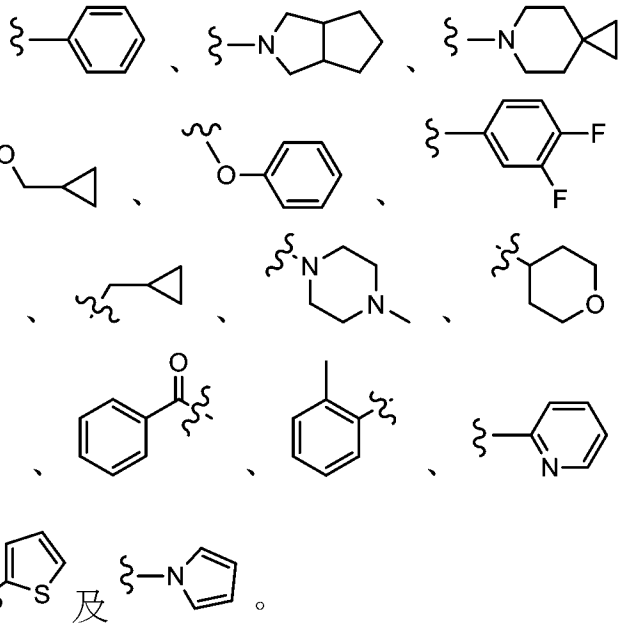
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及$CO_2H$。

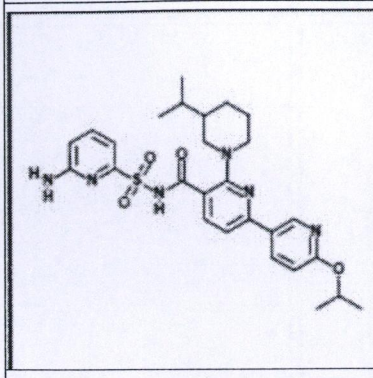
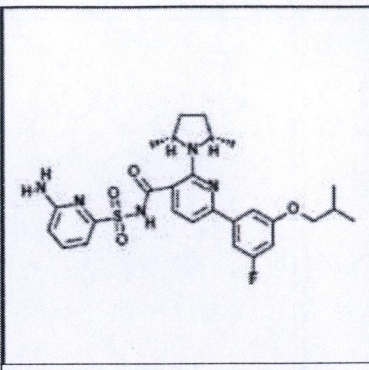
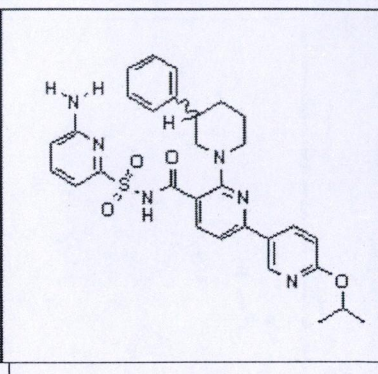
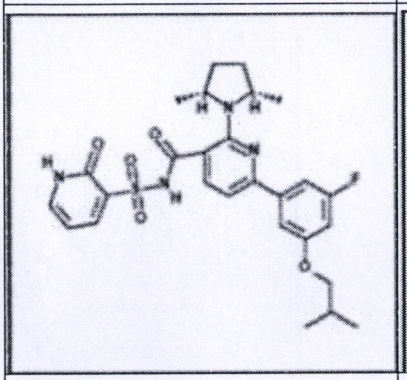
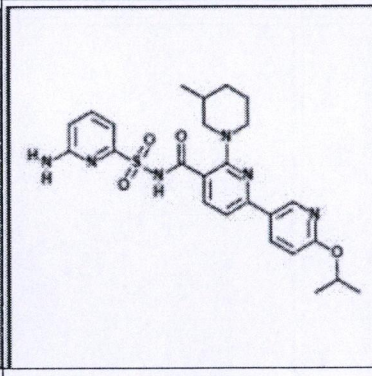
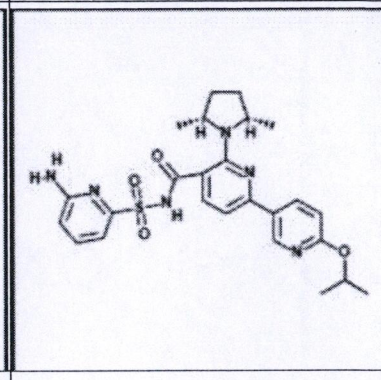
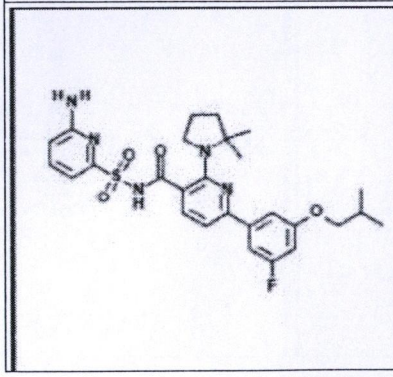
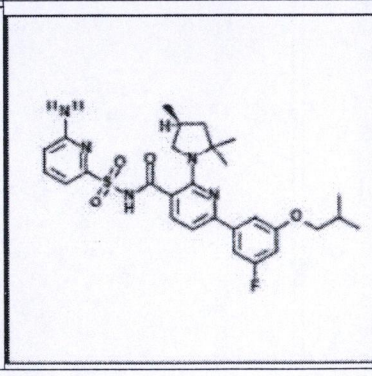
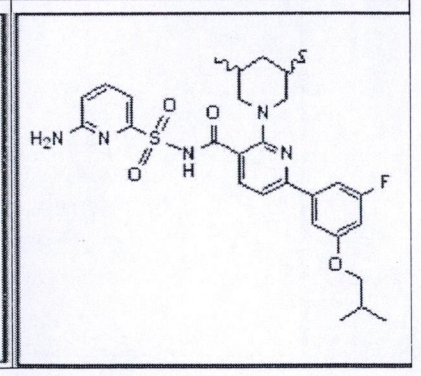
10. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_3$係選自於鹵基、CN、C1-C6烷基或氟烷基、C1-C6烷氧基，以及其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基。

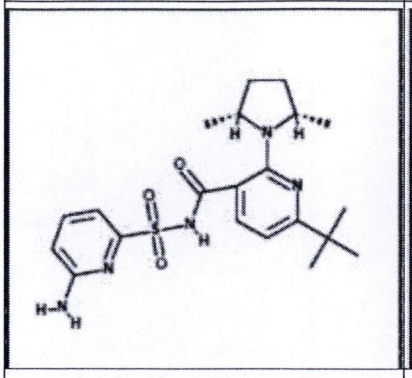
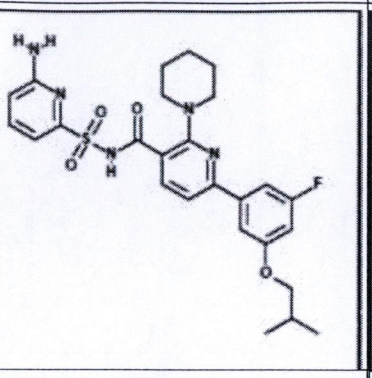
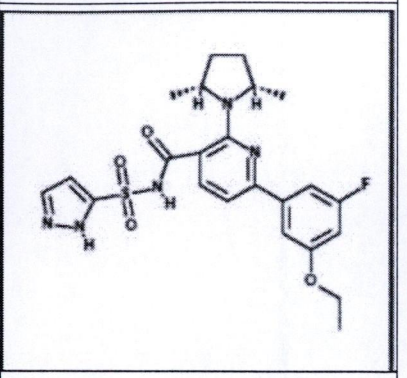
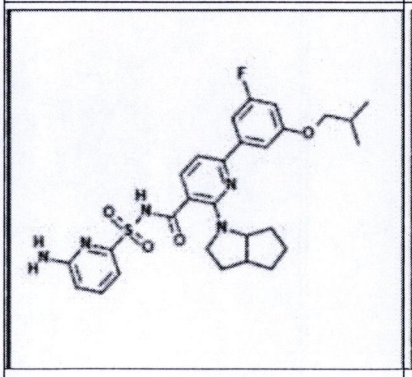
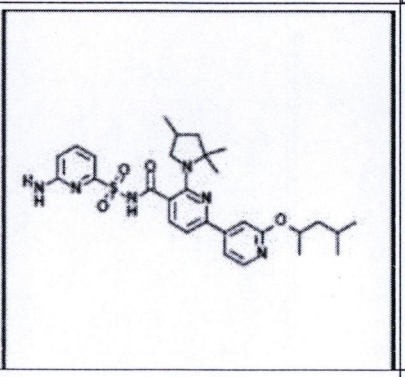
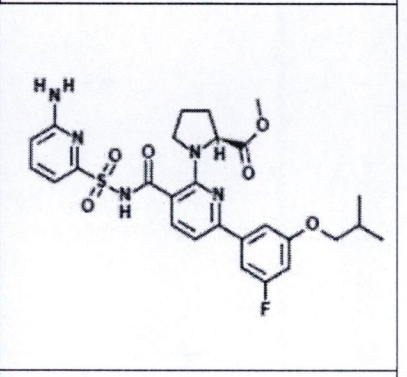
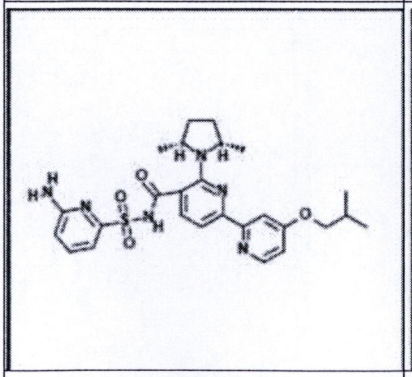
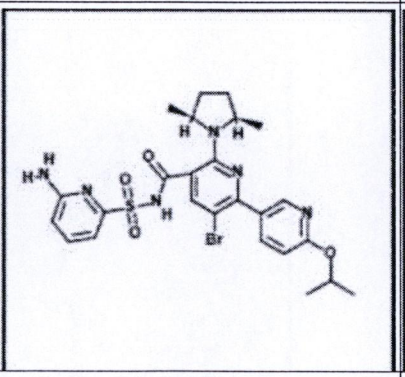
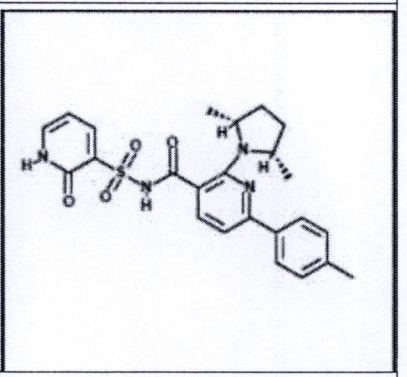
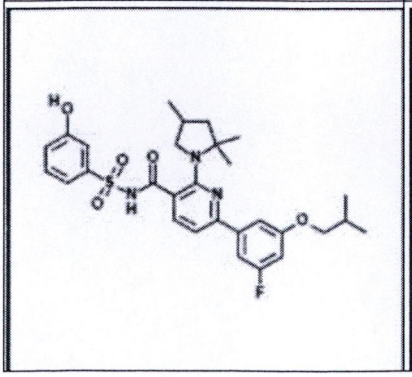
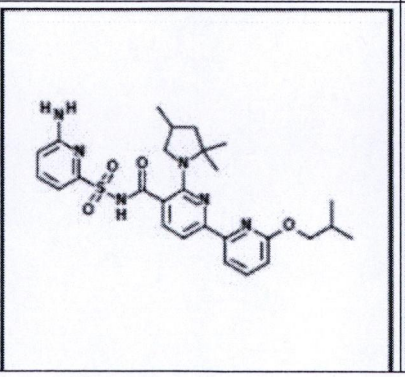
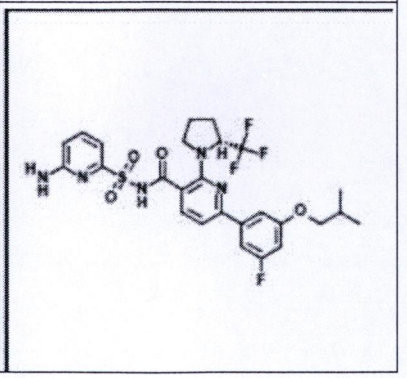
11. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_3$係選自於Cl、I、氘、F、CN、$CH_3$、OH、$OCH_3$、$CF_3$、$CH_2CH_3$、$CH_2CF_3$、$CH_2CH_2CH_3$、$OCH_2CH(CH_3)_2$、$OCH(CH_3)_2$、$CO_2H$、$CO_2NH_2$、$OCH_2CH_3$、$CH_2OCH_3$、$CH(CH_3)_2$、-C≡CH、$CH_2CONH_2$、$CO_2CH_3$、$-CH_2N(CH_3)_2$、$CO_2tBu$、tBu、$=CH_2$、=O、 

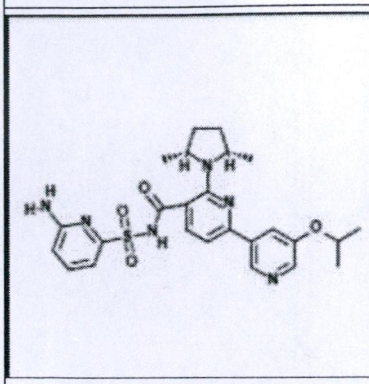
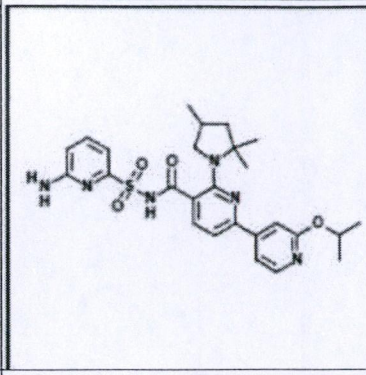
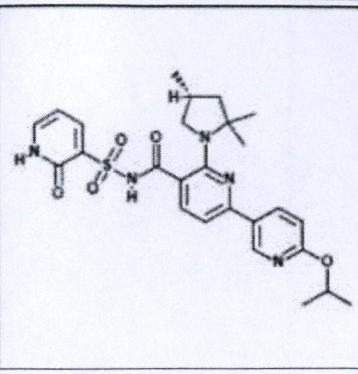
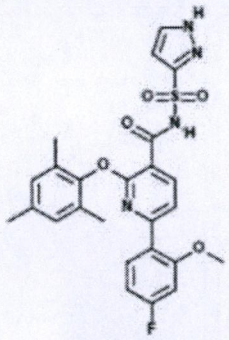
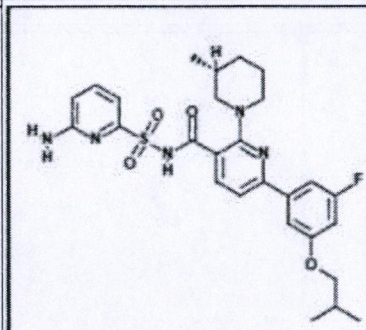
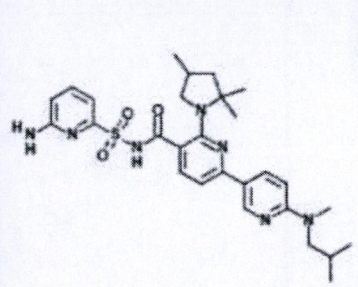
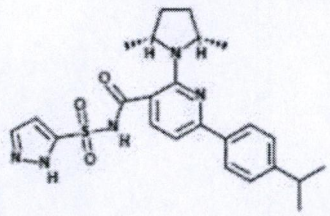
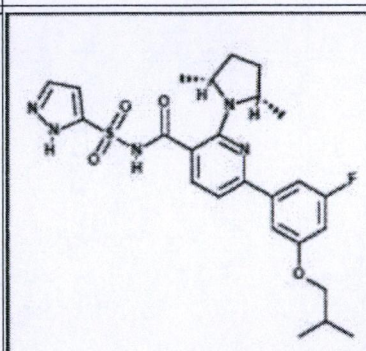
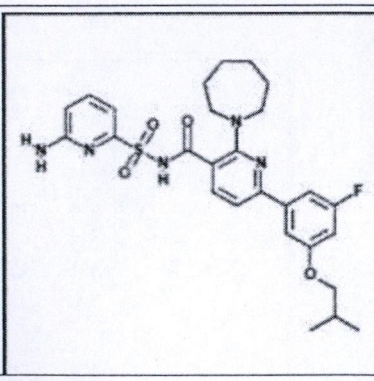
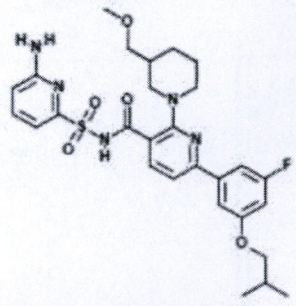
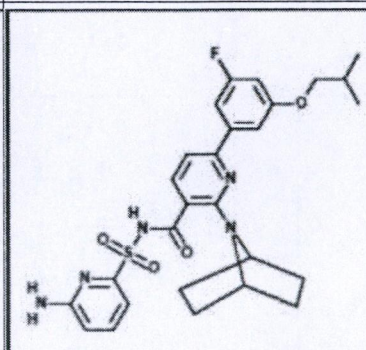
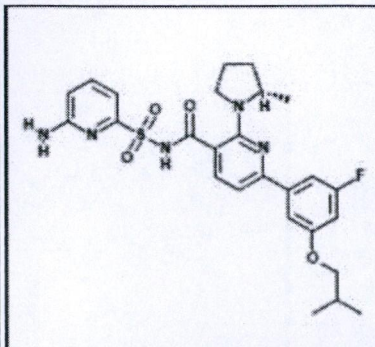
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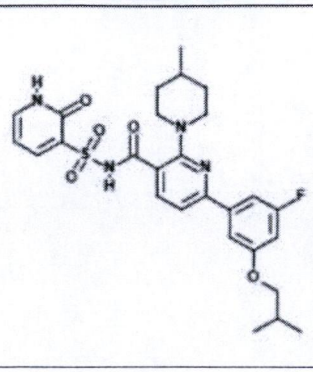
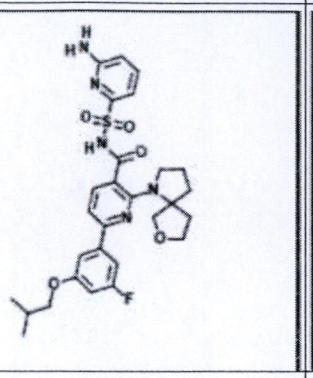
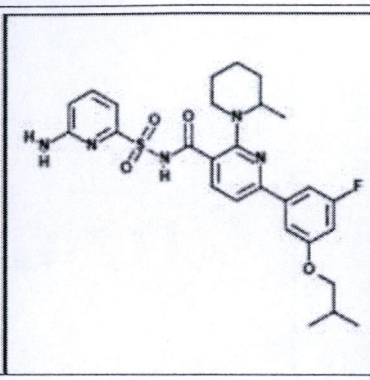
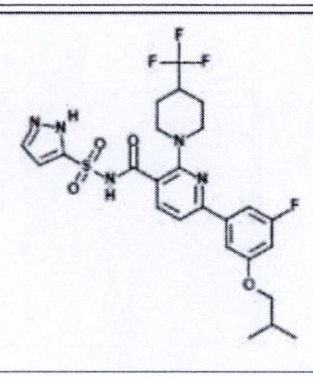
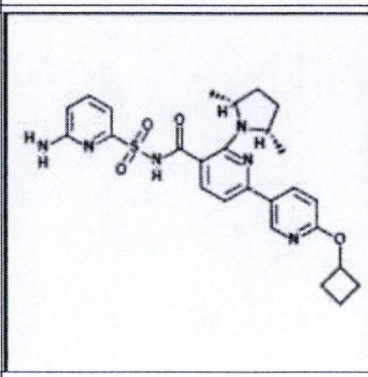
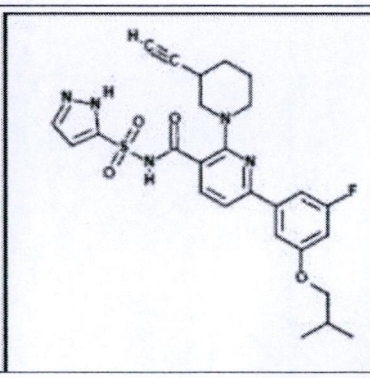
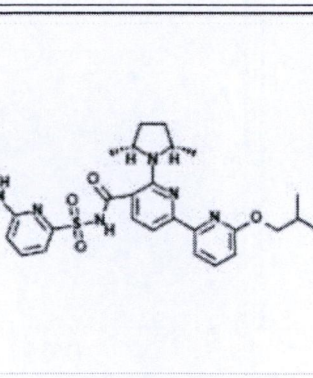
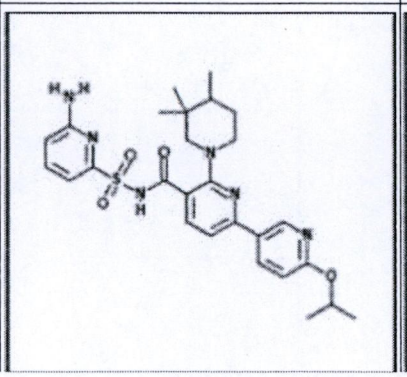
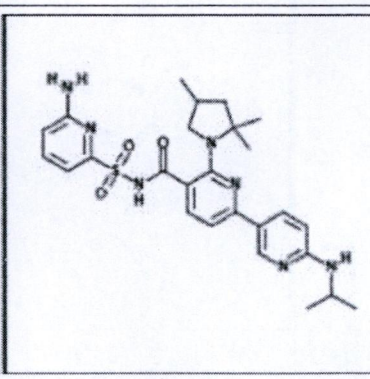
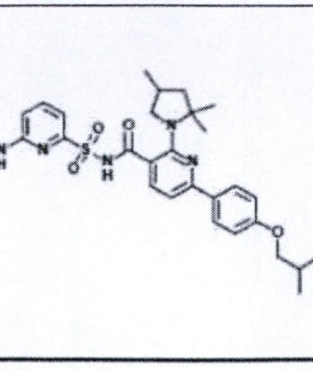
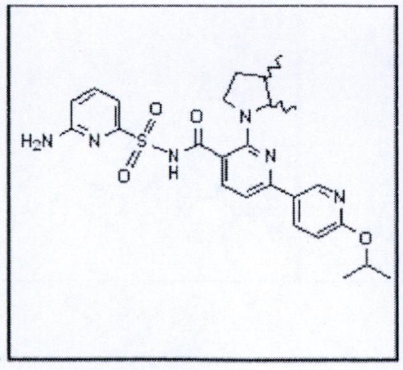
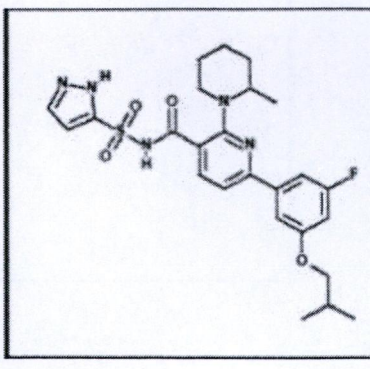
12. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中n為0。

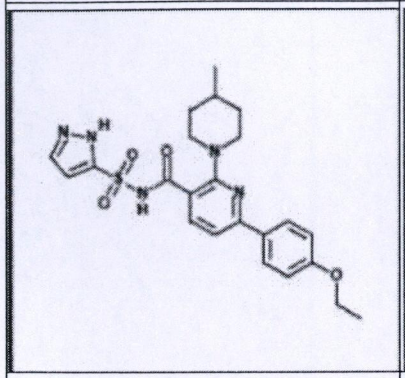
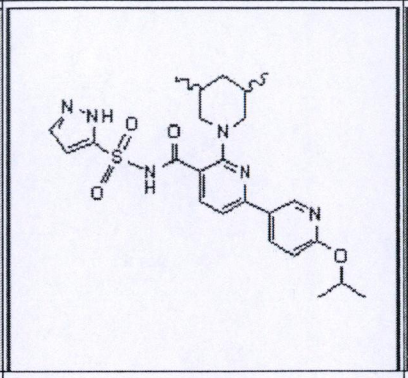
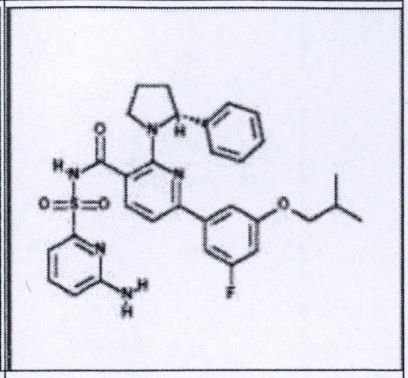
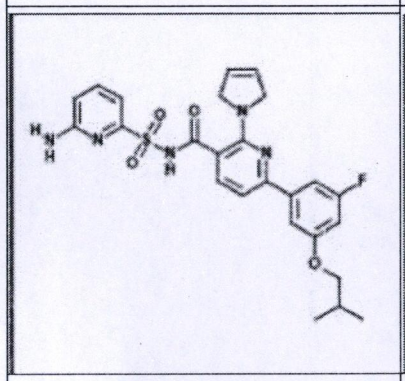
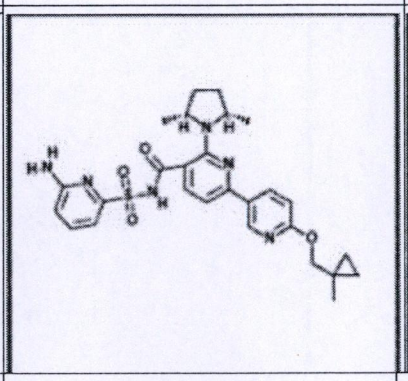
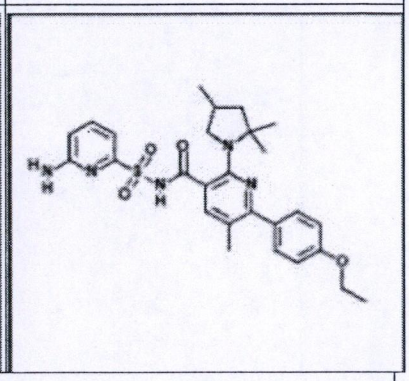
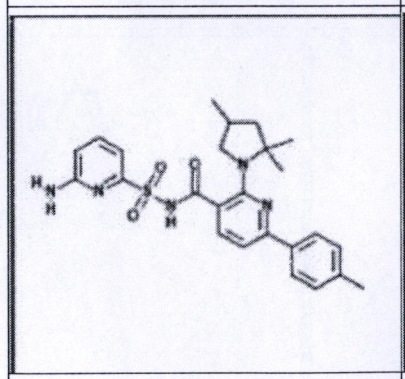
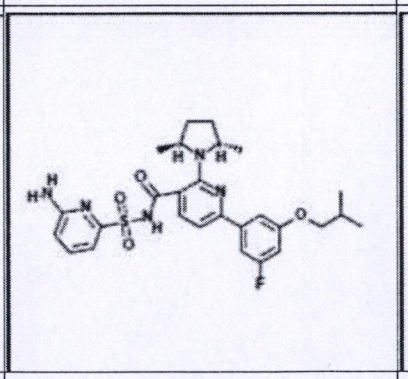
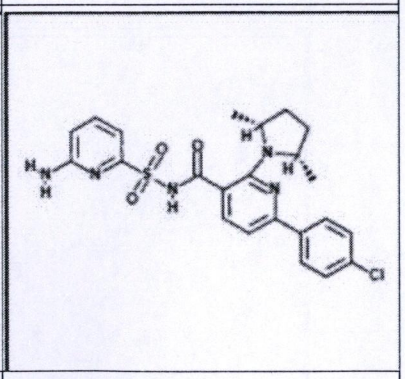
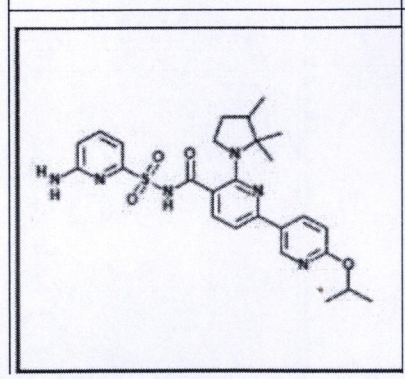
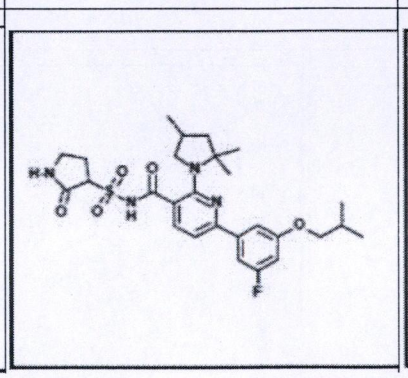
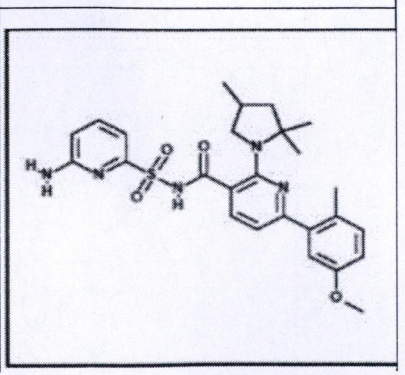
13. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中n為1。
14. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中n為2。
15. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中p為0。
16. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中p為1。
17. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中p為2。
18. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_1$為苯基、吡啶或吡唑，且n為1。
19. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_1$為苯基、吡啶或吡唑，n為1，$R_2$為胺基或烷基，或$R_2$為不存在，且p為0或1。
20. 如請求項1之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中$R_1$為苯基、吡啶或吡唑，n為1，$R_3$為烷基，且q為1、2、3或4。
21. 一種化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中該化合物係選自於：

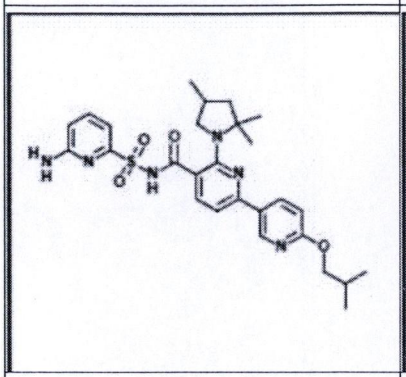
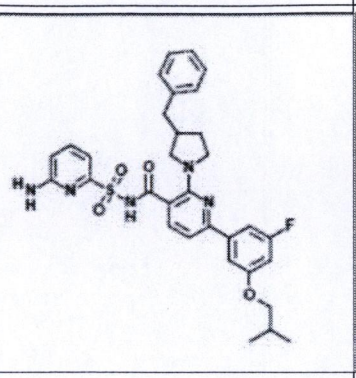
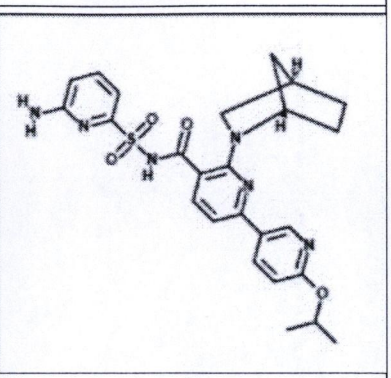
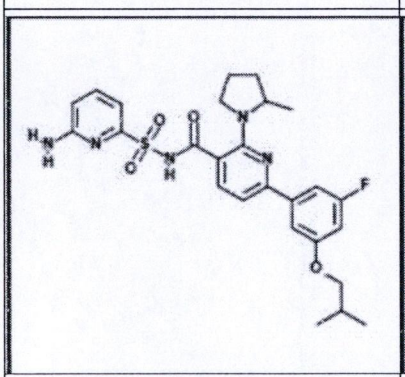
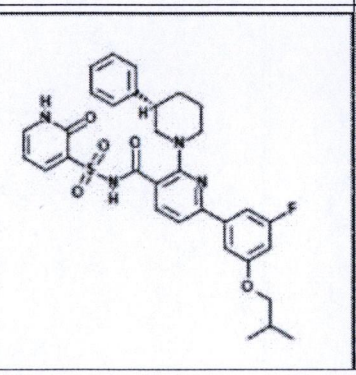
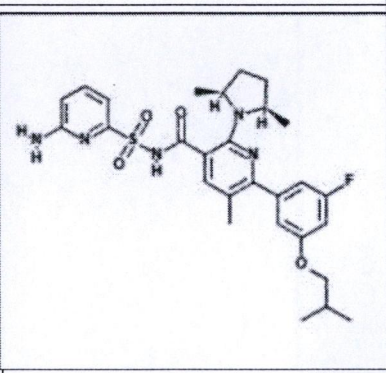
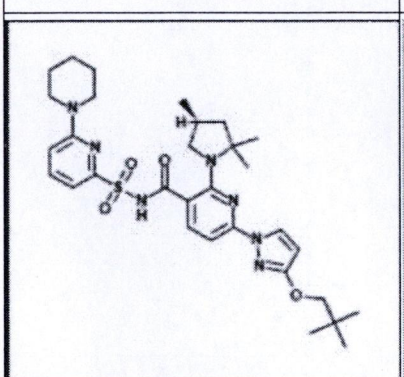
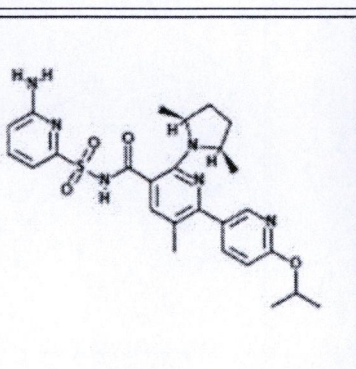
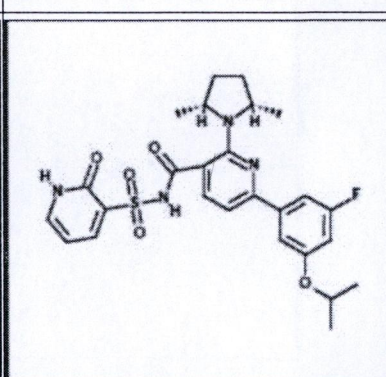
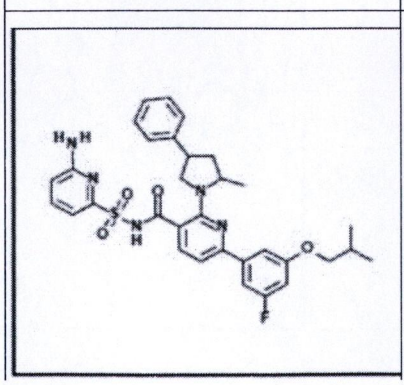
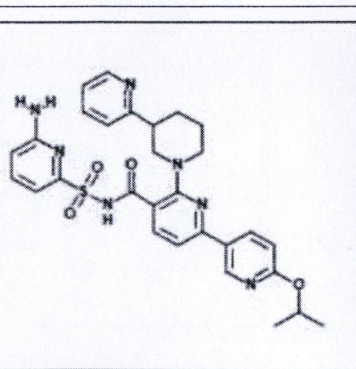
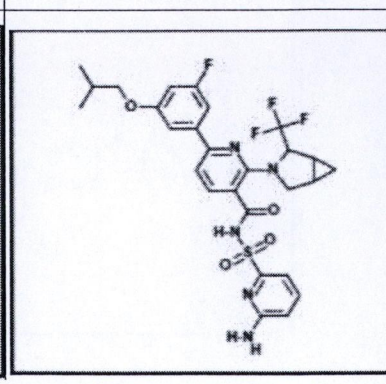
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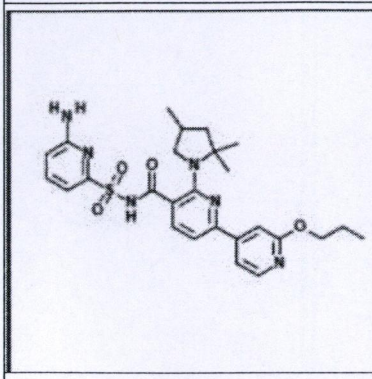
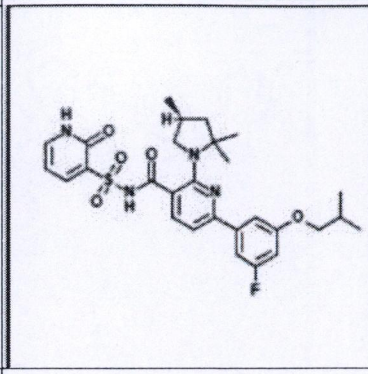
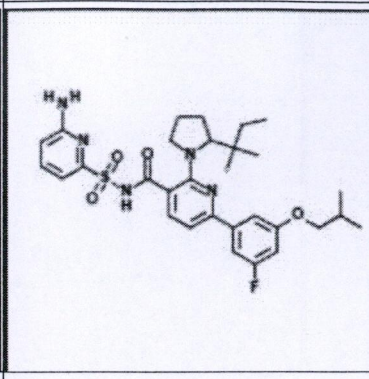
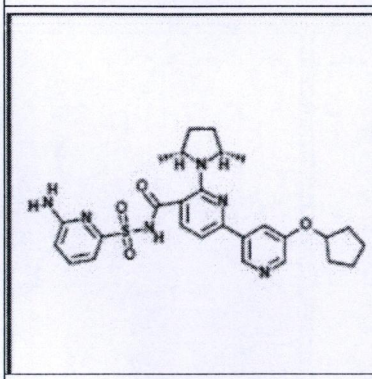
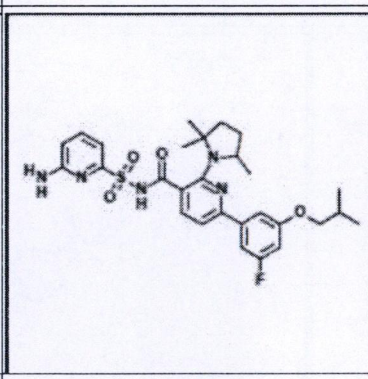
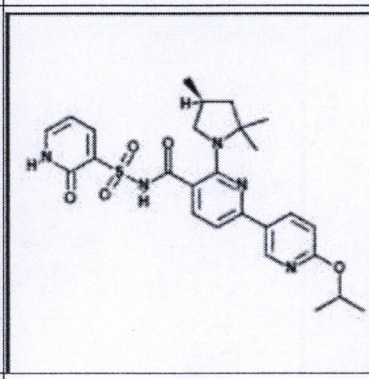
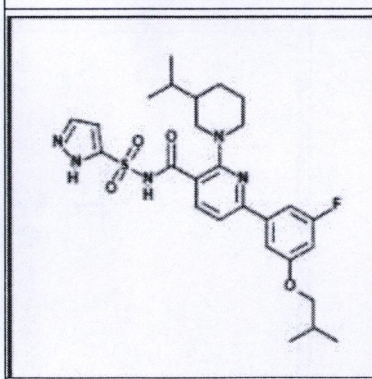
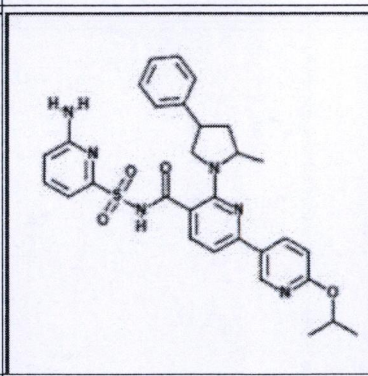
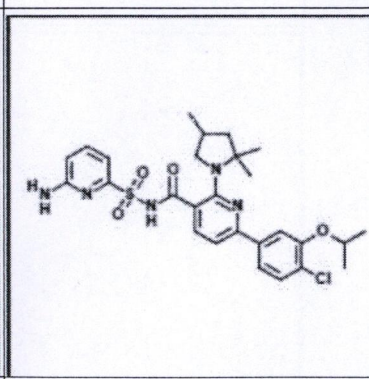
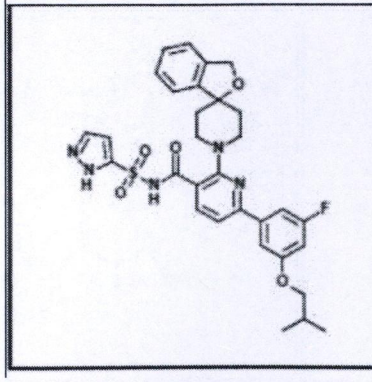
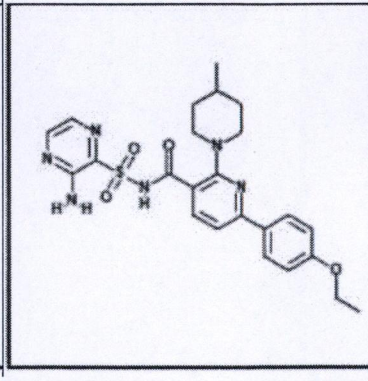
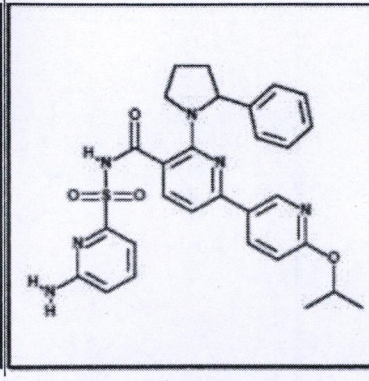
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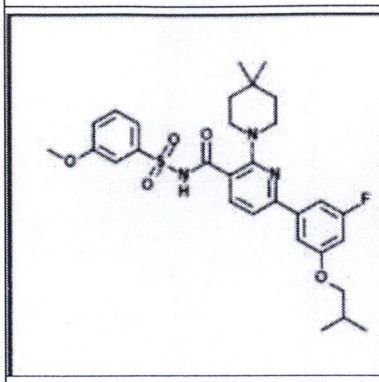
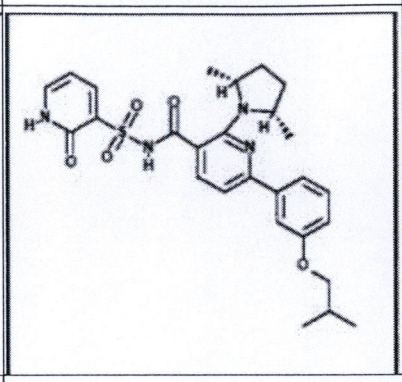
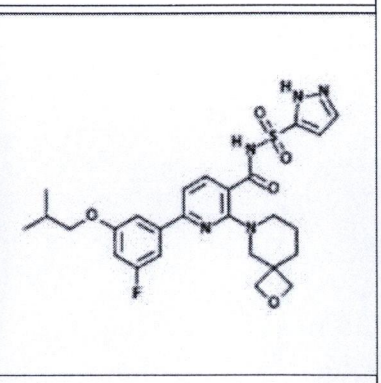
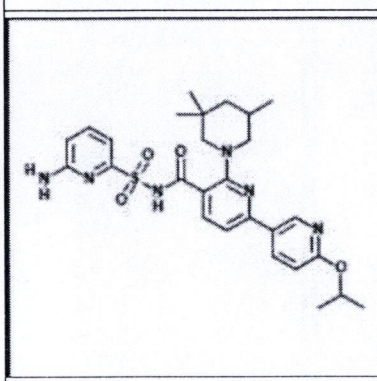
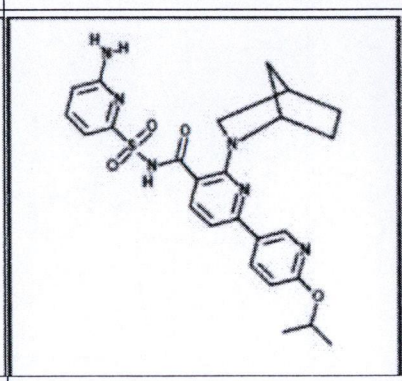
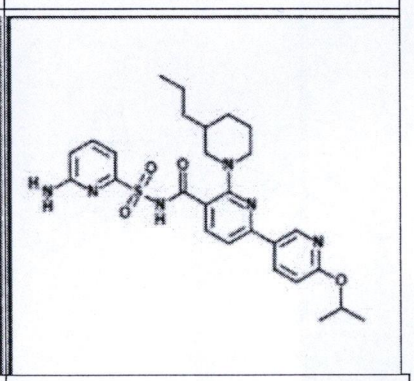
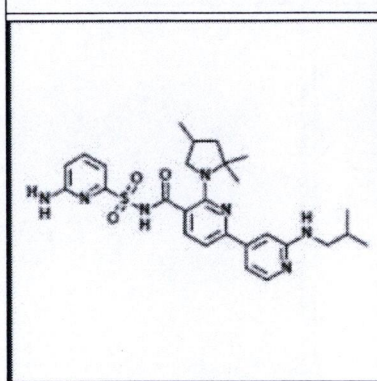
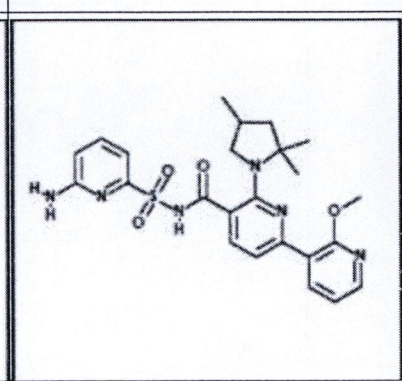
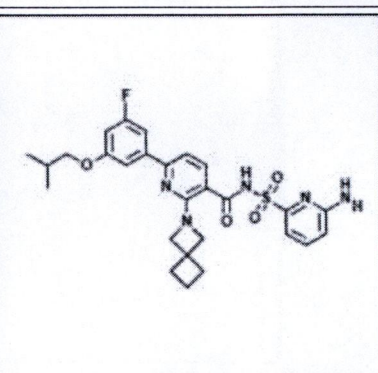
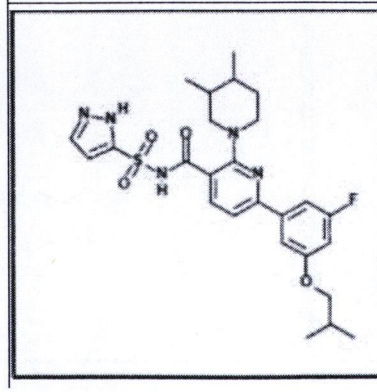
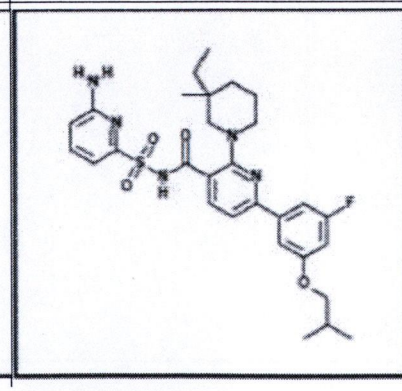
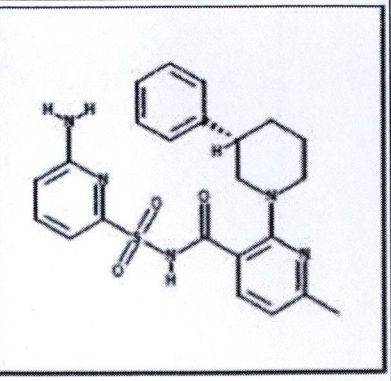
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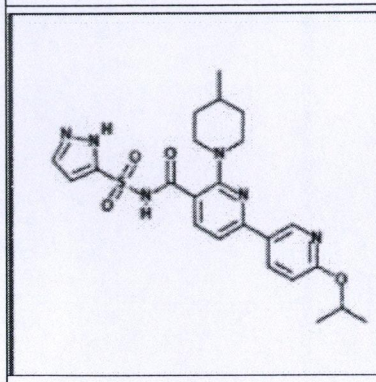
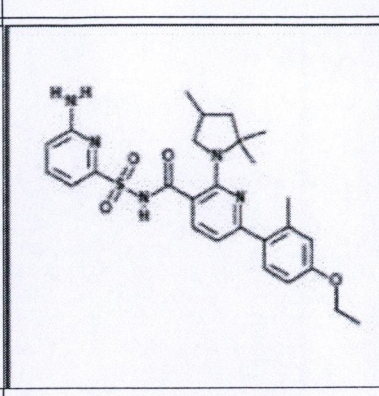
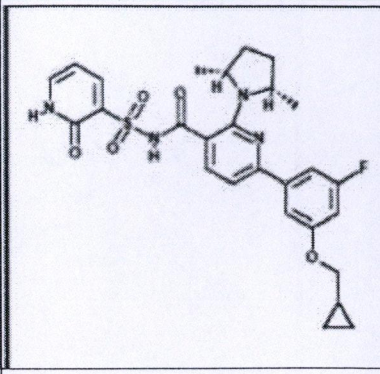
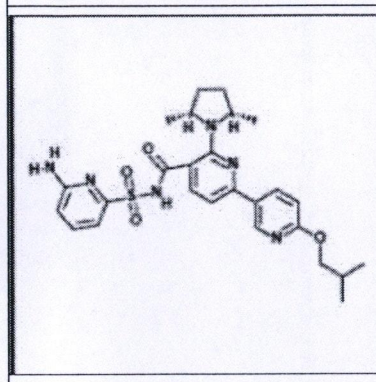
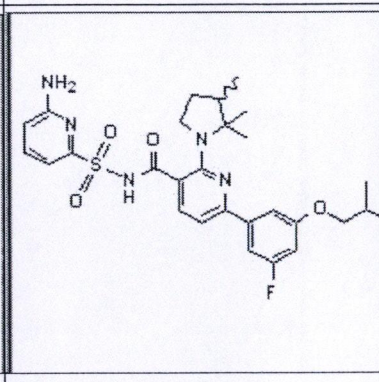
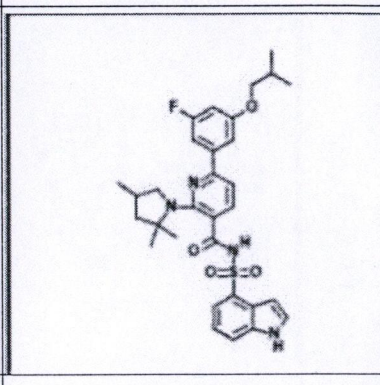
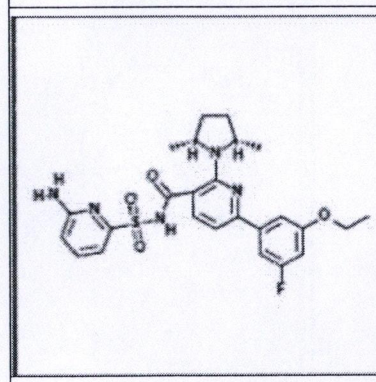
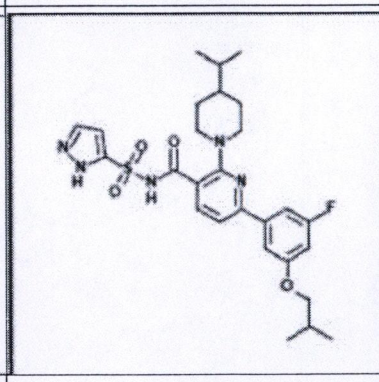
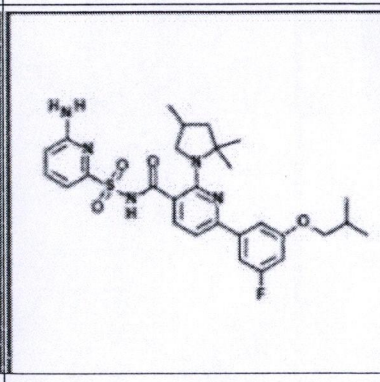
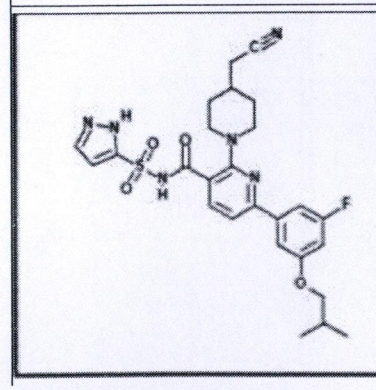
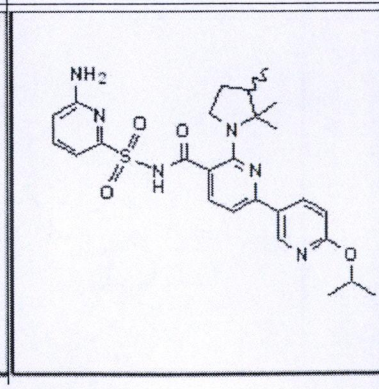
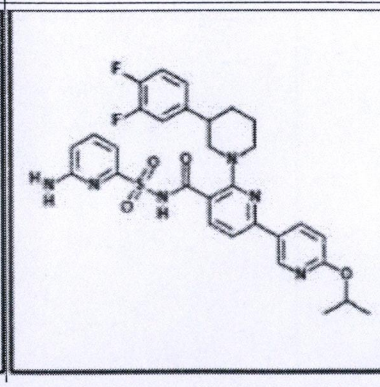
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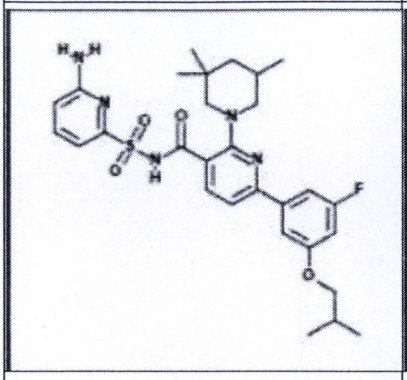
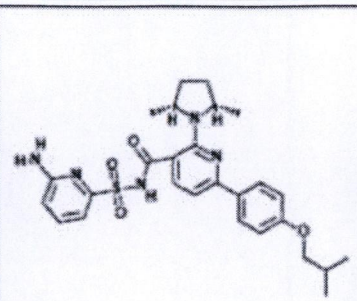
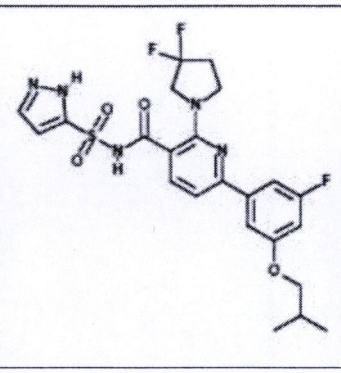
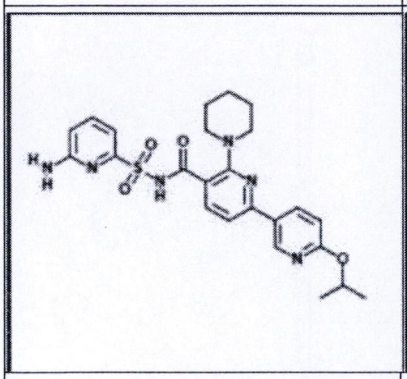
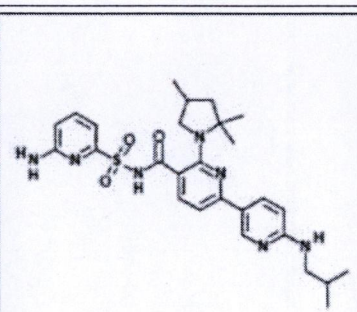
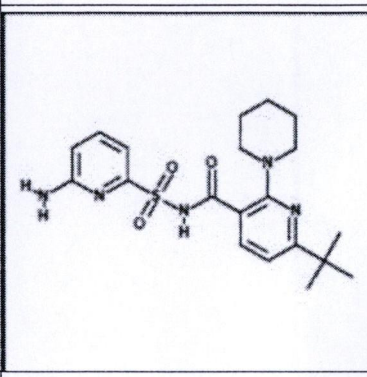
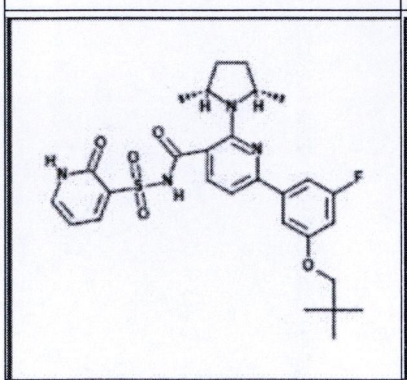
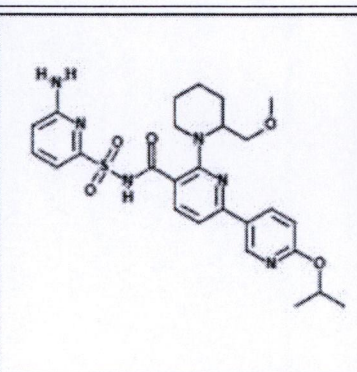
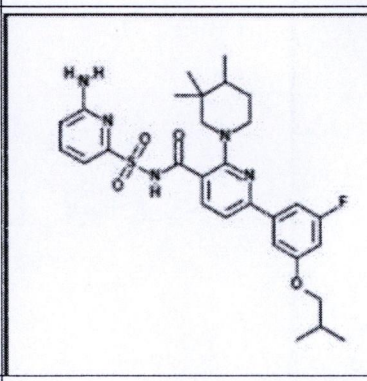
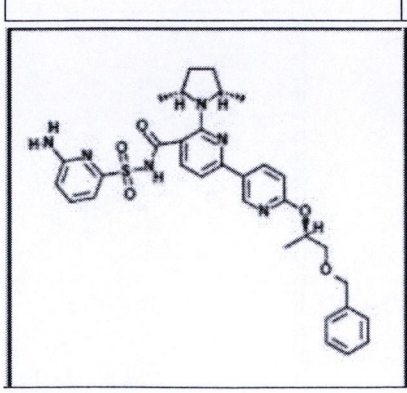
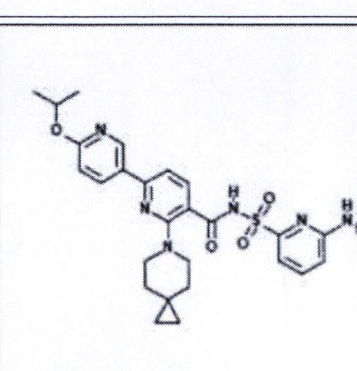
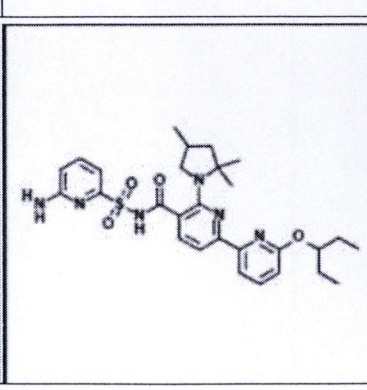
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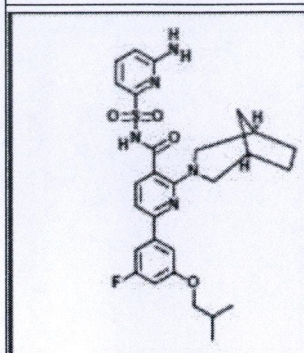
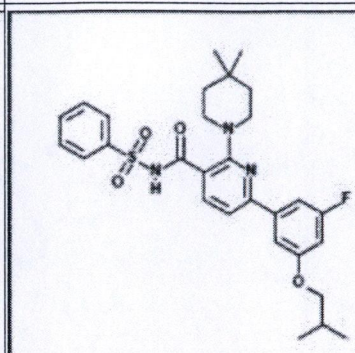
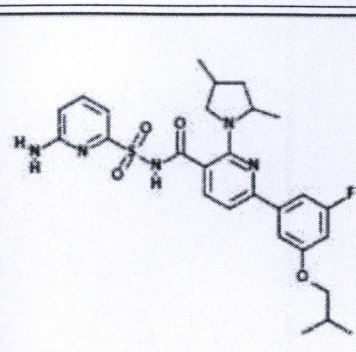
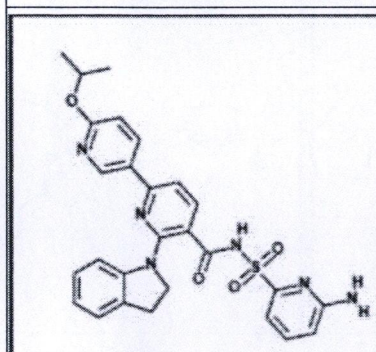
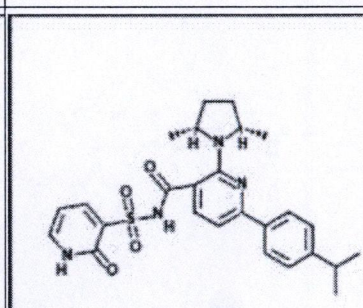
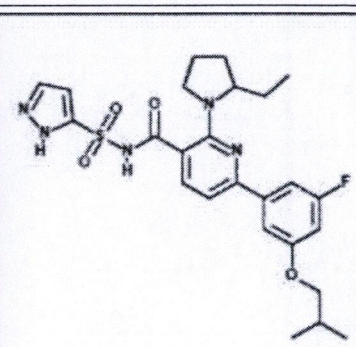
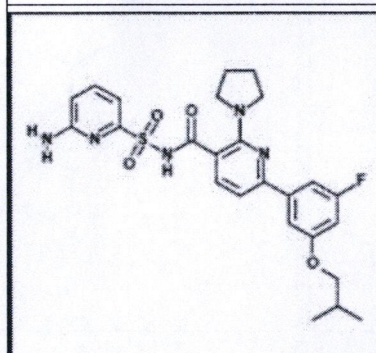
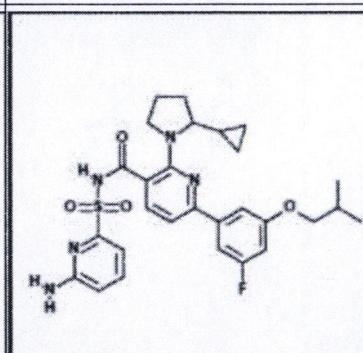
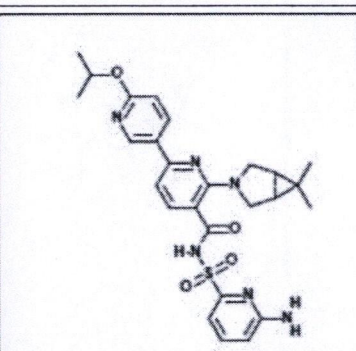
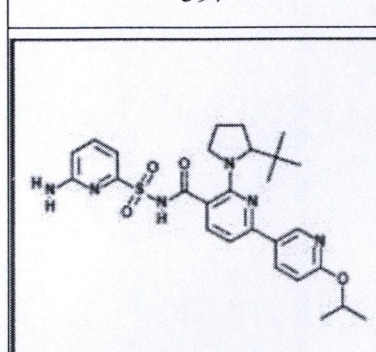
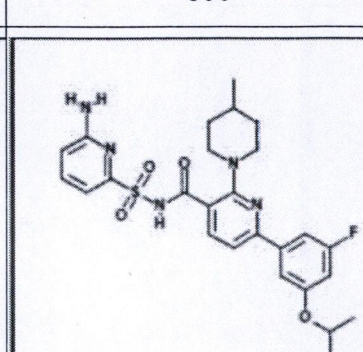
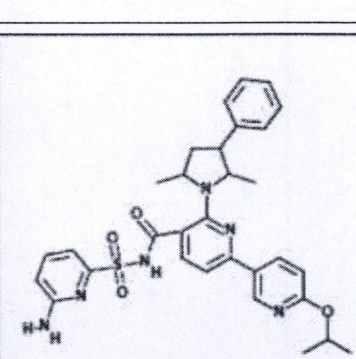
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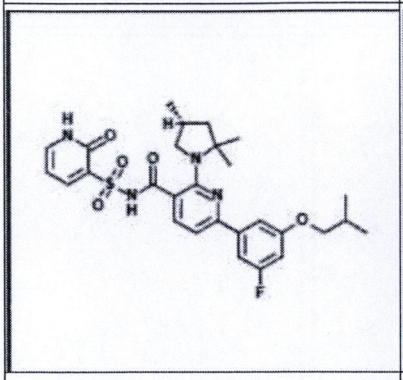
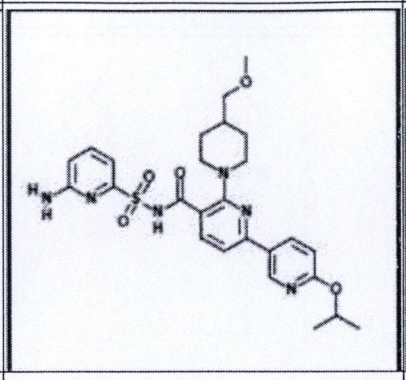
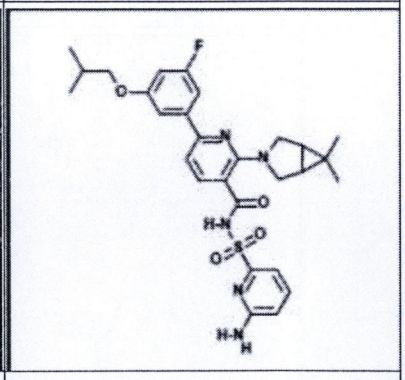
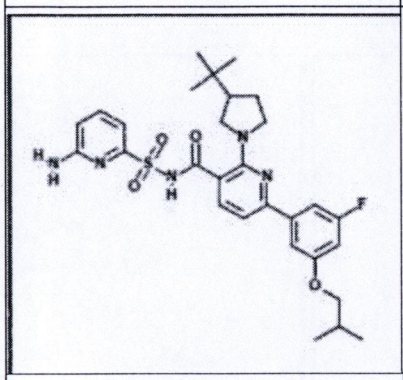
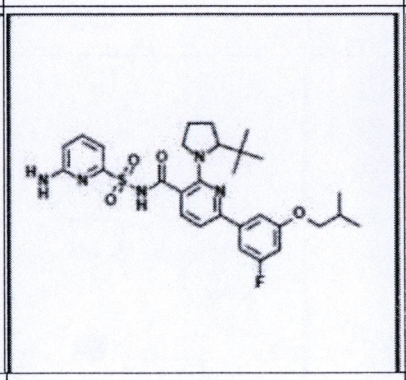
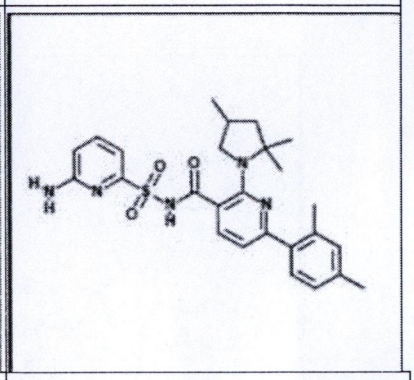
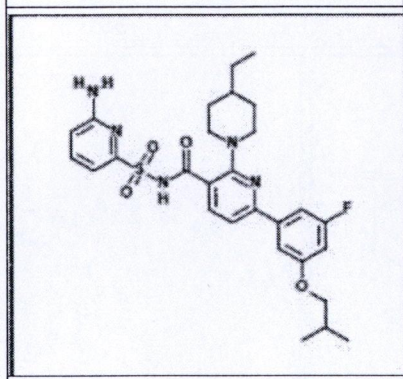
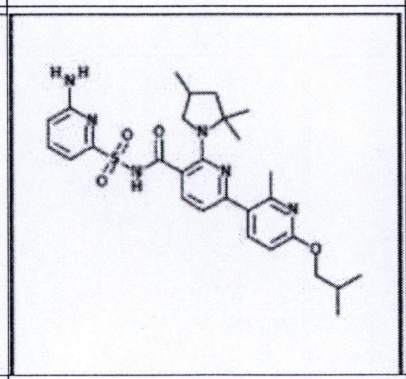
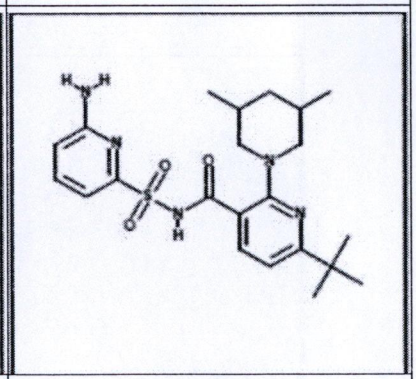
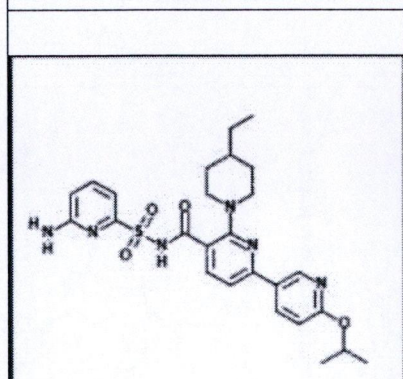
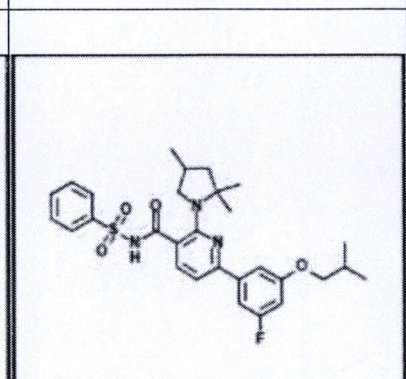
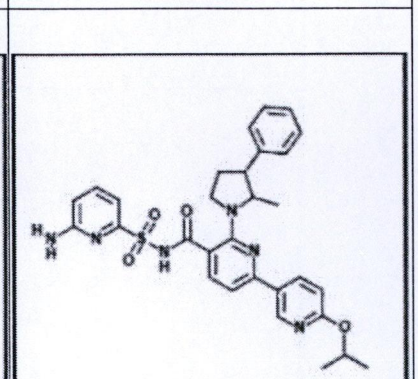
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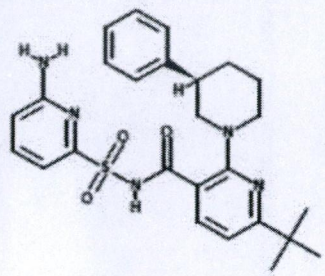
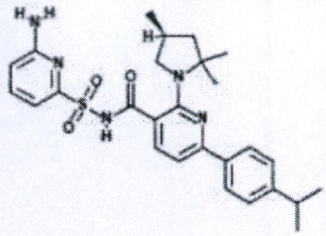
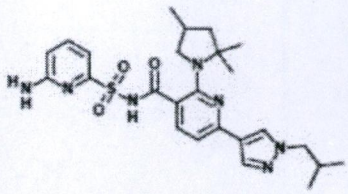
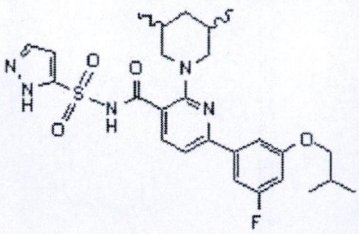
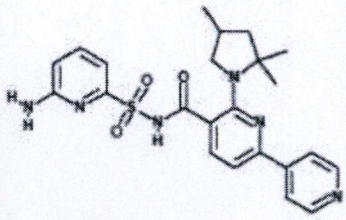
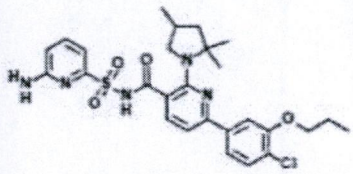
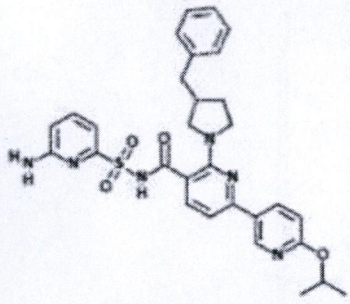
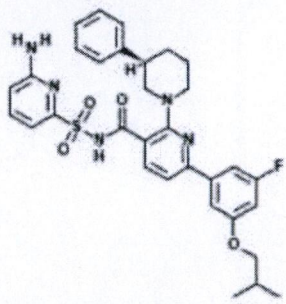
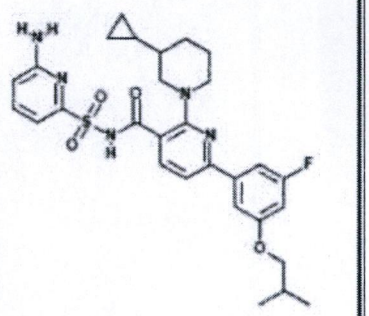
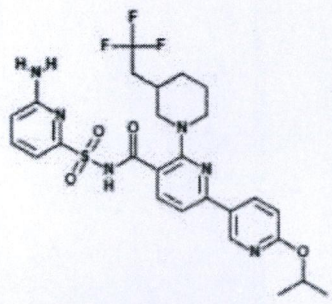
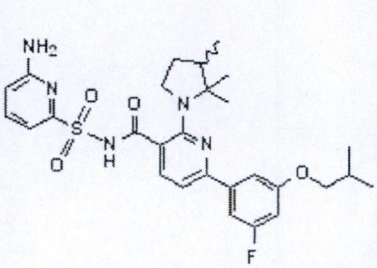
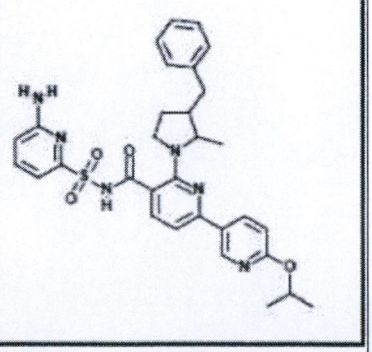
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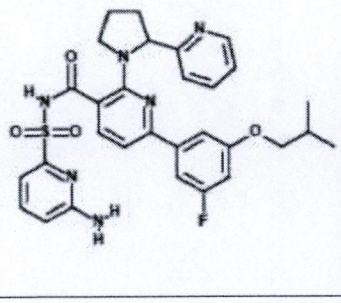
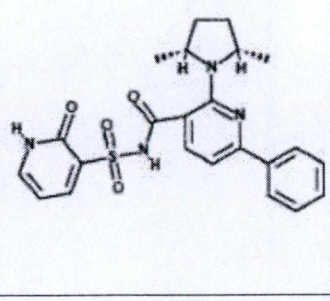
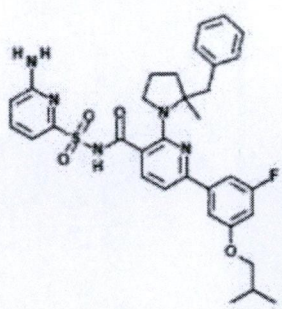
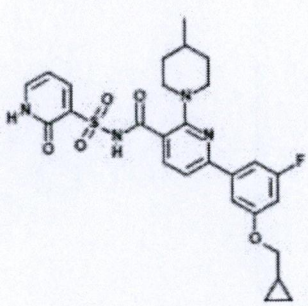
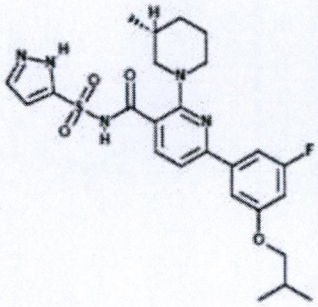
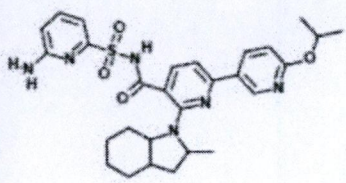
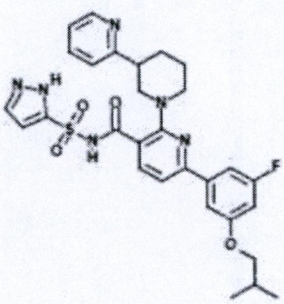
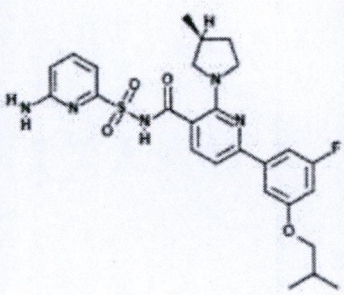
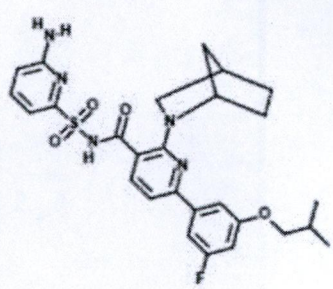
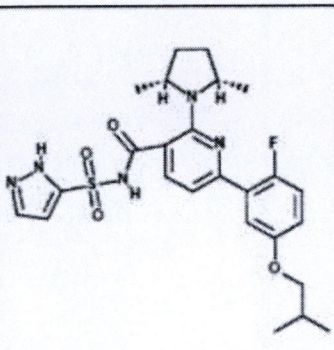
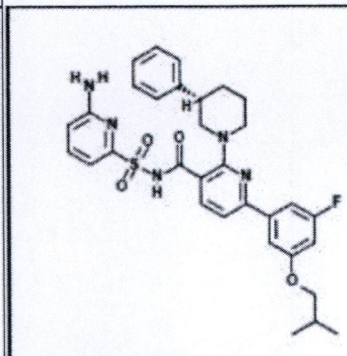
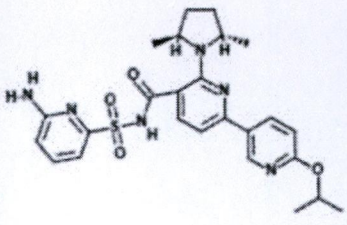
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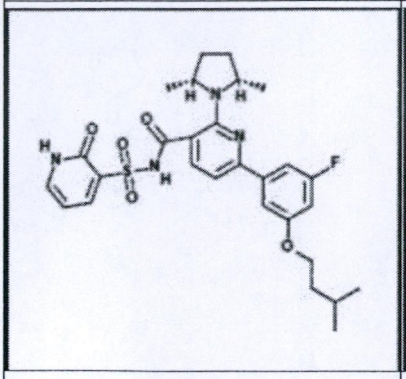
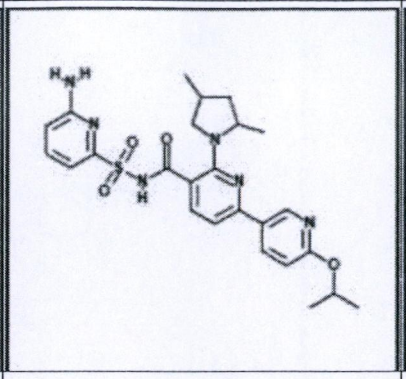
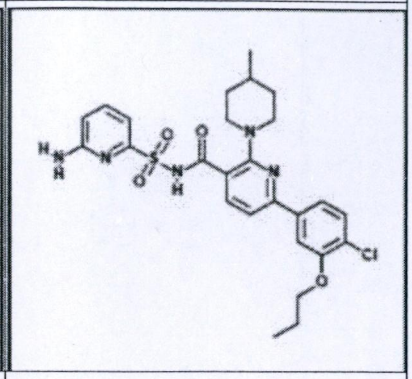
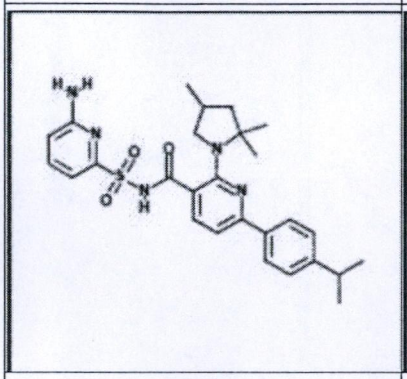
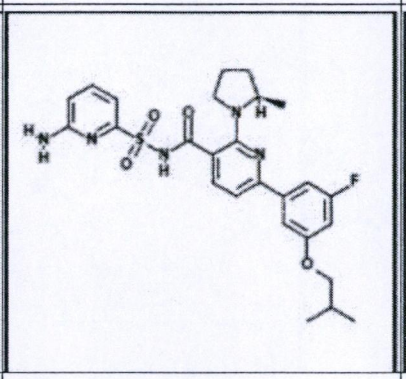
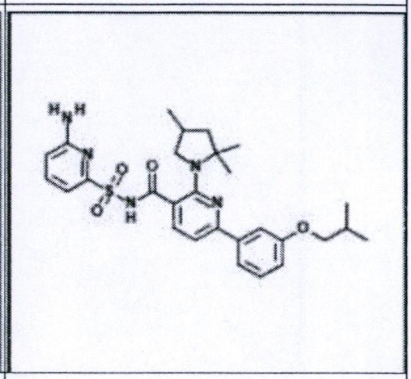
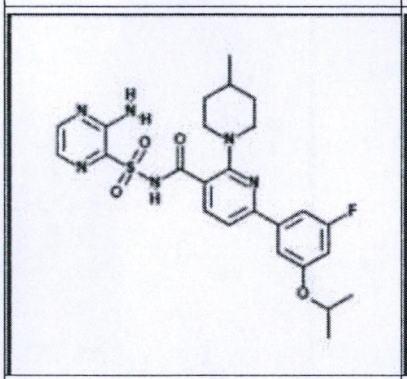
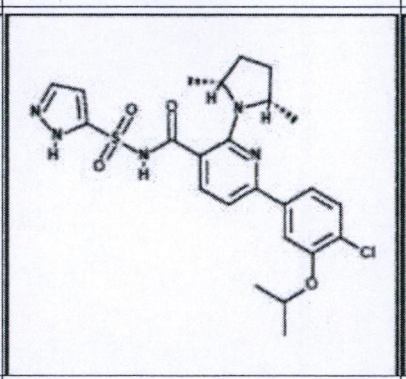
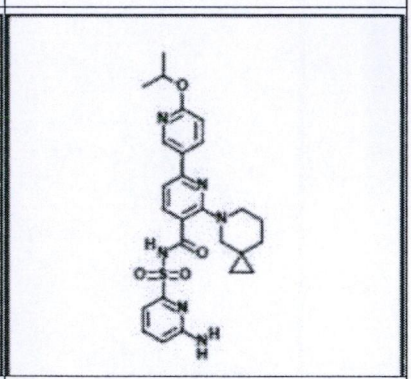
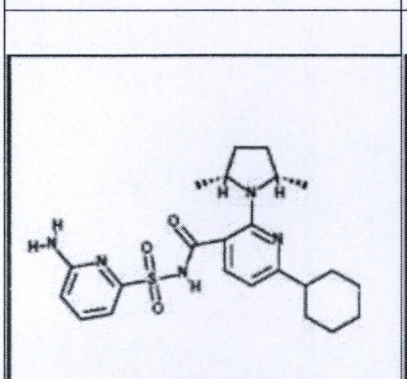
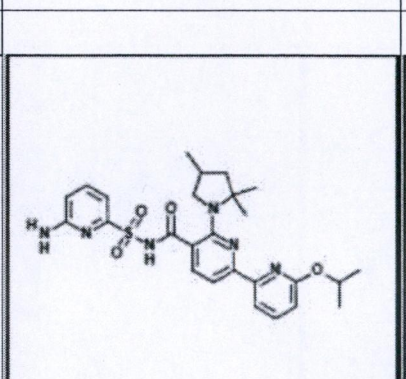
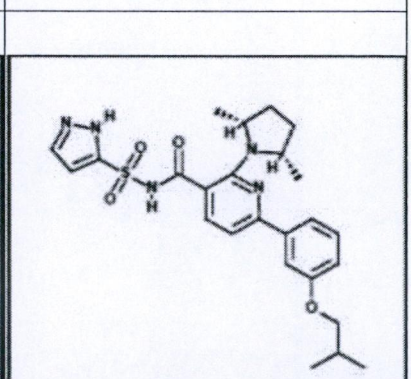
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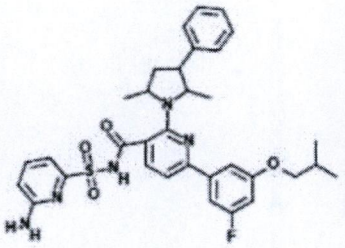
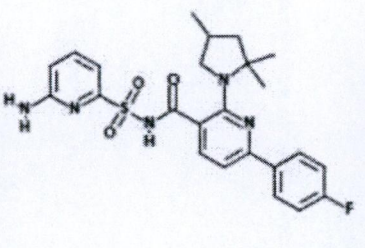
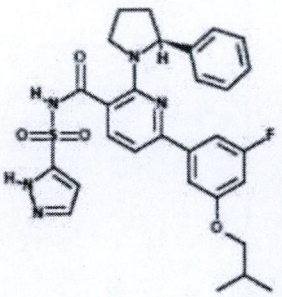
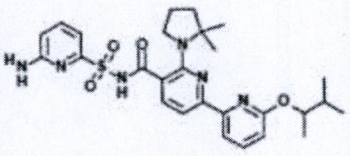
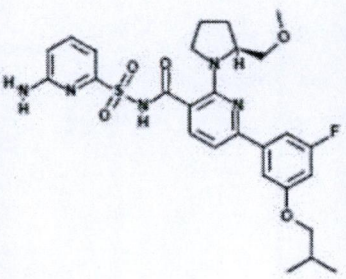
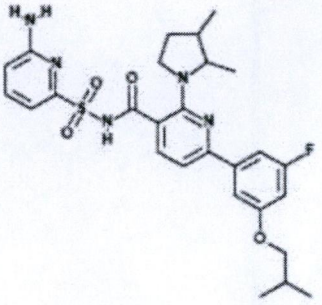
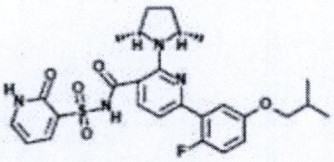
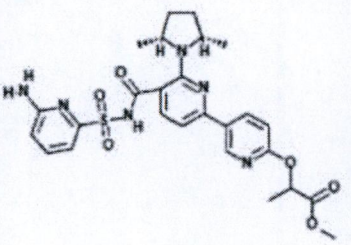
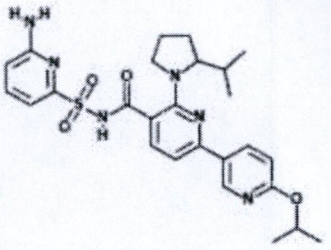
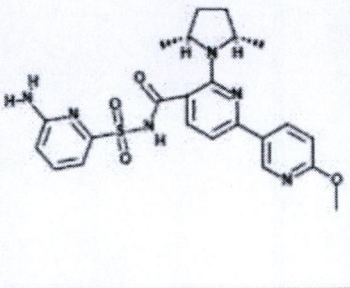
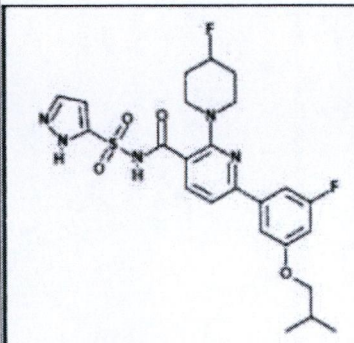
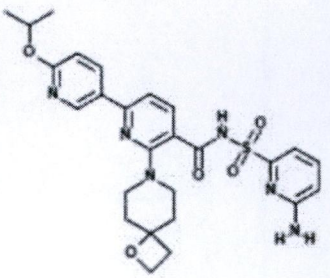
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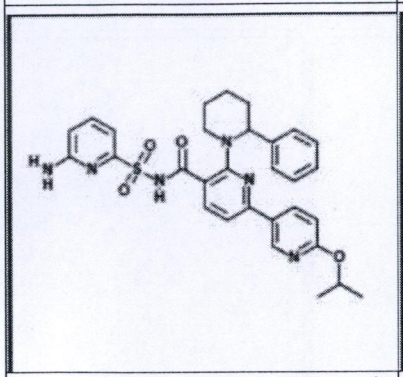
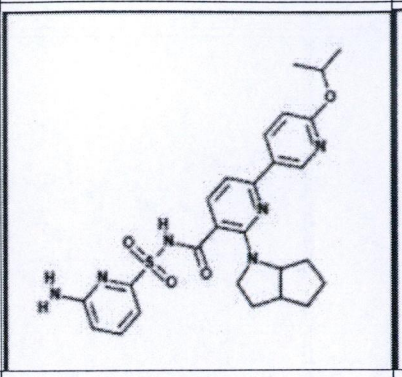
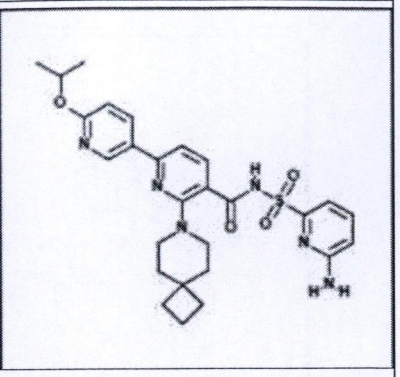
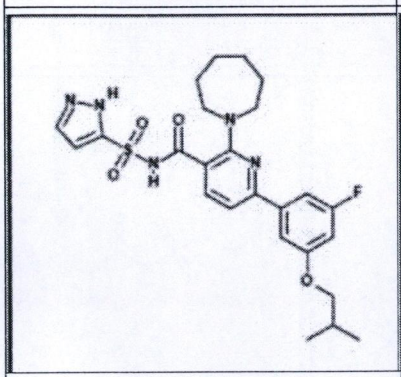
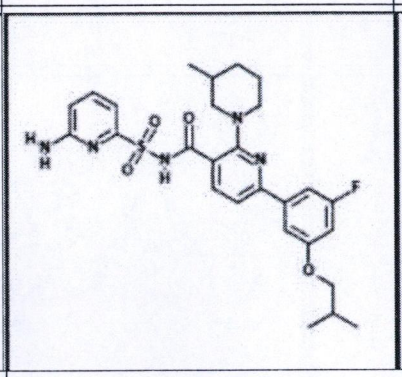
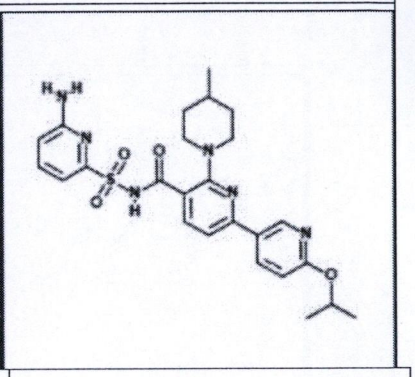
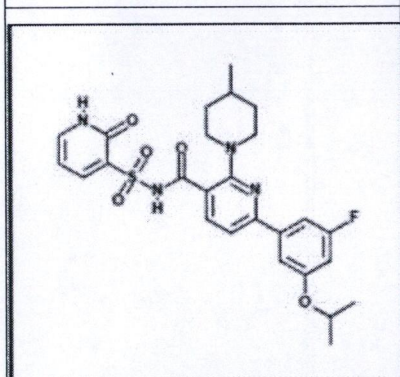
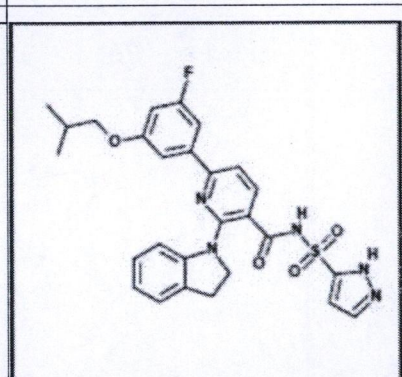
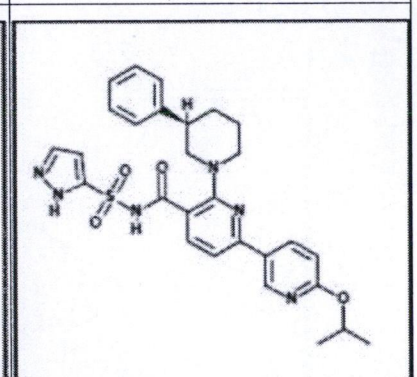
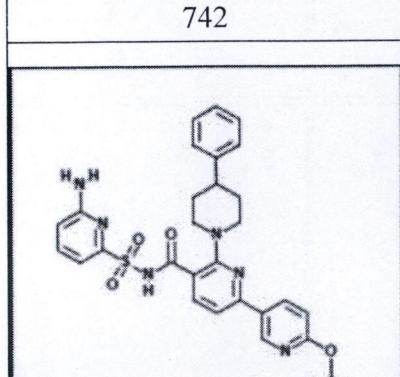
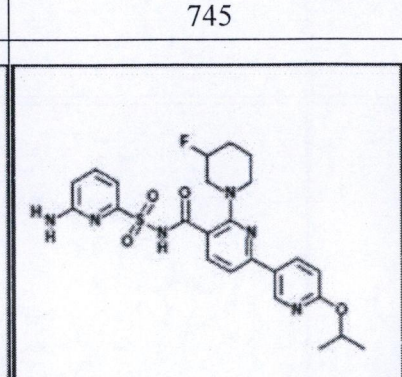
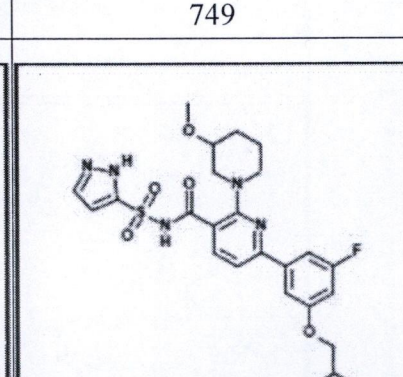
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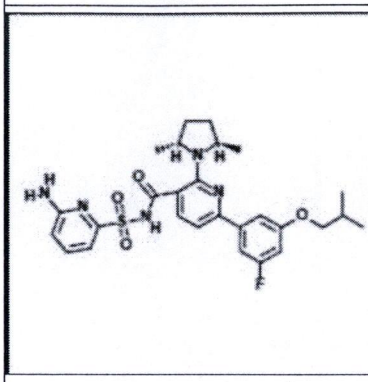
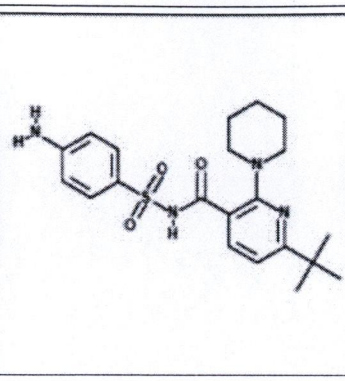
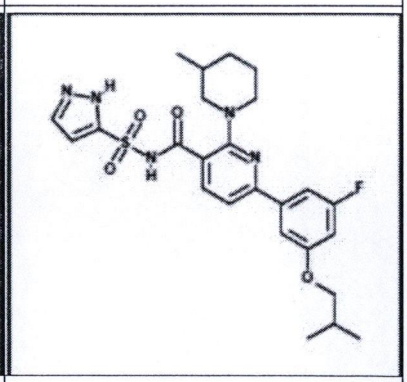
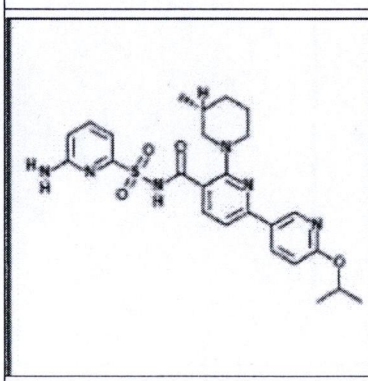
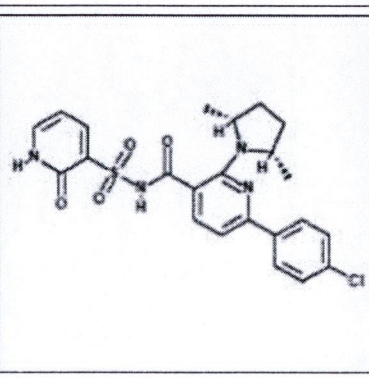
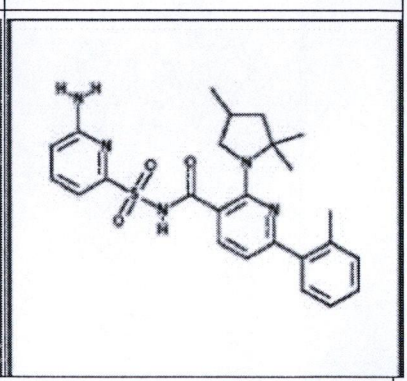
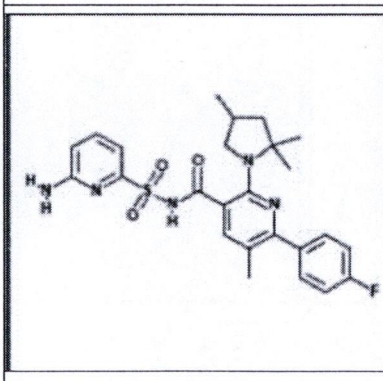
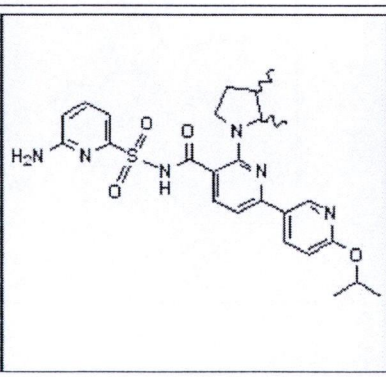
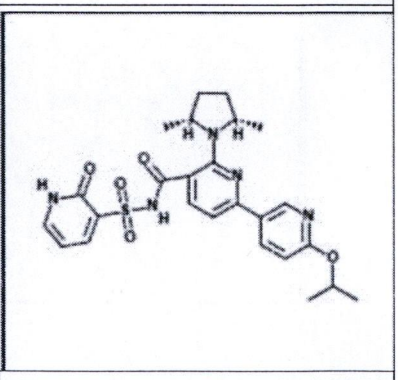
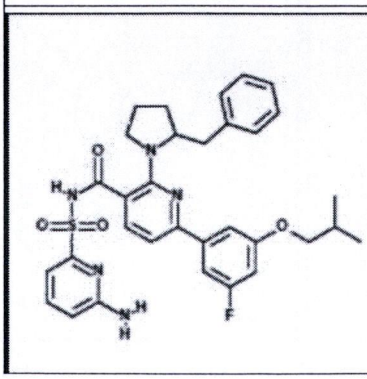
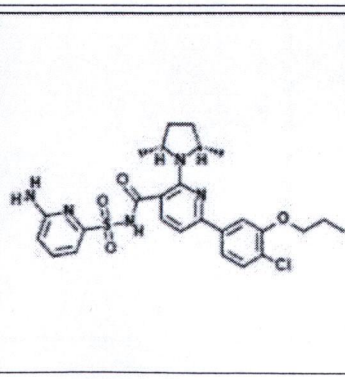
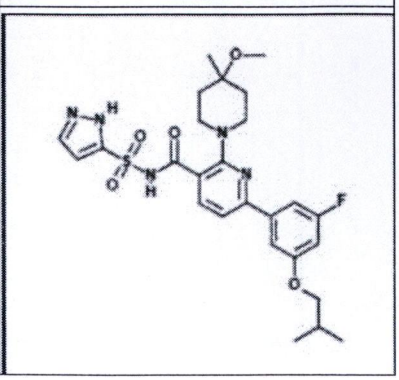
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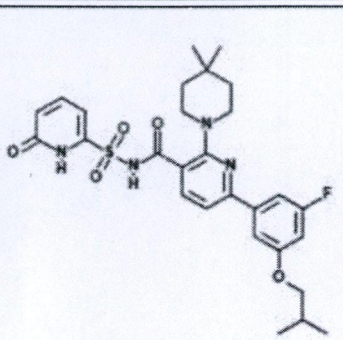
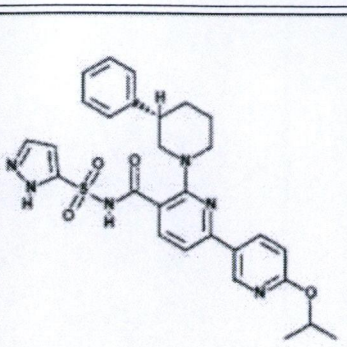
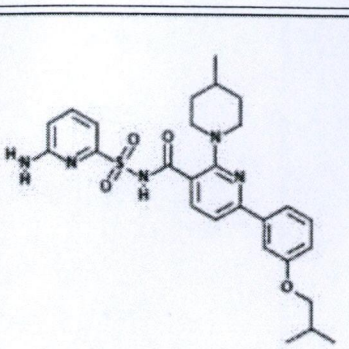
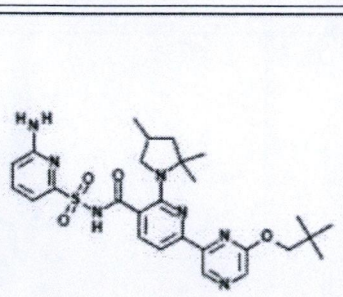
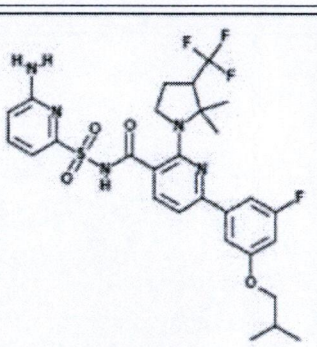
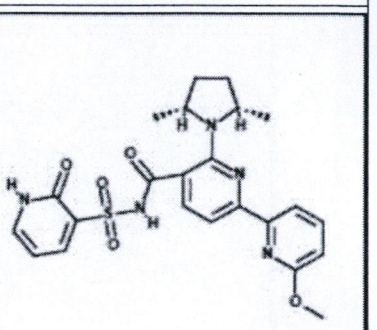
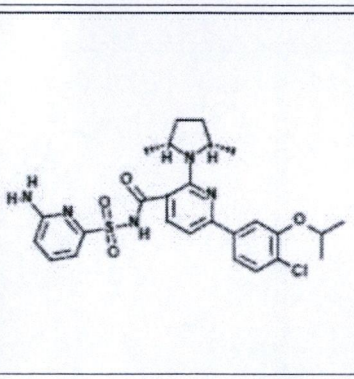
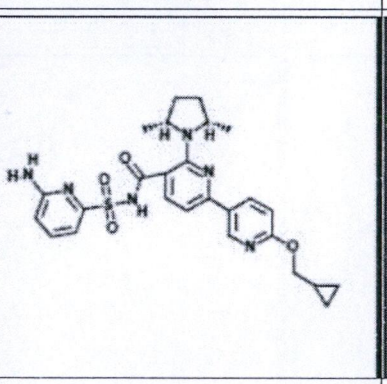
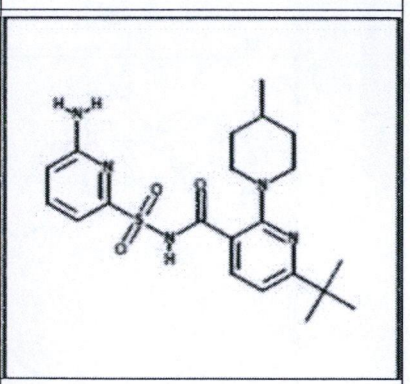
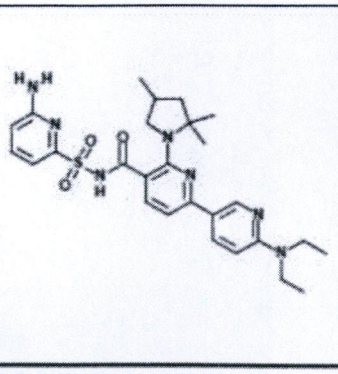
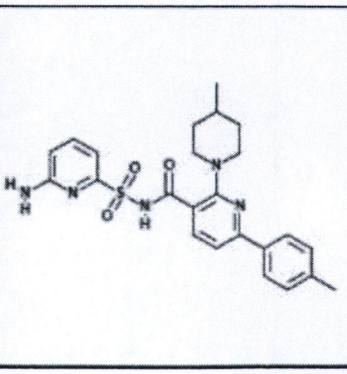
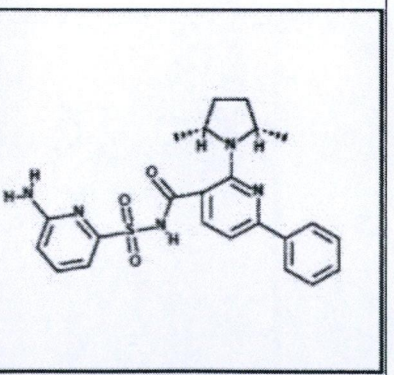
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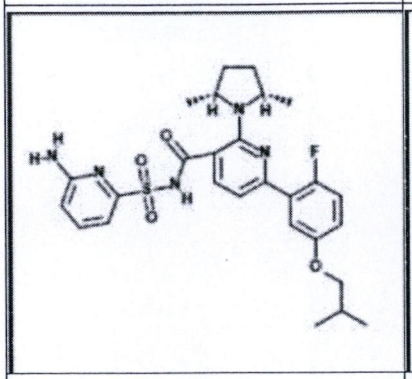
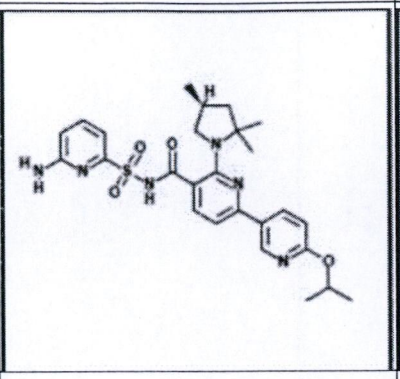
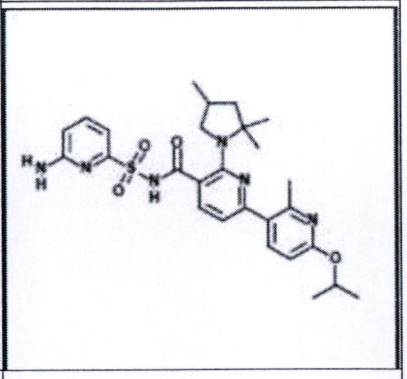
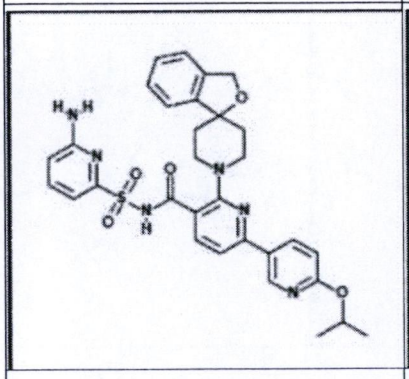
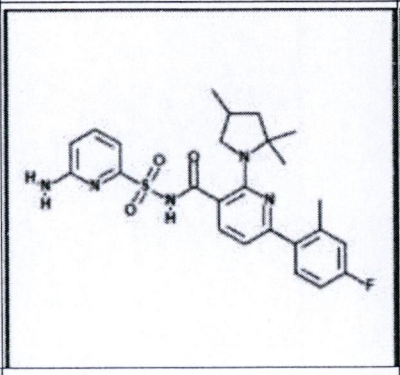
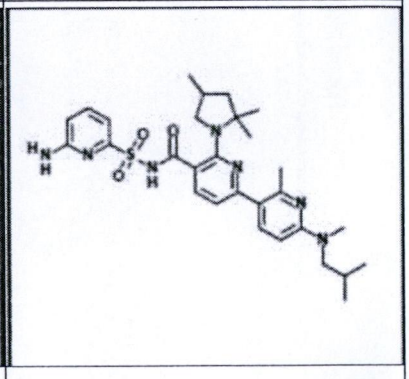
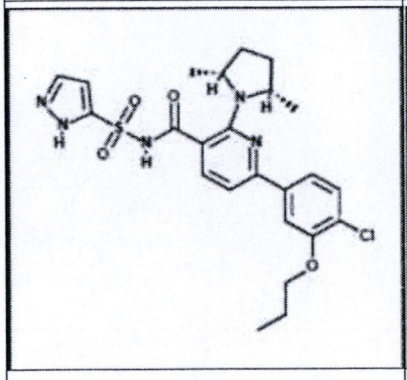
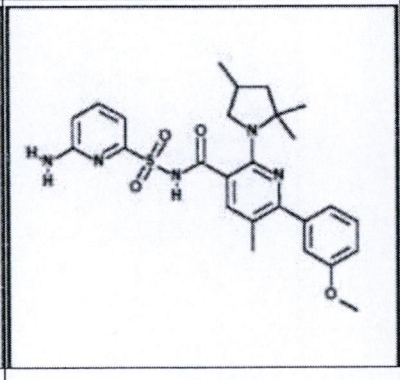
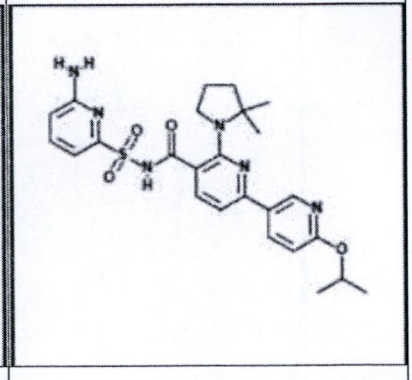
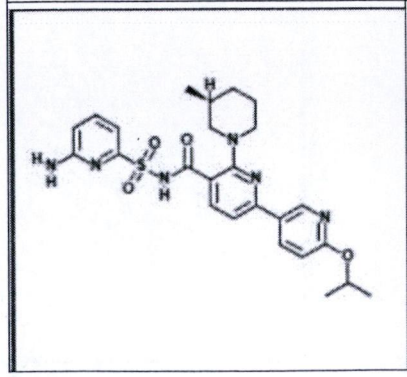
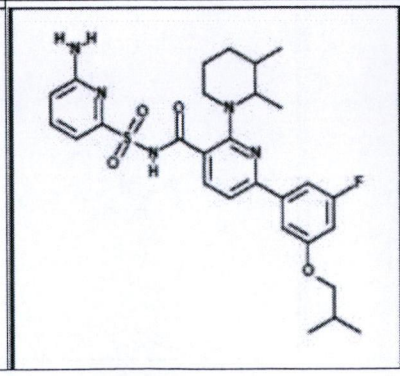
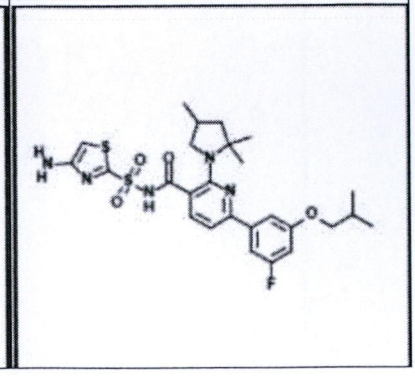
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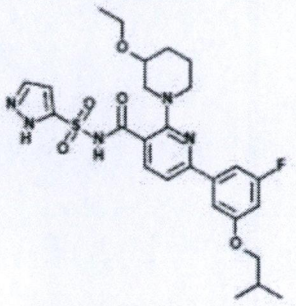
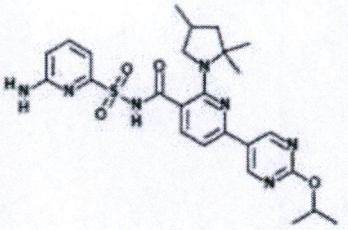
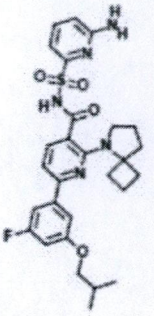
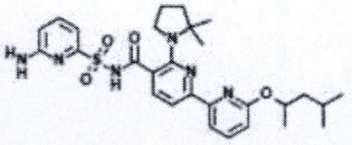
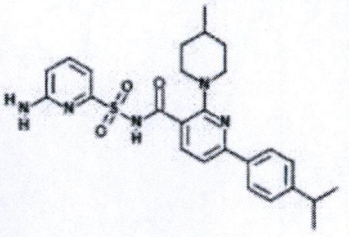
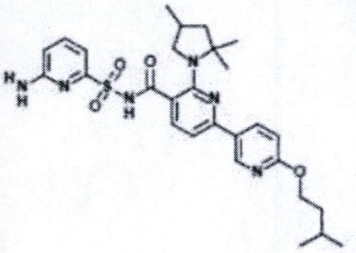
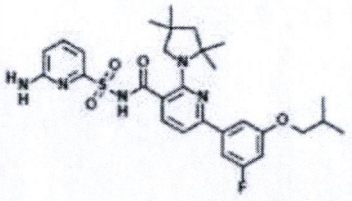
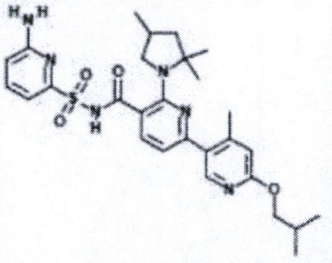
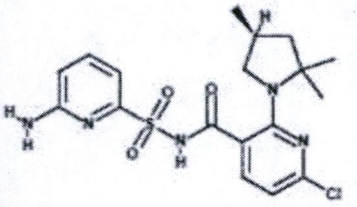
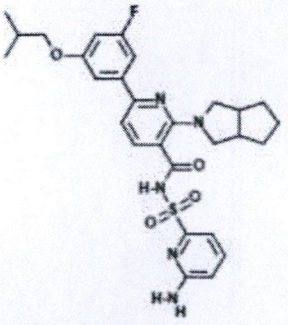
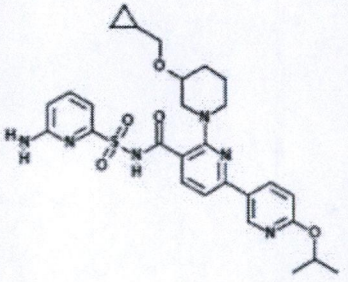
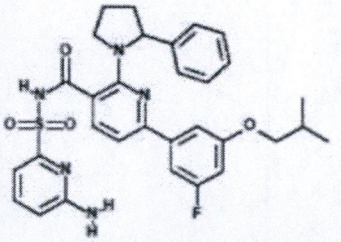
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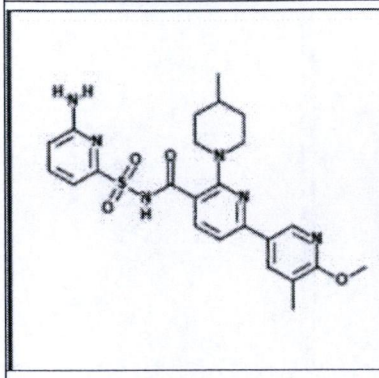
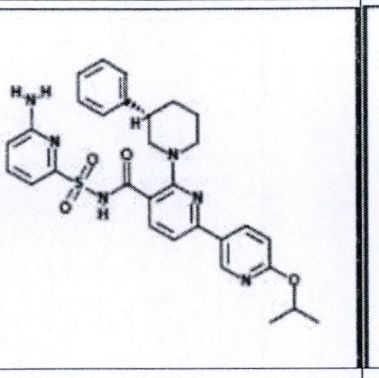
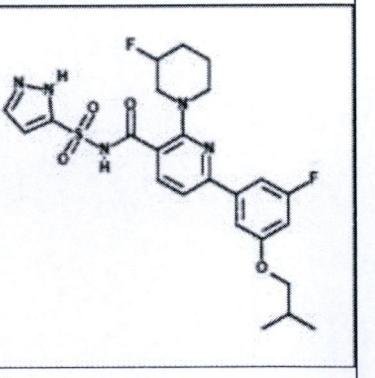
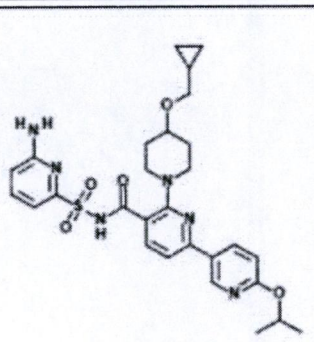
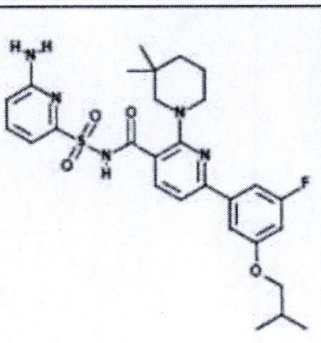
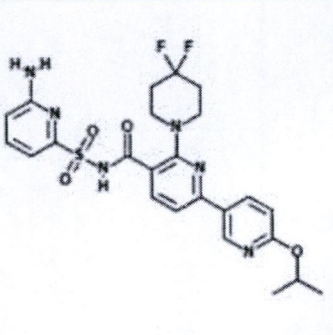
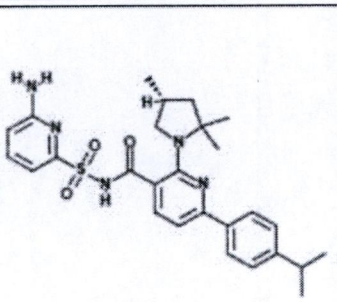
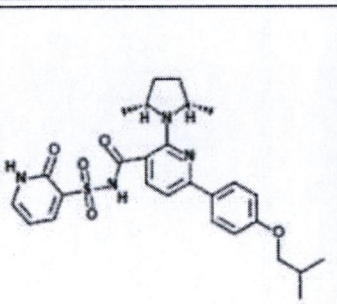
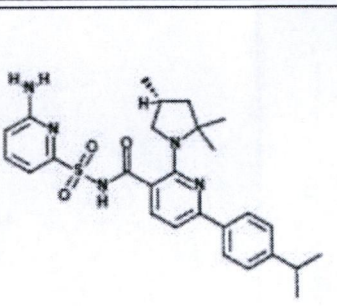
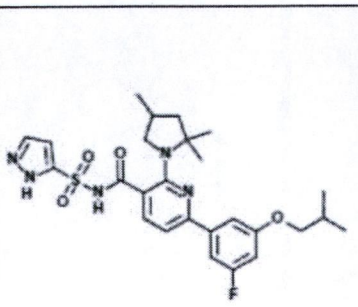
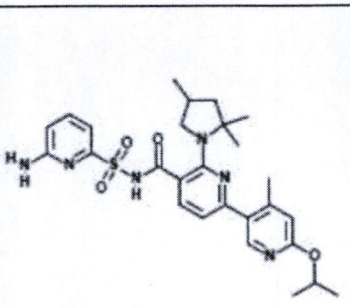
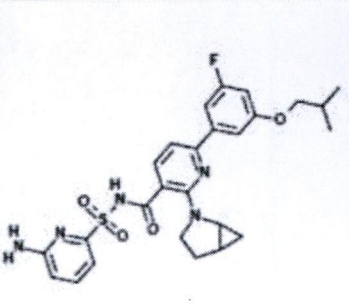
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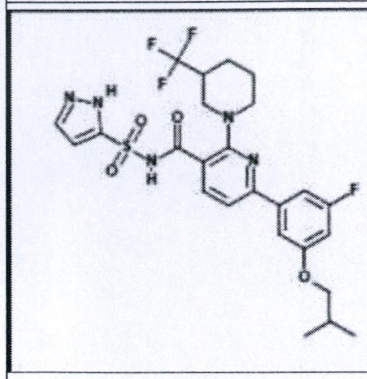
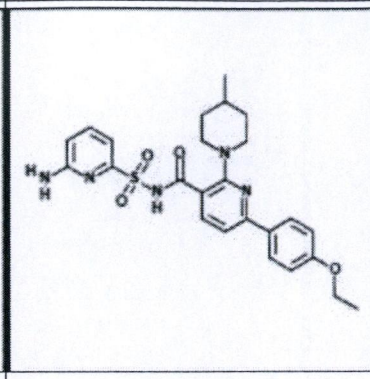
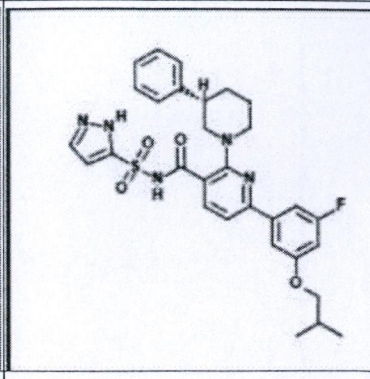
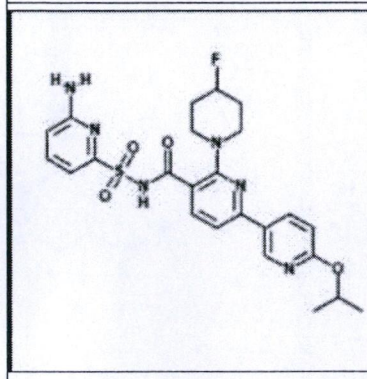
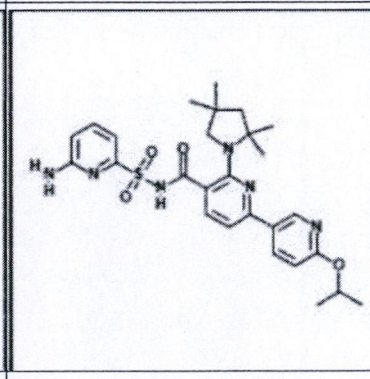
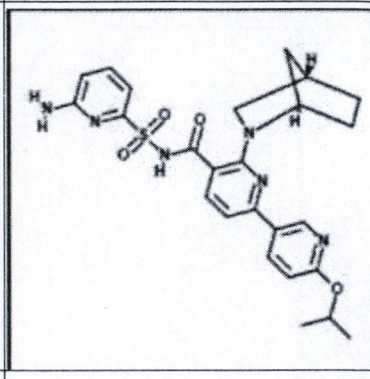
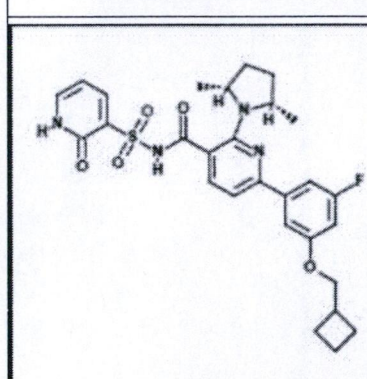
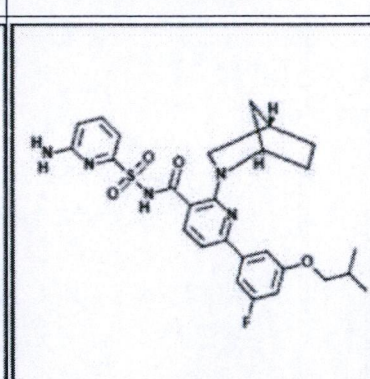
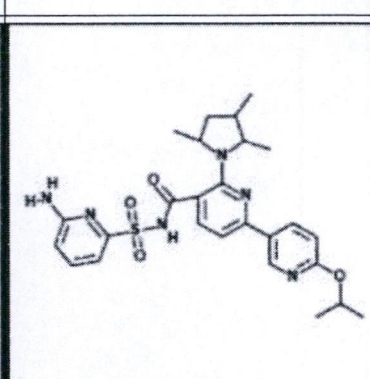
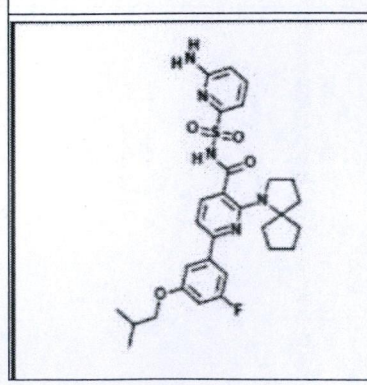
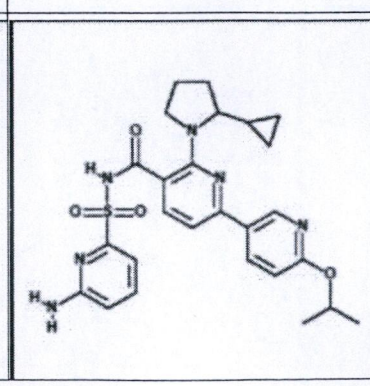
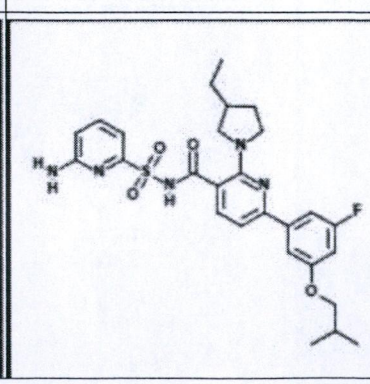
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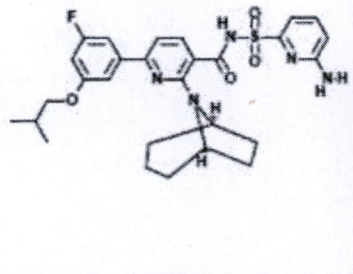
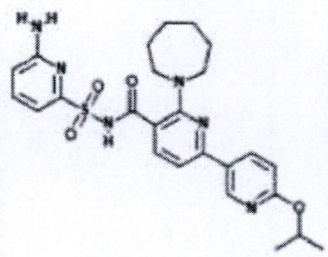
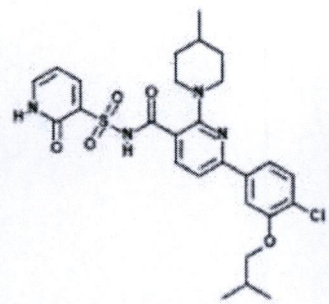
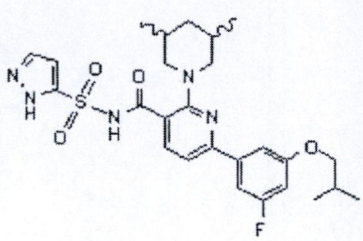
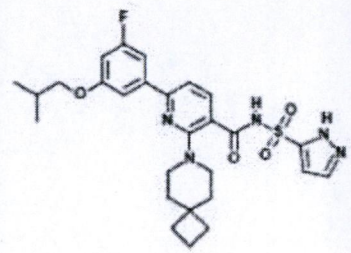
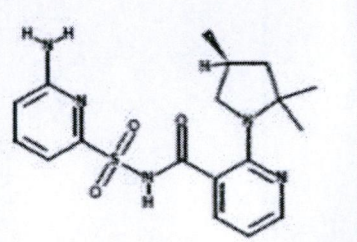
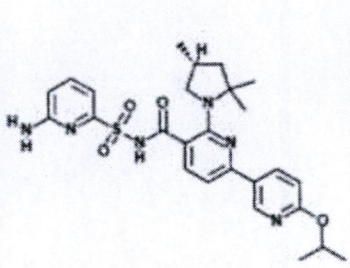
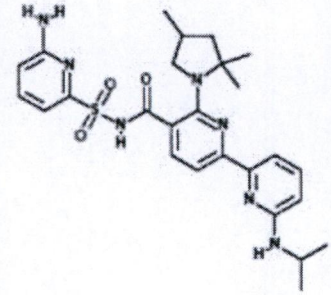
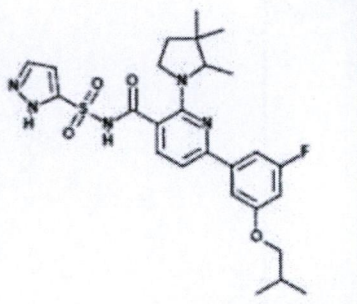
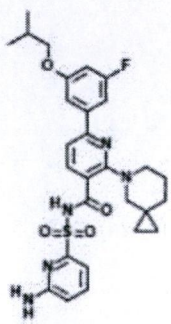
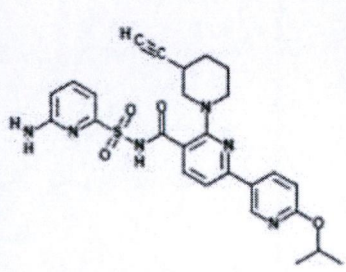
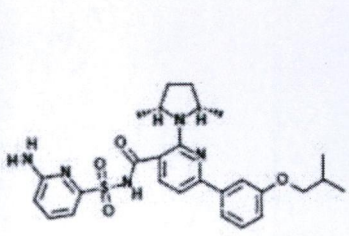
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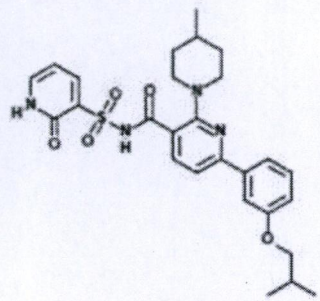
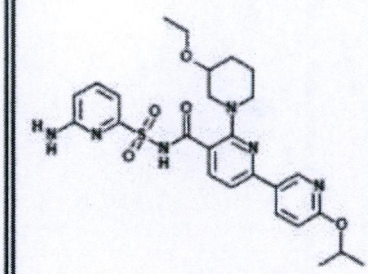
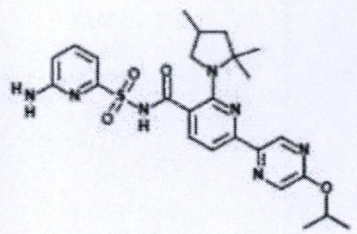
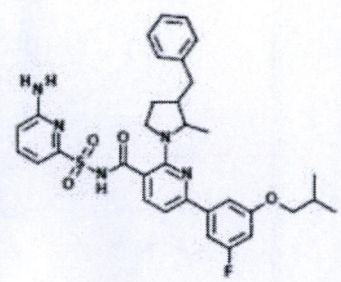
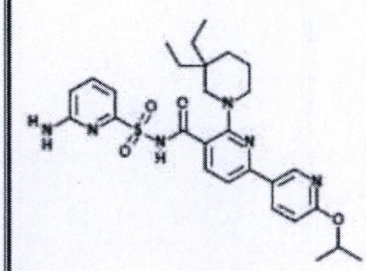
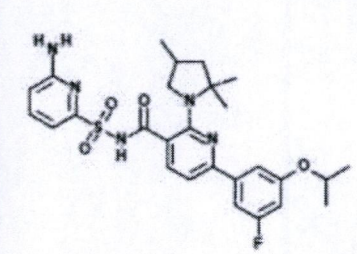
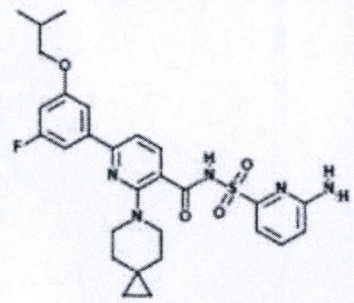
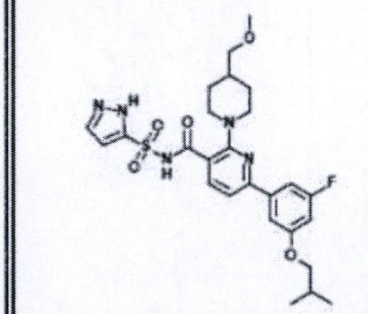
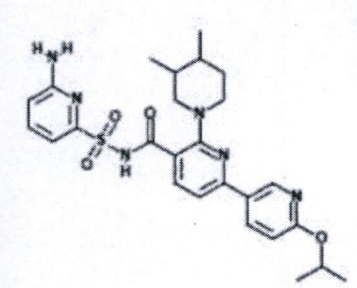
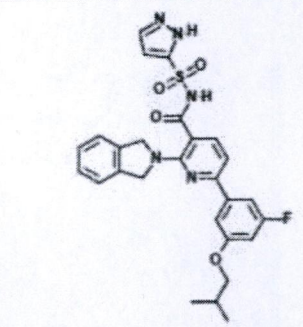
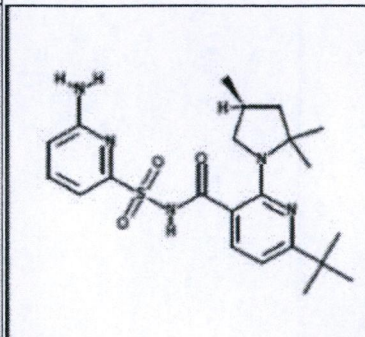
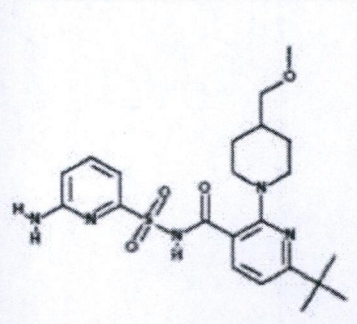
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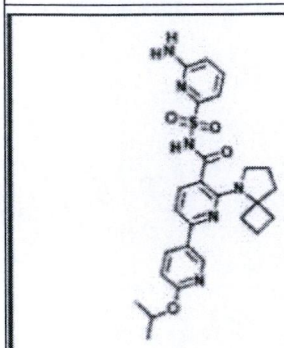
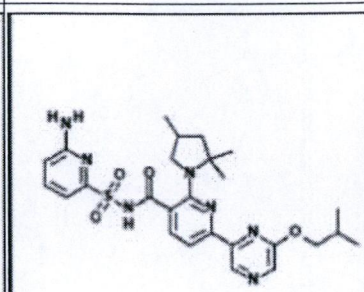
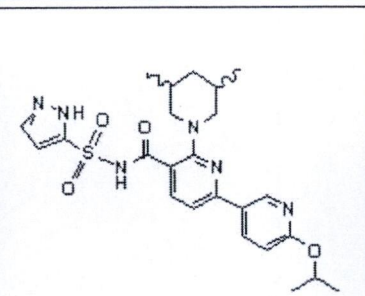
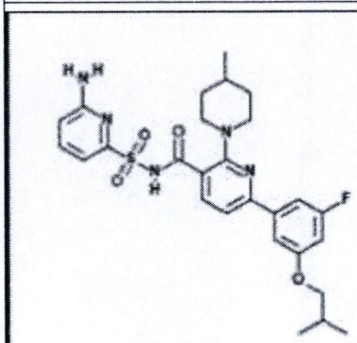
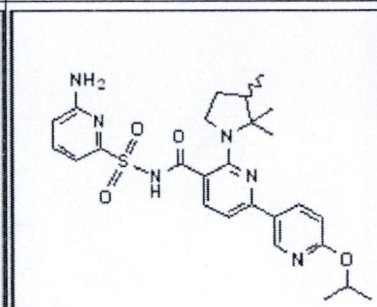
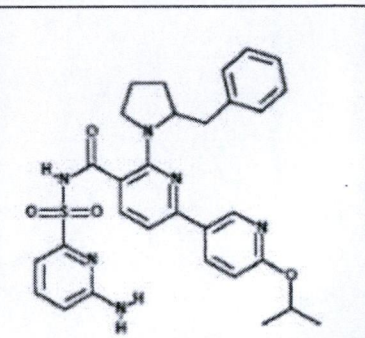
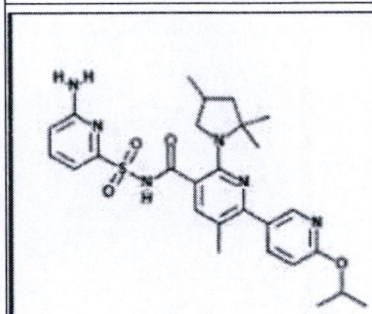
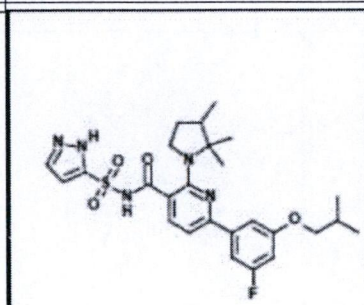
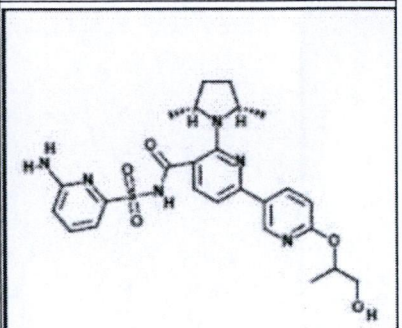
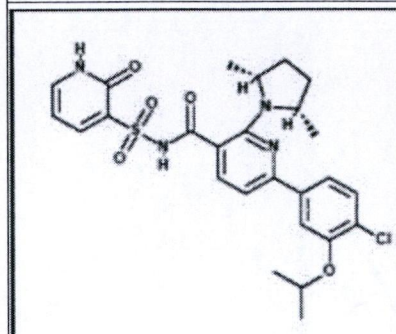
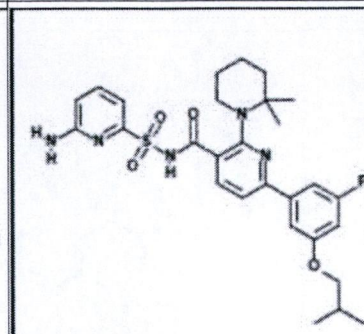
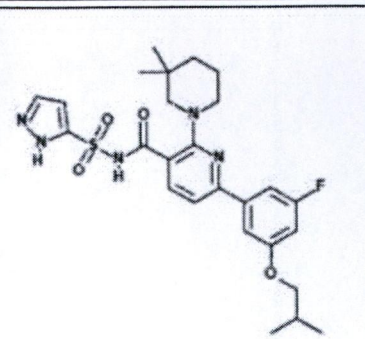
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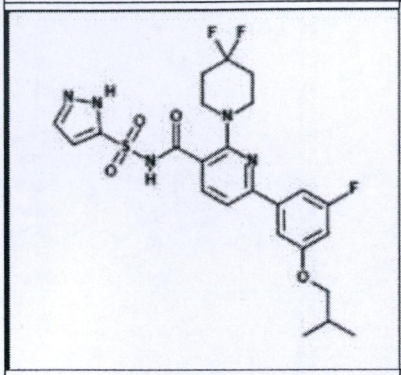
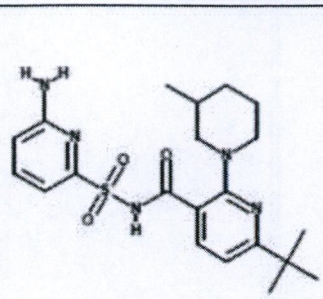
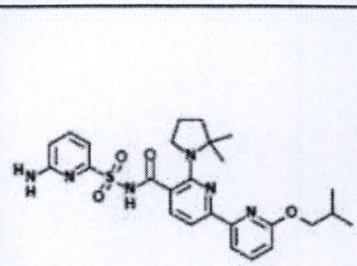
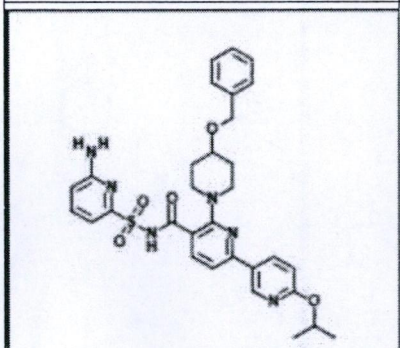
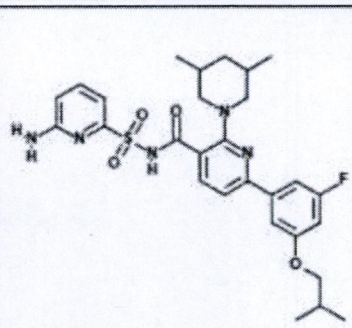
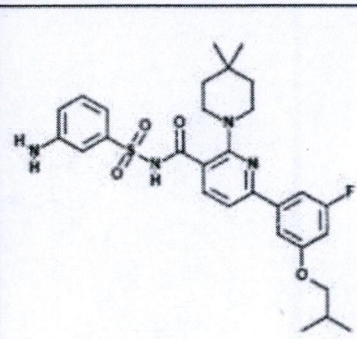
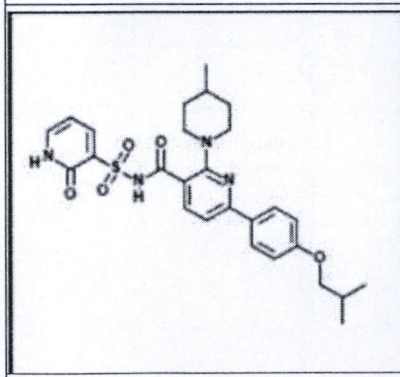
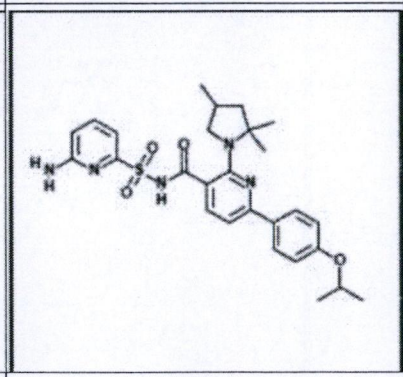
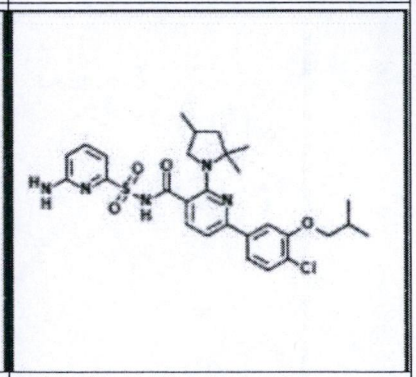
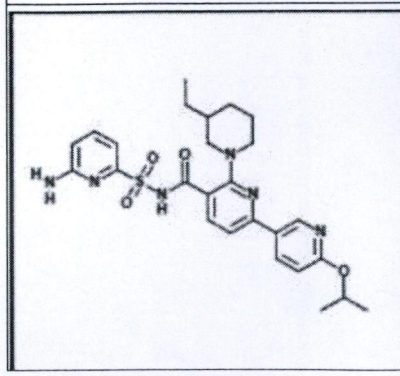
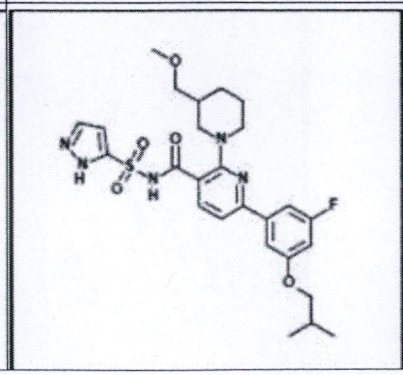
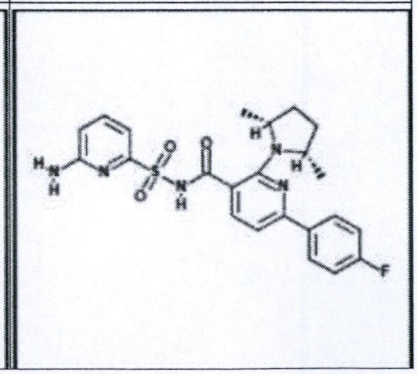
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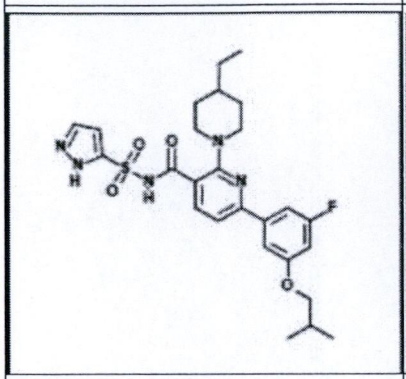
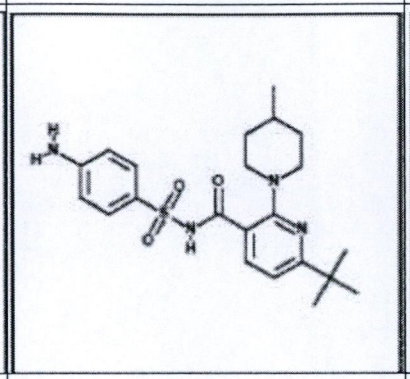
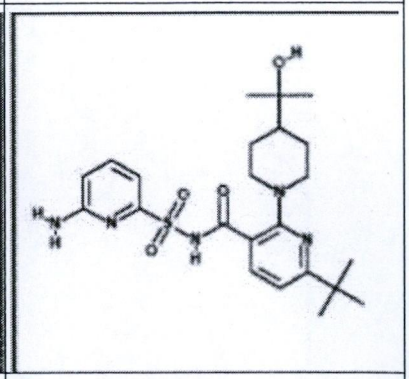
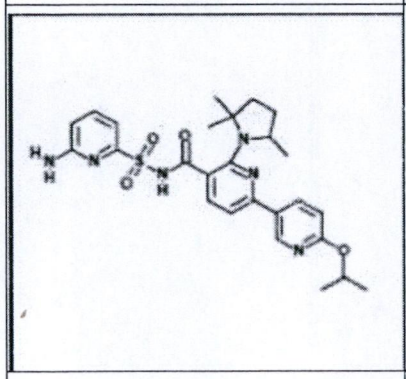
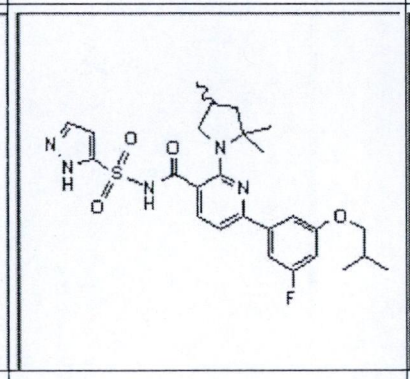
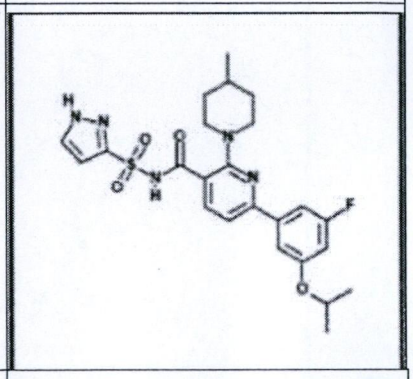
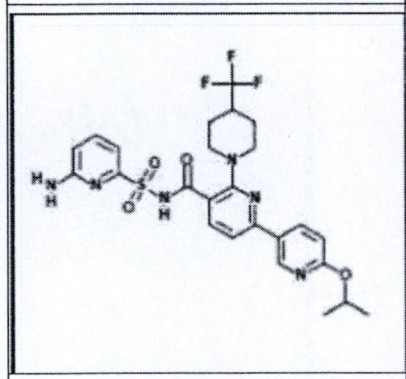
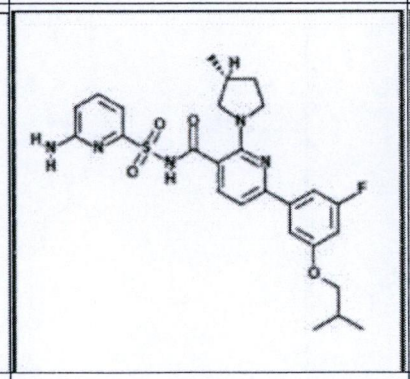
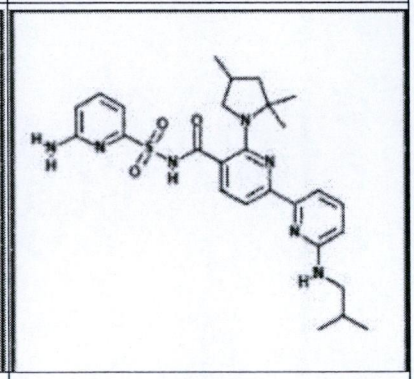
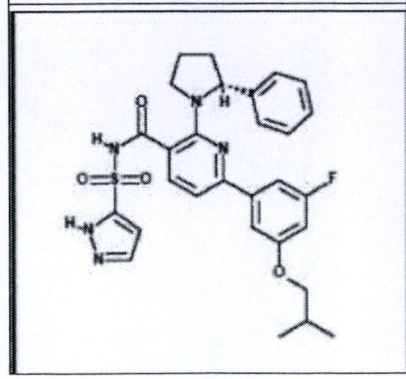
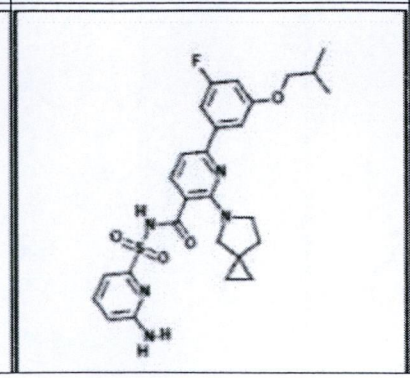
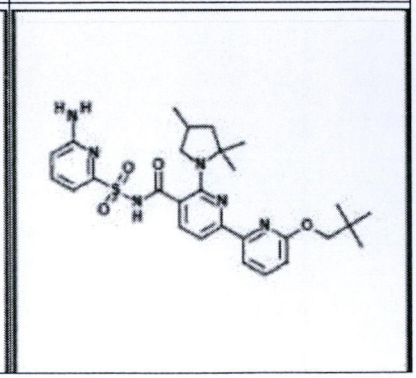
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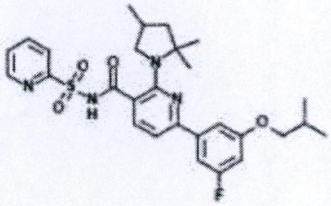
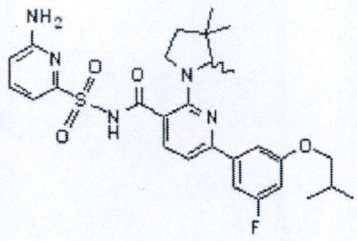
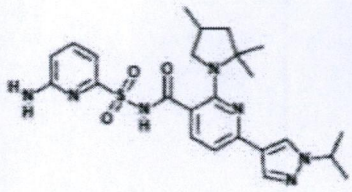
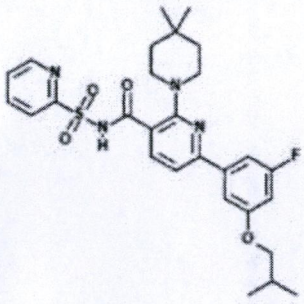
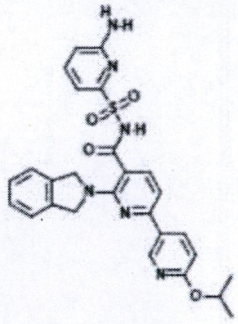
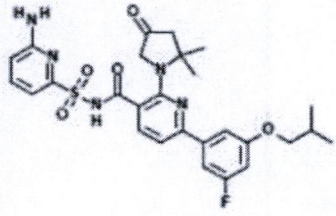
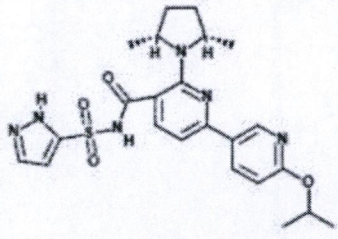
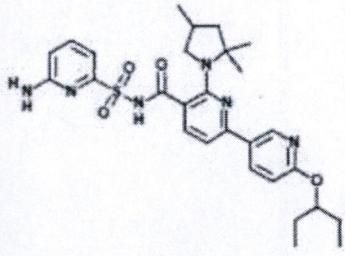
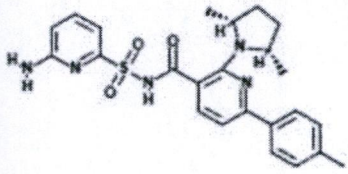
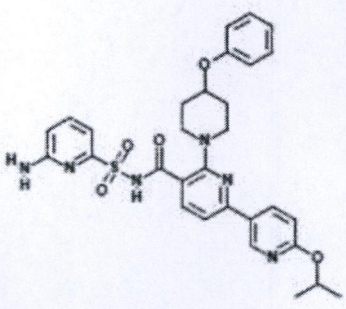
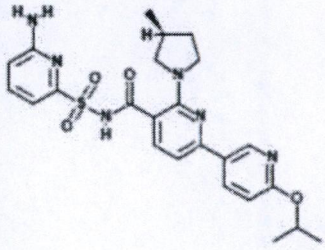
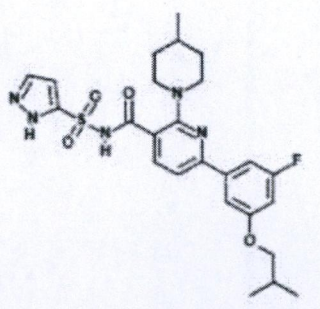
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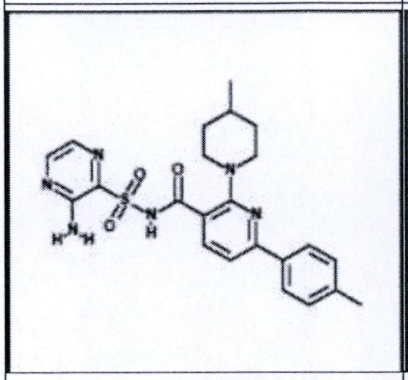
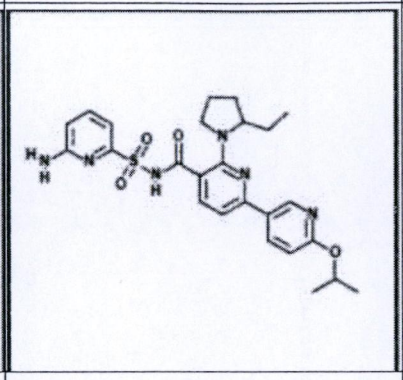
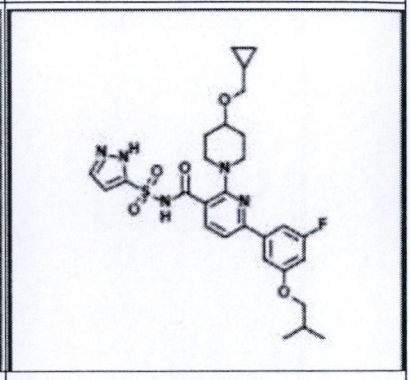
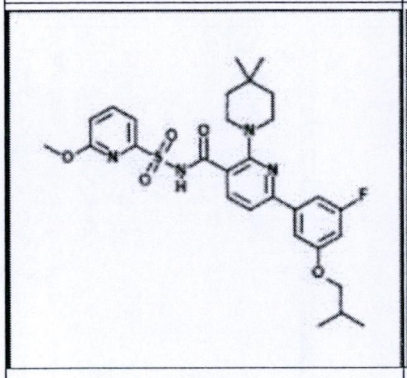
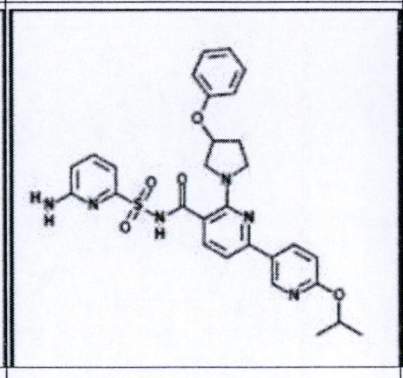
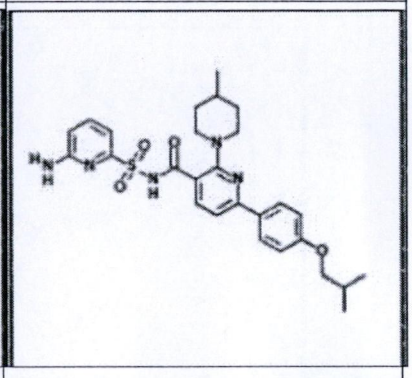
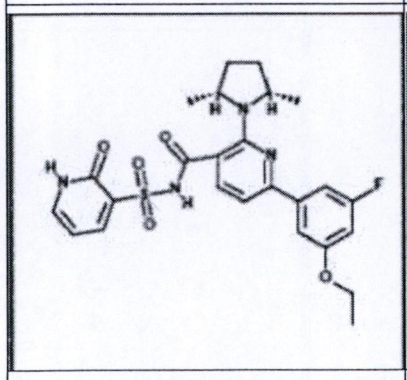
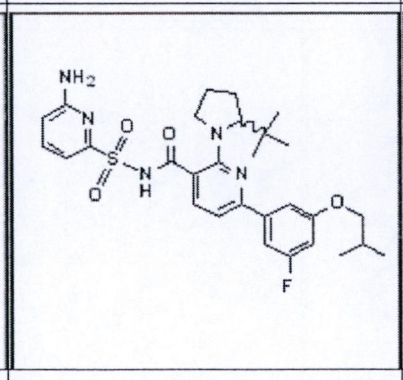
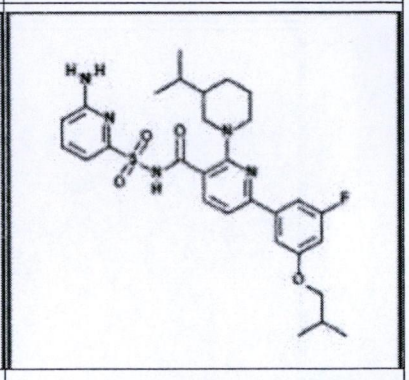
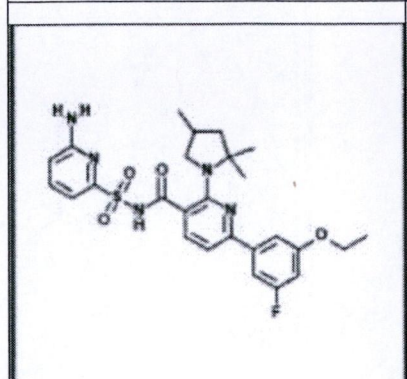
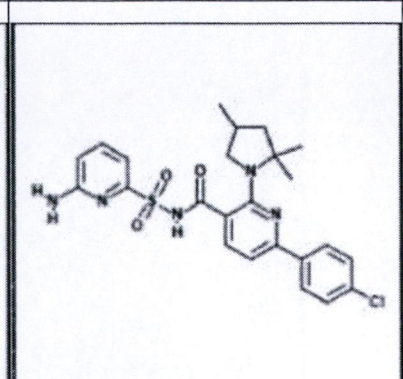
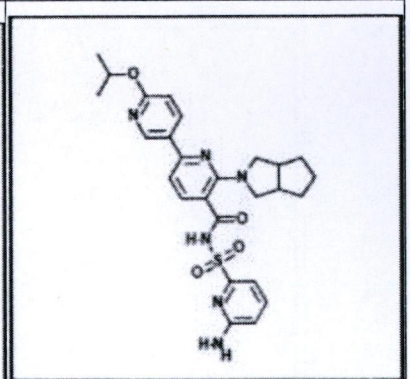
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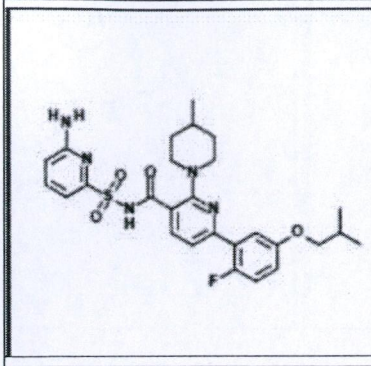
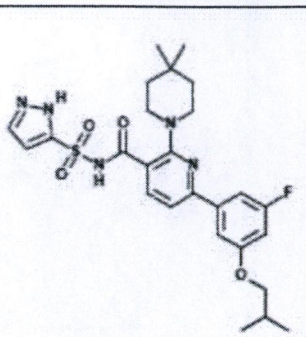
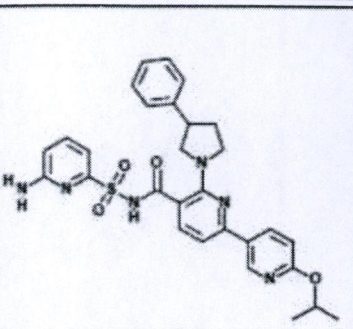
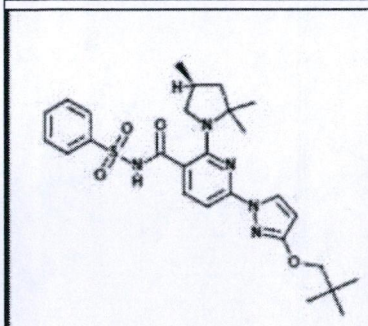
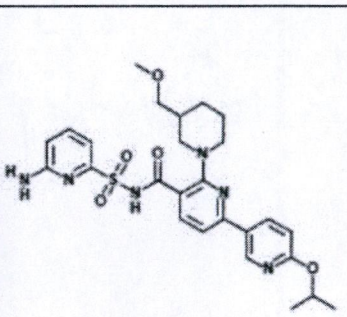
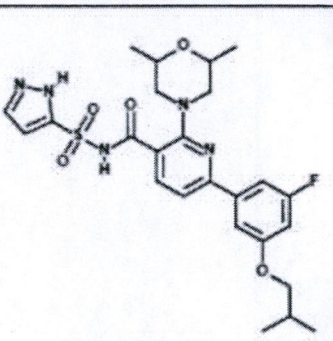
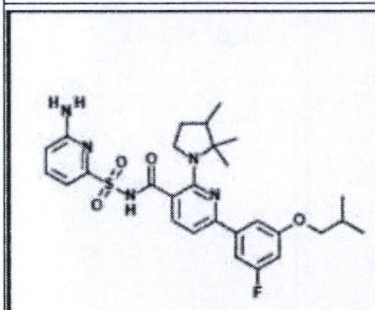
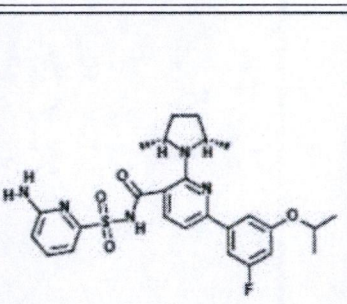
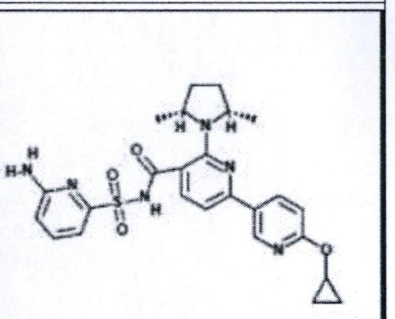
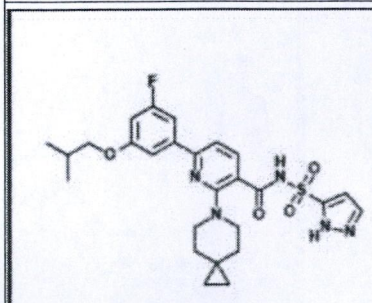
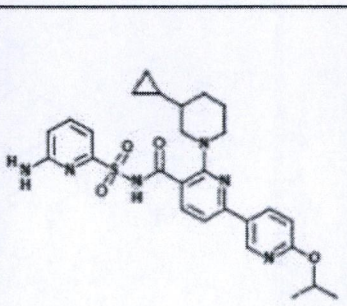
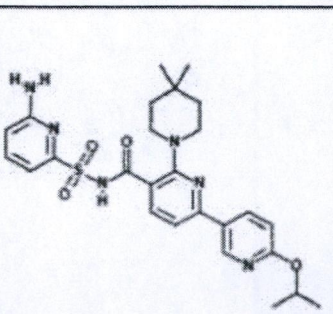
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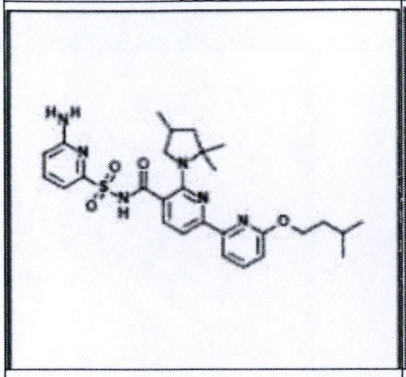
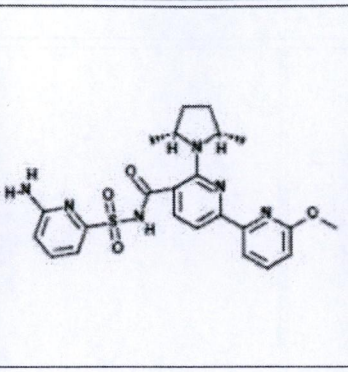
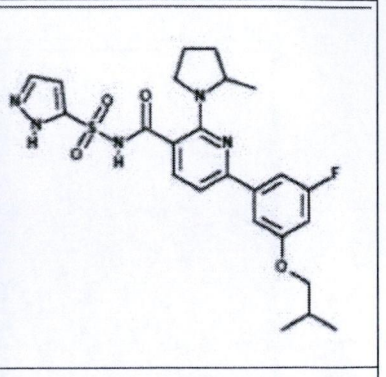
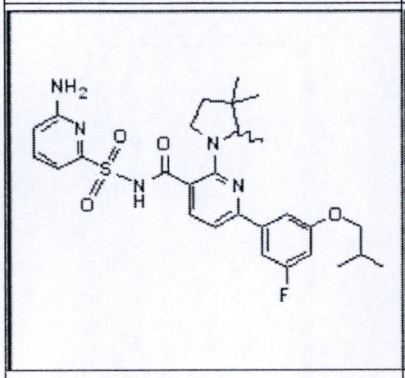
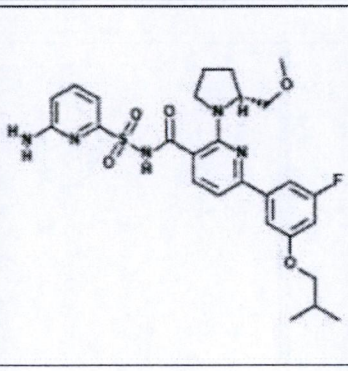
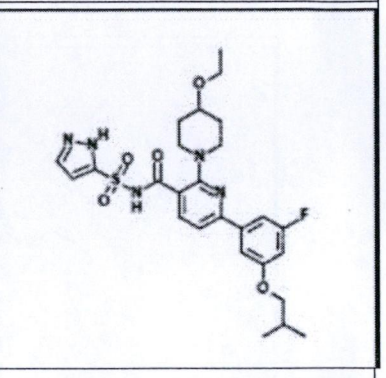
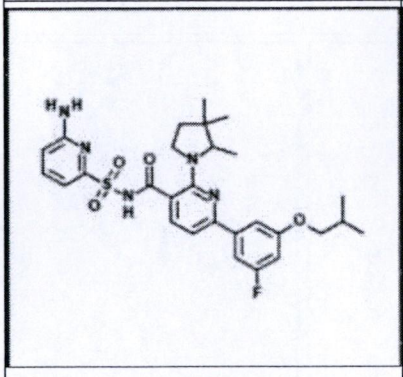
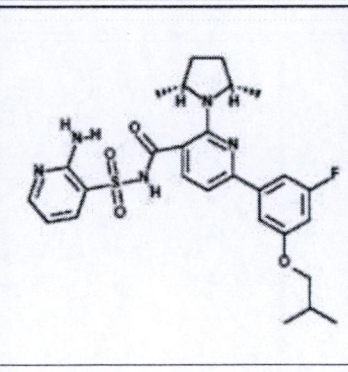
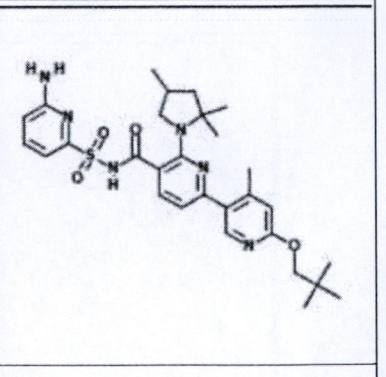
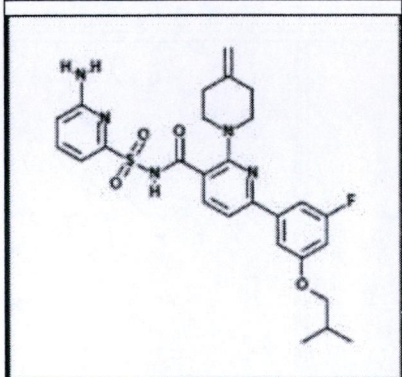
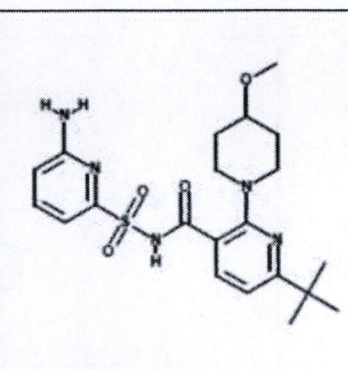
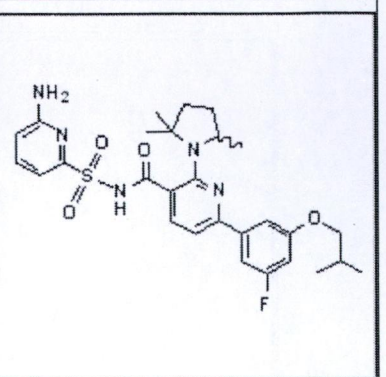
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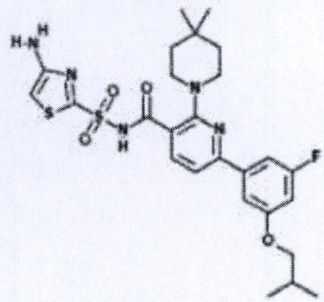
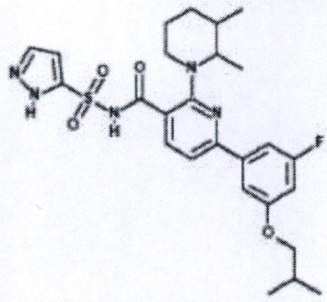
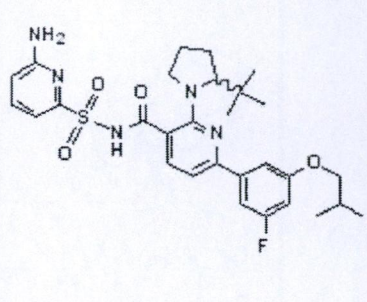
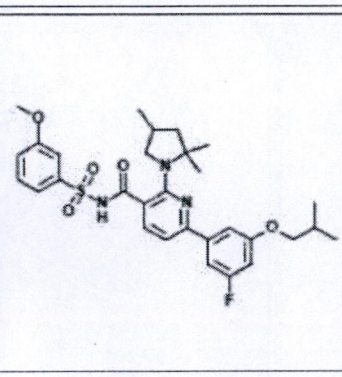
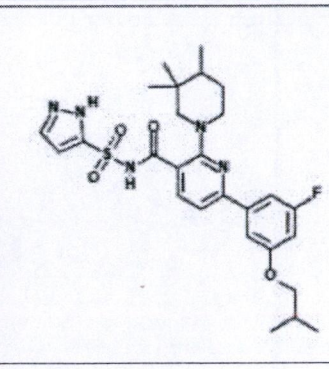
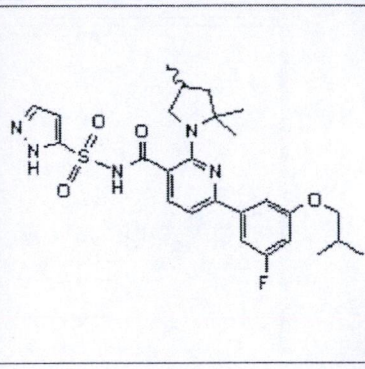
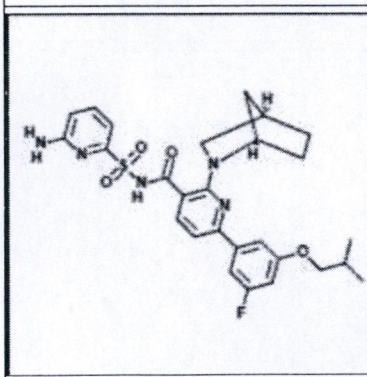
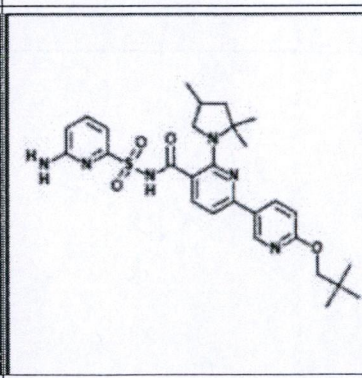
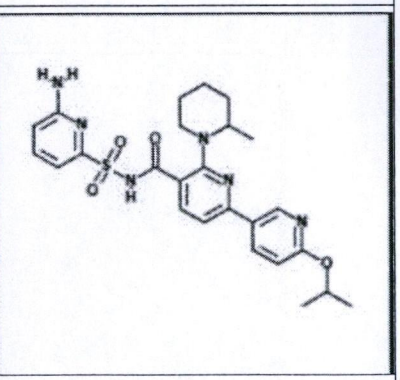
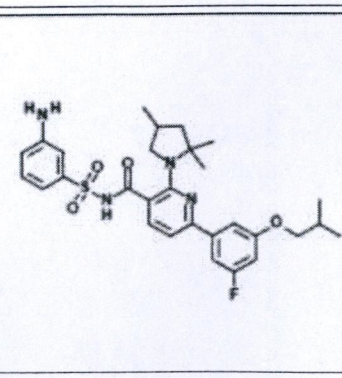
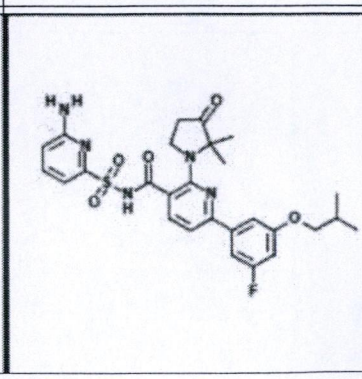
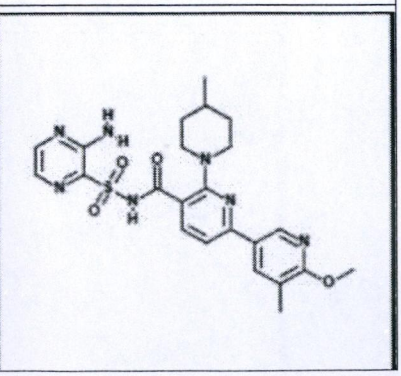
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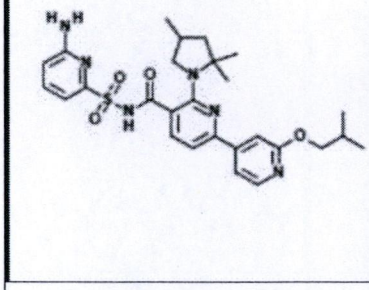
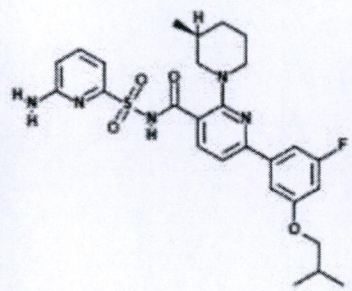
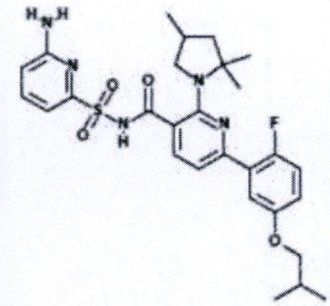
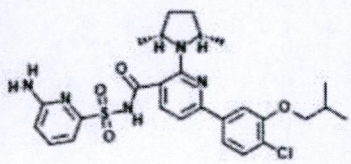
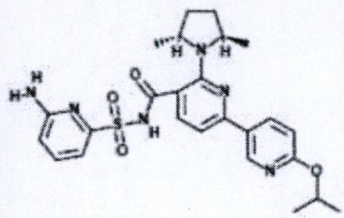
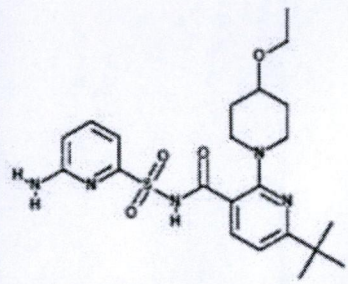
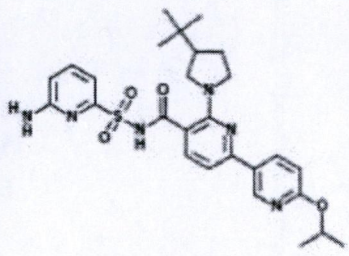
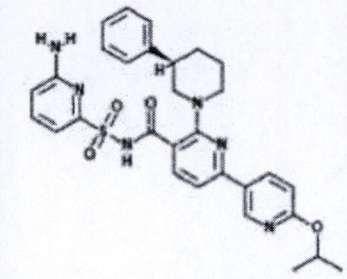
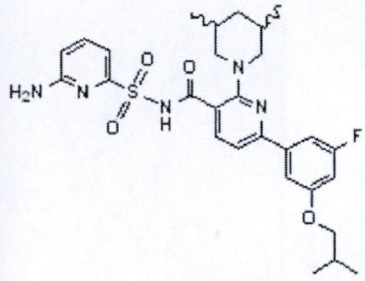
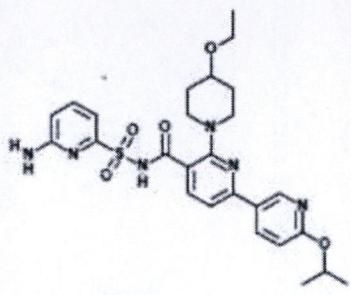
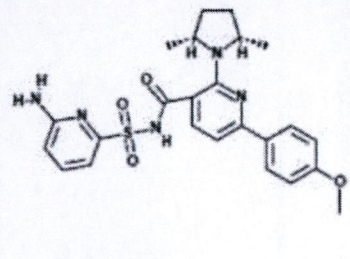
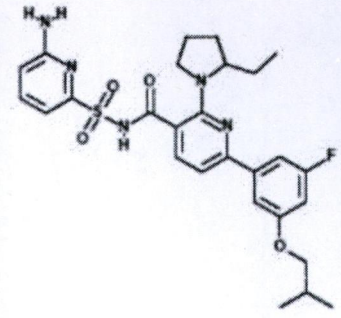
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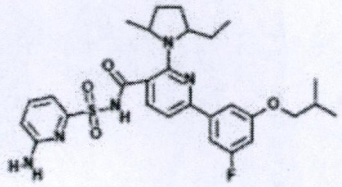
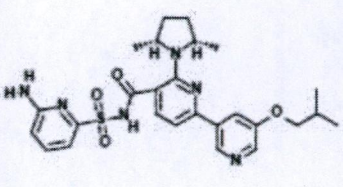
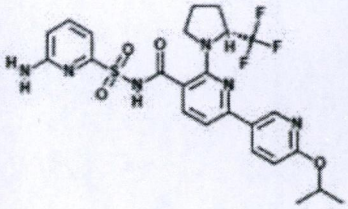
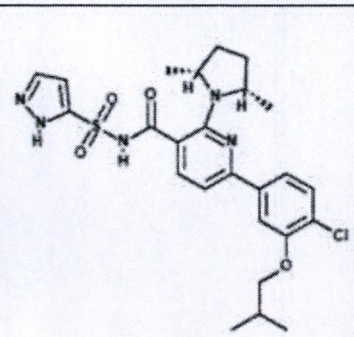
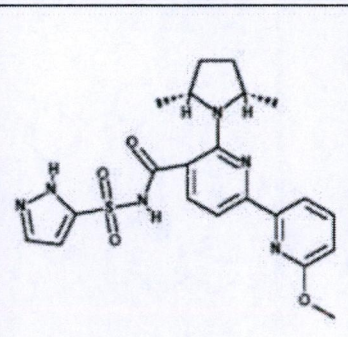
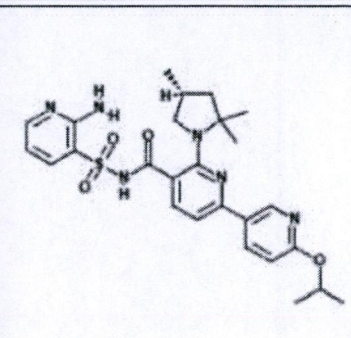
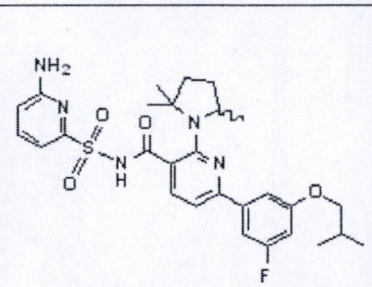
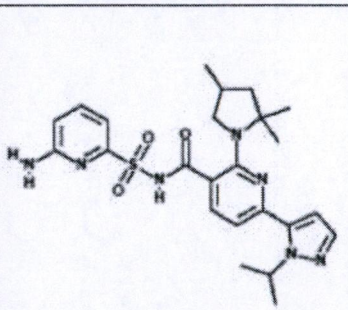
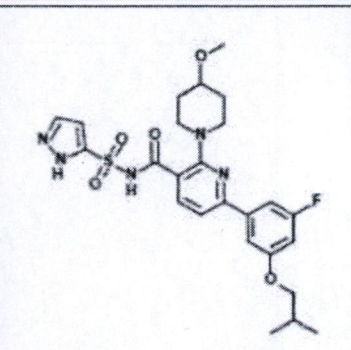
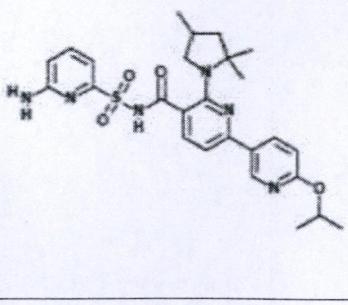
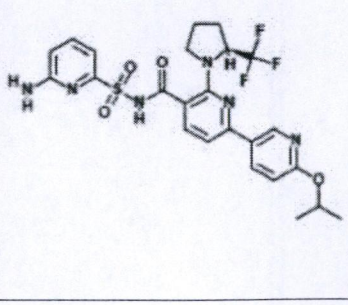
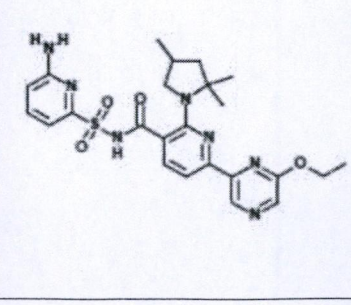
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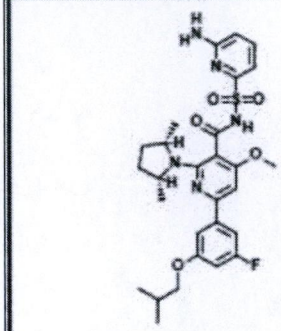
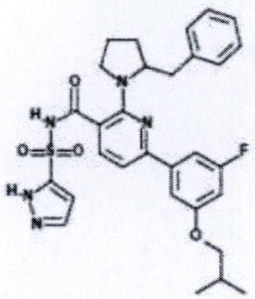
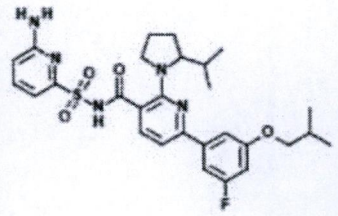
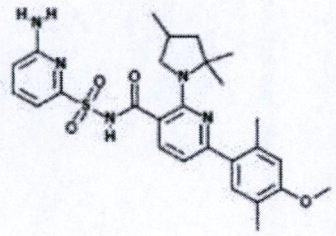
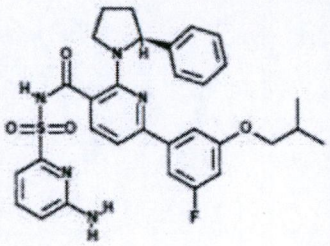
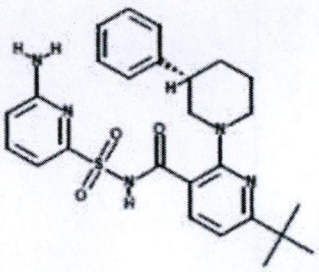
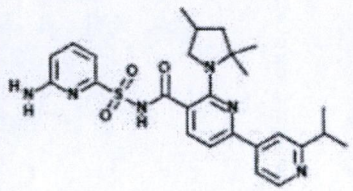
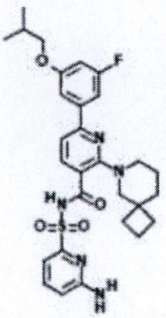
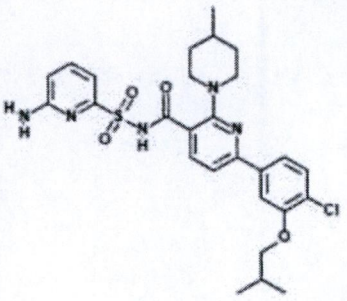
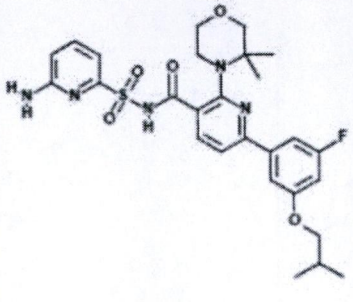
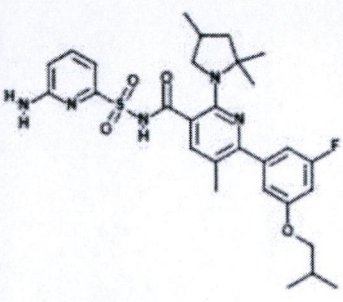
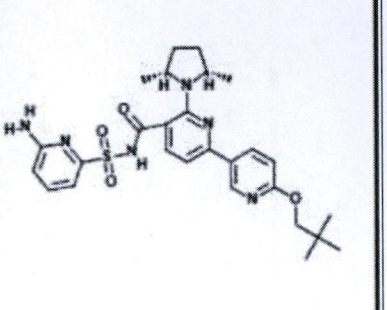
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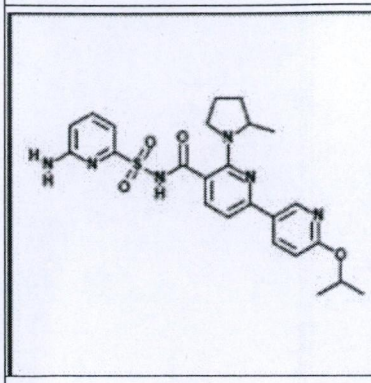
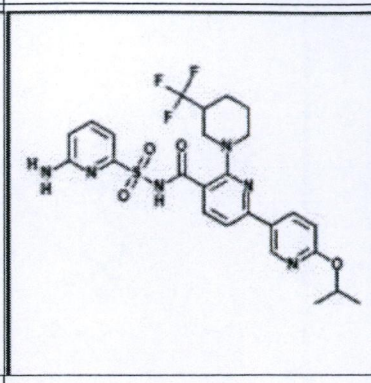
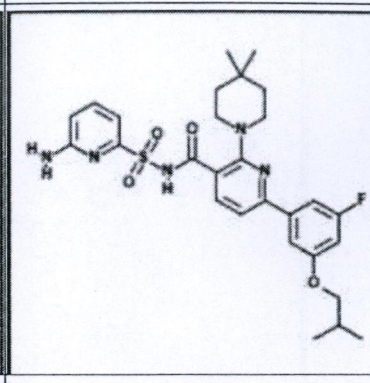
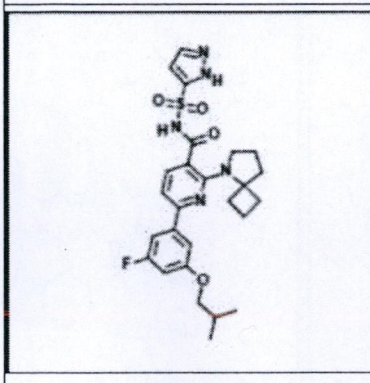
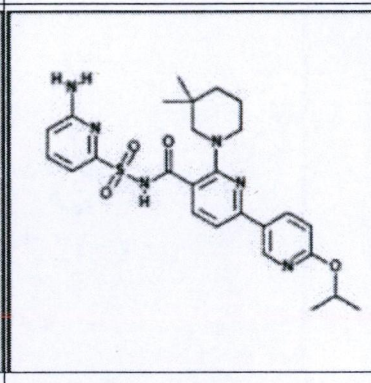
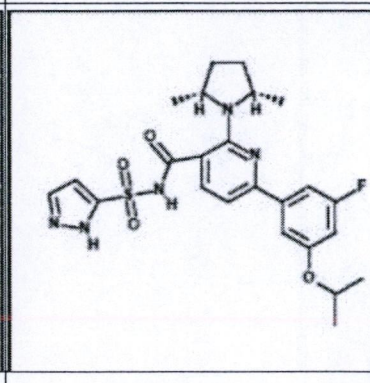
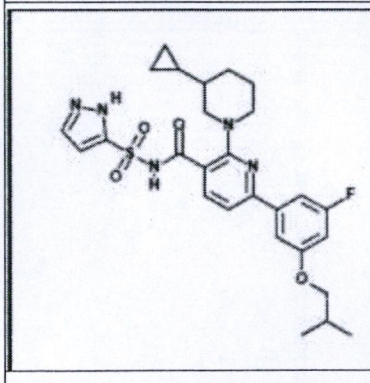
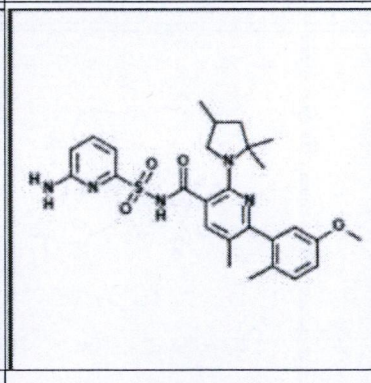
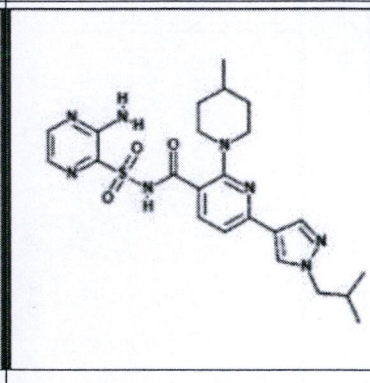
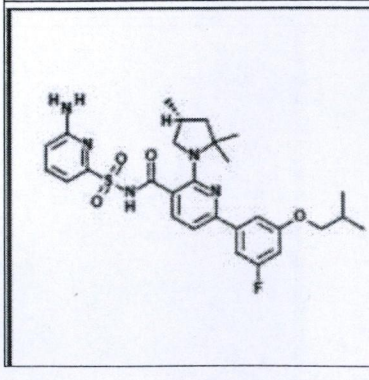
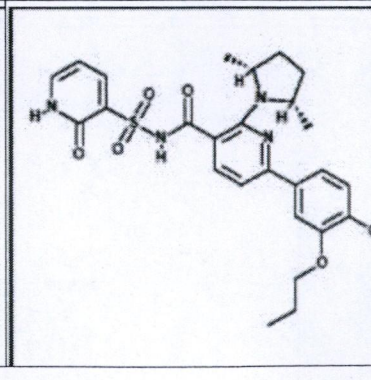
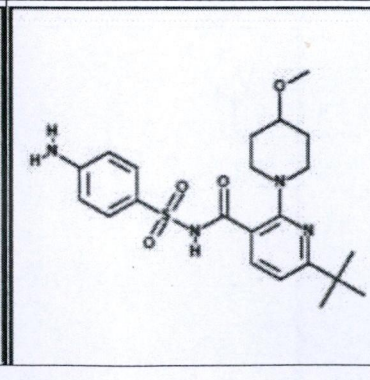
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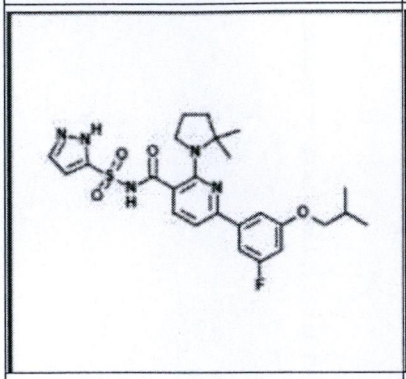
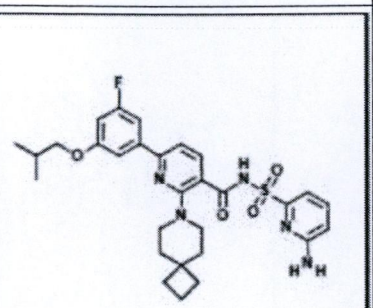
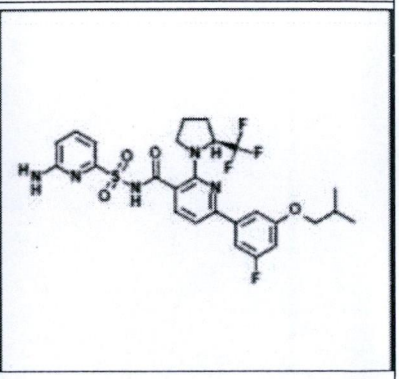
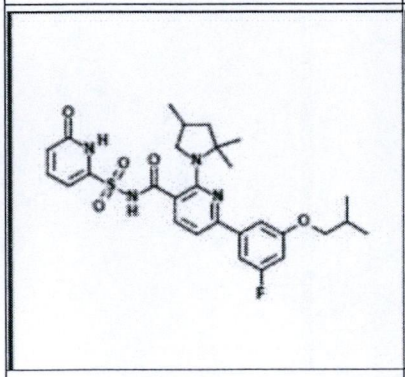
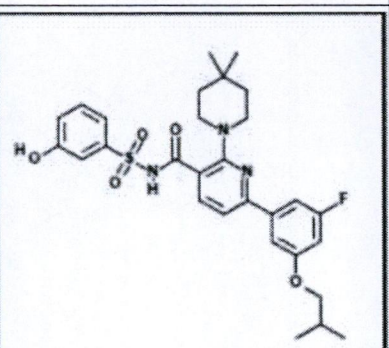
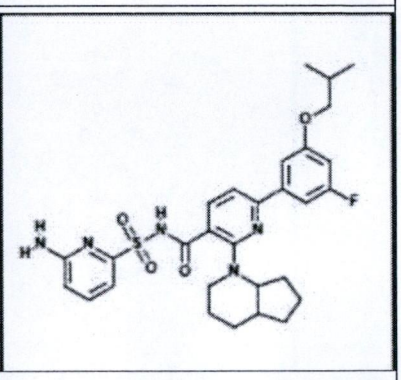
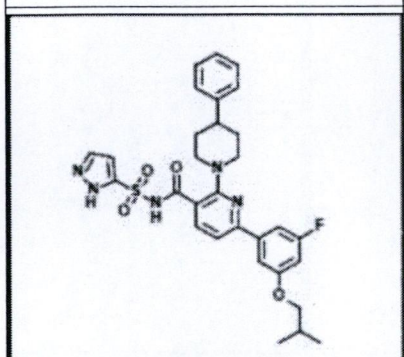
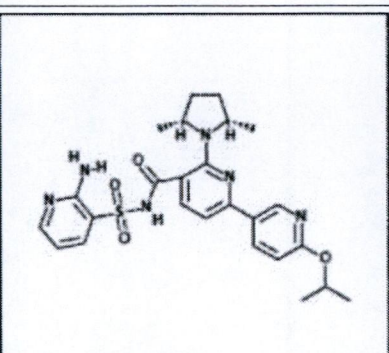
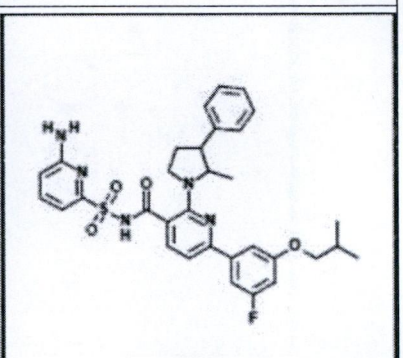
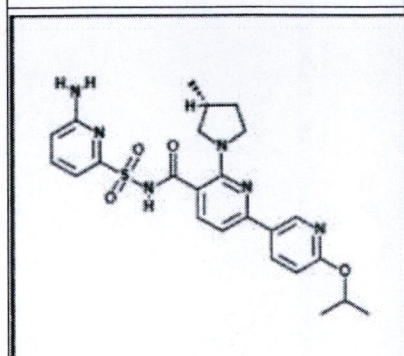
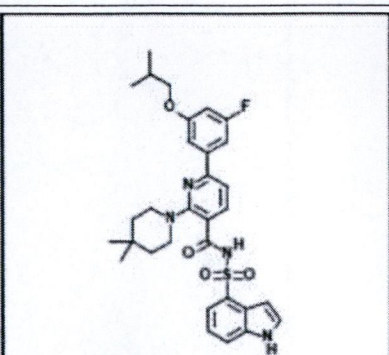
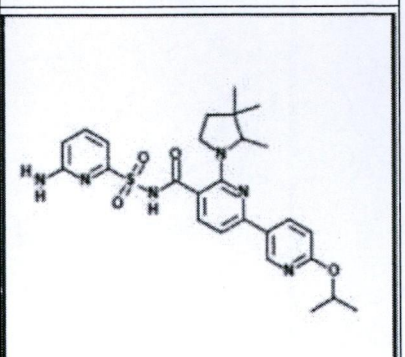
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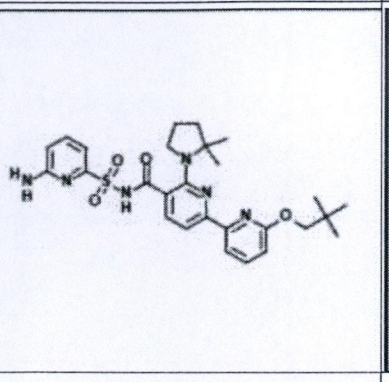
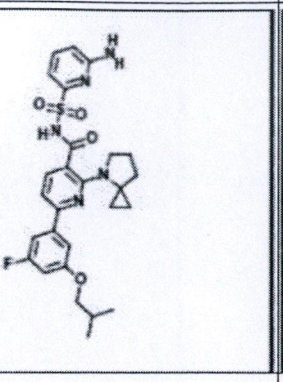
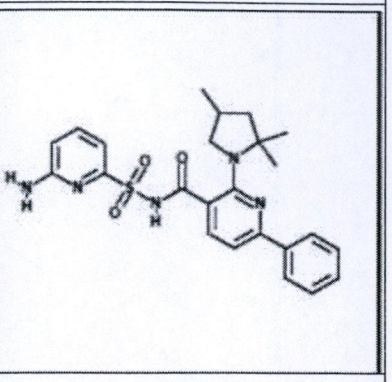
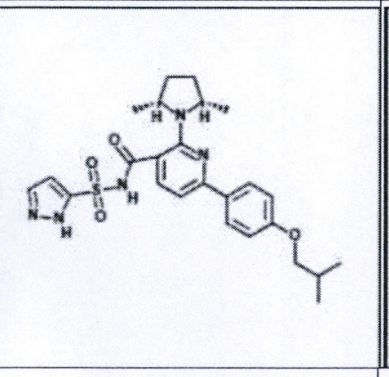
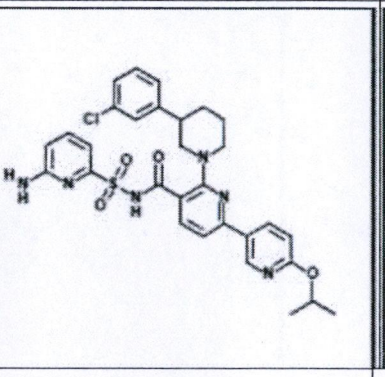
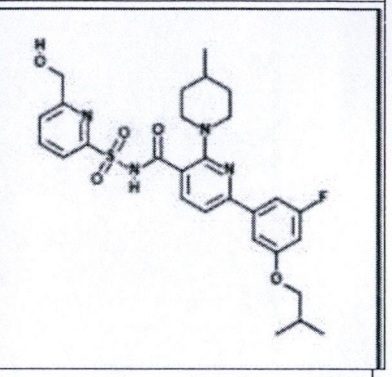
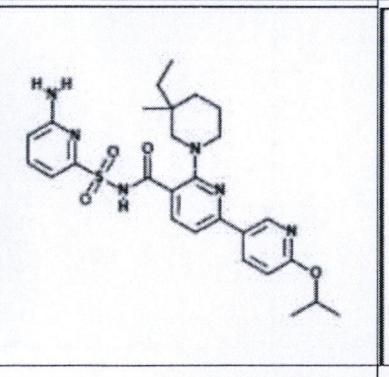
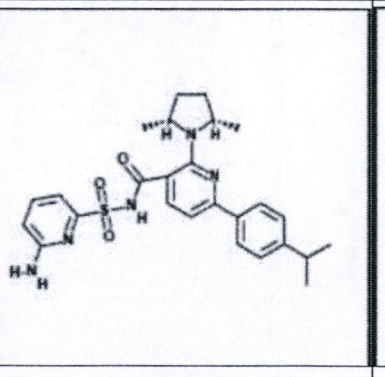
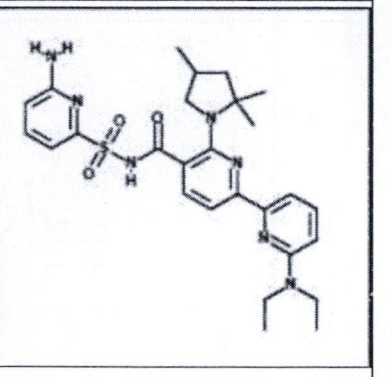
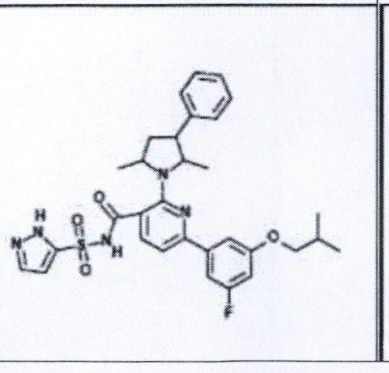
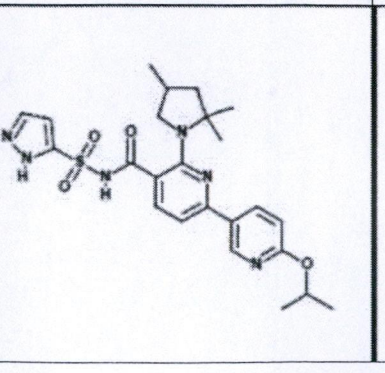
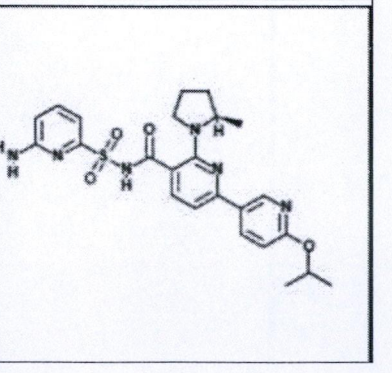
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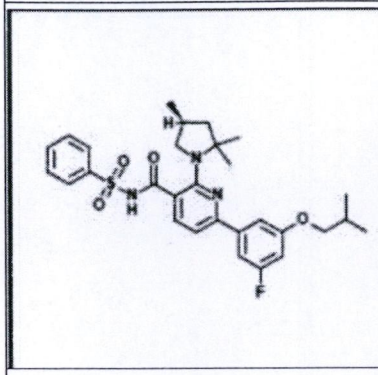
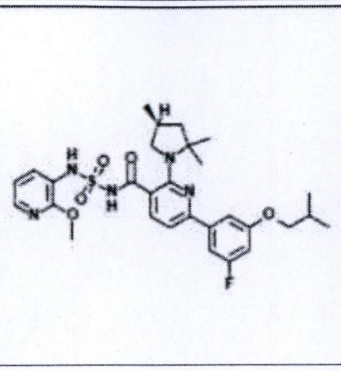
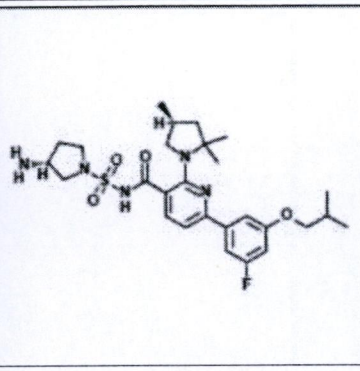
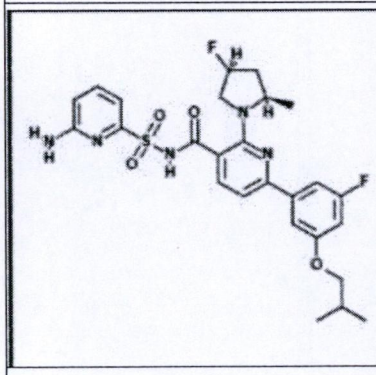
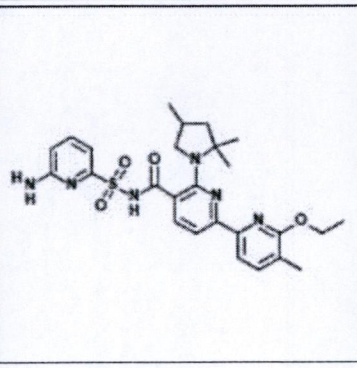
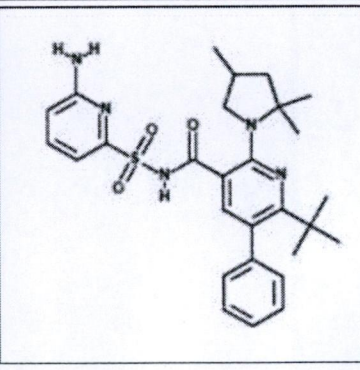
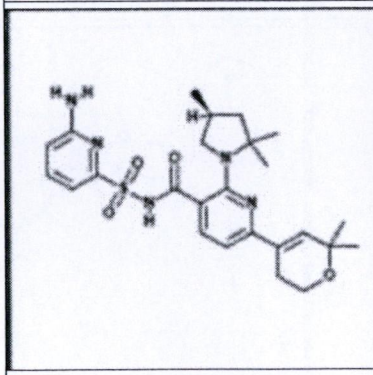
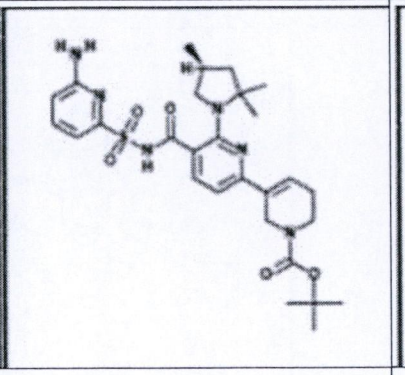
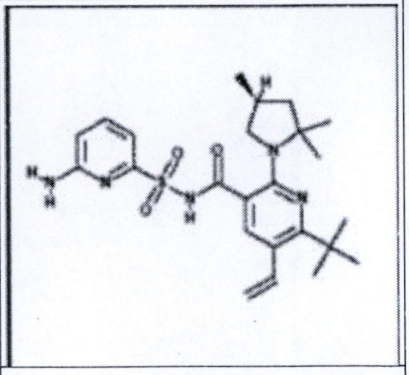
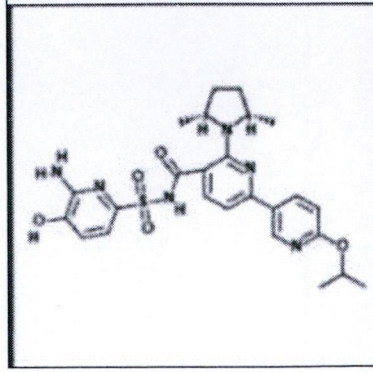
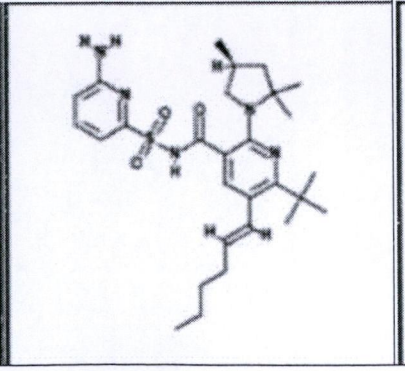
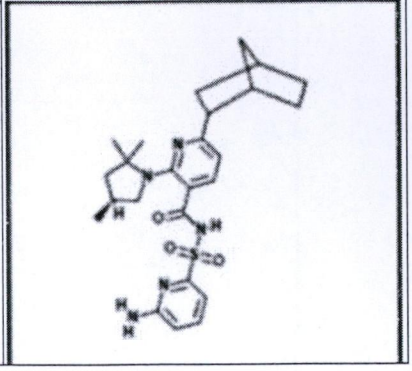
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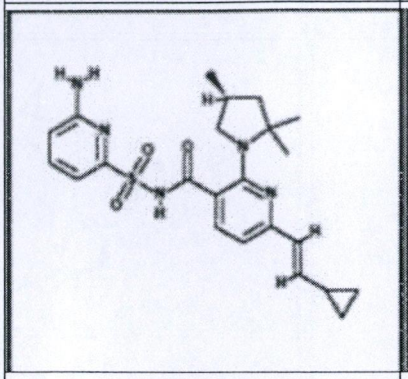
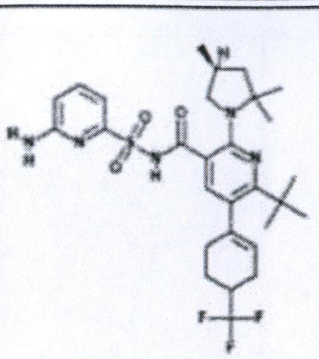
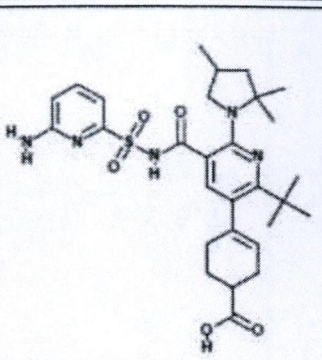
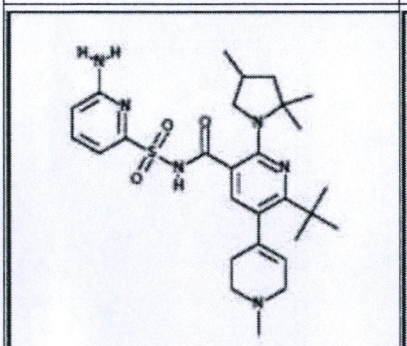
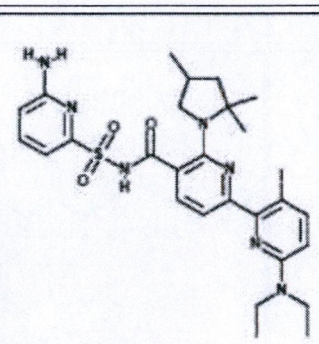
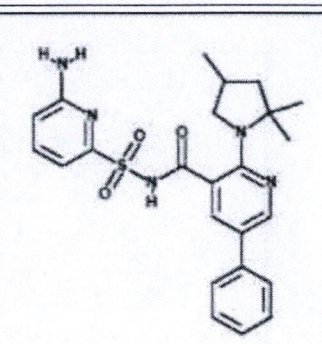
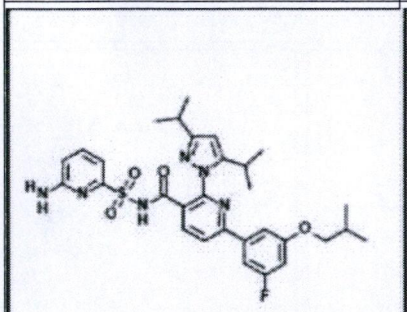
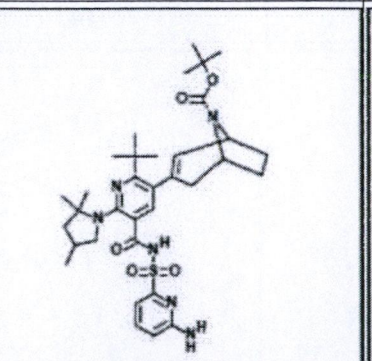
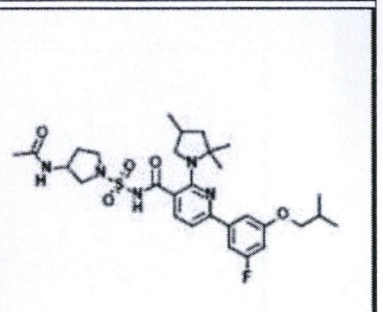
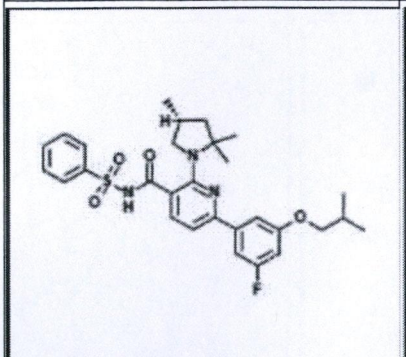
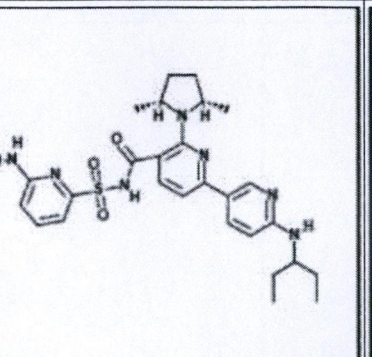
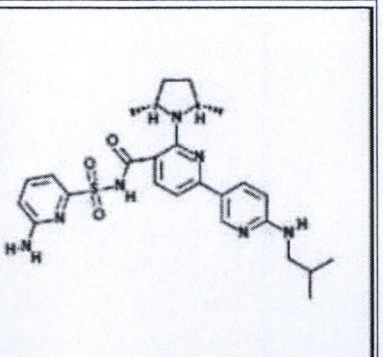
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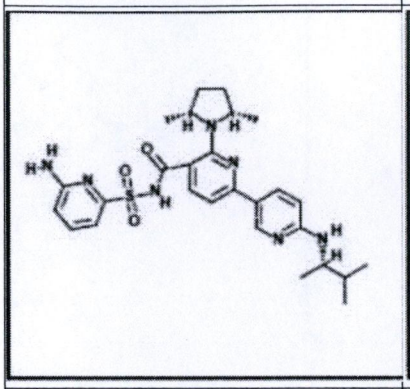
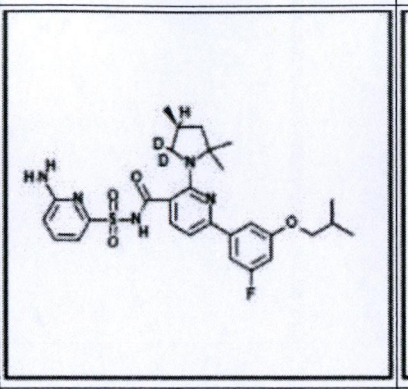
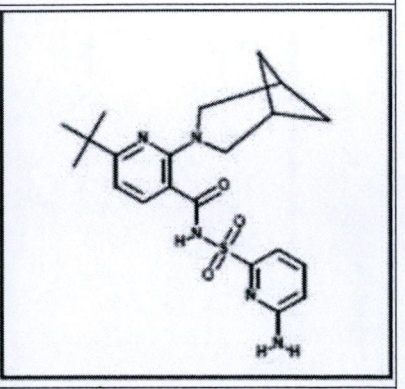
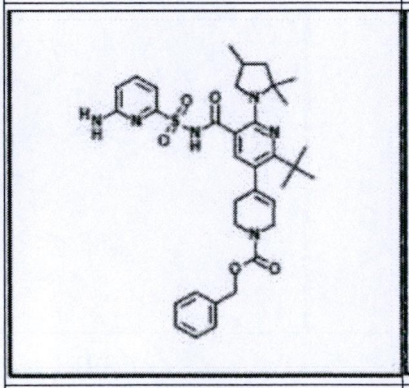
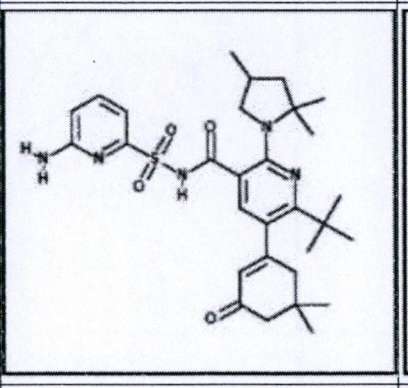
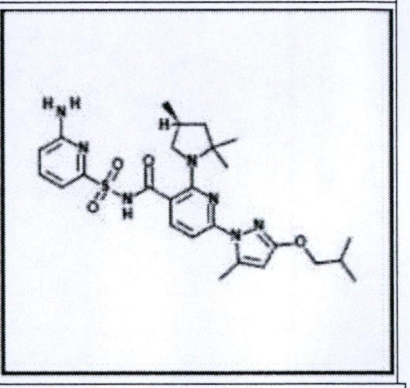
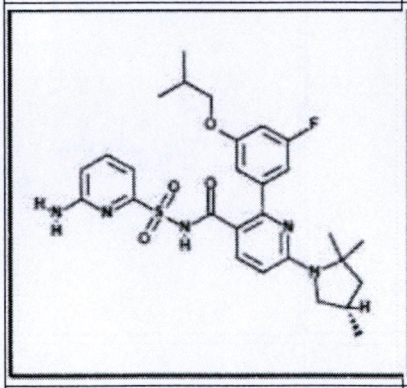
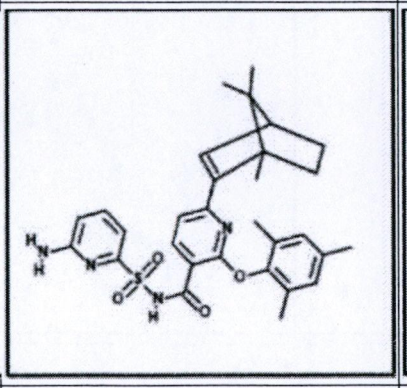
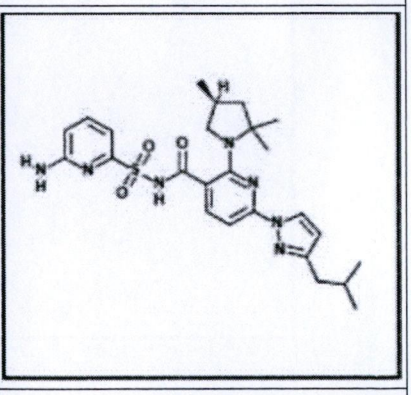
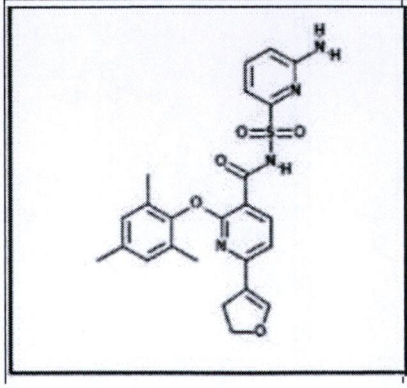
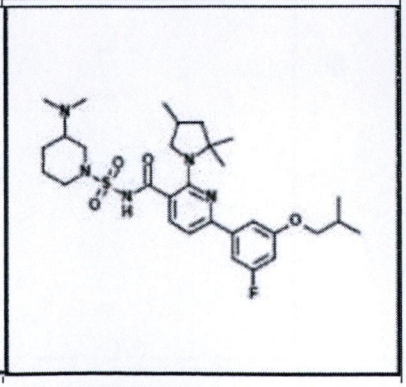
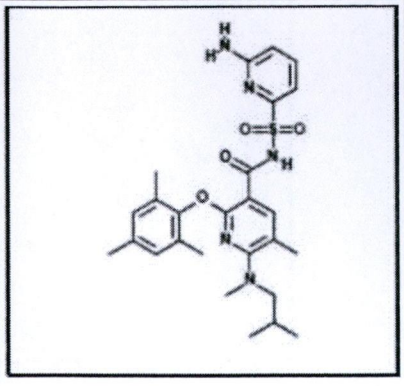
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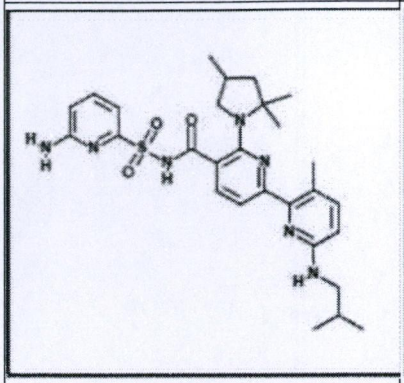
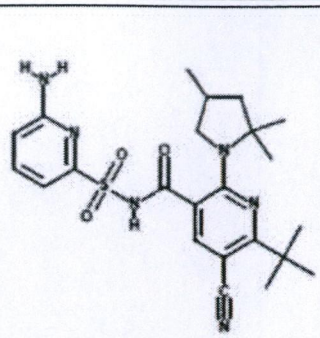
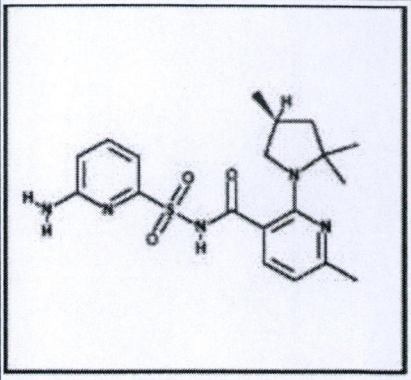
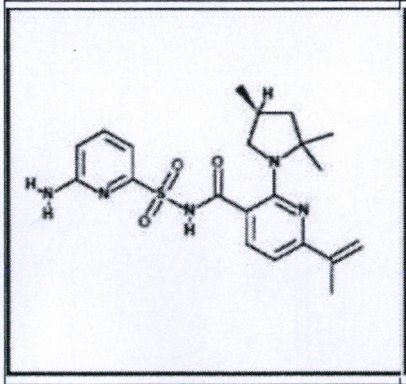
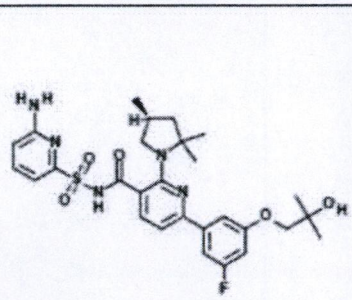
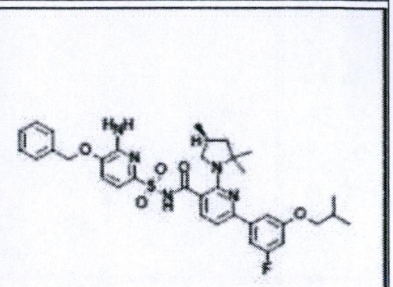
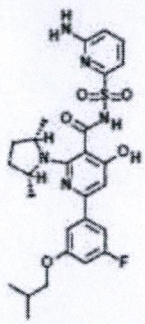
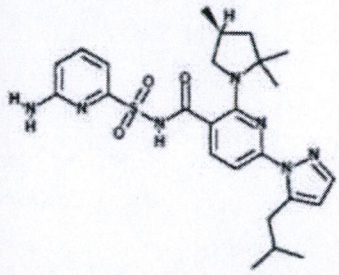
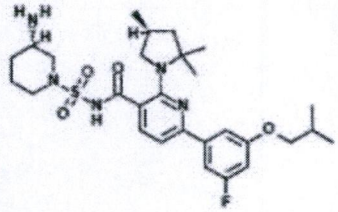
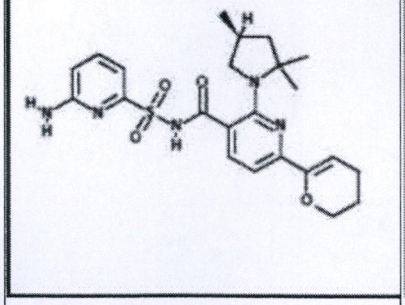
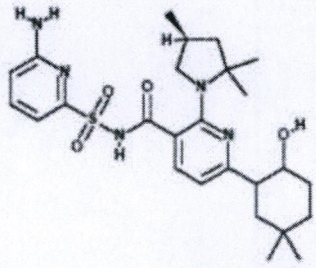
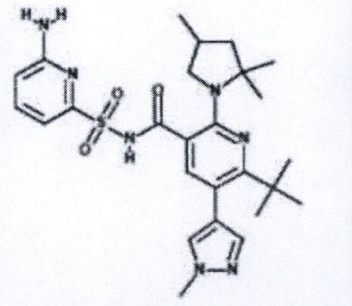
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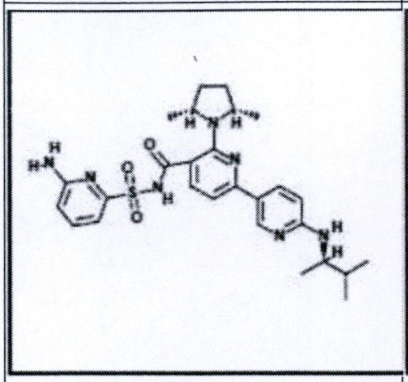
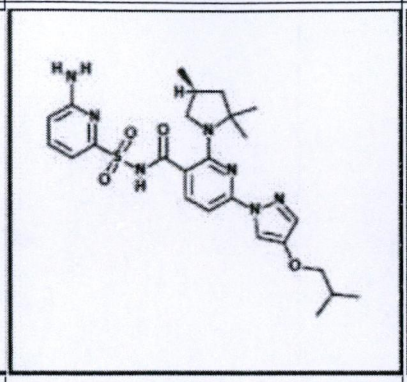
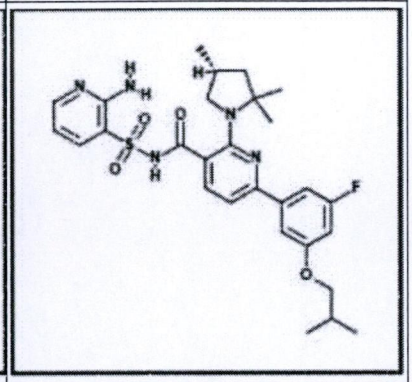
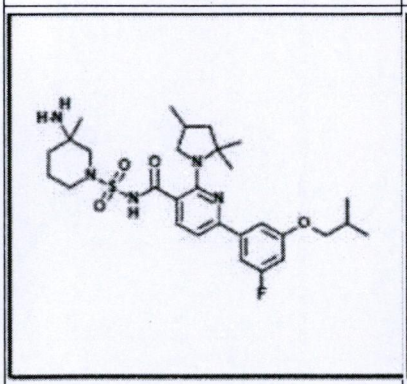
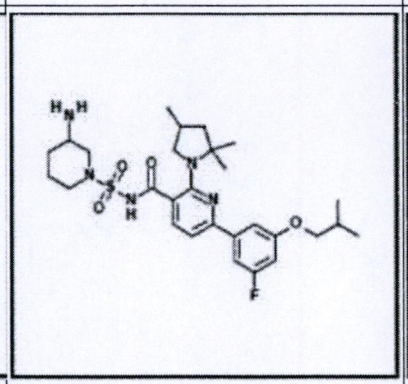
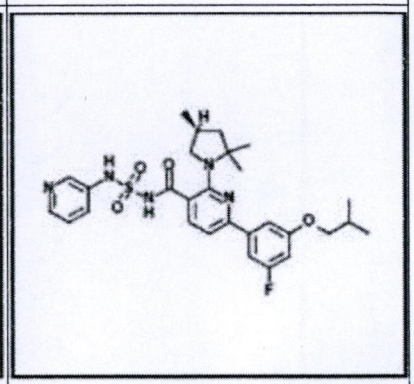
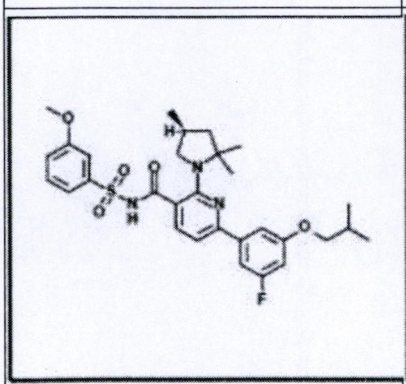
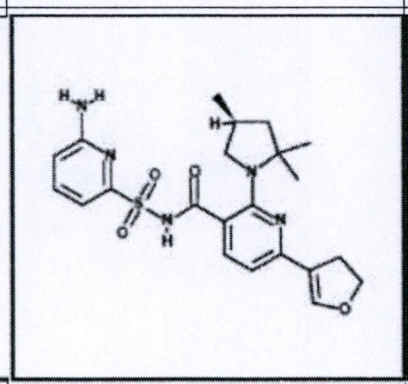
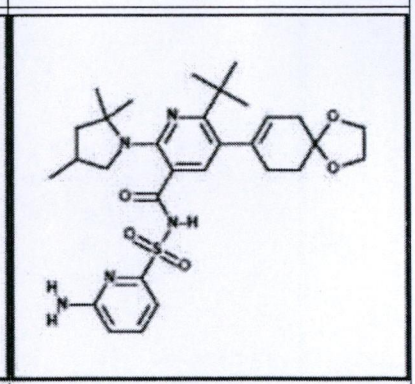
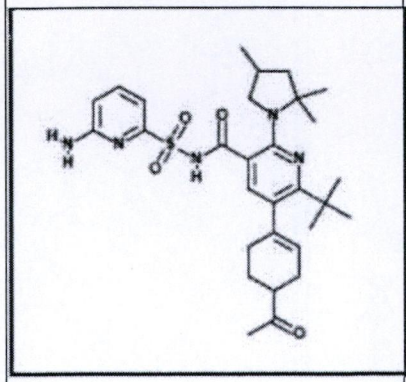
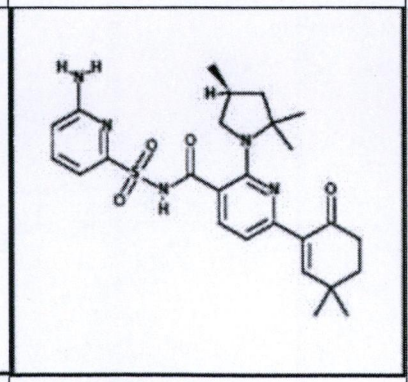
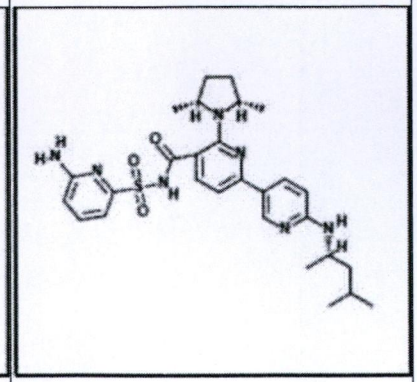
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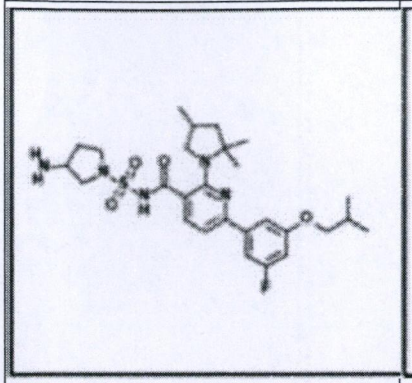
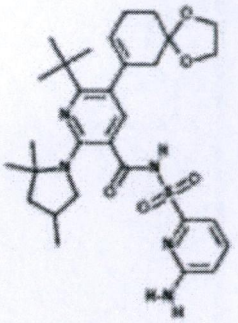
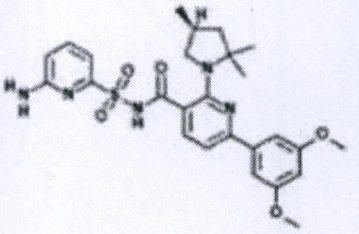
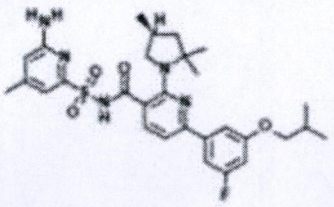
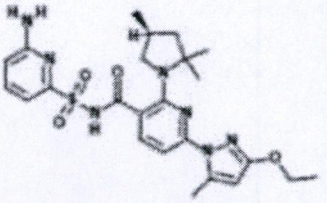
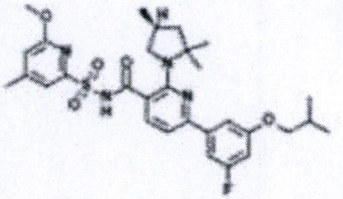
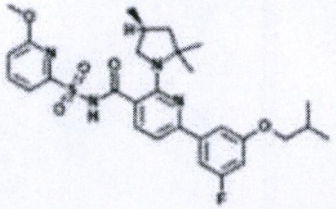
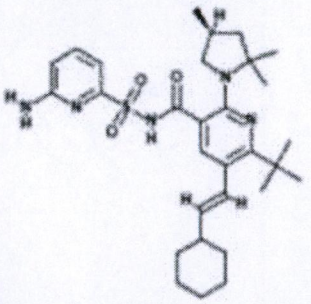
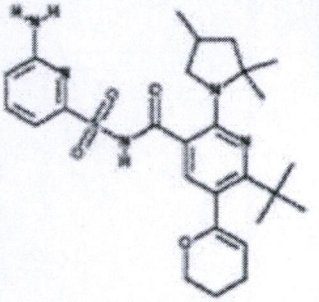
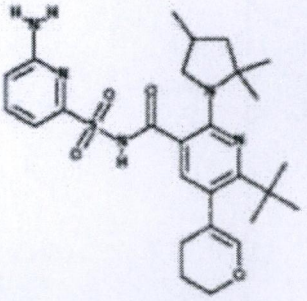
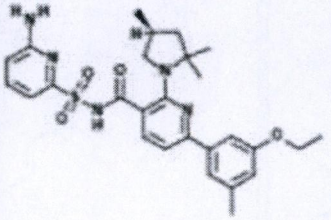
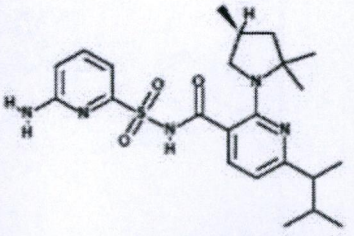
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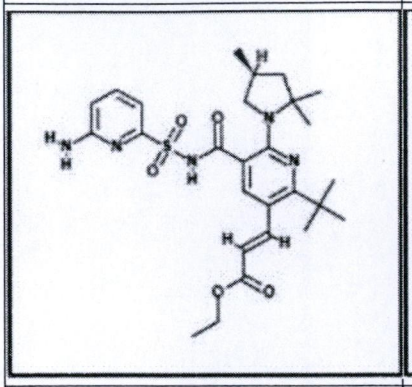
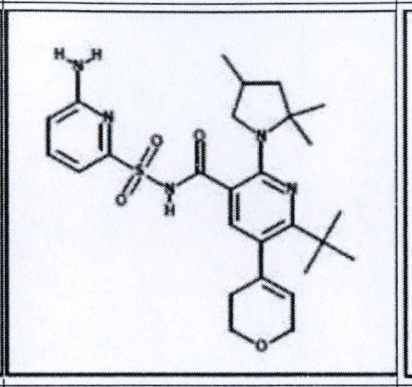
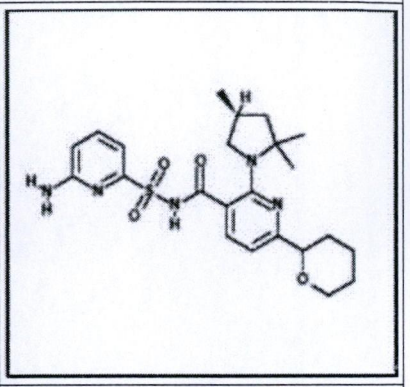
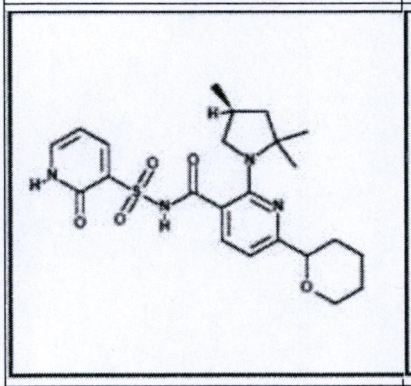
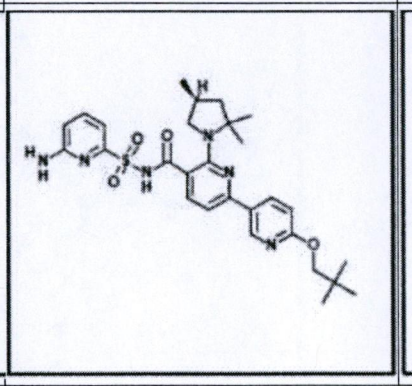
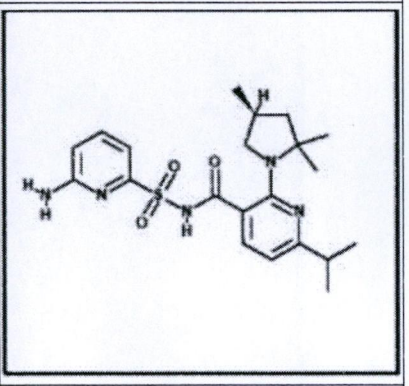
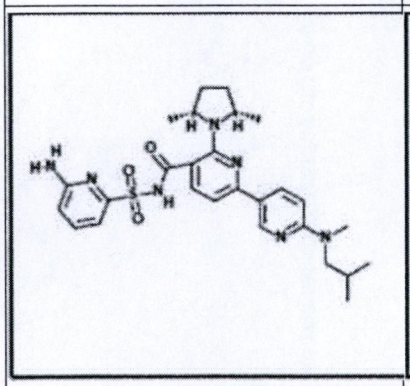
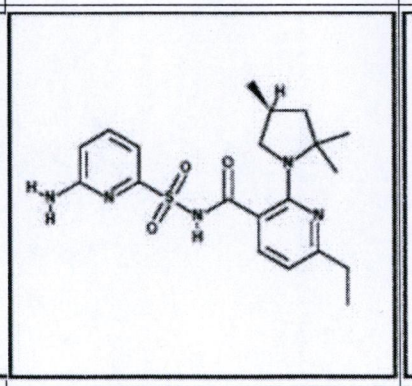
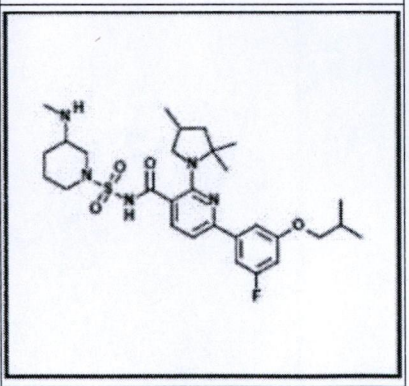
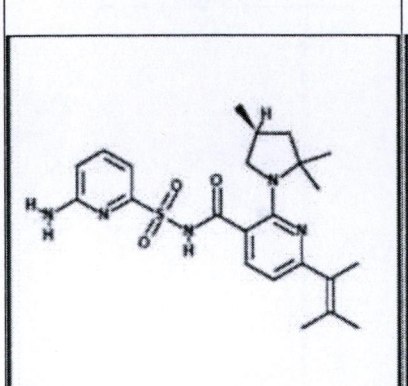
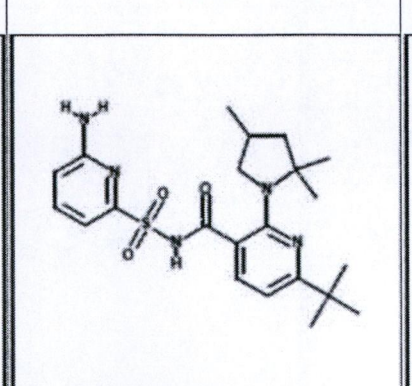
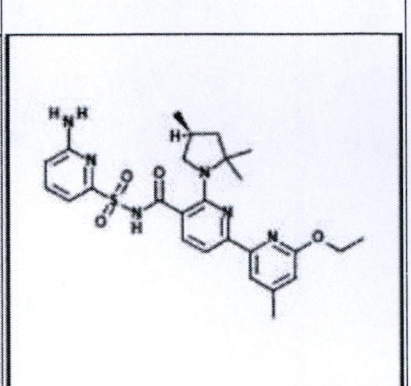
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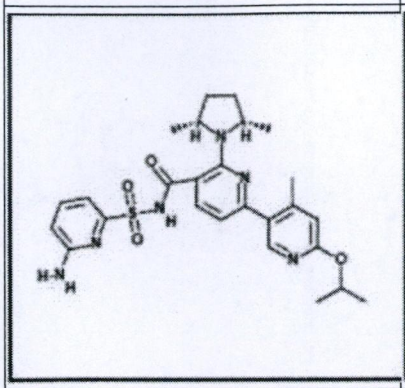
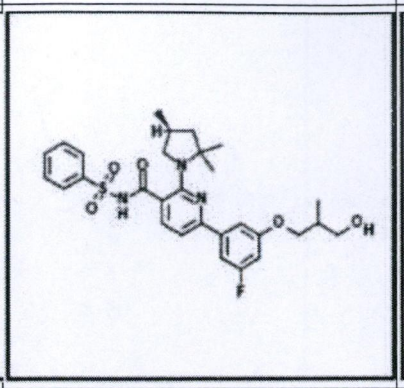
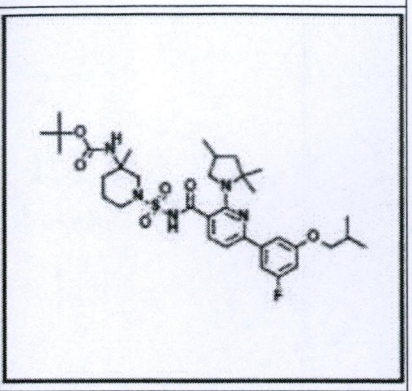
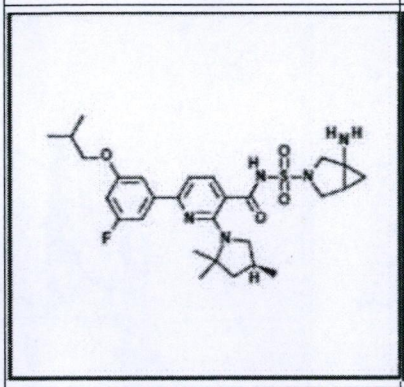
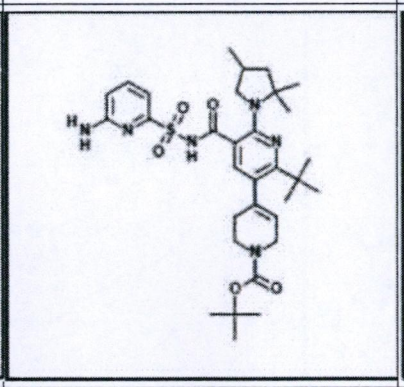
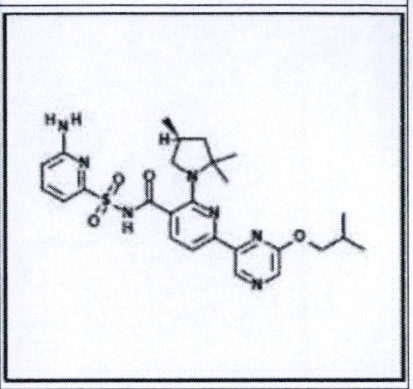
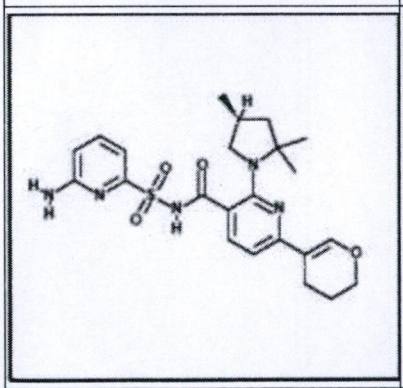
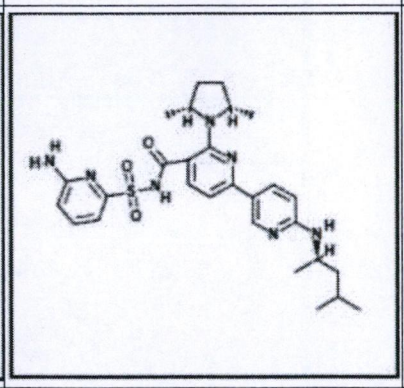
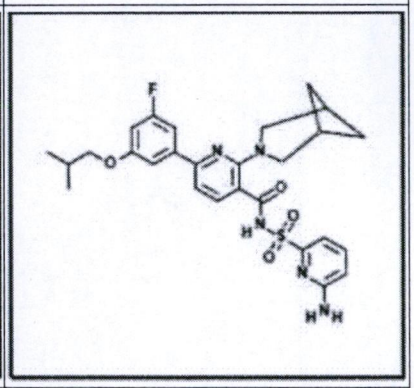
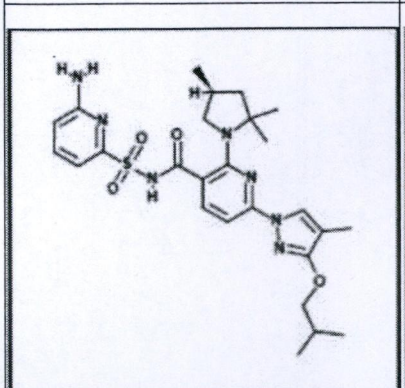
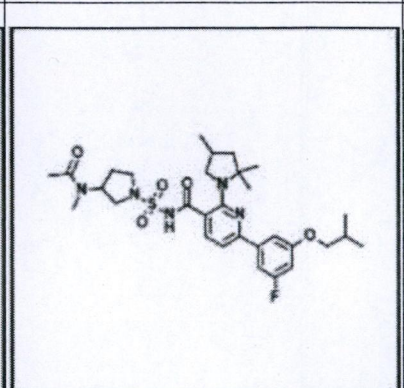
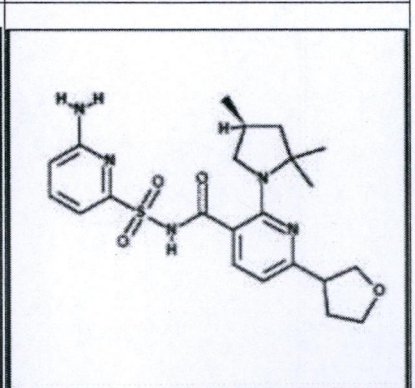
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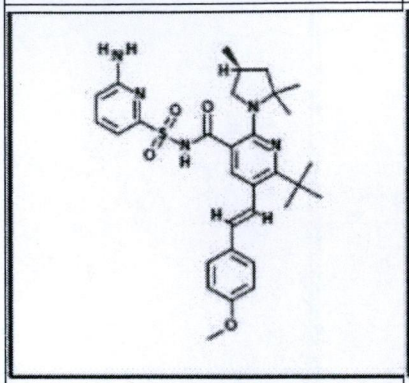
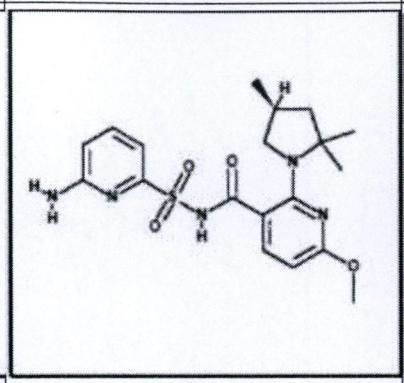
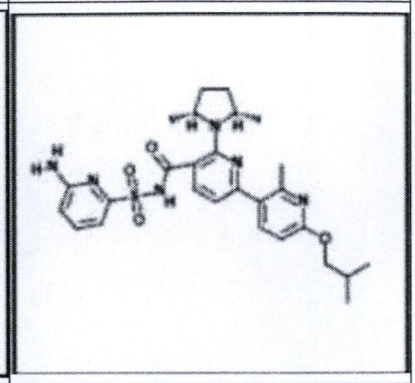
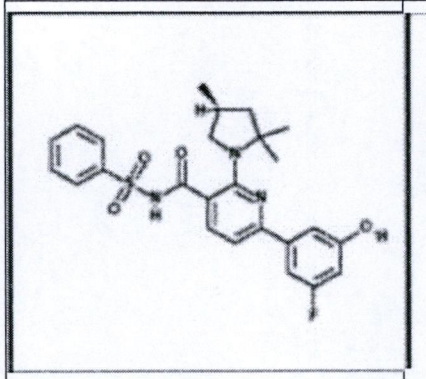
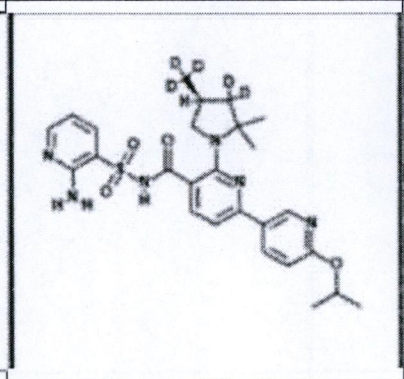
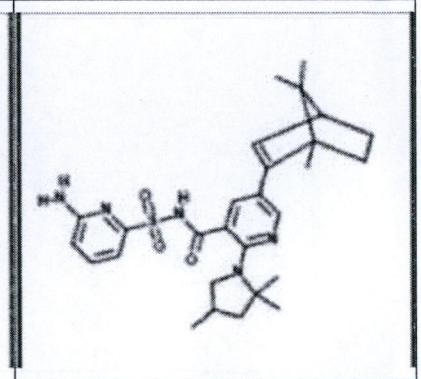
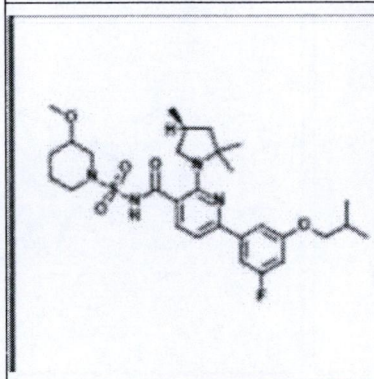
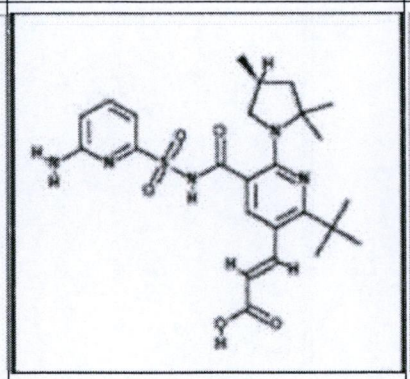
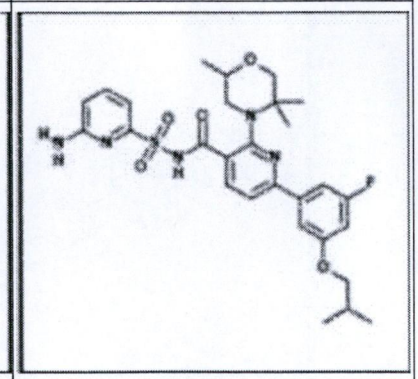
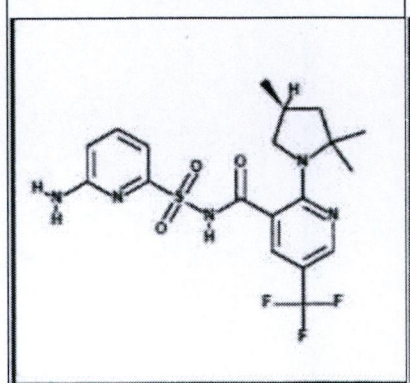
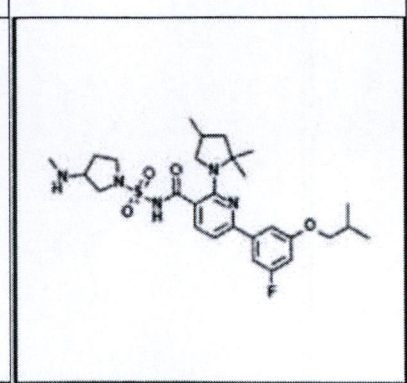
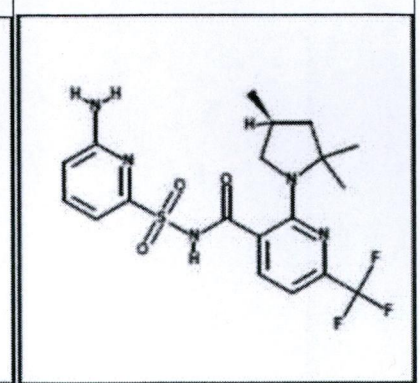
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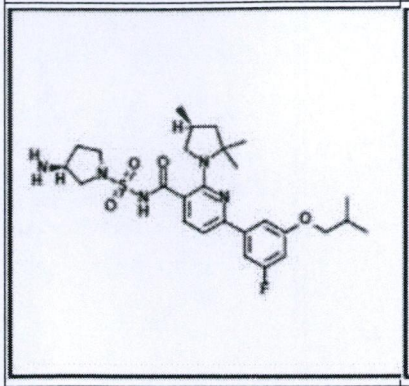
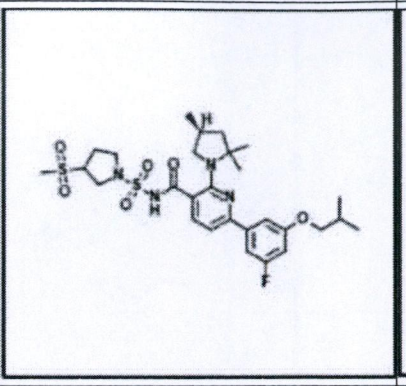
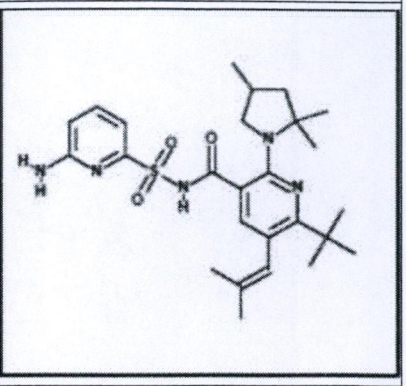
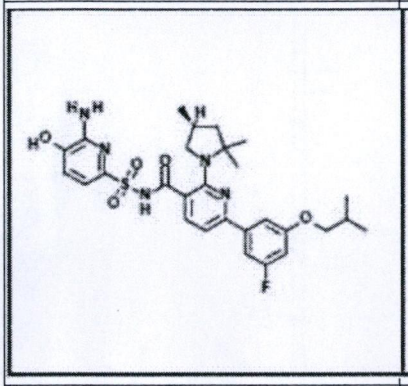
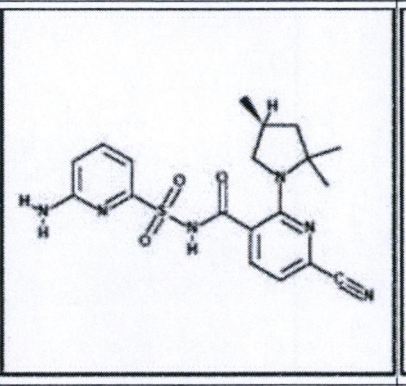
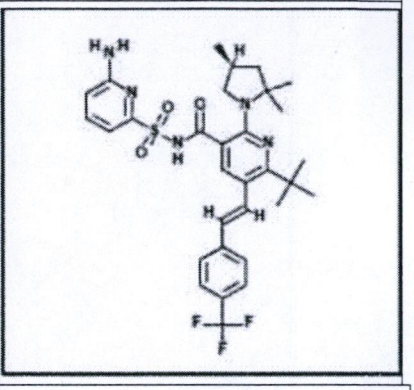
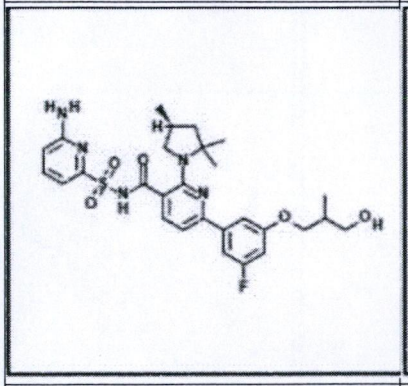
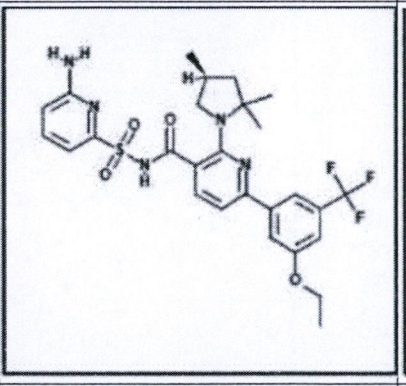
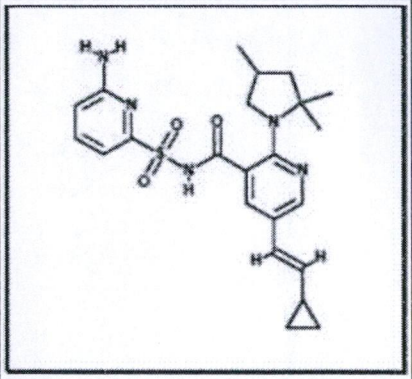
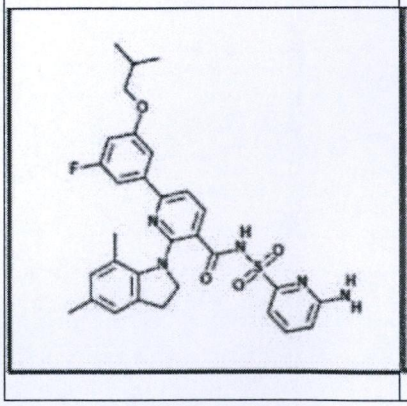
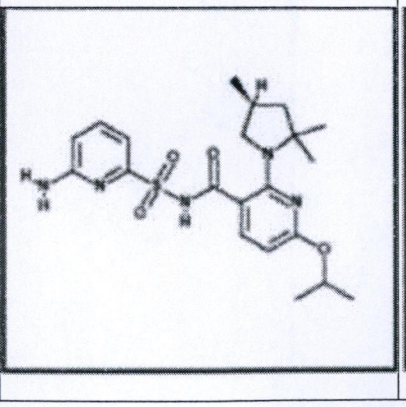
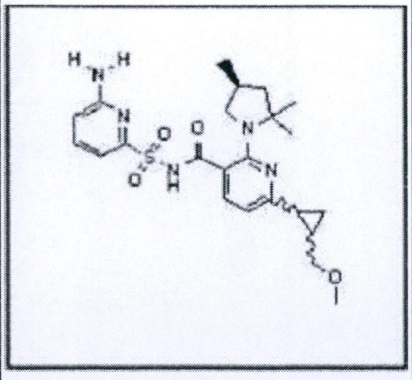
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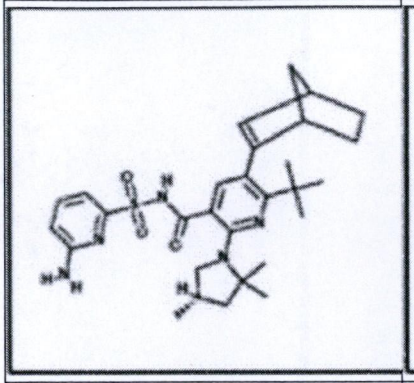
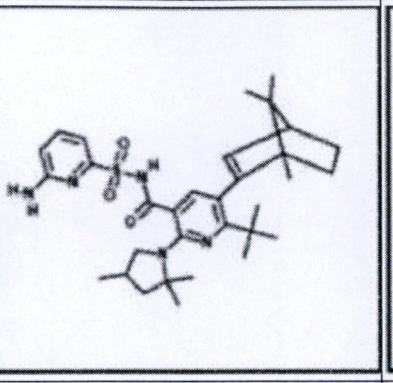
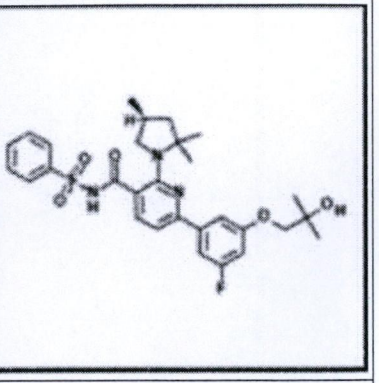
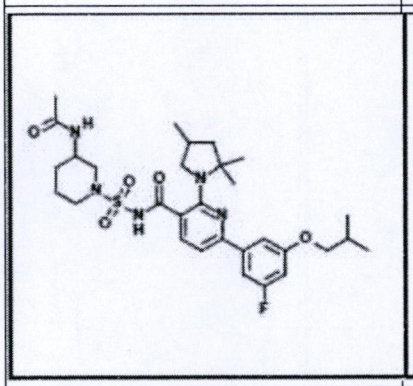
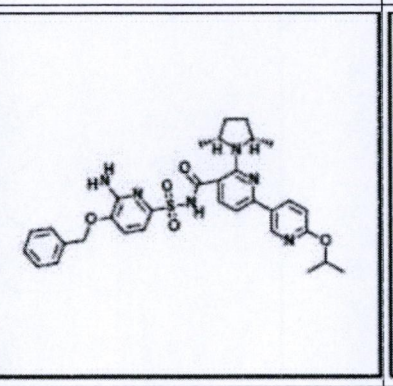
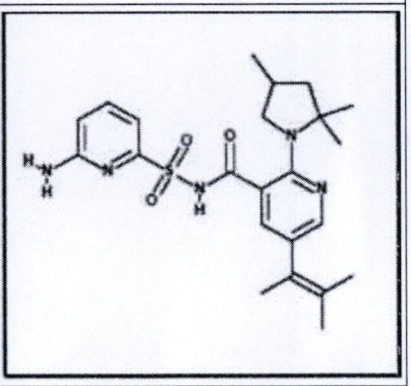
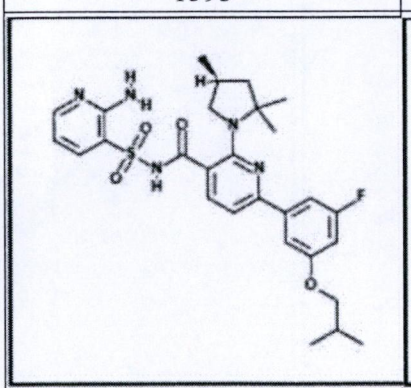
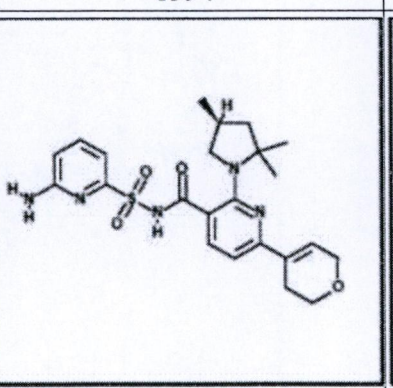
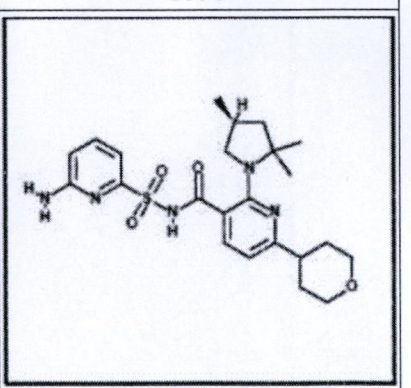
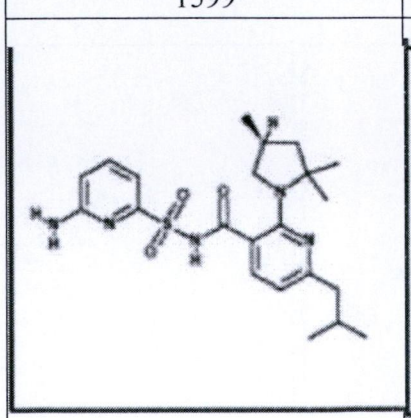
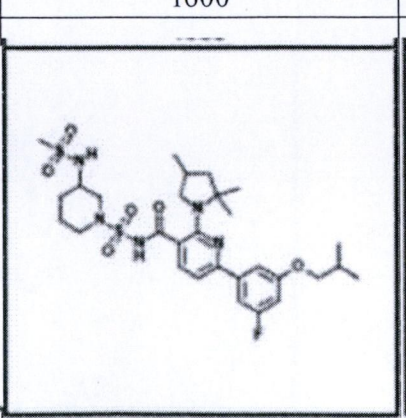
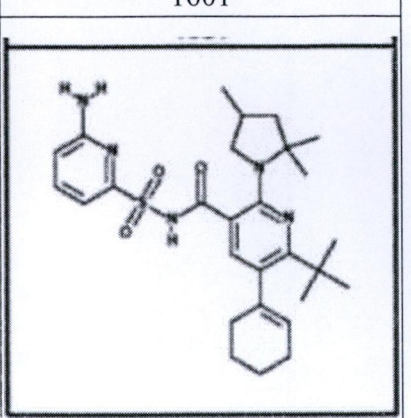
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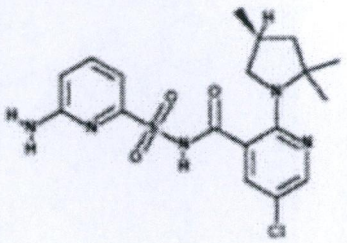
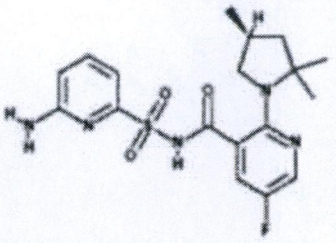
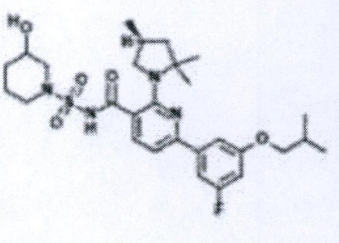
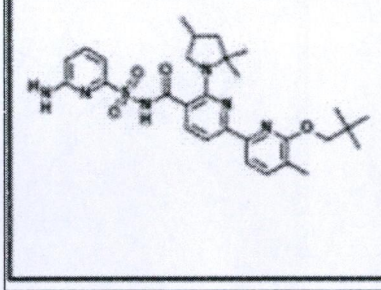
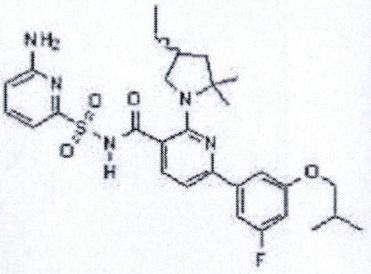
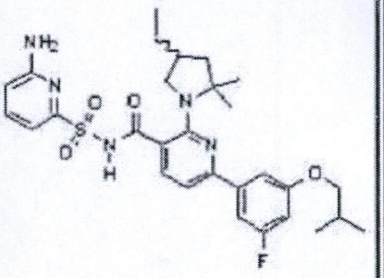
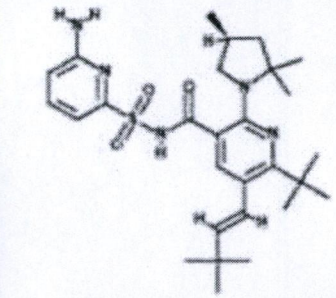
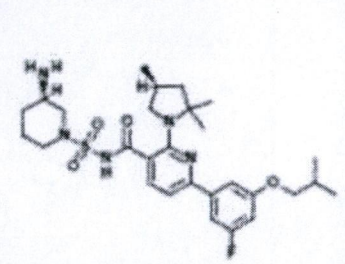
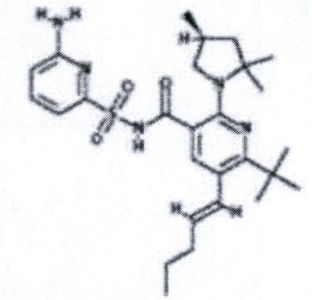
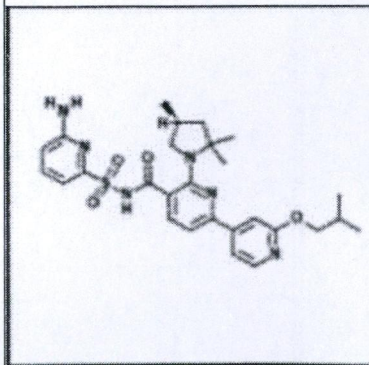
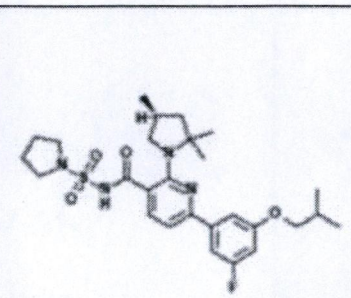
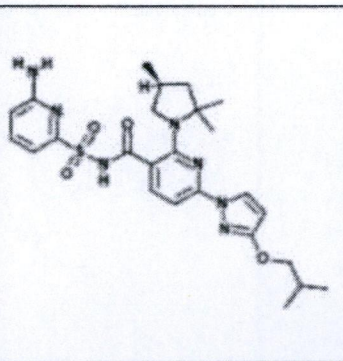
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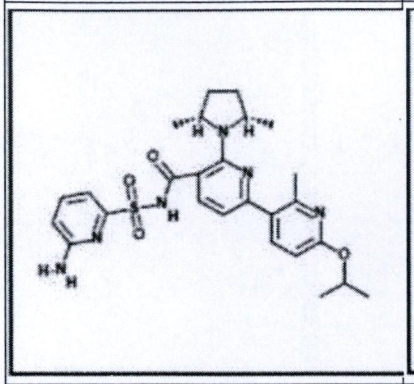
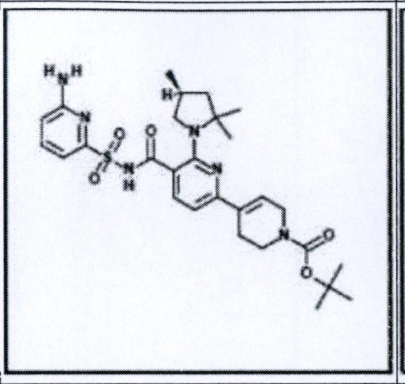
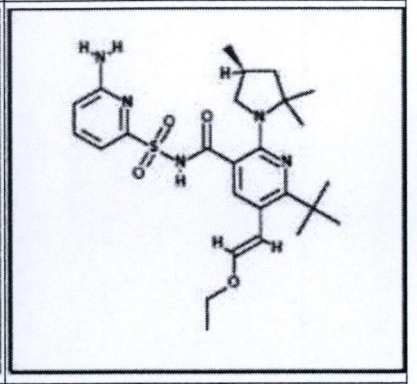
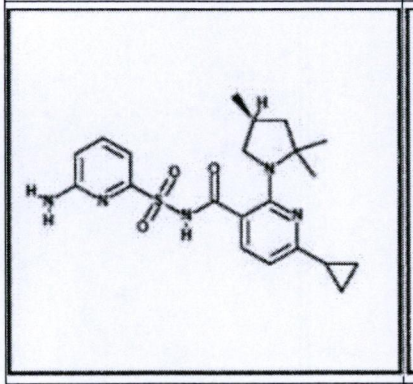
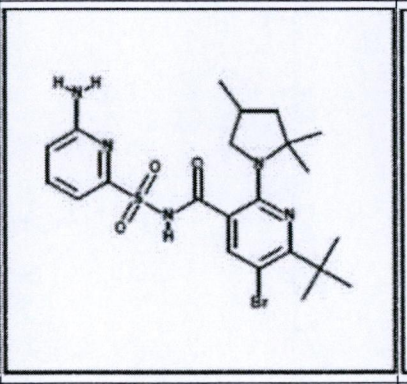
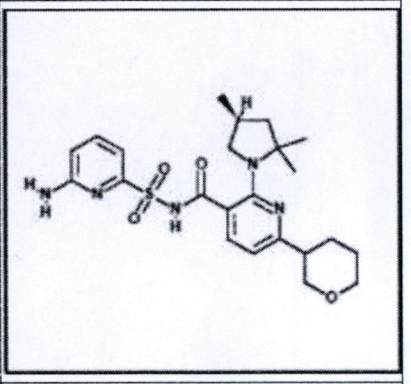
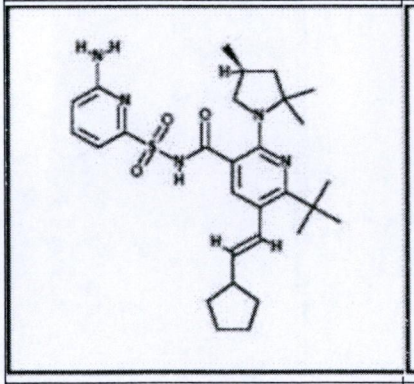
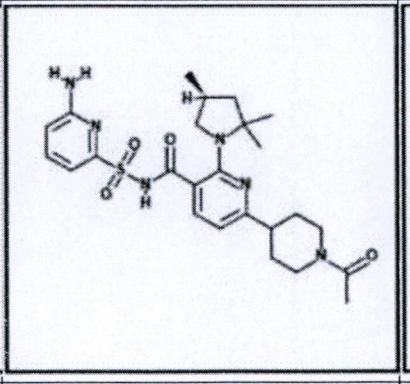
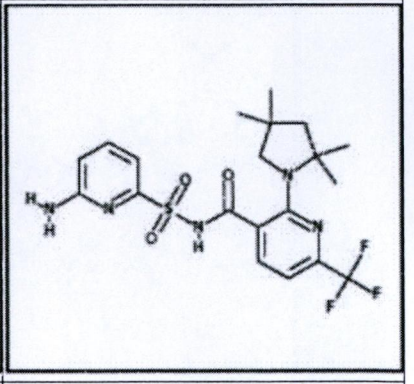
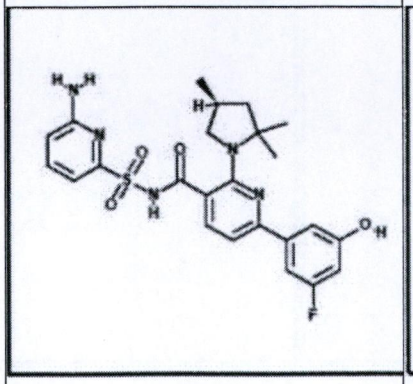
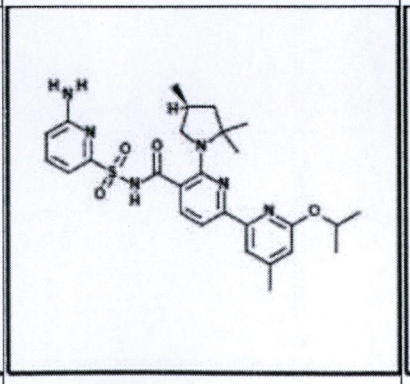
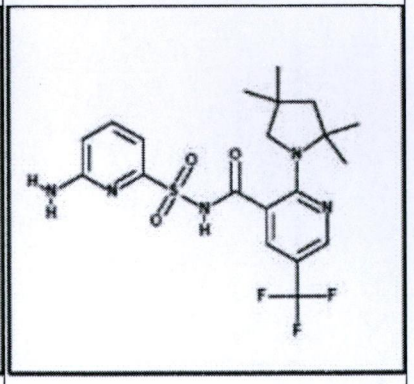
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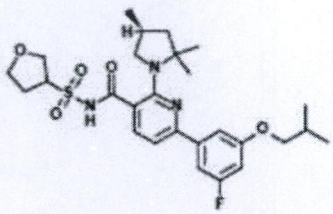
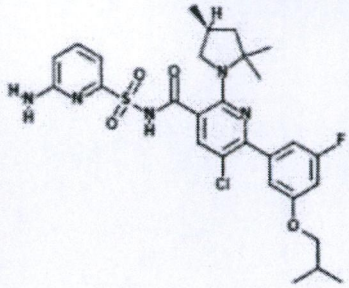
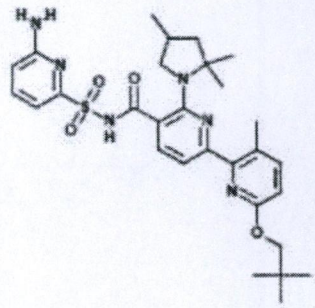
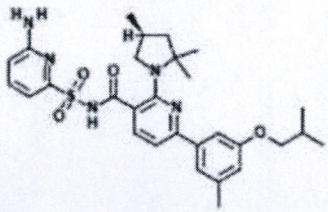
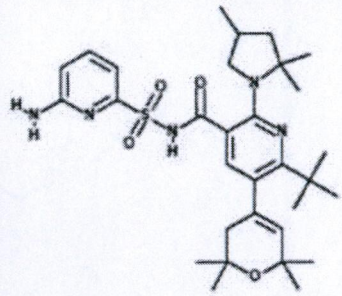
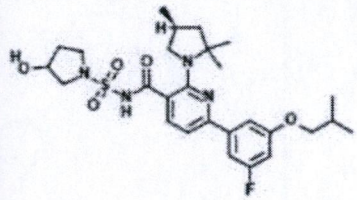
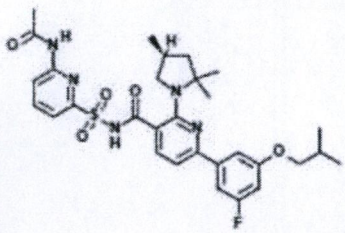
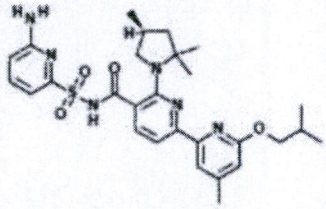
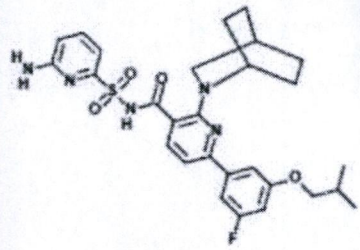
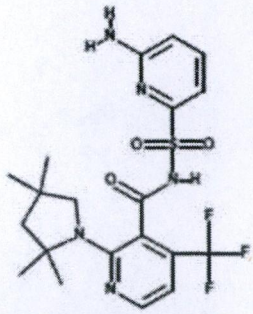
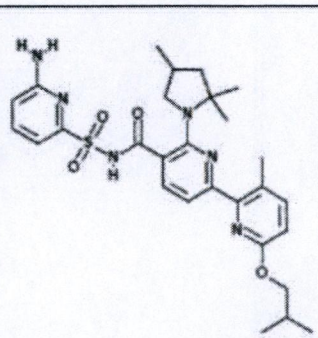
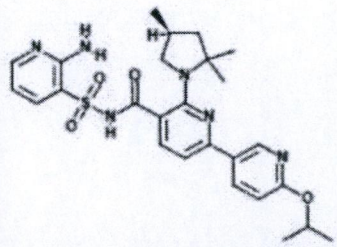
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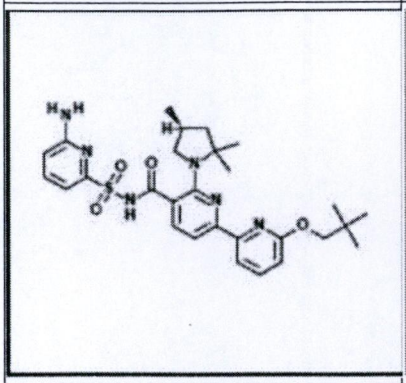
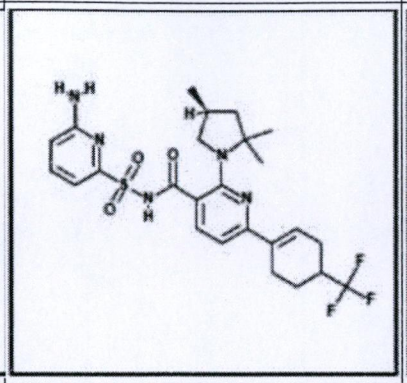
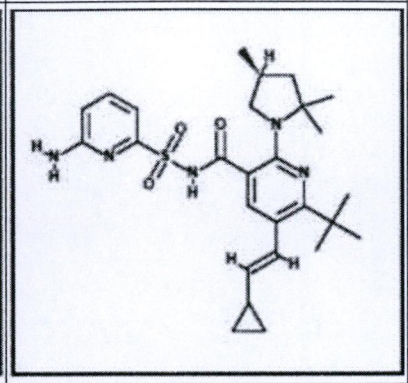
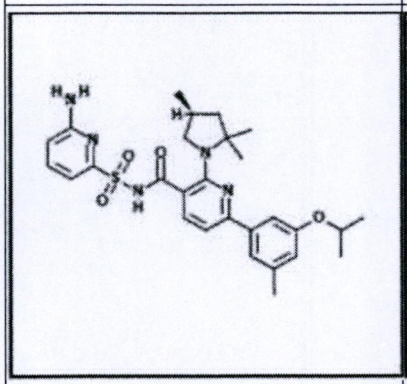
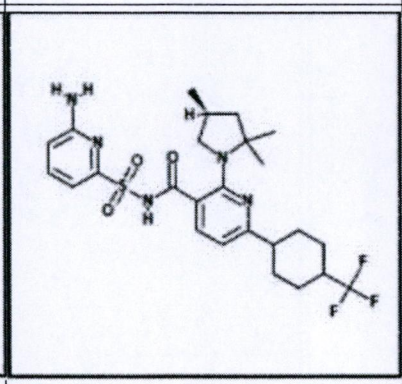
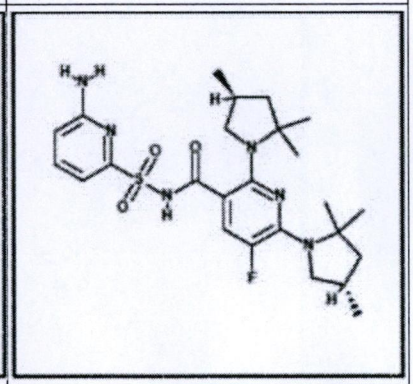
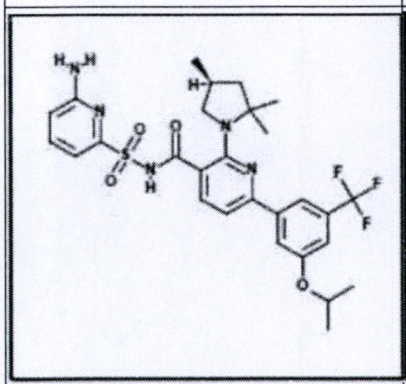
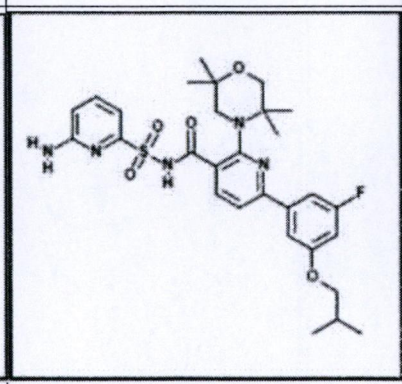
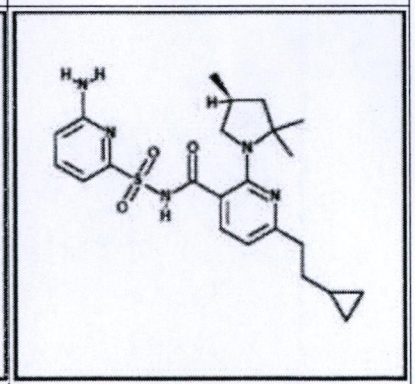
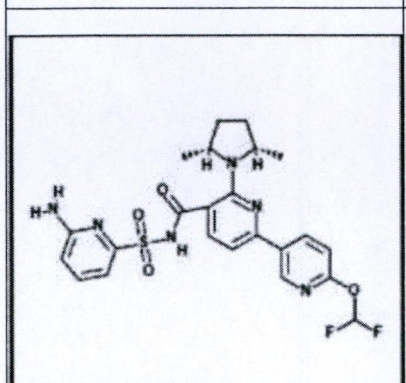
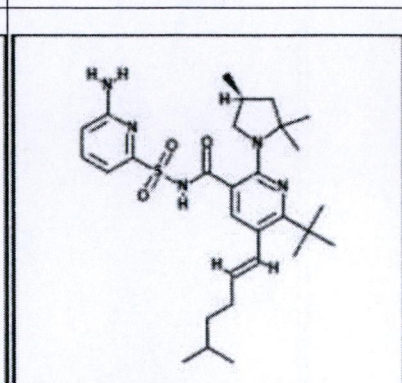
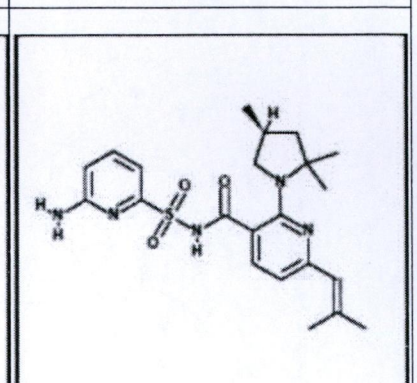
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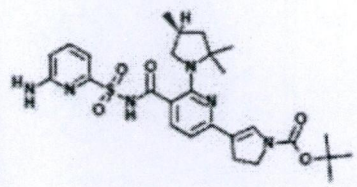
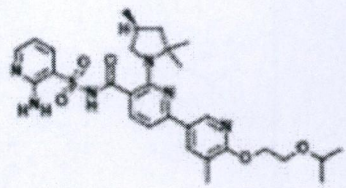
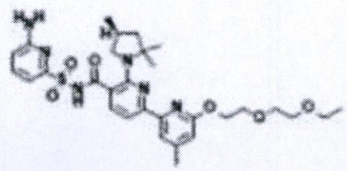
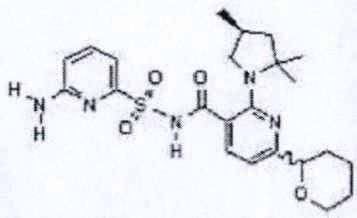
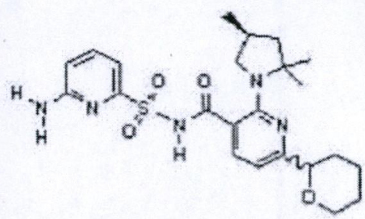
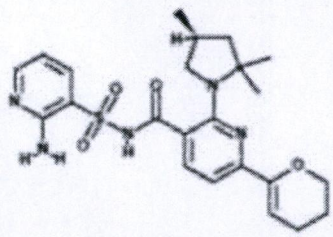
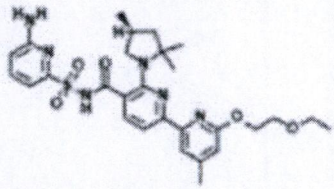
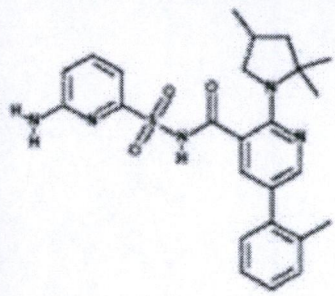
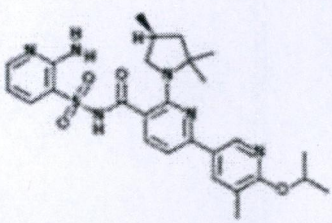
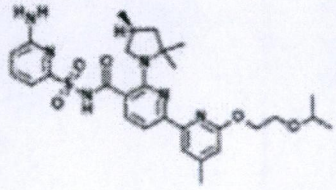
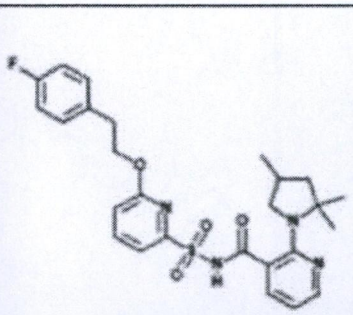
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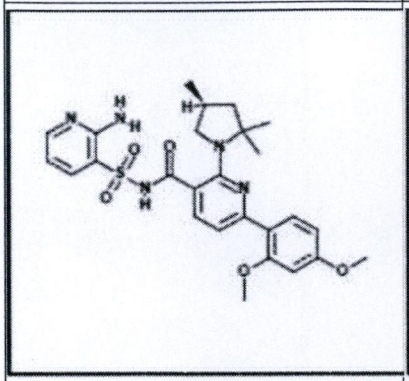
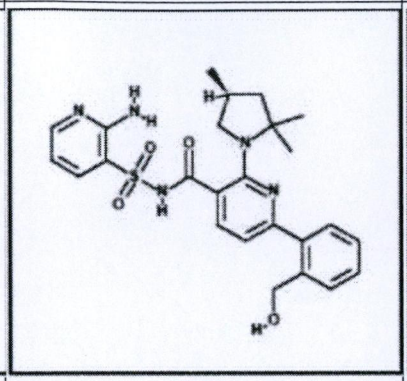
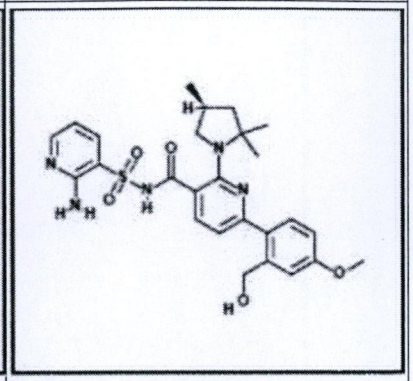
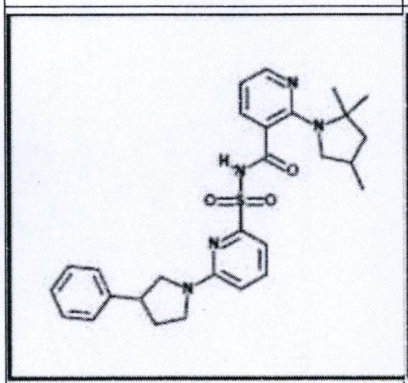
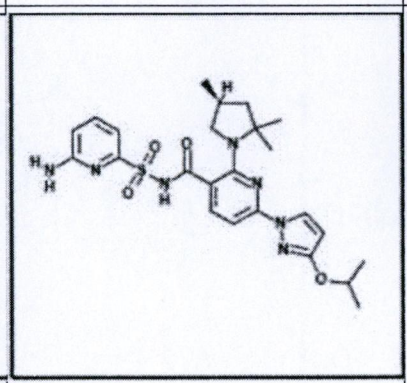
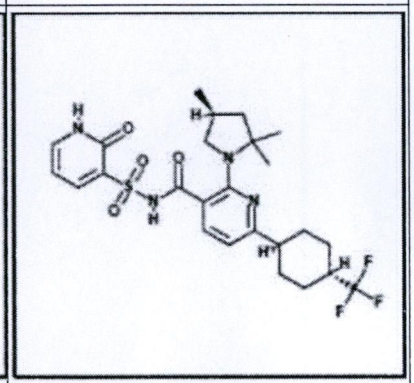
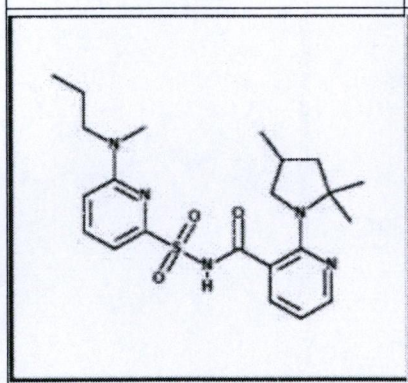
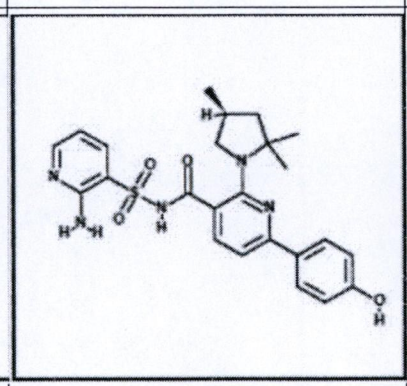
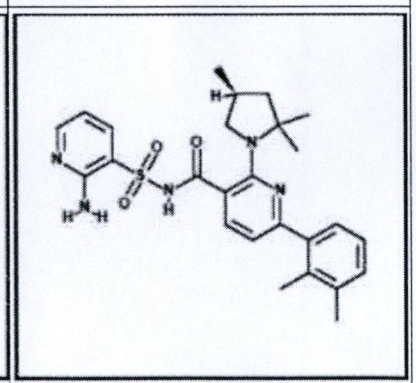
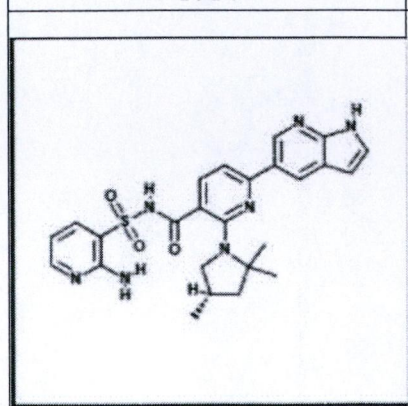
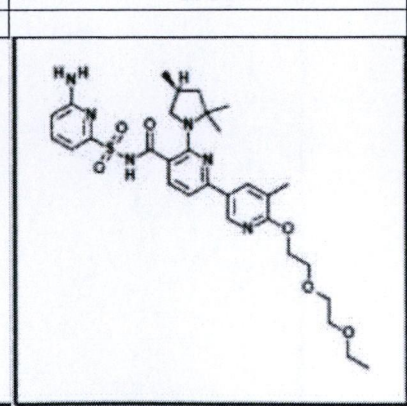
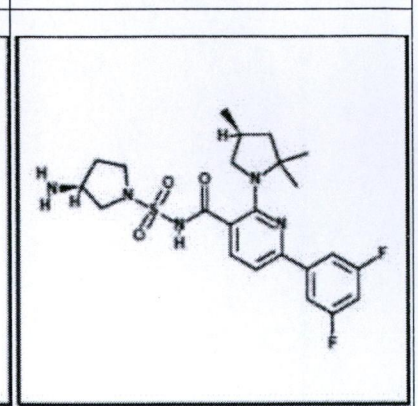
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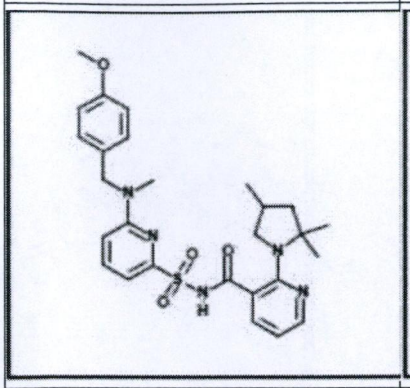
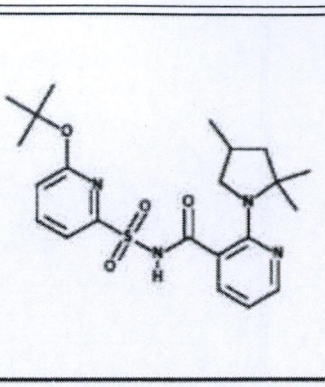
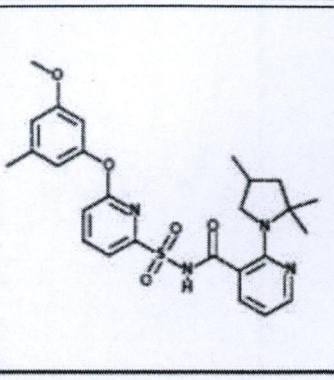
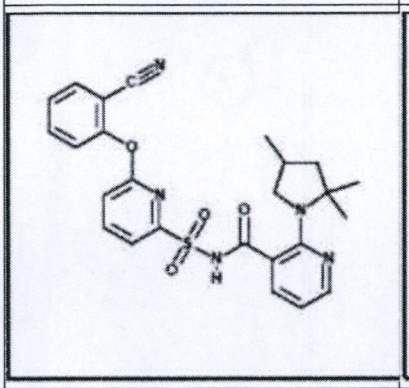
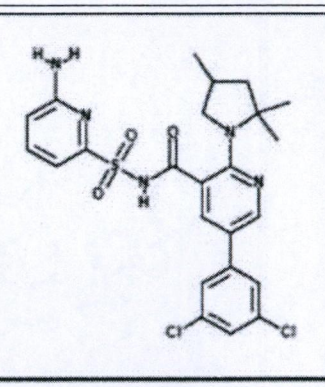
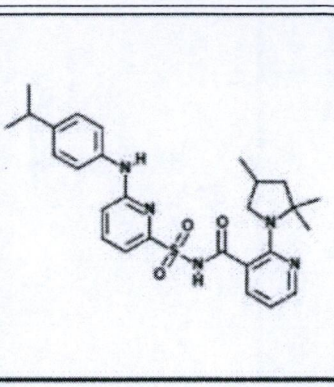
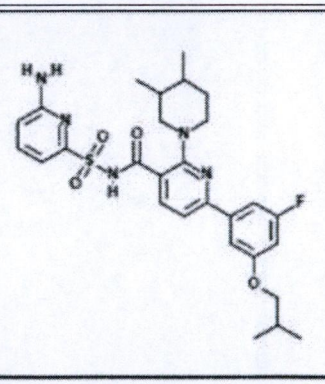
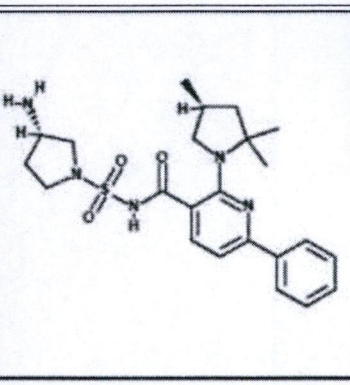
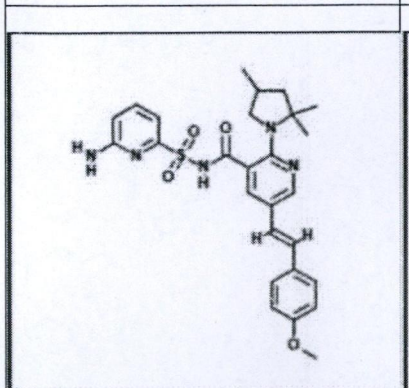
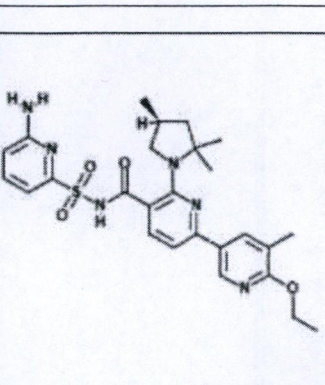
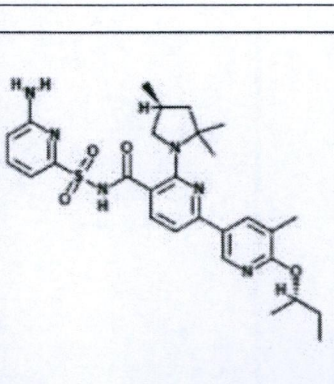
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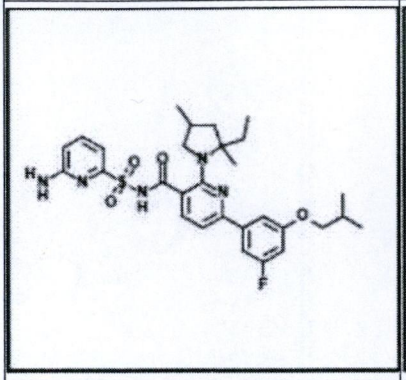
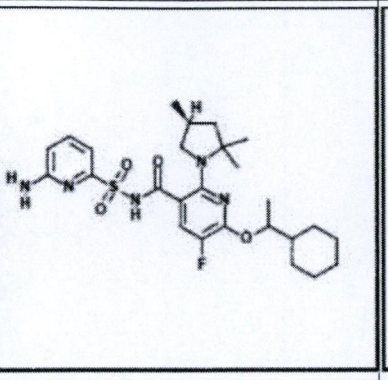
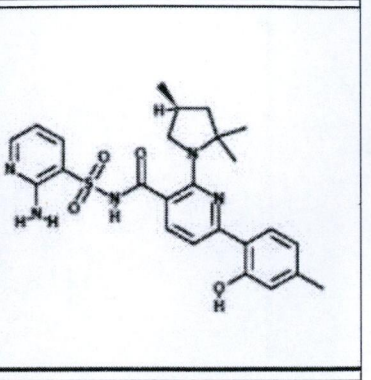
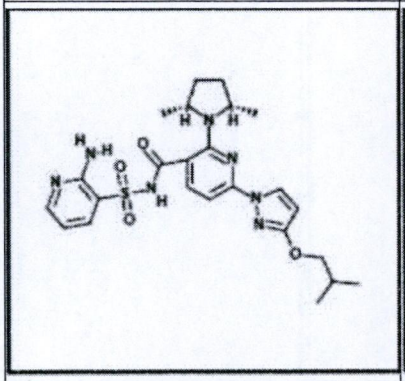
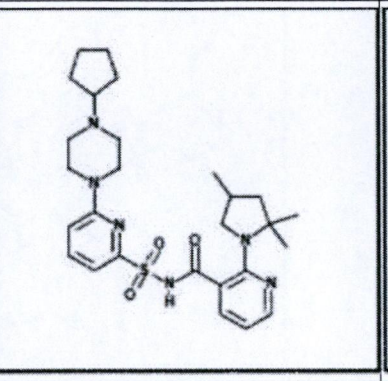
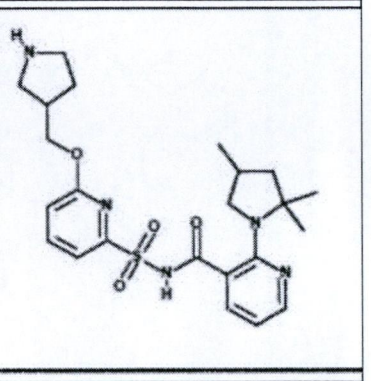
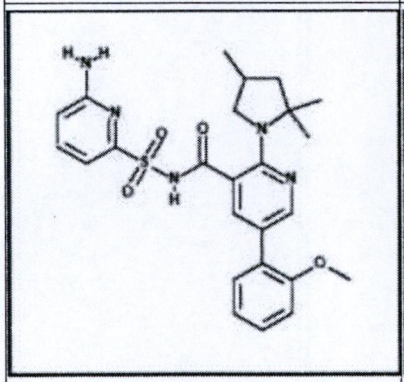
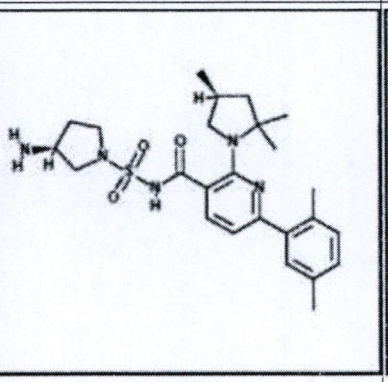
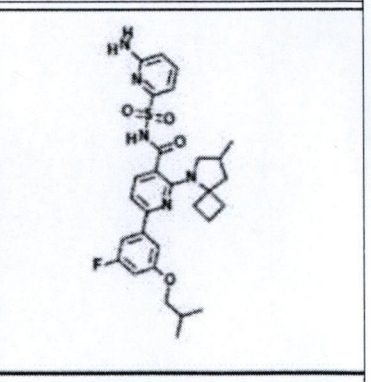
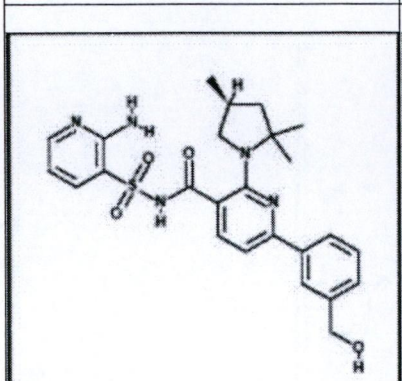
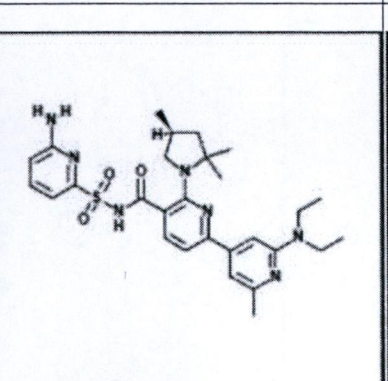
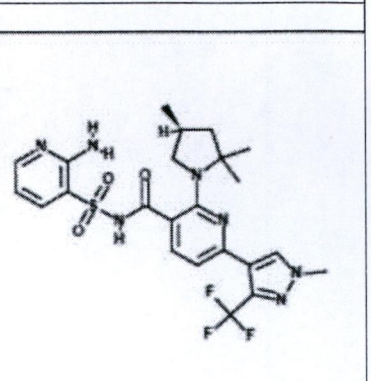
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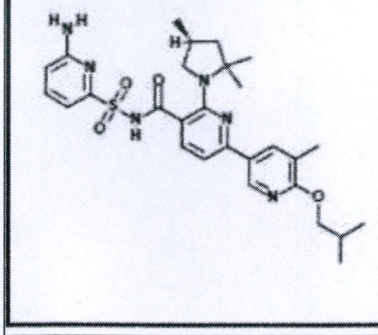
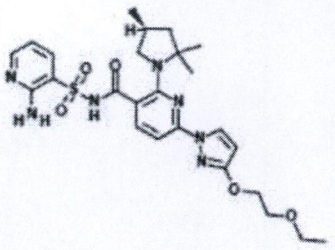
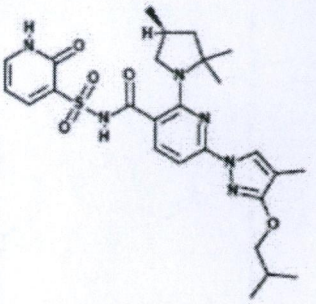
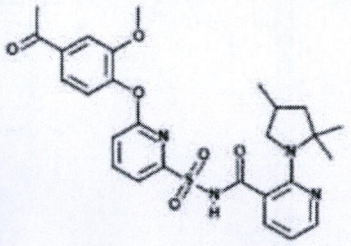
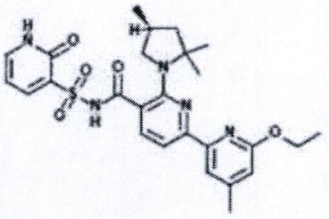
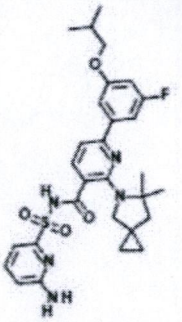
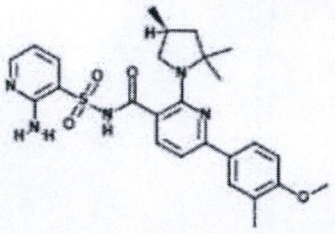
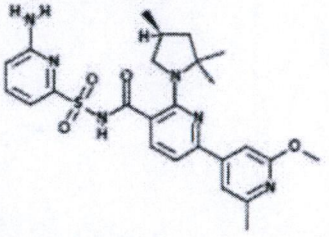
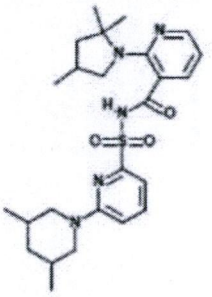
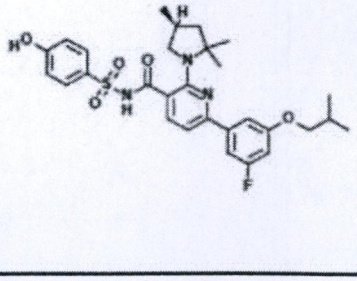
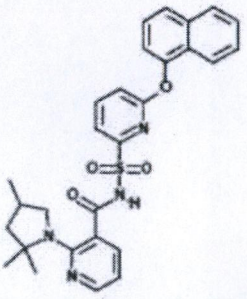
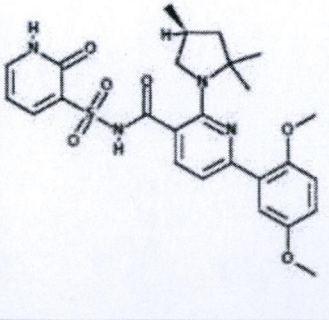
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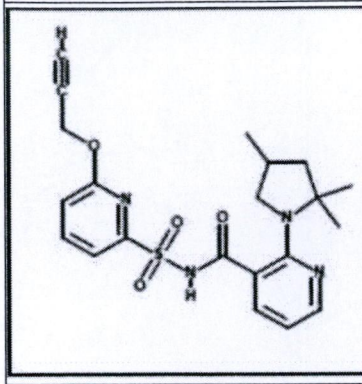
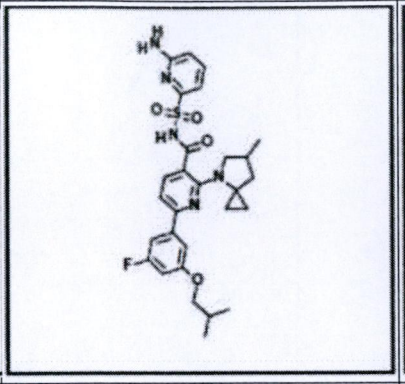
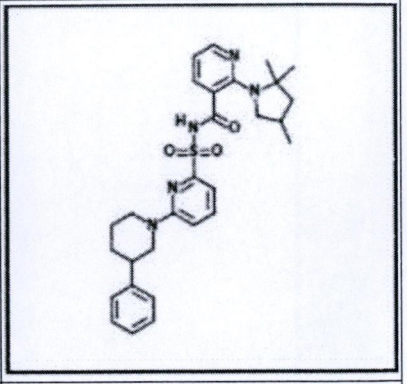
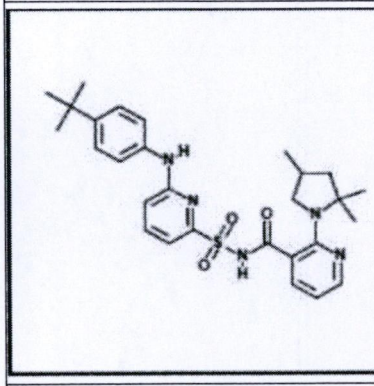
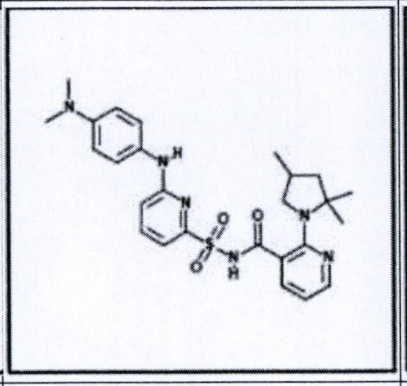
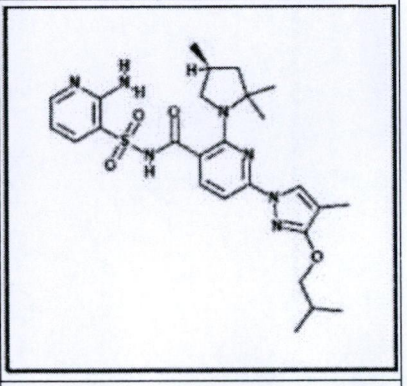
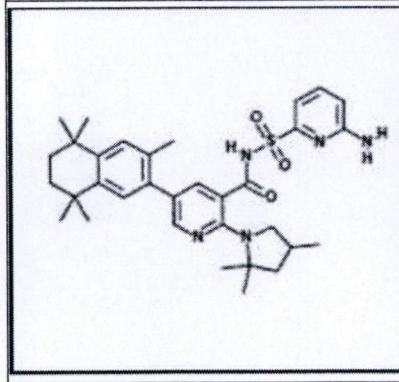
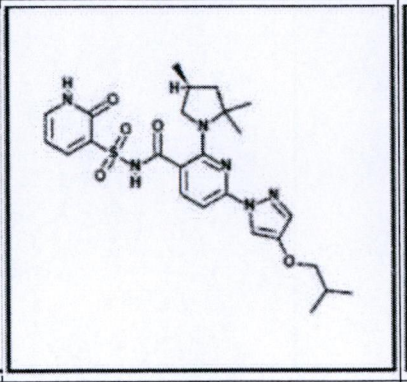
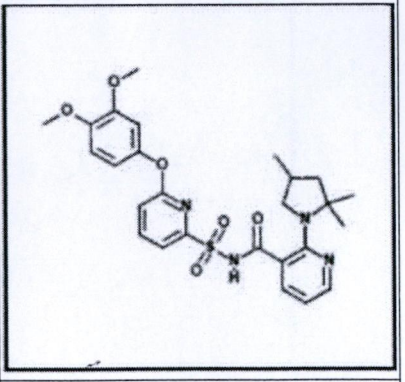
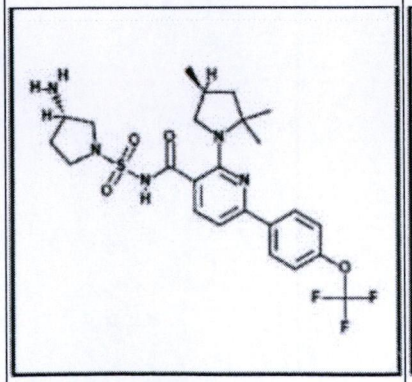
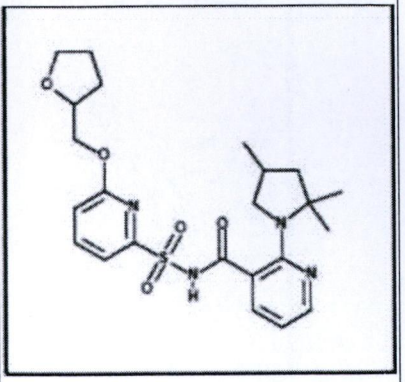
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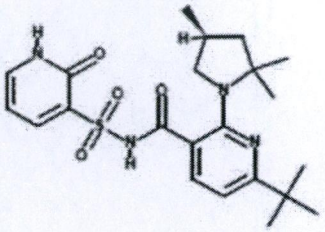
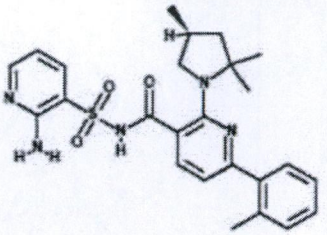
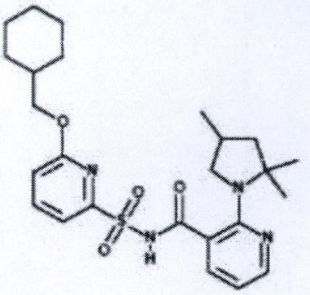
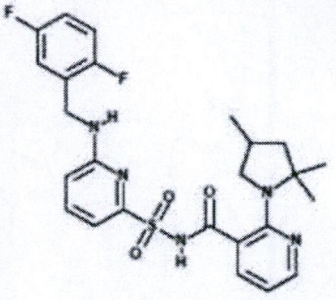
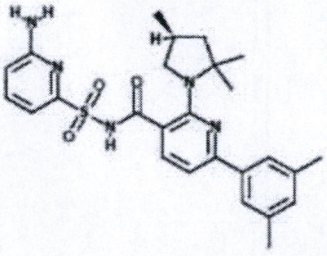
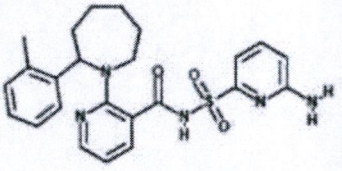
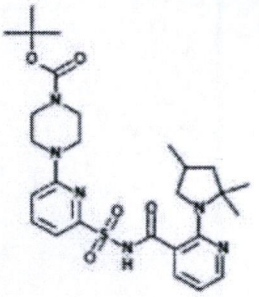
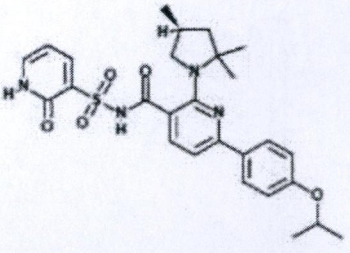
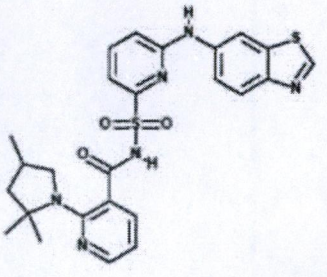
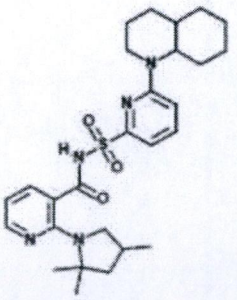
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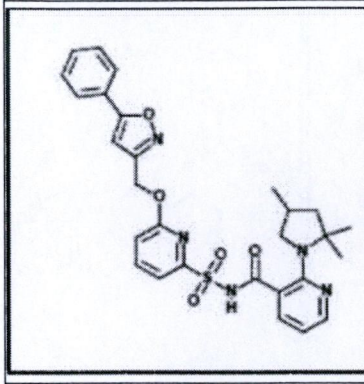
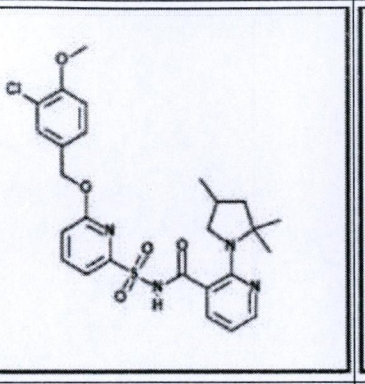
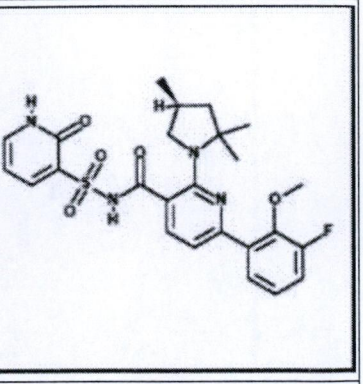
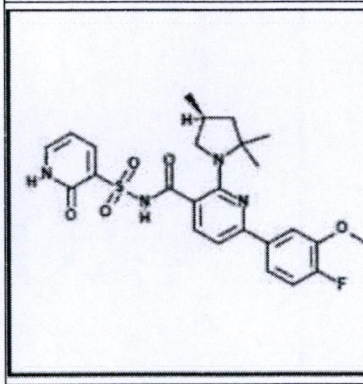
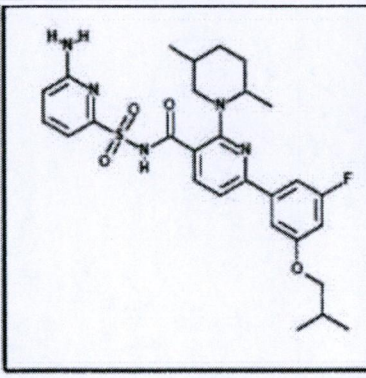
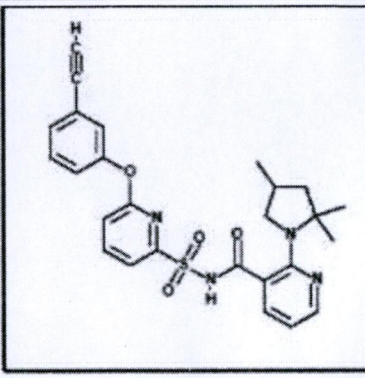
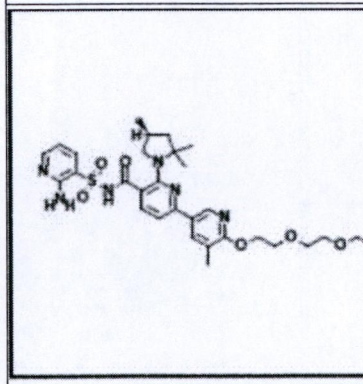
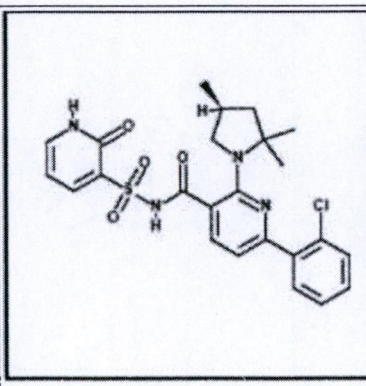
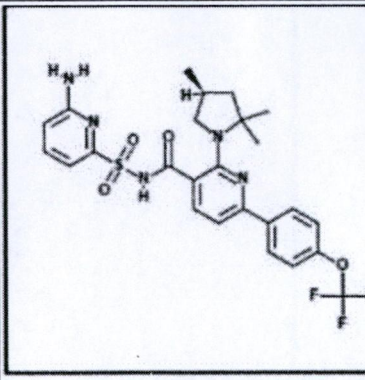
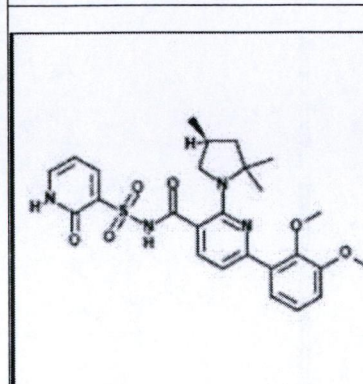
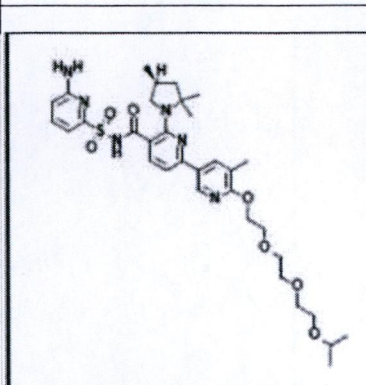
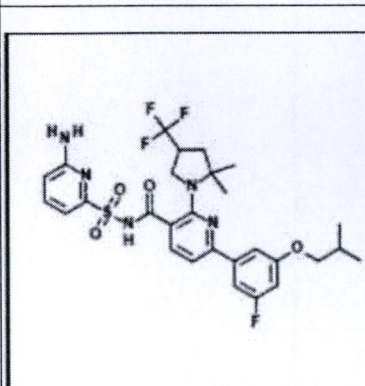
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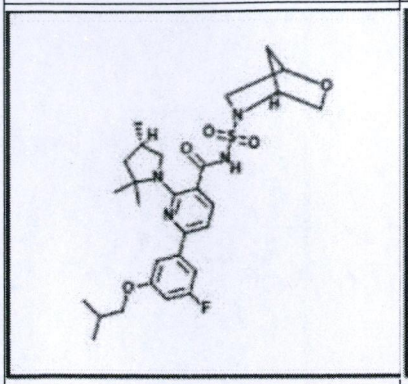
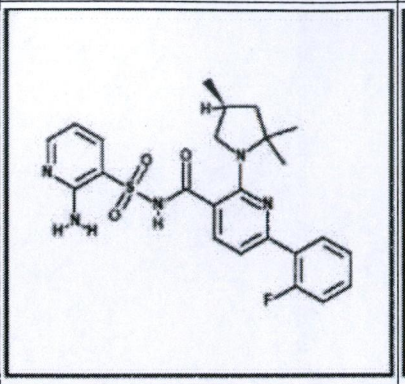
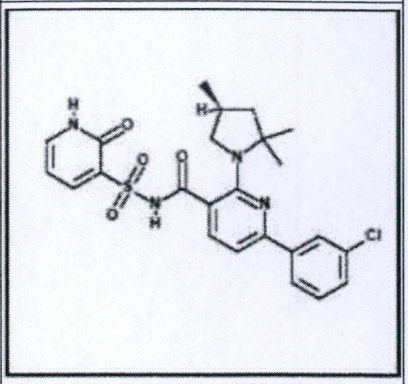
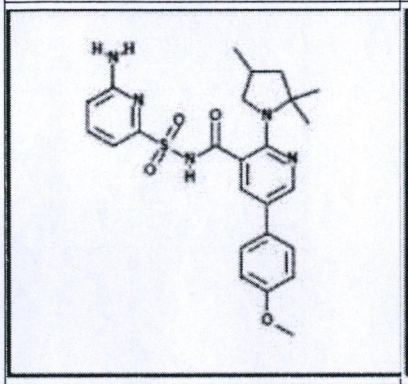
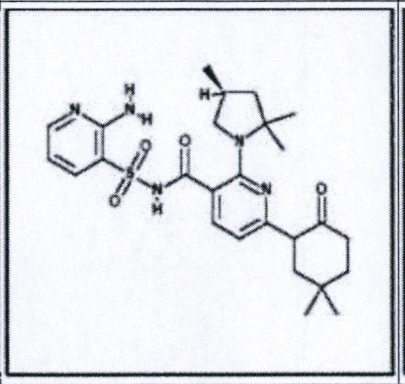
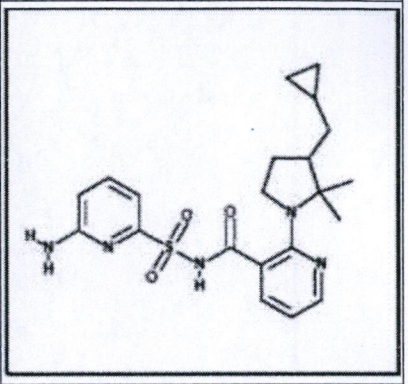
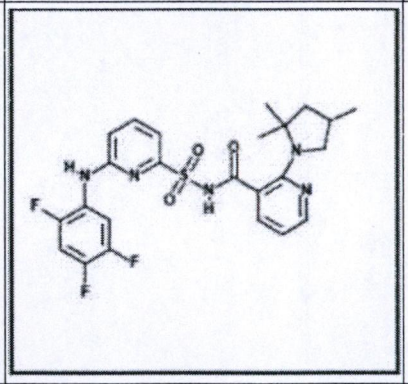
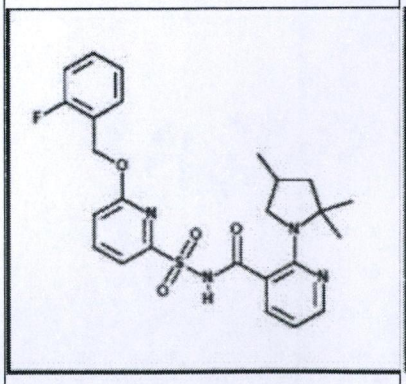
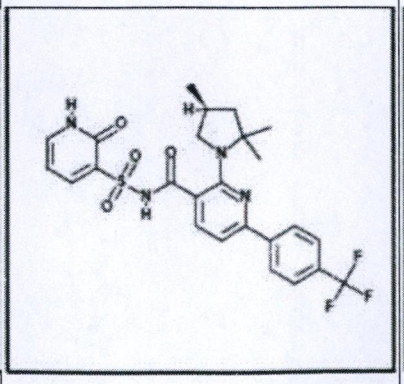
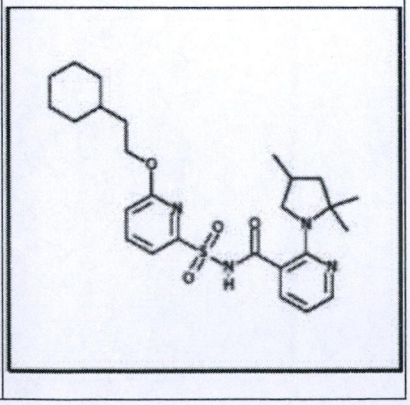
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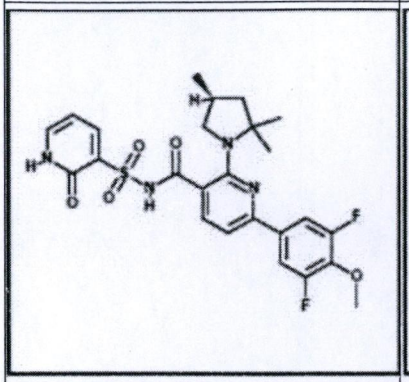
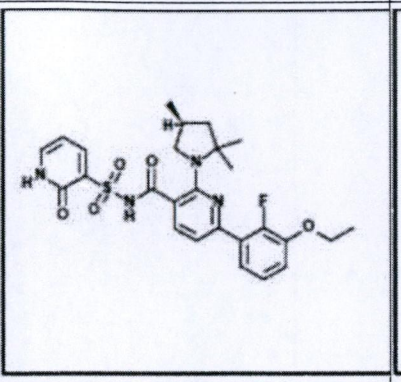
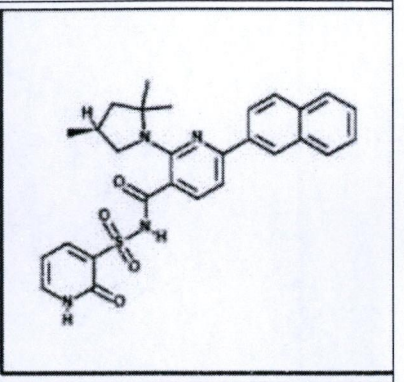
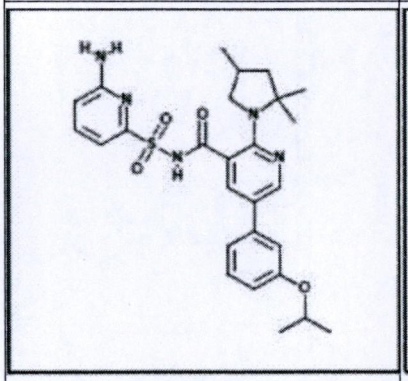
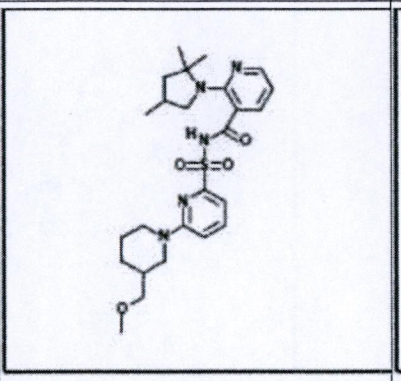
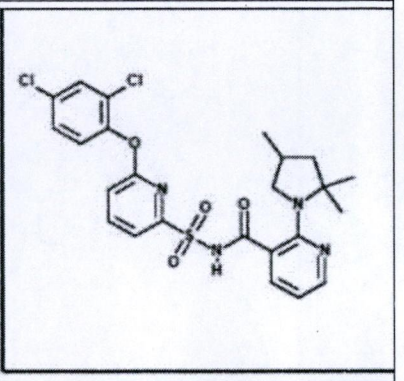
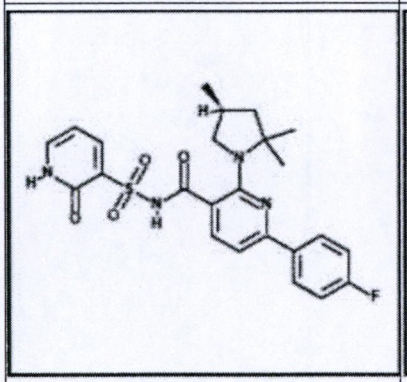
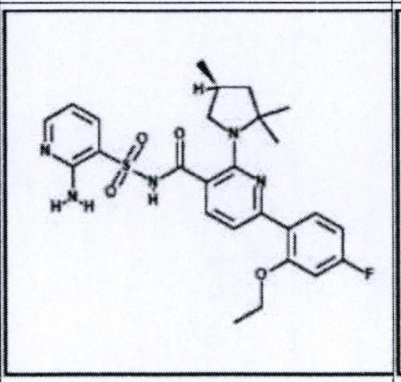
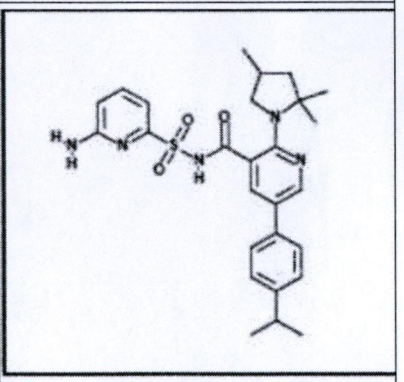
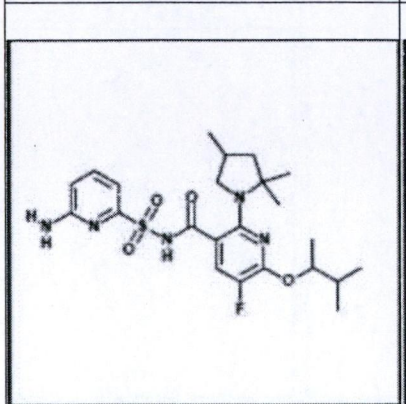
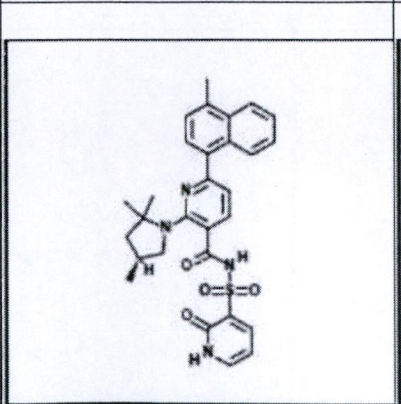
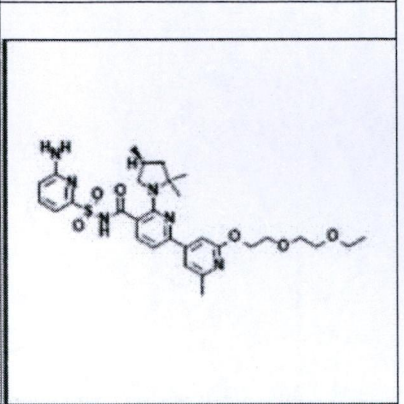
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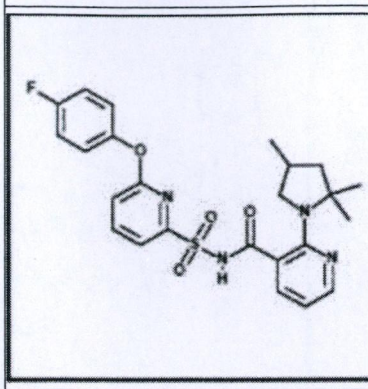
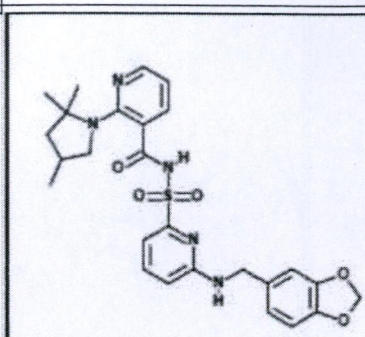
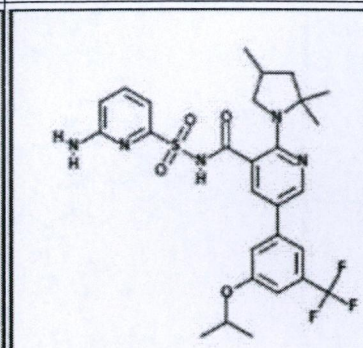
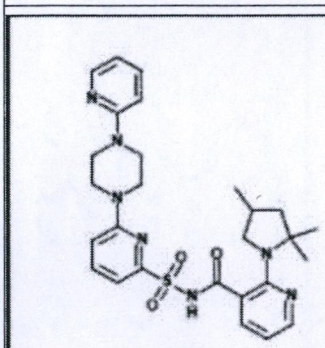
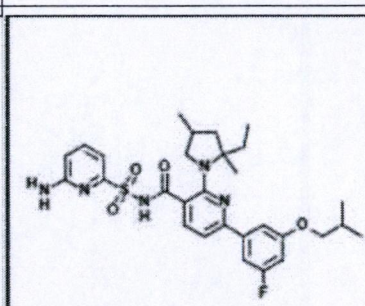
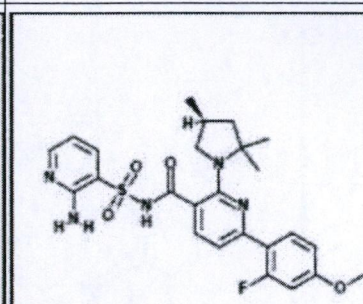
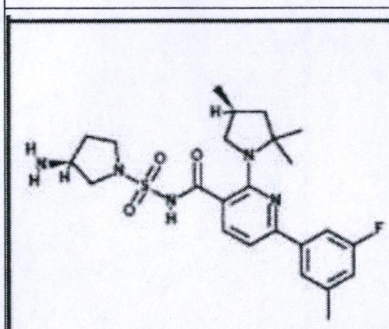
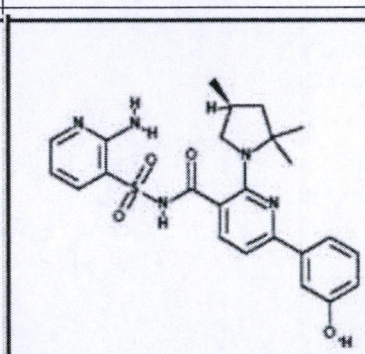
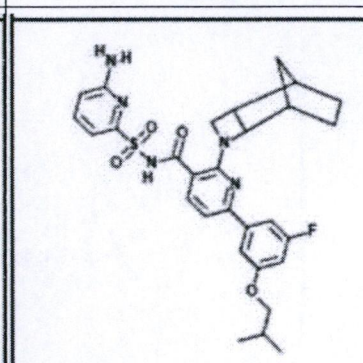
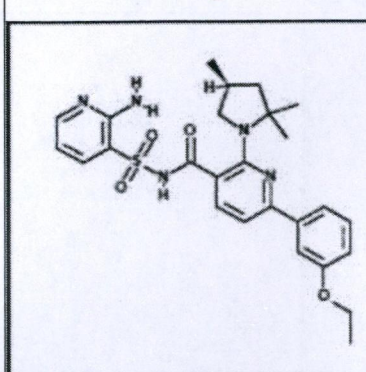
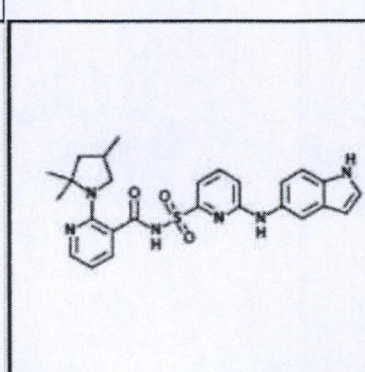
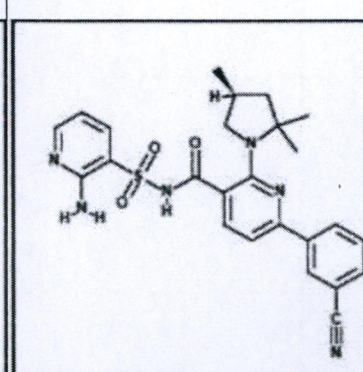
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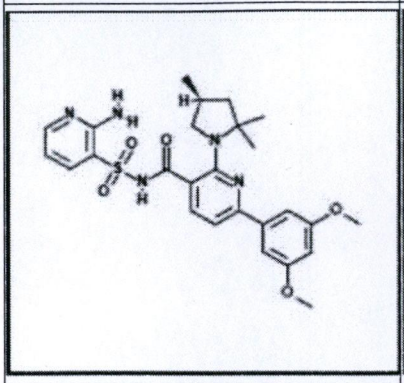
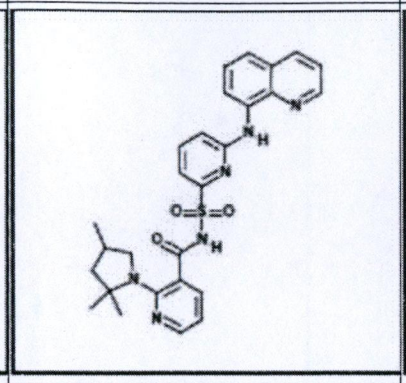
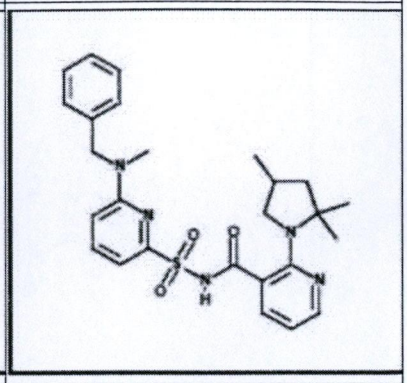
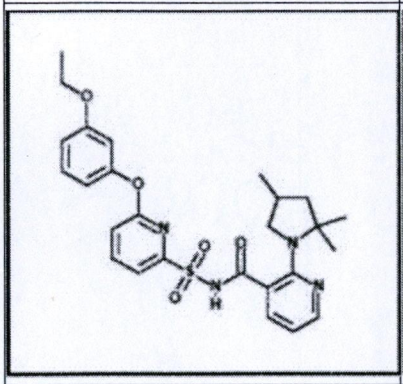
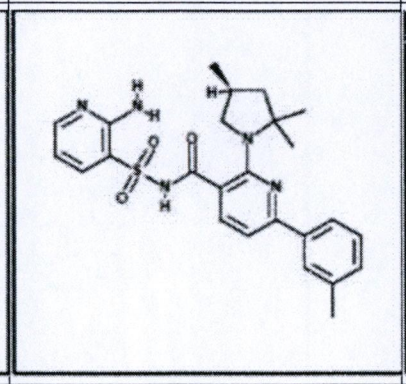
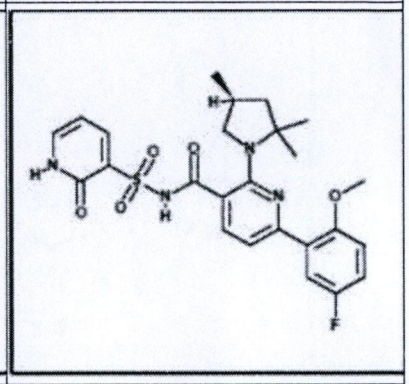
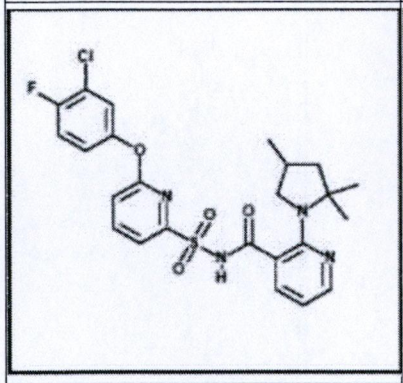
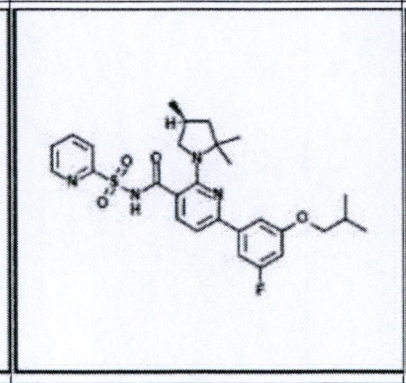
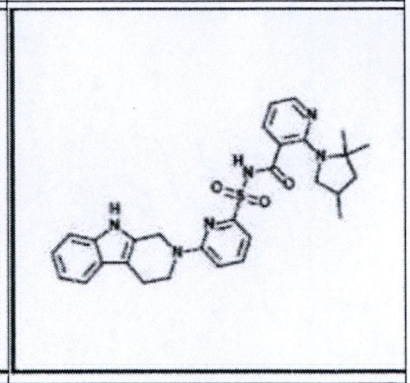
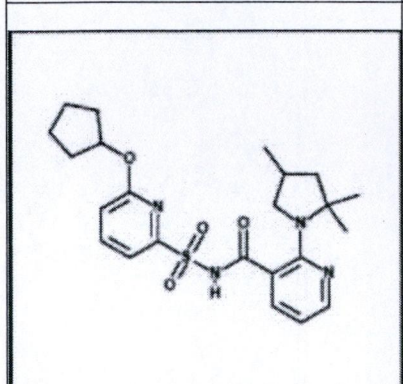
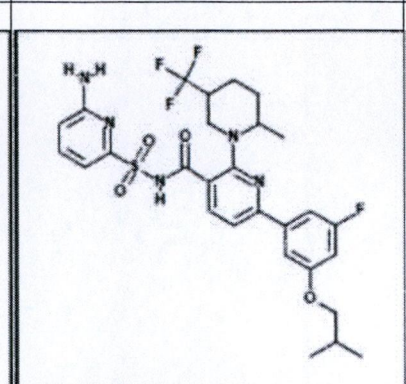
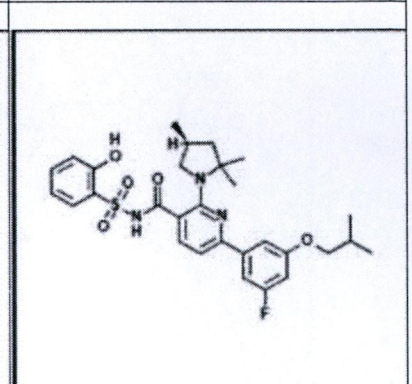
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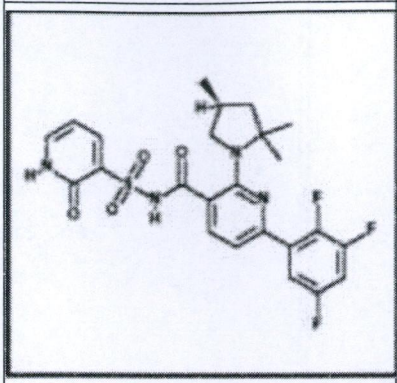
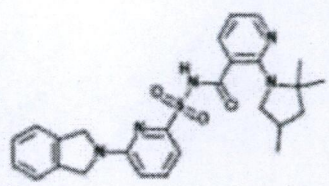
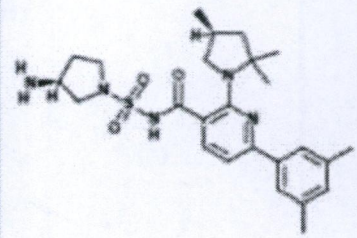
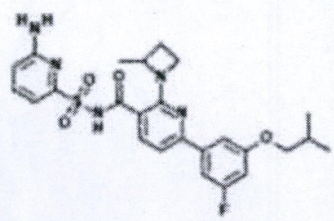
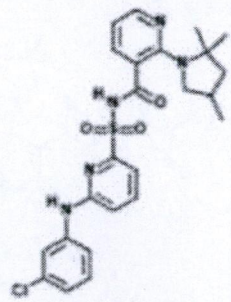
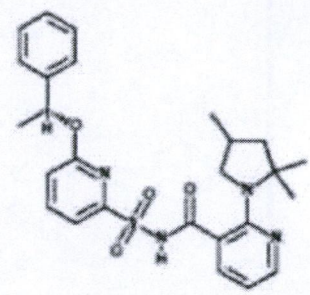
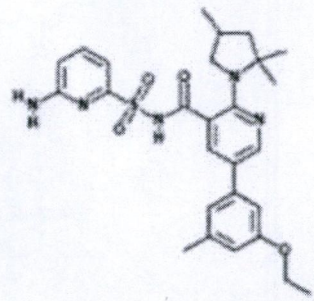
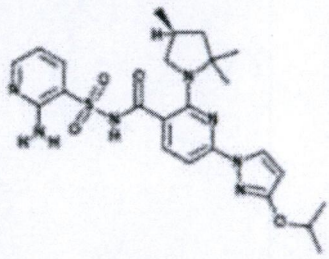
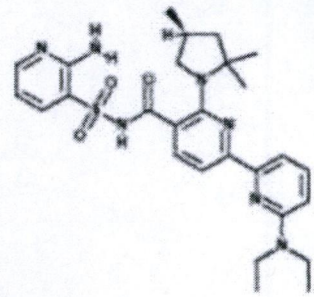
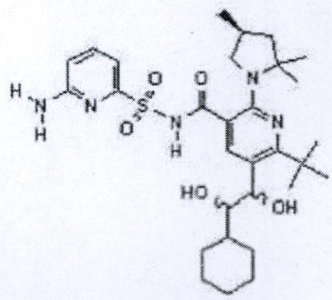
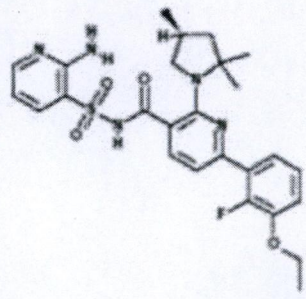
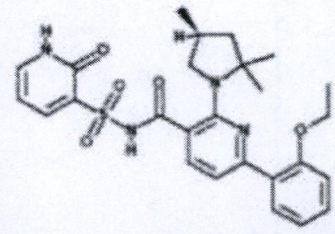
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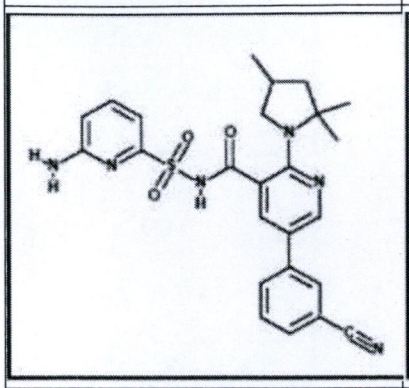
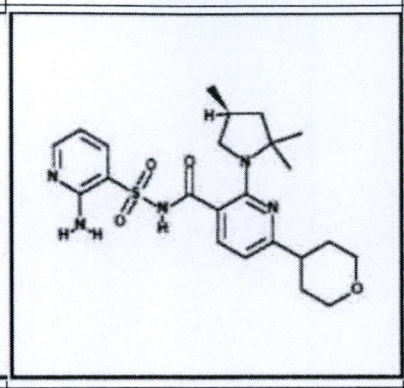
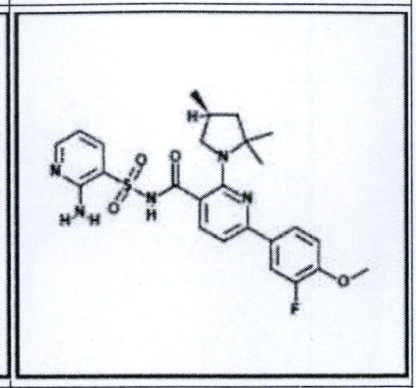
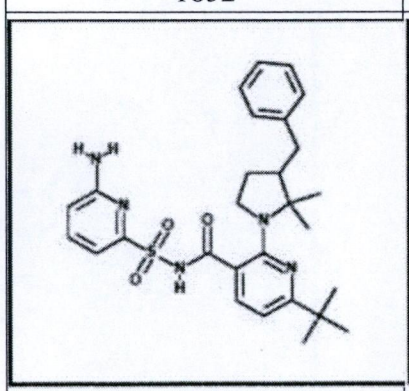
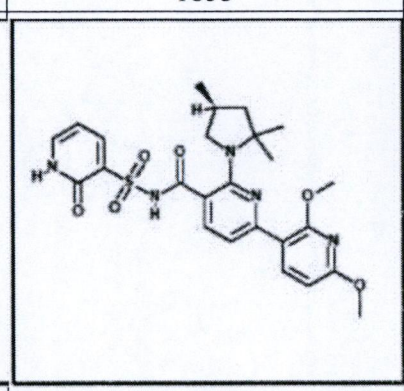
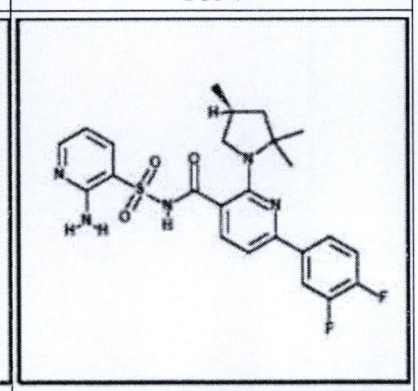
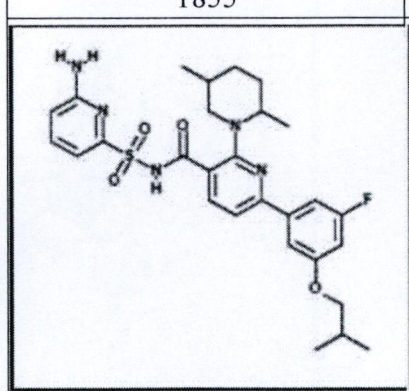
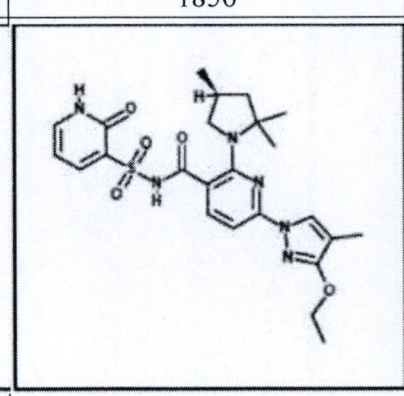
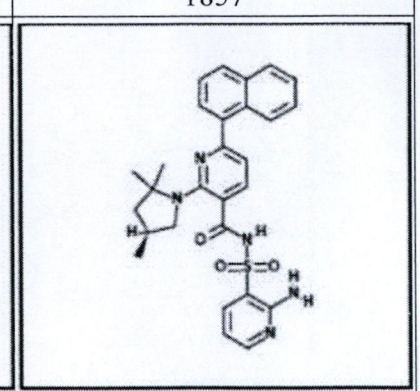
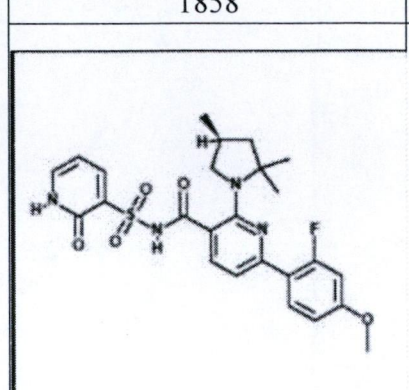
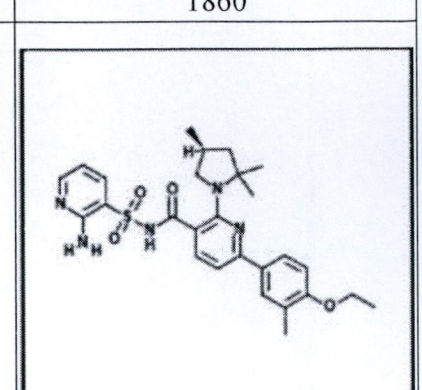
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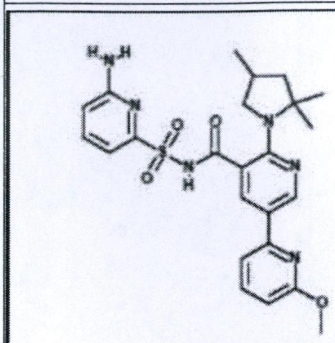
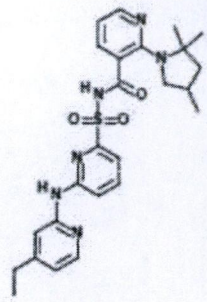
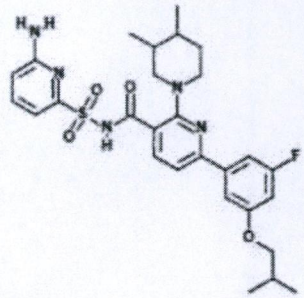
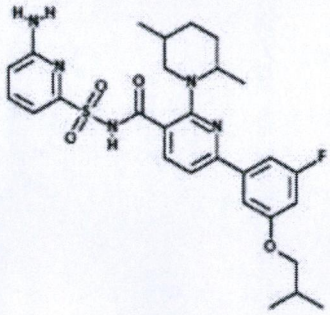
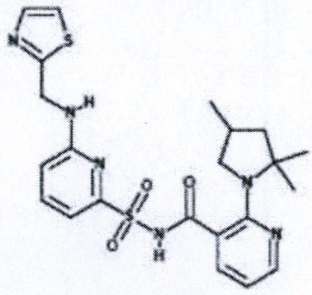
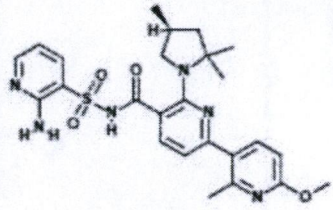
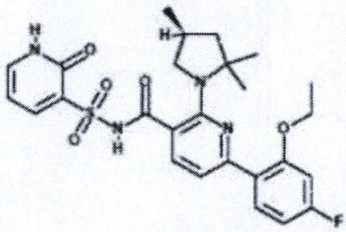
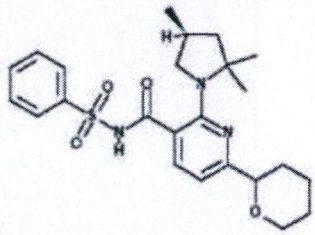
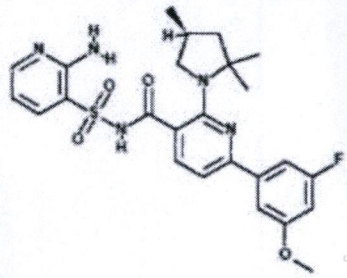
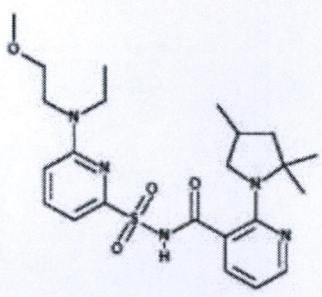
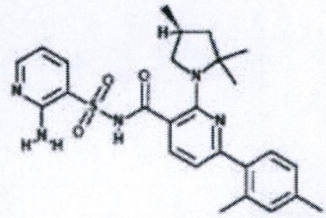
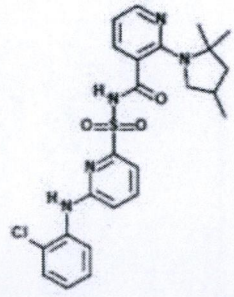
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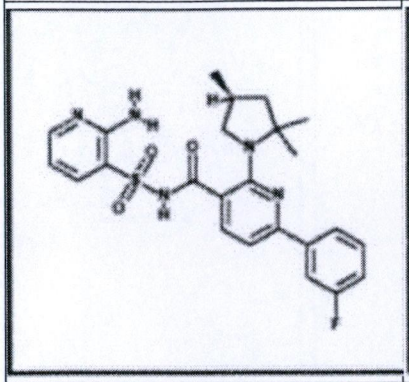
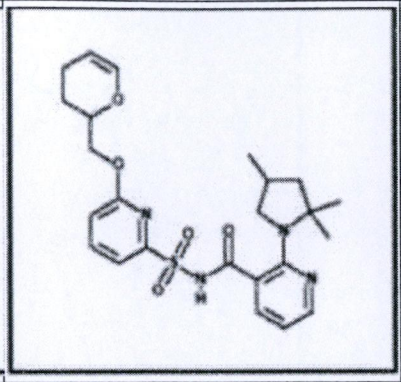
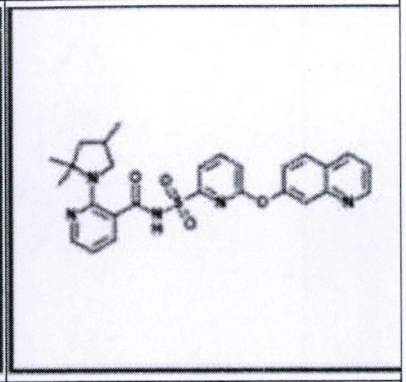
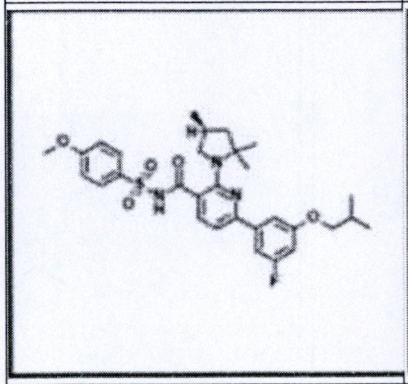
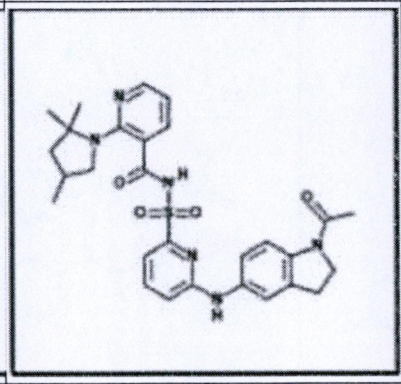
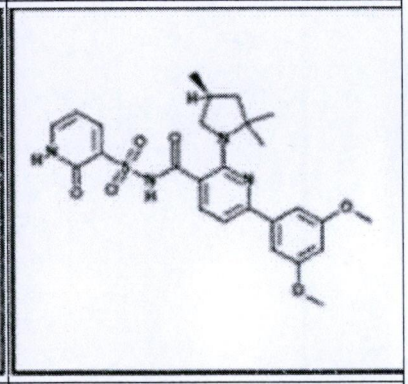
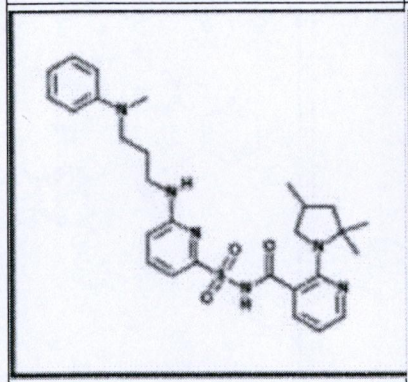
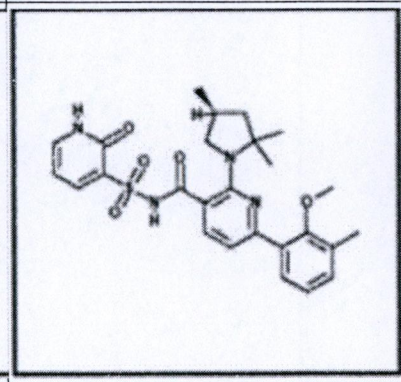
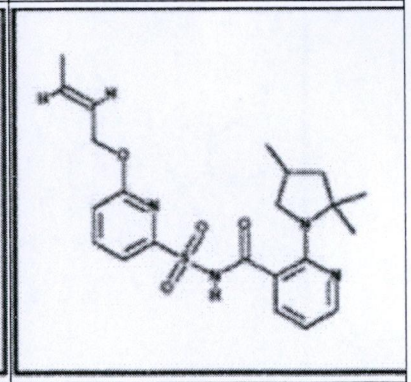
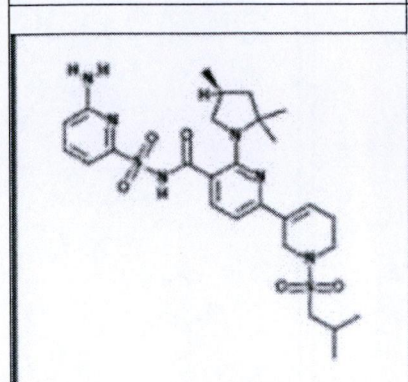
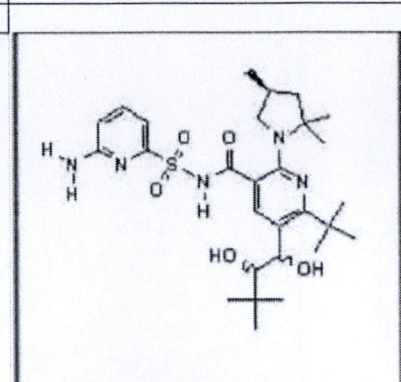
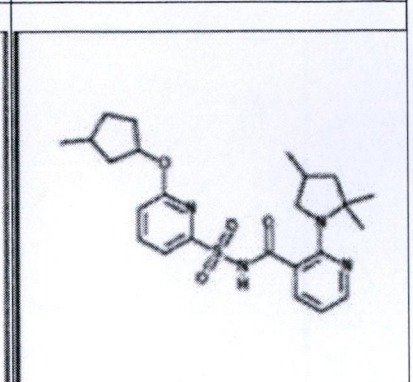
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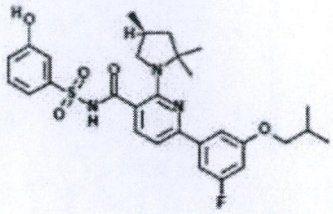
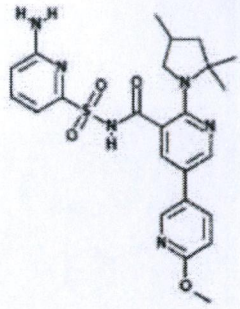
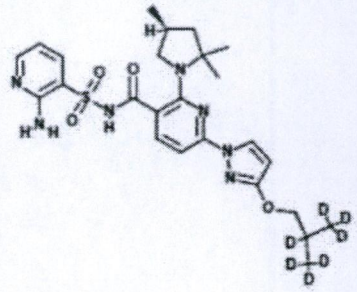
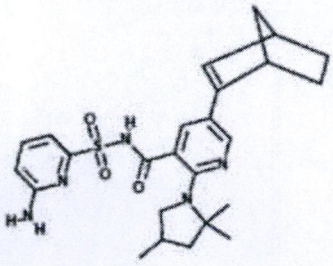
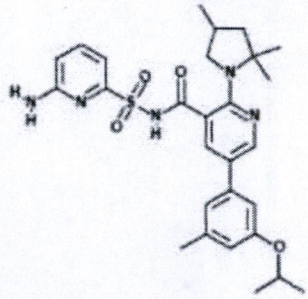
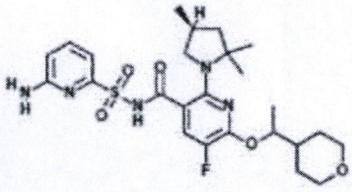
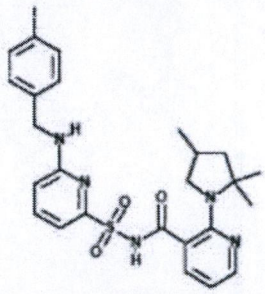
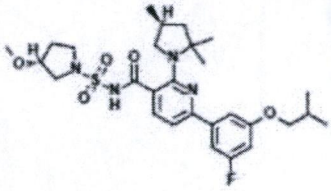
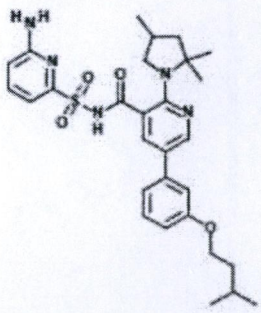
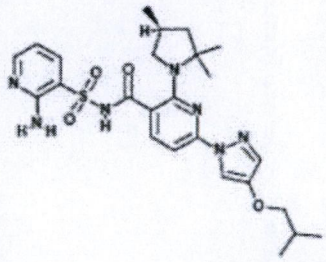
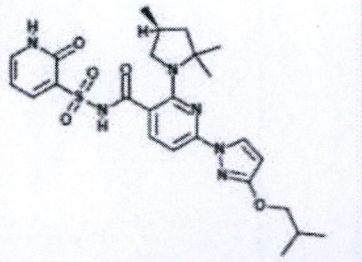
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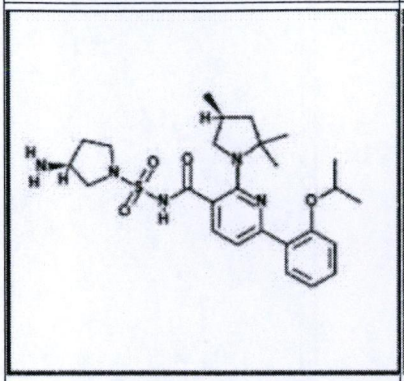
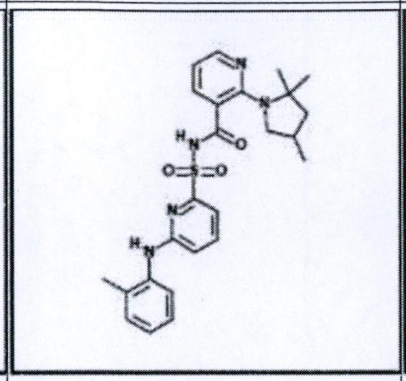
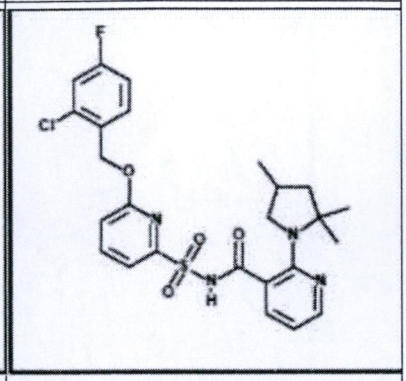
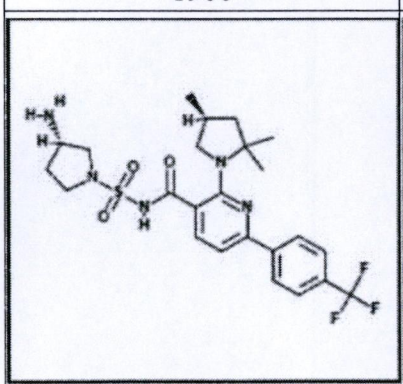
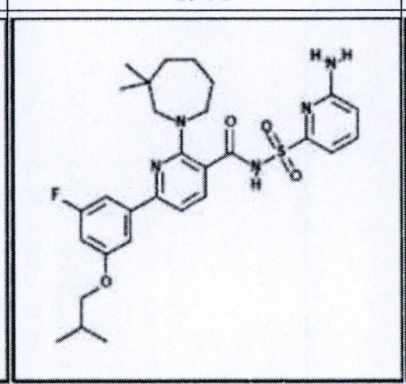
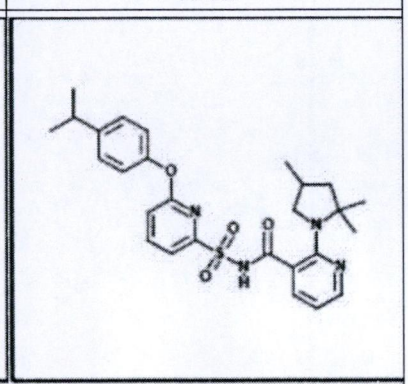
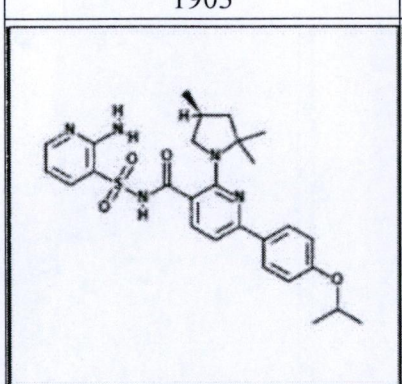
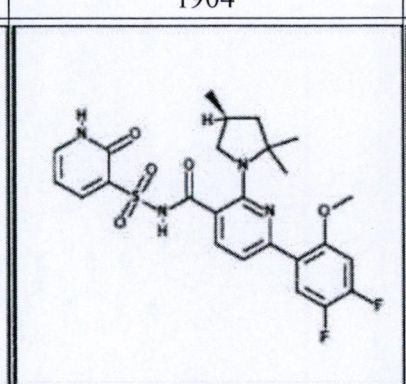
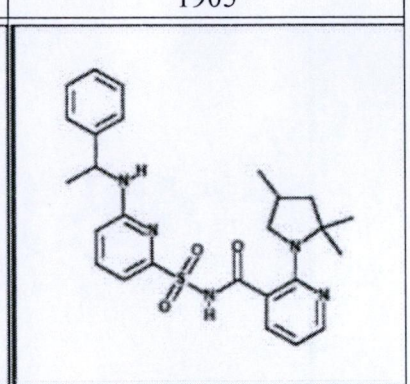
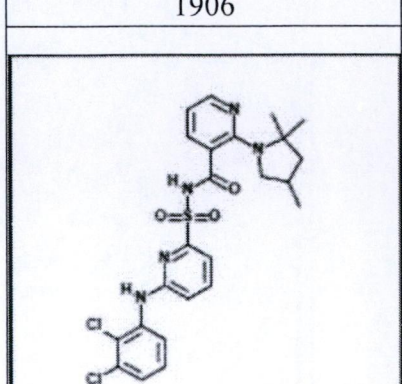
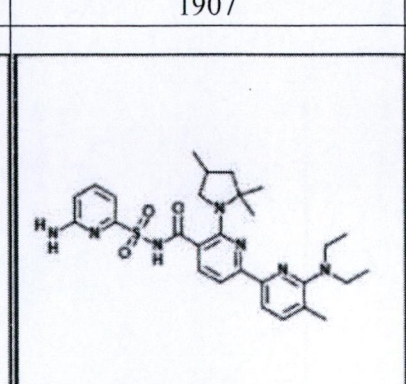
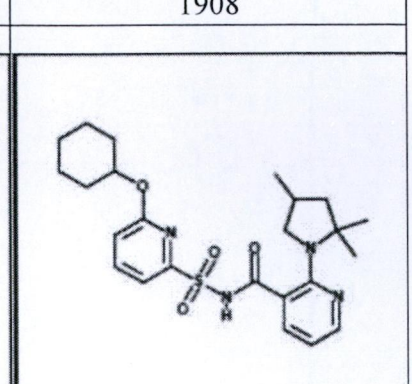
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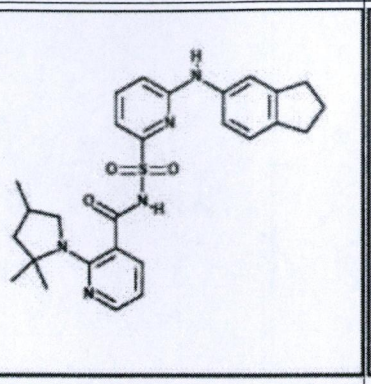
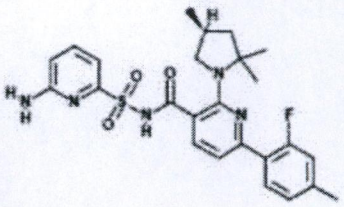
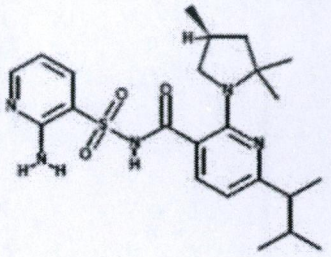
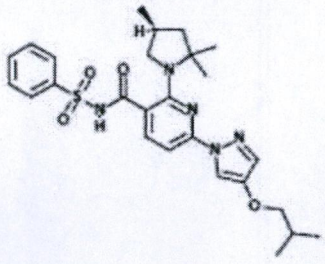
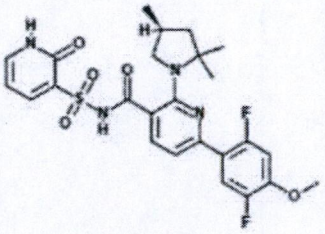
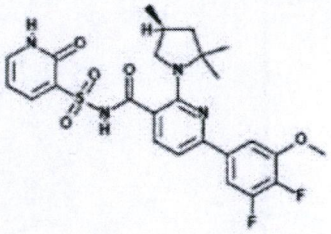
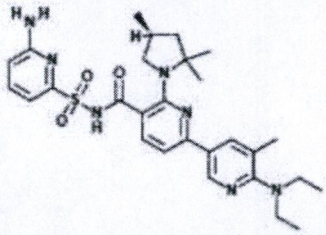
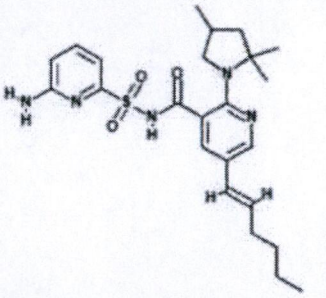
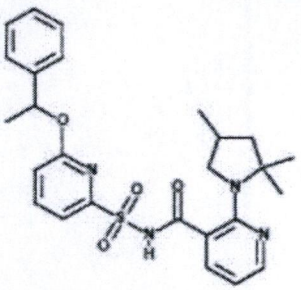
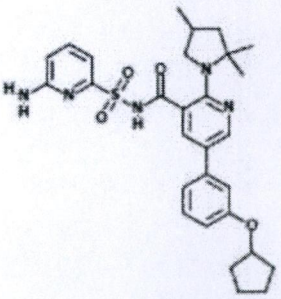
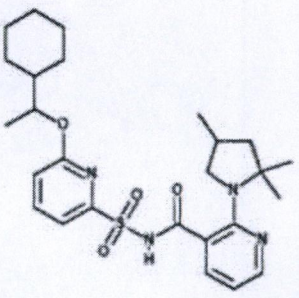
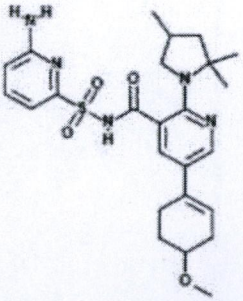
| 1849 | 1850 | 1851 |
|---|---|---|
|  |  |  |
| 1852 | 1853 | 1854 |
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| 1855 | 1856 | 1857 |
|  |  |  |
| 1858 | | 1860 |
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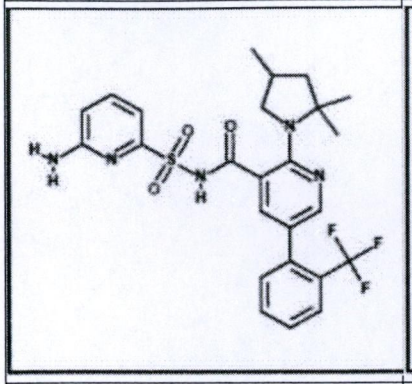
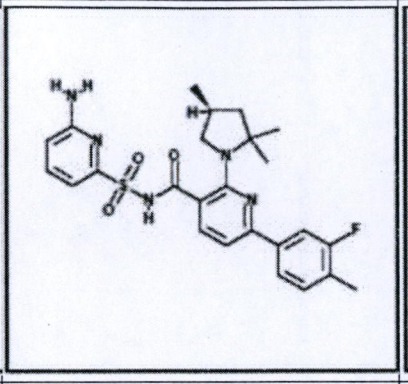
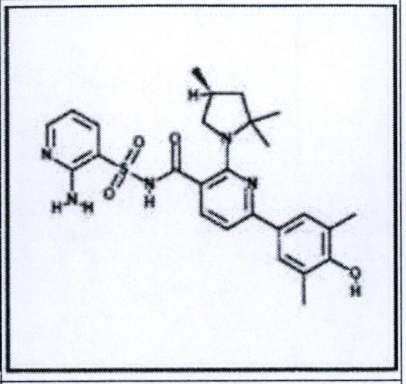
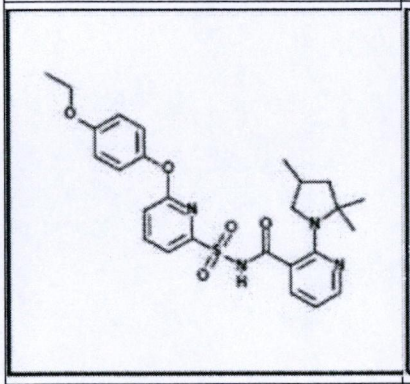
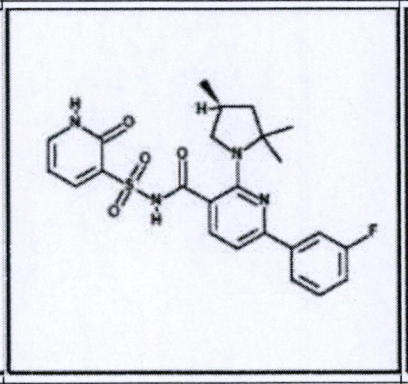
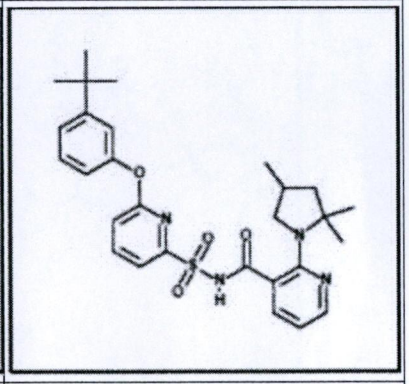
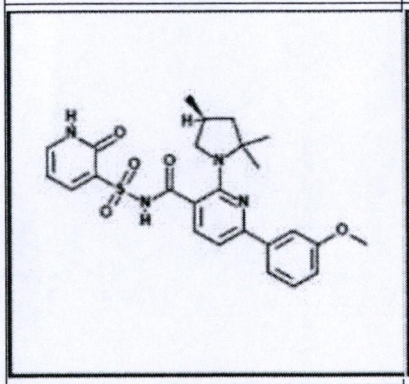
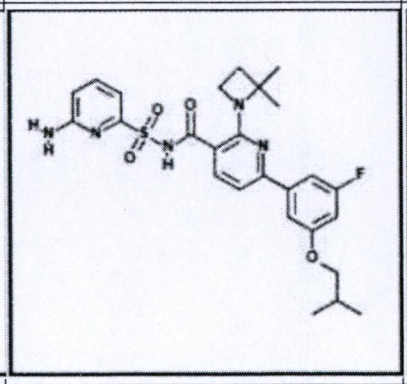
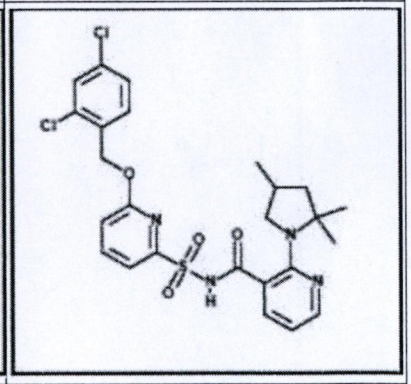
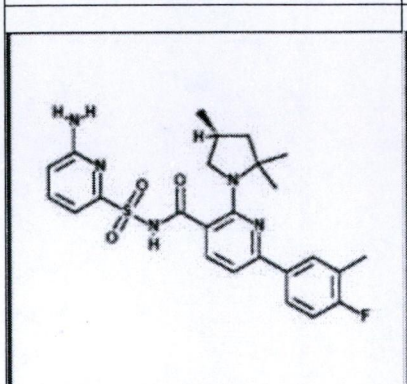
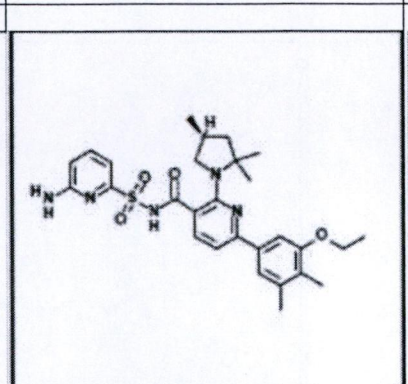
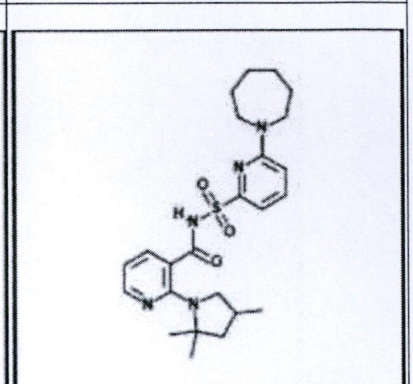
| 1861 | 1862 | 1863 |
|---|---|---|
|  |  |  |
| 1864 | 1865 | 1866 |
|  |  |  |
| 1867 | 1868 | 1869 |
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| 1870 | 1871 | 1872 |
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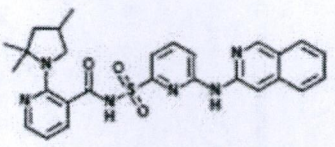
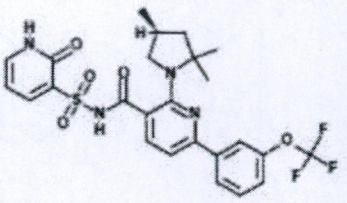
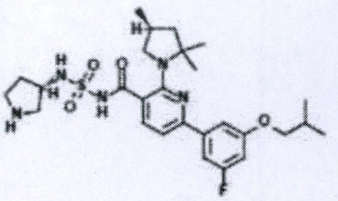
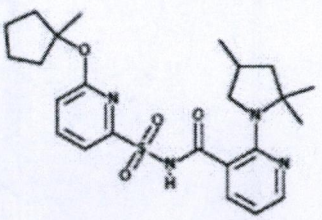
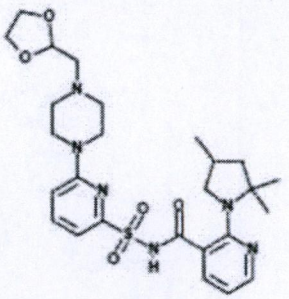
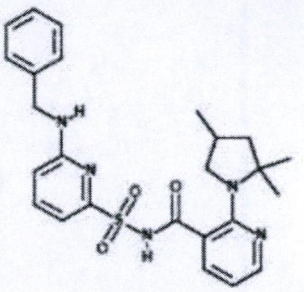
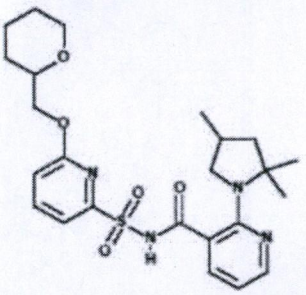
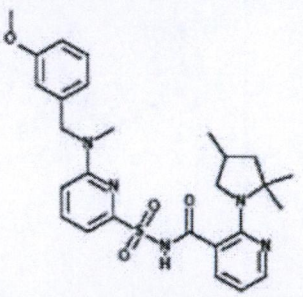
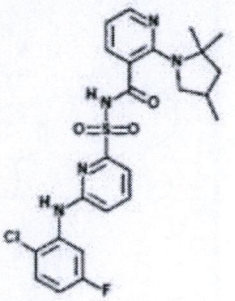
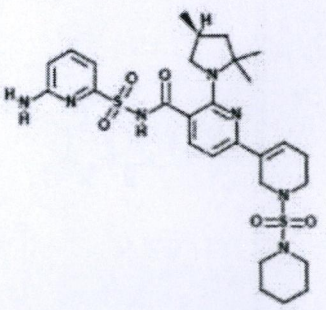
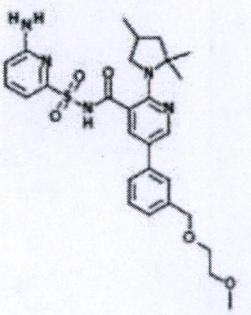
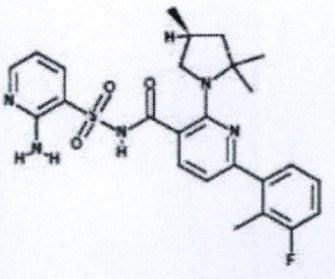
| 1873 | 1874 | 1875 |
|---|---|---|
|  |  |  |
| 1876 | 1877 | 1878 |
|  |  |  |
| 1879 | 1880 | 1881 |
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| 1882 | 1883 | 1884 |
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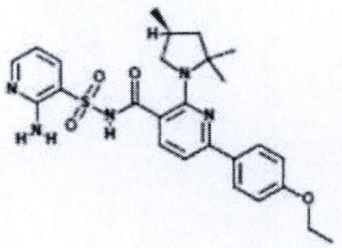
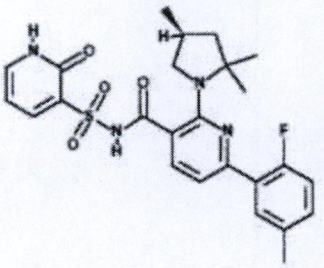
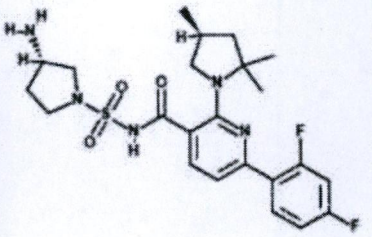
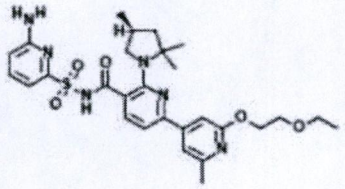
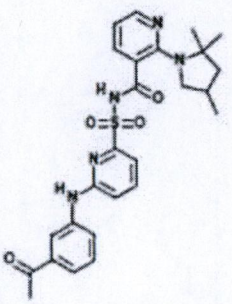
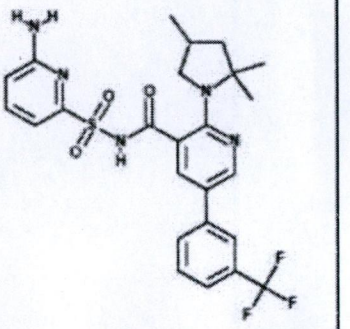
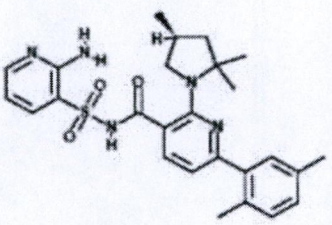
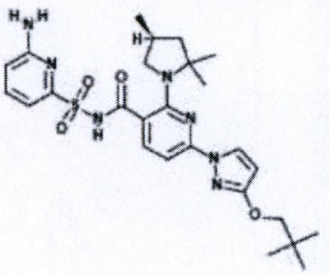
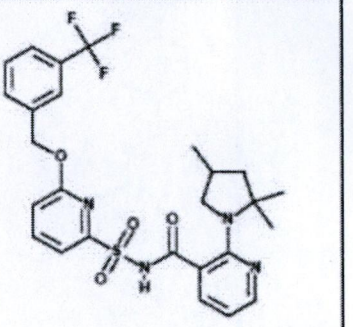
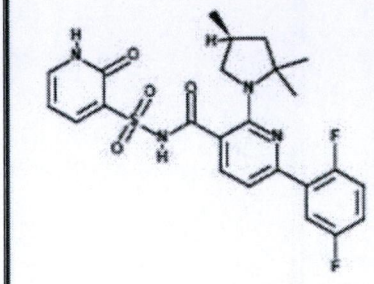
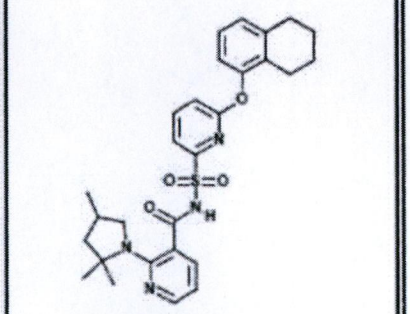
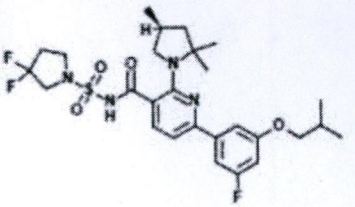
| 1885 | 1886 | 1887 |
|---|---|---|
|  |  |  |
| 1888 | 1889 | |
|  |  | |
| 1891 | 1892 | 1893 |
|  |  |  |
| 1894 | 1895 | 1896 |
|  |  |  |

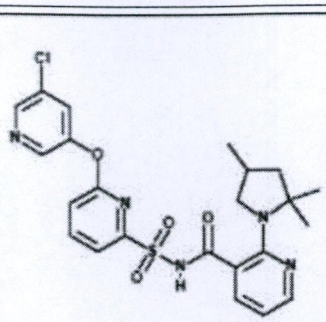
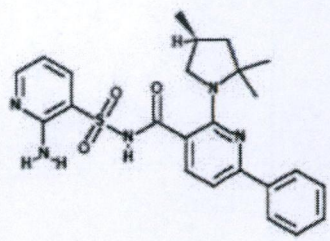
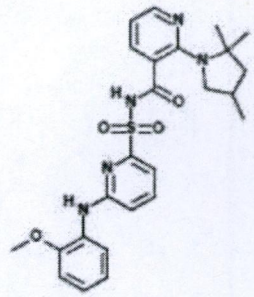
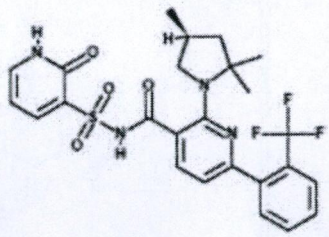
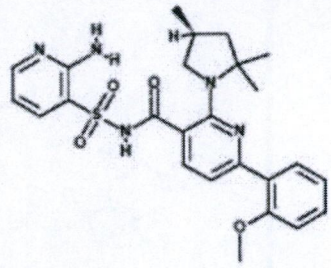
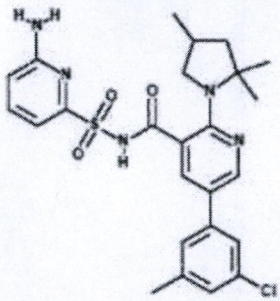
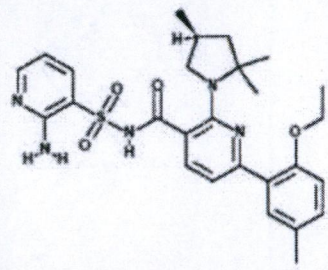
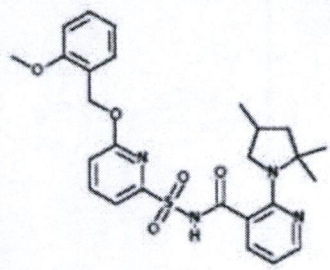
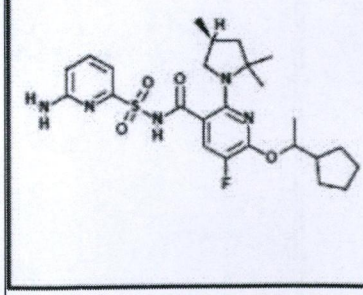
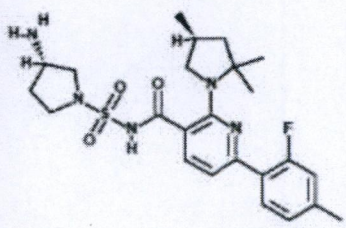
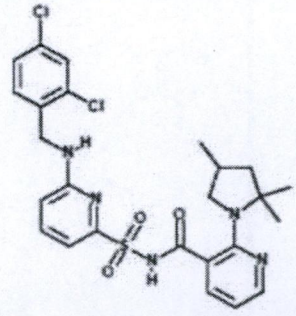
| 1897 | 1898 | 1899 |
|---|---|---|
|  |  |  |
| 1900 | 1901 | 1902 |
|  |  |  |
| 1903 | 1904 | 1905 |
|  |  |  |
| 1906 | 1907 | 1908 |
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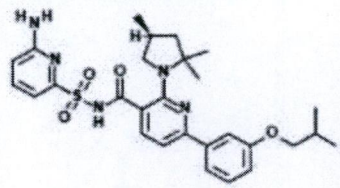
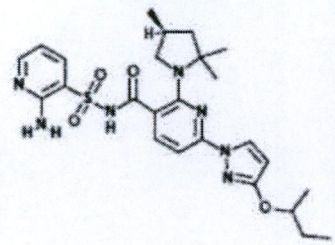
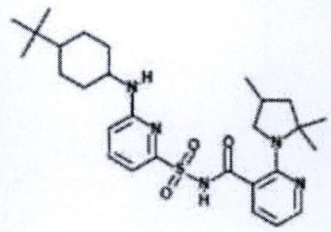
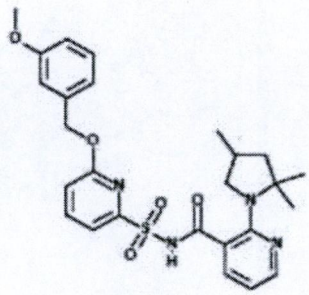
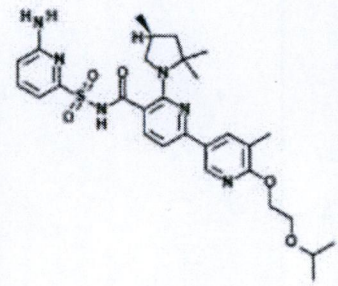
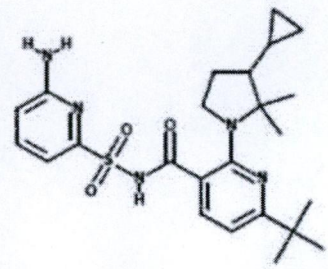
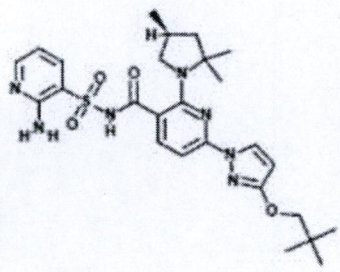
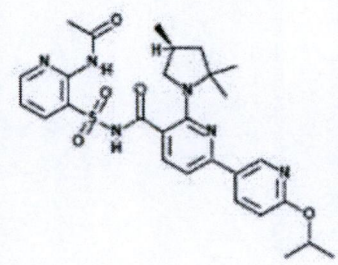
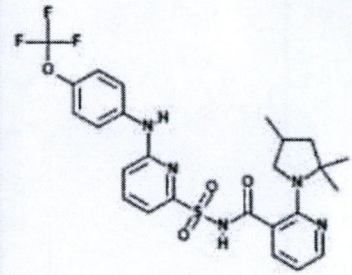
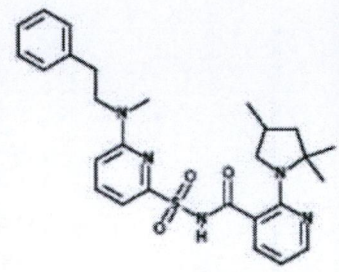
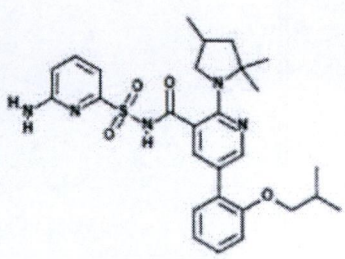
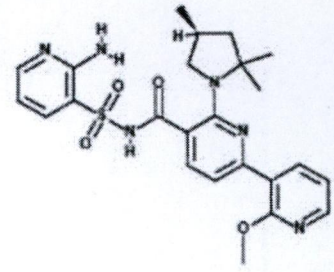
| 1909 | 1910 | 1911 |
|---|---|---|
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| 1912 | 1913 | 1914 |
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| 1915 | 1916 | 1917 |
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| 1918 | 1919 | 1920 |
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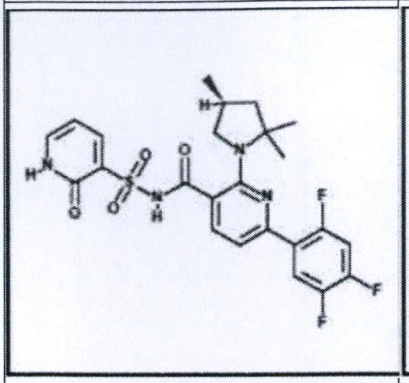
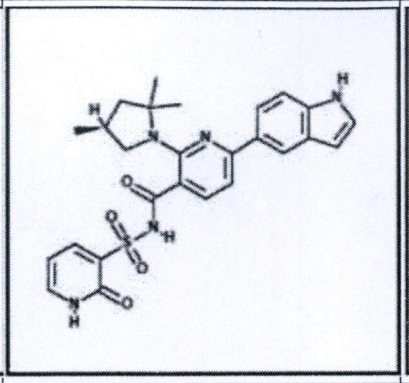
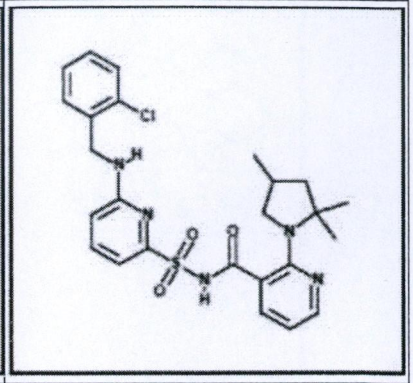
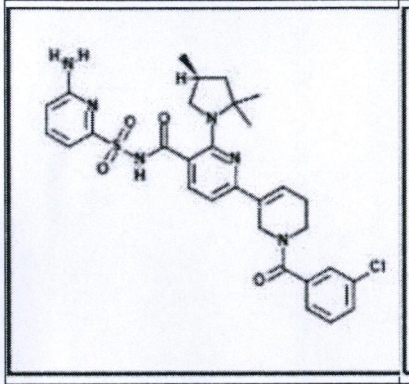
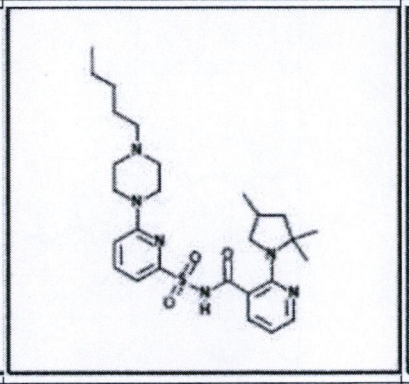
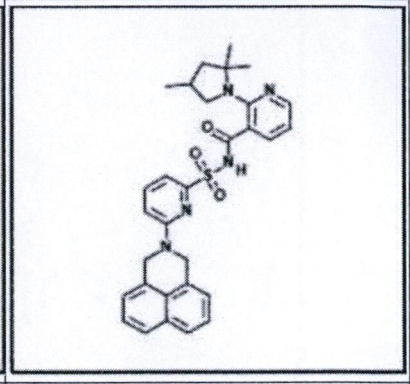
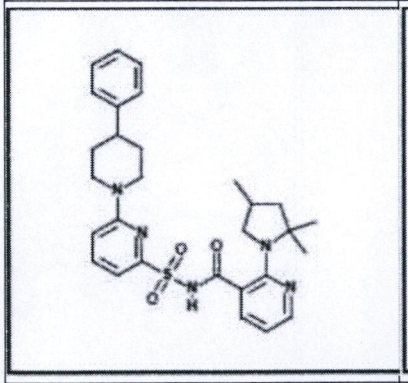
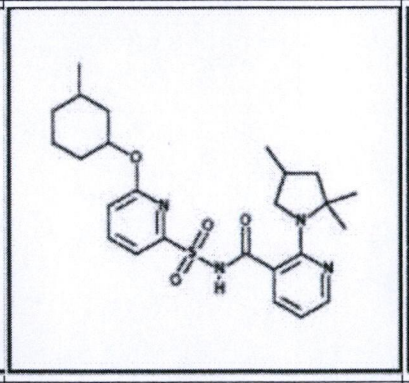
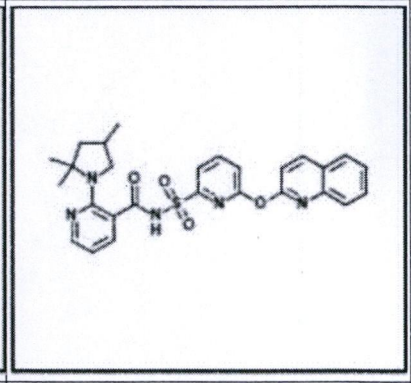
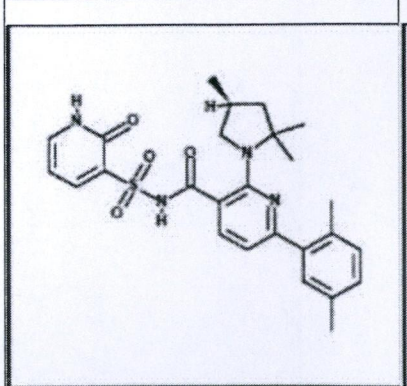
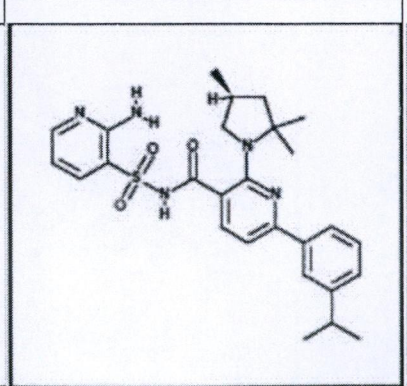
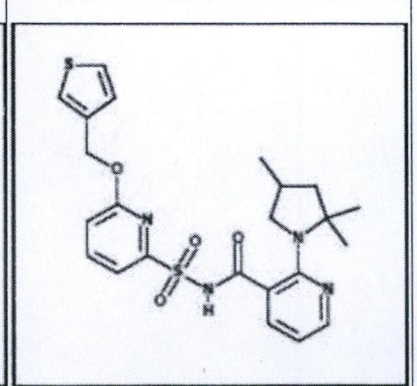
| 1921 | 1922 | 1923 |
|---|---|---|
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| 1924 | 1925 | 1926 |
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| 1927 | 1928 | 1929 |
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| 1930 | 1931 | 1932 |
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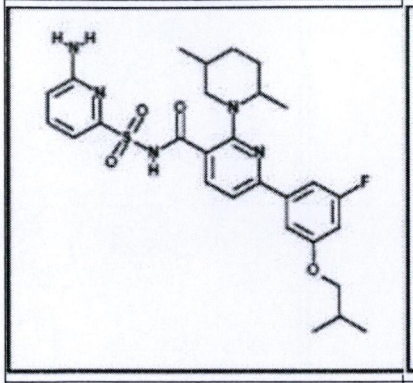
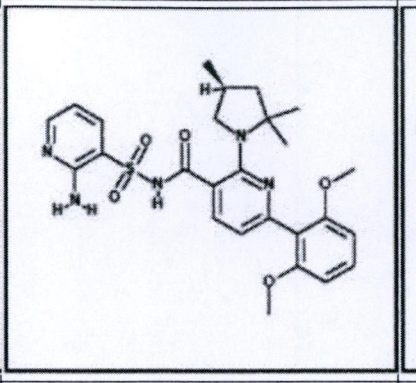
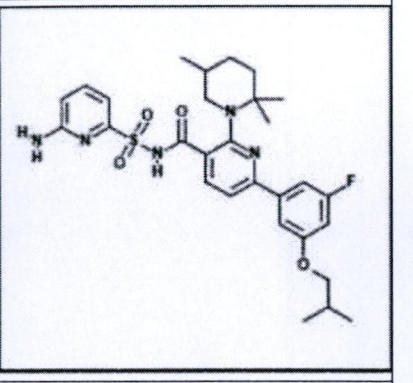
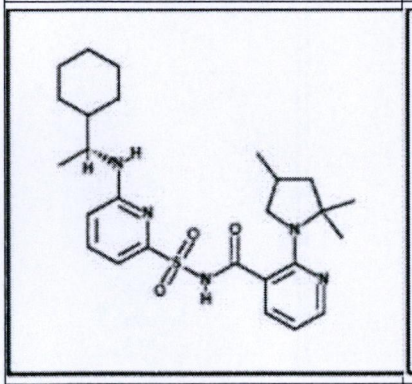
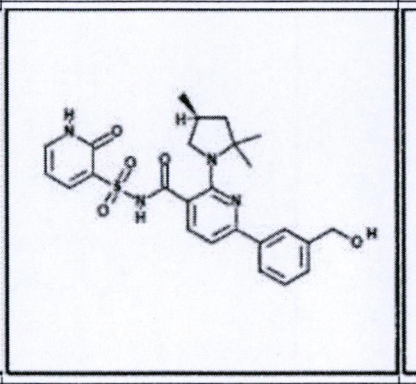
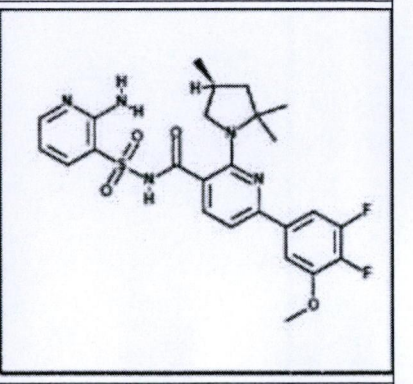
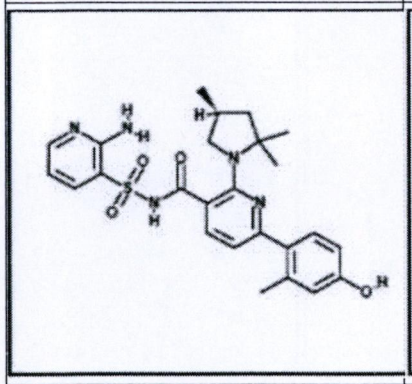
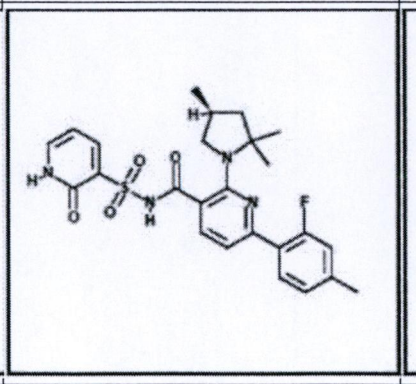
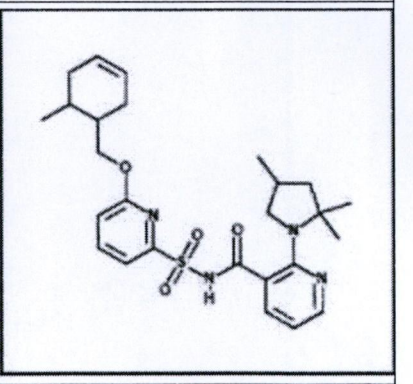
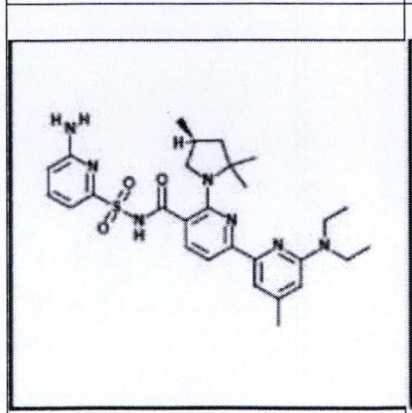
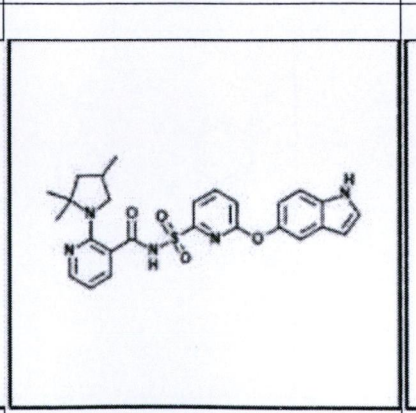
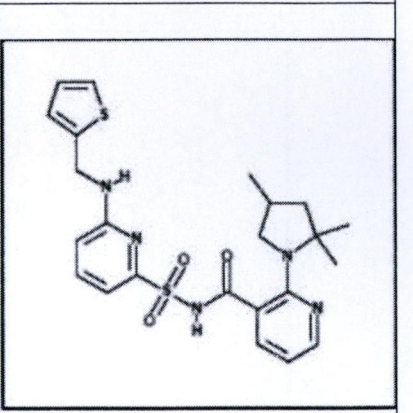
| 1933 | 1934 | 1935 |
|---|---|---|
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| 1939 | 1940 | 1941 |
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| 1942 | 1943 | 1944 |
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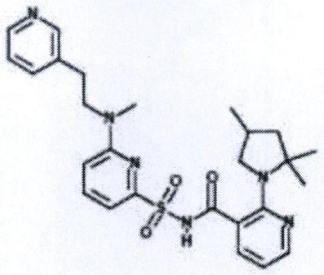
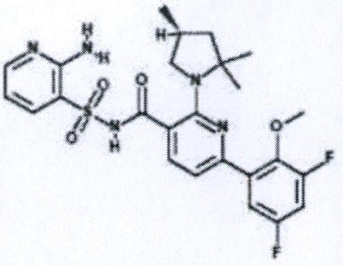
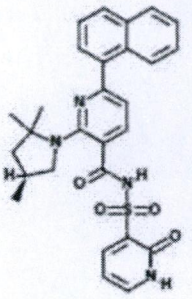
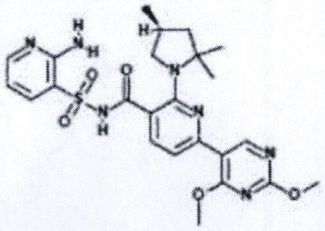
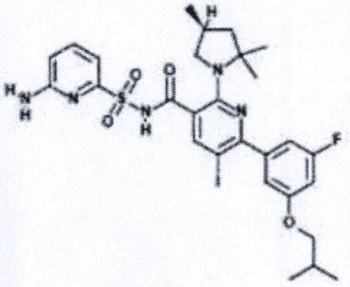
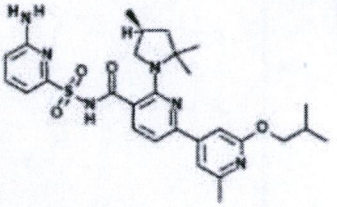
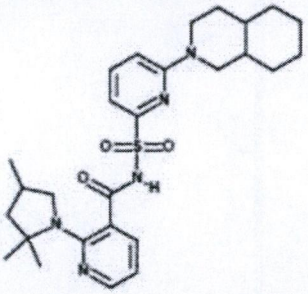
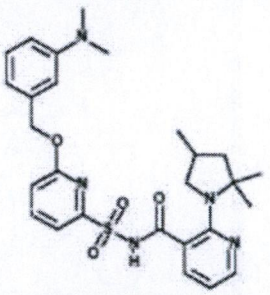
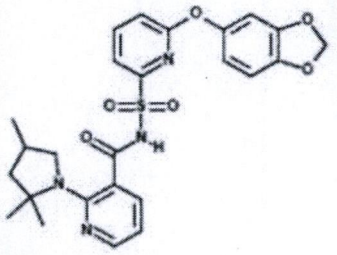
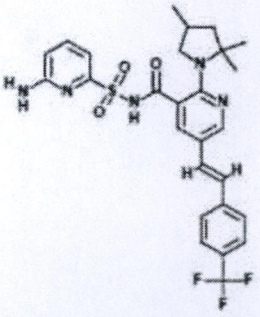
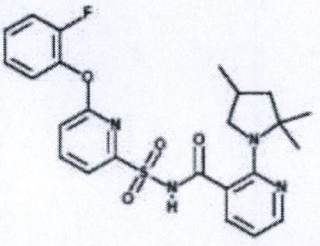
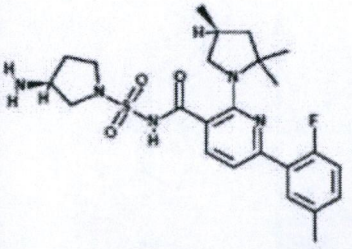
| 1945 | 1946 | 1947 |
|---|---|---|
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| 1948 | 1949 | 1950 |
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| 1951 | 1952 | 1953 |
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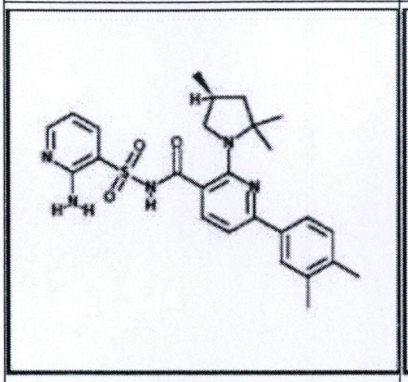
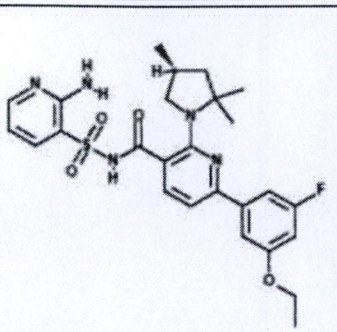
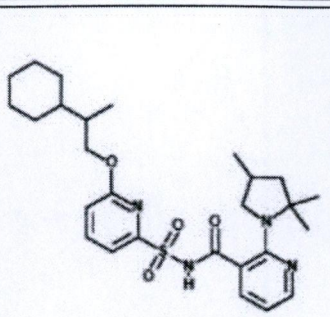
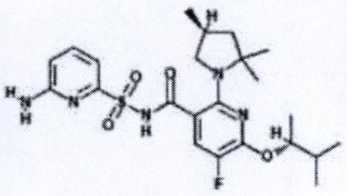
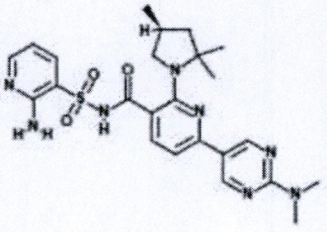
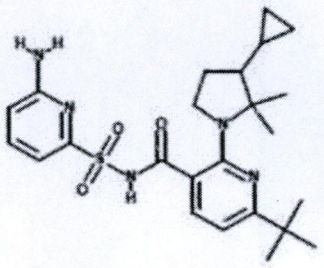
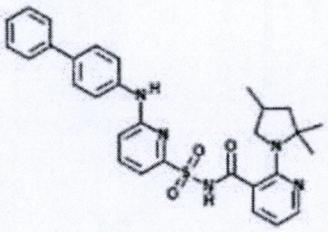
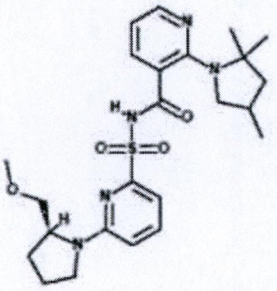
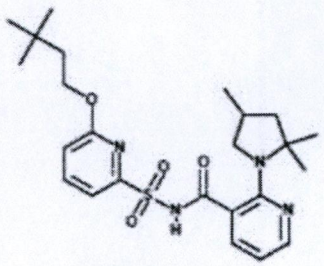
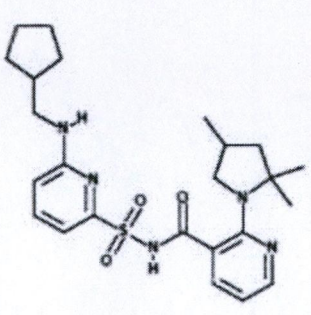
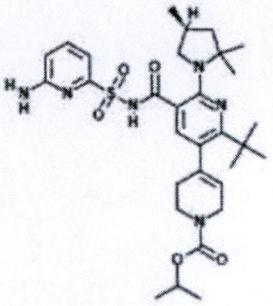
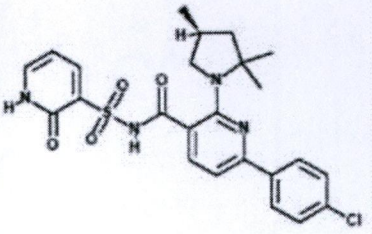
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| 1963 | 1964 | 1965 |
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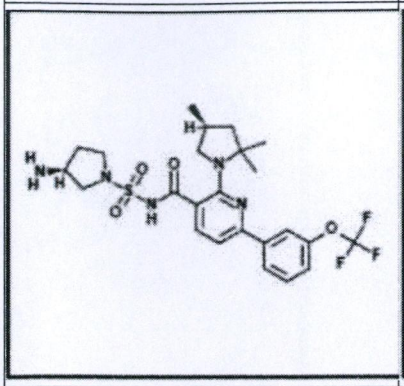
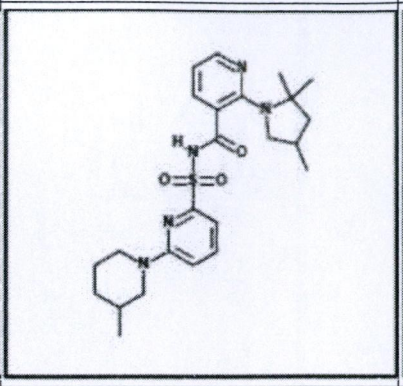
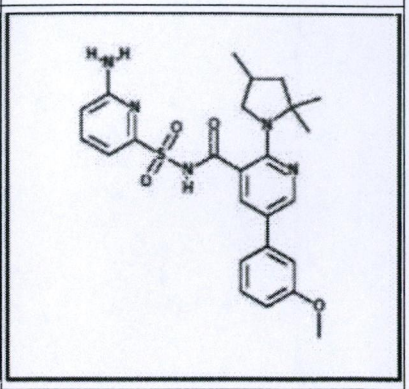
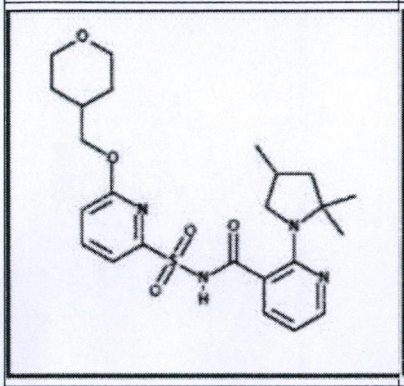
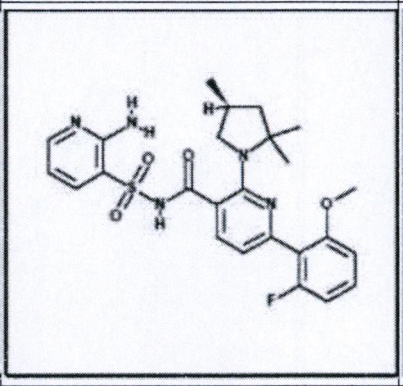
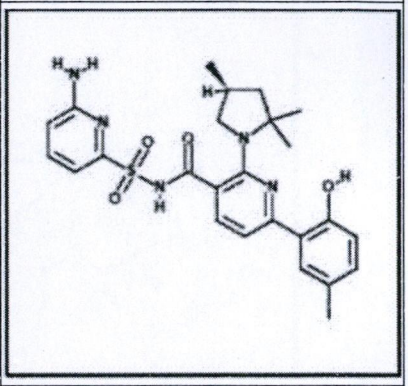
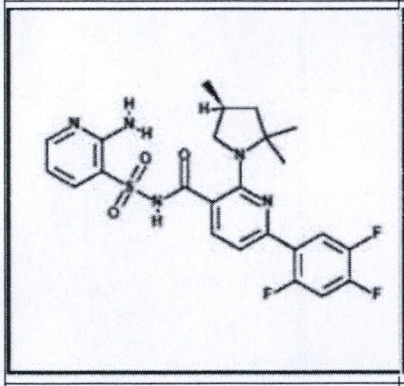
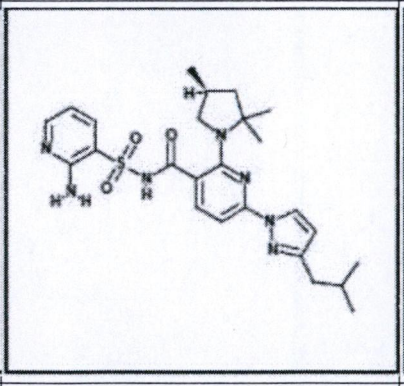
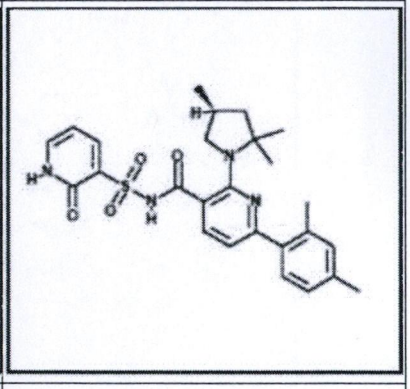
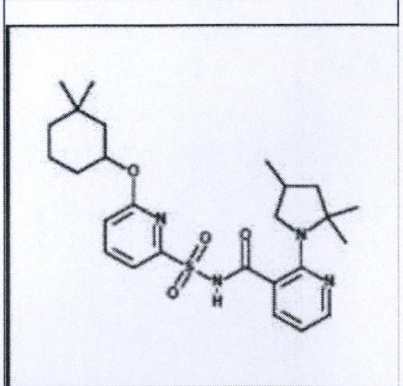
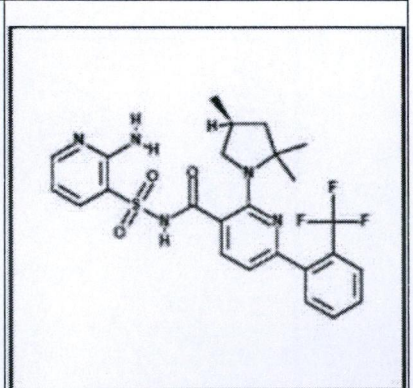
| 1969 | 1970 | 1971 |
|---|---|---|
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| 1975 | 1976 | 1977 |
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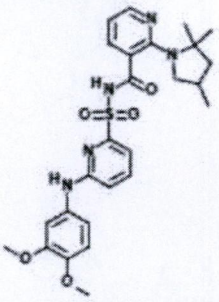
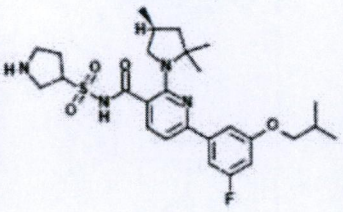
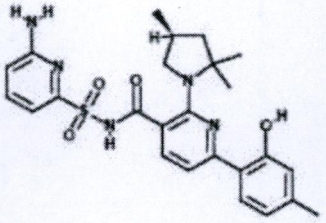
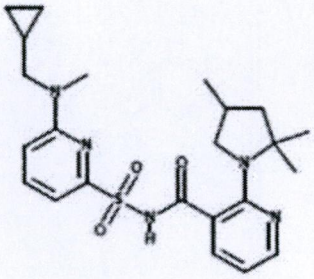
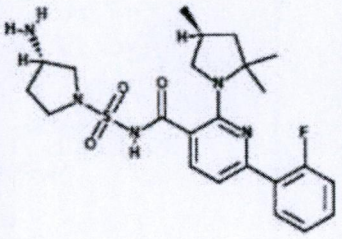
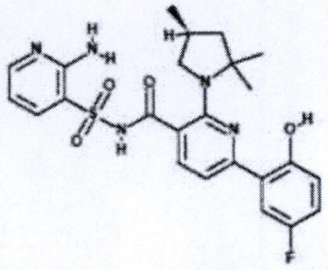
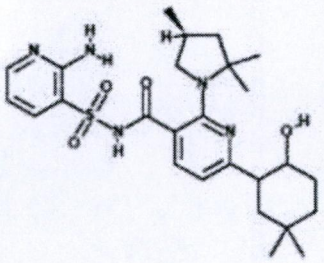
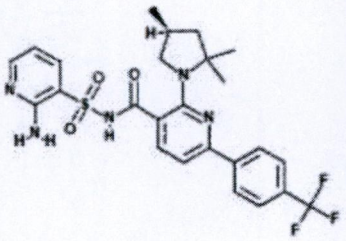
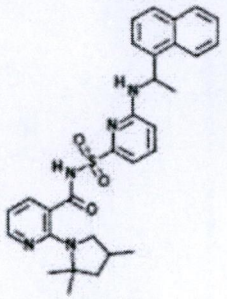
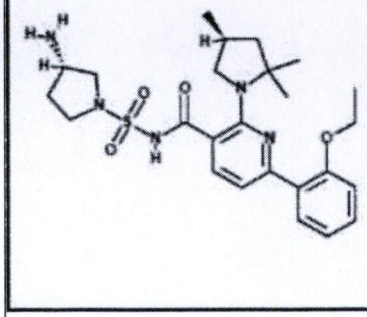
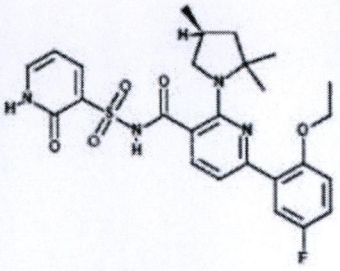
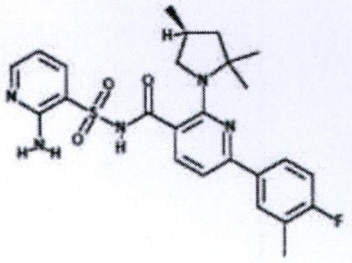
| 1981 | 1982 | 1983 |
|---|---|---|
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| 1987 | 1988 | 1989 |
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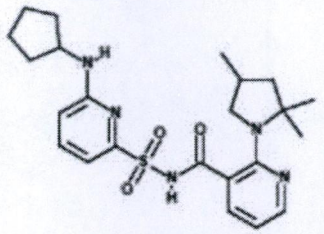
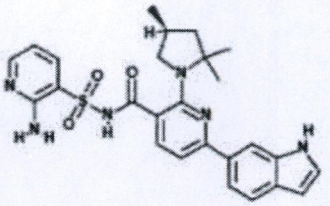
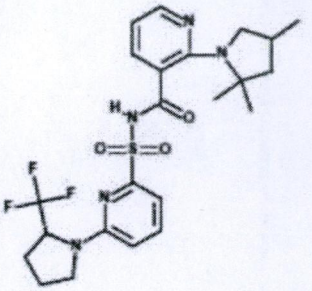
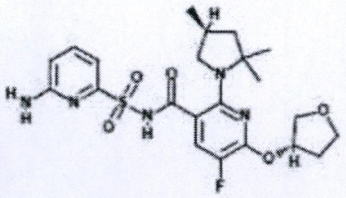
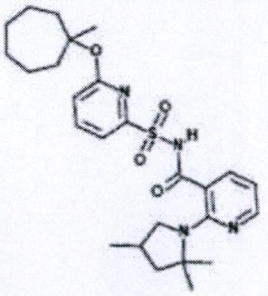
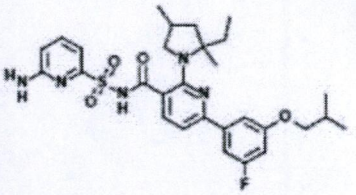
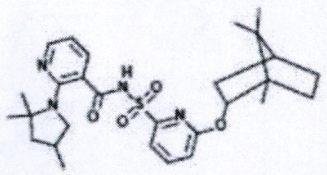
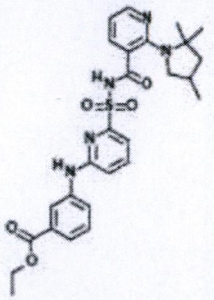
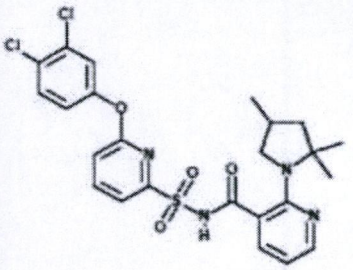
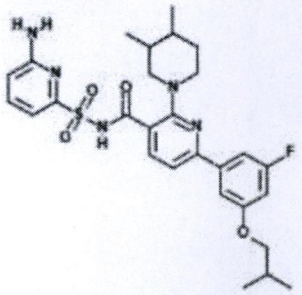
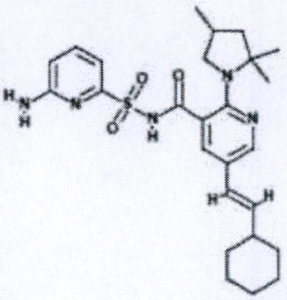
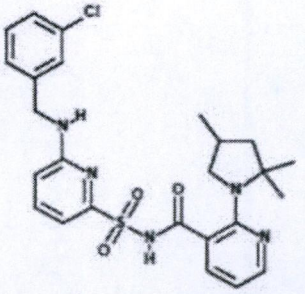
| 1993 | 1994 | 1995 |
|---|---|---|
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| 1999 | 2000 | 2001 |
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| 2002 | 2003 | 2004 |
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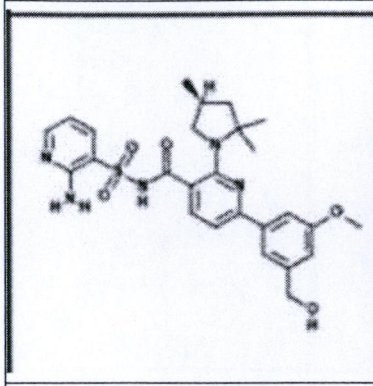
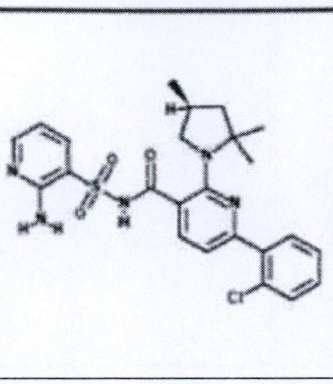
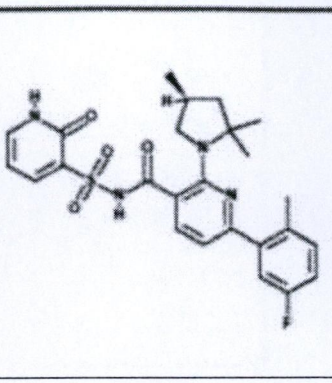
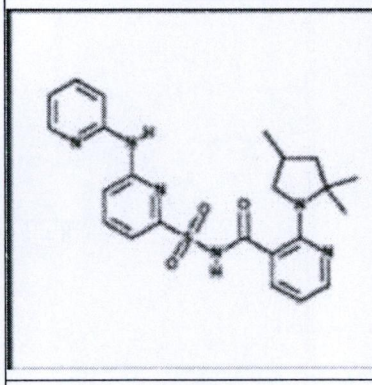
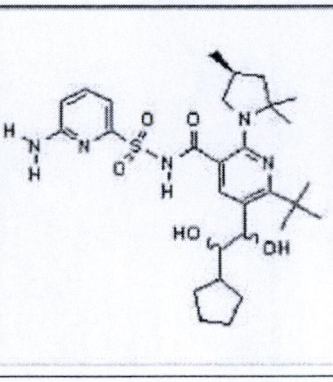
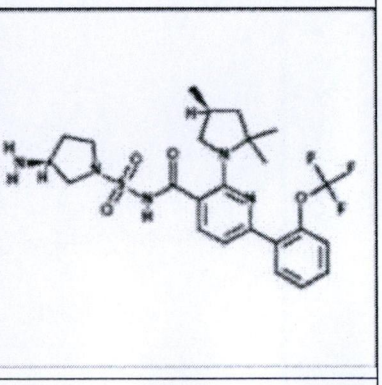
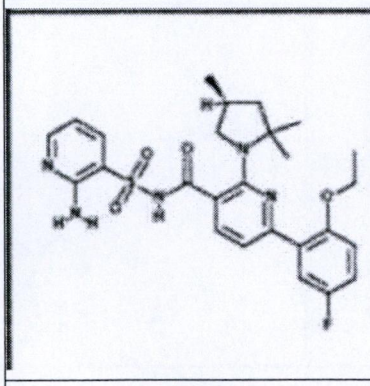
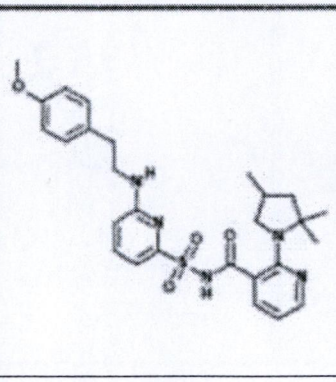
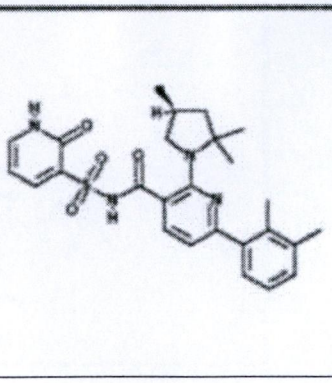
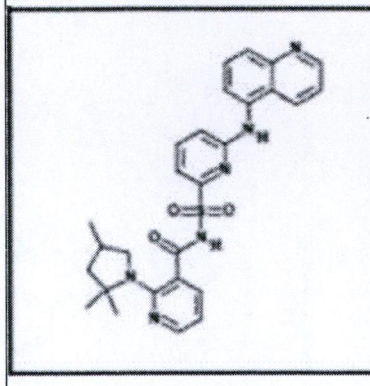
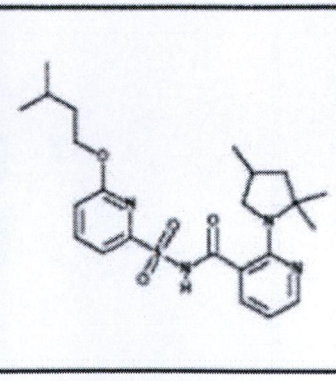
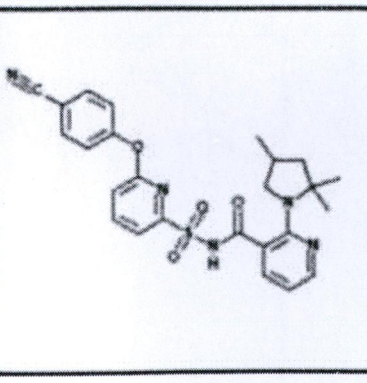
| 2005 | 2006 | 2007 |
|---|---|---|
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| 2008 | 2009 | 2010 |
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| 2011 | 2012 | 2013 |
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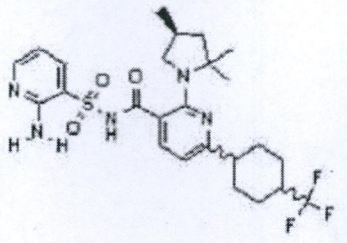
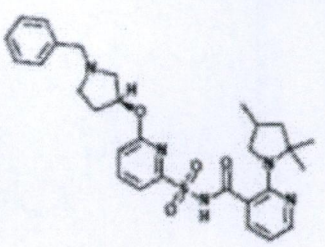
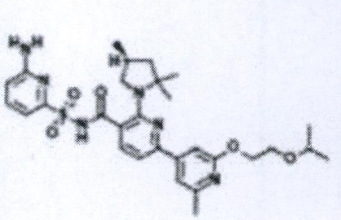
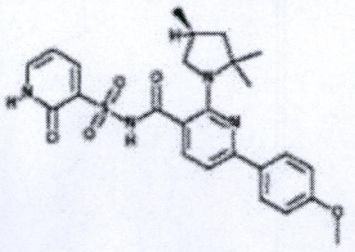
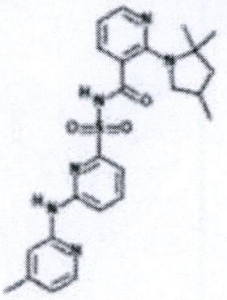
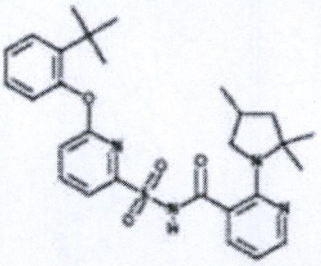
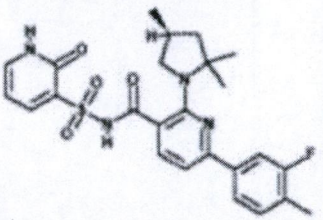
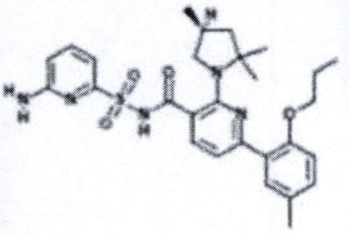
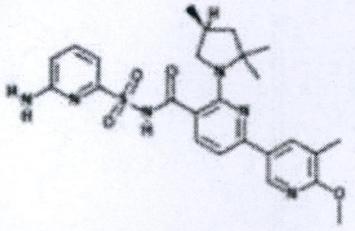
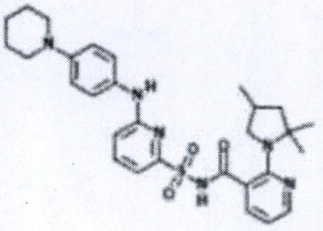
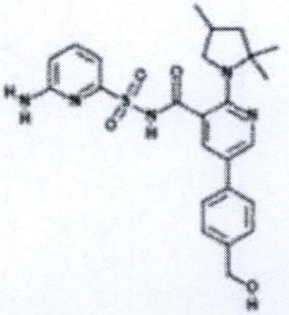
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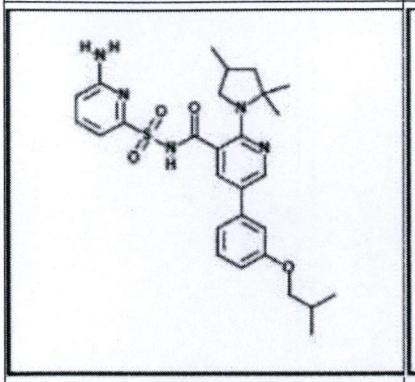
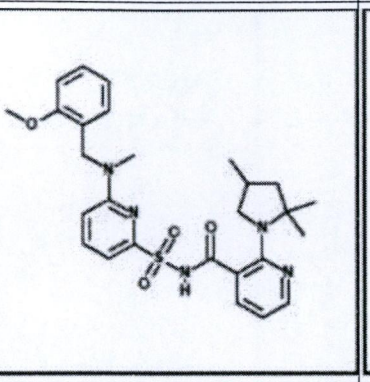
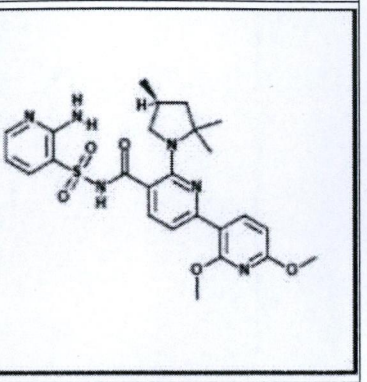
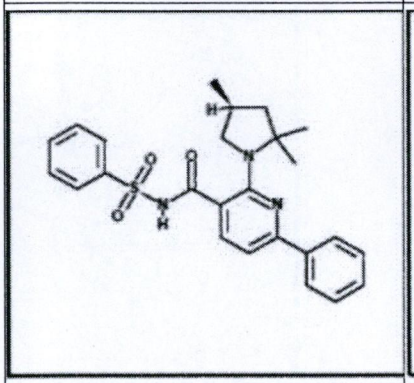
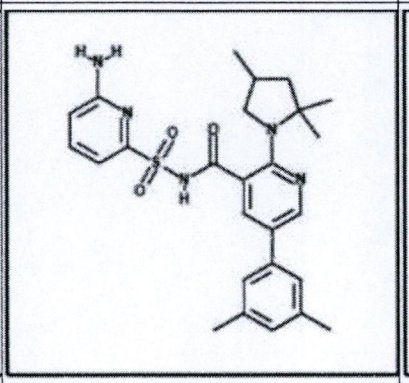
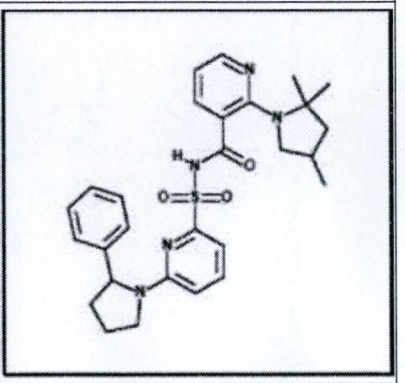
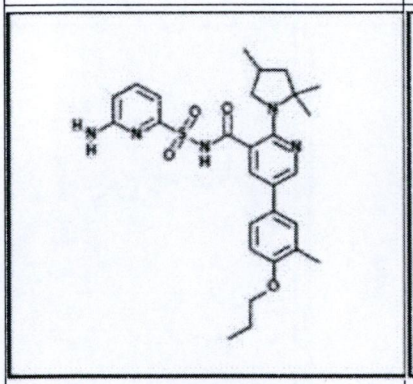
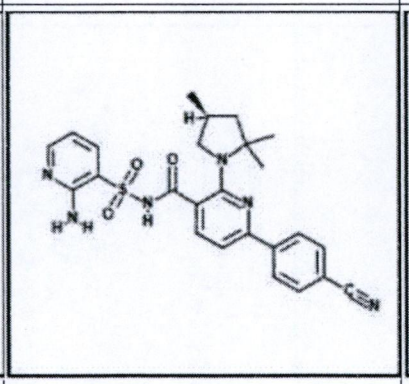
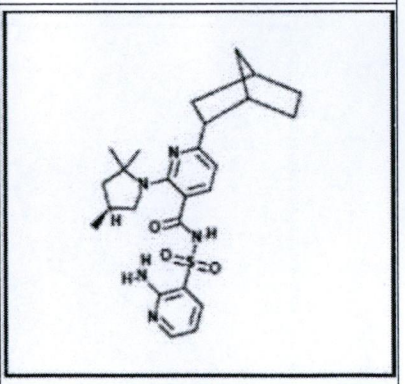
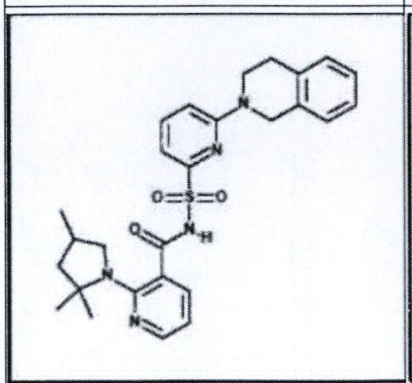
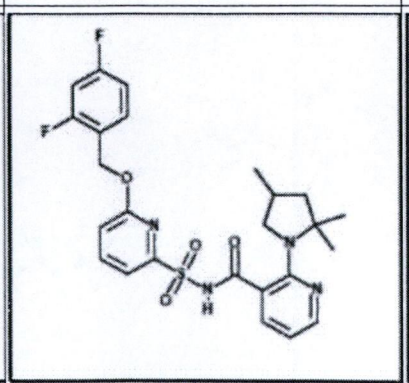
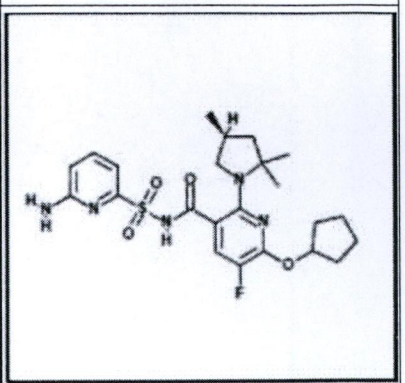
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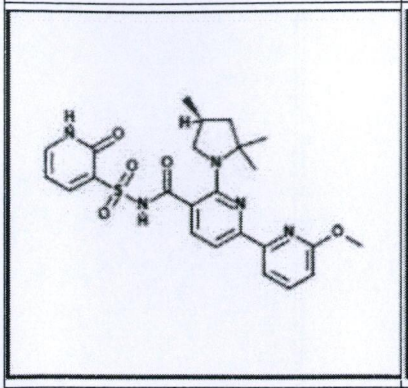
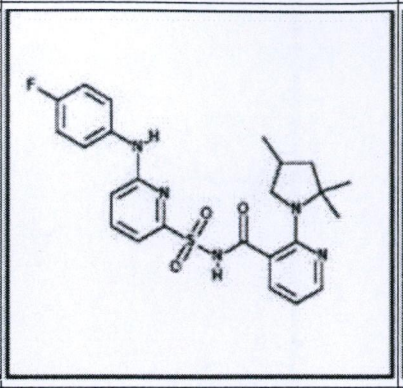
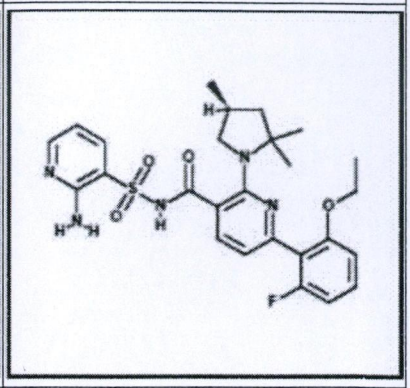
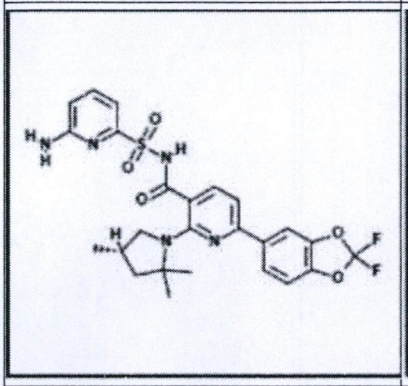
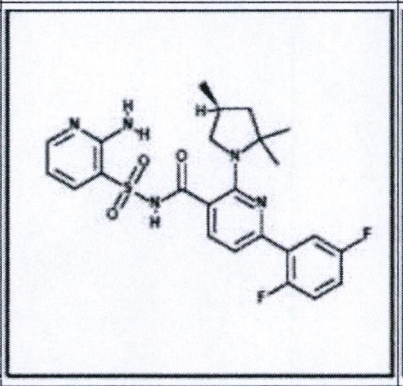
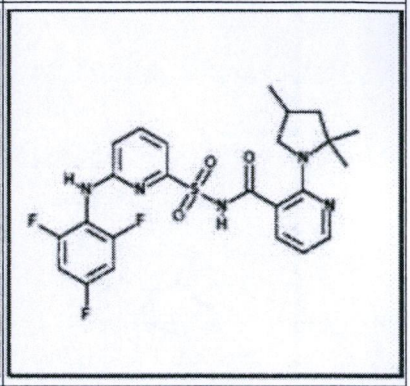
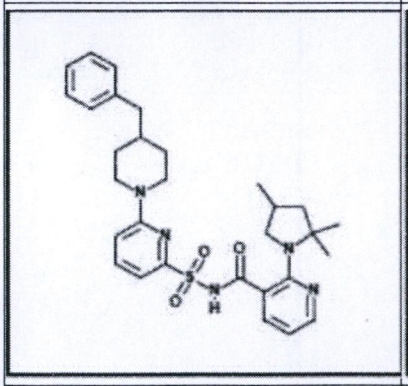
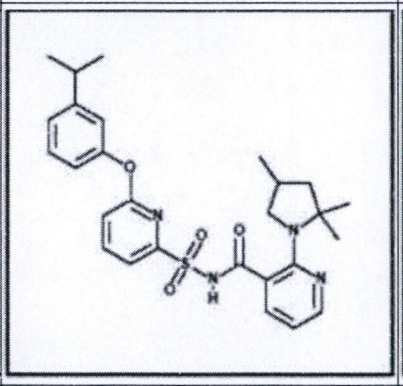
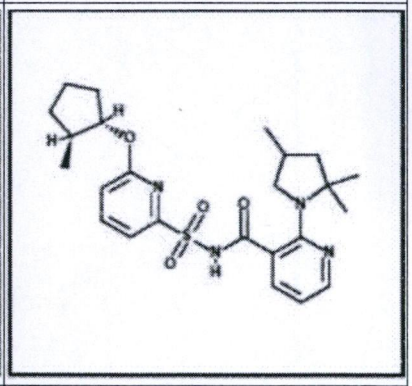
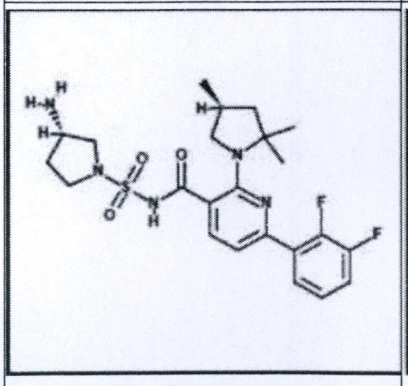
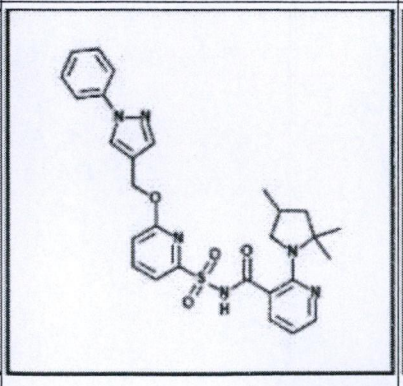
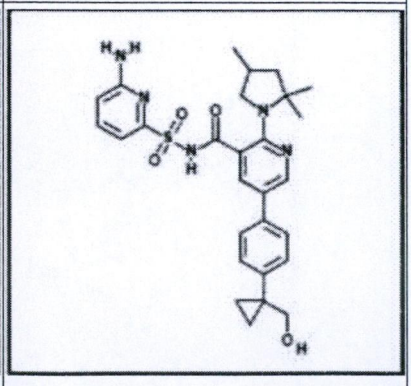
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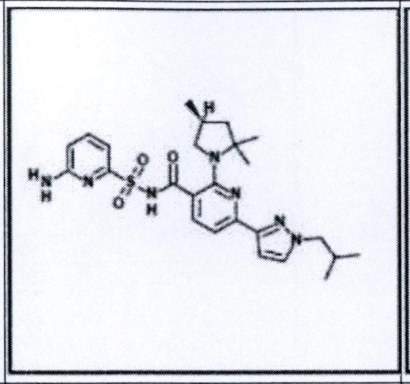
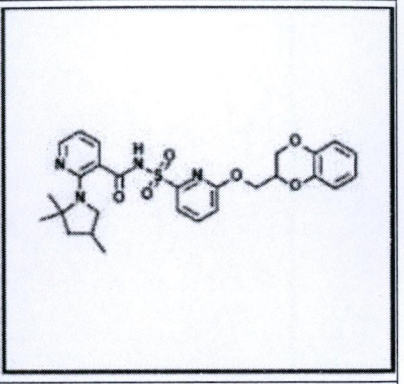
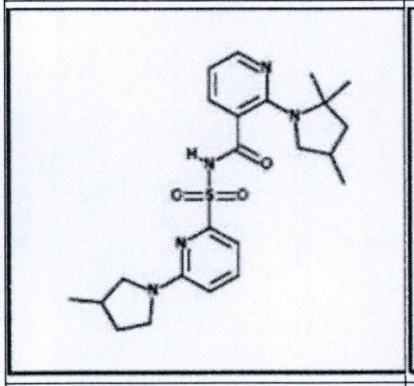
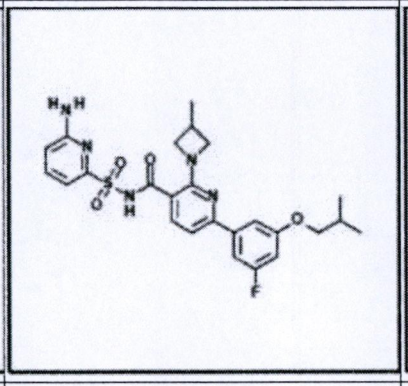
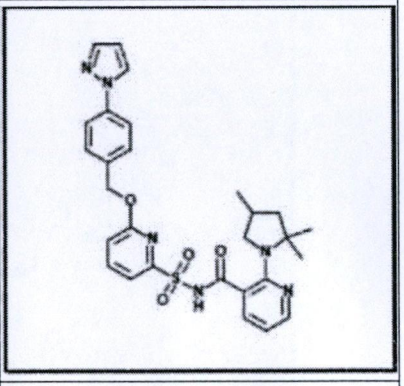
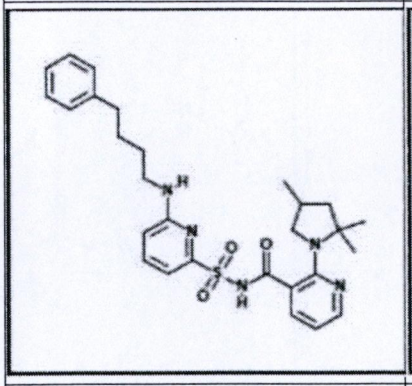
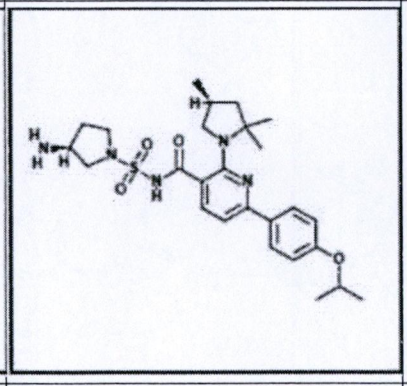
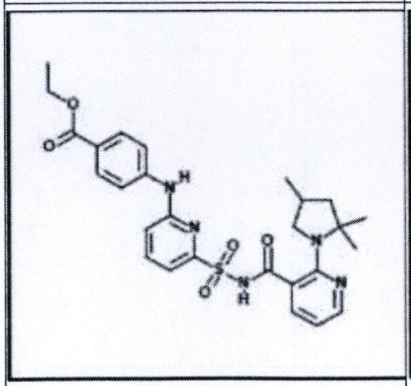
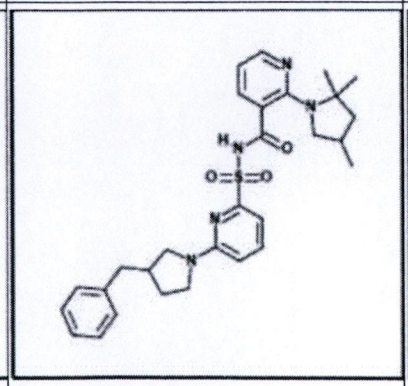
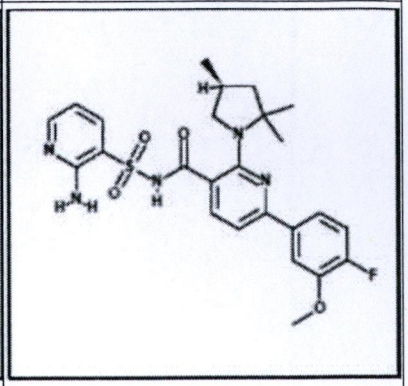
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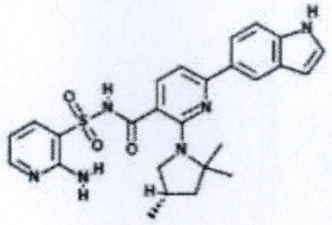
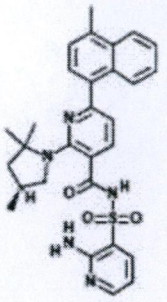
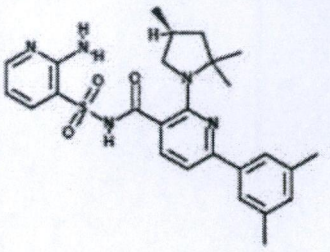
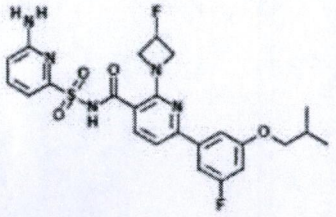
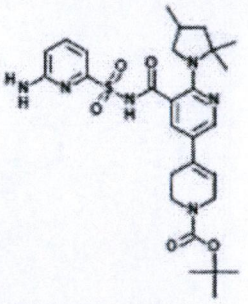
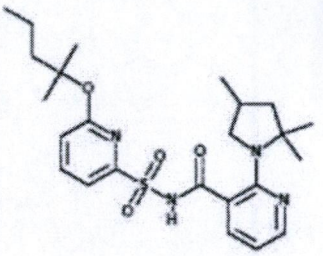
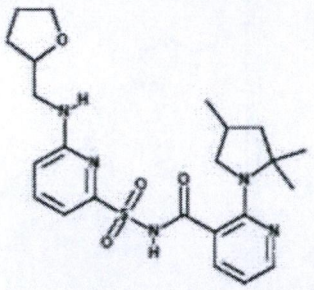
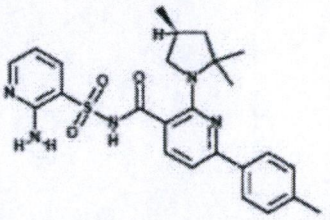
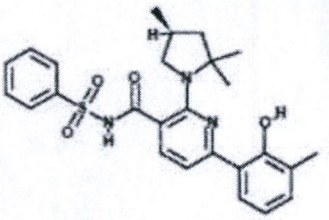
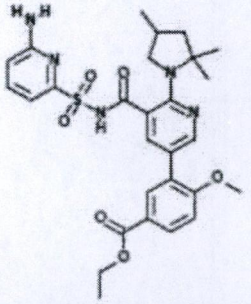
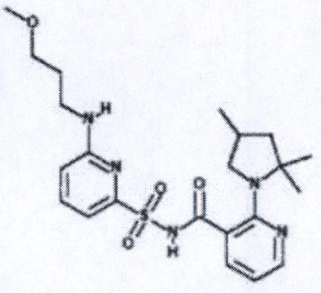
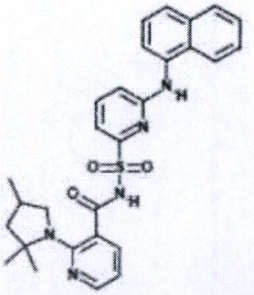
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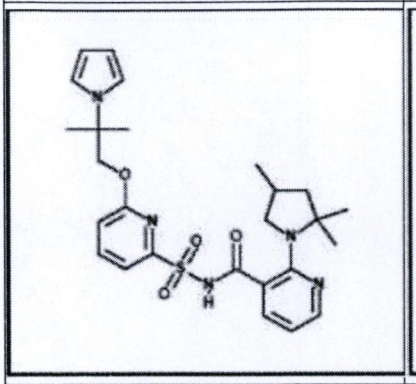
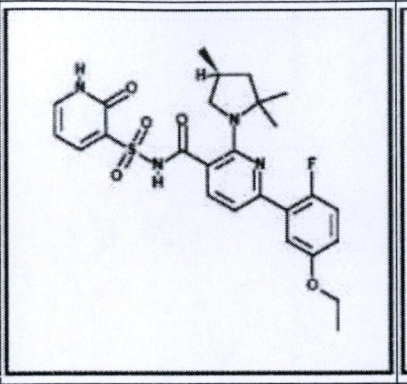
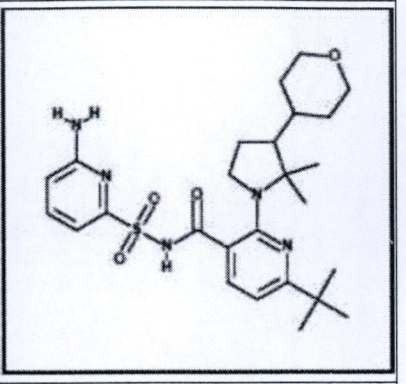
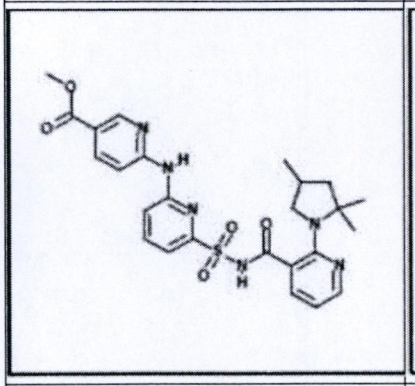
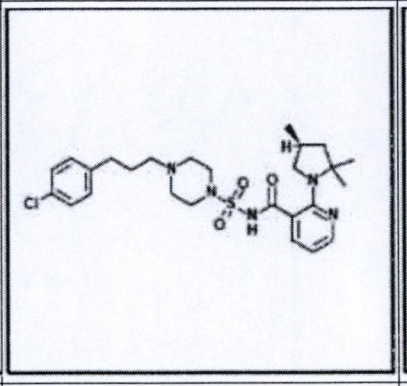
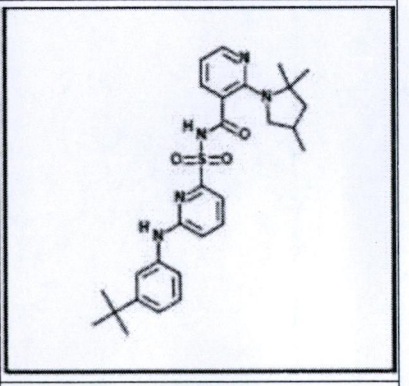
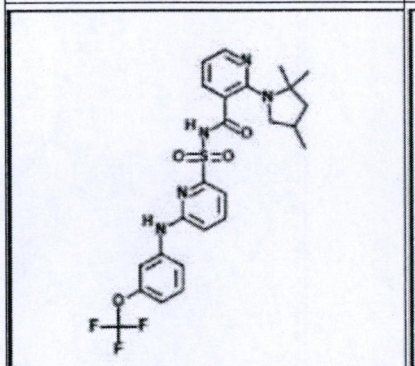
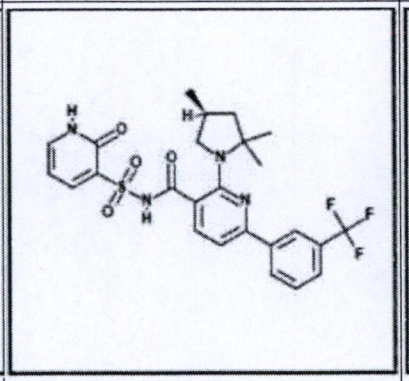
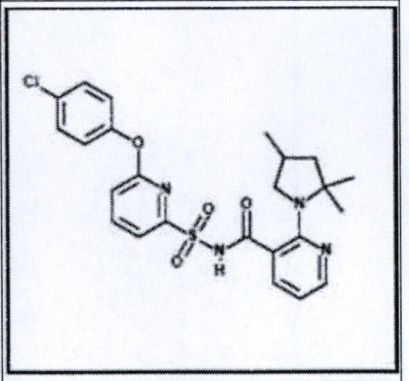
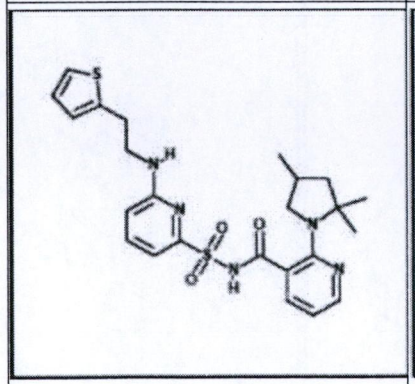
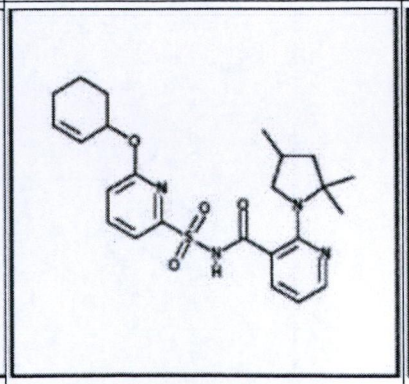
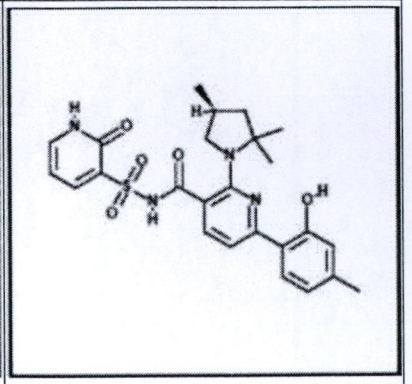
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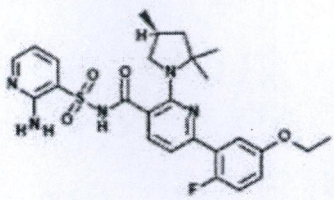
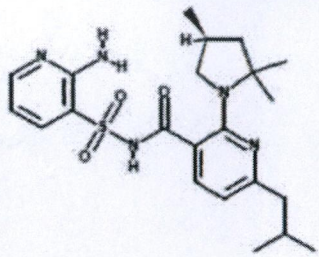
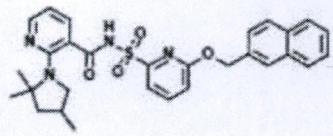
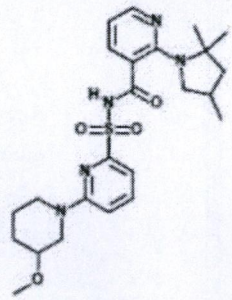
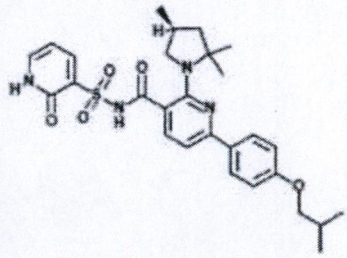
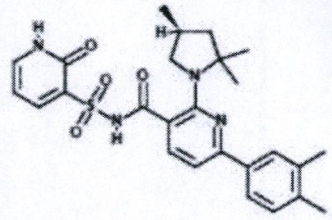
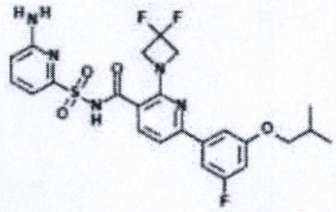
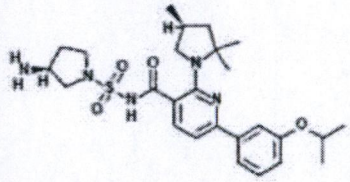
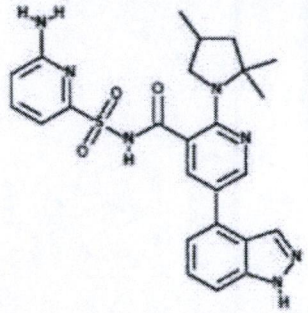
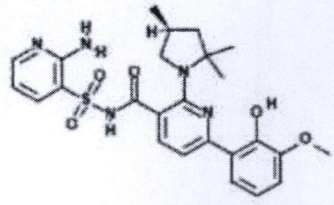
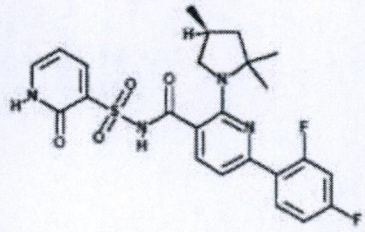
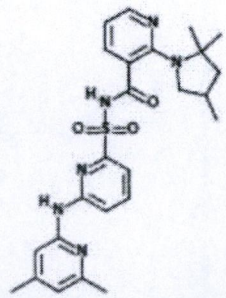
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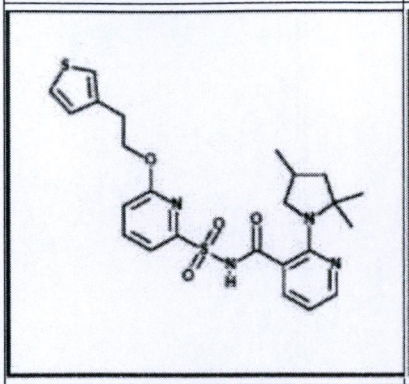
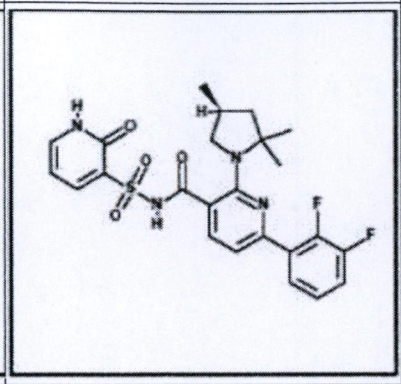
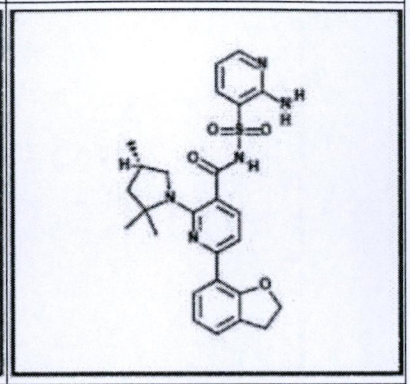
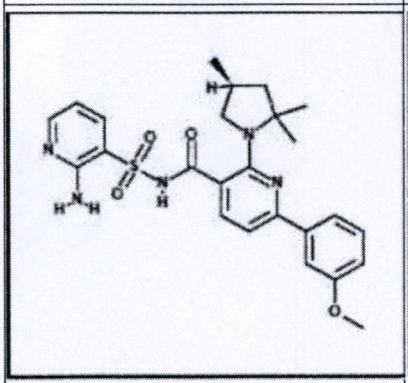
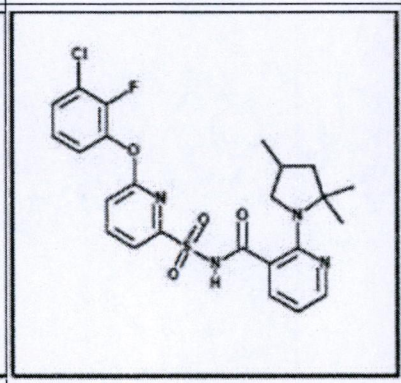
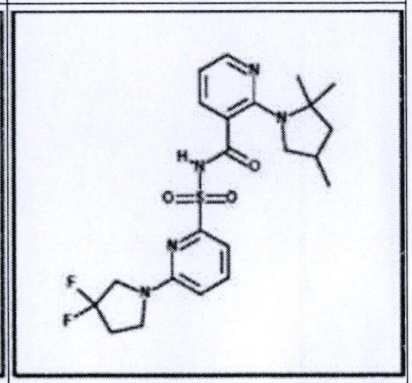
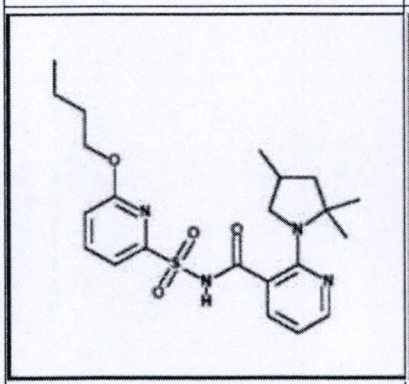
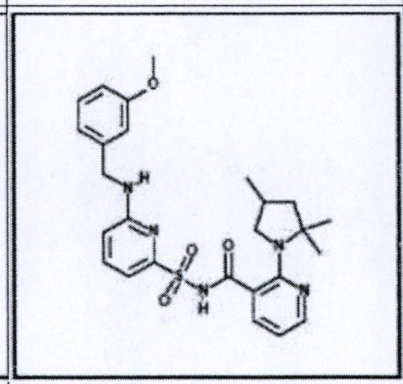
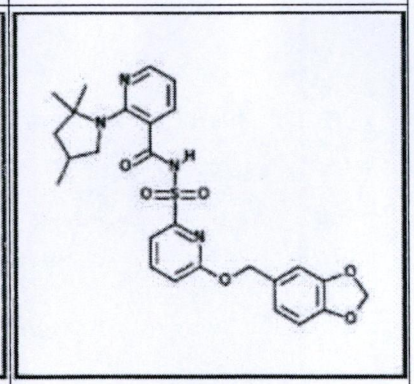
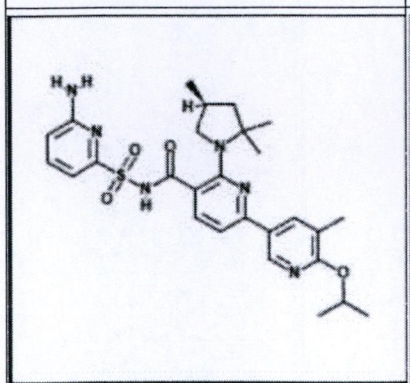
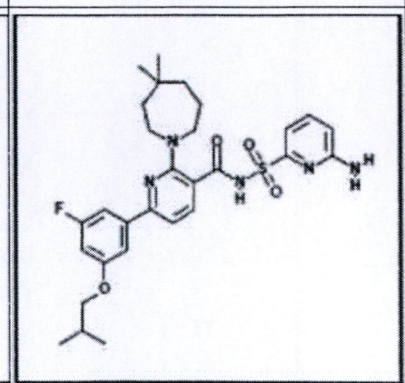
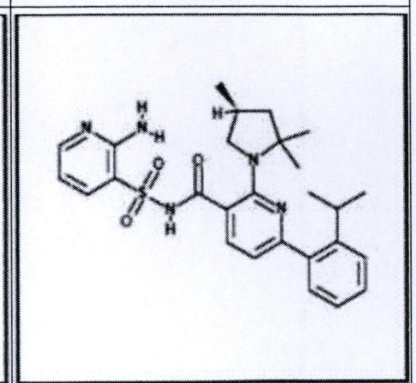
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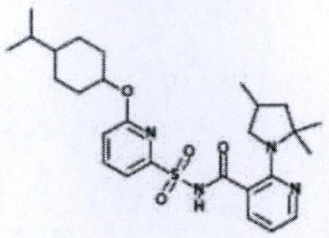
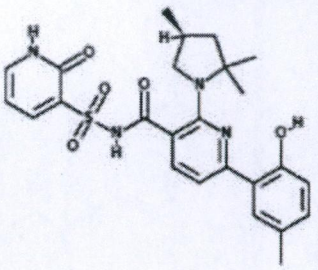
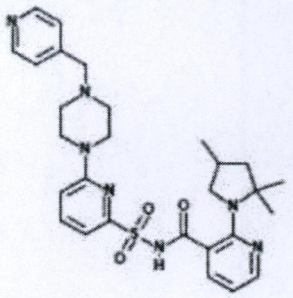
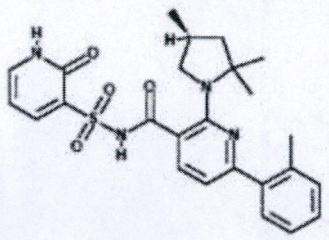
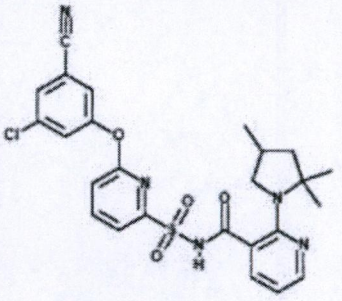
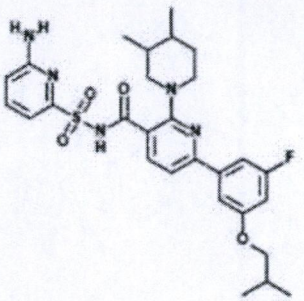
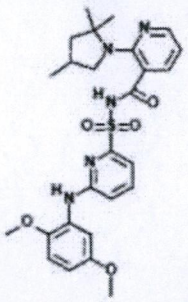
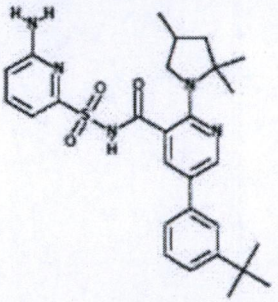
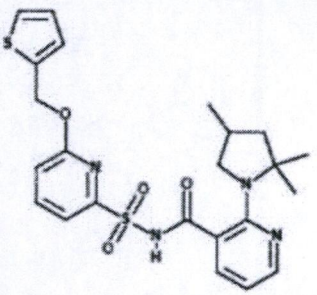
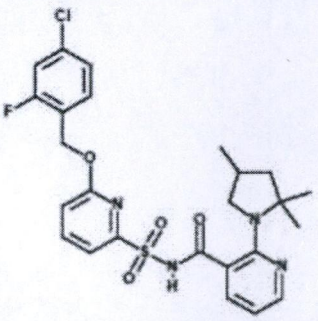
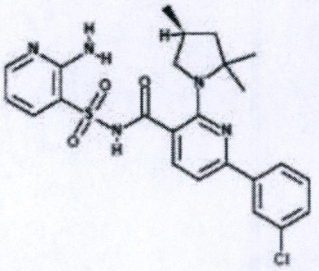
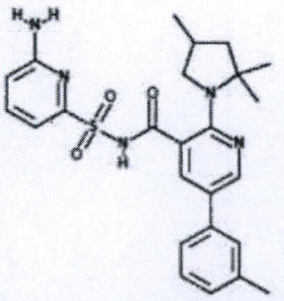
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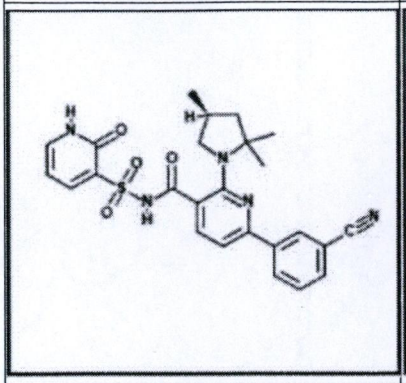
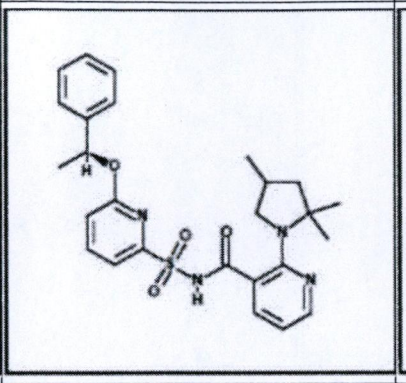
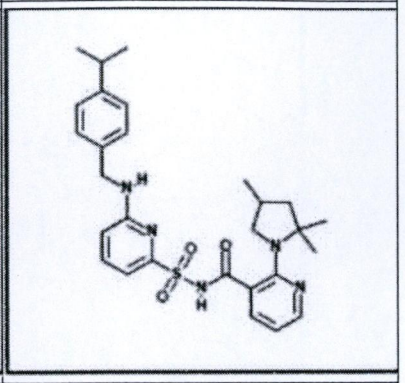
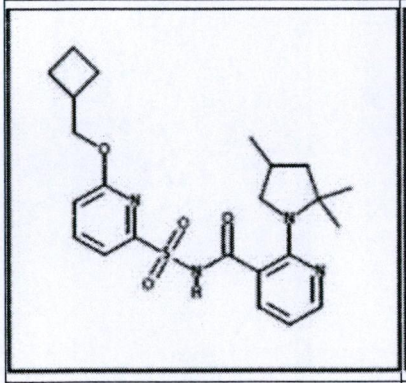
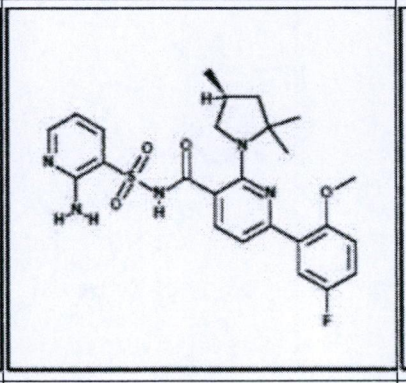
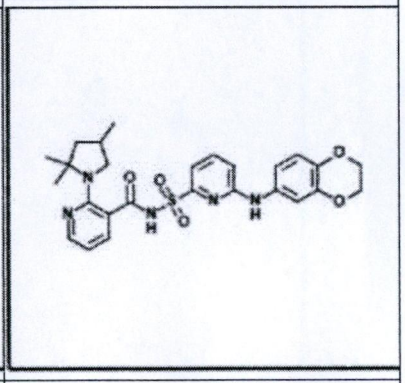
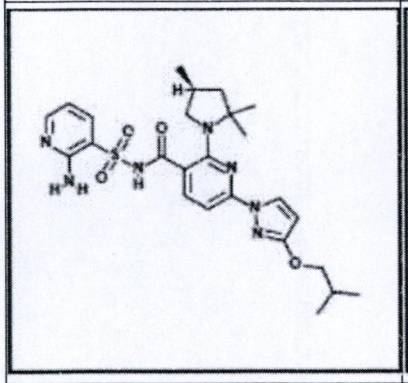
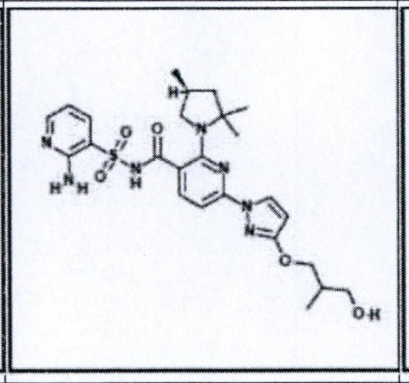
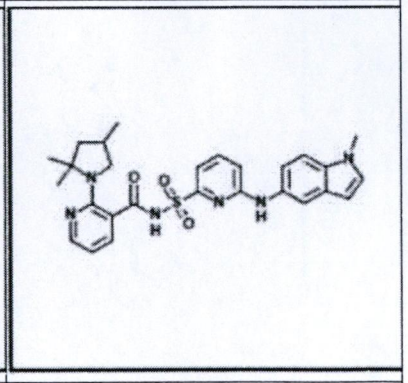
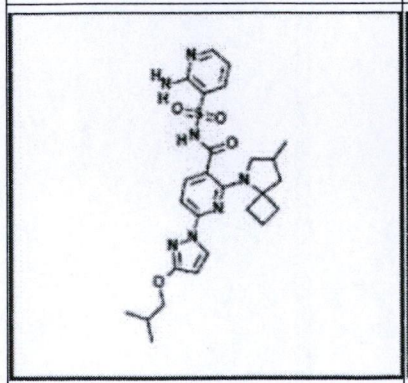
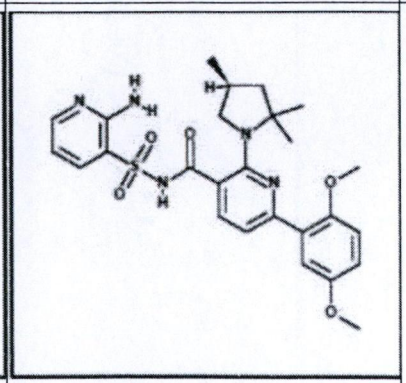
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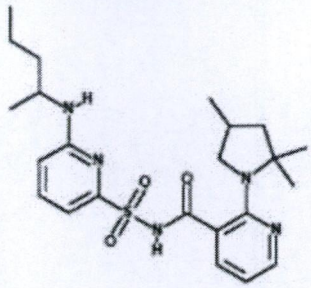
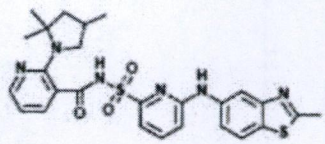
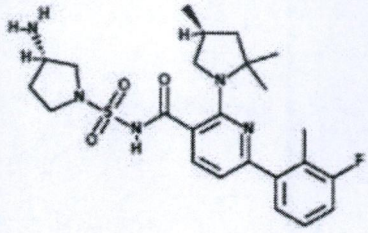
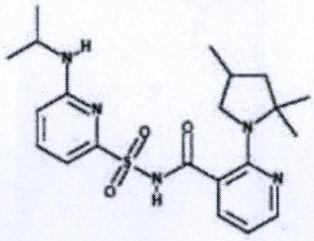
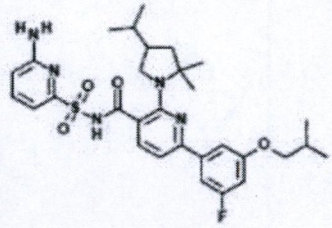
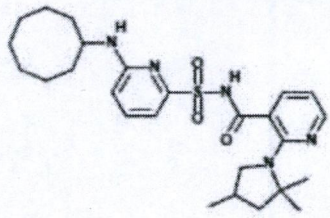
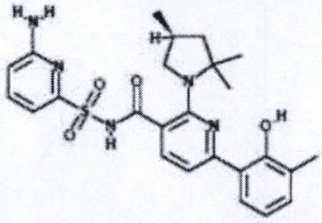
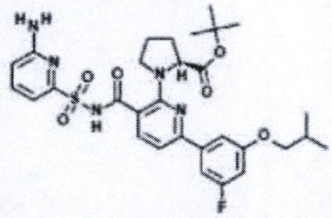
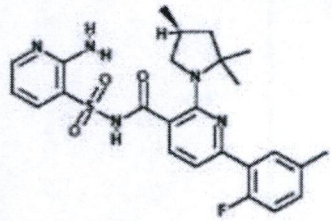
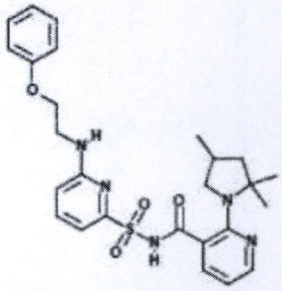
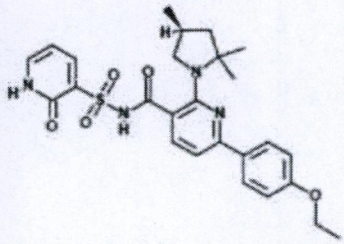
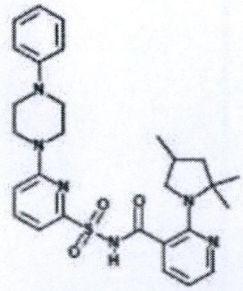
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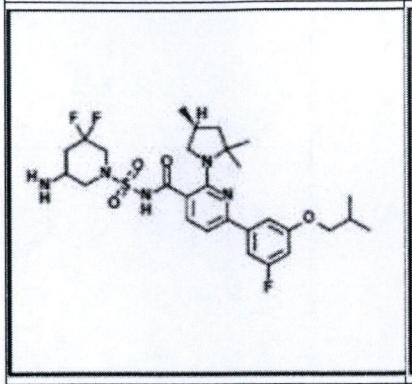
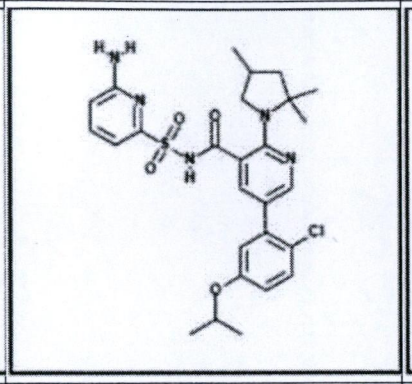
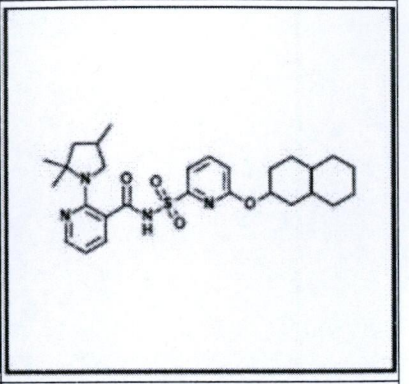
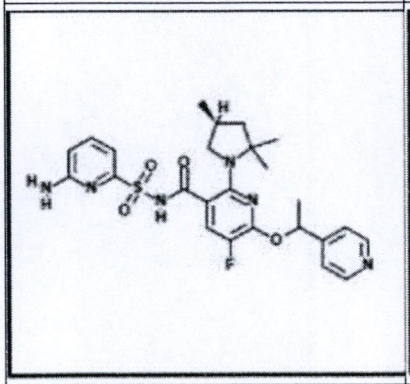
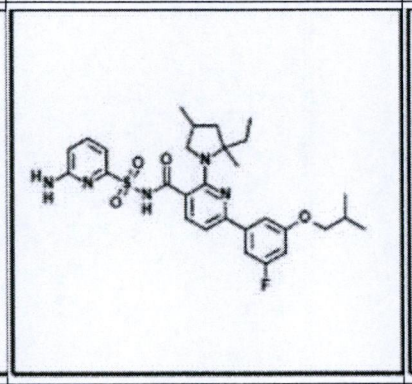
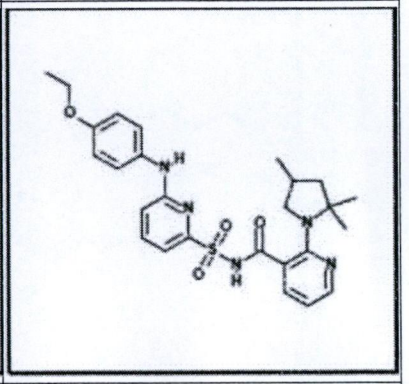
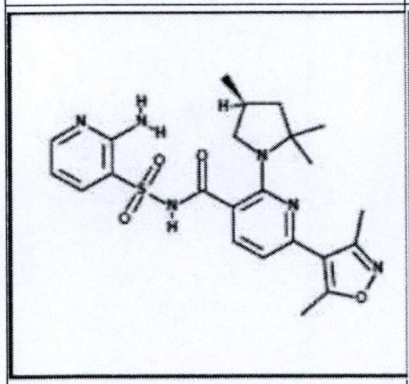
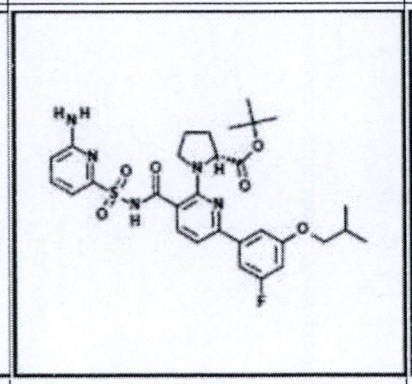
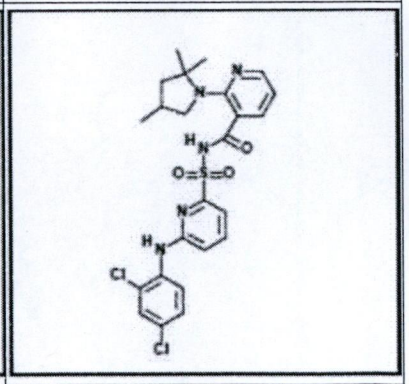
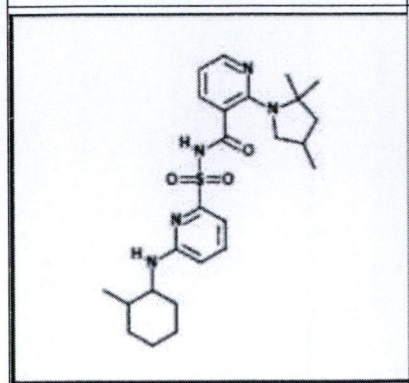
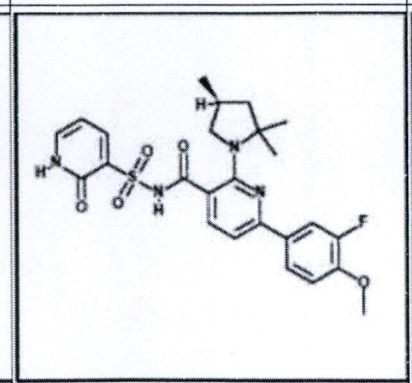
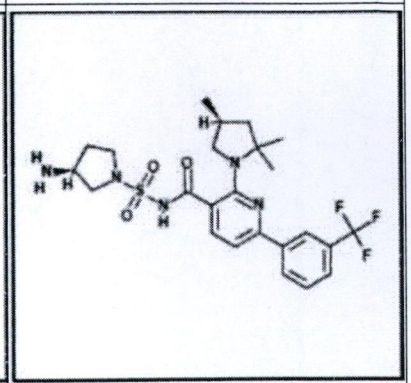
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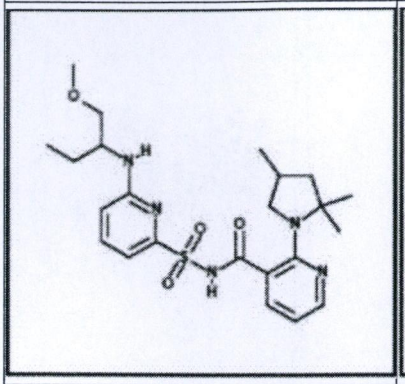
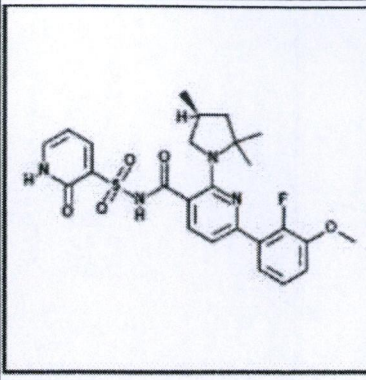
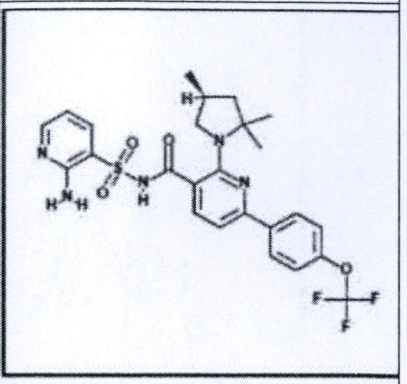
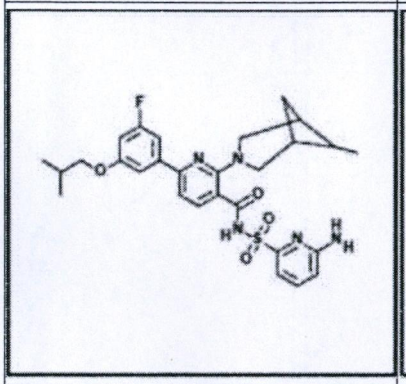
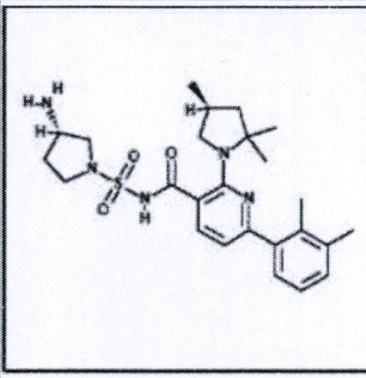
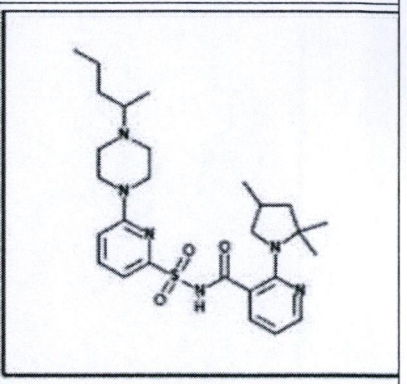
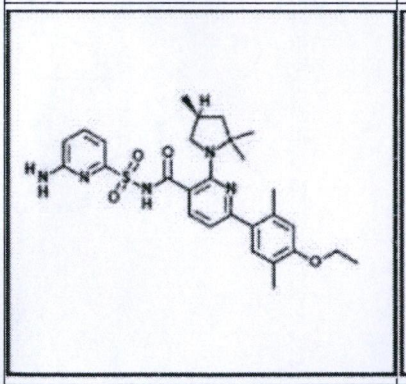
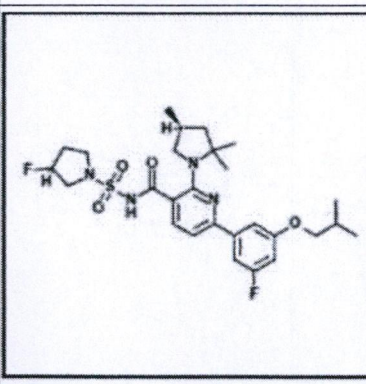
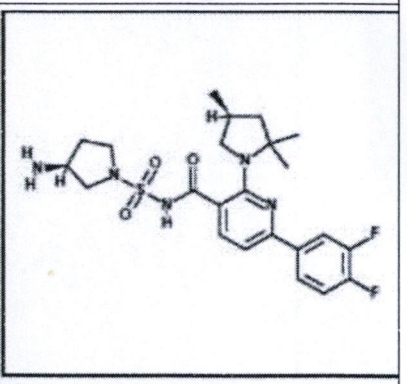
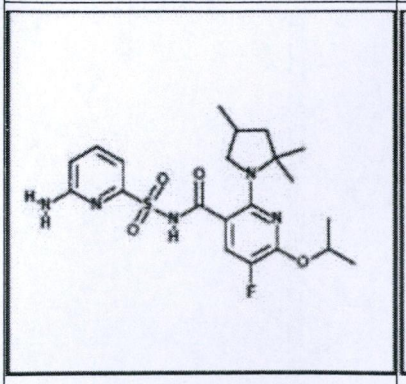
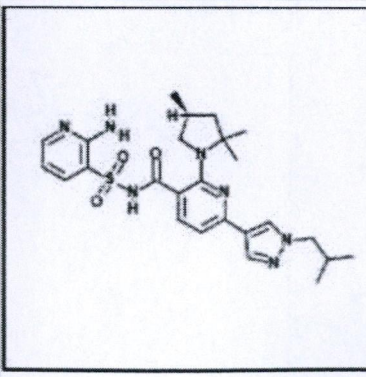
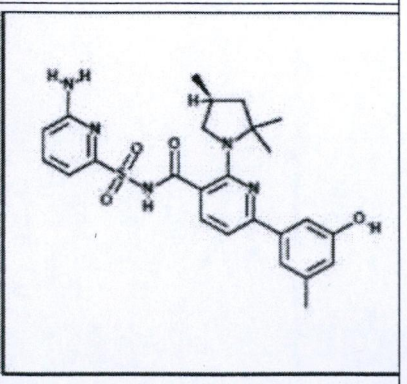
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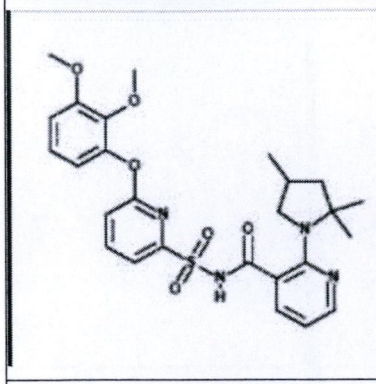
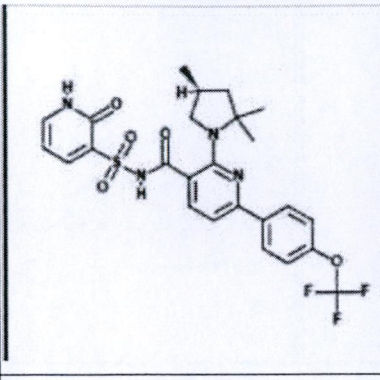
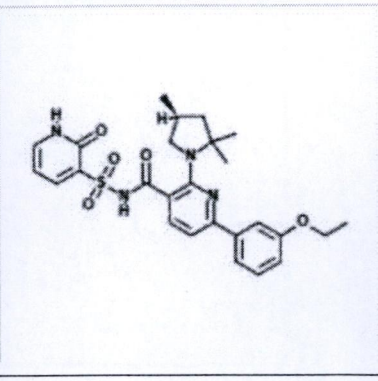
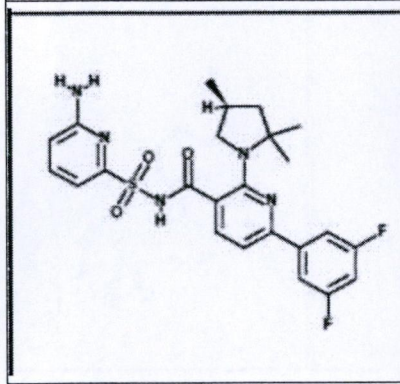
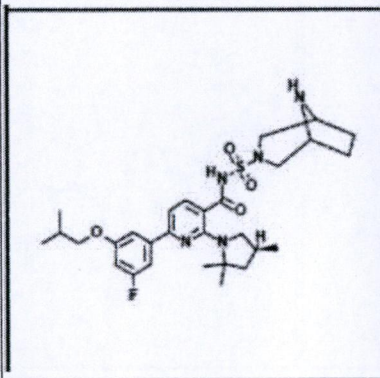
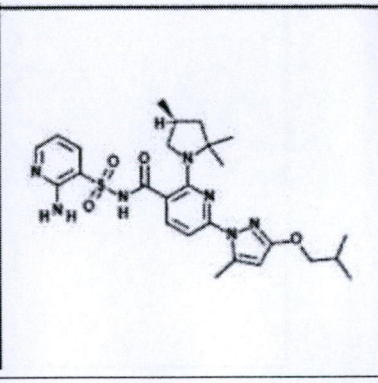
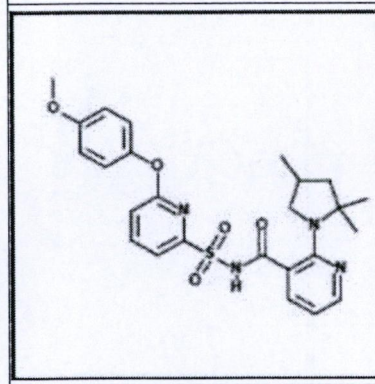
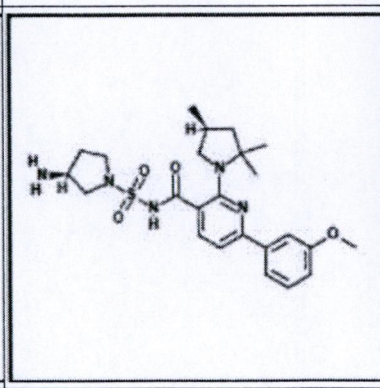
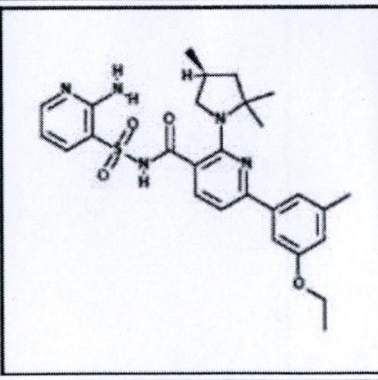
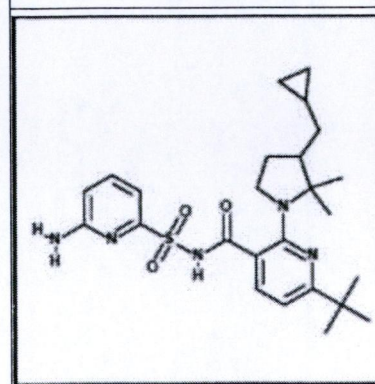
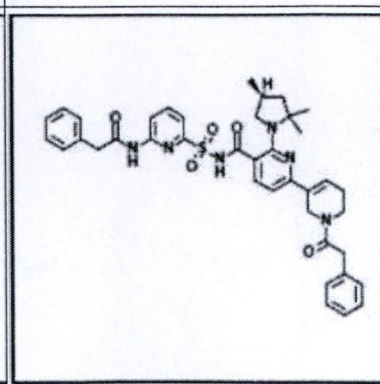
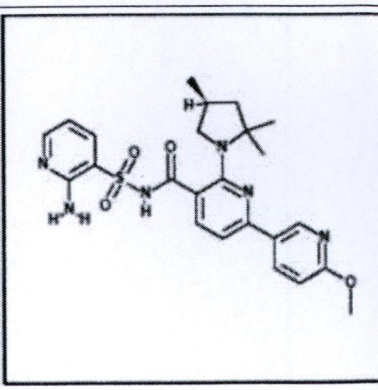
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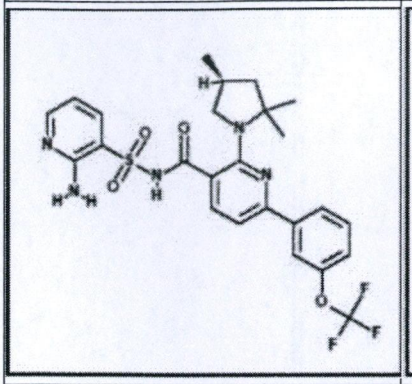
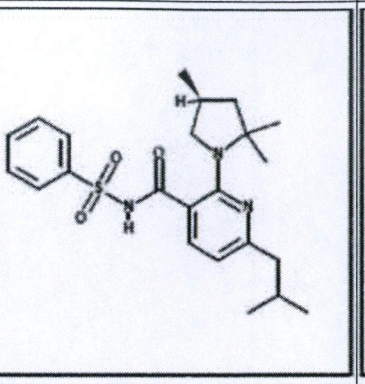
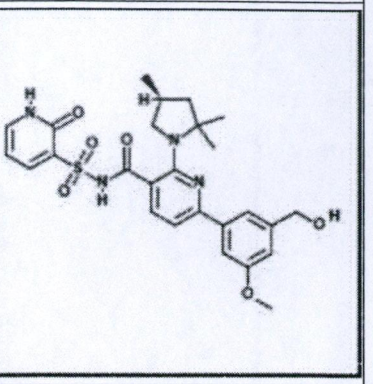
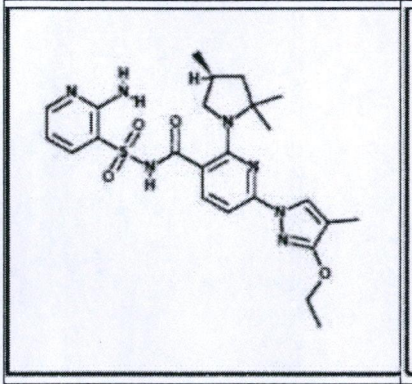
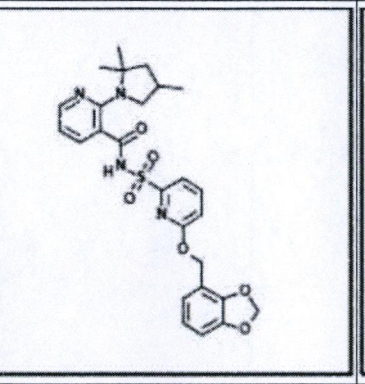
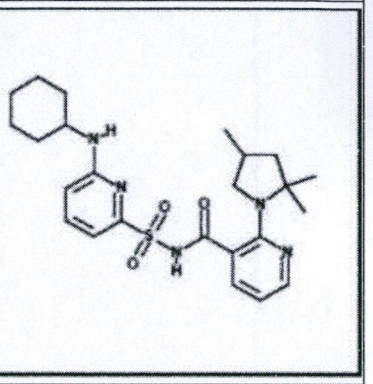
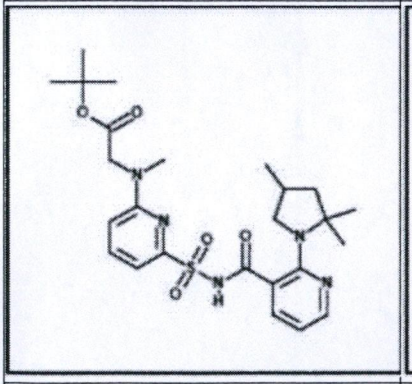
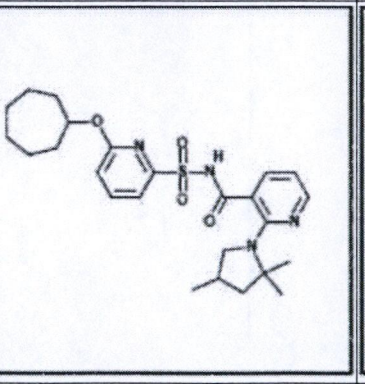
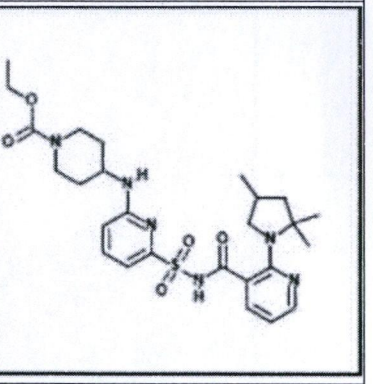
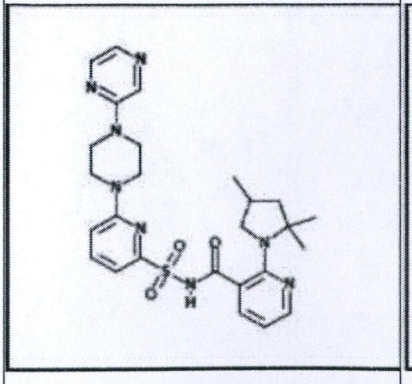
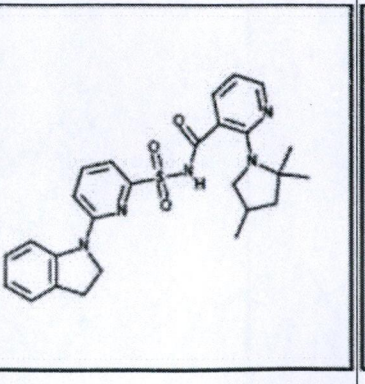
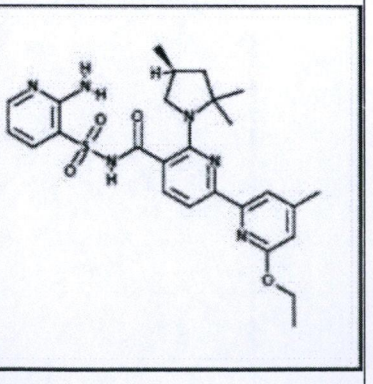
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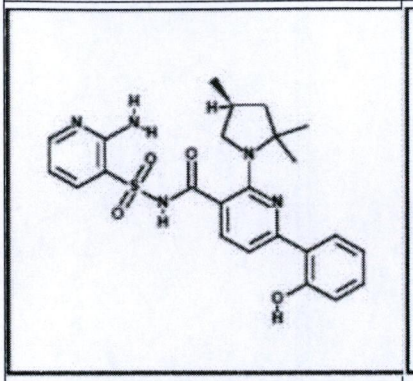
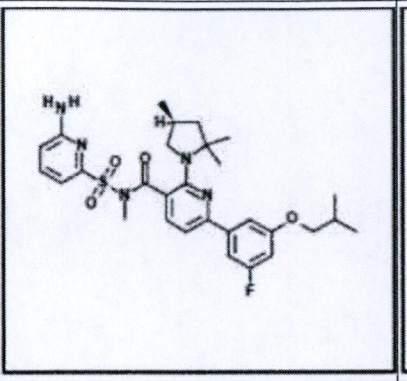
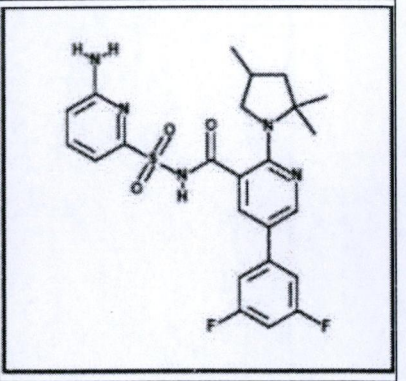
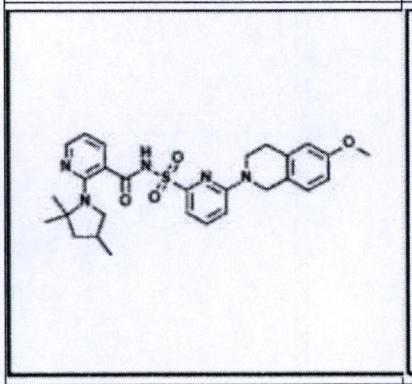
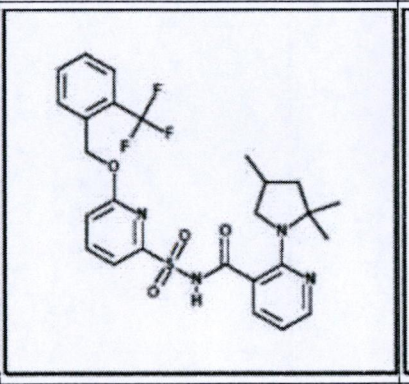
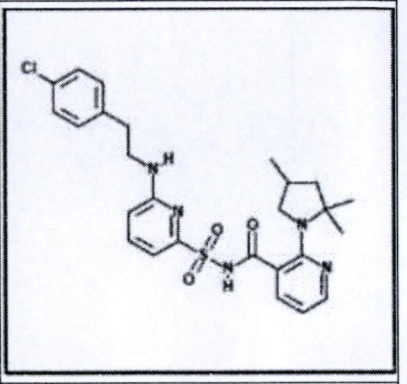
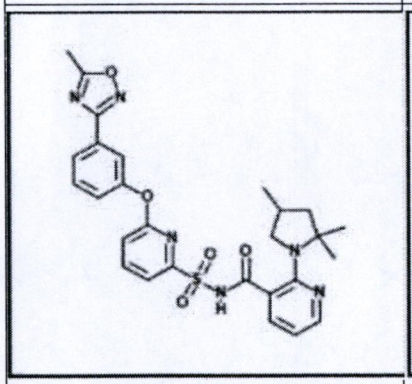
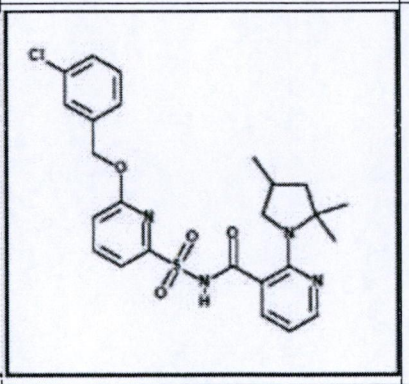
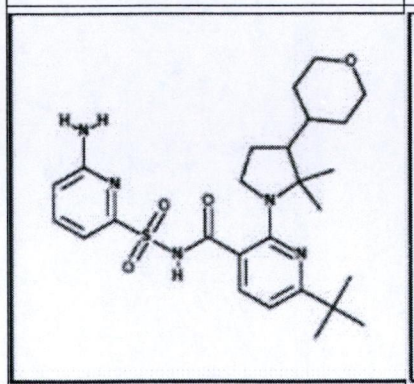
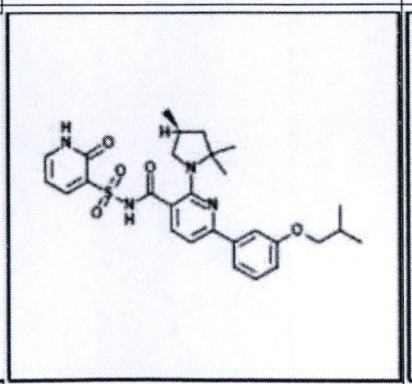
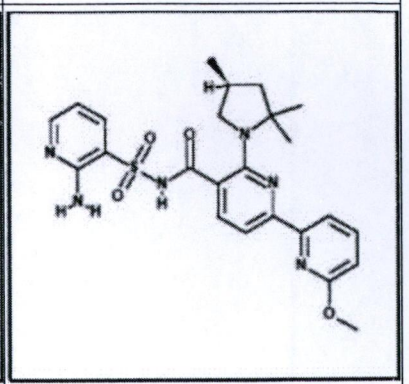
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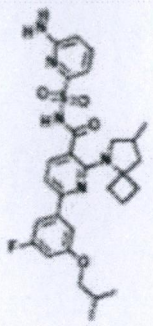
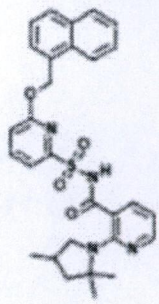
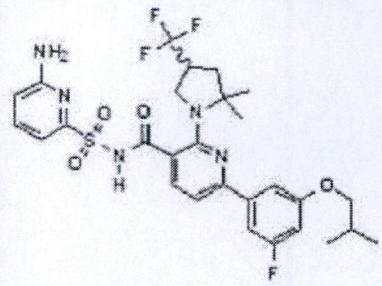
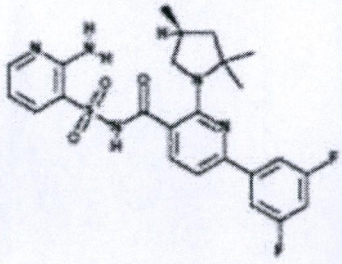
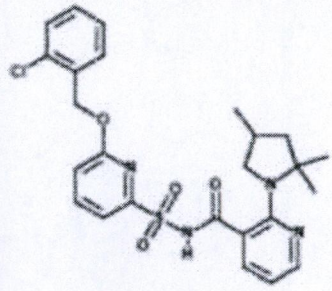
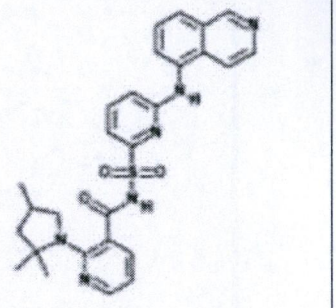
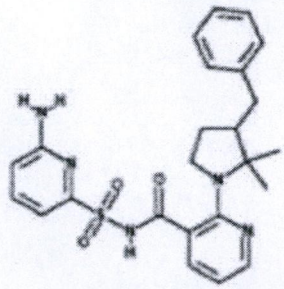
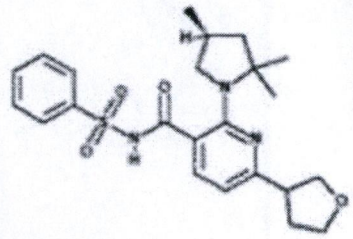
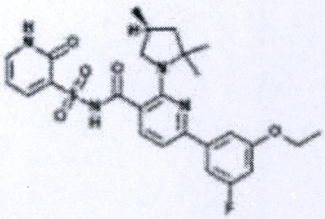
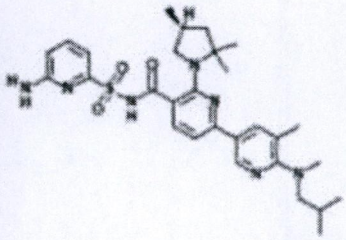
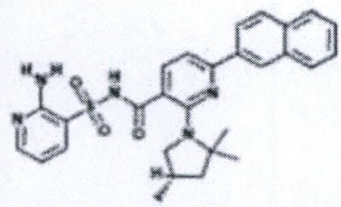
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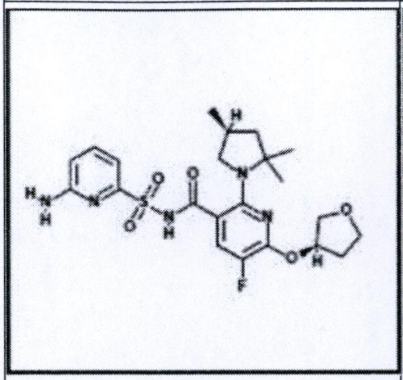
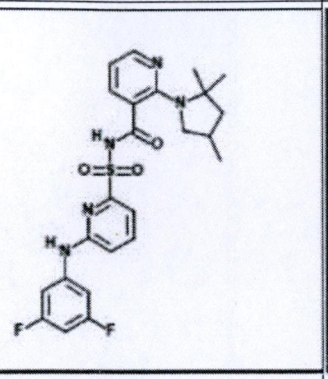
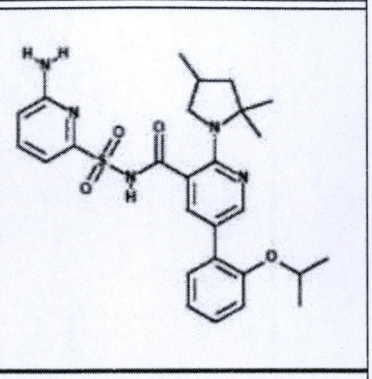
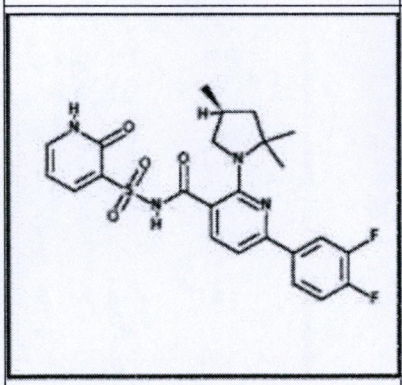
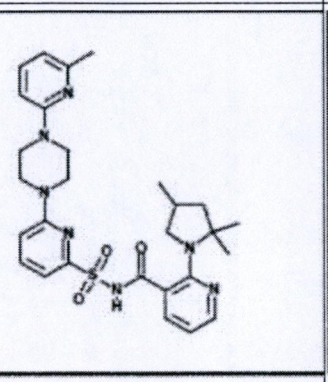
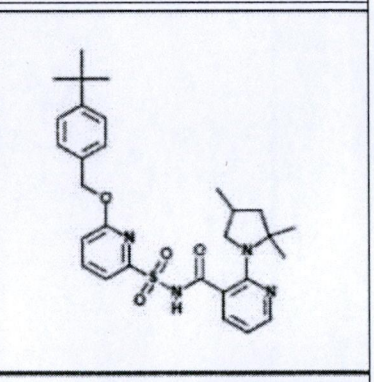
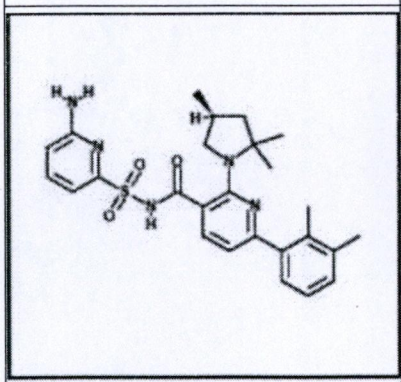
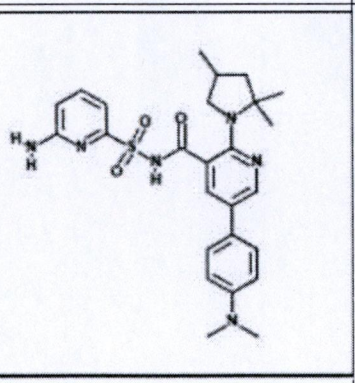
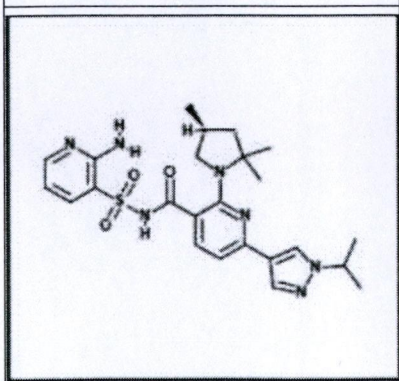
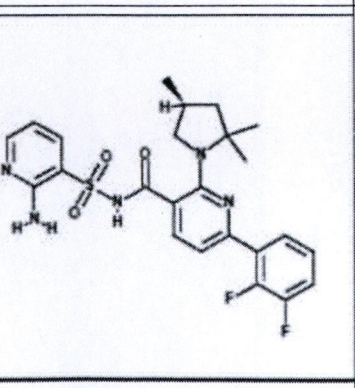
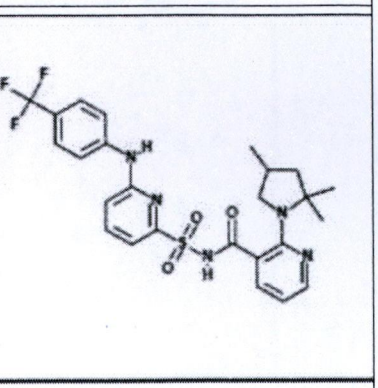
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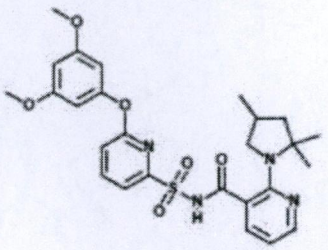
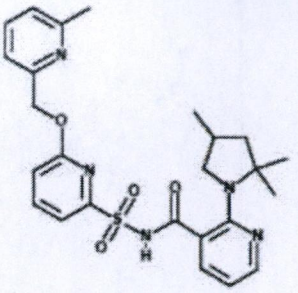
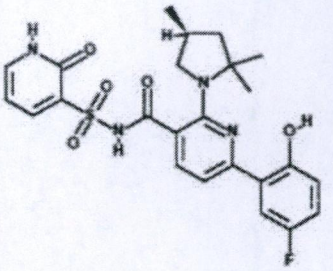
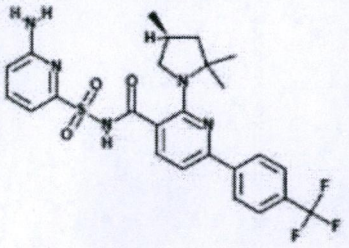
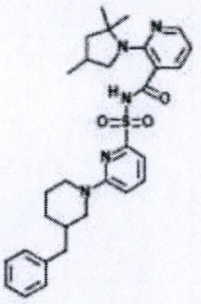
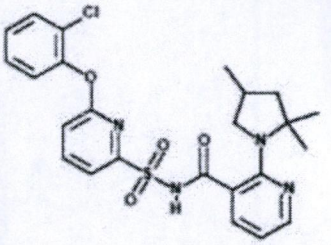
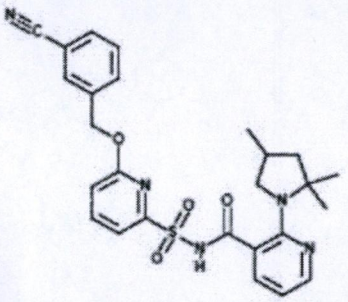
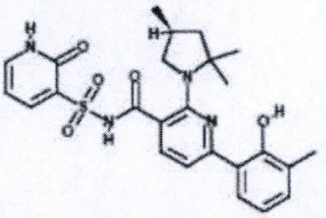
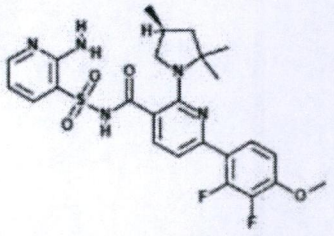
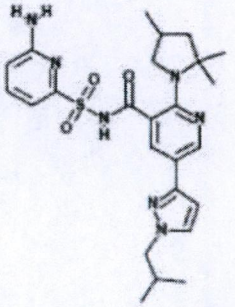
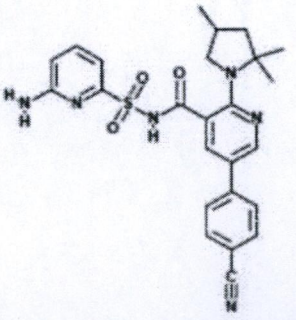
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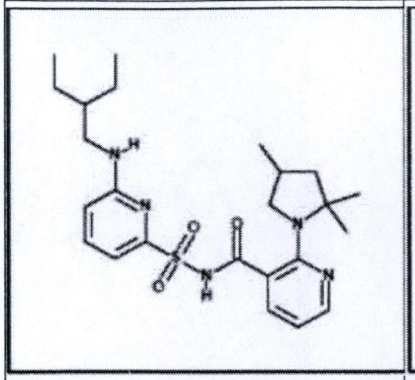
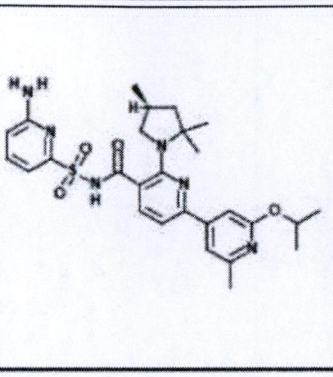
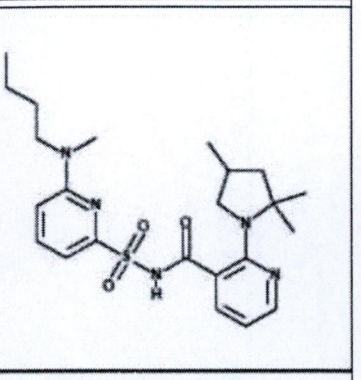
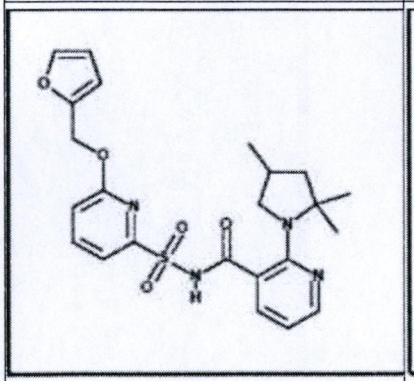
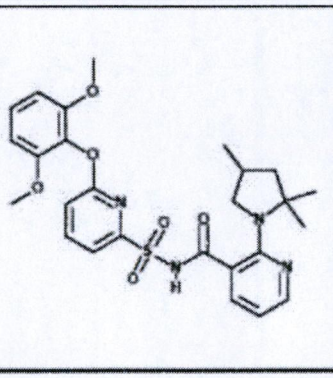
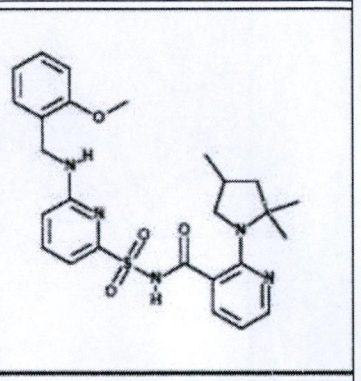
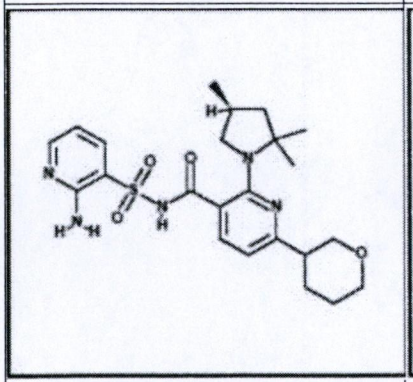
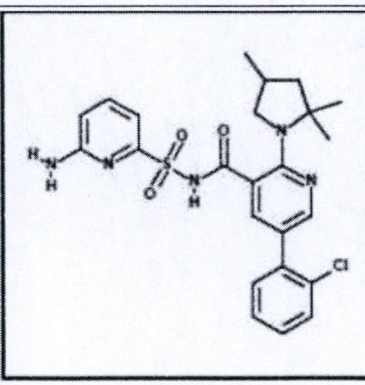
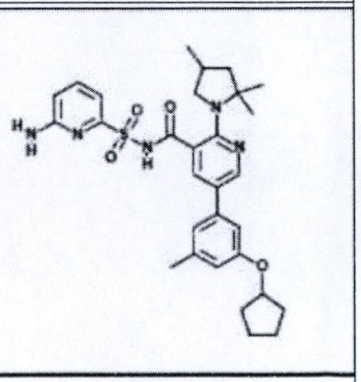
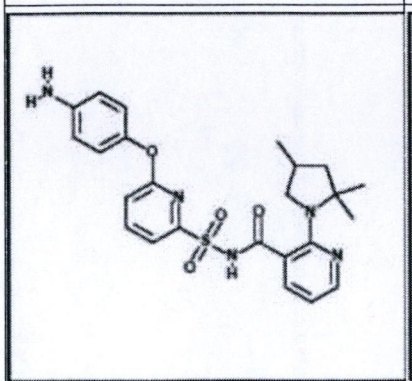
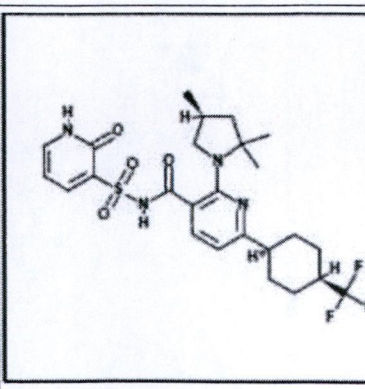
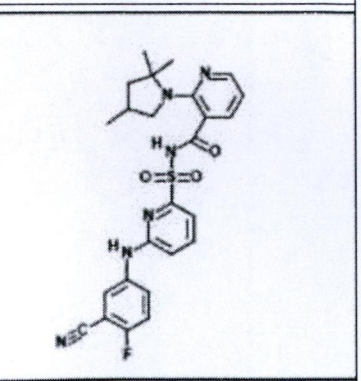
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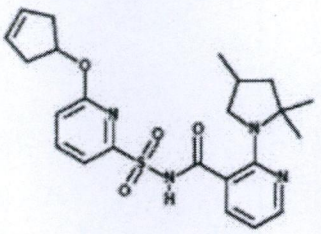
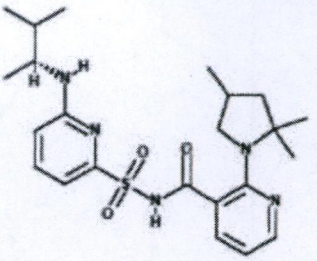
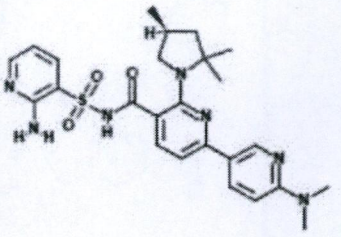
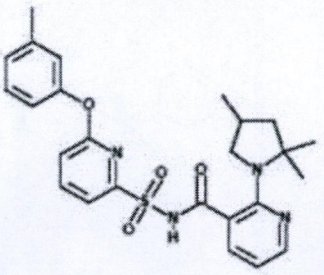
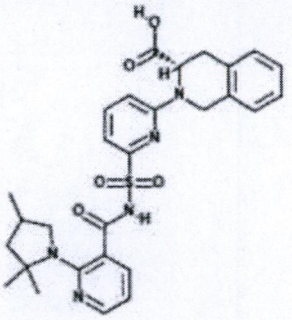
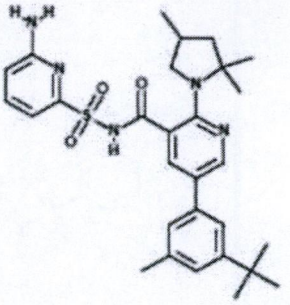
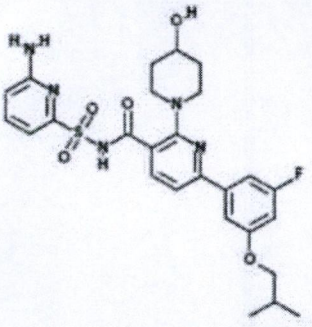
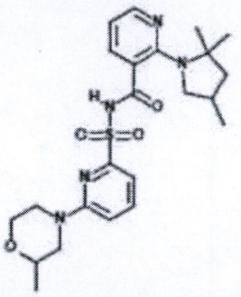
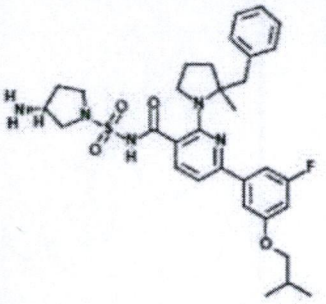
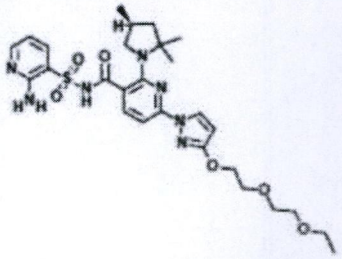
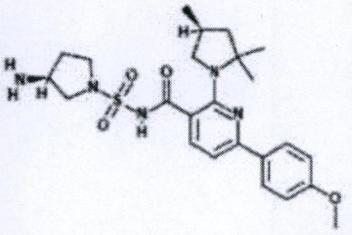
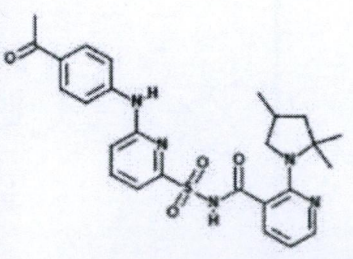
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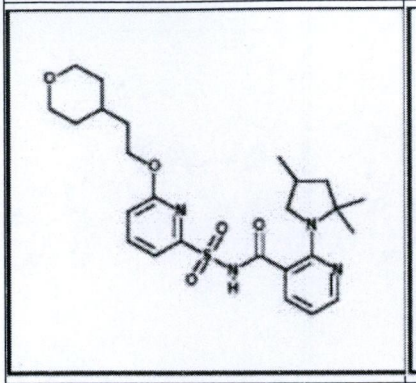
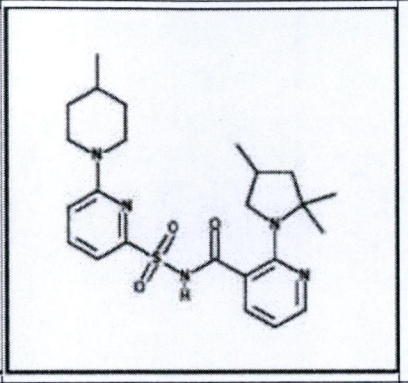
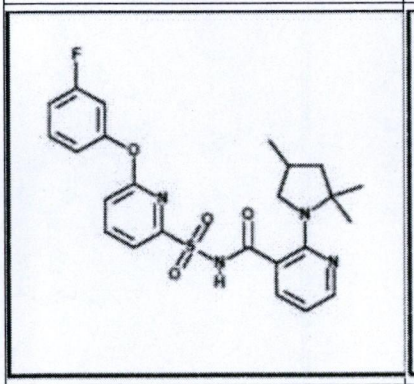
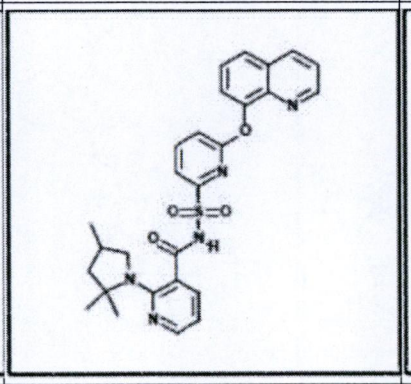
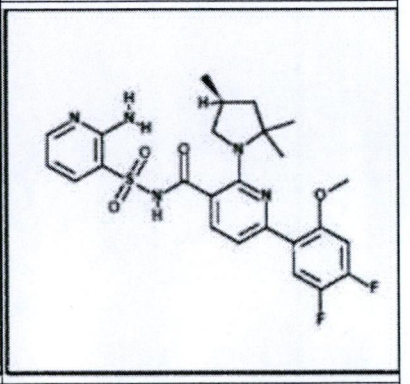
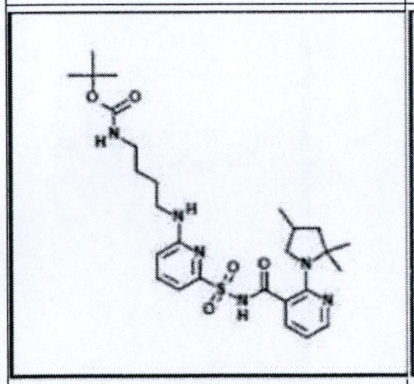
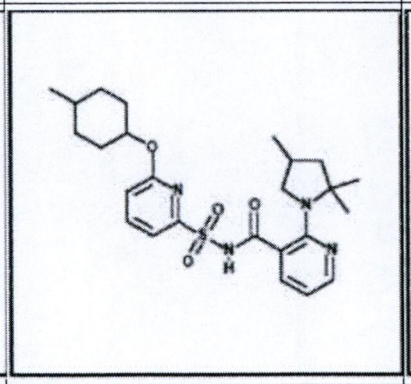
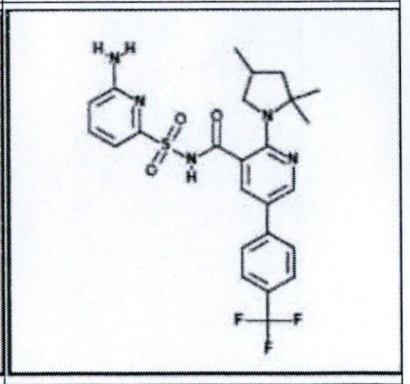
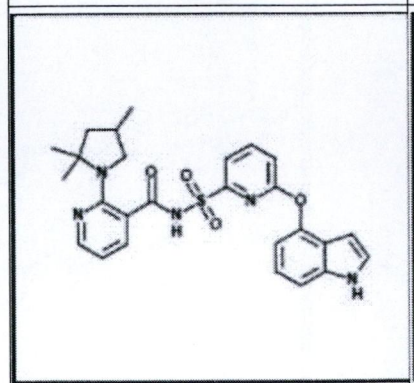
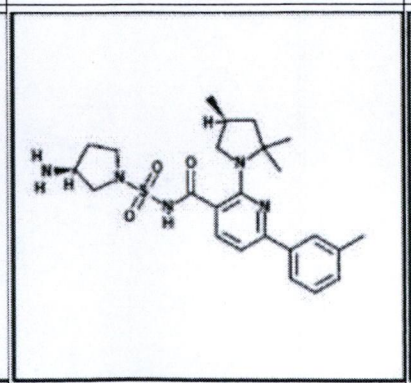
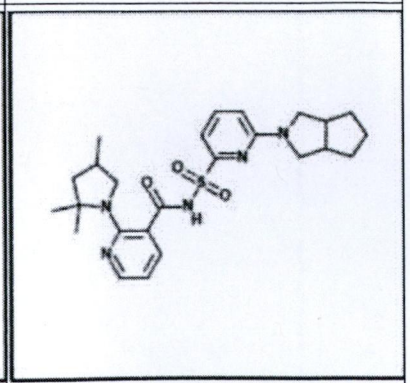
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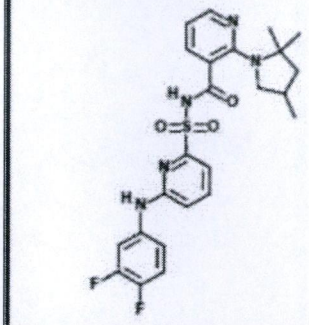
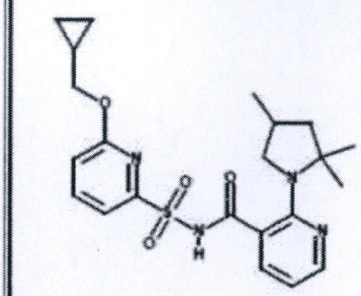
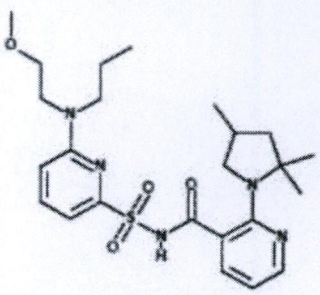
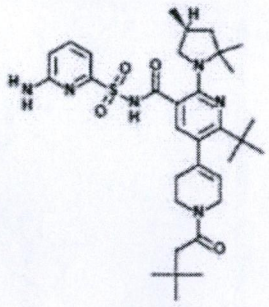
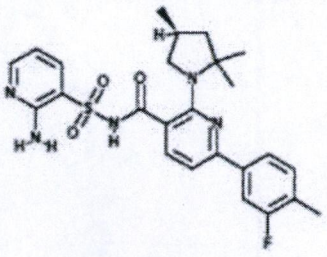
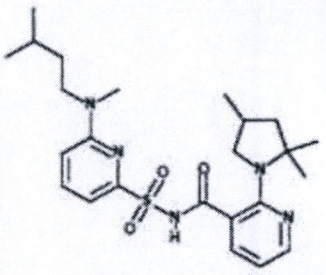
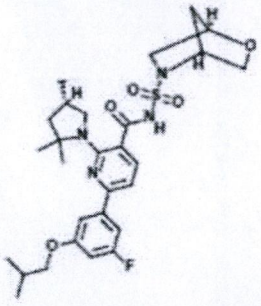
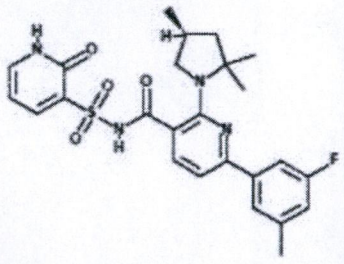
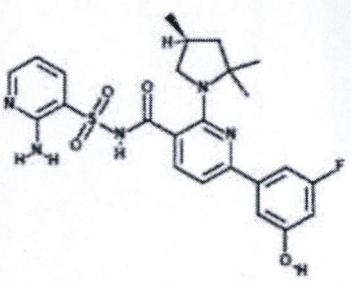
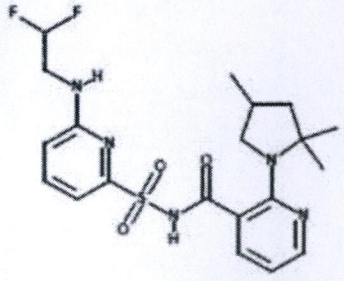
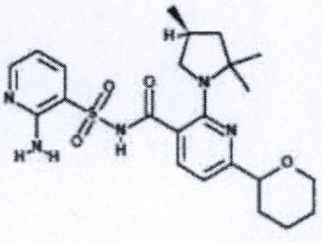
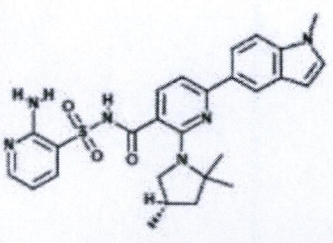
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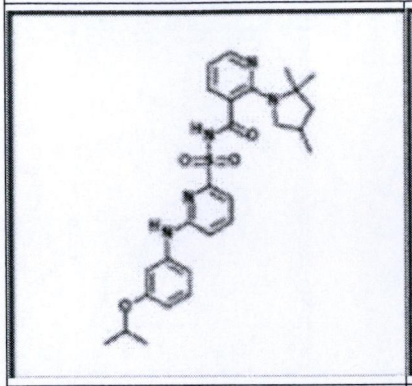
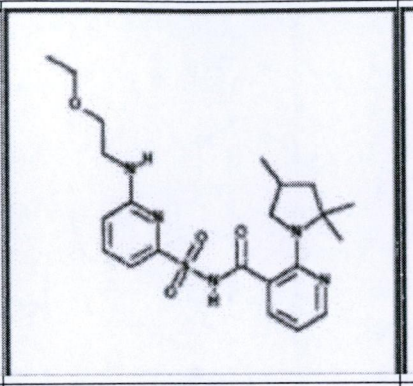
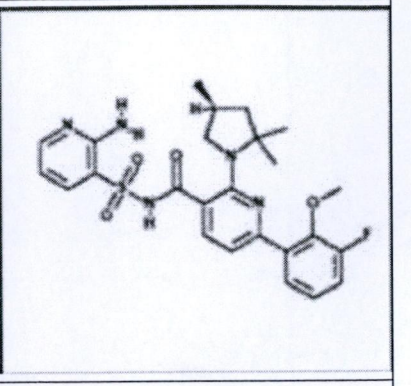
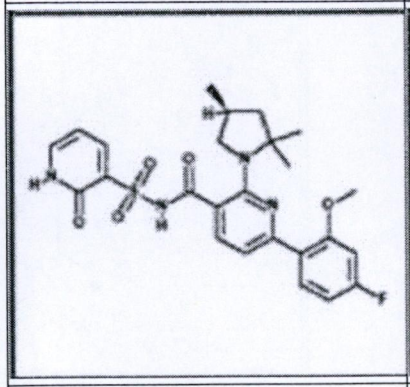
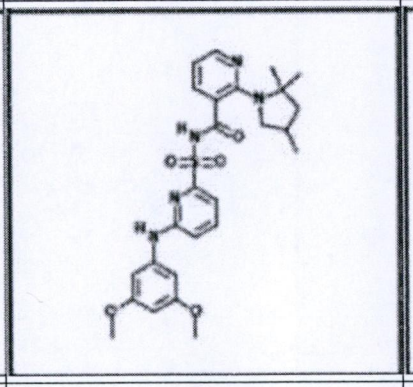
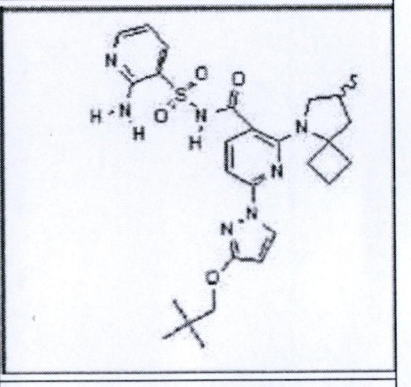
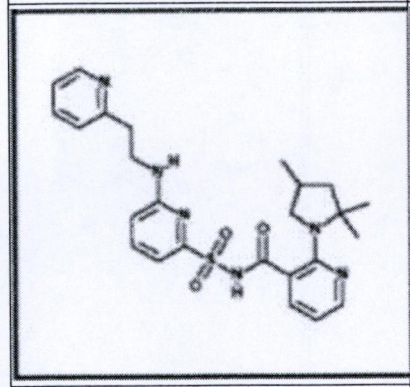
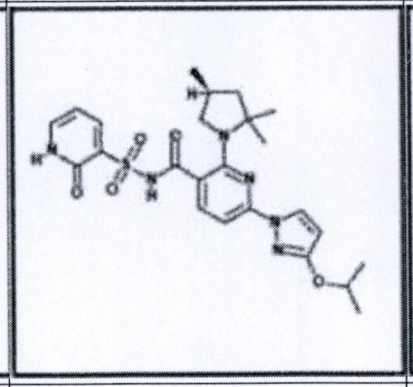
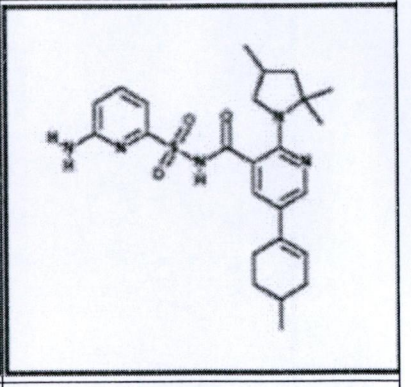
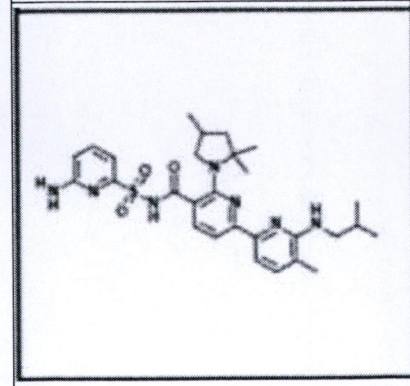
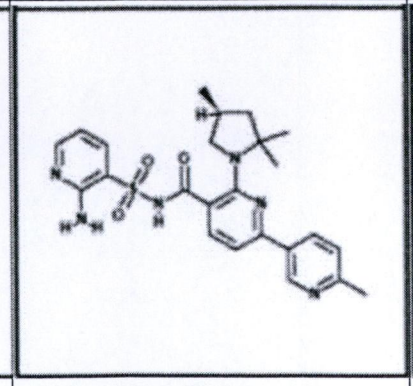
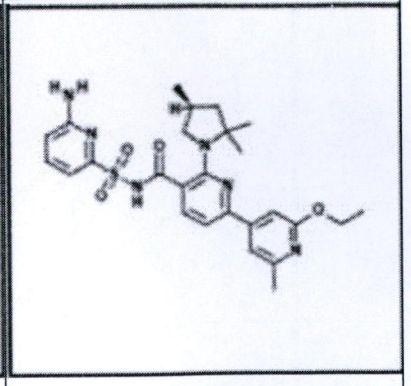
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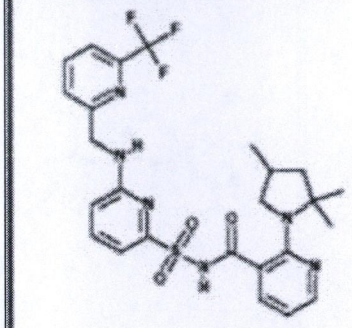
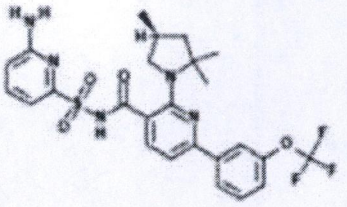
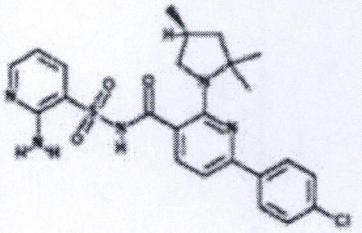
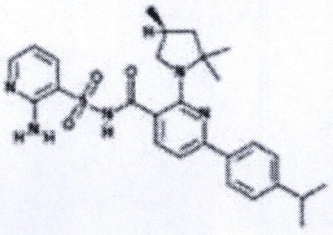
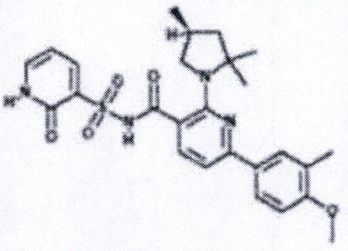
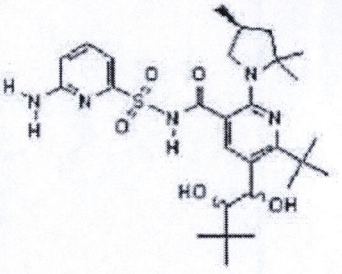
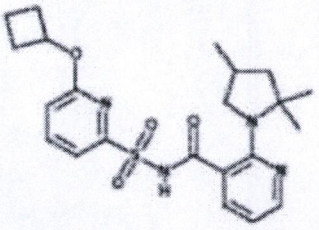
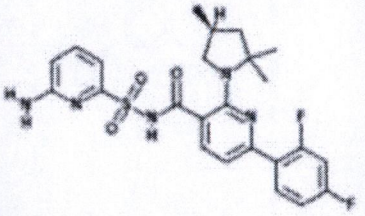
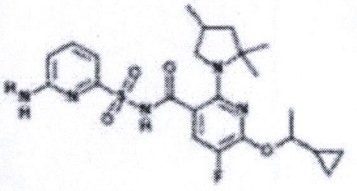
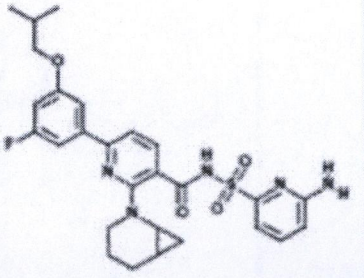
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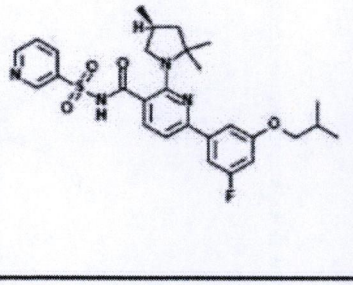
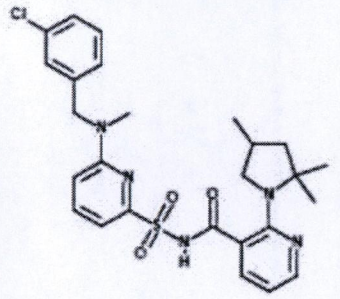
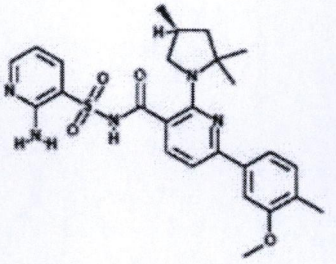
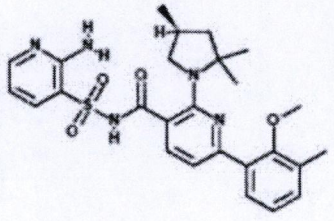
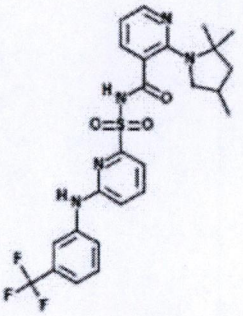
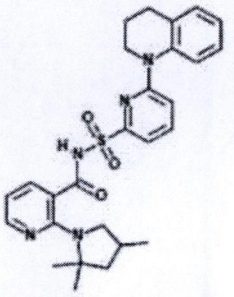
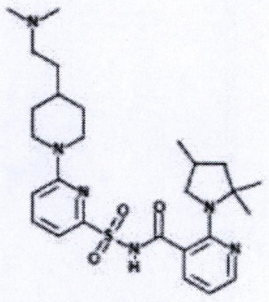
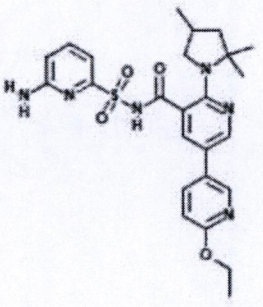
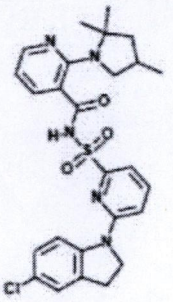
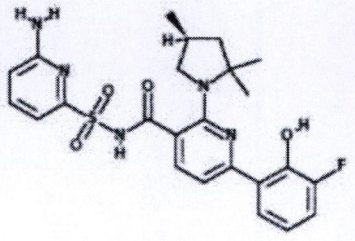
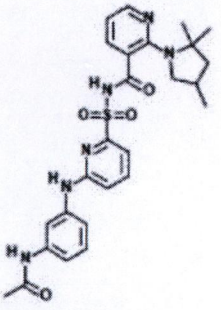
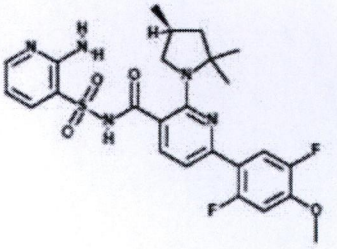
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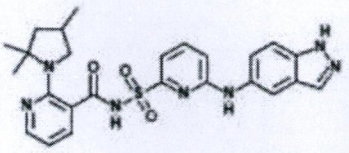
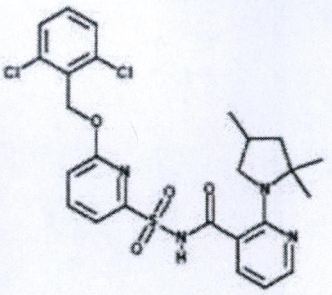
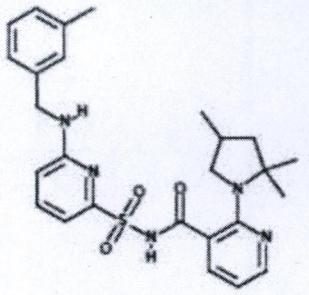
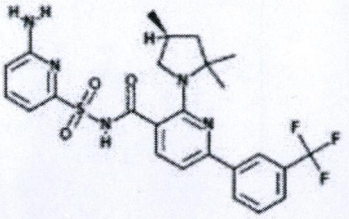
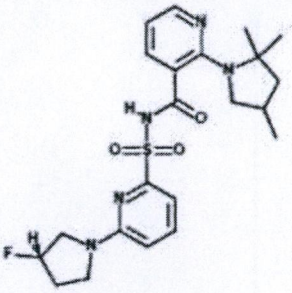
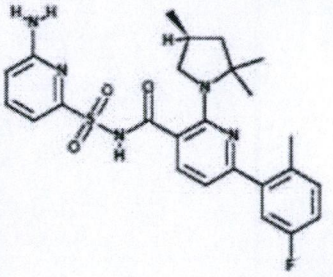
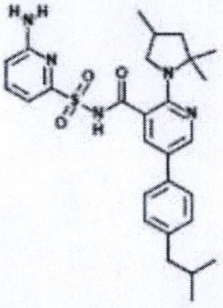
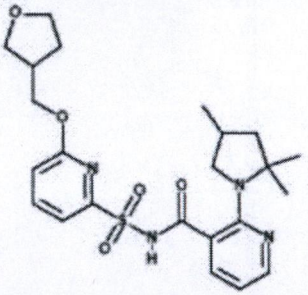
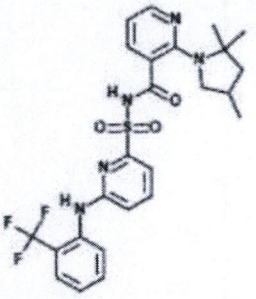
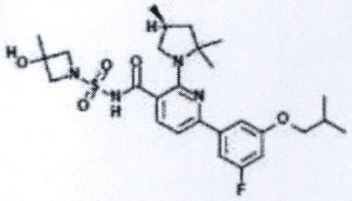
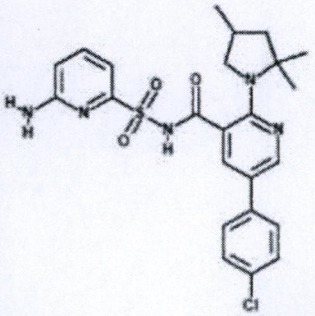
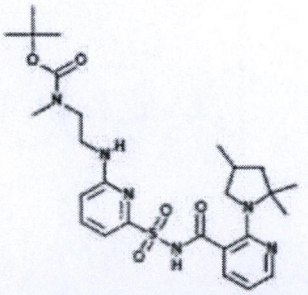
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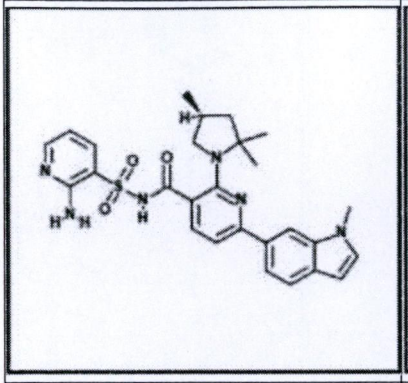
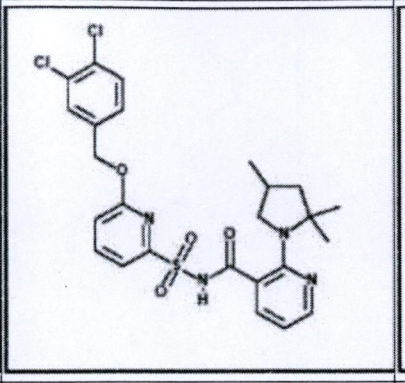
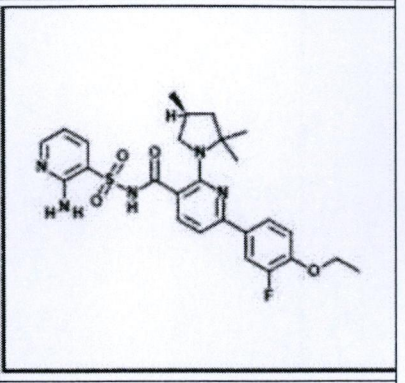
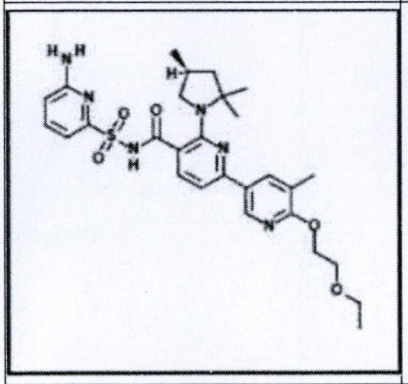
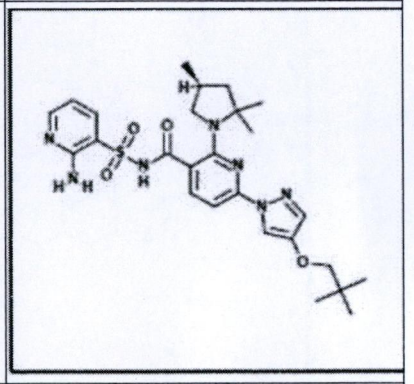
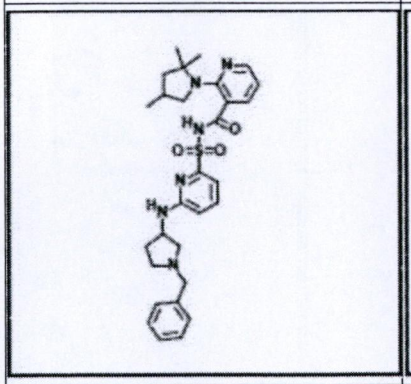
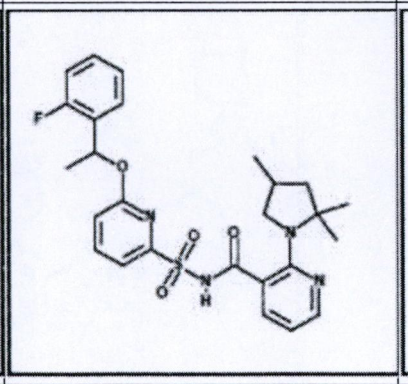
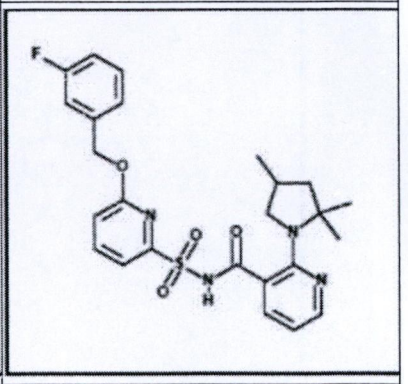
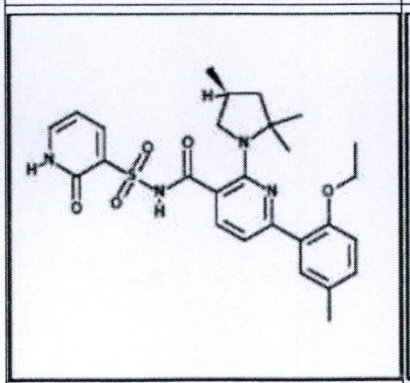
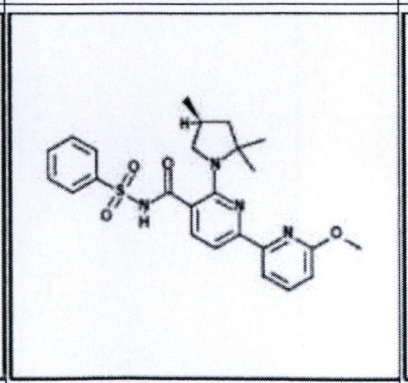
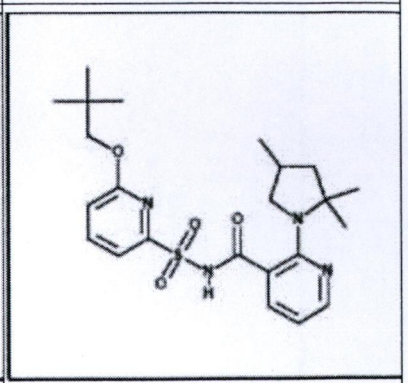
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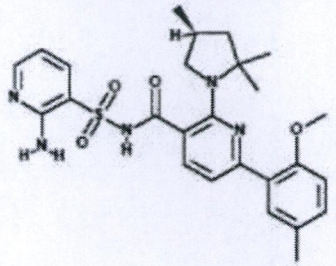
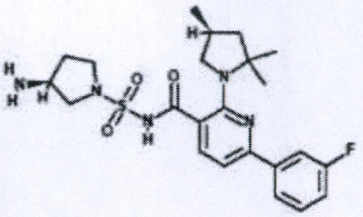
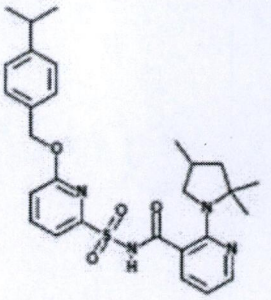
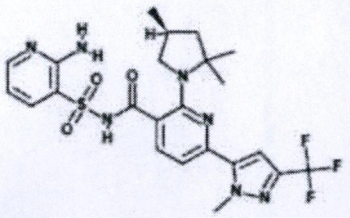
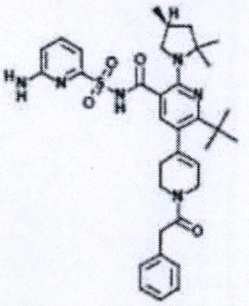
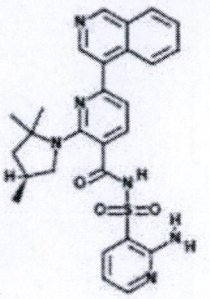
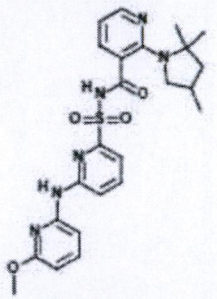
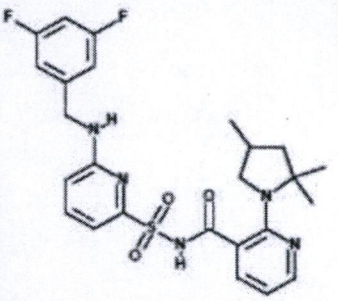
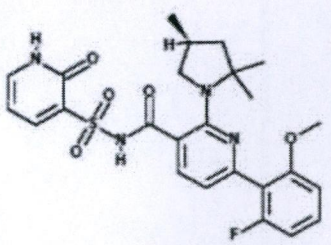
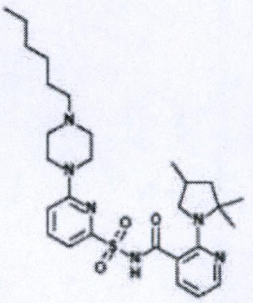
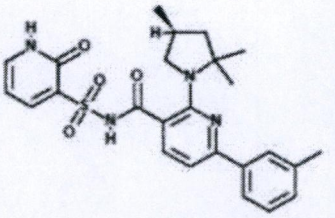
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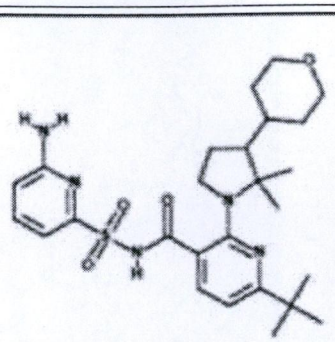
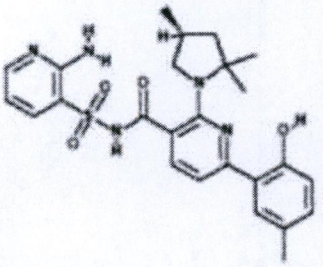
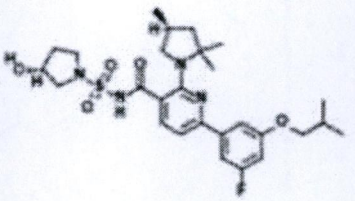
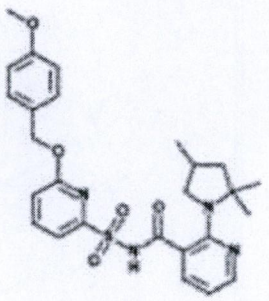
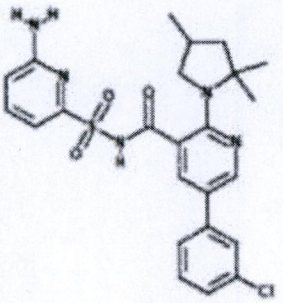
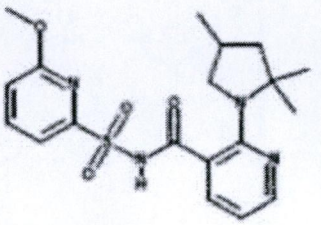
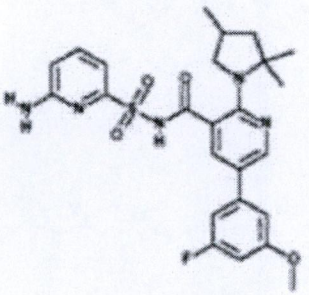
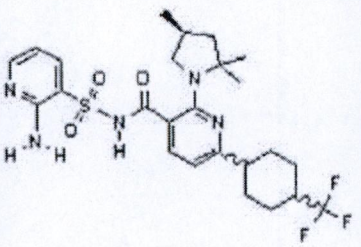
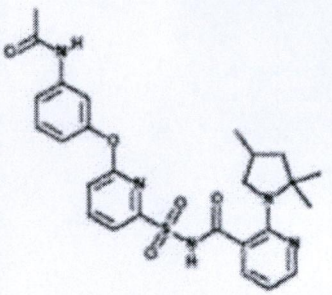
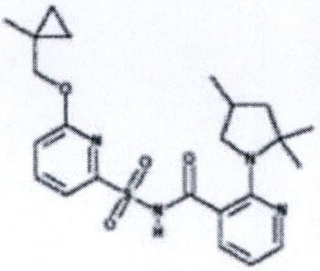
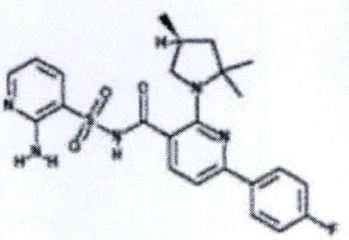
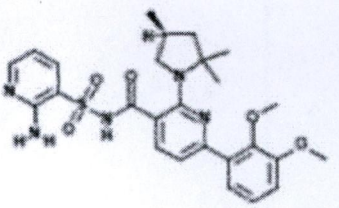
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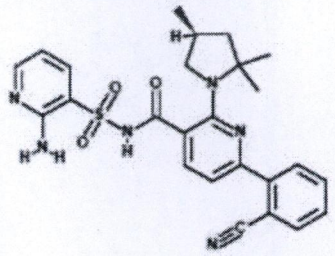
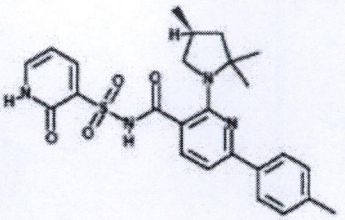
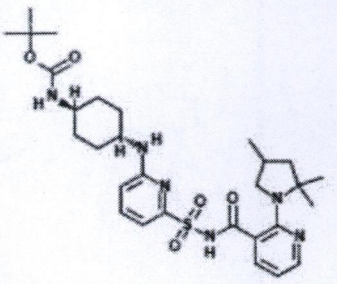
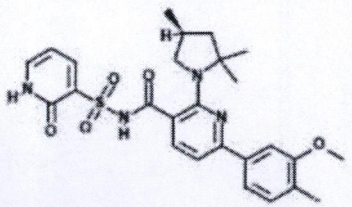
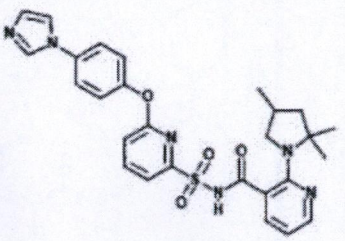
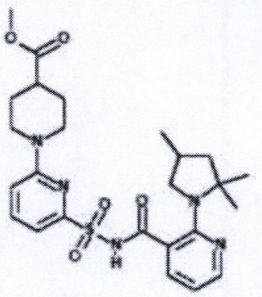
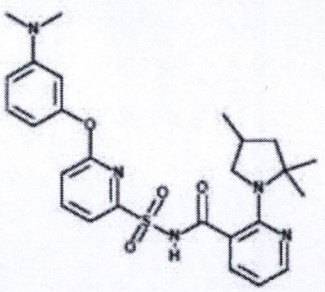
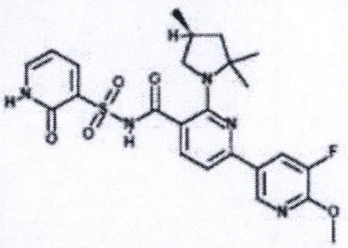
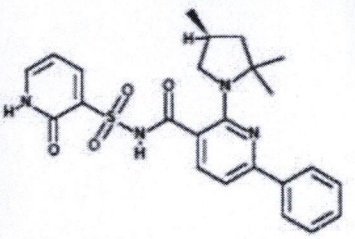
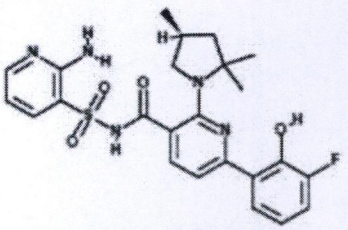
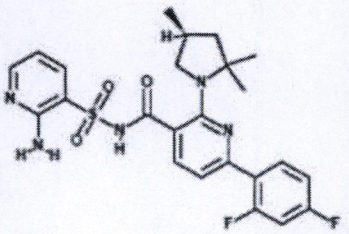
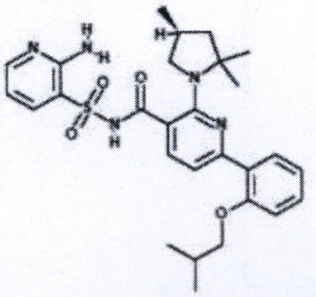
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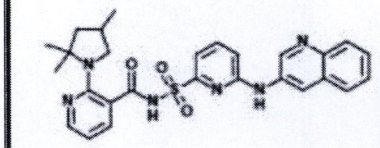
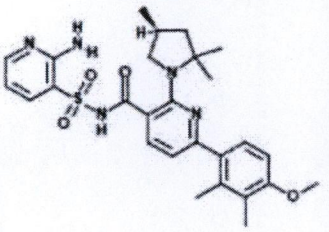
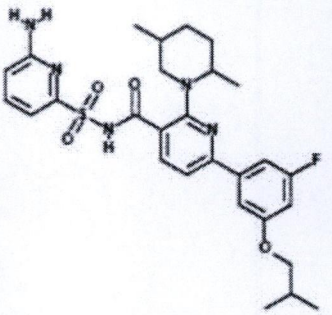
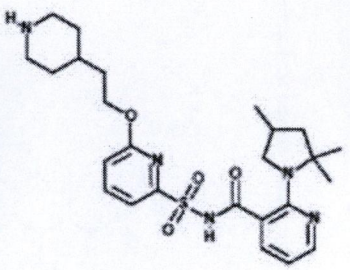
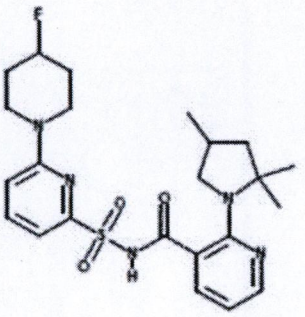
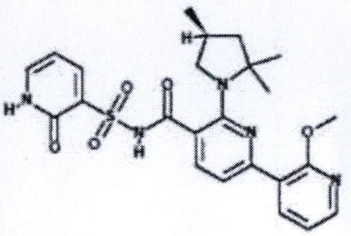
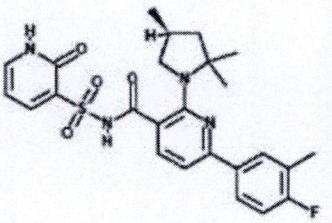
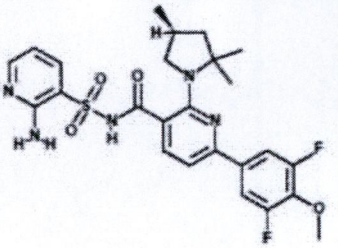
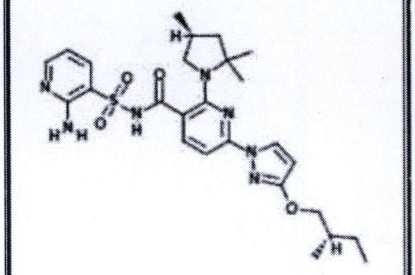
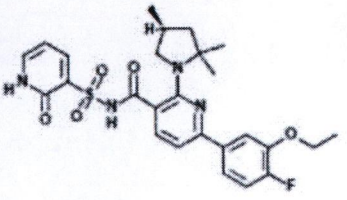
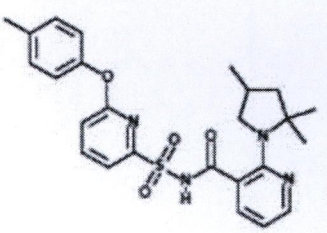
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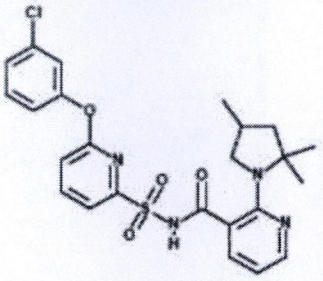
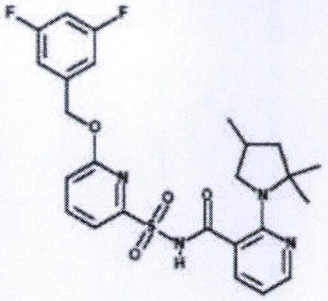
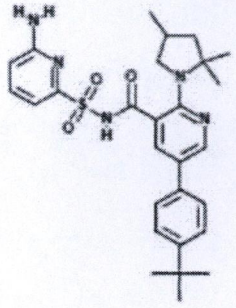
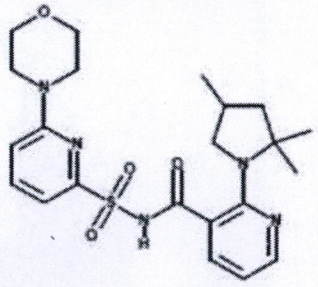
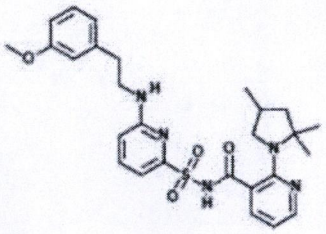
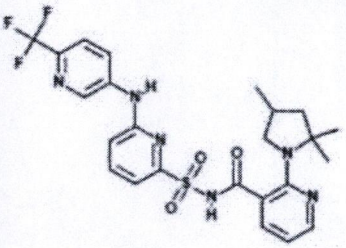
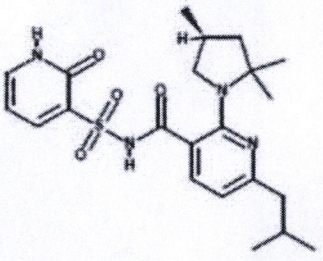
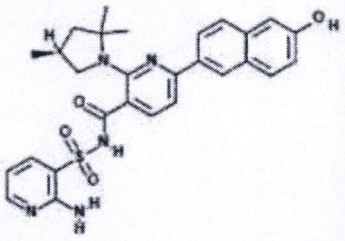
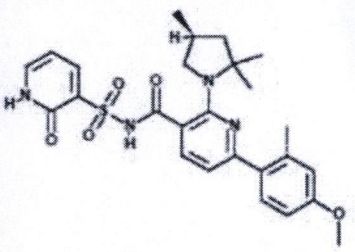
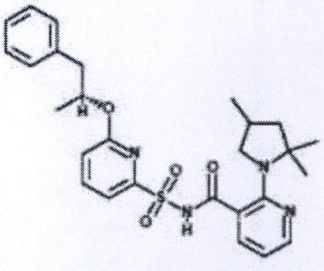
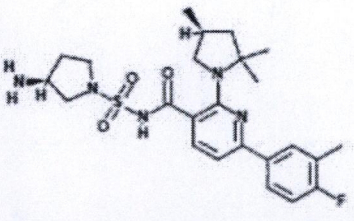
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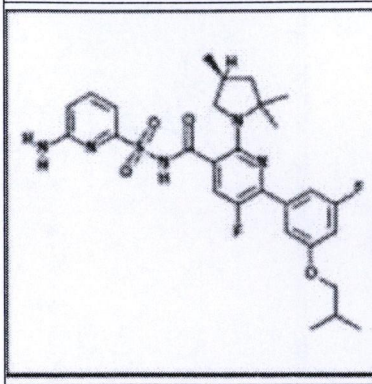
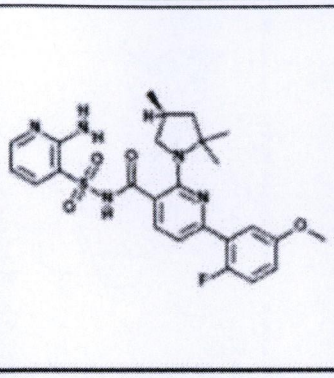
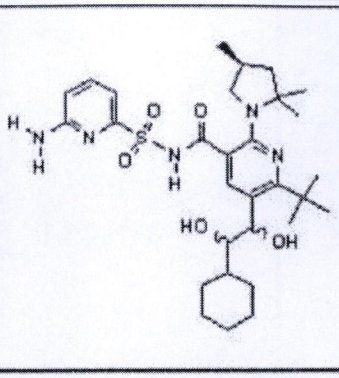
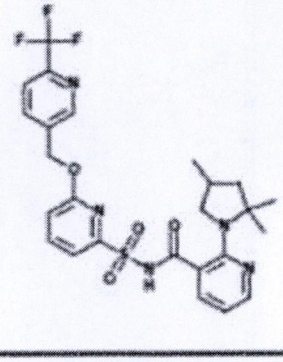
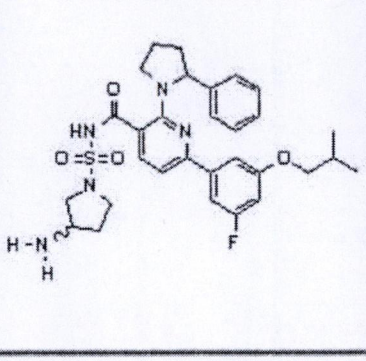
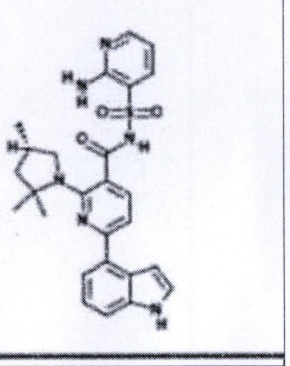
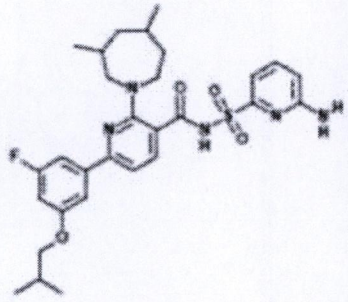
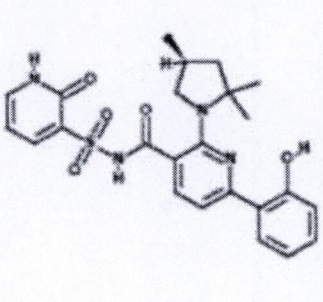
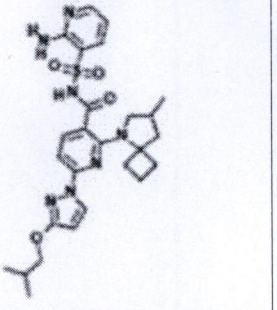
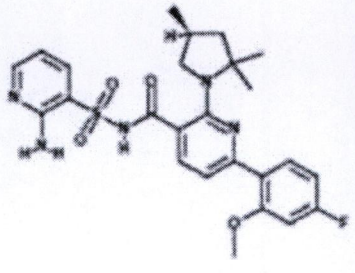
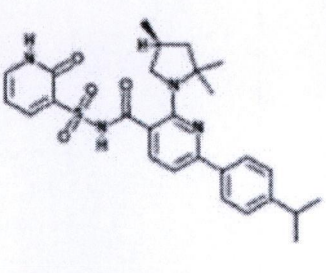
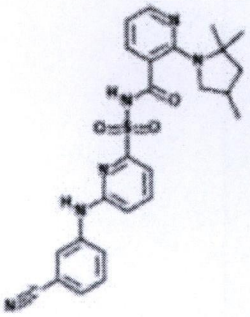
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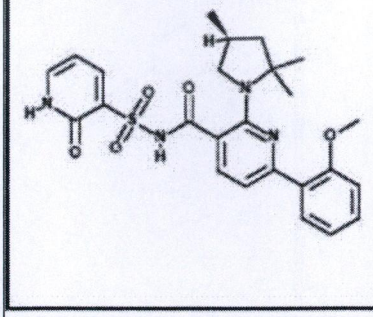
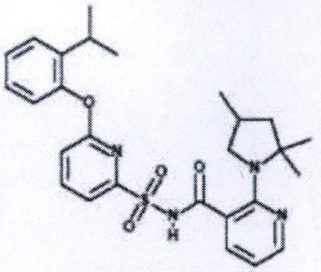
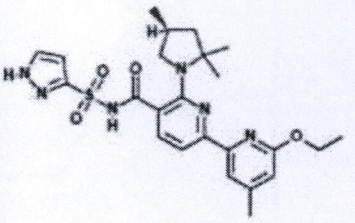
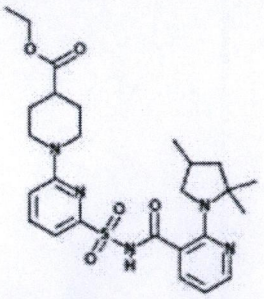
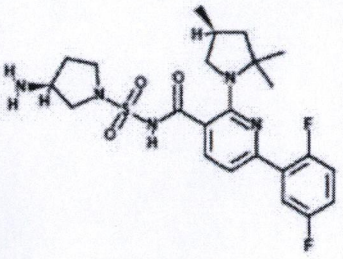
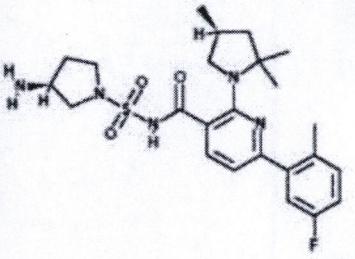
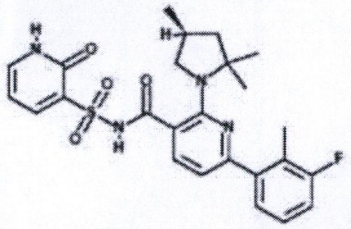
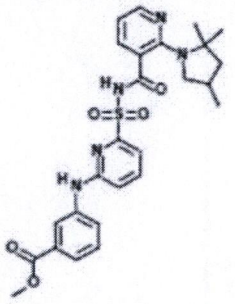
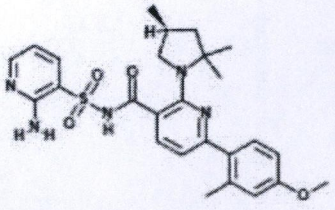
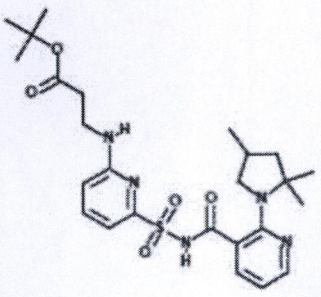
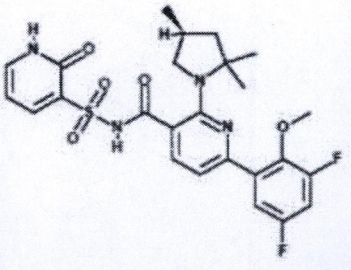
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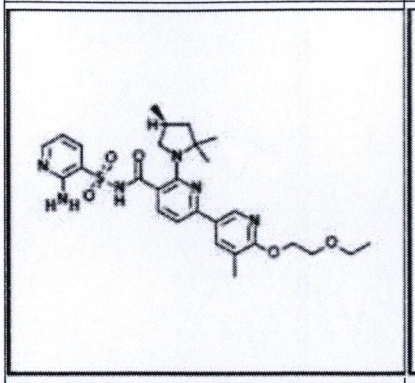
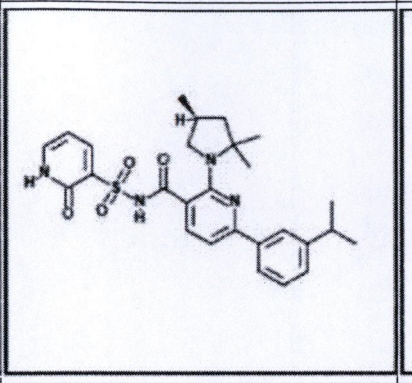
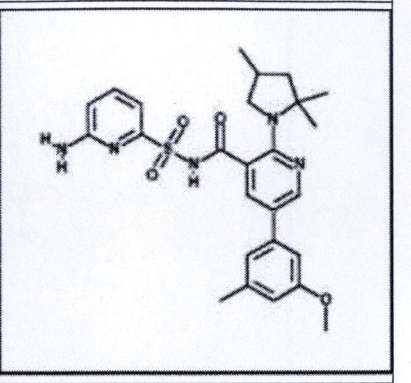
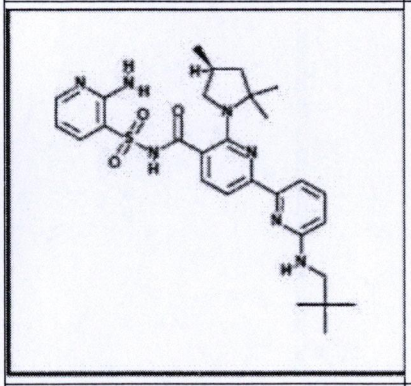
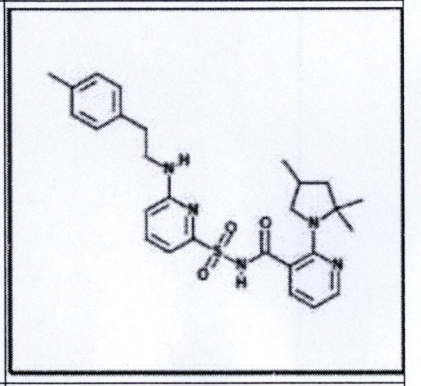
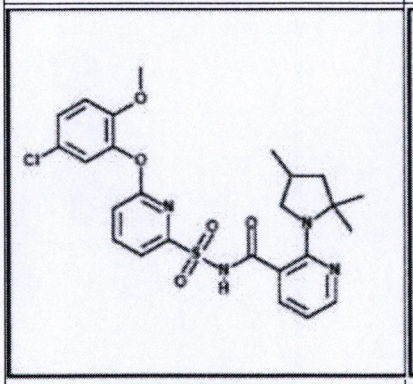
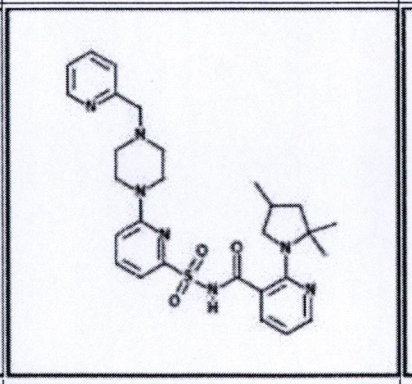
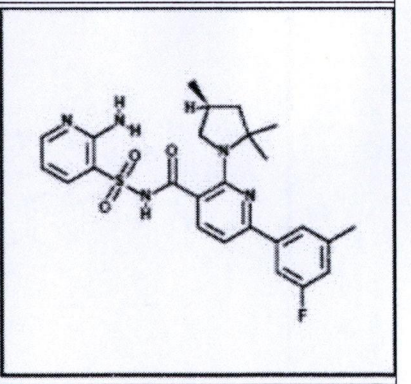
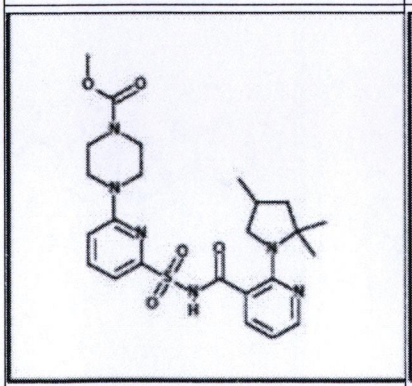
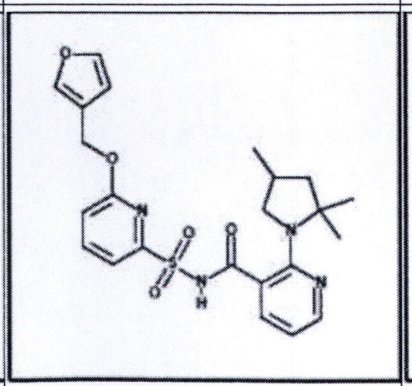
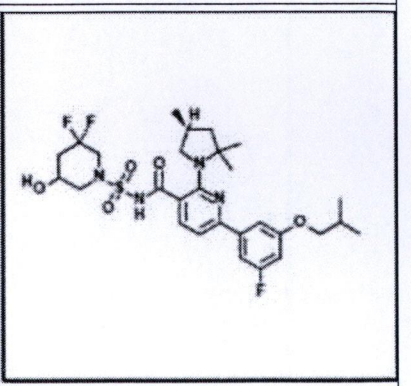
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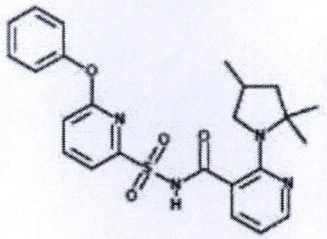
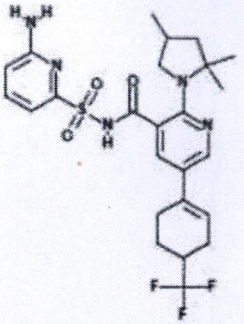
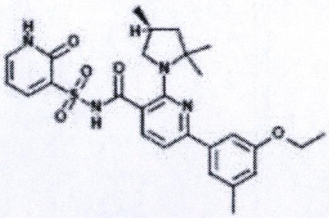
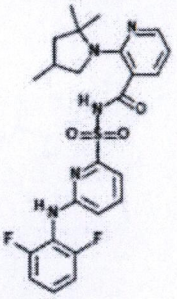
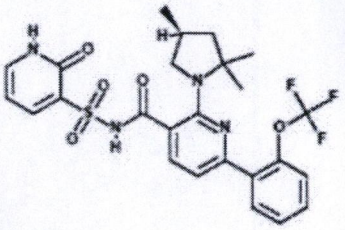
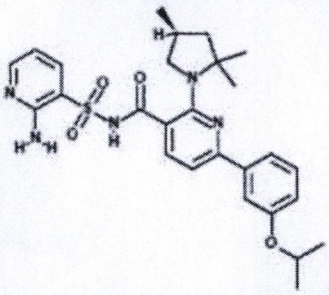
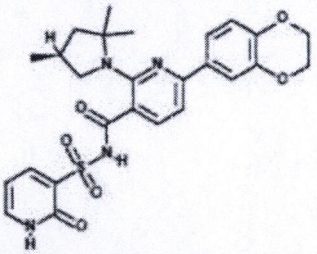
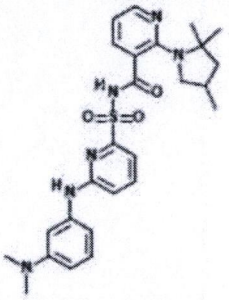
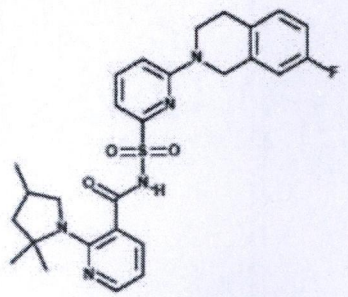
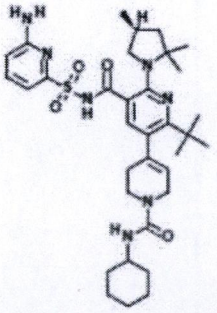
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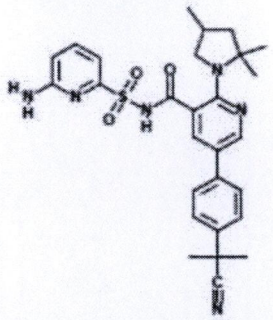
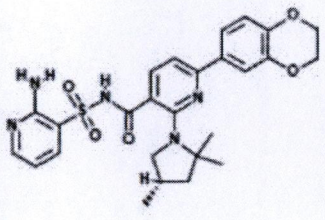
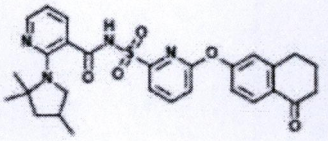
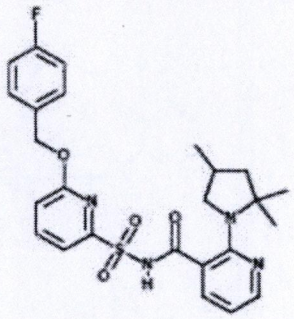
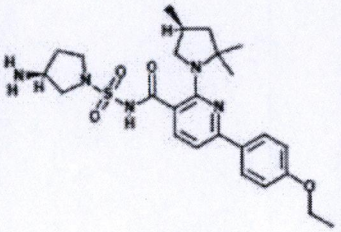
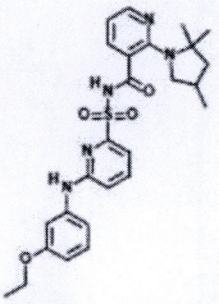
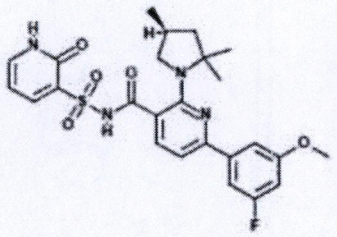
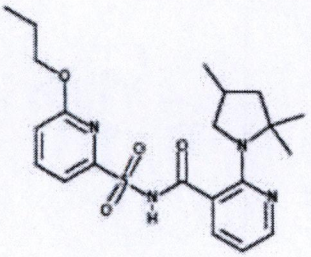
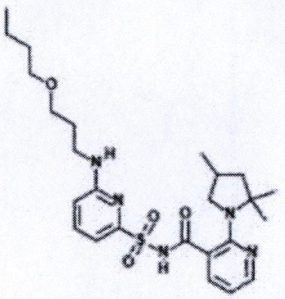
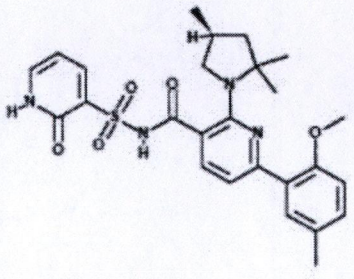
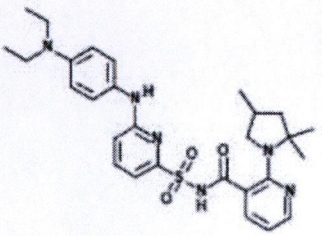
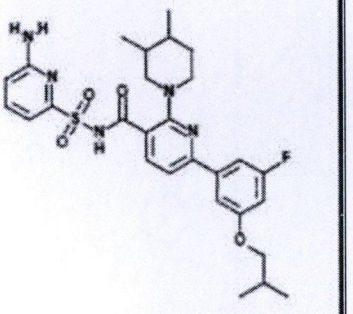
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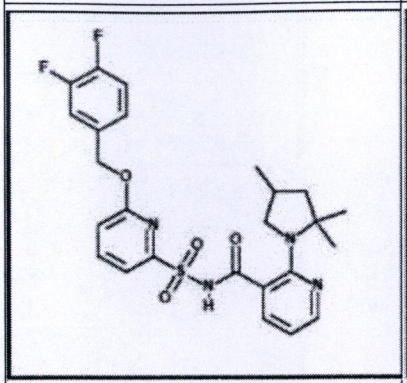
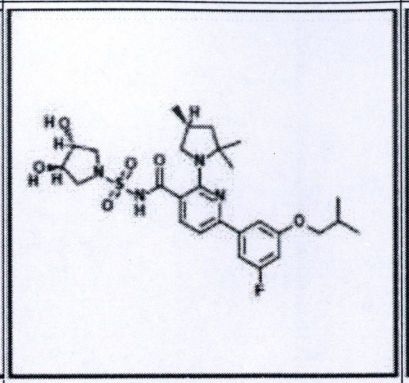
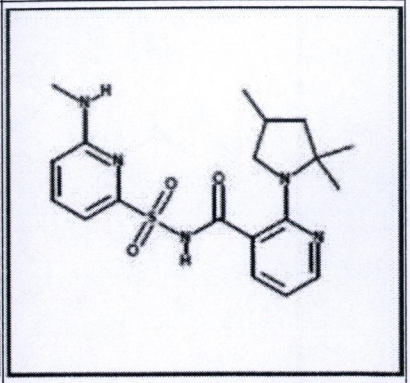
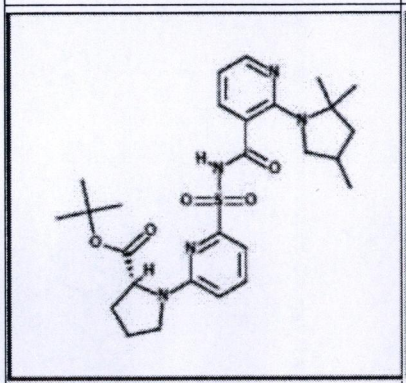
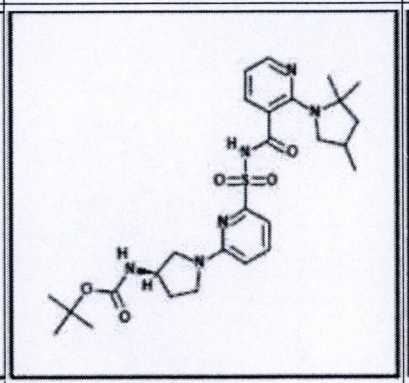
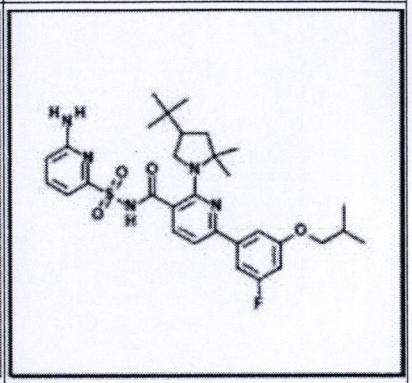
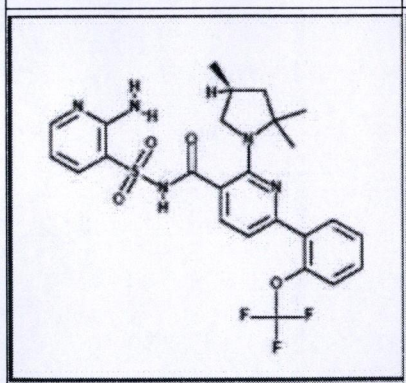
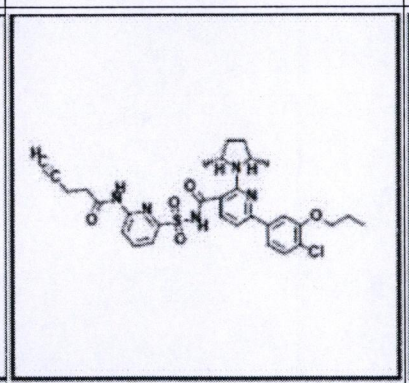
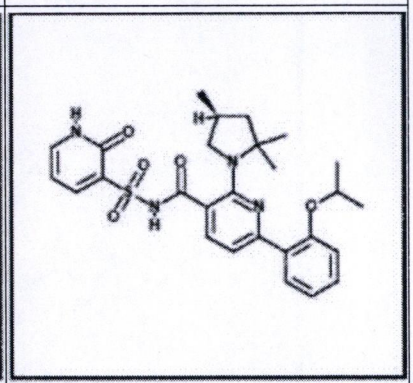
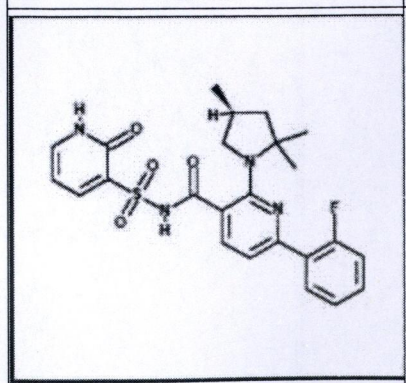
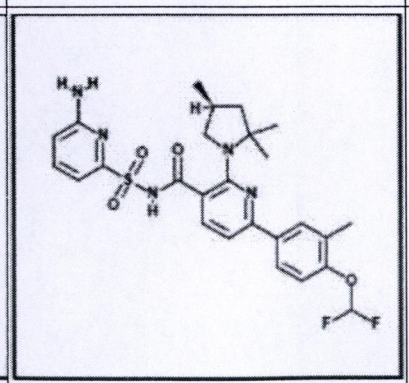
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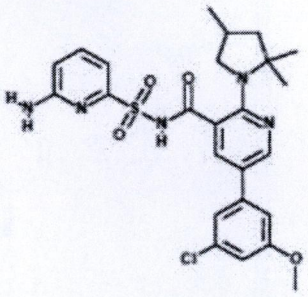
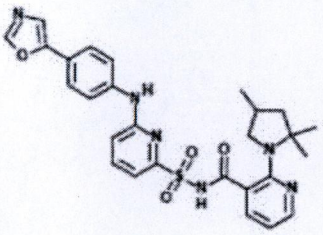
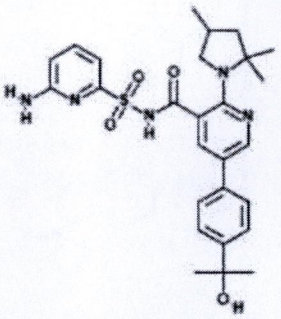
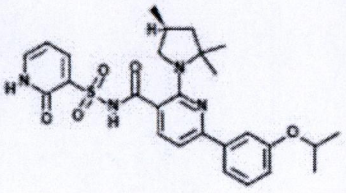
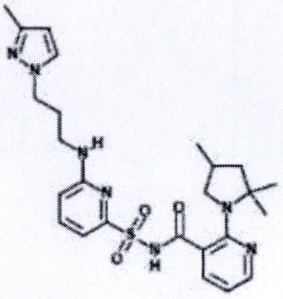
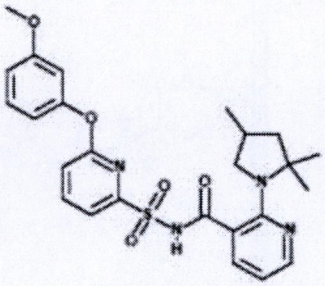
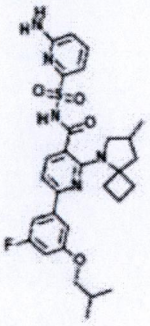
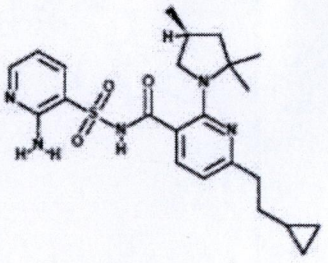
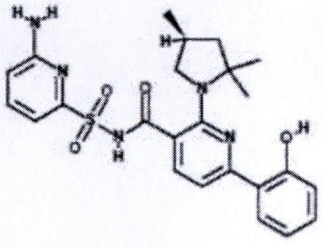
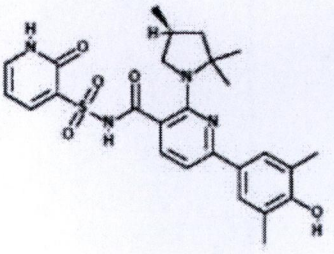
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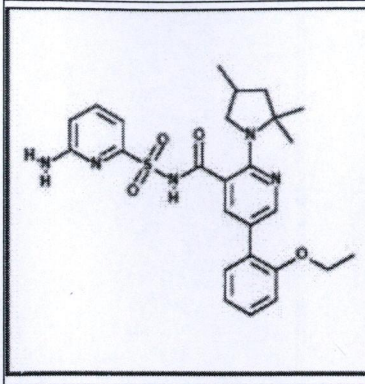
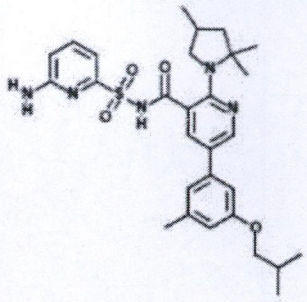
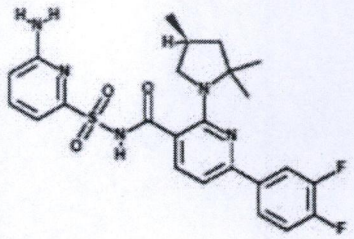
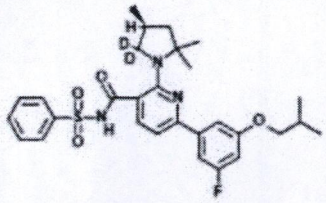
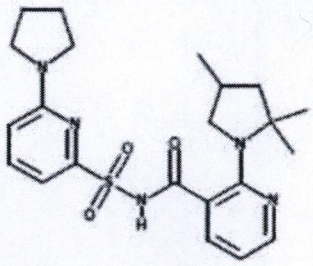
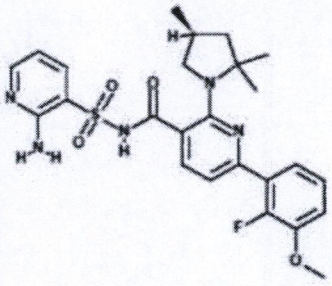
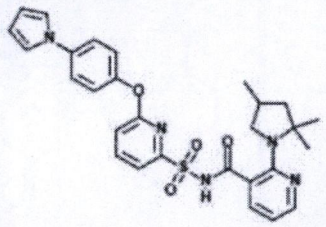
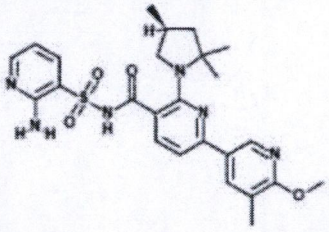
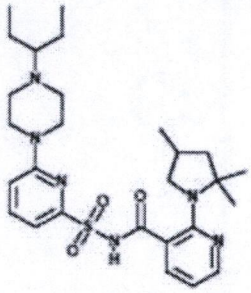
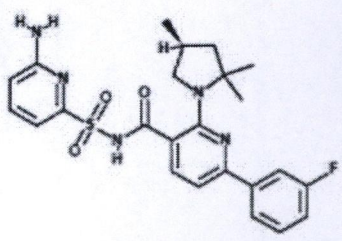
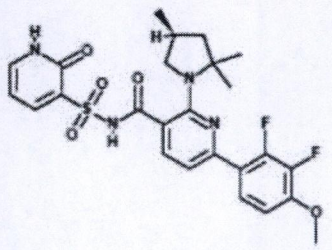
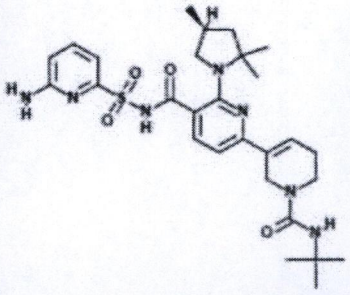
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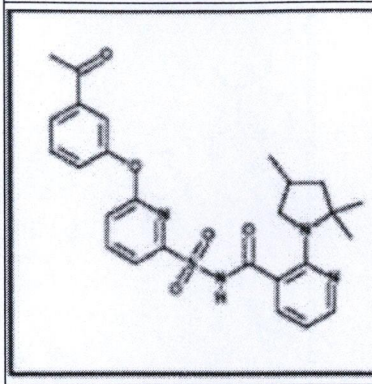
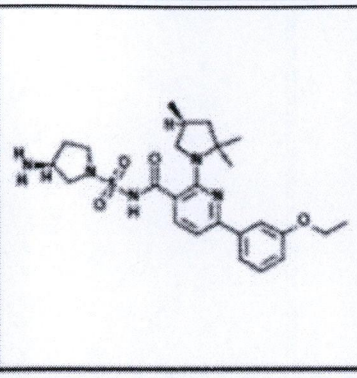
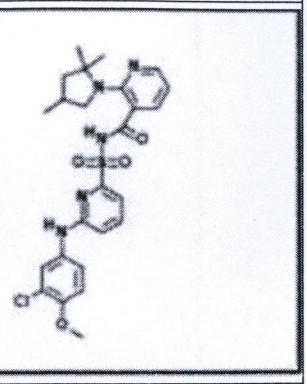
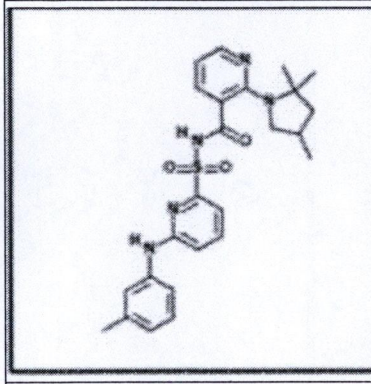
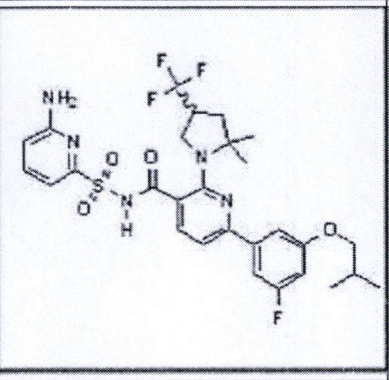
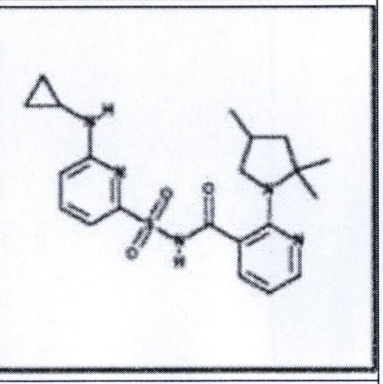
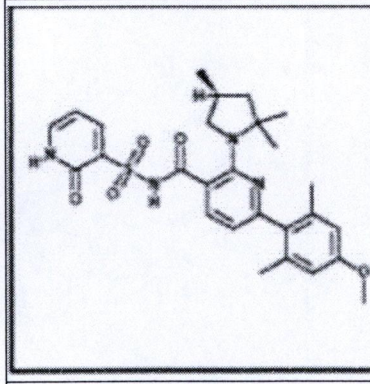
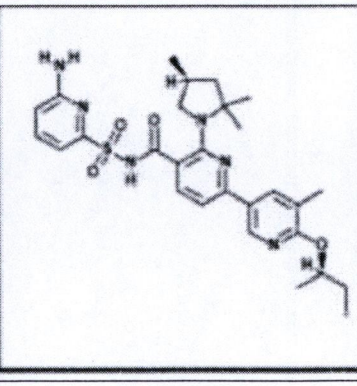
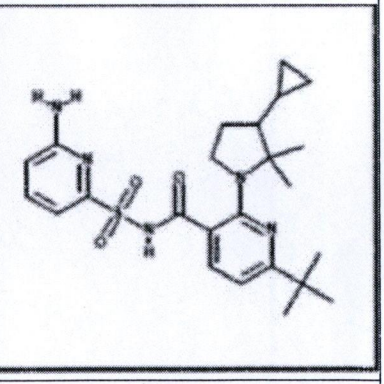
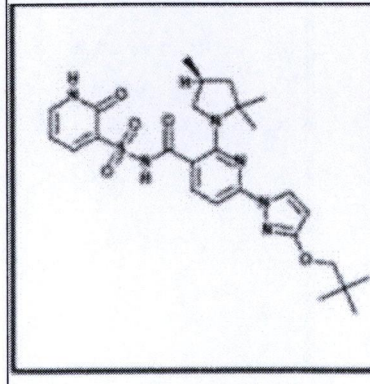
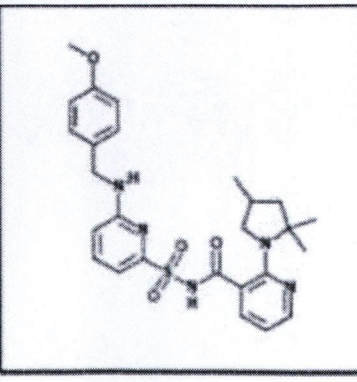
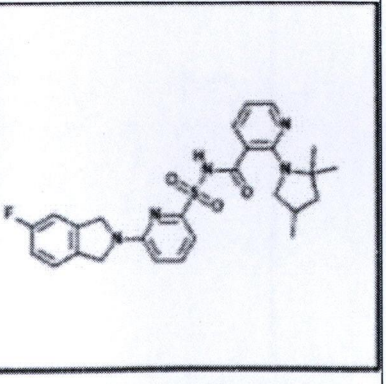
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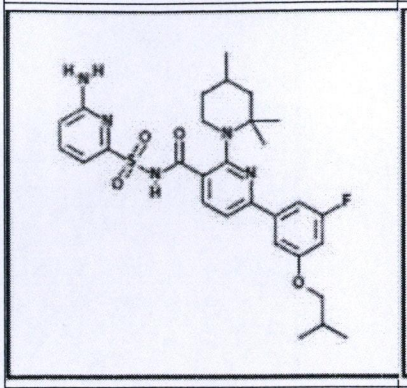
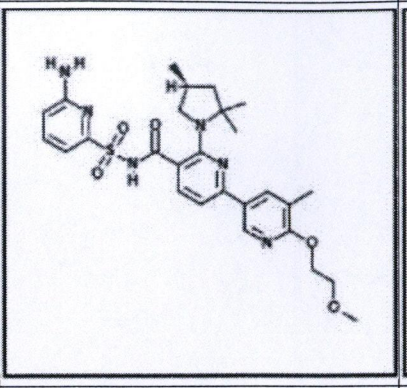
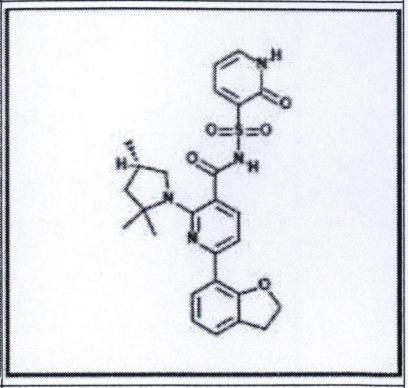
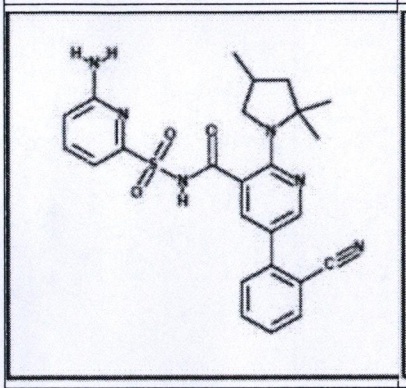
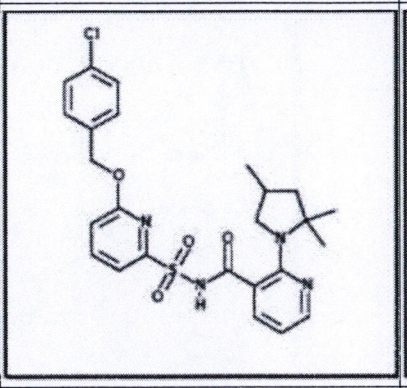
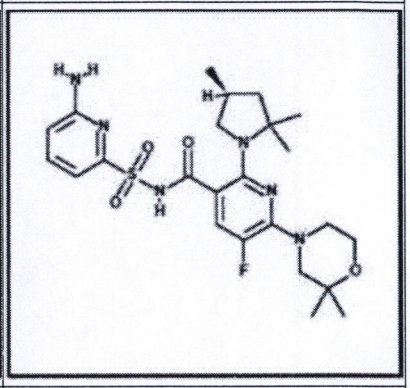
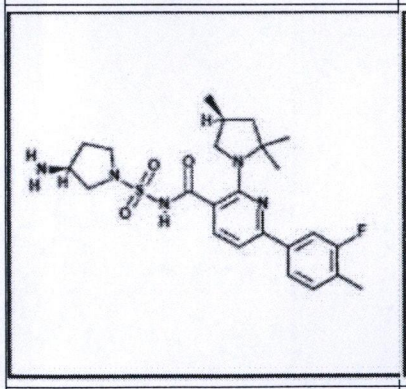
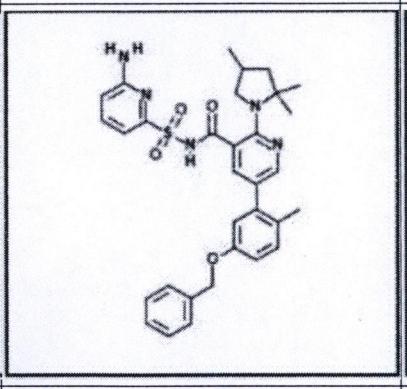
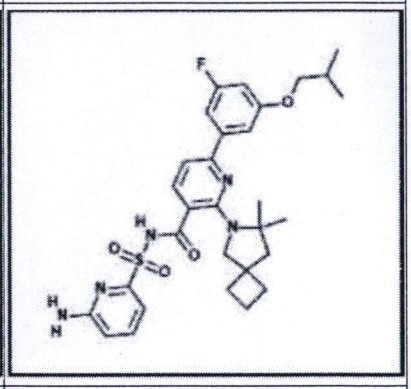
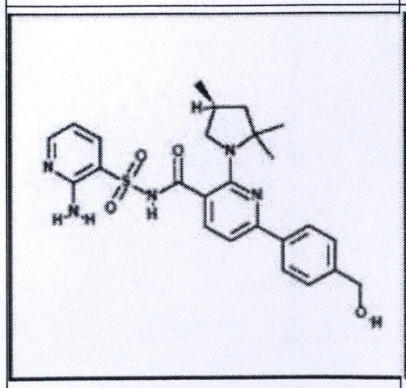
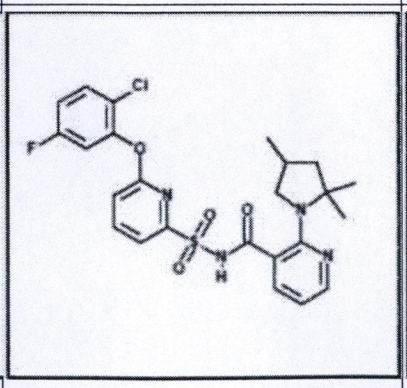
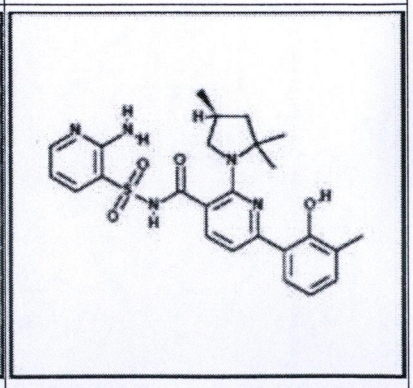
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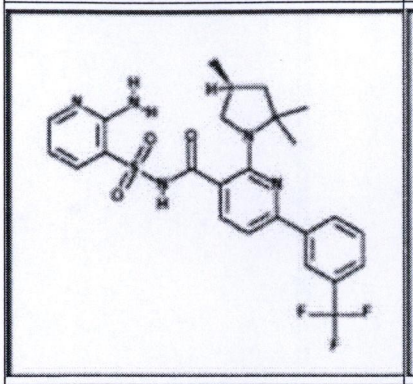
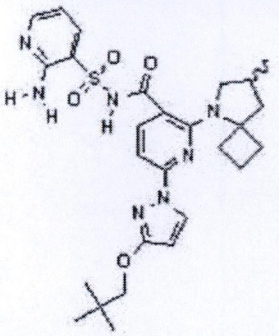
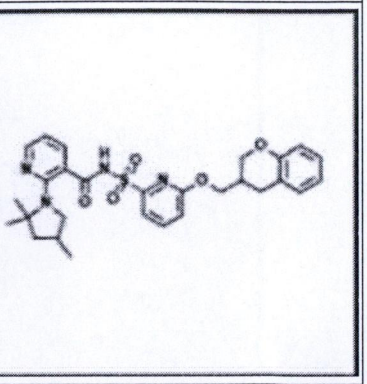
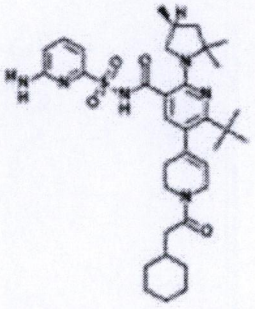
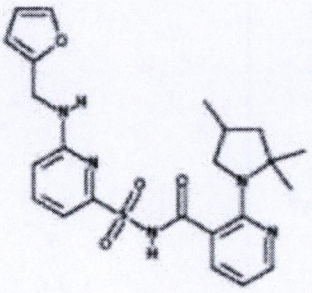
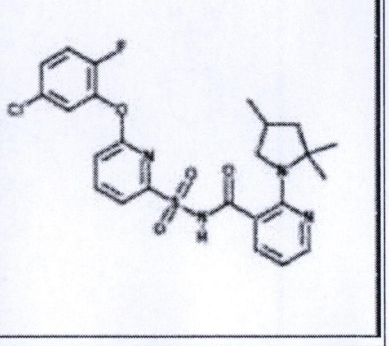
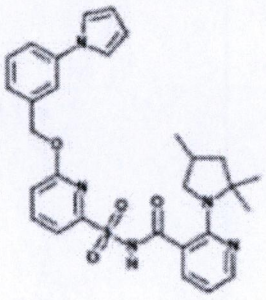
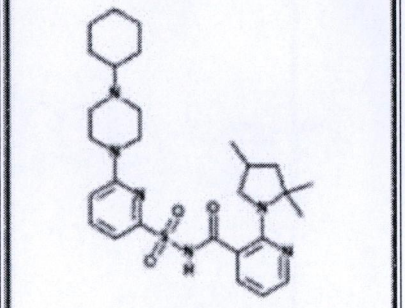
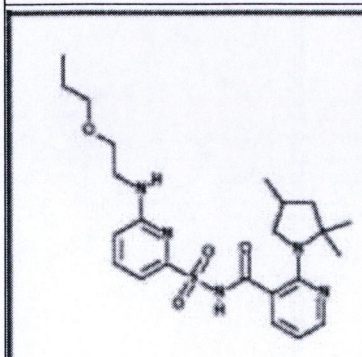
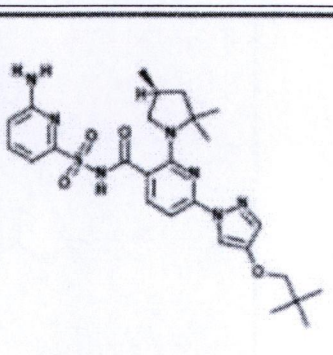
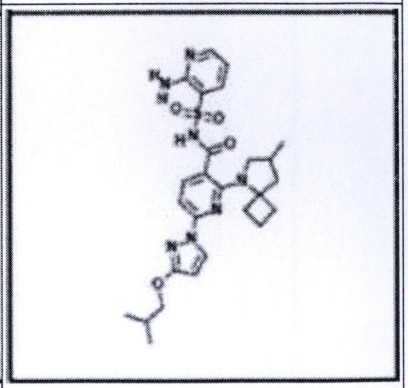
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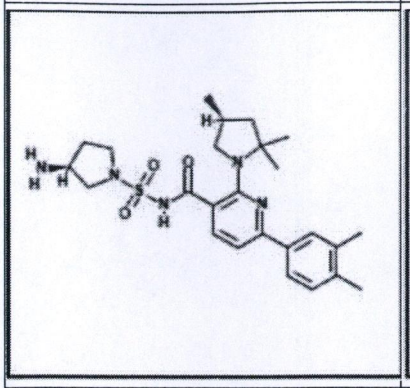
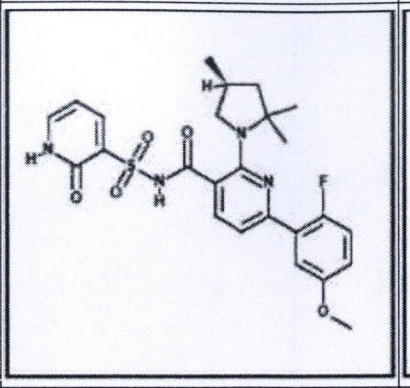
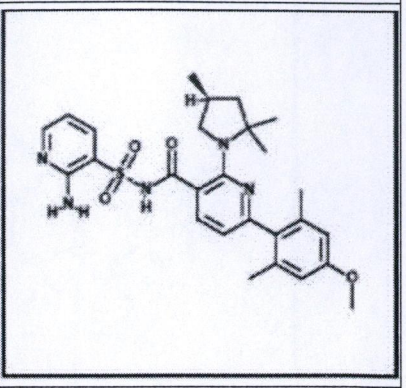
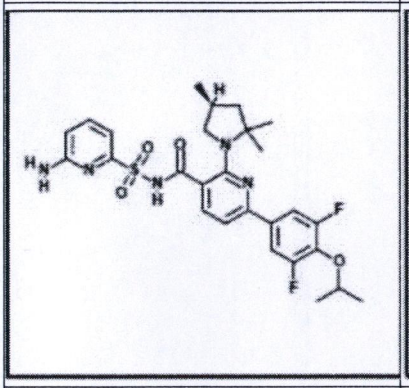
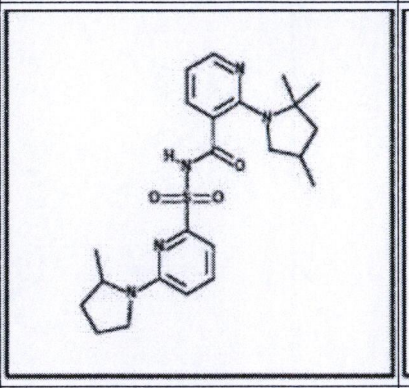
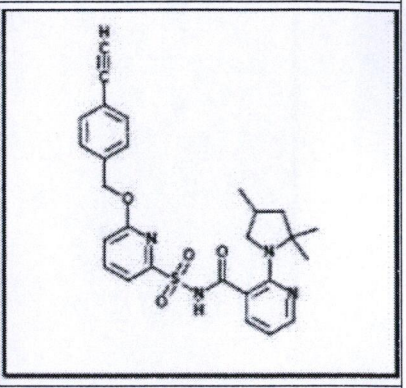
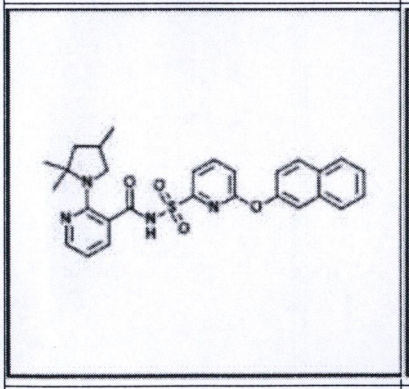
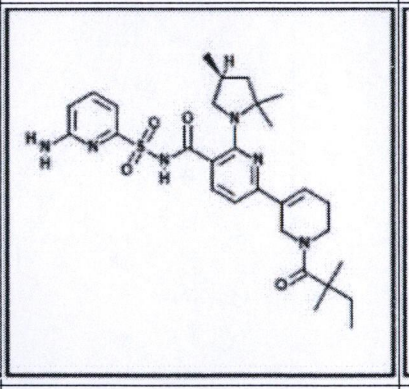
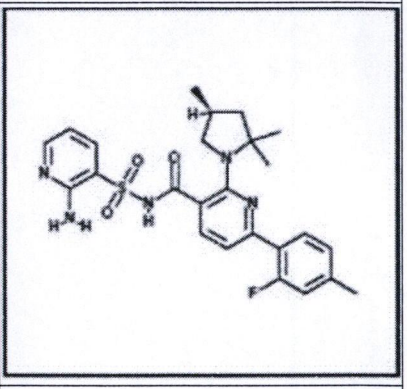
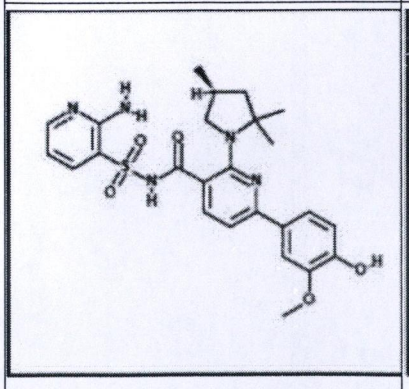
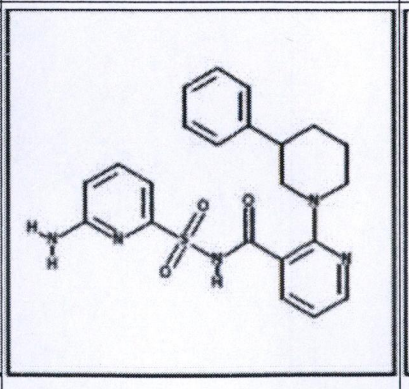
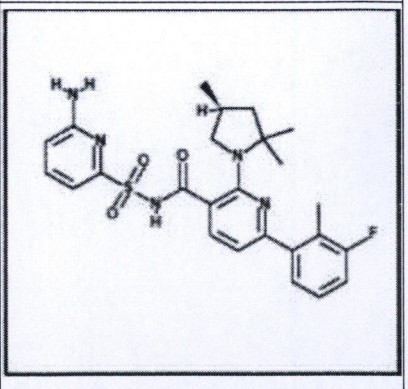
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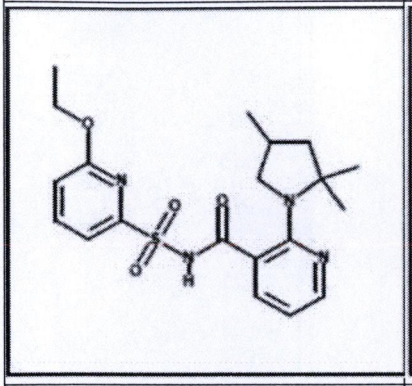
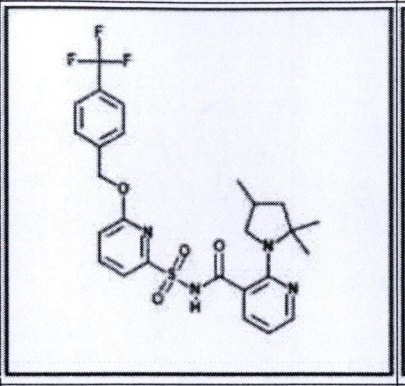
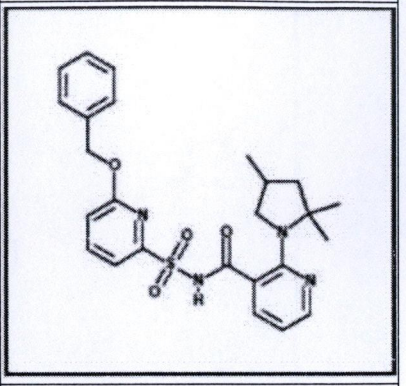
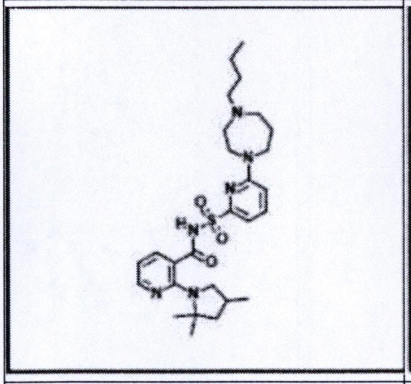
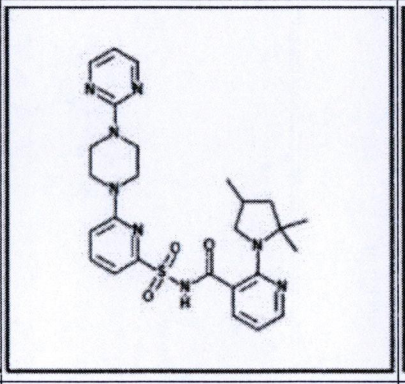
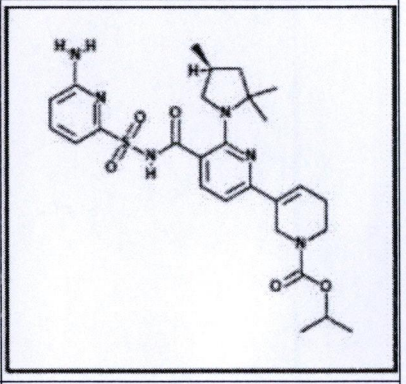
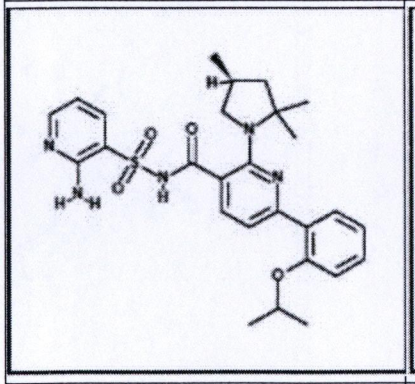
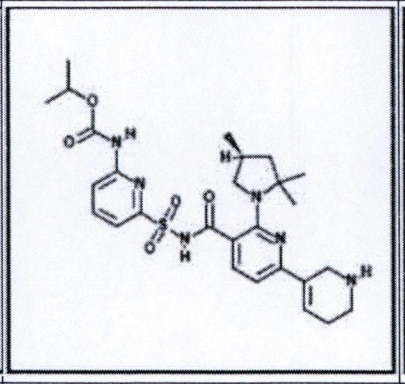
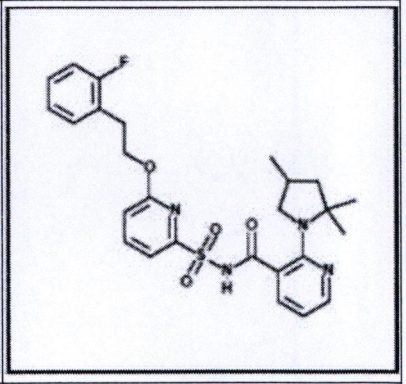
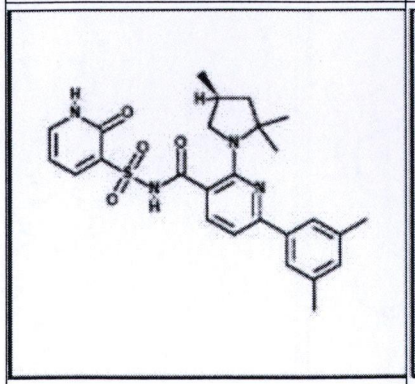
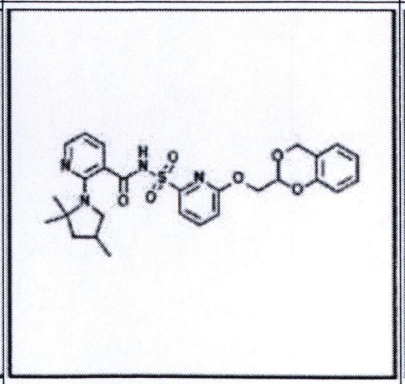
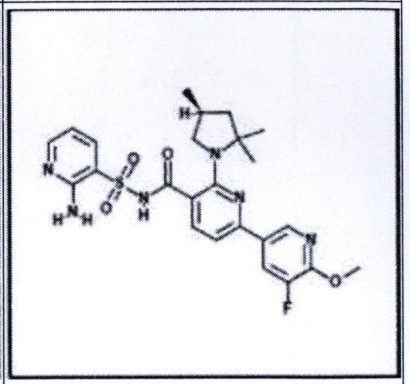
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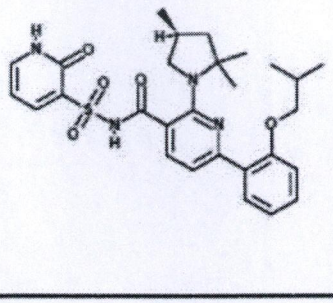
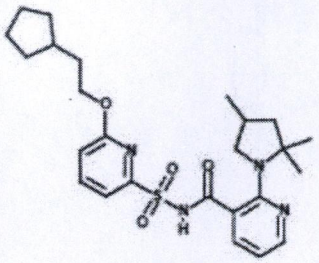
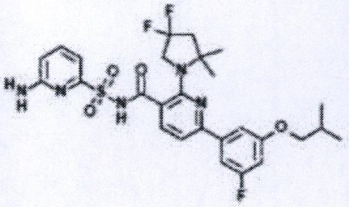
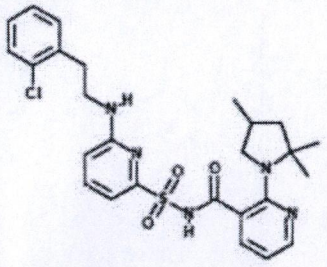
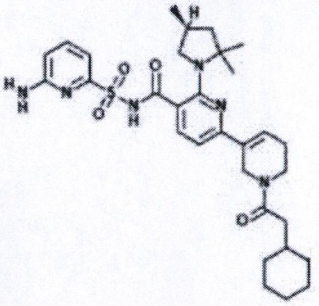
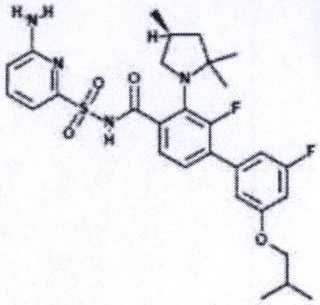
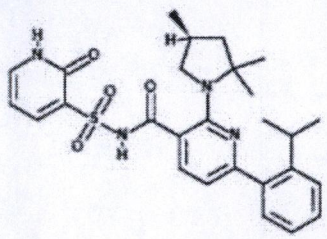
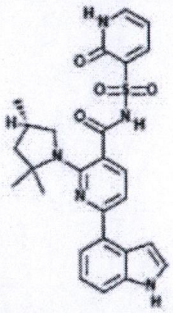
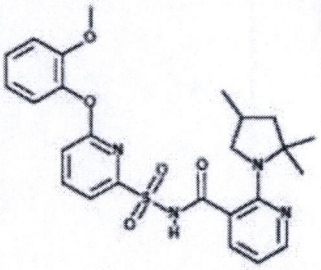
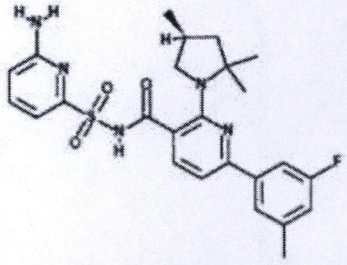
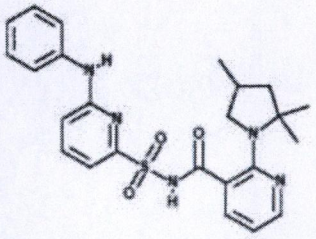
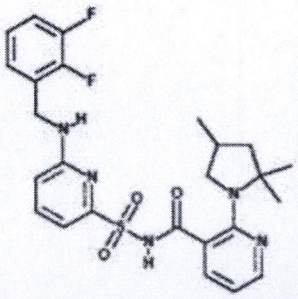
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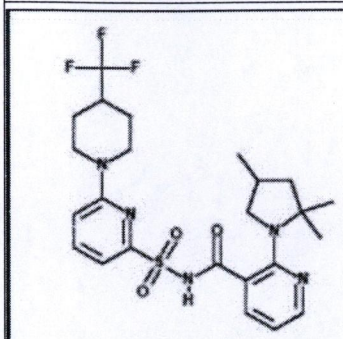
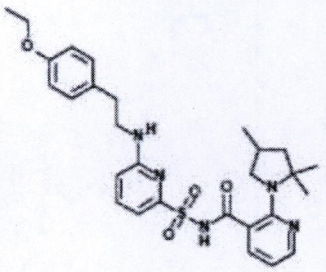
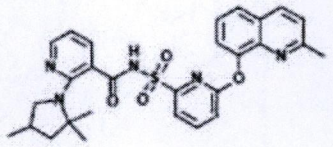
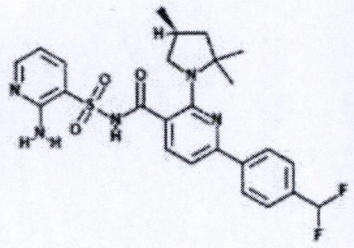
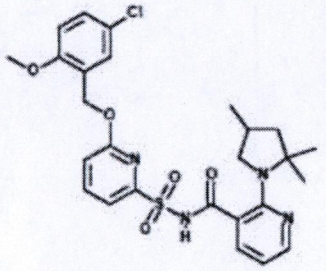
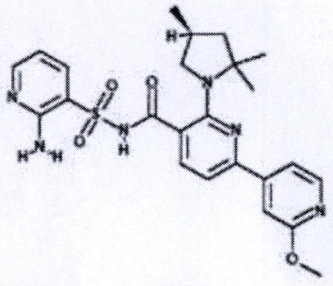
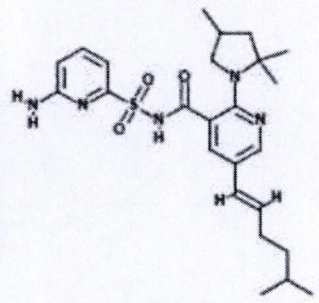
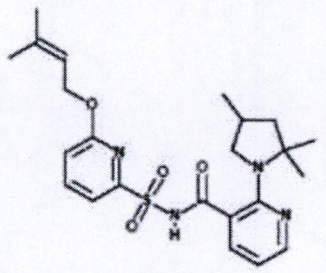
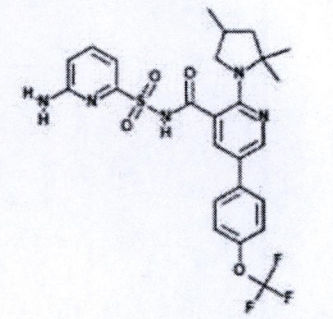
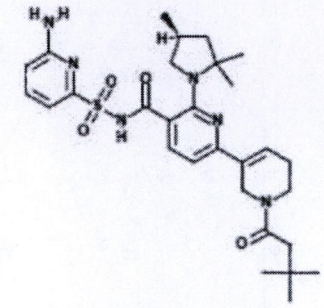
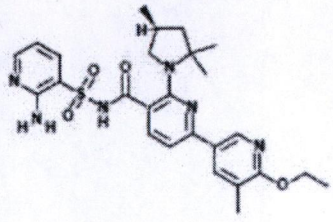
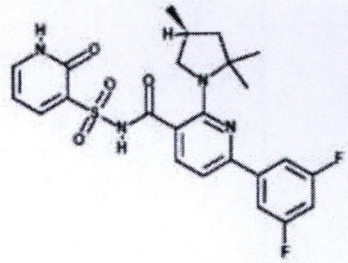
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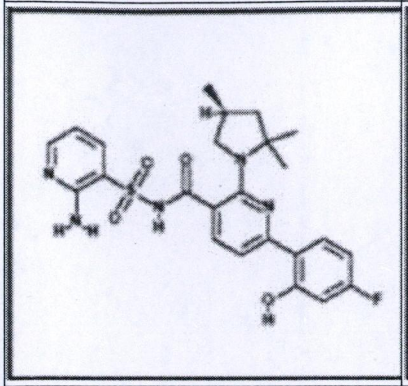
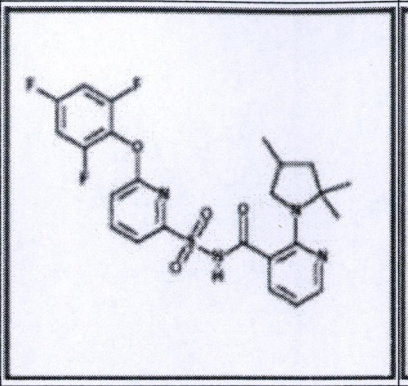
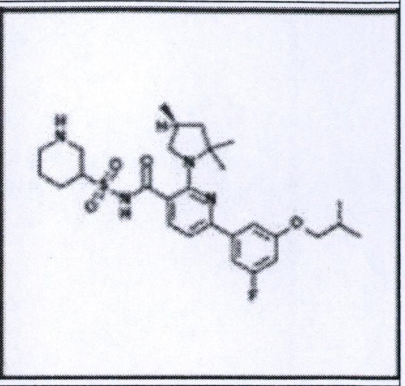
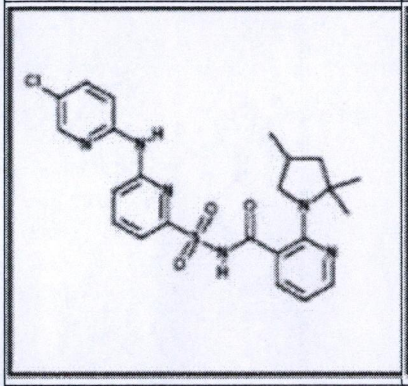
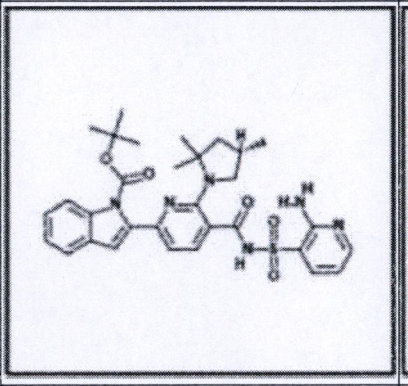
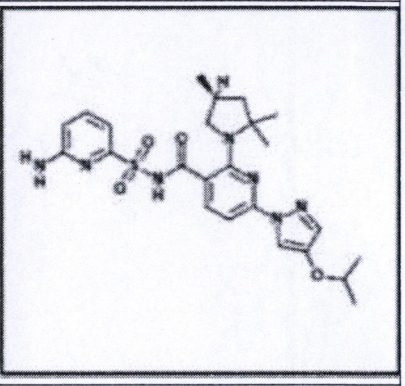
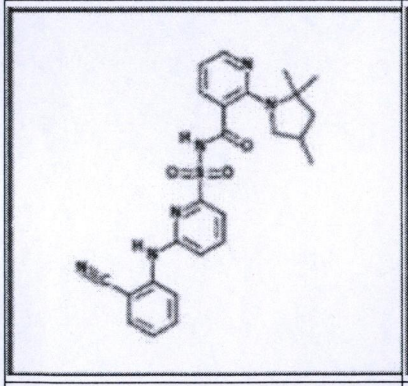
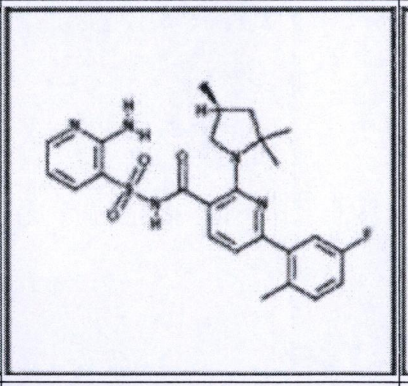
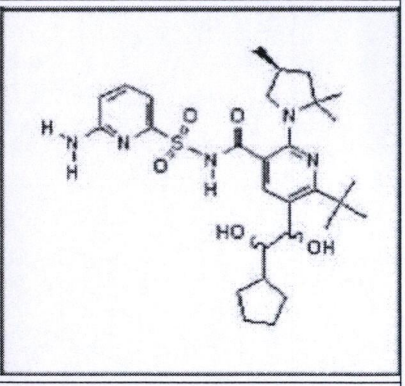
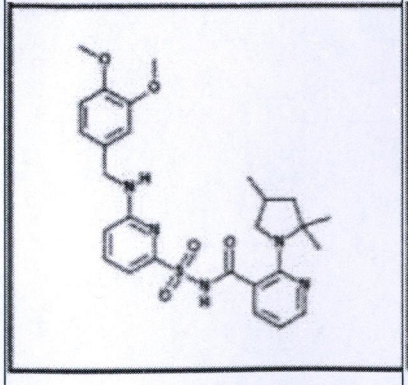
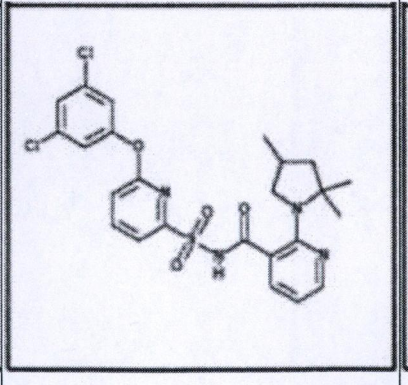
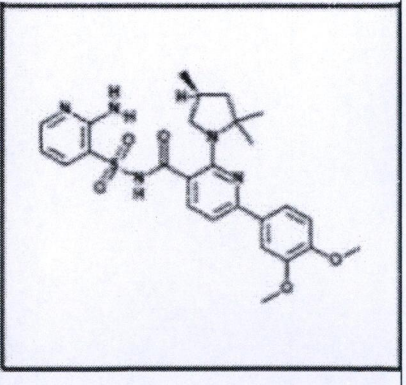
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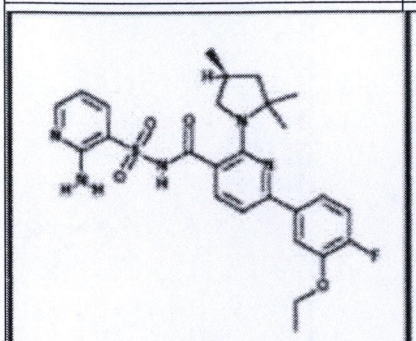
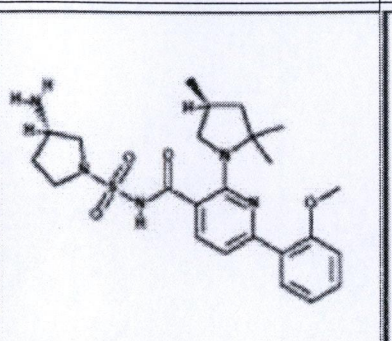
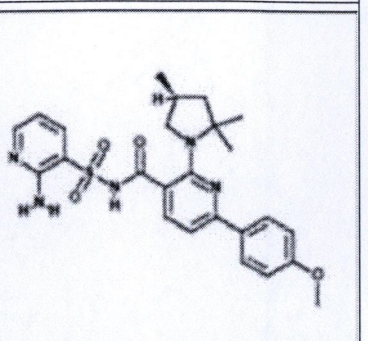
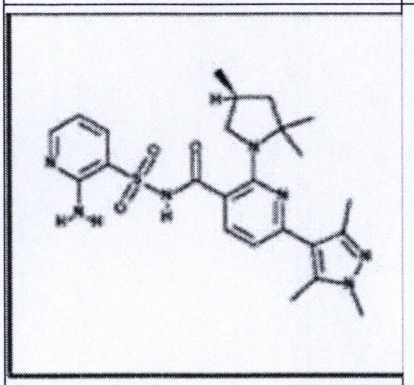
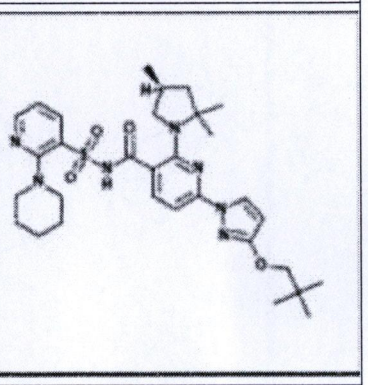
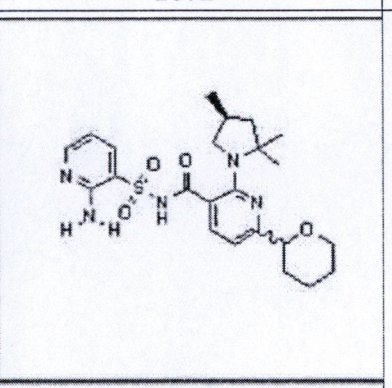
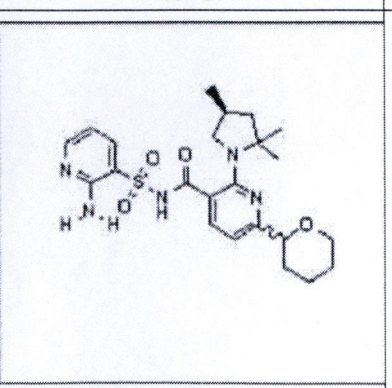
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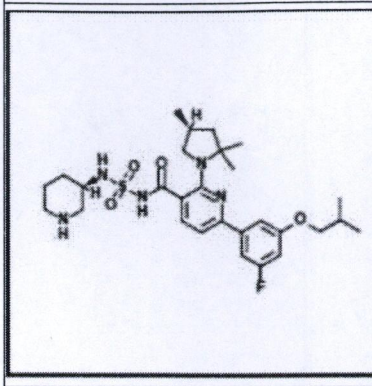
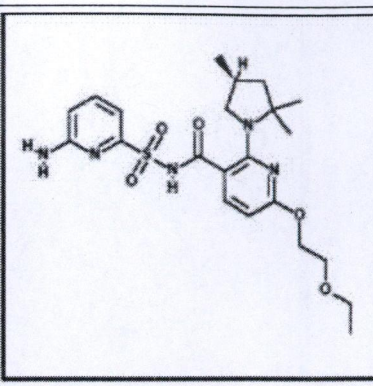
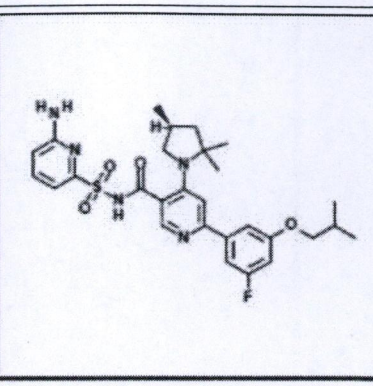
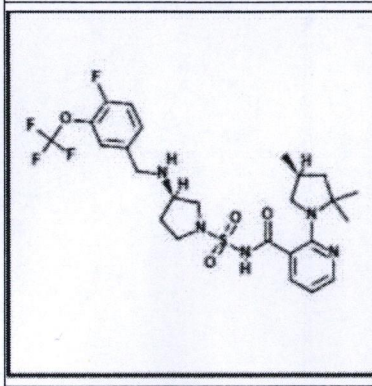
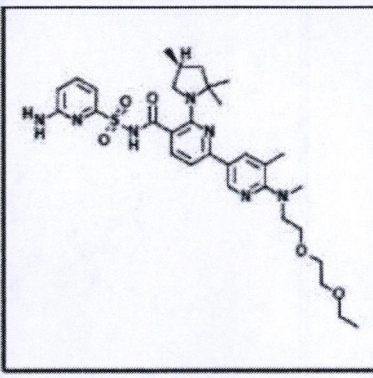
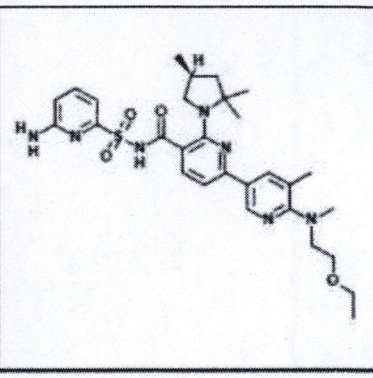
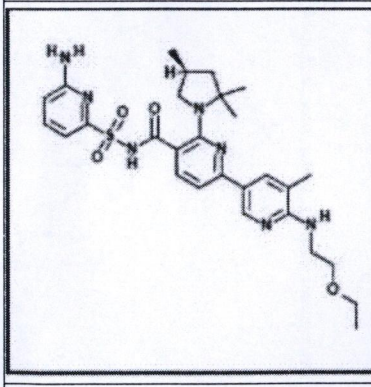
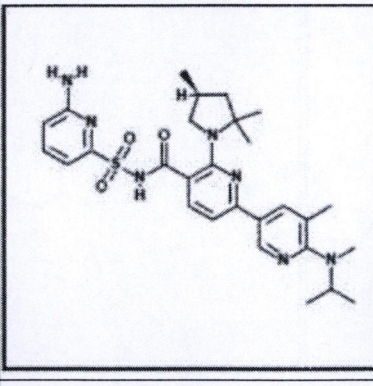
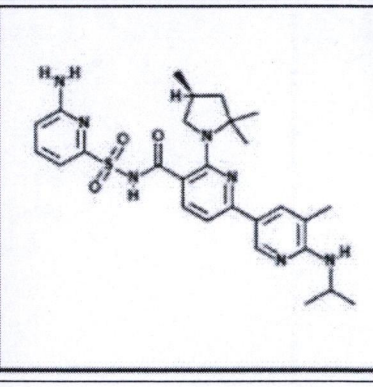
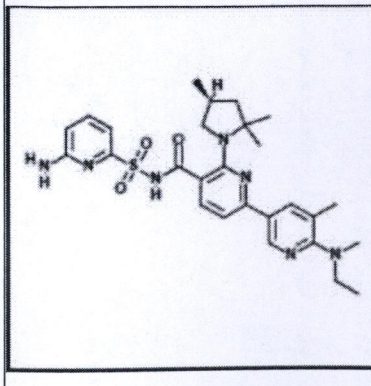
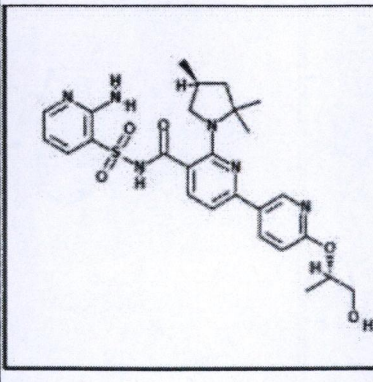
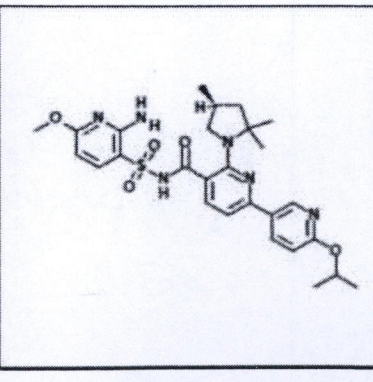
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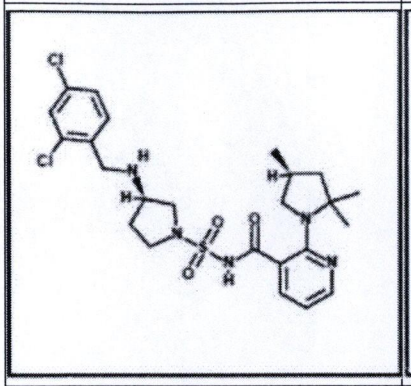
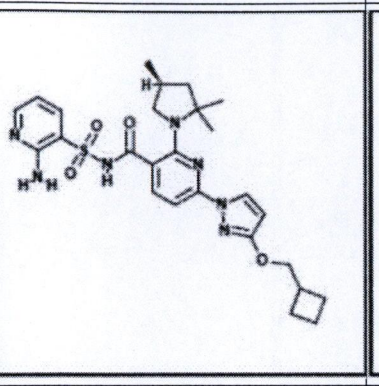
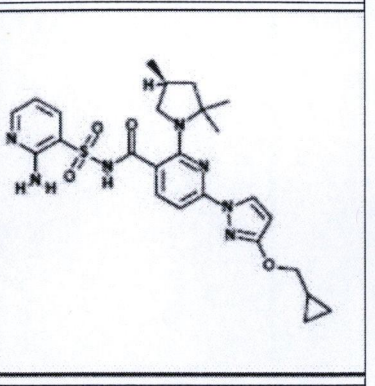
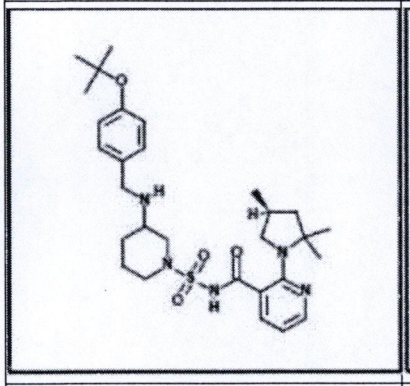
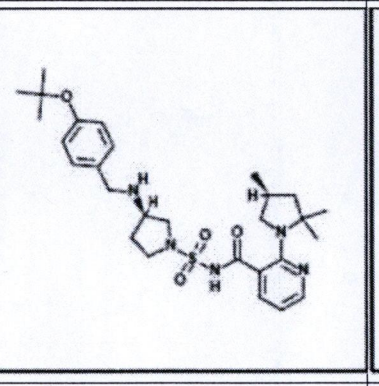
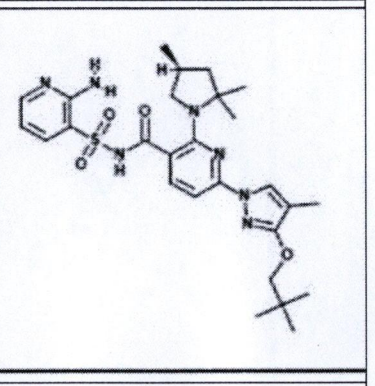
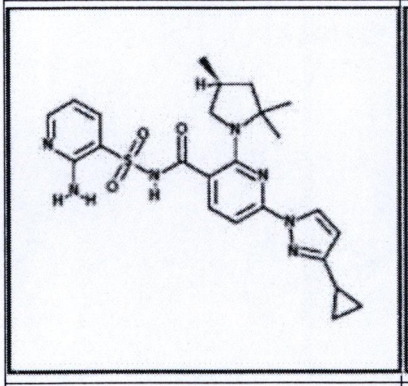
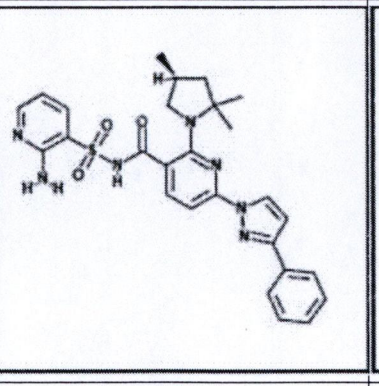
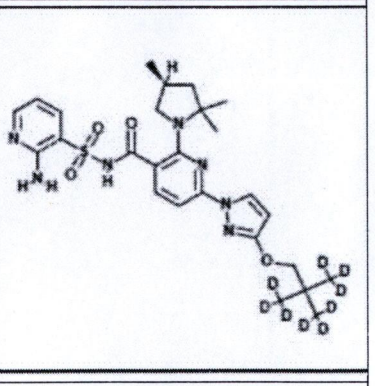
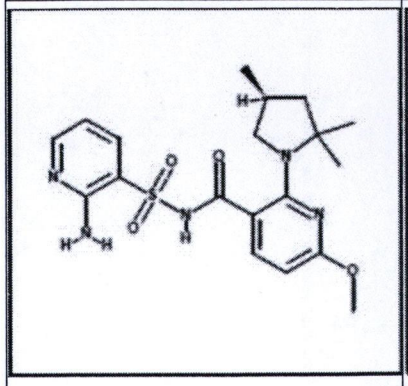
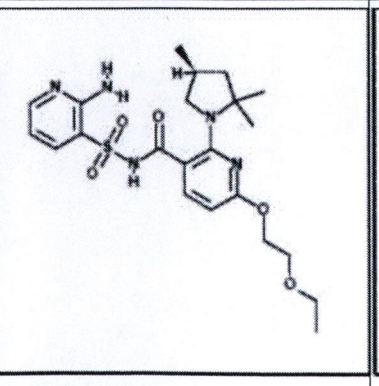
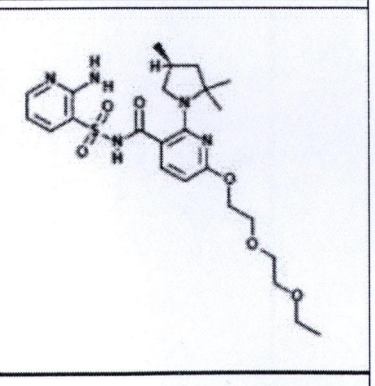
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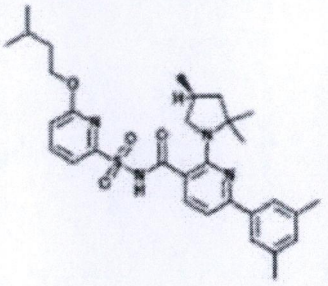
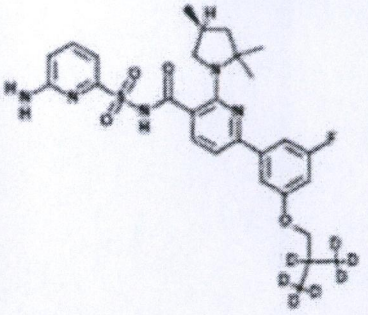
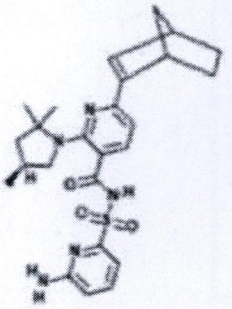
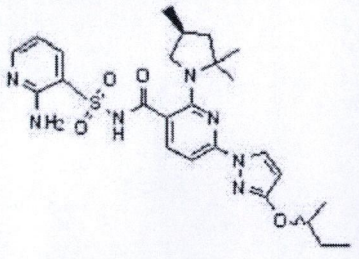
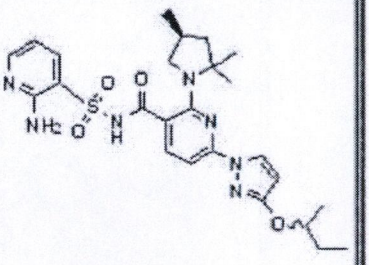
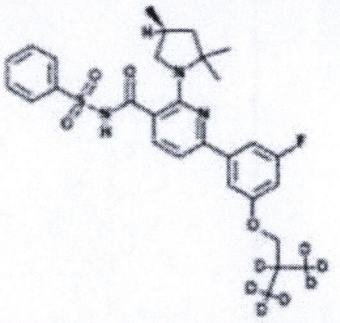
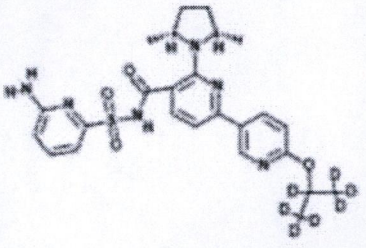
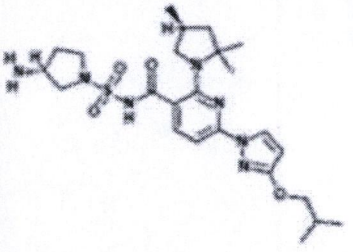
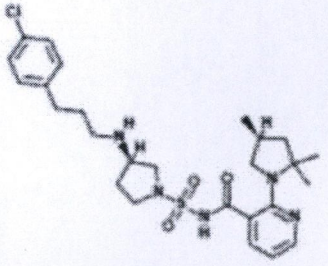
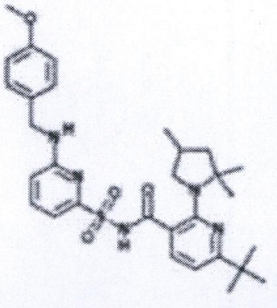
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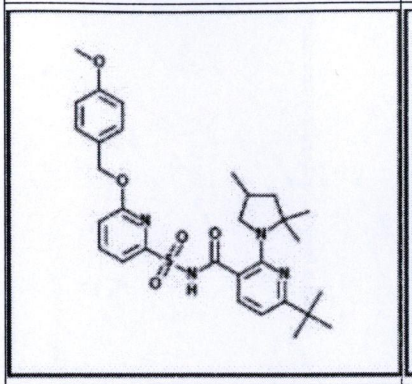
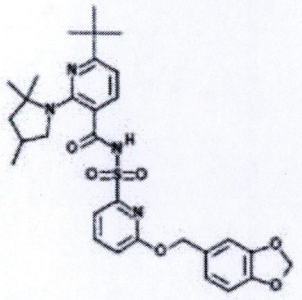
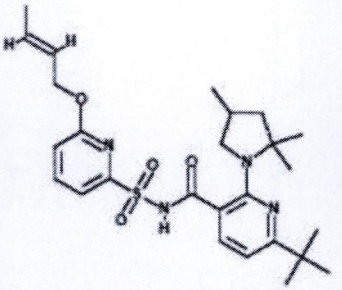
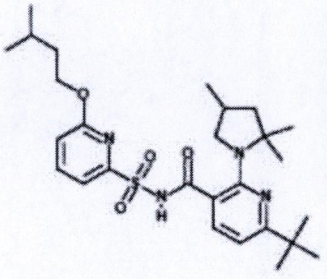
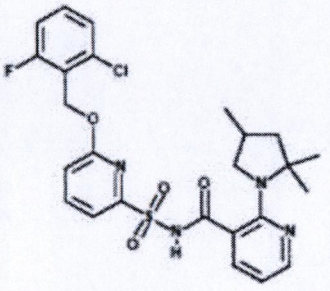
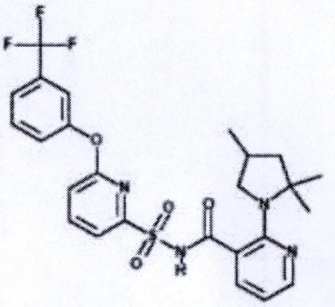
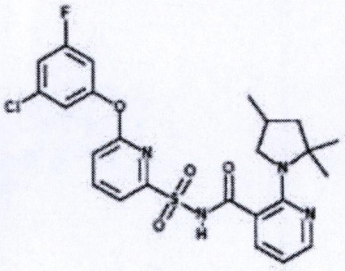
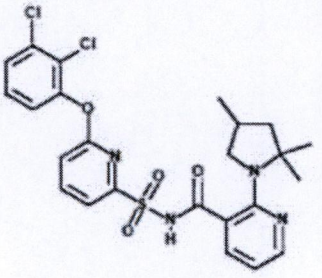
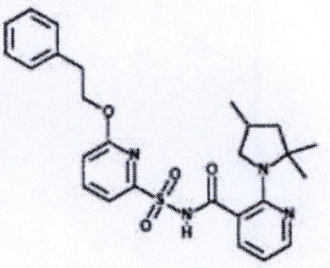
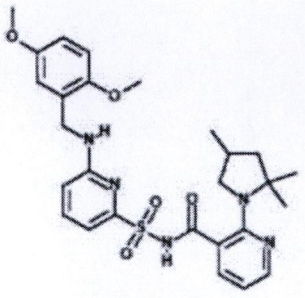
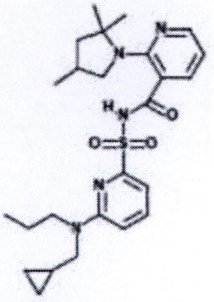
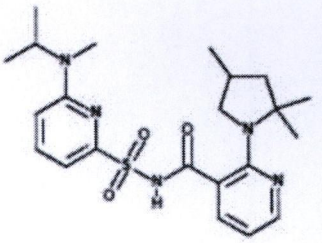
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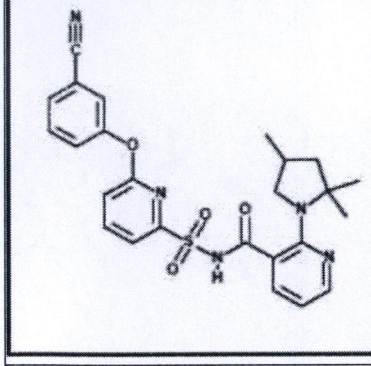
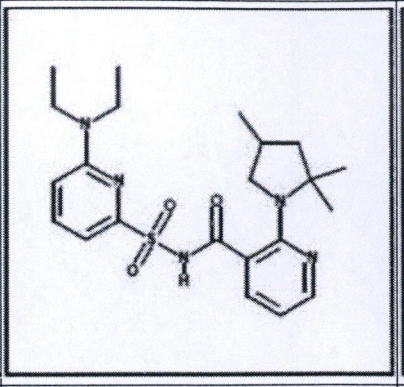
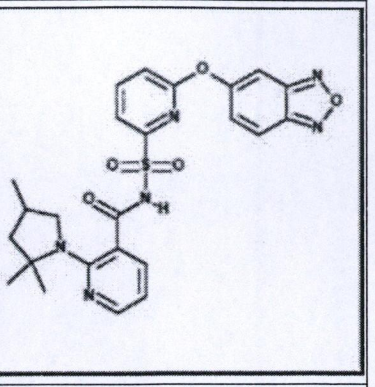
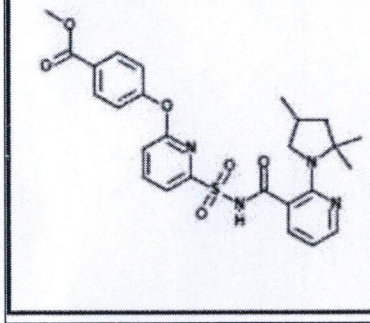
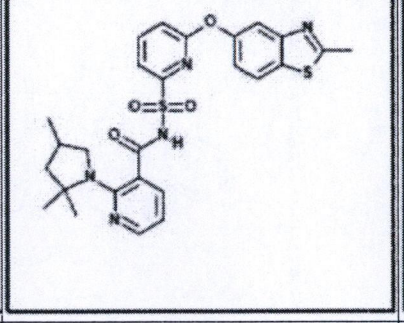
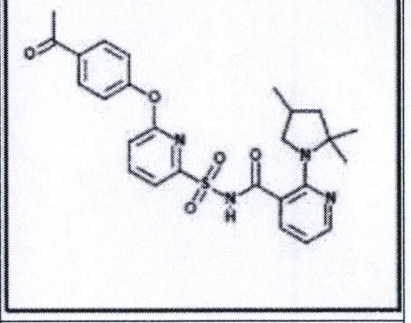
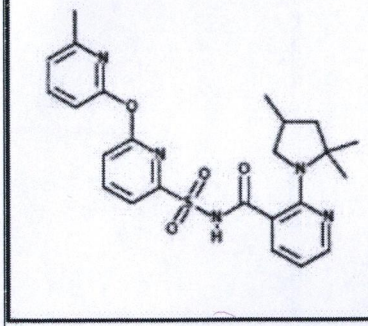
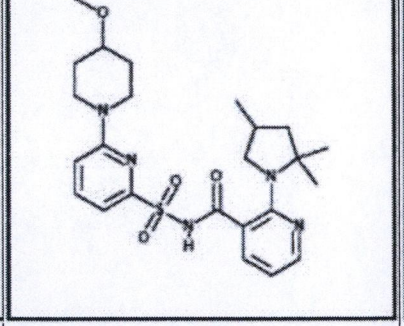
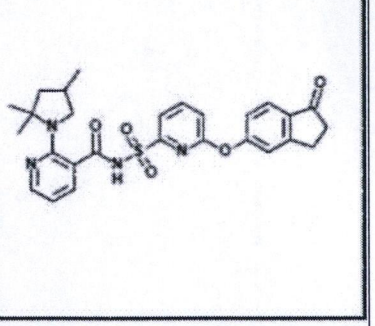
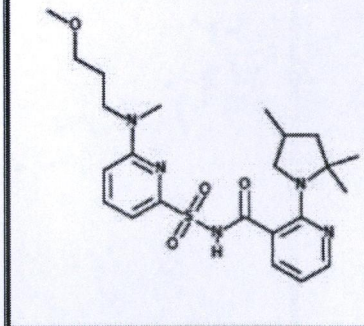
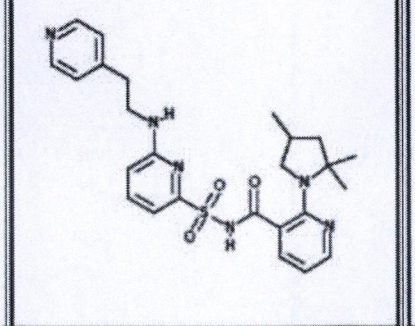
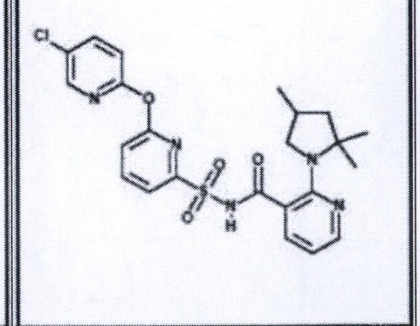
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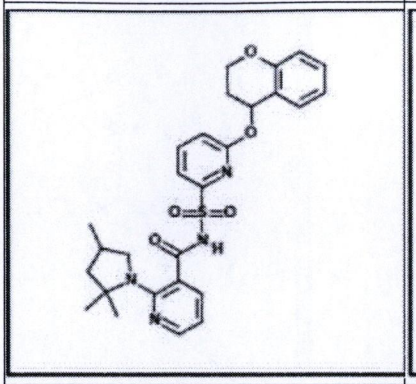
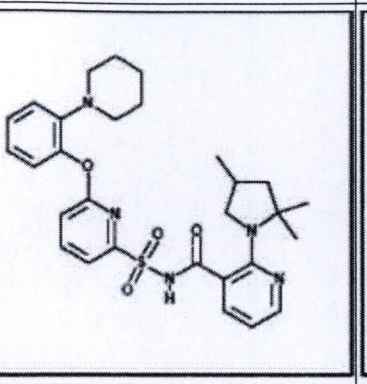
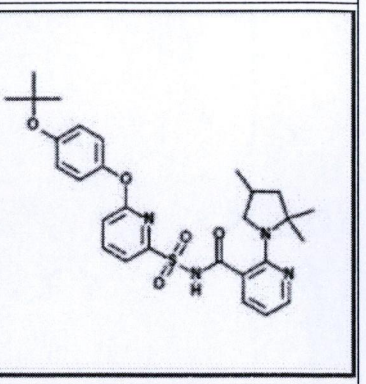
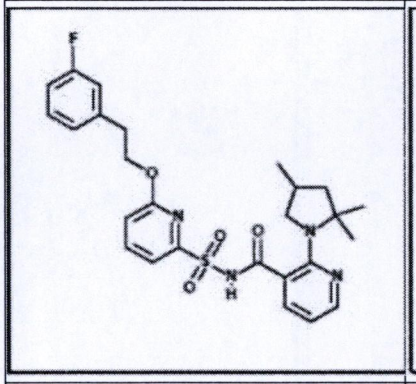
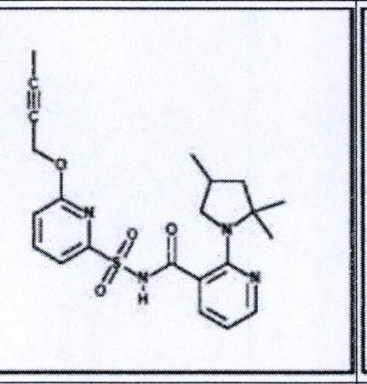
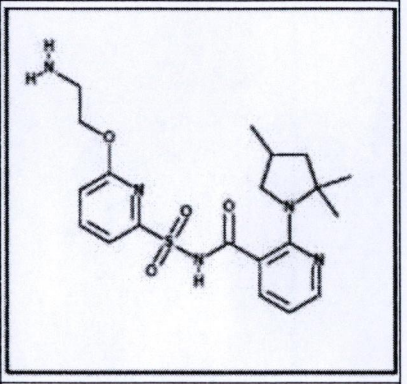
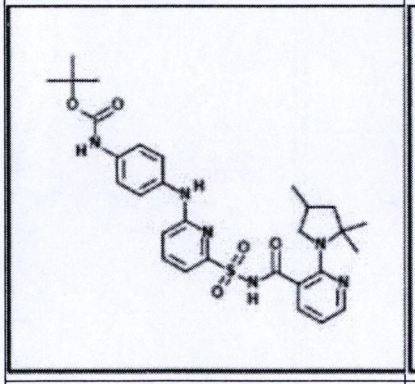
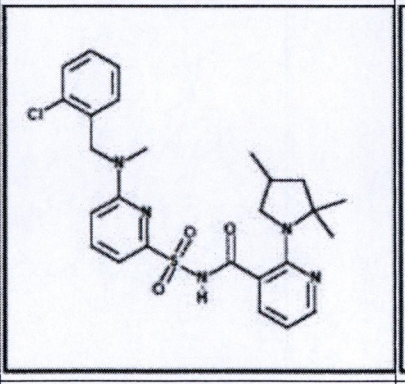
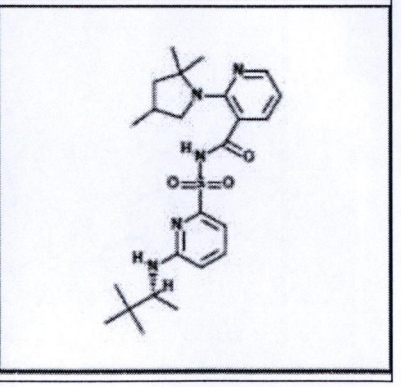
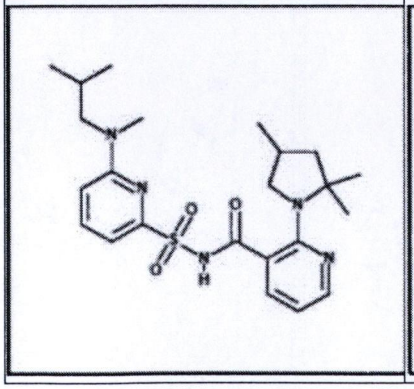
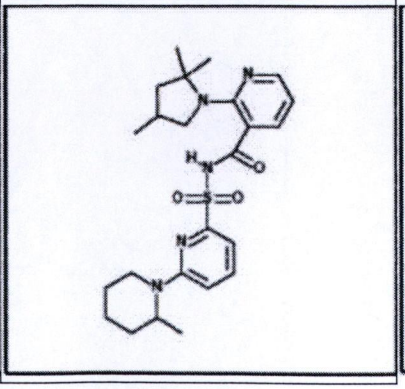
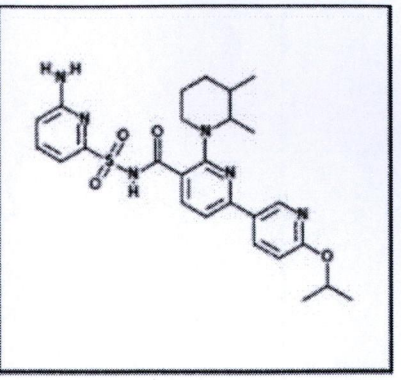
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| 2692 | 2693 | 2694 |
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| 2695 | 2696 | 2697 |
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| 2698 | 2699 | 2700 |
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| 2701 | 2702 | 2703 |
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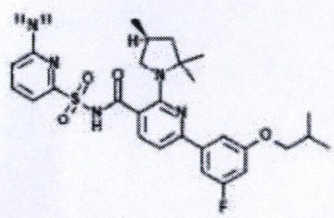
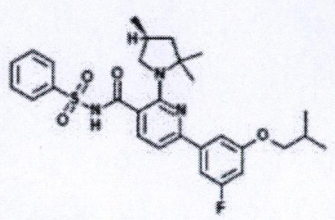
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| 2734 | 2735 | 2736 |
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| 2737 | 2738 | 2739 |
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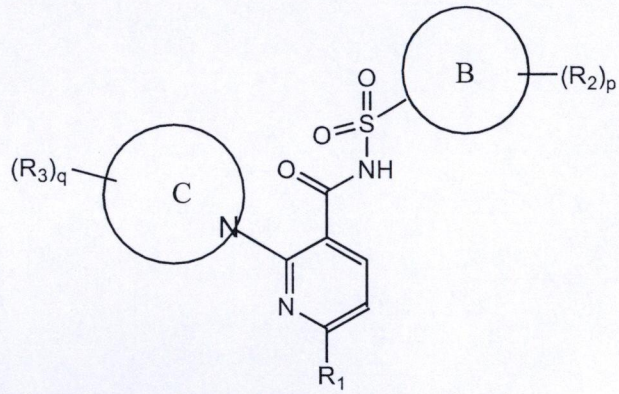
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22. 如請求項21之化合物、其醫藥學上可接受之鹽或前述任一者的氘化衍生物，其中該化合物係選自於：

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23. 一種式Ib-iv化合物：




**Ib-iv**

、其醫藥學上可接受之鹽或前述任一者之氘化衍生物，其中每次出現時獨立地：

環B為C6-C10芳基環或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；

環C為其中1至4個環原子中任一個獨立地為N、O或S的C3-

C14雜芳基或雜環，且其中環C上之一個氮為與吡啶環之附接點；

$R_1$為C6-C10芳基或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C2-C6烯基；C2-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；-C≡CH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

p為0、1、2或3；且

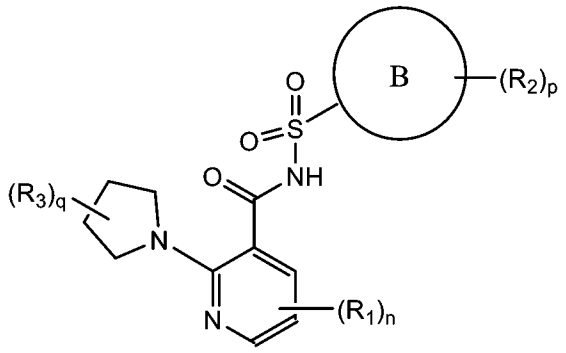
q為0、1、2、3、4或5；

其中變數$R_1$-$R_4$之每一特定基團可視情況經一或多個選自以下各者之基團取代：鹵基、磷醯基、OH、環烷基、雜環烷基、芳基、雜芳基、氟烷基、烷基、烯基、炔基、硝基、CN、羥基及其中至多4個$CH_2$單元獨立地經O、S、$SO_2$、SO、CO、NH、*N*-烷基、*N*-烯基或*N*-炔基置換的(C1-C9伸烷基)-E，且E為H、芳基、環烷基、雜環烷基、雜芳基、烷氧基、CN或$CF_3$，進一步其中芳基、環烷基、雜環烷基及雜芳基每一者視情況經一或多個選自鹵基、烷基、胺基、CN、烯基、炔基及烷氧基之基團取代；及

當兩個烷氧基結合於同一原子或相鄰原子時，兩個烷氧基可與其結合之原子一起形成環；及

其中術語「胺基」係指$NH_2$，其視情況經一或兩個獨立地選自烷基、環烷基及雜環烷基之基團取代。

24. 一種式Ib-v化合物：




**Ib-v**

、其醫藥學上可接受之鹽或前述任一者之氘化衍生物，其中每次出現時獨立地：

環B為C6-C10芳基環或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；

$R_1$為鹵基；CN；$F_5S$；SiRRR；OH；NRR；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；或C3-C10環烷基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C2-C6烯基；C2-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；-C≡CH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任

一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

n為0、1、2或3；

p為0、1、2或3；且

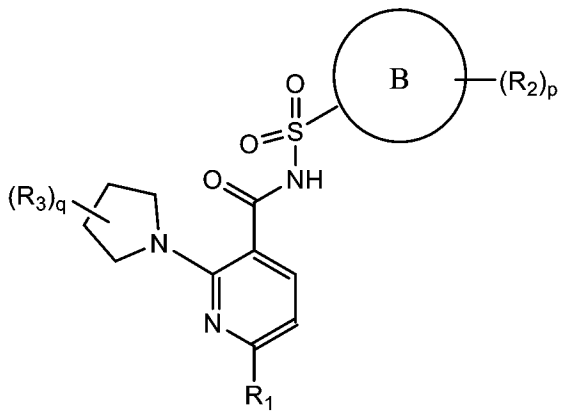
q為0、1、2、3、4或5；

其中變數$R_1$-$R_4$之每一特定基團可視情況經一或多個選自以下各者之基團取代：鹵基、磷醯基、OH、環烷基、雜環烷基、芳基、雜芳基、氟烷基、烷基、烯基、炔基、硝基、CN、羥基及其中至多4個$CH_2$單元獨立地經O、S、$SO_2$、SO、CO、NH、*N*-烷基、*N*-烯基或*N*-炔基置換的(C1-C9伸烷基)-E，且E為H、芳基、環烷基、雜環烷基、雜芳基、烷氧基、CN或$CF_3$，進一步其中芳基、環烷基、雜環烷基及雜芳基每一者視情況經一或多個選自鹵基、烷基、胺基、CN、烯基、炔基及烷氧基之基團取代；及

當兩個烷氧基結合於同一原子或相鄰原子時，兩個烷氧基可與其結合之原子一起形成環；及

其中術語「胺基」係指$NH_2$，其視情況經一或兩個獨立地選自烷基、環烷基及雜環烷基之基團取代。

25. 一種式Ib-vi化合物：




**Ib-vi**

、其醫藥學上可接受之鹽或前述任一者之氘化衍生物，其中每次出現時獨立地：

環B為C6-C10芳基環或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；

$R_1$為C6-C10芳基或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C2-C6烯基；C2-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；-C≡CH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；

C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

p為0、1、2或3；且

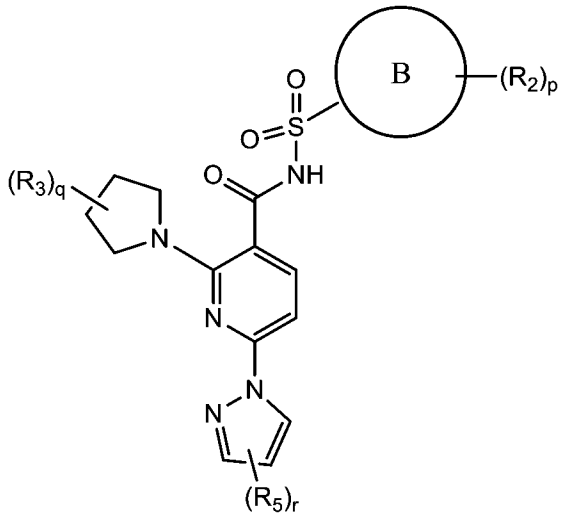
q為0、1、2、3、4或5；

其中變數$R_1$-$R_4$之每一特定基團可視情況經一或多個選自以下各者之基團取代：鹵基、磷醯基、OH、環烷基、雜環烷基、芳基、雜芳基、氟烷基、烷基、烯基、炔基、硝基、CN、羥基及其中至多4個$CH_2$單元獨立地經O、S、$SO_2$、SO、CO、NH、*N*-烷基、*N*-烯基或*N*-炔基置換的(C1-C9伸烷基)-E，且E為H、芳基、環烷基、雜環烷基、雜芳基、烷氧基、CN或$CF_3$，進一步其中芳基、環烷基、雜環烷基及雜芳基每一者視情況經一或多個選自鹵基、烷基、胺基、CN、烯基、炔基及烷氧基之基團取代；及

當兩個烷氧基結合於同一原子或相鄰原子時，兩個烷氧基可與其結合之原子一起形成環；及

其中術語「胺基」係指$NH_2$，其視情況經一或兩個獨立地選自烷基、環烷基及雜環烷基之基團取代。

26. 一種式Ib-ix化合物：



**Ib-ix**

、其醫藥學上可接受之鹽或前述任一者之氘化衍生物，其中每次出現時獨立地：

環B為C6-C10芳基環或其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；

$R_2$為鹵基；OH；NRR；疊氮化物；CN；$CO_2R$；C1-C6烷基或氟烷基；C1-C6烷氧基或氟烷氧基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C13雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_2$基團一起可形成=$CH_2$或=O基團；

$R_3$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C2-C6烯基；C2-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

或兩個$R_3$基團一起可形成=$CH_2$或=O基團；

$R_4$為H；疊氮化物；$CF_3$；$CHF_2$；OR；-C≡CH；$CO_2R$；OH；C6-C10芳基、其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；C3-C10環烷基；NRR、NRCOR、CONRR、CN、鹵基或$SO_2R$；

R獨立地為H；OH；$CO_2H$；$CO_2$C1-C6烷基；C1-C6烷基；C2-C6烯基；C2-C6炔基；C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環烷基；或C3-C10環烷基；

$R_5$為鹵基；CN；$CO_2R$；C1-C6烷基或氟烷基；C2-C6烯基；C2-C6炔基；C1-C6烷氧基或氟烷氧基；或C6-C10芳基；其中1至4個環原子中任一個獨立地為O、S、N或NR的C3-C10雜芳基或雜環；C3-C10環烷基；或其中至多四個$CH_2$單元獨立地經O、CO、S、SO、$SO_2$或NR置換的(C1-C9伸烷基)-$R_4$；

p為0、1、2或3；且

q為0、1、2、3、4或5；

其中變數$R_2$-$R_5$之每一特定基團可視情況經一或多個選自以下各者之基團取代：鹵基、磷醯基、OH、環烷基、雜環烷基、芳基、雜芳基、氟烷基、烷基、烯基、炔基、硝基、CN、羥基及其中至多4個$CH_2$單元獨立地經O、S、$SO_2$、SO、CO、NH、*N*-烷基、*N*-烯基或*N*-炔基置換的(C1-C9伸烷基)-E，且E為H、芳基、環烷基、雜環烷基、雜芳基、烷氧基、CN或$CF_3$，進一步其中芳基、環烷基、雜環烷基及雜芳基每一者視情況經一或多個選自鹵基、烷基、胺基、CN、烯基、炔基及烷氧基之基團取代；及

當兩個烷氧基結合於同一原子或相鄰原子時，兩個烷氧基可與其結合之原子一起形成環；及

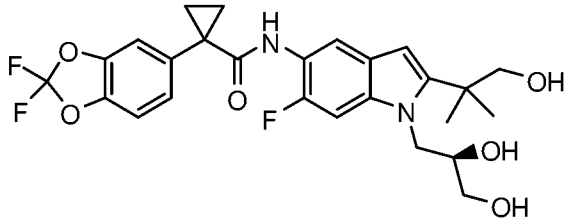
其中術語「胺基」係指$NH_2$，其視情況經一或兩個獨立地選自烷基、環烷基及雜環烷基之基團取代。

27. 一種醫藥組合物，其包含如請求項1至26中任一項之化合物、其醫藥學上可接受之鹽或前述任一者之氘化衍生物及一醫藥學上可接受之載劑。

28. 如請求項27之醫藥組合物，其進一步包含一或多種額外的治療劑。

29. 如請求項28之醫藥組合物，其中該一或多種額外的治療劑包含一CFTR調節劑。

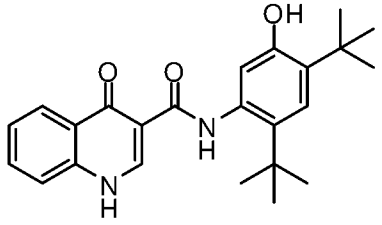
30. 如請求項28之醫藥組合物，其中至少一種額外的治療劑為



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或其醫藥學上可接受之鹽。

31. 如請求項28之醫藥組合物，其中至少一種額外的治療劑為



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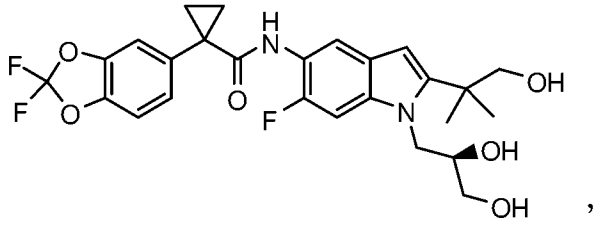
或其醫藥學上可接受之鹽。

32. 一種如請求項1至26中任一項之化合物、其醫藥學上可接受之鹽或前述任一者之氘化衍生物於製造一藥劑之用途，該藥劑係用於治療在一患者中之囊腫纖維化症。

33. 如請求項32之用途，其中該藥劑係配製成在一或多種額外的治療劑之前、與其同時或在其之後投予。

34. 如請求項33之用途，其中該一或多種額外的治療劑包含一CFTR調節劑。

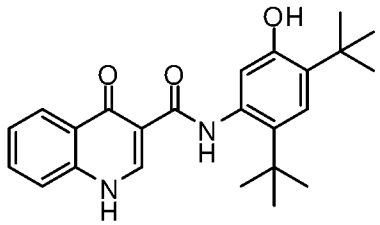
35. 如請求項33之用途，其中至少一種額外的治療劑為



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或其醫藥學上可接受之鹽。

36. 如請求項33之用途，其中至少一種額外的治療劑為



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或其醫藥學上可接受之鹽。

37. 如請求項32之用途，其中該患者在F508del突變中同種接合。

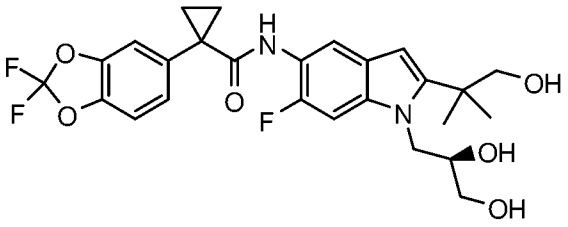
38. 如請求項32之用途，其中該患者在F508del突變中異種接合。

39. 一種如請求項27之醫藥組合物於製造一藥劑之用途，該藥劑係用於治療在一患者中之囊腫纖維化症。

40. 如請求項39之用途，其中該藥劑係配製成在一或多種額外的治療劑之前、與其同時或在其之後投予。

41. 如請求項40之用途，其中該一或多種額外的治療劑包含一CFTR調節劑。

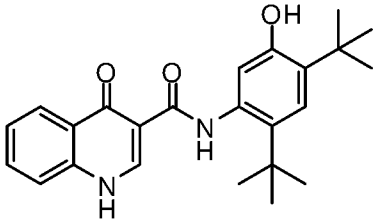
42. 如請求項40之用途，其中至少一種額外的治療劑為



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或其醫藥學上可接受之鹽。

43. 如請求項40之用途，其中至少一種額外的治療劑為



，

或其醫藥學上可接受之鹽。

44. 如請求項39之用途，其中該患者在F508del突變中同種接合。

45. 如請求項39之用途，其中該患者在F508del突變中異種接合。

# 圖式

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.1A>G | p.？(未知) | M1V |
| c.54-5940_273+10250del21kb | p.Ser18ArgfsX16 | CFTRdele2,3 |
| c.91C>T | p.Arg31Cys | R31C |
| c.115C>T | p.Gln39X | Q39X |
| c.137C>A | p.Ala46Asp | A46D |
| c.165-1G>A | 無蛋白質名稱 | 297-1G->A |
| c.166G>A | p.Glu56Lys | E56K |
| c.174_175insA | p.Arg59LysfsX10 | 306insA |
| c.178G>T | p.Glu60X | E60X |
| c.200C>T | p.Pro67Leu | P67L |
| c.220C>T | p.Arg74Trp | R74W |
| c.223C>T | p.Arg75X | R75X |
| c.224G>A | p.Arg75Gln | R75Q |
| c.254G>A | p.Gly85Glu | G85E |
| c.262_263delTT | p.Leu88IlefsX22 | 394delTT |
| c.273+1G>A | 無蛋白質名稱 | 405+1G->A |
| c.274-1G>A | 無蛋白質名稱 | 406-1G->A |
| c.274G>A | p.Glu92Lys | E92K |
| c.274G>T | p.Glu92X | E92X |
| c.292C>T | p.Gln98X | Q98X |
| c.313delA | p.Ile105SerfsX2 | 444delA |
| c.325_327delTATinsG | p.Tyr109GlyfsX4 | 457TAT->G |
| c.328G>C | p.Asp110His | D110H |
| c.349C>T | p.Arg117Cys | R117C |
| c.350G>A | p.Arg117His | R117H |
| c.366T>A | p.Tyr122X | Y122X |
| c.442delA | p.Ile148LeufsX5 | 574delA |
| c.443T>C | p.Ile148Thr | I148T |
| c.489+1G>T | 無蛋白質名稱 | 621+1G->T |

圖1

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.531delT | p.Ile177MetfsX12 | 663delT |
| c.532G>A | p.Gly178Glu | G178R |
| c.543_546delTAGT | p.Leu183PhefsX5 | 675del4 |
| c.579+1G>T | 無蛋白質名稱 | 711+1G->T |
| c.579+3A>G | 無蛋白質名稱 | 711+3A->G |
| c.579+5G>A | 無蛋白質名稱 | 711+5G->A |
| c.580-1G>T | 無蛋白質名稱 | 712-1G->T |
| c.595C>T | p.His199Tyr | H199Y |
| c.613C>T | p.Pro205Ser | P205S |
| c.617T>G | p.Leu206Trp | L206W |
| c.658C>T | p.Gln220X | Q220X |
| c.680T>G | p.Leu227Arg | L227R |
| c.720_741delAGGGAGAATGATGATGAAGTAC | p.Gly241GlufsX13 | 852del22 |
| c.828C>A | p.Cys276X | C276X |
| c.948delT | p.Phe316LeufsX12 | 1078delT |
| c.988G>T | p.Gly330X | G330X |
| c.1000C>T | p.Arg334Trp | R334W |
| c.1007T>A | p.Ile336Lys | I336K |
| c.1013C>T | p.Thr338Ile | T338I |
| c.1021T>C | p.Ser341Pro | S341P |
| c.1022_1023insTC | p.Phe342HisfsX28 | 1154insTC |
| c.1040G>A | p.Arg347His | R347H |
| c.1040G>C | p.Arg347Pro | R347P |
| c.1055G>A | p.Arg352Gln | R352Q |
| c.[1075C>A;1079C>A] | p.[Gln359Lys;Thr360Lys] | Q359K/T360K |

圖1(續)

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.1081delT | p.Trp361GlyfsX8 | 1213delT |
| c.1116+1G>A | 無蛋白質名稱 | 1248+1G->A |
| c.1127_1128insA | p.Gln378AlafsX4 | 1259insA |
| c.1153_1154insAT | p.Asn386IlefsX3 | 1288insTA |
| c.1202G>A or c.1203G>A | p.Trp401X | W401X |
| c.1209+1G>A | 無蛋白質名稱 | 1341+1G->A |
| c.1210-12[5] | 無蛋白質名稱 | 5T |
| c.1210-12[7] | 無蛋白質名稱 | 7T |
| c.1240C>T | p.Gln414X | Q414X |
| c.1329_1330insAGAT | p.Ile444ArgfsX3 | 1461ins4 |
| c.1340delA | p.Lys447ArgfsX2 | 1471delA |
| c.1364C>A | p.Ala455Glu | A455E |
| c.1393-1G>A | 無蛋白質名稱 | 1525-1G->A |
| c.1397C>A or c.1397C>G | p.Ser466X | S466X |
| c.1400T>C | p.Leu467Pro | L467P |
| c.1408A>G | p.Met470Val | M470V |
| c.1418delG | p.Gly473GlufsX54 | 1548delG |
| c.1466C>A | p.Ser489X | S489X |
| c.1475C>T | p.Ser492Phe | S492F |
| c.1477C>T | p.Gln493X | Q493X |
| c.1519_1521delATC | p.Ile507del | I507del |
| c.1521_1523delCTT | p.Phe508del | F508del |
| c.1545_1546delTA | p.Tyr515X | 1677delTA |
| c.1558G>T | p.Val520Phe | V520F |
| c.1573C>T | p.Gln525X | Q525X |
| c.1585-8G>A | 無蛋白質名稱 | 1717-8G->A |
| c.1585-1G>A | 無蛋白質名稱 | 1717-1G->A |
| c.1624G>T | p.Gly542X | G542X |
| c.1645A>C or c.1647T>G | p.Ser549Arg | S549R |

圖1(續)

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.1646G>A | p.Ser549Asn | S549N |
| c.1650delA | p.Gly551ValfsX8 | 1782delA |
| c.1651G>A | p.Gly551Ser | G551S |
| c.1652G>A | p.Gly551Asp | G551D |
| c.1654C>T | p.Gln552X | Q552X |
| c.1657C>T | p.Arg553X | R553X |
| c.1673T>C | p.Leu558Ser | L558S |
| c.1675G>A | p.Ala559Thr | A559T |
| c.1679G>A | p.Arg560Lys | R560K |
| c.1679G>C | p.Arg560Thr | R560T |
| c.1679+1G>C | 無蛋白質名稱 | 1811+1G->C |
| c.1679+1.6kbA>G | 無蛋白質名稱 | 1811+1.6kbA->G |
| c.1680-1G>A | 無蛋白質名稱 | 1812-1G->A |
| c.1682C>A | p.Ala561Glu | A561E |
| c.1692delA | p.Asp565MetfsX7 | 1824delA |
| c.1705T>G | p.Tyr569Asp | Y569D |
| c.1727G>C | p.Gly576Ala | G576A |
| c.1736A>G | p.Asp579Gly | D579G |
| c.1753G>T | p.Glu585X | E585X |
| c.1766+1G>A | 無蛋白質名稱 | 1898+1G->A |
| c.1766+1G>C | 無蛋白質名稱 | 1898+1G->C |
| c.1766+3A>G | 無蛋白質名稱 | 1898+3A->G |
| c.1841A>G | p.Asp614Gly | D614G |
| c.1923_1931del9insA | p.Ser641ArgfsX5 | 2055del9->A |

圖1(續)

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.1973_1985del13insAGAAA | p.Arg658LysfsX4 | 2105-2117del13insAGAAA |
| c.1986_1989delAACT | p.Thr663ArgfsX8 | 2118del4 |
| c.2002C>T | p.Arg668Cys | R668C |
| c.2012delT | p.Leu671X | 2143delT |
| c.2051_2052delAAinsG | p.Lys684SerfsX38 | 2183AA->G‡ |
| c.2051_2052delAAinsG | p.Lys684SerfsX38 | 2183delAA->G‡ |
| c.2052_2053insA | p.Gln685ThrfsX4 | 2184insA |
| c.2052delA | p.Lys684AsnfsX38 | 2184delA |
| c.2125C>T | p.Arg709X | R709X |
| c.2128A>T | p.Lys710X | K710X |
| c.2175_2176insA | p.Glu726ArgfsX4 | 2307insA |
| c.2195T>G | p.Leu732X | L732X |
| c.2215delG | p.Val739TyrfsX16 | 2347delG |
| c.2260G>A | p.Val754Met | V754M |
| c.2290C>T | p.Arg764X | R764X |
| c.2353C>T | p.Arg785X | R785X |
| c.2374C>T | p.Arg792X | R792X |
| c.2424_2425insAT | p.Ser809IlefsX13 | 2556insAT |
| c.2453delT | p.Leu818TrpfsX3 | 2585delT |
| c.2462_2463delGT | p.Ser821ArgfsX4 | No legacy name |
| c.2464G>T | p.Glu822X | E822X |
| c.2490+1G>A | 無蛋白質名稱 | 2622+1G->A |
| c.2491G>T | p.Glu831X | E831X |
| c.2537G>A or c.2538G>A | p.Trp846X | W846X |
| c.2547C>A | p.Tyr849X | Y849X |
| c.2551C>T | p.Arg851X | R851X |
| c.2583delT | p.Phe861LeufsX3 | 2711delT |

圖1(續)

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.2657+2_2657+3insA | 無蛋白質名稱 | 2789+2insA |
| c.2657+5G>A | 無蛋白質名稱 | 2789+5G->A |
| c.2658-1G>C | 無蛋白質名稱 | 2790-1G->C |
| c.2668C>T | p.Gln890X | Q890X |
| c.2735C>A | p.Ser912X | S912X |
| c.2737_2738insG | | 2869insG |
| c.2739T>A | p.Tyr913X | Y913X |
| c.2764_2765insAG | p.Val922GlufsX2 | 2896insAG |
| c.2780T>C | p.Leu927Pro | L927P |
| c.2834C>T | p.Ser945Leu | S945L |
| c.2875delG | p.Ala959HisfsX9 | 3007delG |
| c.2908G>C | p.Gly970Arg | G970R |
| c.2930C>T | p.Ser977Phe | S977F |
| c.2988G>A | 無蛋白質名稱 | 3120G->A |
| c.2988+1G>A | 無蛋白質名稱 | 3120+1G->A |
| c.2989-977_3367+248del | 無蛋白質名稱 | 3121-977_3499+248del2515 |
| c.2989-1G>A | 無蛋白質名稱 | 3121-1G->A |
| c.2991G>C | p.Leu997Phe | L997F |
| c.3002_3003delTG | p.Val1001AspfsX45 | 3132delTG |
| c.3080T>C | p.Ile1027Thr | I1027T |
| c.3140-26A>G | 無蛋白質名稱 | 3272-26A->G |
| c.3154T>G | p.Phe1052Val | F1052V |
| c.3160C>G | p.His1054Asp | H1054D |
| c.3181G>C | p.Gly1061Arg | G1061R |
| c.3194T>C | p.Leu1065Pro | L1065P |
| c.3196C>T | p.Arg1066Cys | R1066C |
| c.3197G>A | p.Arg1066His | R1066H |

圖1(續)

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.3205G>A | p.Gly1069Arg | G1069R |
| c.3208C>T | p.Arg1070Trp | R1070W |
| c.3209G>A | p.Arg1070Gln | R1070Q |
| c.3222T>A | p.Phe1074Leu | F1074L |
| c.3230T>C | p.Leu1077Pro | L1077P |
| c.3266G>A | p.Trp1089X | W1089X |
| c.3276C>A or c.3276C>G | p.Tyr1092X | Y1092X |
| c.3302T>A | p.Met1101Lys | M1101K |
| c.3310G>T | p.Glu1104X | E1104X |
| c.3454G>C | p.Asp1152His | D1152H |
| c.3472C>T | p.Arg1158X | R1158X |
| c.3484C>T | p.Arg1162X | R1162X |
| c.3485G>T | p.Arg1162Leu | R1162L |
| c.3528delC | p.Lys1177SerfsX15 | 3659delC |
| c.3535_3536insTCAA | p.Thr1179IlefsX17 | 3667ins4 |
| c.3587C>G | p.Ser1196X | S1196X |
| c.3605delA | p.Asp1202AlafsX9 | 3737delA |
| c.3611G>A or c.3612G>A | p.Trp1204X | W1204X |
| c.3659delC | p.Thr1220LysfsX8 | 3791delC |
| c.3691delT | p.Ser1231ProfsX4 | 3821delT |
| c.3700A>G | p.Ile1234Val | I1234V |
| c.3705T>G | p.Ser1235Arg | S1235R |
| c.3717+12191C>T | 無蛋白質名稱 | 3849+10kbC->T |

圖1(續)

| 突變<br>cDNA<br>名稱 | 突變<br>蛋白質<br>名稱 | 突變<br>遺留物<br>名稱 |
|---|---|---|
| c.3718-1G>A | 無蛋白質名稱 | 3850-1G->A |
| c.3731G>A | p.Gly1244Glu | G1244E |
| c.3744delA | p.Lys1250ArgfsX9 | 3876delA |
| c.3752G>A | p.Ser1251Asn | S1251N |
| c.3763T>C | p.Ser1255Pro | S1255P |
| c.3764C>A | p.Ser1255X | S1255X |
| c.3773_3774insT | p.Leu1258PhefsX7 | 3905insT |
| c.3808G>A | p.Asp1270Asn | D1270N |
| c.3846G>A | p.Trp1282X | W1282X |
| c.3873+1G>A | 無蛋白質名稱 | 4005+1G->A |
| c.3883delA | p.Ile1295PhefsX33 | 4015delA |
| c.3884_3885insT | p.Ser1297PhefsX5 | 4016insT |
| c.3909C>G | p.Asn1303Lys | N1303K |
| c.3937C>T | p.Gln1313X | Q1313X |
| c.3964-78_4242+577del | NULL | CFTRdele22,23 |
| c.4046G>A | p.Gly1349Asp | G1349D |
| c.4077_4080delTGTTinsAA | 無蛋白質名稱 | 4209TGTT->AA |
| c.4111G>T | p.Glu1371X | E1371X |
| c.4196_4197delTC | p.Cys1400X | 4326delTC |
| c.4234C>T | p.Gln1412X | Q1412X |
| c.4242+1G>T | 無蛋白質名稱 | 4374+1G->T |
| c.4251delA | p.Glu1418ArgfsX14 | 4382delA |
| c.4296_4297insGA | p.Ser1435GlyfsX14 | 4428insGA |

圖1(續)