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(54)名稱

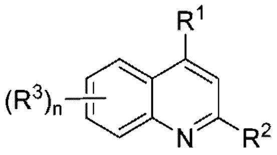
喹啉 cGAS 拮抗劑化合物

(57)摘要

本發明提供作為 cGAS 拮抗劑之化合物、該等化合物之製備方法、包含該等化合物之醫藥組合物及其在醫學療法中之用途。

The present disclosure provides compounds that are cGAS antagonists, methods of preparation of the compounds, pharmaceutical compositions comprising the compounds, and their use in medical therapy.

特徵化學式：



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【發明摘要】

【中文發明名稱】

喹啉cGAS拮抗劑化合物

【英文發明名稱】

QUINOLINE CGAS ANTAGONIST COMPOUNDS

【中文】

本發明提供作為cGAS拮抗劑之化合物、該等化合物之製備方法、包含該等化合物之醫藥組合物及其在醫學療法中之用途。

【英文】

The present disclosure provides compounds that are cGAS antagonists, methods of preparation of the compounds, pharmaceutical compositions comprising the compounds, and their use in medical therapy.

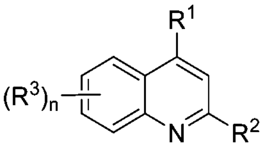
【指定代表圖】

無

【代表圖之符號簡單說明】

無

【特徵化學式】



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【發明說明書】

【中文發明名稱】

喹啉cGAS拮抗劑化合物

【英文發明名稱】

QUINOLINE CGAS ANTAGONIST COMPOUNDS

【技術領域】

【先前技術】

【0001】 環狀GMP-AMP合成酶(cGAS)(UniProtKB-Q8N884)係一種充當DNA感測劑，經由活化干擾素基因刺激蛋白(STING)受體引起針對病原體之免疫反應的酶。經顯示，自身DNA對cGAS之異常活化可致人衰弱且有時引起致命性自體免疫疾病。在動物模型中進行之基因剔除研究指示，抑制cGAS係進行治療干預的一種頗具前景之方法。另外，近期的研究顯示，cGAS-STING路徑在針對腫瘤之先天性免疫反應中起到關鍵作用，且刺激該路徑係臨床上測試癌症免疫療法的一種有前景之策略。

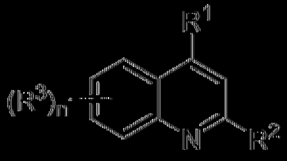
【0002】 此項技術中一直需要存在針對諸如全身性紅斑狼瘡(SLE)、硬皮病、牛皮癬、艾卡迪戈緹耶斯氏症候群(Aicardi Goutières syndrome，AGS)、休格連氏症候群(Sjogren's syndrome)、類風濕性關節炎、發炎性腸病、多發性硬化、糖尿病、心血管疾病及神經退化性疾病之類人類自體免疫疾病及自體發炎性疾病的有效治療。因此，仍需要發現可用於治療此等及其他與cGAS異常活化相關的致人衰弱之人類疾病的強效選擇性小分子cGAS抑制劑。

【發明內容】

【0003】 本發明係關於小分子cGAS拮抗劑化合物、該等化合物之

製備方法、包含該等化合物之醫藥組合物及其在醫學療法中之用途。確切地說，本發明提供可用作cGAS抑制劑之喹啉cGAS拮抗劑化合物。本文所提供之化合物的優勢在於，可能獲得廣泛的藥理學活性，此與cGAS之抑制相符。此外，本發明提供使用本文所描述之化合物治療發炎性疾病、過敏性疾病、自體免疫疾病及感染性疾病的方法。該等化合物亦可用於治療衰老或年齡相關之疾病，諸如神經退化性疾病、心血管疾病、肝臟及腎臟疾病、癌症及早衰。

【0004】現已發現，本發明化合物及其醫藥學上可接受之組合物對cGAS抑制有效。本發明之此等化合物具有通式I：



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或其醫藥學上可接受之鹽，其中各變數如本文所定義及描述。

【0005】本發明化合物及其醫藥學上可接受之組合物可用於治療與cGAS異常活化相關之多種疾病、病症或病況。此類疾病、病症或病況包括本文所描述之疾病、病症或病況。

【0006】本發明所提供之化合物亦可用於研究生物學及病理學現象中之cGAS酶以及在活體外或活體內比較性評估新cGAS拮抗劑或其他cGAS調控劑、信號傳導路徑及細胞介素含量。

【實施方式】

【0007】在以下揭示內容中，闡述某些具體細節以便提供對各種實施例之透徹理解。然而，熟習此項技術者應理解，本文所描述之方法及用途可在無此等細節之情況下實踐。在其他情況下，未詳細顯示或描述熟知結構以避免不必要地混淆實施例之描述。除非上下文另有要求，否則在本

說明書及隨後申請專利範圍中，詞語「包含(comprise)」及其變化形式，諸如「包含(comprises/comprising)」應以開放的包容性含義解釋，亦即，解釋為「包括但不限於」。此外，本文中所提供之標題僅出於方便起見，且不解釋所主張之發明的範圍或含義。

在本說明書通篇提及的「一個實施例(one embodiment)」或「一個實施例(an embodiment)」意謂，結合該實施例描述的特定特徵、結構或特性係包括在至少一個實施例中。因此，在本說明書通篇不同位置中出現的片語「在一個實施例中(in one embodiment)」或「在一個實施例中(in an embodiment)」未必皆指代同一實施例。另外，特定特徵、結構或特性可在一或多個實施例中以任何適合的方式組合。此外，除非上下文另外明確指定，否則如本說明書及所附申請專利範圍中所使用，單數形式「一個(種)(a/an)」及「該(the)」包括複數個(種)參考物。亦應注意，除非上下文另外明確指定，否則術語「或」一般係以其包括「及/或」之含義使用。

3.1. 定義

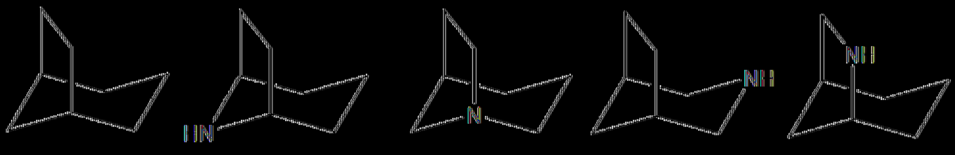
【0008】 本發明之化合物包括本文中大體上描述之化合物，且由本文所揭示之種類、亞類及物種進一步說明。除非另外指明，否則如本文所使用，以下定義應適用。出於本發明之目的，化學元素係根據Periodic Table of the Elements, CAS版, Handbook of Chemistry and Physics, 第75版標識。另外，有機化學之一般原理描述於「Organic Chemistry」, Thomas Sorrell, University Science Books, Sausalito: 1999及「March's Advanced Organic Chemistry」, 第5版, 編輯: Smith, M.B.及March, J., John Wiley & Sons, New York: 2001中，其全部內容以引用之方式併入本

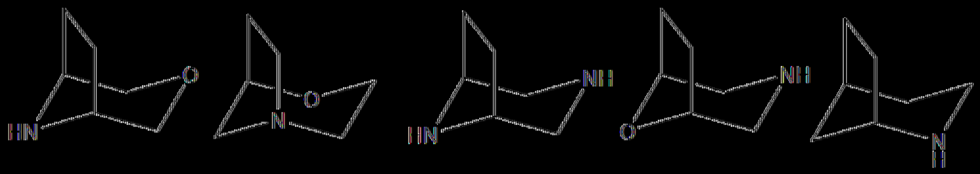
文中。

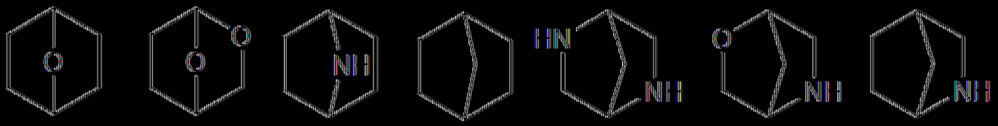
【0009】 如本文所使用，術語「脂族基」或「脂族基團」意謂完全飽和的或含有一或多個不飽和單元的直鏈(亦即，非分支鏈)或分支鏈、經取代或未經取代之烴鏈；或完全飽和的或含有一或多個不飽和單元但非芳族的(在本文中亦稱為「碳環」、「環脂族基」或「環烷基」)的單環烴或雙環烴，其與分子其餘部分具有單一連接點。除非另外說明，否則脂族基團含有1至6個脂族碳原子。在一些實施例中，脂族基團含有1至5個脂族碳原子。在其他實施例中，脂族基團含有1至4個脂族碳原子。在又其他實施例中，脂族基團含有1至3個脂族碳原子，且在又其他實施例中，脂族基團含有1至2個脂族碳原子。在一些實施例中，「環脂族基」(或「碳環」或「環烷基」)係指完全飽和的或含有一或多個不飽和單元但非芳族的單環C_3-C_6烴，其與分子其餘部分具有單一連接點。適合脂族基團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、炔基及其混合物，諸如(環烷基)烷基、(環烯基)烷基或(環烷基)烯基。

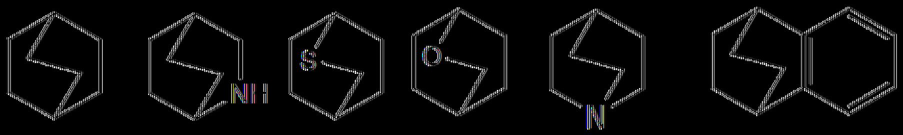
【0010】 如本文所使用，術語「橋連雙環」係指具有至少一個橋鏈的任何飽和或部分不飽和雙環系統，亦即，碳環或雜環基團。如IUPAC所定義，「橋鏈」係含多個原子或一個原子之未分支鏈或連接兩個橋頭之價鏈，其中「橋頭」係環系統中與三個或更多個骨架原子(除氫以外)鍵接之任何骨架原子。在一些實施例中，橋連雙環基團具有7至12個環成員及0至4個獨立地選自氮、氧或硫之雜原子。此類橋連雙環基團係此項技術中熟知的且包括在下文中闡述之基團，其中各基團在任何可取代碳或氮原子處連接至分子其餘部分。除非另外說明，否則橋連雙環基團視情況經一或多個如關於脂族基團所闡述之取代基取代。另外或替代地，橋連雙環基團

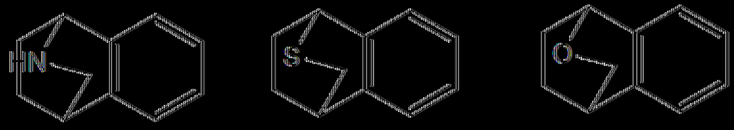
之任何可取代氫視情況經取代。例示性橋連雙環包括：

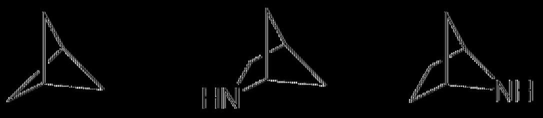












在一些實施例中，雙環[1.1.1.]戊烷係苯基電子等排體。

【0011】 術語「低碳數烷基」係指C_{1-4}直鏈或分支鏈烷基。例示性低碳數烷基係甲基、乙基、丙基、異丙基、丁基、異丁基及三級丁基。

【0012】 術語「低碳數鹵烷基」係指經一或多個鹵素原子取代之C_{1-4}直鏈或分支鏈烷基。

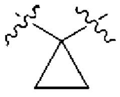
【0013】 術語「雜原子」意謂氧、硫、氮、磷或矽中的一或多個，包括氮、硫、磷或矽之任何氧化形式；任何鹼性氮之四級銨化形式；或雜環中之氧、硫、氮、磷或矽原子。

【0014】 如本文所使用，術語「不飽和」意謂一個部分具有一或多個不飽和單元。

【0015】 如本文所使用，術語「二價C_{1-8} (或C_{1-6})飽和或不飽和直鏈或分支鏈烴鏈」係指如本文所定義的呈直鏈或分支鏈之二價伸烷基、伸烯基及伸炔基鏈。

【0016】 術語「伸烷基」係指二價烷基。「伸烷基鏈」係聚亞甲基，亦即$-(CH_2)_n-$，其中n係正整數，較佳地為1至6、1至4、1至3、1至2或2至3。經取代之伸烷基鏈係一或多個亞甲基氫原子經取代基置換之聚亞甲基。適合的取代基包括下文關於經取代之脂族基團所描述之取代基。

【0017】 術語「伸烯基」係指二價烯基。經取代之伸烯基鏈係含有至少一個雙鍵且一或多個氫原子經取代基置換之聚亞甲基。適合的取代基包括下文關於經取代之脂族基團所描述之取代基。

【0018】 如本文所使用，術語「伸環丙基」係指具有以下結構之二價環丙基：  。

【0019】 術語「鹵素」意謂F、Cl、Br或I。

【0020】 單獨使用或如在「芳烷基」、「芳烷氧基」或「芳氧基烷基」中作為較大部分之一部分使用的術語「芳基」係指具有總計4至14個環成員之單環及雙環系統，其中該系統中之至少一個環係芳族的且其中該系統中之每個環含有3至7個環成員。術語「芳基」可與術語「芳基環」互換使用。在本發明之某些實施例中，「芳基」係指芳族環系統，其包括但不限於苯基、聯苯、萘基、蒽基及其類似基團，其可含有一或多個取代基。如本文所使用，在術語「芳基」範圍內亦包括芳族環與一或多個非芳族環稠合之基團，諸如二氫茚基、鄰苯二甲醯亞胺基、萘醯亞胺基、啡啶基或四氫萘基，及其類似基團。

【0021】 單獨使用或作為例如「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」及「雜芳-」係指這樣一類基團，其具有5至10個環原子，較佳地5、6或9個環原子；在環陣列中共有6、10或14個π電子；且除碳原子外，還具有1至5個雜原子。在「雜芳基」之情形中的術語「雜原子」特定地包括但不限於氮、氧或硫且包括氮或硫之任何氧化形式，及鹼性氮之任何四級銨化形式。雜芳基包括但不限於噻吩基、呋喃基、吡咯基、咪唑基、吡唑基、三唑基、四唑基、噁唑基、異噁唑基、噁二唑基、噻唑基、異噻唑基、噻二唑基、吡啶基、嗒哄基、嘧啶基、吡哄基、吲哚哄基、嘌呤基、㖠啶基及喋啶基。如本文所使用，術語「雜芳基」及「雜芳-」亦包括雜芳族環與一或多個芳基、環脂族基或雜環基環稠合之基團，其中連接基團或連接點在雜芳族環上。非限制性實例包括吲哚基、異吲哚基、苯并噻吩基、苯并呋喃基、二苯并呋喃基、吲唑基、苯并咪唑基、苯并噻唑基、喹啉基、異喹啉基、啐啉基、呔哄基、喹唑啉基、喹喏啉基、4*H*-喹哄基、咔唑基、吖啶基、啡哄基、啡噻哄基、啡噁哄基、四氫喹啉基、四氫異喹啉基及吡啶并[2,3-b]-1,4-噁哄-3(4H)-酮。雜芳基可為單環或雙環的。雜芳基環可包括一或多個側氧基(=O)或硫酮基(=S)取代基。術語「雜芳基」可與術語「雜芳基環」、「雜芳基」或「雜芳族基」互換使用，該等術語中之任一個包括視情況經取代之環。術語「雜芳烷基」係指經雜芳基取代之烷基，其中烷基及雜芳基部分獨立地視情況經取代。

【0022】如本文所使用，術語「雜環(heterocycle)」、「雜環基(heterocyclyl)」、「雜環基團(heterocyclic radical)」及「雜環(heterocyclic ring)」可互換使用且係指穩定的5至7員單環或7至10員雙環雜環部分，其為飽和或部分不飽和的，且除碳原子以外，還具有一或多

個，較佳地1至4個如上文所定義之雜原子。當關於雜環之環原子使用時，術語「氮」包括經取代之氮。舉例而言，在飽和或部分不飽和環中可具有0至3個選自氧、硫或氮之雜原子。

【0023】 雜環可在產生穩定結構之任何雜原子或碳原子處連接至所提供之化合物，且任何環原子均可視情況經取代。此類飽和或部分不飽和雜環基團之實例包括但不限於四氫呋喃基、四氫噻吩基、吡咯啶基、哌啶基、吡咯啉基、四氫喹啉基、四氫異喹啉基、十氫喹啉基、噁唑啶基、哌嗪基、二噁烷基、二氧雜環戊烷基、二氮呯基、噁氮呯基、噻氮呯基、味啉基及嗝啶基。術語「雜環(heterocycle)」、「雜環基(heterocyclyl)」、「雜環基環(heterocyclyl ring)」、「雜環基(heterocyclic group)」、「雜環部分(heterocyclic moiety)」及「雜環基(heterocyclic radical)」在本文中可互換使用，且亦包括雜環基環與一或多個芳基、雜芳基或環脂族環稠合之基團，諸如吲哚啉基、3*H*-吲哚基、𠳭烷基、啡啶基或四氫喹啉基。雜環基可為單環、雙環、橋連雙環或螺環的。雜環可包括一或多個側氧基(=O)或硫酮基(=S)取代基。術語「雜環基烷基」係指經雜環基取代之烷基，其中烷基及雜環基部分獨立地視情況經取代。

【0024】 如本文所使用，術語「部分不飽和」係指包括至少一個雙鍵或參鍵之環部分。術語「部分不飽和」意欲包含具有多個不飽和位點之環，但不意欲包括如本文所定義之芳基或雜芳基部分。

【0025】 如本文所描述，本發明之化合物可含有「經取代」之部分。一般而言，術語「經取代」意謂指定部分中之一或多個氫經適合取代基置換。除非另外指示，否則「視情況經取代」之基團可在該基團之一或多個可取代位置處具有適合的取代基，且當任何給定結構中之超過一個位

置經超過一個選自指定群組之取代基取代時，在每一位置處之取代基可相同或不同。本發明所預想之取代基之組合較佳為使得形成穩定或化學上可行之化合物的取代基。如本文所使用，術語「穩定」係指化合物在經歷允許其產生、偵測且在某些實施例中允許其回收、純化及用於本文所揭示之一或多個目的之條件時實質上無改變。

【0026】在「視情況經取代」之基團之可取代碳原子上的適合單價取代基獨立地為鹵素；$-(CH_2)_{0-6}R^\circ$；$-(CH_2)_{0-6}OR^\circ$；$-O(CH_2)_{0-6}R^\circ$；$-O-(CH_2)_{0-6}C(O)OR^\circ$；$-(CH_2)_{0-6}CH(OR^\circ)_2$；$-(CH_2)_{0-6}SR^\circ$；$-(CH_2)_{0-6}Ph$，該Ph可經$R^\circ$取代；$-(CH_2)_{0-6}O(CH_2)_{0-1}Ph$，該Ph可經$R^\circ$取代；$-CH=CHPh$，該Ph可經$R^\circ$取代；$-(CH_2)_{0-6}O(CH_2)_{0-1}$-吡啶基，該吡啶基可經$R^\circ$取代；$-NO_2$；$-CN$；$-N_3$；$-(CH_2)_{0-6}N(R^\circ)_2$；$-(CH_2)_{0-6}N(R^\circ)C(O)R^\circ$；$-N(R^\circ)C(S)R^\circ$；$-(CH_2)_{0-6}N(R^\circ)C(O)NR^\circ_2$；$-N(R^\circ)C(S)NR^\circ_2$；$-(CH_2)_{0-6}N(R^\circ)C(O)OR^\circ$；$-N(R^\circ)N(R^\circ)C(O)R^\circ$；$-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$；$-N(R^\circ)N(R^\circ)C(O)OR^\circ$；$-(CH_2)_{0-6}C(O)R^\circ$；$-C(S)R^\circ$；$-(CH_2)_{0-6}C(O)OR^\circ$；$-(CH_2)_{0-6}C(O)SR^\circ$；$-(CH_2)_{0-6}C(O)OSiR^\circ_3$；$-(CH_2)_{0-6}OC(O)R^\circ$；$-OC(O)(CH_2)_{0-6}SR^\circ$；$-(CH_2)_{0-6}SC(O)R^\circ$；$-(CH_2)_{0-6}C(O)NR^\circ_2$；$-C(S)NR^\circ_2$；$-C(S)SR^\circ$；$-SC(S)SR^\circ$；$-(CH_2)_{0-6}OC(O)NR^\circ_2$；$-C(O)N(OR^\circ)R^\circ$；$-C(O)C(O)R^\circ$；$-C(O)CH_2C(O)R^\circ$；$-C(NOR^\circ)R^\circ$；$-(CH_2)_{0-6}SSR^\circ$；$-(CH_2)_{0-6}S(O)_2R^\circ$；$-(CH_2)_{0-6}S(O)_2OR^\circ$；$-(CH_2)_{0-6}OS(O)_2R^\circ$；$-S(O)_2NR^\circ_2$；$-(CH_2)_{0-6}S(O)R^\circ$；$-N(R^\circ)S(O)_2NR^\circ_2$；$-N(R^\circ)S(O)_2R^\circ$；$-N(OR^\circ)R^\circ$；$-C(NH)NR^\circ_2$；$-P(O)_2R^\circ$；$-P(O)R^\circ_2$；$-P(O)(OR^\circ)_2$；$-OP(O)(R^\circ)OR^\circ$；$-OP(O)R^\circ_2$；$-OP(O)(OR^\circ)_2$；$SiR^\circ_3$；$-(C_{1-4}$直鏈或分支鏈伸烷基$)O-N(R^\circ)_2$；或$-(C_{1-4}$直鏈或分支鏈伸烷

基)$C(O)O-N(R^{\circ})_2$，其中各R°可如下文所定義經取代且獨立地為氫、C_{1-6}脂族基、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$、$-CH_2-$(5至6員雜芳環)，或具有0至4個獨立地選自氮、氧或硫之雜原子的5至6員飽和、部分不飽和或芳基環，或儘管以上已定義，但兩個獨立出現之R°與其一或多個插入原子一起形成具有0至4個獨立地選自氮、氧或硫之雜原子的3至12員飽和、部分不飽和或芳基單環或雙環，其可如下文所定義經取代。

【0027】 R° (或由兩個獨立出現之R°與其插入原子一起形成的環)上的適合單價取代基獨立地為鹵素、$-(CH_2)_{0-2}R^{\bullet}$、-(鹵基$R^{\bullet}$)、$-(CH_2)_{0-2}OH$、$-(CH_2)_{0-2}OR^{\bullet}$、$-(CH_2)_{0-2}CH(OR^{\bullet})_2$、-O(鹵基$R^{\bullet}$)、-CN、$-N_3$、$-(CH_2)_{0-2}C(O)R^{\bullet}$、$-(CH_2)_{0-2}C(O)OH$、$-(CH_2)_{0-2}C(O)OR^{\bullet}$、$-(CH_2)_{0-2}SR^{\bullet}$、$-(CH_2)_{0-2}SH$、$-(CH_2)_{0-2}NH_2$、$-(CH_2)_{0-2}NHR^{\bullet}$、$-(CH_2)_{0-2}NR^{\bullet}_2$、$-NO_2$、$-SiR^{\bullet}_3$、$-OSiR^{\bullet}_3$、$-C(O)SR^{\bullet}$、$-(C_{1-4}$直鏈或分支鏈伸烷基)$C(O)OR^{\bullet}$或$-SSR^{\bullet}$，其中各$R^{\bullet}$未經取代或在前面有「鹵基」之情況下僅經一或多個鹵素取代，且獨立地選自C_{1-4}脂族基、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或具有0至4個獨立地選自氮、氧或硫之雜原子的5至6員飽和、部分不飽和或芳基環。R°之飽和碳原子上的適合二價取代基包括=O及=S。

【0028】 在「視情況經取代」之基團之飽和碳原子上的適合二價取代基包括以下：=O、=S、$=NNR^{*}_2$、$=NNHC(O)R^{*}$、$=NNHC(O)OR^{*}$、$=NNHS(O)_2R^{*}$、$=NR^{*}$、$=NOR^{*}$、$-O(C(R^{*}_2))_{2-3}O-$或$-S(C(R^{*}_2))_{2-3}S-$，其中R^{*}在每次出現時選自氫、可如下文所定義經取代之C_{1-6}脂族基，或具有0至4個獨立地選自氮、氧或硫之雜原子的未經取代之5至6員飽和、部分不飽和或芳基環。結合至「視情況經取代」之基團之鄰近可取代碳的適合二價取代基包括：$-O(CR^{*}_2)_{2-3}O-$，其中R^{*}在每次出現時選自氫、可如下

文所定義經取代之C_{1-6}脂族基，或具有0至4個獨立地選自氮、氧或硫之雜原子的未經取代之5至6員飽和、部分不飽和或芳基環。

【0029】 在R^*之脂族基上的適合取代基包括鹵素、$-R^\bullet$、-(鹵基$R^\bullet$)、-OH、$-OR^\bullet$、-O(鹵基$R^\bullet$)、-CN、-C(O)OH、$-C(O)OR^\bullet$、$-NH_2$、$-NHR^\bullet$、$-NR^\bullet_2$或$-NO_2$，其中各$R^\bullet$未經取代或在前面有「鹵基」之情況下僅經一或多個鹵素取代，且獨立地為C_{1-4}脂族基、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或具有0至4個獨立地選自氮、氧或硫之雜原子的5至6員飽和、部分不飽和或芳基環。

【0030】 在「視情況經取代」之基團之可取代氮上的適合取代基包括$-R^\dagger$、$-NR^\dagger_2$、$-C(O)R^\dagger$、$-C(O)OR^\dagger$、$-C(O)C(O)R^\dagger$、$-C(O)CH_2C(O)R^\dagger$、$-S(O)_2R^\dagger$、$-S(O)_2NR^\dagger_2$、$-C(S)NR^\dagger_2$、$-C(NH)NR^\dagger_2$或$-N(R^\dagger)S(O)_2R^\dagger$；其中各$R^\dagger$獨立地係氫；可如下文所定義經取代之$C_{1-6}$脂族基；未經取代之-OPh；或具有0至4個獨立地選自氮、氧或硫之雜原子的未經取代之5至6員飽和、部分不飽和或芳基環，或儘管以上已定義，但兩個獨立出現之$R^\dagger$與其一或多個插入原子一起形成具有0至4個獨立地選自氮、氧或硫之雜原子的未經取代之3至12員飽和、部分不飽和或芳基單環或雙環。

【0031】 在$R^\dagger$之脂族基上的適合取代基獨立地為鹵素、$-R^\bullet$、-(鹵基$R^\bullet$)、-OH、$-OR^\bullet$、-O(鹵基$R^\bullet$)、-CN、-C(O)OH、$-C(O)OR^\bullet$、$-NH_2$、$-NHR^\bullet$、$-NR^\bullet_2$或$-NO_2$，其中各$R^\bullet$未經取代或在前面有「鹵基」之情況下僅經一或多個鹵素取代，且獨立地為C_{1-4}脂族基、$-CH_2Ph$、$-O(CH_2)_{0-1}Ph$或具有0至4個獨立地選自氮、氧或硫之雜原子的5至6員飽和、部分不飽和或芳基環。

【0032】 如本文所使用，術語「所提供之化合物」係指本文所闡述

之任何屬、亞屬及/或物種。

【0033】 如本文所使用，術語「醫藥學上可接受之鹽」係指在合理醫學判斷之範圍內適於與人類及低等動物之組織接觸使用而無過度毒性、刺激、過敏反應及其類似情況且與合理的效益/風險比相稱的鹽。醫藥學上可接受之鹽係此項技術中所熟知的。舉例而言，S. M.Berge等人在J. Pharmaceutical Sciences, 1977, 66, 1-19中詳細地描述醫藥學上可接受的鹽，該文獻以引用之方式併入本文中。本發明化合物的醫藥學上可接受之鹽包括衍生自適合無機酸及有機酸以及無機鹼及有機鹼的鹽。醫藥學上可接受之無毒酸加成鹽之實例係胺基與無機酸諸如鹽酸、氫溴酸、磷酸、硫酸及過氯酸，或與有機酸諸如乙酸、草酸、順丁烯二酸、酒石酸、檸檬酸、琥珀酸或丙二酸形成之鹽，或藉由使用此項技術中使用之其他方法，諸如離子交換法形成之鹽。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、特戊酸鹽、丙酸鹽、硬脂酸鹽、琥珀酸鹽、硫酸鹽、酒石酸鹽、硫代氰酸鹽、對甲苯磺酸鹽、十一烷酸鹽、戊酸鹽及其類似鹽。

【0034】 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。代表性鹼金屬或鹼土金屬鹽包括鈉鹽、鋰鹽、鉀鹽、鈣鹽、鎂鹽及其類似鹽。適當時，其他醫藥學上可接受之鹽包括無毒銨、四級銨以及使用相對離子，諸如鹵離子、氫氧根、羧酸根、硫酸根、磷酸根、硝酸根、低碳數烷基磺酸根及芳基磺酸根形成之胺陽離子。

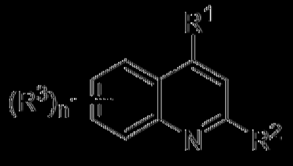
【0035】 除非另外陳述，否則本文所描繪之結構亦意欲包括該結構之所有異構形式(例如鏡像異構、非鏡像異構及幾何異構(或構形異構)形式)；例如，各不對稱中心之R及S組態、Z及E雙鍵異構體及Z及E構形異構體。因此，本發明化合物之單一立體化學異構體以及鏡像異構、非鏡像異構及幾何異構(或構形)混合物均在本發明之範圍內。除非另外陳述，否則本發明化合物之所有互變異構形式均在本發明之範圍內。此外，除非另外說明，否則本文所描繪之結構亦意欲包括不同之處僅在於存在一或多個同位素富集原子的化合物。舉例而言，包括氫經氘或氚置換或碳經^{13}C或^{14}C富集之碳置換的具有本發明結構之化合物係在本發明之範圍內。該等化合物可用作例如分析工具，用作生物分析中之探針，或用作根據本發明之治療劑。

【0036】 如本文所使用，術語「拮抗劑」定義為以可量測之親和力結合至及/或抑制cGAS之化合物。在某些實施例中，cGAS拮抗劑之IC_{50}及/或結合常數小於約30 μM或小於約2 μM。

3.2. 本發明化合物

【0037】 本發明化合物及其組合物可用作cGAS拮抗劑。在一些實施例中，所提供之化合物抑制cGAS。

【0038】 本發明提供一種式**I**化合物：



I

或其醫藥學上可接受之鹽，其中：

R^1 係鹵素、$-OR$、$-NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-NRSO_2R$、$-SR$、$-SO_2R$、$-SO_2NR_2$、$-S(O)R$ 或 R^A，特定言之為 $-NR_2$ 或 R^A；

每個R獨立地係氫或視情況經取代的選自以下之基團：C_{1-6} 脂族基；苯甲基；苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；及具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環，或：

同一氮上的兩個R基團視情況與其插入原子一起形成除氮外還具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和、部分不飽和或雜芳基環；

R^2 係鹵素、$-OR$、$-NR_2$、$-NRNR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-NRSO_2R$、$-SR$、$-SO_2R$、$-SO_2NR_2$、$-S(O)R$ 或 R^B，特定言之為 $-NR_2$ 或 R^B；

每個 R^3 獨立地係鹵素、$-OR$、$-NR_2$、$-SR$ 或 R^C，特定言之為鹵素，諸如氯；

R^A、R^B 及 R^C 獨立地係視情況經取代的選自以下之基團：C_{1-6} 脂族基；苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；及具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；且

n係1、2、3或4。

【0039】 在某些實施例中，本發明提供一種式**I**之化合物，其中：

R^1係R^A，其中R^A係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

R^2係R^B，其中R^B係具有1至3個獨立地選自氮、氧、磷及硫之雜原子的經取代之4至7員飽和雜環(特定言之為吡咯啶、哌啶、味啉及哌哄)，例如其經一個或兩個選自以下之基團取代：鹵素、=O、=CH_2、C_{1-4}烷基、C_{1-4}鹵烷基、C_{3-6}環烷基、-OH、-$(CH_2)_{1-2}$-OH、-OC_{1-4}烷基、-$(CH_2)_{0-2}CO_2H$、-$(CH_2)_{0-2}O(CH_2)_{1-5}CO_2H$、-$(CH_2)_{0-2}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{0-2}CO_2C_{1-4}$烷基、-$NH_2$、-$(CH_2)_{0-2}CONH_2$、-$(CH_2)_{0-2}CONR^a$-$(CH_2)_{1-2}CO_2H$、-$(CH_2)_{0-2}SO_3H$、-$(CH_2)_{0-2}SO_2NH_2$、-$(CH_2)_{0-2}SO_2NHC_{1-4}$烷基或-$(CH_2)_{0-2}NR^aSO_2C_{1-4}$烷基，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0040】 在其他實施例中，本發明提供一種式**I**之化合物，其中：

R^1係R^A，其中R^A係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

R^2係-NR_2，其中一個R係H或低碳數烷基(特定言之為甲基)，且另一個R係經取代之C_{1-6}脂族基，包括視情況經取代之-C_{1-5}伸烷基-X；其中X係選自-OH、-OC_{1-4}烷基、-O-C_{1-4}伸烷基-CO_2H、-O-C_{1-4}伸烷基-CO_2C_{1-4}烷基、-CO_2H、-CO_2C_{1-4}烷基、-NH_2、-$CONH_2$、-$CONHC_{1-4}$烷基、-$CONR^a$-$(CH_2)_{1-2}$-OH、-$CONR^a$-$(CH_2)_{1-2}$-COOH、-$CONR^a$-$(CH_2)_{1-2}$-

$CONH_2$、$-SO_3H$、$-SO_2NH_2$、$-SO_2NHC_{1-4}$烷基、$-NR^aSO_2C_{1-4}$烷基、$-P(O)(OH)_2$及$-OP(O)(H)(OH)$，其中R^a在每次出現時獨立地係H或C_{1-4}烷基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0041】 在一些實施例中，本發明提供一種式**I**之化合物，其中：

R^1係$-NR_2$，其中一個R係H或低碳數烷基(特定言之為甲基)，且另一個R係經取代之C_{1-6}脂族基，包括視情況經取代之$-C_{1-4}$伸烷基-X；其中X係選自-OH、$-OC_{1-4}$烷基、$-CO_2H$、$-O-C_{1-4}$伸烷基$-CO_2H$、$-O-C_{1-4}$伸烷基$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$烷基、$-CONH_2$及$-CONHC_{1-4}$烷基；

R^2係R^B，其中R^B係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0042】 在其他實施例中，本發明提供一種式**I**之化合物，其中：

R^1係R^A，其中R^A係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

R^2係經取代之苯基(特定言之，經一個或兩個選自以下之基團取代：鹵素、C_{1-4}烷基、-OH、$-OC_{1-4}$烷基、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-(CH_2)_{0-2}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-2}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-NH_2$及$-CONH_2$)；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於

喹啉環位在7-或8-位置之R^3係氯。

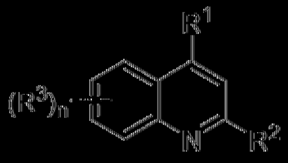
【0043】 在其他實施例中，本發明提供一種式I之化合物，其中：

R^1係R^A，其中R^A係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

R^2係R^B，其中R^B係視情況經取代之C_{1-6}脂族基，較佳地為經取代之C_{1-6}脂族基(特定言之為$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$)；且

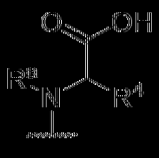
每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

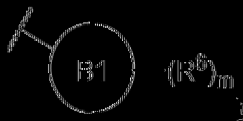
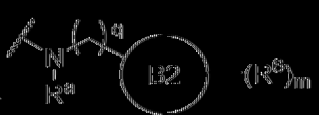
【0044】 在某些實施例中，本發明提供一種化合物，其中該化合物具有式I*：



I*

或其醫藥學上可接受之鹽，其中：

R^1係  或具有1至4個獨立地選自氮、氧及硫之雜原子的視情況經取代之5至6員雜芳基環；

R^2係$-NR^aR^5$、 或 ；

每個R^3獨立地係鹵素、$-OR$、$-NR_2$、$-SR$或R^C；

環B1係苯基，較佳地為經取代之苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

環B2係苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

每個R獨立地係氫或視情況經取代的選自以下之基團：$C_{1\text{-}6}$脂族基；苯甲基；苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；及具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環，

R^4係氫或視情況經取代之$C_{1\text{-}6}$脂族基；

R^5係$-(CR_2)_{0\text{-}4}OR$、$-(CR_2)_{0\text{-}5}CO_2R$、$-(CR_2)_{0\text{-}5}CONR_2$、$-(CR_2)_{0\text{-}4}C(O)NR(CR_2)_{0\text{-}4}CO_2R$、$-(CR_2)_{0\text{-}4}C(O)NR(CR_2)_{0\text{-}4}CONR_2$、$-(CR_2)_{0\text{-}4}NRC(O)R$、$-(CR_2)_{0\text{-}4}SO_3R$、$-(CR_2)_{0\text{-}4}SO_2NR_2$、$-(CR_2)_{0\text{-}4}OSO_2NR_2$、$-(CR_2)_{0\text{-}4}NRSO_2R$、$-(CR_2)_{0\text{-}4}NRSO_2OR$、$-(CR_2)_{0\text{-}4}OP(OR)_2$、$-(CR_2)_{0\text{-}4}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}4}P(O)(OR)_2$、$-(CR_2)_{0\text{-}4}OP(O)(H)OR$或$R^B$；

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0\text{-}4}CO_2R$、$-(CR_2)_{0\text{-}4}CONR_2$、$-OR$、$-(CR_2)_{1\text{-}4}OR$、$-NR_2$、$-(CR_2)_{1\text{-}4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0\text{-}4}SO_3R$、$-(CR_2)_{0\text{-}4}SO_2NR_2$、$-(CR_2)_{0\text{-}4}OSO_2NR_2$、$-(CR_2)_{0\text{-}4}NRSO_2R$、$-(CR_2)_{0\text{-}4}NRSO_2OR$、$-(CR_2)_{0\text{-}4}OP(OR)_2$、$-(CR_2)_{0\text{-}4}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}4}P(O)(OR)_2$、$-(CR_2)_{0\text{-}4}OP(O)(H)OR$、$-B(OR)_2$或$R^B$；

R^B及R^C獨立地係視情況經取代的選自以下之基團：$C_{1\text{-}6}$脂族基；苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；及具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

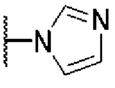
每個R^a獨立地係H或C_{1-6}烷基；

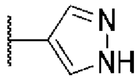
每個m係0、1、2、3或4；

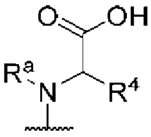
n係1、2、3或4；

q係0、1或2。

【0045】 在一些實施例中，R^1係具有1至4個獨立地選自氮、氧及硫之雜原子的視情況經取代之5至6員雜芳基環。

【0046】 在一些實施例中，R^1係咪唑。在一些實施例中，該咪唑未經取代。在一些實施例中，R^1係。

【0047】 在一些實施例中，R^1係吡唑。在一些實施例中，該吡唑未經取代。在一些實施例中，R^1係。

【0048】 在一些實施例中，R^1係。在一些實施例中，R^4係C_{1-6}烷基。

【0049】 在一些實施例中，至少一個出現之R^3係鹵素。在一些實施例中，至少一個出現之R^3係氯。在一些實施例中，n係2且兩個R^3均為氯。在一些實施例中，n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0050】 在一些實施例中，R^2係$-NR^aR^5$。

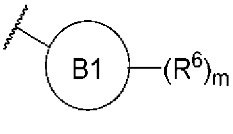
【0051】 在一些實施例中，R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{0-5}CO_2R$、$-(CR_2)_{0-5}CONR_2$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CO_2R$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-4}SO_3R$、$-(CR_2)_{0-4}SO_2NR_2$、$-(CR_2)_{0-4}OSO_2NR_2$、$-(CR_2)_{0-4}NRSO_2R$、$-(CR_2)_{0-4}NRSO_2OR$、$-(CR_2)_{0-4}OP(OR)_2$、$-(CR_2)_{0-4}OP(O)(OR)_2$、$-(CR_2)_{0-4}P(O)(OR)_2$或$-(CR_2)_{0-4}OP(O)(H)OR$。

【0052】在一些實施例中，R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{1-5}CO_2R$、$-(CR_2)_{1-5}CONR_2$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CO_2R$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-4}SO_3R$、$-(CR_2)_{0-4}SO_2NR_2$、$-(CR_2)_{0-4}OSO_2NR_2$、$-(CR_2)_{0-4}NRSO_2R$、$-(CR_2)_{0-4}NRSO_2OR$、$-(CR_2)_{0-4}OP(OR)_2$、$-(CR_2)_{0-4}OP(O)(OR)_2$、$-(CR_2)_{0-4}P(O)(OR)_2$或$-(CR_2)_{0-4}OP(O)(H)OR$。

【0053】在一些實施例中，R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{2-4}OC_{1-4}$烷基、$-(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}CON(C_{1-4}\text{烷基})_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}\text{烷基})_2$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{2-4}SO_3H$、$-(CH_2)_{2-4}SO_3C_{1-4}$烷基、$-(CH_2)_{2-4}SO_2NH_2$、$-(CH_2)_{2-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{2-4}SO_2N(C_{1-4}\text{烷基})_2$、$-(CH_2)_{2-4}OSO_2NH_2$、$-(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{2-4}NR^aSO_3H$、$-(CH_2)_{1-4}OP(OH)_2$、$-(CH_2)_{1-4}P(O)(OH)_2$、$-(CH_2)_{1-4}P(O)(OH)(OC_{1-4}\text{烷基})$或$-(CH_2)_{2-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-6}$烷基。

【0054】在一些實施例中，R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-5}CONH_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{2-4}SO_3H$、$-(CH_2)_{2-4}SO_2NH_2$、$-(CH_2)_{2-4}SO_2NR^aC_{1-4}$烷基、-

$(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{1-4}P(O)(OH)_2$或$-(CH_2)_{2-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【0055】 在一些實施例中，R^2係。在一些實施例中，m係1、2、3或4。

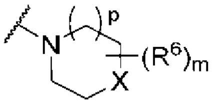
【0056】 在一些實施例中，環B1係經取代之苯基。在一些實施例中，該苯基經一或多個羧基取代。

【0057】 在一些實施例中，環B1係3-羧基苯基，其視情況經一或多個R^6基團取代。

【0058】 在一些實施例中，環B1係3,5-二羧基苯基，其視情況經一或多個R^6基團取代。

【0059】 在一些實施例中，環B1係具有1至3個獨立地選自氮、氧及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。

【0060】 在一些實施例中，環B1係具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環。

【0061】 在一些實施例中，R^2係，其中X係不存在(亦即，為環中的鍵)、$-CR_2-$、$-NR-$、$-O-$、$-S-$或$-SO_2-$；且p係0、1或2。在一些實施例中，X係$-CR_2-$、$-NR-$或$-O-$。在一些實施例中，p係1。在一些實施例中，m係1、2、3或4。

【0062】 在一些實施例中，每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、C_{3-6}環烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、

$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

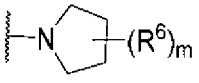
【0063】 在一些實施例中，每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、C_{3-6}環烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO(N$-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$。

【0064】 在一些實施例中，R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、C_{3-6}環烷基、$-(CH_2)_{0-2}CO_2H$、$-(CH_2)_{0-2}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CO(N$-脯胺酸$)$、$-(CH_2)_{0-2}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-2}OH$、$-(CH_2)_{0-2}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-2}OC(O)C_{1-4}$烷基、$-(CH_2)_{0-2}SO_3H$、$-(CH_2)_{0-2}SO_2NH_2$、$-(CH_2)_{0-2}NR^aSO_2C_{0-2}$烷基、$-(CH_2)_{0-2}OP(OH)_2$或$-(CR_2)_{0-2}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【0065】 在一些實施例中，每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、C_{3-6}環烷基、$-(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}CO(N$-脯胺酸$)$、-

$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}SO_3H$、$-(CH_2)_{1-4}SO_2NH_2$、$-(CH_2)_{1-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{1-4}OP(OH)_2$或$-(CR_2)_{1-4}OP(O)(H)OH$。

【0066】在一些實施例中，每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-CO$(N-脯胺酸)、$-CH_2CO_2H$、$-OH$、$-OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-OC(O)C_{1-4}$烷基、$-SO_3H$、$-SO_2NH_2$、$-NR^aSO_2C_{1-4}$烷基、$-OP(OH)_2$或$-OP(O)(H)OH$。

【0067】在一些實施例中，R^2係。在一些實施例中，m係1、2、3或4。在一些實施例中，m係1或2。

【0068】在一些實施例中，每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、C_{3-6}環烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO$(*N*-脯胺酸)、$-(CH_2)_{0-4}CO$(*N*-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NR^aC_{1-4}$烷基、$-(CH_2)_{0-}$

${}_4NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-6}$烷基。

【0069】 在一些實施例中，每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、C_{3-6}環烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO($*N*-脯胺酸)、$-(CH_2)_{0-4}CO($*N*-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基)$-CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

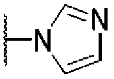
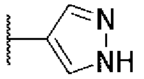
【0070】 在一些實施例中，每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基、$-CO($*N*-脯胺酸)、$-CO($*N*-吡咯啶-3-羧酸)、$-C(O)NR^a(CH_2)_{1-4}CO_2H$、$-C(O)NR^a-CH(C_{1-4}$烷基)$-CO_2H$、$-OH$、$-OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-NR^aC(O)C_{1-4}$烷基、$-NR^aC(O)Ph$、$-NR^aCO(CH_2)_{1-4}OH$、$-SO_3H$、$-SO_2NH_2$、$-NR^aSO_2C_{1-4}$烷基、$-NR^aSO_2Ph$、$-NR^aSO_2(CH_2)_{1-4}CO_2H$、$-OP(OH)_2$或$-OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

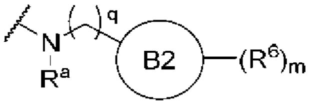
【0071】 在一些實施例中，每個R^6獨立地係氟、$=O$、$=CH_2$、甲基、環己基、味啉基、苯基、$-CF_3$、$-OMe$、$-OtBu$、$-CO_2H$、$-CO_2C_{1-4}$烷

基、$-CO_2C_{1-4}$鹵烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基或-OH。

【0072】在一些實施例中，環B1係具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環，其中該5至6員雜芳基環之碳原子直接鍵接至喹諾酮環2-位置之碳。

【0073】在一些實施例中，環B1係咪唑或吡唑。在一些實施例中，該咪唑或吡唑未經取代。

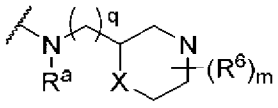
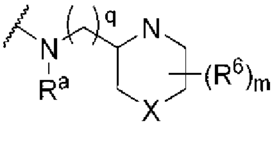
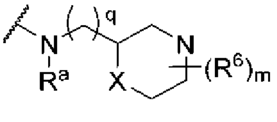
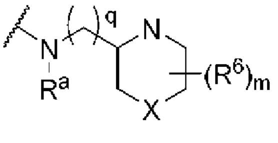
【0074】在一些實施例中，R^2係。在一些實施例中，R^2係。

【0075】在一些實施例中，R^2係。在一些實施例中，m係1、2、3或4。

【0076】在一些實施例中，環B2係苯基。

【0077】在一些實施例中，環B2係具有1至3個獨立地選自氮、氧及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環。

【0078】在一些實施例中，環B2係具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環。

【0079】在一些實施例中，R^2係或，其中X係不存在(亦即，為環中的鍵)、$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$；且m係1、2、3或4。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，X係$-CR_2-$、-NR-或-O-。在一些實施例中，q係1或2。在一些實施例

中，q係1。在一些實施例中，m係1或2。

【0080】 在一些實施例中，每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【0081】 在一些實施例中，每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【0082】 在一些實施例中，每個R^6獨立地係鹵素、$-CO_2H$、$-CO($*N*-脯胺酸$)$、$-C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-SO_3H$、$-SO_2NH_2$、$-NR^aSO_2C_{1-4}$烷基、$-OP(OH)_2$或$-OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【0083】 在一些實施例中，R^6不為R^B。

【0084】 在一些實施例中，m係至少1，且至少一個R^6包括末端$-CO_2H$或$-CO_2C_{1-4}$烷基。

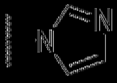
【0085】 在一些實施例中，至少一個R^6係$-(CH_2)_{0-4}O(CH_2)_{1-}$

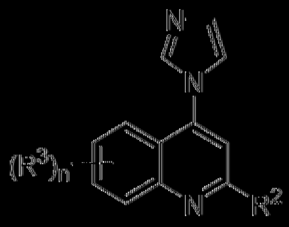
$_{5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2H$或$-(CH_2)_{0-4}CO_2C_{1-4}$烷基。

【0086】在一些實施例中，本發明提供一種醫藥組合物，其包含式I*之化合物或其醫藥學上可接受之鹽。

【0087】在一些實施例中，本發明提供一種拮抗有需要患者體內之環狀GMP-AMP合成酶(cGAS)的方法，其包含投與有效量的式I*之化合物或其醫藥學上可接受之鹽，或其醫藥組合物。

【0088】在一些實施例中，本發明提供一種治療有需要患者之發炎性疾病、過敏性疾病或自體免疫疾病的方法，其包含投與有效量的式I*之化合物或其醫藥學上可接受之鹽，或其醫藥組合物。

【0089】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係，由此形成式I-a-1之化合物：



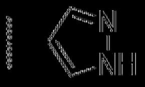
I-a-1

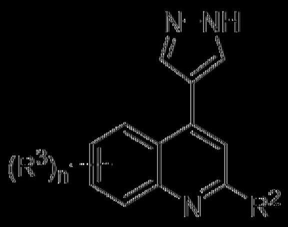
或其醫藥學上可接受之鹽，其中R^2、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0090】在某些實施例中，本發明提供一種式I-a-1之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0091】在某些實施例中，本發明提供一種式I-a-1之化合物，其中R^2係R^B，其中R^B係視情況經取代之C_{1-6}脂族基，較佳地為經取代之C_{1-6}脂族基，諸如$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-4}O(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-}$

$_4CO_2R$、$-(CR_2)_{1-4}OH$、$-(CR_2)_{1-4}NH_2$、$-(CR_2)_{1-4}C(O)NH_2$、$-(CR_2)_{1-4}C(O)NHC_{1-4}$烷基或$-(CR_2)_{1-4}C(O)N(C_{1-4}$烷基$)_2$，特定言之為$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$或$-(CR_2)_{1-4}CO_2R$。在一些實施例中，$R^2$係$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2R^a$，諸如$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係$-(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2R^a$，諸如為$-(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係$-(CR_2)_{1-4}CO_2R$，諸如$-(CR_2)_{1-4}CO_2H$，包括$-(CH_2)_{1-4}CO_2H$。在某些實施例中，$R^2$包括末端$-CO_2H$基團。舉例而言，在某些情形中，$R^2$包括末端$-(CH_2)_{0-4}CO_2H$基團。

【0092】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係，由此形成式I-a-2之化合物：



I-a-2

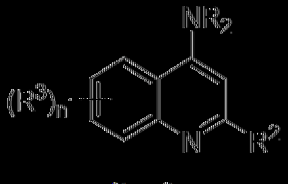
或其醫藥學上可接受之鹽，其中R^2、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0093】在某些實施例中，本發明提供一種式I-a-2之化合物，其中R^2係R^B，其中R^B係視情況經取代之C_{1-6}脂族基，較佳地為經取代之C_{1-6}脂族基，諸如$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-4}O(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}OH$、$-(CR_2)_{1-4}NH_2$、$-(CR_2)_{1-4}C(O)NH_2$、$-(CR_2)_{1-4}C(O)NHC_{1-4}$烷基或$-(CR_2)_{1-4}C(O)N(C_{1-4}$烷基$)_2$，特定言之為$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$或$-(CR_2)_{1-4}CO_2R$。在一些實施例中，$R^2$係$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2R^a$，

諸如-$(CH_2)_{1\text{-}4}NR^a(CH_2)_{0\text{-}4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1\text{-}4}$烷基。在其他實施例中，$R^2$係-$(CH_2)_{1\text{-}4}N(SO_2C_{1\text{-}4}$烷基$)(CH_2)_{0\text{-}4}CO_2R^a$，諸如為-$(CH_2)_{1\text{-}4}N(SO_2C_{1\text{-}4}$烷基$)(CH_2)_{0\text{-}4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1\text{-}4}$烷基。在其他實施例中，$R^2$係-$(CR_2)_{1\text{-}4}CO_2R$，諸如-$(CR_2)_{1\text{-}4}CO_2H$，包括-$(CH_2)_{1\text{-}4}CO_2H$。在某些實施例中，$R^2$包括末端-$CO_2H$基團。舉例而言，在某些情形中，$R^2$包括末端-$(CH_2)_{0\text{-}4}CO_2H$基團。

【0094】 在某些實施例中，本發明提供一種式I-a-2之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

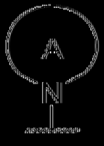
【0095】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係-NR_2，由此形成式I-a-3之化合物：

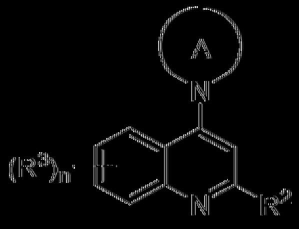


I-a-3

或其醫藥學上可接受之鹽，其中R、R^2、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0096】 在某些實施例中，本發明提供一種式I-a-3之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0097】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  ，由此形成式I-a-4之化合物：



I-a-4

或其醫藥學上可接受之鹽，其中：

環A係具有0至3個獨立地選自氮、氧、磷及硫之雜原子(除環A中已描繪之氮外)的視情況經取代之4至7員飽和或部分不飽和雜環或雜芳基環；

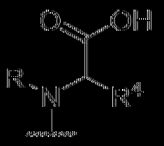
R^2、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0098】 在某些實施例中，本發明提供一種式I-a-4之化合物，其中R^2係R^B，其中R^B係視情況經取代之C_{1-6}脂族基，較佳地為經取代之C_{1-6}脂族基，諸如-$(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$、-$(CR_2)_{1-4}O(CR_2)_{0-6}CO_2R$、-$(CR_2)_{1-4}CO_2R$、-$(CR_2)_{1-4}OH$、-$(CR_2)_{1-4}NH_2$、-$(CR_2)_{1-4}C(O)NH_2$、-$(CR_2)_{1-4}C(O)NHC_{1-4}$烷基或-$(CR_2)_{1-4}C(O)N(C_{1-4}$烷基$)_2$，特定言之為-$(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$或-$(CR_2)_{1-4}CO_2R$。在一些實施例中，$R^2$係-$(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2R^a$，諸如-$(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係-$(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2R^a$，諸如為-$(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係-$(CR_2)_{1-4}CO_2R$，諸如-$(CR_2)_{1-4}CO_2H$，包括-$(CH_2)_{1-4}CO_2H$。在某些實施例中，$R^2$包括末端-$CO_2H$基團。舉例而言，在某些情形中，$R^2$包括末端-$(CH_2)_{0-4}CO_2H$基團。

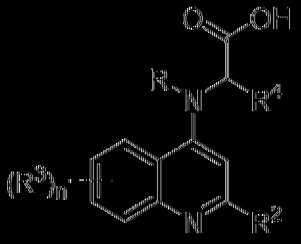
【0099】 在某些實施例中，本發明提供一種式I-a-4之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在

7-或8-位置之R^3係氯。

【0100】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係



，由此形成式I-a-5之化合物：



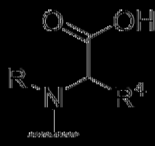
I-a-5

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；且

R、R^2、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

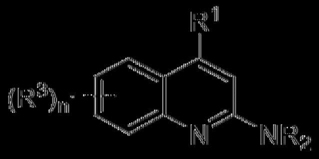
【0101】在一些實施例中，本發明提供一種式I-a-5之化合物，其中



中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0102】在某些實施例中，本發明提供一種式I-a-5之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0103】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^2係$-NR_2$，由此形成式I-b-1之化合物：



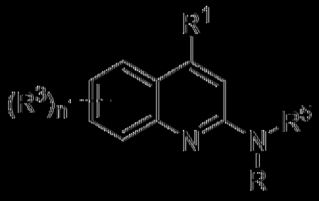
I-b-1

或其醫藥學上可接受之鹽，其中R、R^1、R^3及n各自如上文所定義且

單獨及以組合形式描述於本文實施例中。

【0104】 在某些實施例中，本發明提供一種式I-b-1之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0105】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^2係-NRR^5，由此形成式I-b-2之化合物：



I-b-2

或其醫藥學上可接受之鹽，其中：

R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$；且

R、R^1、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0106】 在某些實施例中，本發明提供一種式I-b-2之化合物，其中R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$。

【0107】 在一些實施例中，本發明提供一種式**I-b-2**之化合物，其中R^5不為R^B。

【0108】 在一些實施例中，本發明提供一種式**I-b-2**之化合物，其中$-NRR^5$中之R係R^a，其係H或C_{1-6}烷基。

【0109】 在某些實施例中，本發明提供一種式**I-b-2**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0110】 在某些實施例中，本發明提供一種式**I-b-2**之化合物，其中：

R^1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

$-NRR^5$中之R係H或低碳數烷基，特定言之為甲基；

R^5係$-(CR_2)_{0-6}OR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$或$-(CR_2)_{0-6}OP(O)(H)OR$；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0111】 在特定實施例中，本發明提供一種式**I-b-2**之化合物，其中：

R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

-NRR^{5}中之R係H或低碳數烷基，特定言之為甲基；

R^{5}係-$(CH_2)_{2-4}OH$、-$(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、-$(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{0-3}CH(CH_2OH)_2$、-$(CH_2)_{2-4}OC_{1-4}$烷基、-$(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}CO_2C_{1-4}$烷基、-$(CH_2)_{1-4}CONH_2$、-$(CH_2)_{1-4}CONHC_{1-4}$烷基、-$(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-$(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、-$(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{2-4}SO_3H$、-$(CH_2)_{2-4}SO_3C_{1-4}$烷基、-$(CH_2)_{2-4}SO_2NH_2$、-$(CH_2)_{2-4}SO_2NHC_{1-4}$烷基、-$(CH_2)_{2-4}SO_2N(C_{1-4}$烷基$)_2$、-$(CH_2)_{2-4}OSO_2NH_2$、-$(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、-$(CH_2)_{2-4}NR^aSO_3H$、-$(CH_2)_{1-4}OP(OH)_2$、-$(CH_2)_{1-4}P(O)(OH)_2$、-$(CH_2)_{1-4}P(O)(OH)$（$OC_{1-4}$烷基）或-$(CH_2)_{2-4}OP(O)(H)OH$，其中R^{a}在每次出現時獨立地係H或$C_{1-4}$烷基；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0112】 在其他特定實施例中，本發明提供一種式**I-b-2**之化合物，其中：

R^{1}係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

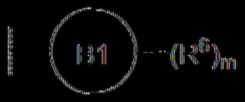
-NRR^{5}中之R係H或低碳數烷基，特定言之為甲基；

R^{5}係-$(CH_2)_{2-4}OH$、-$(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、-$(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{0-3}CH(CH_2OH)_2$、-$(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}CONH_2$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、-$(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、-$(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{2-4}SO_3H$、-

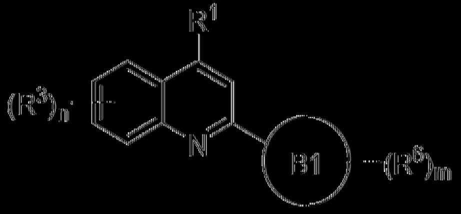
$(CH_2)_{2\text{-}4}SO_2NH_2$、$-(CH_2)_{2\text{-}4}SO_2NR^aC_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}NR^aSO_2C_{1\text{-}4}$烷基、$-(CH_2)_{1\text{-}4}P(O)(OH)_2$或$-(CH_2)_{2\text{-}4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1\text{-}4}$烷基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0113】 在某些實施例中，對於以上揭示的式I-b-2之化合物，R^5包括末端-CO_2H基團。舉例而言，在某些情形中，R^5包括末端-$(CH_2)_{0\text{-}4}CO_2H$基團。

【0114】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^2係

，由此形成式I-b-3之化合物：



I-b-3

或其醫藥學上可接受之鹽，其中：

環B1係苯基，較佳地為經取代之苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

每個R^6獨立地係鹵素、-COR、$-(CR_2)_{0\text{-}6}CO_2R$、$-(CR_2)_{0\text{-}6}CONR_2$、-OR、$-(CR_2)_{1\text{-}4}OR$、$-NR_2$、$-(CR_2)_{1\text{-}4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0\text{-}6}SO_3R$、$-(CR_2)_{0\text{-}6}SO_2NR_2$、$-(CR_2)_{0\text{-}6}OSO_2NR_2$、$-(CR_2)_{0\text{-}6}NRSO_2R$、$-(CR_2)_{0\text{-}6}NRSO_2OR$、$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}}$

${}_6$OP(O)(H)OR、-B(OR)$_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

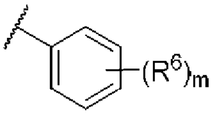
R、R^1、R^3、R^{B}及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

【0115】 在某些實施例中，本發明提供一種式**I-b-3**之化合物，其中環B1係苯基，特定言之為經取代之苯基。在其他實施例中，環B1不為苯基。舉例而言，環B1可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

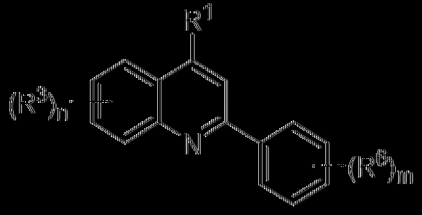
【0116】 在一些實施例中，本發明提供一種式**I-b-3**之化合物，其中R^{6}不為R^B。

【0117】 在某些實施例中，本發明提供一種式**I-b-3**之化合物，其中R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0118】 在某些實施例中，對於以上揭示的式**I-b-3**之化合物，m係1或2，且至少一個R^{6}包括末端-CO$_2$H基團。舉例而言，在某些情形中，至少一個R^{6}係-(CH$_2$)$_{0\text{-}4}$CO$_2$H。

【0119】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其中R^{2}係

，由此形成式**I-b-4**之化合物：



I-b-4

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

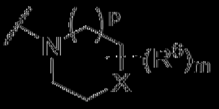
R、R^1、R^3、R^B及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

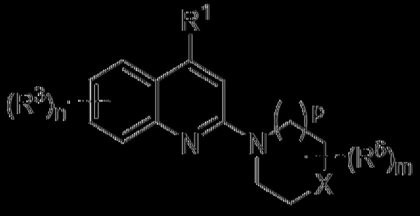
【0120】 在一些實施例中，本發明提供一種式I-b-4之化合物，其中R^6不為R^B。

【0121】 在某些實施例中，本發明提供一種式I-b-4之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0122】 在某些實施例中，對於以上揭示的式I-b-4之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0123】 在一些實施例中，本發明提供一種式I或式I*之化合物，其

中R^2係  ，由此形成式I-b-5之化合物：



I-b-5

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

X係不存在(亦即，為環中的鍵)、$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$；特定言之為$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$；更特定言之為$-CR_2-$、-NR-或-O-；

m係0、1、2、3或4，特定言之為1、2、3或4；

p係0、1或2，特定言之為1；且

R、R^1、R^3、R^B及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

[0124] 在一些實施例中，本發明提供一種式I-b-5之化合物，其中R^6不為R^B。

[0125] 在某些實施例中，本發明提供一種式I-b-5之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0126】 在某些實施例中，本發明提供一種式**I-b-5**之化合物，其中：

R^1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CR_2$、$=O$、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；

p係0或1，特定言之為1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0127】 在特定實施例中，本發明提供一種式**I-b-5**之化合物，其中：

R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CH_2$、$=O$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、-

$(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

X係$-CH_2-$、-NH-或-O-；

m係1、2、3或4，特定言之為1或2；

p係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0128】 在其他特定實施例中，本發明提供一種式**I-b-5**之化合物，其中：

R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CH_2$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$；

X係$-CH_2-$、-NH-或-O-；

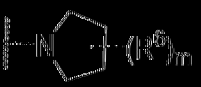
m係1或2；

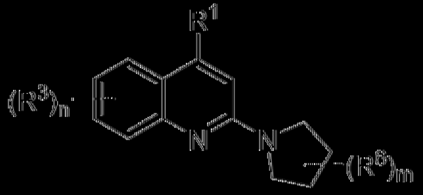
p係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於

喹啉環位在7-或8-位置之R^3係氯。

【0129】在某些實施例中，對於以上揭示的式I-b-5之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0130】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^2係，由此形成式I-b-6之化合物：



I-b-6

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、$=O$、$=CR_2$、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^1、R^3、R^B及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

【0131】在一些實施例中，本發明提供一種式I-b-6之化合物，其中R^6不為R^B。

【0132】在某些實施例中，本發明提供一種式I-b-6之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在

7-或8-位置之R^3係氯。

【0133】在某些實施例中，本發明提供一種式**I-b-6**之化合物，其中：

R^1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CR_2$、$=O$、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0134】在特定實施例中，本發明提供一種式**I-b-6**之化合物，其中：

R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CH_2$、$=O$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}CO(N$-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}(N$-吡唑)-$(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N$-吡唑)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}(N$-吡

咯)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-吡咯)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($苯基$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($苯基$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($環烷烴$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($環烷烴$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON\ (C_{1-4}$烷基$)_2$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2C_{1-4}$烷基、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2C_{1-4}$烷基、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHCF_3(CH_2)_{1-4}O-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^a{}_2$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aOH$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aCN$、$-(CH_2)_{1-4}O(CH_2)_{1-5}P(O)OH_2$、$-NH_2$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NR^aC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於

喹啉環位在7-或8-位置之R^3係氯。

【0135】 在其他特定實施例中，本發明提供一種式**I-b-6**之化合物，其中：

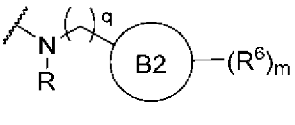
R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CH_2$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO$(*N*-脯胺酸)、$-(CH_2)_{0-4}CO$(*N*-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

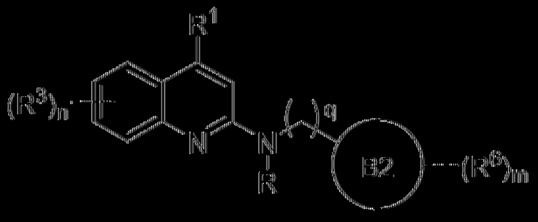
m係1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0136】 在某些實施例中，對於以上揭示的式**I-b-6**之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0137】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其中R^2係

，由此形成式**I-b-7**之化合物：



I-b-7

或其醫藥學上可接受之鹽，其中：

環B2係苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；

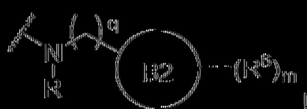
q係0、1或2；且

R、R^1、R^3、R^B及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

【0138】 在某些實施例中，本發明提供一種式I-b-7之化合物，其中環B2係苯基，特定言之為經取代之苯基。在其他實施例中，環B2不為苯基。舉例而言，環B2可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B2係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

【0139】 在一些實施例中，本發明提供一種式I-b-7之化合物，其中R^6不為R^B。

【0140】 在一些實施例中，本發明提供一種式I-b-7之化合物，其中

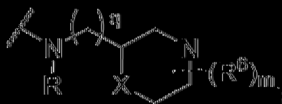


中之R係R^a，其係H或C_{1-6}烷基。

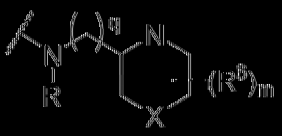
【0141】 在某些實施例中，本發明提供一種式I-b-7之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0142】 在某些實施例中，對於以上揭示的式I-b-7之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

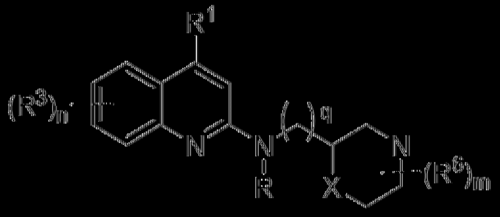
【0143】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^2係



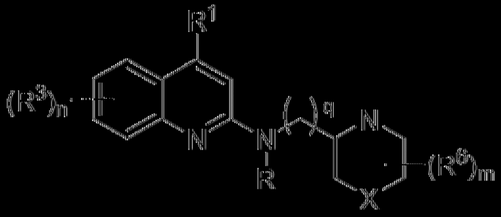
或



，由此分別形成式I-b-8或式I-b-8*之化合物：



I-b-8



I-b-8*

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係氫(僅在N上)、鹵素(不在N上)、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-}$

$_6$NRSO$_2$OR、-(CR$_2$)$_{0\text{-}6}$OP(OR)$_2$、-(CR$_2$)$_{0\text{-}6}$OP(O)(OR)$_2$、-(CR$_2$)$_{0\text{-}6}$P(O)(OR)$_2$、-(CR$_2$)$_{0\text{-}6}$OP(O)(H)OR、-B(OR)$_2$或R^B；

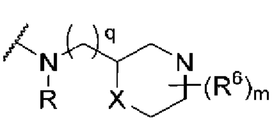
X係不存在(亦即，為環中的鍵)、-CR$_2$-、-NR-、-O-、-S-或-SO$_2$-，特定言之為-CR$_2$-、-NR-或-O；

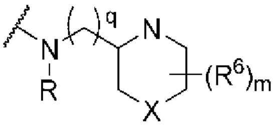
m係1、2、3或4；

q係0、1或2；且

R、R^1、R^3、R^{B}及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

【0144】 在一些實施例中，本發明提供一種式**I-b-8**或式**I-b-8***之化合物，其中R^{6}不為R^B。

【0145】 在一些實施例中，本發明提供一種式**I-b-8**或式**I-b-8***之化合物，其中

或

中之R係R^a，其係H或C$_{1\text{-}6}$烷基。

【0146】 在某些實施例中，本發明提供一種式**I-b-8**或式**I-b-8***之化合物，其中R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0147】 在某些實施例中，本發明提供一種式**I-b-8**或式**I-b-8***之化合物，其中：

R^{1}係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環(特定言之為咪唑或吡唑，包括1-咪唑或4-吡唑)；

每個R^{6}獨立地係鹵素、=O、-COR、-(CR$_2$)$_{0\text{-}6}$CO$_2$R、-(CR$_2$)$_{0\text{-}6}$CONR$_2$、-OR、-(CR$_2$)$_{1\text{-}4}$OR、-NR$_2$、-(CR$_2$)$_{1\text{-}4}$NR$_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR$_2$、-SR、-SO$_2$R、-S(O)R、-(CR$_2$)$_{0\text{-}6}$SO$_3$R、-

$(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；

q係1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0148】 在特定實施例中，本發明提供一種式**I-b-8**或式**I-b-8***之化合物，其中：

R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

每個R^6獨立地係鹵素、=O、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1、2、3或4，特定言之為1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於

喹啉環位在7-或8-位置之R^3係氯。

【0149】 在其他特定實施例中，本發明提供一種式I-b-8或式I-b-8*之化合物，其中：

R^1係視情況經取代之咪唑或吡唑，包括1-咪唑或4-吡唑，特定言之為未經取代之1-咪唑或4-吡唑；

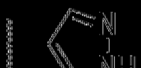
每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

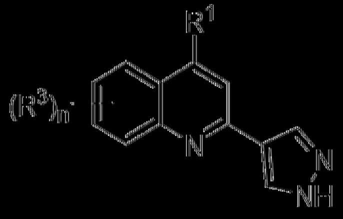
m係1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0150】 在某些實施例中，對於以上揭示的式I-b-8或I-b-8*之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0151】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^2係，由此形成式I-b-9之化合物：

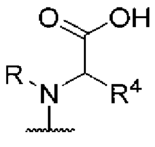


I-b-9

或其醫藥學上可接受之鹽，其中R、R^1、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

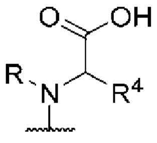
【0152】 在某些實施例中，本發明提供一種式**I-b-9**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0153】 在某些實施例中，本發明提供一種式**I-b-9**之化合物，其中：

R^1係  ，其中R及R^4獨立地係氫或視情況經取代之C_{1-6}脂族基；且

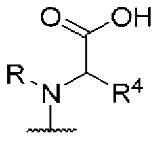
每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0154】 在特定實施例中，本發明提供一種式**I-b-9**之化合物，其中：

R^1係  ，其中R及R^4獨立地係氫或低碳數烷基，特定言之為甲基；且

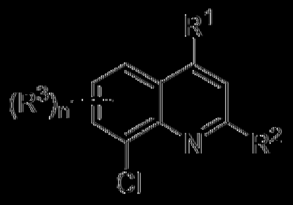
每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0155】 在其他特定實施例中，本發明提供一種式**I-b-9**之化合物，其中：

R^1係  ，其中R係氫且R^4係氫或低碳數烷基，特定言之為甲基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

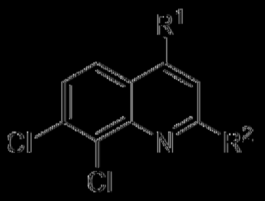
【0156】在一些實施例中，本發明提供一種式I或式I*之化合物，其中至少一個R^3係鹵素，諸如在8位之氯，由此形成式I-c-1之化合物：



I-c-1

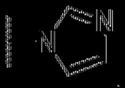
或其醫藥學上可接受之鹽，其中單獨地及組合地，R^1、R^2及R^3各自如上文所定義且描述於本文實施例中，且n係0、1、2或3。

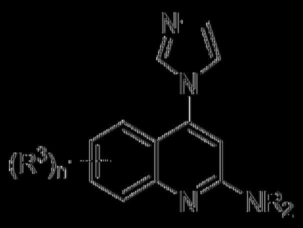
【0157】在一些實施例中，本發明提供一種式I或式I*之化合物，其中n係2且R^3係在7位及8位之氯，由此形成式I-c-2之化合物：



I-c-2

或其醫藥學上可接受之鹽，其中R^1及R^2各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0158】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係$-NR_2$，由此形成式I-d-1之化合物：

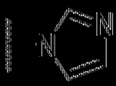


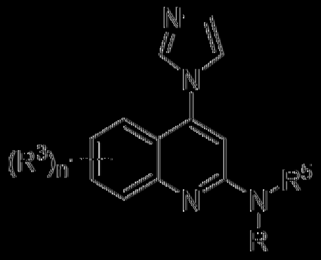
I-d-1

或其醫藥學上可接受之鹽，其中R、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0159】在某些實施例中，本發明提供一種式I-d-1之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在

7-或8-位置之R^3係氫。

【0160】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係-NRR^5，由此形成式I-d-2之化合物：



I-d-2

或其醫藥學上可接受之鹽，其中：

R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-4}NR^aC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0161】 在某些實施例中，本發明提供一種式I-d-2之化合物，其中R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-4}NR^aC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$。

【0162】 在一些實施例中，本發明提供一種式I-d-2之化合物，其中R^5不為R^B。

【0163】 在一些實施例中，本發明提供一種式**I-d-2**之化合物，其中$-NRR^5$中之R係R^a，其係H或C_{1-6}烷基。

【0164】 在某些實施例中，本發明提供一種式**I-d-2**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0165】 在特定實施例中，本發明提供一種式**I-d-2**之化合物，其中：

$-NRR^5$中之R係H或低碳數烷基，特定言之為甲基；

R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{2-4}OC_{1-4}$烷基、$-(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{2-4}SO_3H$、$-(CH_2)_{2-4}SO_3C_{1-4}$烷基、$-(CH_2)_{2-4}SO_2NH_2$、$-(CH_2)_{2-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{2-4}SO_2N(C_{1-4}$烷基$)_2$、$-(CH_2)_{2-4}OSO_2NH_2$、$-(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{2-4}NR^aSO_3H$、$-(CH_2)_{1-4}OP(OH)_2$、$-(CH_2)_{1-4}P(O)(OH)_2$、$-(CH_2)_{1-4}P(O)(OH)(OC_{1-4}$烷基$)$或$-(CH_2)_{2-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

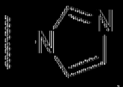
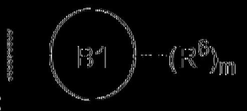
【0166】 在其他特定實施例中，本發明提供一種式**I-d-2**之化合物，其中：

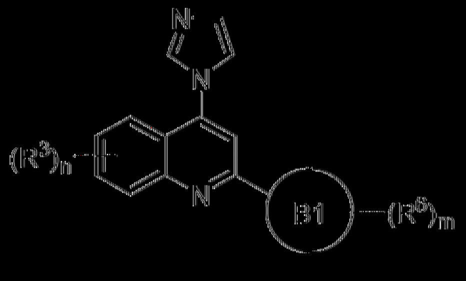
-NRR^{5}中之R係H或低碳數烷基，特定言之為甲基；

R^{5}係-$(CH_2)_{2-4}OH$、-$(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、-$(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{0-3}CH(CH_2OH)_2$、-$(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}CONH_2$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、-$(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、-$(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{2-4}SO_3H$、-$(CH_2)_{2-4}SO_2NH_2$、-$(CH_2)_{2-4}SO_2NR^aC_{1-4}$烷基、-$(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、-$(CH_2)_{1-4}P(O)(OH)_2$或-$(CH_2)_{2-4}OP(O)(H)OH$，其中R^{a}在每次出現時獨立地係H或C$_{1-4}$烷基；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0167】 在某些實施例中，對於以上揭示的式I-d-2之化合物，R^{5}包括末端-CO$_2$H基團。舉例而言，在某些情形中，R^{5}包括末端-$(CH_2)_{0-4}CO_2H$基團。

【0168】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^{1}係且R^{2}係 ，由此形成式I-d-3之化合物：



I-d-3

或其醫藥學上可接受之鹽，其中：

環B1係苯基，較佳地為經取代之苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基

環；

每個R^6獨立地係鹵素、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

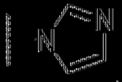
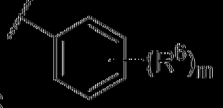
【0169】 在某些實施例中，本發明提供一種式**I-d-3**之化合物，其中環B1係苯基，特定言之為經取代之苯基。在其他實施例中，環B1不為苯基。舉例而言，環B1可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

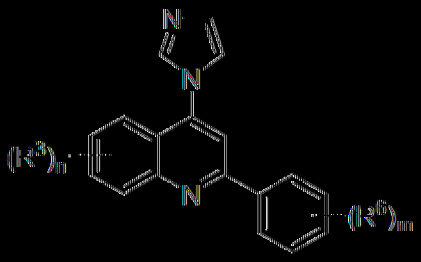
【0170】 在一些實施例中，本發明提供一種式**I-d-3**之化合物，其中R^6不為R^B。

【0171】 在某些實施例中，本發明提供一種式**I-d-3**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0172】 在某些實施例中，對於以上揭示的式**I-d-3**之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至

少一個R^6係-$(CH_2)_{0-4}CO_2H$。

【0173】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-d-4之化合物：



I-d-4

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

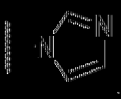
R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

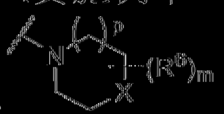
【0174】 在一些實施例中，本發明提供一種式I-d-4之化合物，其中R^6不為R^B。

【0175】 在某些實施例中，本發明提供一種式I-d-4之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

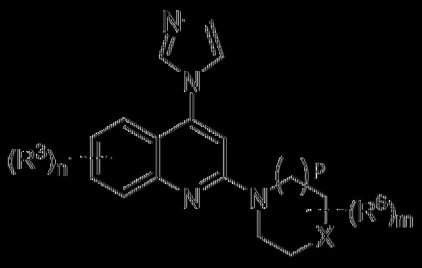
【0176】 在某些實施例中，對於以上揭示的式I-d-4之化合物，m係

1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0177】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係 

且R^2係 

，由此形成式I-d-5之化合物：



I-d-5

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、=O、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

X係$-CR_2-$、$-NR-$、$-O-$、$-S-$或$-SO_2-$，特定言之為$-CR_2-$、$-NR-$或$-O-$；

m係0、1、2、3或4，特定言之為1、2、3或4；

p係0、1或2，特定言之為1；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0178】 在一些實施例中，本發明提供一種式I-d-5之化合物，其中R^6不為R^B。

【0179】 在某些實施例中，本發明提供一種式**I-d-5**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0180】 在特定實施例中，本發明提供一種式**I-d-5**之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CH_2$、$=O$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2C_{1-4}$烷基、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2C_{1-4}$烷基、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHCF_3(CH_2)_{1-4}O-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^a{}_2$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aOH$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aCN$、$-(CH_2)_{1-4}O(CH_2)_{1-5}P(O)OH_2$、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}($*N*-吡唑$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-吡唑$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}($*N*-吡咯$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-吡咯$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($苯基$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($苯基$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($環烷烴$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($環烷烴$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON\ (C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{0-}$

$_4NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}N[(CH_2)_{1-4}CO_2C_{1-4}$烷基$]_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

X係$-CH_2-$、-NH-或-O-；

m係1、2、3或4，特定言之為1或2；

p係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0181】 在其他特定實施例中，本發明提供一種式**I-b-5**之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$=CH_2$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N$-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{0-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$；

X係$-CH_2-$、-NH-或-O-；

m係1或2；

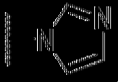
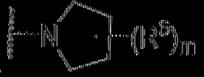
p係1；且

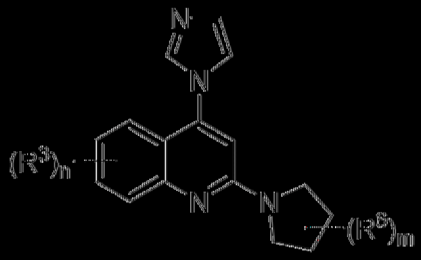
每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0182】 在特定實施例中，本發明提供一種式**I-b-5**之化合物，其中

每個R^6獨立地係氟、-甲基、-甲氧基、$-(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基或-OH；且m係1、2或3，特定言之為1或2。

【0183】 在某些實施例中，對於以上揭示的式I-d-5之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0184】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-d-6之化合物：



I-d-6

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0185】 在一些實施例中，本發明提供一種式I-d-6之化合物，其中

R^6不為R^B。

【0186】 在某些實施例中，本發明提供一種式**I-d-6**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0187】 在某些實施例中，本發明提供一種式**I-d-6**之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-C_{3-6}$環烷基、$=CR_2$、$=O$、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0188】 在特定實施例中，本發明提供一種式**I-d-6**之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-C_{3-6}$環烷基、$=CH_2$、$=O$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2C_{1-4}$烷基、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2C_{1-4}$烷基、-

$CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHCF_3(CH_2)_{1-4}O-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^a{}_2$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aOH$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aCN$、$-(CH_2)_{1-4}O(CH_2)_{1-5}P(O)OH_2$、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO(N-$脯胺酸)、$-(CH_2)_{0-4}CO(N-$吡咯啶-3-羧酸)、$-(CH_2)_{0-4}(N-$吡唑$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N-$吡唑$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}(N-$吡咯$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N-$吡咯$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($苯基$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($苯基$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($環烷烴$)-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($環烷烴$)-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-NH_2$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NR^aC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於

喹啉環位在7-或8-位置之R^3係氯。

【0189】 在其他特定實施例中，本發明提供一種式**I-d-6**之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-C_{3-6}$環烷基、$=CH_2$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO$(*N*-脯胺酸)、$-(CH_2)_{0-4}CO$(*N*-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

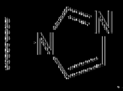
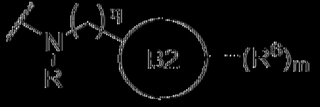
m係1或2；且

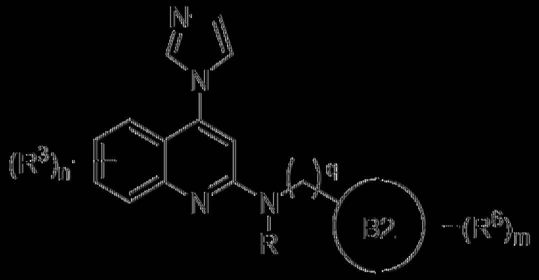
每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0190】 在其他特定實施例中，本發明提供一種式**I-d-6**之化合物，其中每個R^6獨立地係氟、-甲基、環己基、-甲氧基、-OtBu、$-CF_3$、$-(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基或-OH；且m係1、2或3，特定言之為1或2。

【0191】 在某些實施例中，對於以上揭示的式**I-d-6**之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0192】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其

中R^1係且R^2係，由此形成式I-d-7之化合物：



I-d-7

或其醫藥學上可接受之鹽，其中：

環B2係苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；

q係0、1或2；且

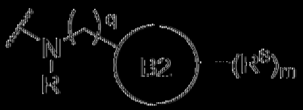
R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0193】 在某些實施例中，本發明提供一種式I-d-7之化合物，其中環B2係苯基，特定言之為經取代之苯基。在其他實施例中，環B2不為苯基。舉例而言，環B2可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例

中，環B2係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

【0194】 在一些實施例中，本發明提供一種式I-d-7之化合物，其中R^6不為R^B。

【0195】 在一些實施例中，本發明提供一種式I-d-7之化合物，其中

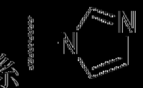


中之R係R^a，其係H或C_{1-6}烷基。

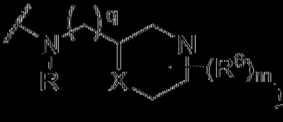
【0196】 在某些實施例中，本發明提供一種式I-d-7之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0197】 在某些實施例中，對於以上揭示的式I-d-7之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

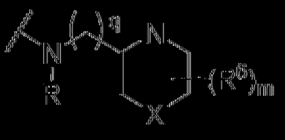
【0198】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係



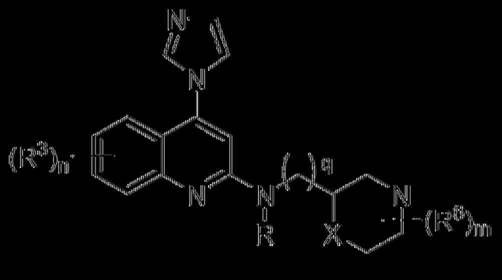
且R^2係



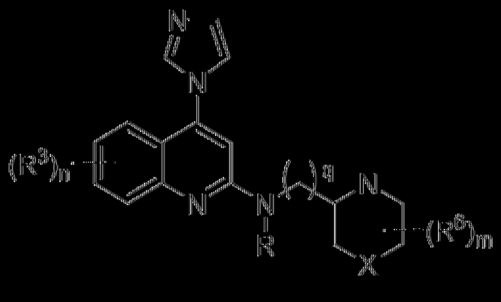
或



，由此分別形成式I-d-8或式I-d-8*之化合物：



I-d-8



I-d-8*

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係氫(僅在N上)、鹵素(不在N上)、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$ 、 -OR 、 -$(CR_2)_{1-4}OR$ 、 -NR_2 、 -$(CR_2)_{1-4}NR_2$ 、 -

NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；

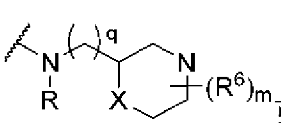
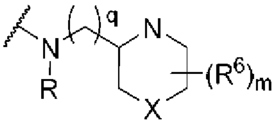
X係-CR_2-、-NR-、-O-、-S-或-SO_2-，特定言之為-CR_2-、-NR-或-O；

m係1、2、3或4；

q係0、1或2；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0199】 在一些實施例中，本發明提供一種式**I-d-8**或式**I-d-8***之化合物，其中R^6不為R^B。

【0200】 在一些實施例中，本發明提供一種式**I-d-8**或式**I-d-8***之化合物，其中  或  中之R係R^a，其係H或C_{1-6}烷基。

【0201】 在某些實施例中，本發明提供一種式**I-d-8**或式**I-d-8***之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0202】 在某些實施例中，本發明提供一種式**I-d-8**或式**I-d-8***之化合物，其中：

每個R^6獨立地係鹵素、=O、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-

$(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；

q係1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0203】 在特定實施例中，本發明提供一種式**I-d-8**或式**I-d-8***之化合物，其中：

每個R^6獨立地係鹵素、=O、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1、2、3或4，特定言之為1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0204】 在其他特定實施例中，本發明提供一種式**I-d-8**或式**I-d-8***

之化合物，其中：

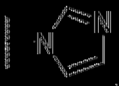
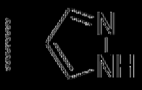
每個R^6獨立地係鹵素、-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}CO$(*N*-脯胺酸)、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-OH、-$(CH_2)_{1-4}OH$、-$(CH_2)_{0-4}SO_3H$、-$(CH_2)_{0-4}SO_2NH_2$、-$(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、-$(CH_2)_{0-4}OP(OH)_2$或-$(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

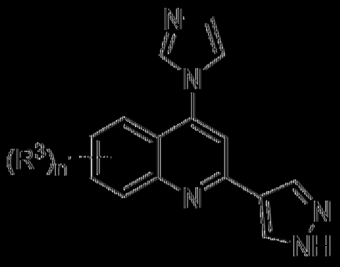
m係1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0205】 在某些實施例中，對於以上揭示的式I-d-8或I-d-8*之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

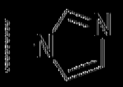
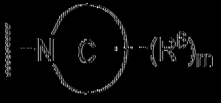
【0206】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-d-9之化合物：

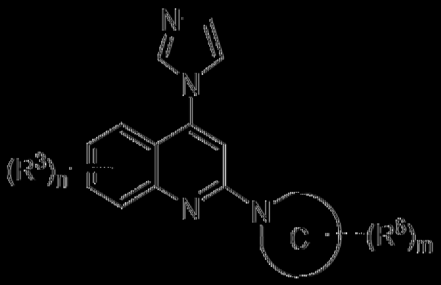


I-d-9

或其醫藥學上可接受之鹽，其中R、R^1、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0207】 在某些實施例中，本發明提供一種式I-d-9之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0208】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-d-10之化合物：



I-d-10

或其醫藥學上可接受之鹽，其中：

環C係吡咯基或具有0至3個獨立地選自氮、氧及硫之雜原子(除環C中已描繪之氮外)的4至10員飽和或部分不飽和單環、雙環、橋連雙環或螺環雜環；

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係1、2、3或4；且

R、R^B、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0209】 在一些實施例中，本發明提供一種式I-d-10之化合物，其中環C係氮雜環丁烷基、吡咯基、2,3-二氫-1H-吡咯基、吡咯啶基、哌啶基、味啉基、噻唑啶基、吲哚啉基、異吲哚啉基、八氫吲哚基、氮雜環庚烷基、氧氮雜環庚烷、氮雜雙環己烷、氮雜雙環庚烷、氮雜雙環辛烷、氮

雜雙環壬烷、氮雜螺庚烷或八氫環戊并吡咯。

【0210】在特定實施例中，本發明提供一種式**I-d-10**之化合物，其中環C係吡咯基、2-氮雜雙環[3.1.0]己基、3-氮雜雙環[3.1.0]己烷、5-氮雜螺[2.4]庚基或八氫環戊并[b]吡咯基。

【0211】在特定實施例中，本發明提供一種式**I-d-10**之化合物，其中環C係3-羥基脯胺酸、C_{1-6}烷基3-羥基脯胺酸酯或C_{1-6}鹵烷基3-羥基脯胺酸酯。

【0212】在一些實施例中，本發明提供一種式**I-d-10**之化合物，其中：

每個R^6獨立地係氟、-CN、甲基、$-C_{3-6}$環烷基、$-CF_3$、$-CO_2H$、$-NH_2$、-OH、$-OC_{1-4}$烷基、$=CH_2$、=O、四唑基、咪唑基、噻吩基、1,2,4-噁二唑-3(2H)-酮基、味啉基、苯基、$-(CH_2)_{1-4}OC_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2C_{1-4}$烷基、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2C_{1-4}$烷基、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHOH-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CONR^a{}_2$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aOH$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aCN$、$-(CH_2)_{1-4}O(CH_2)_{1-5}P(O)OH_2$、$-CH(OH)CF_3$、$-COH(CF_3)_2$、$-(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CHCHCO_2H$、$-(CH_2)_{0-4}CHCHCO_2C_{1-4}$烷基、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基、$-OCOC_{1-4}$烷基、$-O(CH_2)_{1-4}CO_2H$、$-O(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-OCONR^a(CH_2)_{0-4}CO_2H$、-

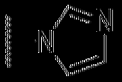
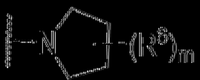
$OCONR^a(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-OCO-($*N*-味啉)、$-CONH_2$、$-CONHOH$、$-CONHOC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}($吡咯啶-2-酮)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}($哌啶-2-酮)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}C(OH)(CF_3)_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}CONR^aSO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO($*N*-吡咯啶)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-吡咯啶)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}($*N*-吡唑)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-吡唑)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}($*N*-吡咯)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-吡咯)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O-($苯基)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O-($苯基)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O($環烷烴)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O($環烷烴)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO($*N*-吡咯啶)$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}CO($*N*-吡咯啶)-(四唑)、$-(CH_2)_{0-4}CO($*N*-哌啶)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO($*N*-哌啶)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO($*N*-味啉)$-(CH_2)_{0-4}CO_2H$、$-CONR^a($雙環[1.1.1]戊烷)$-(CH_2)_{0-4}CO_2H$、$-NH_2$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}N[(CH_2)_{1-4}CO_2C_{1-4}$烷基$]_2$、$-(CH_2)_{0-4}NR^aCO($異噚唑$)-OH$、$-(CH_2)_{0-4}NR^aSO_2($苯$)-CO_2H$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}($咪唑啶-2,4-二酮)、$-(CH_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；且

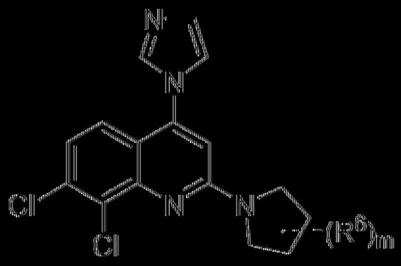
m係1、2、3或4。

【0213】 在特定實施例中，本發明提供一種式**I-d-10**之化合物，其中每個R^6獨立地係氟、-甲基、環己基、$-CF_3$、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基或-OH；且m係1、2或3，特定言之為1或2。

【0214】 在特定實施例中，本發明提供一種式I-d-10之化合物，其中每個R^6獨立地係氟、-甲基、環己基、$-CF_3$、-甲氧基、$-(CH_2)_{1\text{-}5}CO_2H$、$-(CH_2)_{1\text{-}5}CO_2C_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}O(CH_2)_{1\text{-}5}CO_2H$、$-(CH_2)_{0\text{-}4}O(CH_2)_{1\text{-}5}CO_2C_{1\text{-}4}$烷基或-OH；且m係1、2或3，特定言之為1或2。

【0215】 在某些實施例中，本發明提供一種式I-d-10之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0216】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係，R^2係，且R^3係在7位及8位之氯，由此形成式I-d-11之化合物：



I-d-11

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0\text{-}6}CO_2R$、$-(CR_2)_{0\text{-}6}CONR_2$、-OR、$-(CR_2)_{1\text{-}4}OR$、$-NR_2$、$-(CR_2)_{1\text{-}4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0\text{-}6}SO_3R$、$-(CR_2)_{0\text{-}6}SO_2NR_2$、$-(CR_2)_{0\text{-}6}OSO_2NR_2$、$-(CR_2)_{0\text{-}6}NRSO_2R$、$-(CR_2)_{0\text{-}6}NRSO_2OR$、$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(H)OR$、$-B(OR)_2$或$R^B$；

m係1、2、3或4；且

R及R^B各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0217】 在一些實施例中，本發明提供一種式**I-d-11**之化合物，其中：

每個R^6獨立地係氟、-CN、甲基、=O、=CH_2、-C_{3-6}環烷基、-CF_3、-CO_2H、-NH_2、-OH、-OC_{1-4}烷基、四唑基、咪唑基、噻吩基、1,2,4-噚二唑-3(2H)-酮基、味啉基、苯基、-$(CH_2)_{1-4}OC_{1-4}$烷基、-$(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、-$(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2H$、-$(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2C_{1-4}$烷基、-$(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2H$、-$(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2C_{1-4}$烷基、-$(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2H$、-$(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2C_{1-4}$烷基、-$CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、-$CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、-$CHCF_3(CH_2)_{1-4}O$-$(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{1-4}O(CH_2)_{1-5}CONR^a{}_2$、-$(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aOH$、-$(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aCN$、-$(CH_2)_{1-4}O(CH_2)_{1-5}P(O)OH_2$、-$CH(OH)CF_3$、-$COH(CF_3)_2$、-$(CH_2)_{1-5}CO_2H$、-$(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}CHCHCO_2H$、-$(CH_2)_{0-4}CHCHCO_2C_{1-4}$烷基、-$CO_2C_{1-4}$烷基、-$CO_2C_{1-4}$鹵烷基、-$OCOC_{1-4}$烷基、-$O(CH_2)_{1-4}CO_2H$、-$O(CH_2)_{1-4}CO_2C_{1-4}$烷基、-$OCONR^a(CH_2)_{0-4}CO_2H$、-$OCONR^a(CH_2)_{0-4}CO_2C_{1-4}$烷基、-OCO-(*N*-味啉)、-$CONH_2$、-CONHOH、-$CONHOC_{1-4}$烷基、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}$(吡咯啶-2-酮)、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}$(哌啶-2-酮)、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}C(OH)(CF_3)_2$、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、-$(CH_2)_{0-4}CONR^aSO_2C_{1-4}$鹵烷基、-$(CH_2)_{0-4}CO$(*N*-吡咯啶)-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}CO$(*N*-吡咯啶)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}$(*N*-吡

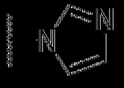
唑)-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}CO$(*N*-吡唑)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}$(*N*-吡咯)-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}CO$(*N*-吡咯)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}$-O(苯基)-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}$-O(苯基)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}$-O(環烷烴)-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}$-O(環烷烴)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}CO$(*N*-吡咯啶)-$(CH_2)_{0-4}SO_2NH_2$、-$(CH_2)_{0-4}CO$(*N*-吡咯啶)-(四唑)、-$(CH_2)_{0-4}CO$(*N*-哌啶)-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}CO$-(*N*-哌啶)-$(CH_2)_{0-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}CO$(*N*-味啉)-$(CH_2)_{0-4}CO_2H$、-$CONR^a$(雙環[1.1.1]戊烷)-$(CH_2)_{0-4}CO_2H$、-NH_2、-$(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2H$、-$(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}N[(CH_2)_{1-4}CO_2C_{1-4}$烷基$]_2$、-$(CH_2)_{0-4}NR^aCO$(異噚唑)OH、-$(CH_2)_{0-4}NR^aSO_2$(苯基)-$CO_2H$、-$(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、-$(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}$(咪唑啶-2,4-二酮)、-$(CH_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；且

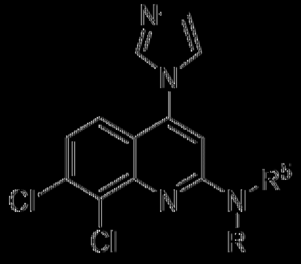
m係1、2、3或4。

【0218】在特定實施例中，本發明提供一種式**I-d-11**之化合物，其中每個R^6獨立地係氟、=O、=CH_2、-甲基、環己基、-CF_3、-CO_2H、-CO_2C_{1-4}烷基、-CO_2C_{1-4}鹵烷基或-OH；m係1、2或3，特定言之為1或2。

【0219】在特定實施例中，本發明提供一種式**I-d-11**之化合物，其中每個R^6獨立地係氟、=O、=CH_2、-甲基、環己基、-CF_3、-甲氧基、-OtBu、-$(CH_2)_{1-5}CO_2H$、-$(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、-$(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、-$(CH_2)_{1-4}O(CH_2)_{1-5}CONR^a{}_2$或-OH；且m係1、2或3，特定言之為1或2。

【0220】在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其

中R^1係，R^2係$-NRR^5$，且R^3係在7位及8位之氯，由此形成式I-d-12之化合物：



I-d-12

或其醫藥學上可接受之鹽，其中：

R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}NRCOR$、$-(CR_2)_{0-4}NR^aC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$；且

R及R^B各自如上文所定義且單獨及以組合形式描述於本文實施例中。

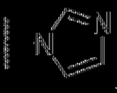
【0221】 在一些實施例中，本發明提供一種式I-d-12之化合物，其中R^5不為R^B。

【0222】 在特定實施例中，本發明提供一種式I-d-12之化合物，其中R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{2-4}OC_{1-4}$烷基、$-(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CHMe)CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、-

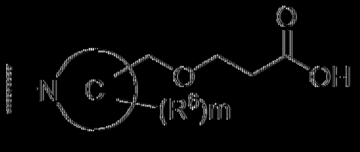
$(CH_2)_{2\text{-}4}SO_3H$、$-(CH_2)_{2\text{-}4}SO_3C_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}SO_2NH_2$、$-(CH_2)_{1\text{-}4}C(O)NR^a(CH_2)_{2\text{-}4}SO_2NH_2$、$-(CH_2)_{1\text{-}4}CO$(*N*-吡咯啶)$-SO_2NH_2$、$-(CH_2)_{2\text{-}4}SO_2NHC_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}SO_2N(C_{1\text{-}4}$烷基$)_2$、$-(CH_2)_{2\text{-}4}OSO_2NH_2$、$-(CH_2)_{2\text{-}4}NR^a(CH_2)_{2\text{-}4}CO_2H$、$-(CH_2)_{2\text{-}4}NR^aCO(CH_2)_{2\text{-}4}CO_2H$、$-(CH_2)_{2\text{-}4}NR^aCO$(環戊烷)$-CO_2H$、$-(CH_2)_{2\text{-}4}NR^aCO$(苯)$-OH$、$-(CH_2)_{2\text{-}4}NR^aCO$(苯)$-CO_2H$、$-(CH_2)_{2\text{-}4}NR^aSO_3H$、$-(CH_2)_{2\text{-}4}NR^aSO_2C_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}NR^aSO_2(CH_2)_{2\text{-}4}OH$、$-(CH_2)_{2\text{-}4}NR^aSO_2(CH_2)_{2\text{-}4}OC_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}NR^aSO_2(CH_2)_{2\text{-}4}CO_2H$、$-(CH_2)_{2\text{-}4}NR^aSO_2$(苯)$-CO_2H$、$-(CH_2)_{2\text{-}4}NR^aSO_2$(苯)$-CO_2C_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}SO_2NR^a(CH_2)_{2\text{-}4}OH$、$-(CH_2)_{2\text{-}4}$(*N*-糖精)、$-(CH_2)_{2\text{-}4}SO_2NR^a(CH_2)_{2\text{-}4}CO_2H$、$-(CH_2)_{2\text{-}4}SO_2NR^a$(環戊烷)$-CO_2H$、$-(CH_2)_{2\text{-}4}NR^a$(環己烷)$-CO_2C_{1\text{-}4}$烷基、$-(CH_2)_{2\text{-}4}SO_2$(*N*-吡咯啶)$-CO_2H$、$-(CH_2)_{2\text{-}4}SO_2$(*N*-哌啶)$-CO_2H$、$-(CH_2)_{1\text{-}4}OP(OH)_2$、$-(CH_2)_{1\text{-}4}P(O)(OH)_2$、$-(CH_2)_{1\text{-}4}P(O)(OH)(OC_{1\text{-}4}$烷基)或$-(CH_2)_{2\text{-}4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H、$C_{1\text{-}4}$烷基或$-SO_2C_{1\text{-}4}$烷基。

【0223】在一些實施例中，本發明提供一種式I-d-12之化合物，其中$-NRR^5$中之R係R^a，其係H或$C_{1\text{-}6}$烷基，特定言之為甲基。

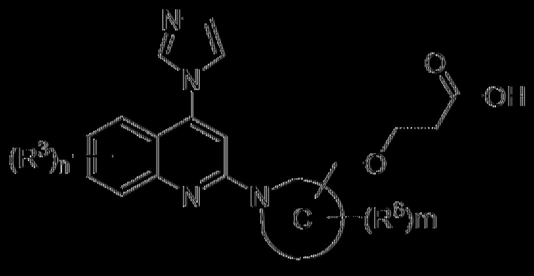
【0224】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係



且R^2係



，由此形成式I-d-13之化合物：



I-d-13

或其醫藥學上可接受之鹽，其中：

環C係吡咯基或具有0至3個獨立地選自氮、氧及硫之雜原子(除環C中已描繪之氮外)的4至10員飽和或部分不飽和單環、雙環、橋連雙環或螺環雜環；

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2或3；且

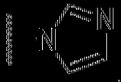
R、R^B、R^3及n各自係如上文所定義且單獨及以組合形式描述於本文實施例中。

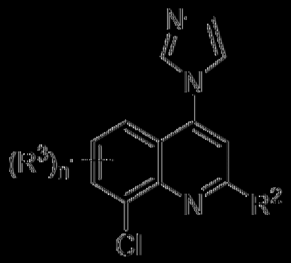
【0225】 在一些實施例中，本發明提供一種式**I-d-13**之化合物，其中環C係氮雜環丁烷基、吡咯基、2,3-二氫-1H-吡咯基、吡咯啶基、哌啶基、味啉基、噻唑啶基、吲哚啉基、異吲哚啉基、八氫吲哚基、氮雜環庚烷基、氧氮雜環庚烷、氮雜雙環己烷、氮雜雙環庚烷、氮雜雙環辛烷、氮雜雙環壬烷、氮雜螺庚烷或八氫環戊并吡咯。

【0226】 在特定實施例中，本發明提供一種式**I-d-13**之化合物，其中每個R^6獨立地係氟、-甲基、=O、$=CH_2$、-環己基、苯基、味啉基、-OMe、-OtBu、$-CF_3$、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基或-OH；且m係0或1或2，特定言之為0或1。

【0227】 在某些實施例中，本發明提供一種式**I-d-13**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位

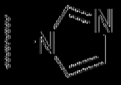
在7-或8-位置之R^3係氯。

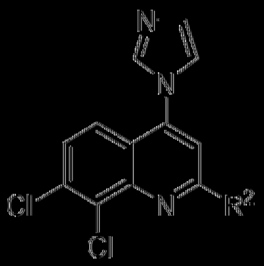
【0228】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且至少一個R^3係鹵素，諸如在8位之氯，由此形成式I-e-1之化合物：



I-e-1

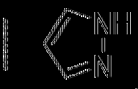
或其醫藥學上可接受之鹽，其中單獨地及組合地，R^2及R^3各自如上文所定義且描述於本文實施例中，且n係0、1、2或3。

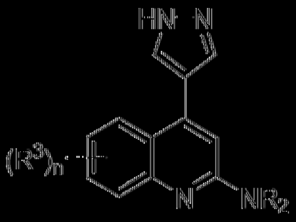
【0229】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係，n係2，且R^3係在7位及8位之氯，由此形成式I-e-2之化合物：



I-e-2

或其醫藥學上可接受之鹽，其中R^2係如上文所定義且描述於本文實施例中。

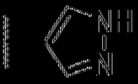
【0230】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係$-NR_2$，由此形成式I-f-1之化合物：

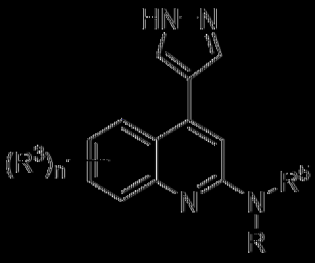


I-f-1

或其醫藥學上可接受之鹽，其中R、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0231】 在某些實施例中，本發明提供一種式I-f-1之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0232】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係-NRR^5，由此形成式I-f-2之化合物：



I-f-2

或其醫藥學上可接受之鹽，其中：

R^5係-$(CR_2)_{2\text{-}4}OR$、-$(CR_2)_{0\text{-}6}CO_2R$、-$(CR_2)_{0\text{-}6}CONR_2$、-$(CR_2)_{0\text{-}6}C(O)NR(CR_2)_{0\text{-}6}CO_2R$、-$(CR_2)_{0\text{-}6}C(O)NR(CR_2)_{0\text{-}6}CONR_2$、-$(CR_2)_{0\text{-}4}NRC(O)R$、-$(CR_2)_{0\text{-}6}SO_3R$、-$(CR_2)_{0\text{-}6}SO_2NR_2$、-$(CR_2)_{0\text{-}6}OSO_2NR_2$、-$(CR_2)_{0\text{-}6}NRSO_2R$、-$(CR_2)_{0\text{-}6}NRSO_2OR$、-$(CR_2)_{0\text{-}6}OP(OR)_2$、-$(CR_2)_{0\text{-}6}OP(O)(OR)_2$、-$(CR_2)_{0\text{-}6}P(O)(OR)_2$、-$(CR_2)_{0\text{-}6}OP(O)(H)OR$或$R^B$；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0233】 在某些實施例中，本發明提供一種式I-f-2之化合物，其中

R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$。

【0234】 在一些實施例中，本發明提供一種式**I-f-2**之化合物，其中R^5不為R^B。

【0235】 在一些實施例中，本發明提供一種式**I-f-2**之化合物，其中$-NRR^5$中之R係R^a，其係H或C_{1-6}烷基。

【0236】 在某些實施例中，本發明提供一種式**I-f-2**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0237】 在特定實施例中，本發明提供一種式**I-f-2**之化合物，其中：

$-NRR^5$中之R係H或低碳數烷基，特定言之為甲基；

R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{2-4}OC_{1-4}$烷基、$-(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{2-4}SO_3H$、$-(CH_2)_{2-4}SO_3C_{1-4}$烷基、$-(CH_2)_{2-4}SO_2NH_2$、$-(CH_2)_{2-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{2-}$

$_4SO_2N(C_{1-4}$烷基$)_2$、$-(CH_2)_{2-4}OSO_2NH_2$、$-(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{2-4}NR^aSO_3H$、$-(CH_2)_{1-4}OP(OH)_2$、$-(CH_2)_{1-4}P(O)(OH)_2$、$-(CH_2)_{1-4}P(O)(OH)(OC_{1-4}$烷基$)$或$-(CH_2)_{2-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0238】 在其他特定實施例中，本發明提供一種式**I-f-2**之化合物，其中：

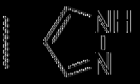
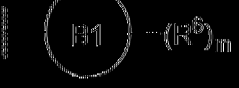
$-NRR^5$中之R係H或低碳數烷基，特定言之為甲基；

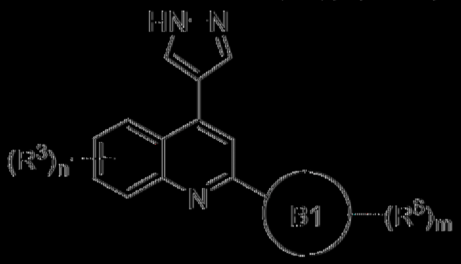
R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}NR^aC(O)(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{2-4}SO_3H$、$-(CH_2)_{2-4}SO_2NH_2$、$-(CH_2)_{2-4}SO_2NR^aC_{1-4}$烷基、$-(CH_2)_{2-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{1-4}P(O)(OH)_2$或$-(CH_2)_{2-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0239】 在某些實施例中，對於以上揭示的式**I-f-2**之化合物，R^5包括末端$-CO_2H$基團。舉例而言，在某些情形中，R^5包括末端$-(CH_2)_{0-4}CO_2H$基團。

【0240】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其

中R^1係且R^2係，由此形成式I-f-3之化合物：



I-f-3

或其醫藥學上可接受之鹽，其中：

環B1係苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

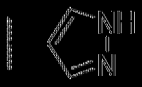
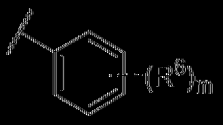
【0241】 在某些實施例中，本發明提供一種式I-f-3之化合物，其中環B1係苯基，特定言之為經取代之苯基。在其他實施例中，環B1不為苯基。舉例而言，環B1可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜

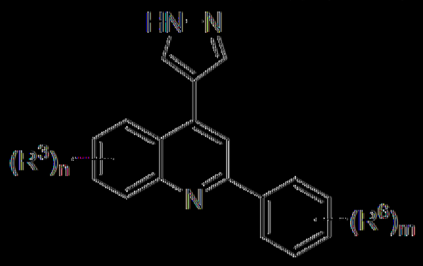
芳基環。

【0242】 在一些實施例中，本發明提供一種式I-f-3之化合物，其中R^6不為R^B。

【0243】 在某些實施例中，本發明提供一種式I-f-3之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0244】 在某些實施例中，對於以上揭示的式I-f-3之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

【0245】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-f-4之化合物：



I-f-4

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

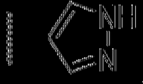
R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

[0246] 在一些實施例中，本發明提供一種式I-f-4之化合物，其中R^6不為R^B。

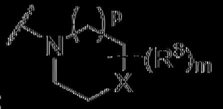
[0247] 在某些實施例中，本發明提供一種式I-f-4之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

[0248] 在某些實施例中，對於以上揭示的式I-f-4之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

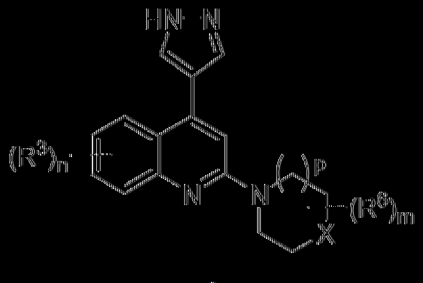
[0249] 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係



且R^2係



，由此形成式I-f-5之化合物：



I-f-5

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、=O、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；

X係$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$，特定言之為$-CR_2-$、-NR-或-O；

m係0、1、2、3或4，特定言之為1、2、3或4；

p係0、1或2，特定言之為1；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0250】 在一些實施例中，本發明提供一種式**I-f-5**之化合物，其中R^6不為R^B。

【0251】 在某些實施例中，本發明提供一種式**I-f-5**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0252】 在特定實施例中，本發明提供一種式**I-f-5**之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-C_{3-6}$環烷基、$=CH_2$、=O、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-}$

$_4$OP(O)(H)OH，其中R^{a}在每次出現時獨立地係H或C$_{1-4}$烷基；

X係-CH$_2$-、-NH-或-O-；

m係1、2、3或4，特定言之為1或2；

p係1；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0253】 在其他特定實施例中，本發明提供一種式**I-f-5**之化合物，其中：

每個R^{6}獨立地係鹵素、-C$_{1-4}$烷基、-C$_{1-4}$鹵烷基、-C$_{3-6}$環烷基、=CH$_2$、-(CH$_2$)$_{0-4}$CO$_2$H、-(CH$_2$)$_{1-4}$O(CH$_2$)$_{1-5}$CO$_2$H、-(CH$_2$)$_{1-4}$O(CH$_2$)$_{1-5}$CO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$CO(*N*-脯胺酸)、-(CH$_2$)$_{0-4}$C(O)NR^a(CH$_2$)$_{1-4}$CO$_2$H、-OH、-(CH$_2$)$_{1-4}$OH、-(CH$_2$)$_{0-4}$SO$_3$H、-(CH$_2$)$_{0-4}$SO$_2$NH$_2$、-(CH$_2$)$_{0-4}$NR^{a}SO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$OP(OH)$_2$或-(CR$_2$)$_{0-4}$OP(O)(H)OH；

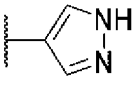
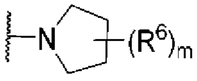
X係-CH$_2$-、-NH-或-O-；

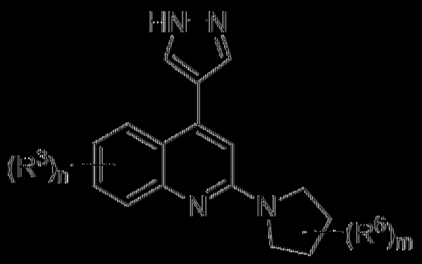
m係1或2；

p係1；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0254】 在某些實施例中，對於以上揭示的式**I-f-5**之化合物，m係1或2，且至少一個R^{6}包括末端-CO$_2$H基團。舉例而言，在某些情形中，至少一個R^{6}係-(CH$_2$)$_{0-4}$CO$_2$H。

【0255】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其中R^{1}係  且R^{2}係 ，由此形成式**I-f-6**之化合物：



I-f-6

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係鹵素、=O、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0256】 在一些實施例中，本發明提供一種式I-f-6之化合物，其中R^6不為R^B。

【0257】 在某些實施例中，本發明提供一種式I-f-6之化合物，其中R^3獨立地係鹵素，諸如氟，包括二氟，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氟。

【0258】 在某些實施例中，本發明提供一種式I-f-6之化合物，其中：

每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-C_{3-6}$環烷基、$=CR_2$、=O、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-}$

$_4$OR、-NR$_2$、-(CR$_2$)$_{1-4}$NR$_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR$_2$、-SR、-SO$_2$R、-S(O)R、-(CR$_2$)$_{0-6}$SO$_3$R、-(CR$_2$)$_{0-6}$SO$_2$NR$_2$、-(CR$_2$)$_{0-6}$OSO$_2$NR$_2$、-(CR$_2$)$_{0-6}$NRSO$_2$R、-(CR$_2$)$_{0-6}$NRSO$_2$OR、-(CR$_2$)$_{0-6}$OP(OR)$_2$、-(CR$_2$)$_{0-6}$OP(O)(OR)$_2$、-(CR$_2$)$_{0-6}$P(O)(OR)$_2$、-(CR$_2$)$_{0-6}$OP(O)(H)OR或-B(OR)$_2$；

m係1、2、3或4，特定言之為1或2；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0259】 在特定實施例中，本發明提供一種式**I-f-6**之化合物，其中：

每個R^{6}獨立地係鹵素、-C$_{1-4}$烷基、-C$_{1-4}$鹵烷基、-C$_{3-6}$環烷基、=CH$_2$、=O、-(CH$_2$)$_{0-4}$CO$_2$H、-(CH$_2$)$_{0-4}$CO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$O(CH$_2$)$_{1-5}$CO$_2$H、-(CH$_2$)$_{0-4}$O(CH$_2$)$_{1-5}$CO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$CONH$_2$、-(CH$_2$)$_{0-4}$CONHC$_{1-4}$烷基、-(CH$_2$)$_{0-4}$CON(C$_{1-4}$烷基)$_2$、-(CH$_2$)$_{0-4}$CO(*N*-脯胺酸)、-(CH$_2$)$_{0-4}$CO(*N*-吡咯啶-3-羧酸)、-(CH$_2$)$_{0-4}$C(O)NR^a(CH$_2$)$_{1-4}$CO$_2$H、-(CH$_2$)$_{0-4}$C(O)NR^a-CH(C$_{1-4}$烷基)-CO$_2$H、-(CH$_2$)$_{0-4}$C(O)NR^a(CH$_2$)$_{1-4}$CONH$_2$、-(CH$_2$)$_{0-4}$C(O)NR^a(CH$_2$)$_{1-4}$CONHC$_{1-4}$烷基、-(CH$_2$)$_{0-4}$C(O)NR^a(CH$_2$)$_{1-4}$CON(C$_{1-4}$烷基)$_2$、-OH、-(CH$_2$)$_{1-4}$OH、-(CH$_2$)$_{0-4}$OC$_{1-4}$烷基、-NH$_2$、-(CH$_2$)$_{1-4}$NH$_2$、-(CH$_2$)$_{0-4}$NHC$_{1-4}$烷基、-(CH$_2$)$_{0-4}$NR^{a}C(O)C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$NR^{a}C(O)Ph、-(CH$_2$)$_{0-4}$NR^{a}CO(CH$_2$)$_{1-4}$OH、-(CH$_2$)$_{0-4}$N(C$_{1-4}$烷基)$_2$、-(CH$_2$)$_{0-4}$SO$_3$H、-(CH$_2$)$_{0-4}$SO$_2$NH$_2$、-(CH$_2$)$_{0-4}$SO$_2$NR^{a}C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$NR^{a}SO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{0-4}$NR^{a}SO$_2$Ph、-(CH$_2$)$_{0-4}$NR^{a}SO$_2$(CH$_2$)$_{1-4}$CO$_2$H、-(CH$_2$)$_{0-4}$OP(OH)$_2$、-(CH$_2$)$_{0-4}$OP(OH)(OC$_{1-4}$烷基)或-(CR$_2$)$_{0-4}$OP(O)(H)OH，其中

R^a在每次出現時獨立地係H或C_{1-4}烷基；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

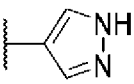
【0260】 在其他特定實施例中，本發明提供一種式**I-f-6**之化合物，其中：

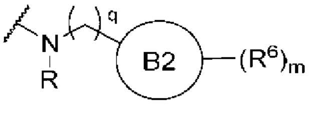
每個R^6獨立地係鹵素、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-C_{3-6}$環烷基、$=CH_2$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}CO($*N*-吡咯啶-3-羧酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1或2；且

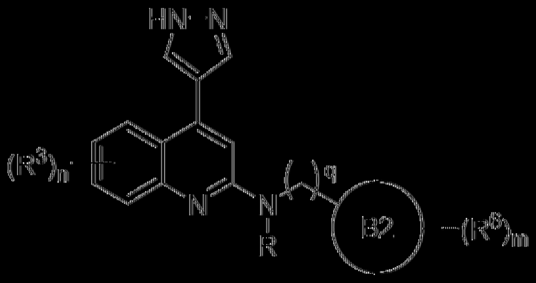
每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0261】 在某些實施例中，對於以上揭示的式**I-f-6**之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0262】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其中R^1係

且R^2係

，由此形成式**I-f-7**之化合物：



I-ff-7

或其醫藥學上可接受之鹽，其中：

環B2係苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0\text{-}6}CO_2R$、$-(CR_2)_{0\text{-}6}CONR_2$、$-OR$、$-(CR_2)_{1\text{-}4}OR$、$-NR_2$、$-(CR_2)_{1\text{-}4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0\text{-}6}SO_3R$、$-(CR_2)_{0\text{-}6}SO_2NR_2$、$-(CR_2)_{0\text{-}6}OSO_2NR_2$、$-(CR_2)_{0\text{-}6}NRSO_2R$、$-(CR_2)_{0\text{-}6}NRSO_2OR$、$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(H)OR$、$-B(OR)_2$或$R^B$；

m係0、1、2、3或4，特定言之為1、2、3或4；

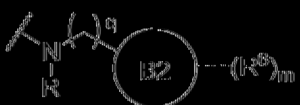
q係0、1或2；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0263】 在某些實施例中，本發明提供一種式I-ff-7之化合物，其中環B2係苯基，特定言之為經取代之苯基。在其他實施例中，環B2不為苯基。舉例而言，環B2可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B2係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜

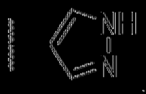
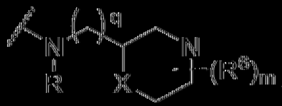
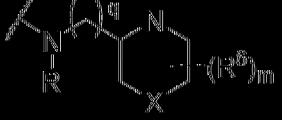
芳基環。

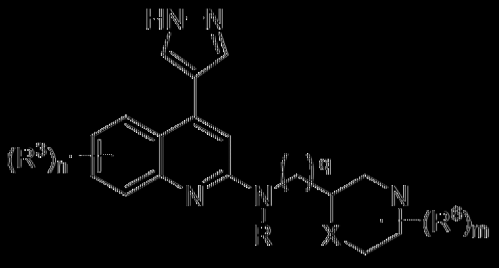
【0264】 在一些實施例中，本發明提供一種式I-f-7之化合物，其中R^6不為R^B。

【0265】 在一些實施例中，本發明提供一種式I-f-7之化合物，其中中之R係R^a，其係H或C_{1-6}烷基。

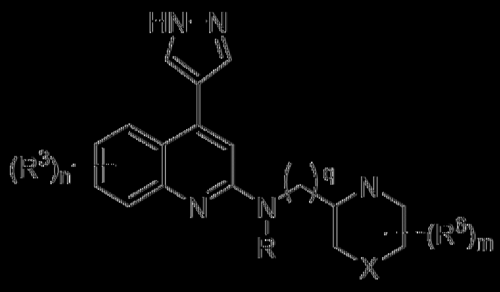
【0266】 在某些實施例中，本發明提供一種式I-f-7之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0267】 在某些實施例中，對於以上揭示的式I-f-7之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0268】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係或，由此分別形成式I-f-8或式I-f-8*之化合物：



I-f-8



I-f-8*

或其醫藥學上可接受之鹽，其中：

每個R^6獨立地係氫(僅在N上)、鹵素(不在N上)、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-}$

$_6SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

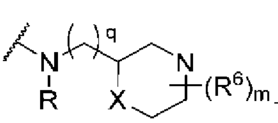
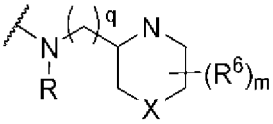
X係$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$，特定言之為$-CR_2-$、-NR-或-O；

m係1、2、3或4；

q係0、1或2；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0269】 在一些實施例中，本發明提供一種式**I-f-8**或式**I-f-8***之化合物，其中R^6不為R^B。

【0270】 在一些實施例中，本發明提供一種式**I-f-8**或式**I-f-8***之化合物，其中或中之R係R^a，其係H或C_{1-6}烷基。

【0271】 在某些實施例中，本發明提供一種式**I-f-8**或式**I-f-8***之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0272】 在某些實施例中，本發明提供一種式**I-f-8**或式**I-f-8***之化合物，其中：

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、

$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；

q係1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0273】 在特定實施例中，本發明提供一種式**I-f-8**或式**I-f-8***之化合物，其中：

每個R^6獨立地係鹵素、=O、$-(CH_2)_{0\text{-}4}CO_2H$、$-(CH_2)_{0\text{-}4}CO_2C_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}CONH_2$、$-(CH_2)_{0\text{-}4}CONHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}CON(C_{1\text{-}4}$烷基$)_2$、$-(CH_2)_{0\text{-}4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CO_2H$、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CONH_2$、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CONHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CON(C_{1\text{-}4}$烷基$)_2$、-OH、$-(CH_2)_{1\text{-}4}OH$、$-(CH_2)_{0\text{-}4}OC_{1\text{-}4}$烷基、$-NH_2$、$-(CH_2)_{1\text{-}4}NH_2$、$-(CH_2)_{0\text{-}4}NHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}N(C_{1\text{-}4}$烷基$)_2$、$-(CH_2)_{0\text{-}4}SO_3H$、$-(CH_2)_{0\text{-}4}SO_2NH_2$、$-(CH_2)_{0\text{-}4}SO_2NHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}NR^aSO_2C_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}OP(OH)_2$、$-(CH_2)_{0\text{-}4}OP(OH)(OC_{1\text{-}4}$烷基$)$或$-(CR_2)_{0\text{-}4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1\text{-}4}$烷基；

m係1、2、3或4，特定言之為1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0274】 在其他特定實施例中，本發明提供一種式**I-f-8**或式**I-f-8***

之化合物，其中：

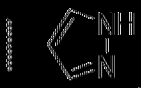
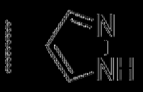
每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

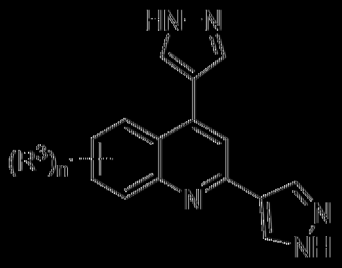
m係1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

[0275] 在某些實施例中，對於以上揭示的式I-f-8或I-f-8*之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

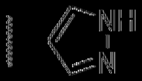
[0276] 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-f-9之化合物：

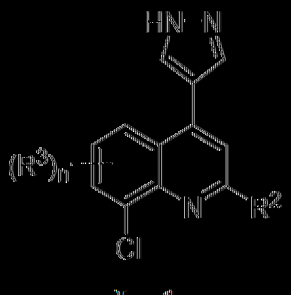


I-f-9

或其醫藥學上可接受之鹽，其中R、R^1、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

[0277] 在某些實施例中，本發明提供一種式I-f-9之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

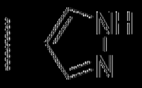
【0278】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且至少一個R^3係鹵素，諸如在8位之氯，由此形成式I-g-1之化合物：



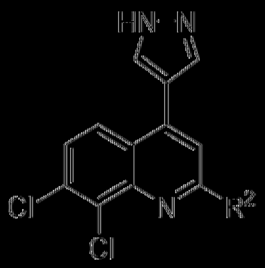
I-g-1

或其醫藥學上可接受之鹽，其中單獨地及組合地，R^2及R^3各自如上文所定義且描述於本文實施例中，且n係0、1、2或3。

【0279】 在某些實施例中，本發明提供一種式I-g-1之化合物，其中R^2係R^B，其中R^B係視情況經取代之C_{1-6}脂族基，較佳地為經取代之C_{1-6}脂族基，諸如$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-4}O(CR_2)_{0-4}CO_2R$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}OH$、$-(CR_2)_{1-4}NH_2$、$-(CR_2)_{1-4}C(O)NH_2$、$-(CR_2)_{1-4}C(O)NHC_{1-4}$烷基或$-(CR_2)_{1-4}C(O)N(C_{1-4}$烷基$)_2$，特定言之為$-(CR_2)_{1-4}NR(CR_2)_{0-4}CO_2R$或$-(CR_2)_{1-4}CO_2R$。在一些實施例中，$R^2$係$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2R^a$，諸如為$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係$-(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2R^a$，諸如為$-(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係$-(CR_2)_{1-4}CO_2R$，諸如$-(CR_2)_{1-4}CO_2H$，包括$-(CH_2)_{1-4}CO_2H$。在某些實施例中，$R^2$包括末端$-CO_2H$基團。舉例而言，在某些情形中，$R^2$包括末端$-(CH_2)_{0-4}CO_2H$基團。

【0280】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係，n係2，且R^3係在7位及8位之氯，由此形成式I-g-2之化合

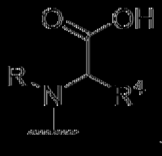
物：

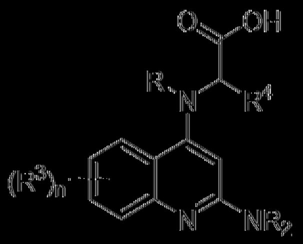


I-g-2

或其醫藥學上可接受之鹽，其中R^2係如上文所定義且描述於本文實施例中。

【0281】 在某些實施例中，本發明提供一種式I-g-2之化合物，其中R^2係R^B，其中R^B係視情況經取代之C_{1-6}脂族基，較佳地為經取代之C_{1-6}脂族基，諸如$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-4}O(CR_2)_{0-6}CO_2R$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}OH$、$-(CR_2)_{1-4}NH_2$、$-(CR_2)_{1-4}C(O)NH_2$、$-(CR_2)_{1-4}C(O)NHC_{1-4}$烷基或$-(CR_2)_{1-4}C(O)N(C_{1-4}$烷基$)_2$，特定言之為$-(CR_2)_{1-4}NR(CR_2)_{0-6}CO_2R$或$-(CR_2)_{1-4}CO_2R$。在一些實施例中，$R^2$係$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2R^a$，諸如為$-(CH_2)_{1-4}NR^a(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係$-(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2R^a$，諸如為$-(CH_2)_{1-4}N(SO_2C_{1-4}$烷基$)(CH_2)_{0-4}CO_2H$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。在其他實施例中，$R^2$係$-(CR_2)_{1-4}CO_2R$，諸如為$-(CR_2)_{1-4}CO_2H$，包括$-(CH_2)_{1-4}CO_2H$。在某些實施例中，$R^2$包括末端$-CO_2H$基團。舉例而言，在某些情形中，$R^2$包括末端$-(CH_2)_{0-4}CO_2H$基團。

【0282】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係$-NR_2$，由此形成式I-h-1之化合物：

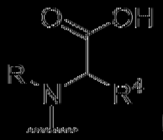


I-h-1

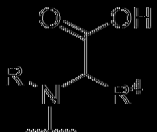
或其醫藥學上可接受之鹽，其中：

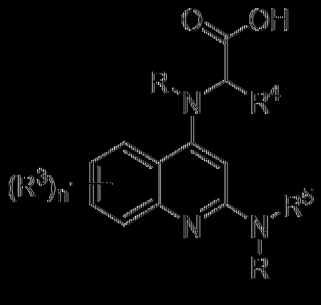
R^4係氫或視情況經取代之C_{1-6}脂族基；且

R、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0283】在一些實施例中，本發明提供一種式I-h-1之化合物，其中  中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0284】在某些實施例中，本發明提供一種式I-h-1之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0285】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係$-NRR^5$，由此形成式I-h-2之化合物：



I-h-2

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；

R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-}$

${}_6CO_2R$、$-(CR_2)_{0\text{-}6}C(O)NR(CR_2)_{0\text{-}6}CONR_2$、$-(CR_2)_{0\text{-}6}SO_3R$、$-(CR_2)_{0\text{-}6}SO_2NR_2$、$-(CR_2)_{0\text{-}6}OSO_2NR_2$、$-(CR_2)_{0\text{-}6}NRSO_2R$、$-(CR_2)_{0\text{-}6}NRSO_2OR$、$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(H)OR$或$R^B$；且

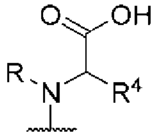
R、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0286】在某些實施例中，本發明提供一種式**I-h-2**之化合物，其中R^5係$-(CR_2)_{2\text{-}4}OR$、$-(CR_2)_{1\text{-}4}CO_2R$、$-(CR_2)_{1\text{-}4}CONR_2$、$-(CR_2)_{0\text{-}6}C(O)NR(CR_2)_{0\text{-}6}CO_2R$、$-(CR_2)_{0\text{-}6}C(O)NR(CR_2)_{0\text{-}6}CONR_2$、$-(CR_2)_{0\text{-}6}SO_3R$、$-(CR_2)_{0\text{-}6}SO_2NR_2$、$-(CR_2)_{0\text{-}6}OSO_2NR_2$、$-(CR_2)_{0\text{-}6}NRSO_2R$、$-(CR_2)_{0\text{-}6}NRSO_2OR$、$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(H)OR$或$R^B$。

【0287】在一些實施例中，本發明提供一種式**I-h-2**之化合物，其中R^5不為R^B。

【0288】在一些實施例中，本發明提供一種式**I-h-2**之化合物，其中$-NRR^5$中之R係R^a，其係H或$C_{1\text{-}6}$烷基。

【0289】在一些實施例中，本發明提供一種式**I-h-2**之化合物，其中



中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0290】在某些實施例中，本發明提供一種式**I-h-2**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0291】在特定實施例中，本發明提供一種式**I-h-2**之化合物，其

中：

-NRR^{5}中之R係H或低碳數烷基，特定言之為甲基；

R^{5}係-(CH$_2$)$_{2-4}$OH、-(CH$_2$)$_{0-3}$CH(CH$_2$OH)$_2$、-(CH$_2$)$_{2-4}$OC$_{1-4}$烷基、-(CH$_2$)$_{1-4}$CO$_2$H、-(CH$_2$)$_{1-4}$CO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{1-4}$CONH$_2$、-(CH$_2$)$_{1-4}$CONHC$_{1-4}$烷基、-(CH$_2$)$_{1-4}$CON(C$_{1-4}$烷基)$_2$、-(CH$_2$)$_{1-4}$C(O)NR^a(CH$_2$)$_{1-4}$CO$_2$H、-(CH$_2$)$_{1-4}$C(O)NR^a(CH$_2$)$_{1-4}$CONH$_2$、-(CH$_2$)$_{1-4}$C(O)NR^a(CH$_2$)$_{1-4}$CONHC$_{1-4}$烷基、-(CH$_2$)$_{1-4}$C(O)NR^a(CH$_2$)$_{1-4}$CON(C$_{1-4}$烷基)$_2$、-(CH$_2$)$_{2-4}$SO$_3$H、-(CH$_2$)$_{2-4}$SO$_3$C$_{1-4}$烷基、-(CH$_2$)$_{2-4}$SO$_2$NH$_2$、-(CH$_2$)$_{2-4}$SO$_2$NHC$_{1-4}$烷基、-(CH$_2$)$_{2-4}$SO$_2$N(C$_{1-4}$烷基)$_2$、-(CH$_2$)$_{2-4}$OSO$_2$NH$_2$、-(CH$_2$)$_{2-4}$NR^{a}SO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{2-4}$NR^{a}SO$_3$H、-(CH$_2$)$_{1-4}$OP(OH)$_2$、-(CH$_2$)$_{1-4}$P(O)(OH)$_2$、-(CH$_2$)$_{1-4}$P(O)(OH)(OC$_{1-4}$烷基)或-(CH$_2$)$_{2-4}$OP(O)(H)OH，其中R^{a}在每次出現時獨立地係H或C$_{1-4}$烷基；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^{3}係氯。

【0292】 在其他特定實施例中，本發明提供一種式**I-h-2**之化合物，其中：

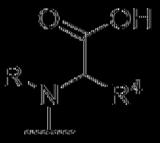
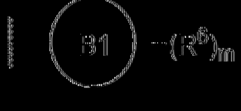
-NRR^{5}中之R係H或低碳數烷基，特定言之為甲基；

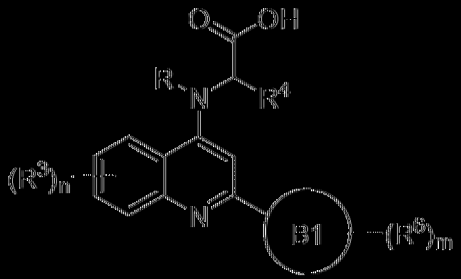
R^{5}係-(CH$_2$)$_{2-4}$OH、-(CH$_2$)$_{0-3}$CH(CH$_2$OH)$_2$、-(CH$_2$)$_{1-4}$CO$_2$H、-(CH$_2$)$_{1-4}$CONH$_2$、-(CH$_2$)$_{1-4}$C(O)NR^a(CH$_2$)$_{1-4}$CO$_2$H、-(CH$_2$)$_{1-4}$C(O)NR^a(CH$_2$)$_{1-4}$CONH$_2$、-(CH$_2$)$_{2-4}$SO$_3$H、-(CH$_2$)$_{2-4}$SO$_2$NH$_2$、-(CH$_2$)$_{2-4}$SO$_2$NR^{a}C$_{1-4}$烷基、-(CH$_2$)$_{2-4}$NR^{a}SO$_2$C$_{1-4}$烷基、-(CH$_2$)$_{1-4}$P(O)(OH)$_2$或-(CH$_2$)$_{2-4}$OP(O)(H)OH，其中R^{a}在每次出現時獨立地係H或C$_{1-4}$烷基；且

每個R^{3}獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於

喹啉環位在7-或8-位置之R^3係氫。

【0293】在某些實施例中，對於以上揭示的式I-h-2之化合物，R^5包括末端-CO_2H基團。舉例而言，在某些情形中，R^5包括末端-$(CH_2)_{0-4}CO_2H$基團。

【0294】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係  ，由此形成式I-h-3之化合物：



I-h-3

或其醫藥學上可接受之鹽，其中：

環B1係苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

R^4係氫或視情況經取代之C_{1-6}脂族基；

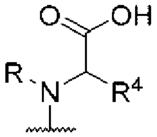
每個R^6獨立地係鹵素、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0295】 在某些實施例中，本發明提供一種式**I-h-3**之化合物，其中環B1係苯基，特定言之為經取代之苯基。在其他實施例中，環B1不為苯基。舉例而言，環B1可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

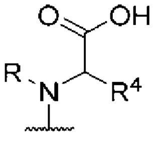
【0296】 在一些實施例中，本發明提供一種式**I-h-3**之化合物，其中R^6不為R^B。

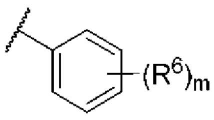
【0297】 在一些實施例中，本發明提供一種式**I-h-3**之化合物，其中 

中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

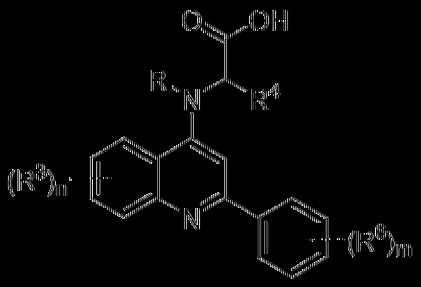
【0298】 在某些實施例中，本發明提供一種式**I-h-3**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0299】 在某些實施例中，對於以上揭示的式**I-h-3**之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

【0300】 在一些實施例中，本發明提供一種式**I**或式**I***之化合物，其中R^1係 

且R^2係 

，由此形成式**I-h-4**之化合物：



I-h-4

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；

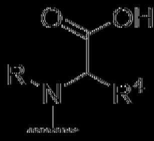
每個R^6獨立地係鹵素、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-$NRC(O)NR_2$、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

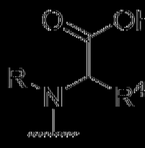
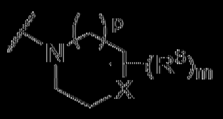
[0301] 在一些實施例中，本發明提供一種式I-h-4之化合物，其中R^6不為R^B。

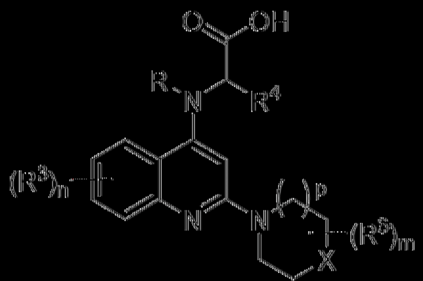
[0302] 在一些實施例中，本發明提供一種式I-h-4之化合物，其中



中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

[0303] 在某些實施例中，本發明提供一種式I-h-4之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0304】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係  ，由此形成式I-h-5之化合物：



I-h-5

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

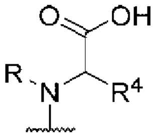
X係$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$，特定言之為$-CR_2-$、-NR-或-O-；

m係0、1、2、3或4，特定言之為1、2、3或4；

p係0、1或2，特定言之為1；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0305】 在一些實施例中，本發明提供一種式I-h-5之化合物，其中R^6不為R^B。

【0306】在一些實施例中，本發明提供一種式**I-h-5**之化合物，其中

中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0307】在某些實施例中，本發明提供一種式**I-h-5**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0308】在特定實施例中，本發明提供一種式**I-h-5**之化合物，其中：

每個R^6獨立地係鹵素、=O、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸$)$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

X係$-CH_2-$、-NH-或-O-；

m係1、2、3或4，特定言之為1或2；

p係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0309】 在其他特定實施例中，本發明提供一種式I-h-5之化合物，其中：

每個R^6獨立地係鹵素、-$(CH_2)_{0-4}CO_2H$、-$(CH_2)_{0-4}CO$(*N*-脯胺酸)、-$(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、-OH、-$(CH_2)_{1-4}OH$、-$(CH_2)_{0-4}SO_3H$、-$(CH_2)_{0-4}SO_2NH_2$、-$(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、-$(CH_2)_{0-4}OP(OH)_2$或-$(CR_2)_{0-4}OP(O)(H)OH$；

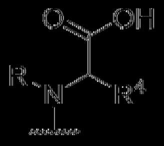
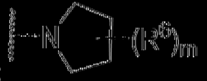
X係-CH_2-、-NH-或-O-；

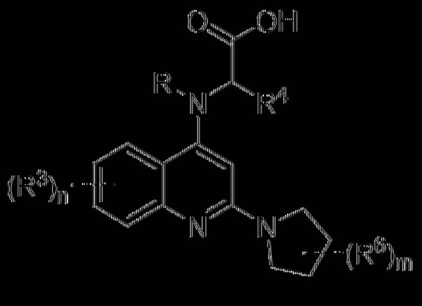
m係1或2；

p係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0310】 在某些實施例中，對於以上揭示的式I-h-5之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

【0311】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係 ，由此形成式I-h-6之化合物：



I-h-6

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；

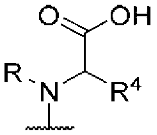
每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0312】 在一些實施例中，本發明提供一種式**I-h-6**之化合物，其中R^6不為R^B。

【0313】 在一些實施例中，本發明提供一種式**I-h-6**之化合物，其中



中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0314】 在某些實施例中，本發明提供一種式**I-h-6**之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0315】 在某些實施例中，本發明提供一種式**I-h-6**之化合物，其中：

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、

$-(CR_2)_{0\text{-}6}OP(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(OR)_2$、$-(CR_2)_{0\text{-}6}P(O)(OR)_2$、$-(CR_2)_{0\text{-}6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0316】 在特定實施例中，本發明提供一種式**I-h-6**之化合物，其中：

每個R^6獨立地係鹵素、=O、$-(CH_2)_{0\text{-}4}CO_2H$、$-(CH_2)_{0\text{-}4}CO_2C_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}CONH_2$、$-(CH_2)_{0\text{-}4}CONHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}CON(C_{1\text{-}4}$烷基$)_2$、$-(CH_2)_{0\text{-}4}CO($*N*-脯胺酸)、$-(CH_2)_{0\text{-}4}CO($*N*-吡咯啶-3-羧酸)、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CO_2H$、$-(CH_2)_{0\text{-}4}C(O)NR^a\text{-}CH(C_{1\text{-}4}$烷基$)\text{-}CO_2H$、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CONH_2$、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CONHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}C(O)NR^a(CH_2)_{1\text{-}4}CON(C_{1\text{-}4}$烷基$)_2$、-OH、$-(CH_2)_{1\text{-}4}OH$、$-(CH_2)_{0\text{-}4}OC_{1\text{-}4}$烷基、$-NH_2$、$-(CH_2)_{1\text{-}4}NH_2$、$-(CH_2)_{0\text{-}4}NHC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}NR^aC(O)C_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}NR^aC(O)Ph$、$-(CH_2)_{0\text{-}4}NR^aCO(CH_2)_{1\text{-}4}OH$、$-(CH_2)_{0\text{-}4}N(C_{1\text{-}4}$烷基$)_2$、$-(CH_2)_{0\text{-}4}SO_3H$、$-(CH_2)_{0\text{-}4}SO_2NH_2$、$-(CH_2)_{0\text{-}4}SO_2NR^aC_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}NR^aSO_2C_{1\text{-}4}$烷基、$-(CH_2)_{0\text{-}4}NR^aSO_2Ph$、$-(CH_2)_{0\text{-}4}NR^aSO_2(CH_2)_{1\text{-}4}CO_2H$、$-(CH_2)_{0\text{-}4}OP(OH)_2$、$-(CH_2)_{0\text{-}4}OP(OH)(OC_{1\text{-}4}$烷基)或$-(CR_2)_{0\text{-}4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1\text{-}4}$烷基；

m係1、2、3或4，特定言之為1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

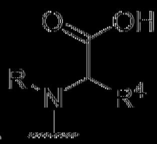
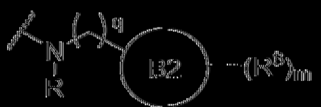
【0317】 在其他特定實施例中，本發明提供一種式I-h-6之化合物，其中：

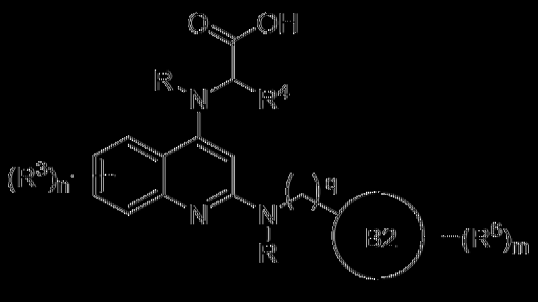
每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-脯胺酸)、$-(CH_2)_{0-4}CO$(*N*-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a$-CH($C_{1-4}$烷基)-$CO_2H$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0318】 在某些實施例中，對於以上揭示的式I-h-6之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0319】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係且R^2係，由此形成式I-h-7之化合物：



I-h-7

或其醫藥學上可接受之鹽，其中：

環B2係苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環；

R^4係氫或視情況經取代之C_{1-6}脂族基；

每個R^6獨立地係鹵素、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

m係0、1、2、3或4，特定言之為1、2、3或4；

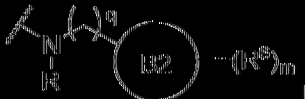
q係0、1或2；且

R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0320】 在某些實施例中，本發明提供一種式**I-h-7**之化合物，其中環B2係苯基，特定言之為經取代之苯基。在其他實施例中，環B2不為苯基。舉例而言，環B2可為具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B2係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

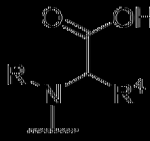
【0321】 在一些實施例中，本發明提供一種式**I-h-7**之化合物，其中R^6不為R^B。

【0322】 在一些實施例中，本發明提供一種式**I-h-7**之化合物，其中



中之R係R^a，其係H或C_{1-6}烷基。

【0323】在一些實施例中，本發明提供一種式I-h-7之化合物，其中

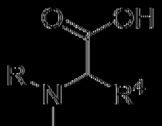


中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

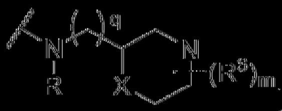
【0324】在某些實施例中，本發明提供一種式I-h-7之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0325】在某些實施例中，對於以上揭示的式I-h-7之化合物，m係1或2，且至少一個R^6包括末端-CO_2H基團。舉例而言，在某些情形中，至少一個R^6係-$(CH_2)_{0-4}CO_2H$。

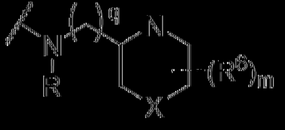
【0326】在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係



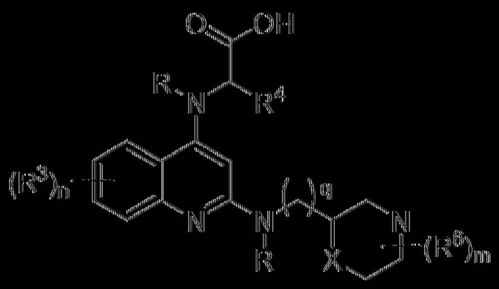
且R^2係



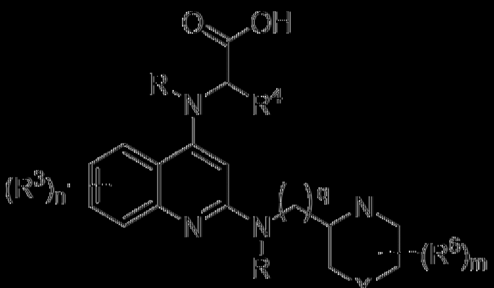
或



，由此分別形成式I-h-8或式I-h-8*之化合物：



I-h-8



I-h-8*

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；

每個R^6獨立地係氫(僅在N上)、鹵素(不在N上)、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-}$

${}_6SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B；

X係$-CR_2-$、$-NR-$、$-O-$、$-S-$或$-SO_2-$，特定言之為$-CR_2-$、$-NR-$或$-O$；

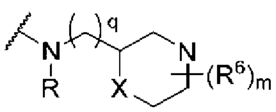
m係1、2、3或4；

q係0、1或2；且

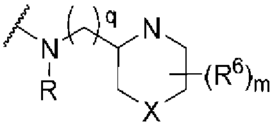
R、R^3、R^B及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0327】 在一些實施例中，本發明提供一種式**I-h-8**或式**I-h-8***之化合物，其中R^6不為R^B。

【0328】 在一些實施例中，本發明提供一種式**I-h-8**或式**I-h-8***之化合物，其中

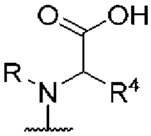


或



中之R係R^a，其係H或C_{1-6}烷基。

【0329】 在一些實施例中，本發明提供一種式**I-h-8**或式**I-h-8***之化合物，其中



中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0330】 在某些實施例中，本發明提供一種式**I-h-8**或式**I-h-8***之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0331】 在某些實施例中，本發明提供一種式**I-h-8**或式**I-h-8***之化合物，其中：

每個R^6獨立地係鹵素、=O、-COR、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、-OR、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、$-NRC(O)NR_2$、-SR、$-SO_2R$、-S(O)R、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$-B(OR)_2$；

m係1、2、3或4，特定言之為1或2；

q係1或2；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0332】 在特定實施例中，本發明提供一種式**I-h-8**或式**I-h-8***之化合物，其中：

每個R^6獨立地係鹵素、=O、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO($*N*-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

m係1、2、3或4，特定言之為1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0333】 在其他特定實施例中，本發明提供一種式I-h-8或式I-h-8*之化合物，其中：

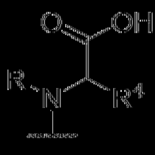
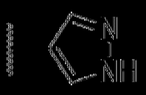
每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基；

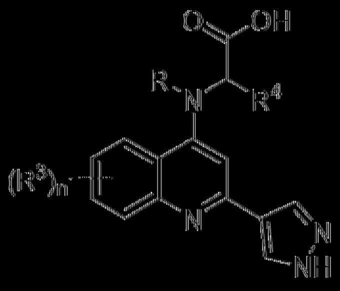
m係1或2；

q係1；且

每個R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0334】 在某些實施例中，對於以上揭示的式I-h-8或I-h-8*之化合物，m係1或2，且至少一個R^6包括末端$-CO_2H$基團。舉例而言，在某些情形中，至少一個R^6係$-(CH_2)_{0-4}CO_2H$。

【0335】 在一些實施例中，本發明提供一種式I或式I*之化合物，其中R^1係  且R^2係  ，由此形成式I-h-9之化合物：

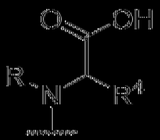


I-h-9

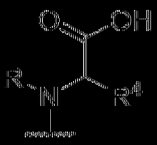
或其醫藥學上可接受之鹽，其中：

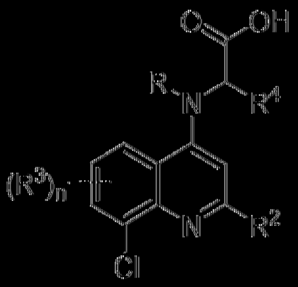
R^4係氫或視情況經取代之C_{1-6}脂族基；且

R、R^3及n各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0336】 在一些實施例中，本發明提供一種式I-h-9之化合物，其中中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0337】 在某些實施例中，本發明提供一種式I-h-9之化合物，其中R^3獨立地係鹵素，諸如氯，包括二氯，包括其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【0338】 在一些實施例中，本發明提供一種式I之化合物，其中R^1係且至少一個R^3係鹵素，諸如在8位之氯，由此形成式I-i-1之化合物：



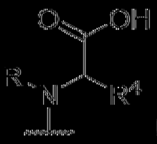
I-i-1

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；且

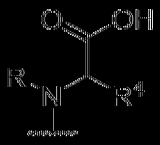
單獨地及組合地，R、R^2及R^3各自如上文所定義且描述於本文實施例中，且n係0、1、2或3。

【0339】 在一些實施例中，本發明提供一種式I-i-1之化合物，其中

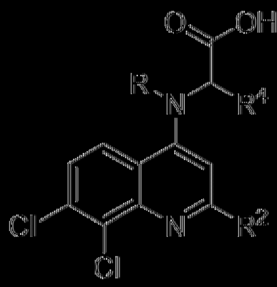


中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0340】 在一些實施例中，本發明提供一種式I之化合物，其中R^1係



，n係2，且R^3係在7位及8位之氯，由此形成式I-i-2之化合物：



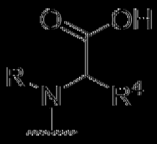
I-i-2

或其醫藥學上可接受之鹽，其中：

R^4係氫或視情況經取代之C_{1-6}脂族基；且

R及R^2各自如上文所定義且單獨及以組合形式描述於本文實施例中。

【0341】 在一些實施例中，本發明提供一種式I-i-2之化合物，其中

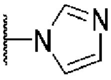
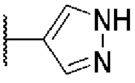
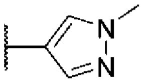
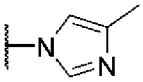
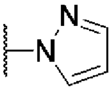
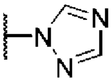
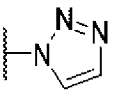
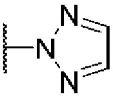
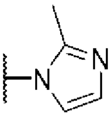
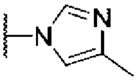
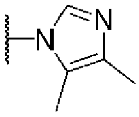
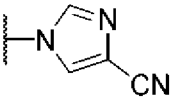
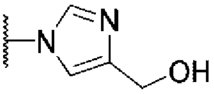
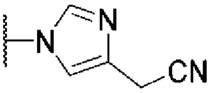
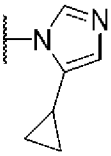
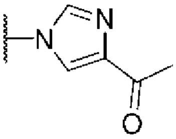
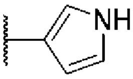
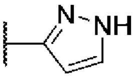
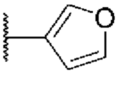
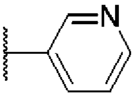
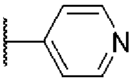
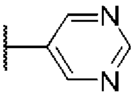
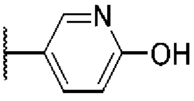
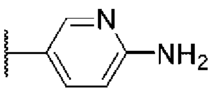
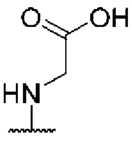
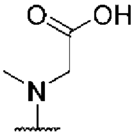
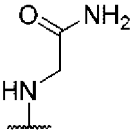


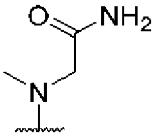
中之R及R^4獨立地係氫或低碳數烷基，特定言之為甲基。

【0342】 如上文所定義及本文所描述，R^1係鹵素、-OR、-NR_2、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-$NRSO_2R$、-SR、-SO_2R、-SO_2NR_2、-S(O)R或R^A，特定言之為-NR_2或R^A。

【0343】 在一些實施例中，R^1係鹵素。在一些實施例中，R^1係-OR。在一些實施例中，R^1係-NR_2。在一些實施例中，R^1係-NRC(O)OR。在一些實施例中，R^1係-NRC(O)R。在一些實施例中，R^1係-NRC(O)NR_2。在一些實施例中，R^1係-$NRSO_2R$。在一些實施例中，R^1係

-SR。在一些實施例中，R^1係$-SO_2R$。在一些實施例中，R^1係$-SO_2NR_2$。在一些實施例中，R^1係$-S(O)R$。在一些實施例中，R^1係R^A。

【0344】在一些實施例中，R^1係氫。在一些實施例中，R^1係氯。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係。在一些實施例中，R^1係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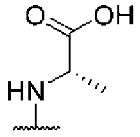
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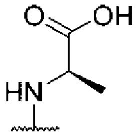
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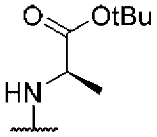
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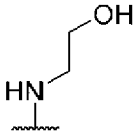
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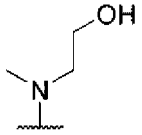
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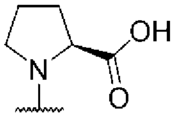
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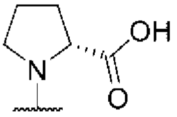
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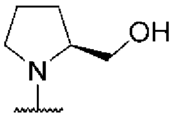
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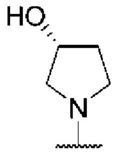
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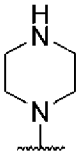
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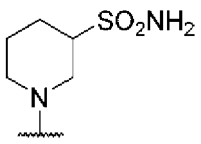
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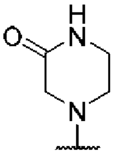
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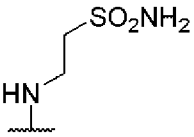
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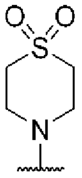
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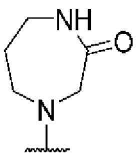
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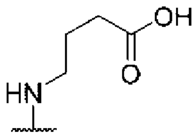
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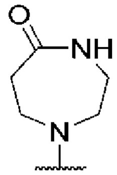
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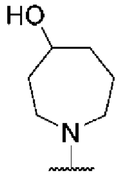
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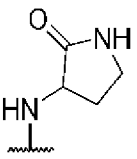
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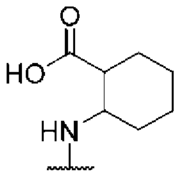

。

【0345】在一些實施例中，R^1係選自**表1**中所描繪之基團。

【0346】如上文所定義及本文所描述，每個R獨立地係氫或視情況經取代的選自以下之基團：$C_{1\text{-}6}$脂族基；苯甲基；苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；及具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環，或同一氮上的兩個R基團視情況與其插入原子一起形成除氮外還具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和、部分不飽和或雜芳基環。

【0347】在一些實施例中，R係氫。在一些實施例中，R係視情況經取代之$C_{1\text{-}6}$脂族基。在一些實施例中，R係視情況經取代之苯甲基。在一些實施例中，R係視情況經取代之苯基。在一些實施例中，R係具有1至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，R係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環。在一些實施例中，同一氮上的兩個R基團視情況與其插入原子一起形成除氮外還具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和、部分不飽和或雜芳基環。

【0348】在一些實施例中，同一碳原子上之兩個R基團(例如-(CR_2)-等)視情況與其插入原子一起形成具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和或部分不飽和環。

【0349】在一些實施例中，不同原子上之兩個R基團(例如-$P(O)(OR)_2$、-$B(OR)_2$等)視情況與其插入原子一起形成具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和或部分不飽和

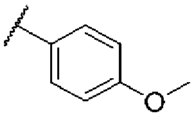
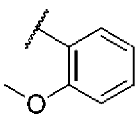
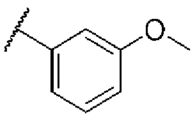
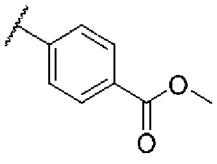
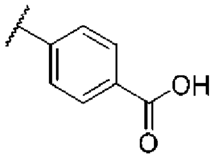
環。

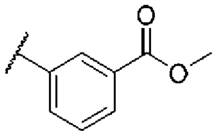
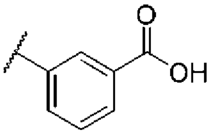
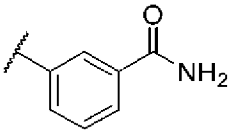
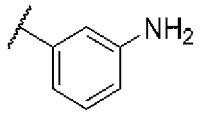
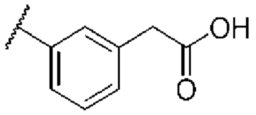
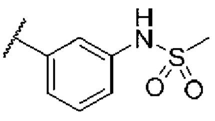
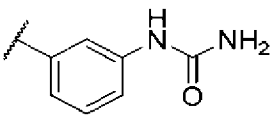
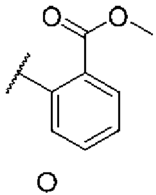
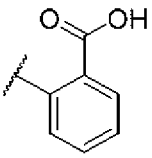
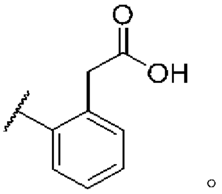
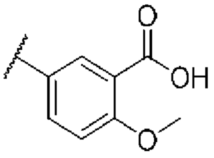
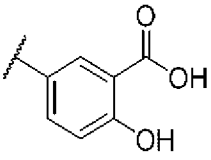
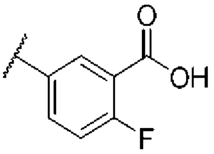
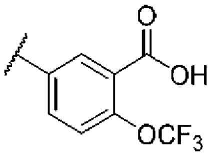
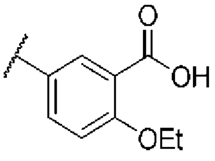
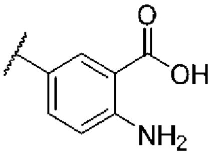
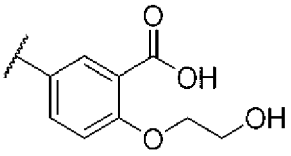
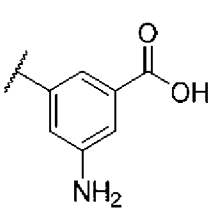
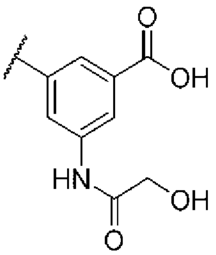
【0350】 在一些實施例中，R係氫。在一些實施例中，R係甲基。在一些實施例中，R係乙基。在一些實施例中，R係異丙基。在一些實施例中，R係苯基。在一些實施例中，R係苯甲基。在一些實施例中，R係-$(CH_2)_{1-5}CO_2H$。在一些實施例中，R係-$(CH_2)_{1-5}CO_2C_{1-4}$烷基。

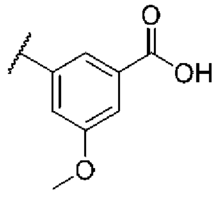
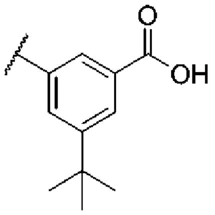
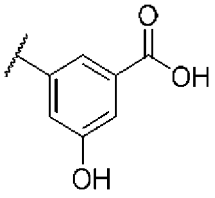
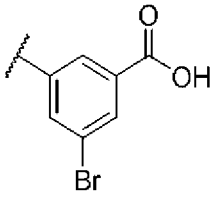
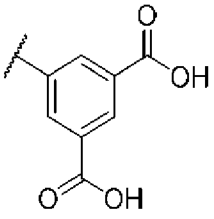
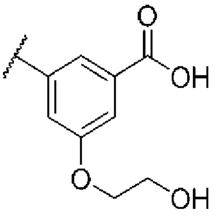
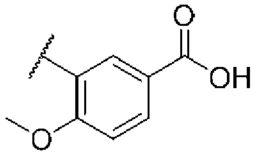
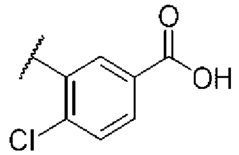
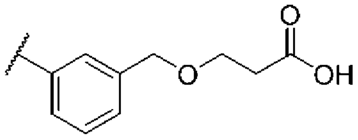
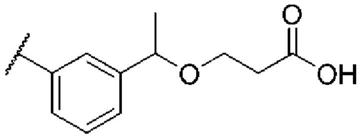
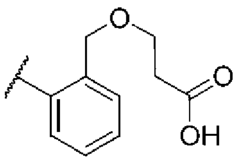
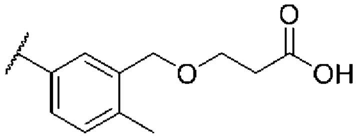
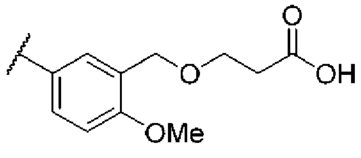
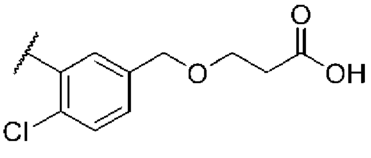
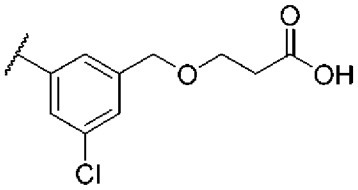
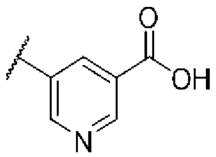
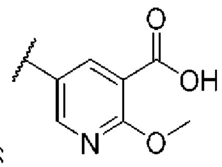
【0351】 在一些實施例中，R係選自**表1**中所描繪之基團。

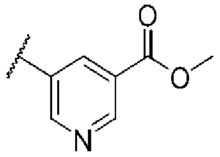
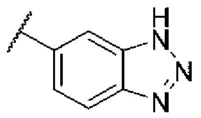
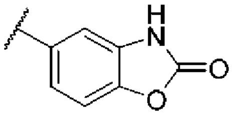
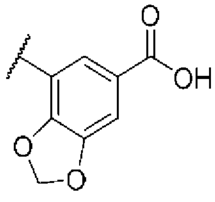
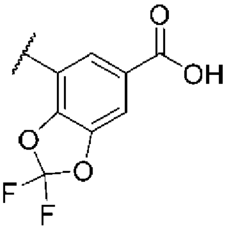
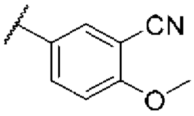
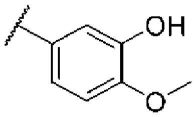
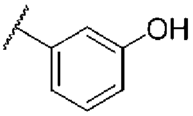
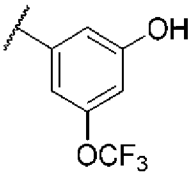
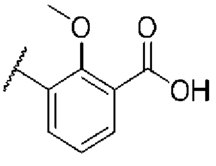
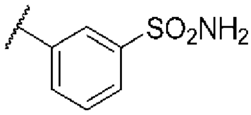
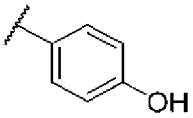
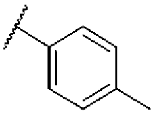
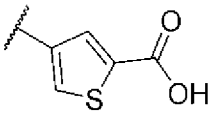
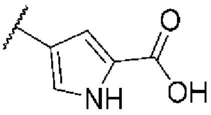
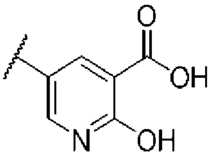
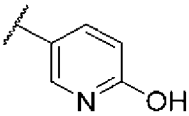
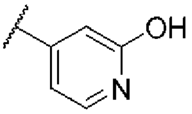
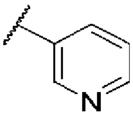
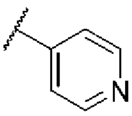
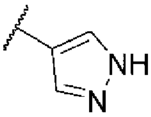
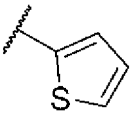
【0352】 如上文所定義及本文所描述，R^2係鹵素、-OR、-NR_2、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-$NRSO_2R$、-SR、-SO_2R、-SO_2NR_2、-S(O)R或R^B，特定言之為-NR_2或R^B。

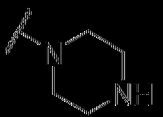
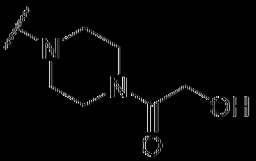
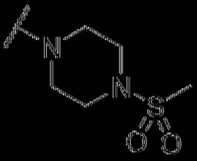
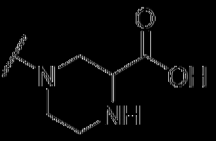
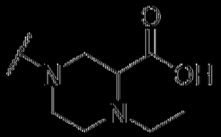
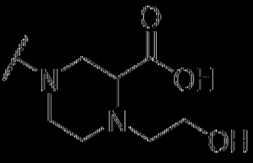
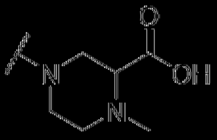
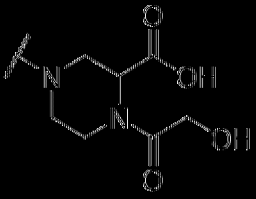
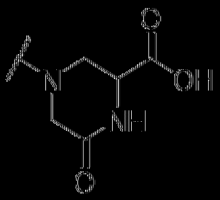
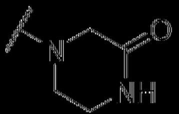
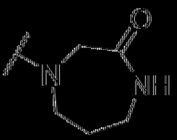
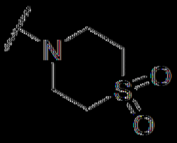
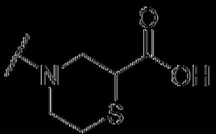
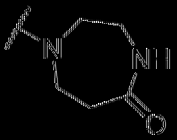
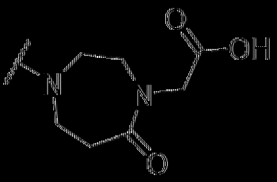
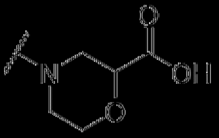
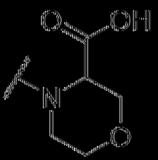
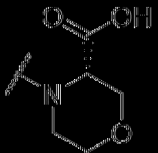
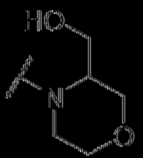
【0353】 在一些實施例中，R^2係鹵素。在一些實施例中，R^2係-OR。在一些實施例中，R^2係-NR_2。在一些實施例中，R^2係-NRC(O)OR。在一些實施例中，R^2係-NRC(O)R。在一些實施例中，R^2係-NRC(O)NR_2。在一些實施例中，R^2係-$NRSO_2R$、-SR。在一些實施例中，R^2係-SO_2R。在一些實施例中，R^2係-SO_2NR_2。在一些實施例中，R^2係-S(O)R。在一些實施例中，R^2係R^B。

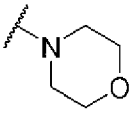
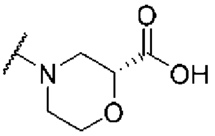
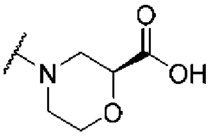
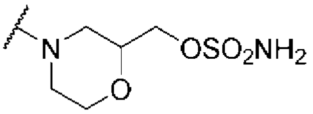
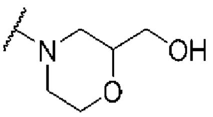
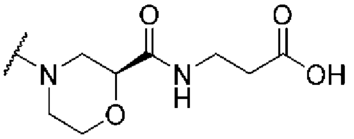
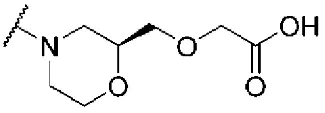
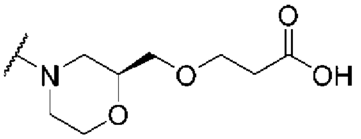
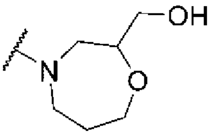
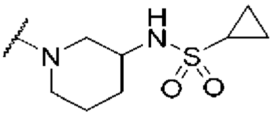
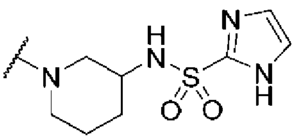
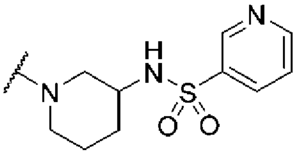
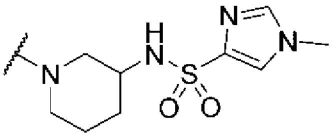
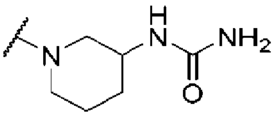
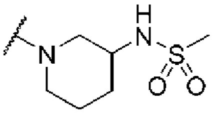
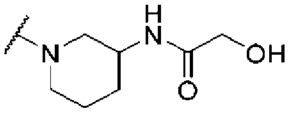
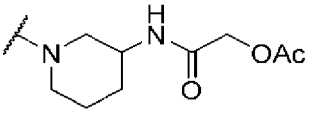
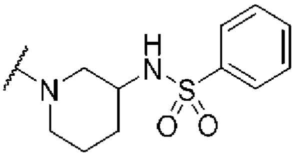
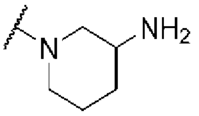
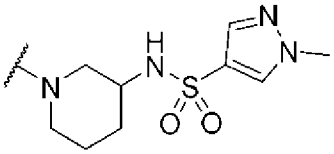
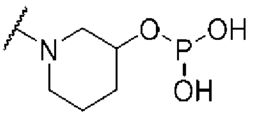
【0354】 在一些實施例中，R^2係氫。在一些實施例中，R^2係氯。在一些實施例中，R^2係甲基。在一些實施例中，R^2係-CF_3。在一些實施例中，R^2係苯基。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2

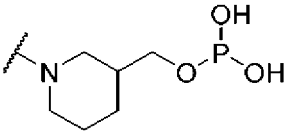
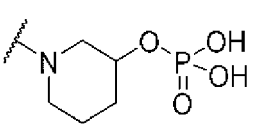
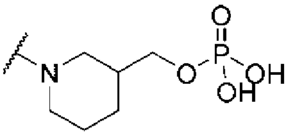
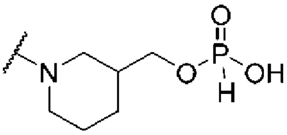
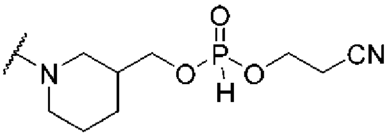
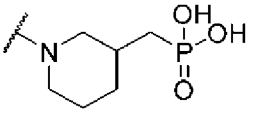
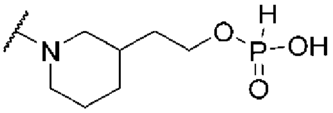
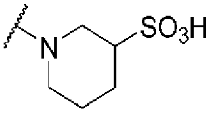
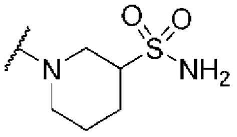
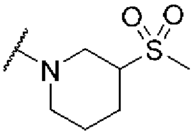
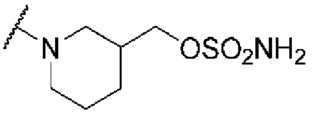
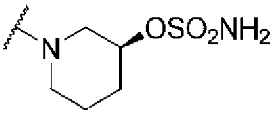
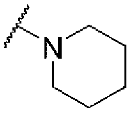
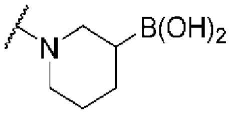
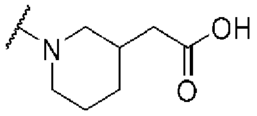
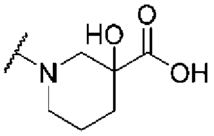
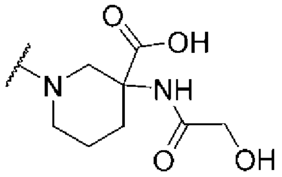
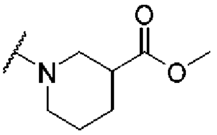
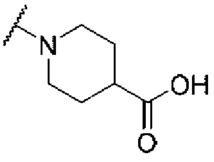
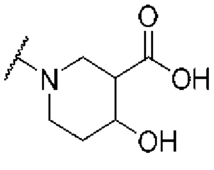
係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2

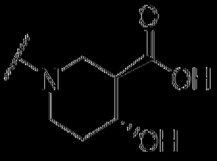
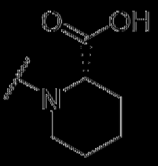
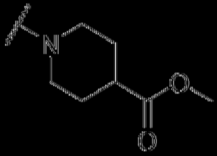
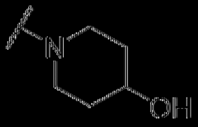
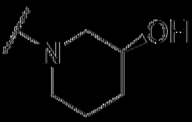
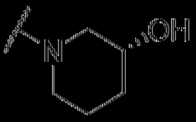
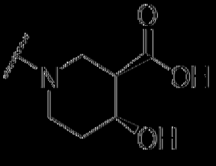
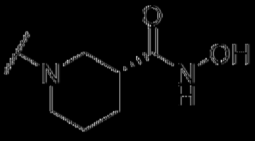
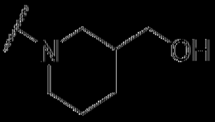
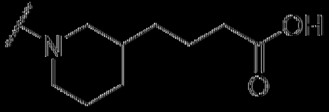
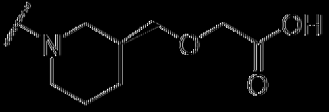
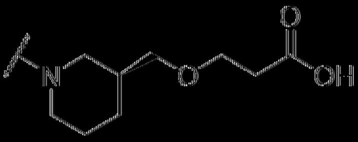
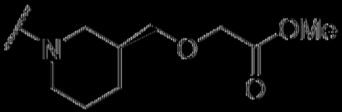
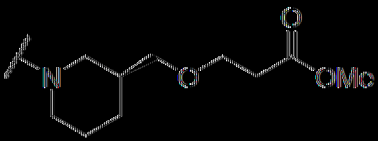
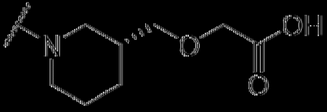
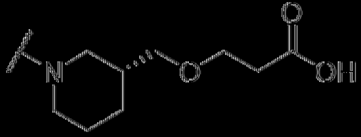
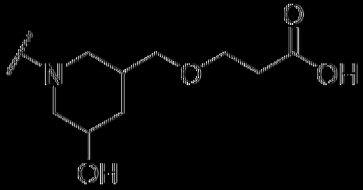
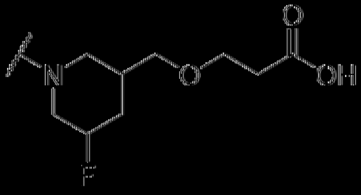
係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^2

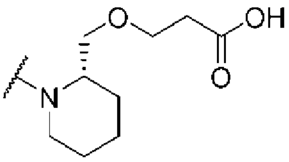
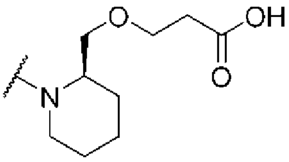
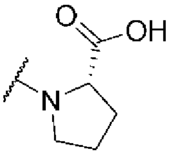
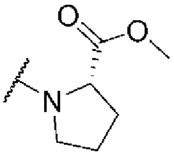
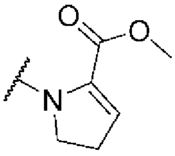
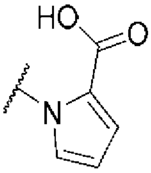
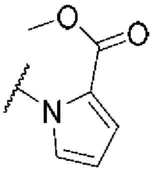
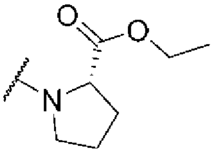
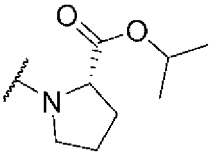
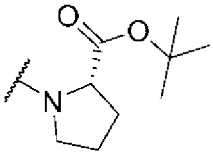
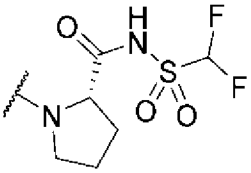
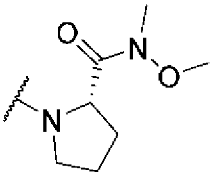
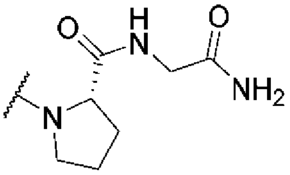
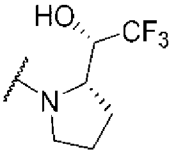
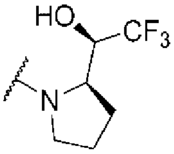
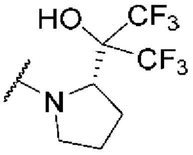
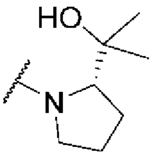
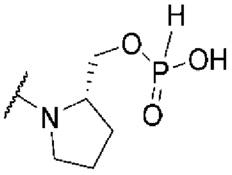
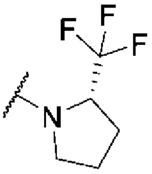
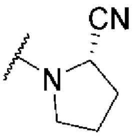
係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例

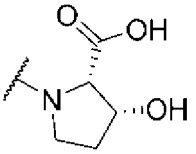
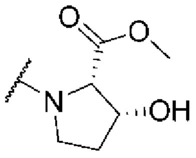
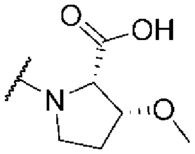
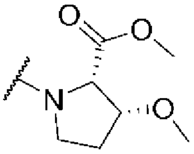
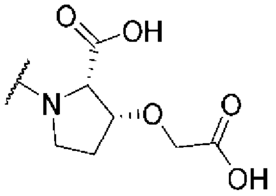
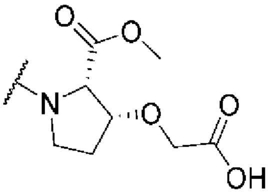
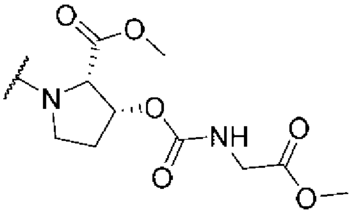
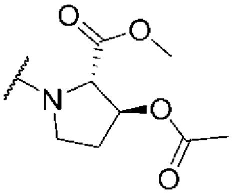
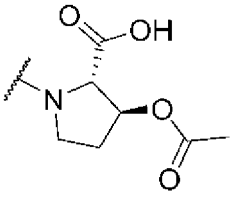
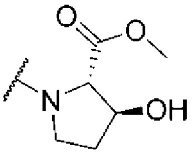
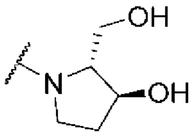
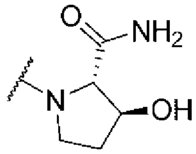
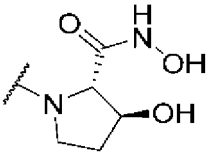
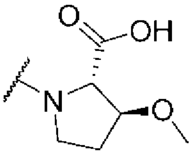
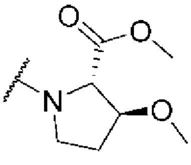
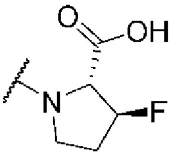
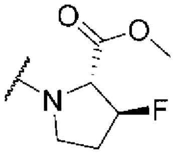
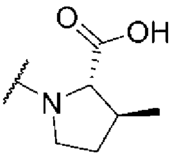
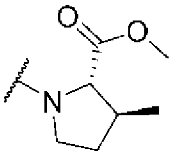
中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係

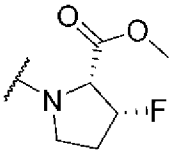
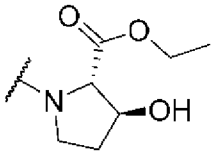
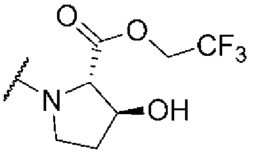
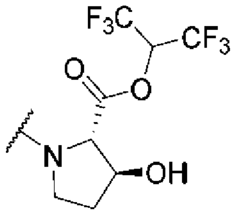
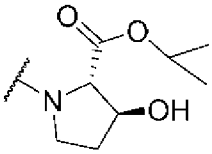
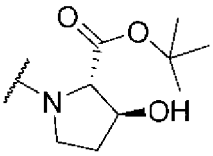
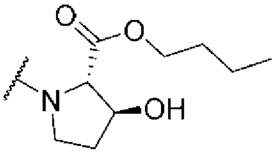
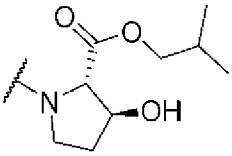
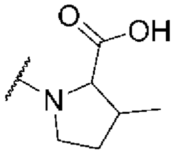
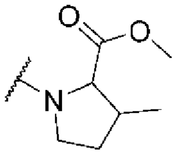
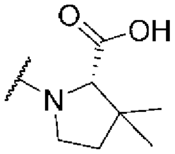
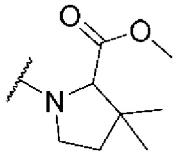
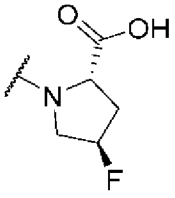
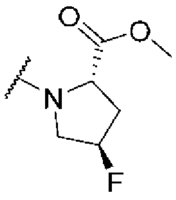
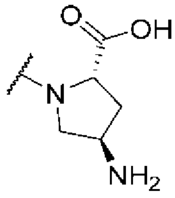
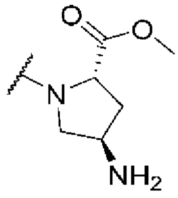
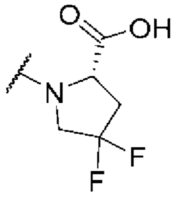
。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在

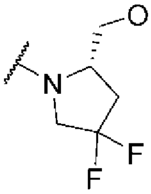
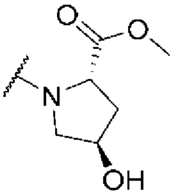
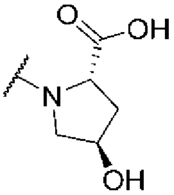
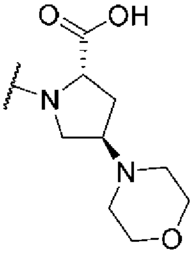
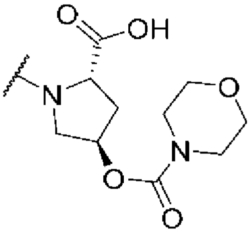
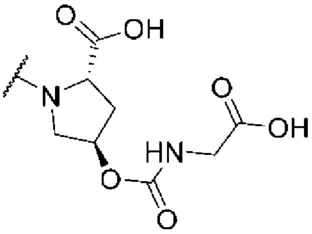
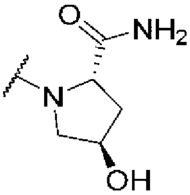
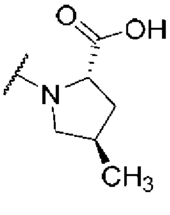
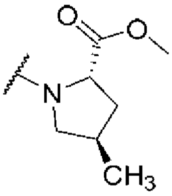
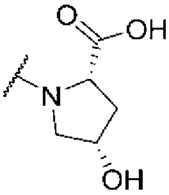
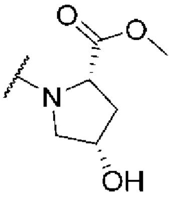
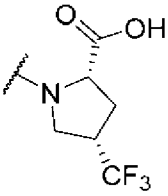
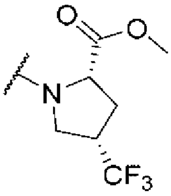
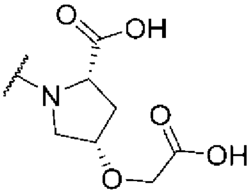
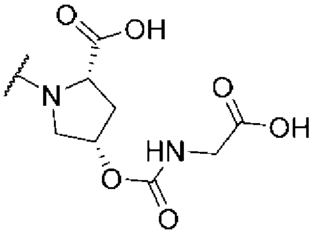
一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施

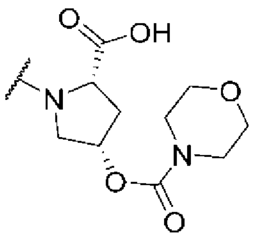
例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係。在一典實施例中，R²係

。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些

實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些

實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例

中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係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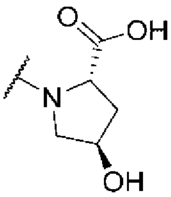
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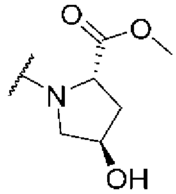
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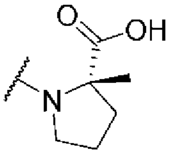
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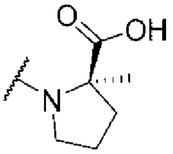
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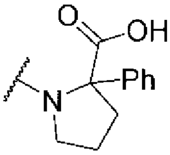
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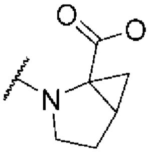
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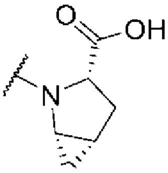
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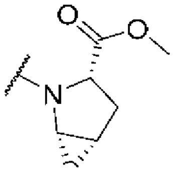
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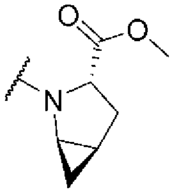
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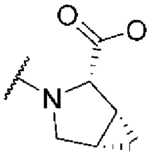
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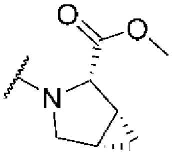
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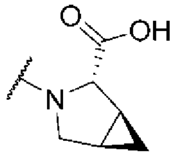
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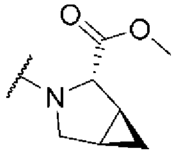
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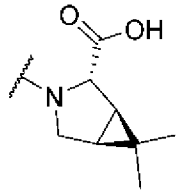
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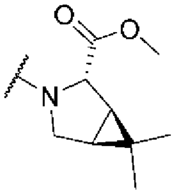
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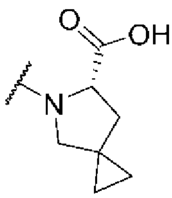
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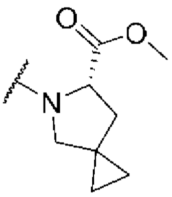
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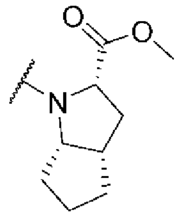
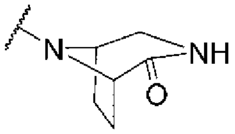
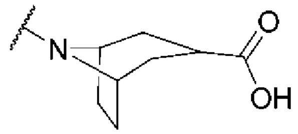
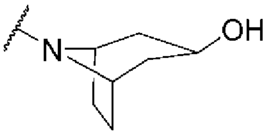
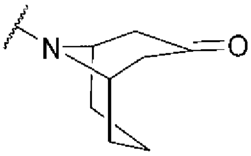
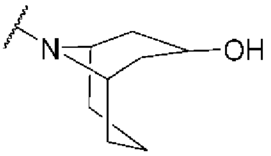
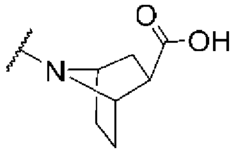
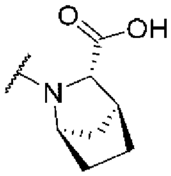
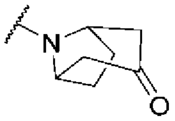
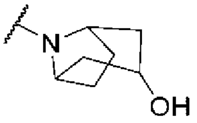
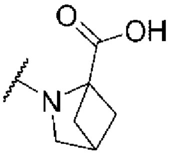
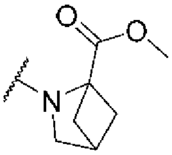
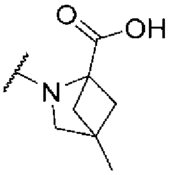
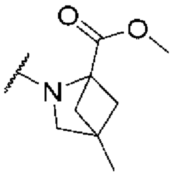
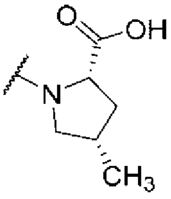
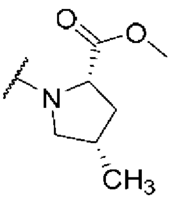
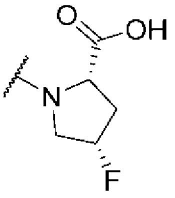
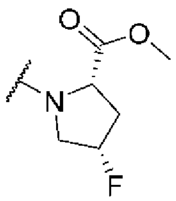
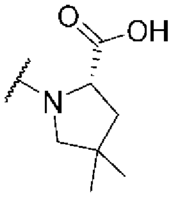
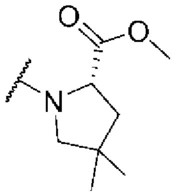
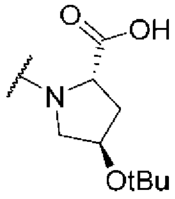
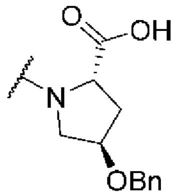
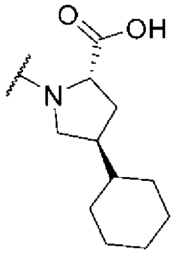
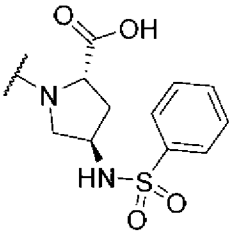
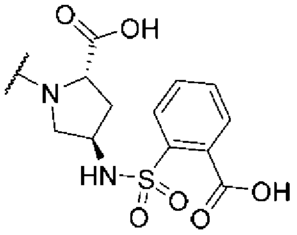
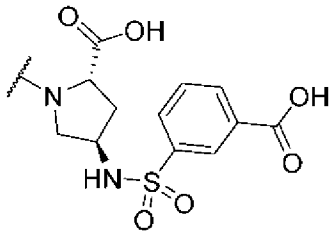
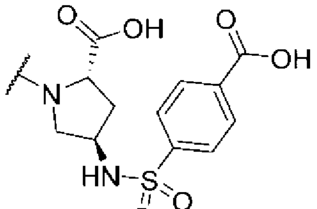
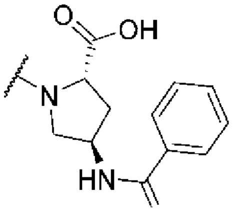
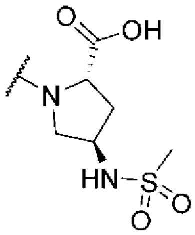
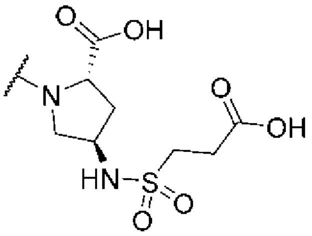
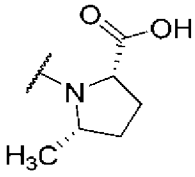
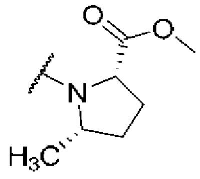
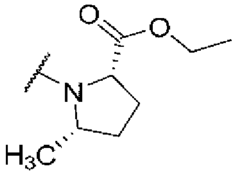
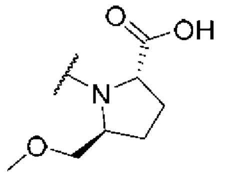
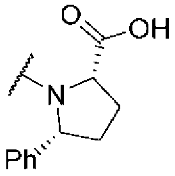
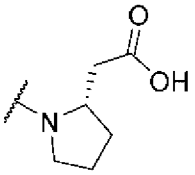
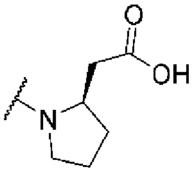
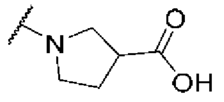
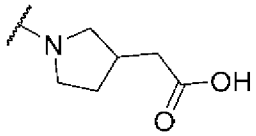
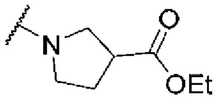
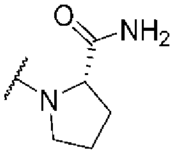
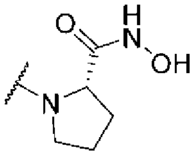
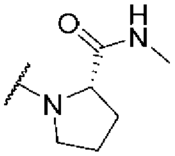
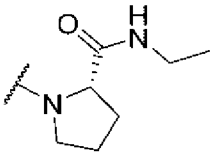
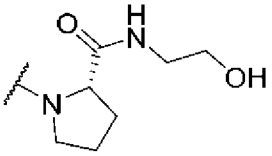
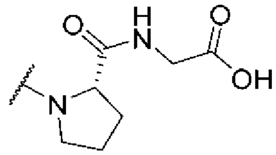
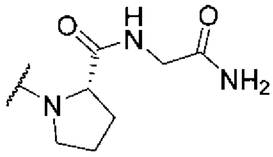
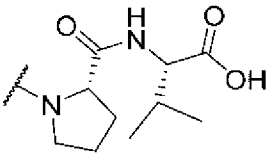
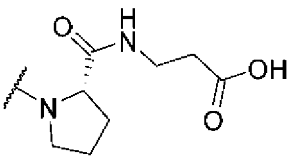
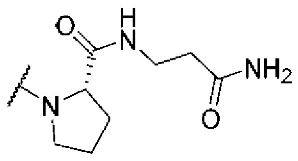
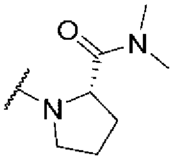
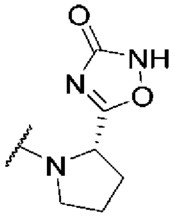
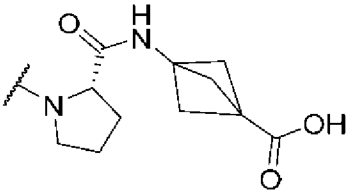
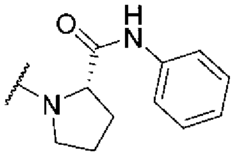
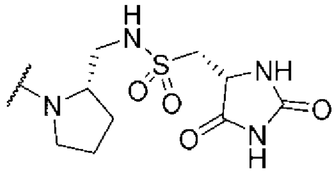
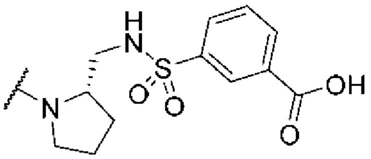
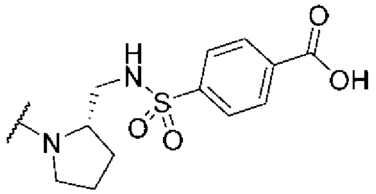
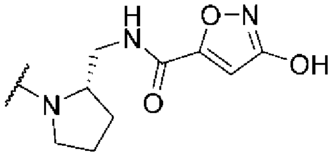
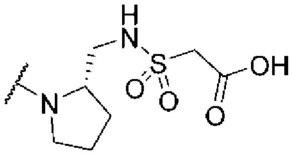
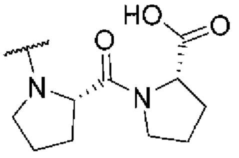
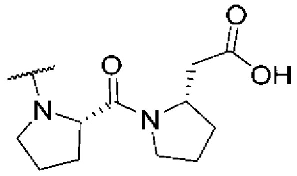
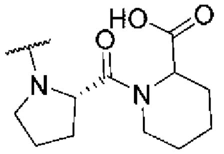
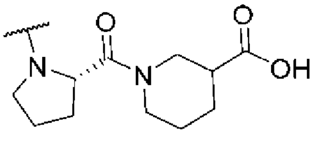
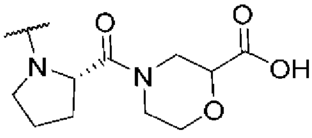
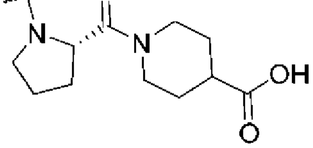
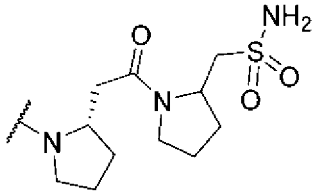
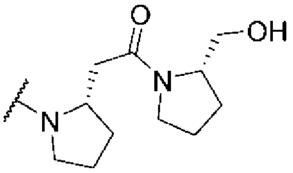
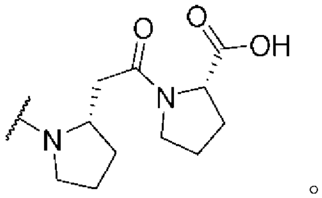
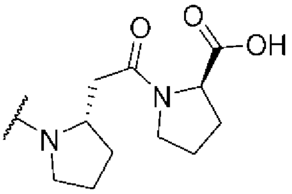
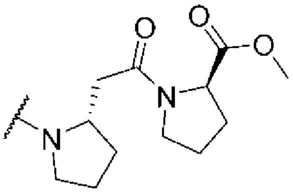
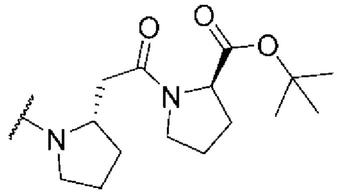
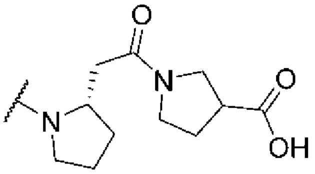
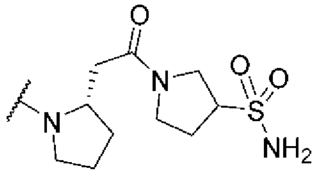
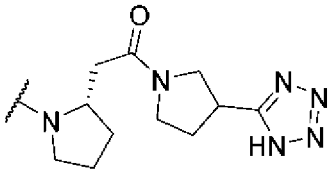
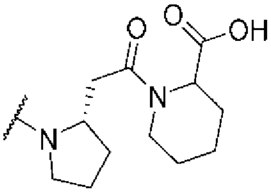
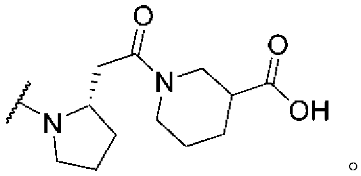
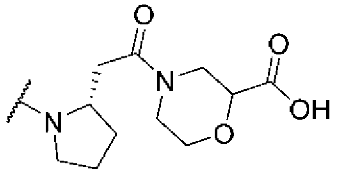
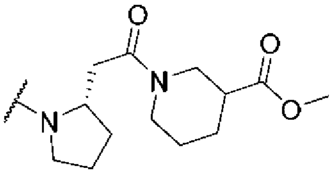
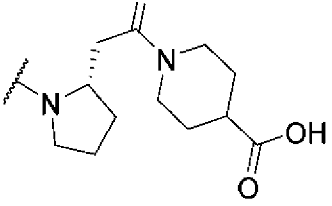
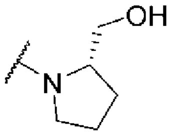
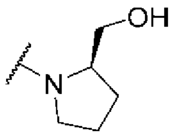
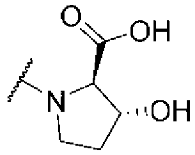
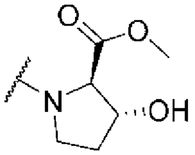
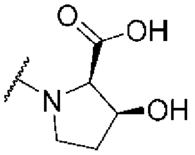
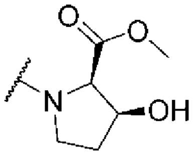
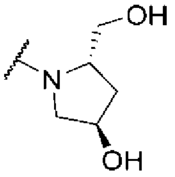
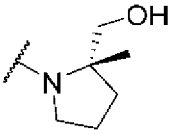
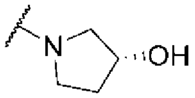
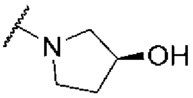
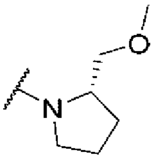
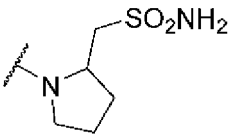
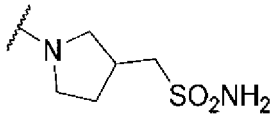
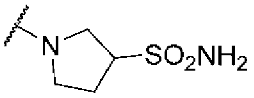
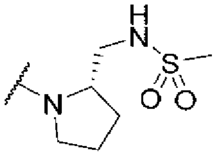
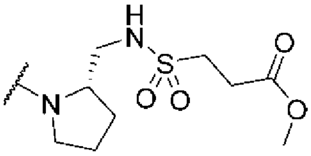
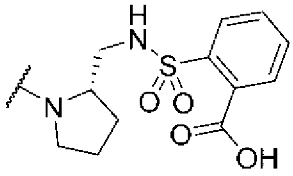
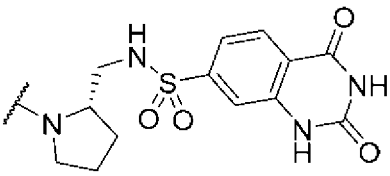
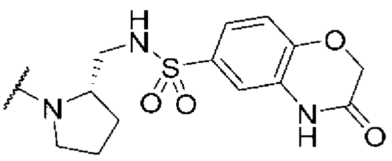
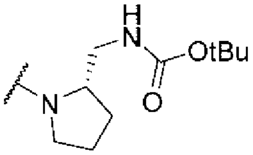
。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係

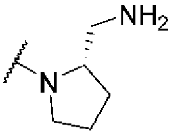
。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些

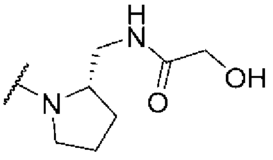
實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施

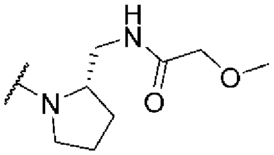
例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實

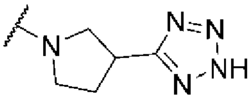
施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些

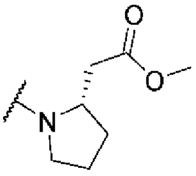
實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些實施例中，R²係  。在一些

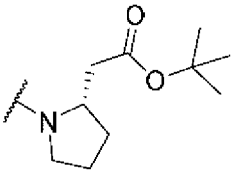
實施例中，R^{2}係

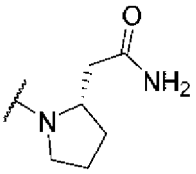
。在一些實施例中，R^{2}係

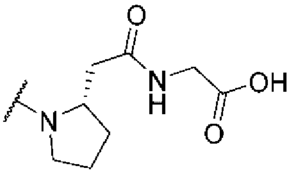
。在一些實施例中，R^{2}係

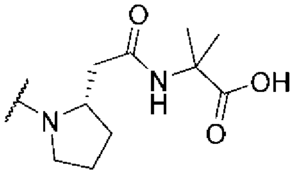
。在一些實施例中，R^{2}係

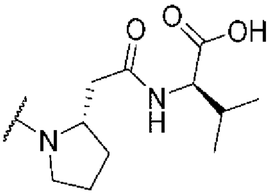
。在一些實施例中，R^{2}係

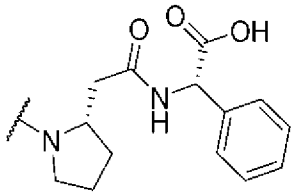
。在一些實施例中，R^{2}係

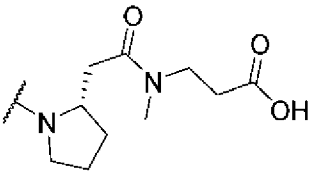
。在一些實施例中，R^{2}係

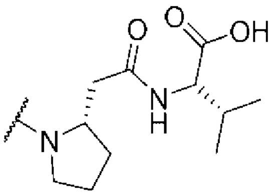
。在一些實施例中，R^{2}係

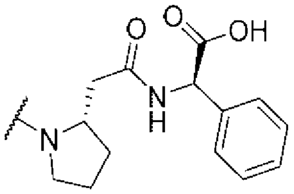
。在一些實施例中，R^{2}係

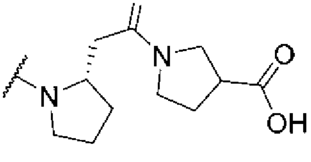
。在一些實施例中，R^{2}係

。在一些實施例中，R^{2}係

。在一些實施例中，R^{2}係

。在一些實施例中，R^{2}係

。在一些實施例中，R^{2}係

。在一些實施例中，R^{2}係

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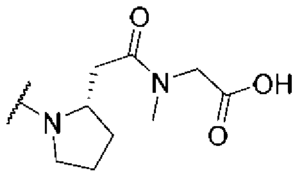
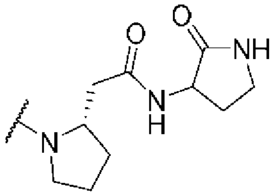
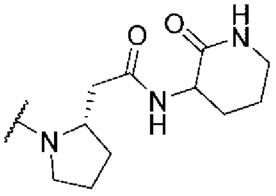
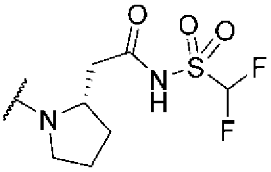
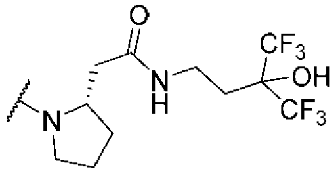
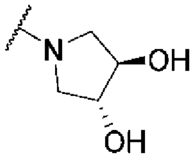
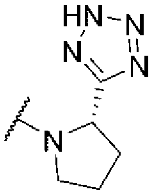
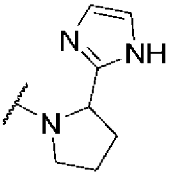
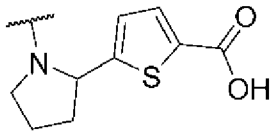
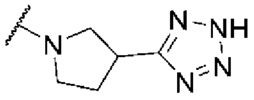
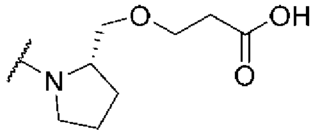
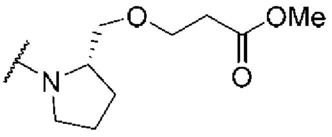
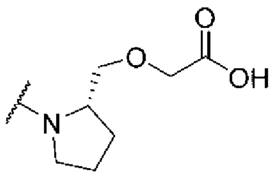
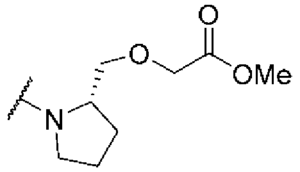
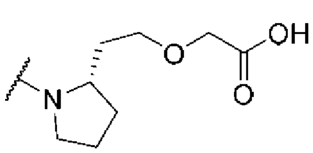
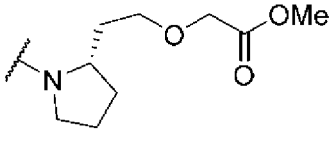
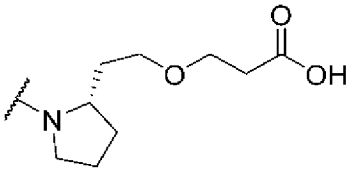
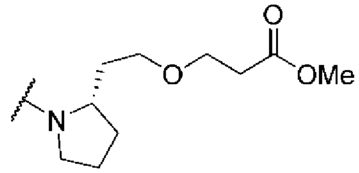
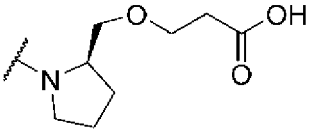
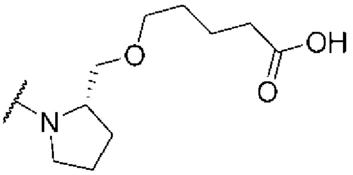
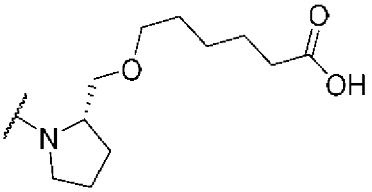
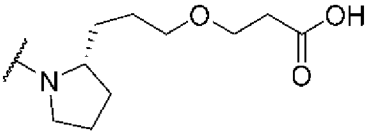
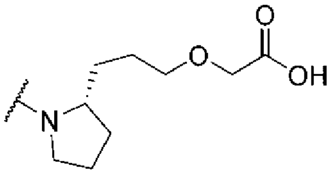
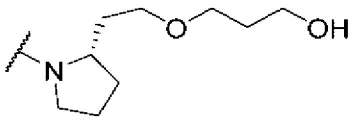
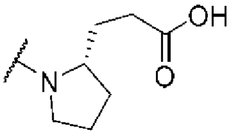
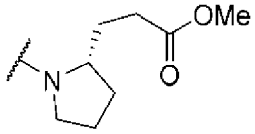
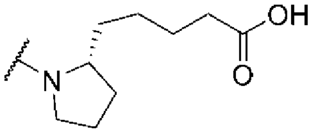
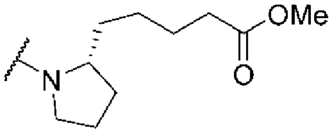
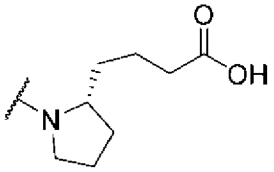
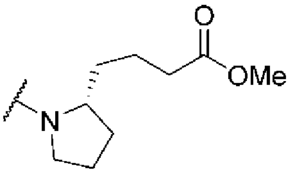
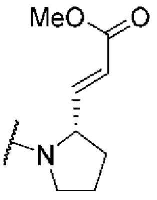
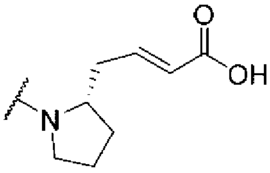
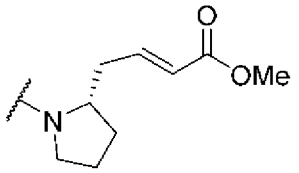
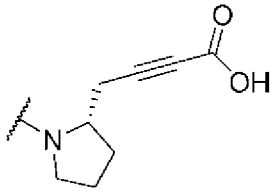
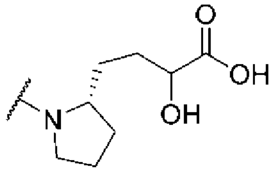
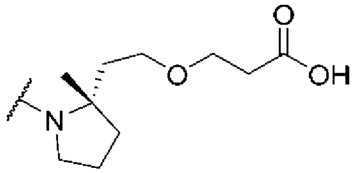
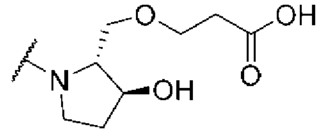
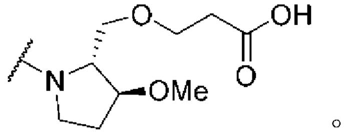
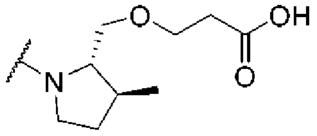
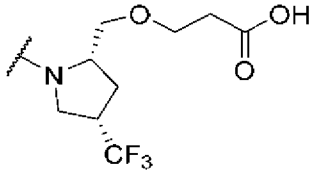
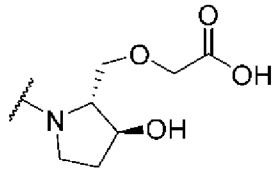
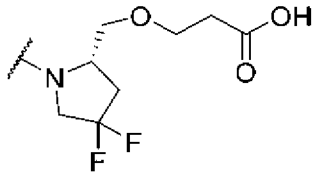
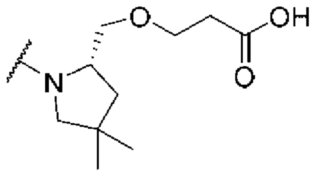
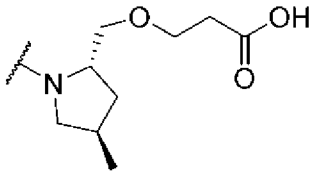
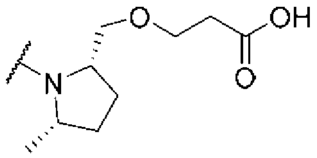
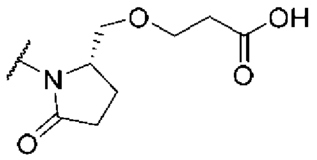
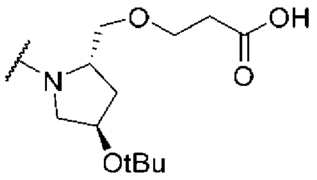
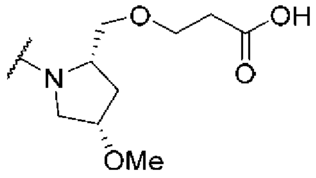
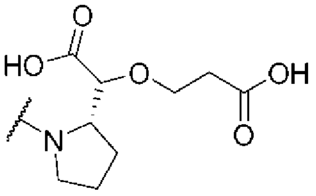
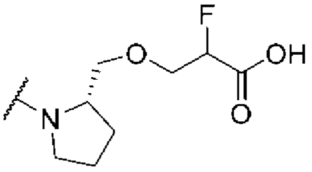
施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係

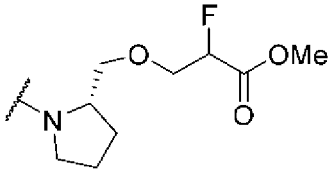
。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實

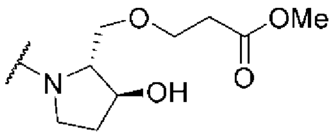
施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實

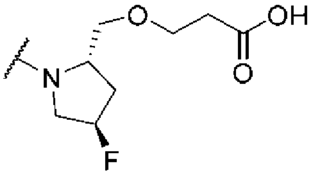
施例中，R^{2}係 

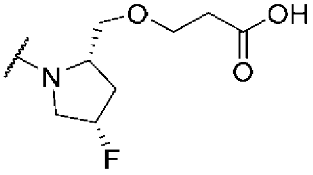
。在一些實施例中，R^{2}係 

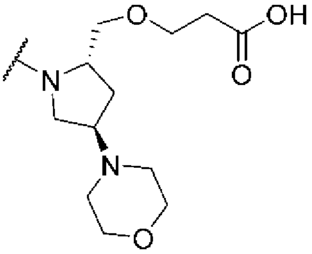
。在一些實施例中，R^{2}係 

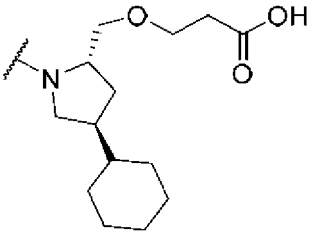
。在一些實施例中，R^{2}係 

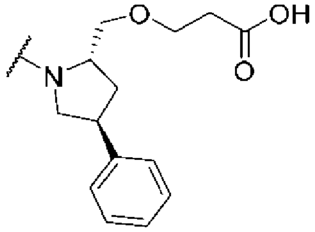
。在一些實施例中，R^{2}係 

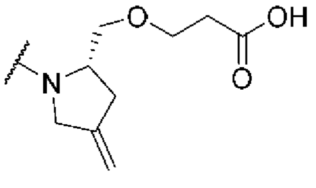
。在一些實施例中，R^{2}係 

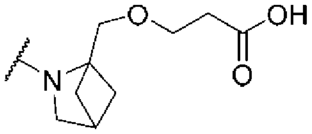
。在一些實施例中，R^{2}係 

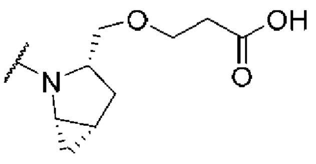
。在一些實施例中，R^{2}係 

。在一些實施例中，R^{2}係 

。在一些實施例中，R^{2}係 

。在一些實施例中，R^{2}係 

。在一些實施例中，R^{2}係 

。在一些實施例中，R^{2}係 

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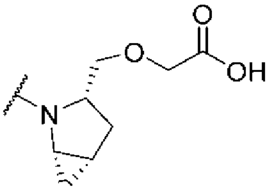
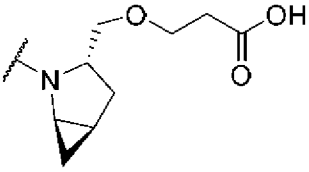
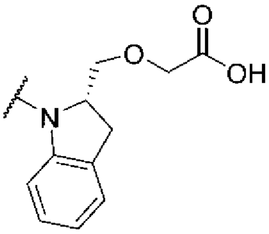
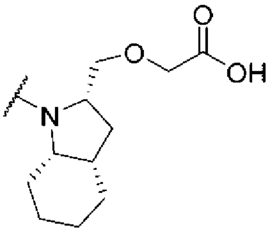
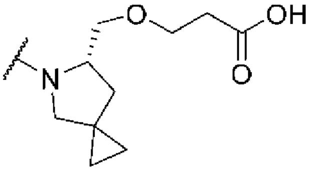
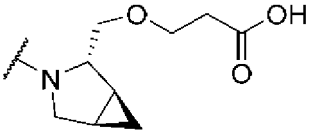
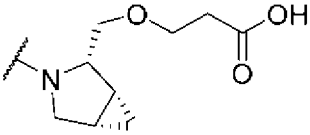
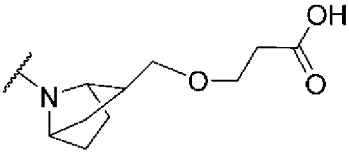
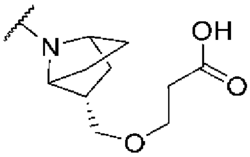
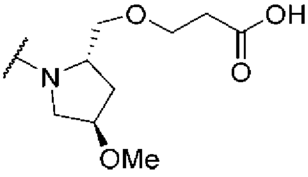
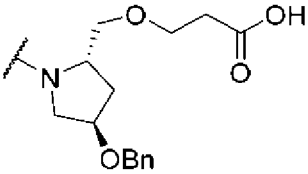
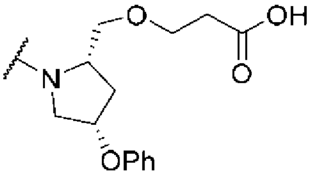
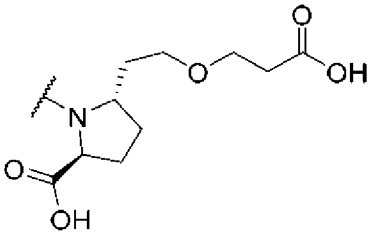
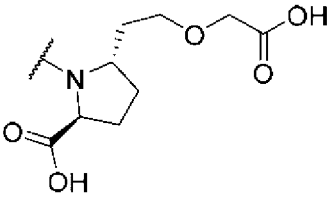
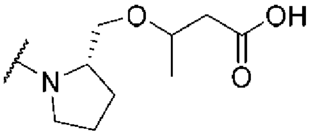
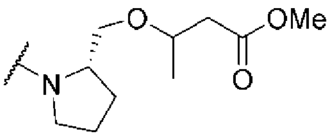
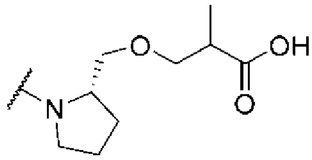
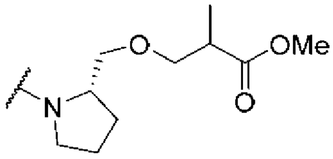
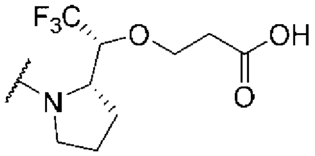
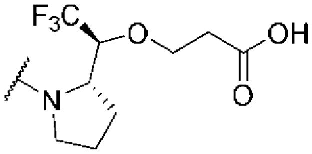
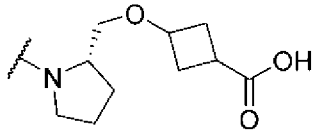
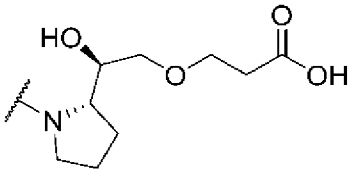
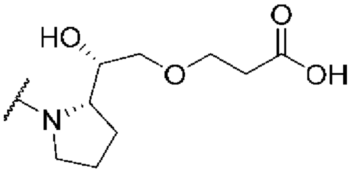
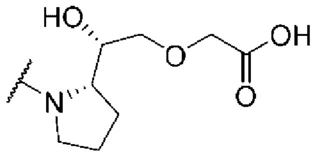
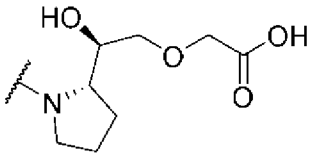
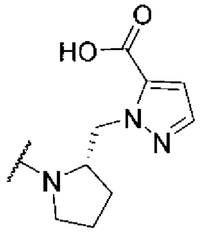
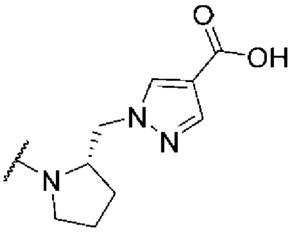
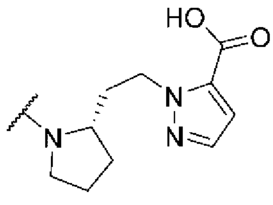
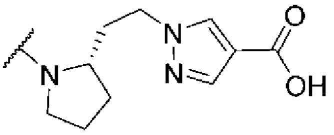
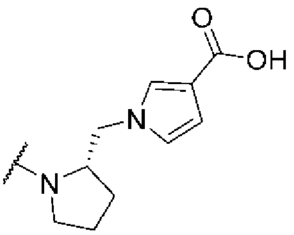
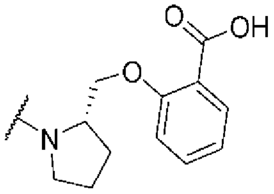
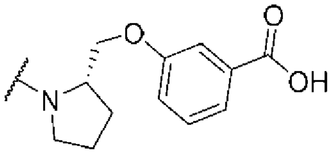
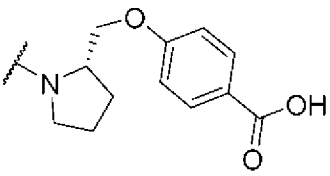
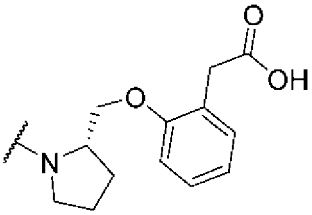
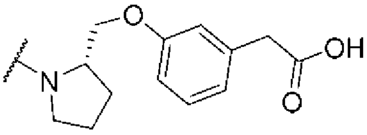
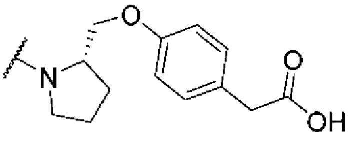
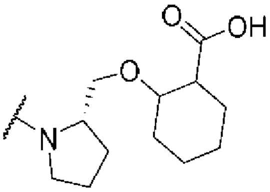
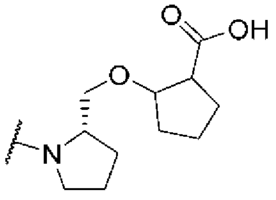
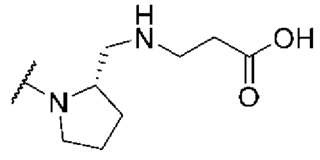
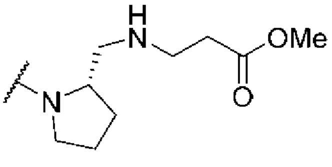
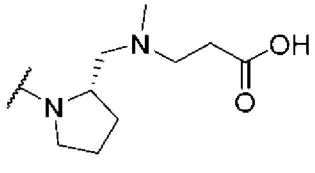
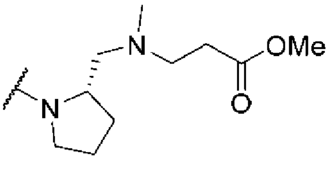
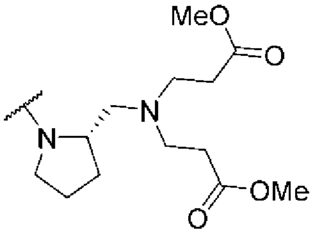
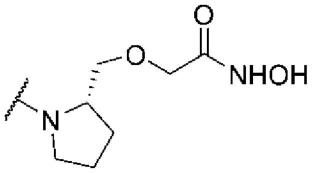
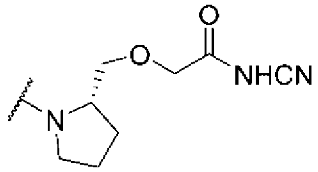
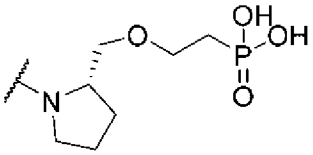
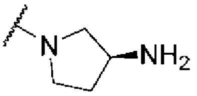
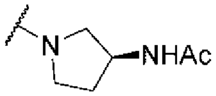
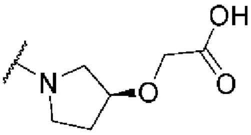
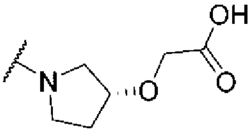
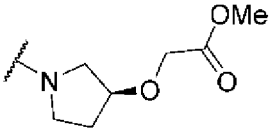
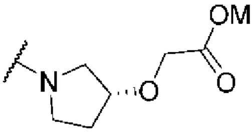
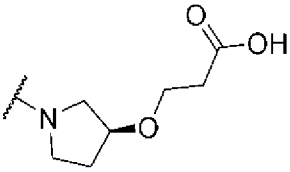
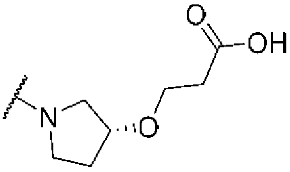
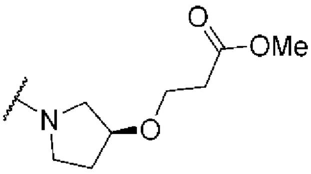
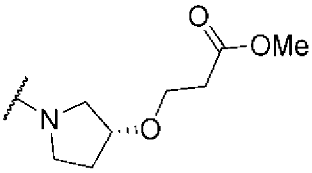
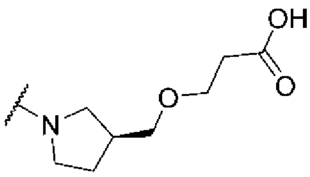
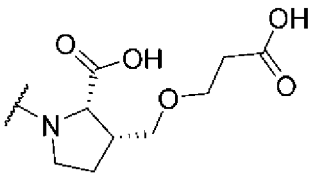
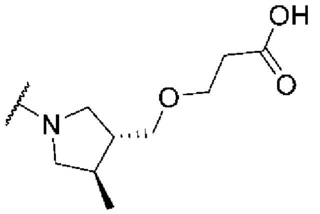
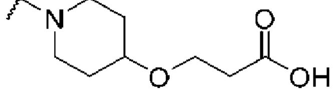
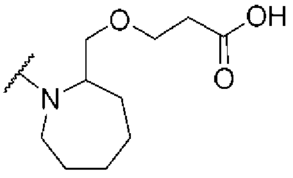
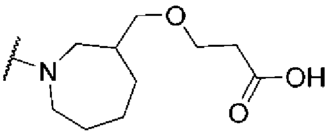
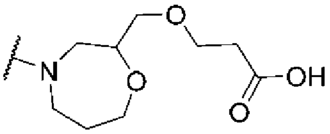
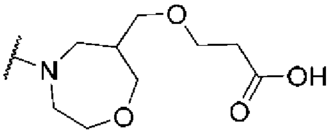
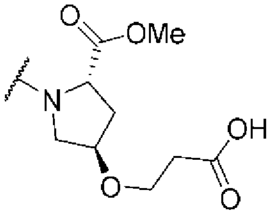
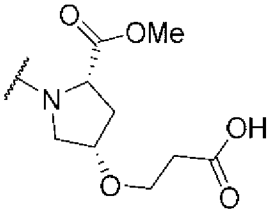
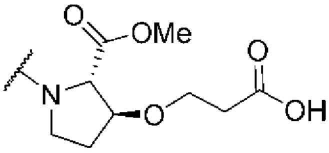
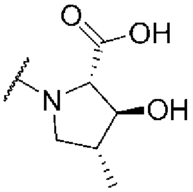
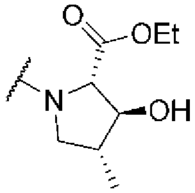
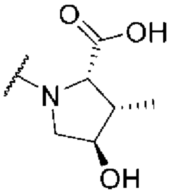
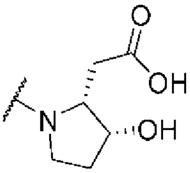
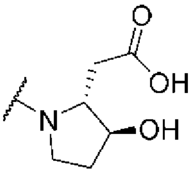
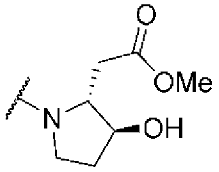
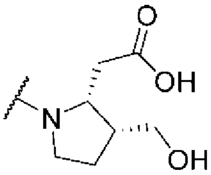
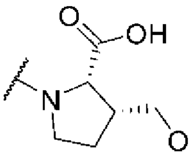
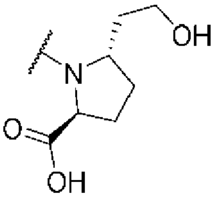
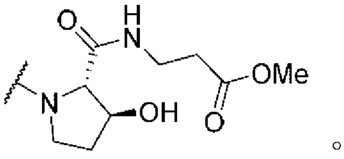
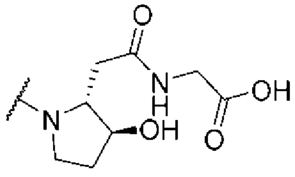
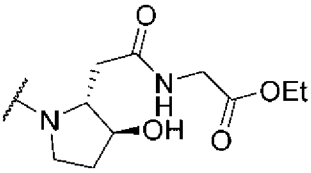
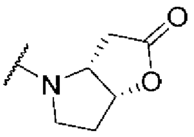
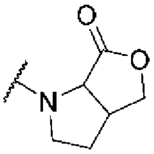
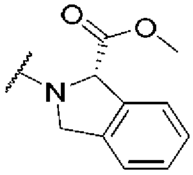
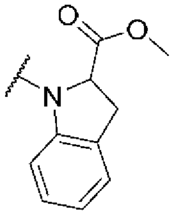
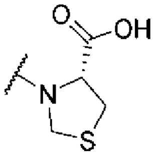
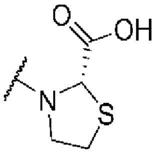
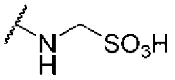
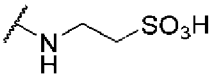
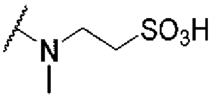
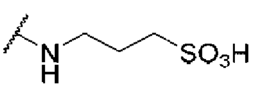
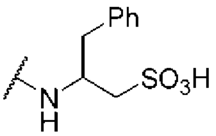
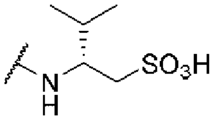
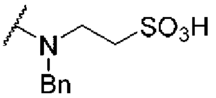
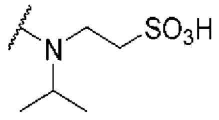
 。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係  。在一些實施例中，R^2係

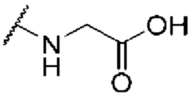
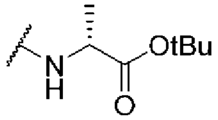
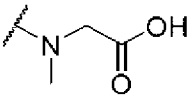
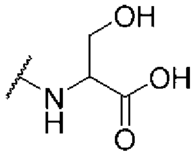
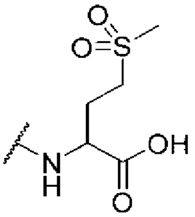
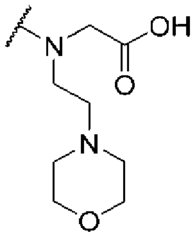
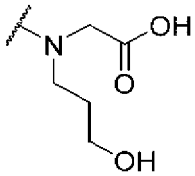
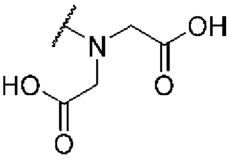
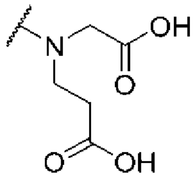
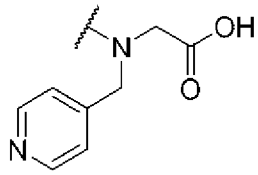
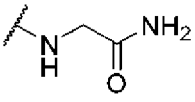
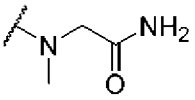
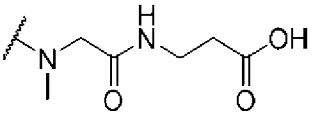
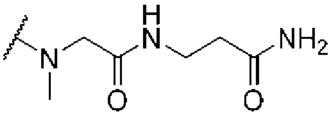
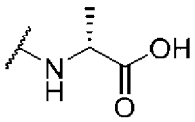
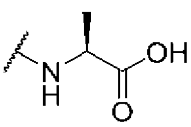
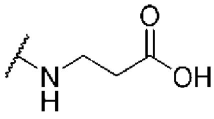
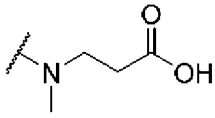
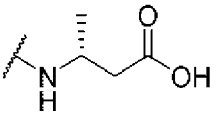
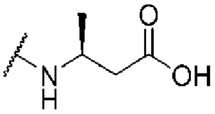
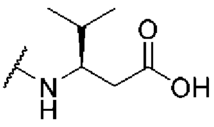
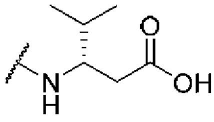
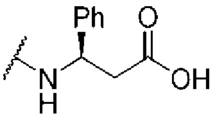
。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係

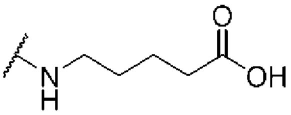
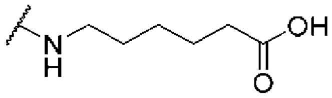
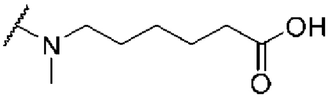
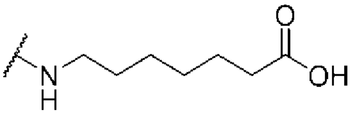
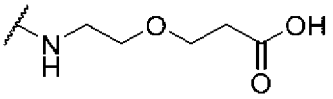
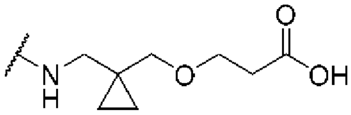
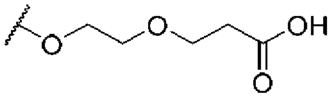
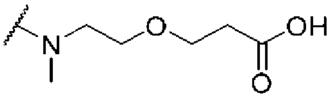
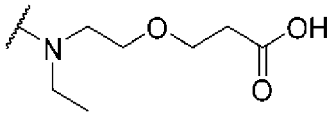
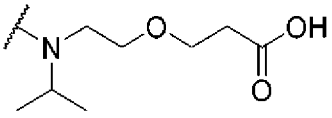
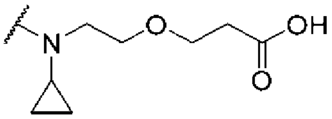
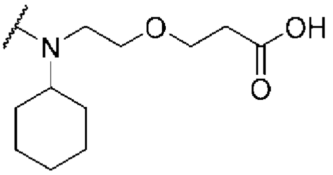
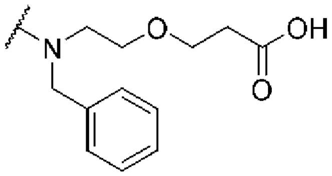
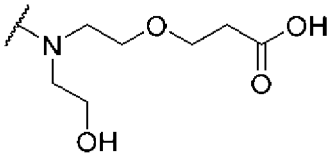
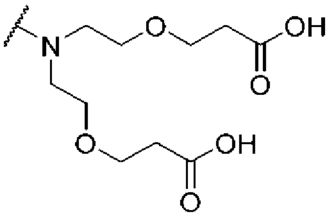
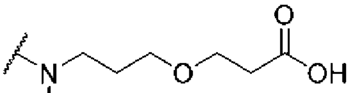
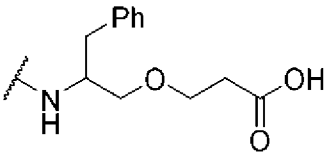
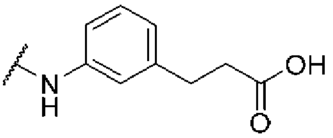
。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些

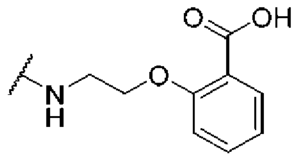
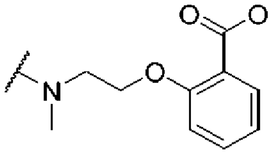
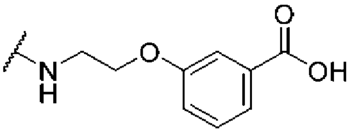
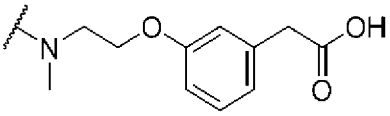
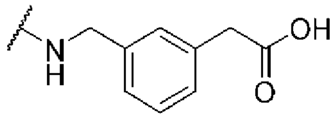
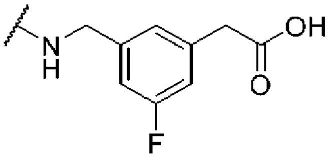
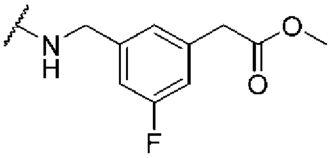
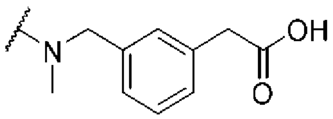
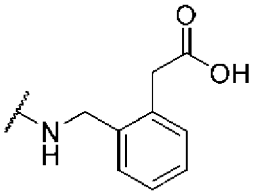
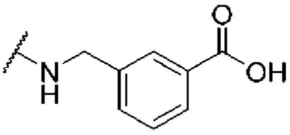
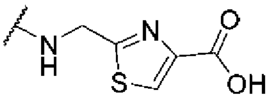
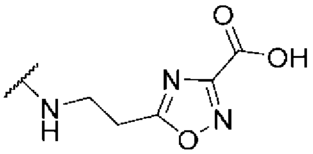
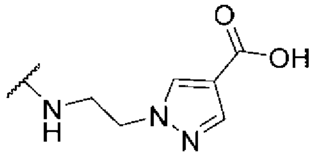
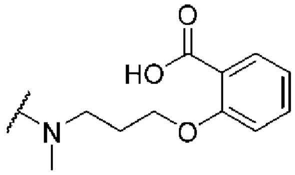
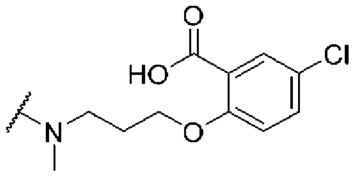
實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實

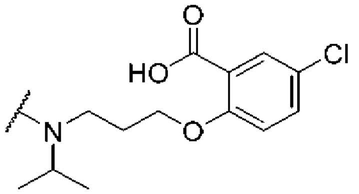
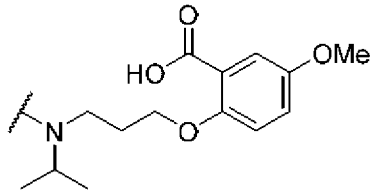
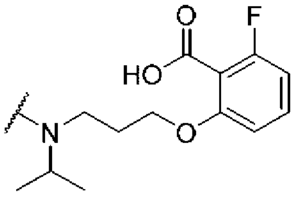
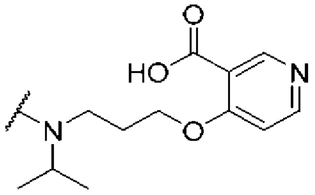
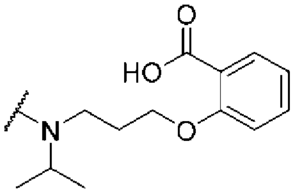
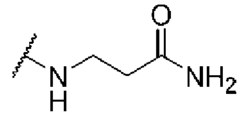
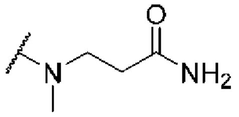
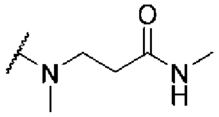
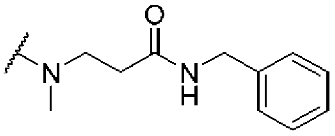
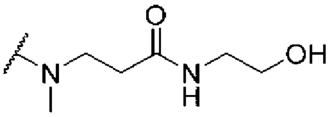
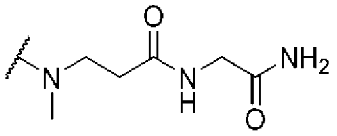
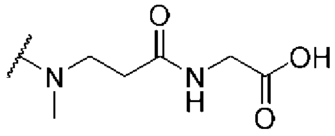
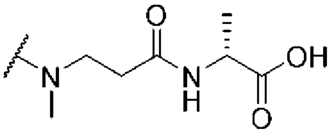
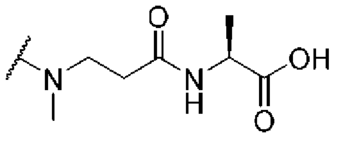
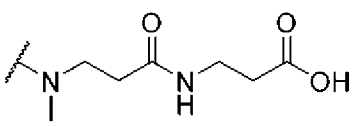
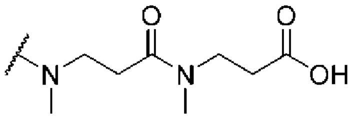
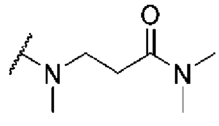
施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些

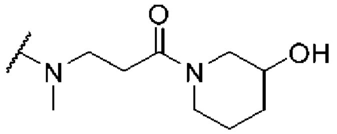
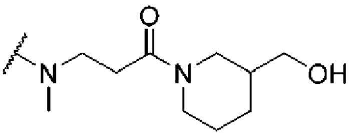
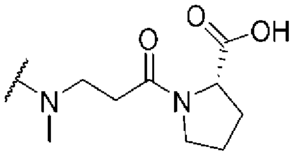
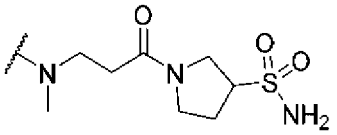
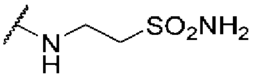
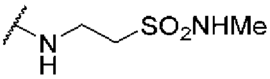
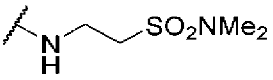
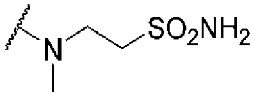
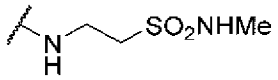
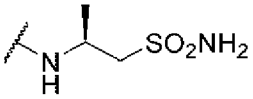
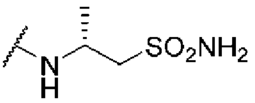
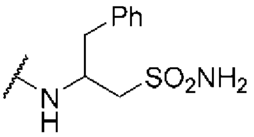
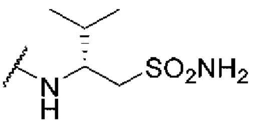
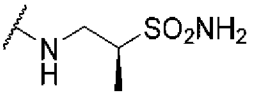
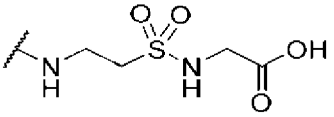
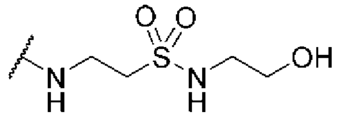
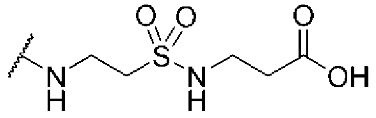
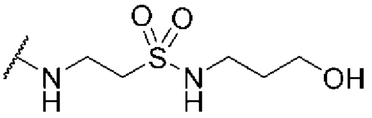
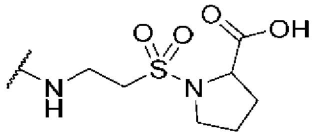
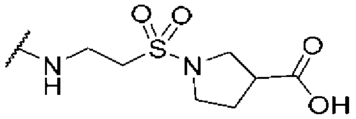
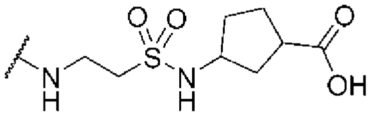
實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係

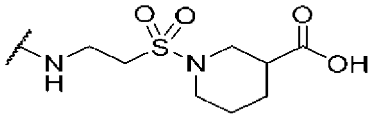
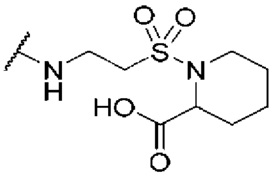
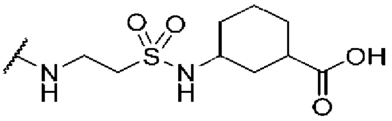
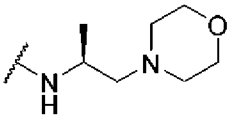
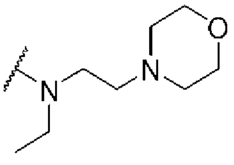
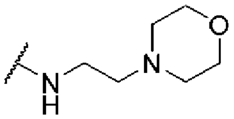
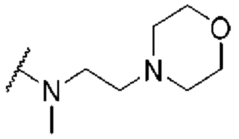
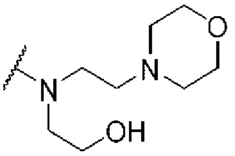
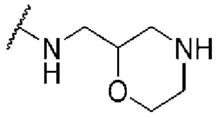
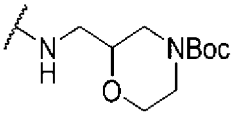
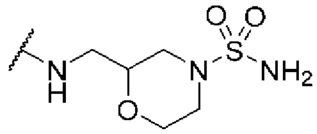
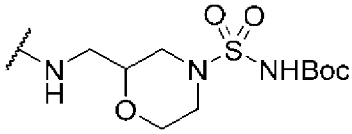
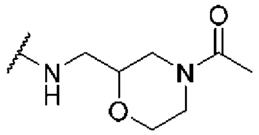
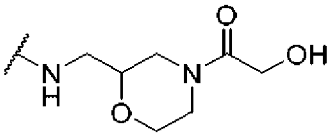
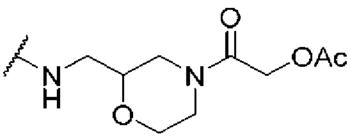
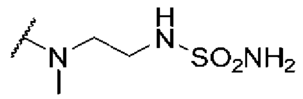
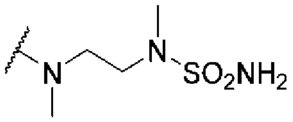
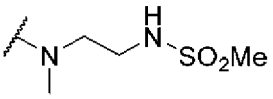
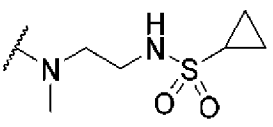
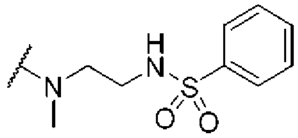
。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一些實施例中，R²係。在一

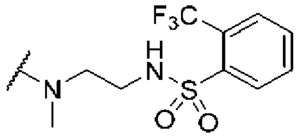
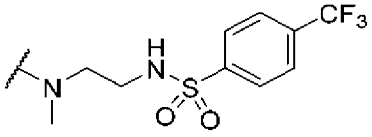
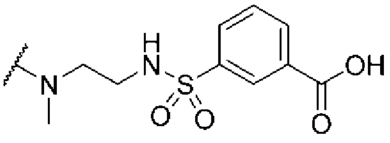
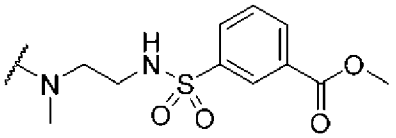
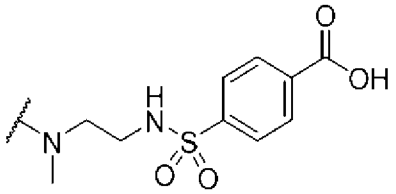
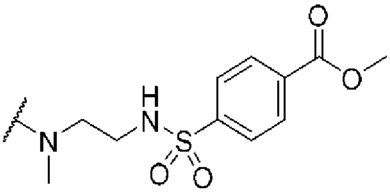
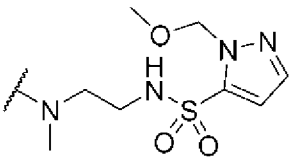
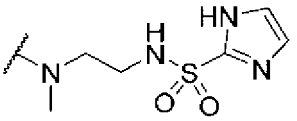
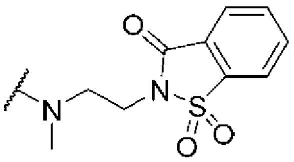
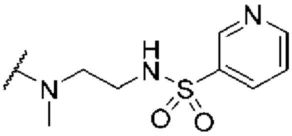
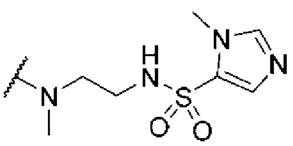
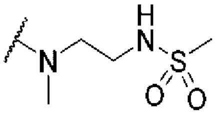
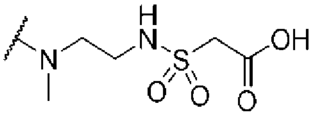
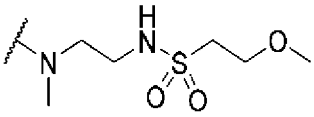
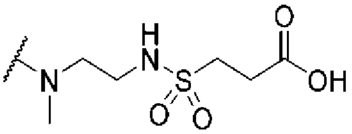
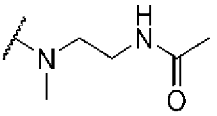
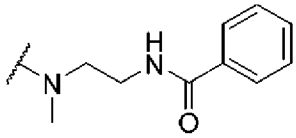
些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些實施例中，R^2係 。在一些

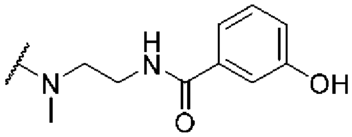
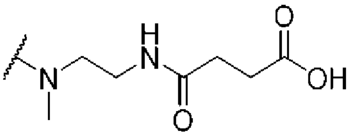
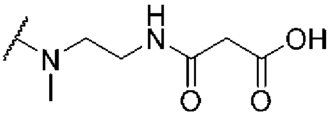
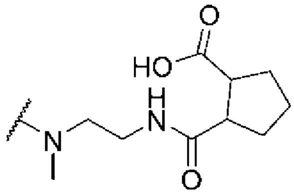
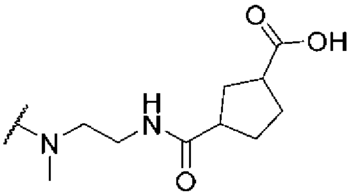
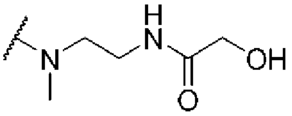
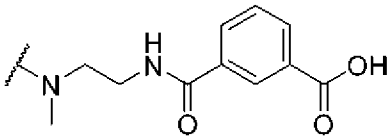
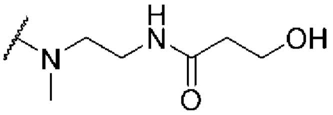
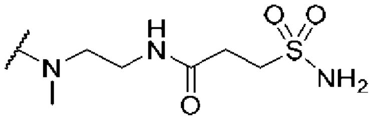
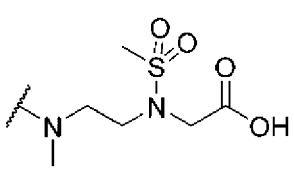
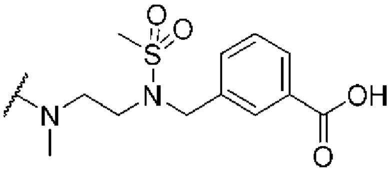
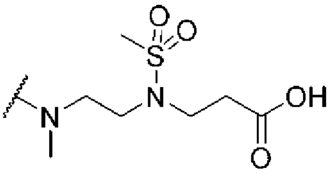
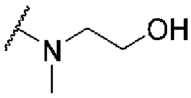
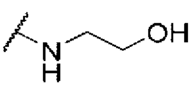
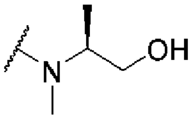
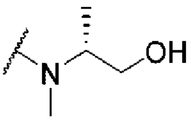
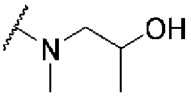
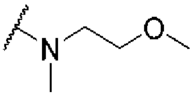
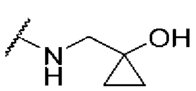
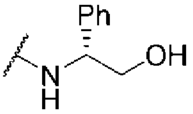
實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係  。在一些實施例中，R^{2}係

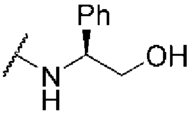
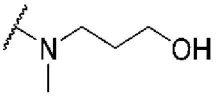
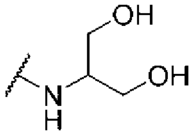
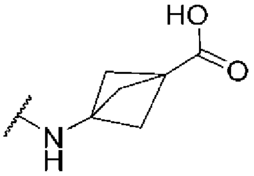
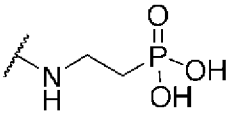
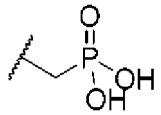
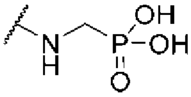
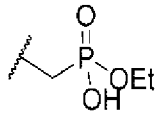
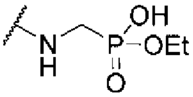
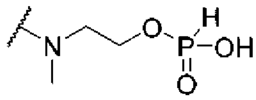
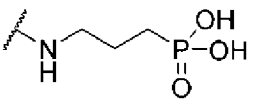
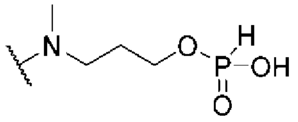
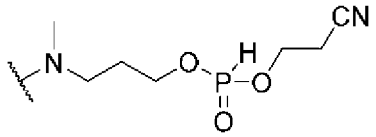
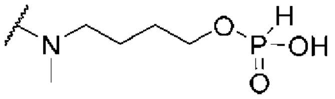
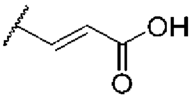
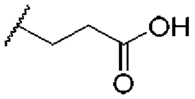
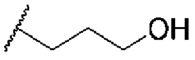
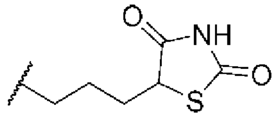
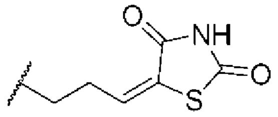
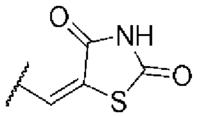
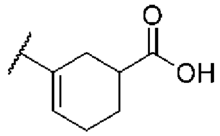
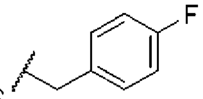
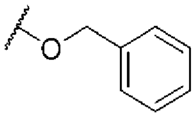
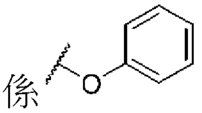
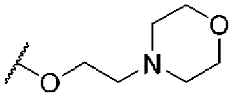
。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係

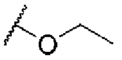
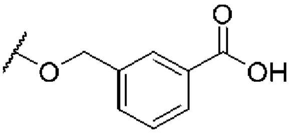
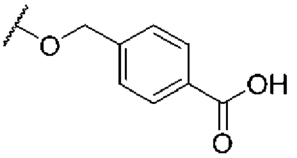
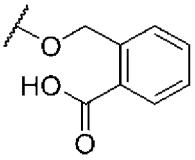
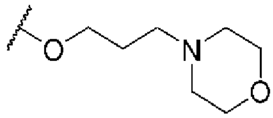
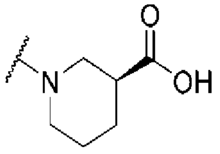
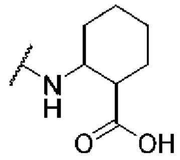
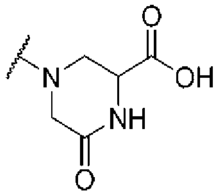
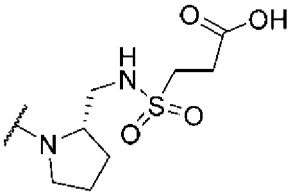
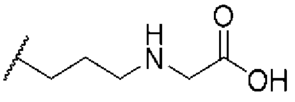
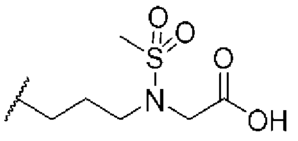
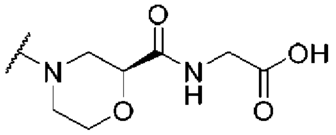
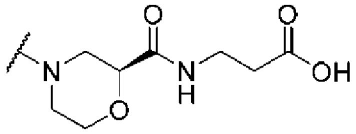
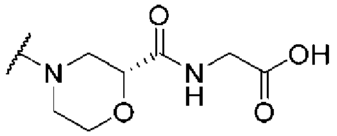
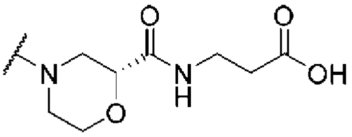
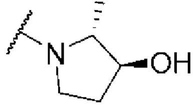
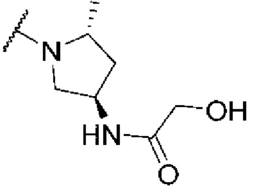
。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係

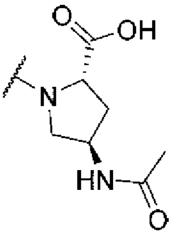
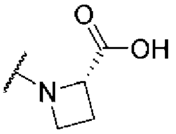
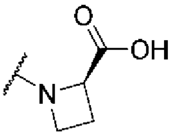
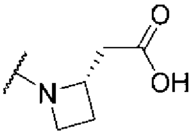
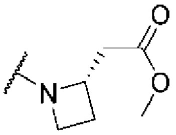
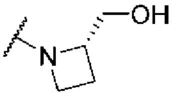
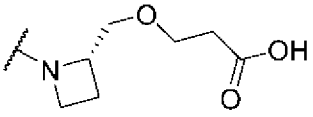
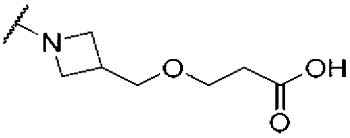
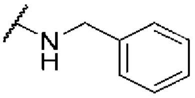
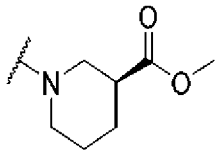
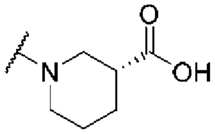
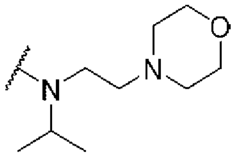
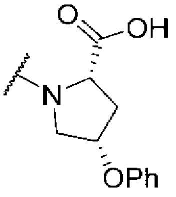
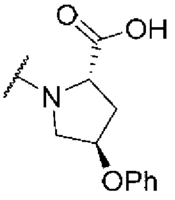
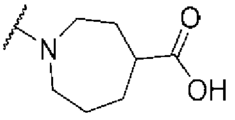
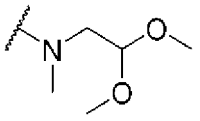
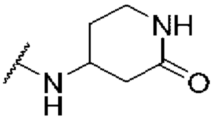
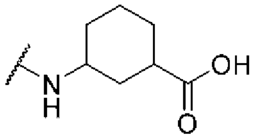
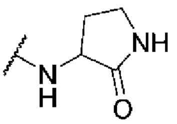
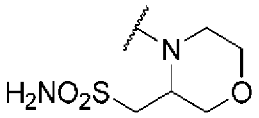
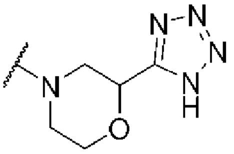
。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係

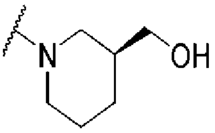
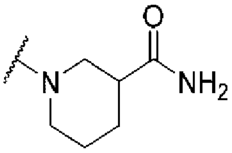
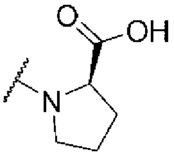
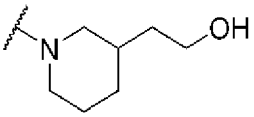
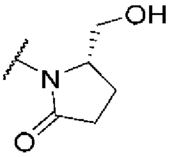
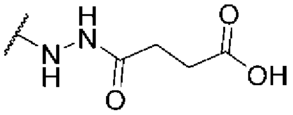
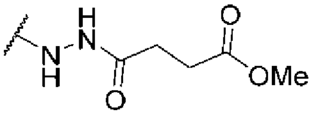
。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係

。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係

。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在一些實施例中，R^{2}係。在

一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，

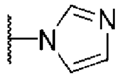
R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例中，R^{2}係 。在一些實施例

中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。在一些實施例中，R^2係。

【0355】 在一些實施例中，R^2係選自**表1**中所描繪之基團。

【0356】 如上文所定義及本文所描述，每個R^3獨立地係鹵素、-OR、-NR_2、-SR或R^C，特定言之為鹵素，諸如氯。

【0357】 在一些實施例中，R^3係鹵素。在一些實施例中，R^3係-OR。在一些實施例中，R^3係-NR_2。在一些實施例中，R^3係-SR。在一些實施例中，R^3係R^C。

【0358】 在一些實施例中，R^3係氟。在一些實施例中，R^3係氯。在一些實施例中，R^3係溴。在一些實施例中，R^3係-OH。在一些實施例中，R^3係-OMe。在一些實施例中，R^3係-OEt。在一些實施例中，R^3係甲基。在一些實施例中，R^3係異丙基。在一些實施例中，R^3係三級丁基。在一些實施例中，R^3係-CF_3。在一些實施例中，R^3係苯基。在一些實施例中，R^3係。

【0359】 在一些實施例中，R^3係選自**表1**中所描繪之基團。

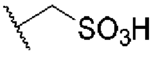
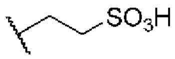
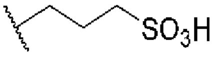
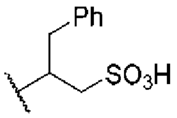
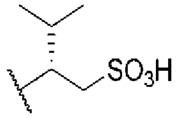
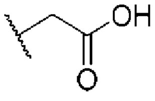
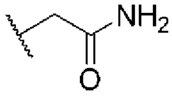
【0360】 如上文所定義及本文所描述，R^4係氫或視情況經取代之C_{1-6}脂族基。

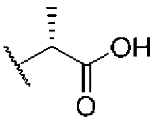
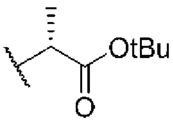
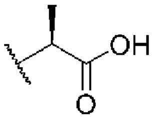
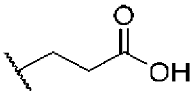
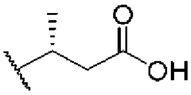
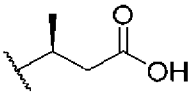
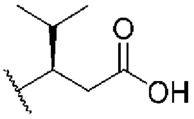
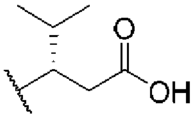
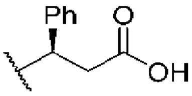
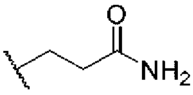
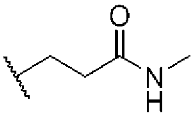
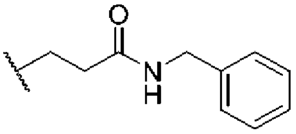
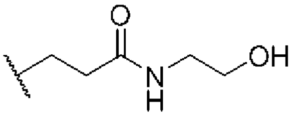
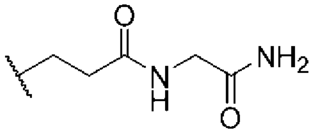
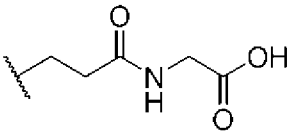
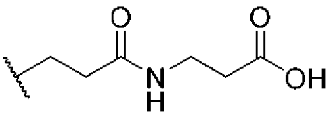
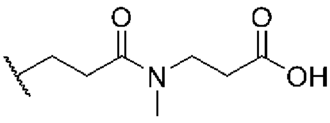
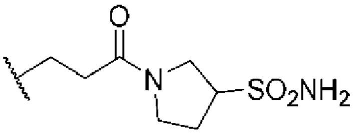
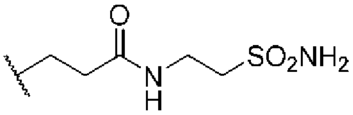
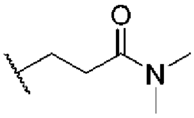
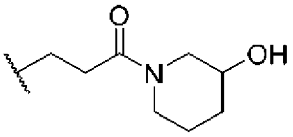
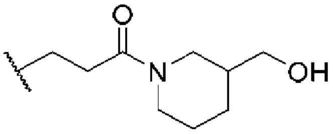
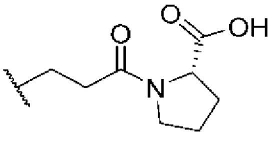
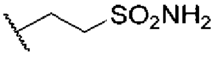
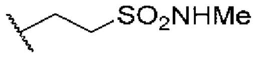
【0361】在一些實施例中，R^4係氫。在一些實施例中，R^4係視情況經取代之C_{1-6}脂族基。在一些實施例中，R^4係甲基。

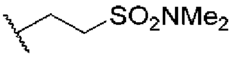
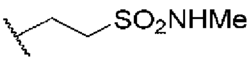
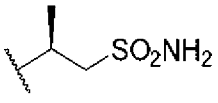
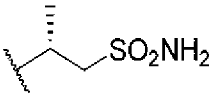
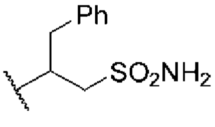
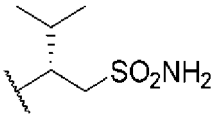
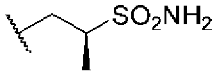
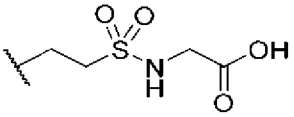
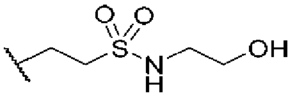
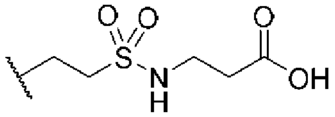
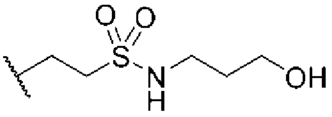
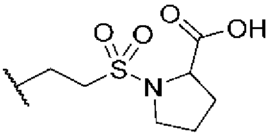
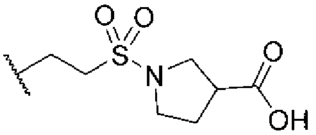
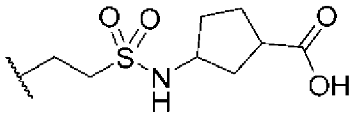
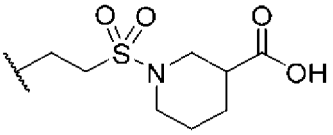
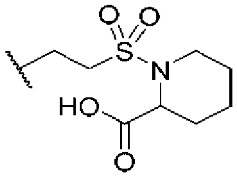
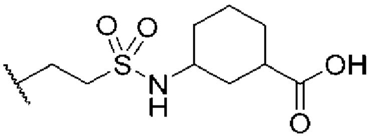
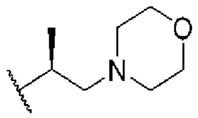
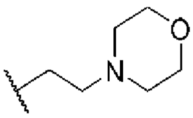
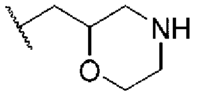
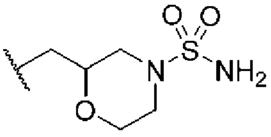
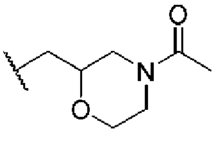
【0362】在一些實施例中，R^4係選自**表1**中所描繪之基團。

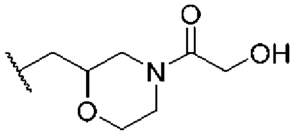
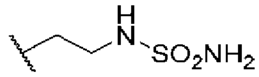
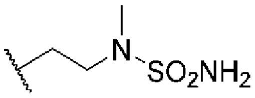
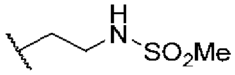
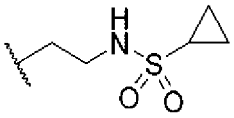
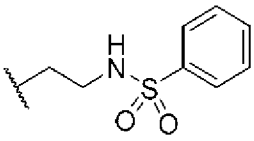
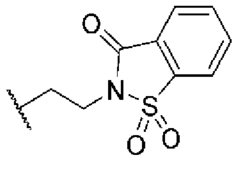
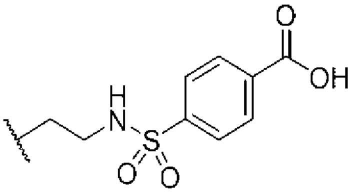
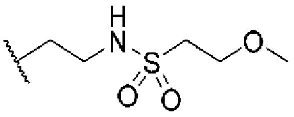
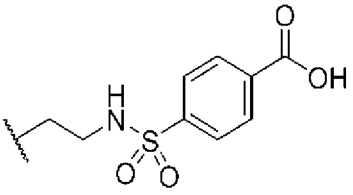
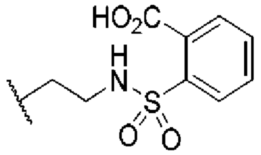
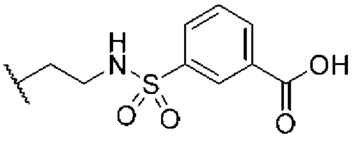
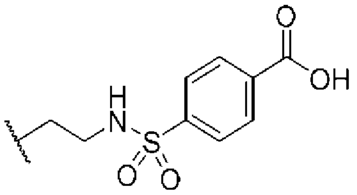
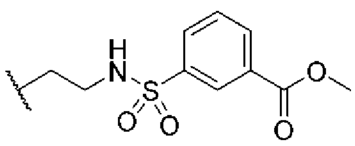
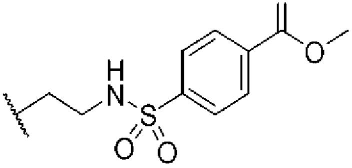
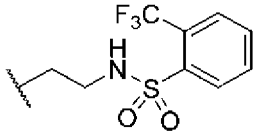
【0363】如上文所定義及本文所描述，R^5係$-(CR_2)_{0-6}OR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$或$R^B$。

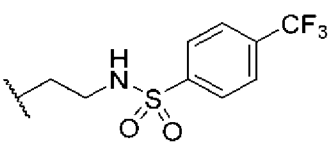
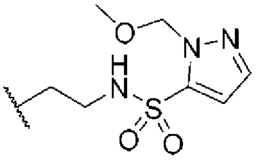
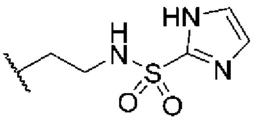
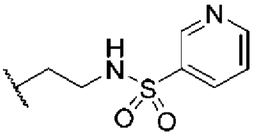
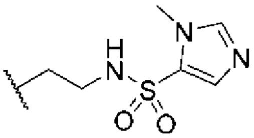
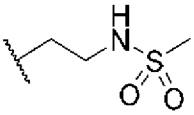
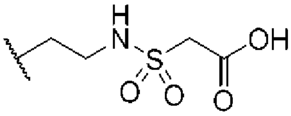
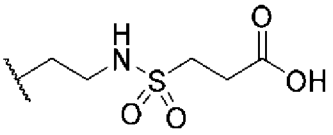
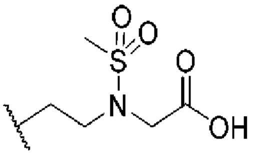
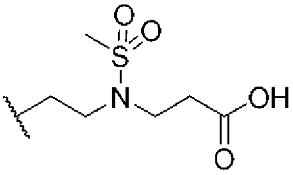
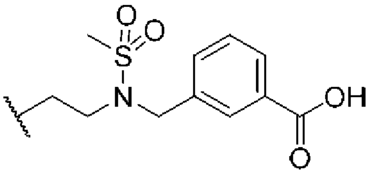
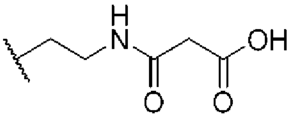
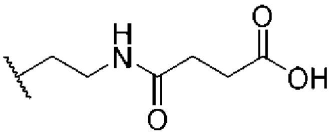
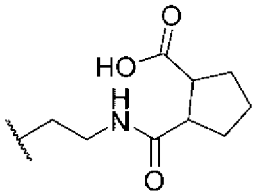
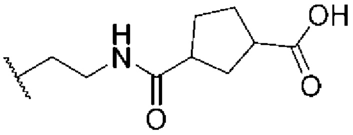
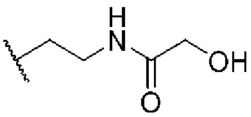
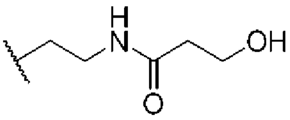
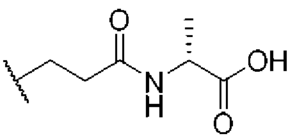
【0364】在一些實施例中，R^5係$-(CR_2)_{0-6}OR$。在一些實施例中，R^5係$-(CR_2)_{0-6}CO_2R$。在一些實施例中，R^5係$-(CR_2)_{0-6}CONR_2$。在一些實施例中，R^5係$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CO_2R$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}C(O)NR(CR_2)_{0-6}CONR_2$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}SO_3R$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}SO_2NR_2$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}OSO_2NR_2$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}NRSO_2R$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}NRSO_2OR$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}OP(OR)_2$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}OP(O)(OR)_2$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}P(O)(OR)_2$。在一些實施例中，$R^5$係$-(CR_2)_{0-6}OP(O)(H)OR$。在一些實施例中，$R^5$係$R^B$。

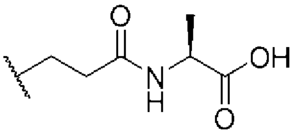
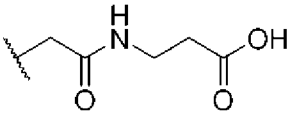
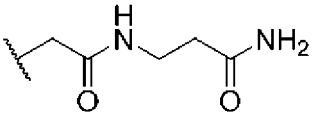
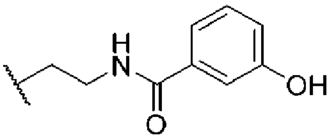
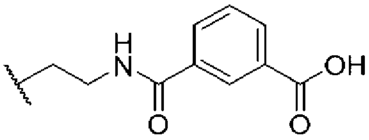
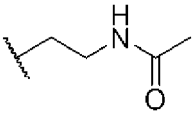
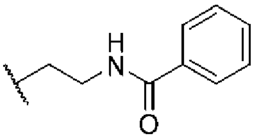
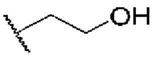
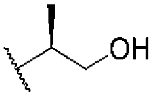
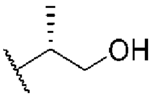
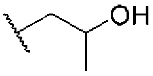
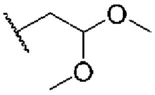
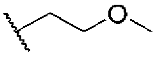
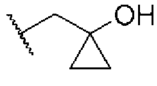
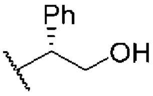
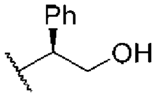
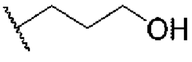
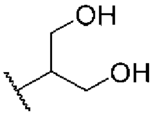
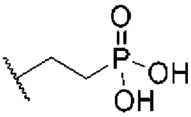
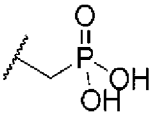
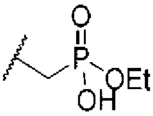
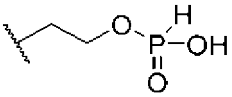
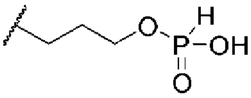
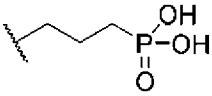
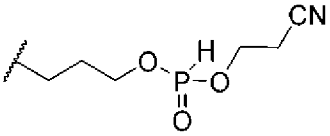
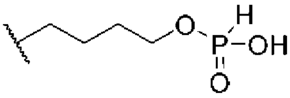
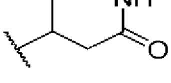
【0365】在一些實施例中，R^5係  。在一些實施例中，R^5係  。在一些實施例中，R^5係  。在一些實施例中，R^5係  。在一些實施例中，R^5係  。在一些實施例中，R^5係  。在一些實施例中，R^5係  。在一些實施例中，R^5係

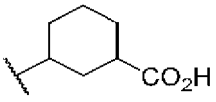
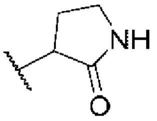
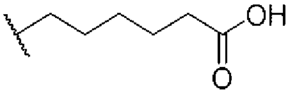
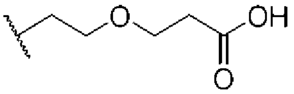
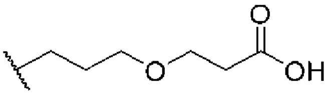
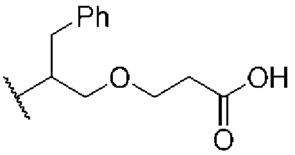
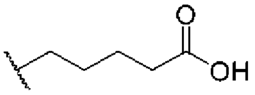
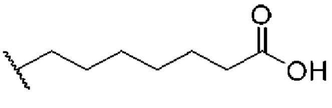
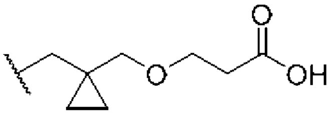
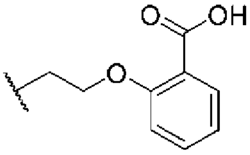
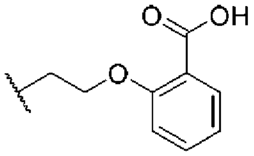
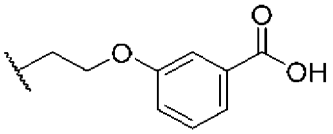
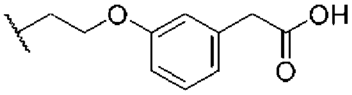
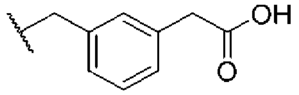
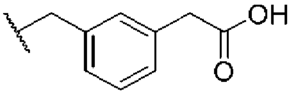
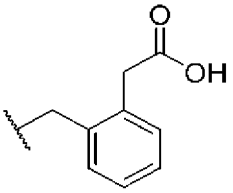
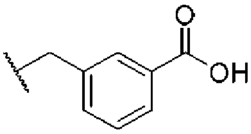
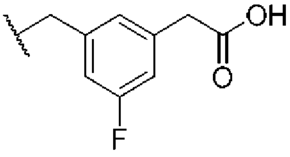
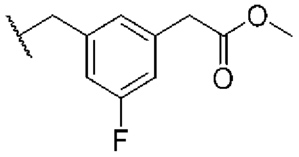
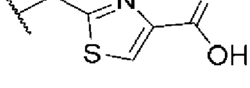
。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，R^{5}係。在一些實施例中，

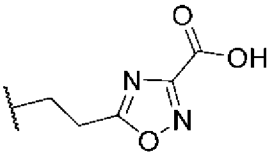
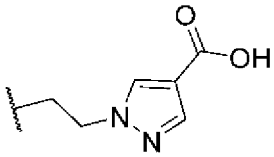
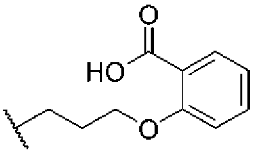
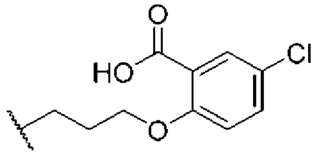
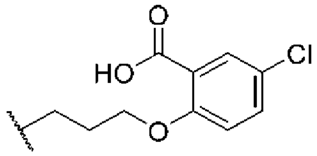
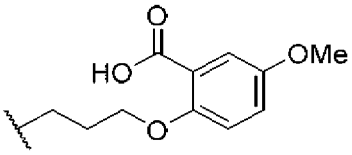
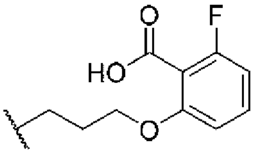
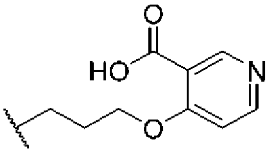
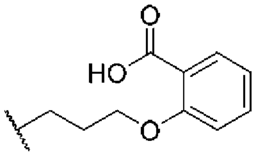
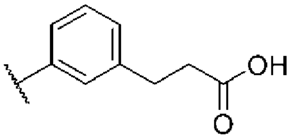
R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係

。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係

。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係

。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。

在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例

中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。在一些實施例中，R^5係。

【0366】 在一些實施例中，R^5係選自**表1**中所描繪之基團。

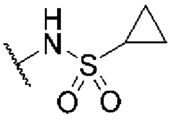
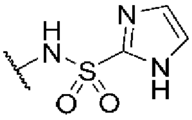
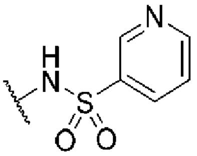
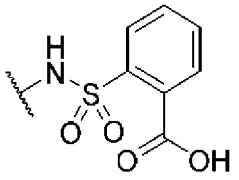
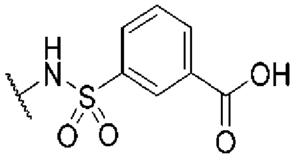
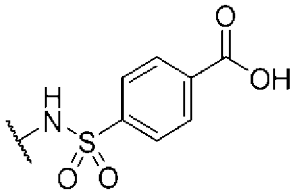
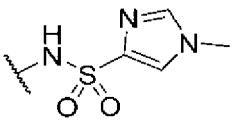
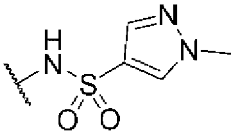
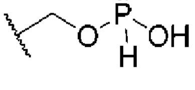
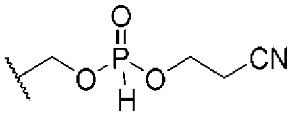
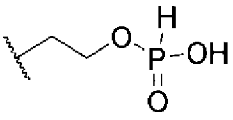
【0367】 如上文所定義及本文所描述，每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0-6}CO_2R$、$-(CR_2)_{0-6}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-6}SO_3R$、$-(CR_2)_{0-6}SO_2NR_2$、$-(CR_2)_{0-6}OSO_2NR_2$、$-(CR_2)_{0-6}NRSO_2R$、$-(CR_2)_{0-6}NRSO_2OR$、$-(CR_2)_{0-6}OP(OR)_2$、$-(CR_2)_{0-6}OP(O)(OR)_2$、$-(CR_2)_{0-6}P(O)(OR)_2$、$-(CR_2)_{0-6}OP(O)(H)OR$、$-B(OR)_2$或R^B。

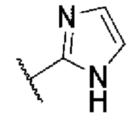
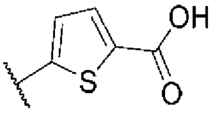
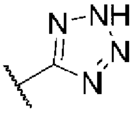
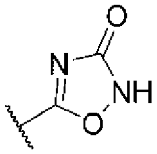
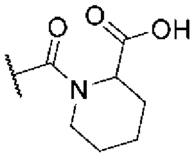
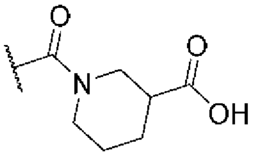
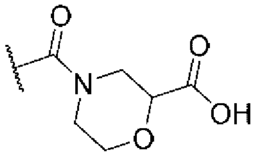
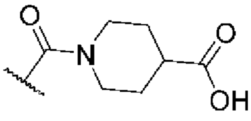
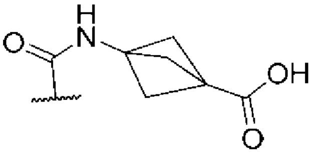
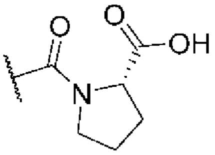
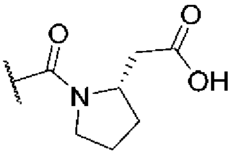
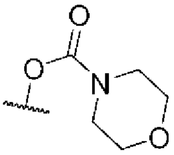
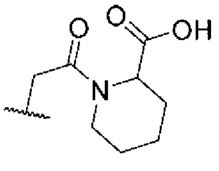
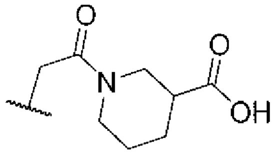
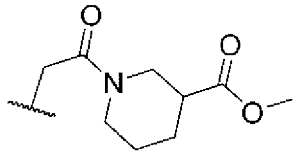
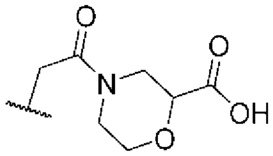
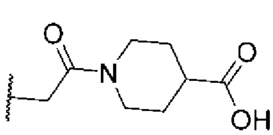
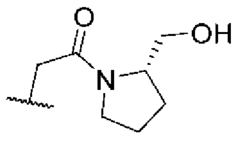
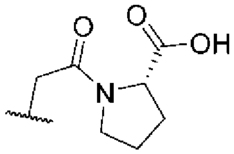
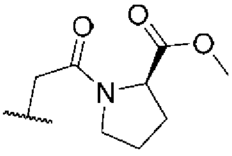
【0368】 在一些實施例中，R^6係鹵素。在一些實施例中，R^6係$-COR$。在一些實施例中，R^6係$-(CR_2)_{0-6}CO_2R$。在一些實施例中，R^6係$-(CR_2)_{0-6}CONR_2$。在一些實施例中，R^6係$-OR$。在一些實施例中，R^6係$-(CR_2)_{1-}$

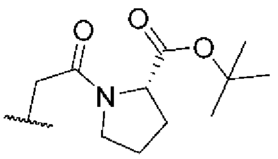
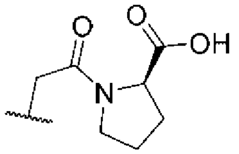
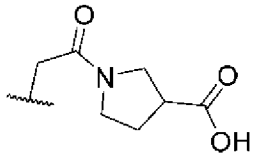
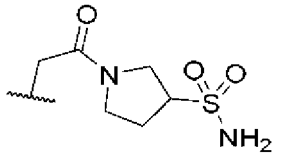
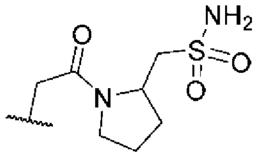
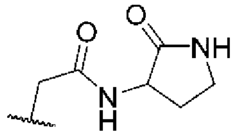
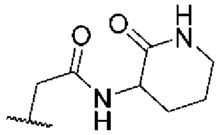
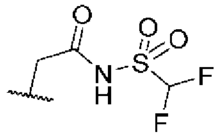
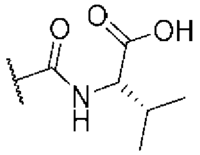
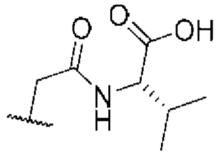
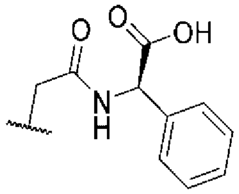
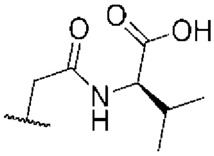
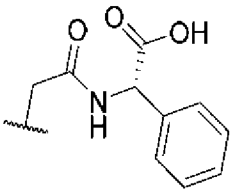
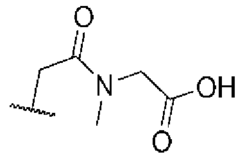
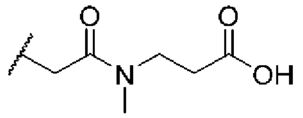
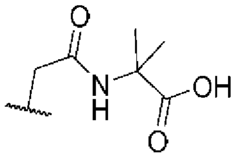
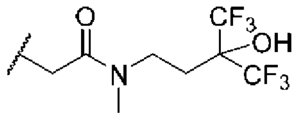
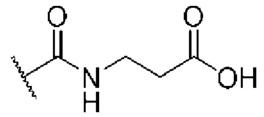
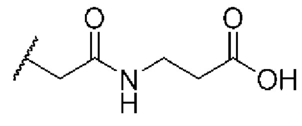
$_4$OR。在一些實施例中，R^{6}係-NR$_2$。在一些實施例中，R^{6}係-(CR$_2$)$_{1-4}$NR$_2$。在一些實施例中，R^{6}係-NRC(O)OR。在一些實施例中，R^{6}係-NRC(O)R。在一些實施例中，R^{6}係-NRC(O)NR$_2$。在一些實施例中，R^{6}係-SR。在一些實施例中，R^{6}係-SO$_2$R。在一些實施例中，R^{6}係-S(O)R。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$SO$_3$R。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$SO$_2$NR$_2$。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$OSO$_2$NR$_2$。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$NRSO$_2$R。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$NRSO$_2$OR。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$OP(OR)$_2$。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$OP(O)(OR)$_2$。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$P(O)(OR)$_2$。在一些實施例中，R^{6}係-(CR$_2$)$_{0-6}$OP(O)(H)OR。在一些實施例中，R^{6}係-B(OR)$_2$。在一些實施例中，R^{6}係R^B。

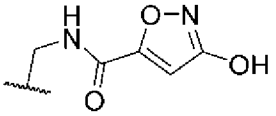
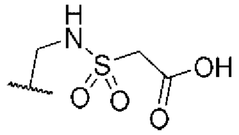
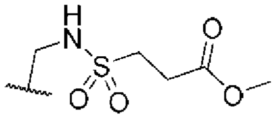
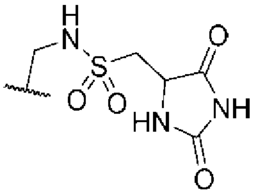
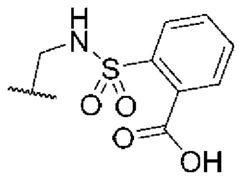
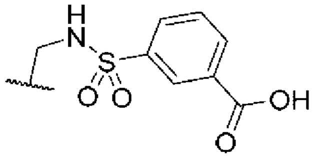
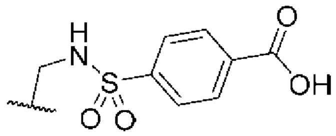
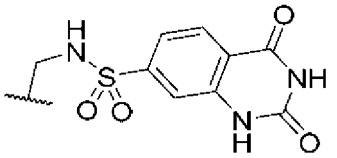
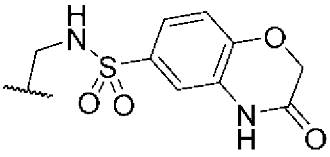
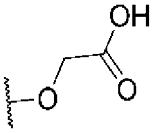
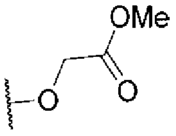
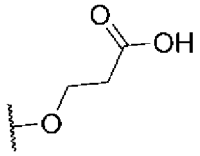
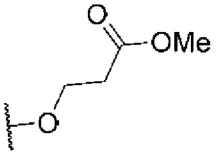
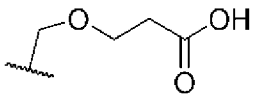
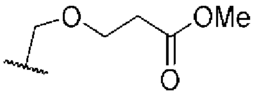
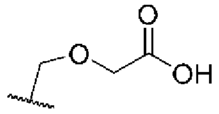
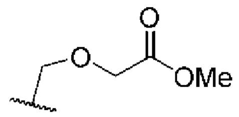
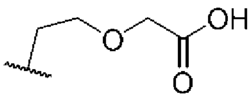
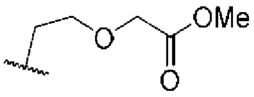
【0369】 在一些實施例中，R^{6}係氟。在一些實施例中，R^{6}係氯。在一些實施例中，R^{6}係溴。在一些實施例中，R^{6}係-OH。在一些實施例中，R^{6}係-OMe。在一些實施例中，R^{6}係-OEt。在一些實施例中，R^{6}係-OtBu。在一些實施例中，R^{6}係-OBn。在一些實施例中，R^{6}係-OCH$_2$CH$_2$OH。在一些實施例中，R^{6}係-OCH$_2$CO$_2$H。在一些實施例中，R^{6}係-OCONHCH$_2$CO$_2$H。在一些實施例中，R^{6}係-CF$_3$。在一些實施例中，R^{6}係-OCF$_3$。在一些實施例中，R^{6}係-CH(OH)CF$_3$。在一些實施例中，R^{6}係-C(OH)(CF$_3$)$_2$。在一些實施例中，R^{6}係氰基。在一些實施例中，R^{6}係甲基。在一些實施例中，R^{6}係=CH$_2$。在一些實施例中，R^{6}係乙基。在一些實施例中，R^{6}係-CH$_2$OH。在一些實施例中，R^{6}係-CH$_2$OMe。在一些實施例中，R^{6}係乙醯基。在一些實施例中，R^{6}係-OAc。在一些實施例中，R^{6}係-NH$_2$。在一些實施例中，R^{6}係-NHBoc。在一些實施例中，

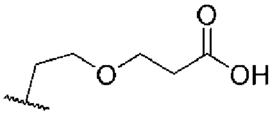
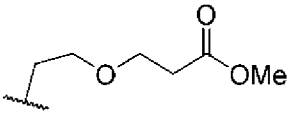
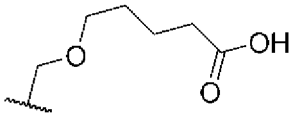
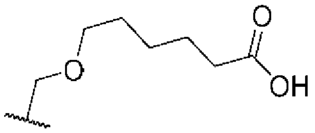
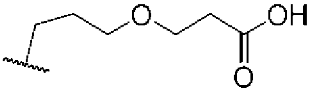
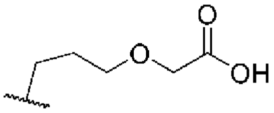
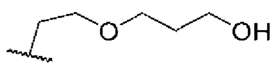
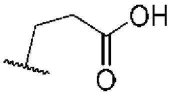
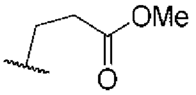
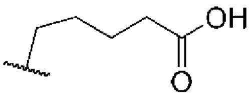
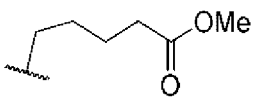
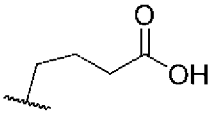
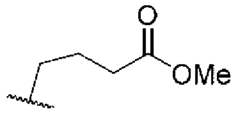
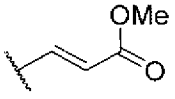
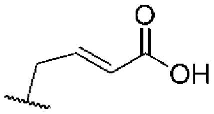
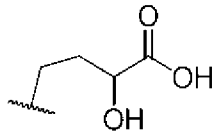
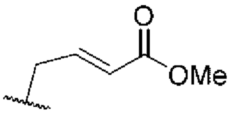
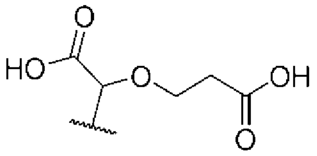
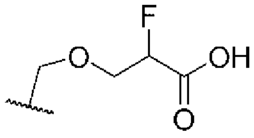
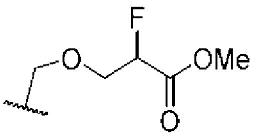
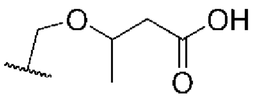
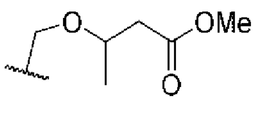
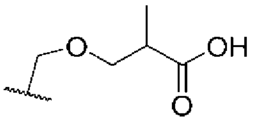
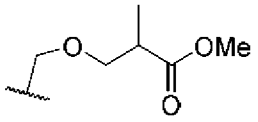
R^6係$-CH_2NH_2$。在一些實施例中，R^6係$-CH_2NHBoc$。在一些實施例中，R^6係$-CH_2CH_2OH$。在一些實施例中，R^6係三級丁基。在一些實施例中，R^6係$-C_{3-6}$環烷基。在一些實施例中，R^6係環己基。在一些實施例中，R^6係苯基。在一些實施例中，R^6係*N*-味啉基。在一些實施例中，R^6係$-CO_2H$。在一些實施例中，R^6係$-CO_2Me$。在一些實施例中，R^6係$-CO_2Et$。在一些實施例中，R^6係$-CO_2iPr$。在一些實施例中，R^6係$-CO_2nBu$。在一些實施例中，R^6係$-CO_2isoBu$。在一些實施例中，R^6係$-CO_2tBu$。在一些實施例中，R^6係$-CO_2CH_2CF_3$。在一些實施例中，R^6係$-CO_2CH(CF_3)_2$。在一些實施例中，R^6係$-CONH_2$。在一些實施例中，R^6係$-CONHOH$。在一些實施例中，R^6係$-CONHOMe$。在一些實施例中，R^6係$-CONHMe$。在一些實施例中，R^6係$-CONHEt$。在一些實施例中，R^6係$-CONMe_2$。在一些實施例中，R^6係$-COCH_2OH$。在一些實施例中，R^6係$-COCH_2OAc$。在一些實施例中，R^6係$-CONHCH_2CH_2OH$。在一些實施例中，R^6係$-CONHCH_2CONH_2$。在一些實施例中，R^6係$-CONHCH_2CH_2CONH_2$。在一些實施例中，R^6係$-CONHCH_2CO_2Me$。在一些實施例中，R^6係$-CONHCH_2CH_2CO_2H$。在一些實施例中，R^6係$-NH_2$。在一些實施例中，R^6係$-NHAc$。在一些實施例中，R^6係$-CH_2CO_2H$。在一些實施例中，R^6係$-CH_2CO_2Me$。在一些實施例中，R^6係$-CH_2CO_2tBu$。在一些實施例中，R^6係$-CH_2CONH_2$。在一些實施例中，R^6係$-CH_2NHSO_2Me$。在一些實施例中，R^6係$-NHSO_2Me$。在一些實施例中，R^6係$-NHSO_2Ph$。在一些實施例中，R^6係$-NHCONH_2$。在一些實施例中，R^6係$-NHCOPh$。在一些實施例中，R^6係$-NHCOCH_2OH$。在一些實施例中，R^6係$-NHCOCH_2OAc$。在一些實施例中，R^6係-

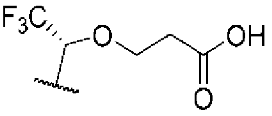
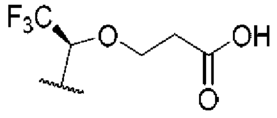
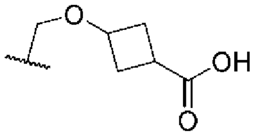
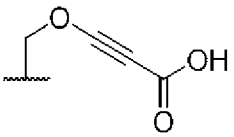
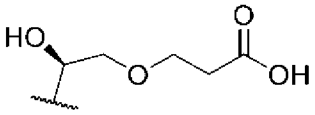
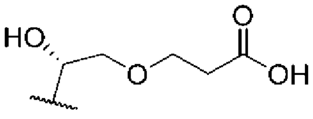
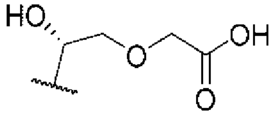
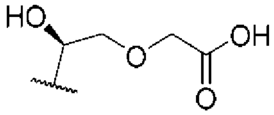
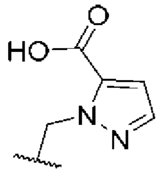
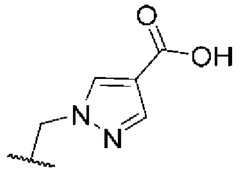
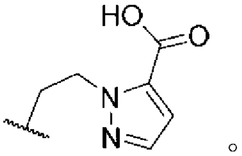
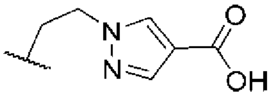
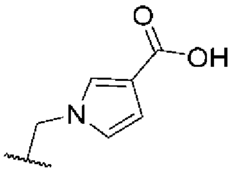
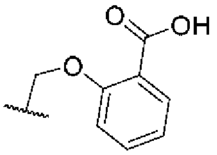
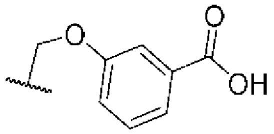
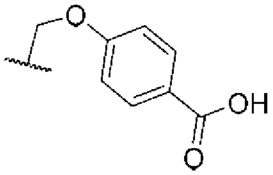
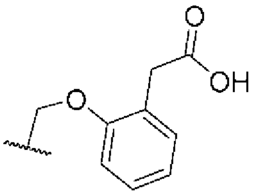
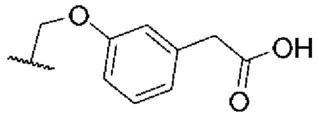
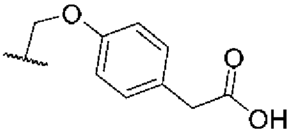
$NHSO_2CH_2CH_2CO_2H$。在一些實施例中，R^6係$-CH_2NHCOCH_2OH$。在一些實施例中，R^6係$-CH_2NHCOCH_2CO_2H$。在一些實施例中，R^6係$-SO_3H$。在一些實施例中，R^6係$-SO_2Me$。在一些實施例中，R^6係$-SO_2NH_2$。在一些實施例中，R^6係$-SO_2NHBoc$。在一些實施例中，R^6係$-CH_2SO_2NH_2$。在一些實施例中，R^6係$-OSO_2NH_2$。在一些實施例中，R^6係$-OCONHCH_2CO_2Me$。在一些實施例中，R^6係$-B(OH)_2$。在一些實施例中，R^6係$-CH_2OSO_2NH_2$。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係$-OP(OH)_2$。在一些實施例中，R^6係$-CH_2OP(OH)_2$。在一些實施例中，R^6係$-CH_2OP(O)(H)OH$。在一些實施例中，R^6係$-OP(O)(OH)_2$。在一些實施例中，R^6係$-CH_2OP(O)(OH)_2$。在一些實施例中，R^6係$-CH_2P(O)(OH)_2$。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實

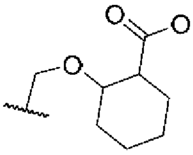
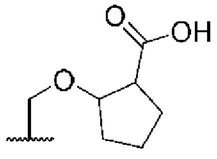
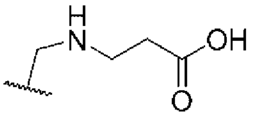
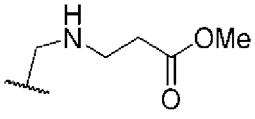
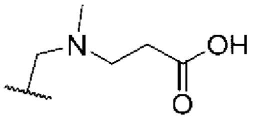
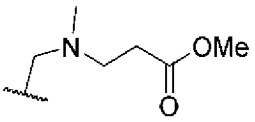
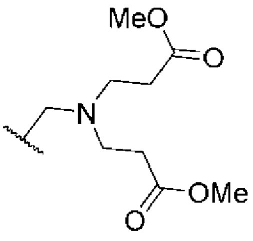
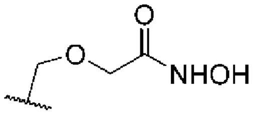
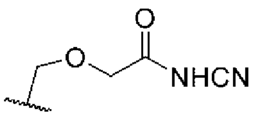
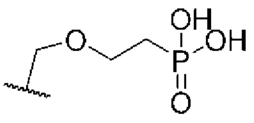
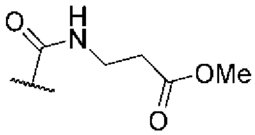
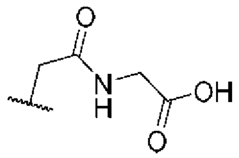
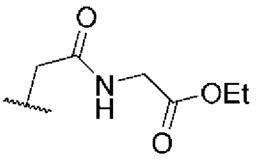
施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實

施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係

。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例中，R^{6}係。在一些實施例

中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係

 。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實施例中，R^6係  。在一些實

施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。在一些實施例中，R^6係。

【0370】 在一些實施例中，R^6係選自**表1**中所描繪之基團。

【0371】 如上文所定義及本文所描述，R^A、R^B及R^C獨立地係視情況經取代的選自以下之基團：C_{1-6}脂族基；苯基，包括經取代之苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；及具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

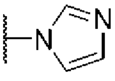
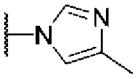
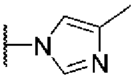
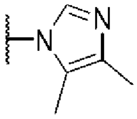
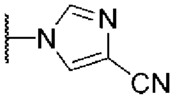
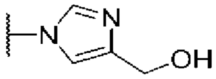
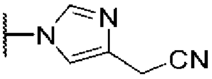
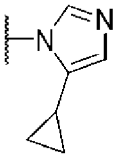
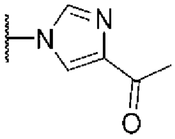
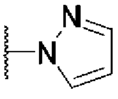
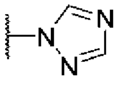
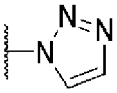
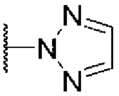
【0372】 在一些實施例中，R^A、R^B或R^C係視情況經取代之C_{1-6}脂族

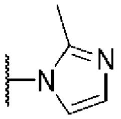
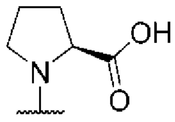
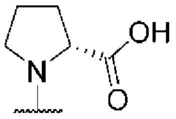
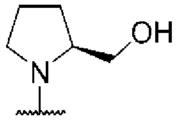
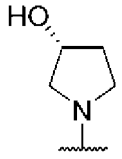
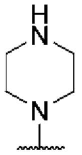
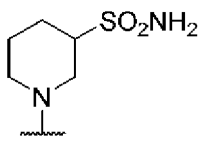
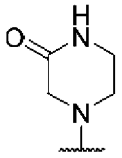
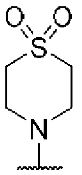
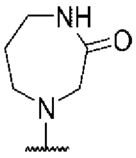
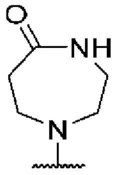
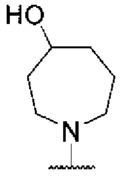
基。在一些實施例中，R^A、R^B或R^C係視情況經取代之苯基。在一些實施例中，R^A、R^B或R^C係具有1至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，R^A、R^B或R^C係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之5至6員雜芳基環。

【0373】 在一些實施例中，R^A、R^B或R^C係選自**表1**中所描繪之基團。

【0374】 如上文所定義及本文所描述，環A係除氮外還具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和、部分不飽和或雜芳基環。

【0375】 在一些實施例中，環A係除氮外還具有0至3個獨立地選自氮、氧、磷及硫之雜原子的視情況經取代之4至7員飽和、部分不飽和或雜芳基環。

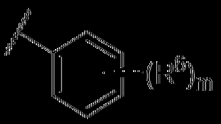
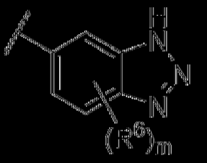
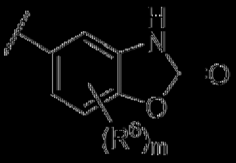
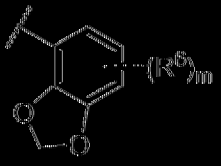
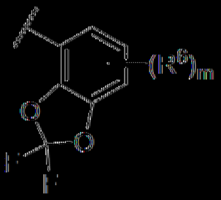
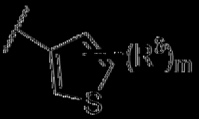
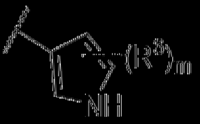
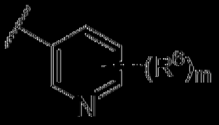
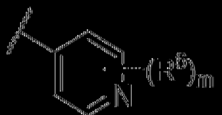
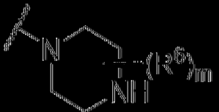
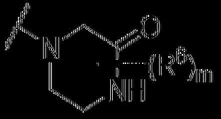
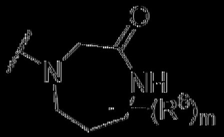
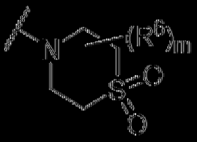
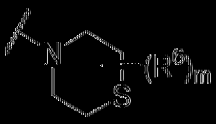
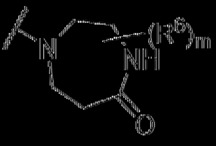
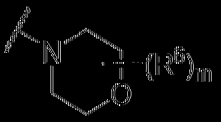
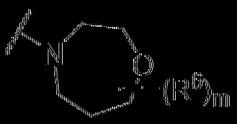
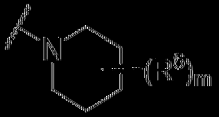
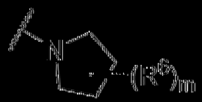
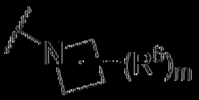
【0376】 在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係

。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。在一些實施例中，環A係。

【0377】 在一些實施例中，環A係選自**表1**中所描繪之基團。

【0378】 如上文所定義及本文所描述，環B1係苯基，特定言之為經取代之苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

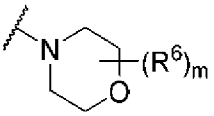
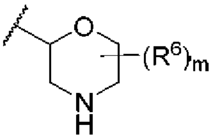
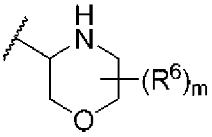
【0379】 在一些實施例中，環B1係苯基，特定言之為經取代之苯基。在一些實施例中，環B1係具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。在一些實施例中，環B1係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

【0380】 在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。在一些實施例中，環B1係 。

【0381】 在一些實施例中，環B1係選自表1中所描繪之基團。

【0382】 如上文所定義及本文所描述，環B2係苯基，包括經取代之苯基；具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

【0383】 在一些實施例中，環B2係苯基。在一些實施例中，環B2係具有1至3個獨立地選自氮、氧、磷及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環。在一些實施例中，環B2係具有1至4個獨立地選自氮、氧、磷及硫之雜原子的5至6員雜芳基環。

【0384】 在一些實施例中，環B2係  。在一些實施例中，環B2係  。在一些實施例中，環B2係  。

【0385】 在一些實施例中，環B2係選自**表1**中所描繪之基團。

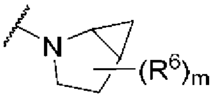
【0386】 如上文所定義及本文所描述，環C係吡咯啶基或具有0至3個獨立地選自氮、氧及硫之雜原子(除環C中已描繪之氮外)的4至10員飽和或部分不飽和單環、雙環、橋連雙環或螺環雜環。

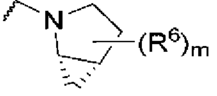
【0387】 在一些實施例中，環C係吡咯啶基。在一些實施例中，環C係具有0至3個獨立地選自氮、氧及硫之雜原子(除環C中已描繪之氮外)的4至10員飽和或部分不飽和單環、雙環、橋連雙環或螺環雜環。

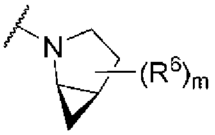
【0388】 在一些實施例中，環C係氮雜環丁烷基。在一些實施例中，環C係吡咯基。在一些實施例中，環C係2,3-二氫-1H-吡咯基。在一些實施例中，環C係味啉基。在一些實施例中，環C係噻唑啶基。在一些

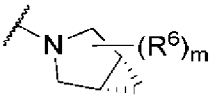
實施例中，環C係吲哚啉基。在一些實施例中，環C係異吲哚啉基。在一些實施例中，環C係八氫吲哚基。在一些實施例中，環C係氮雜環庚烷基。在一些實施例中，環C係氧氮雜環庚烷基。在一些實施例中，環C係氮雜雙環己烷。在一些實施例中，環C係氮雜雙環庚烷。在一些實施例中，環C係氮雜雙環辛烷。在一些實施例中，環C係氮雜雙環壬烷。在一些實施例中，環C係氮雜螺庚烷。在一些實施例中，環C係八氫環戊并吡咯。

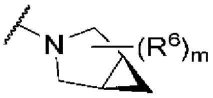
【0389】 在特定實施例中，環C係吡咯啶基、2-氮雜雙環[3.1.0]己基、3-氮雜雙環[3.1.0]己烷、5-氮雜螺[2.4]庚基或八氫環戊并[b]吡咯基。

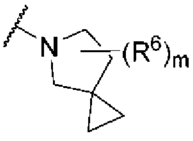
【0390】 在一些實施例中，環C係 

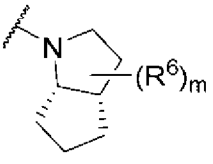
。在一些實施例中，環C係 

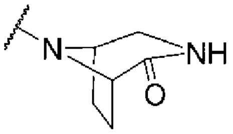
。在一些實施例中，環C係 

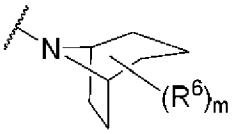
。在一些實施例中，環C係 

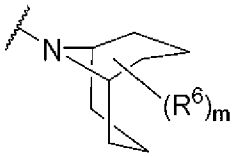
。在一些實施例中，環C係 

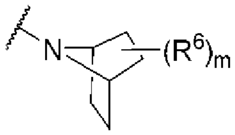
。在一些實施例中，環C係 

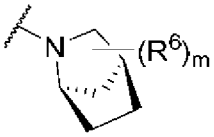
。在一些實施例中，環C係 

。在一些實施例中，環C係 

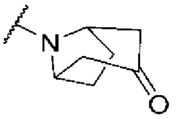
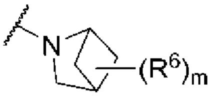
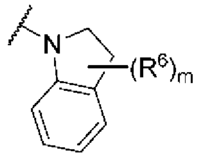
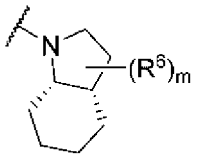
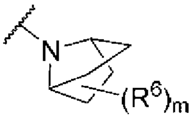
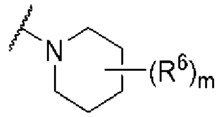
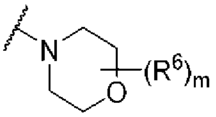
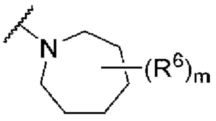
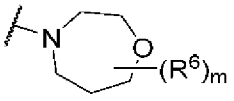
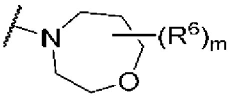
。在一些實施例中，環C係 

。在一些實施例中，環C係 

。在一些實施例中，環C係 

。在一些實施例中，環C係 

。在一些

實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。在一些實施例中，環C係。

【0391】 在一些實施例中，環C係選自**表1**中所描繪之基團。

【0392】 如上文所定義及本文所描述，n係1、2、3或4。

【0393】 在一些實施例中，n係1。在一些實施例中，n係2。在一些實施例中，n係3。在一些實施例中，n係4。

【0394】 在一些實施例中，n係選自**表1**中所描繪之基團。

【0395】 如上文所定義及本文所描述，m係0、1、2、3或4。

【0396】 在一些實施例中，m係0。在一些實施例中，m係1、2、3或4。在一些實施例中，m係1。在一些實施例中，m係2。在一些實施例中，m係3。在一些實施例中，m係4。

【0397】 在一些實施例中，m係選自**表1**中所描繪之基團。

【0398】 如上文所定義及本文所描述，p係0、1或2。

【0399】 在一些實施例中，p係0。在一些實施例中，p係1。在一些

實施例中，p係2。

【0400】 在一些實施例中，p係選自表1中所描繪之基團。

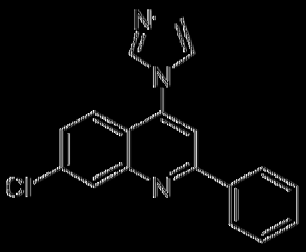
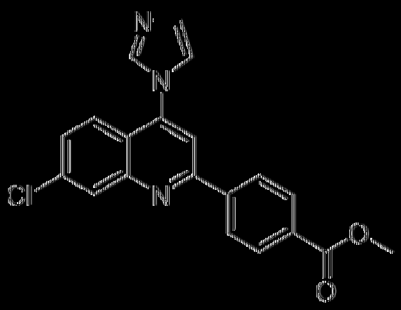
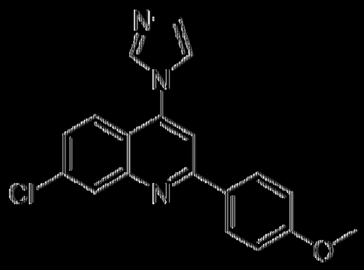
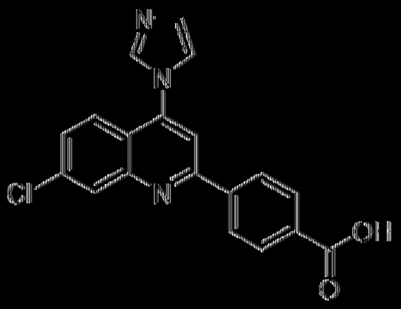
【0401】 如上文所定義及本文所描述，q係0、1或2。

【0402】 在一些實施例中，q係0。在一些實施例中，q係1。在一些實施例中，q係2。

【0403】 在一些實施例中，q係選自表1中所描繪之基團。

【0404】 例示性本發明化合物示於下表1中。

表1. 例示性化合物

I-#	結構	I-#	結構
I-1		I-3	
I-2		I-4	

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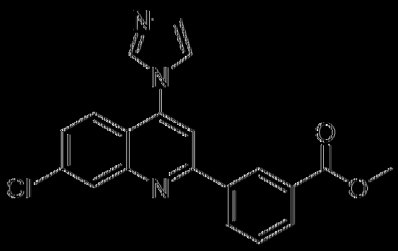
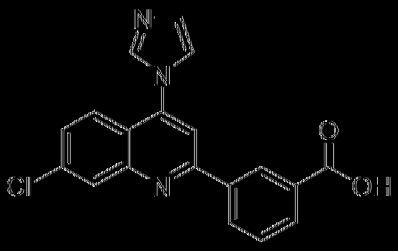
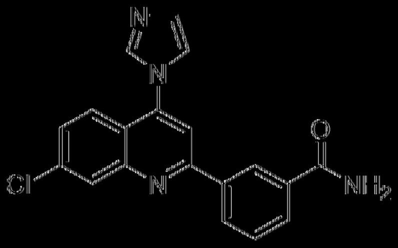
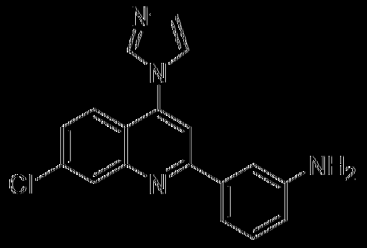
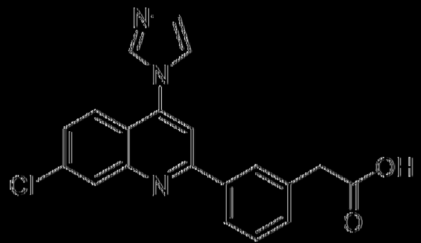
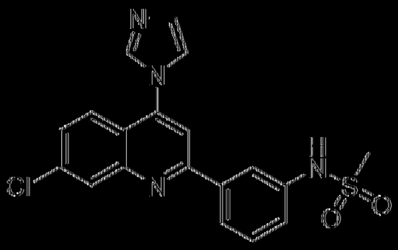
I-5	
I-6	
I-7	
I-8	
I-9	
I-10	

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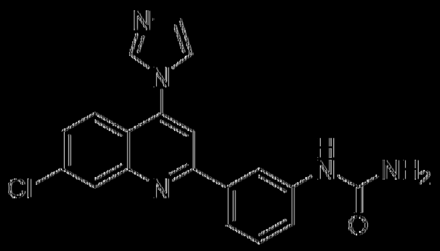
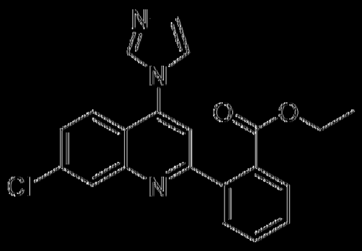
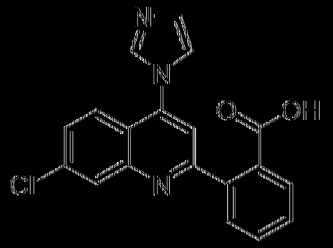
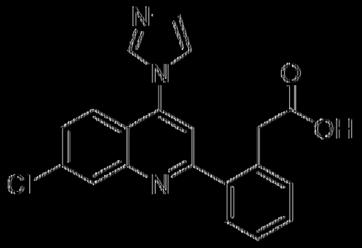
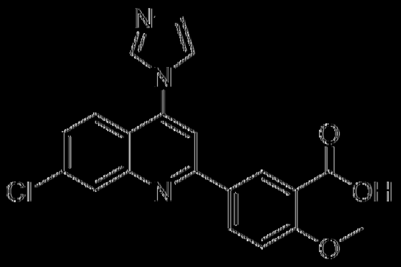
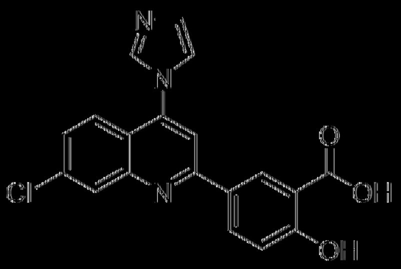
I-11	
I-12	
I-13	
I-14	
I-15	
I-16	

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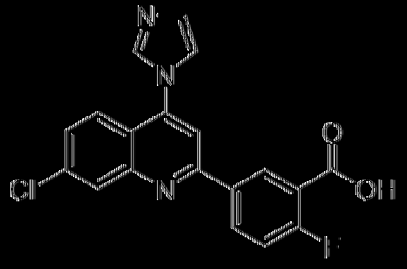
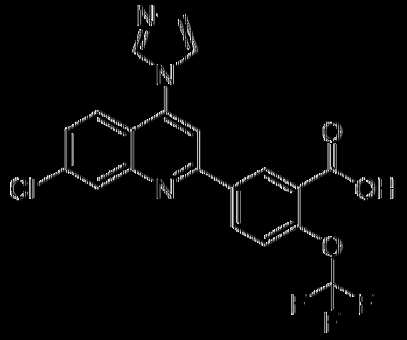
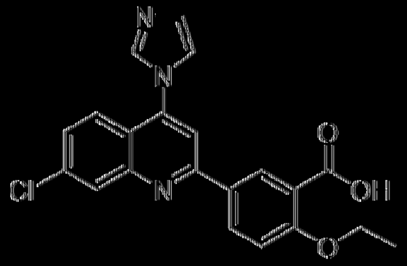
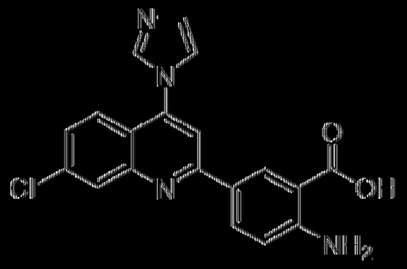
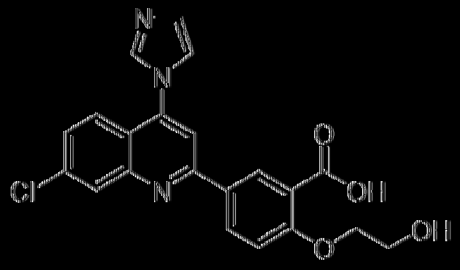
I-17	
I-18	
I-19	
I-20	
I-21	

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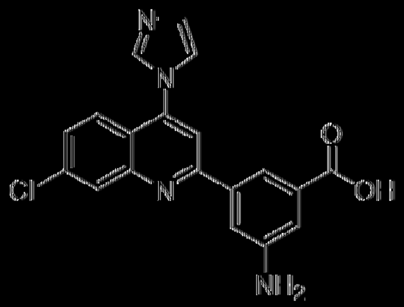
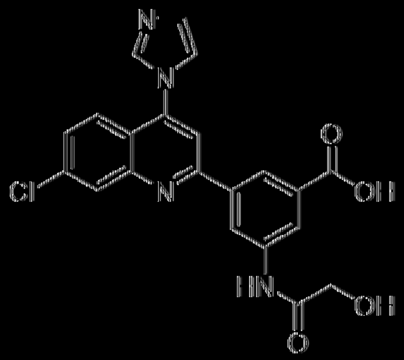
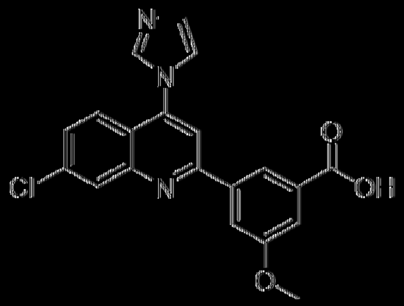
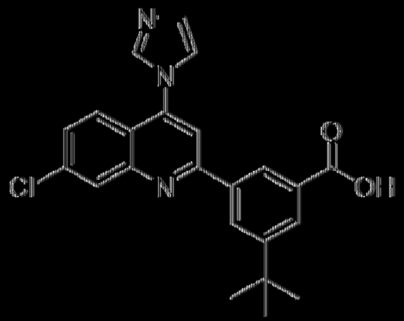
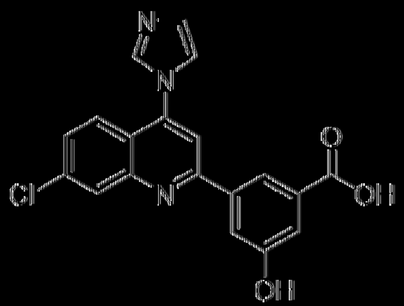
I-22	
I-23	
I-24	
I-25	
I-26	

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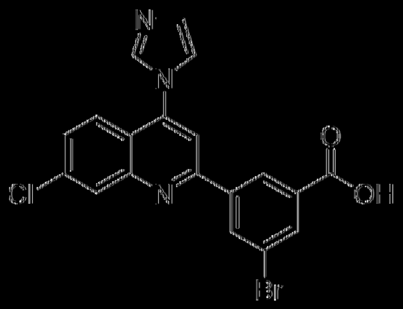
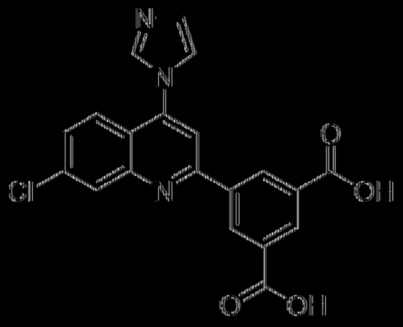
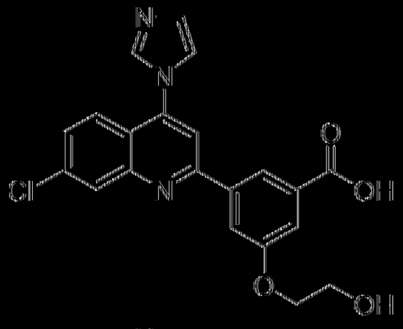
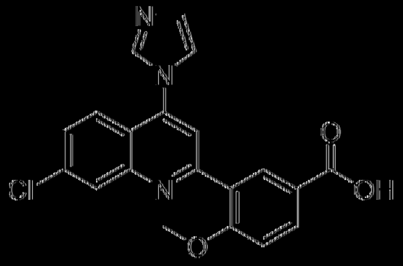
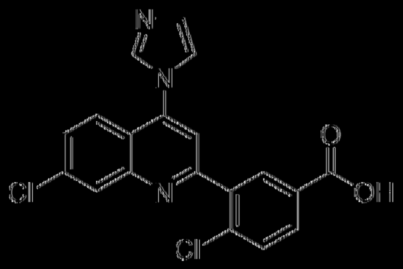
I-27	
I-28	
I-29	
I-30	
I-31	

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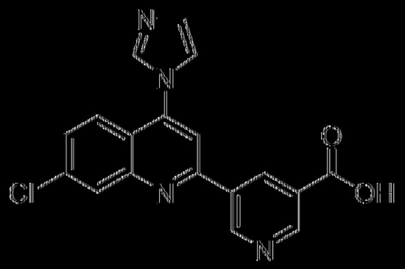
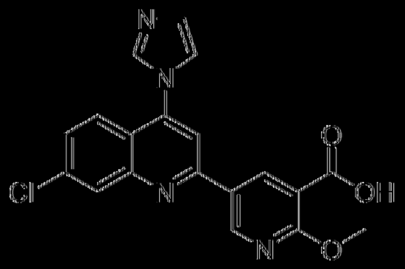
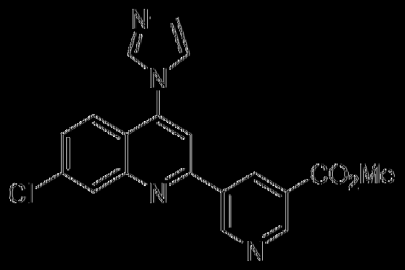
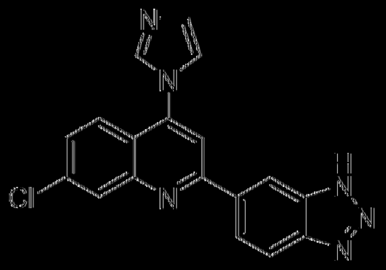
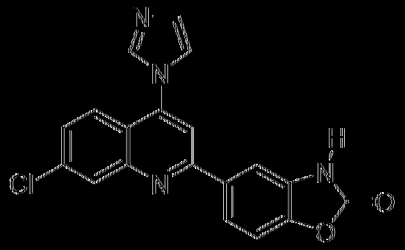
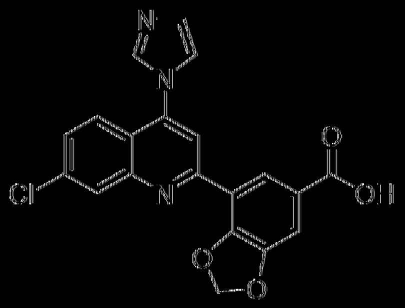
I-32	
I-33	
I-34	
I-35	
I-36	
I-37	

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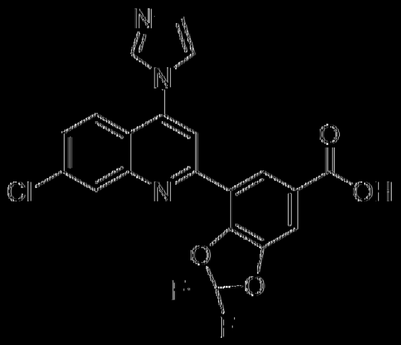
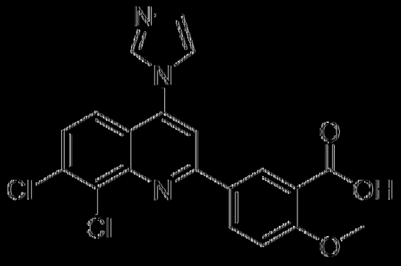
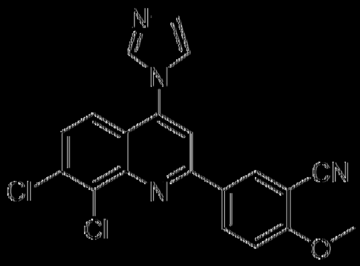
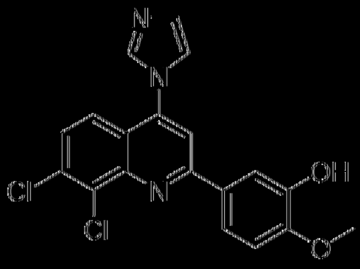
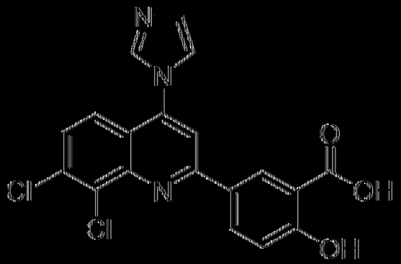
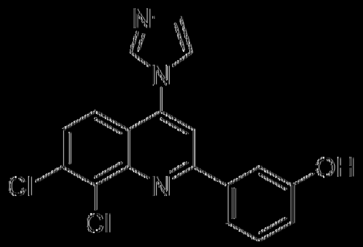
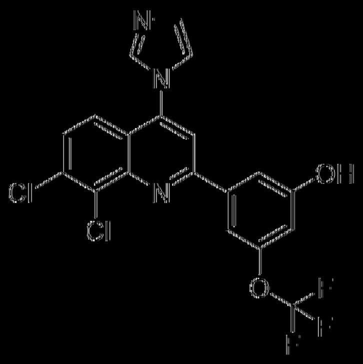
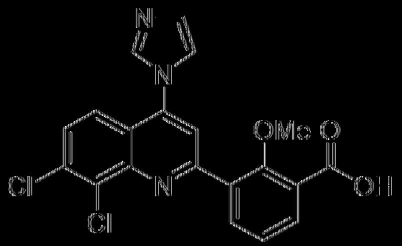
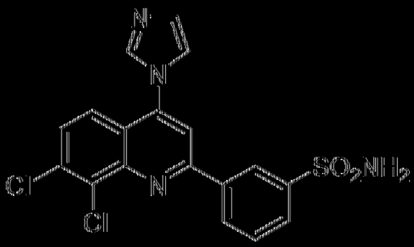
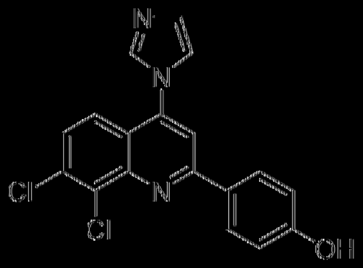
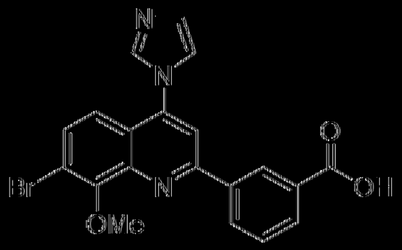
I-38	
I-39	
I-40	
I-41	
I-42	
I-43	
I-44	
I-45	
I-46	
I-47	
I-48	

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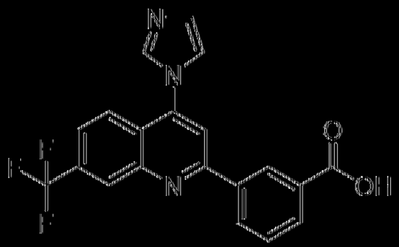
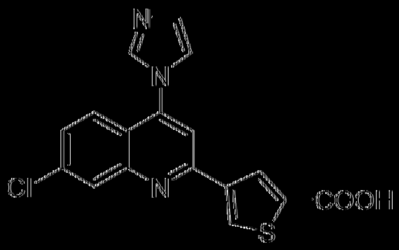
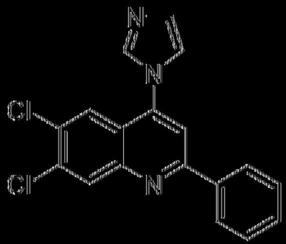
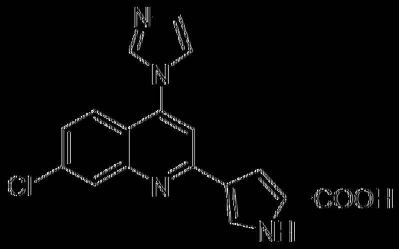
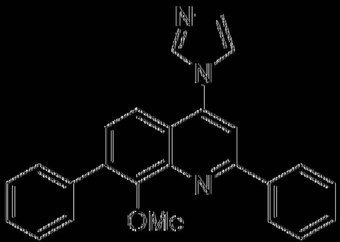
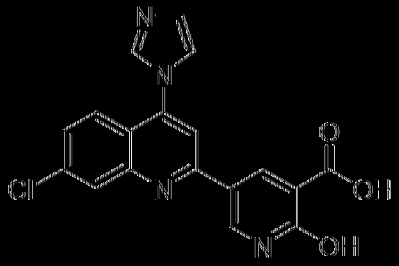
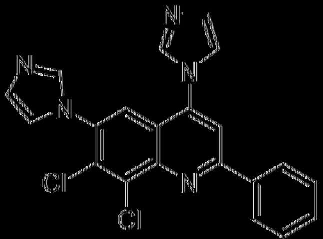
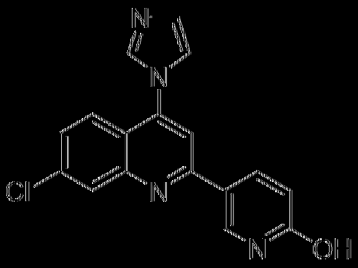
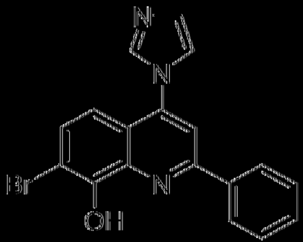
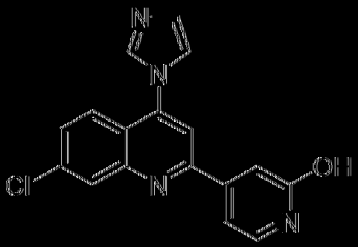
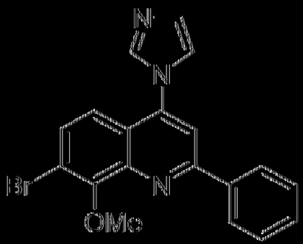
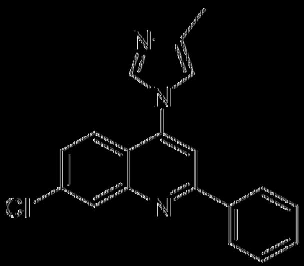
I-49		I-55	
I-50		I-56	
I-51		I-57	
I-52		I-58	
I-53		I-59	
I-54		I-60	

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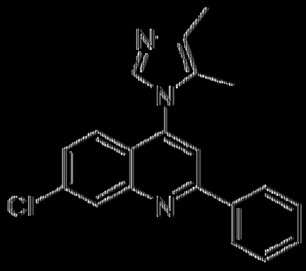
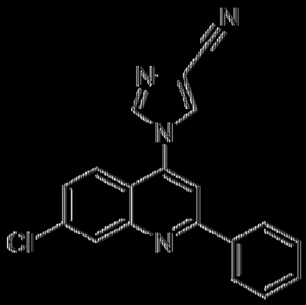
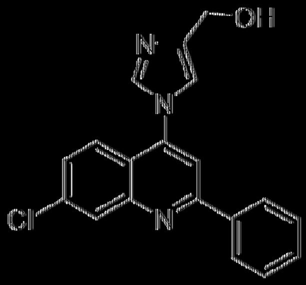
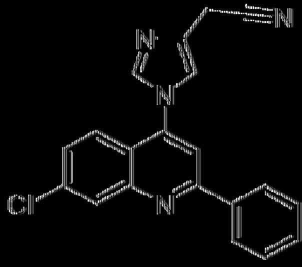
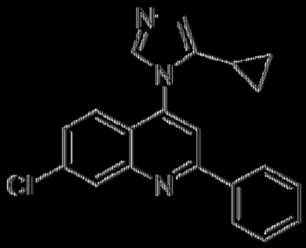
I-61	
I-62	
I-63	
I-64	
I-65	

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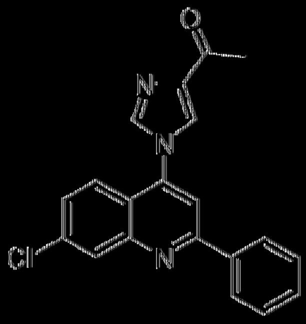
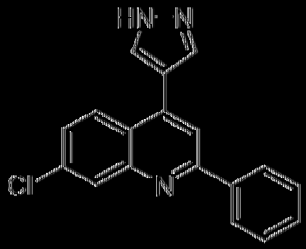
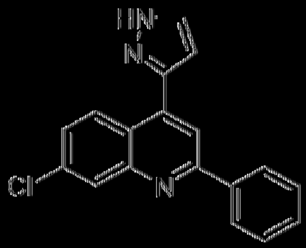
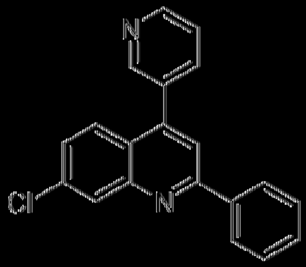
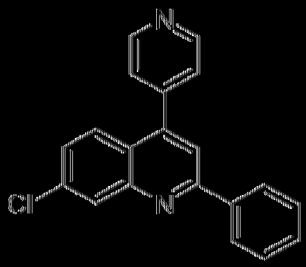
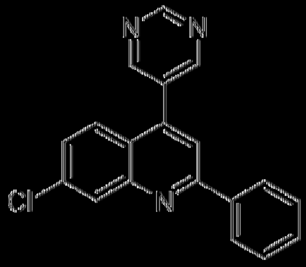
I-66	
I-67	
I-68	
I-69	
I-70	
I-71	

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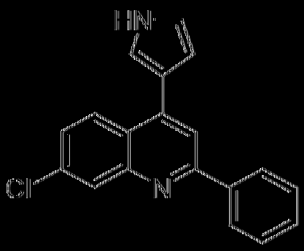
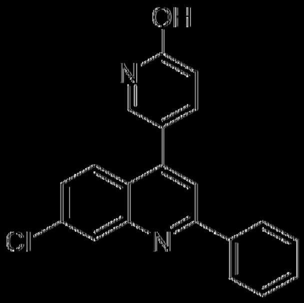
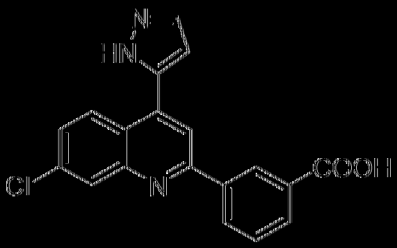
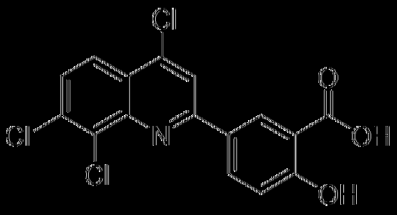
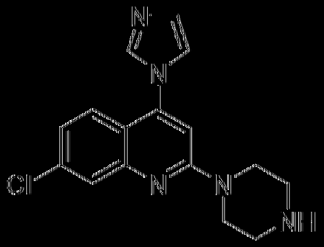
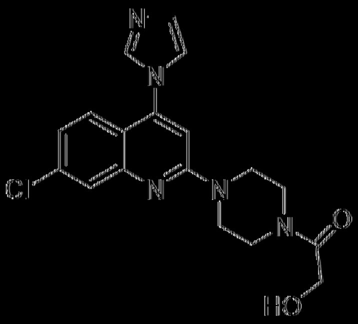
I-72	
I-73	
I-74	
I-75	
I-76	
I-77	

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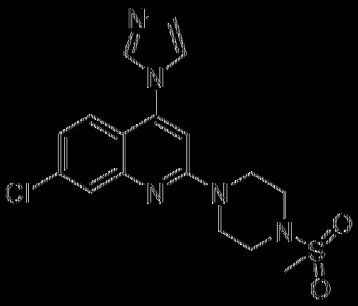
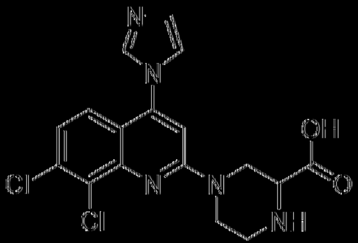
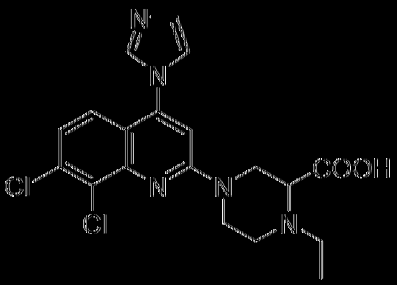
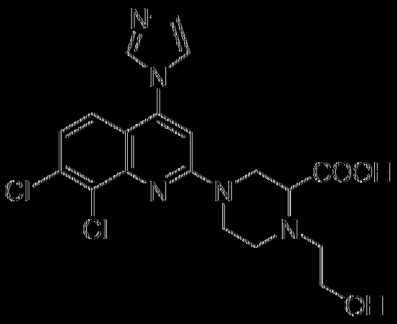
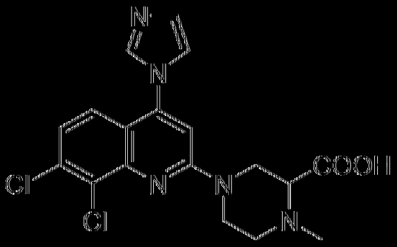
I-78	
I-79	
I-80	
I-81	
I-82	

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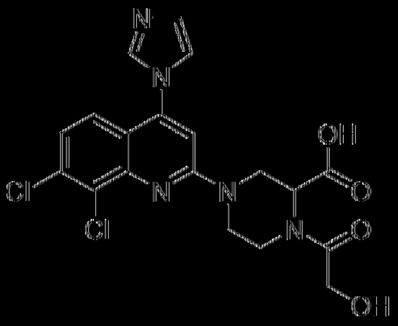
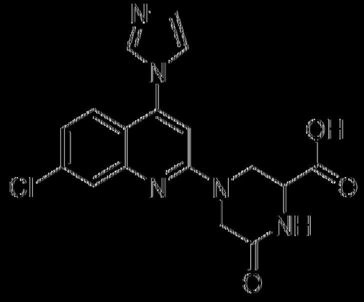
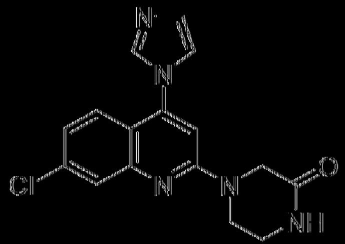
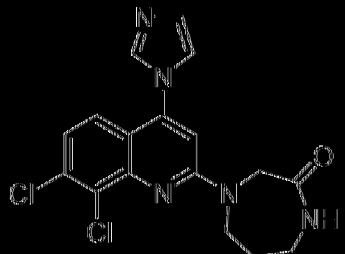
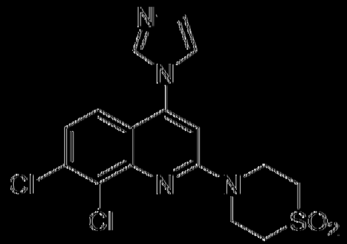
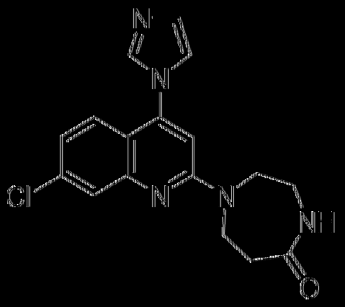
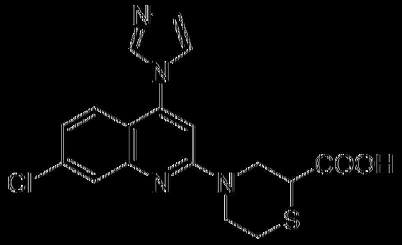
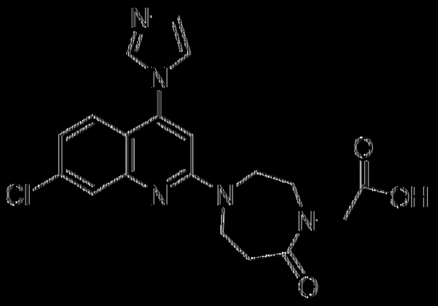
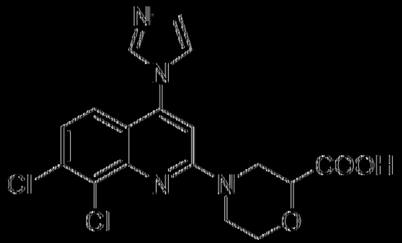
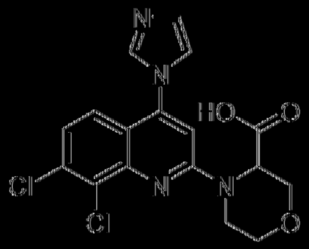
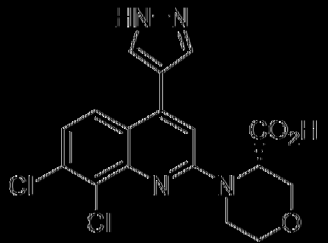
I-83	
I-84	
I-85	
I-86	
I-87	
I-88	
I-89	
I-90	
I-91	
I-92	
I-93	

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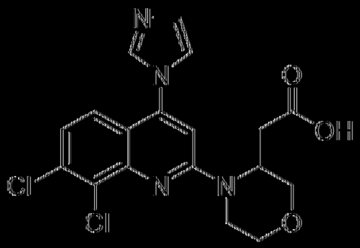
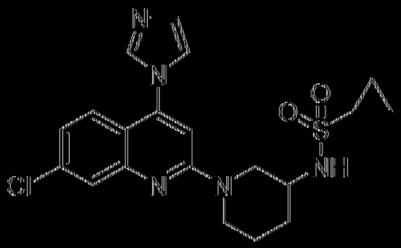
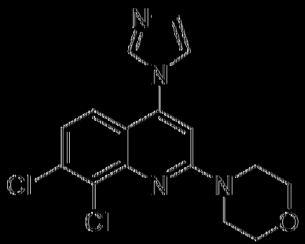
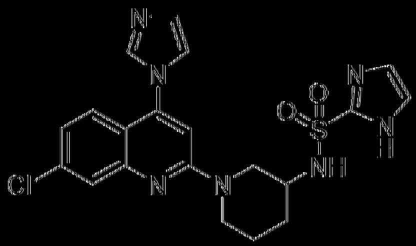
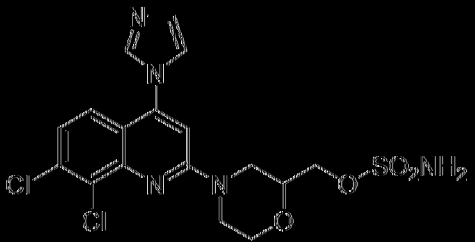
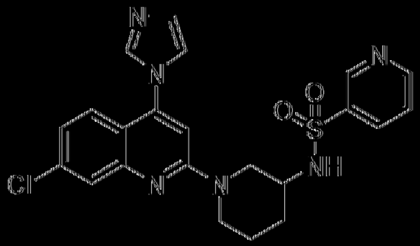
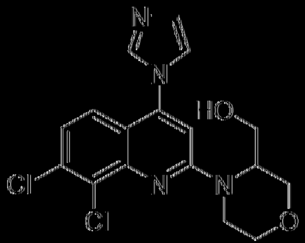
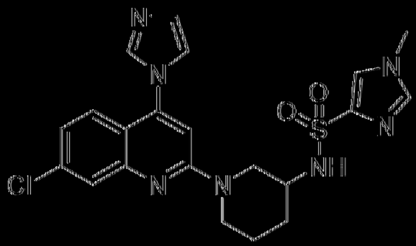
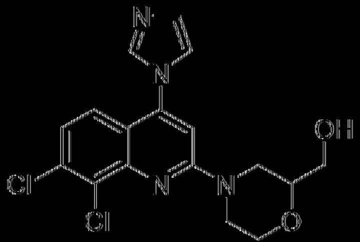
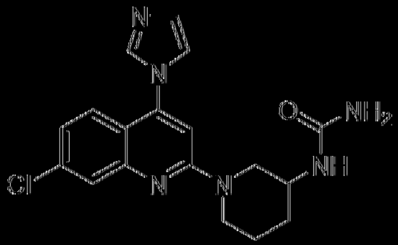
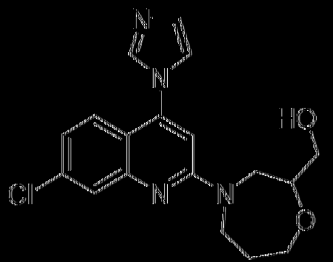
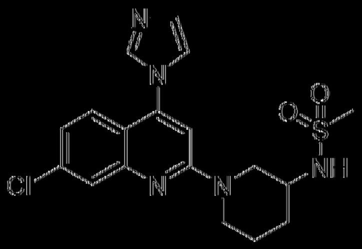
I-94		I-100	
I-95		I-101	
I-96		I-102	
I-97		I-103	
I-98		I-104	
I-99		I-105	

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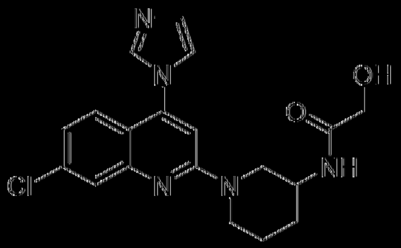
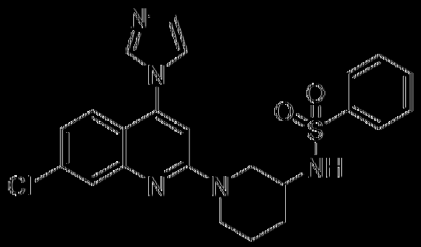
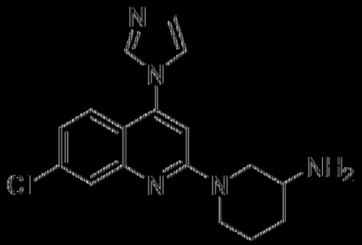
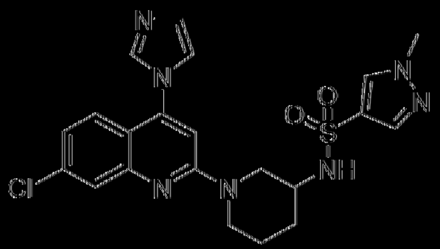
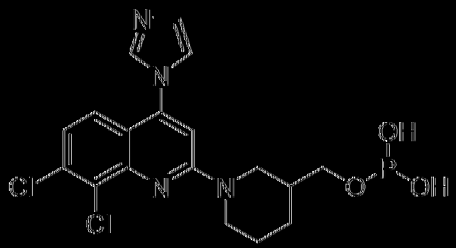
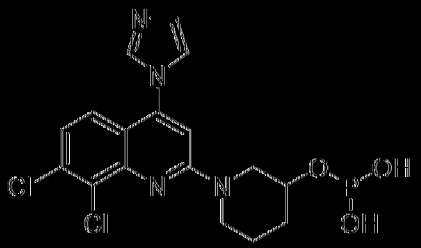
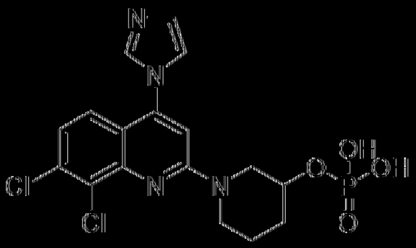
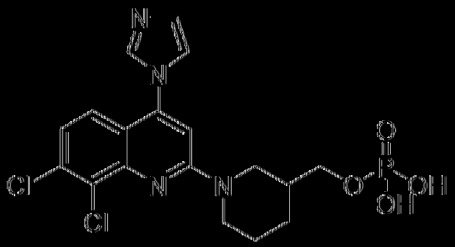
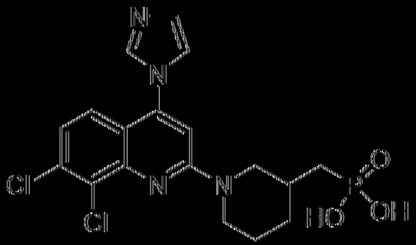
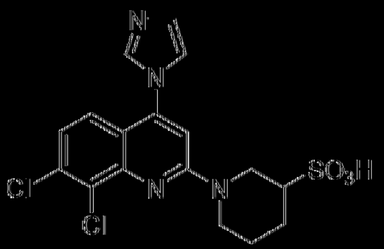
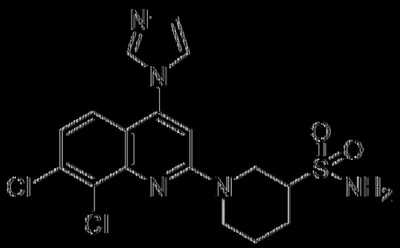
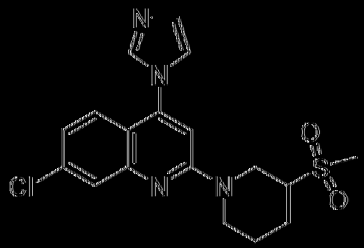
I-106	
I-107	
I-108	
I-109	
I-110	
I-111	
I-112	
I-113	
I-114	
I-115	
I-116	
I-117	

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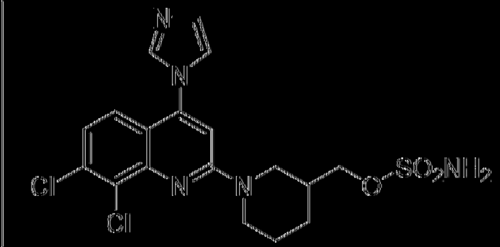
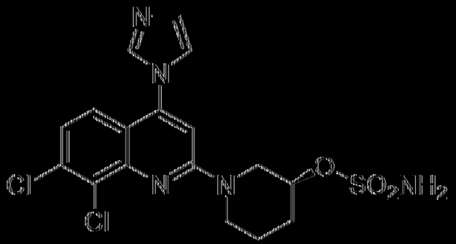
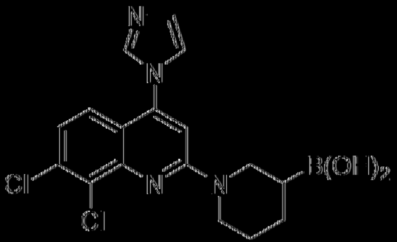
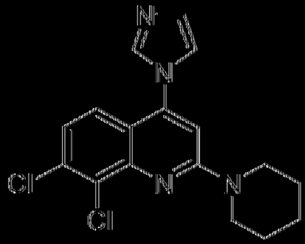
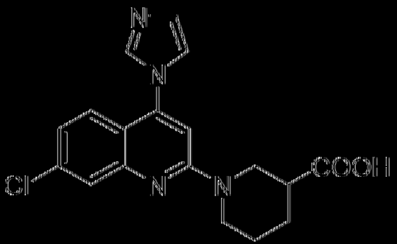
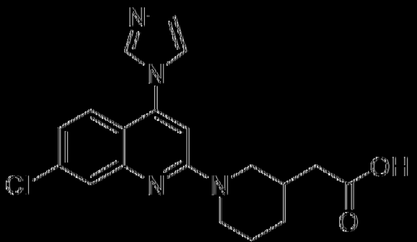
I-118	
I-119	
I-120	
I-121	
I-122	
I-123	

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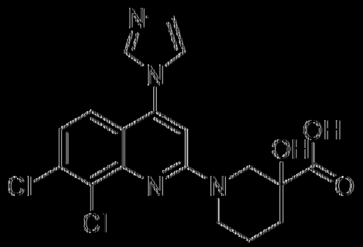
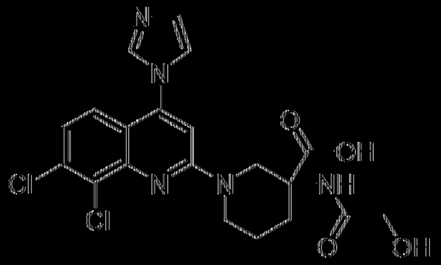
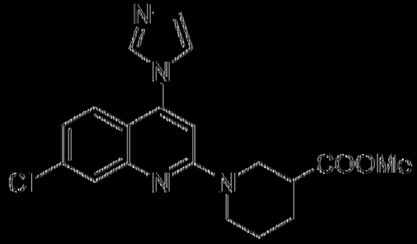
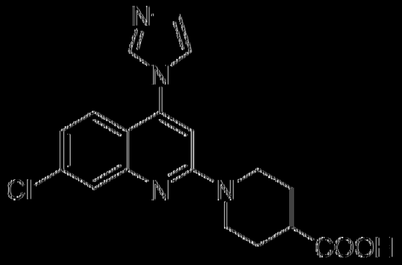
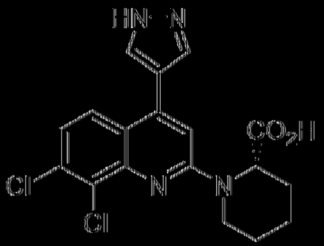
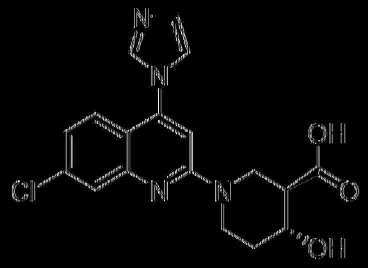
I-124	
I-125	
I-126	
I-127	
I-128	
I-130	

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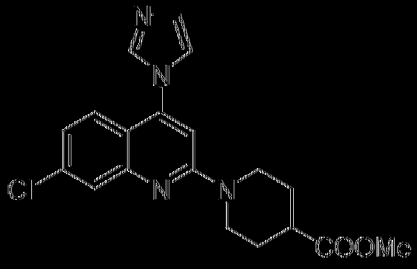
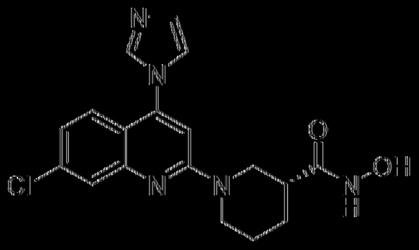
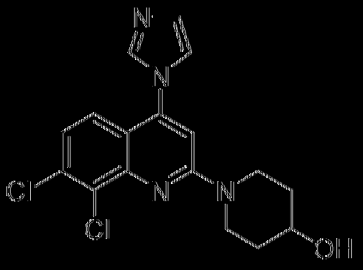
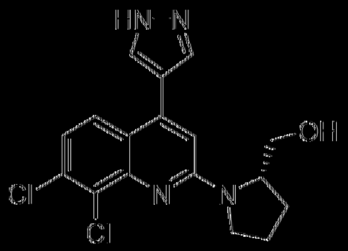
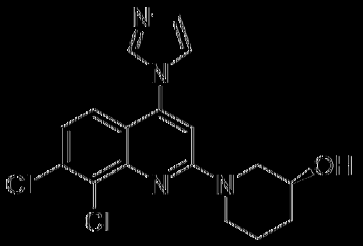
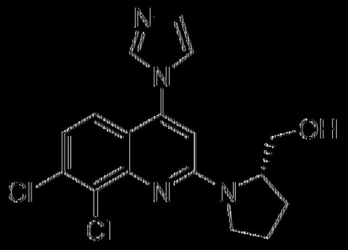
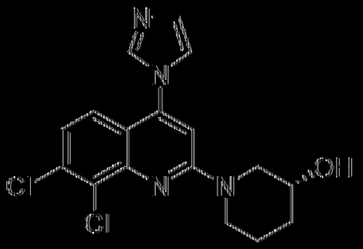
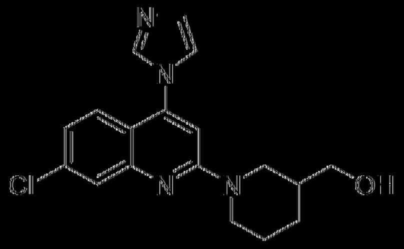
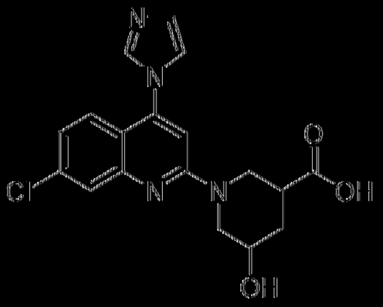
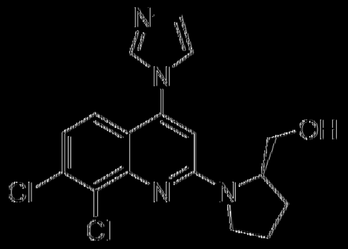
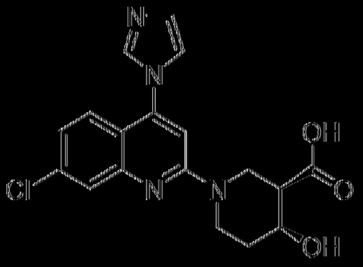
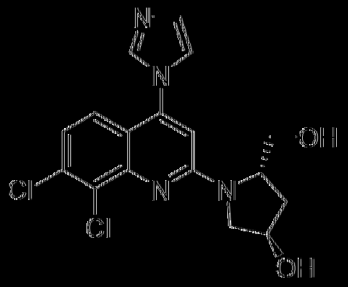
I-131		I-137	
I-132		I-138	
I-133		I-139	
I-134		I-140	
I-135		I-141	
I-136		I-142	

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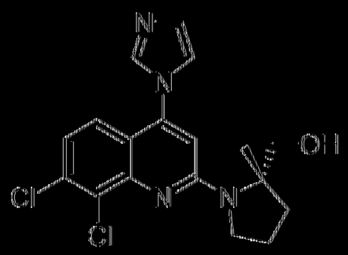
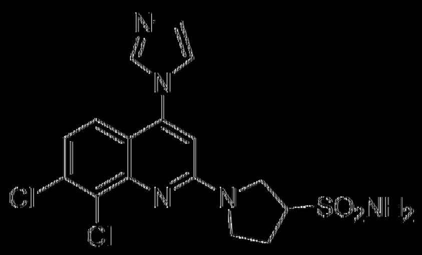
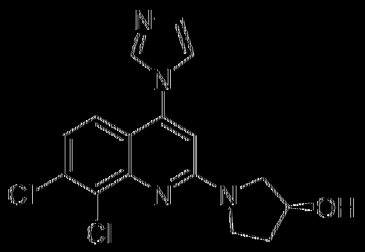
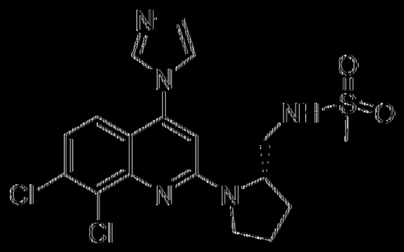
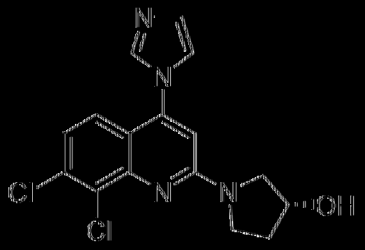
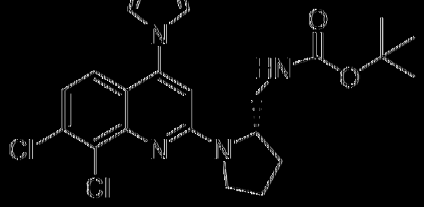
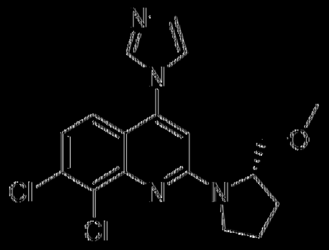
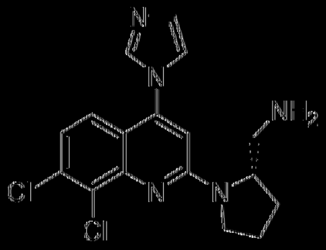
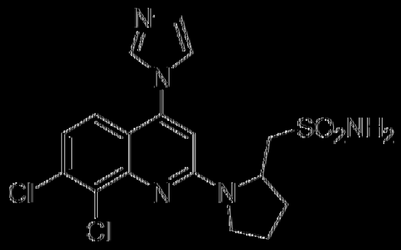
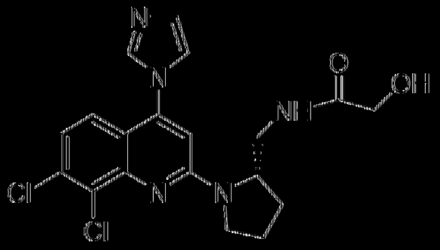
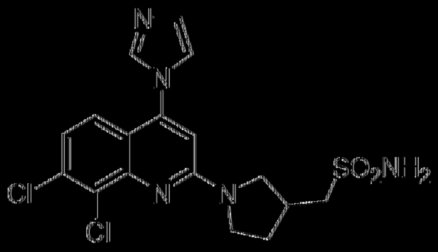
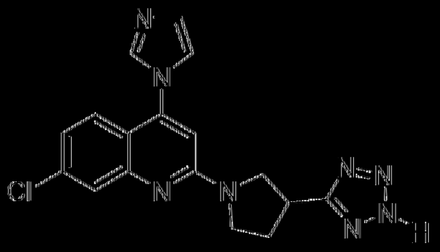
I-143		I-150	
I-144		I-151	
I-145		I-152	
I-147		I-153	
I-148		I-154	
I-149		I-155	

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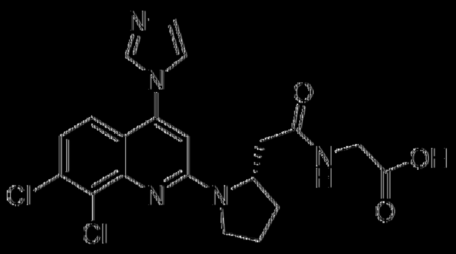
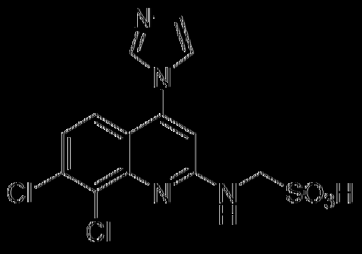
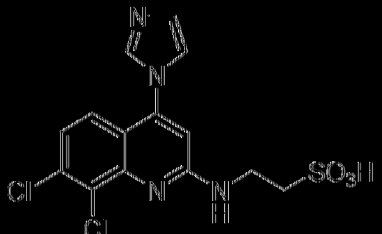
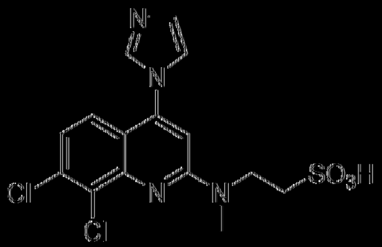
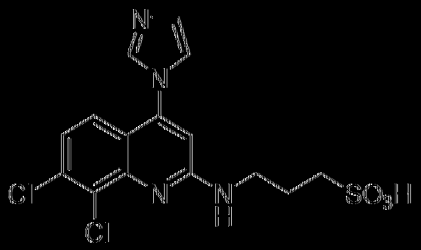
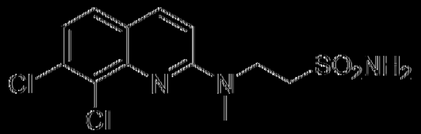
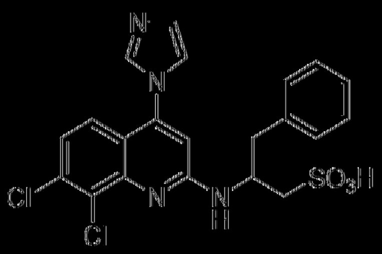
I-156	
I-157	
I-158	
I-159	
I-160	
I-161	
I-162	

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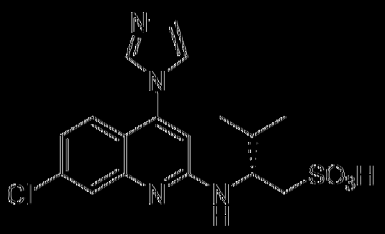
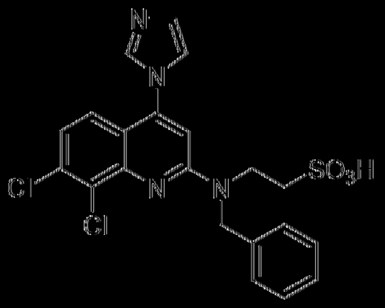
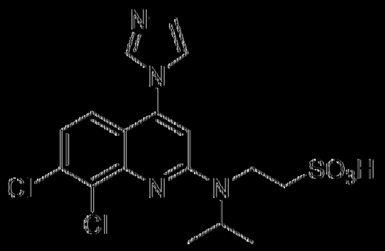
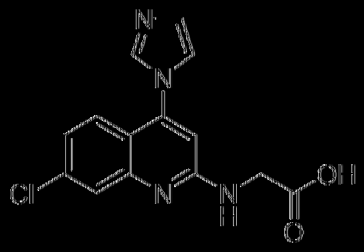
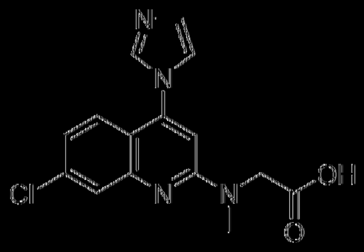
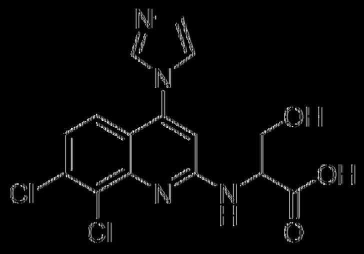
I-163	
I-164	
I-165	
I-166	
I-167	
I-168	

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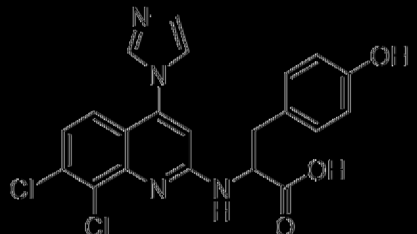
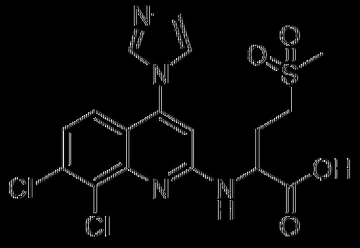
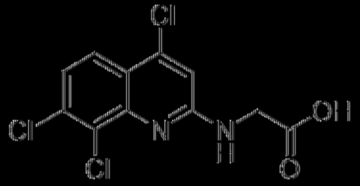
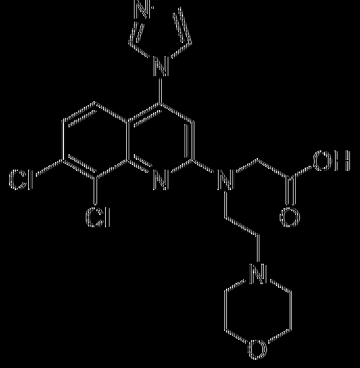
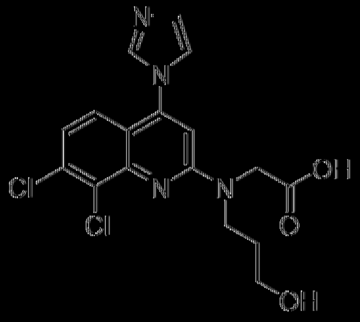
I-169	
I-170	
I-171	
I-172	
I-173	

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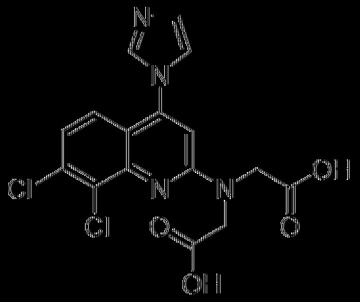
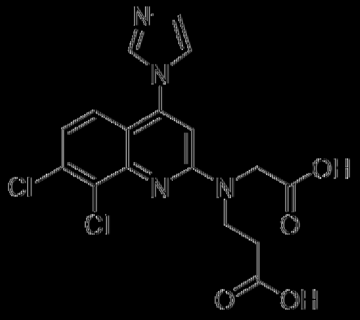
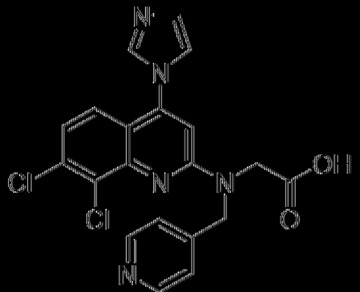
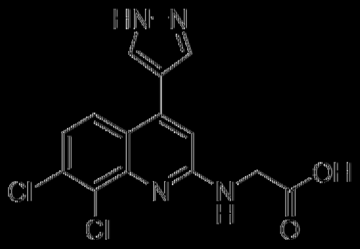
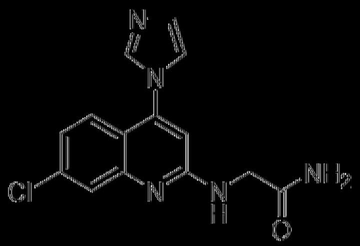
I-174	
I-175	
I-176	
I-177	
I-178	

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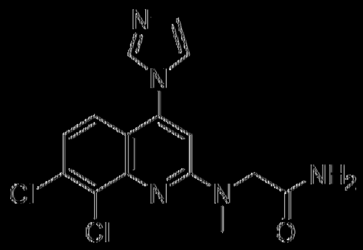
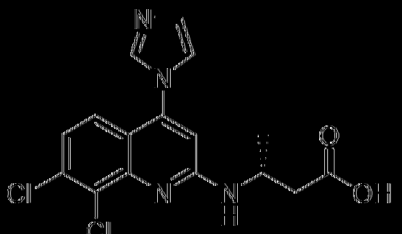
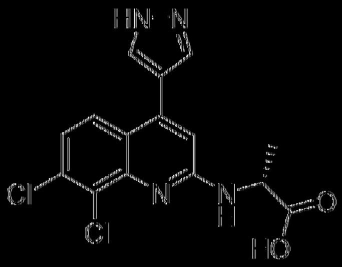
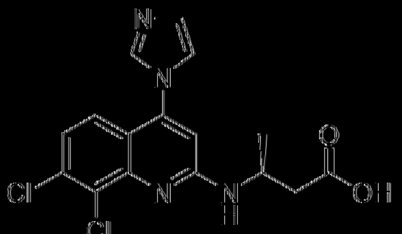
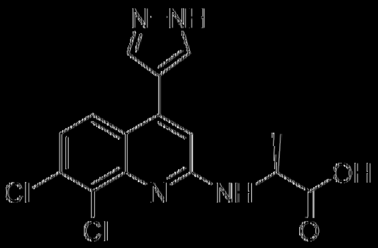
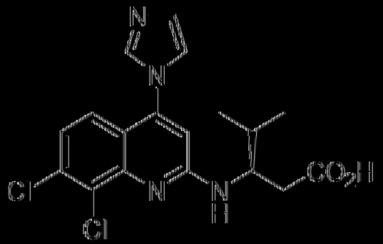
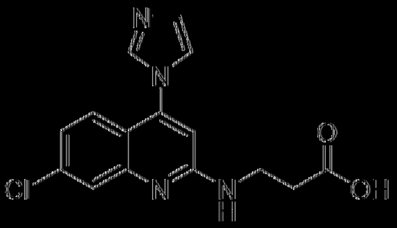
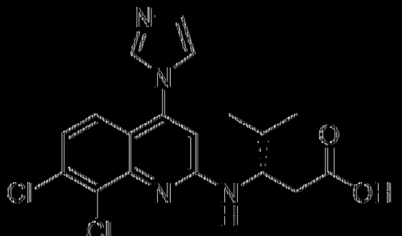
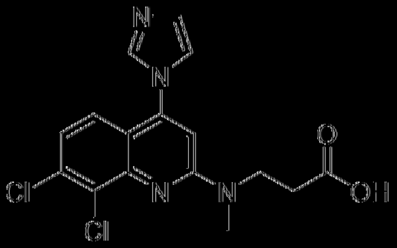
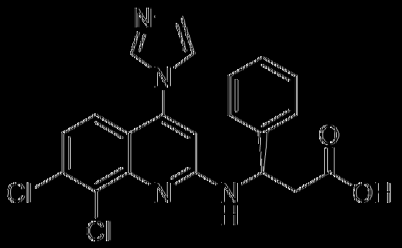
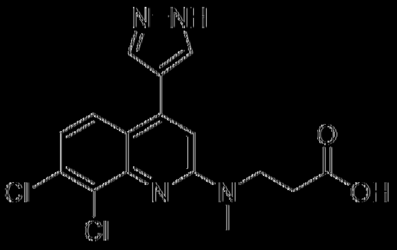
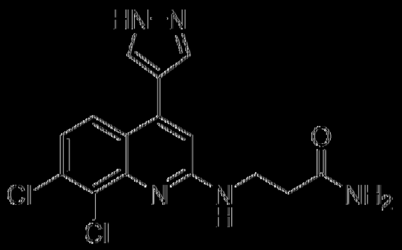
I-179		I-185	
I-180		I-186	
I-181		I-187	
I-182		I-188	
I-183		I-189	
I-184		I-190	

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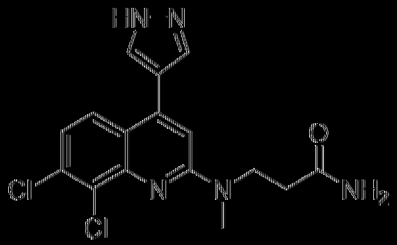
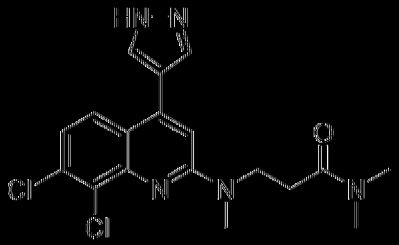
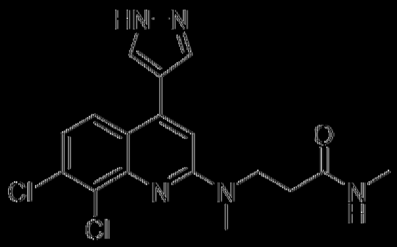
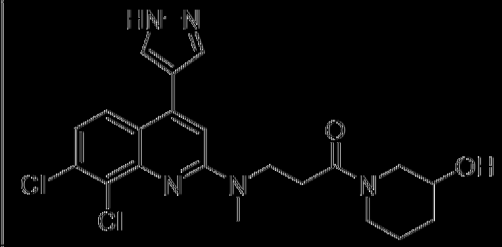
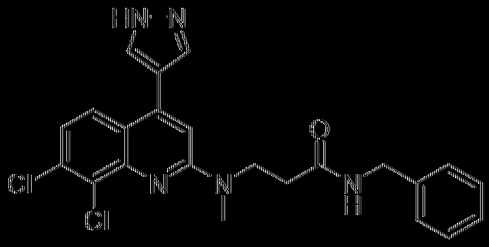
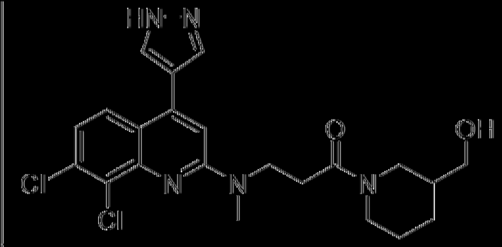
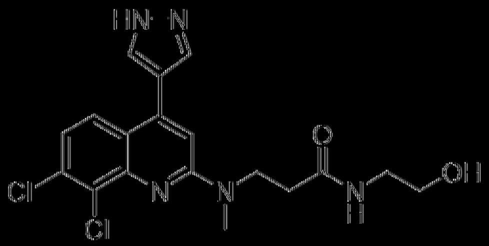
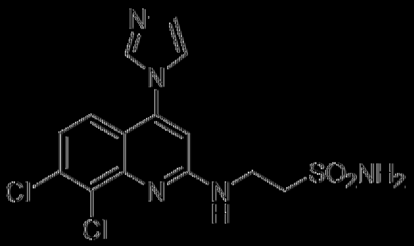
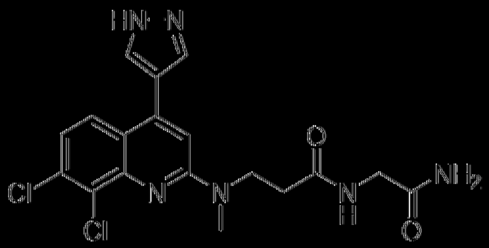
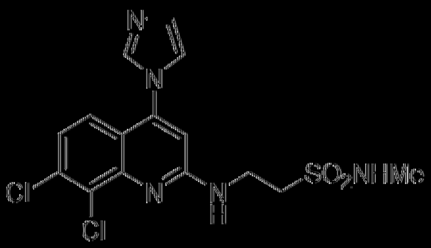
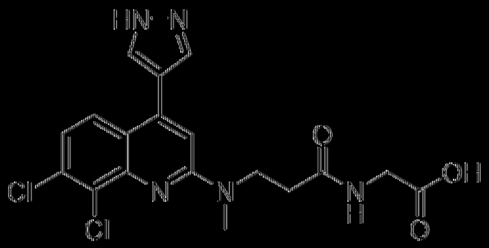
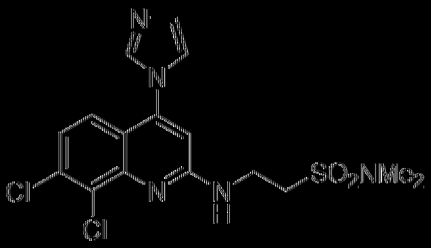
I-191		I-197	
I-192		I-198	
I-193		I-199	
I-194		I-200	
I-195		I-201	
I-196		I-202	

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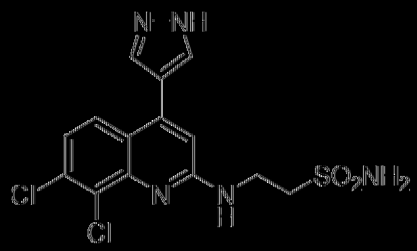
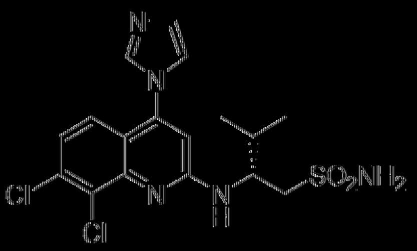
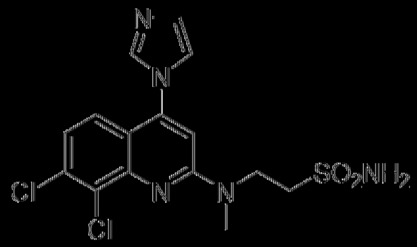
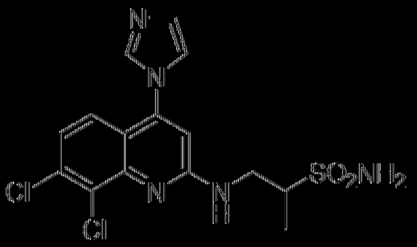
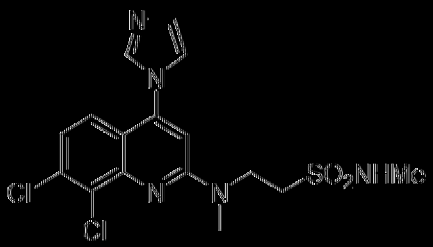
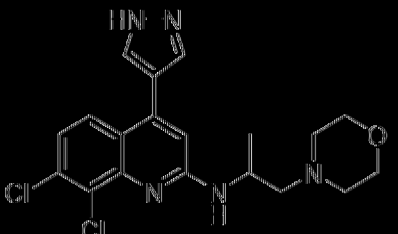
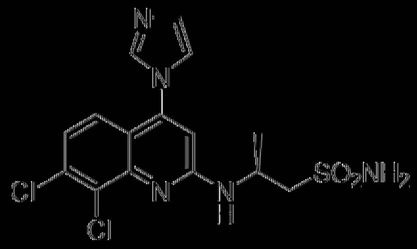
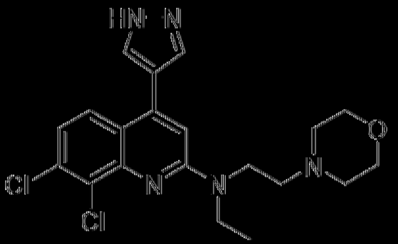
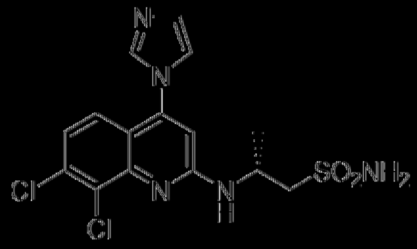
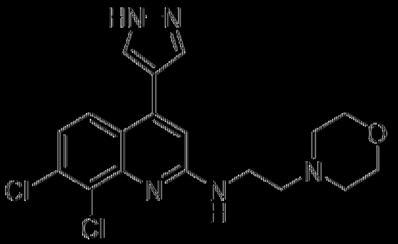
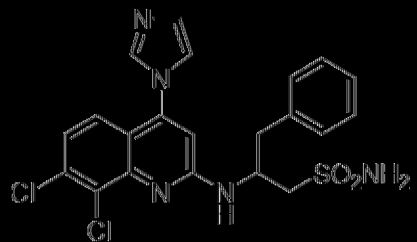
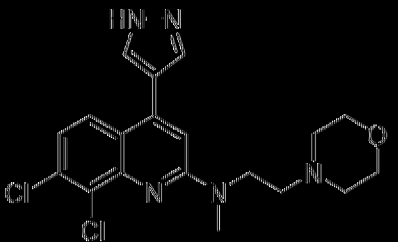
I-203		I-209	
I-204		I-210	
I-205		I-211	
I-206		I-212	
I-207		I-213	
I-208		I-214	

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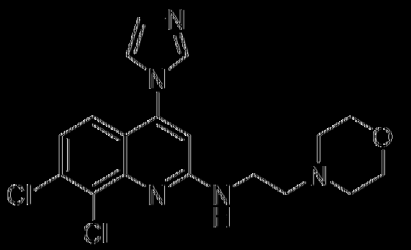
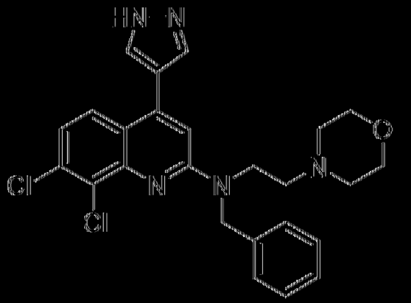
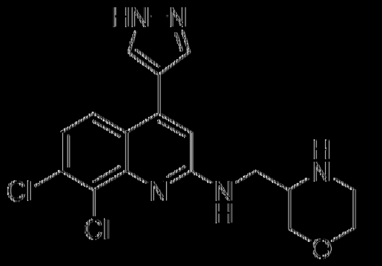
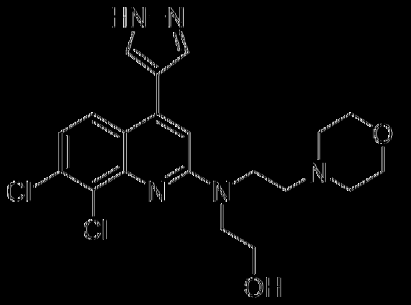
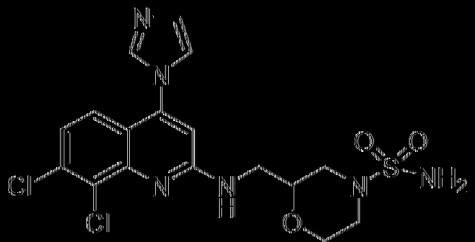
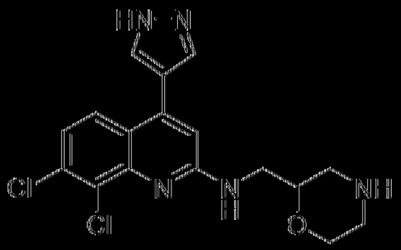
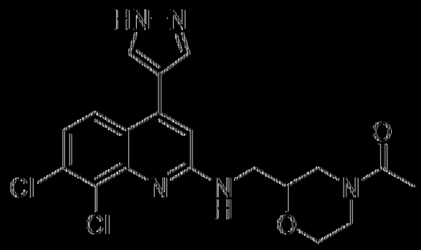
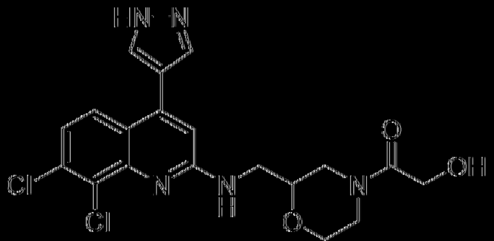
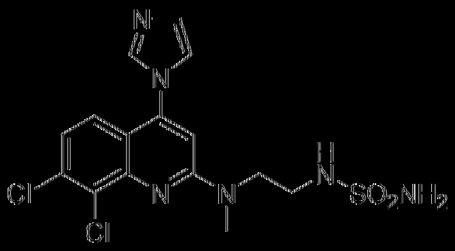
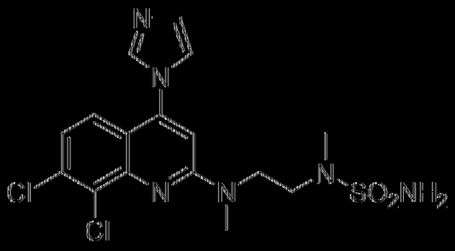
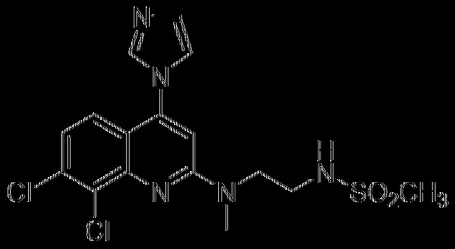
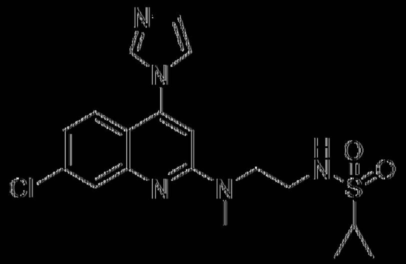
I-215	
I-216	
I-217	
I-218	
I-219	
I-220	
I-221	
I-222	
I-223	
I-224	
I-225	
I-226	

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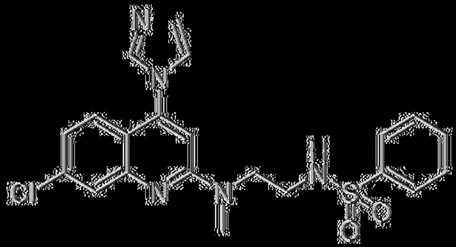
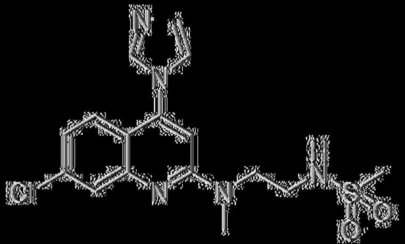
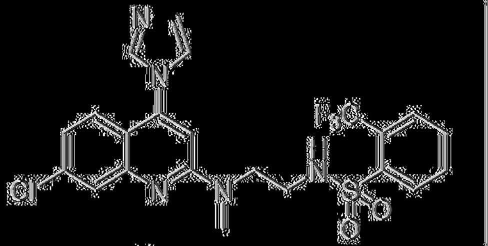
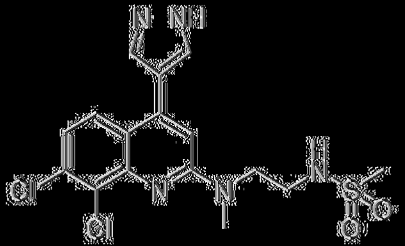
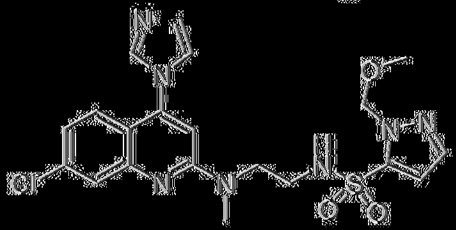
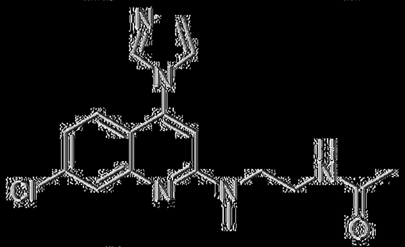
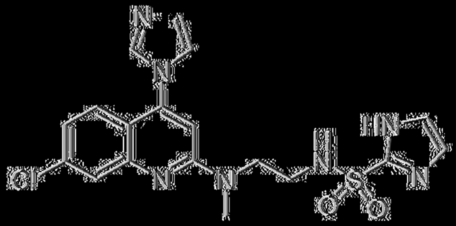
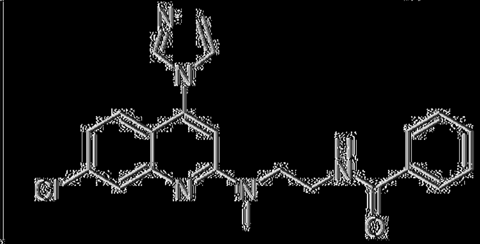
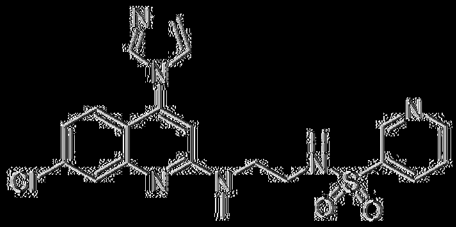
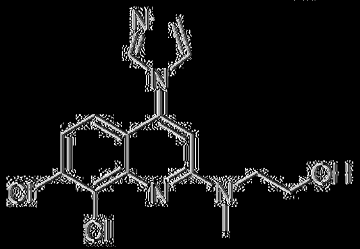
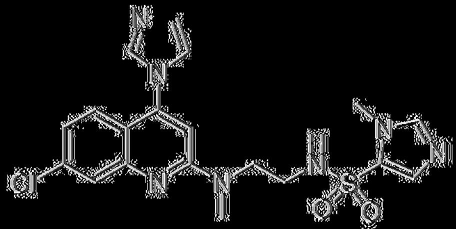
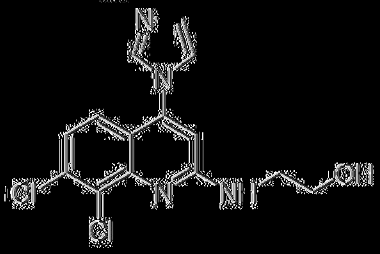
I-227		I-234	
I-228		I-235	
I-229		I-236	
I-230		I-237	
I-231		I-238	
I-232		I-239	

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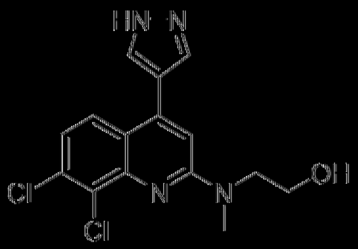
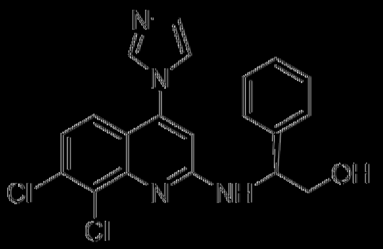
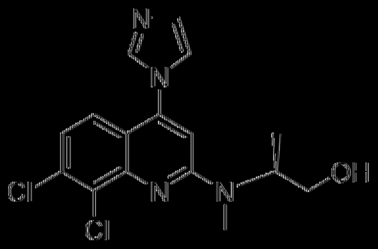
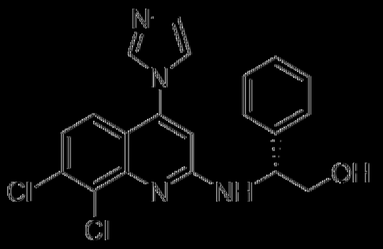
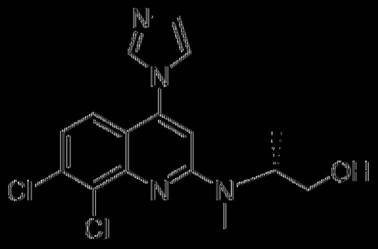
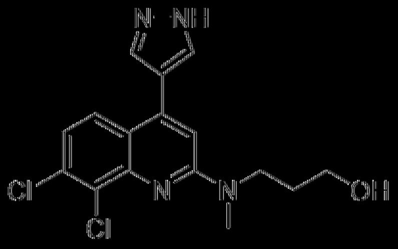
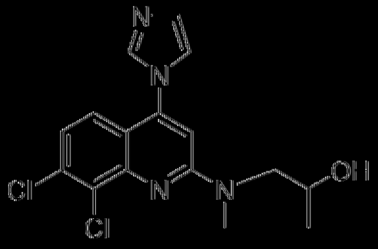
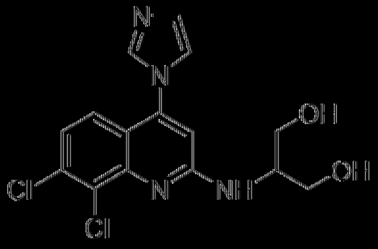
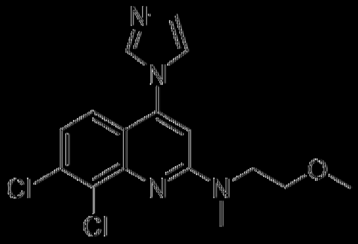
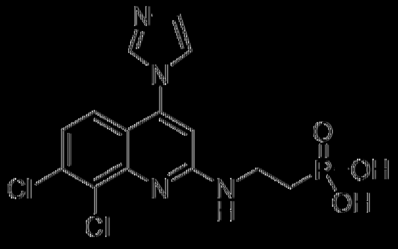
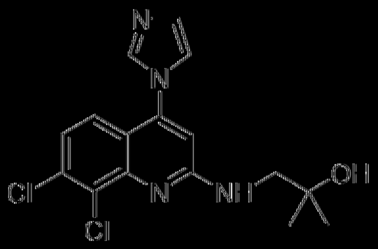
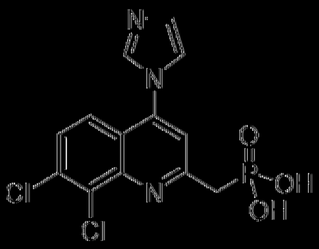
I-240		I-246	
I-241		I-247	
I-242		I-248	
I-243		I-249	
I-244		I-250	
I-245		I-251	

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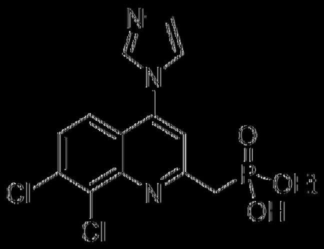
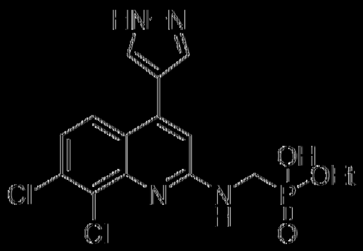
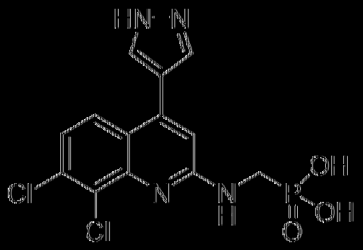
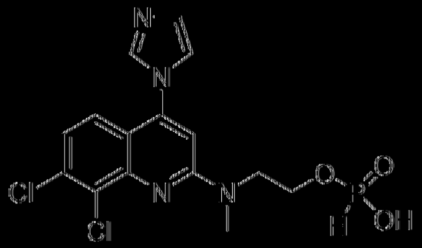
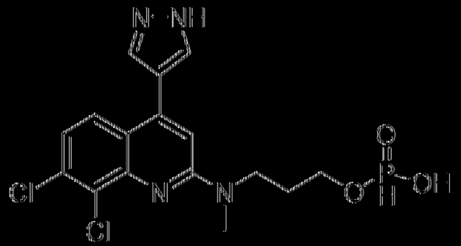
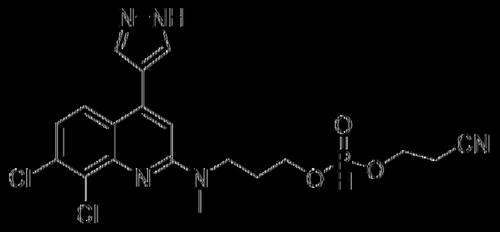
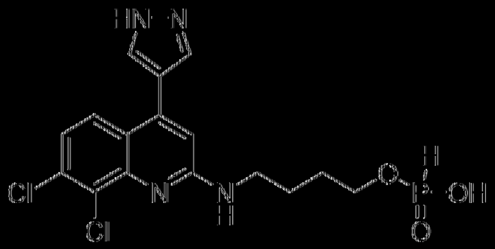
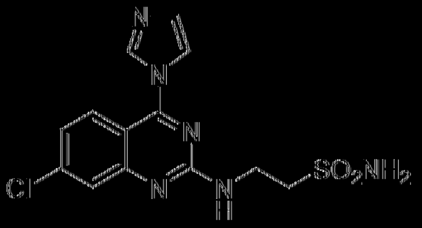
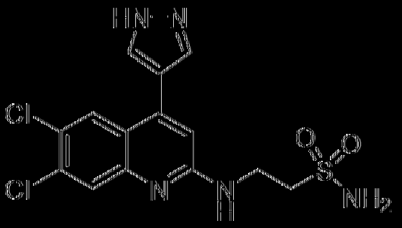
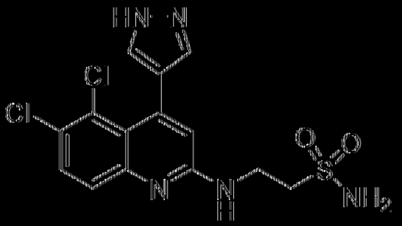
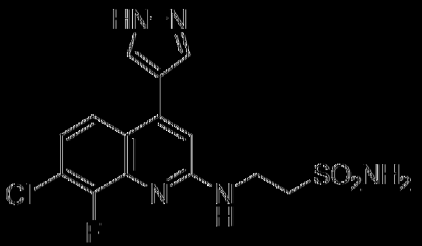
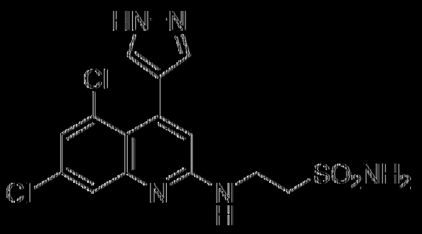
I-252	
I-253	
I-254	
I-255	
I-256	
I-257	
I-258	
I-259	
I-260	
I-261	
I-262	
I-263	

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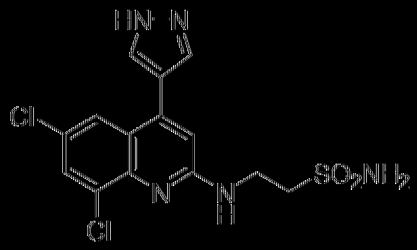
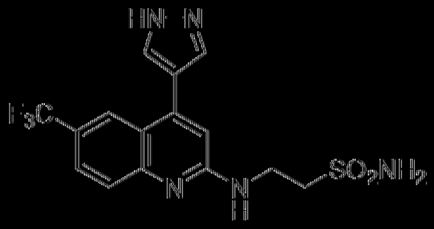
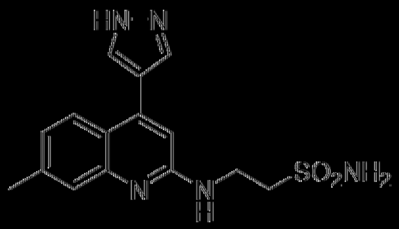
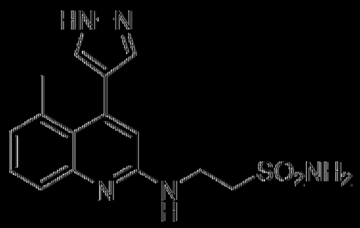
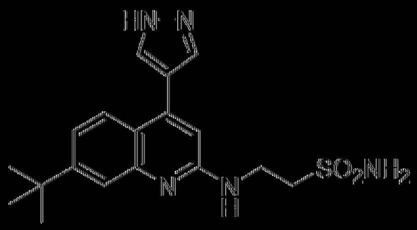
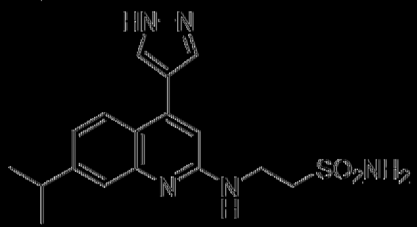
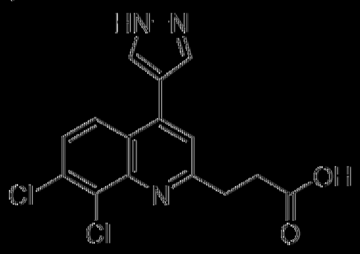
I-264	
I-265	
I-266	
I-267	
I-268	
I-269	
I-270	

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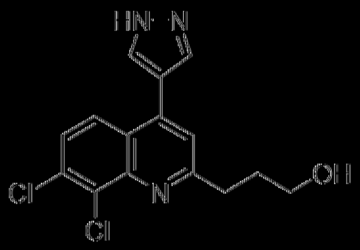
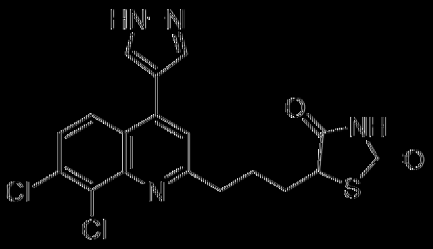
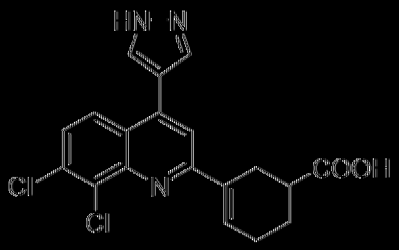
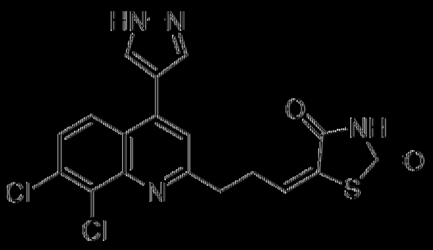
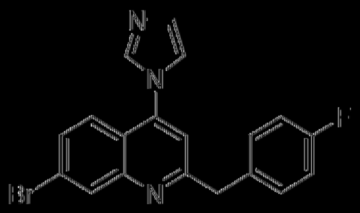
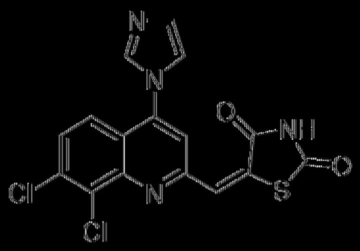
I-271	
I-272	
I-273	
I-274	
I-275	
I-276	

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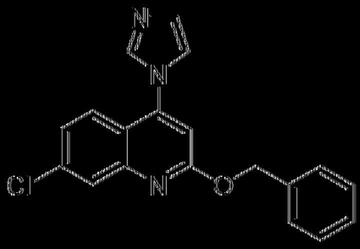
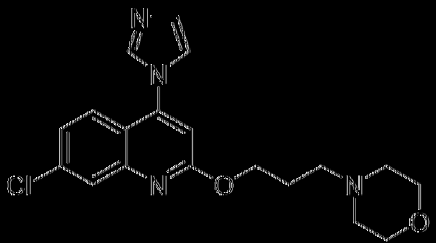
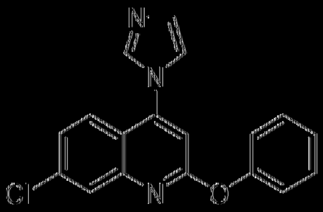
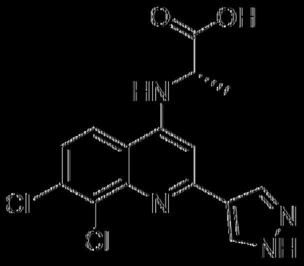
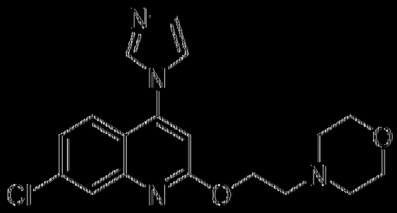
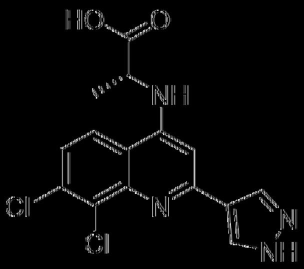
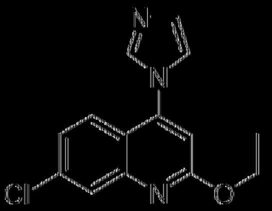
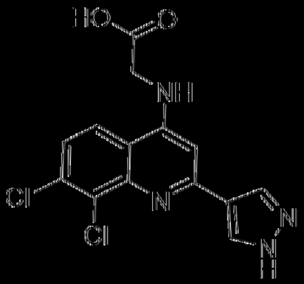
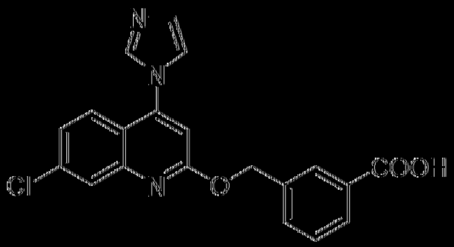
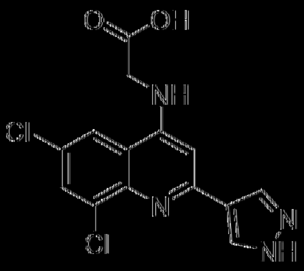
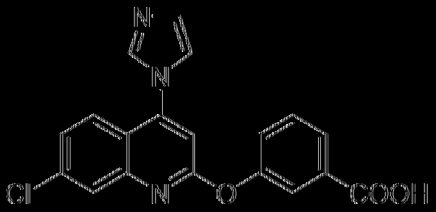
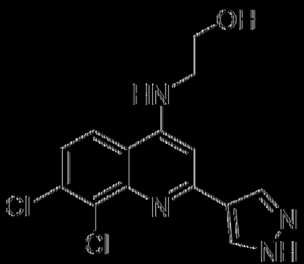
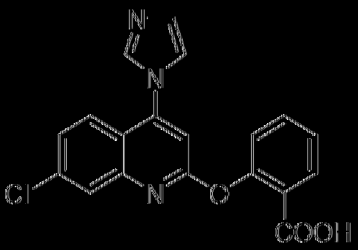
I-277		I-284	
I-278		I-285	
I-279		I-286	
I-280		I-287	
I-281		I-288	
I-282		I-289	
I-283			

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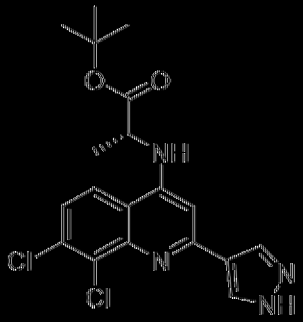
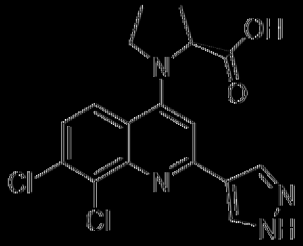
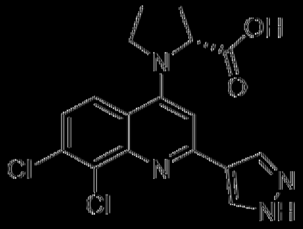
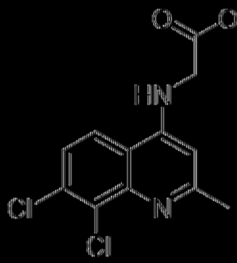
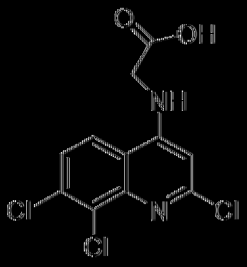
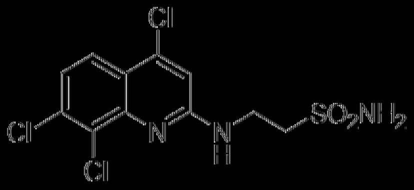
I-290	
I-291	
I-292	
I-293	
I-294	
I-295	

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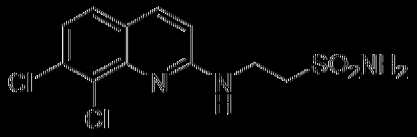
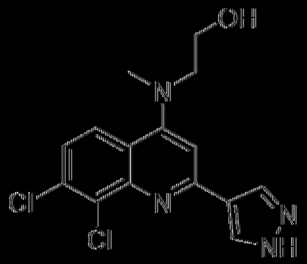
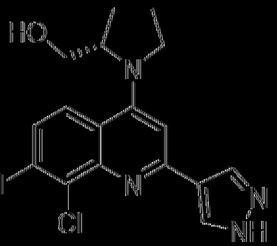
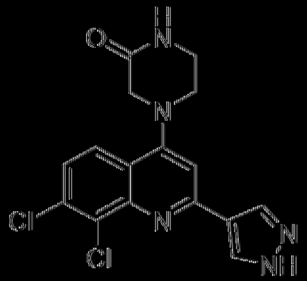
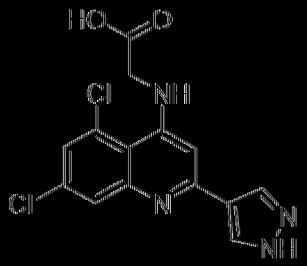
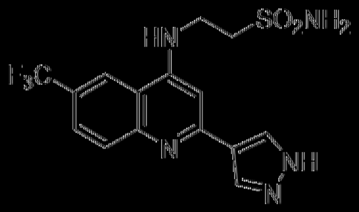
I-296	
I-297	
I-298	
I-299	
I-300	
I-301	

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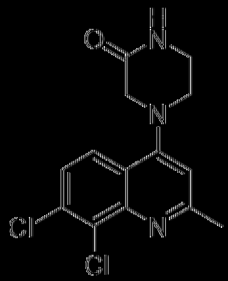
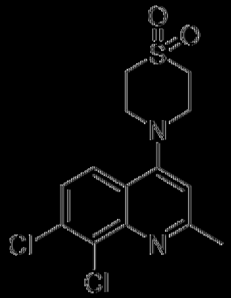
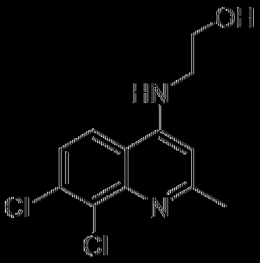
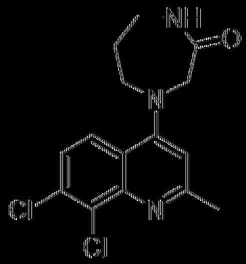
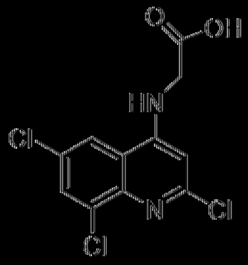
I-302	
I-303	
I-304	
I-305	
I-306	

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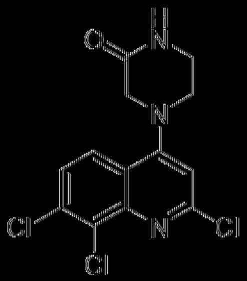
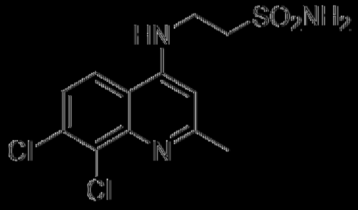
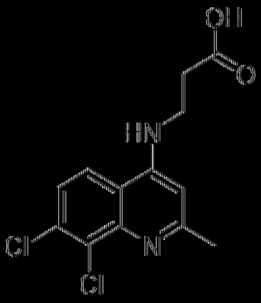
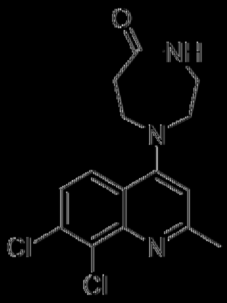
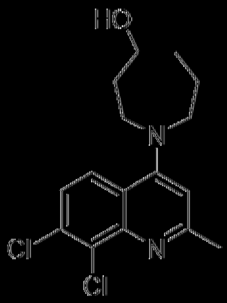
I-307	
I-308	
I-309	
I-310	
I-311	

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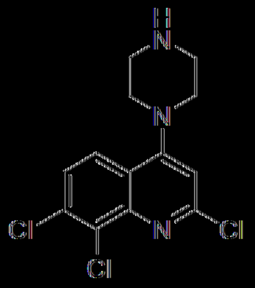
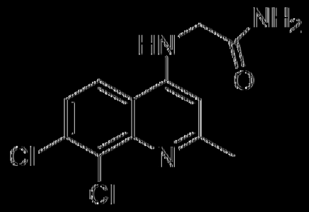
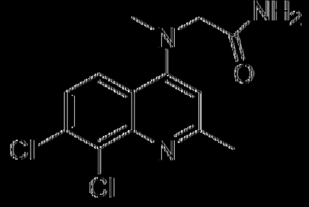
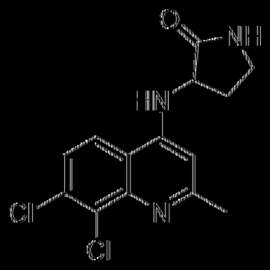
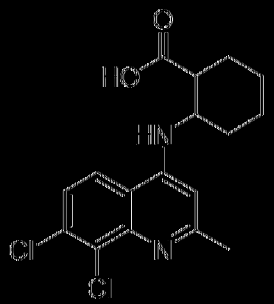
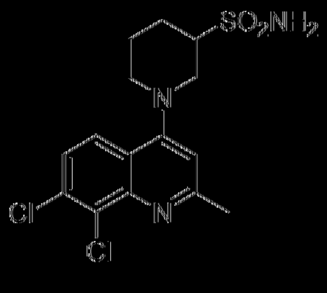
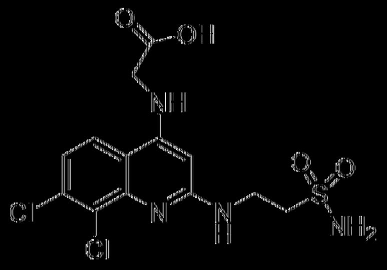
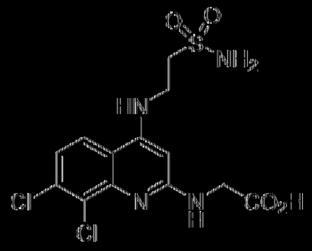
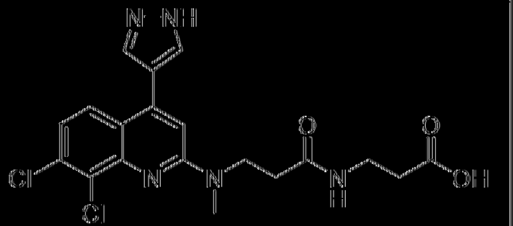
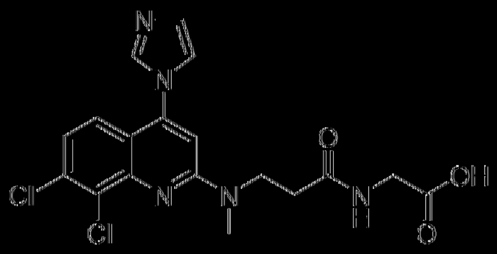
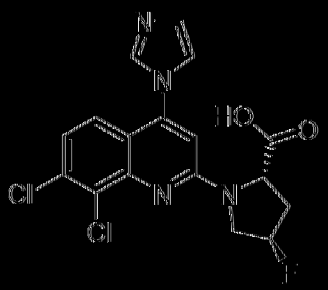
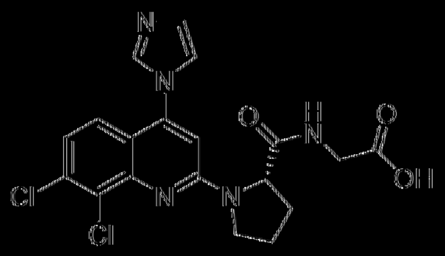
I-312	
I-313	
I-314	
I-315	
I-316	
I-317	
I-318	
I-319	
I-320	
I-321	
I-322	
I-323	

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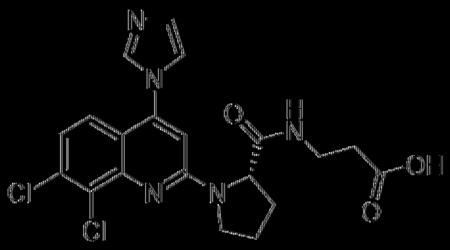
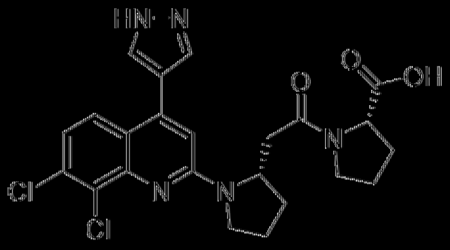
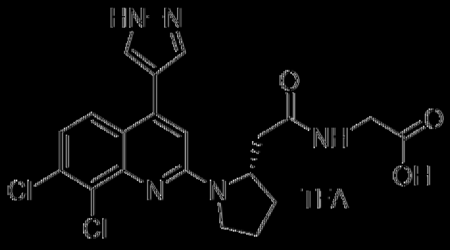
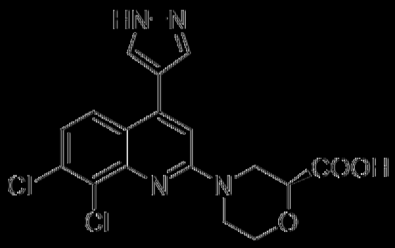
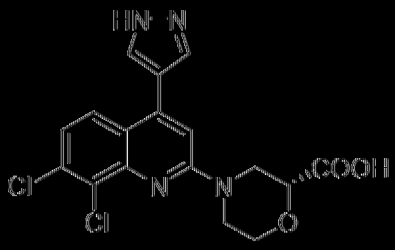
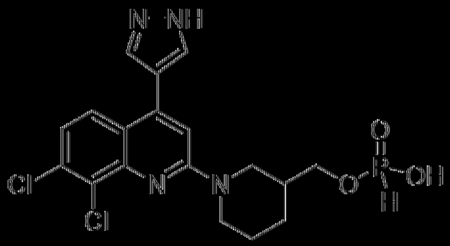
I-324	
I-325	
I-326	
I-327	
I-328	
I-329	

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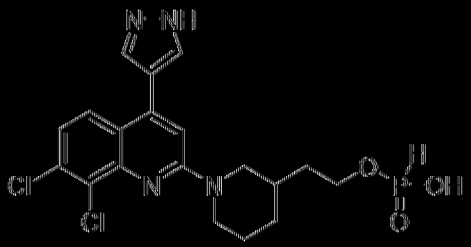
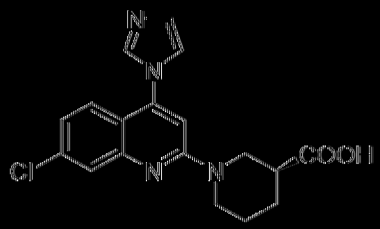
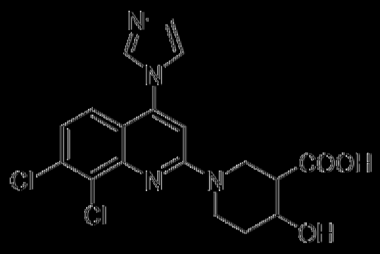
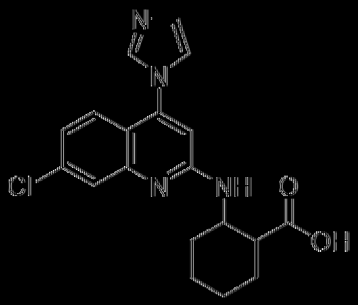
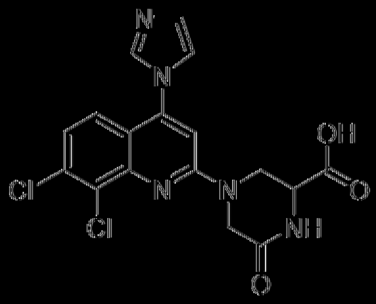
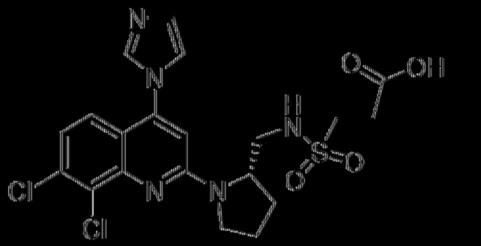
I-330	
I-331	
I-332	
I-333	
I-334	
I-335	

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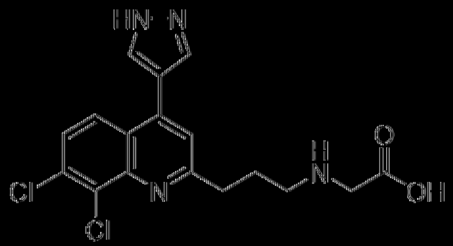
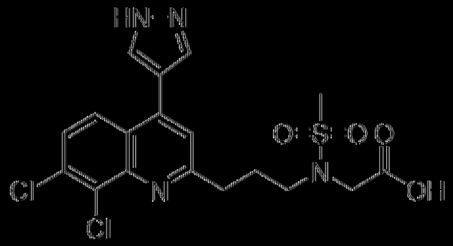
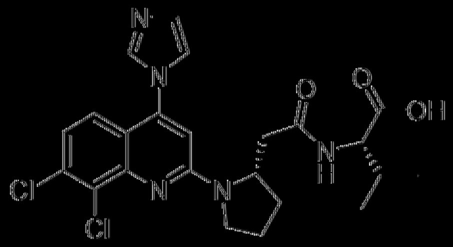
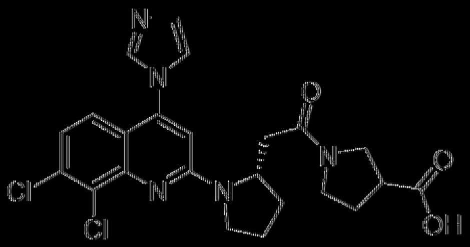
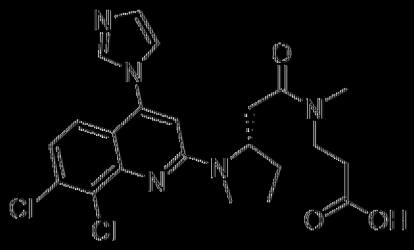
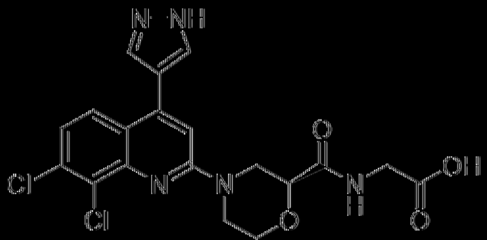
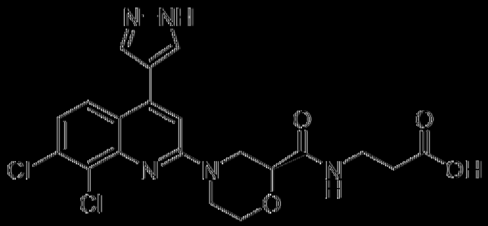
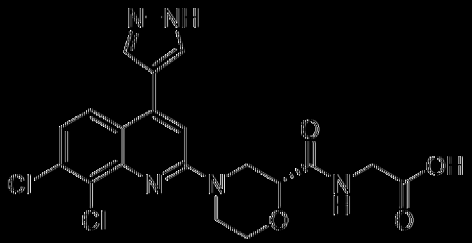
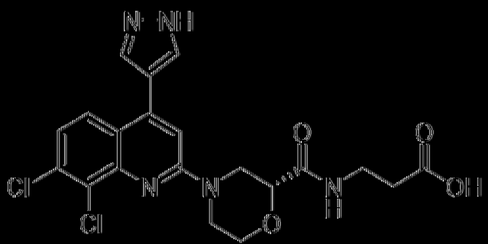
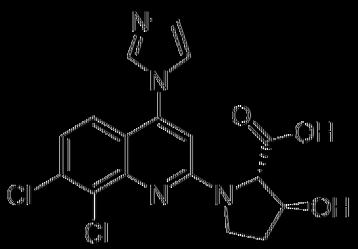
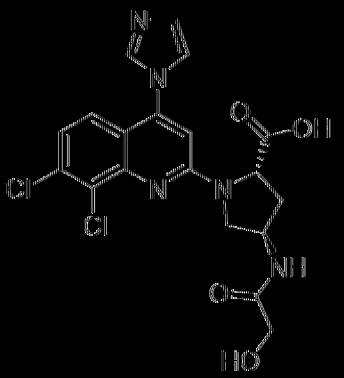
I-336	
I-337	
I-338	
I-339	
I-340	
I-341	
I-342	
I-343	
I-344	
I-345	
I-346	

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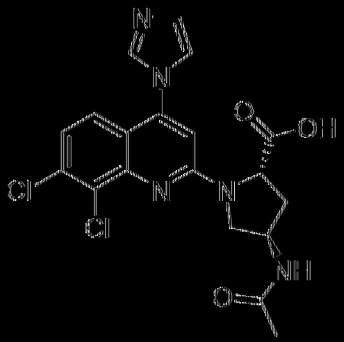
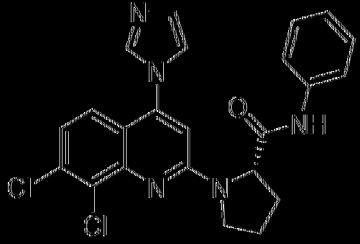
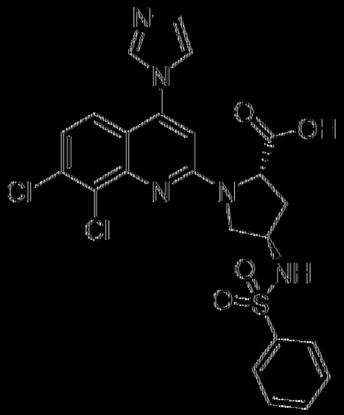
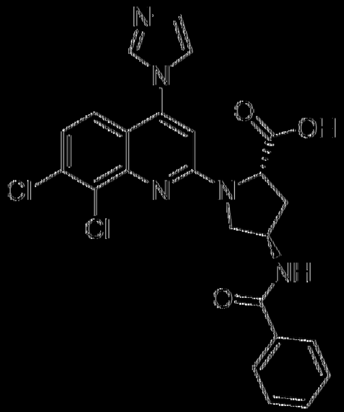
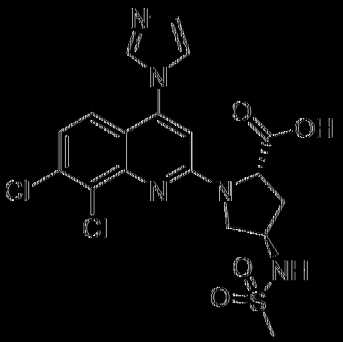
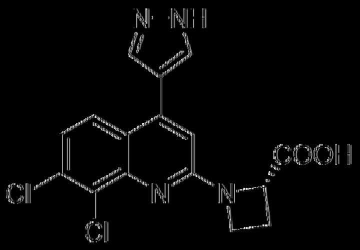
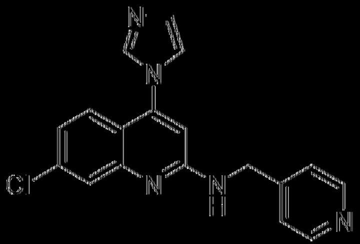
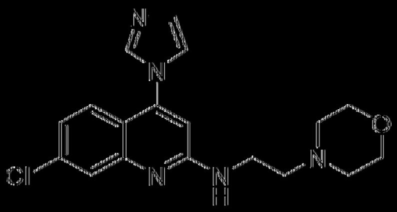
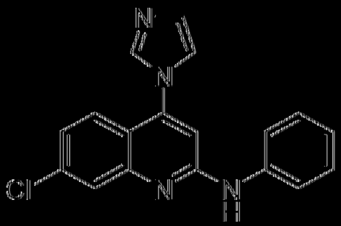
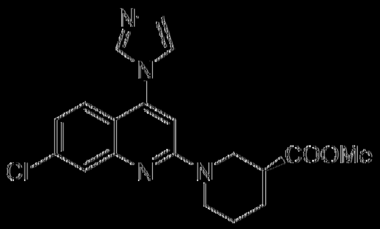
I-347	
I-348	
I-349	
I-350	
I-351	
I-352	
I-353	
I-354	
I-355	
I-356	

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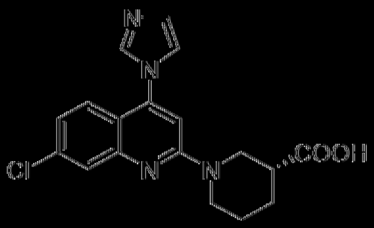
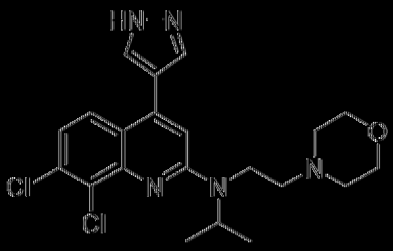
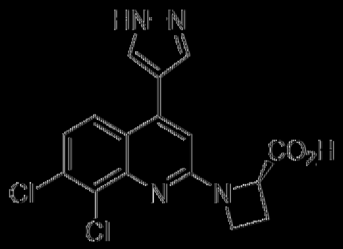
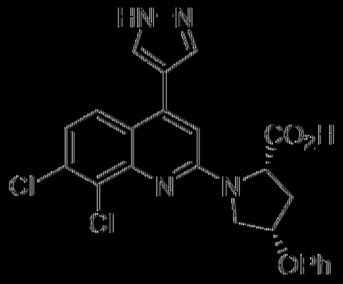
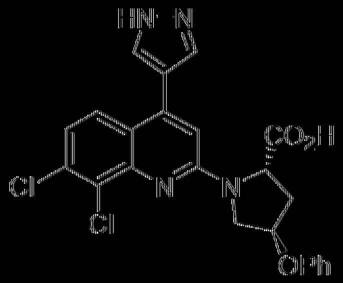
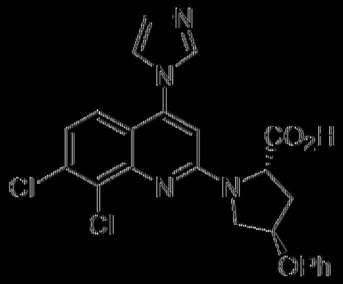
I-357	
I-358	
I-359	
I-360	
I-361	
I-362	

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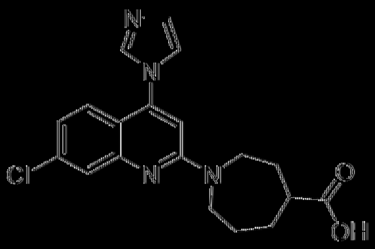
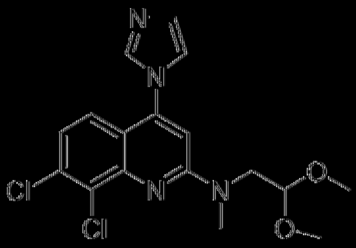
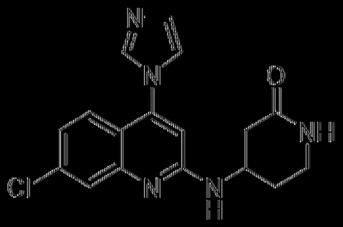
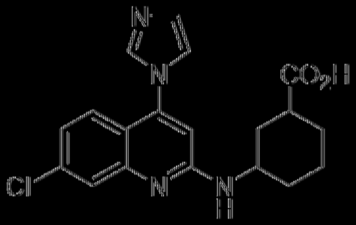
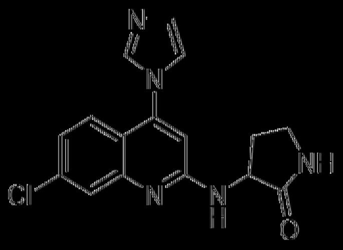
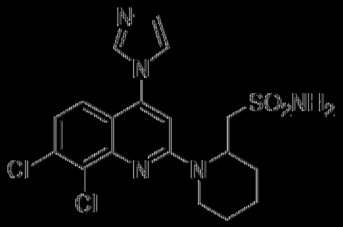
I-363	
I-364	
I-365	
I-366	
I-367	
I-368	

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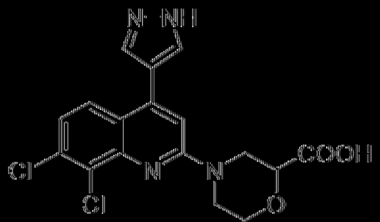
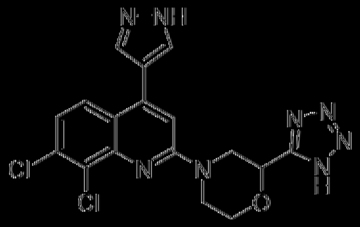
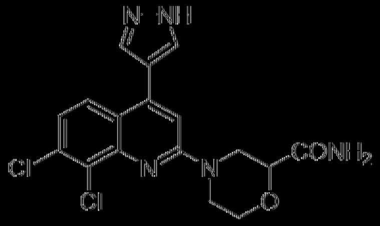
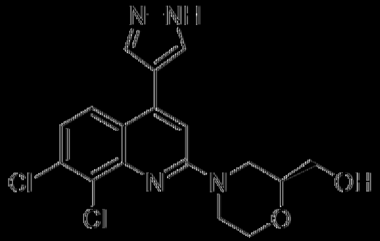
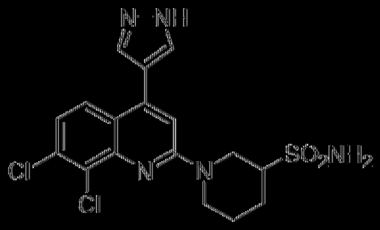
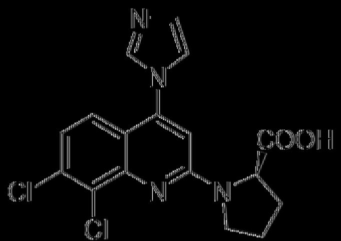
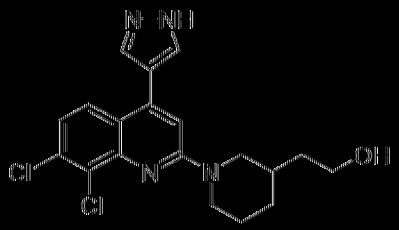
I-369	
I-370	
I-371	
I-372	
I-373	
I-374	
I-375	

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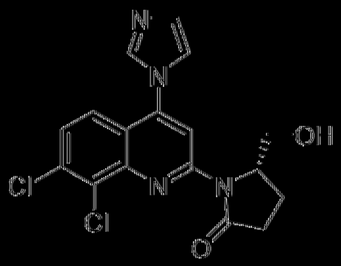
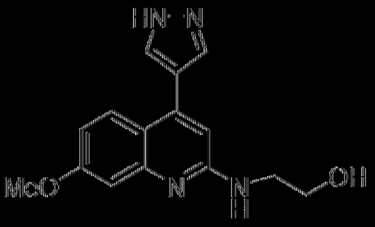
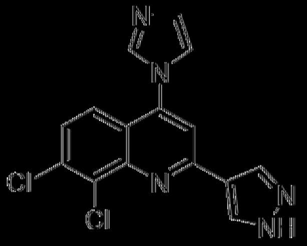
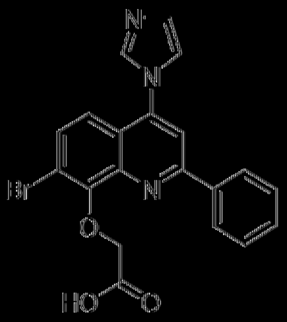
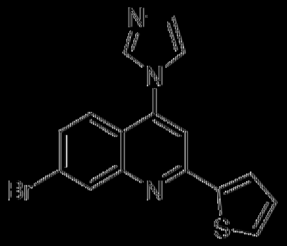
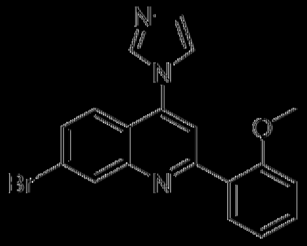
I-376	
I-377	
I-378	
I-379	
I-380	
I-381	

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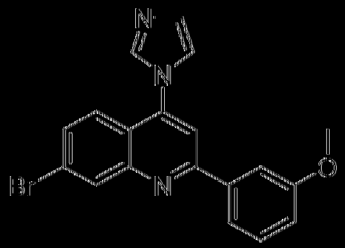
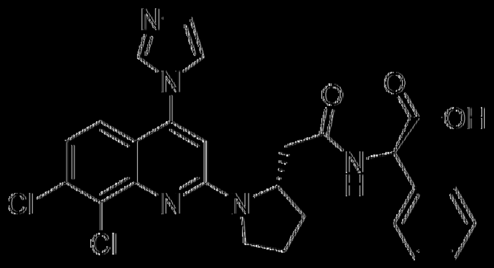
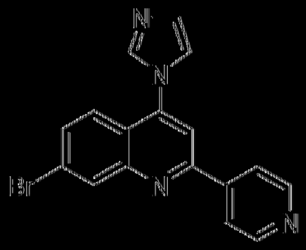
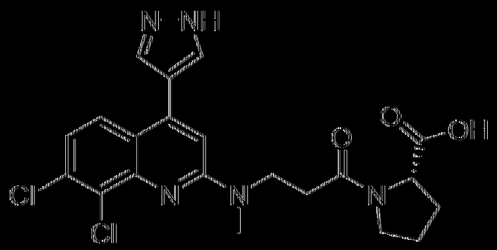
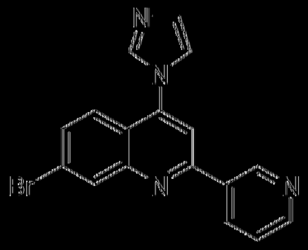
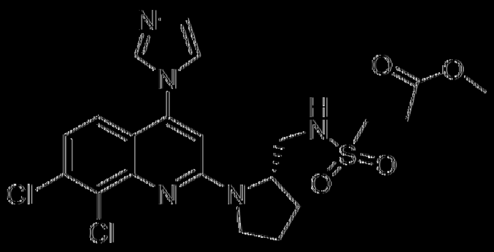
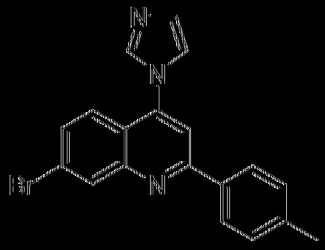
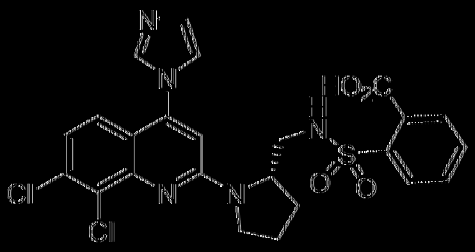
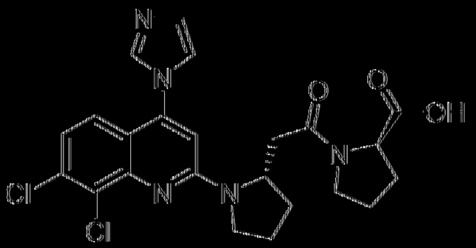
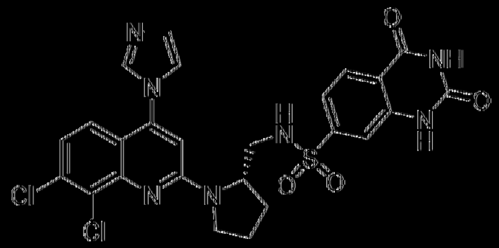
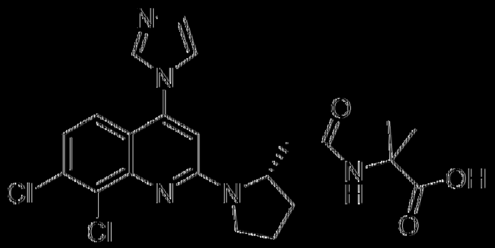
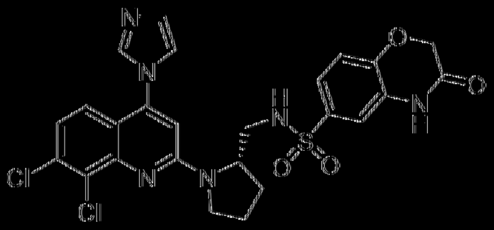
I-382		I-388	
I-383		I-389	
I-384		I-390	
I-385		I-391	
I-386		I-392	
I-387		I-393	

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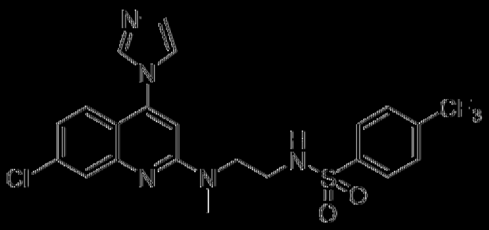
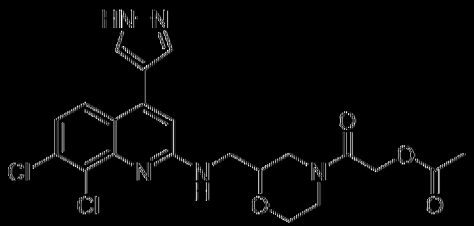
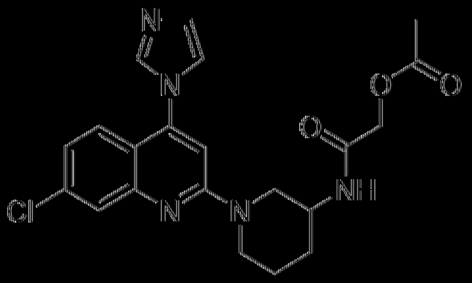
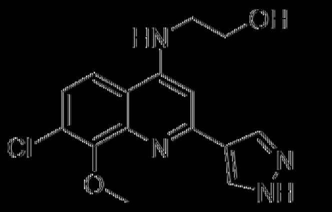
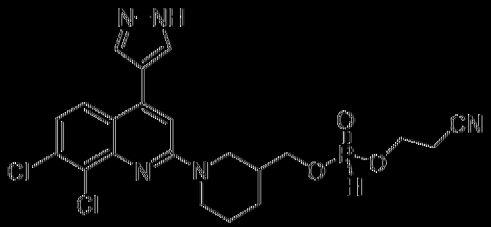
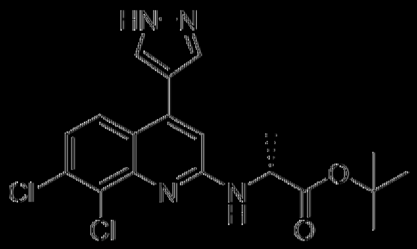
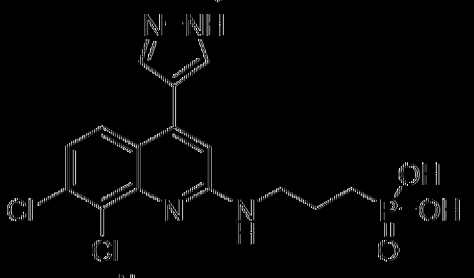
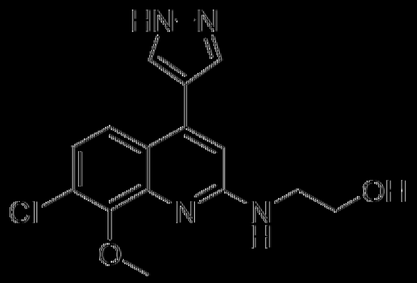
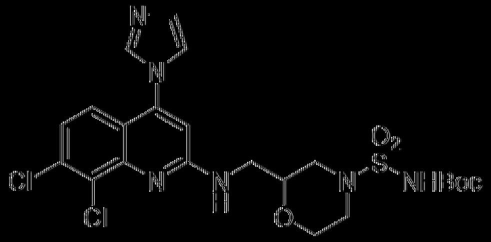
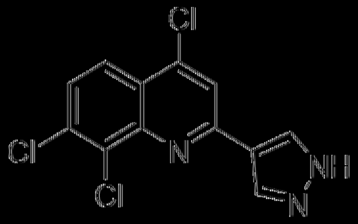
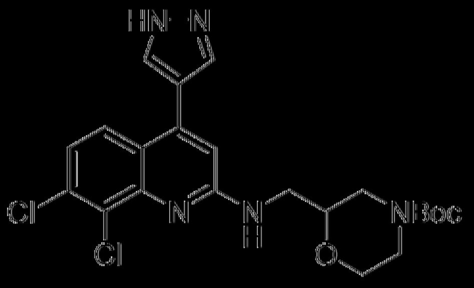
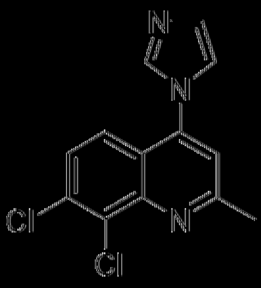
I-394		I-400	
I-395		I-401	
I-396		I-402	
I-397		I-403	
I-398		I-404	
I-399		I-405	

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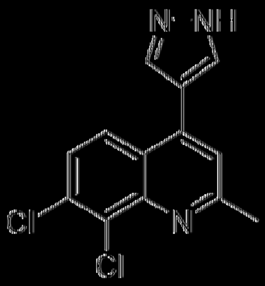
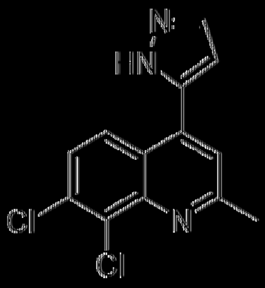
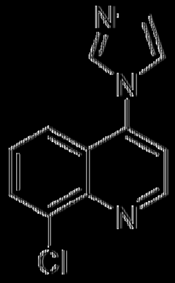
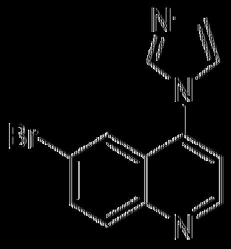
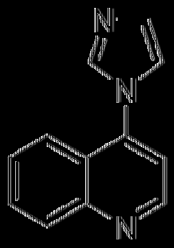
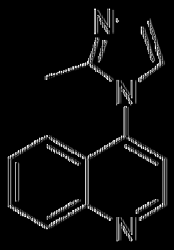
I-406	
I-407	
I-408	
I-409	
I-410	
I-411	

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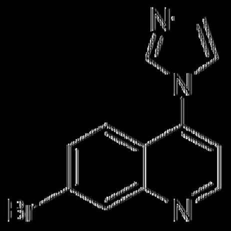
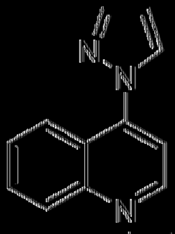
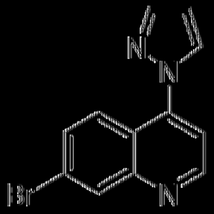
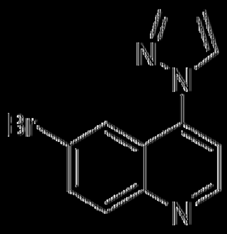
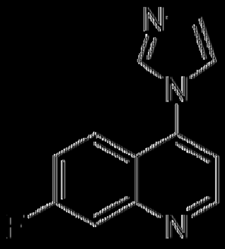
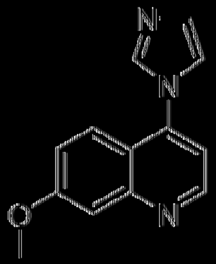
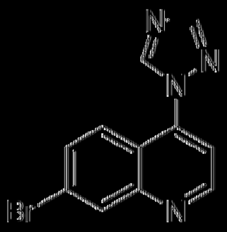
I-412	
I-413	
I-414	
I-415	
I-416	
I-417	
I-418	

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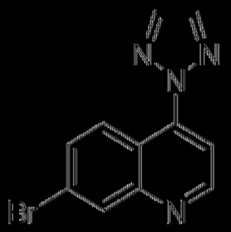
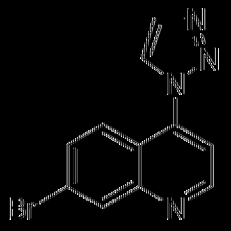
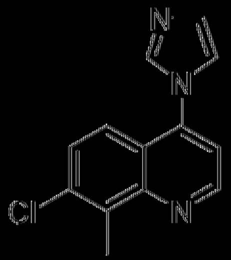
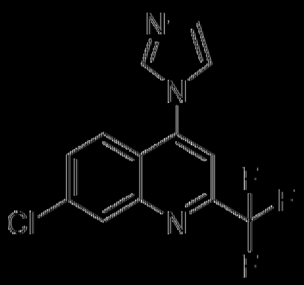
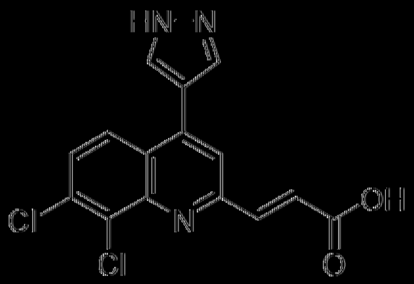
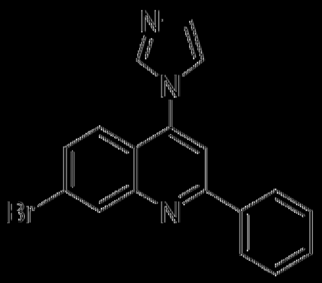
I-419	
I-420	
I-421	
I-422	
I-423	
I-424	

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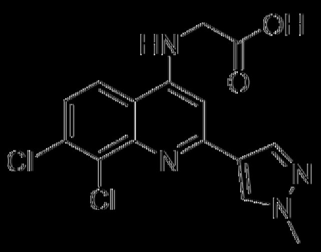
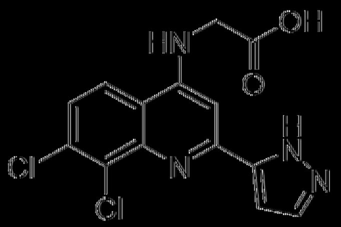
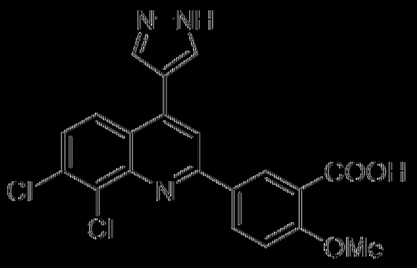
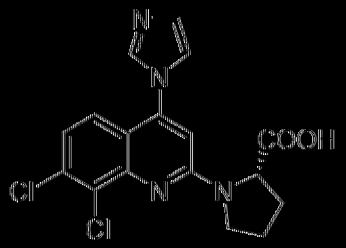
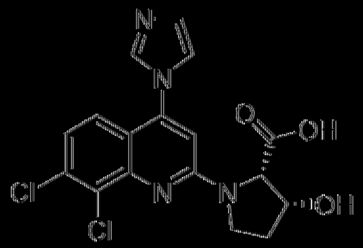
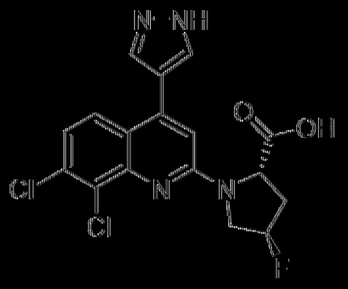
I-425	
I-426	
I-427	
I-428	
I-429	
I-430	

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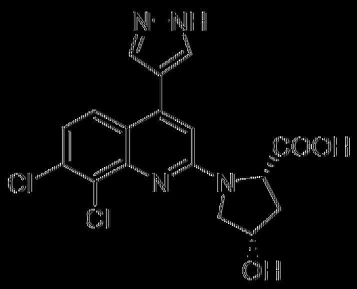
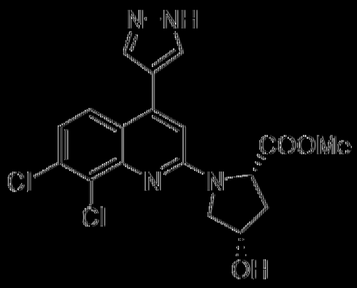
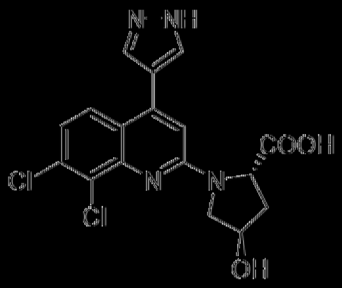
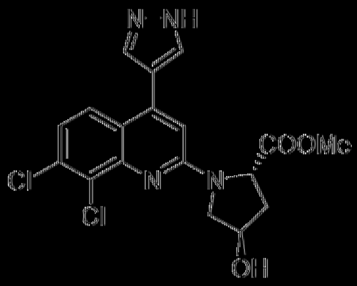
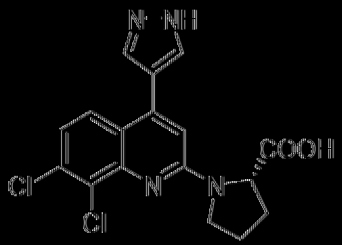
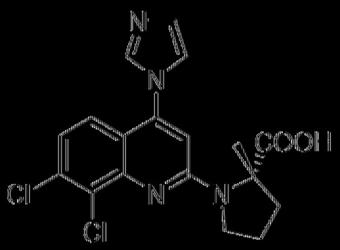
I-431	
I-432	
I-433	
I-434	
I-435	
I-436	

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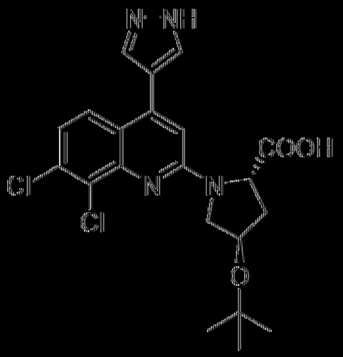
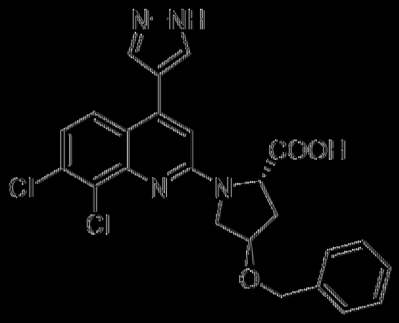
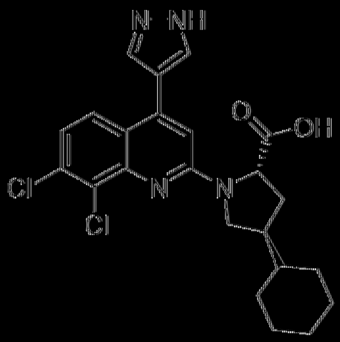
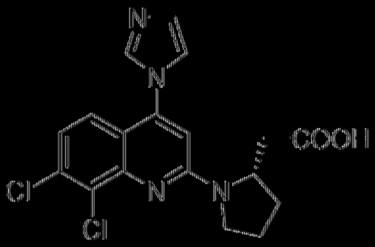
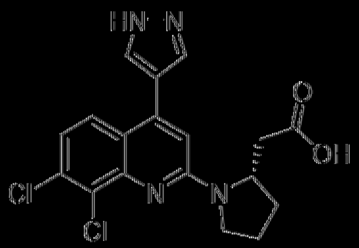
I-437	
I-438	
I-439	
I-443	
I-444	

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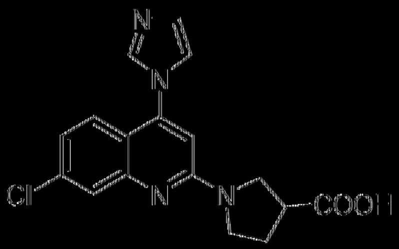
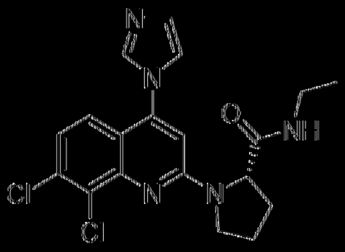
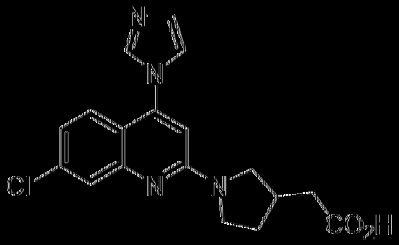
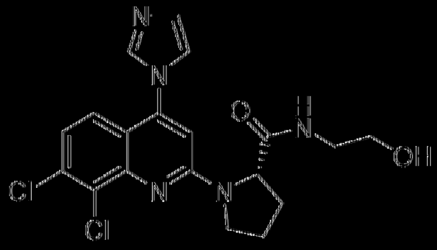
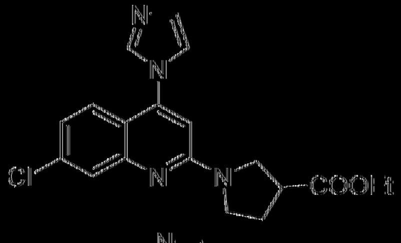
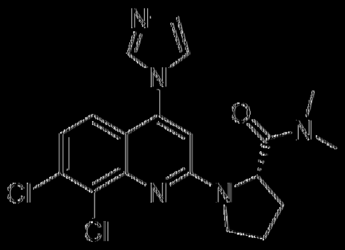
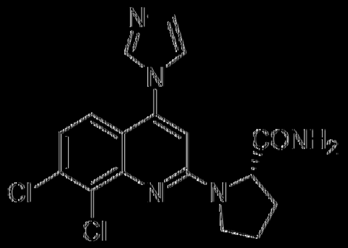
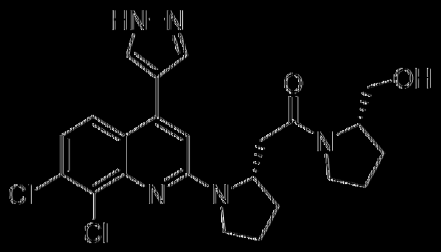
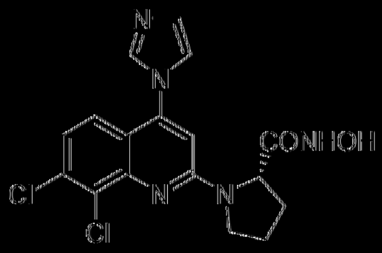
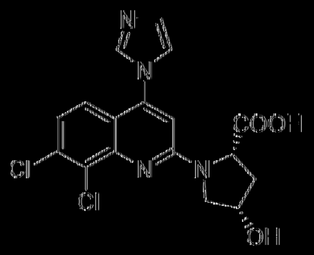
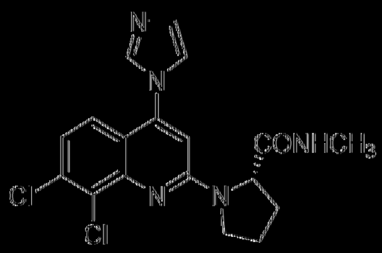
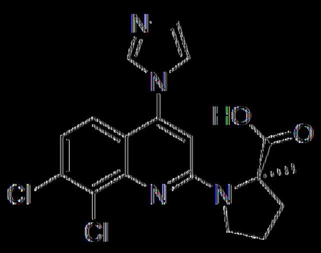
I-445		I-451	
I-446		I-452	
I-447		I-453	
I-448		I-454	
I-449		I-455	
I-450		I-456	

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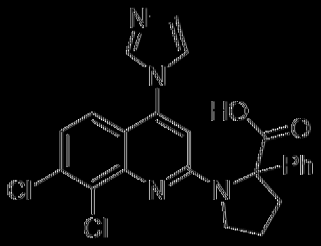
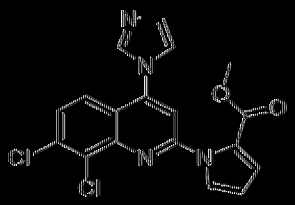
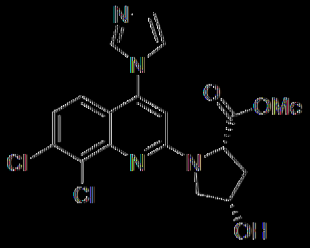
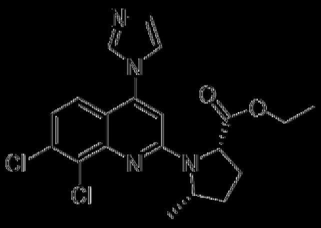
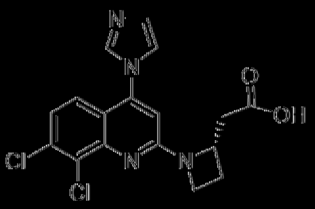
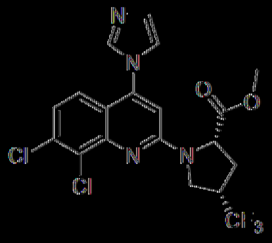
I-457	
I-458	
I-459	
I-460	
I-461	
I-462	

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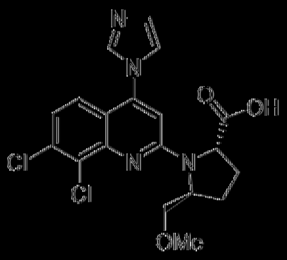
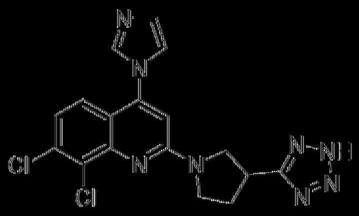
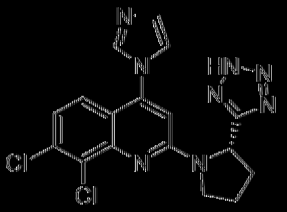
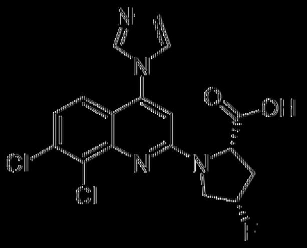
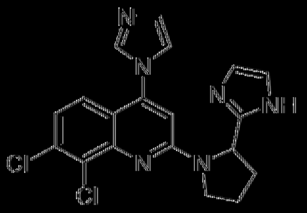
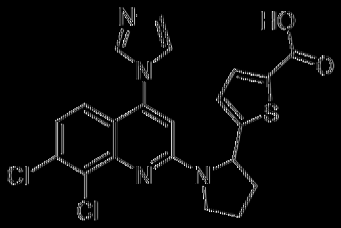
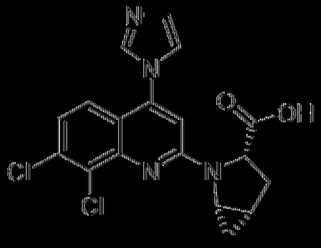
I-463	
I-464	
I-465	
I-466	
I-467	
I-468	
I-469	

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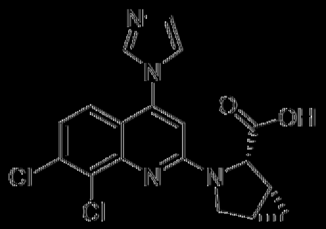
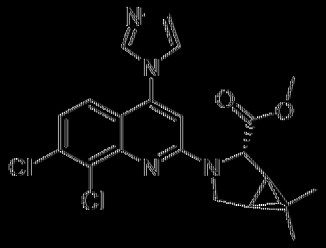
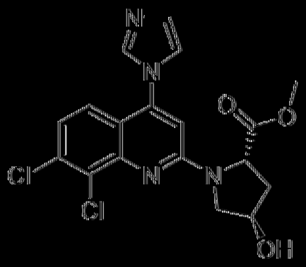
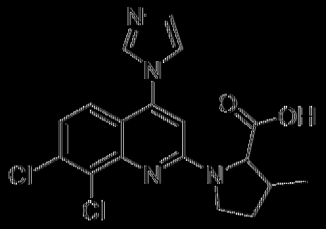
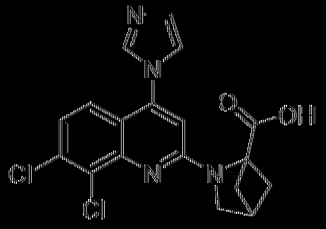
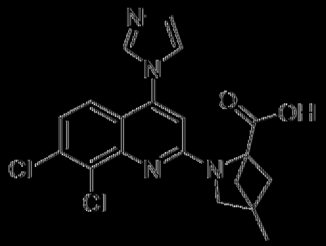
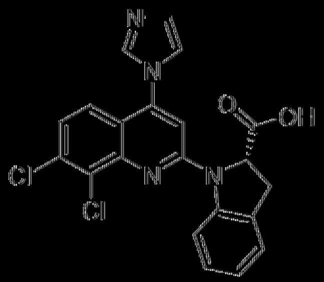
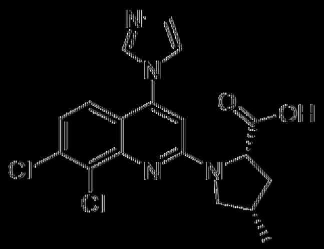
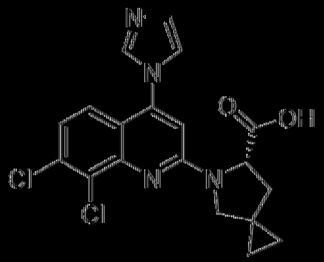
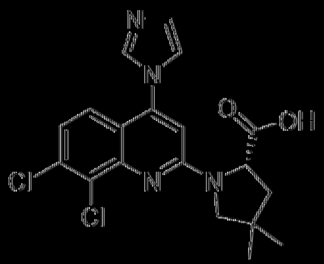
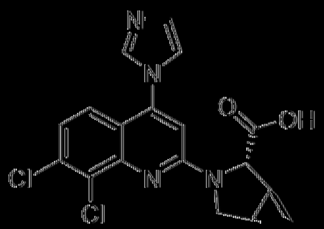
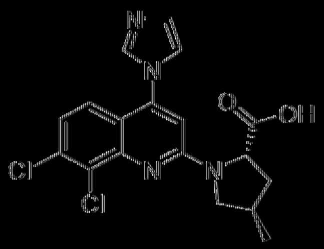
I-470	
I-471	
I-472	
I-473	
I-474	
I-475	
I-476	
I-477	
I-478	
I-479	
I-480	
I-481	

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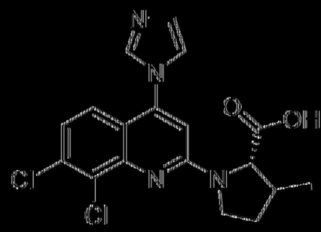
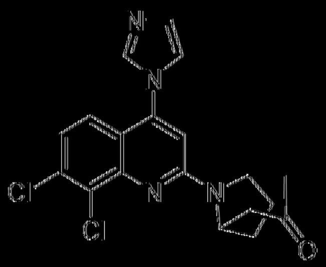
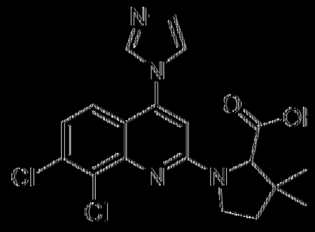
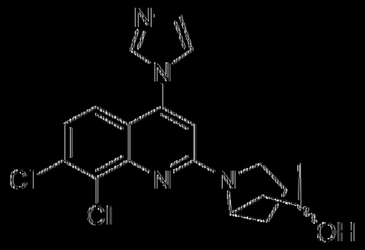
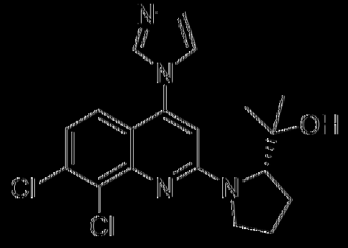
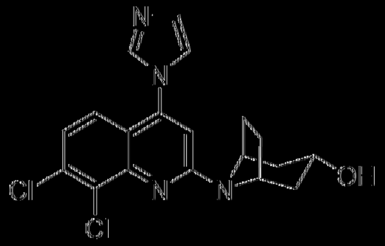
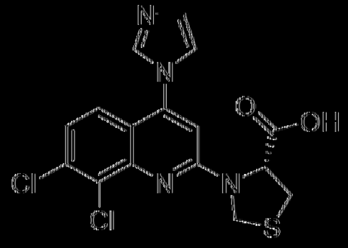
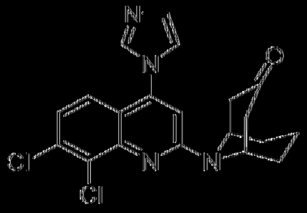
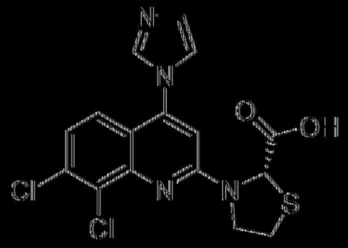
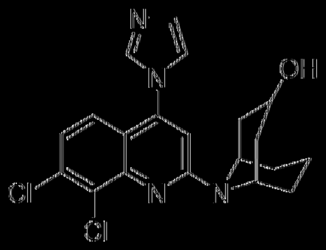
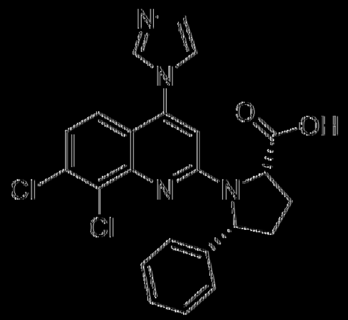
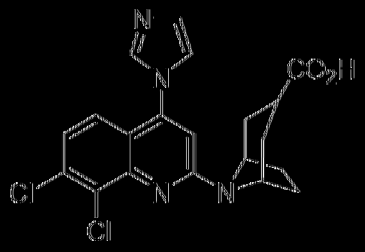
I-482		I-488	
I-483		I-489	
I-484		I-490	
I-485		I-491	
I-486		I-492	
I-487		I-493	

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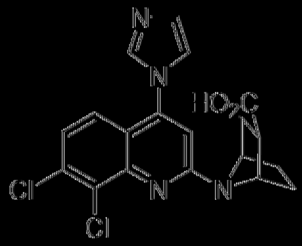
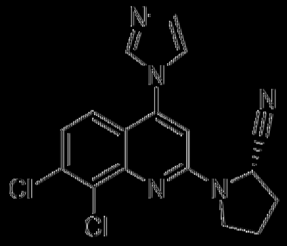
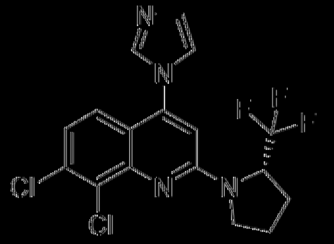
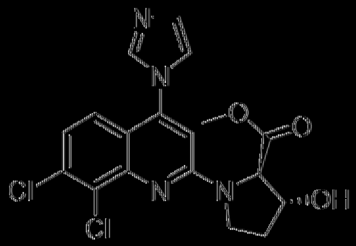
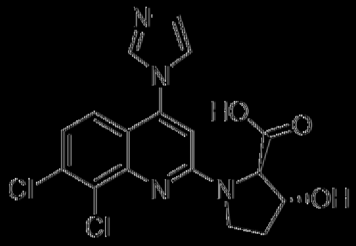
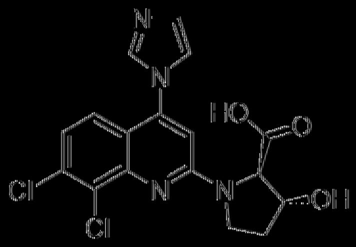
I-494	
I-495	
I-496	
I-497	
I-498	
I-499	

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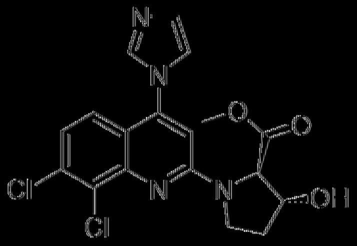
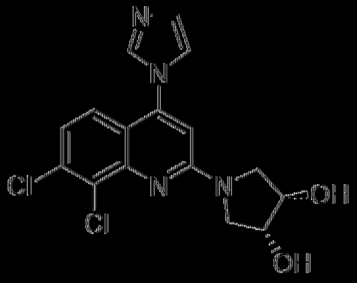
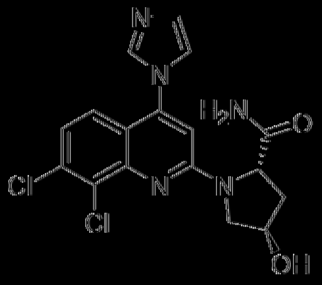
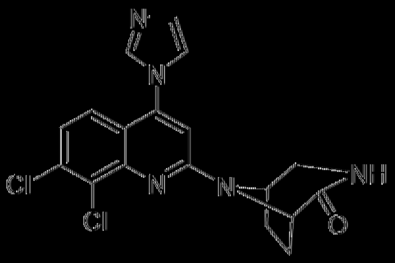
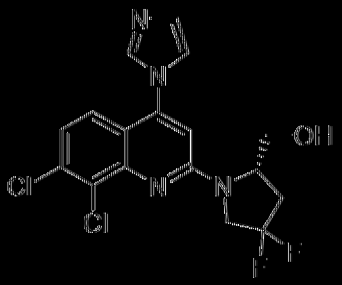
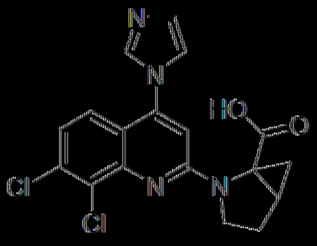
I-500	
I-501	
I-502	
I-503	
I-504	
I-505	

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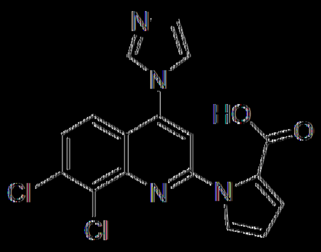
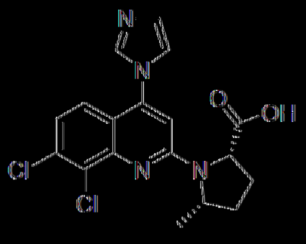
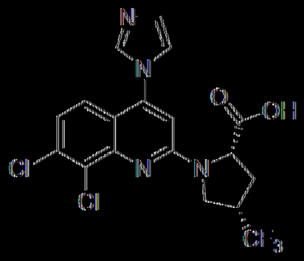
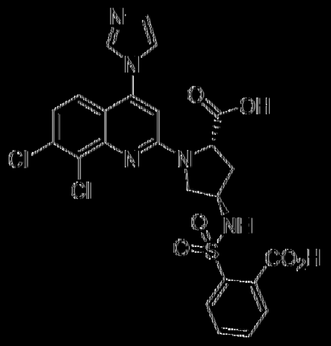
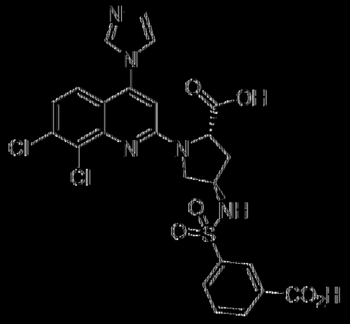
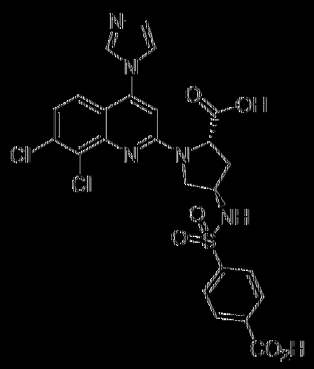
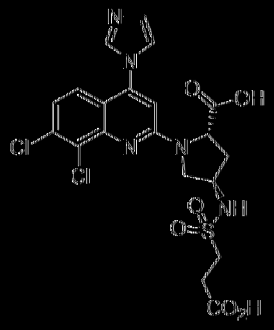
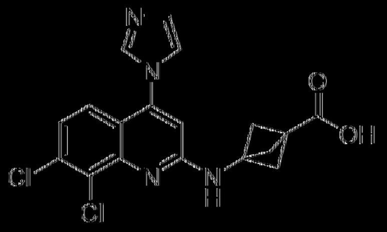
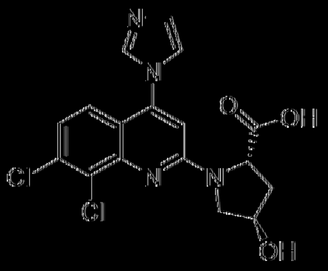
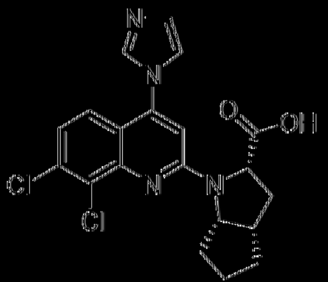
I-506	
I-507	
I-508	
I-509	
I-510	
I-511	
I-512	
I-513	
I-514	
I-515	

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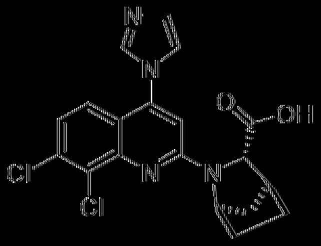
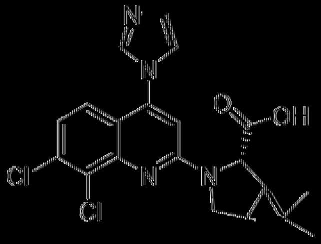
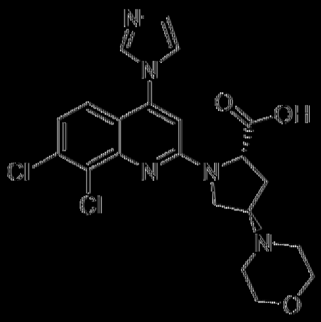
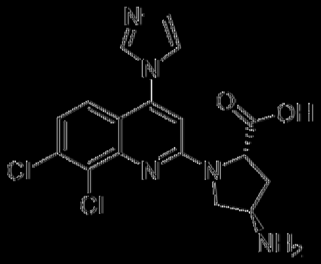
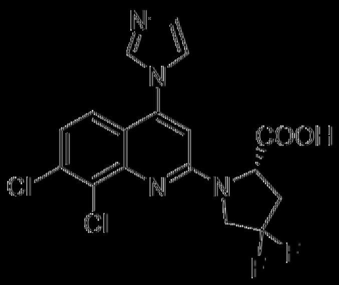
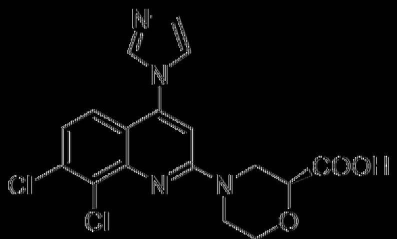
I-516	
I-517	
I-518	
I-519	
I-520	
I-521	

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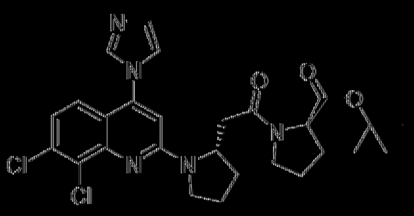
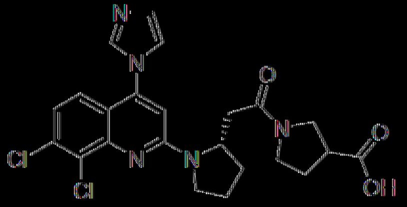
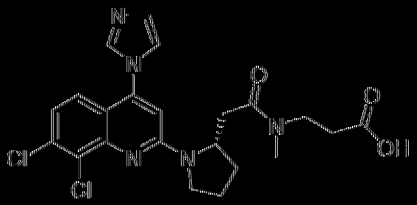
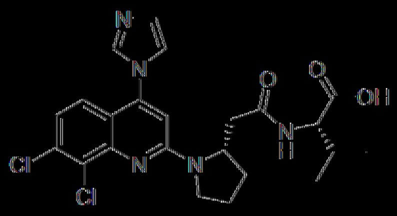
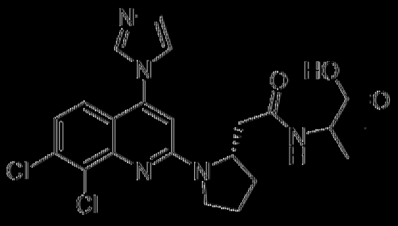
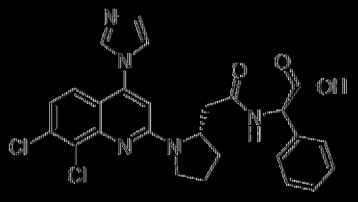
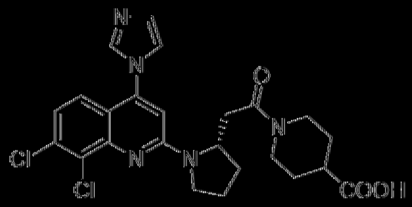
I-522	
I-524	
I-525	
I-526	
I-527	
I-528	
I-529	

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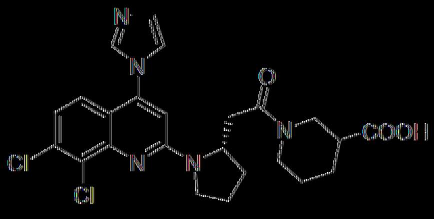
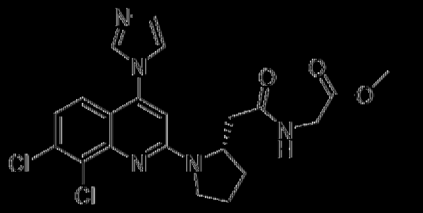
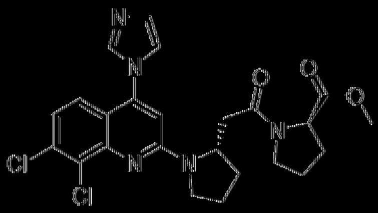
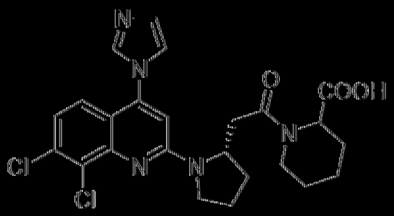
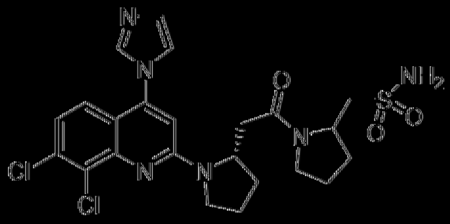
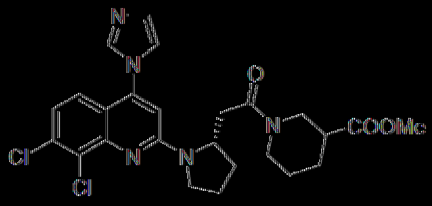
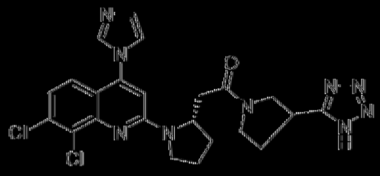
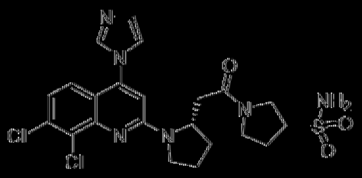
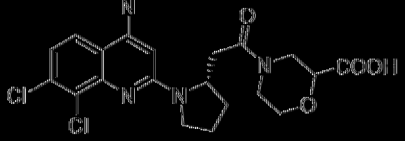
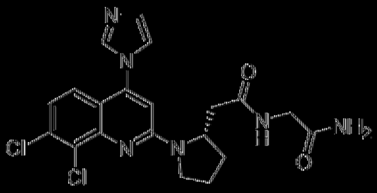
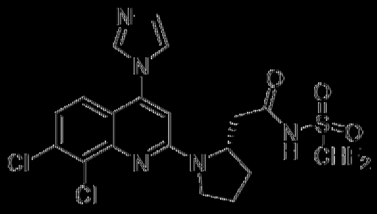
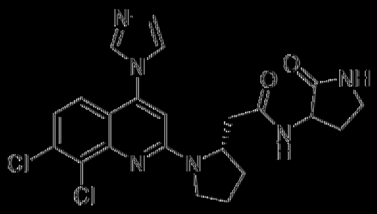
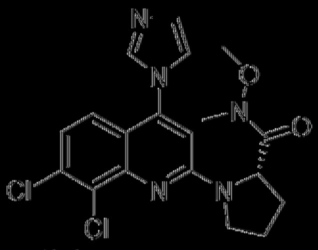
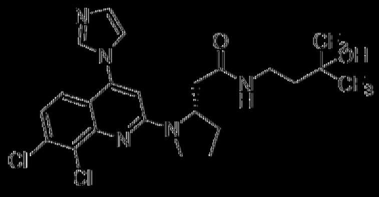
I-530	
I-531	
I-532	
I-533	
I-534	
I-535	
I-536	
I-537	
I-538	
I-539	
I-540	
I-541	
I-542	
I-543	

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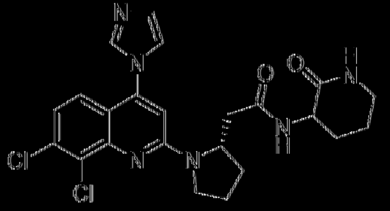
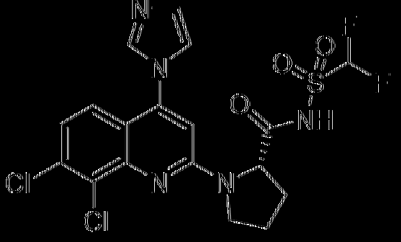
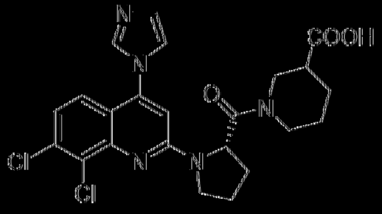
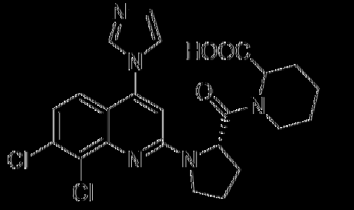
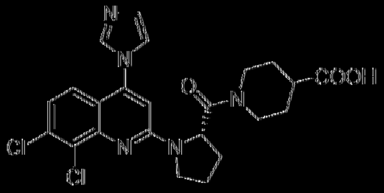
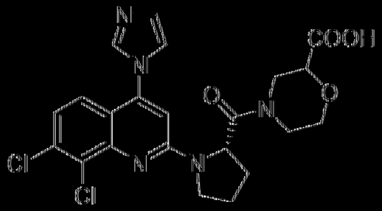
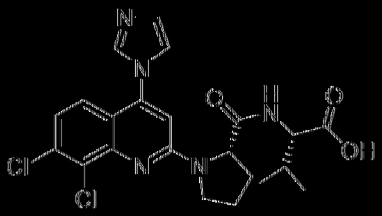
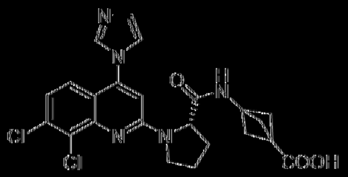
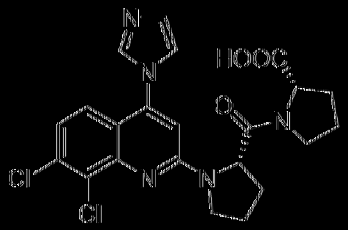
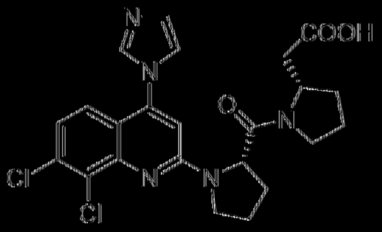
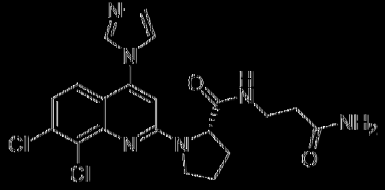
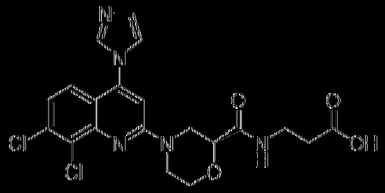
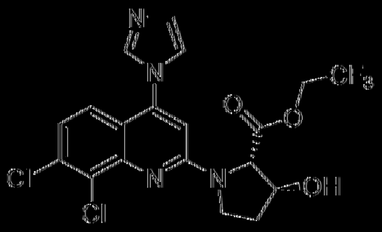
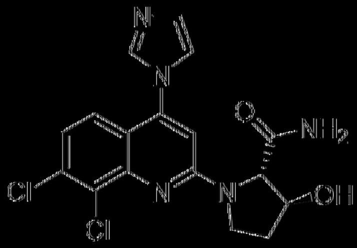
I-544	
I-545	
I-546	
I-547	
I-548	
I-549	
I-550	
I-551	
I-552	
I-553	
I-554	
I-555	
I-556	
I-557	

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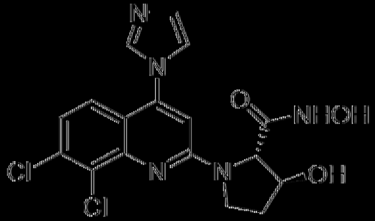
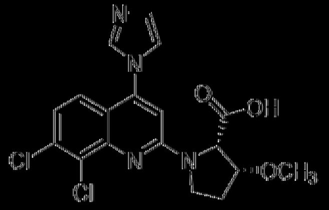
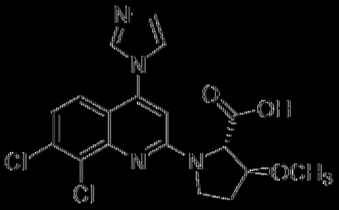
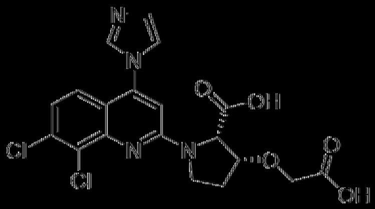
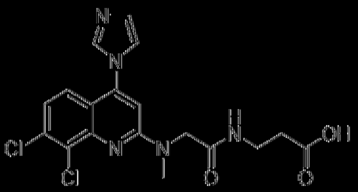
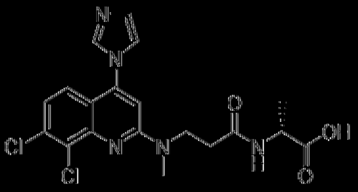
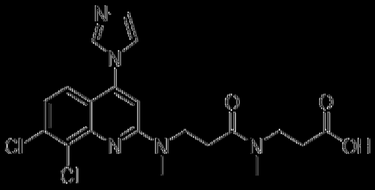
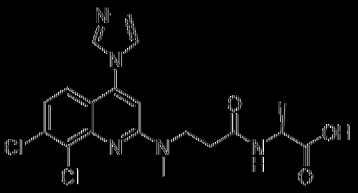
I-558	
I-559	
I-560	
I-561	
I-562	
I-563	
I-564	
I-565	

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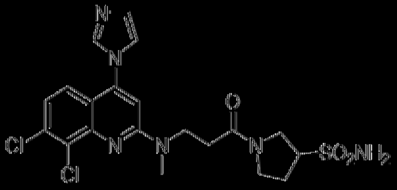
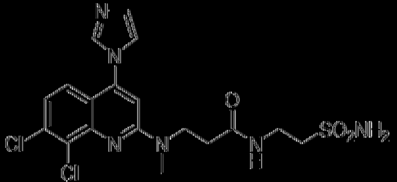
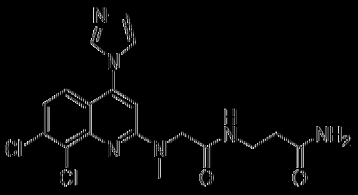
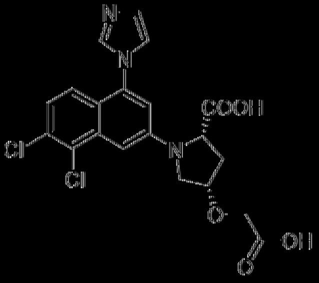
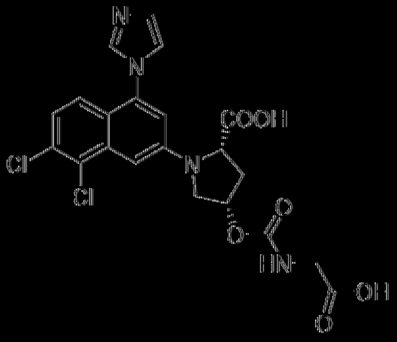
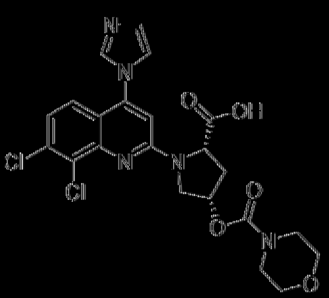
I-566	
I-567	
I-568	
I-569	
I-570	
I-571	

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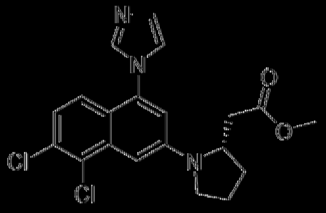
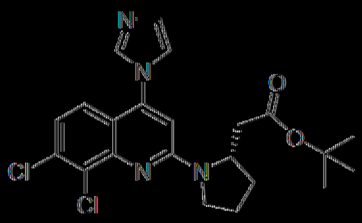
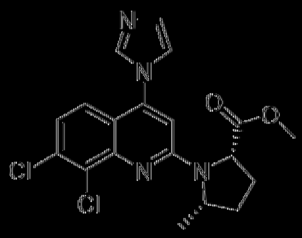
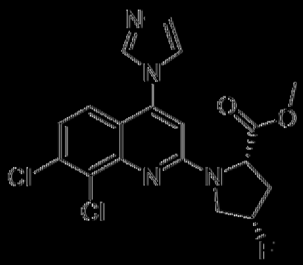
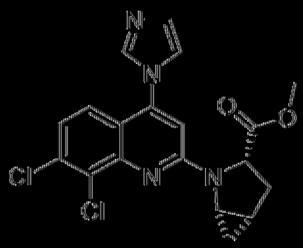
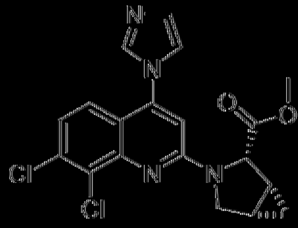
I-572	
I-573	
I-574	
I-575	
I-576	
I-577	

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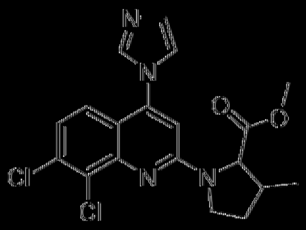
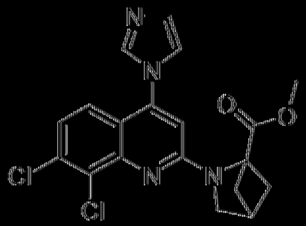
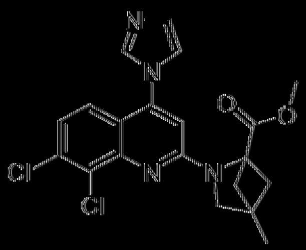
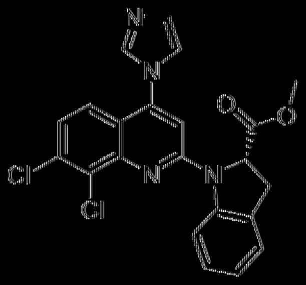
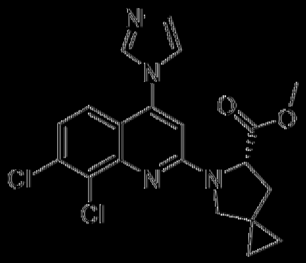
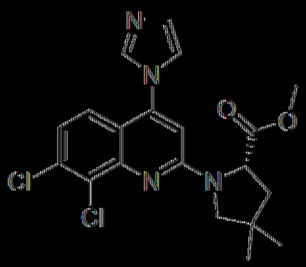
I-578	
I-579	
I-580	
I-581	
I-582	
I-583	

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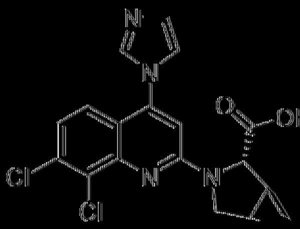
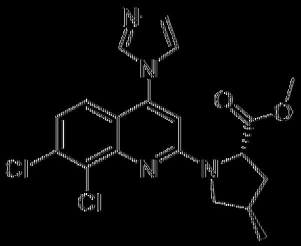
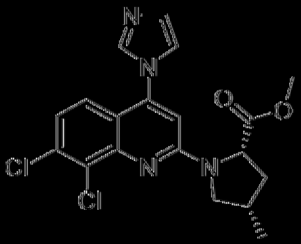
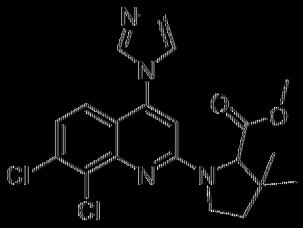
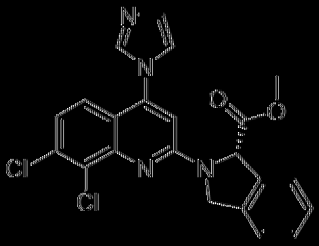
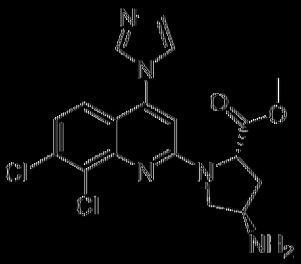
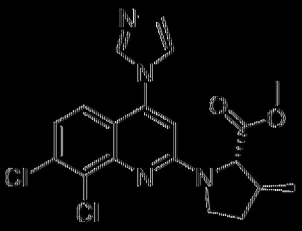
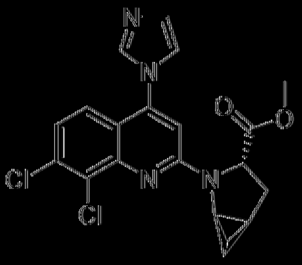
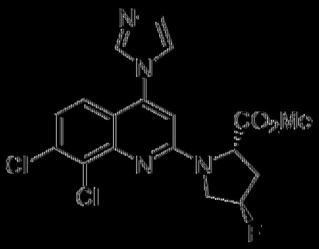
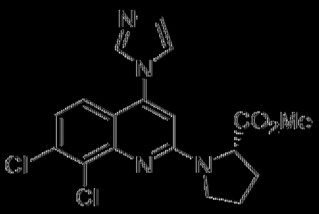
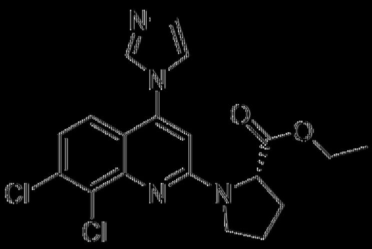
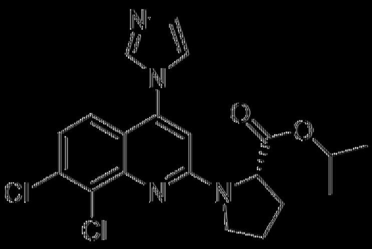
I-584	
I-585	
I-586	
I-587	
I-588	
I-589	
I-590	
I-591	
I-592	
I-593	
I-594	
I-595	

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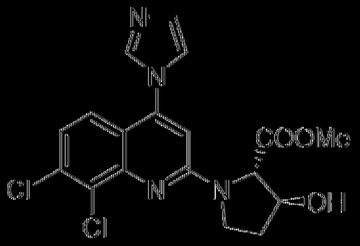
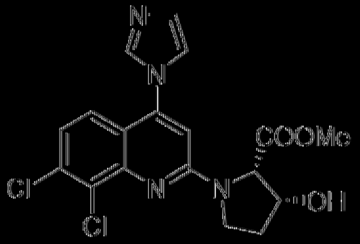
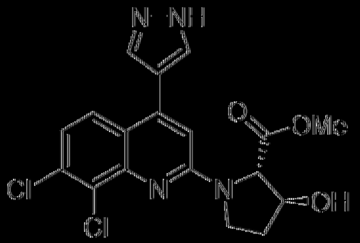
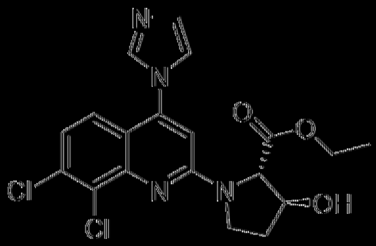
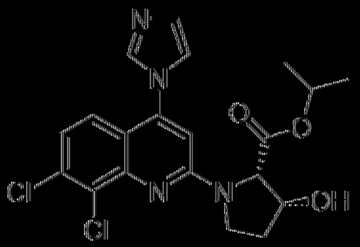
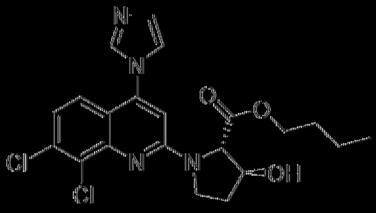
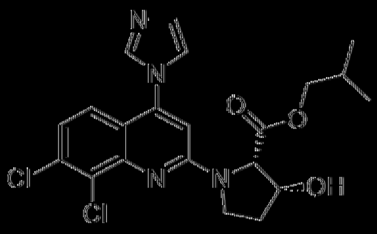
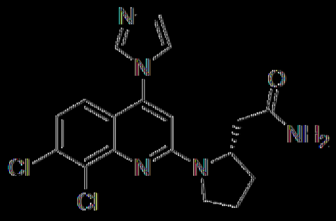
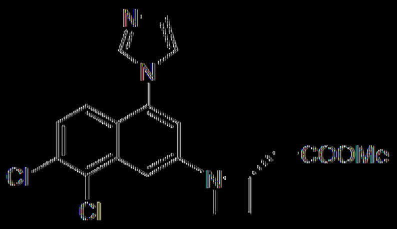
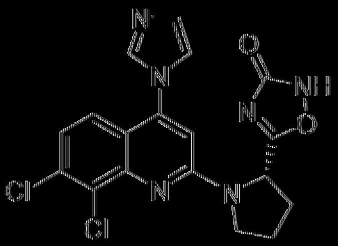
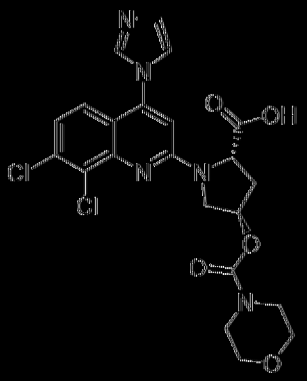
I-596	
I-597	
I-598	
I-599	
I-600	
I-601	
I-602	
I-603	
I-604	
I-605	
I-606	

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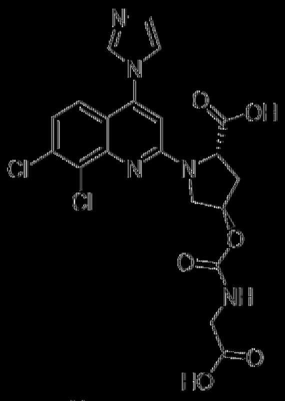
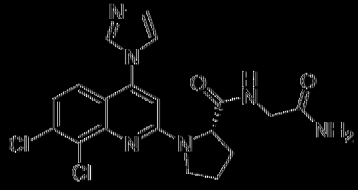
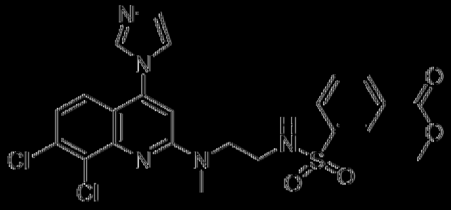
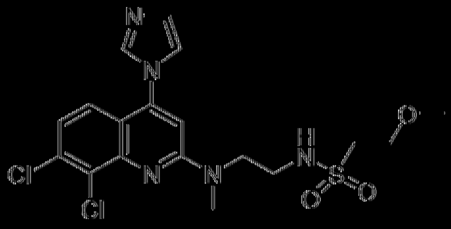
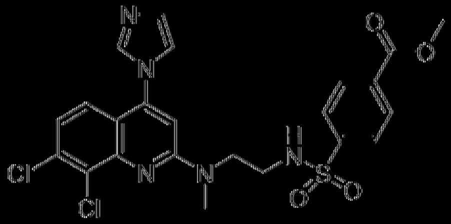
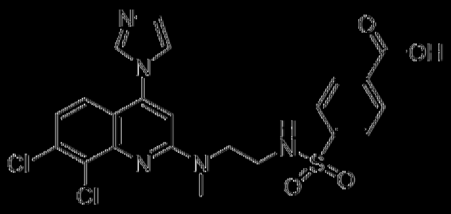
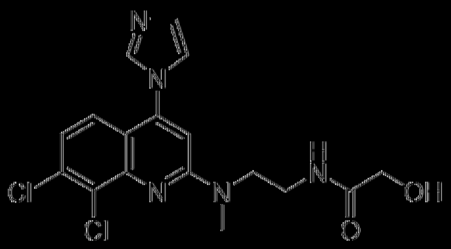
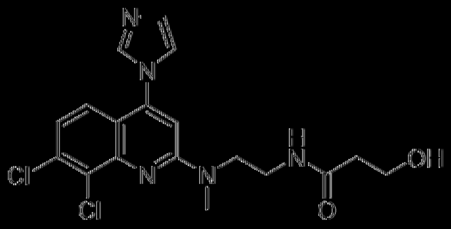
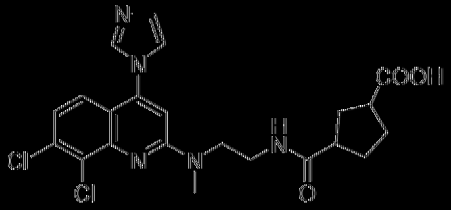
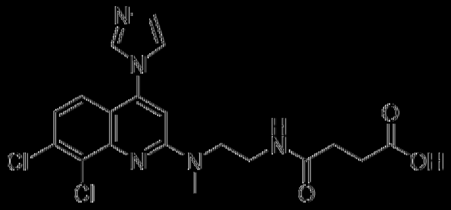
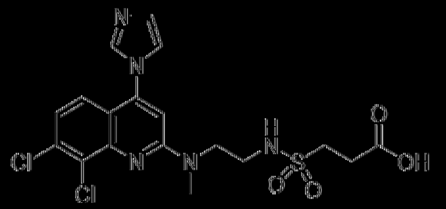
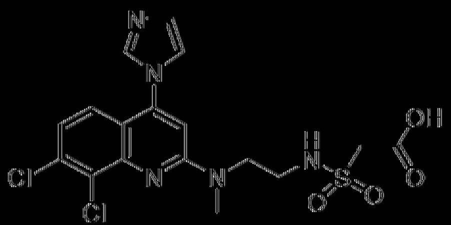
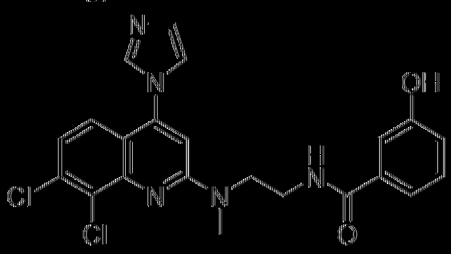
I-607	
I-608	
I-609	
I-610	
I-611	
I-612	
I-613	
I-614	
I-615	
I-616	
I-617	
I-618	
I-619	

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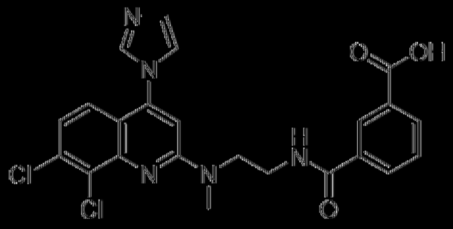
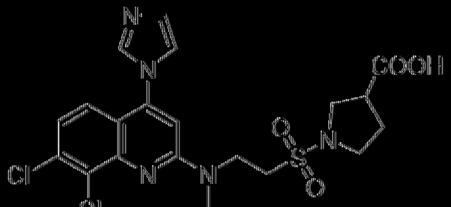
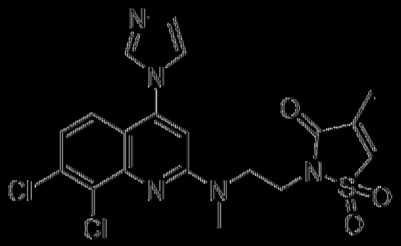
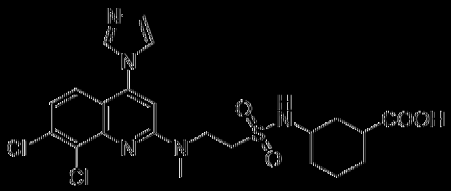
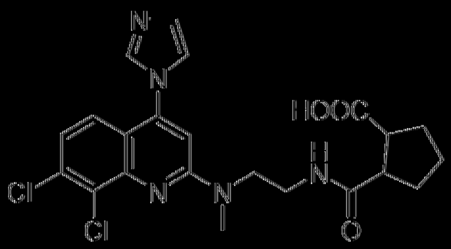
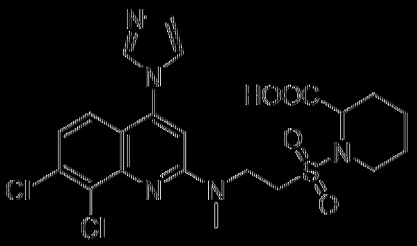
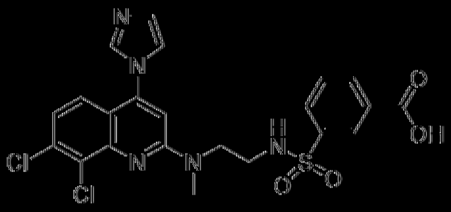
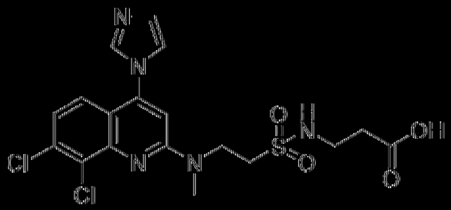
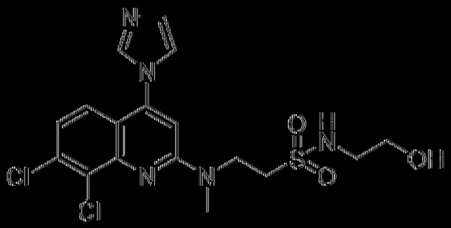
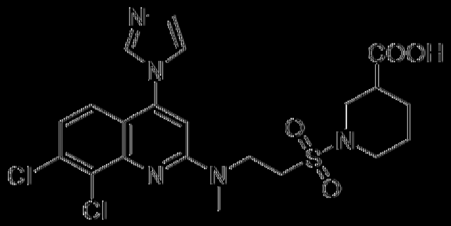
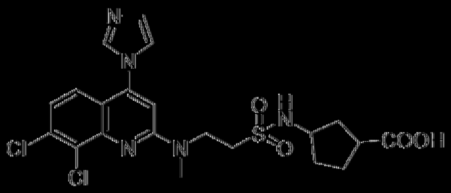
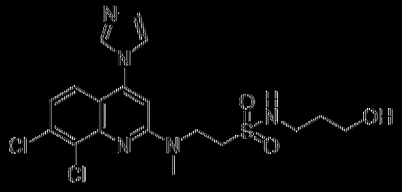
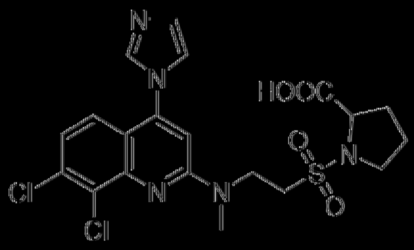
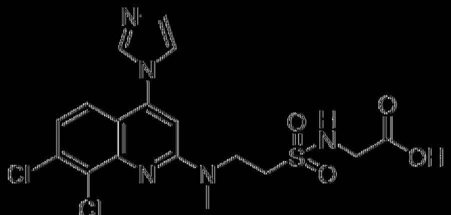
I-620		I-627	
I-621		I-628	
I-622		I-629	
I-623		I-630	
I-624		I-631	
I-625		I-632	
I-626		I-633	

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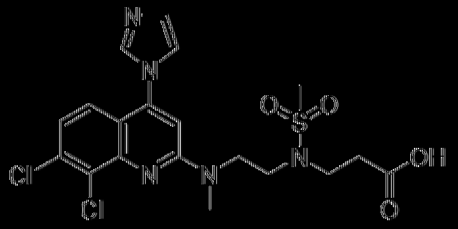
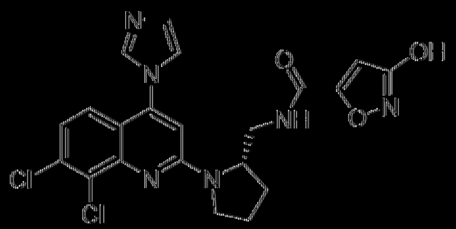
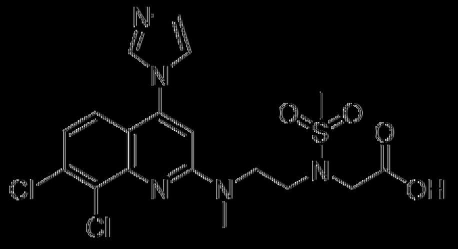
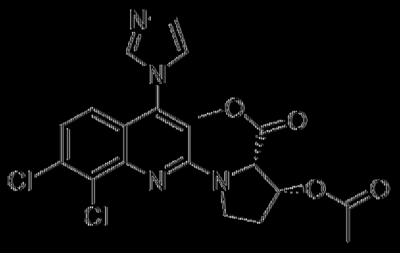
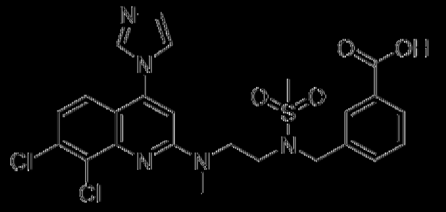
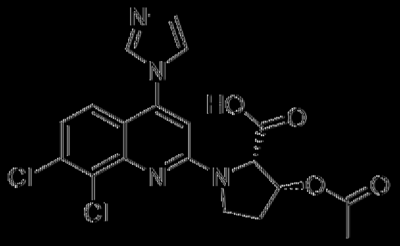
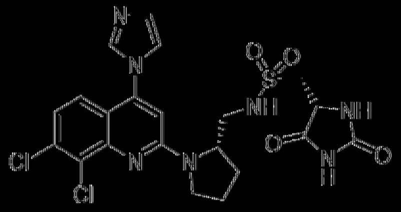
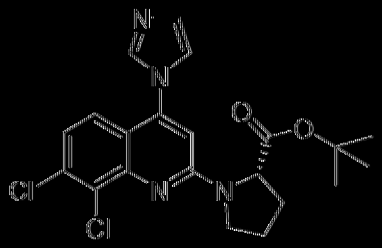
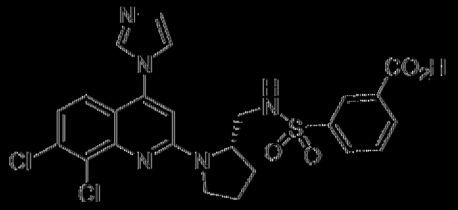
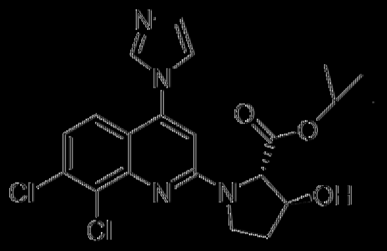
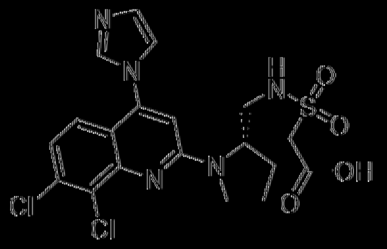
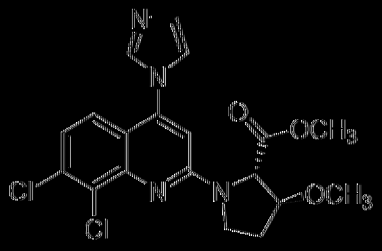
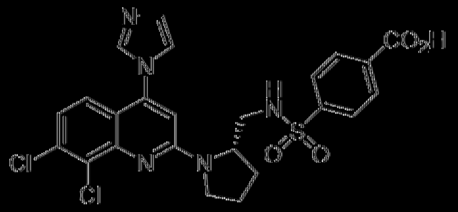
I-634		I-641	
I-635		I-642	
I-636		I-643	
I-637		I-644	
I-638		I-645	
I-639		I-646	
I-640			

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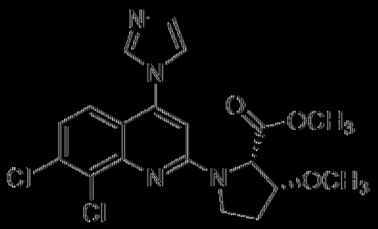
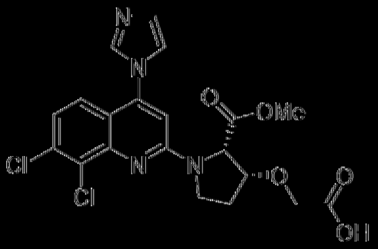
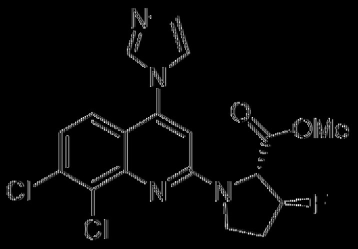
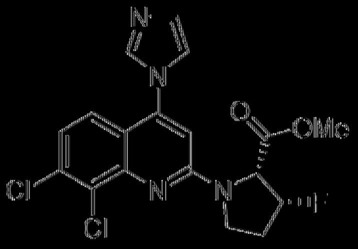
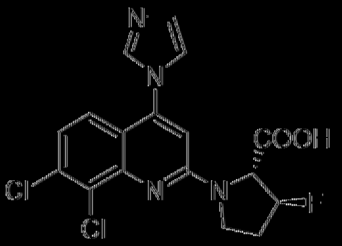
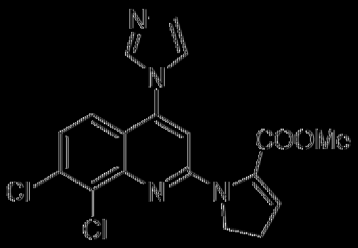
I-647	
I-648	
I-649	
I-650	
I-651	
I-652	

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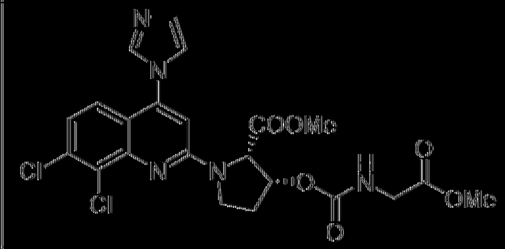
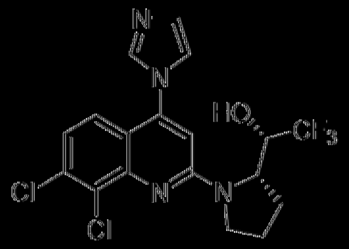
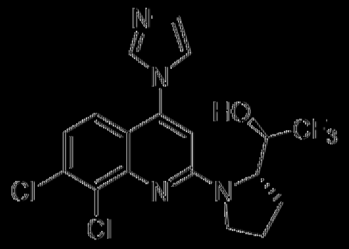
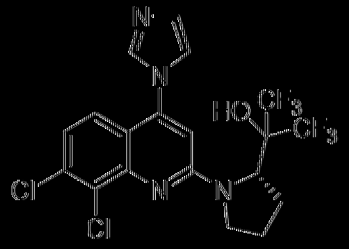
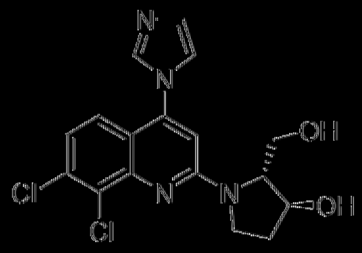
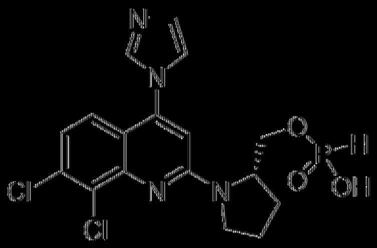
I-653	
I-654	
I-655	
I-656	
I-657	
I-658	

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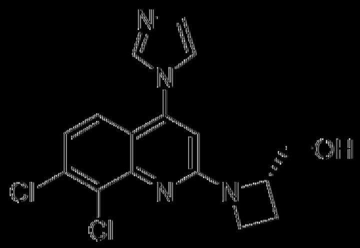
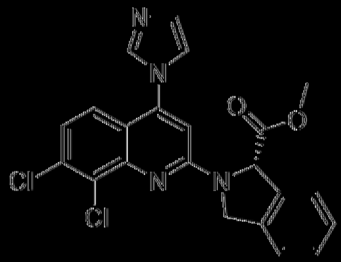
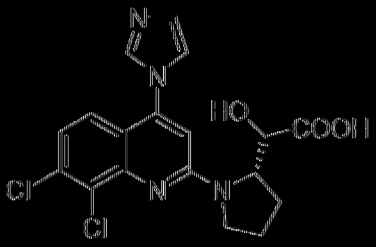
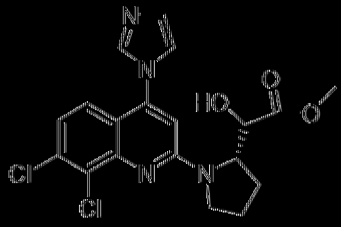
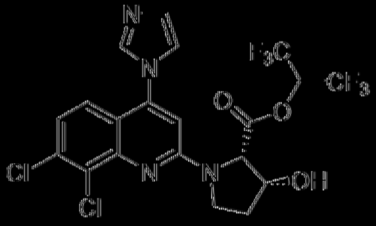
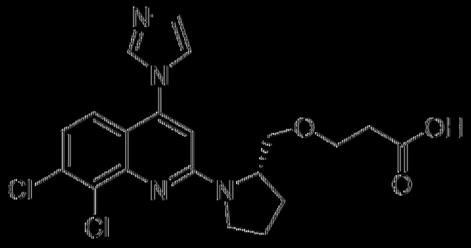
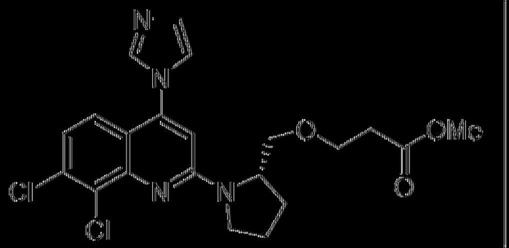
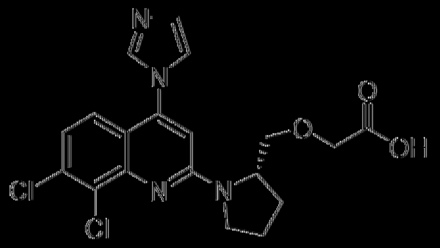
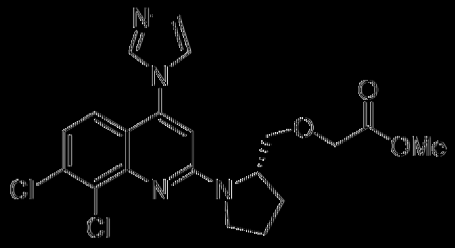
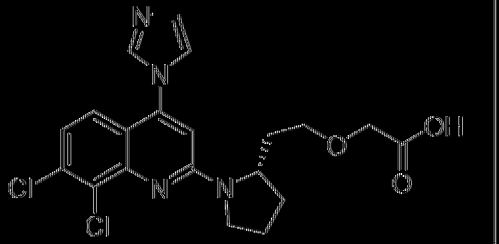
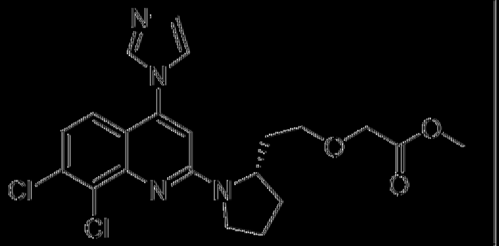
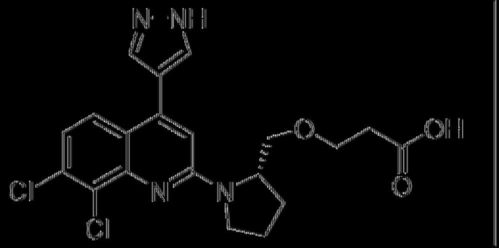
I-659	
I-660	
I-661	
I-662	
I-663	
I-664	
I-665	
I-666	
I-667	
I-668	
I-669	
I-670	

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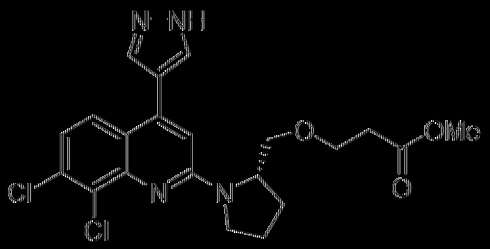
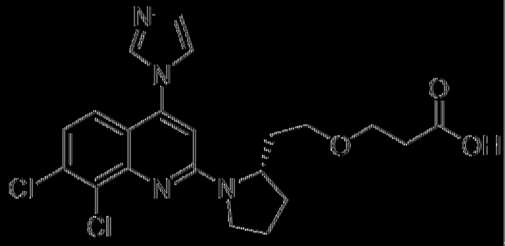
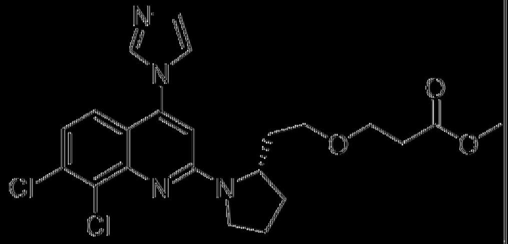
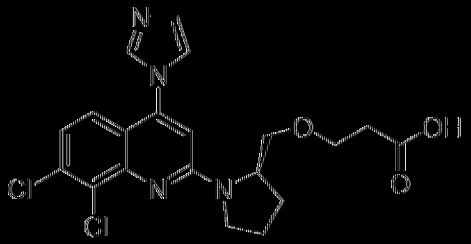
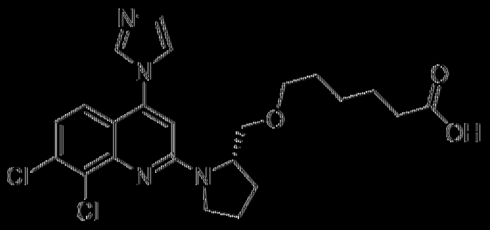
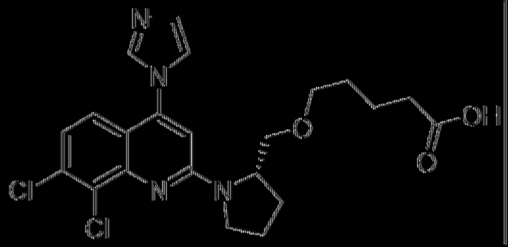
I-671	
I-672	
I-673	
I-674	
I-675	
I-676	

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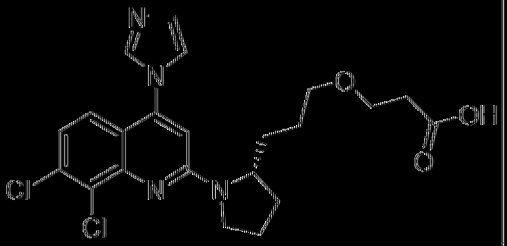
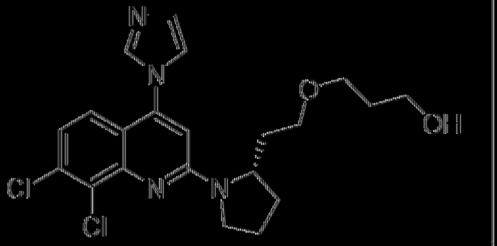
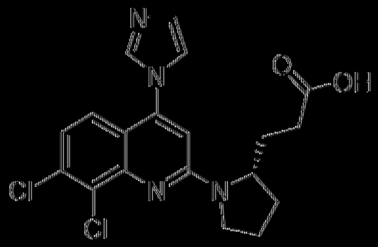
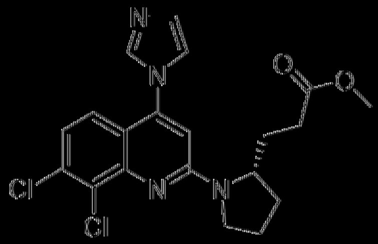
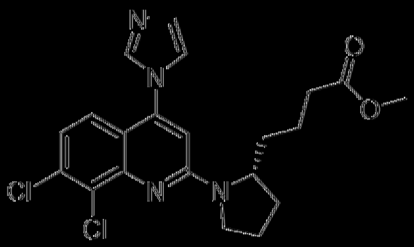
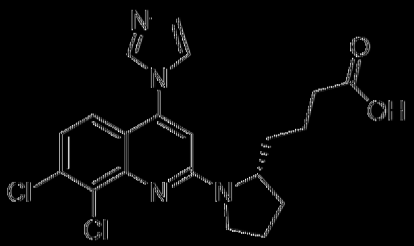
I-677	
I-678	
I-679	
I-680	
I-681	
I-682	

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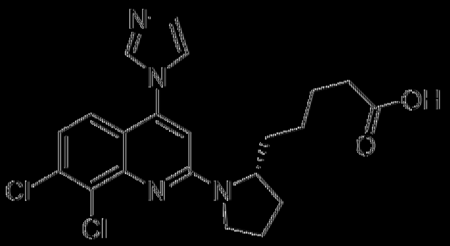
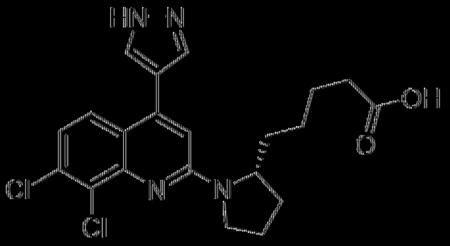
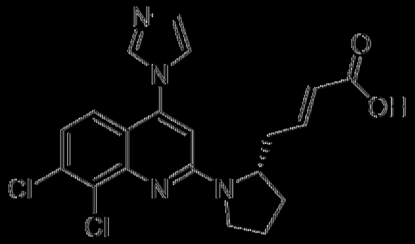
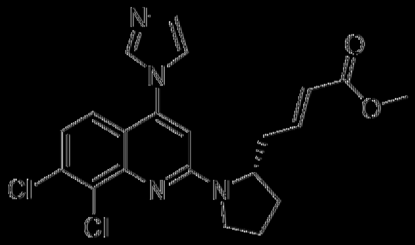
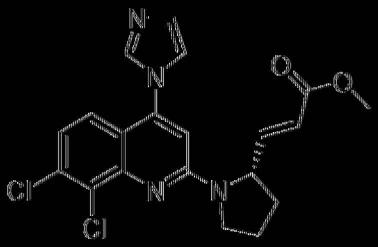
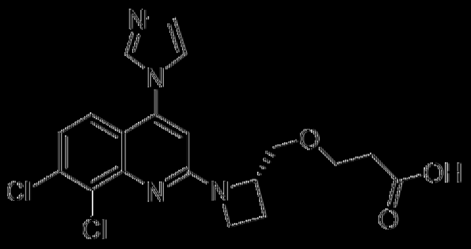
I-683	
I-684	
I-685	
I-686	
I-687	
I-688	

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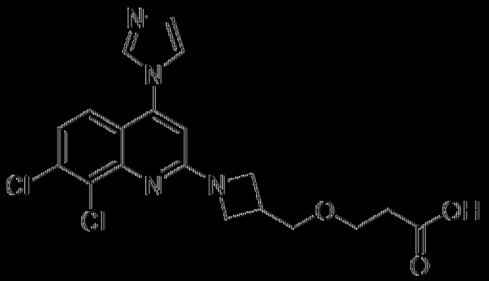
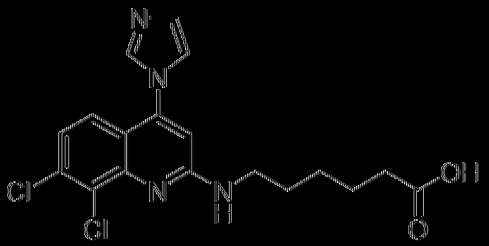
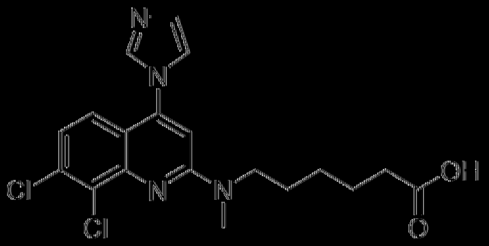
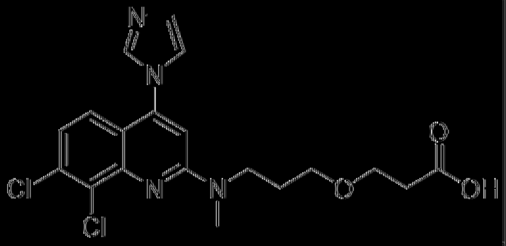
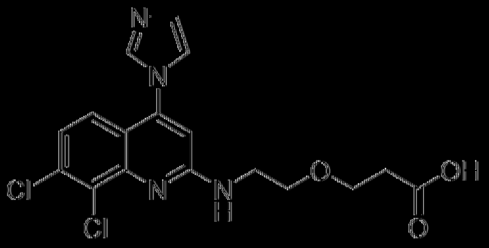
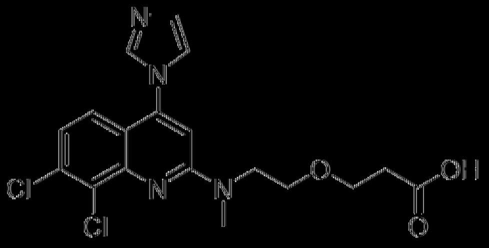
I-689	
I-690	
I-691	
I-692	
I-693	
I-694	

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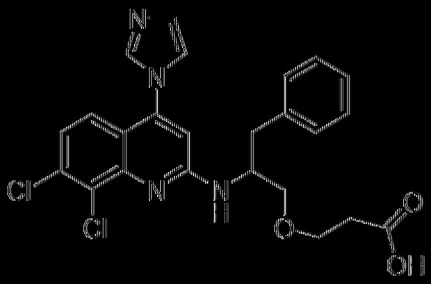
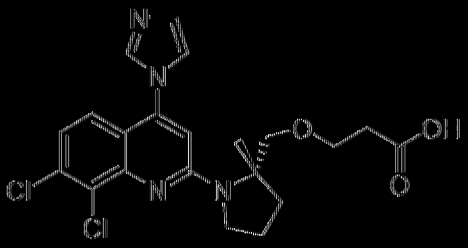
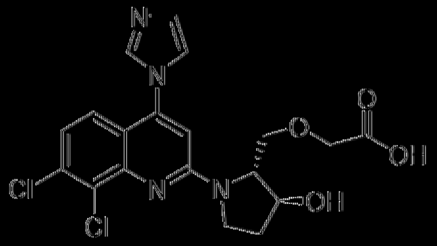
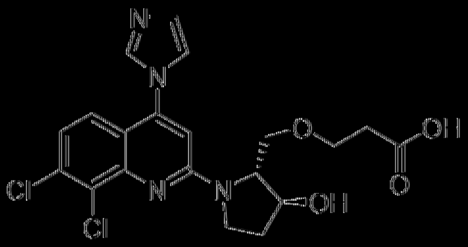
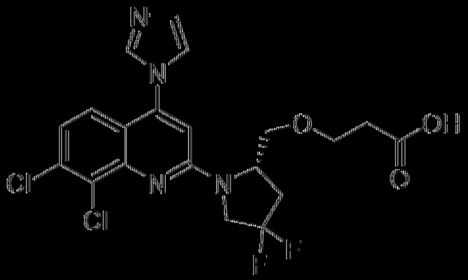
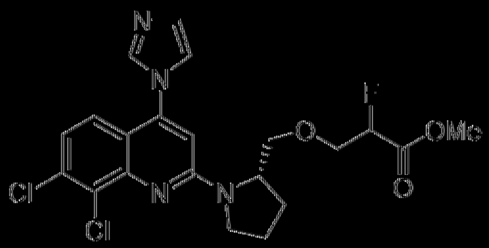
I-695	
I-696	
I-697	
I-698	
I-699	
I-700	

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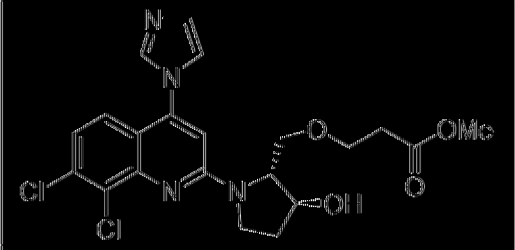
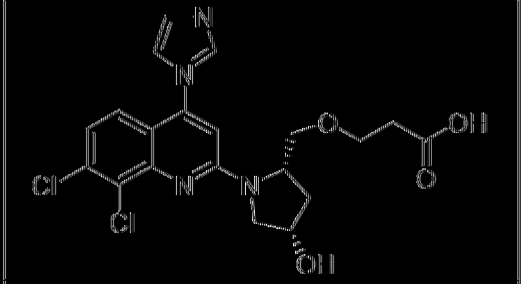
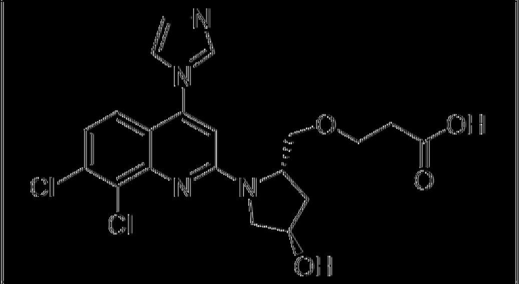
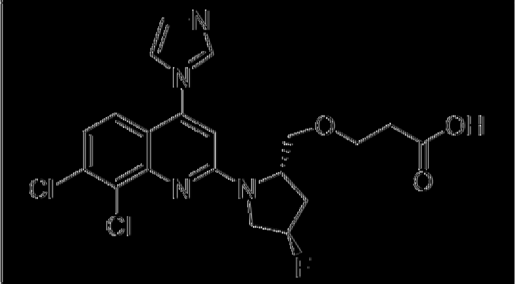
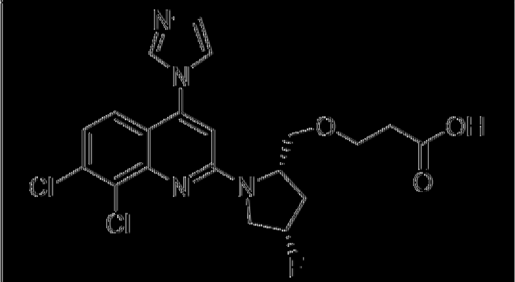
I-701	
I-702	
I-703	
I-704	
I-705	

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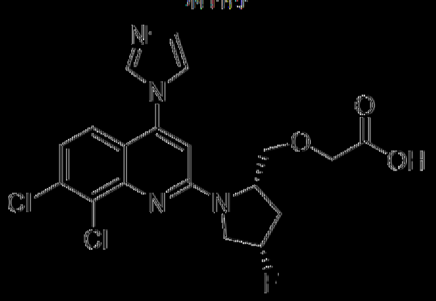
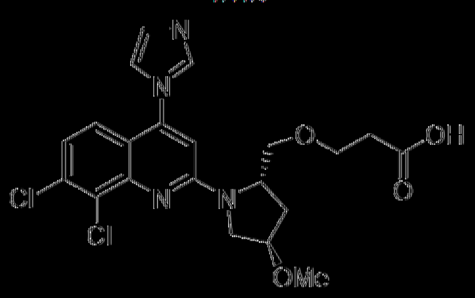
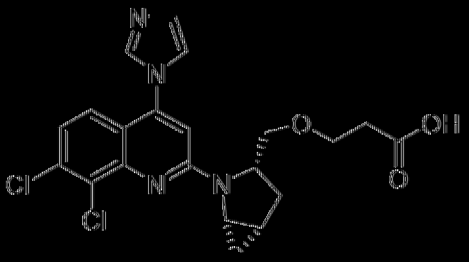
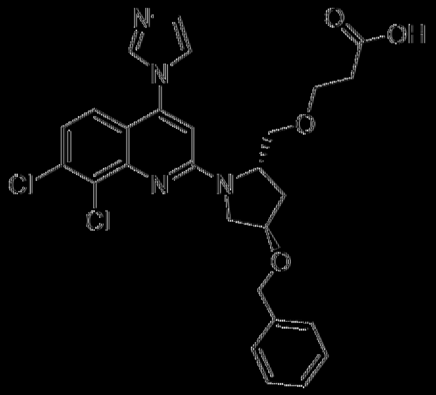
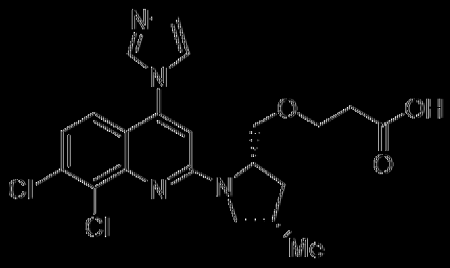
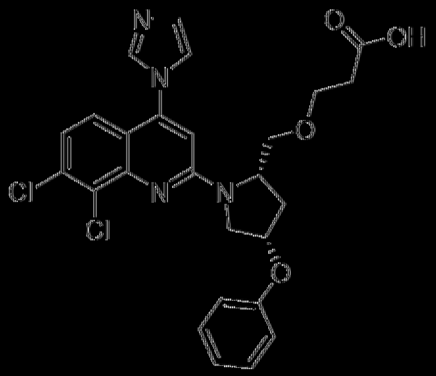
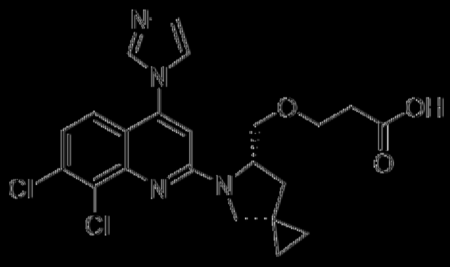
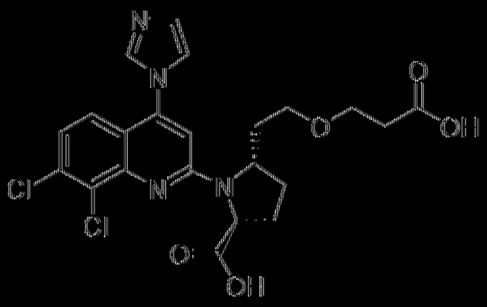
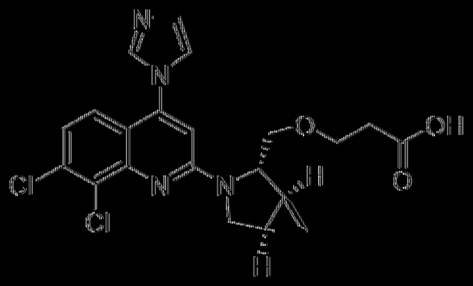
I-706		I-711	
I-707		I-712	
I-708		I-713	
I-709		I-714	
I-710			

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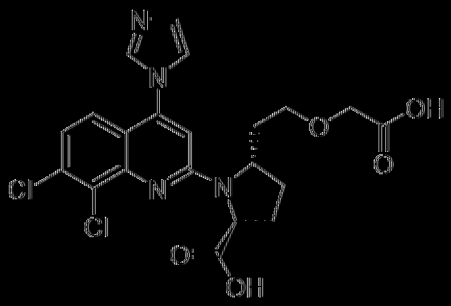
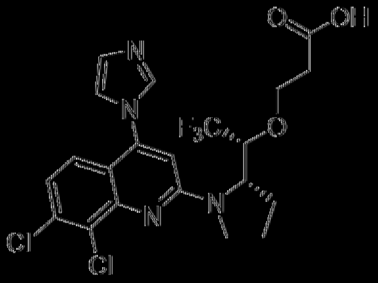
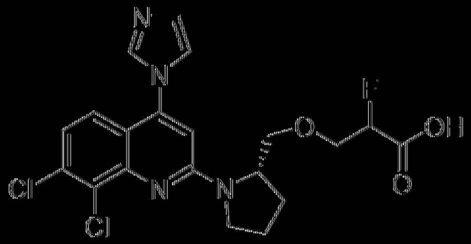
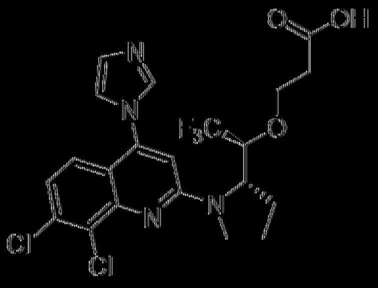
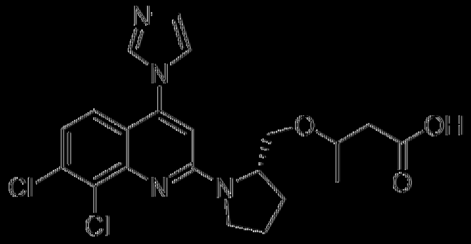
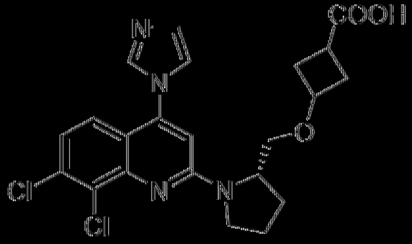
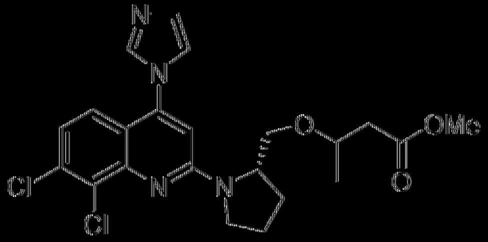
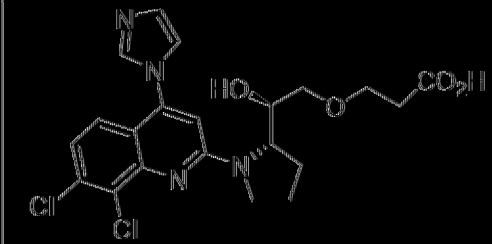
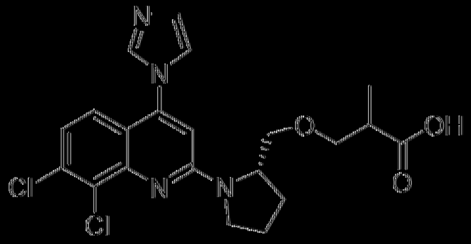
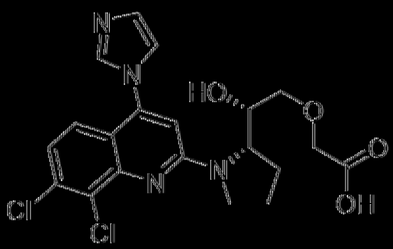
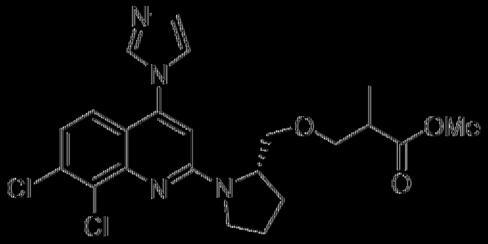
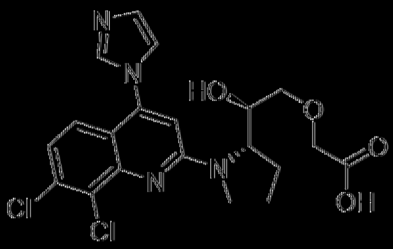
I-715		I-721	
I-716		I-722	
I-717		I-723	
I-718		I-724	
I-719		I-725	
I-720		I-726	

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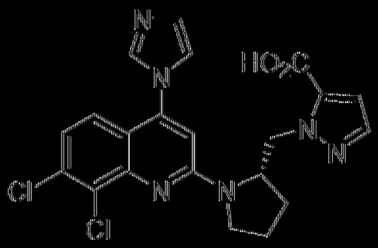
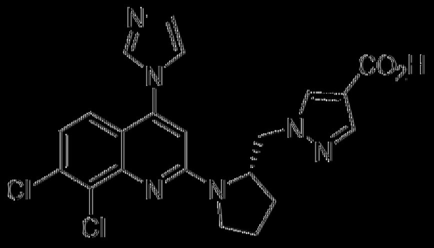
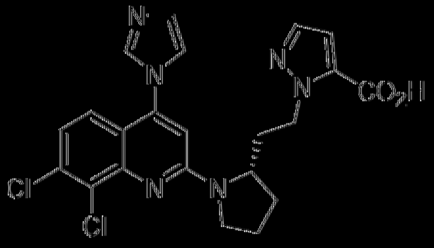
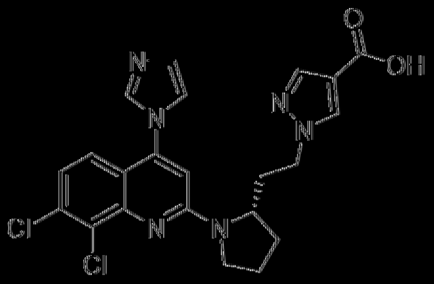
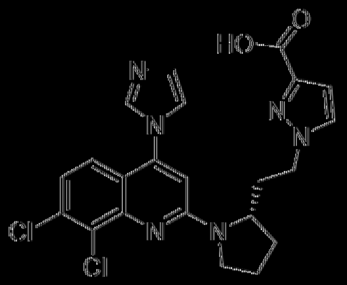
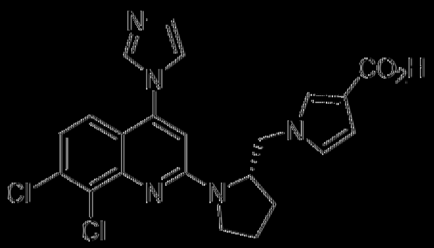
I-727	
I-728	
I-729	
I-730	
I-731	
I-732	

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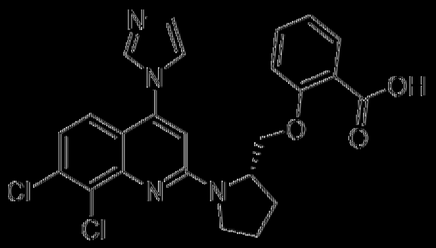
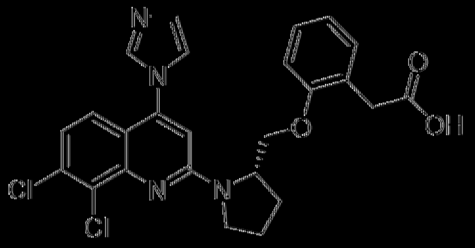
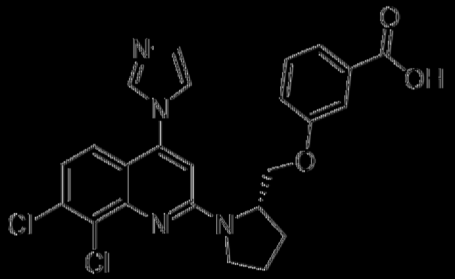
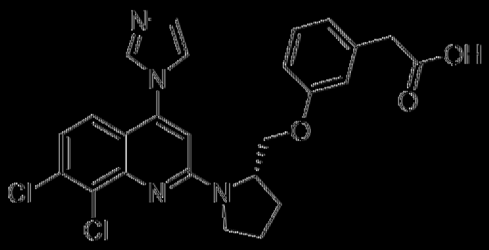
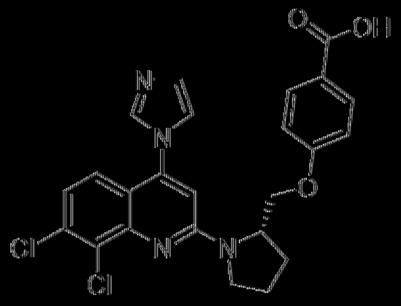
I-733	
I-734	
I-735	
I-736	
I-737	

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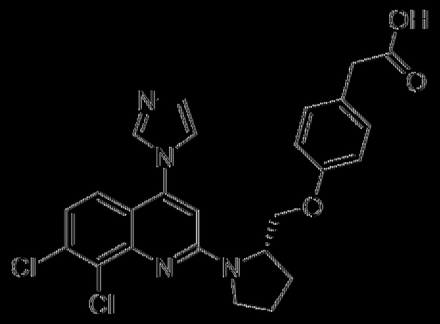
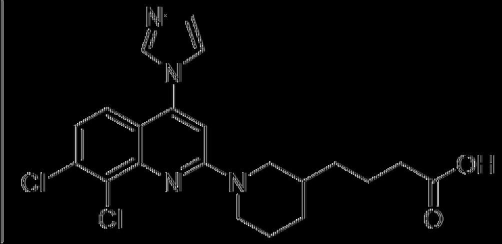
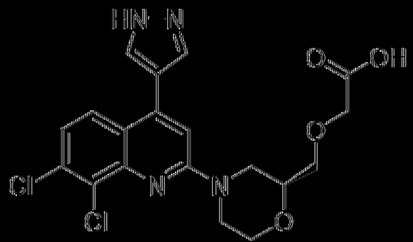
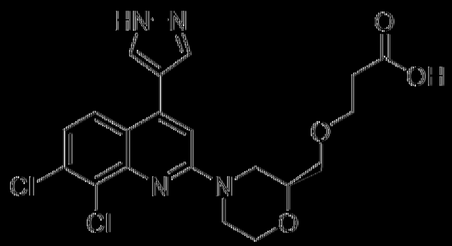
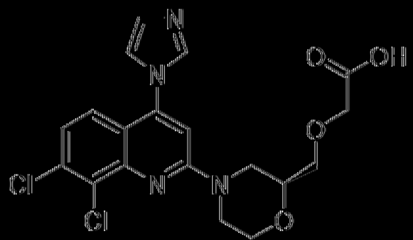
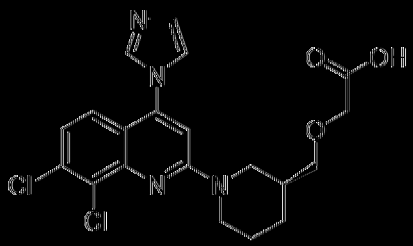
I-738	
I-739	
I-740	
I-741	
I-742	
I-743	

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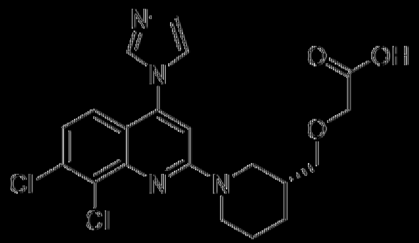
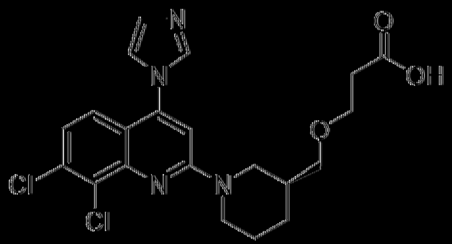
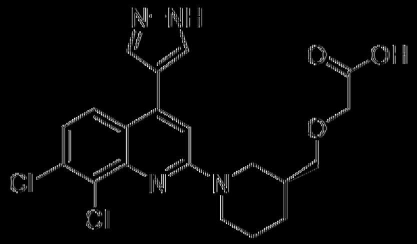
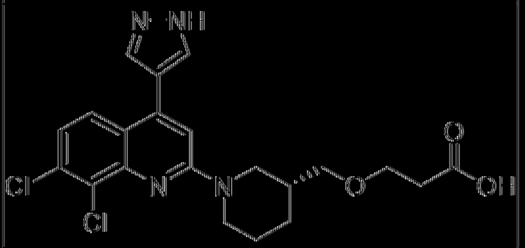
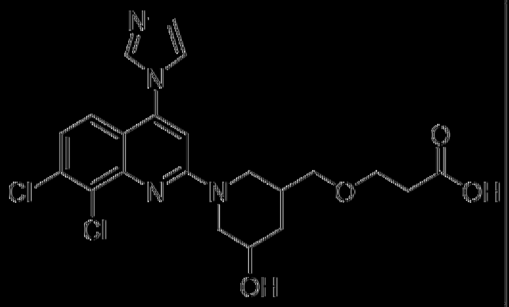
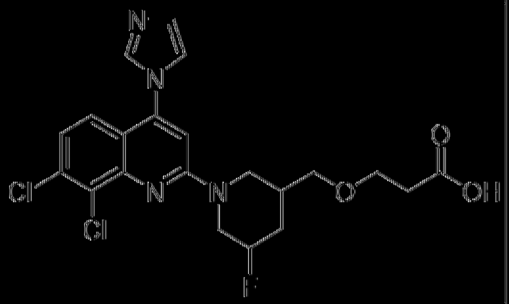
I-744	
I-745	
I-746	
I-747	
I-748	
I-749	

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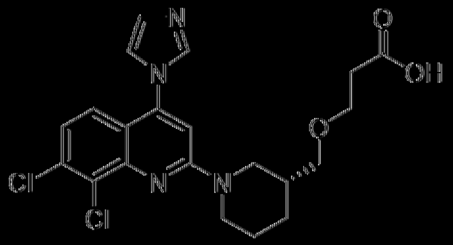
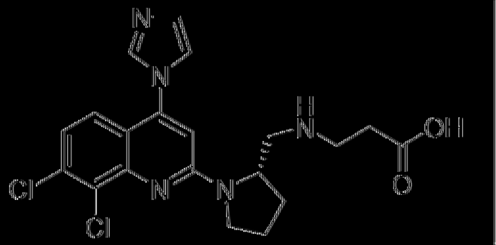
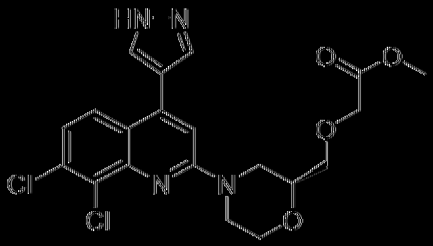
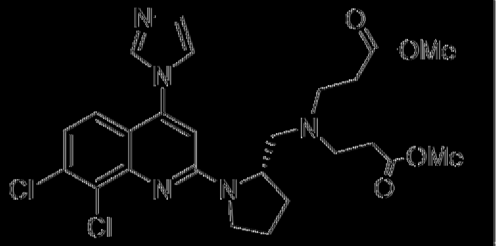
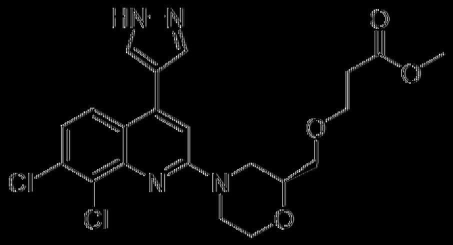
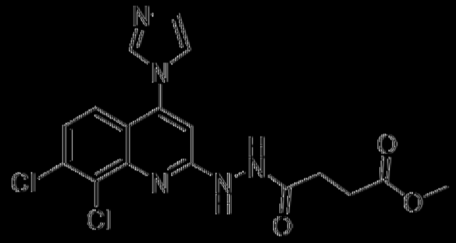
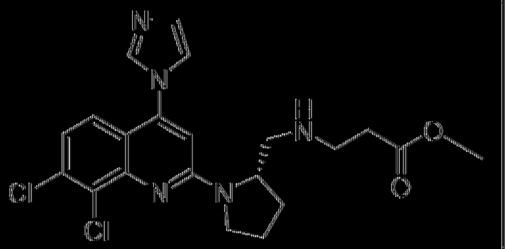
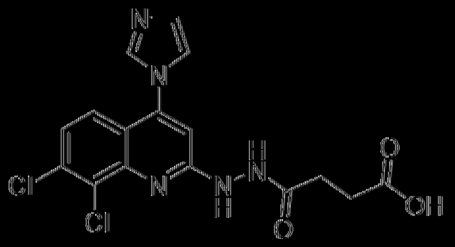
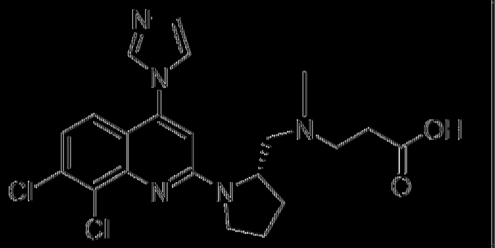
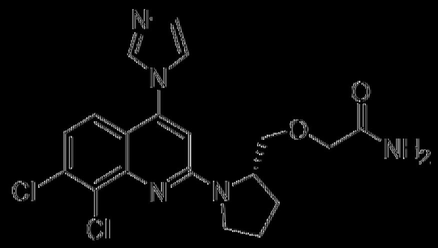
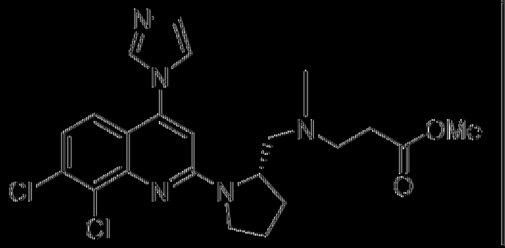
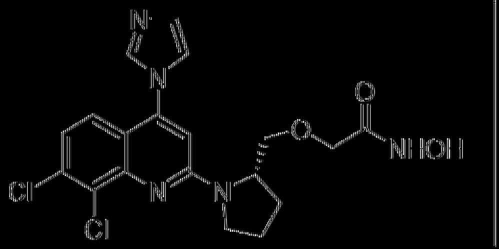
I-750		I-756	
I-751		I-757	
I-752		I-758	
I-753		I-759	
I-754		I-760	
I-755		I-761	

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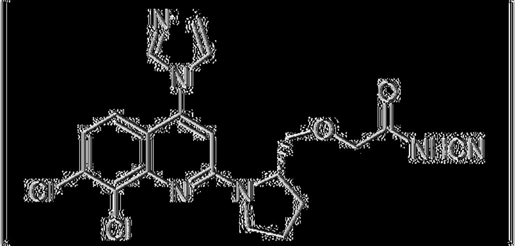
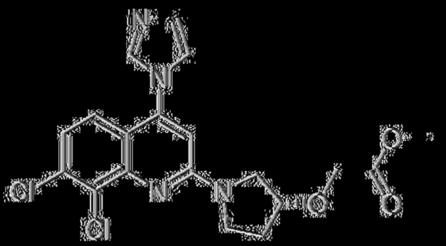
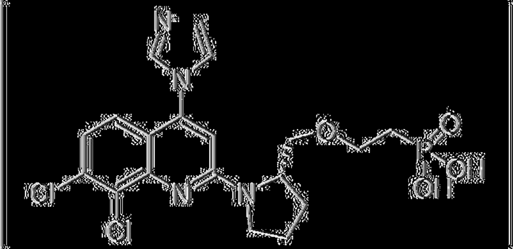
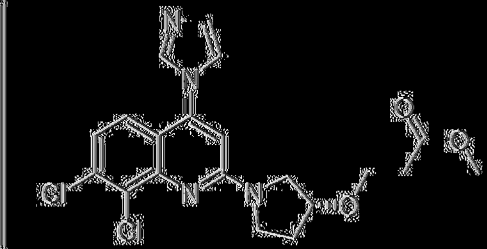
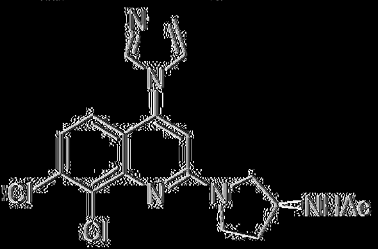
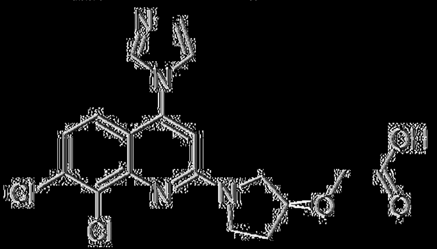
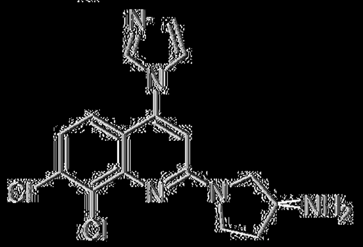
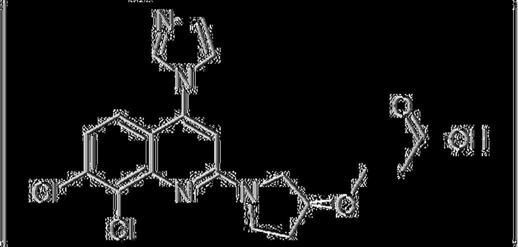
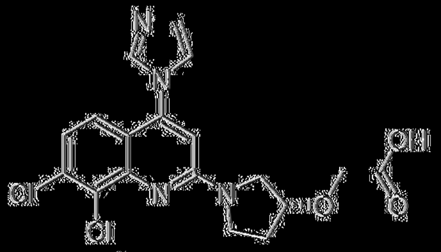
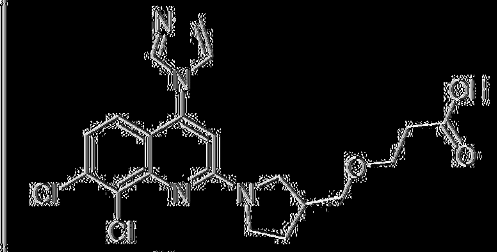
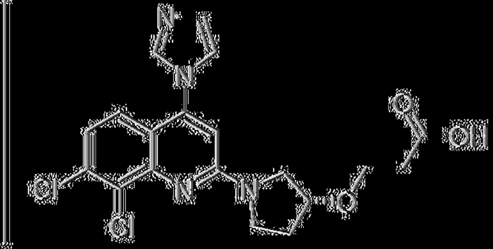
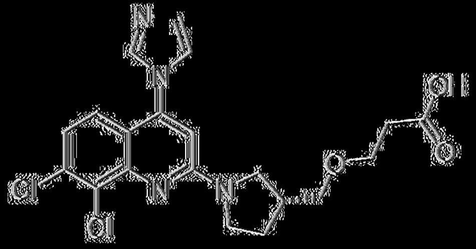
I-762		I-768	
I-763		I-769	
I-764		I-770	
I-765		I-771	
I-766		I-772	
I-767		I-773	

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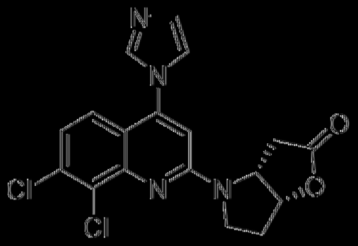
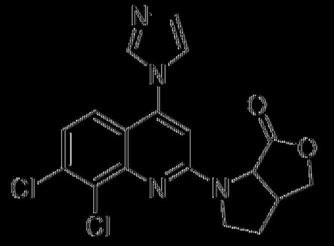
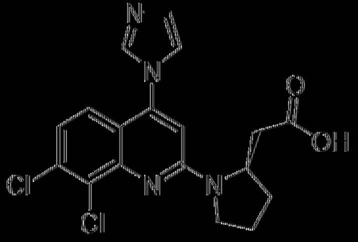
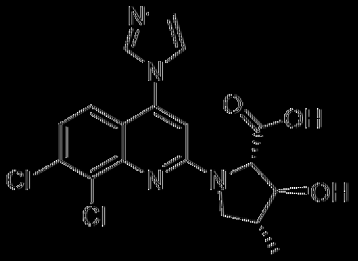
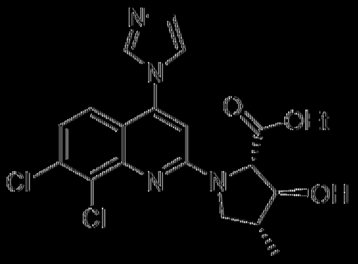
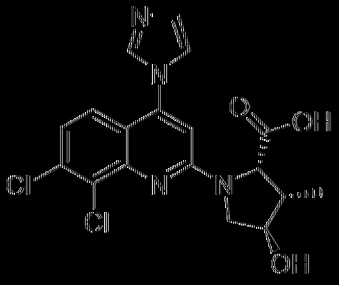
I-774	
I-775	
I-776	
I-778	
I-779	
I-780	

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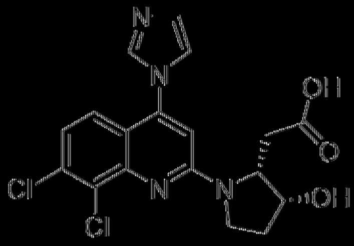
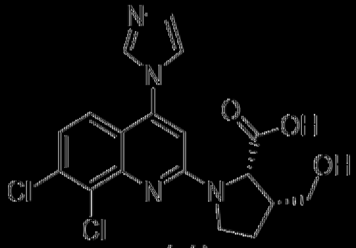
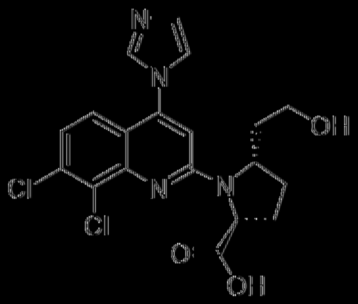
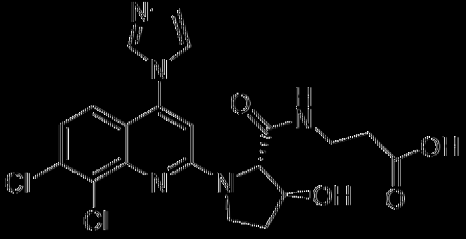
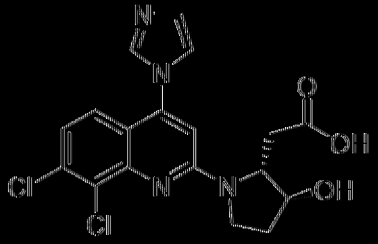
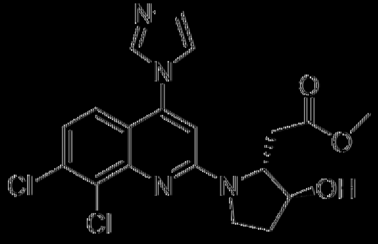
I-781	
I-782	 (+/-)
I-783	
I-784	
I-785	
I-786	

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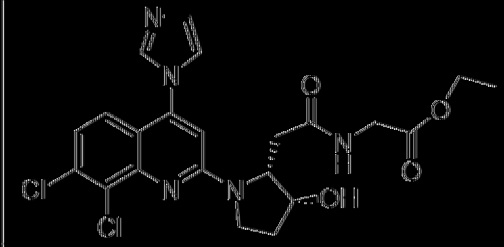
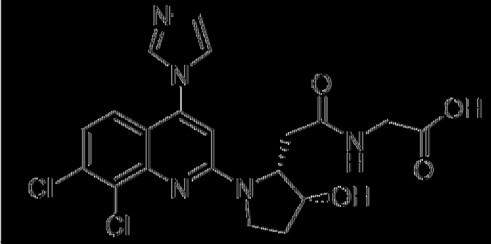
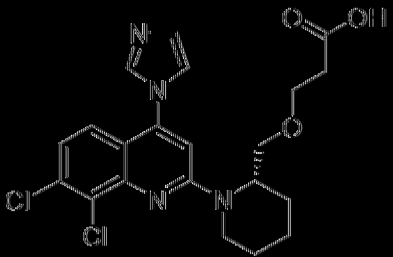
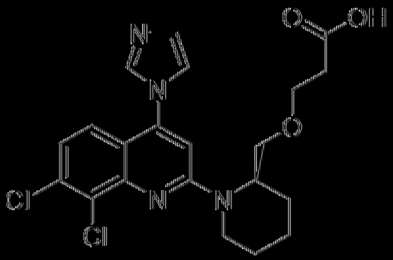
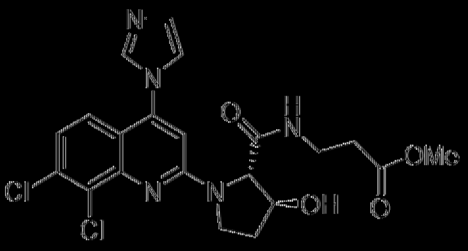
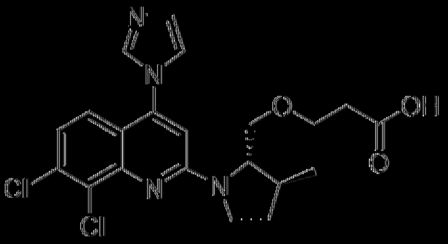
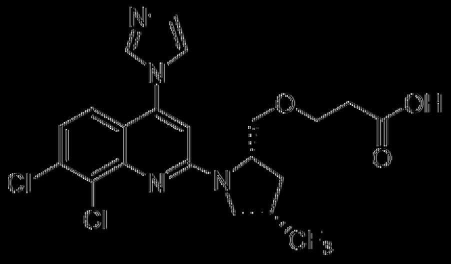
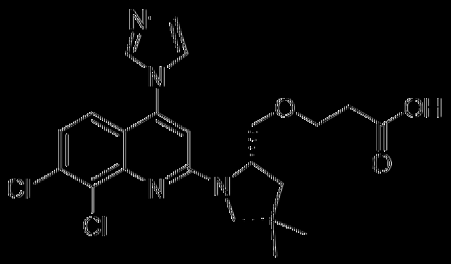
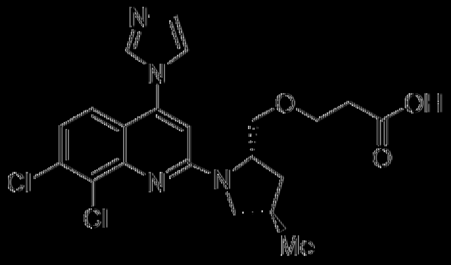
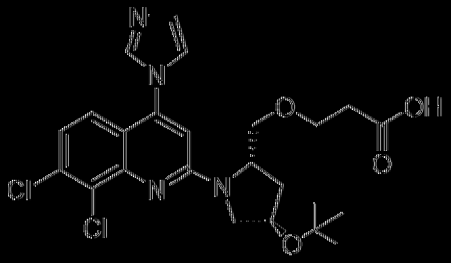
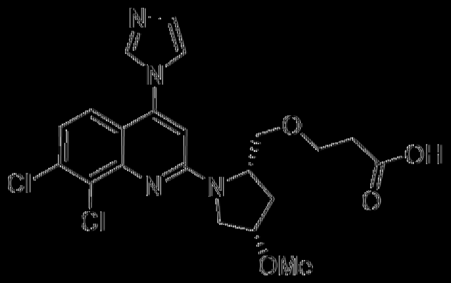
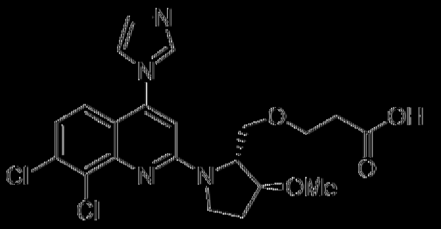
I-787	
I-788	
I-789	
I-790	
I-791	
I-792	
I-793	
I-794	
I-795	
I-796	
I-797	
I-798	

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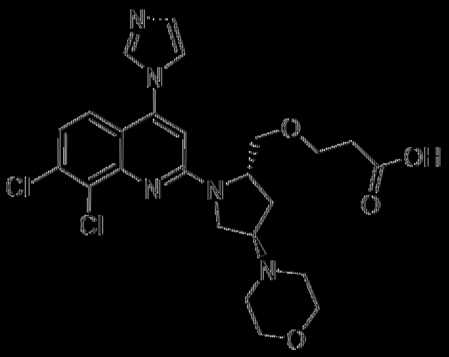
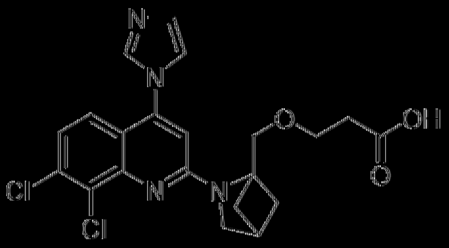
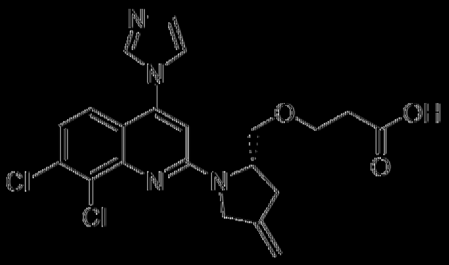
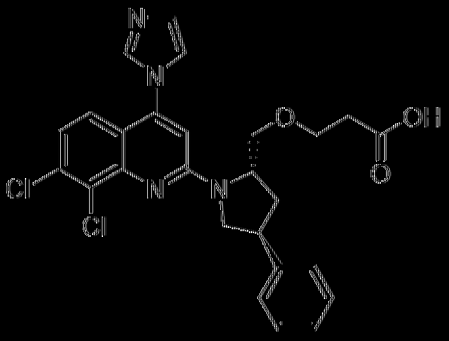
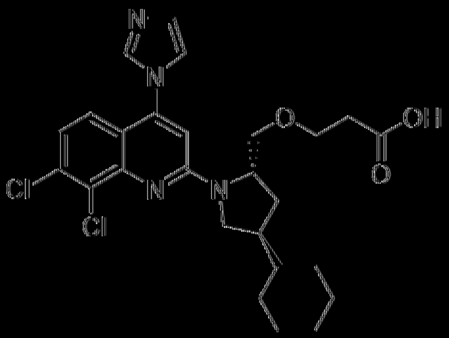
I-799	
I-800	
I-801	
I-802	
I-803	

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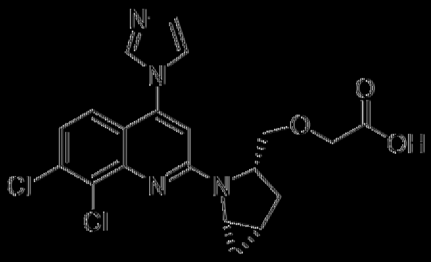
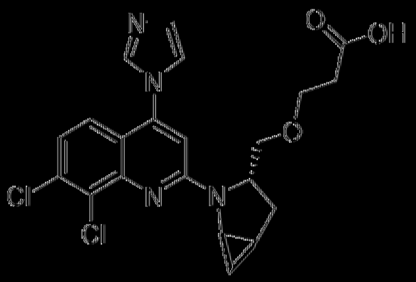
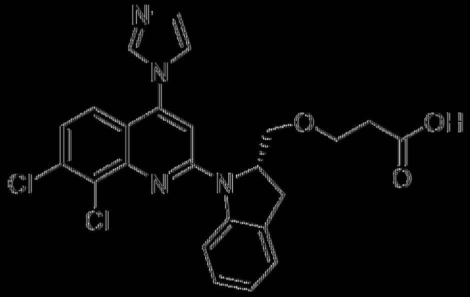
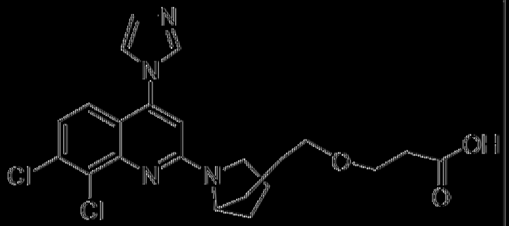
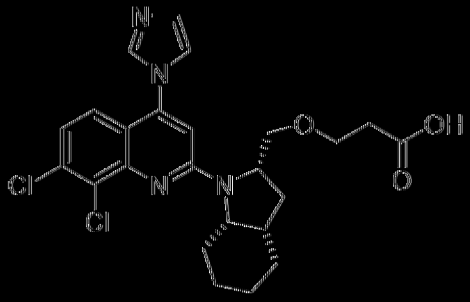
I-804	
I-805	
I-806	
I-807	
I-808	

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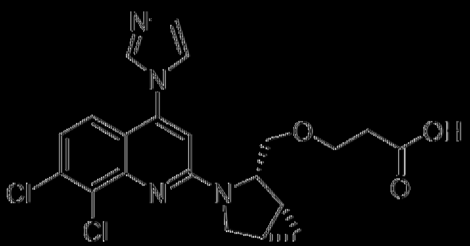
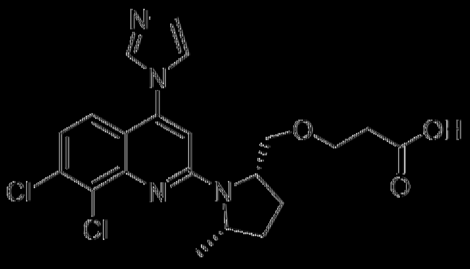
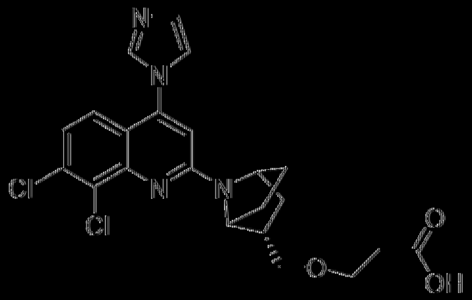
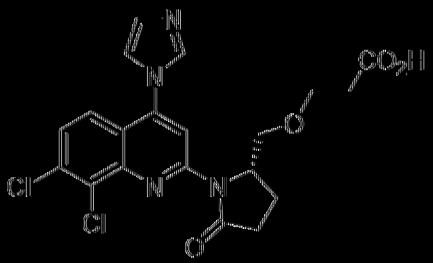
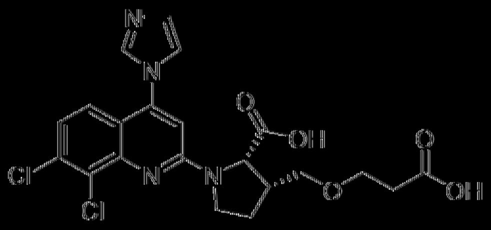
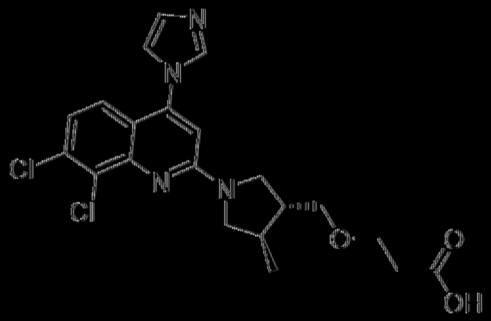
I-809	
I-810	
I-811	
I-812	
I-813	
I-814	

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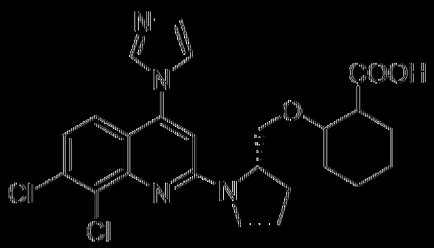
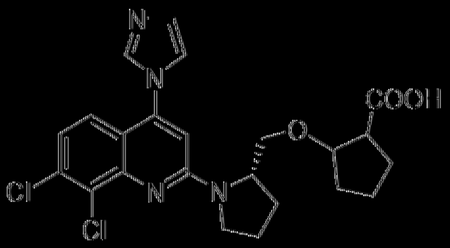
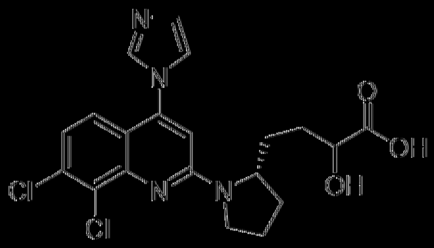
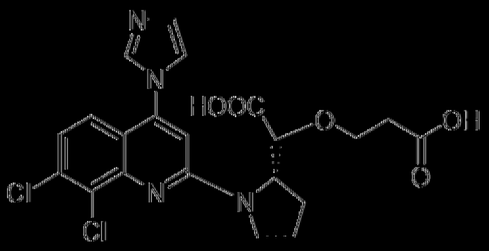
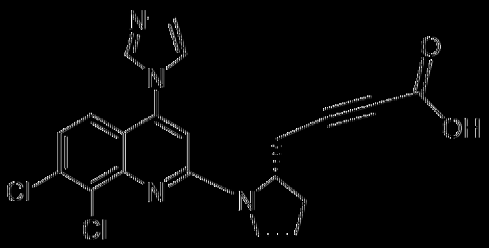
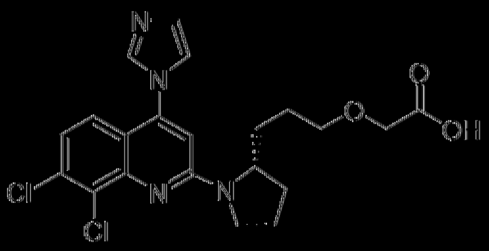
I-815	
I-816	
I-817	
I-818	
I-819	
I-820	

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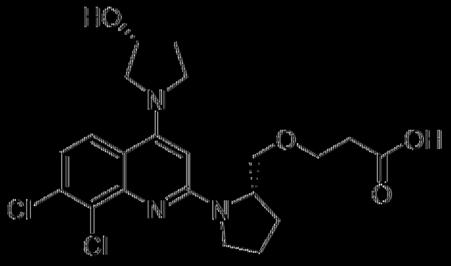
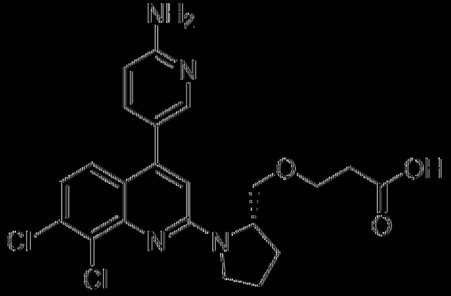
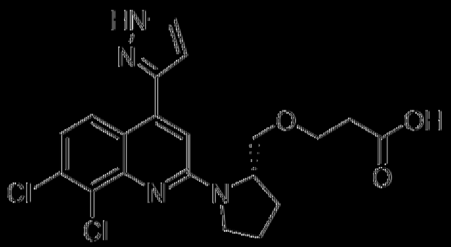
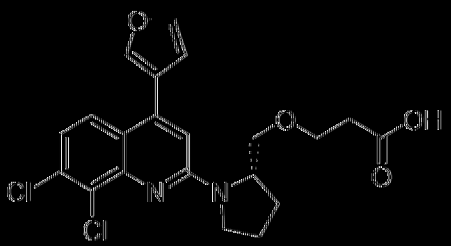
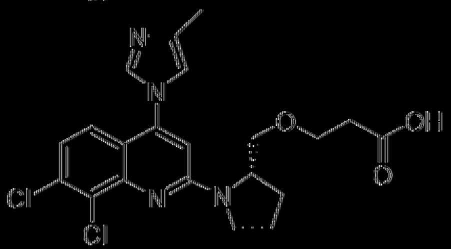
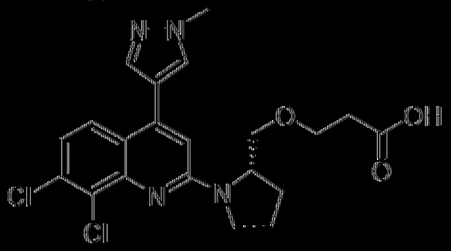
I-821	
I-822	
I-823	
I-824	
I-825	
I-826	

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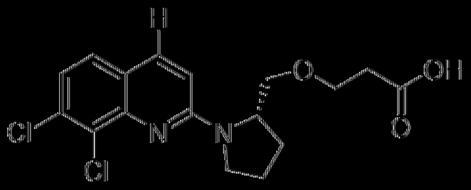
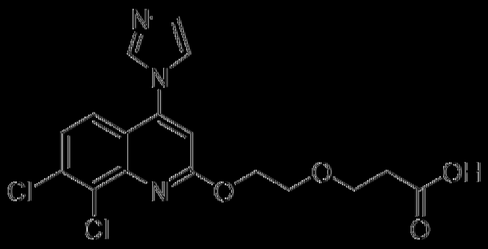
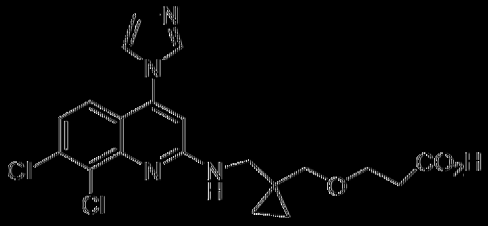
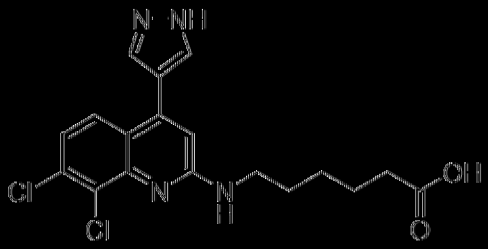
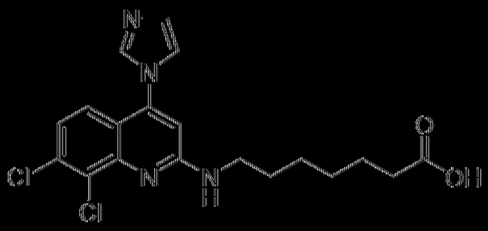
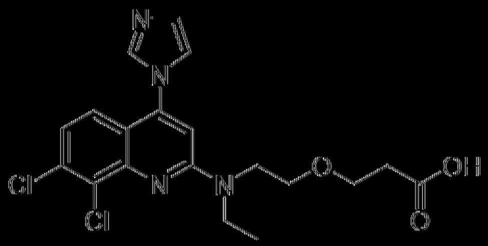
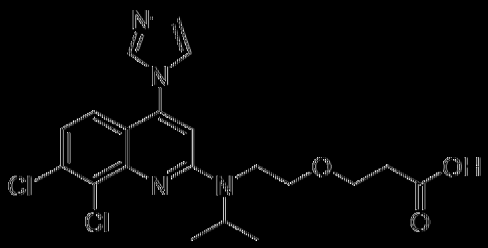
I-827	
I-828	
I-829	
I-830	
I-831	
I-832	
I-833	

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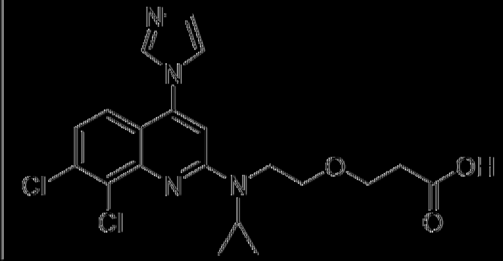
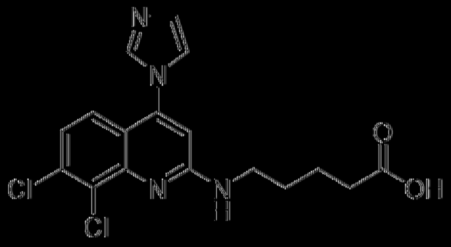
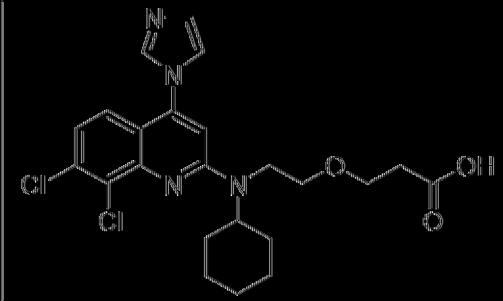
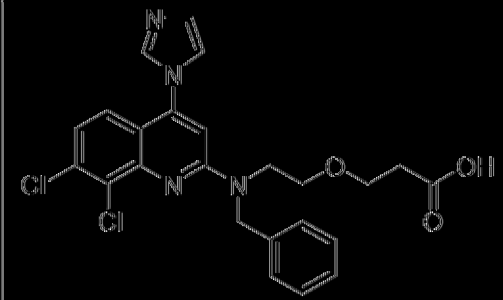
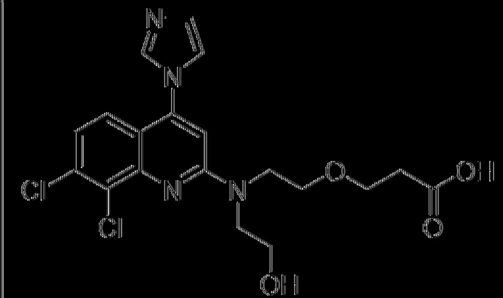
I-834	
I-835	
I-836	
I-837	
I-838	

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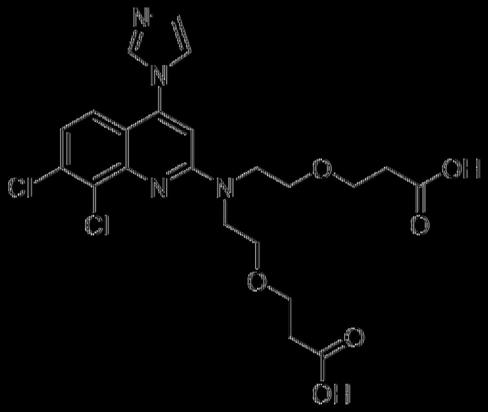
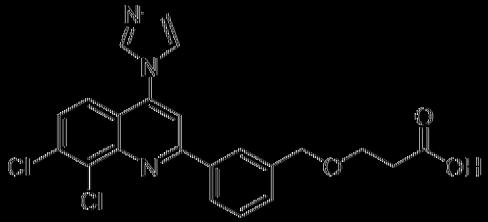
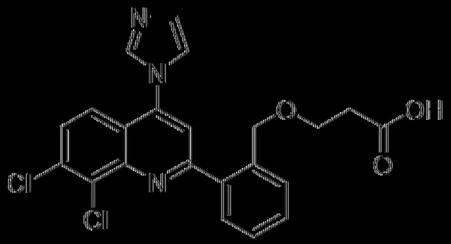
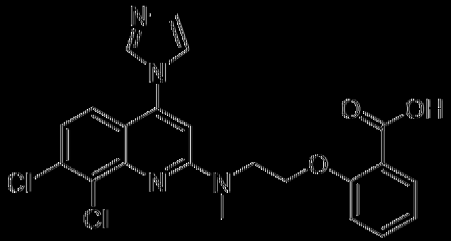
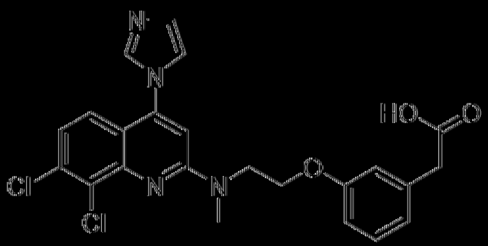
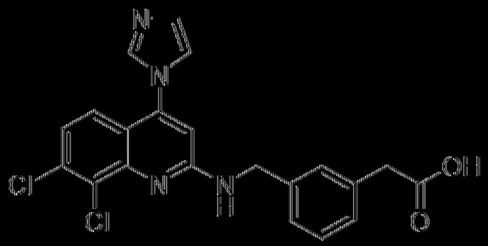
I-839	
I-840	
I-841	
I-842	
I-843	
I-844	

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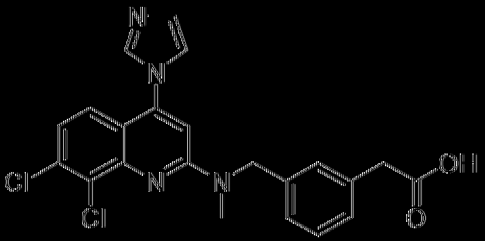
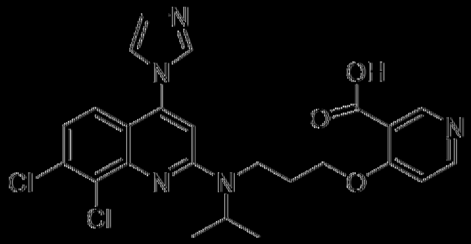
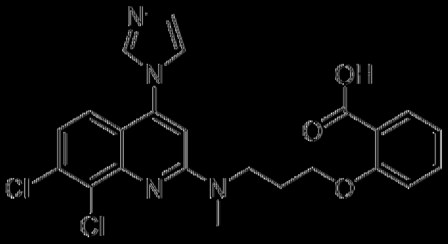
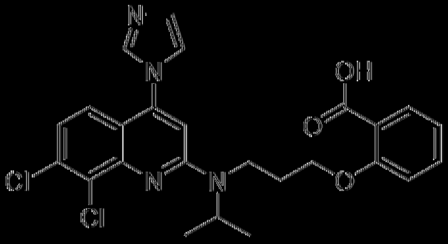
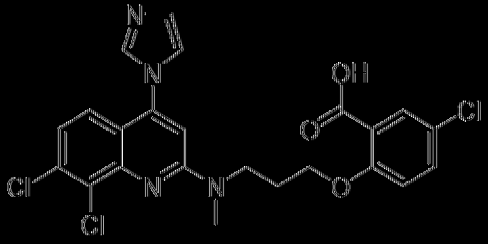
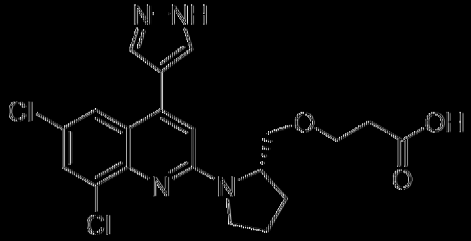
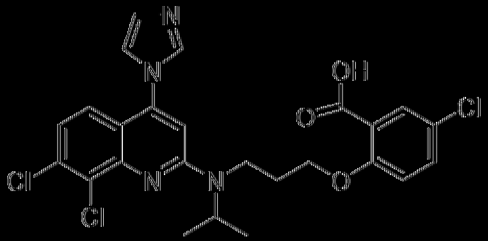
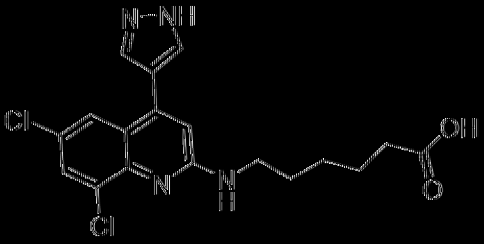
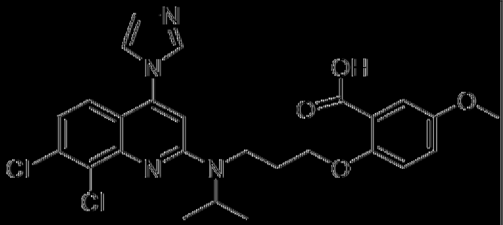
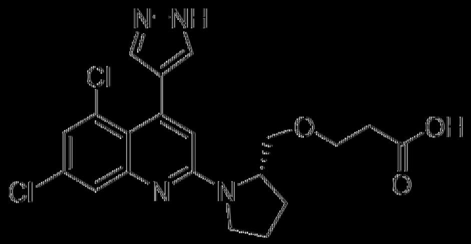
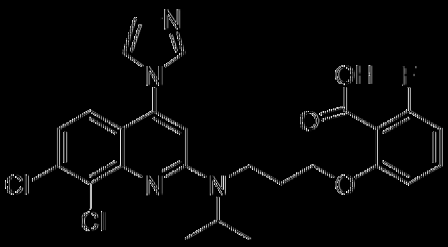
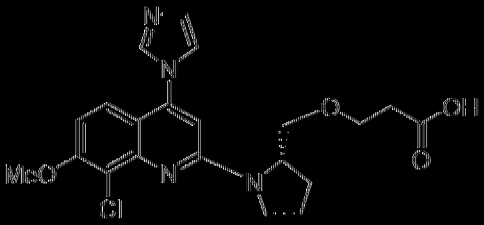
I-845		I-851	
I-846		I-852	
I-847		I-853	
I-848		I-854	
I-849		I-855	
I-850		I-856	

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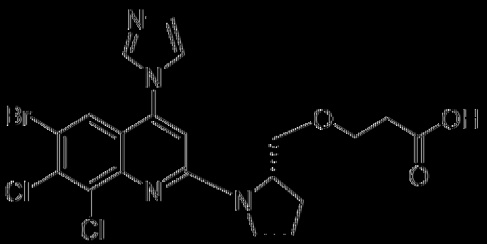
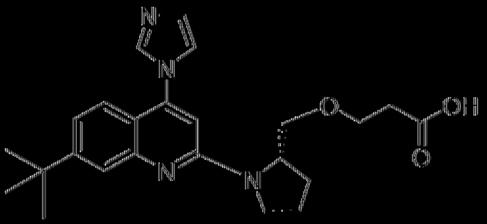
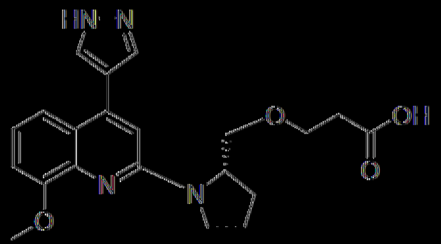
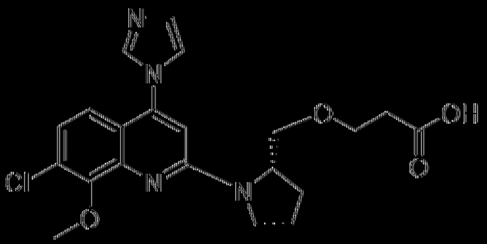
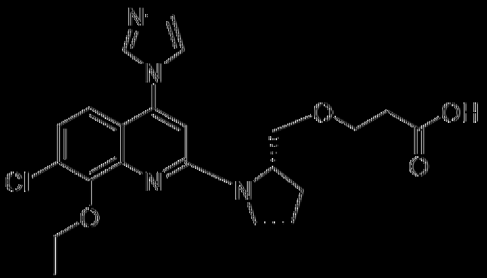
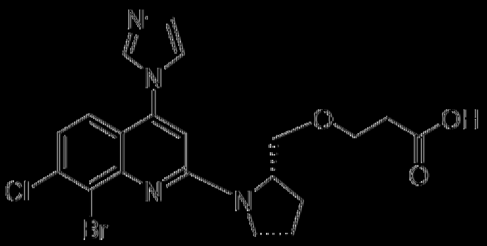
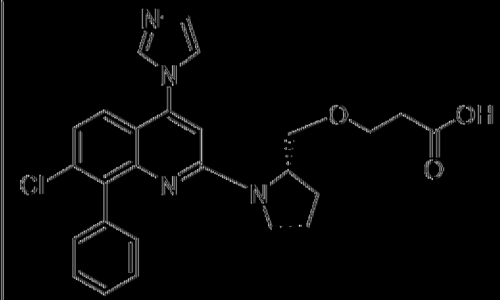
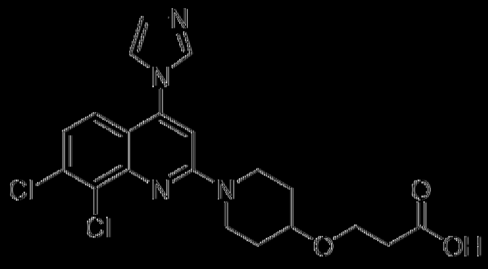
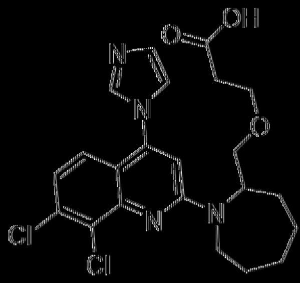
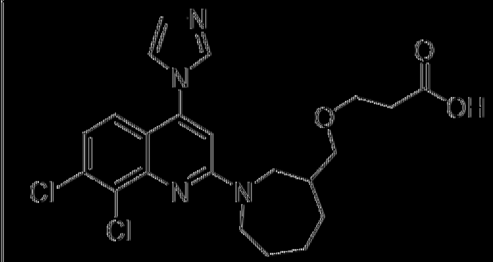
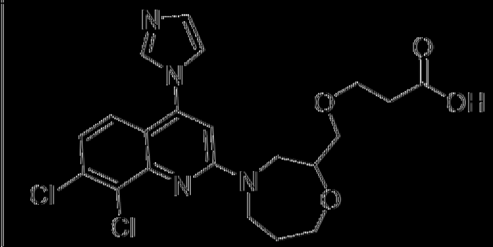
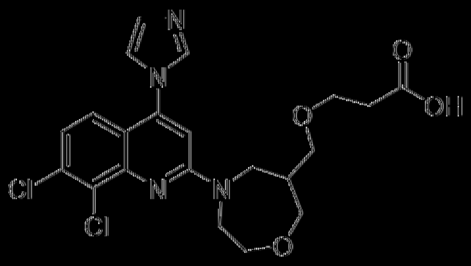
I-857	
I-858	
I-859	
I-860	
I-861	
I-862	
I-863	
I-864	
I-865	
I-866	
I-867	
I-868	

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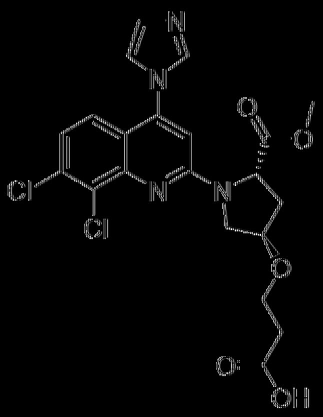
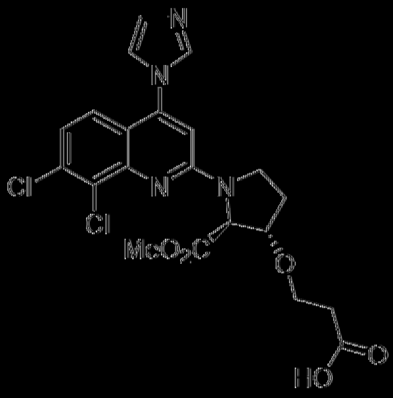
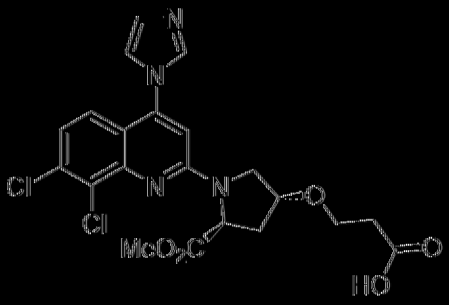
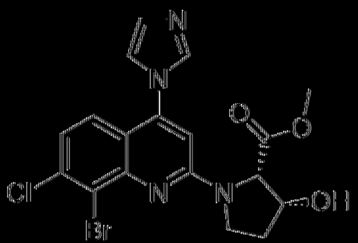
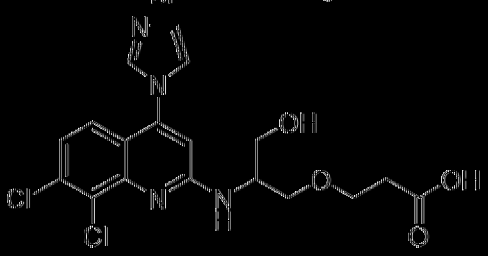
I-869	
I-870	
I-871	
I-872	
I-873	

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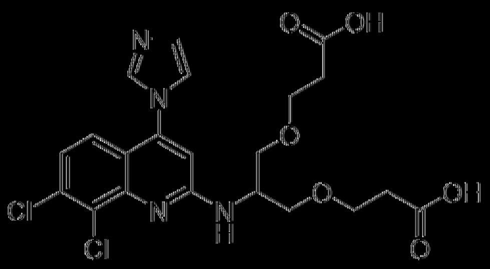
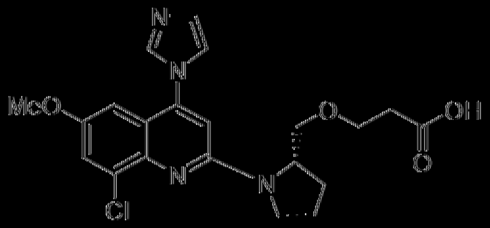
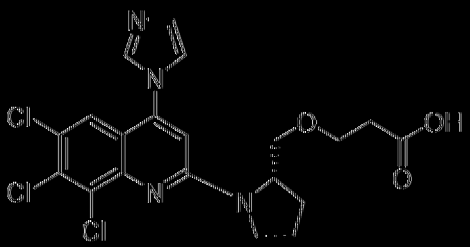
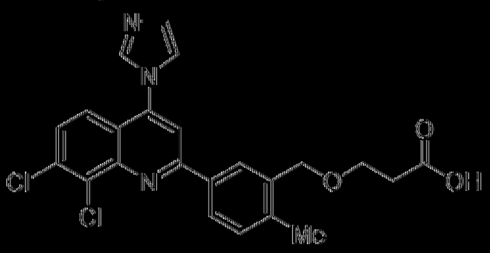
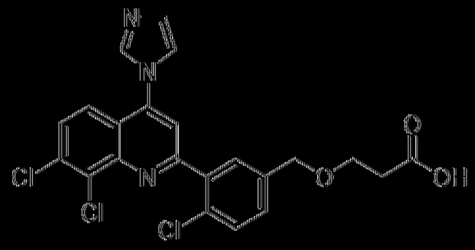
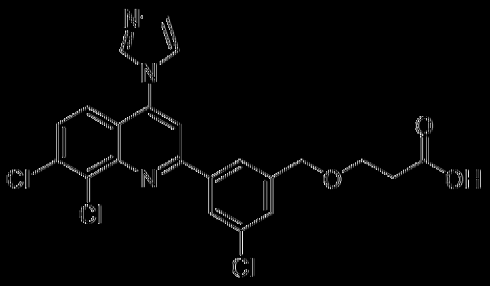
I-874	
I-875	
I-876	
I-877	
I-878	
I-879	

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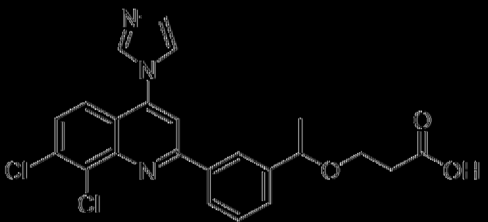
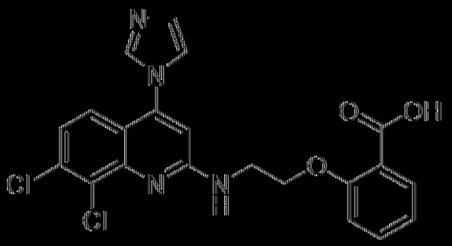
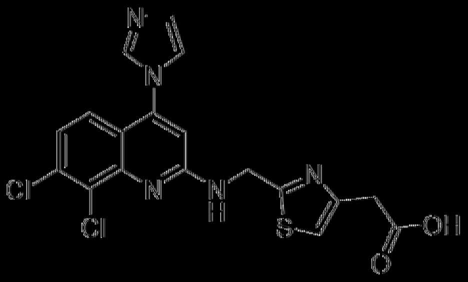
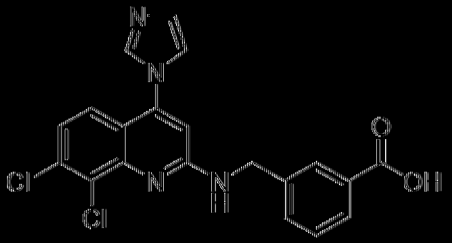
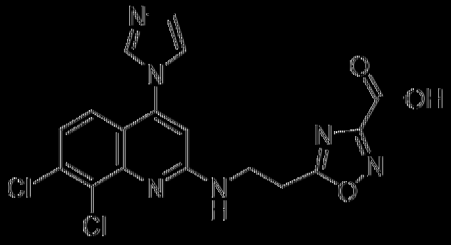
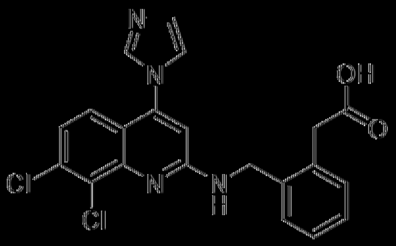
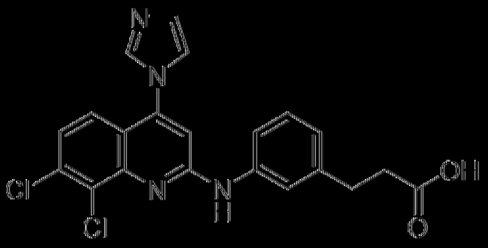
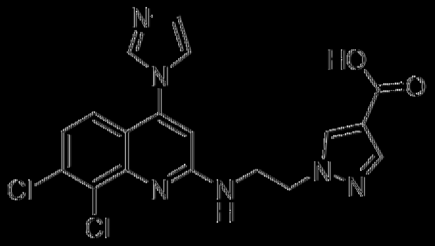
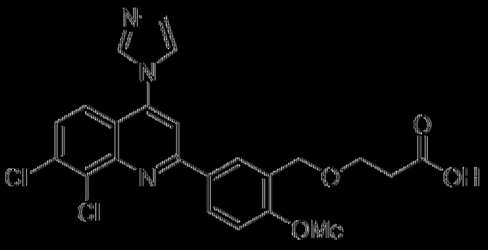
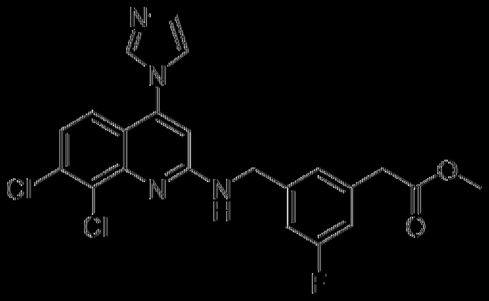
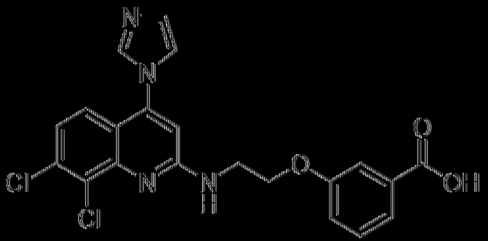
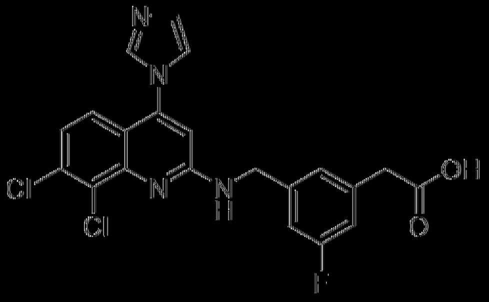
I-880		I-886	
I-881		I-887	
I-882		I-888	
I-883		I-889	
I-884		I-890	
I-885		I-891	

【0405】 在一些實施例中，本發明提供一種上**表1**中所示之化合物或其醫藥學上可接受之鹽。

3.3. 本發明化合物之醫藥組合物

【0406】 儘管所提供之化合物在用於療法中時可以化學原料形式投與，但所提供之化合物亦可作為醫藥組合物中之活性成分提供。此等組合物可依醫藥技術中熟知之方式製備且包含至少一種活性化合物。因此，在一個實施例中，本發明進一步提供醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及一或多種醫藥學上可接受之賦形劑。該一或多種賦形劑在與組合物之其他成分相容且對其接受者無害之意義上必須為「可接受的」。根據本發明之另一態樣，亦提供一種用於製備醫藥組合物之方法，該醫藥組合物包括所提供之化合物或其醫藥學上可接受之鹽，及一或多種醫藥學上可接受之賦形劑。該醫藥組合物可用於治療及/或預防任何本文所描述之病況。

【0407】 一般而言，所提供之化合物係以醫藥有效量投與。化合物之實際投與量通常由醫師根據相關情況確定，包括所治療之病況；所選擇之投與途徑；所投與之實際化合物；個別患者之年齡、體重及反應；患者症狀之嚴重程度，及其類似情況。醫藥組合物可呈每單位劑量含有預定量活性成分的單位劑型提供。術語「單位劑型」係指適合以單式劑量用於人類個體及其他哺乳動物的物理性離散單位，每個單位含有經過計算可產生所希望治療作用的預定量之活性材料，其與合適醫藥賦形劑、媒劑或載劑結合。典型單位劑型包括含液體組合物之預填充、預計量之安瓿或注射器，或在固體組合物情形下包括丸劑、錠劑、膠囊或其類似物。

【0408】 較佳之單位劑量組合物係含有每日劑量或子劑量或其適當

部分之活性成分的組合物。因此，此等單位劑量可一天投與一次或超過一次。此類醫藥組合物可藉由藥學技術中熟知之任何方法製備。

【0409】 醫藥組合物可適於藉由任何適當途徑投與，例如藉由經口(包括經頰或舌下)、經直腸、吸入、鼻內、表面(包括經頰、舌下或經皮)、經陰道或非經腸(包括皮下、肌肉內、靜脈內或皮內)途徑投與。此類組合物可藉由藥學技術中已知之任何方法製備，例如藉由使活性成分與一或多種載劑或賦形劑相結合來製備。

【0410】 適於經口投與之醫藥組合物可呈離散單元形式，諸如膠囊或錠劑；呈粉末或顆粒形式；呈於水性或非水性液體中之溶液或懸浮液形式；呈可食用泡沫產品或乳油甜點形式；或呈水包油液體乳液或油包水液體乳液形式。

【0411】 舉例而言，對於以錠劑或膠囊形式經口投與，活性藥物組分可與經口、無毒的醫藥學上可接受之惰性賦形劑，諸如乙醇、甘油、水及其類似物組合。粉末係藉由將化合物減小至適合的精細大小且與以類似方式製備之醫藥賦形劑，諸如可食用碳水化合物，如澱粉或甘露糖醇混合來製備。亦可存在調味劑、防腐劑、分散劑及著色劑。

【0412】 膠囊係藉由製備上述粉末混合物且填充成形之明膠外殼製備。在填充操作之前，可將賦形劑添加至粉末混合物中，該等賦形劑包括助流劑及潤滑劑，諸如膠態二氧化矽、滑石、硬脂酸鎂、硬脂酸鈣或固體聚乙二醇。亦可添加崩解劑或增溶劑，諸如瓊脂、碳酸鈣或碳酸鈉，以改善攝取膠囊時藥劑之可用率。

【0413】 此外，當需要或必要時，亦可將包括適合黏合劑、助流劑、潤滑劑、甜味劑、調味劑、崩解劑及著色劑在內之賦形劑併入混合物

中。適合黏合劑包括澱粉；明膠；天然糖，諸如葡萄糖或β-乳糖；玉米甜味劑；天然及合成膠，諸如阿拉伯膠、黃蓍膠或海藻酸鈉；羧甲基纖維素；聚乙二醇；蠟，及其類似物。用於此等劑型中之潤滑劑包括油酸鈉、硬脂酸鈉、硬脂酸鎂、苯甲酸鈉、乙酸鈉、氯化鈉及其類似物。崩解劑包括但不限於澱粉、甲基纖維素、瓊脂、膨潤土、三仙膠及其類似物。錠劑係例如藉由製備粉末混合物，粒化或擊壓(slugging)，添加潤滑劑及崩解劑並壓製成錠劑來調配。粉末混合物係藉由將適當地搗碎的所提供之化合物與如上文所述之稀釋劑或基劑混合，且視情況混入黏合劑，諸如羧甲基纖維素、海藻酸鹽、明膠或聚乙烯吡咯啶酮；溶解延遲劑，諸如石蠟；吸收促進劑，諸如四級鹽及/或吸收劑，諸如膨潤土、高嶺土或磷酸二鈣來製備。粉末混合物可藉由用黏合劑，諸如糖漿、澱粉漿料、阿卡迪亞膠漿(acadia mucilage)或纖維素或聚合材料之溶液潤濕且迫使其通過篩網來粒化。作為粒化之替代方案，可使粉末混合物穿過壓錠機，且由此得到不完美成形之塊，將其破碎成顆粒。該等顆粒可藉助於添加硬脂酸、硬脂酸鹽、滑石或礦物油潤滑以防止黏著於成錠模具上。接著，將經潤滑之混合物壓縮成錠劑。所提供之化合物亦可與自由流動之惰性載劑組合且直接壓縮為錠劑，無需經歷粒化或擊壓步驟。可提供由蟲膠形成之密封塗層組成之透明或不透明保護塗層、糖或聚合材料形成之塗層及蠟形成之拋光塗層。可將染料添加至此等塗層中以區分不同單位劑量。

【0414】 口服流體，諸如溶液、懸浮液、糖漿及酏劑可以單位劑型製備以使得給定量含有預定量之化合物。糖漿可藉由將化合物溶解於適當調味之水溶液中製備，而酏劑係經由使用無毒醇性媒劑製備。懸浮液可藉由將化合物分散於無毒媒劑中調配。亦可添加增溶劑及乳化劑，諸如乙氧

基化異硬脂醇及聚氧乙烯山梨糖醇醚；防腐劑；風味添加劑，諸如薄荷油；或天然甜味劑或糖精或其他人工甜味劑，及其類似物。

【0415】 適當時，供經口投與之劑量單位組合物可經微膠囊化。該組合物亦可例如藉由將粒狀材料包覆或包埋於聚合物、蠟或其類似物中來製備以延長或持續釋放。

【0416】 本發明化合物亦可以脂質體遞送系統之形式投與，諸如單層小囊泡、單層大囊泡及多層囊泡。脂質體可由多種磷脂，諸如膽固醇、硬脂胺或磷脂醯膽鹼形成。適於經皮投與之醫藥組合物可呈離散貼片形式，以便與接受者之表皮保持長時段之緊密接觸。

【0417】 適於表面投與之醫藥組合物可調配為軟膏、乳膏、懸浮液、洗劑、散劑、溶液、糊劑、凝膠、噴霧劑、氣霧劑或油形式。

【0418】 對於眼睛或其他外部組織，例如口腔及皮膚之治療，組合物較佳以表面用軟膏或乳膏形式施用。當調配為軟膏時，活性成分可與石蠟或可與水混溶之軟膏基劑一起使用。替代地，活性成分可利用水包油乳膏基劑或油包水基劑調配成乳膏。

【0419】 適於表面投與眼睛之醫藥組合物包括滴眼劑，其中活性成分溶解或懸浮於適合載劑、尤其是水性溶劑中。

【0420】 適於口中表面投與之醫藥組合物包括口含錠、片劑及漱口水。

【0421】 適於直腸投與之醫藥組合物可呈栓劑或灌腸劑形式。

【0422】 供經鼻或吸入投與之劑型可適宜地調配為氣霧劑、溶液、懸浮滴劑、凝膠或乾粉形式。

【0423】 供鼻內投與之組合物包括藉由滴劑或藉由加壓泵投與鼻部

之水性組合物。出於此目的，適合組合物含有水作為稀釋劑或載劑。供投與肺部或鼻部之組合物可含有一或多種賦形劑，例如一或多種懸浮劑、一或多種防腐劑、一或多種界面活性劑、一或多種張力調節劑、一或多種共溶劑，且可包括控制組合物之pH值的組分，例如緩衝液系統。另外，該等組合物可含有其他賦形劑，諸如抗氧化劑，例如偏亞硫酸氫鈉，及遮味劑。組合物亦可藉由噴霧投與鼻部或呼吸道其他區域。鼻內組合物可容許將所提供之化合物或其醫藥學上可接受之鹽遞送至鼻腔(目標組織)之所有區域且亦可容許使所提供之化合物或其醫藥學上可接受之鹽與目標組織保持長時段接觸。適合鼻內組合物之給藥方案將為患者在清理鼻腔之後經由鼻緩慢吸入。在吸入期間，將該組合物投與一個鼻孔，同時手動擠壓另一個鼻孔。接著，對另一個鼻孔重複此程序。典型地，每天將一次、兩次或三次藉由以上程序投與每個鼻孔一次或兩次噴霧，理想的是，每天投與一次。備受關注的是適於每天投與一次的鼻內組合物。

【0424】 若包括一或多種懸浮劑，則該一或多種懸浮劑的存在量以組合物之總重量計典型地將為0.1至5%(w/w)，諸如1.5%至2.4%(w/w)。醫藥學上可接受之懸浮劑的實例包括但不限於Avicef (微晶纖維素及羧甲基纖維素鈉)、羧甲基纖維素鈉、維格姆(veegum)、黃蓍膠、膨潤土、甲基纖維素、三仙膠、卡波莫(carbopol)及聚乙二醇。

【0425】 供投與肺部或鼻部之組合物可含有一或多種賦形劑，且可藉由包括一或多種防腐劑來防止微生物或真菌污染及生長。醫藥學上可接受之抗微生物劑或防腐劑的實例包括但不限於四級銨化合物(例如苯紮氯銨(benzalkonium chloride)、苄索氯銨(benzethonium chloride)、西曲溴胺(cetrimide)、氯化十六烷基吡錠、勞拉氯銨(lauralkonium chloride)及

氯化肉豆蔻基甲吡錠)、汞劑(例如硝酸苯汞、乙酸苯汞及硫柳汞)、醇劑(例如氯丁醇、苯乙醇及苯甲醇)、抗細菌酯(例如對羥基苯甲酸酯)、螯合劑諸如依地酸二鈉(EDTA)，以及其他抗微生物劑，諸如氯己定(chlorhexidine)、氯甲酚、山梨酸及其鹽(諸如山梨酸鉀)，及多黏菌素。醫藥學上可接受之抗真菌劑或防腐劑的實例包括但不限於苯甲酸鈉、山梨酸、丙酸鈉、對羥基苯甲酸甲酯、對羥基苯甲酸乙酯、對羥基苯甲酸丙酯及對羥基苯甲酸丁酯。若包括一或多種防腐劑，則該一或多種防腐劑的存在量以組合物之總重量計可為0.001至1%(w/w)，諸如0.015%至0.5%(w/w)。組合物(例如其中至少一種化合物係在懸浮液中)可包括一或多種界面活性劑，其用以促進藥劑粒子溶解於組合物之水相中。舉例而言，界面活性劑之用量係在混合期間不會引起發泡的量。醫藥學上可接受之界面活性劑的實例包括脂肪醇、酯及醚，諸如聚氧乙烯(20)脫水山梨糖醇單油酸酯(聚山梨醇酯80)、聚乙二醇醚及泊洛沙姆(poloxamers)。界面活性劑的存在量以組合物之總重量計可在約0.01至10% (w/w)之間，諸如為0.01至0.75% (w/w)，例如為約0.5% (w/w)。

【0426】 可包括一或多種張力調節劑以達到體液(例如鼻腔之流體)的張力，由此降低刺激水準。醫藥學上可接受之張力調節劑的實例包括但不限於氯化鈉、右旋糖、木糖醇、氯化鈣、葡萄糖、甘油及山梨糖醇。若存在張力調節劑，則所包括的張力調節劑之量以組合物之總重量計可為0.1至10% (w/w)，諸如為4.5至5.5% (w/w)，例如為約5.0% (w/w)。

【0427】 本發明之組合物可藉由添加適合緩衝劑，諸如檸檬酸鈉、檸檬酸、胺丁三醇、磷酸鹽諸如磷酸二鈉(例如十二水合物、七水合物、二水合物及無水形式)或磷酸鈉及其混合物來進行緩衝。

【0428】 若存在緩衝劑，則所包括的緩衝劑的量以組合物之總重量計可為0.1至5% (w/w)，例如為1至3% (w/w)。

【0429】 遮味劑之實例包括蔗糖素、蔗糖、糖精或其鹽、果糖、右旋糖、甘油、玉米糖漿、阿斯巴甜糖、乙醯磺胺酸-K、木糖醇、山梨糖醇、赤藻糖醇、甘草酸銨、索馬甜(thaumatin)、紐甜(neotame)、甘露糖醇、薄荷醇、桉油、樟腦、天然調味劑、人工調味劑及其組合。

【0430】 可包括一或多種共溶劑以幫助藥劑化合物及/或其他賦形劑溶解。醫藥學上可接受之共溶劑的實例包括但不限於丙二醇、二丙二醇、乙二醇、甘油、乙醇、聚乙二醇(例如PEG300或PEG400)及甲醇。在一個實施例中，共溶劑係丙二醇。

【0431】 若存在共溶劑，則所包括的共溶劑之量以組合物之總重量計可為0.05至30% (w/w)，諸如為1至25% (w/w)，例如為1至10% (w/w)。

【0432】 供吸入投與之組合物包括藉由加壓泵或吸入器投與呼吸道之水性、有機或水性/有機混合物、乾粉或結晶組合物，該吸入器例如為儲槽式乾粉吸入器、單位劑量乾粉吸入器、預計量多劑量乾粉吸入器、鼻吸入器或加壓氣霧劑吸入器、噴霧器或吹入器。適合組合物含有水作為稀釋劑或載劑以達成此目的，且可具有習知賦形劑，諸如緩衝劑、張力調節劑及其類似物。水性組合物亦可藉由噴霧投與鼻部及呼吸道其他區域。此類組合物可為自加壓包裝，諸如定計量吸入器遞送的水性溶液或懸浮液或氣霧劑，其中使用適合液化推進劑。

【0433】 供表面投與鼻部(例如用於治療鼻炎)或肺部的組合物包括藉由加壓泵遞送至鼻腔的加壓氣霧劑組合物及水性組合物。未加壓且適於表面投與鼻腔的組合物特別值得關注。出於此目的，適合組合物含有水作

為稀釋劑或載劑。供投與肺部或鼻部之水性組合物可具有習知賦形劑，諸如緩衝劑、張力調節劑及其類似物。水性組合物亦可藉由噴霧向鼻部投與。

【0434】 典型地，可使用流體施配器將流體組合物遞送至鼻腔。流體組合物可為水性或非水性的，但典型地為水性的。此類流體施配器可具有施配噴嘴或施配孔口，在使用者外施力施加至流體施配器之泵機構時，經由該施配噴嘴或施配孔口施配經計量之劑量的流體組合物。此類流體施配器一般具有含多個經計量之劑量之流體組合物的儲槽，劑量可在連續泵致動時施配。施配噴嘴或孔口可經組態用於插入至使用者之鼻孔中以向鼻腔中噴霧施配流體組合物。

【0435】 藉由吸入經表面遞送至肺部的乾粉組合物可例如提供於例如明膠或例如層壓鋁箔制泡殼形成之膠囊及藥筒中，以用於吸入器或吹入器。粉末摻合物組合物一般含有粉末混合物以供吸入所提供之化合物或其醫藥學上可接受之鹽，及適合粉末基劑(載劑/稀釋劑/賦形劑物質)，諸如單醣、二醣或多醣(例如乳糖或澱粉)。除藥物及載劑外，乾粉組合物亦可包括另一賦形劑(例如三元試劑，諸如糖酯，例如八乙酸纖維二糖酯、硬脂酸鈣或硬脂酸鎂)。

【0436】 適於非經腸投與之醫藥組合物包括水性及非水性無菌注射溶液，其可含有抗氧化劑、緩衝劑、抑菌劑及使組合物與預期接受者之血液等張之溶質；以及水性及非水性無菌懸浮液，其可包括懸浮劑及增稠劑。組合物可提供於單位劑量或多劑量容器，例如密封安瓿及小瓶中，且可在冷凍乾燥(凍乾)條件下儲存，其只需要在臨用前添加無菌液體載劑，例如注射用水。即用型注射溶液和懸浮液可由無菌粉末、顆粒及錠劑製

備。

【0437】 應理解，除上文特別提及之成分以外，組合物亦可包括此項技術中習知與所討論之調配物類型相關之其他試劑，例如適於經口投與之調配物可包括調味劑。

3.4. 本發明醫藥組合物及化合物在療法中之用途

【0438】 試劑之治療有效量將取決於多種因素，包括例如個體之年齡及體重、需要治療之精確病況及其嚴重程度、調配物之性質及投與途徑，且最終將由主治醫師或獸醫酌情處理。確切地說，待治療之個體係哺乳動物，尤其是人類。

【0439】 該試劑可以日劑量投與。此量可每天以單次劑量給與，或更通常地，每天以多次(例如兩個、三個、四個、五個或六個)子劑量給與，由此使總日劑量係相同的。

【0440】 適當地，投與的本發明化合物之量可為每天選自0.01 mg至10 g之量(以游離或無鹽化合物計算)。

【0441】 在一些實施例中，所提供之化合物或其醫藥學上可接受之鹽可單獨或與其他治療劑組合使用。所提供之化合物或其醫藥學上可接受之鹽及其他醫藥活性劑可一起或分開投與，且當分開投與時，投與可藉由任何適宜途徑以獨立或組合之醫藥組合物同時或按任何次序依序進行。所提供之化合物或其醫藥學上可接受之鹽及其他醫藥活性劑之量以及相對投與時序經選擇以便實現所希望的組合治療作用。所提供之化合物或其醫藥學上可接受之鹽及其他治療劑可藉由以包括兩種化合物之單式醫藥組合物同時投與來組合使用。替代地，該組合可以獨立醫藥組合物形式，以依序方式分開投與，該等獨立醫藥組合物各自包括一種化合物，其中例如，先

投與本發明化合物且再投與另一種化合物，且反之亦然。此類依序投與在時間上可極接近(例如同時)或在時間上可間隔很遠。另外，化合物是否以相同劑型投與並不重要，例如一種化合物可表面投與，而另一化合物可經口投與。適當地，兩種化合物均經口投與。

【0442】 該等組合可呈組合套組形式。如本文所使用，術語「組合套組」或「分裝部分之套組」意思指用於投與根據本發明之組合的一或多種醫藥組合物。當同時投與兩種化合物時，該組合套組可含有呈單一醫藥組合物形式(諸如錠劑)或呈獨立醫藥組合物形式之兩種化合物。當化合物並非同時投與時，該組合套組將含有呈在單一包裝中之獨立醫藥組合物形式或呈在獨立包裝中之獨立醫藥組合物形式的每種化合物。組合套組亦可提供有說明書，諸如劑量及投與說明書。此類劑量及投與說明書可為被提供給醫生之種類，例如藥物產品標籤，或其可為由醫生提供之種類，諸如給患者之說明書。

【0443】 當組合係以依序方式分開投與，其中先投與一種且再投與另一種，或反之亦然時，此類依序投與在時間上可極接近或在時間上間隔很遠。舉例而言，包括在投與第一試劑之後數分鐘至數十分鐘投與另一試劑，以及在投與第一試劑之後數小時至數天投與另一試劑，其中時間之流逝不受限制。舉例而言，一種試劑可一天投與一次，且另一試劑可一天投與2次或3次，或一種試劑可一週投與一次，且另一試劑可一天投與一次，及其類似情形。熟習此項技術者應瞭解，適當時，所用其他治療成分可呈鹽形式，例如呈鹼金屬或胺鹽形式或呈酸加成鹽形式；或呈前藥形式；或呈酯形式，例如低碳數烷基酯；或呈溶劑合物形式，例如水合物，以使治療成分之活性及/或穩定性及/或物理特性，諸如溶解度達到最佳。亦應瞭

解，適當時，所用治療成分可呈光學純形式。

【0444】 當組合於同一組合物中時，應瞭解，兩種化合物必須穩定且彼此及與組合物中之其他組分相容，且可經調配用於投與。當分開調配時，其可提供於任何適宜組合物中，便利地以諸如此項技術中關於此類化合物已知的方式提供。

【0445】 當將所提供之化合物或其醫藥學上可接受之鹽與針對同種疾病、病況或病症具有活性的第二治療劑組合使用時，每種化合物之劑量可不同於單獨使用該化合物時的劑量。熟習此項技術者將容易地瞭解適合的劑量。

【0446】 在一個實施例中，本發明之方法及用途中的哺乳動物係人類。所提供之化合物或其醫藥學上可接受之鹽可用於治療調節cGAS有益的疾病及病況。作為免疫反應調節劑，所提供之化合物一其醫藥學上可接受之鹽亦可單獨使用、組合使用或作為佐劑使用，以治療調節cGAS有益的疾病及病況。

【0447】 在一個實施例中，該疾病或病況係發炎性疾病、過敏性疾病或自體免疫疾病，諸如全身性紅斑狼瘡、牛皮癬、胰島素依賴性糖尿病(IDDM)、硬皮病、艾卡迪戈緹耶斯氏症候群、皮肌炎、發炎性腸病、多發性硬化、類風濕性關節炎及休格倫氏症候群(SS)。

【0448】 在另一個實施例中，該疾病或病況係調節cGAS活性有益的感染性疾病，諸如細菌、病毒或寄生蟲疾病。

【0449】 在另一個實施例中，該疾病或病況係衰老或年齡相關之疾病，包括神經退化性疾病，諸如阿茲海默氏病或帕金森氏病；心血管疾病，諸如動脈粥樣硬化或心肌梗塞；肝臟或腎臟疾病；癌症；或早衰。

【0450】 發炎表示一組針對外傷之血管、細胞及神經反應。發炎的特徵可為發炎細胞，諸如單核球、嗜中性白血球及顆粒球向組織內之移動。此通常與內皮障壁功能減弱及組織內水腫相關。發炎可分為急性或慢性的。急性發炎係身體對有害刺激之初始反應且藉由增加血漿及白血球自血液至受傷組織之移動達成。一連串生化事件傳播且促成發炎反應，涉及局部血管系統、免疫系統及受傷組織內之各種細胞。長期發炎，稱為慢性發炎，引起存在於發炎部位之細胞類型之進行性移位且以由發炎過程引起的同時發生之組織破壞及癒合為特徵。

【0451】 當發炎係作為對感染之免疫反應的一部分或作為對外傷之急性反應出現時，發炎可為有益的且通常具有自限性。然而，在多種情況下，發炎可為有害的。此包括回應於感染物而產生過度發炎，此可導致顯著器官損傷及死亡(例如在敗血症之情況中)。此外，慢性發炎一般係有害的且為多種慢性疾病之根源，會對組織造成嚴重且不可逆的損害。在此類情況中，免疫反應通常係針對自身組織(自體免疫)，但對外來實體之慢性反應亦可能導致對自身組織之旁觀者損傷。因此，抗炎療法之目標係減少此發炎、抑制自體免疫(若存在)及允許生理過程或癒合及組織修復進展。

【0452】 在一些實施例中，所提供之化合物或其醫藥學上可接受之鹽可用於治療身體任何組織及器官之發炎，包括肌肉骨胳發炎、血管發炎、神經發炎、消化系統發炎、眼部發炎、生殖系統發炎及其他發炎，如下文所例示。

【0453】 肌肉骨胳發炎係指肌肉骨胳系統之任何發炎性病況，尤其是影響包括手、腕、肘、肩、頜、脊椎、頸、髖、膝、踝及足關節在內之骨骼關節的病況，及影響諸如肌腱之類連接肌肉與骨之組織的病況。可用

本發明化合物治療之肌肉骨胳發炎的實例包括關節炎(包括例如骨關節炎、類風濕性關節炎、牛皮癬性關節炎、僵直性脊椎炎、急性及慢性感染性關節炎、與痛風及偽痛風相關的關節炎及幼年特發性關節炎)、肌腱炎、滑膜炎、腱鞘炎、滑囊炎、纖維組織炎(纖維肌痛)、上髁炎、肌炎及骨炎(包括例如佩吉特氏病(Paget's disease)、恥骨炎及囊性纖維性骨炎)。眼部發炎係指包括眼瞼在內之眼睛任何結構的發炎。可用本發明化合物治療之眼部發炎的實例包括瞼緣炎、眼瞼鬆弛(blepharochalasis)、結膜炎、淚腺炎、角膜炎、乾燥性角膜結膜炎(乾眼症)、鞏膜炎、倒睫及葡萄膜炎。可用本發明化合物治療的神經系統發炎之實例包括腦炎、格-巴二氏症候群(Guillain-Barre syndrome)、腦膜炎、神經肌強直、發作性睡病、多發性硬化、脊髓炎及精神分裂症。

【0454】 可用所提供之化合物或其醫藥學上可接受之鹽治療的血管或淋巴系統發炎之實例包括關節硬化、關節炎、靜脈炎、血管炎及淋巴管炎。

【0455】 可用所提供之化合物或其醫藥學上可接受之鹽治療之消化系統發炎性病況的實例包括膽管炎、膽囊炎、腸炎、小腸結腸炎、胃炎、胃腸炎、發炎性腸病(諸如克羅恩氏病(Crohn's disease)及潰瘍性結腸炎)、迴腸炎及直腸炎。

【0456】 可用所提供之化合物或其醫藥學上可接受之鹽治療的生殖系統發炎性病況之實例包括子宮頸炎、絨膜羊膜炎、子宮內膜炎、附睪炎、臍炎、卵巢炎、睪丸炎、輸卵管炎、輸卵管-卵巢囊腫、尿道炎、陰道炎、外陰炎及外陰疼痛。

【0457】 該等試劑可用於治療具有發炎性組分之自體免疫病況。此

類病況包括全身性紅斑狼瘡、急性播散性普禿、白塞氏病(Behcet's disease)、卻格司氏病(Chagas' disease)、慢性疲勞症候群、自主神經失調、腦脊髓炎、僵直性脊椎炎、再生不全性貧血、化膿性汗腺炎、自體免疫肝炎、自體免疫卵巢炎、乳糜瀉、克羅恩氏病、1型糖尿病、巨大細胞動脈炎、古巴士德氏症候群(goodpasture's syndrome)、格雷夫氏病(Grave's disease)、格-巴二氏症候群、橋本氏病(Hashimoto's disease)、亨偌-絲奇恩賴氏紫癜(Henoch-Schonlein purpura)、川崎氏病(Kawasaki's disease)、顯微鏡下結腸炎、顯微鏡下多動脈炎、混合性結締組織病、多發性硬化、重症肌無力、眼陣攣肌陣攣症候群、視神經炎、奧德氏甲狀腺炎(ord's thyroiditis)、天疱瘡、結節性多動脈炎、多肌痛、類風濕性關節炎、萊特氏症候群(Reiter's syndrome)、休格連氏症候群、艾卡迪戈緹耶斯氏症候群、顳動脈炎、韋格納氏肉芽腫病(Wegener's granulomatosis)、溫型自體免疫溶血性貧血、間質性膀胱炎、萊姆病(lyme disease)、硬斑病、牛皮癬、類肉瘤病、硬皮病、潰瘍性結腸炎及白斑病。

【0458】 在一些實施例中，所提供之化合物或其醫藥學上可接受之鹽可用於治療具有炎性組分的T細胞介導之過敏疾病。此類病況包括接觸過敏、接觸性皮炎(包括因毒葛引起之接觸性皮炎)、蕁麻疹、皮膚過敏、呼吸過敏(枯草熱、過敏性鼻炎)及麩質敏感性腸病(賽利亞病(Celliac disease))。

【0459】 可用所提供之化合物或其醫藥學上可接受之鹽治療之其他發炎性病況包括例如闌尾炎、皮炎、皮肌炎、心內膜炎、纖維組織炎、齒齦炎、舌炎、肝炎、化膿性汗腺炎、虹膜炎、喉炎、乳腺炎、心肌炎、腎炎、耳炎、胰臟炎、腮腺炎、心包炎、腹膜炎、咽炎、胸膜炎、肺炎、前

列腺炎、腎盂腎炎及口腔炎、移植排斥反應(涉及諸如腎臟、肝臟、心臟、肺、胰臟(例如胰島細胞)、骨髓、角膜、小腸之類器官、皮膚同種異體移植、皮膚同種移植及心瓣膜異種移植、血清病及移植物抗宿主疾病)、急性胰臟炎、慢性胰臟炎、急性呼吸窘迫症候群、塞氏症候群(Sexary's syndrome)、先天性腎上腺增生、非化膿性甲狀腺炎、癌症相關高鈣血症、天疱瘡、大皰性疱疹樣皮炎、重度多形性紅斑、剝脫性皮炎、脂溢性皮炎、季節性或常年性過敏性鼻炎、支氣管哮喘、接觸性皮炎、異位性皮炎、藥物過敏反應、過敏性結膜炎、角膜炎、帶狀疱疹病毒眼症、虹膜炎及虹膜睫狀體炎、脈絡膜視網膜炎、視神經炎、有症狀之類肉瘤病、暴發性或播散性肺結核化學療法、成人特發性血小板減少性紫癜、成人繼發性血小板減少症、獲得性(自體免疫性)溶血性貧血、成人白血病及淋巴瘤、兒童急性白血病、區域性腸炎、自體免疫脈管炎、多發性硬化、慢性阻塞性肺病、實體器官移植排斥反應、敗血症。較佳之治療包括移植排斥反應、類風濕性關節炎、牛皮癬性關節炎、多發性硬化、第1型糖尿病、哮喘、發炎性腸病、全身性紅斑狼瘡、牛皮癬、慢性肺病及伴隨感染性病況之發炎(例如敗血症)之治療。

【0460】 在一些實施例中，本發明提供用於治療發炎性疾病、過敏性疾病或自體免疫疾病的所提供之化合物或其醫藥學上可接受之鹽。

【0461】 在一些實施例中，本發明提供一種治療發炎性疾病、過敏性疾病或自體免疫疾病之方法，其包含：向有需要之患者投與治療有效量的所提供之化合物或其醫藥學上可接受之鹽。

【0462】 在一些實施例中，本發明提供所提供之化合物或其醫藥學上可接受之鹽在製造用於治療發炎性疾病、過敏性疾病或自體免疫疾病之

藥劑中的用途。

【0463】 在一些實施例中，所提供之化合物或其醫藥學上可接受之鹽可與一或多種其他試劑組合使用以預防或治療過敏性疾病、發炎性疾病或自體免疫疾病，其中此類其他試劑可包括：抗原免疫療法試劑；抗組織胺；類固醇、NSAID；支氣管擴張劑(例如β2促效劑、腎上腺素激導性促效劑、抗膽鹼劑、茶鹼)；甲胺喋呤(methotrexate)；白三烯調節劑；單株抗體劑，諸如抗lgE、抗TNF、抗IL-5、抗IL-6、抗IL-12、抗IL-1及類似試劑；受體治療劑，諸如依那西普(entanercept)；及抗原非特異性免疫治療劑，諸如干擾素或其他細胞介素/趨化因子、細胞介素/趨化因子受體調節劑、細胞介素促效劑或拮抗劑，及TLR拮抗劑。

【0464】 在一些實施例中，本發明提供一種醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療過敏性疾病、發炎性疾病或自體免疫疾病之治療劑。

【0465】 在一些實施例中，本發明提供一種用於療法中之醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療過敏性疾病、發炎性疾病或自體免疫疾病之治療劑。

【0466】 在一些實施例中，本發明提供一種用於治療過敏性疾病、發炎性疾病或自體免疫疾病之醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療過敏性疾病、發炎性疾病或自體免疫疾病之治療劑。

【0467】 在一些實施例中，本發明提供醫藥組合物在製造用於治療過敏性疾病、發炎性疾病或自體免疫疾病之藥劑中的用途，該醫藥組合物包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治

療過敏性疾病、發炎性疾病或自體免疫疾病之治療劑。

【0468】 在一些實施例中，本發明提供一種治療過敏性疾病、發炎性疾病或自體免疫疾病之方法，其包含：向有需要之患者投與治療有效量之醫藥組合物，該醫藥組合物包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療過敏性疾病、發炎性疾病或自體免疫疾病之治療劑。

【0469】 在一些實施例中，本發明提供一種醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽、至少一種其他可用於治療過敏性疾病、發炎性疾病或自體免疫疾病之治療劑，及一或多種醫藥學上可接受之賦形劑。

【0470】 在一些實施例中，本發明提供用於治療感染性疾病的所提供之化合物或其醫藥學上可接受之鹽。

【0471】 在一些實施例中，本發明提供一種治療感染性疾病之方法，其包含向有需要之患者投與治療有效量的所提供之化合物或其醫藥學上可接受之鹽。

【0472】 在一些實施例中，本發明提供所提供之化合物或其醫藥學上可接受之鹽在製造用於治療感染性疾病之藥劑中的用途。在一個實施例中，本發明化合物可與治療感染性疾病之其他治療方法一起使用。確切地說，利用I型干擾素路徑發揮其優勢之細菌及寄生蟲感染，分別諸如結核分支桿菌及瘧疾，可用cGAS抑制劑治療。

【0473】 在一些實施例中，所提供之化合物或其醫藥學上可接受之鹽可與一或多種可用於預防或治療細菌及病毒感染之試劑組合使用。此類試劑之實例包括：聚合酶抑制劑；複製抑制劑，諸如阿克洛韋

(acyclovir)、泛昔洛韋(famciclovir)、更昔洛韋(ganciclovir)、西多福韋(cidofovir)及拉米夫定(lamivudine)；蛋白酶抑制劑，諸如HIV蛋白酶抑制劑沙奎那韋(saquinavir)、利托那韋(ritonavir)、茚地那韋(indinavir)、奈非那韋(nelfinavir)、安普那韋(amprenavir)、夫沙那韋(fosamprenavir)、貝卡那韋(brecanavir)、阿紮那韋(atazanavir)、替拉那韋(tipranavir)、帕利那韋(palinavir)、拉西那韋(lasinavir)及HCV蛋白酶抑制劑BILN2061、VX-950、SCH503034；核苷及核苷酸逆轉錄酶抑制劑，諸如齊多夫定(zidovudine)、地達諾新(didanosine)、拉米夫定(lamivudine)、紮西他濱(zalcitabine)、阿巴卡韋(abacavir)、司他夫定(stavidine)、阿德福韋(adefovir)、阿德福韋雙匹酯(adefovir dipivoxil)、福齊夫定(fozivudine)、托多西爾(todoxil)、恩曲他濱(emtricitabine)、阿洛夫定(alovudine)、安多索韋(amdoxovir)及艾夫他濱(elvucitabine)；非核苷逆轉錄酶抑制劑(包括具有抗氧化活性之試劑，諸如怡妙康(immunocal)或奧替普拉(oltipraz))，諸如奈韋拉平(nevirapine)、迪拉韋啶(delavirdine)、依法韋侖(efavirenz)、洛韋胺(loviride)、怡妙康、奧替普拉、卡普拉林(capravirine)、TMC-278、TMC-125及依曲韋林(etravirine)；進入抑制劑，諸如恩夫韋地(enfuvirtide)(T-20)、T-1249、PRO-542、PRO-140、TNX-355、BMS-806、5-螺旋及類似試劑；整合酶抑制劑，諸如L-870及180；出芽抑制劑，諸如PA-344及PA-457；趨化因子受體抑制劑，諸如維克維若(vicriviroc)(Sch-C)、Sch-D、TAK779、馬拉韋羅(maraviroc)(UK-427,857)及TAK449；神經胺糖酸酶抑制劑，諸如CS-8958、紮那米韋(zanamivir)、奧司他韋(oseltamivir)及帕拉米韋(peramivir)；離子通道阻斷劑，諸如金剛胺(amantadine)或金剛烷乙胺

(rimantadine)；干擾RNA及反義寡核苷酸，諸如ISIS-14803；以及作用機制不確定之抗病毒劑，諸如利巴韋林(ribavirin)。

【0474】 在一些實施例中，所提供之化合物或其醫藥學上可接受之鹽亦可與可用於預防或治療病毒感染之一或多種其他試劑組合使用，該一或多種其他試劑諸如免疫療法(例如干擾素或其他細胞介素/趨化因子、細胞介素/趨化因子受體調節劑、細胞介素促效劑或拮抗劑及類似試劑)；治療性疫苗；抗纖維化劑；及抗炎劑，諸如皮質類固醇或NSAID(非類固醇抗炎劑)。

【0475】 在一些實施例中，本發明提供一種醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療感染性疾病之治療劑。

【0476】 在一些實施例中，本發明提供一種用於療法中之醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療感染性疾病之治療劑。

【0477】 在一些實施例中，本發明提供一用於治療感染性疾病之醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療感染性疾病之治療劑。

【0478】 在一些實施例中，本發明提供醫藥組合物在製造用於治療感染性疾病之藥劑中的用途，該醫藥組合物包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療感染性疾病之治療劑。

【0479】 在一些實施例中，本發明提供一種治療感染性疾病之方法，其包含向有需要之患者投與治療有效量之醫藥組合物，該醫藥組合物包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治

療感染性疾病之治療劑。

【0480】在一些實施例中，本發明提供一種醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽、至少一種其他可用於治療感染性疾病之治療劑及一或多種醫藥學上可接受之賦形劑。

【0481】在一些實施例中，本發明提供用於治療衰老或年齡相關之疾病的所提供之化合物或其醫藥學上可接受之鹽。

【0482】在一些實施例中，本發明提供一種治療衰老或年齡相關之疾病的方法，其包含：向有需要之患者投與治療有效量的所提供之化合物或其醫藥學上可接受之鹽。

【0483】在一些實施例中，本發明提供所提供之化合物或其醫藥學上可接受之鹽在製造用於治療衰老或年齡相關之疾病之藥劑中的用途。

【0484】在一些實施例中，本發明提供一種醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療衰老或年齡相關之疾病的治療劑。

【0485】在一些實施例中，本發明提供一種用於療法中之醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療衰老或年齡相關之疾病的治療劑。

【0486】在一些實施例中，本發明提供一種用於治療衰老或年齡相關之疾病的醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療衰老或年齡相關之疾病的治療劑。

【0487】在一些實施例中，本發明提供醫藥組合物在製造用於治療衰老或年齡相關之疾病之藥劑中的用途，該醫藥組合物包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療衰老或年齡相關

之疾病的治療劑。

【0488】 在一些實施例中，本發明提供一種治療衰老或年齡相關之疾病的方法，其包含向有需要之患者投與治療有效量之醫藥組合物，該醫藥組合物包含所提供之化合物或其醫藥學上可接受之鹽，及至少一種其他可用於治療衰老或年齡相關之疾病的治療劑。

【0489】 在一些實施例中，本發明提供一種醫藥組合物，其包含所提供之化合物或其醫藥學上可接受之鹽、至少一種其他可用於治療衰老或年齡相關之疾病的治療劑及一或多種醫藥學上可接受之賦形劑。

【0490】 所提供之化合物可藉由以下方案及/或以下描述之具體實例中所示的有機合成領域中已知之方法製備。在所有方法中，應充分理解，必要時，可根據一般化學原理，對敏感性或反應性基團使用保護基。保護基係根據標準有機合成方法操作(T. W. Green及P. G. M. Wuts (1999) Protective Groups in Organic Synthesis, 第3版, John Wiley & Sons)。此等基團係使用熟習此項技術者顯而易見之方法，在化合物合成之適宜階段移除。方法以及反應條件及其執行次序的選擇應與所提供之化合物的製備相符。

【0491】 以下清單提供如本文所使用之某些縮寫的定義。應瞭解，該清單並不詳盡，但未在下文中定義之縮寫的含義將為熟習此項技術者顯而易見：AIBN係2,2'-偶氮二異丁腈；ATP係腺苷5'-三磷酸；BPO係過氧化苯甲醯；*n*-BuLi係正丁基鋰；BzCl係苯甲醯氯；CDI係1,1'-羰基二咪唑；cGAS係環狀GMP-AMP合成酶；CO係一氧化碳；Cu(OAc)$_2$係乙酸銅(II)；CuCN係氰化銅(I)；CuI係碘化銅(I)；DAST係三氟化(二乙基胺基)硫；DBU係1,8-二氮雜雙環[5.4.0]十一碳-7-烯；DCE係二氯乙烷；DCM係二氯甲烷；DDQ係2,3-二氯-5,6-二氰基-對苯醌；DHP係3,4-二氫-2*H*-

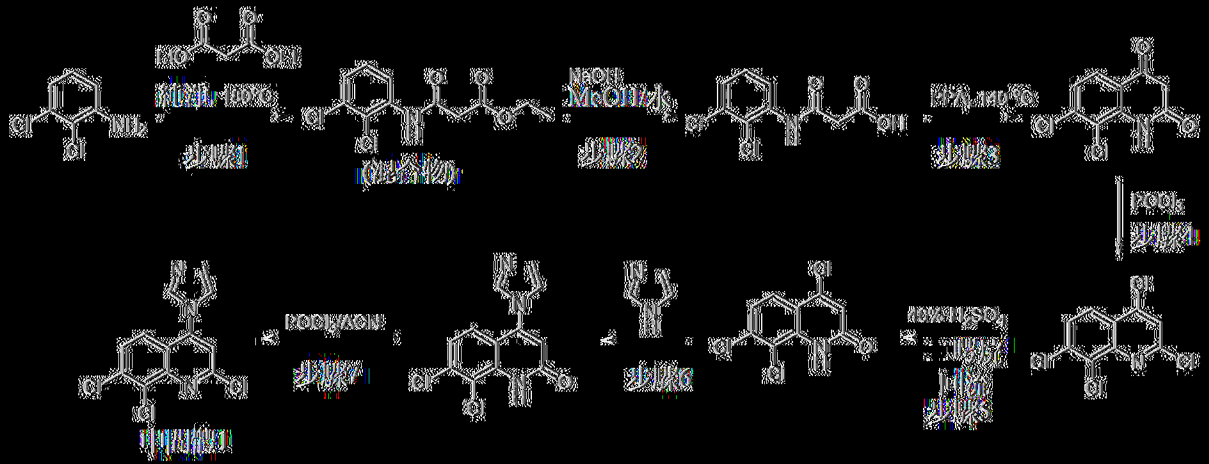
哌喃；DIAD係偶氮二甲酸二異丙酯；DIBAL-H係氫化二異丁基鋁；DIPA係二異丙胺；DIPEA係*N*,*N*-二異丙基乙胺；DMAP係4-(二甲基胺基)吡啶；DMB係2,4-二甲氧基苯甲基；DMF係*N*,*N*-二甲基甲醯胺；DMP係戴斯-馬丁高碘烷(Dess-Martin periodinane)；DMSO係二甲亞碸；EA係乙酸乙酯；EtMgBr係溴化乙基鎂；Et_2O係乙醚；EtOH係乙醇；GTP係鳥苷三磷酸；HCl係鹽酸；HMTA係六亞甲基四胺；HOAc係乙酸；HPLC係高效液相層析法；LAH係氫化鋰鋁；*m*CPBA係3-氯過氧苯甲酸；MeCN係乙腈；MeI係碘甲烷；MeOH係甲醇；MeMgBr係溴化甲基鎂；MOMCl係氯甲基甲基醚；MOM係甲氧基甲氧基；MS係質譜儀或質譜；MsCl係甲烷磺醯氯；MTBE係甲基三級丁基醚；NaH係氫化鈉；NaOH係氫氧化鈉；NBS係*N*-溴代琥珀醯亞胺；NMM係*N*-甲基味啉；NMR係核磁共振；$Pd(dba)_2$係雙(二苯亞甲基丙酮)鈀(0)；$Pd(dppf)Cl_2$係[1,1'-雙(二苯基膦基)二茂鐵]二氯鈀(II)；$Pd(OAc)_2$係乙酸鈀(II)；$Pd(PPh_3)_2Cl_2$係二氯化雙(三苯膦)鈀(II)；$Pd(PPh_3)_4$係肆(三苯基膦)鈀(0)；Pd/C係鈀/碳；PDC係重鉻酸吡錠；PE係石油醚；PMB係4-甲氧基苯甲基；PPh_3係三苯膦；prep-HPLC係製備型高效液相層析法；prep-TLC係製備型薄層層析法；Py係吡啶；TBAF係氟化四正丁基銨；TBSCl係三級丁基二甲基矽基氯；TEA係三乙胺；TFA係三氟乙酸；THF係四氫呋喃；THP係四氫哌喃基；TLC係薄層層析法；TSA係單水合對甲苯磺酸及TsCl係對甲苯磺醯氯。

4. 實例

【0492】 以下實例提供所提供之化合物之合成及其活體外活性。

中間體

【0493】 製備2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(中間體1)



【0494】 步驟1：製備3-((2,3-二氯苯基)胺基)-3-側氧基丙酸乙酯. 將2,3-二氯苯胺(10.33 g，64 mmol，1.0 eq)與丙二酸二乙酯1-2 (24 mL，24.3 g，158 mmol)混合並在180℃下加熱16小時，直至停止產物形成(藉由LC-MS確認)。將所得油混合物用於下一步驟中。MS (ES): $[M+1]^+$ 276。

【0495】 步驟2：製備3-((2,3-二氯苯基)胺基)-3-側氧基丙酸. 將第一步驟之混合物用MeOH (80 mL)及水(80 mL)稀釋並用冰-水浴冷卻。向上述溶液中緩慢添加NaOH (12 g，相對於丙二酸二乙酯為約2 eq)於50 mL水中之溶液。在攪拌30至60分鐘後，有固體沈澱。添加水以幫助攪拌。在室溫下攪拌3至4小時後，起始物質消耗(藉由LC-MS確認)，用濃HCl將反應混合物酸化至pH 1以形成沈澱。在過濾，用水沖洗並真空乾燥後，將標題化合物(10.57 g)不經進一步純化即用於下一步驟中。MS (ES): $[M+1]^+$ 248。

【0496】 步驟3：製備7,8-二氯喹啉-2,4(1H,3H)-二酮. 使步驟2之產物(10.57 g)懸浮並在140℃下與PPA (55 g)一起攪拌3小時，直至所有固體均溶解。在起始物質消耗(藉由LC-MS確認)後，用冰淬滅反應混合物。藉由過濾收集所形成之固體並用水沖洗。真空乾燥後，將標題化合物(17 g)不經進一步純化即用於下一步驟中。MS (ES): $[M+1]^+$ 230

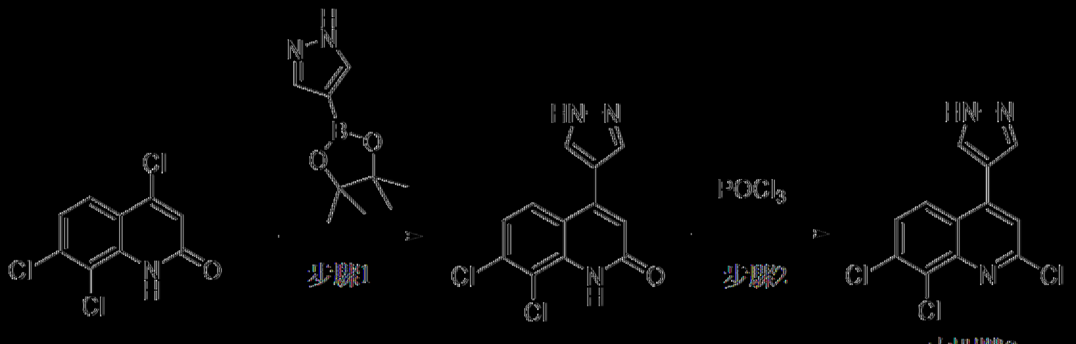
【0497】 步驟4：製備2,4,7,8-四氯喹啉(1.6). 使步驟3之產物懸浮於$POCl_3$ (45 g)中並在130℃下加熱，直至所有固體均溶解。在起始物質消耗(藉由LC-MS確認)後，在真空下移除過量$POCl_3$。用冰-水處理殘餘物(放熱)，得到固體，並將懸浮之固體攪拌4小時。過濾，用水沖洗並真空乾燥，得到呈褐色固體狀之粗產物(9.25 g)，將其懸浮於己烷(400 mL)中並在回流下加熱。趁熱過濾以移除殘留固體並緩慢冷卻至室溫後，獲得5.73 g呈淺褐色固體狀之標題化合物。將自濾液濃縮之固體及上述重結晶中未溶解之固體藉由急驟二氧化矽管柱純化，又得到產物(1.7 g)。MS (ES): $[M+1]^+$ 266.0。^{1}H NMR (400 Hz, $CDCl_3$): δ 8.074-8.046 (dd, *J* = 9.2及2.4 Hz, 1H), 7.705-7.677 (dd, *J* = 9.2及2.4 Hz, 1H), 7.571 (s, 1H) ppm。

【0498】 步驟5：製備4,7,8-三氯喹啉-2(1H)-酮. 將步驟4之產物(4.93 g)懸浮於二噁烷(80 mL)、濃H_2SO_4 (16 mL)、水(24 mL)中，並加熱至回流，保持12至16小時。最初形成澄清溶液，隨後固體沈澱。在起始物質消耗(藉由LC-MS確認)並將反應混合物冷卻後，添加100 mL ACN以形成沈澱。過濾，用CAN沖洗並真空乾燥，得到呈無色粉末狀之標題化合物(4.12 g)。MS (ES): $[M+1]^+$ 248.0。

【0499】 步驟6：製備7,8-二氯-4-(1H-咪唑-1-基)喹啉-2(1H)-酮(1-8). 將步驟5之產物(4.12 g)懸浮於含咪唑(4 g)之DMF (20 mL)中並加熱至130℃，直至起始物質消耗(藉由LC-MS確認)。可再添加咪唑以推動反應完成。冷卻後，添加ACN (150 mL)以形成沈澱，藉由過濾收集該沈澱並用CAN沖洗，得到標題化合物(1.8，3.90 g)。MS (ES): $[M+1]^+$ 280.0。^{1}H NMR (400 Hz, DMSO-d6): δ 8.089 (s, 1H), 7.650 (s, 1H), 7.494-7.516 (d, *J* = 8.8 Hz, 1H), 7.316-7.338 (d, *J* = 8.8 Hz, 1H), 7.225 (s. 1H), 6.795 (s, 1H) ppm。

【0500】 步驟7：2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(中間體1). 將步驟6之產物(3.90 g)懸浮於ACN (100 mL)及$POCl_3$ (8 mL)中並加熱至回流，直至所有固體均溶解且起始物質消耗(藉由LC-MS確認)。真空濃縮後，在冰浴中冷卻殘餘物並藉由5% NaOH小心地中和至pH 7以沈澱得到中間體1。過濾，用水沖洗並真空乾燥，得到呈淺棕色固體狀之中間體1 (3.8 g)。MS (ES): $[M+1]^+$ 298。^1H NMR (400 Hz, DMSO-d6): δ 8.200 (s, 1H), 8.005 (s, 1H), 7.925-7.948 (d, *J* = 9.2 Hz, 1H), 7.785-7.808 (d, *J* = 9.2 Hz, 1H), 7.772 (s. 1H), 7.286 (s, 1H) ppm。

【0501】 製備2,7,8-三氯-4-(1H-吡唑-4-基)喹啉(中間體2)



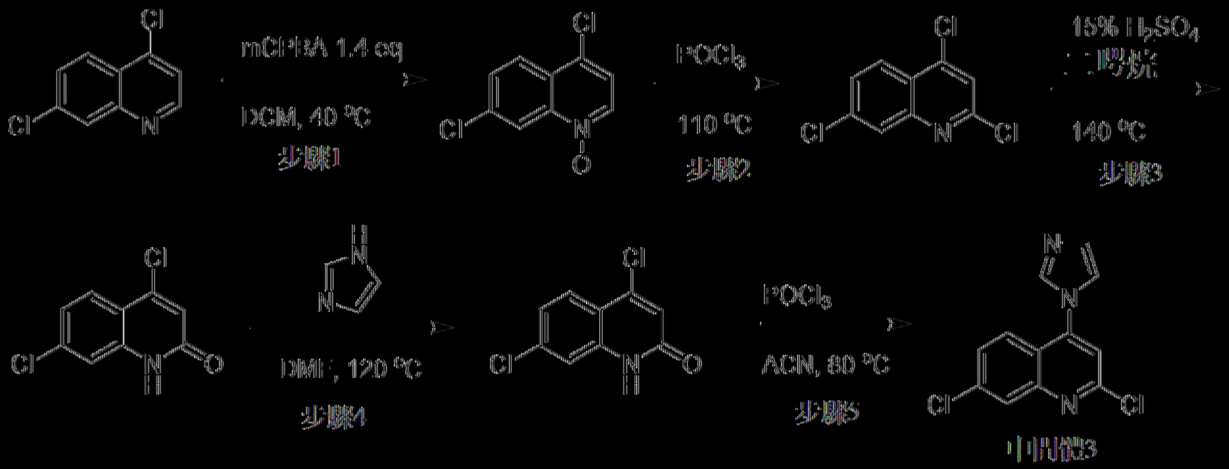
中間體2

【0502】 步驟1：製備7,8-二氯-4-(1H-吡唑-4-基)喹啉-2(1H)-酮. 將4,7,8-三氯喹啉-2(1H)-酮(300 mg，1.21 mmol)、Na_2CO_3 (321 mg，3.03 mmol)及$Pd(PPh_3)_4$ (140 mg，0.121 mmol)添加至圓底燒瓶中並用二噁烷(10 mL)及水(5 mL)稀釋。在冰浴中冷卻混合物，並抽真空且用N_2吹掃三次。製備硼酯2.1 (703 mg，3.62 mmol)於二噁烷(3 mL)中之溶液並脫氣。在N_2下，經由注射器將在二噁烷中之硼酯2.1的一部分(1 mL，1.0 eq)添加至反應混合物中。在110℃下，將反應混合物加熱2小時，同時LC-MS顯示約50%之1.7消耗。在N_2下，添加在二噁烷中之硼酯2.1的其餘部分。在加熱且再攪拌3小時後，化合物1.7消耗(藉由LC-MS確認)。在冷卻至室溫後，再用水(20 mL)稀釋反應混合物。藉由離心機或過濾收集沈澱之固體

並用DCM (5 mL × 3)洗滌。在真空乾燥後，得到標題化合物(2.2, 315 mg)。MS: $[M+1]^+$ 280。

【0503】 步驟2：製備2,7,8-三氯-4-(1H-吡唑-4-基)喹啉(中間體2). 將步驟1之產物(208 mg，0.743 mmol)懸浮於ACN (2.5 mL)及$POCl_3$ (0.42 mL)中。在80℃下，將所得混合物加熱3小時或直至不到10%之化合物2.2殘留(藉由LC-MS確認)。在真空濃縮後，在冰浴中冷卻殘餘物並藉由5% NaOH小心地中和至pH 7，沈澱得到呈黃色固體狀之中間體2。藉由離心機或過濾收集固體並用水(15 mL × 3)洗滌。真空乾燥後，得到中間體2 (180 mg)。MS: $[M+1]^+$ 298。^{1}HNMR (400 MHz, DMSO-D6) δ: 8.8.25-8.30 (m, 3H), 7.84 (d, J = 9.2 Hz, 1H)及7.72 (s, 1H) ppm。

【0504】 製備2,7-二氯-4-(1H-咪唑-1-基)喹啉(中間體3).



【0505】 步驟1：製備4,7-二氯喹啉1-氧化物. 在室溫下，向4,7-二氯喹啉(20.0 g，101.5 mmol)於DCM (400mL)中之溶液中分數份添加3-氯過氧苯甲酸(mCPBA) (28.8 g，85%純度，142.1 mmol)並在40℃下將所得溶液攪拌2小時。接著，用$NaHCO_3$水溶液(2 × 50 mL)、$Na_2S_2O_3$水溶液(100 mL × 2)洗滌溶液，經無水Mg_2SO_4乾燥，過濾，減壓濃縮，並在高真空下乾燥，得到呈白色固體狀之標題產物(21 g)。MS: $[M+1]^+$ 214.1。

【0506】 步驟2：製備2,4,7-三氯喹啉. 在室溫下，將步驟1之產物

(20.0 g，1.0 eq)溶解於$POCl_3$ (74 mL)並在110℃下，將所得溶液攪拌2小時。減壓濃縮混合物並用10% NaOH溶液將其調至pH 9。收集沈澱，用水洗滌並乾燥，得到呈灰白色固體狀之標題化合物(18 g，產率83%)。MS: $[M+1]^+$ 234.0。^1H NMR (400 Hz, $CDCl_3$): δ 8.148-8.126 (d, *J* = 8.8 Hz, 1H), 8.033 (s, 1H), 7.622-7.596 (dd, *J* = 1.4 Hz, 1H), 7.510 (s, 1H) ppm。

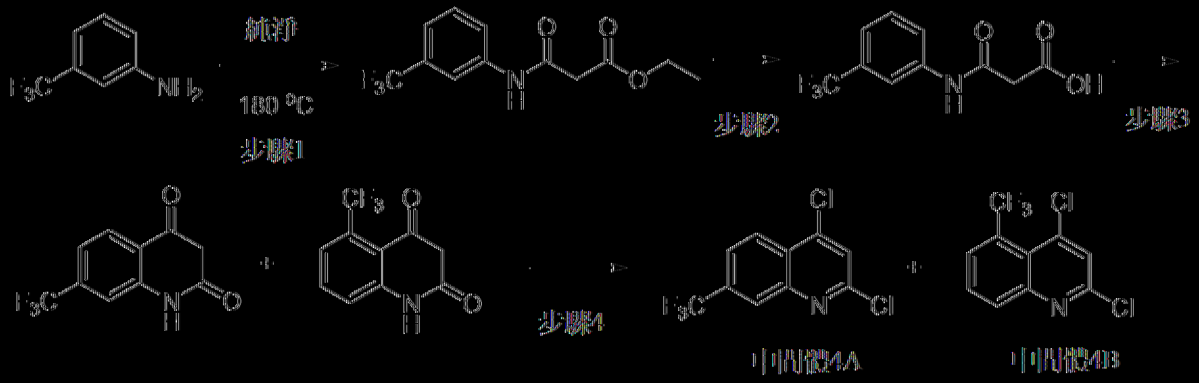
【0507】 步驟3：製備4,7-二氯喹啉-2(1H)-酮. 在25℃下，向步驟2之產物(5.0 g，1.0 eq)於1,4-二噁烷(125 mL)中之溶液中添加15% H_2SO_4 (250 mL)。在140℃下，將所得混合物攪拌12小時。藉由過濾收集沈澱之固體，用水洗滌並乾燥，得到呈灰色固體狀之標題化合物(3.9 g)。MS: $[M+1]^+$ 214.1。^1H NMR (400 Hz, $CDCl_3$): δ 12.122 (s, 1H), 7.880-7.859 (d, *J* = 8.4 Hz, 1H), 7.406 (s, 1H), 7.368-7.343 (dd, *J* = 1.4 Hz, 1H), 6.865 (s, 1H) ppm。

【0508】 步驟4：製備7-氯-4-(1H-咪唑-1-基)喹啉-2(1H)-酮. 向4,7-二氯喹啉-2(1H)-酮(9.0 g，1.0 eq)於DMF (18 mL)中之溶液中添加咪唑(48.8 g，17 eq)。在120℃下攪拌21小時後，用ACN (100mL)稀釋反應混合物並攪拌0.5小時。收集沈澱之固體，用ACN洗滌並真空乾燥，得到呈灰色固體狀之粗標題化合物(6.7 g)。MS: $[M+1]^+$ 246.1。^1H NMR (400 MHz, DMSO): δ 12.19 (s, 1H), 8.09 (s, 1H), 7.65 (s, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.21 (s, 1H), 6.66 (s, 1H) ppm。

【0509】 步驟5：製備2,7-二氯-4-(1H-咪唑-1-基)喹諾酮(中間體3). 向化合物3.5 (5.0 g，1.0 eq)於ACN (50mL)中之溶液中添加$POCl_3$ (10 mL)並在80℃下將所得混合物攪拌0.5小時。真空濃縮混合物並在冰浴中小心地用5-10% NaOH溶液達到pH 7來淬滅殘餘物。收集沈澱之固體，用

水洗滌並真空乾燥，得到呈白色固體狀之中間體3 (4.1 g)。MS (ES): $[M+1]^+$ 264。^{1}H NMR (400 Hz, $CDCl_3$): δ 8.164 (s, 1H), 7.970 (s, 1H) ,7.786-7.763(d, *J* = 9.2 Hz, 1H), 7.631-7.608 (d, *J* = 9.2 Hz, 1H), 7.422 (s, 1H), 7.357 (s, 1H) ppm。

【0510】 製備2,4-二氯-7-(三氟甲基)喹啉(中間體4A)及2,4-二氯-5-(三氟甲基)喹啉(中間體4B).



【0511】 步驟1：3-側氧基-3-((3-(三氟甲基)苯基)胺基)丙酸. 攪拌3-(三氟甲基)苯胺(5.74 g)及丙二酸二乙酯(14.9 g)之混合物並在180℃下加熱4小時。將所得混合物溶解於MeOH (30 mL)及水(10 mL)中。在冰浴中冷卻溶液並用NaOH (7.1 g)處理。在室溫下攪拌2小時並在真空下移除MeOH後，再用水(60 mL)稀釋所得混合物並用濃HCl酸化到pH 1至2。用EtOAc (30 mL × 4)萃取後，將合併之有機層藉由鹽水洗滌且經Na_2SO_4乾燥。減壓蒸發EtOAc，得到呈油狀之4.3 (8.76 g)。MS: $[M+1]^+$ 276。

【0512】 步驟2：7-(三氟甲基)喹啉-2,4(1H,3H)-二酮4-4及5-(三氟甲基)喹啉-2,4(1H,3H)-二酮. 將純4.3 (8.76 g)懸浮於PPA (42 g)中並在130℃下加熱4小時。再用水(120 mL)稀釋所得混合物並用EtOAc (40 mL × 3)萃取水層。用鹽水洗滌合併之有機層且經Na_2SO_4乾燥。減壓蒸發，得到呈黏性固體狀的兩種標題區位異構體之混合物(5.99 g)。MS: $[M+1]^+$ 230。

【0513】 步驟3：2,4-二氯-7-(三氟甲基)喹啉(中間體4A)及2,4-二氯-5-(三氟甲基)喹啉(中間體4B). 將來自前一步驟的4.4及4.5之混合物(5.99 g)懸浮於$POCl_3$中，攪拌，並在回流下加熱3小時。減壓移除$POCl_3$並小心地用冰淬滅所得混合物。用EtOAc (30 mL × 3)萃取水層並將合併之有機層用鹽水洗滌且經Na_2SO_4乾燥。進行管柱層析法，用0至50%之DCM/己烷梯度溶離，得到中間體4A (3.1 g)及中間體4B (0.59 g)。4A：MS [M+1]: 266.1。^{1}HNMR (400 MHz, CD3Cl) δ: 8.38 (s, 1H), 8.37 (d, J = 8 Hz, 1H), 7.86 (dd, J =8及4 Hz)及7.66 (s, 1H) ppm。4B: MS [M+1]: 266.1。^{1}HNMR (400 MHz, CD3Cl) δ: 8.29 (d, J = 8Hz, 1H), 8.18 (d, J = 8 Hz, 1H), 7.85 (t, J =8 Hz)及7.72 (s, 1H) ppm。

【0514】 遵循以上製備中間體1及4之程序，製備以下中間體。

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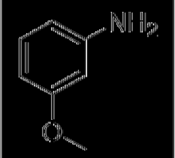
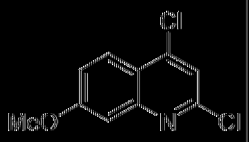
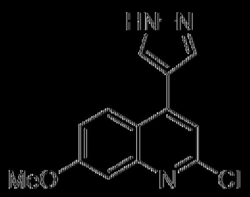
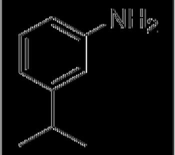
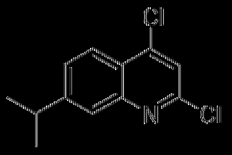
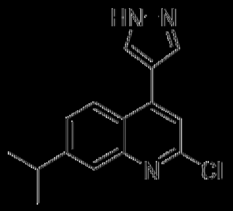
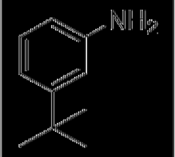
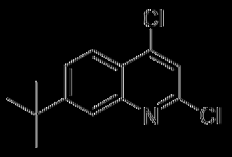
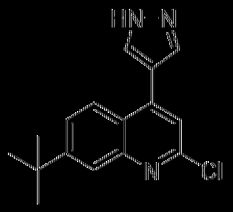
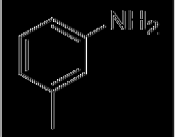
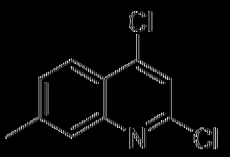
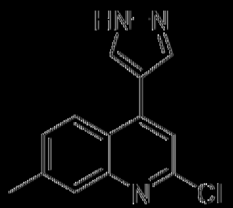
	5A		228	5B		260
	6A		240	6B		272
	7A		254	7B		286
	8A		212	8B		244

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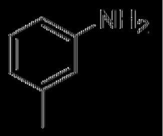
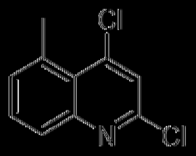
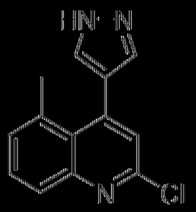
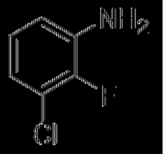
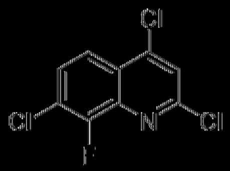
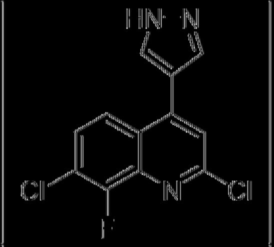
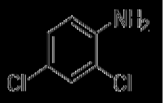
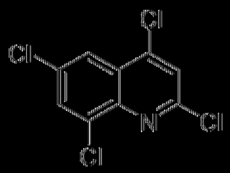
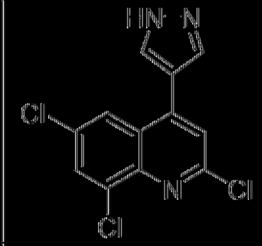
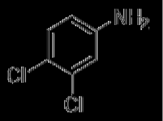
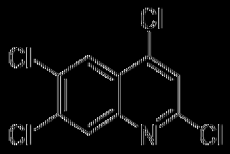
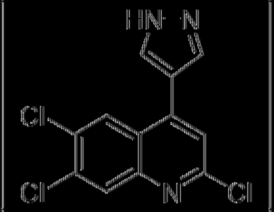
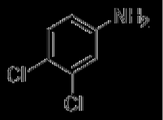
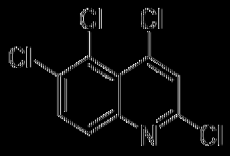
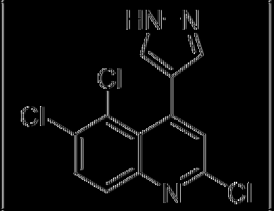
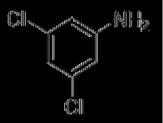
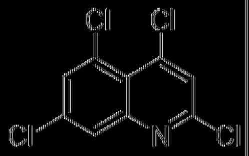
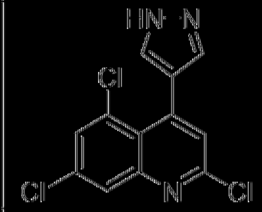
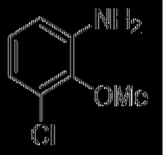
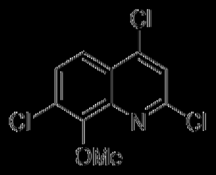
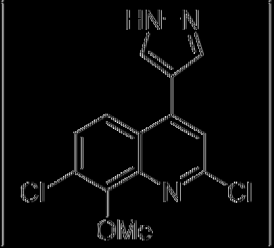
	9A		212	9B		244
	10A		250	10B		282
	11A		266	11B		298
	12A		266	12B		298
	13A		266	13B		298
	14A		266	14B		298
	15A		262	15B		294

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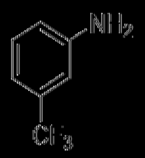
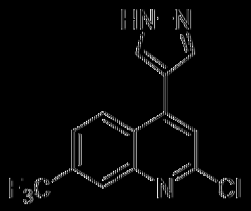
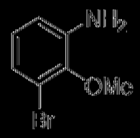
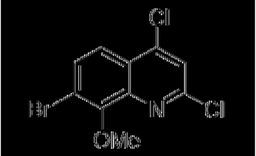
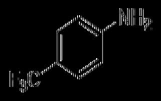
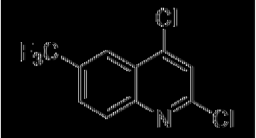
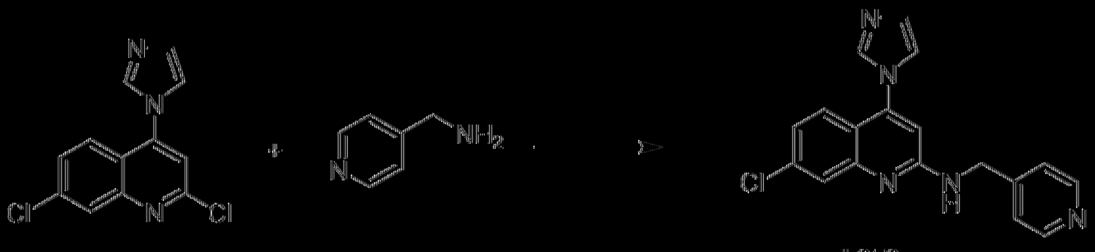
	-	-	-	16		298
	17		306	-	-	-
	18		266	-	-	-

實例1：合成7-氯-4-(1H-咪唑-1-基)-N-(吡啶-4-基甲基)喹啉-2-胺(I-353)



I-353

【0515】 向2,7-二氯-4-(1H-咪唑-1-基)喹啉(132 mg，0.5 mmol)於DMF (2 mL)中之溶液中添加吡啶-4-基甲胺(0.15 mL，1.5 mmol)。在120℃下將溶液劇烈攪拌3小時。冷卻至室溫後，藉由蒸發移除溶劑，得到粗品。將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(115 mg，68%產率)。MS: [M+1]$^+$ 336.1。

【0516】 以下化合物基本上藉由與以上關於製備I-353所描述相同的方法製備。

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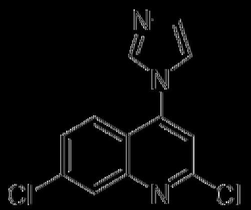
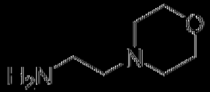
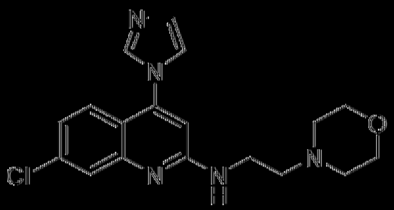
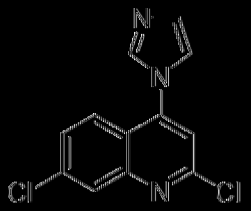
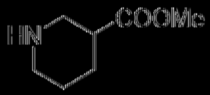
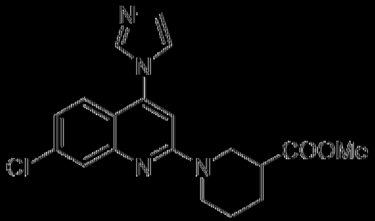
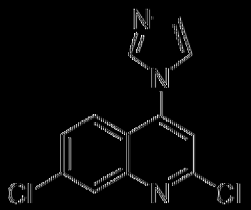
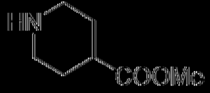
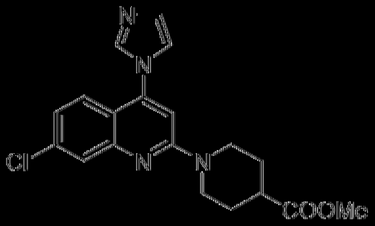
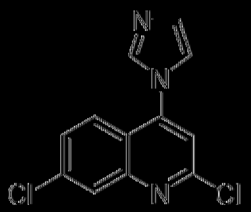
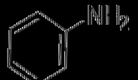
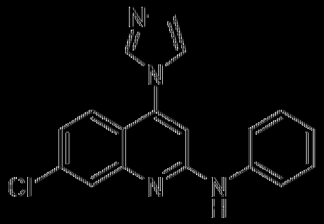
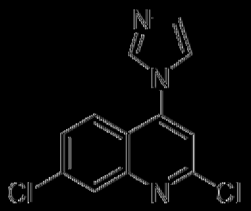
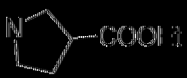
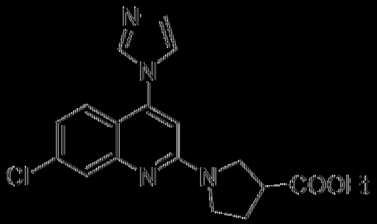
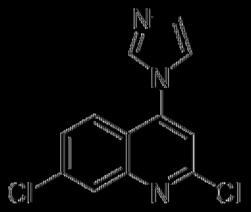
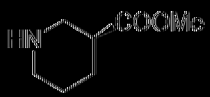
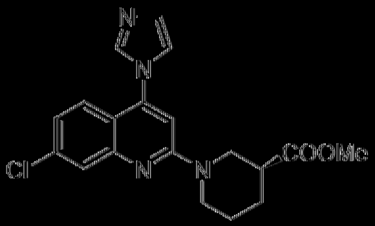
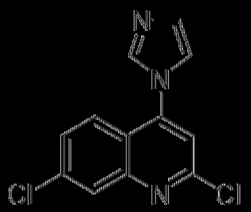
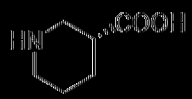
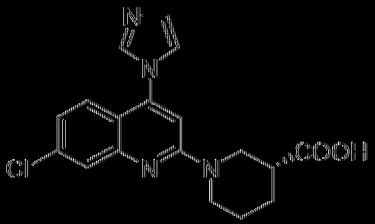
I-354				358
I-126				371
I-131				371
I-355				321
I-447				371
I-356				371
I-357				357

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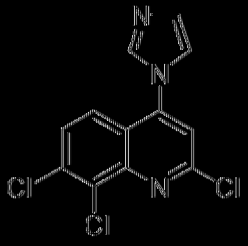
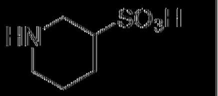
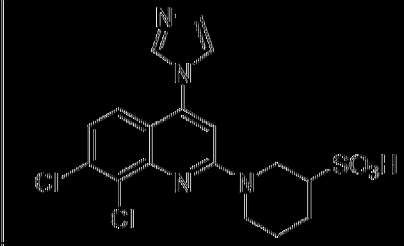
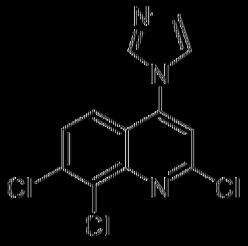
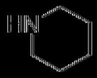
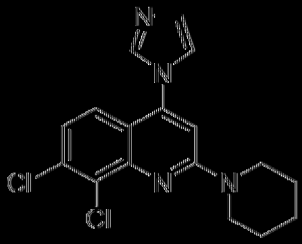
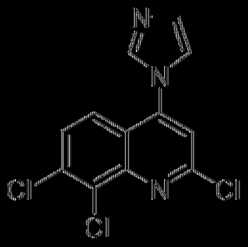
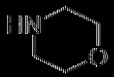
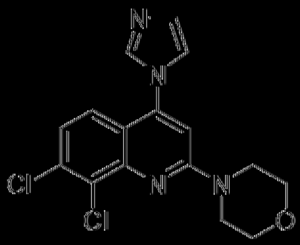
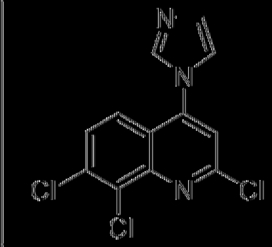
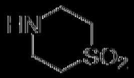
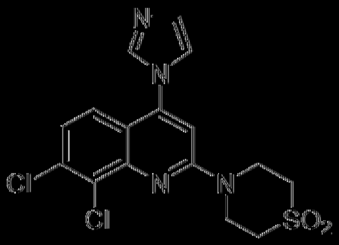
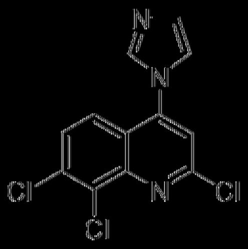
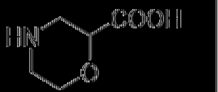
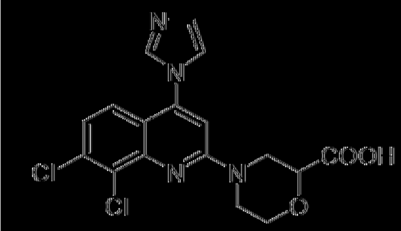
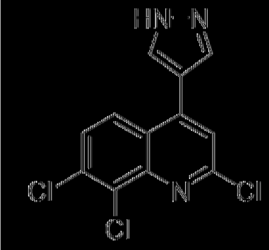
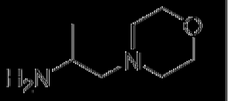
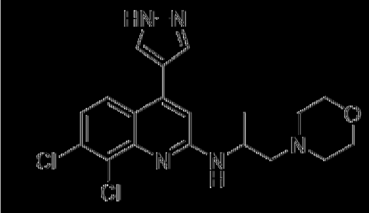
I-115				427
I-121				347
I-95				349
I-87				397
I-91				393
I-211				406

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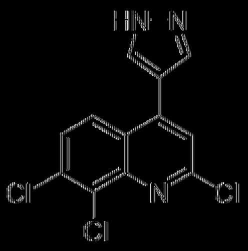
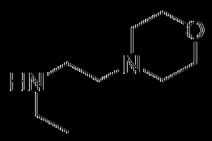
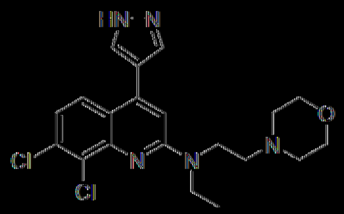
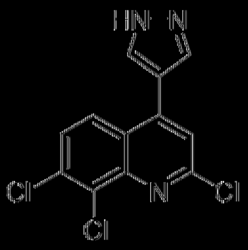
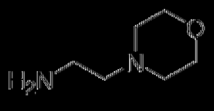
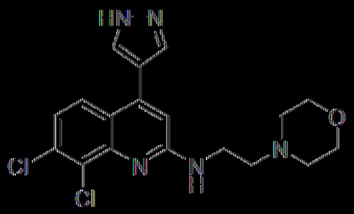
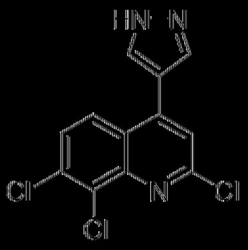
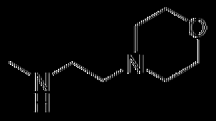
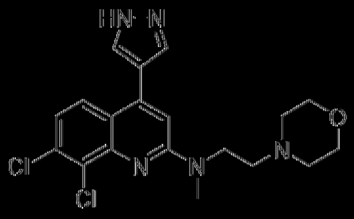
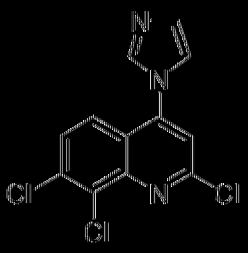
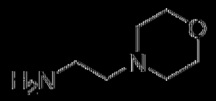
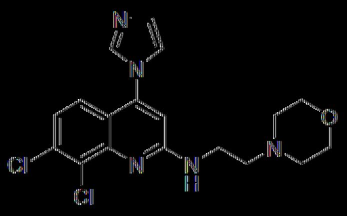
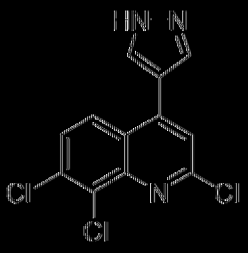
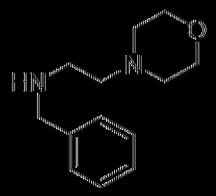
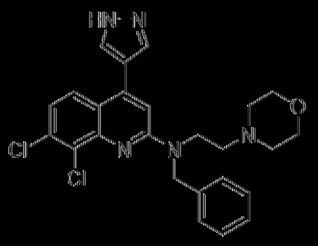
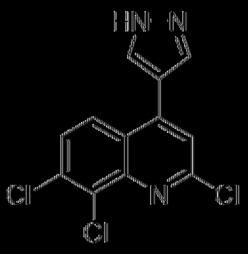
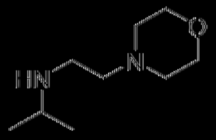
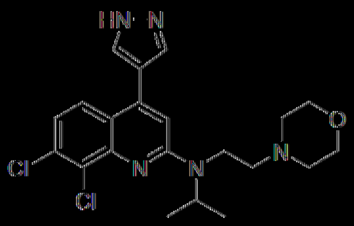
I-212				420
I-213				392
I-214				406
I-215				392
I-216				482
I-368				434

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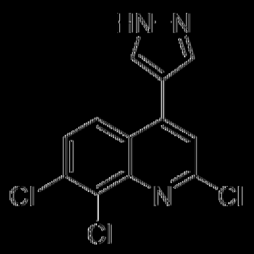
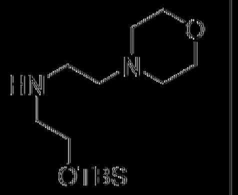
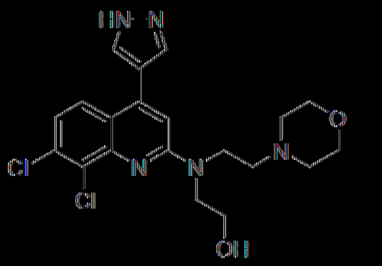
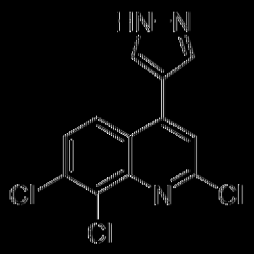
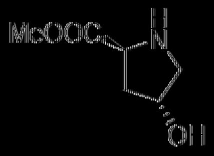
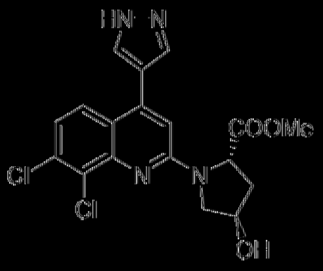
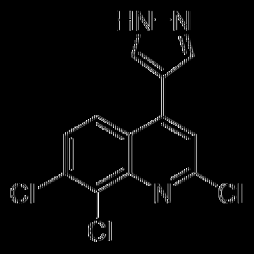
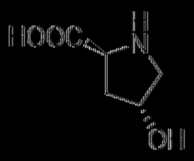
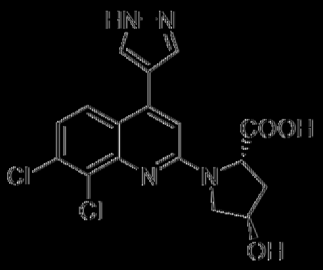
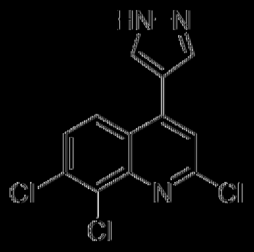
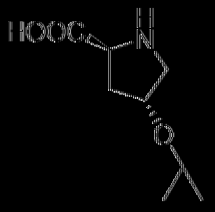
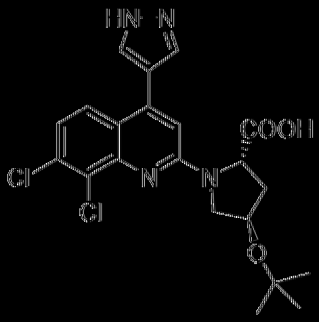
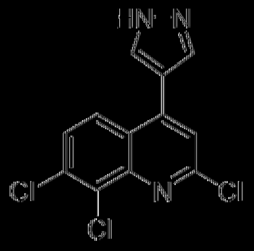
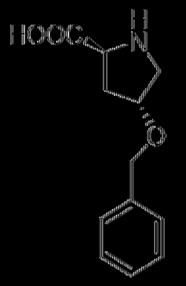
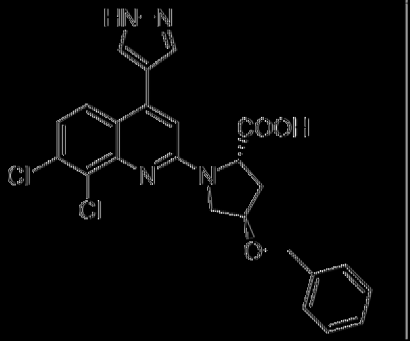
I-218				436
I-434				407
I-433				393
I-437				449
I-438				483

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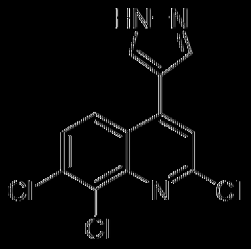
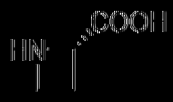
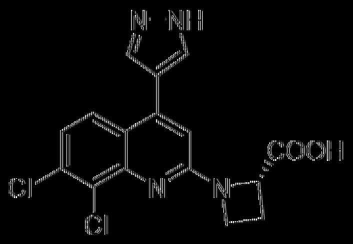
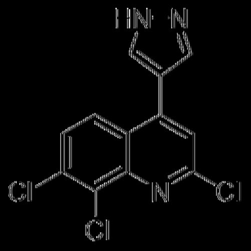
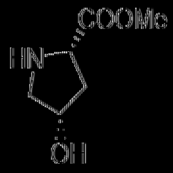
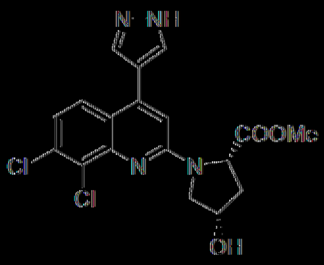
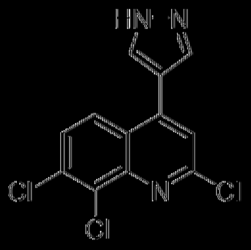
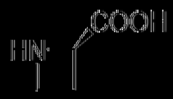
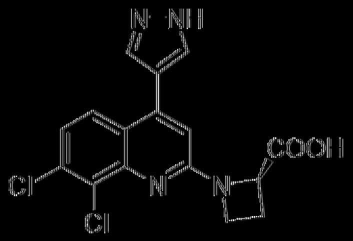
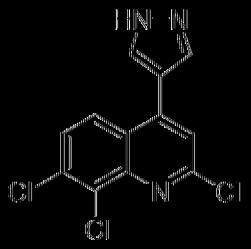
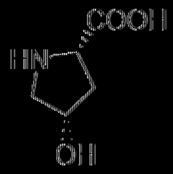
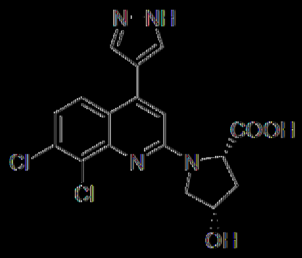
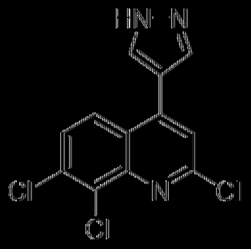
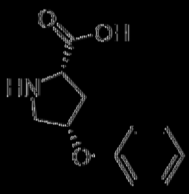
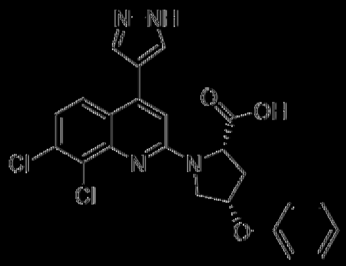
I-362				363
I-432				407
I-359				363
I-431				393
I-360				469

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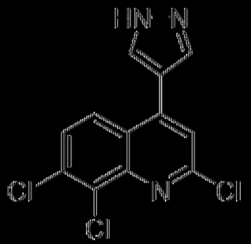
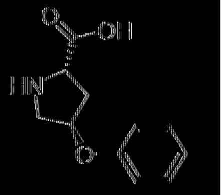
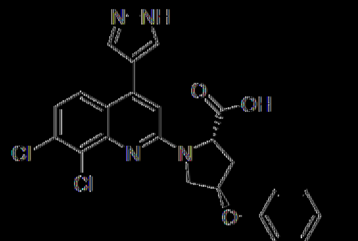
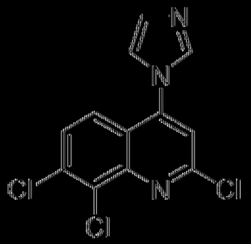
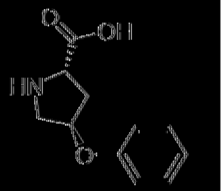
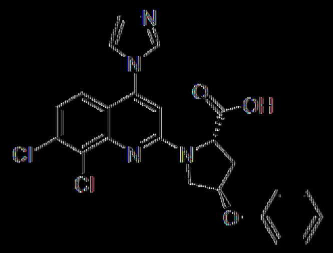
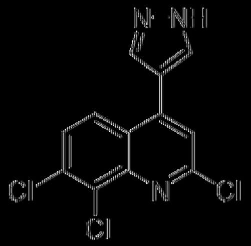
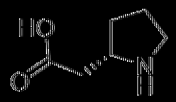
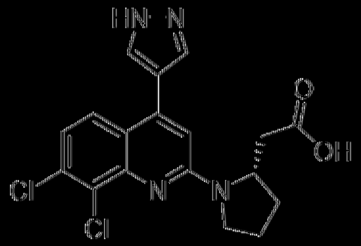
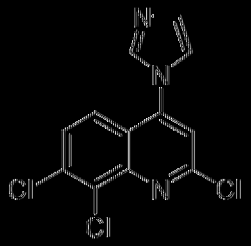
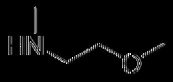
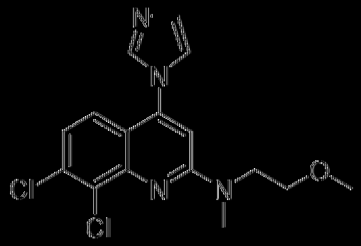
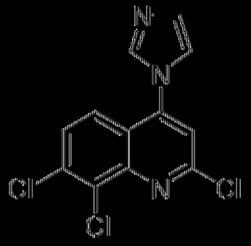
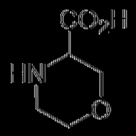
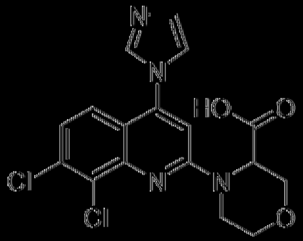
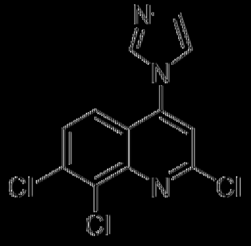
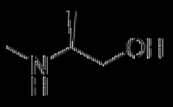
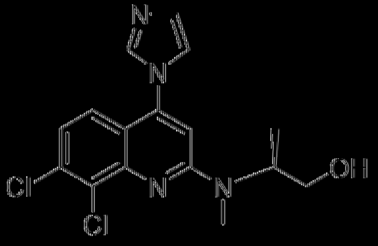
I-361				469
I-362				469
I-444				391
I-244				351
I-92				393
I-241				351

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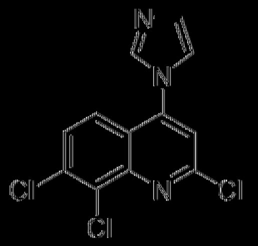
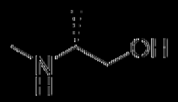
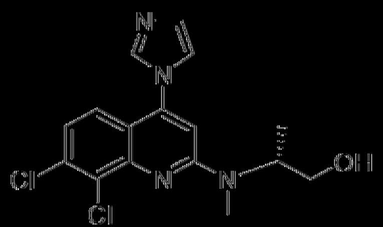
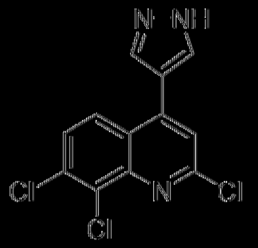
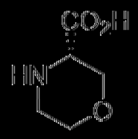
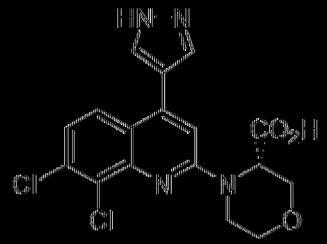
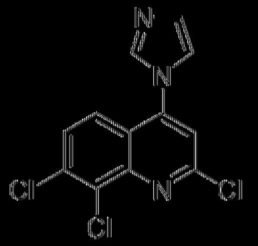
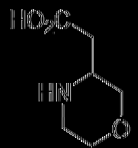
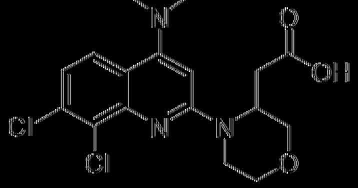
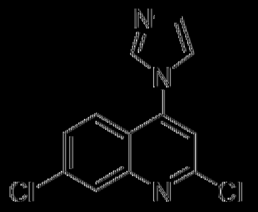
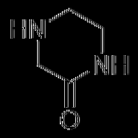
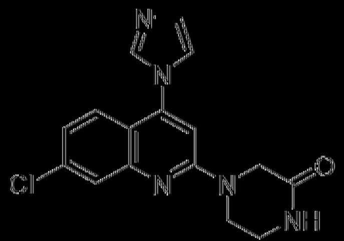
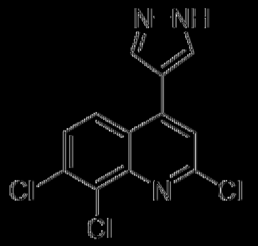
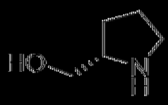
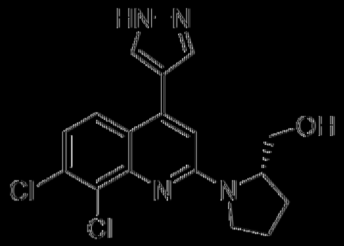
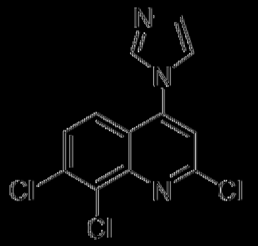
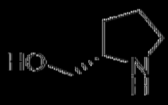
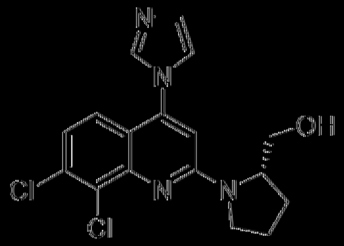
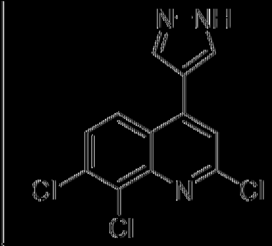
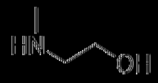
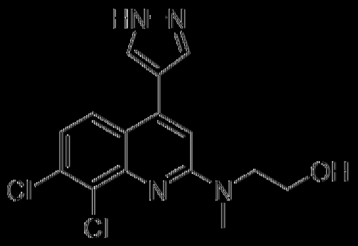
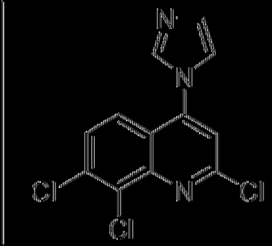
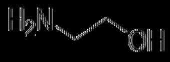
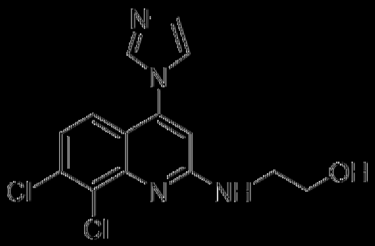
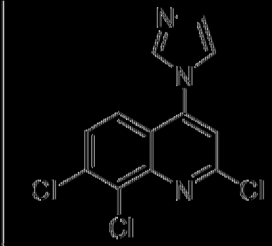
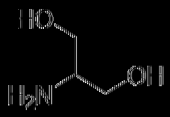
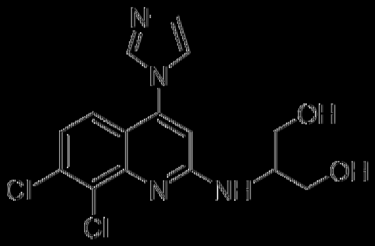
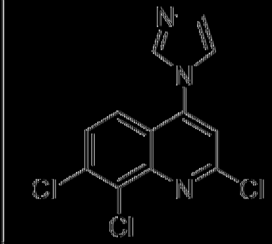
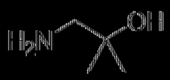
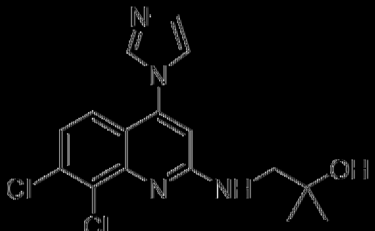
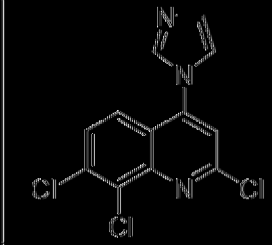
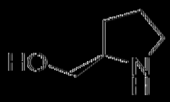
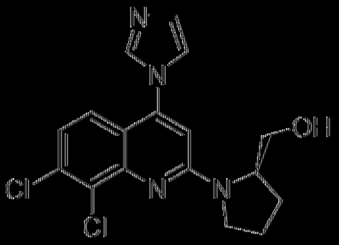
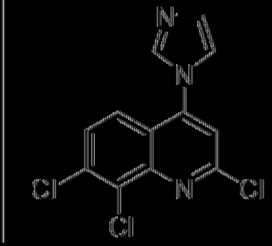
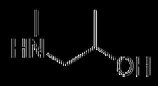
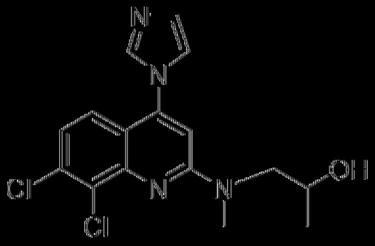
I-242				351
I-93				393
I-94				407
I-85				328
I-138				363
I-139				363

I-#	起始材料		結構	MS [M+1]+
I-240				337
I-239				323
I-249				353
I-245				349
I-141				363
I-243				351

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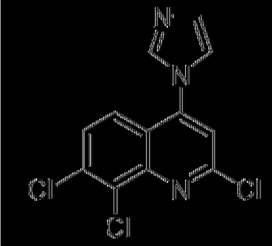
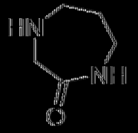
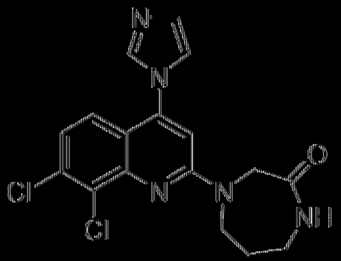
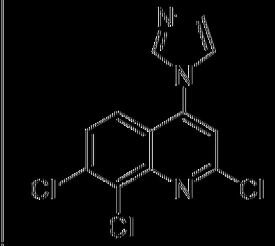
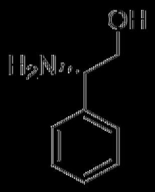
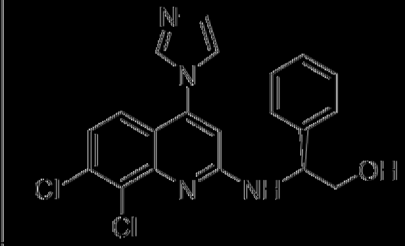
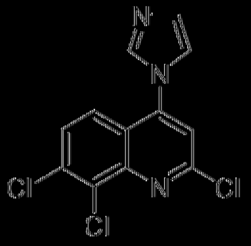
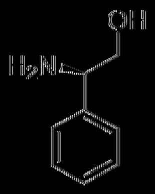
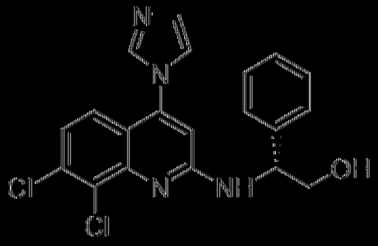
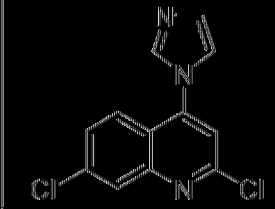
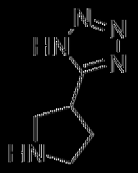
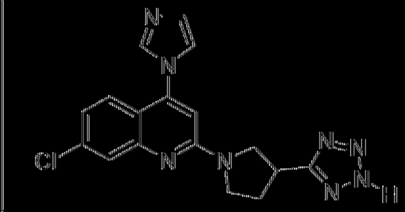
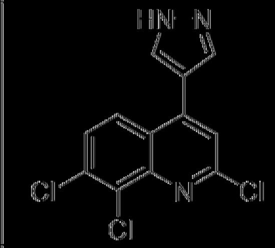
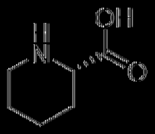
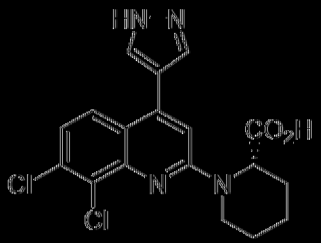
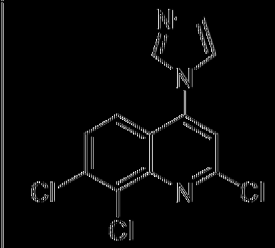
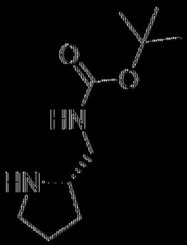
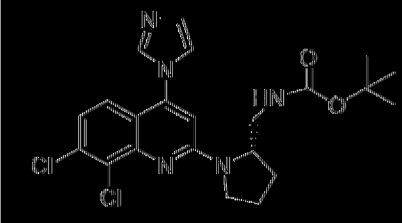
I-86				376
I-246				399
I-247				399
I-155				367
I-128				391
I-152				462

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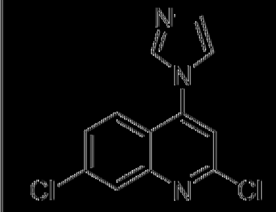
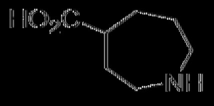
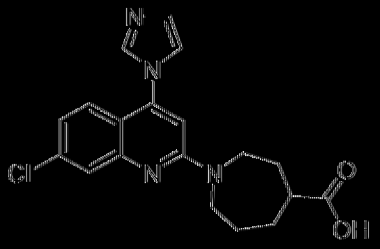
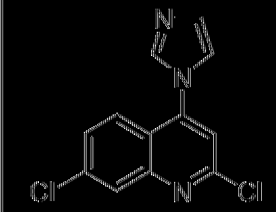
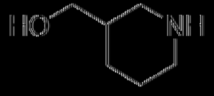
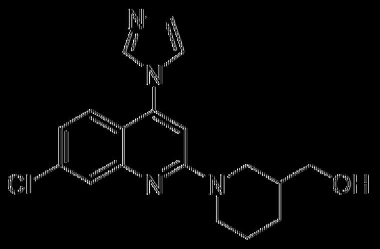
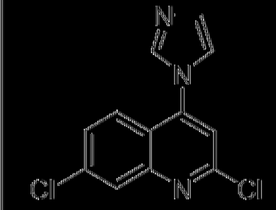
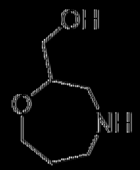
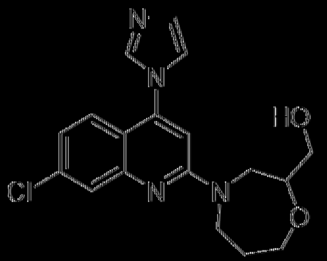
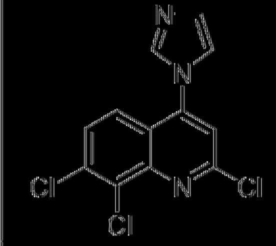
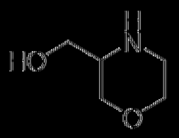
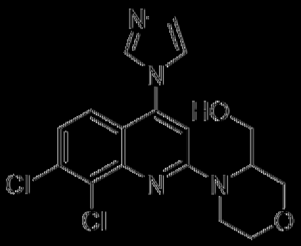
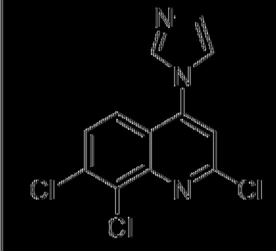
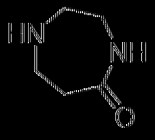
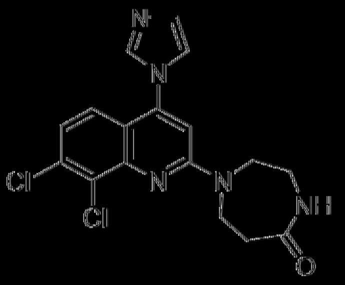
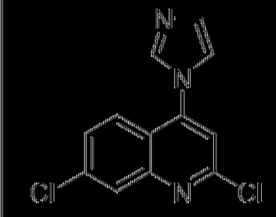
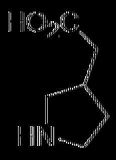
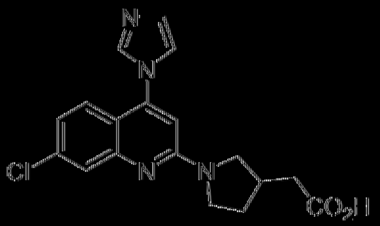
I-363				371
I-140				343
I-99				359
I-97				379
I-88				342
I-446				357

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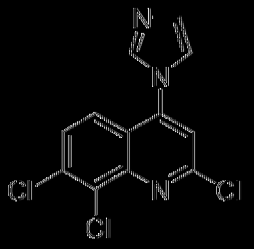
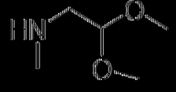
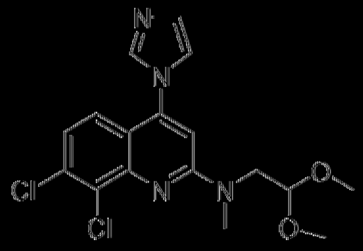
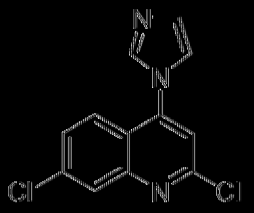
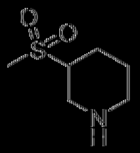
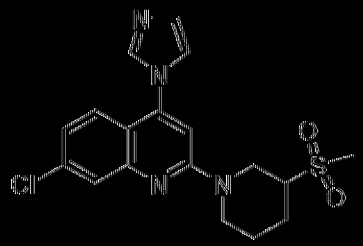
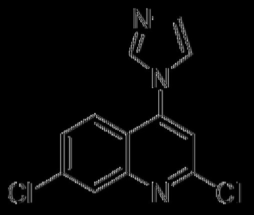
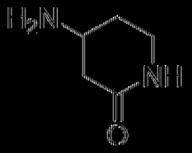
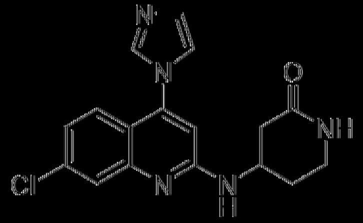
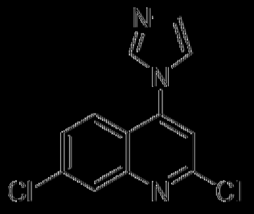
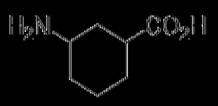
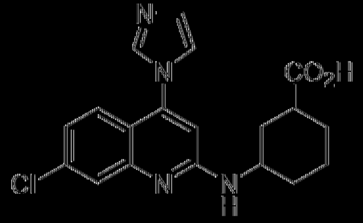
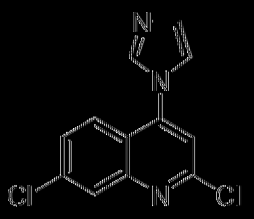
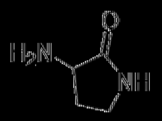
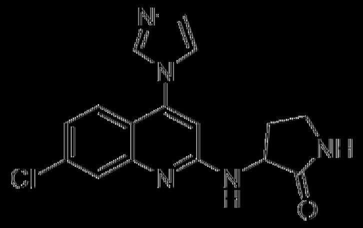
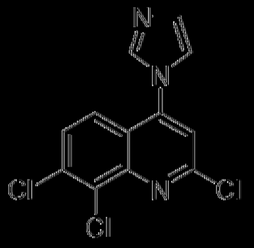
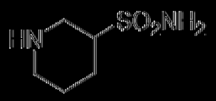
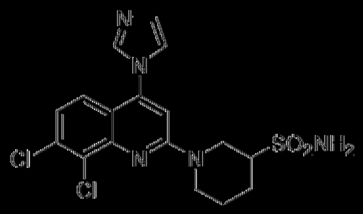
I-364				381
I-117				391
I-365				342
I-366				371
I-367				328
I-116				426

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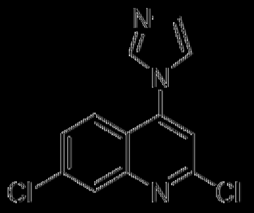
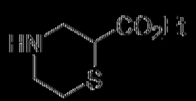
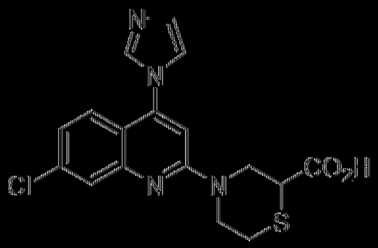
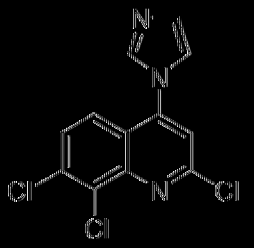
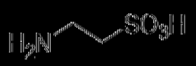
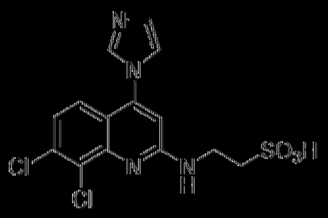
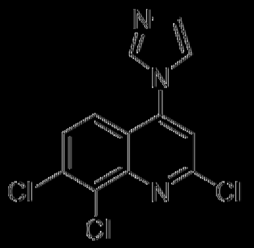
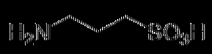
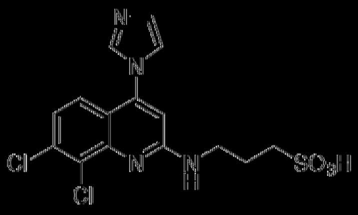
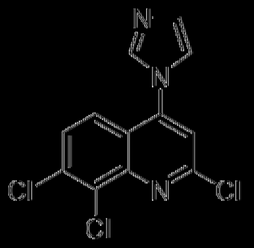
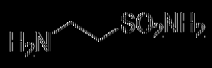
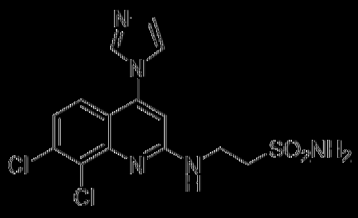
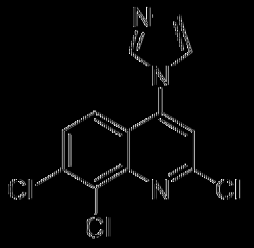
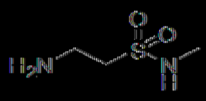
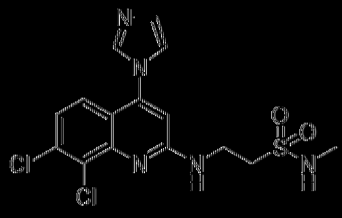
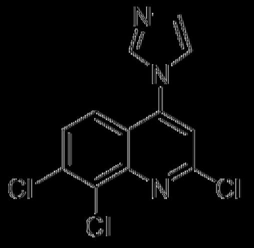
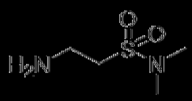
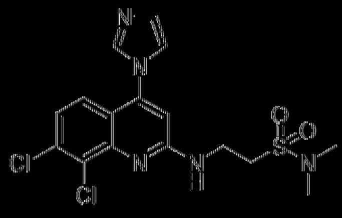
I-89				375
I-158				387
I-160				401
I-200				386
I-201				400
I-202				414

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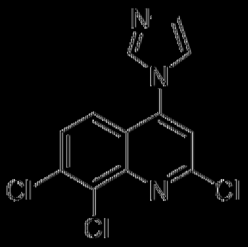
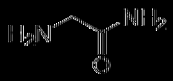
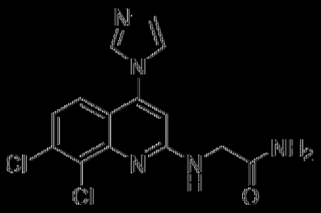
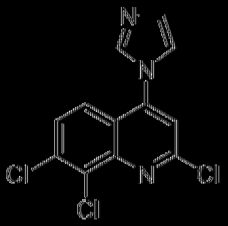
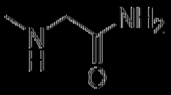
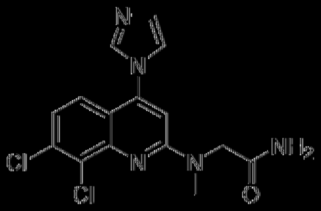
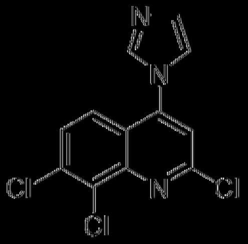
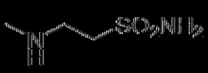
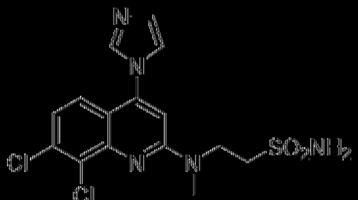
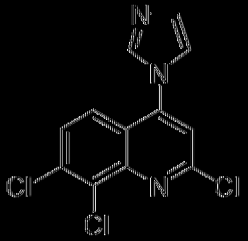
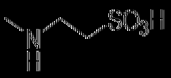
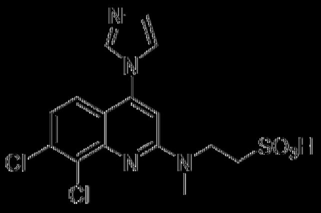
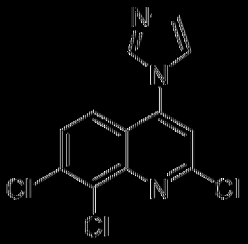
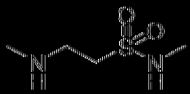
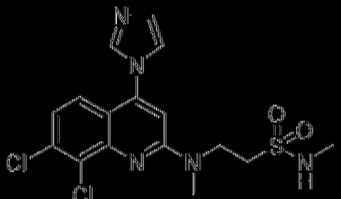
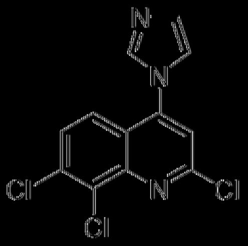
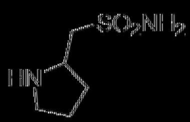
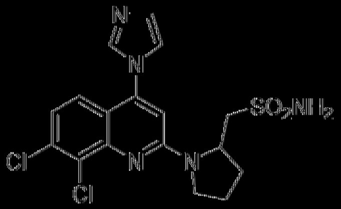
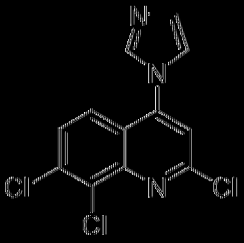
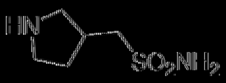
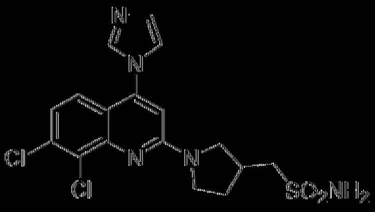
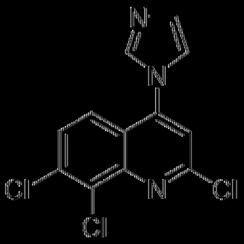
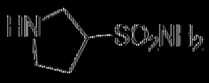
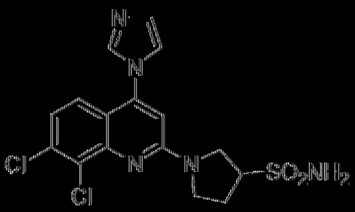
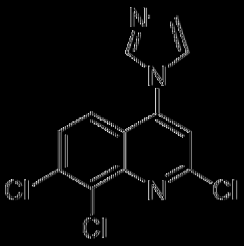
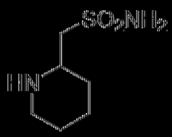
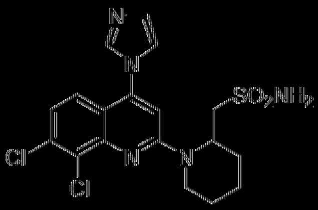
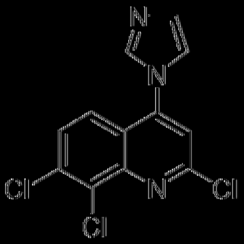
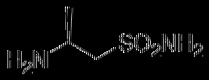
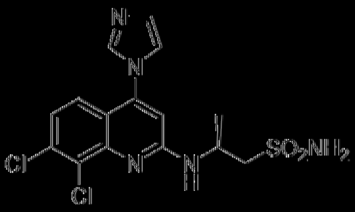
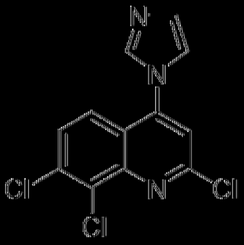
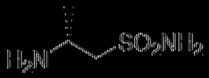
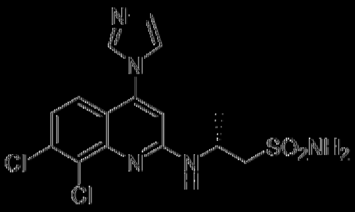
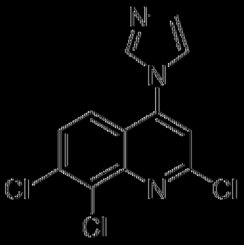
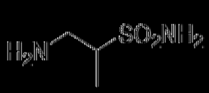
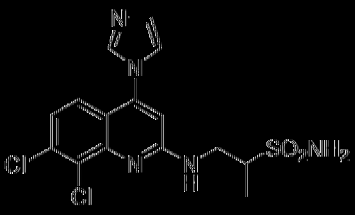
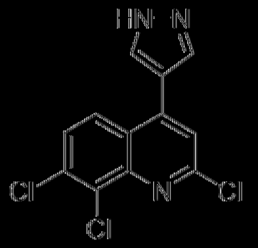
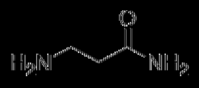
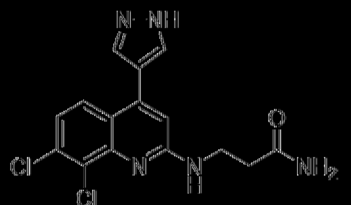
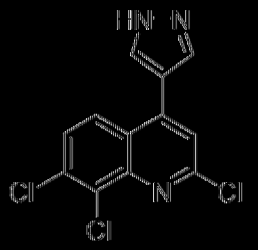
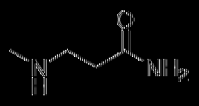
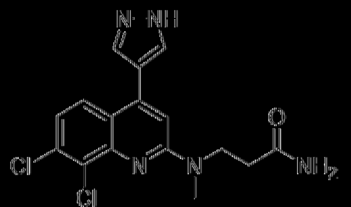
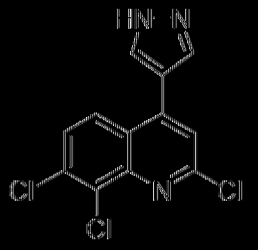
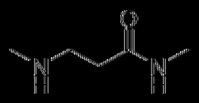
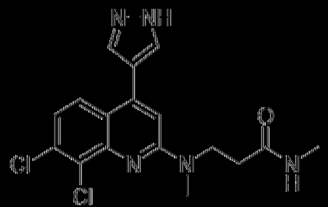
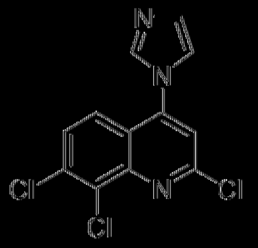
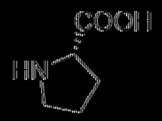
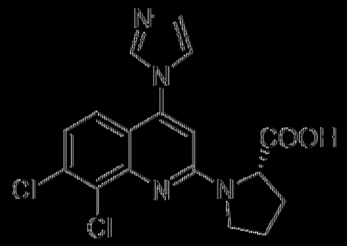
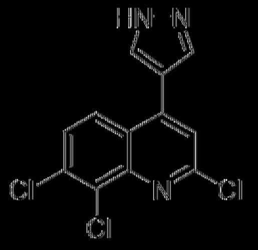
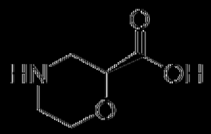
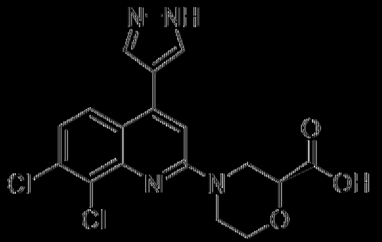
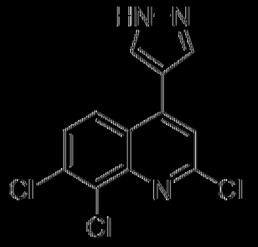
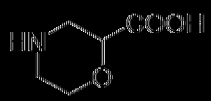
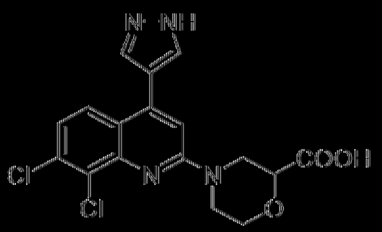
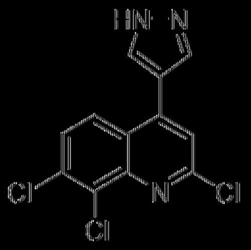
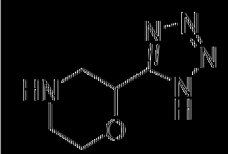
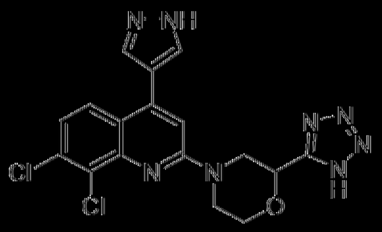
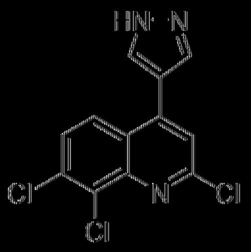
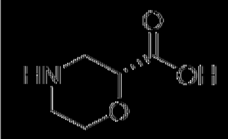
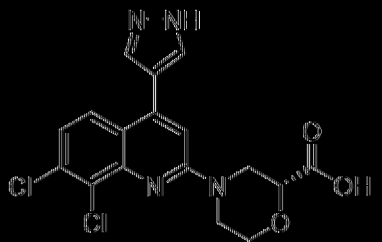
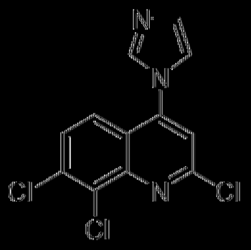
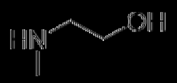
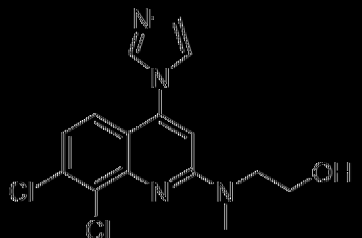
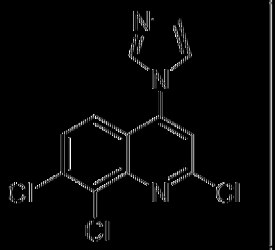
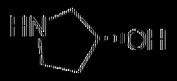
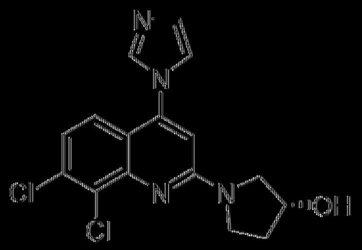
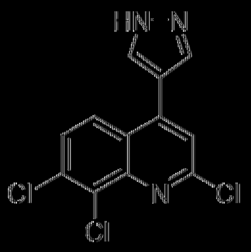
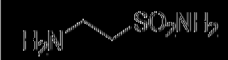
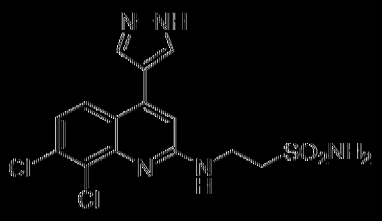
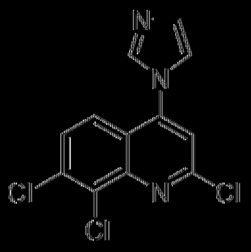
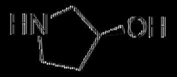
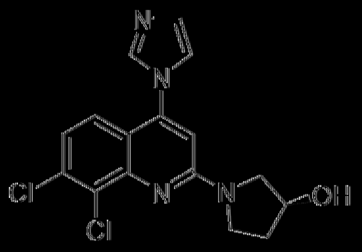
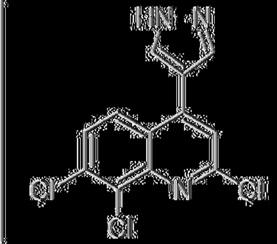
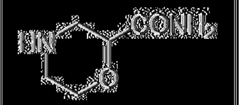
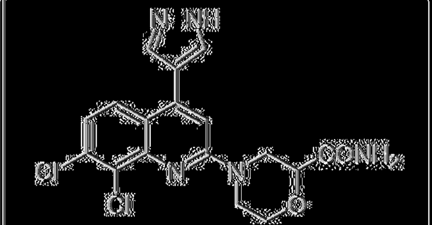
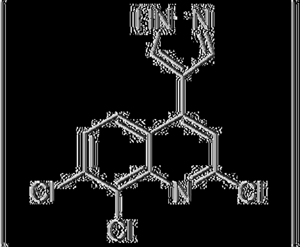
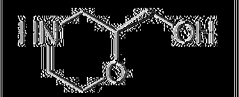
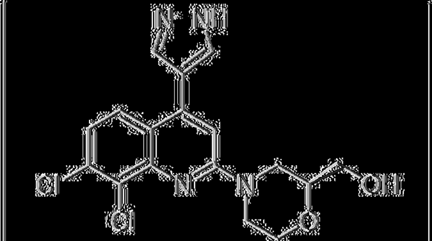
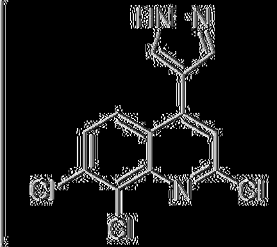
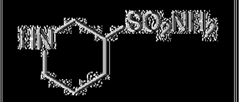
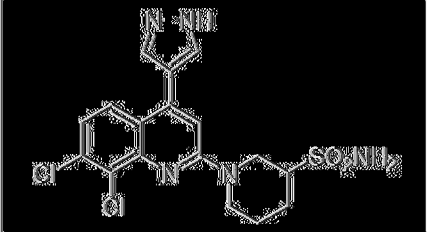
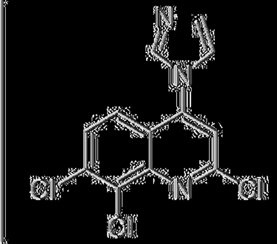
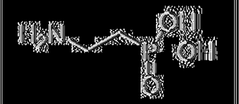
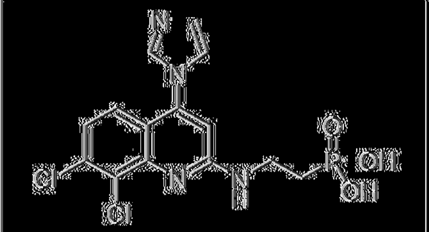
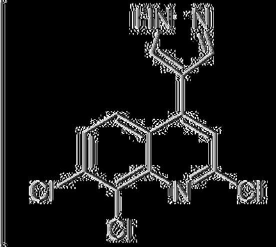
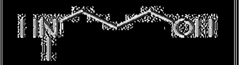
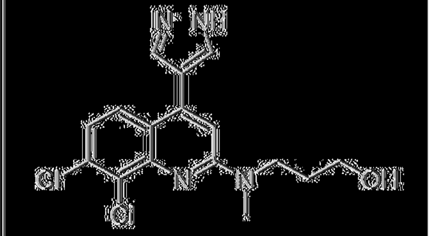
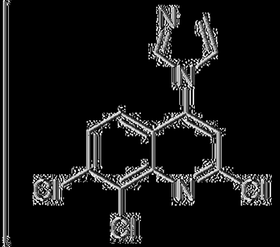
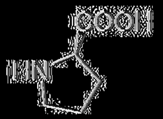
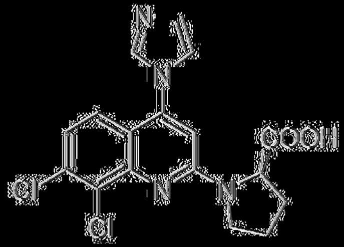
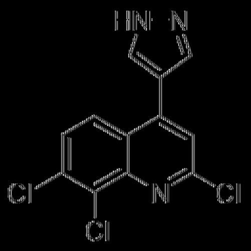
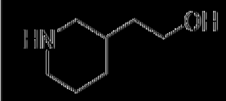
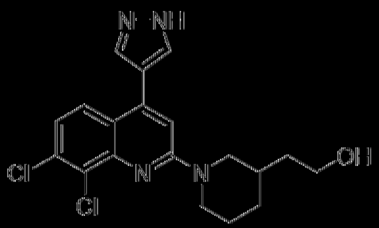
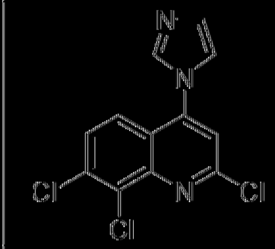
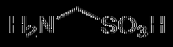
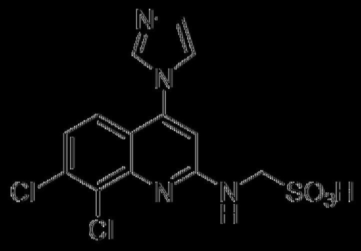
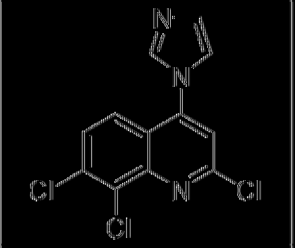
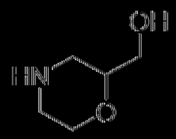
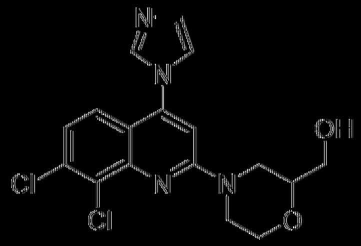
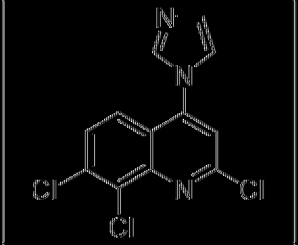
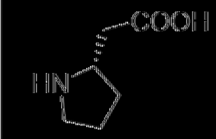
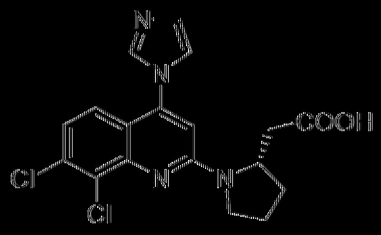
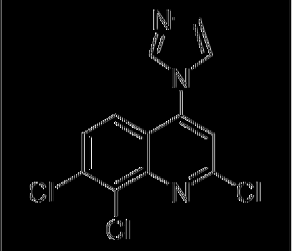
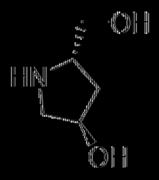
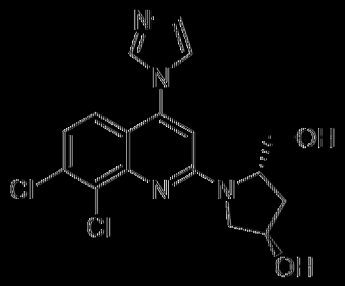
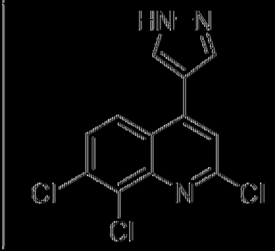
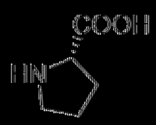
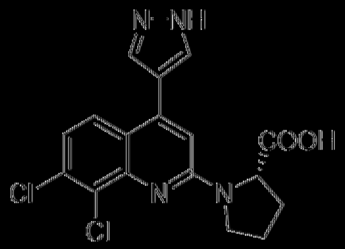
I-178				336
I-179				350
I-204				400
I-169				401
I-205				414
I-148				426

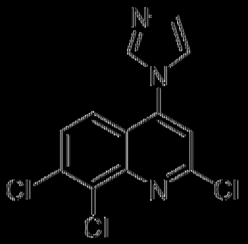
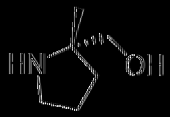
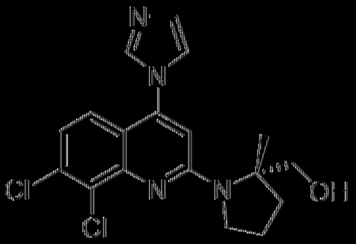
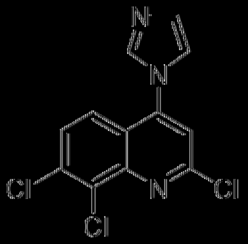
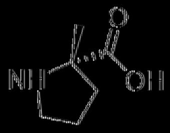
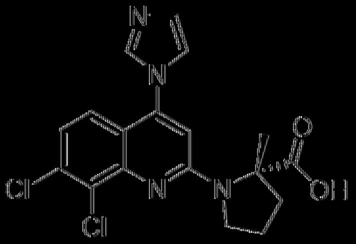
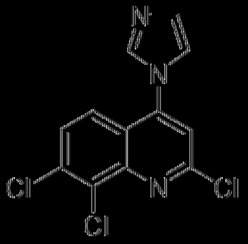
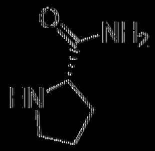
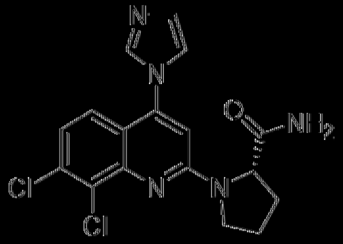
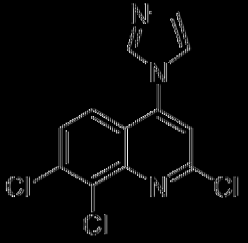
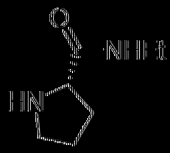
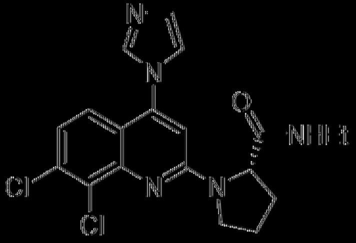
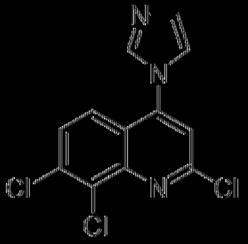
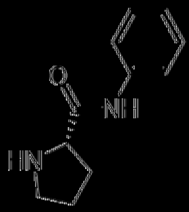
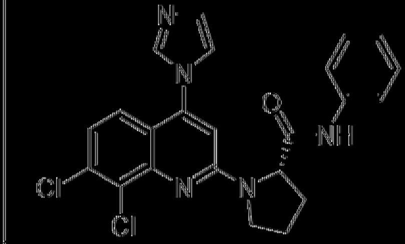
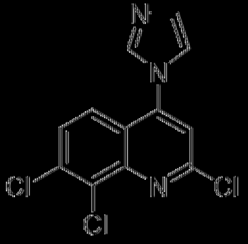
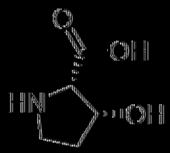
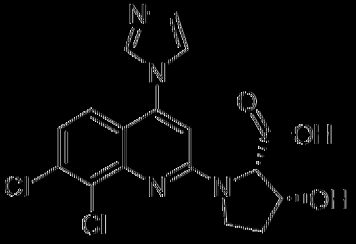
I-#	起始材料		結構	MS $[M+1]^+$
I-149				426
I-150				412
I-368				440
I-206				400
I-207				400
I-210				400

I-#	起始材料		結構	MS $[M+1]^+$
I-190				350
I-191				364
I-192				378
I-428				377
I-327				393
I-369				393

I#	起始材料		結構	MS [M+1]+
I-370				417
I-328				393
I-238				337
I-145				349
I-203				386
I-144				349

I-#	起始材料		結構	MS [M+1]+
I-371				392
I-372				379
I-373				426
I-250				387
I-248				351
I-374				377

I-#	起始材料		結構	MS [M+1]+
I-375				391
I-157				373
I-98				379
I-443				391
I-142				379
I-435				377

I-#	起始材料		結構	MS [M+1]+
I-143				377
I-436				391
I-448				376
I-461				404
I-348				452
I-429				393

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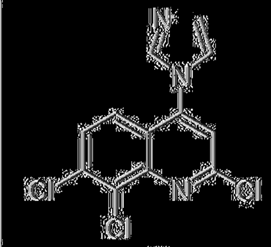
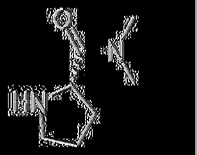
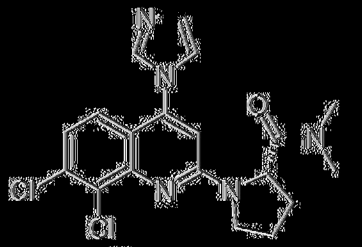
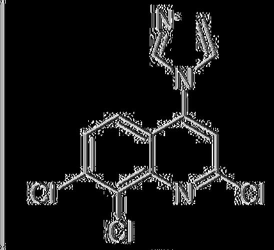
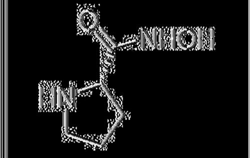
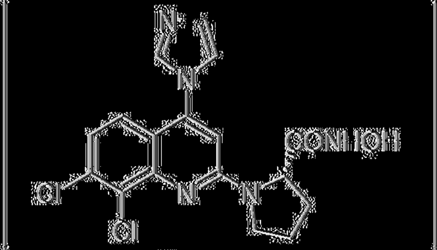
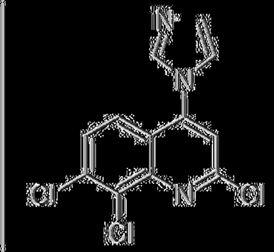
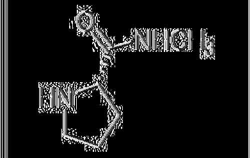
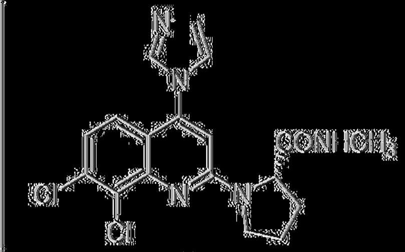
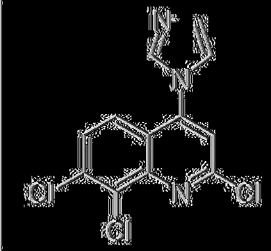
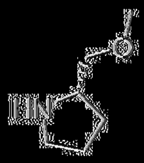
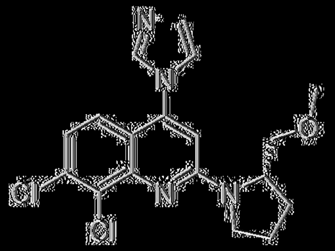
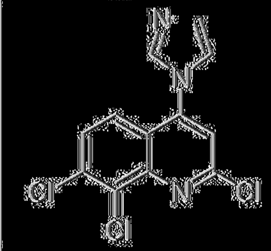
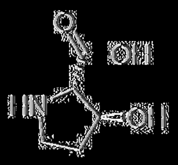
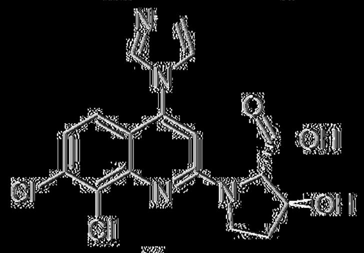
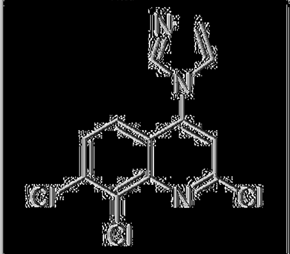
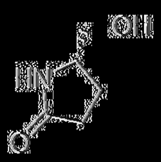
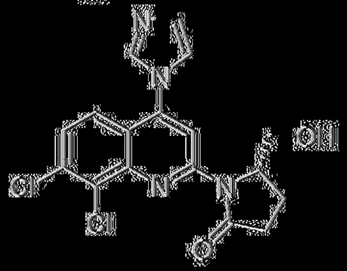
I-458				404
I-449				392
I-450				390
I-147				377
I-345				393
I-376				377

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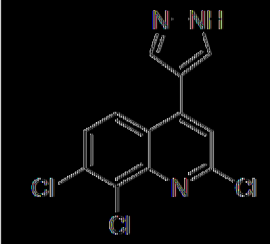
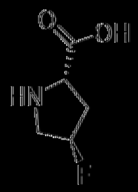
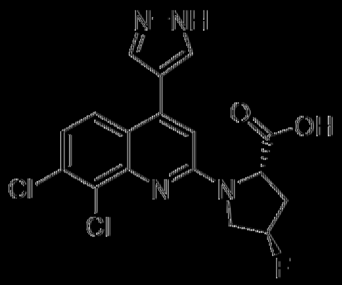
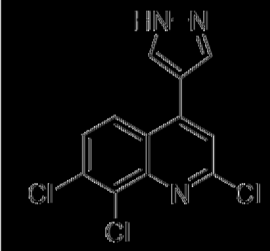
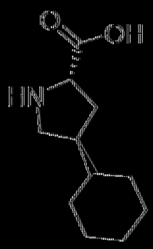
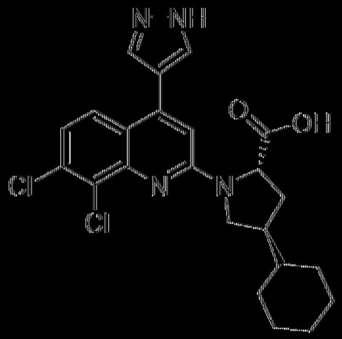
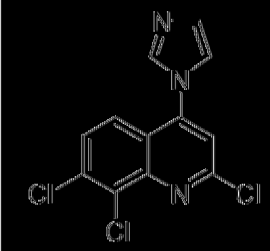
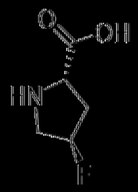
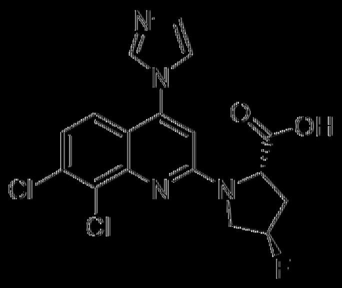
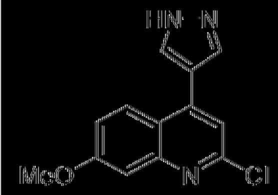
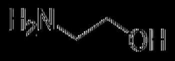
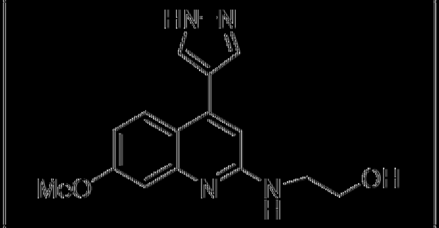
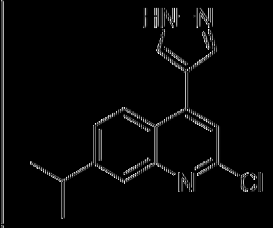
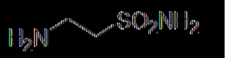
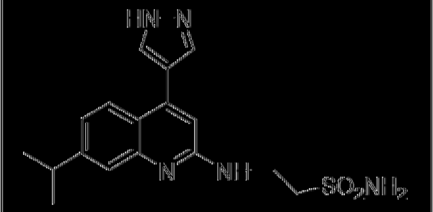
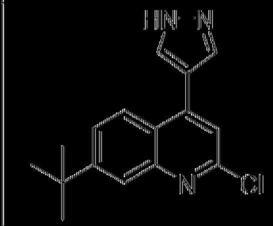
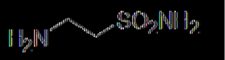
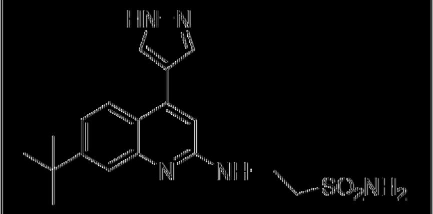
I-430				395
I-439				459
I-322				395
I-377				285
I-269				360
I-268				374

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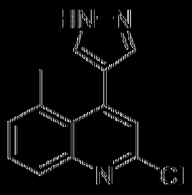
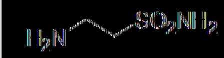
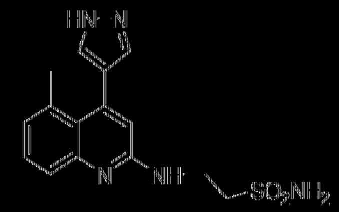
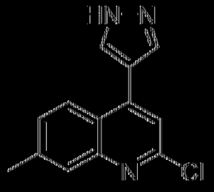
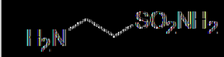
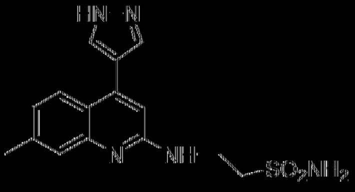
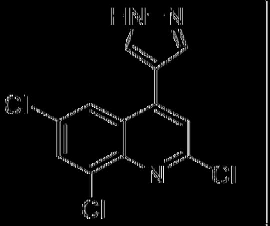
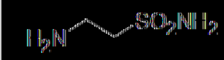
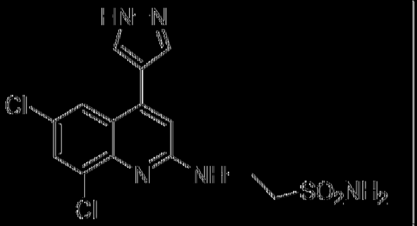
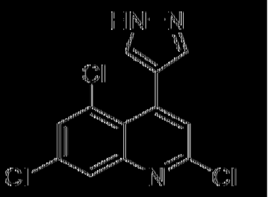
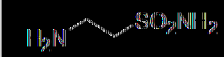
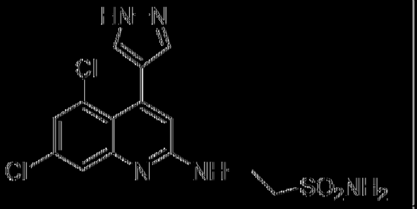
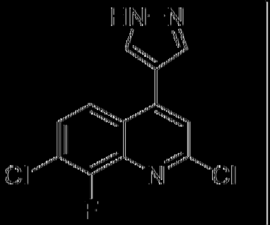
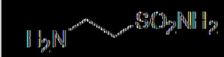
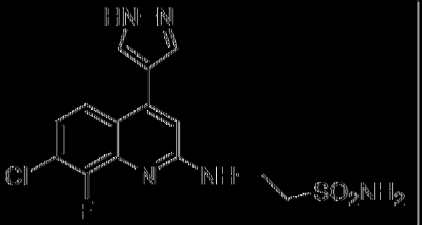
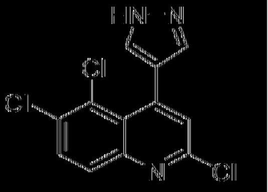
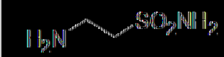
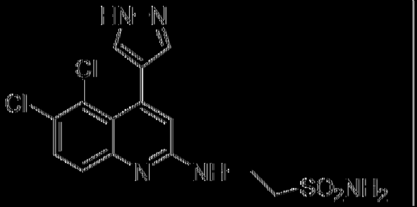
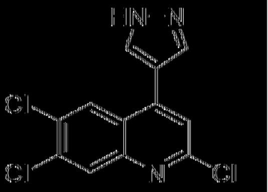
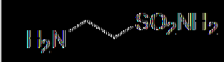
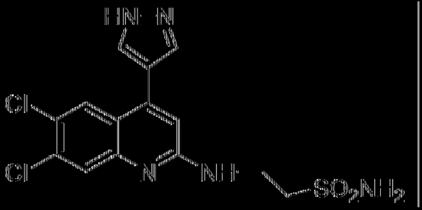
I-267				332
I-266				332
I-264				386
I-263				386
I-262				370
I-261				386
I-260				386

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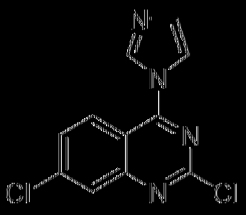
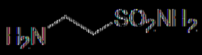
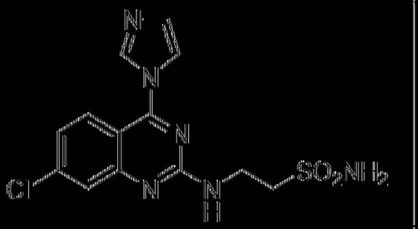
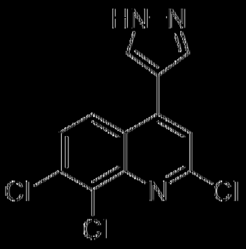
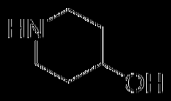
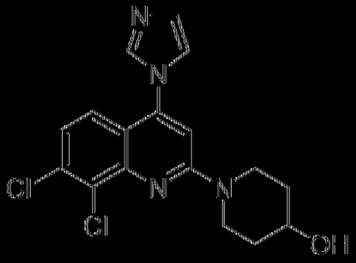
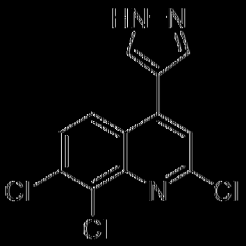
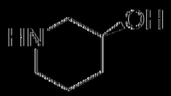
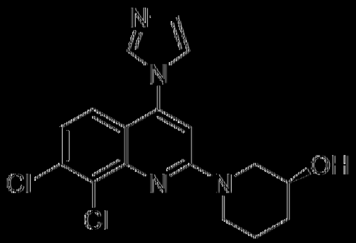
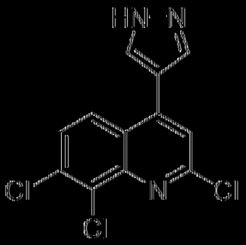
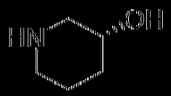
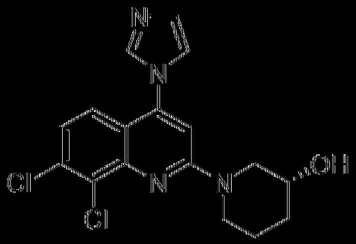
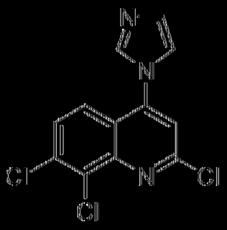
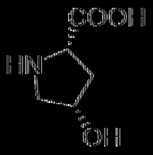
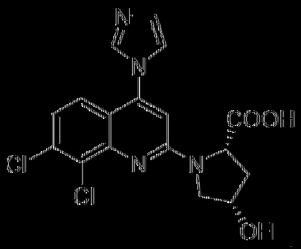
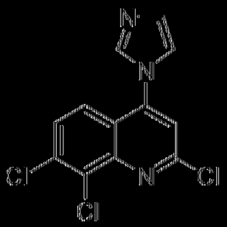
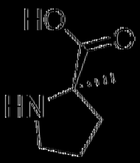
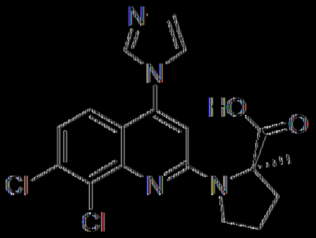
I-259				353
I-132				363
I-133				363
I-134				363
I-455				393
I-456				391

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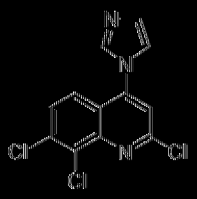
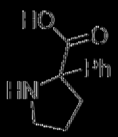
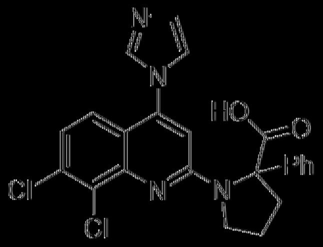
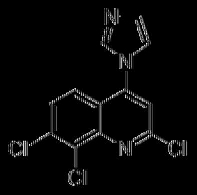
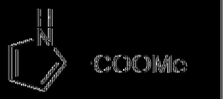
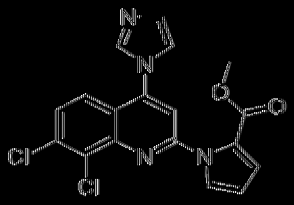
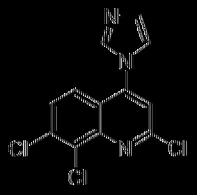
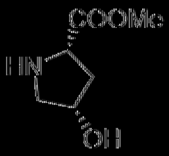
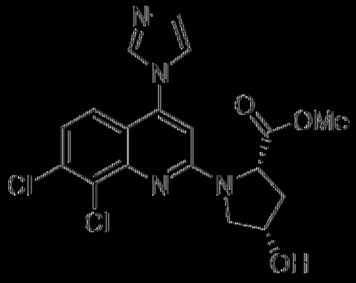
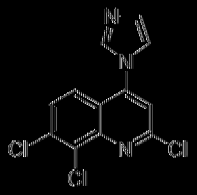
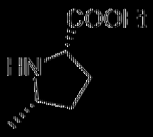
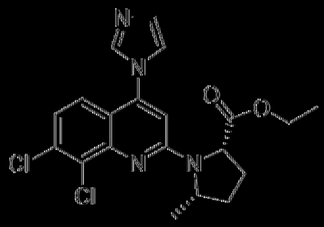
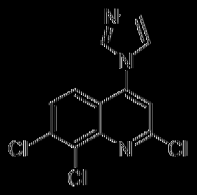
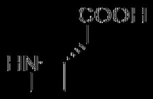
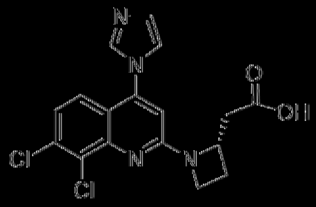
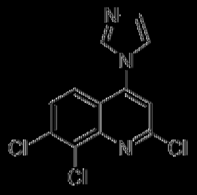
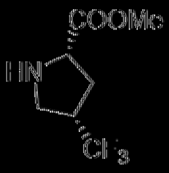
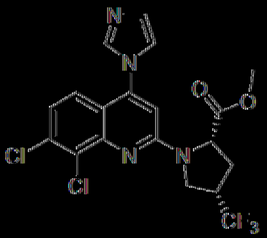
I-457				453
I-458				387
I-459				407
I-460				419
I-461				377
I-462				459

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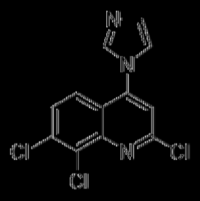
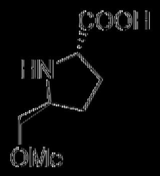
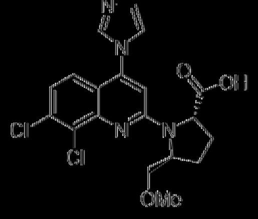
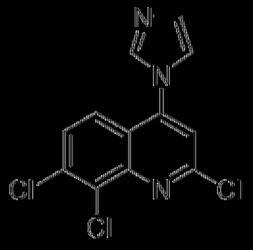
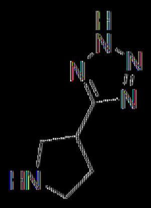
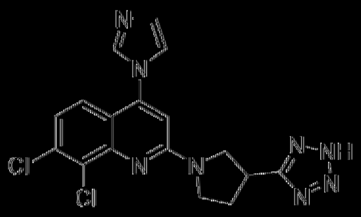
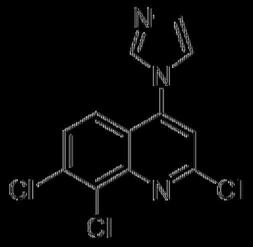
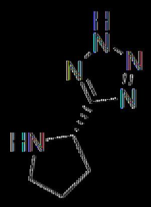
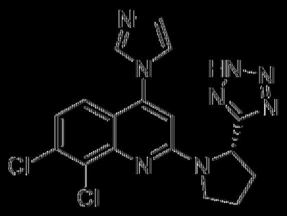
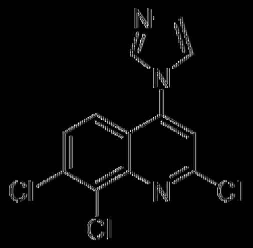
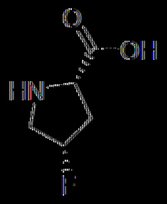
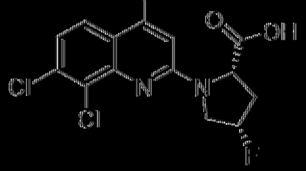
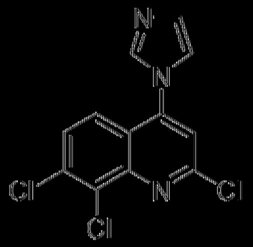
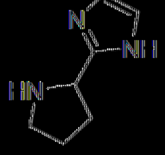
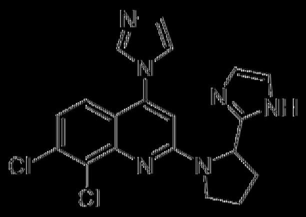
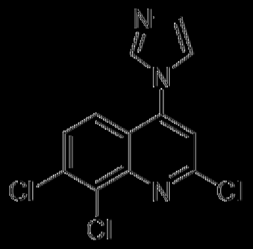
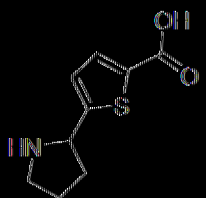
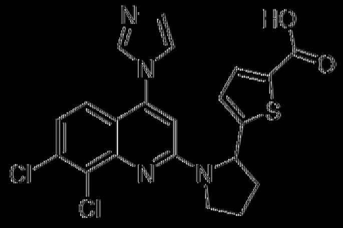
I-463				421
I-464				401
I-465				401
I-466				395
I-467				399
I-468				459

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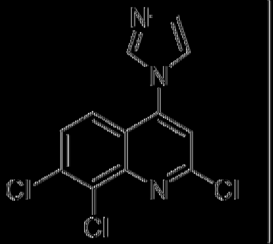
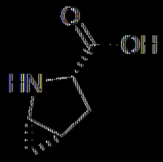
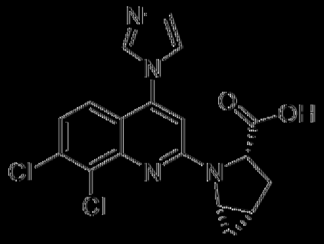
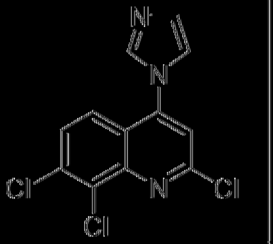
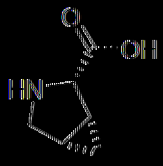
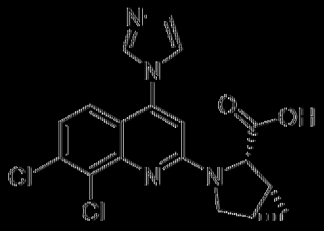
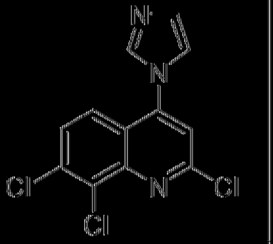
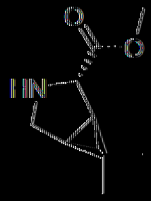
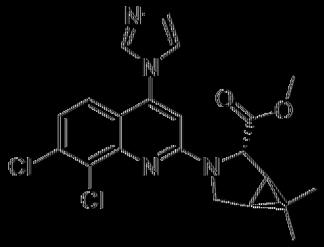
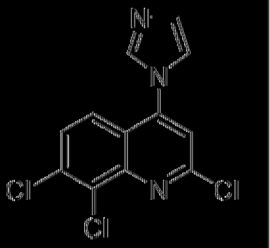
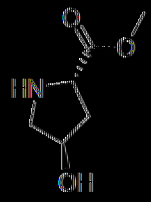
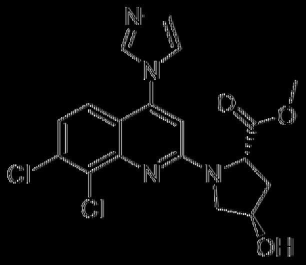
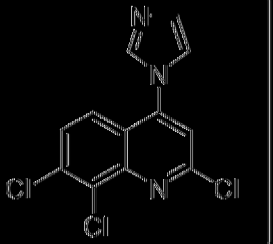
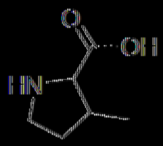
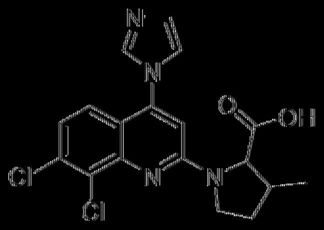
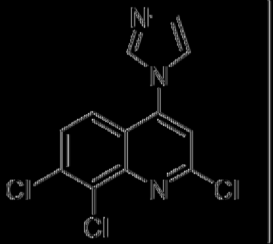
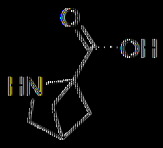
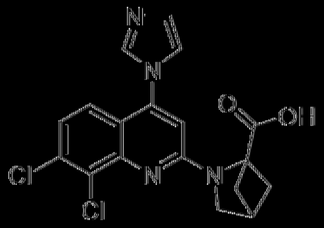
I-469				389
I-470				389
I-471				431
I-472				407
I-473				391
I-474				389

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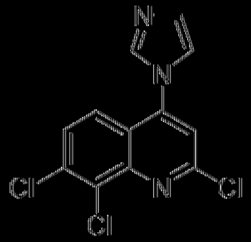
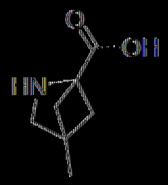
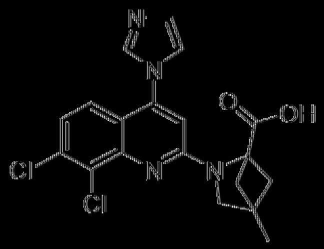
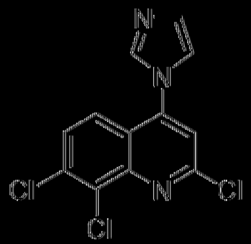
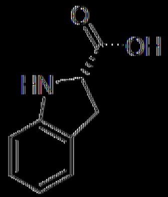
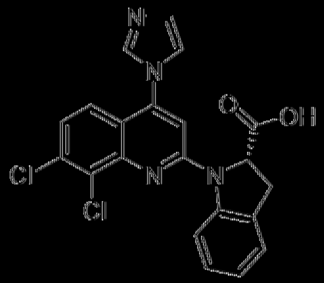
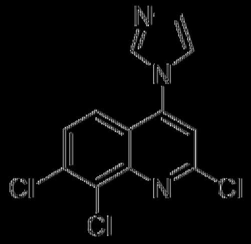
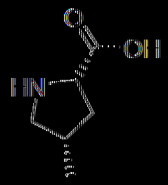
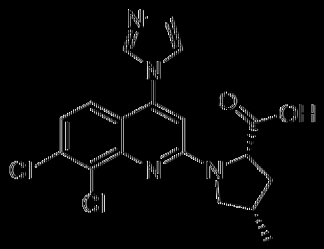
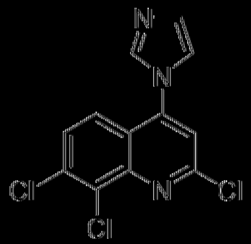
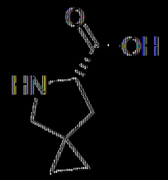
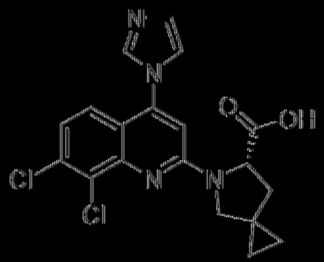
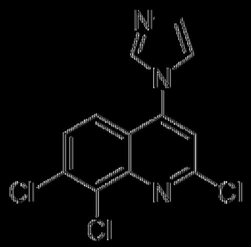
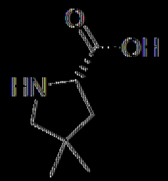
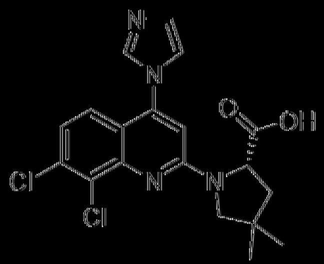
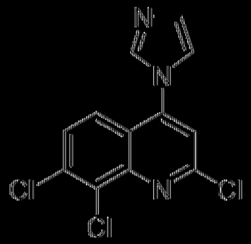
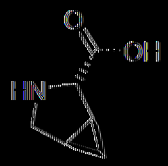
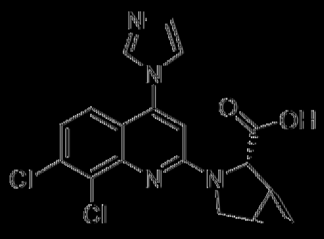
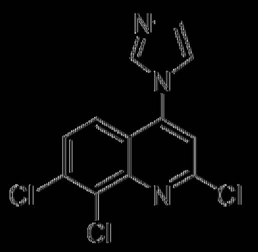
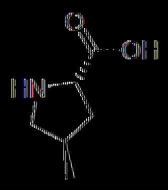
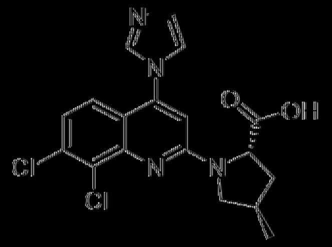
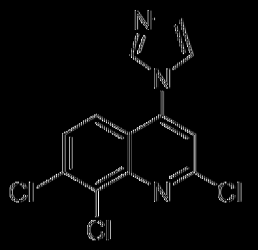
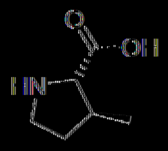
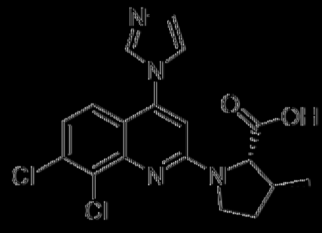
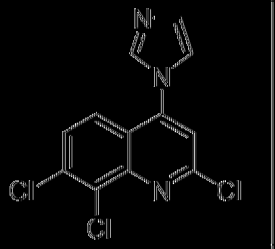
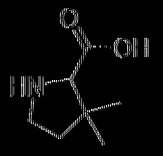
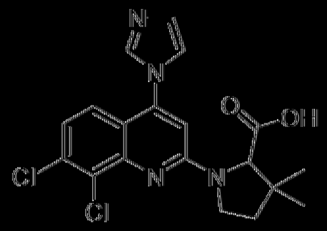
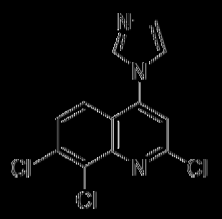
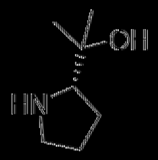
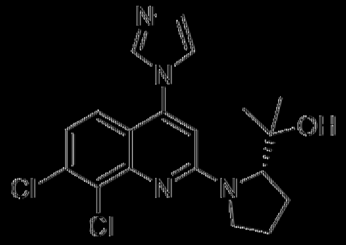
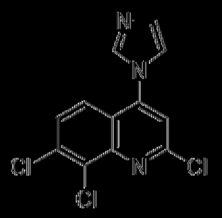
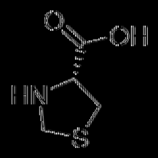
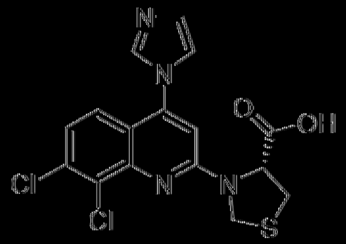
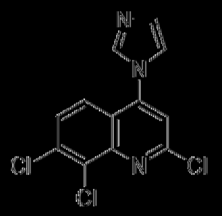
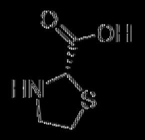
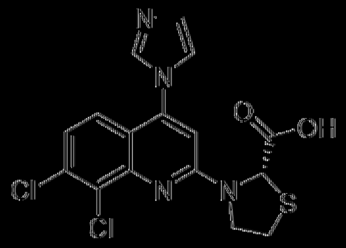
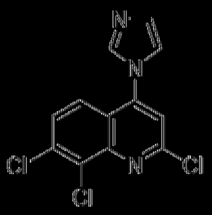
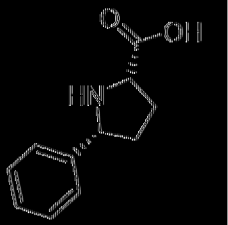
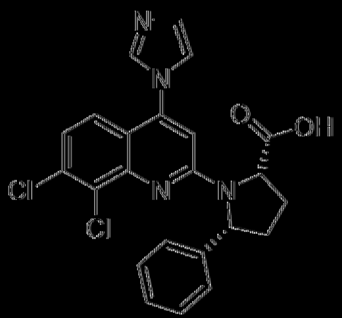
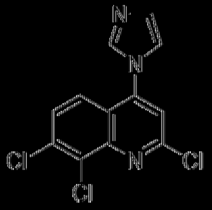
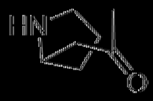
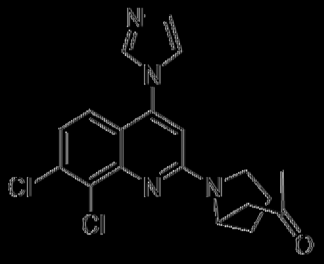
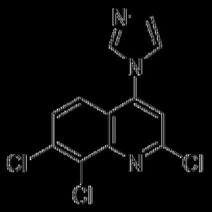
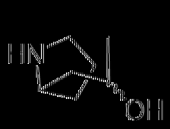
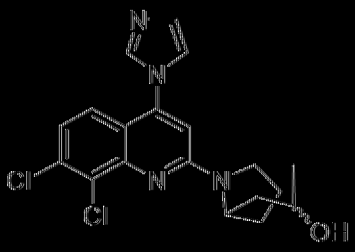
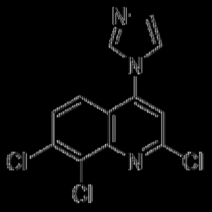
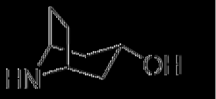
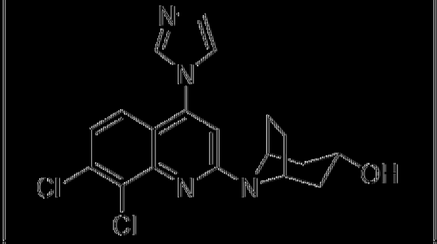
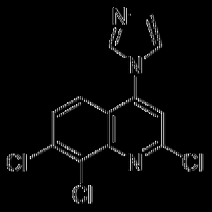
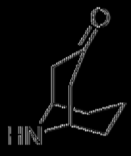
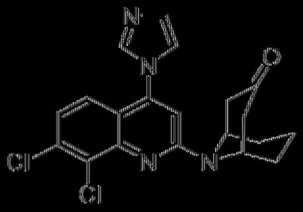
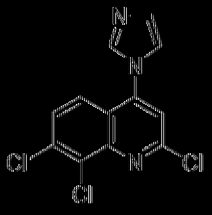
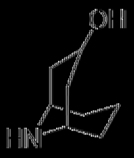
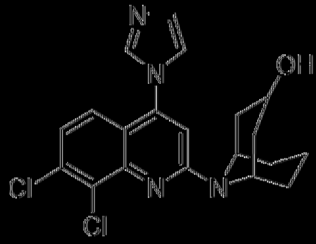
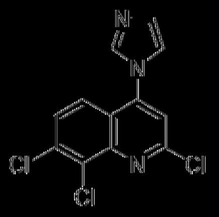
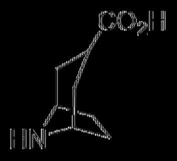
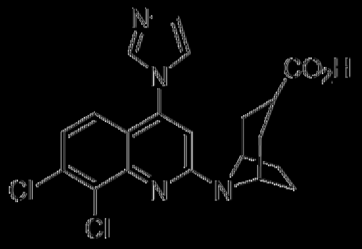
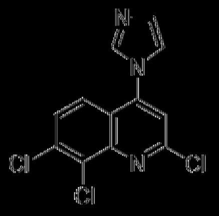
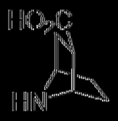
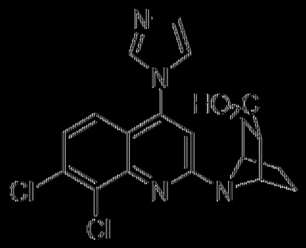
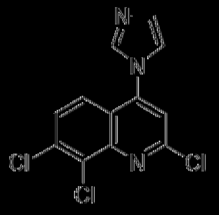
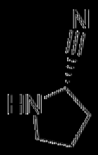
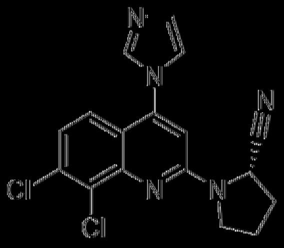
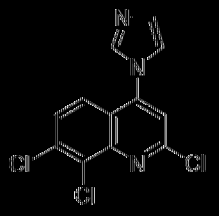
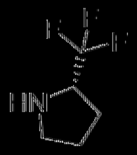
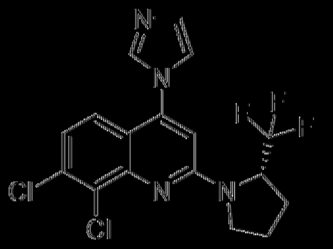
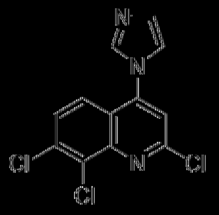
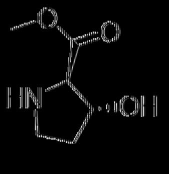
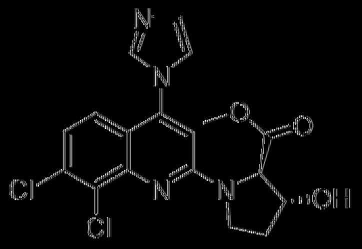
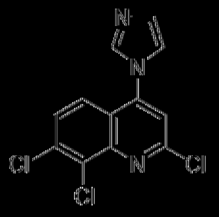
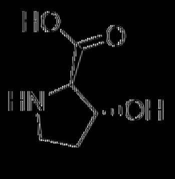
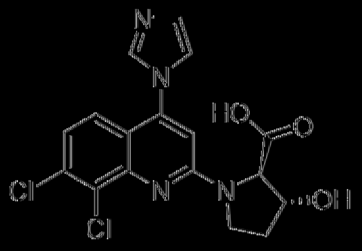
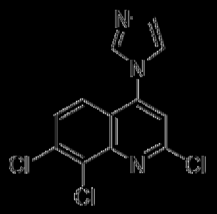
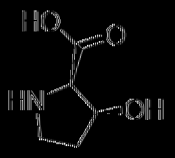
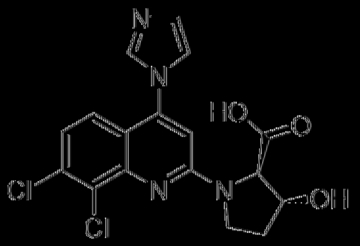
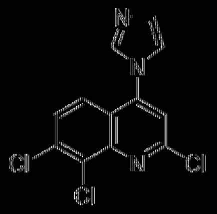
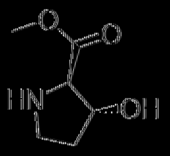
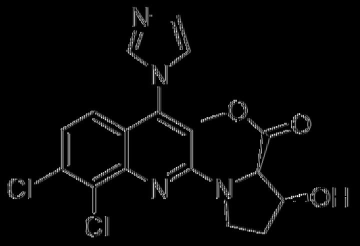
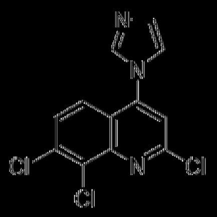
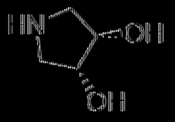
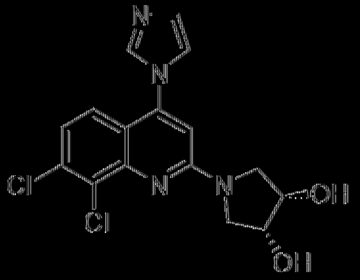
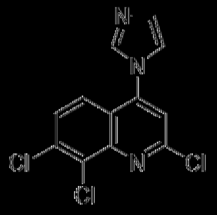
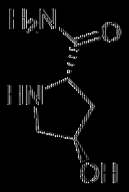
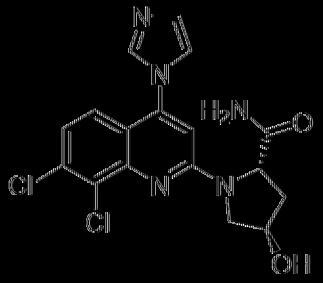
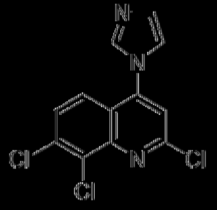
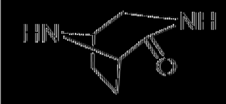
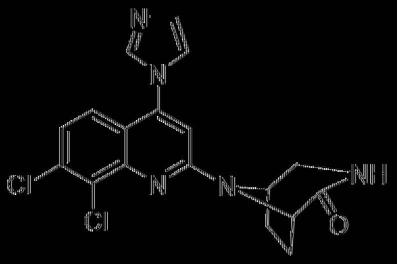
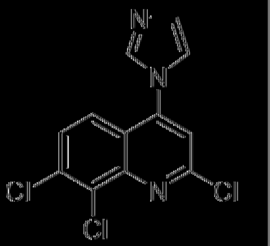
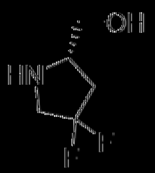
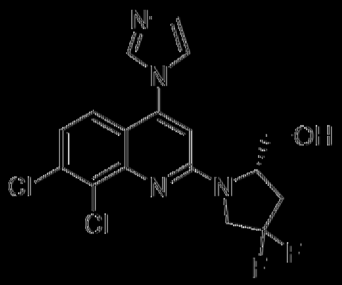
I-475				403
I-476				425
I-477				391
I-478				403
I-479				405
I-480				389

I-#	起始材料		結構	MS [M+1]+
I-481				391
I-482				391
I-483				405
I-484				391
I-485				395
I-486				395

I-#	起始材料		結構	MS [M+1]+
I-487				453
I-488				387
I-489				389
I-490				389
I-491				401
I-492				403

I-#	起始材料		結構	MS [M+1]+
I-493				417
I-494				403
I-495				358
I-496				401
I-497				407
I-498				393

I-#	起始材料		結構	MS [M+1]+
I-499				393
I-500				407
I-501				365
I-502				392
I-503				388
I-504				399

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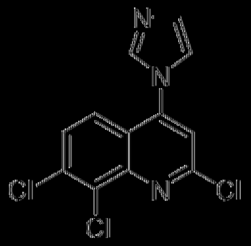
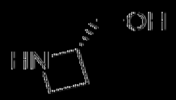
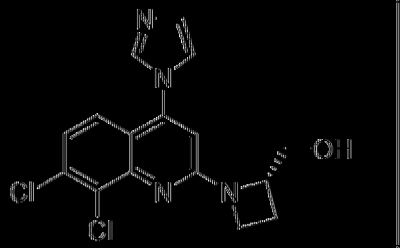
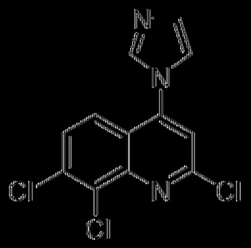
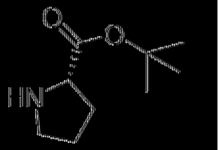
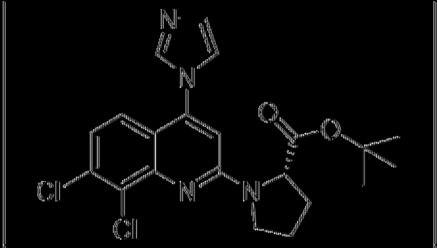
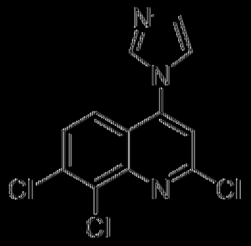
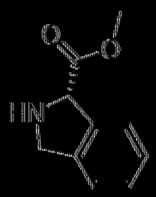
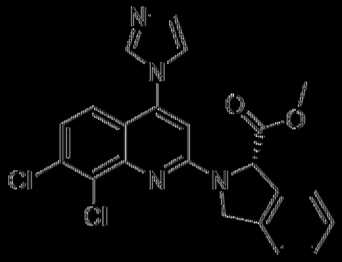
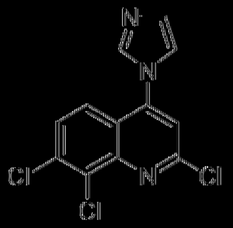
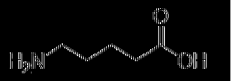
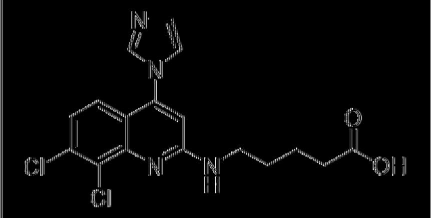
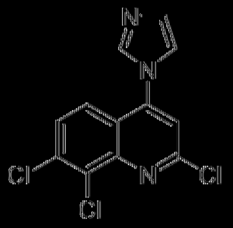
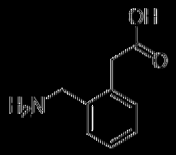
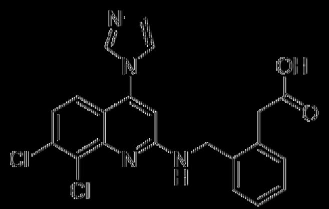
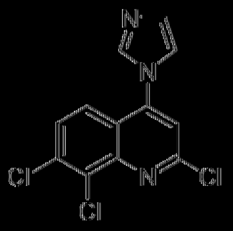
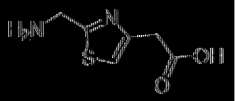
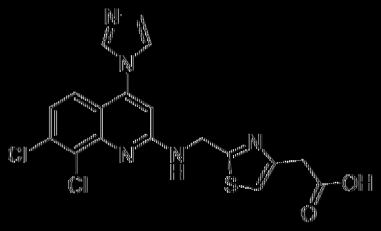
I-659				349
I-644				433
I-660				439
I-835				379
I-888				427
I-881				434

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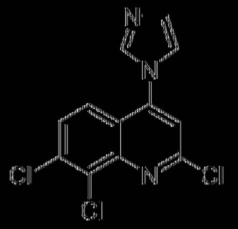
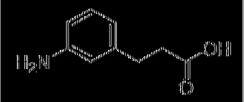
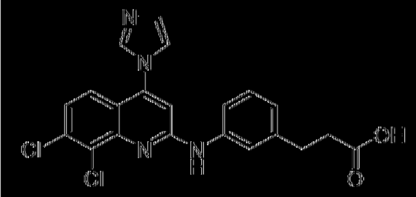
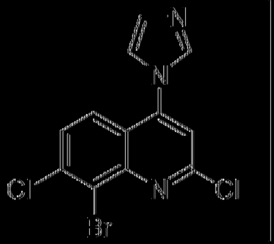
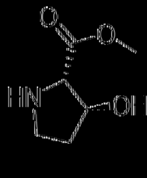
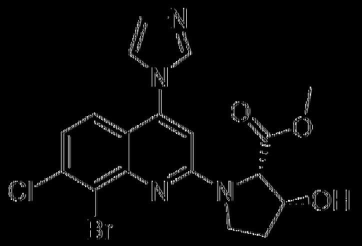
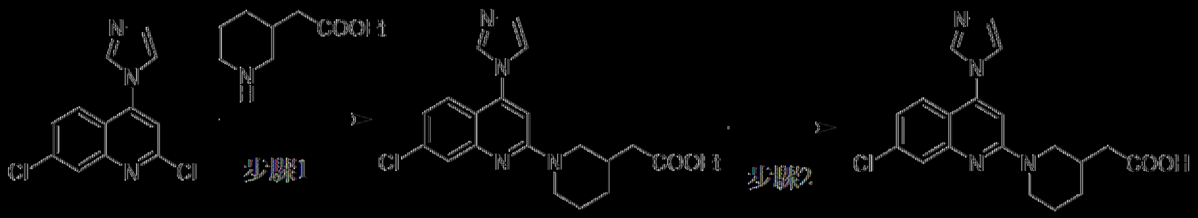
I-883				427
I-872				451

實例2：合成2-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)乙酸(I-123)



I-123

【0517】 步驟1：2-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)乙酸乙酯. 向2,7-二氯-4-(1H-咪唑-1-基)喹啉(38 mg，0.144 mmol)於DMF (1 mL)中之溶液中添加2-(哌啶-3-基)乙酸乙酯(50 mg，0.3 mmol)。在140℃下將溶液劇烈攪拌3小時。冷卻至室溫後，藉由蒸發移除溶劑並在矽膠上藉由管柱層析法純化殘餘物，得到呈油狀之標題產物(MS: $[M+1]^+$ 399.1)。

【0518】 步驟2：2-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)乙酸. 向2-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)乙酸乙酯(20 mg，0.05 mmol)於MeOH (2 mL)中之溶液中添加10% NaOH (水溶液，0.5 mL)。在50℃下將混合物攪拌1小時。在冷卻至室溫後，藉由1 N HCl (2.5 mL)酸化粗品。藉由過濾收集到呈固體狀之標題化合物(MS: $[M+1]^+$ 371.1)。

【0519】 以下化合物基本上藉由與上文關於I-123所描述相同的方法製備。

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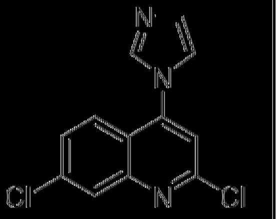
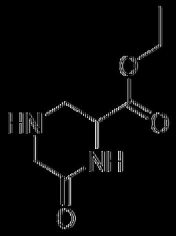
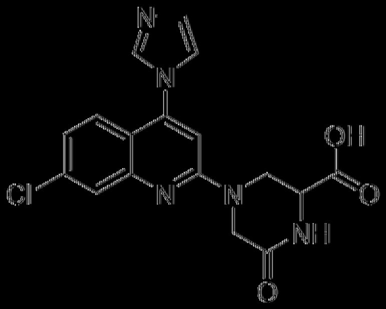
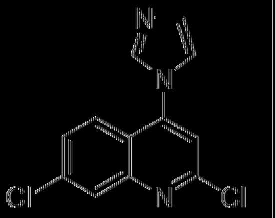
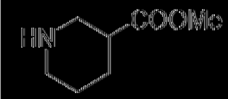
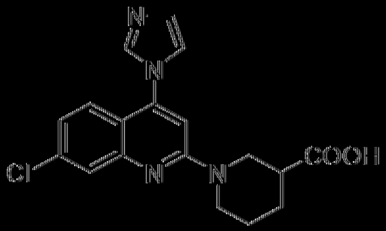
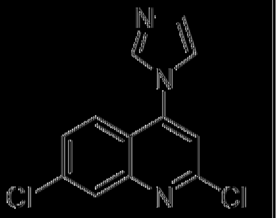
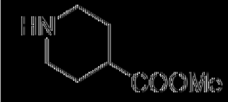
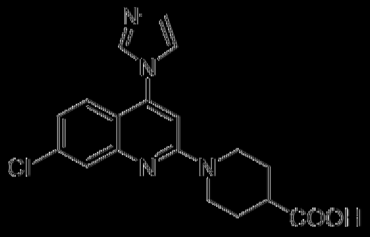
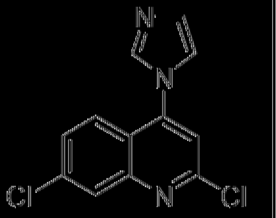
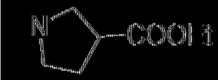
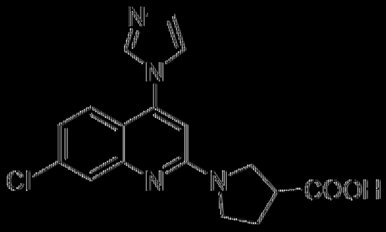
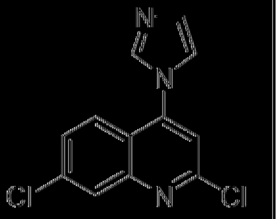
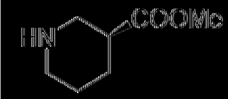
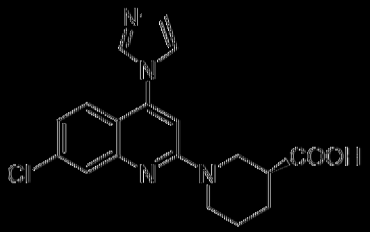
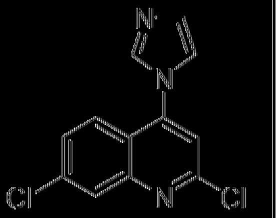
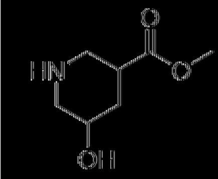
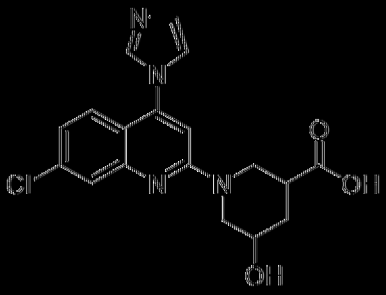
I-84				372
I-122				357.1
I-127				357.1
I-445				343.0
I-331				357.1
I-135				373.1

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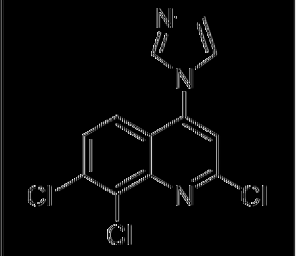
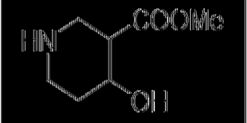
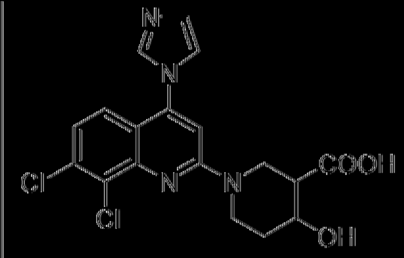
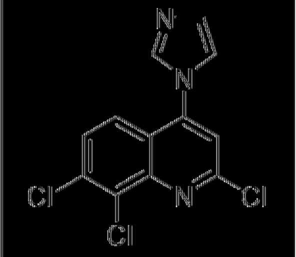
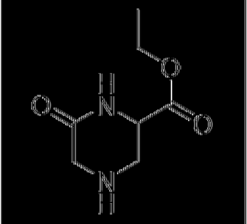
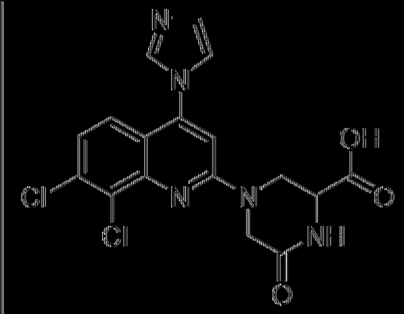
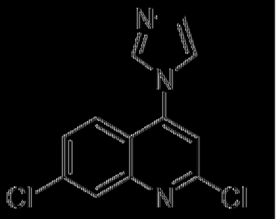
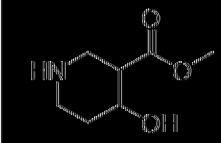
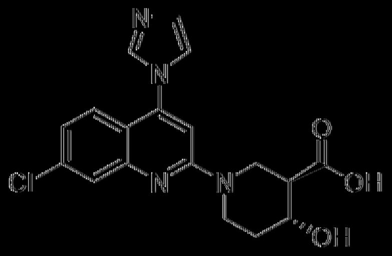
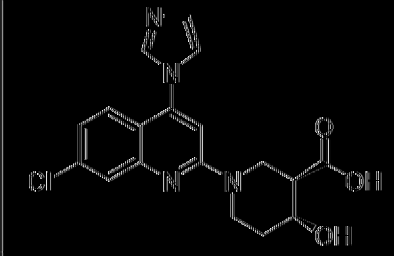
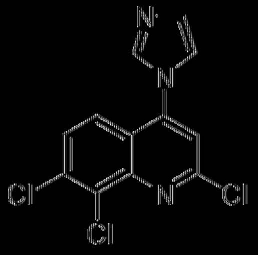
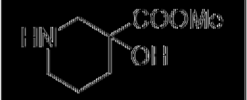
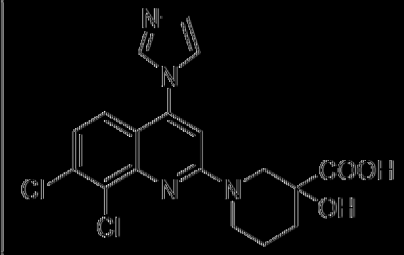
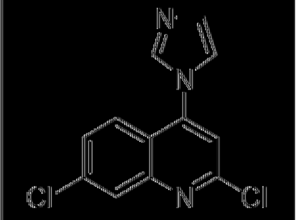
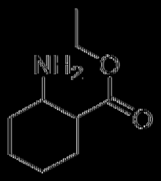
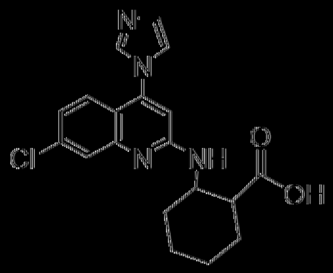
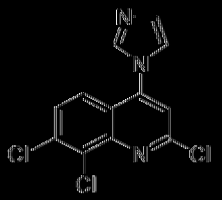
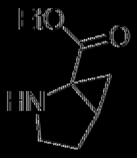
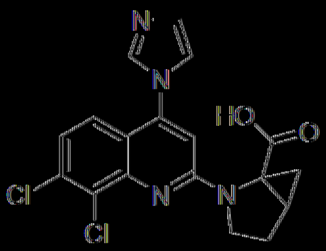
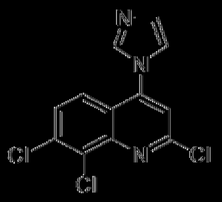
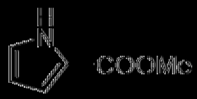
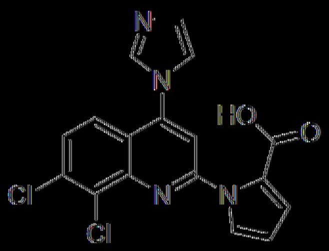
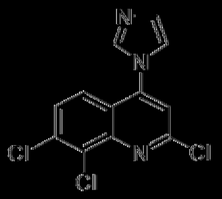
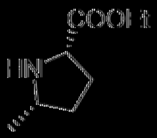
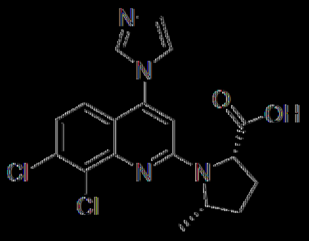
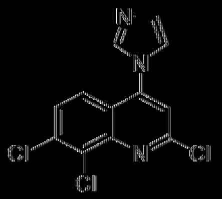
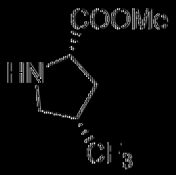
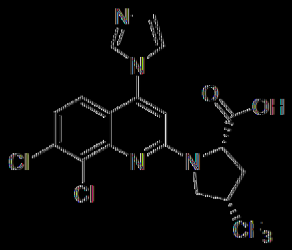
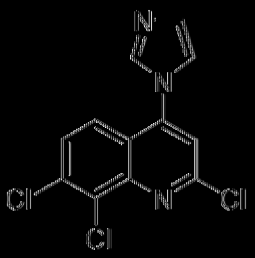
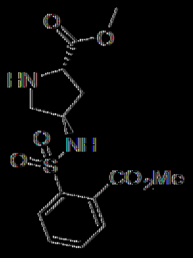
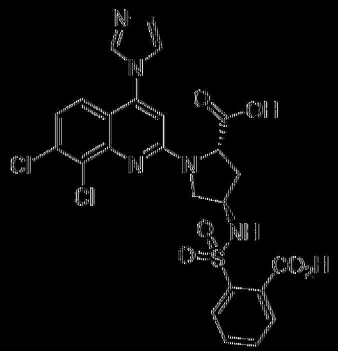
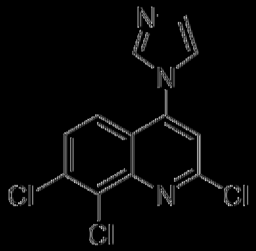
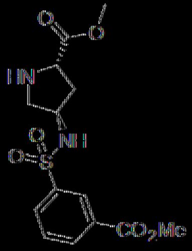
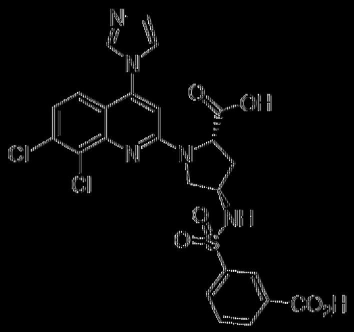
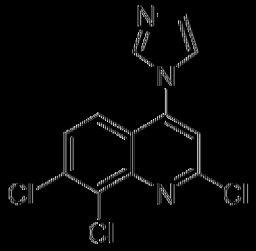
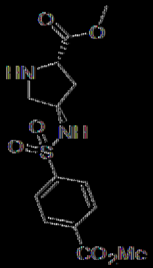
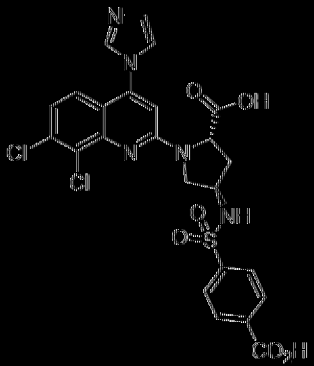
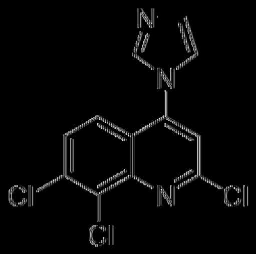
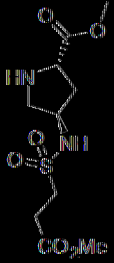
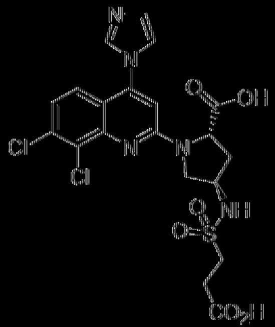
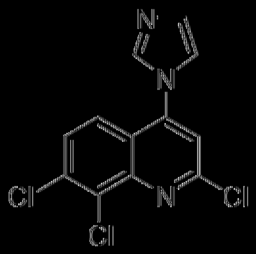
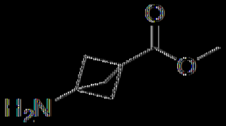
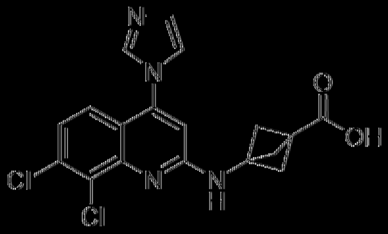
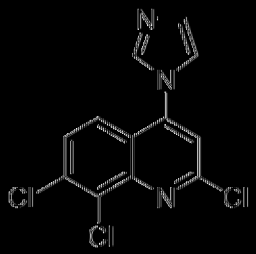
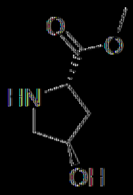
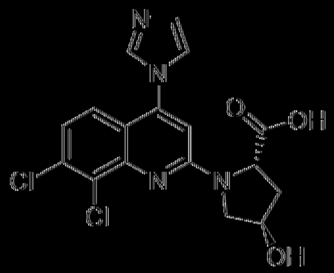
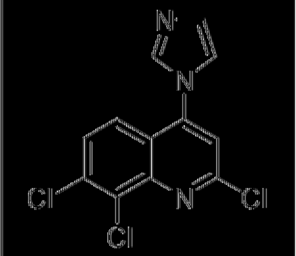
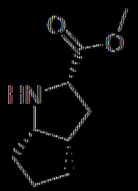
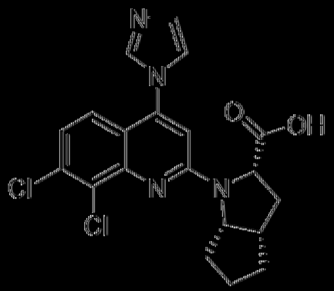
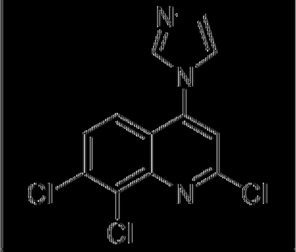
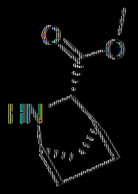
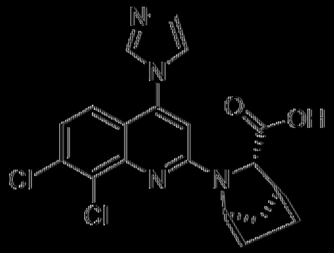
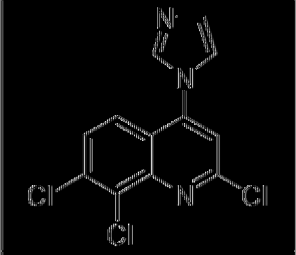
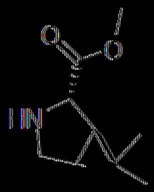
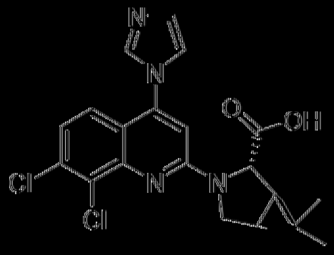
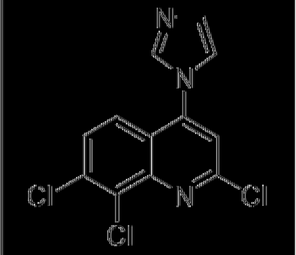
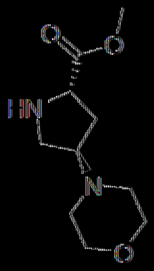
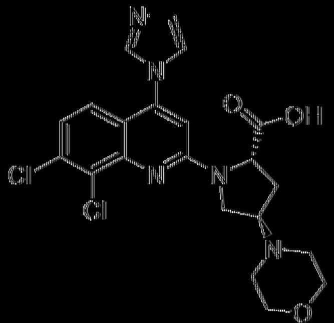
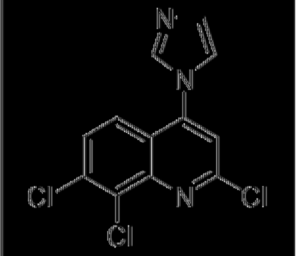
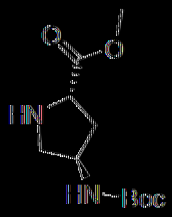
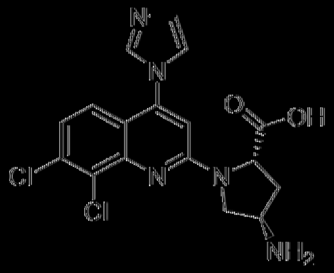
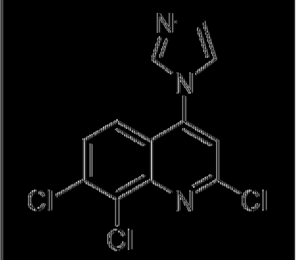
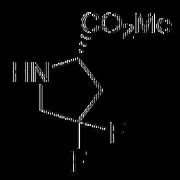
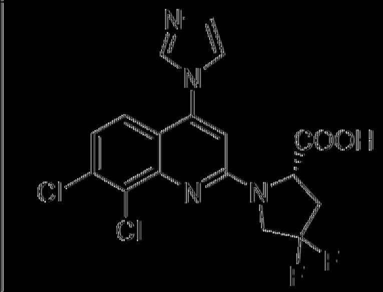
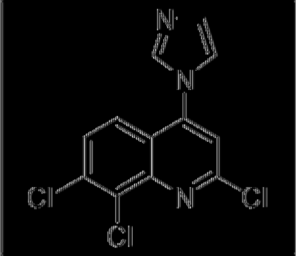
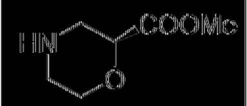
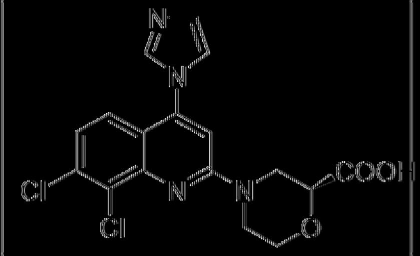
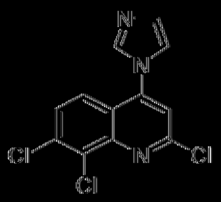
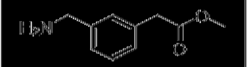
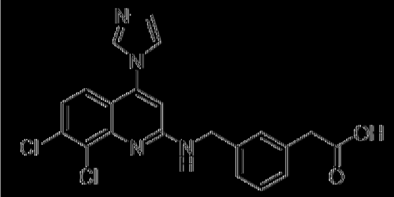
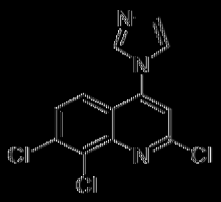
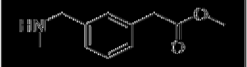
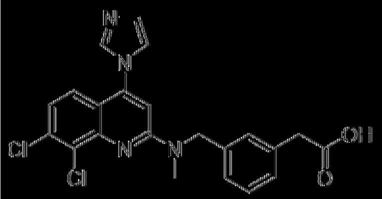
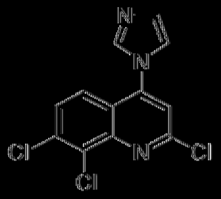
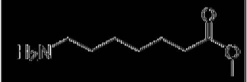
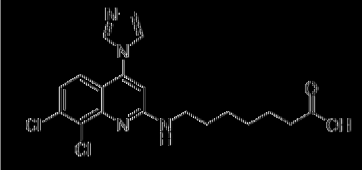
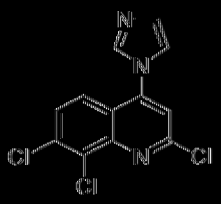
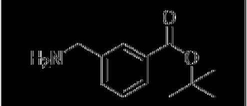
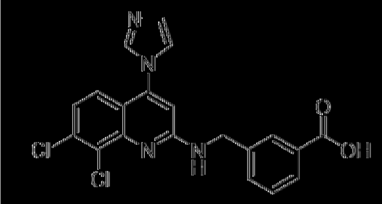
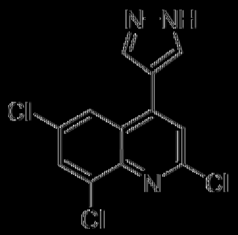
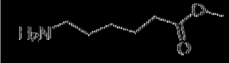
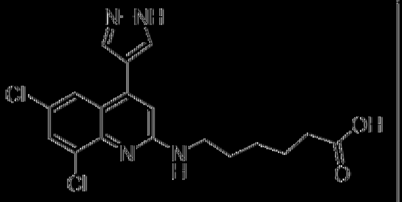
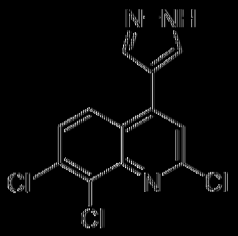
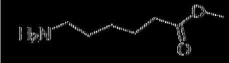
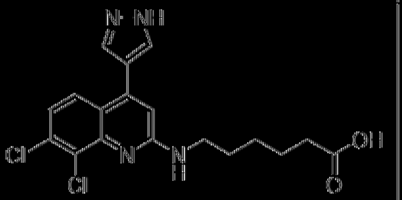
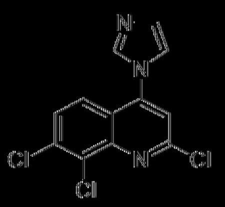
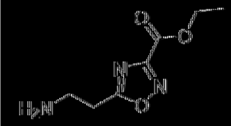
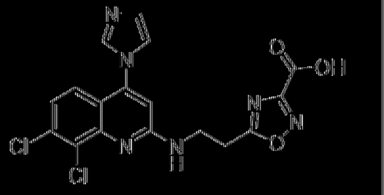
I-332				373
I-334				406
I-130				373.1
I-136				373.1
I-124				407
I-333				371

I-#	起始材料		結構	MS $[M+1]^+$
I-505				389
I-506				373
I-507				391
I-508				445
I-509				576

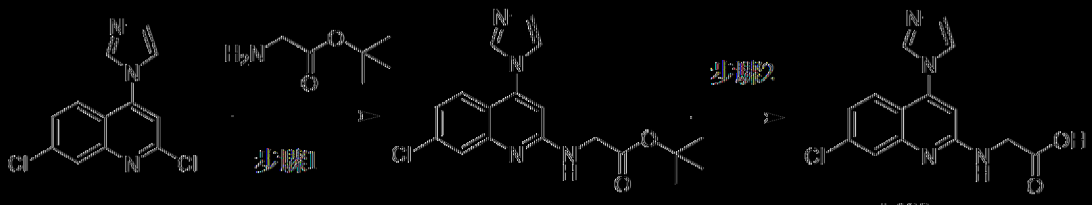
I-#	起始材料		結構	MS [M+1]⁺
I-510				576
I-511				576
I-512				528
I-513				389
I-514				393

I#	起始材料		結構	MS $[M+1]^+$
I-515				417
I-516				403
I-517				417
I-518				462
I-519				392

I-#	起始材料		結構	MS $[M+1]^+$
I-520				413
I-521				393
I-844				427
I-845				441
I-831				407
I-887				413

I-#	起始材料		結構	MS $[M+1]^+$
I-854				393
I-830				393
I-882				419

實例3. 合成(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)甘胺酸(I-166)



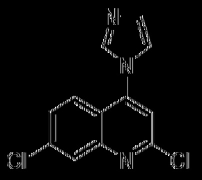
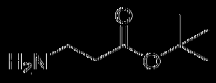
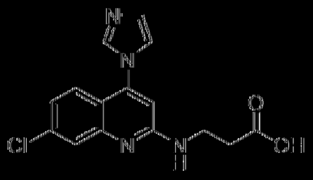
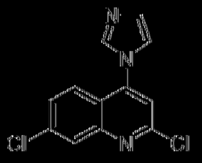
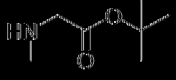
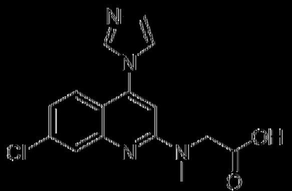
I-166

[0520] 步驟1：(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)甘胺酸三級丁酯. 在100 ℃下，將2,7-二氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.114 mmol)、甘胺酸三級丁酯(38 mg，0.228 mmol)、三乙胺(0.2 mL)及二噁烷(2 mL)之混合物加熱16小時。在冷卻至室溫後，用水(5 mL)稀釋粗品並藉由EtOAc (2 × 5 mL)萃取。將合併之有機層乾燥並濃縮。在矽膠上藉由管柱層析法(25-100% EtOAc/己烷)純化殘餘物，得到呈固體狀之(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)甘胺酸三級丁酯(MS: $[M+1]^+$ 359.1)。

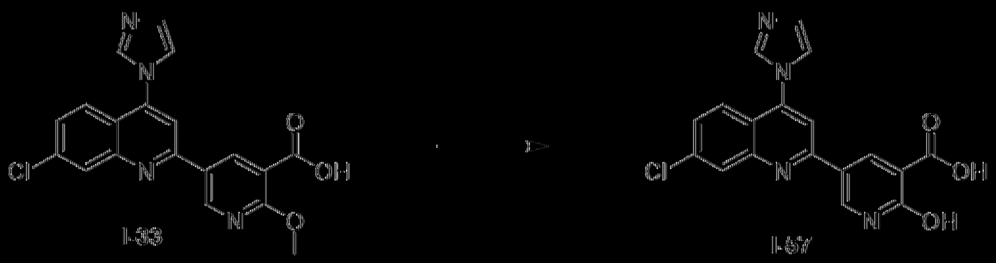
[0521] 步驟2：(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)甘胺酸. 將(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)甘胺酸三級丁酯(20 mg，0.056 mmol)放入含

二氯甲烷(3 mL)之小瓶中。添加鹽酸(2.0 M於乙醚中)並在室溫下攪拌反應16小時。濃縮去除揮發性物質並將所得固體用二氯甲烷濕磨，接著真空乾燥，得到呈固體狀之(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)甘胺酸(MS: [M+1]$^+$ 303.1)。

【0522】 以下化合物基本上藉由與以上關於製備I-166所描述相同的方法製備：

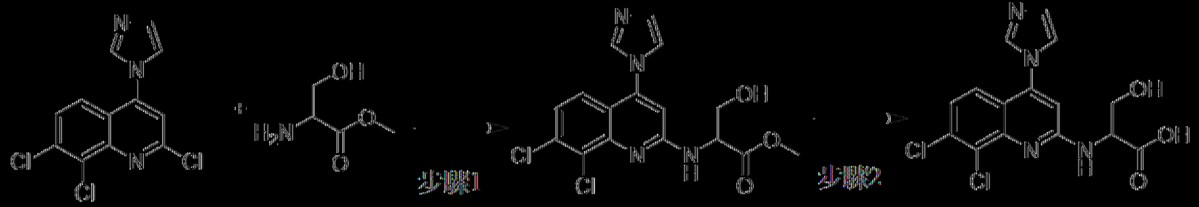
I#	起始材料		結構	MS [M+1]$^+$
I-182				317.1
I-167				317.1

實例4：合成5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基菸鹼酸(I-57)


I-33
I-57

【0523】 將5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-甲氧基菸鹼酸(I-33，15 mg，0.04 mmol)放入含乙酸(1 mL)之小瓶中。添加氫溴酸(33%於乙酸中，0.2 mL)並在室溫下攪拌反應16小時。濃縮去除揮發性物質並在二氧化矽製備板上純化所得殘餘物，得到標題化合物(MS: [M+1]$^+$ 367.0)。

實例5：合成(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)絲胺酸(I-168)

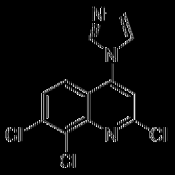
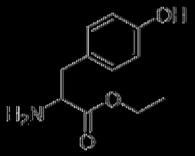
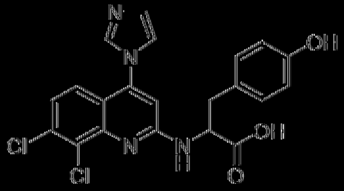
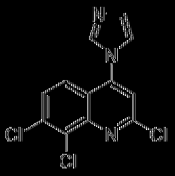
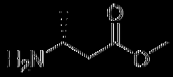
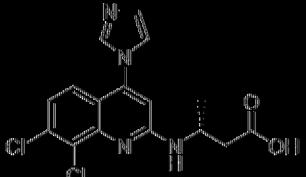
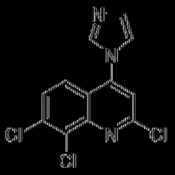
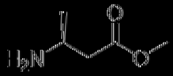
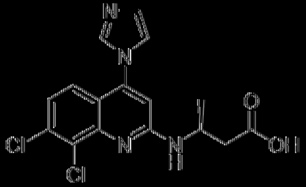
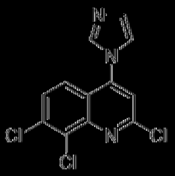
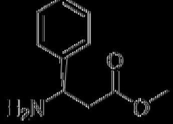
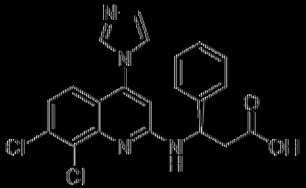
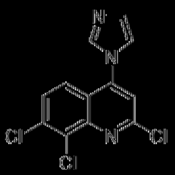
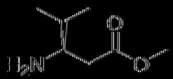
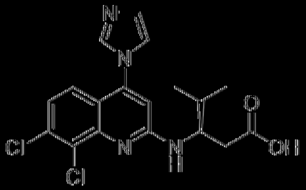
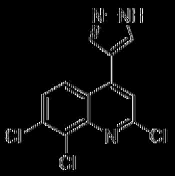
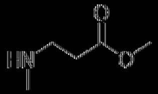
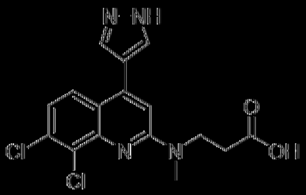
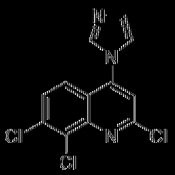
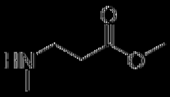
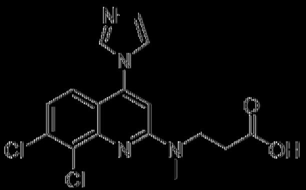
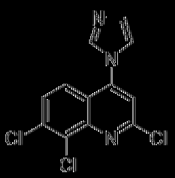
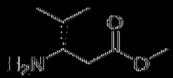
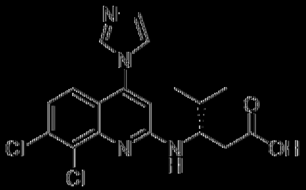


I-168

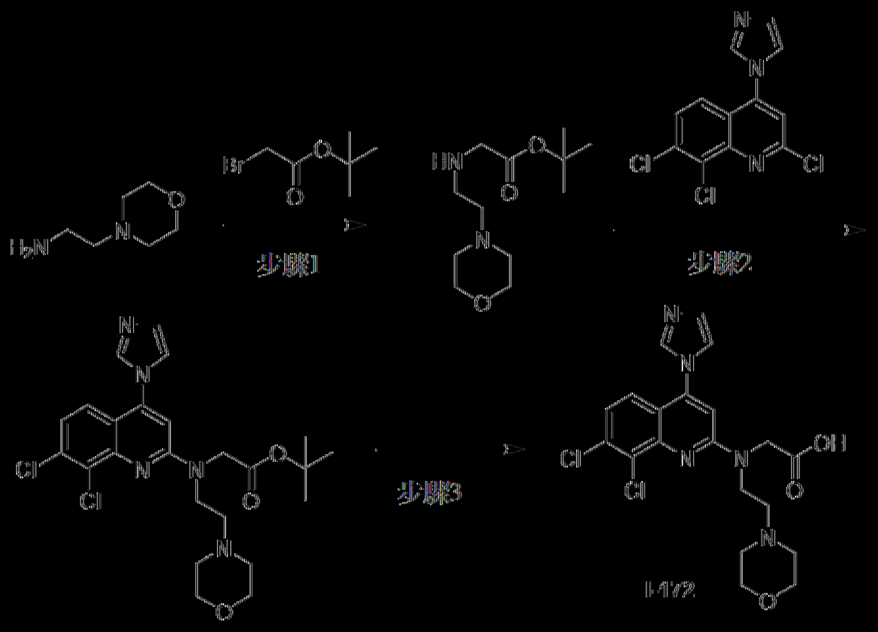
【0524】 步驟1：(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)絲胺酸甲酯. 向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)於DMSO (0.2 mL)中之溶液中添加*DL*-絲胺酸甲酯HCl (39 mg，0.25 mmol)及N,N-二異丙基乙胺(0.1 mL)並在95℃下將溶液攪拌16小時。在冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5 mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽層析法，使用0-15% MeOH/二氯甲烷純化，得到(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)絲胺酸甲酯(MS: $[M+1]^+$ 381.0)。

【0525】 步驟2：(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)絲胺酸. 將(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)絲胺酸甲酯(12 mg，0.031 mmol)放入含THF (0.6 mL)、甲醇(0.2 mL)及水(0.2 mL)之小瓶中。添加單水合氫氧化鋰(4 mg，0.09 mmol)並在室溫下攪拌反應16小時。濃縮去除揮發性物質並藉由添加1 N鹽酸中和所得殘餘物。將所得溶液凍乾，得到標題化合物(MS: $[M+1]^+$ 367.0)。

【0526】 以下化合物基本上藉由與以上關於製備I-168所描述相同之方法製備：

I-#	起始材料		結構	MS [M+1]+
I-169				443.0
I-185				365.0
I-186				365.0
I-189				427.0
I-187				393.0
I-184				365.0
I-183				365.1
I-188				393.0

實例6：合成N-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-(2-(N-味啉基)乙基)甘胺酸(I-172)



I-172

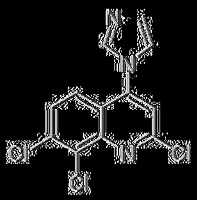
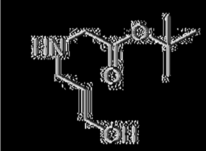
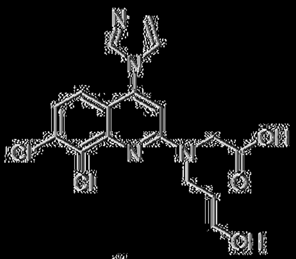
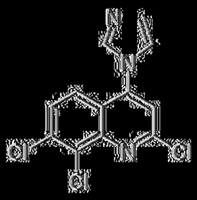
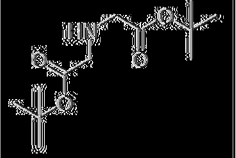
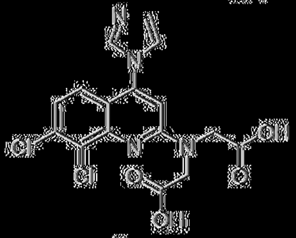
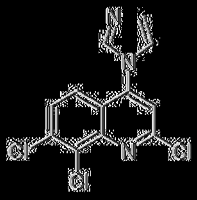
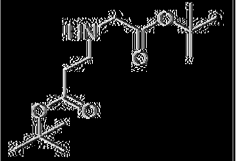
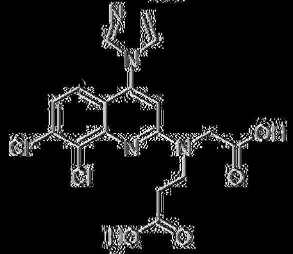
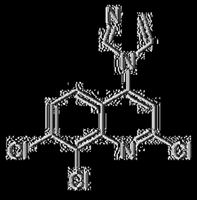
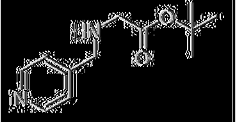
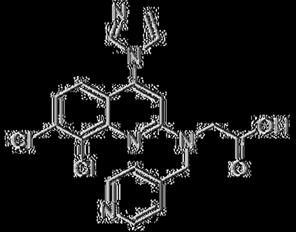
【0527】 步驟1：(2-(N-𠰌啉基)乙基)甘胺酸三級丁酯. 向2-(N-𠰌啉基)乙-1-胺(260 mg，2.0 mmol)於乙腈(5 mL)中之溶液中添加K_2CO_3(1.38g, 10 mmol)。將反應物冷卻至0℃並逐滴添加於乙腈(5 mL)中之2-溴乙酸三級丁酯(390 mg，2.0 mmol)。在0℃下攪拌反應1小時，接著經由矽藻土過濾並濃縮。將殘餘物藉由管柱層析法純化，得到呈油狀之(2-(N-𠰌啉基)乙基)甘胺酸三級丁酯(200 mg) (MS: $[M+1]^+$ 245.2)。

【0528】 步驟2：N-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-(2-(N-𠰌啉基)乙基)甘胺酸三級丁酯. 向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)於DMSO (0.2 mL)中之溶液中添加(2-(N-𠰌啉基)乙基)甘胺酸三級丁酯(200 mg)及N,N-二異丙基乙胺(0.1 mL)。在95℃下將溶液攪拌16小時。冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5 mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽層析法，使用0-15% MeOH/二氯甲烷純化，得到N-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-(2-(N-𠰌啉基)乙基)甘胺酸三級丁酯(10 mg) (MS: $[M+1]^+$ 506.1)。

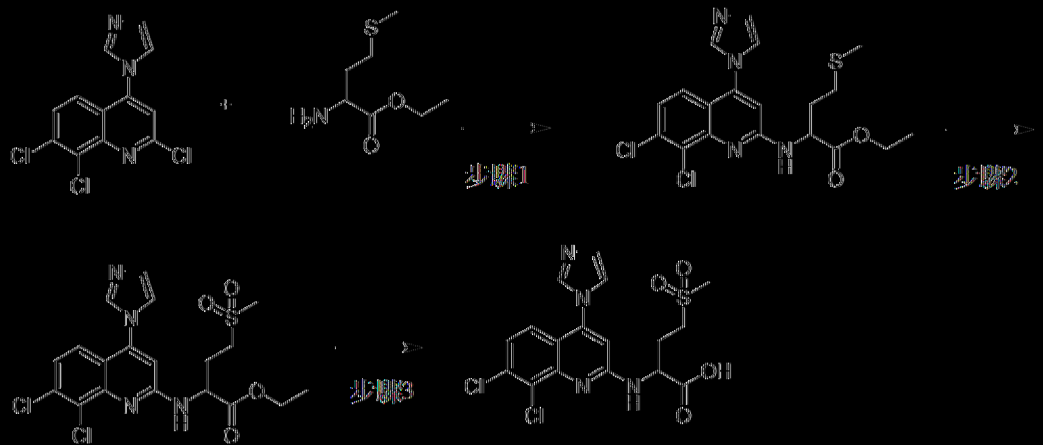
【0529】 步驟3：N-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-(2-

(N-味啉基)乙基)甘胺酸. 將N-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-(2-(N-味啉基)乙基)甘胺酸三級丁酯(10 mg，0.02 mmol)放入含二氯甲烷(1 mL)之小瓶中。添加三氟乙酸(0.1 mL)並在室溫下攪拌反應16小時。藉由旋轉蒸發移除揮發性物質並真空乾燥殘餘物，得到N-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-(2-(N-味啉基)乙基)甘胺酸(MS: $[M+1]^+$ 450.1)。

【0530】 以下化合物基本上藉由與以上關於製備I-172所描述相同之方法製備：

I-#	起始材料		結構	MS $[M+1]^+$
I-173				395.0
I-174				395.1
I-175				409.1
I-176				428.0

實例7：合成2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-4-(甲基磺醯基)丁酸(I-170)



I-170

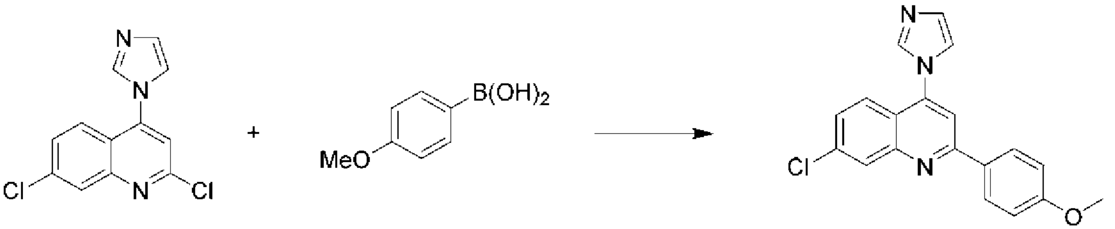
【0531】 步驟1：(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲硫胺酸乙酯. 向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)於DMSO (0.2 mL)中之溶液中添加甲硫胺酸乙酯(47 mg，0.2 mmol)及N,N-二異丙基乙胺(0.1 mL)。在95℃下將溶液攪拌16小時。冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5 mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽層析法，使用0-100% EtOAc/己烷純化，得到(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲硫胺酸乙酯(20 mg) (MS: $[M+1]^+$ 439.0)。

【0532】 步驟2：2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-4-(甲基磺醯基)丁酸乙酯. 將(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲硫胺酸乙酯(20 mg，0.045 mmol)放入含二氯甲烷(2 mL)之小瓶中。添加*m*-CPBA (20 mg，0.09 mmol)並在室溫下攪拌反應16小時。添加亞硫酸鈉(2 mL，10%水溶液)並將有機層乾燥(Na_2SO_4)且藉由二氧化矽層析法，使用0-10% MeOH/CH_2Cl_2純化，得到2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-4-(甲基磺醯基)丁酸乙酯(10 mg) (MS: $[M+1]^+$ 471.1)。

【0533】 步驟3：2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-4-(甲基磺醯基)丁酸. 將2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-4-

(甲基磺醯基)丁酸乙酯(20 mg，0.042 mmol)放入含THF (1 mL)及水(0.25 mL)之小瓶中。添加單水合氫氧化鋰(5 mg，0.13 mmol)並在室溫下將反應混合物攪拌3小時。藉由旋轉蒸發移除揮發性物質並藉由添加1N HCl (水溶液)中和殘餘物。將所得溶液凍乾，得到2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-4-(甲基磺醯基)丁酸(12 mg) (MS: $[M+1]^+$ 443.0)。

實例8：合成7-氯-4-(1H-咪唑-1-基)-2-(4-甲氧基苯基)喹啉(**I-2**)



I-2

【0534】 藉由N_2將2,7-二氯-4-(1H-咪唑-1-基)喹啉(132 mg，0.5 mmol)、(4-甲氧基苯基)硼酸(boronic acid) (114 mg，0.75 mmol)、Na_2CO_3 (265 mg，2.5 mmol)、1,4-二噁烷(4 mL)及H_2O (1 mL)之混合物吹掃30分鐘。在N_2下，將肆(三苯基膦)鈀(55 mg，0.05 mmol)添加至上述混合物中。在100℃下將混合物劇烈攪拌3小時。冷卻至室溫後，將粗品用EtOAc (20 mL)稀釋並用水(5 mL × 2)及鹽水(5 mL × 2)洗滌。將有機相濃縮並在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物**I-2** (MS: $[M+1]^+$ 336.1)。

【0535】 以下化合物基本上藉由與以上關於製備**I-2**所描述相同之方法製備。

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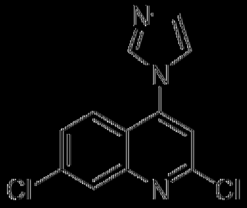
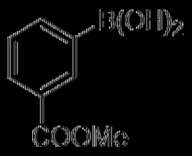
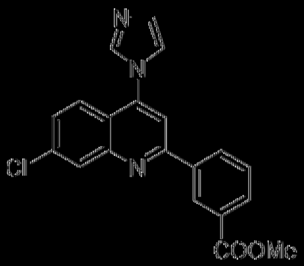
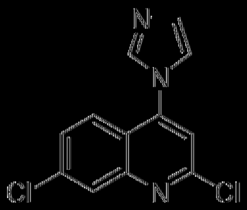
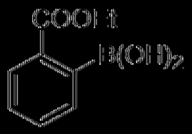
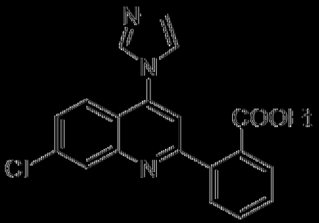
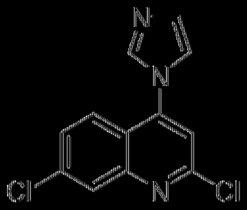
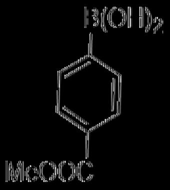
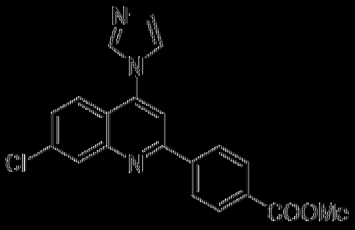
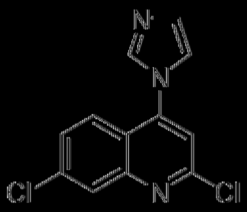
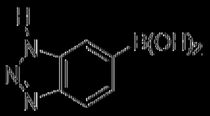
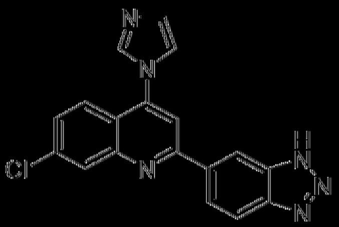
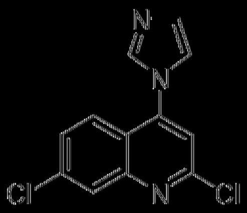
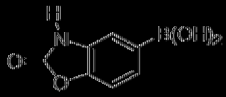
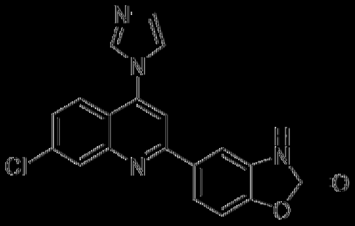
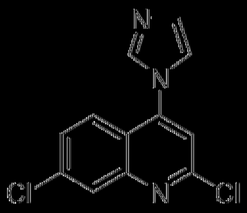
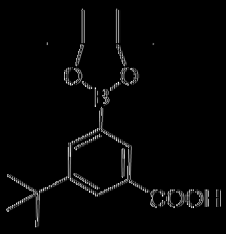
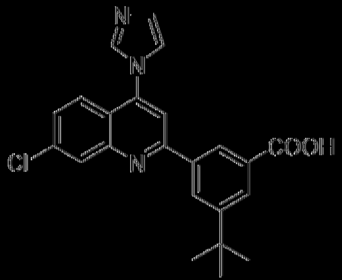
I-5				364.1
I-12				378.1
I-3				364.1
I-35				347
I-36				363
I-25				406.1

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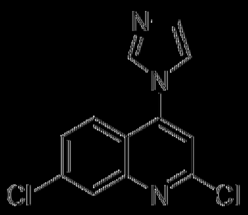
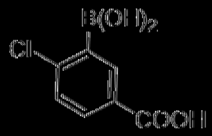
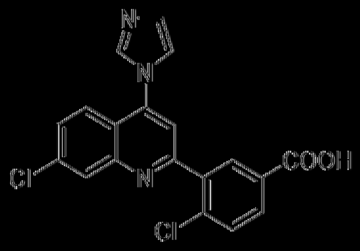
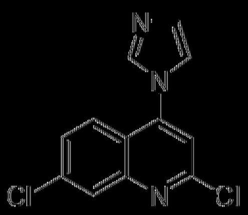
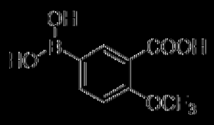
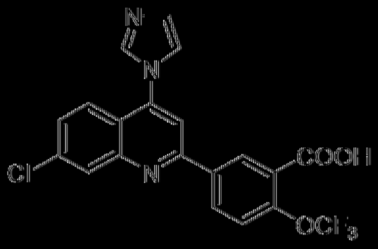
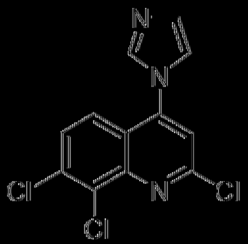
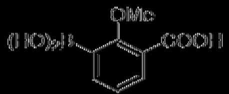
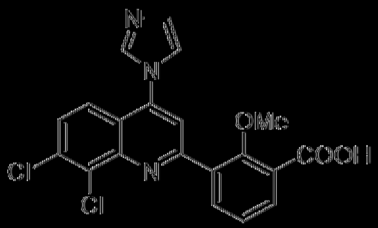
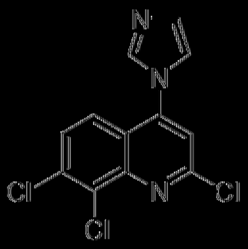
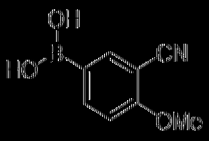
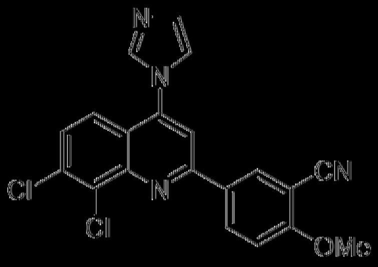
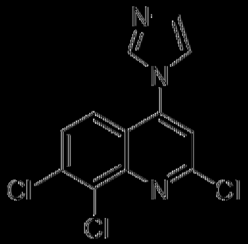
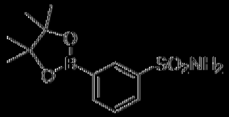
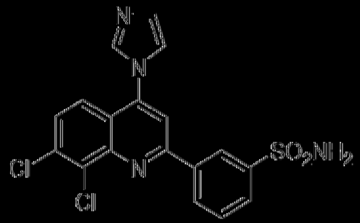
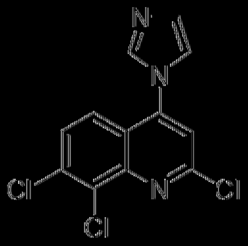
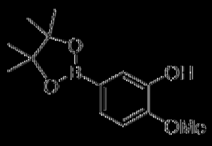
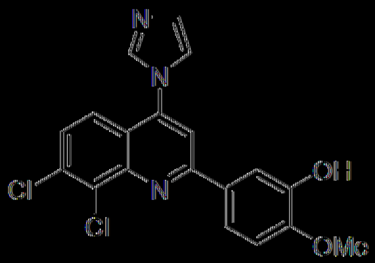
I-31				384.0
I-18				434
I-45				414
I-40				395
I-46				419
I-41				386

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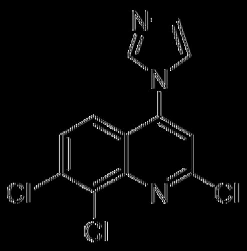
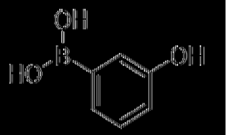
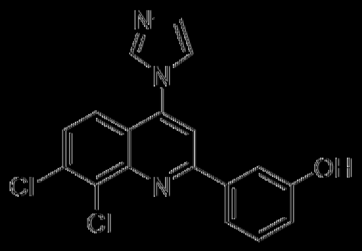
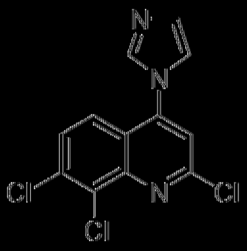
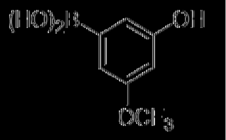
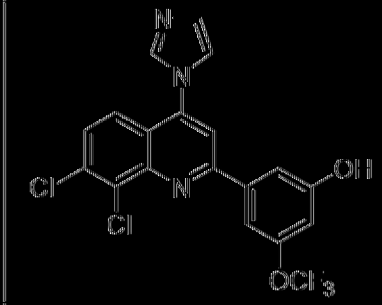
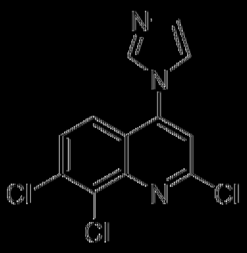
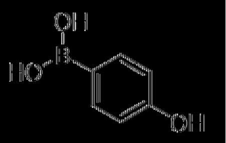
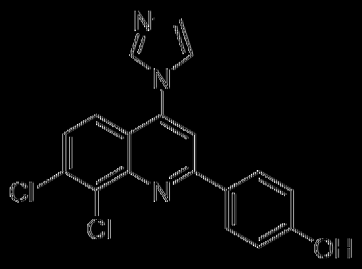
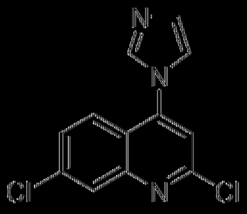
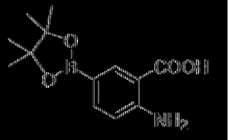
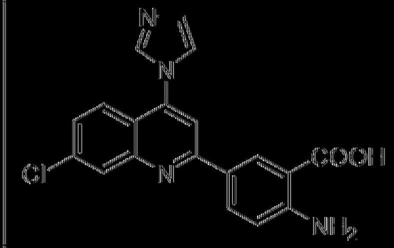
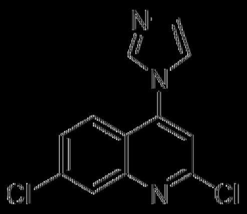
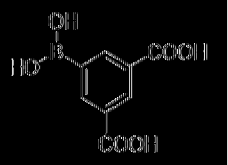
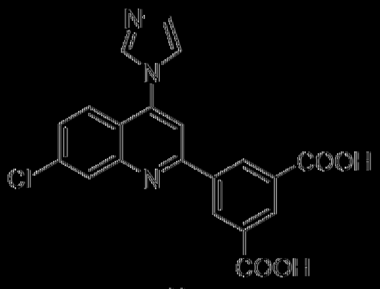
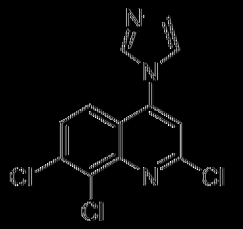
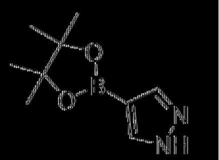
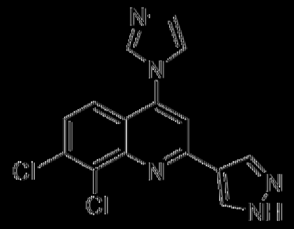
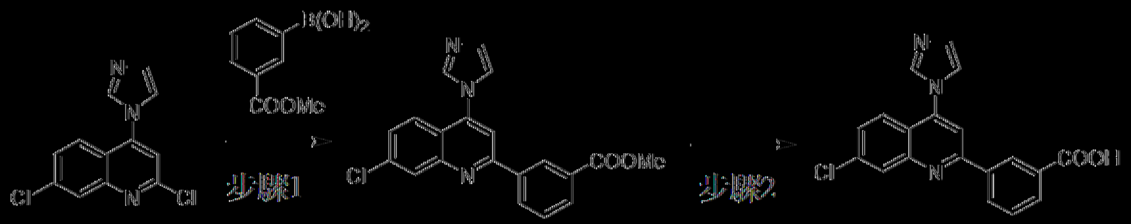
I-43				356
I-44				440
I-47				356
I-20				365
I-28				394
I-378				330.0

實例9：合成7-氯-4-(1H-咪唑-1-基)-2-(4-甲氧基苯基)喹啉(I-6)



I-6

【0536】 步驟1：3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸甲酯. 藉由N_2將2,7-二氯-4-(1H-咪唑-1-基)喹啉(132 mg，0.5 mmol)、(3-(甲氧基羰基)苯基)硼酸(136 mg，0.75 mmol)、Na_2CO_3 (265 mg，2.5 mmol)、1,4-二噁烷(4 mL)及H_2O (1 mL)之混合物吹掃30分鐘。在N_2下，將肆(三苯基膦)鈀(55 mg，0.05 mmol)添加至上述混合物中。在100℃下將混合物劇烈攪拌2小時。冷卻至室溫後，將粗品用EtOAc (20 mL)稀釋並用水(5 mL × 2)及鹽水(5 mL × 2)洗滌。將有機相濃縮並在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(MS: $[M+1]^+$ 364.1)。

【0537】 步驟2：3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸. 向3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸甲酯(80 mg，0.22 mmol)於MeOH (4 mL)中之溶液中添加10% NaOH (水溶液，1 mL)。在50℃下將混合物攪拌1小時。冷卻至室溫後，藉由1 N HCl (5 mL)酸化粗品。藉由過濾收集呈固體狀之標題化合物(MS: $[M+1]^+$ 350.1)。

【0538】 以下化合物基本上藉由與以上關於製備I-6所描述相同的方法製備：

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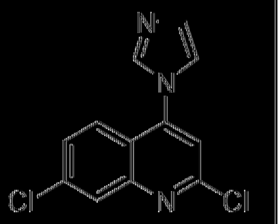
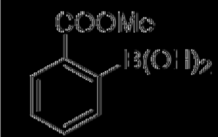
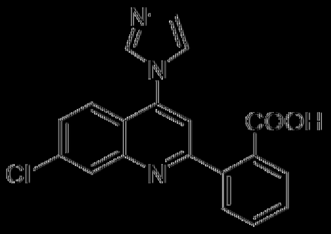
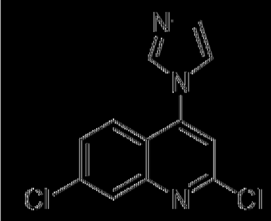
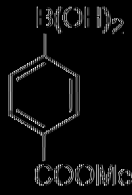
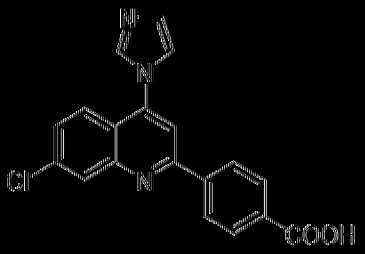
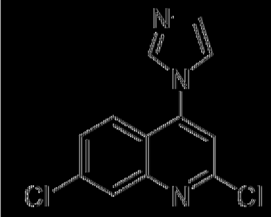
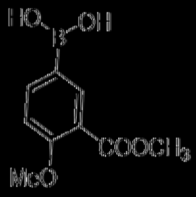
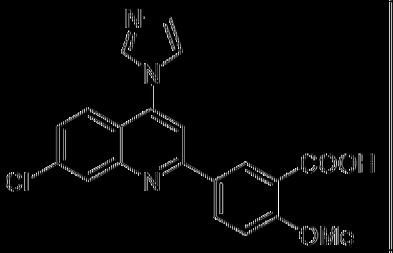
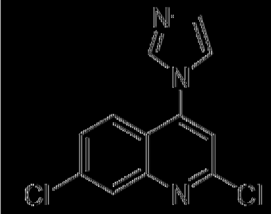
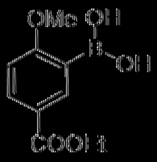
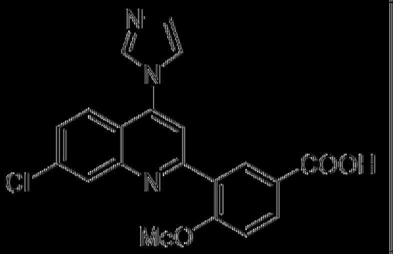
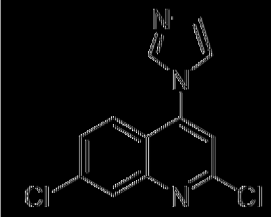
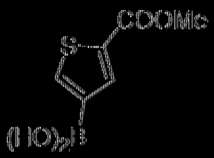
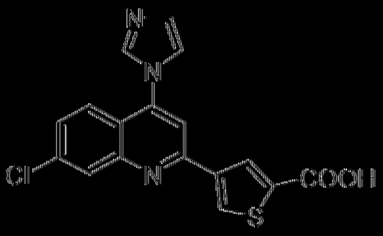
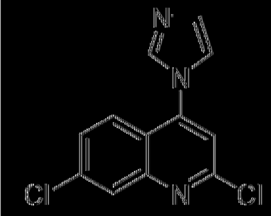
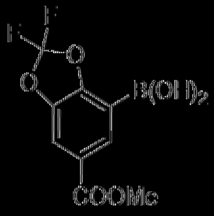
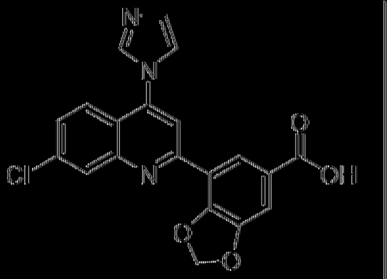
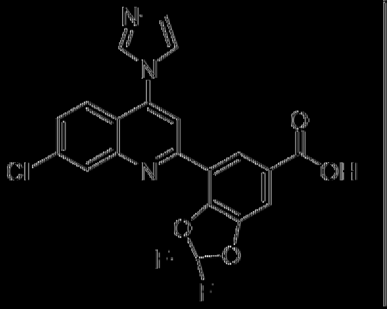
I-13				350.1

I-#	起始材料		結構	MS [M+1]+
I-4				350.1
I-15				380
I-30				380
I-55				356
I-37			 副產物	394.0
I-38				430.0

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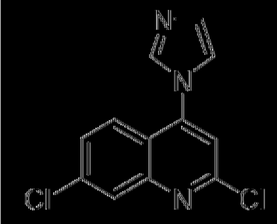
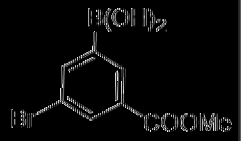
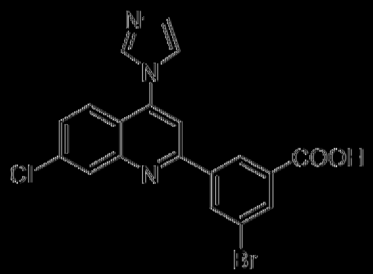
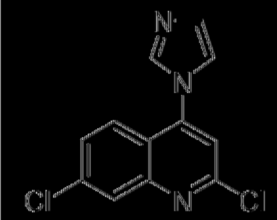
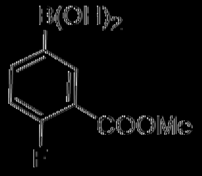
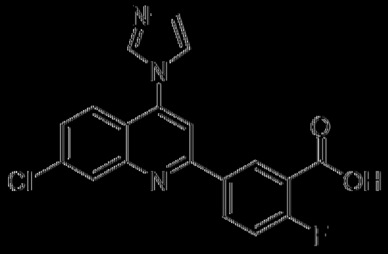
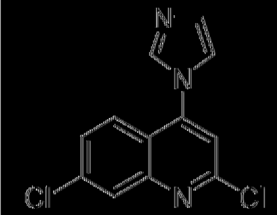
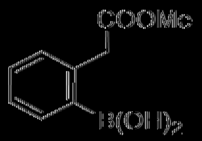
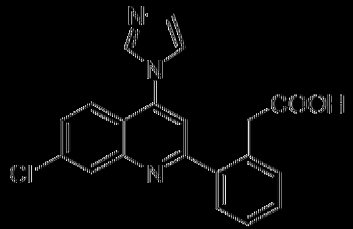
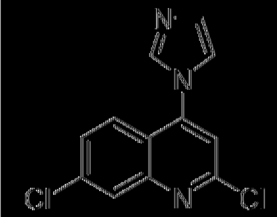
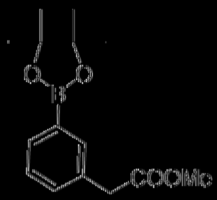
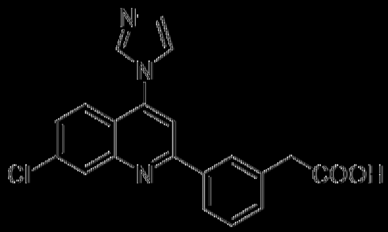
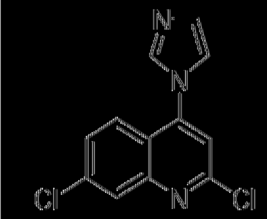
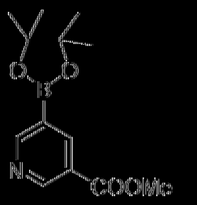
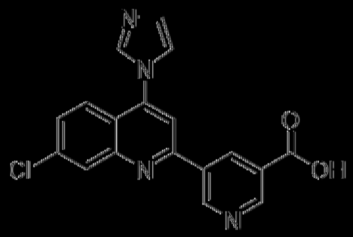
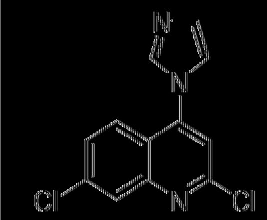
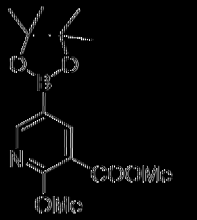
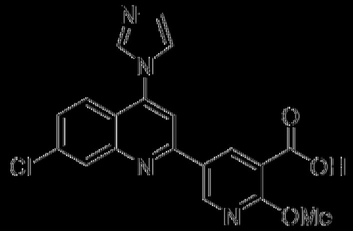
I-27				428.0
I-17				368.0
I-14				364.1
I-9				364.1
I-32				351.0
I-33				381.1

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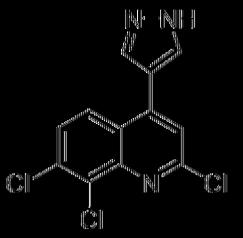
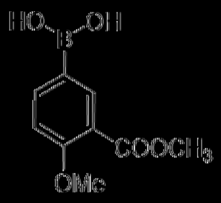
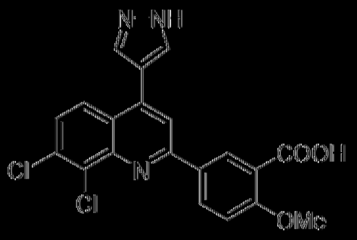
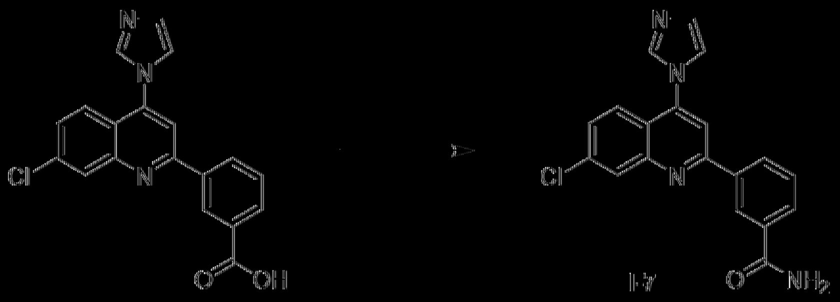
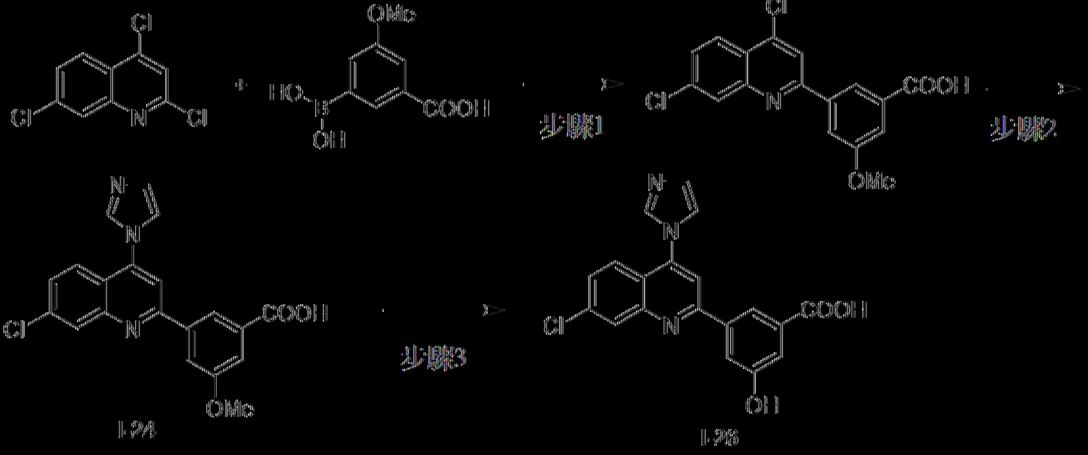
I-427				414

實例10：合成3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲醯胺(I-7)



【0539】 向3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸(25 mg，0.07 mmol)於THF (1 mL)中之溶液中添加$SOCl_2$ (0.015 mL，0.2 mmol)。1小時後，添加NH_4OH (水溶液，0.5 mL)。3小時後，藉由蒸發移除溶劑，得到粗品。將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(MS: $[M+1]^+$ 349.1)。

實例11：合成3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-甲氧基苯甲酸(I-24)及3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-羥基苯甲酸(I-26)



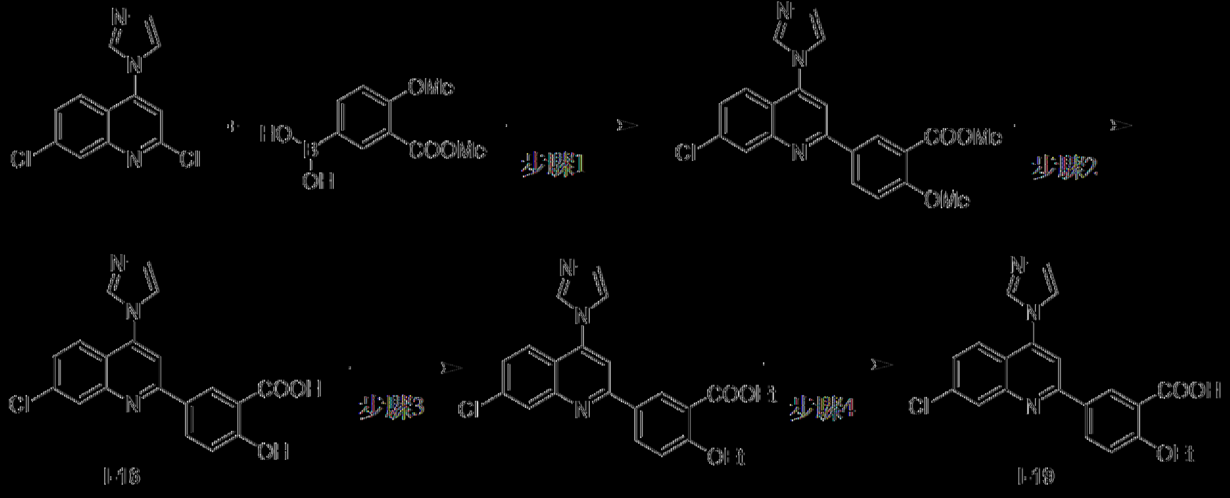
【0540】 步驟1：3-(4,7-二氯喹啉-2-基)-5-甲氧基苯甲酸基本上藉

由與以上關於製備I-2所描述相同之方法製備。

【0541】 步驟2：3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-甲氧基苯甲酸. 向小瓶中添加3-(4,7-二氯喹啉-2-基)-5-甲氧基苯甲酸(50 mg，0.144 mmol)、咪唑(49 mg，0.718 mmol)、Cs_2CO_3 (70 mg，0.216 mmol)及DMF (1.0 mL)。在110℃下將所得反應混合物攪拌隔夜。在室溫下將反應混合物用H_2O (4 mL)稀釋並藉由HCl (1 N)酸化至約pH 3。有許多白色固體沈澱，離心並用H_2O (2 × 4 mL)洗滌。將殘餘物真空乾燥，得到呈白色固體狀之標題化合物(30 mg)。MS: $[M+1]^+$ 380。

【0542】 步驟3：3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-羥基苯甲酸. 向小瓶中添加3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-甲氧基苯甲酸(7.9 mg，0.0208 mmol)、NaI (20 mg，0.133 mmol)及HBr之HOAc溶液(33%，1.0 mL)。在50℃下將所得混合物攪拌隔夜。將混合物冷卻至室溫並藉由H_2O (10 mL)稀釋，離心，並用H_2O (4 mL)洗滌。在高真空下乾燥殘餘物，得到呈灰白色固體狀之標題產物(18 mg) (MS: $[M+1]^+$ 366)。

實例12：合成5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸(I-16)及5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-乙氧基苯甲酸(I-19)



【0543】 步驟1：5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-甲氧基苯

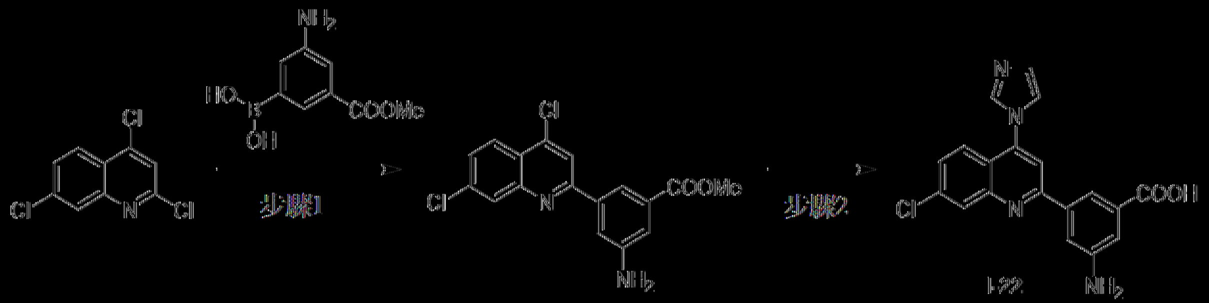
甲酸甲酯係根據以上製備化合物I-2之程序製備。

【0544】 步驟2：5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸(I-16)係根據以上製備化合物I-26之程序製備。(MS: $[M+1]^+$ 366)。

【0545】 步驟3：基5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-乙氧基苯甲酸乙酯. 向小瓶中添加5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸(14 mg，0.0383 mmol)、碘乙烷(22 μl，0.274 mmol)、Cs_2CO_3 (62 mg，0.191 mmol)及DMF (1.0 mL)。在室溫下將所得反應混合物攪拌隔夜。將混合物用乙酸乙酯(40 mL)稀釋，用H_2O (4 × 20 mL)及鹽水(15 mL)洗滌。濃縮後，將粗品用於下一步驟。

【0546】 步驟4：5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-乙氧基苯甲酸. 向以上粗產物中添加MeOH (0.6 mL)、THF (0.4 mL)及NaOH於H_2O中之溶液(7.66 mg/0.2 mL)。在室溫下將所得反應混合物攪拌隔夜。接著，將混合物用H_2O (3 mL)稀釋並藉由HOAc酸化至pH 4。將渾濁混合物離心並將殘餘物用H_2O (2 × 1.5 mL)洗滌，經高真空乾燥，得到呈灰白色固體狀之標題產物(6 mg) (MS: $[M+1]^+$ 394)。

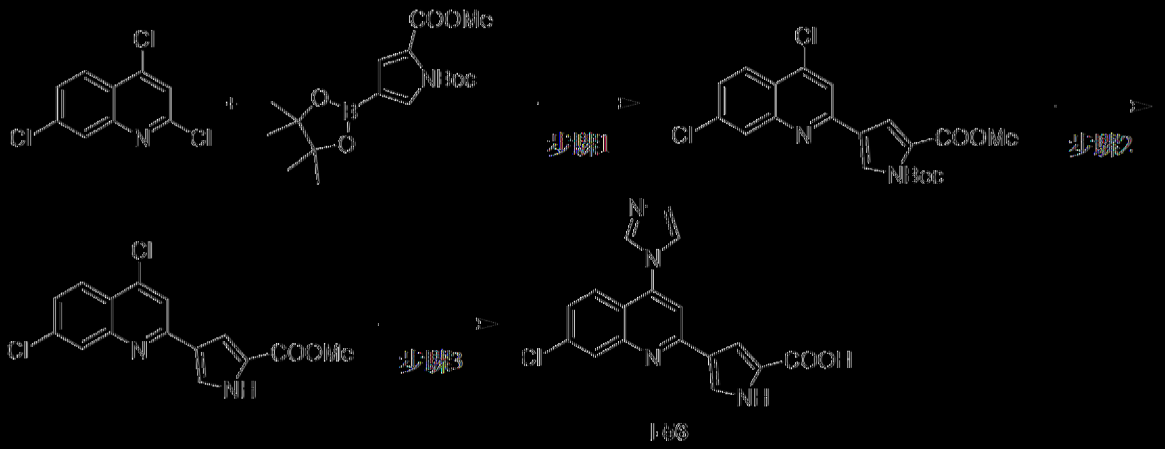
實例13：合成3-胺基-5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸(I-22)



【0547】 步驟1：3-胺基-5-(4,7-二氯喹啉-2-基)苯甲酸甲酯係根據以上製備化合物I-2之程序製備。

【0548】 步驟2：3-胺基-5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸係根據以上製備化合物I-24之程序製備(MS: $[M+1]^+$ 365)。

實例14：合成4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-1H-吡咯-2-甲酸(I-56)

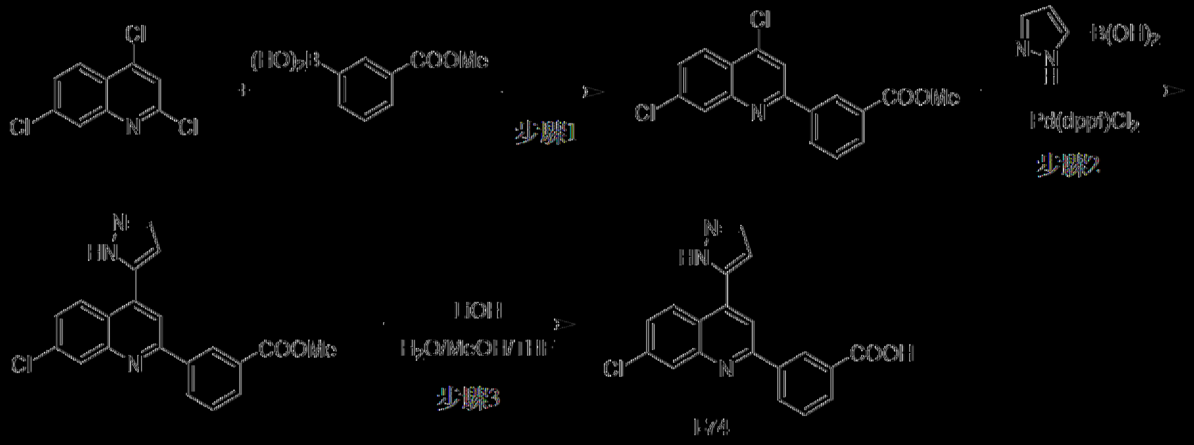


【0549】 步驟1：4-(4,7-二氯喹啉-2-基)-1H-吡咯-1,2-二甲酸1-(三級丁基)酯2-甲酯係根據以上關於製備化合物I-2所描述之程序製備。

【0550】 步驟2：4-(4,7-二氯喹啉-2-基)-1H-吡咯-2-甲酸甲酯係根據以上關於製備化合物I-172 (步驟3)所描述之程序製備。

【0551】 步驟3：4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-1H-吡咯-2-甲酸係根據以上關於製備化合物I-24 (步驟2)所描述之程序製備。(MS: $[M+1]^+$ 339)。

實例15：合成3-(7-氯-4-(1H-吡唑-5-基)喹啉-2-基)苯甲酸(I-74)



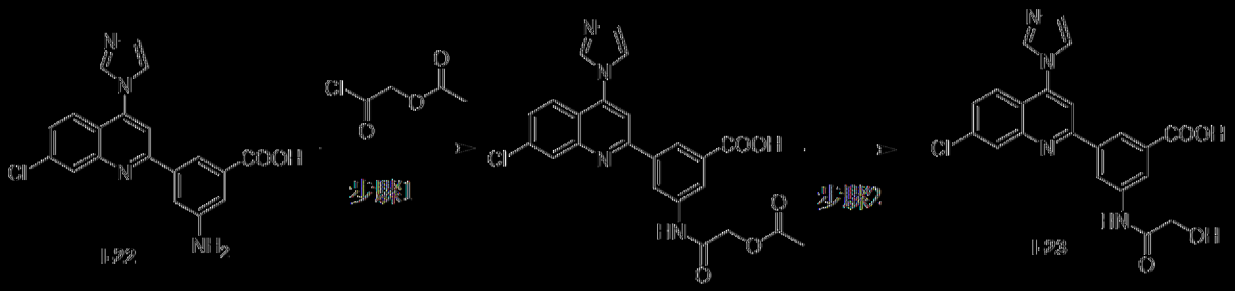
【0552】 步驟1：3-(4,7-二氯喹啉-2-基)苯甲酸甲酯係根據以上關於製備化合物I-2所描述之程序製備。

【0553】 步驟2：3-(7-氯-4-(1H-吡唑-5-基)喹啉-2-基)苯甲酸甲酯係

根據以上關於製備化合物I-2所描述之程序製備。

【0554】 步驟3：3-(7-氯-4-(1H-吡唑-5-基)喹啉-2-基)苯甲酸係根據以上關於製備化合物I-24 (步驟2)所描述之程序製備。(MS: $[M+1]^+$ 350)。

實例16：合成3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-羥基乙醯胺基)苯甲酸(I-23)

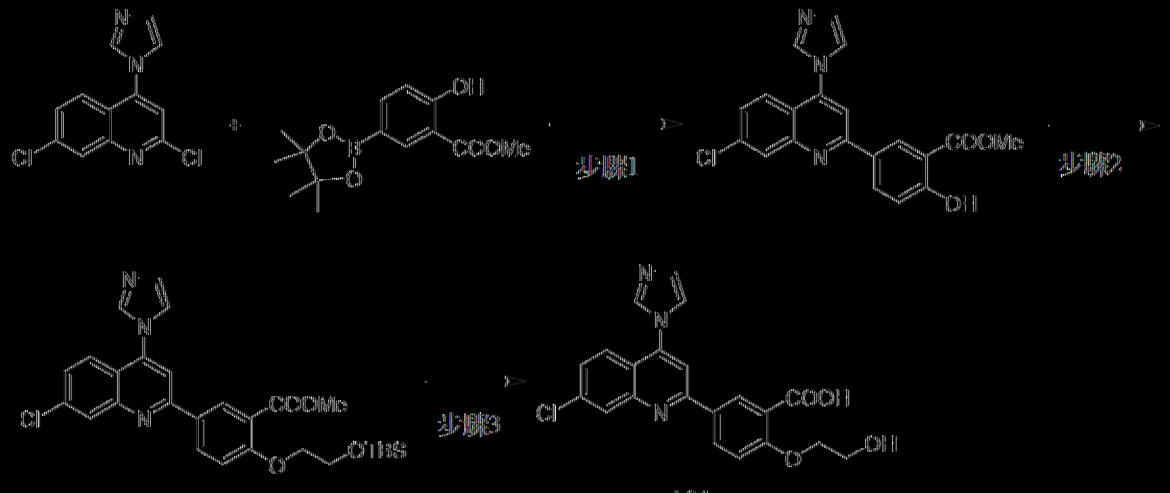


【0555】 步驟1：3-(2-乙醯氧基乙醯胺基)-5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸. 向小瓶中添加3-胺基-5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸(9.3 mg，0.0255 mmol)、DCM (0.5 mL)及TEA (8.9 µl，0.0637 mmol)。添加乙酸2-氯-2-側氧基乙酯於DCM中之溶液(4.18 mg/0.1 mL，0.0306 mmol)並在室溫下將所得反應混合物攪拌1小時。添加H_2O (0.5 mL)以淬滅反應。減壓移除大部分DCM並將粗品用於下一步驟。

【0556】 步驟2：3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-羥基乙醯胺基)苯甲酸. 向以上粗產物(3-(2-乙醯氧基乙醯胺基)-5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸)中添加MeOH (0.5 mL)、THF (1.0 mL)及$LiOH\text{-}H_2O$於H_2O中之溶液(5.36 mg/0.2 mL，0.127 mmol)。在室溫下將所得反應混合物攪拌16小時。移除所有揮發性物質並用H_2O (2.5 mL)稀釋混合物。離心後，將殘餘物用H_2O (2 × 3 mL)洗滌，在高真空下乾燥，得到呈白色固體狀之標題產物(MS: $[M+1]^+$ 423)。

實例17：合成5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-(2-羥基乙氧基)苯甲

酸(I-21)



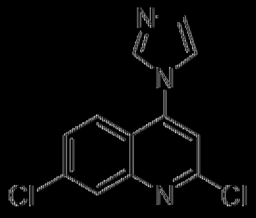
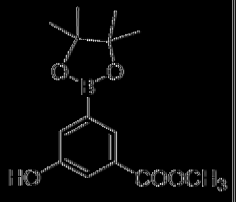
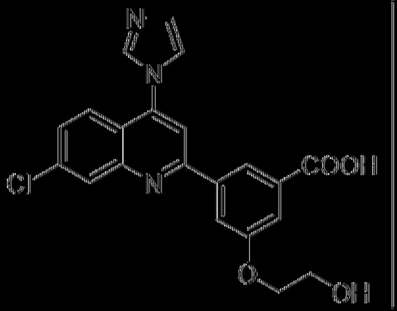
I-21

【0557】 步驟1：5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸甲酯係根據以上關於製備化合物I-2所描述之程序製備。

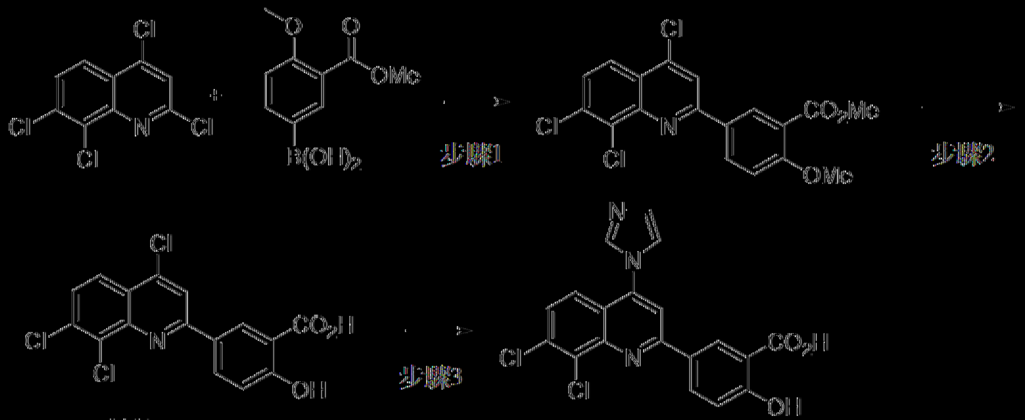
【0558】 步驟2：2-(2-((三級丁基二甲基矽基)氧基)乙氧基)-5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲酸甲酯. 向小瓶中添加5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸甲酯(10 mg，0.0263 mmol)、Cs_2CO_3 (10.3 mg，0.0316 mmol)及(2-溴乙氧基)(三級丁基)二甲基矽烷於DMF中之溶液(6.8 µl/0.5 mL，0.0316 mmol)。在室溫下將所得反應混合物攪拌1小時。接著，將混合物用乙酸乙酯(30 mL)稀釋，用H_2O (4 × 10 mL)及鹽水(10 mL)洗滌，經Na_2SO_4乾燥。濃縮後，將粗品用於下一步驟。

【0559】 步驟3：5-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-(2-羥基乙氧基)苯甲酸. 向步驟2之粗品中添加MeOH (0.5 mL)、THF (1.0 mL)及LiOH·H_2O於H_2O中之溶液(5.5 mg/0.5 mL，0.132 mmol)。在室溫下將所得反應混合物攪拌48小時。藉由乙酸將混合物酸化至pH 5。移除大部分揮發性物質並將殘餘物用H_2O (1.5 mL)稀釋，離心，用H_2O (2 × 1.5 mL)洗滌，在高真空下乾燥，得到呈灰白色固體狀之標題產物(MS: $[M+1]^+$ 410)。

【0560】 以下化合物基本上藉由與以上關於製備I-21所描述相同的方法製備。

I#	起始材料		結構	MS $[M+1]^+$
I-29				410

實例18：合成5-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸(I-42)



I-75　　　　I-42

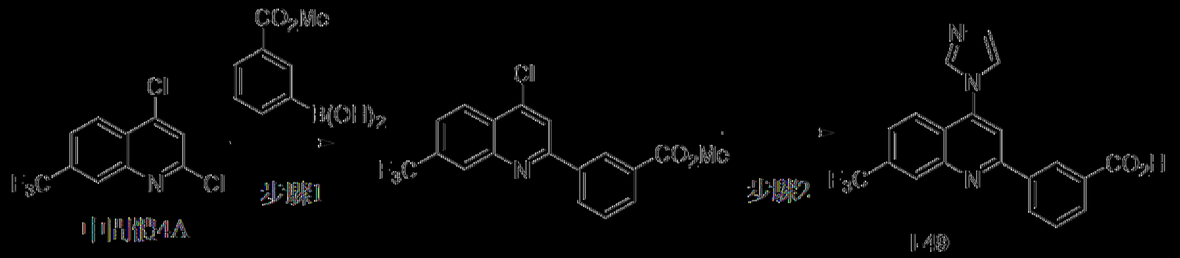
【0561】 步驟1：2-甲氧基-5-(4,7,8-三氯喹啉-2-基)苯甲酸甲酯. 向2,4,7,8-四氯喹啉(200 mg，0.75 mmol)與(4-甲氧基-3-(甲氧基羰基)苯基)硼酸(205.3 mg，0.98 mmol)及Na_2CO_3 (178 mg，1.68 mmol)於二㗁烷(8.0 mL)及水(2.0 mL)中之懸浮液中添加$Pd(PPh_3)_4$ (79.2 mg)。將所得混合物抽真空且用N_2吹掃，持續三個循環，接著攪拌並在80°C下加熱兩小時。在冷卻至室溫後，將反應混合物溶解於DCM (50 mL)中並用水及鹽水洗滌。將所得有機層分離且經無水Na_2SO_4乾燥。進行矽膠急驟管柱層析，用DCM/己烷溶離，得到所需無色產物(MS: $[M+1]^+$ 396)。

【0562】 步驟2：2-羥基-5-(4,7,8-三氯喹啉-2-基)苯甲酸(I-75). 在

室溫下，用1M BBr_3之DCM溶液(0.1 mL)處理於DCM (1.5 mL)中之2-甲氧基-5-(4,7,8-三氯喹啉-2-基)苯甲酸甲酯(17 mg) 8小時。將所得混合物用EtOAc (25 mL)稀釋，用水(10 mL)洗滌且經Na_2SO_4乾燥。真空濃縮，得到所需淺褐色固體(11 mg)，即2-羥基-5-(4,7,8-三氯喹啉-2-基)苯甲酸(MS: $[M+1]^+$ 368)。

【0563】 步驟3：5-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-羥基苯甲酸. 向2-羥基-5-(4,7,8-三氯喹啉-2-基)苯甲酸(11 mg)於DMF (0.5 mL)中之溶液中添加咪唑(55 mg)及K_2CO_3 (50 mg)。攪拌所得溶液並在120℃下加熱5小時，直至起始材料完全消耗。將反應混合物用水(3 mL)稀釋並用Dowex樹脂處理，直至pH值達到3。藉由過濾將所得無色固體分離並用水(3 mL)洗滌。真空乾燥後，獲得所需產物(MS: $[M+1]^+$ 400)。

實例19：合成3-(4-(1H-咪唑-1-基)-7-(三氟甲基)喹啉-2-基)苯甲酸(I-49)

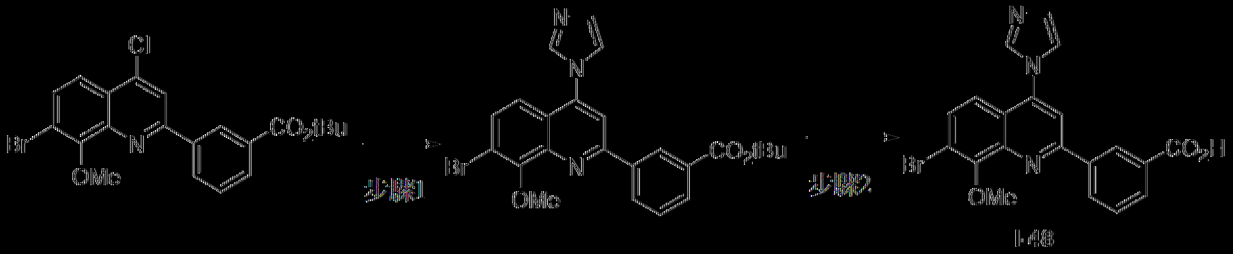


【0564】 步驟1：3-(4-氯-7-(三氟甲基)喹啉-2-基)苯甲酸甲酯. 向2,4-二氯-7-(三氟甲基)喹啉(217 mg，0.82 mmol)與(3-(甲氧基羰基)苯基)硼酸(190.9 mg，1.06 mmol)於二噁烷(7 mL)及水(3 mL)中之混合物中添加Na_2CO_3 (191 mg，1.804 mmol)及$Pd(PPh_3)_4$ (95 mg，0.082 mmol)。將所得混合物置於真空下且用氮氣反覆吹掃三次，接著攪拌並在90℃下加熱3小時。將反應混合物用水(25 mL)稀釋並用EtOAc (20 mL)萃取。在分離有機層並進行管柱層析，用0至60%之DCM/己烷梯度溶離後，得到所需產物(254 mg)，即3-(4-氯-7-(三氟甲基)喹啉-2-基)苯甲酸甲酯(MS: $[M+1]^+$

366)。

【0565】 步驟2：3-(4-(1H-咪唑-1-基)-7-(三氟甲基)喹啉-2-基)苯甲酸. 向3-(4-氯-7-(三氟甲基)喹啉-2-基)苯甲酸甲酯(42 mg，0.12 mmol)、咪唑(40 mg)及Cs_2CO_3之混合物中添加DMF (0.6 mL)。攪拌懸浮溶液並在100℃下加熱6小時。將反應混合物用水(2 mL)稀釋並用HOAc酸化至pH 3以沈澱得到產物。將產物藉由離心機分離並用水及50%乙腈/水沖洗。真空乾燥濕固體，得到標題化合物(30 mg) ($[M+1]^+$: 384)。

實例20：合成3-(7-溴-4-(1H-咪唑-1-基)-8-甲氧基喹啉-2-基)苯甲酸(I-48)



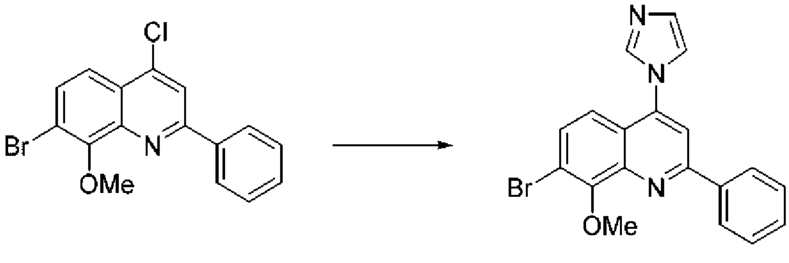
【0566】 遵循I-49之製備中之步驟1，由中間體17製備3-(7-溴-4-氯-8-甲氧基喹啉-2-基)苯甲酸三級丁酯。

【0567】 步驟1：3-(7-溴-4-(1H-咪唑-1-基)-8-甲氧基喹啉-2-基)苯甲酸三級丁酯. 向3-(7-溴-4-氯-8-甲氧基喹啉-2-基)苯甲酸三級丁酯(125 mg)及Cs_2CO_3 (136.8 mg)於DMF (2 mL)中之混合物中添加咪唑(96 mg)。攪拌懸浮溶液並在130℃下加熱2小時。用EtOAc進行水性處理並進行管柱層析，用EtOAc/己烷溶離，得到所需產物3-(7-溴-4-(1H-咪唑-1-基)-8-甲氧基喹啉-2-基)苯甲酸三級丁酯(120 mg) (MS: $[M+1]^+$ 480)。

【0568】 步驟2：3-(7-溴-4-(1H-咪唑-1-基)-8-甲氧基喹啉-2-基)苯甲酸. 向3-(7-溴-4-(1H-咪唑-1-基)-8-甲氧基喹啉-2-基)苯甲酸三級丁酯(65 mg)於DCM (0.2 mL)及MeOH (0.2 mL)中之溶液中添加TFA (0.4 mL)。將所得溶液攪拌5小時並濃縮至乾。將所得油性殘餘物懸浮於水(0.5 mL)中

並凍乾，得到呈淺褐色粉末狀之標題化合物3-(7-溴-4-(1H-咪唑-1-基)-8-甲氧基喹啉-2-基)苯甲酸(60 mg) (MS: $[M+1]^+$ 424)。

實例21：合成7-溴-4-(1H-咪唑-1-基)-8-甲氧基-2-苯基喹啉(**I-54**)

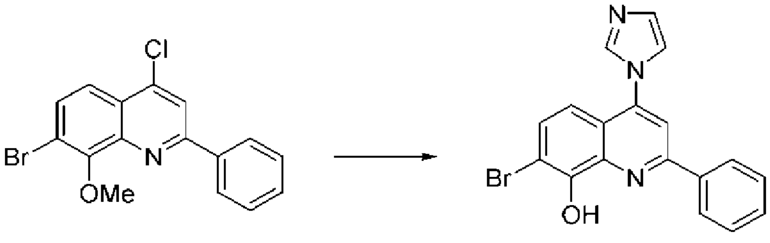


I-54

【0569】 7-溴-4-氯-8-甲氧基-2-苯基喹啉係遵循3-(4-氯-7-(三氟甲基)喹啉-2-基)苯甲酸甲酯之製備程序中的步驟1製備。

【0570】 向7-溴-4-氯-8-甲氧基-2-苯基喹啉(63 mg)於DMF (2.0 mL)中之溶液中添加咪唑(129 mg)及Cs_2CO_3 (62 mg)。在80℃下，將反應混合物用水(4 mL)稀釋以沈澱得到所需產物。分離產物並用水(2 mL)沖洗，得到標題化合物(55 mg)，即7-溴-4-(1H-咪唑-1-基)-8-甲氧基-2-苯基喹啉(MS:$[M+1]^+$ 380)。

實例22：合成7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉-8-醇(**I-53**)

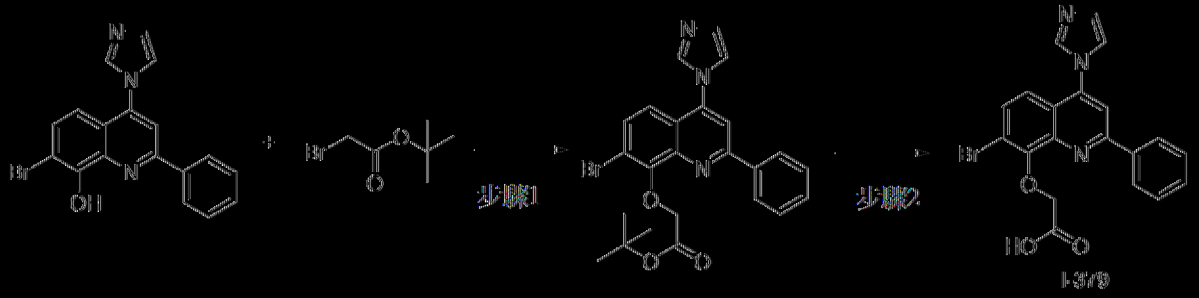


I-53

【0571】 向7-溴-4-氯-8-甲氧基-2-苯基喹啉(20 mg)於DMF (0.5 mL)中之溶液中添加咪唑(50 mg)及Cs_2CO_3 (50 mg)。在120℃下將所得混合物攪拌隔夜。將反應混合物用水(3 mL)稀釋以沈澱得到所需產物。分離產物並用水(1 mL)沖洗，得到標題化合物(MS:$[M+1]^+$ 366)。

實例23：合成2-((7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉-8-基)氧基)乙酸(**I-**

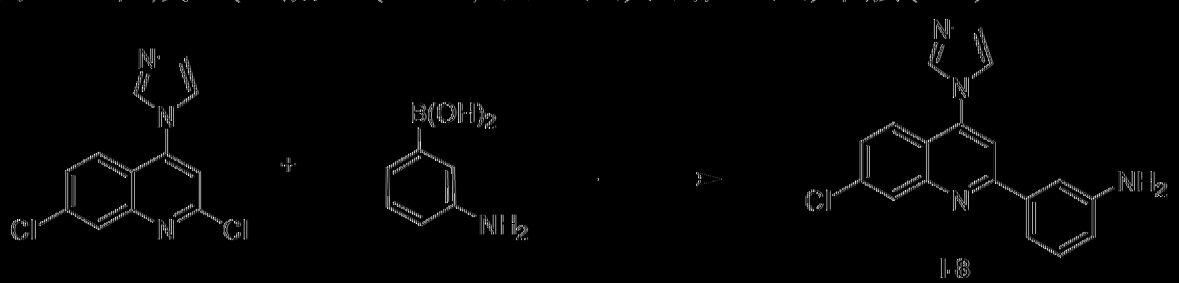
379)



【0572】 步驟1：2-((7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉-8-基)氧基)乙酸三級丁酯. 向7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉-8-醇(10 mg)於DMSO (2 mL)中之溶液中添加2-溴乙酸三級丁酯(40 mg)及K_2CO_3 (40 mg)。在室溫下將所得溶液攪拌3小時並用水/EtOAc (20 mL)稀釋。分離有機層，用鹽水洗滌並經Na_2SO_4乾燥，接著進行管柱層析，用己烷/EtOAc溶離，得到所需產物(9 mg)。MS:$[M+1]^+$ 480。

【0573】 步驟2：2-((7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉-8-基)氧基)乙酸. 向2-((7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉-8-基)氧基)乙酸三級丁酯(9 mg)於DCM (0.8 mL)中之溶液中添加TFA (0.2 mL)。將所得溶液攪拌隔夜並濃縮至乾。凍乾，得到所需產物(6.6 mg) (MS:$[M+1]^+$ 424)。

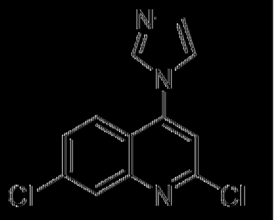
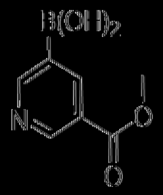
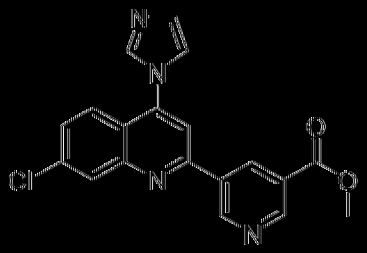
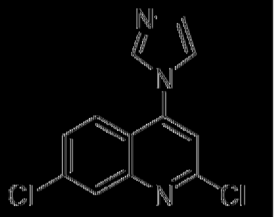
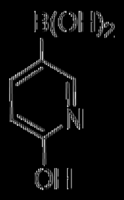
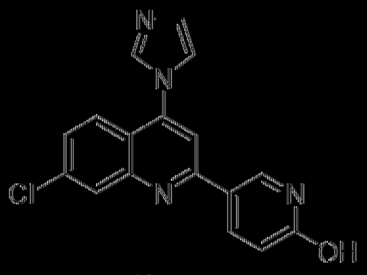
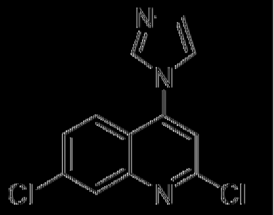
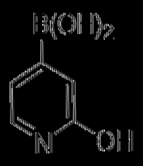
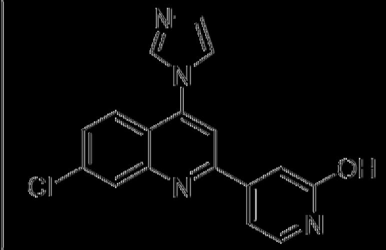
實例24：合成3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯胺(I-8)



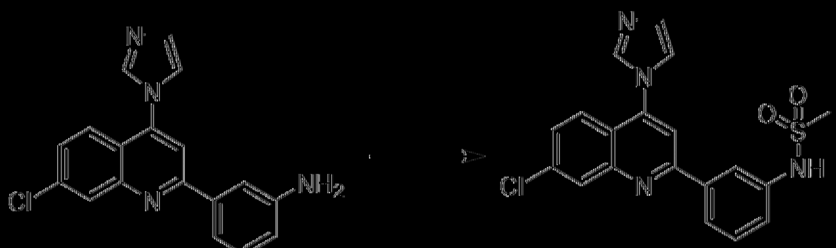
【0574】 在N_2下，將2,7-二氯-4-(1H-咪唑-1-基)喹啉(26 mg，0.10 mmol)放入含二噁烷(2.3 mL)及水(0.5 mL)之小瓶中。添加(3-胺基苯基)硼酸(21 mg，0.15 mmol)及碳酸鉀(70 mg，0.50 mmol)，隨後添加肆(三苯基膦)鈀(0) (6 mg，0.005 mmol)。在100℃下將混合物攪拌16小時。添加

水(5mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5 mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。藉由二氧化矽層析法純化，得到3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯胺(MS: $[M+1]^+$ 321.1)。

【0575】 以下化合物基本上藉由與以上關於製備I-8所描述相同的方法製備。

I#	起始材料		結構	MS $[M+1]^+$
I-34				365.0
I-58				323.1
I-59				323.0

實例25：合成N-(3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯基)甲烷磺醯胺(I-10)

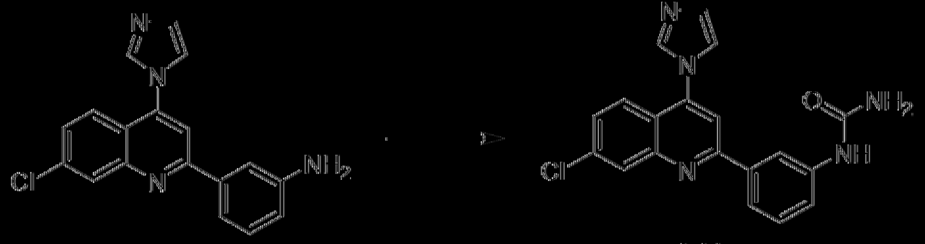


I-10

【0576】 將3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯胺(12 mg，0.04 mmol)放入含二氯甲烷(2 mL)及TEA (0.1 mL)之小瓶中並冷卻至0℃。添

加甲烷磺醯氯(6 mg，0.06 mmol)並在室溫下將溶液攪拌16小時。添加水(3mL)並用乙酸乙酯(2 × 5 mL)萃取水溶液。將合併之有機層乾燥並濃縮，並將殘餘物藉由二氧化矽層析法純化，得到N-(3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯基)甲烷磺醯胺(MS: $[M+1]^+$ 399.0)。

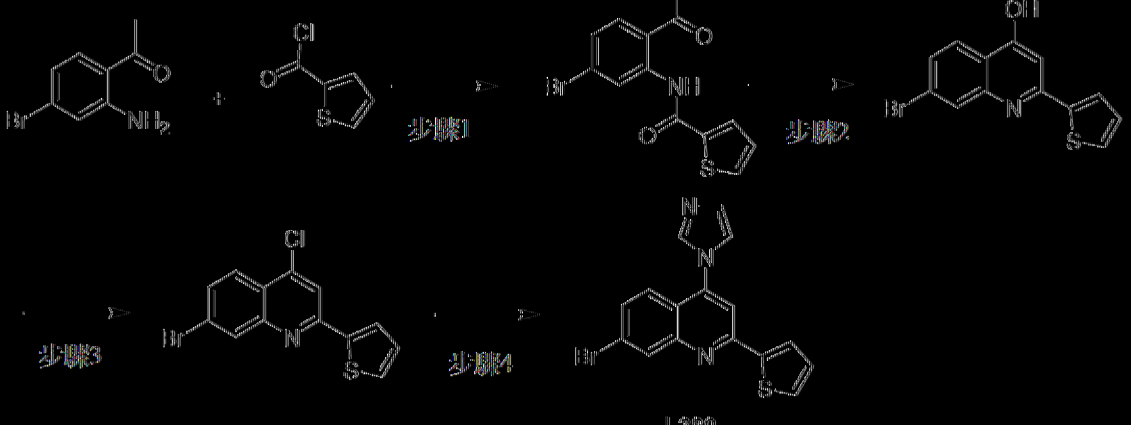
實例26：合成1-(3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯基)脲(I-11)



I-11

【0577】 將3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯胺(10 mg，0.03 mmol)放入含乙酸(0.2 mL)之小瓶中。接著，將於水中之氰酸鉀(25 mg，0.31 mmol)逐滴添加至該小瓶中，並在室溫下將溶液攪拌1.5小時。添加水(3mL)並用10%甲醇/二氯甲烷(2 × 5 mL)萃取水溶液。將合併之有機層乾燥並濃縮，並將殘餘物藉由二氧化矽層析法純化，得到1-(3-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)苯基)脲(MS: $[M+1]^+$ 364.1)。

實例27：合成7-溴-4-(1H-咪唑-1-基)-2-(噻吩-2-基)喹啉(I-380)



I-380

【0578】 步驟1：N-(2-乙醯基-5-溴苯基)噻吩-2-甲醯胺. 將1-(2-胺基-4-溴苯基)乙-1-酮(214 mg，1.00 mmol)放入含二氯甲烷(5 mL)及三乙

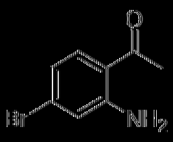
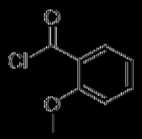
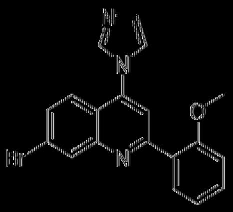
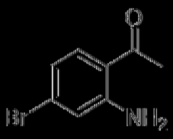
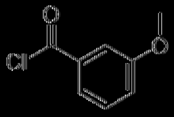
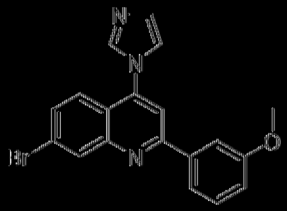
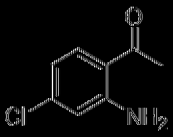
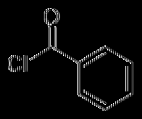
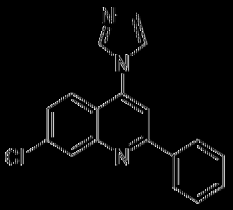
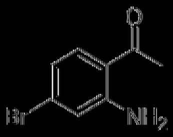
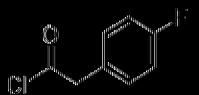
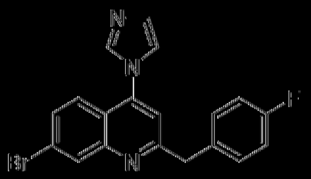
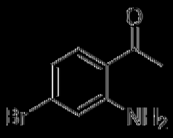
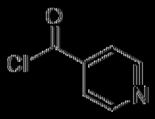
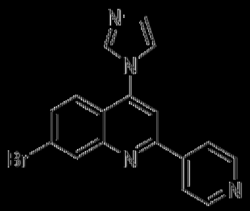
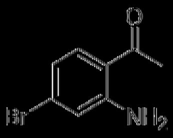
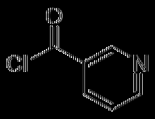
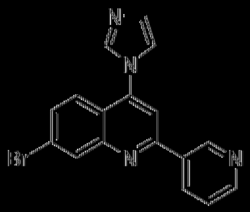
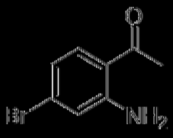
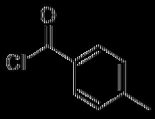
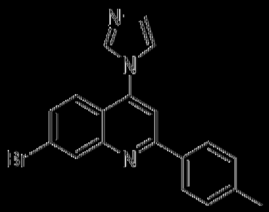
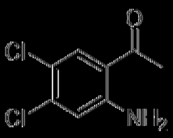
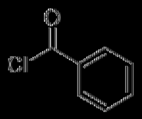
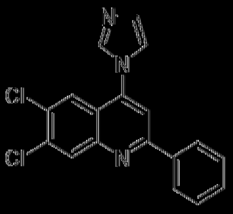
胺(0.15 mL，1.10 mmol)之燒瓶中，接著冷卻至0℃。逐滴添加噻吩-2-羰基氯(147 mg，1.10 mmol)。使反應物升溫至室溫並攪拌16小時。移除揮發性物質並將所得固體用二氯甲烷濕磨，過濾並真空乾燥，得到呈固體狀之N-(2-乙醯基-5-溴苯基)噻吩-2-甲醯胺(MS: $[M+1]^+$ 323.9)。

【0579】 步驟2：7-溴-2-(噻吩-2-基)喹啉-4-醇. 將N-(2-乙醯基-5-溴苯基)噻吩-2-甲醯胺(250 mg，0.77 mmol)放入含二噁烷(10 mL)之燒瓶中。添加氫氧化鈉(108 mg，2.7 mmol)並將混合物加熱至110℃，保持2小時。添加乙醇(2 mL)並過濾出所得固體。將濾液濃縮至乾。添加水(4 mL)及己烷(1mL)並將混合物攪拌5分鐘。將溶液用HCl (1.0 N水溶液)酸化並過濾所得固體且真空乾燥，得到呈固體狀之7-溴-2-(噻吩-2-基)喹啉-4-醇(MS: $[M+1]^+$ 306.0)。

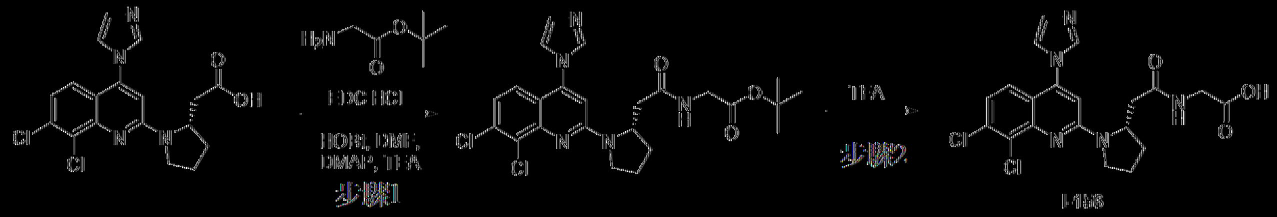
【0580】 步驟3：7-溴-4-氯-2-(噻吩-2-基)喹啉. 將7-溴-2-(噻吩-2-基)喹啉-4-醇(180 mg，0.59 mmol)放入含氧氯化磷(3 mL)之燒瓶中。將反應物加熱至110℃，保持3小時。冷卻至室溫後，添加冰。用乙酸乙酯(2 × 5 mL)萃取水溶液部分並乾燥(Na_2SO_4)合併之有機層，接著濃縮，得到7-溴-4-氯-2-(噻吩-2-基)喹啉(MS: $[M+1]^+$ 323.9)。

【0581】 步驟4：7-溴-4-(1H-咪唑-1-基)-2-(噻吩-2-基)喹啉. 在N_2下，將7-溴-4-氯-2-(噻吩-2-基)喹啉(65 mg，0.2 mmol)放入含咪唑(34 mg，0.50 mmol)、三級丁醇鉀(34 mg，0.30 mmol)、二氯化雙(三苯基膦)鈀(II)(7 mg，0.01 mmol)及DMA (3 mL)之燒瓶中。在110℃下將混合物加熱2小時。冷卻至室溫後，將粗品用EtOAc (20 mL)稀釋並用水(5 mL × 2)及鹽水(5 mL × 2)洗滌。將有機相濃縮並在矽膠上藉由管柱層析法純化，得到呈固體狀之7-溴-4-(1H-咪唑-1-基)-2-(噻吩-2-基)喹啉(MS: $[M+1]^+$ 356.0)。

【0582】以下化合物基本上藉由與以上關於製備I-380所描述相同的方法製備。

I#	起始材料		結構	MS $[M+1]^+$
I-381				380.0
I-382				380.0
I-1				306.1
I-275				382.1
I-383				351.0
I-384				351.0
I-385				364.0
I-50				340.0

實例28：合成(S)-(2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)乙醯基)甘胺酸(I-156)



【0583】 步驟1：(S)-(2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)乙醯基)甘胺酸三級丁酯. 向(S)-2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)乙酸(9.4 mg)、甘胺酸三級丁酯(8.05 mg)、EDC HCl (9.2 mg)、HOBt (6.5 mg)及DMAP (8.7 mg)之混合物中添加DMF (0.2 mL)及TEA (0.05 mL)。在室溫下將所得混合物攪拌隔夜並用EtOAc (20 mL)稀釋。將有機溶液用水、鹽水洗滌且經無水Na_2SO_4乾燥。進行管柱層析，用己烷及EtOAc梯度溶離，得到呈黃色固體狀之所需產物(9.0 mg) (MS: $[M+1]^+$ 544.2)。

【0584】 步驟2：(S)-(2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)乙醯基)甘胺酸. 向(S)-(2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)乙醯基)甘胺酸三級丁酯(9.0 mg)於DCM (0.4 mL)中之溶液中添加TFA (0.1 mL)。攪拌4小時後，將反應混合物減壓濃縮至乾並用水稀釋以凍乾。得到總計9.2 mg標題化合物(S)-(2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)乙醯基)甘胺酸(MS $[M+1]^+$: 448)。

【0585】 以下化合物基本上藉由與以上關於製備I-156所描述相同的方法製備。

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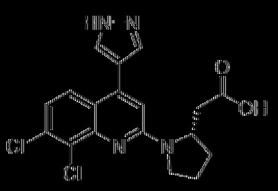
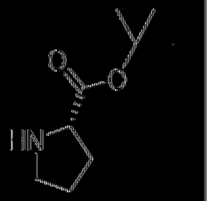
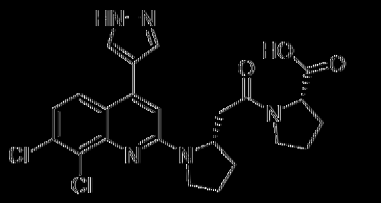
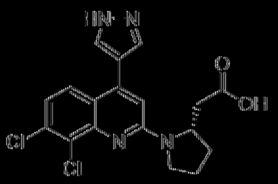
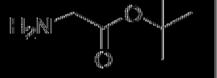
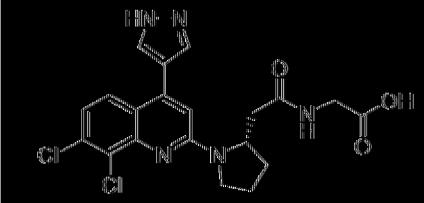
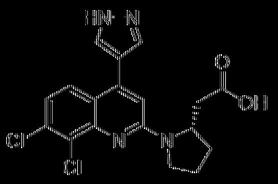
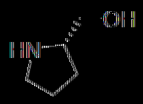
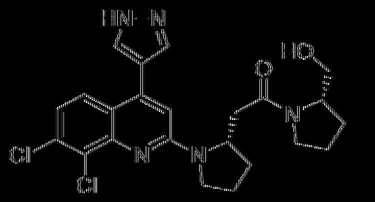
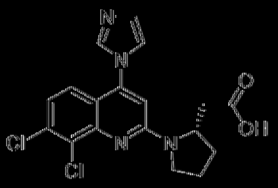
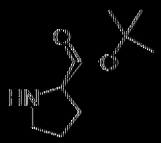
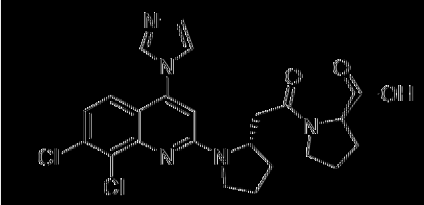
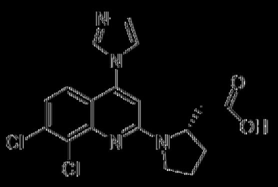
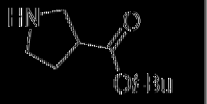
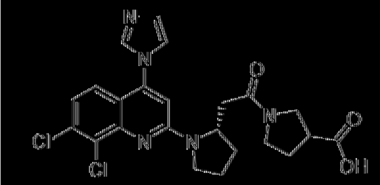
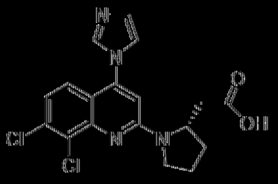
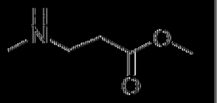
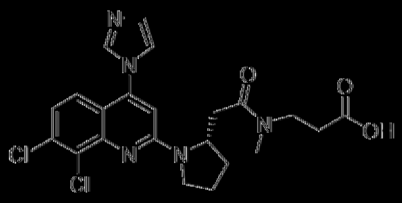
I-325				488
I-326				448
I-454				474
I-386	 2242			488
I-339				488
I-340				476

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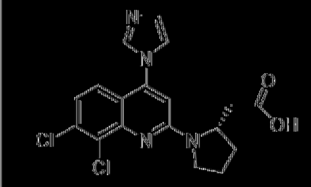
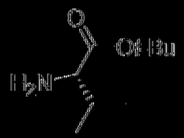
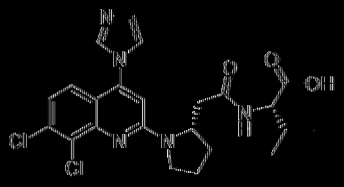
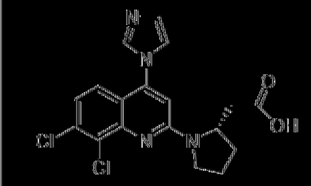
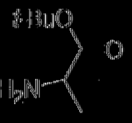
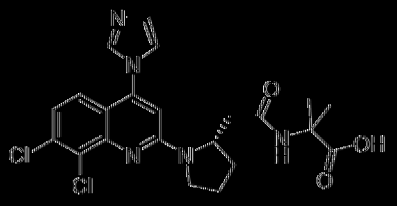
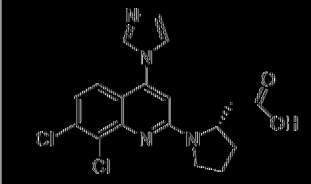
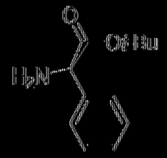
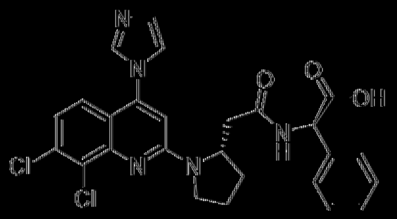
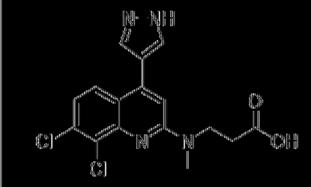
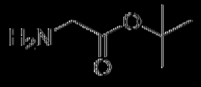
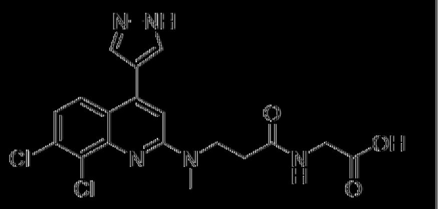
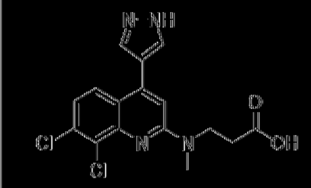
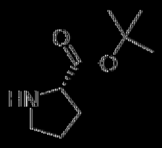
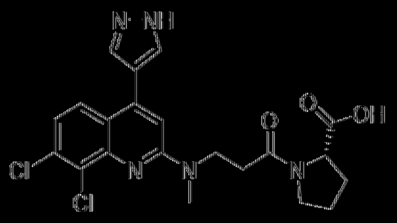
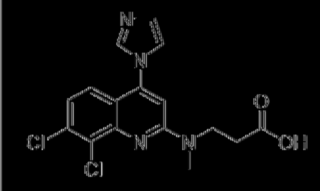
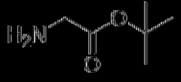
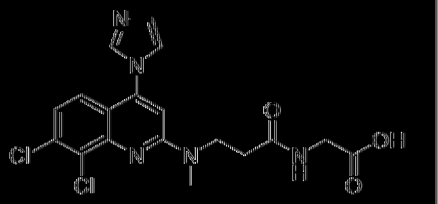
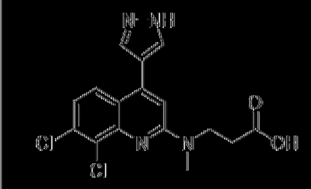
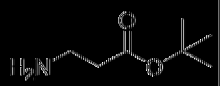
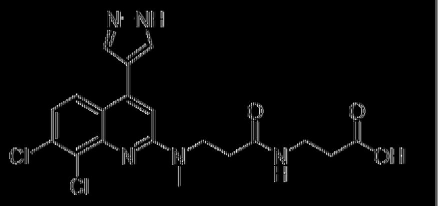
I-338				490
I-387				476
I-388				524.1
I-196				422
I-389				462
I-321				422
I-320				436

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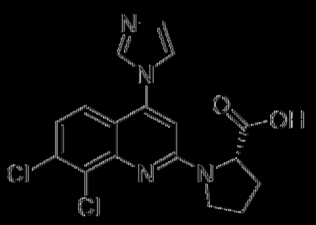
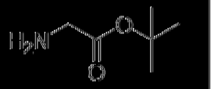
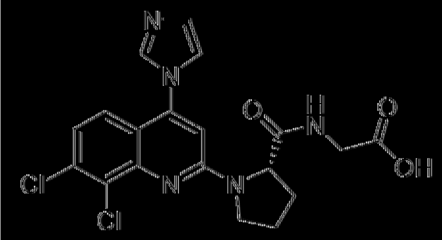
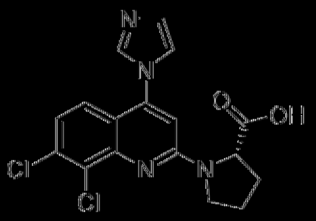
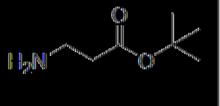
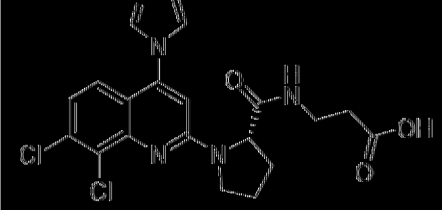
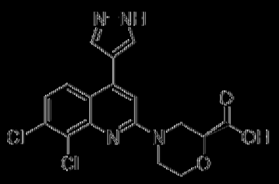
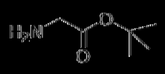
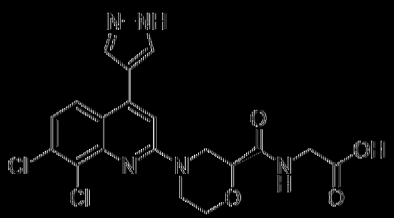
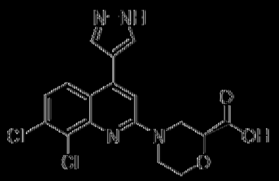
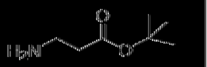
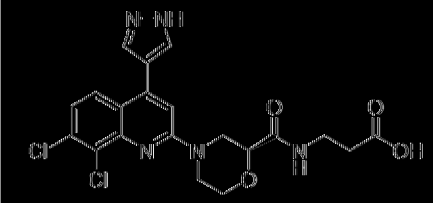
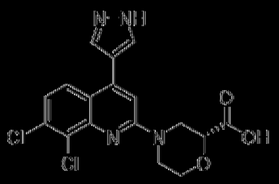
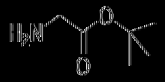
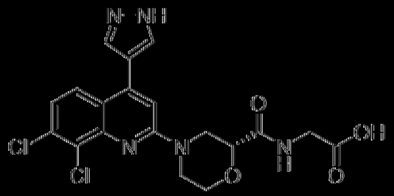
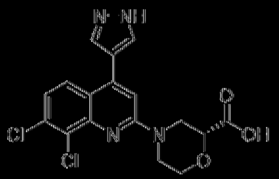
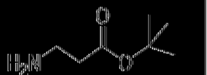
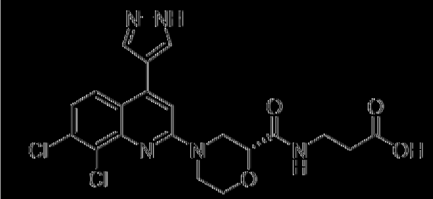
I-323				434
I-324				448
I-341				450
I-342				464
I-343				450
I-344				464

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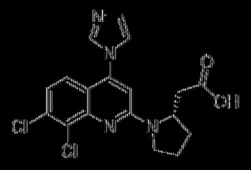
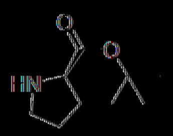
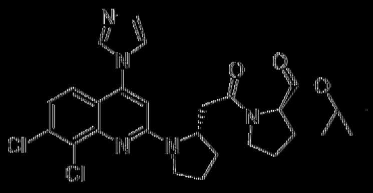
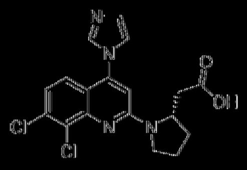
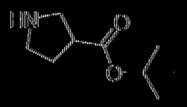
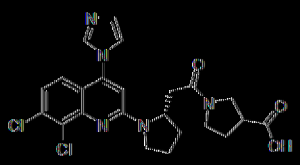
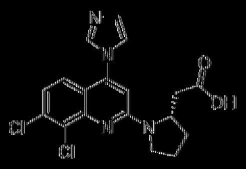
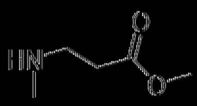
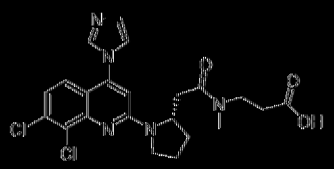
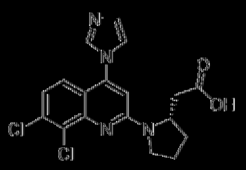
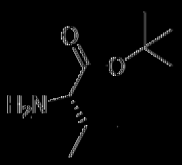
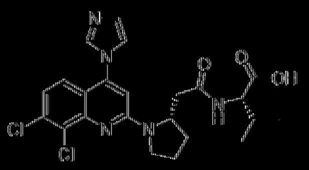
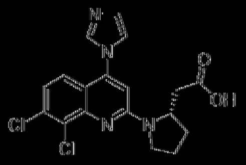
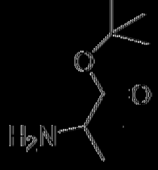
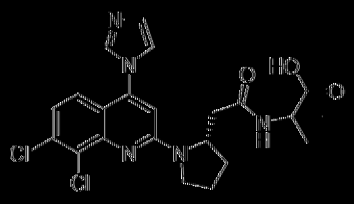
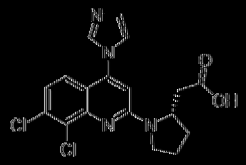
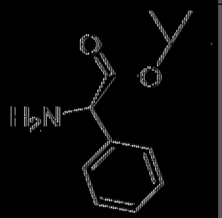
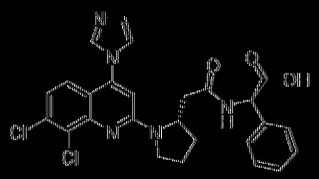
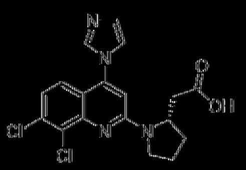
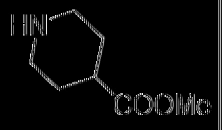
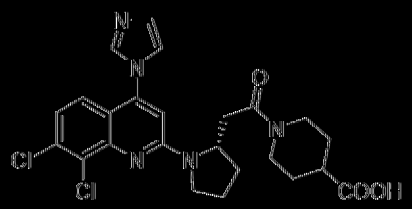
I-522				544
I-524				488
I-525				476
I-526				490
I-527				476
I-528				524
I-529				502

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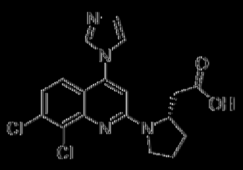
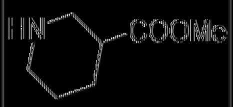
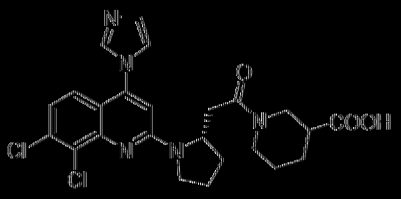
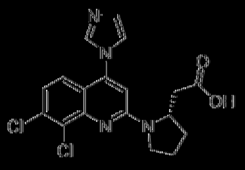
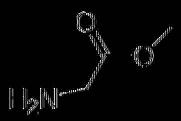
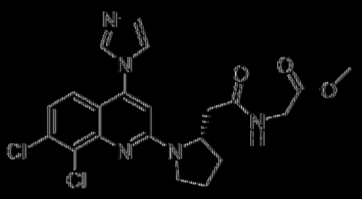
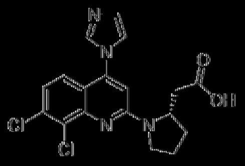
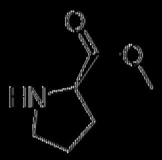
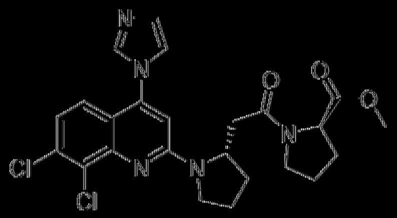
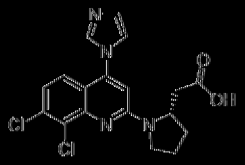
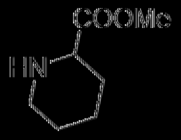
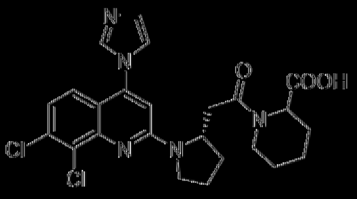
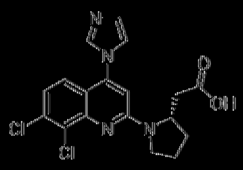
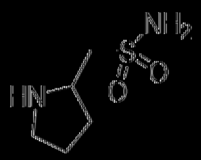
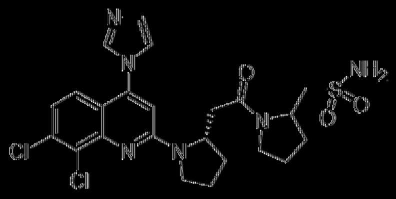
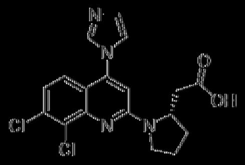
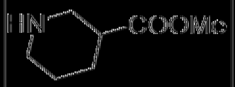
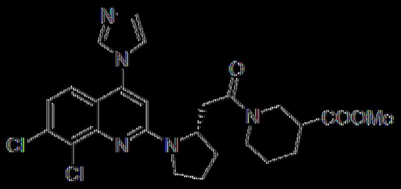
I-530				502
I-531				462
I-532				502
I-533				502
I-534				537
I-535				516

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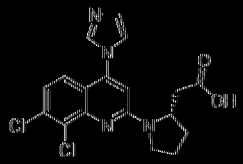
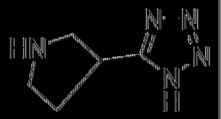
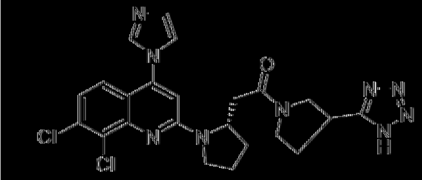
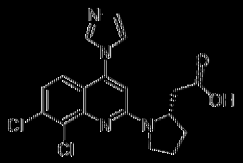
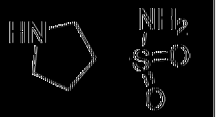
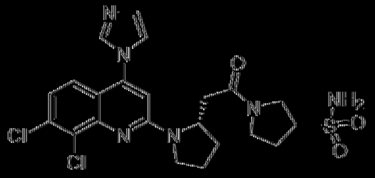
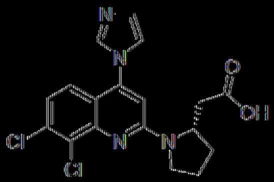
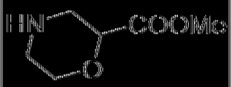
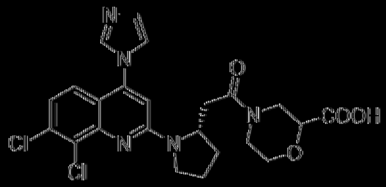
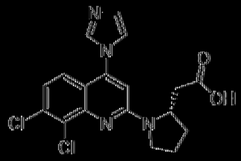
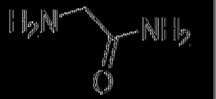
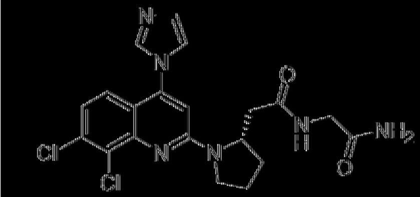
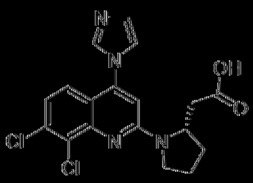
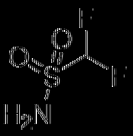
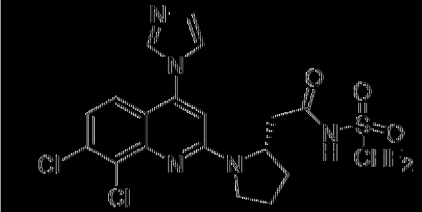
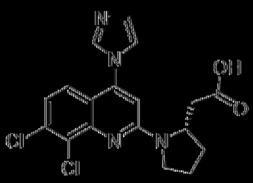
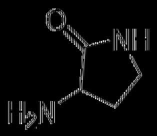
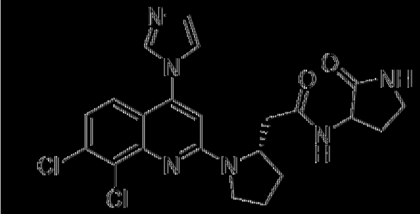
I-536				512
I-537				523
I-538				504
I-539				447
I-540				504
I-541				473

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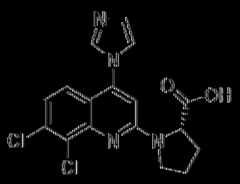
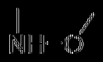
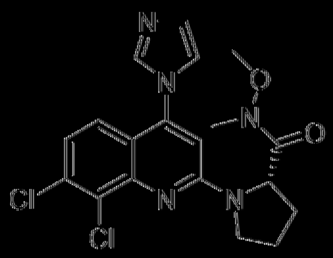
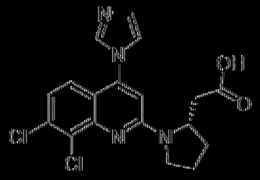
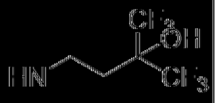
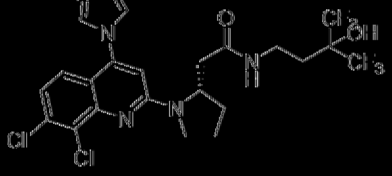
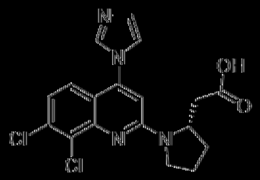
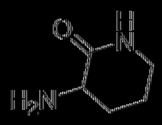
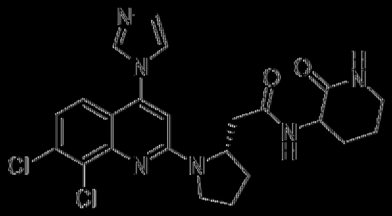
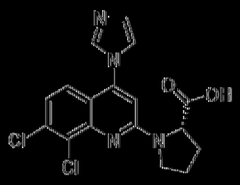
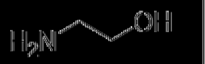
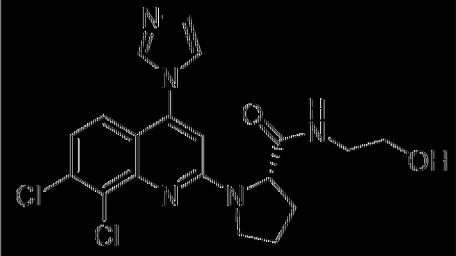
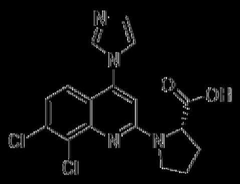
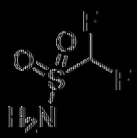
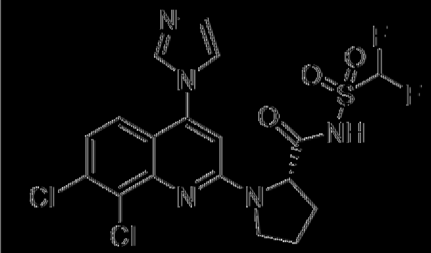
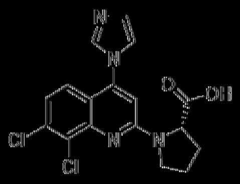
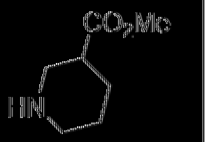
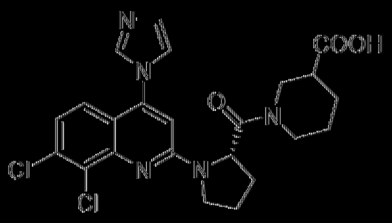
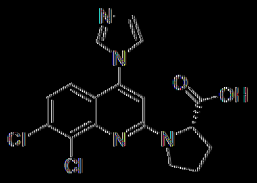
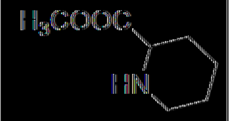
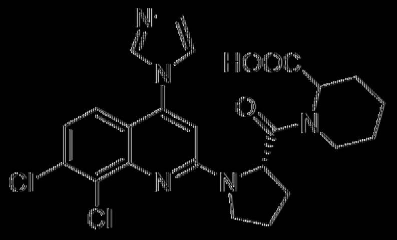
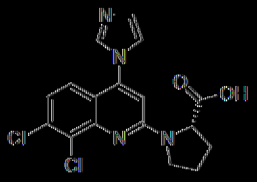
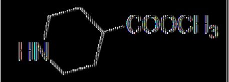
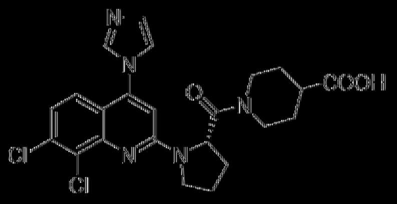
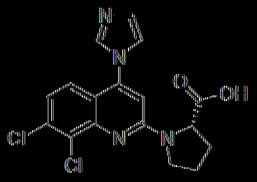
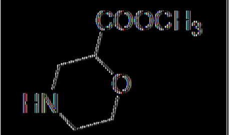
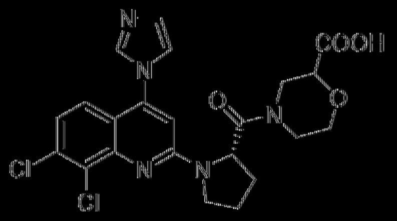
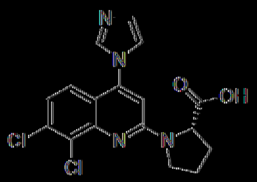
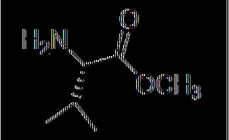
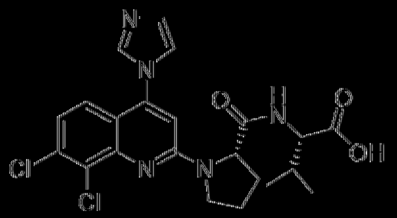
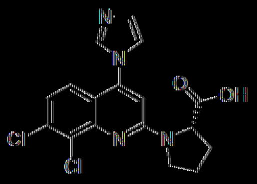
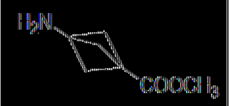
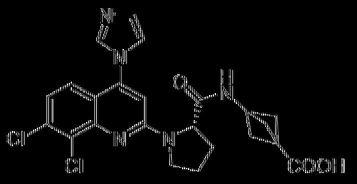
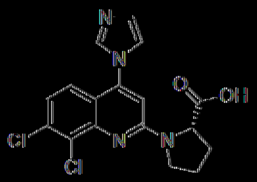
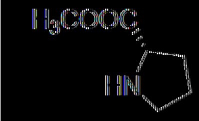
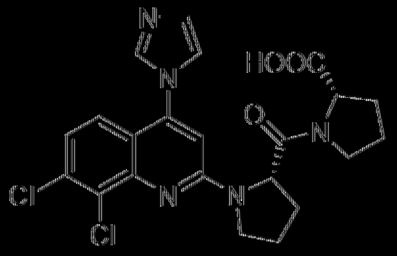
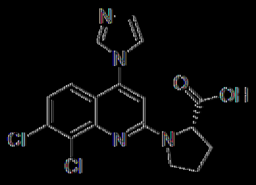
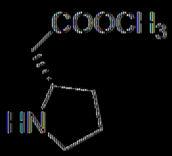
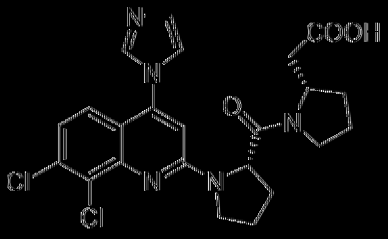
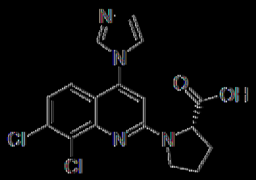
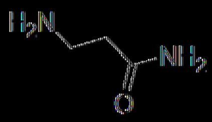
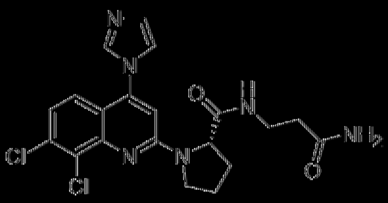
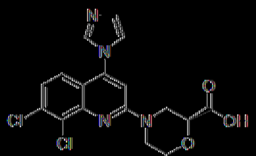
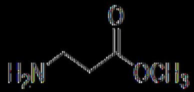
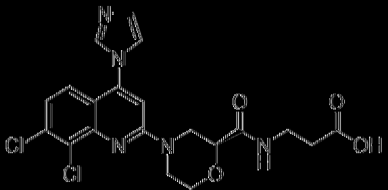
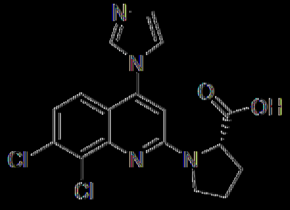
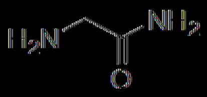
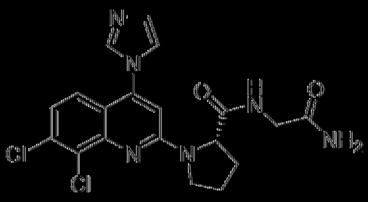
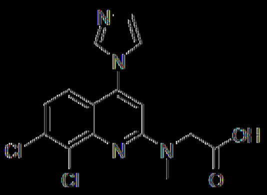
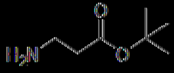
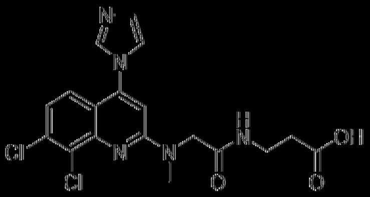
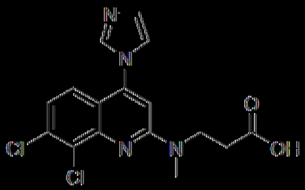
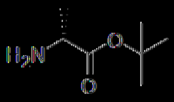
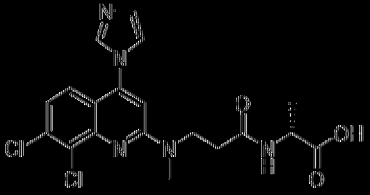
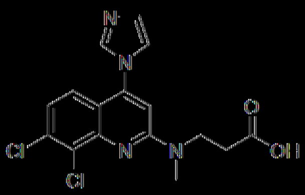
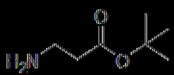
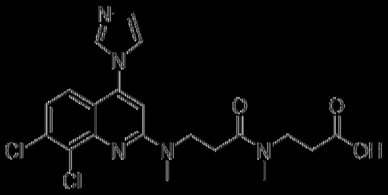
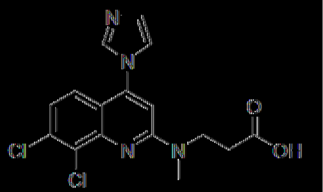
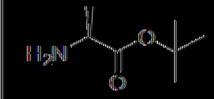
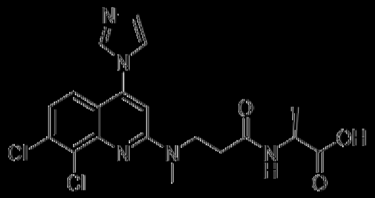
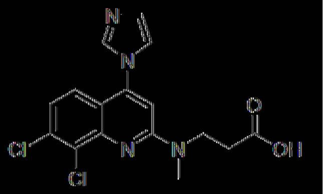
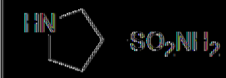
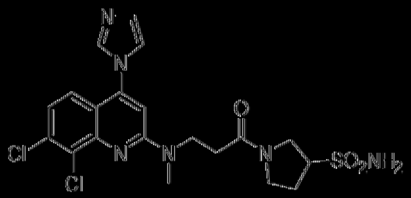
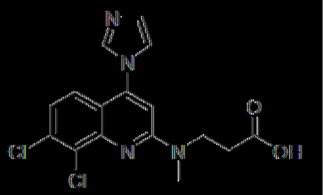
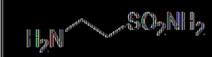
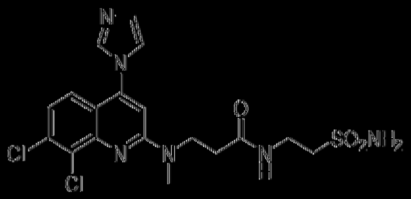
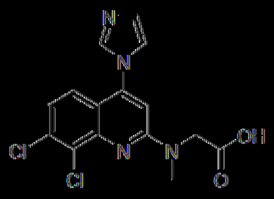
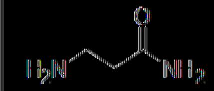
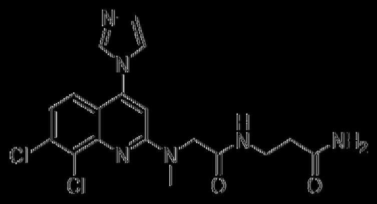
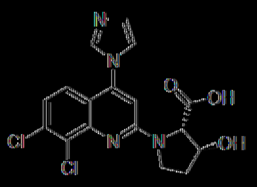
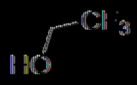
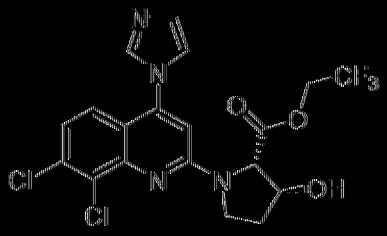
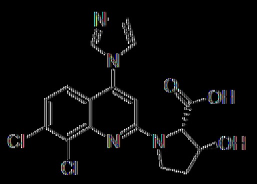
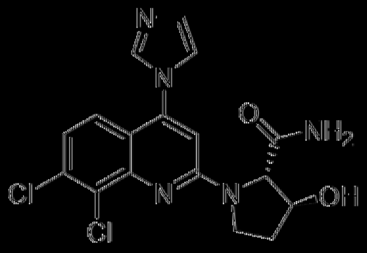
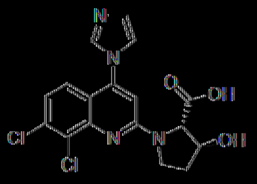
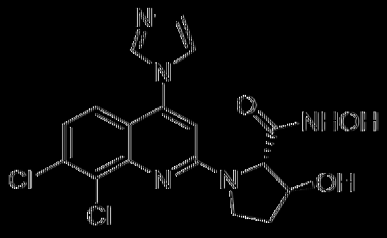
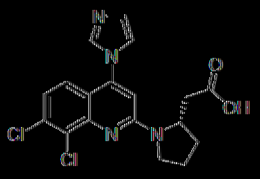
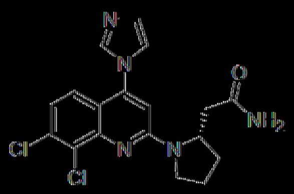
I-542				420
I-543				584
I-544				487
I-452				420
I-545				490
I-546				488

I-#	起始材料		結構	MS [M+1]+
I-547				488
I-548				488
I-549				490
I-550				476
I-551				486
I-552				474

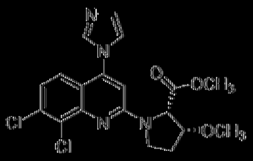
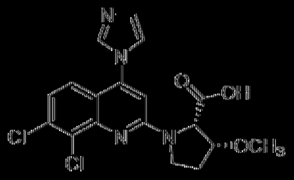
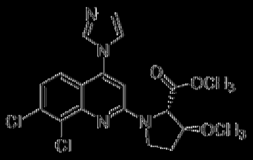
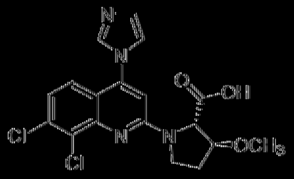
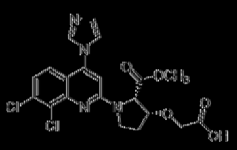
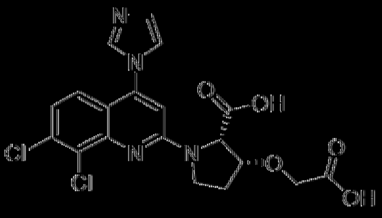
I-#	起始材料		結構	MS [M+1]$^+$
I-553				488
I-554				448
I-555				464
I-608				433
I-562				422
I-563				436
I-564				450

I-#	起始材料		結構	MS [M+1]$^+$
I-565				436
I-566				497
I-567				471
I-568				421

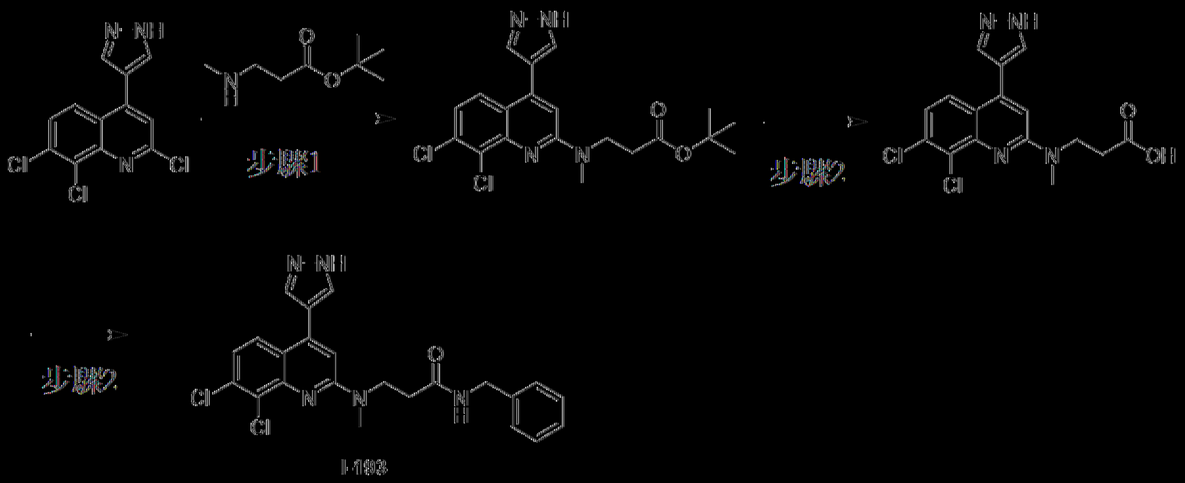
【0586】以下化合物基本上藉由與以上關於I-156所描述之步驟1相同的方法製備。

I#	起始材料		結構	MS [M+1]$^+$
I-566				475
I-567		NH_4Cl		392
I-568		NH_2OH		408
I-603		NH_3		390

【0587】 以下化合物基本上藉由與以上關於I-156所描述之步驟2相同的方法製備。

I-#	起始材料		結構	MS $[M+1]^+$
I-559		LiOH		407
I-560		LiOH		407
I-561		LiOH		451

實例29：合成N-苯甲基-3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙醯胺(I-193)



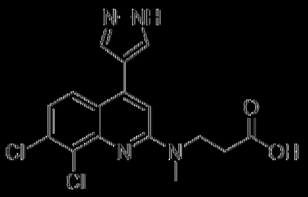
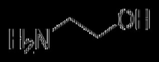
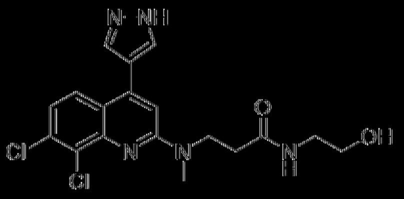
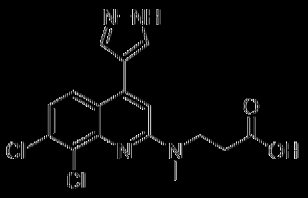
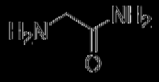
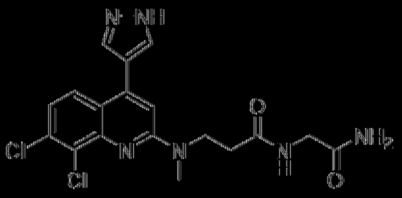
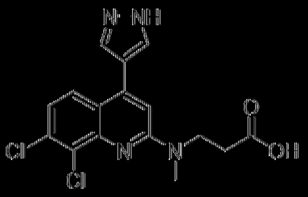
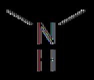
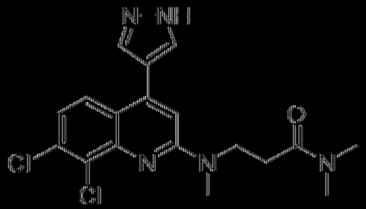
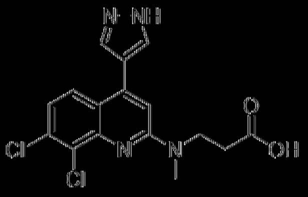
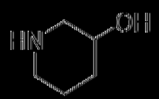
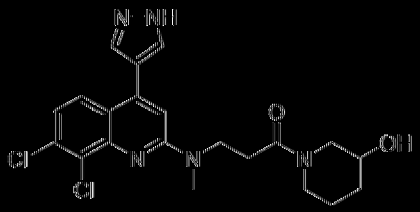
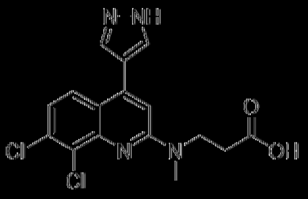
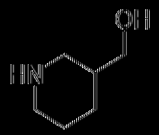
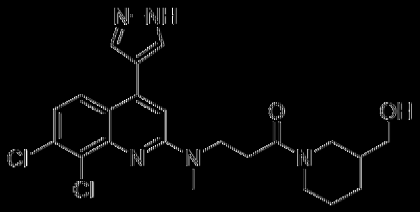
【0588】 步驟1：3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙酸三級丁酯. 向2,7,8-三氯-4-(1H-吡唑-4-基)喹啉(125 mg，0.42 mmol)於DMSO (0.5 mL)中之溶液中添加3-(甲基胺基)丙酸三級丁酯(133 mg，0.84 mmol)及N,N-二異丙基乙胺(0.22 mL，1.26 mmol)。在95℃下

將溶液攪拌16小時。冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽層析法，使用20-80% EtOAc/己烷純化，得到3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙酸三級丁酯(120 mg) (MS: $[M+1]^+$ 421)。

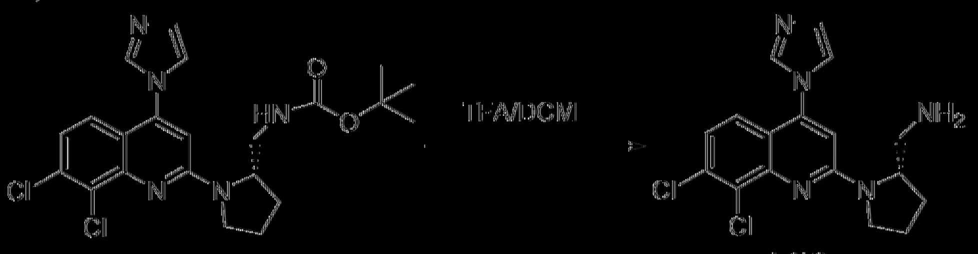
【0589】 步驟2：3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙酸. 向3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙酸三級丁酯(100 mg，0.24 mmol)於二氯甲烷(3 mL)中之溶液中添加鹽酸(0.5 mL，4.0 M於二噁烷中)。在室溫下攪拌反應16小時。藉由旋轉蒸發移除揮發性物質且所得固體不經進一步純化即使用(MS: $[M+1]^+$ 365)。

【0590】 步驟3：N-苯甲基-3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙醯胺. 向3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)(甲基)胺基)丙酸(20 mg，0.055 mmol)於二甲基甲醯胺(0.3 mL)中之溶液中添加HATU (31 mg，0.082 mmol)、N,N-二異丙基乙胺(0.1 mL，0.57 mmol)及苯甲胺(9 mg，0.082 mmol)。在室溫下攪拌反應16小時。添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽層析法，使用0-15% MeOH/CH_2Cl_2純化，得到標題化合物(MS: $[M+1]^+$ 454)。

【0591】 以下化合物基本上藉由與以上關於製備**I-193**所描述相同的方法製備。

I-#	起始材料		結構	MS [M+1]+
I-194				408
I-195				421
I-197				392
I-198				448
I-199				462

實例30：合成(S)-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲胺(I-153)

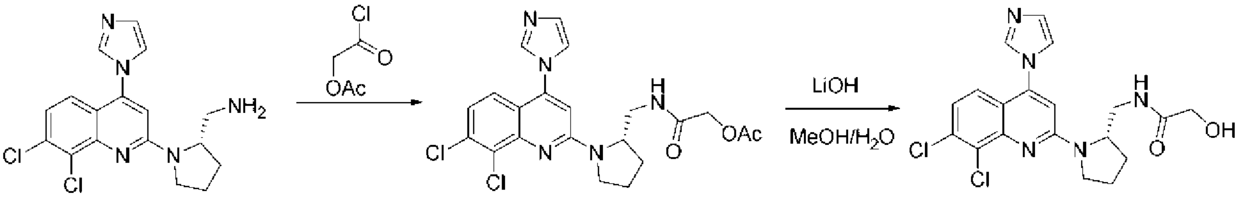


I-152 I-153

【0592】 向(S)-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)胺基甲酸三級丁酯(174 mg)於DCM (2 mL)中之溶液中添加TFA

(0.4 mL)。將所得溶液攪拌6小時後，減壓蒸發並凍乾，得到呈褐色粉末狀之標題化合物(200 mg) (MS: $[M+1]^+$ 362)。

實例31：合成(S)-N-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)-2-羥基乙醯胺(**I-154**)



I-153

I-154

【0593】 向(S)-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲胺三氟乙酸鹽(50 mg)於DCM (0.4 mL)及TEA (0.05 mL)中之溶液中添加乙酸2-氯-2-側氧基乙酯(17 mg)。在攪拌4小時後，用EtOAc (20 mL)稀釋反應混合物並將有機層用$NaHCO_3$及鹽水洗滌。用己烷及含5% MeOH之EtOAc梯度進行管柱層析，得到所需中間體13.4 mg (MS: $[M+1]^+$ 462.)。將中間體(13.4 mg)溶解於MeOH (0.4 mL)及水(0.1 mL)中並用$LiOH·H_2O$ (4 mg)處理2小時。將反應混合物用水(1 mL)稀釋並用HOAc (0.02 mL)酸化以沈澱析出產物，將其進一步凍乾，得到呈粉末狀之終產物2260 (7.8 mg) (MS: $[M+1]^+$ 420)。

【0594】 以下化合物基本上藉由與以上關於製備**I-154**所描述相同的方法製備。

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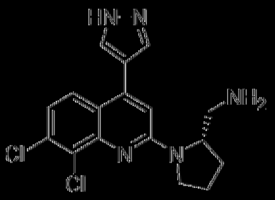
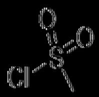
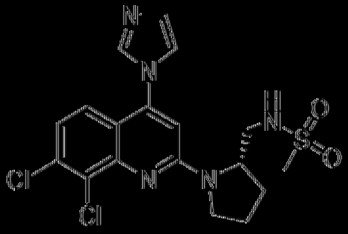
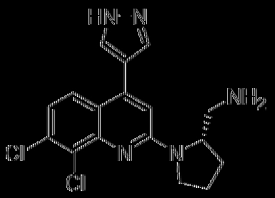
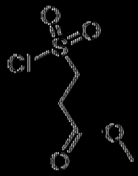
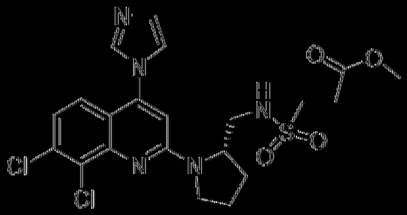
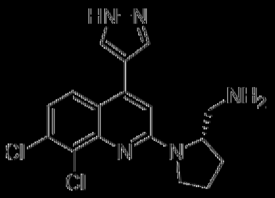
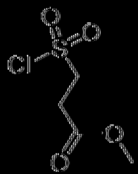
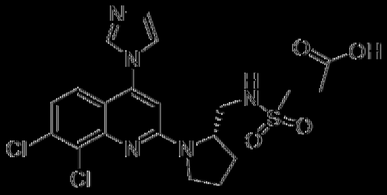
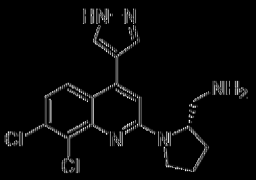
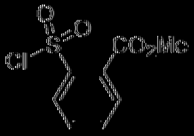
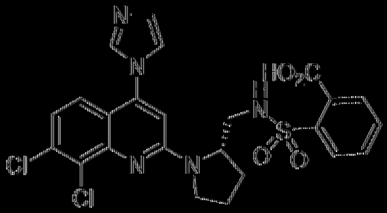
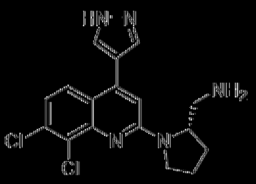
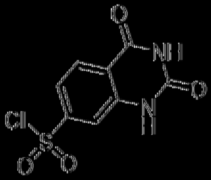
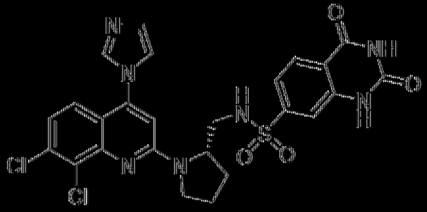
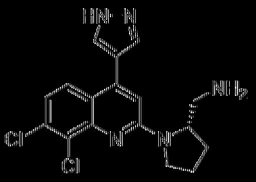
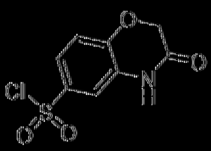
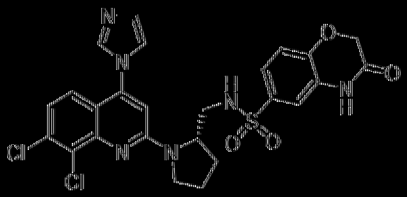
I-151				440
I-390				512
I-335				498
I-391				546
I-392				586
I-393				573

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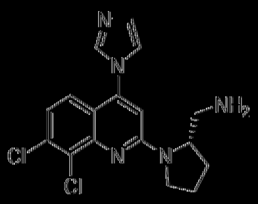
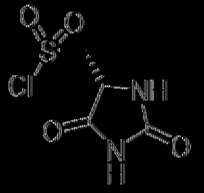
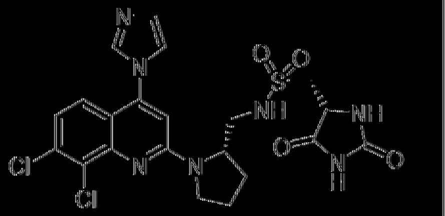
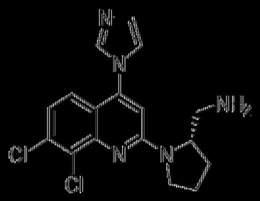
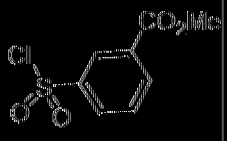
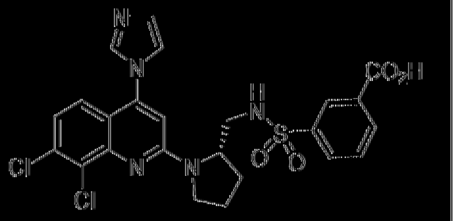
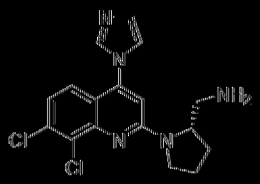
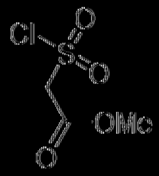
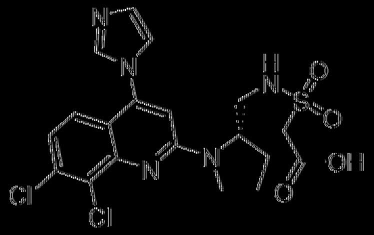
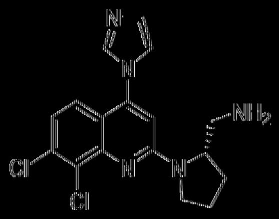
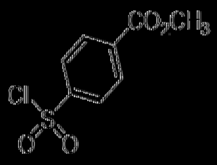
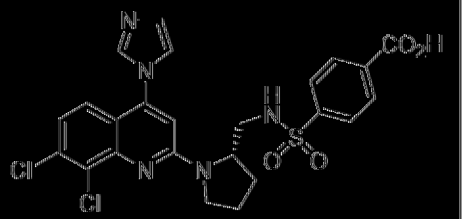
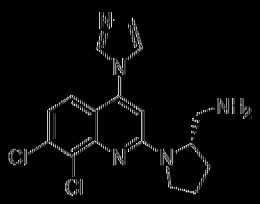
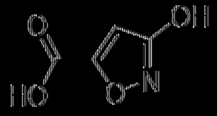
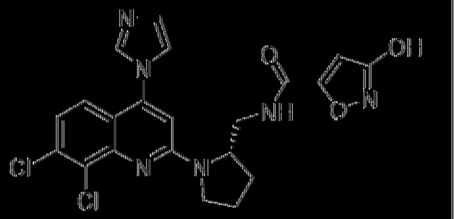
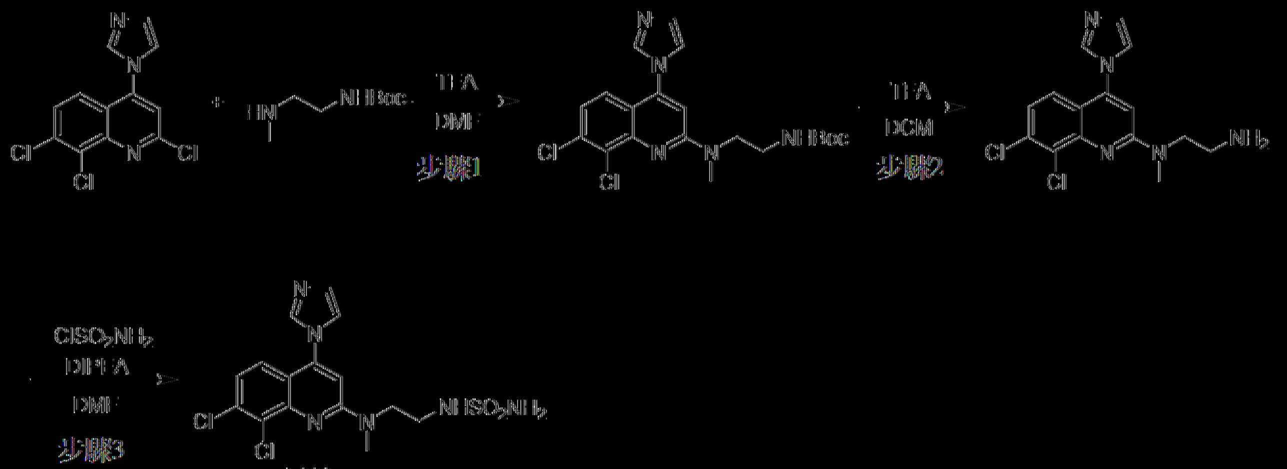
I-637				538
I-638				546
I-639				484
I-640				546
I-641				473

實例32：合成N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)胺基磺醯胺(I-223)



I-223

【0595】 步驟1：2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基胺基甲酸三級丁酯. 向小瓶中添加2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(100 mg，0.335 mmol)、2-(甲基胺基)乙基胺基甲酸三級丁酯(175 mg，1.01 mmol)、DMF (2.0 mL)及TEA (187 µl，1.34 mmol)。在70℃下將所得反應混合物攪拌3小時並冷卻至室溫，隨後添加H_2O (20 mL)。將渾濁混合物離心並藉由DCM (2 × 10 mL)萃取殘餘物。將有機相用H_2O (10 mL)、鹽水(10 mL)洗滌，經Na_2SO_4乾燥，濃縮，得到灰白色固體(132 mg) (MS: $[M+1]^+$ 436)。

【0596】 步驟2：N-(2-胺基乙基)-7,8-二氯-4-(1H-咪唑-1-基)-N-甲基喹啉-2-胺. 向小瓶中添加2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基胺基甲酸三級丁酯(131 mg，0.300 mmol)、DCM (1.5 mL)及TFA (1.5 mL)。在室溫下將所得混合物攪拌2小時。接著，減壓移除所有揮發性溶劑並在高真空下乾燥殘餘物，得到標題產物。將粗品用於下一步驟。

【0597】 步驟3：N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)胺基磺醯胺. 向小瓶中添加N-(2-胺基乙基)-7,8-二氯-4-(1H-咪唑-1-基)-N-甲基喹啉-2-胺(12.5 mg，0.0373 mmol)、DMF (0.5 mL)、胺磺醯氯(26 mg，0.224 mmol)及DIPEA (52 µl，0.296 mmol)。在50℃下將所得反應混合物攪拌隔夜。將反應混合物用乙酸乙酯(15 mL)稀釋。將有機相用H_2O (3 × 5 mL)、鹽水(5 mL)洗滌，經Na_2SO_4乾燥。濃縮後，將30%粗品藉由PTLC純化，得到呈灰白色固體狀之標題產物(1.3 mg) (MS: $[M+1]^+$ 415)。

【0598】 以下化合物基本上藉由與以上關於製備**I-223**所描述相同的方法製備。

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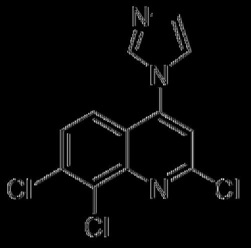
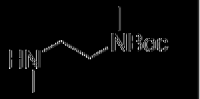
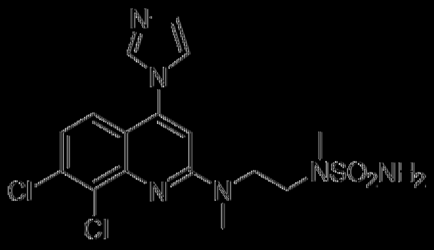
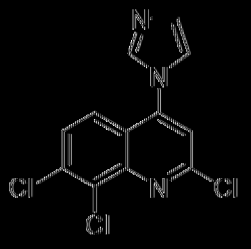
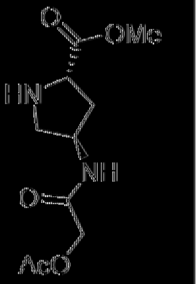
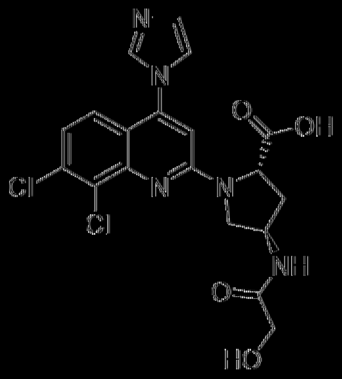
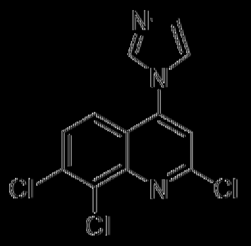
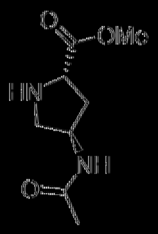
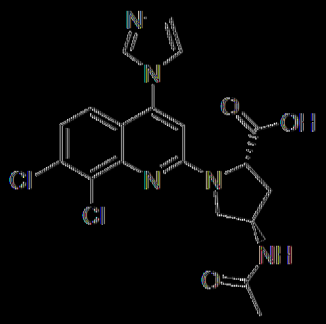
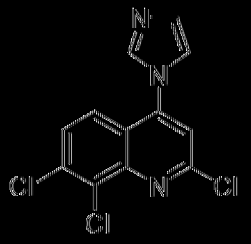
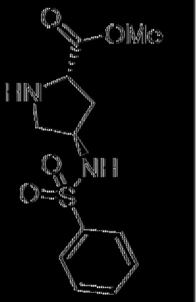
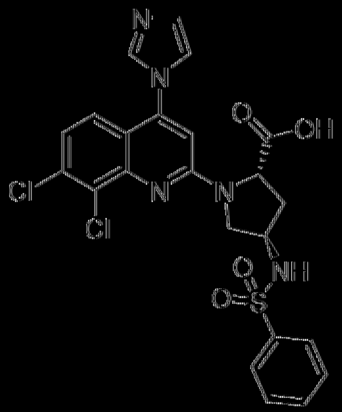
I-224				429
I-346				450
I-347				434
I-349				532

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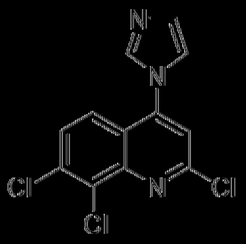
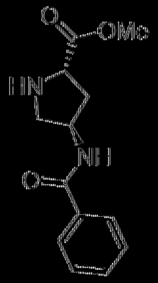
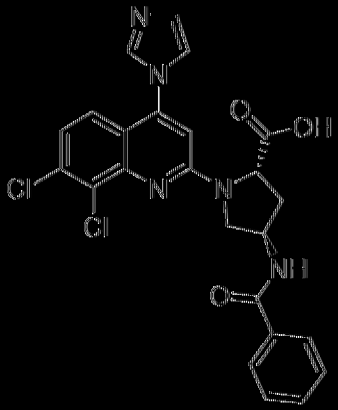
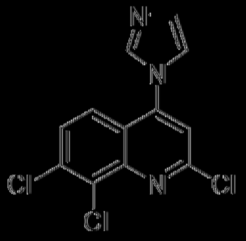
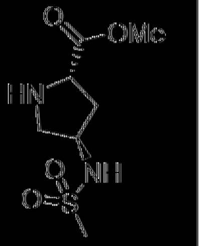
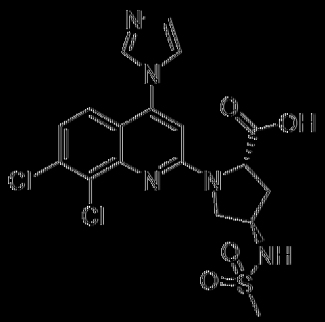
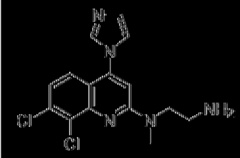
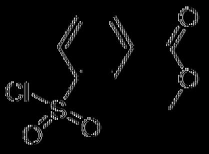
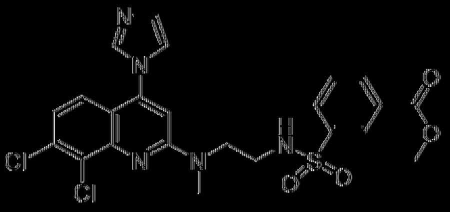
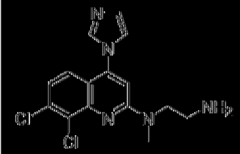
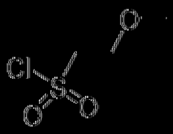
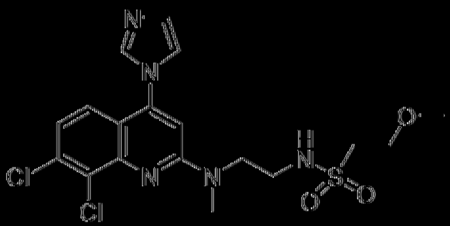
I-360				496
I-351				470

【0599】以下化合物基本上藉由與製備I-223相同之方法製備。一些類似物係由一般醯胺形成法且隨後水解酯以形成相應酸來製備。

I-#	起始材料		結構	MS [M+1]+
I-609				534
I-610				458

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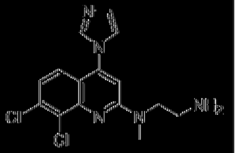
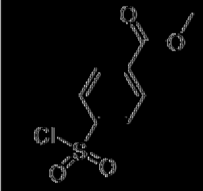
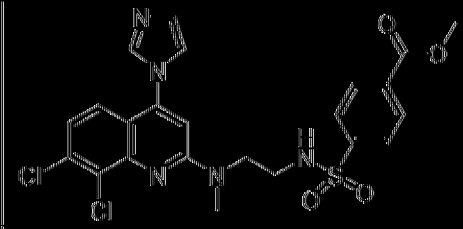
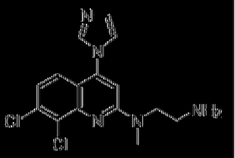
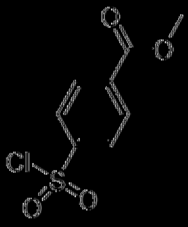
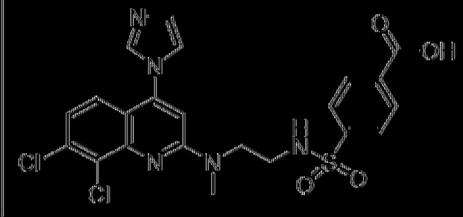
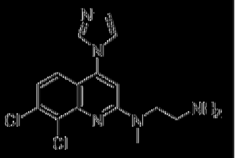
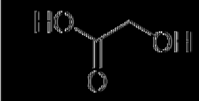
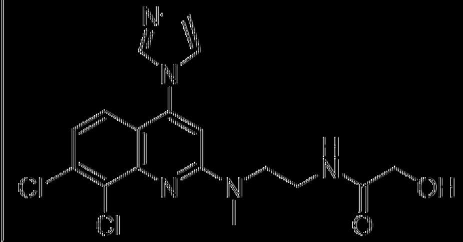
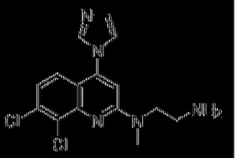
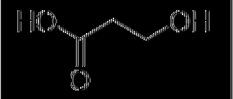
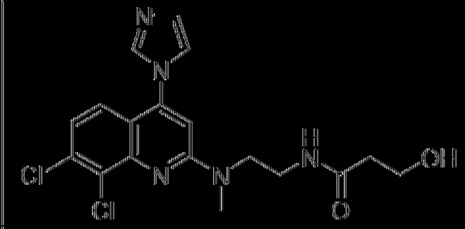
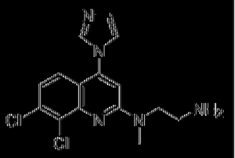
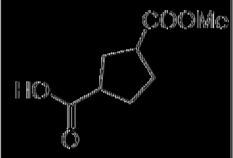
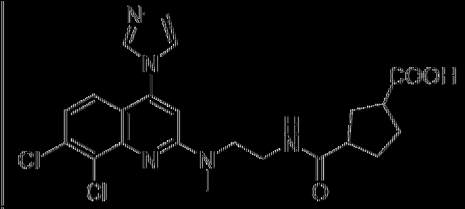
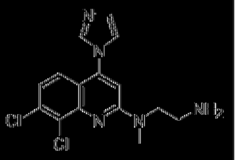
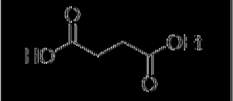
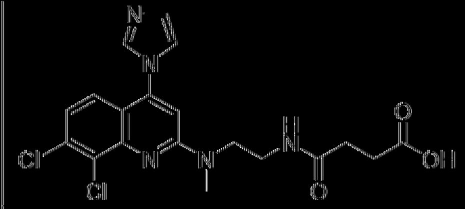
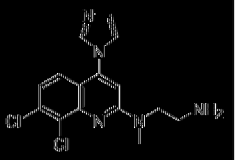
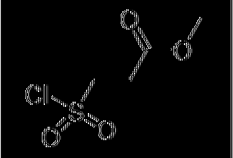
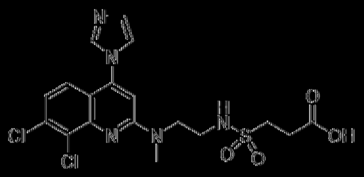
I-611				534
I-612				520
I-613				394
I-614				408
I-615				476
I-616				436
I-617				472

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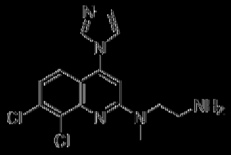
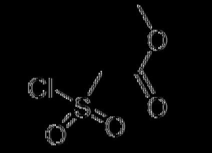
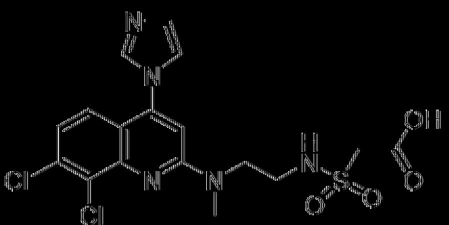
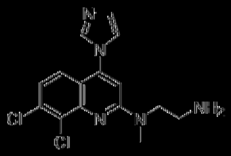
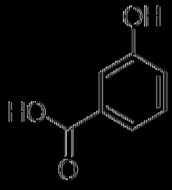
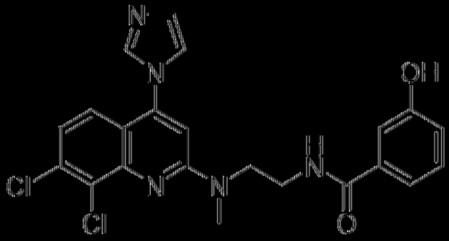
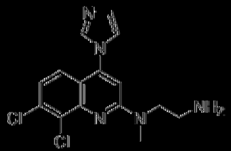
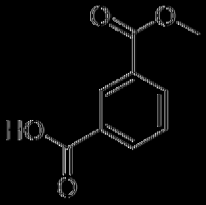
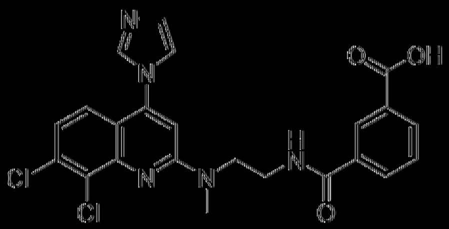
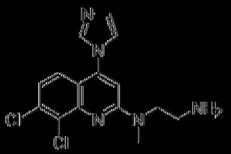
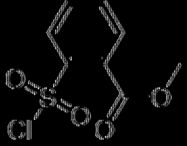
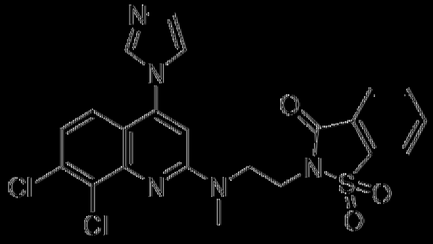
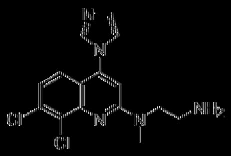
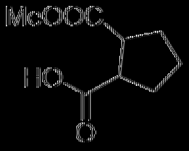
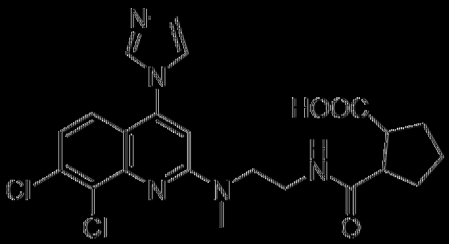
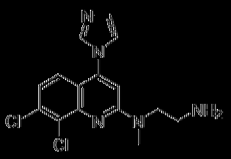
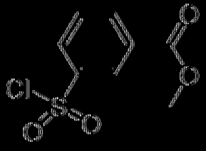
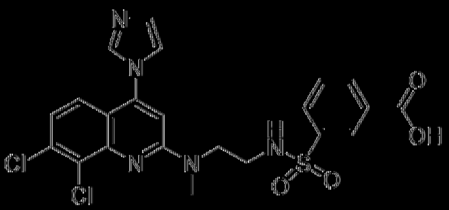
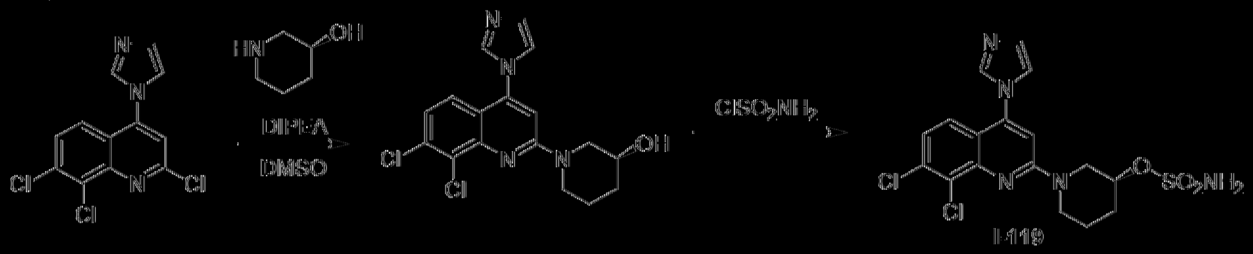
I-618				458
I-619				456
I-620				484
I-621				502
I-622				476
I-623				520

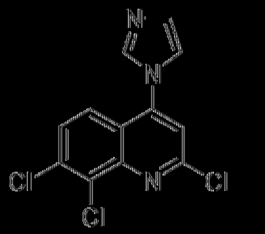
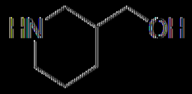
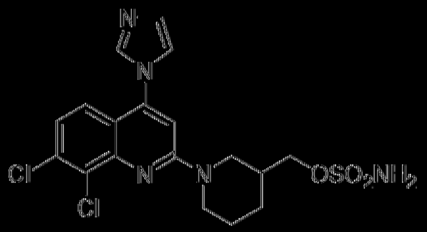
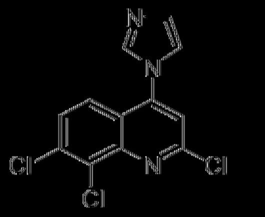
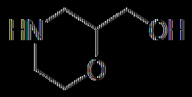
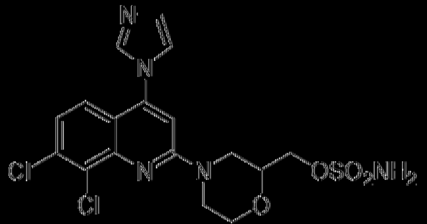
實例33：合成(S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-醇(I-119)



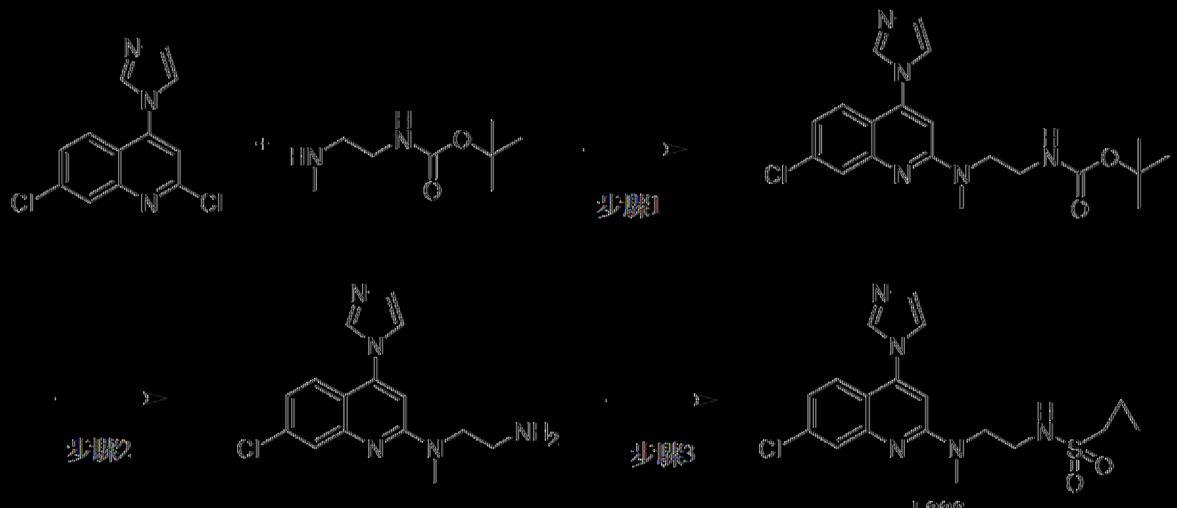
【0600】 步驟1：1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-醇係與關於化合物I-353之方法相同(MS: [M+1]+ 263)。

【0601】 步驟2：胺基磺酸(S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基酯. 向小瓶中添加1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-醇(20 mg，0.0551 mmol)、DMF (0.3 mL)及TEA (50 µl，0.364 mmol)。添加胺磺醯氯於DMF中之儲備溶液(38 mg/100 µl，0.33 mmol)。在100℃下將所得反應混合物攪拌6小時並冷卻至室溫，隨後添加14 mL水。將混合物離心並將殘餘物藉由PTLC (30% MeOH/DCM)純化，得到呈白色固體狀之所需產物(1 mg) (MS: [M+1]+ 442)。

【0602】 以下化合物基本上藉由與I-223相同之方法製備。

I-#	起始材料		結構	MS [M+1]+
I-118				456
I-96				458

實例34：合成N-(2-((7-氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)環丙烷磺醯胺(I-226)



I-228

【0603】 步驟1：(2-((7-氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)胺基甲酸三級丁酯. 向2,7-二氯-4-(1H-咪唑-1-基)喹啉(528 mg，2.0 mmol)於DMF (2 mL)中之溶液中添加(2-(甲基胺基)乙基)胺基甲酸三級丁酯(871 mg，mmol)及漢氏鹼(Hunig's base) (0.5 mL)。在95℃下將溶液攪拌16小時。冷卻至室溫後，添加水(10 mL)並將有機物萃取至10%甲醇/二氯甲烷(2 × 5 mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽管柱層析法，使用50-100% EtOAc/Hex純化，得到呈固體狀之(2-((7-氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)胺基甲酸三級丁酯(MS: $[M+1]^+$-Boc 302)。

【0604】 步驟2：N1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-N1-甲基乙-1,2-二胺. 向小瓶中添加(2-((7-氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)胺基甲酸三級丁酯(120 mg，0.30 mmol)。添加鹽酸(4.0M於二㗁烷中，1.0 mL)並在室溫下攪拌反應16小時。過濾出所得固體並乾燥，得到呈固體狀之N1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-N1-甲基乙-1,2-二胺鹽酸鹽(MS: $[M+1]^+$ 302)。

【0605】 步驟3：N-(2-((7-氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)環丙烷磺醯胺. 向小瓶中添加於DMF (0.5 mL)及漢氏鹼(0.1 mL)中之N1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-N1-甲基乙-1,2-二胺鹽酸鹽

(20 mg，0.06 mmol)。添加環丙烷磺醯氯(17 mg，0.12 mmol)並在室溫下攪拌反應16小時。添加水(5 mL)並用乙酸乙酯(2 × 5 mL)萃取水溶液。將合併之有機層乾燥(Na_2SO_4)，接著藉由二氧化矽層析法，使用0-10% MeOH/CH_2Cl_2純化，得到12 mg N-(2-((7-氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)環丙烷磺醯胺(MS: $[M+1]^+$ 406)。

【0606】 以下化合物基本上藉由與以上關於製備I-226所描述相同的方法製備。

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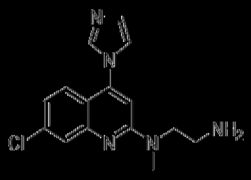
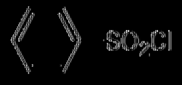
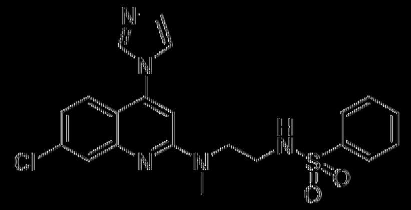
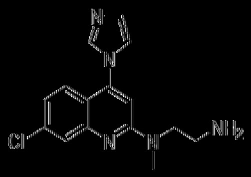
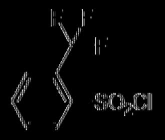
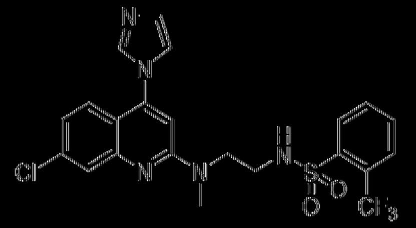
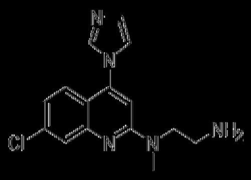
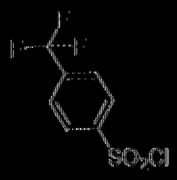
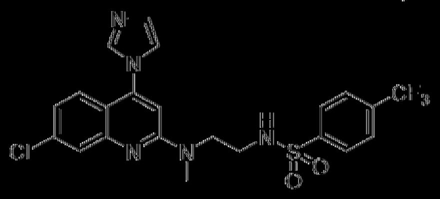
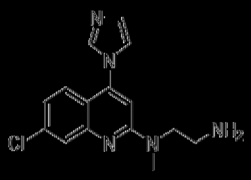
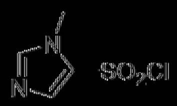
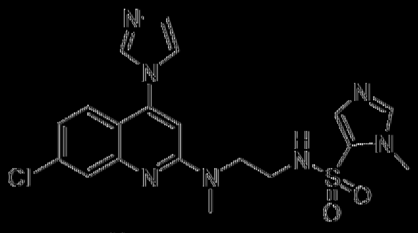
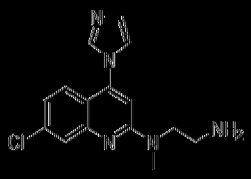
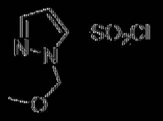
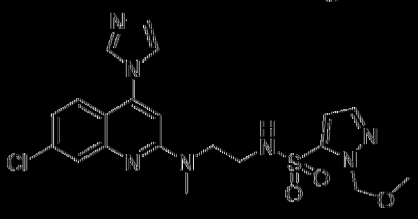
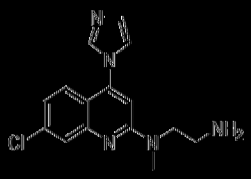
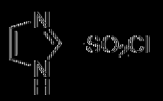
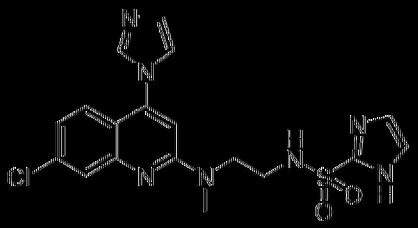
I-227				442
I-228				510
I-394				510
I-232				446
I-229				476
I-230				432

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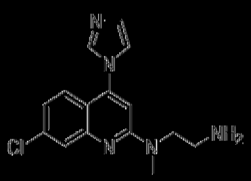
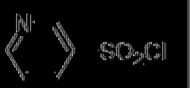
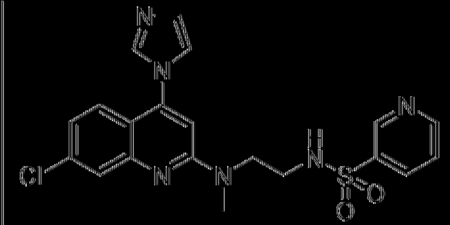
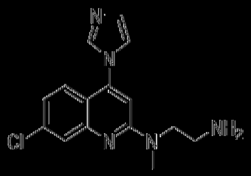
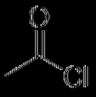
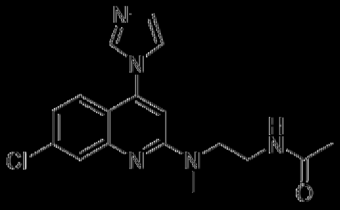
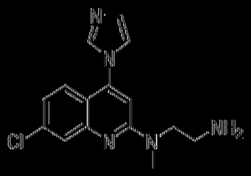
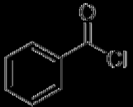
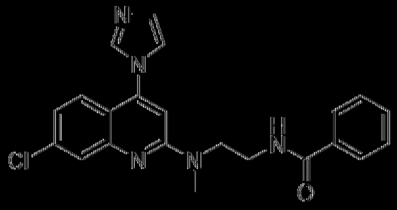
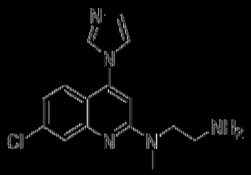
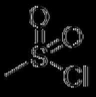
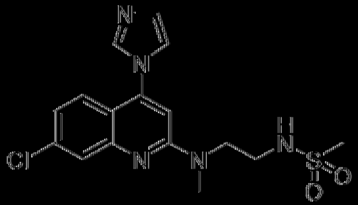
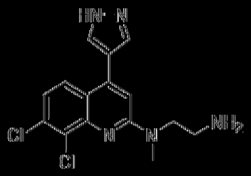
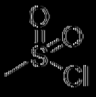
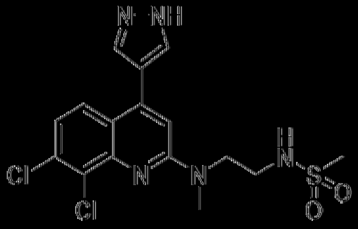
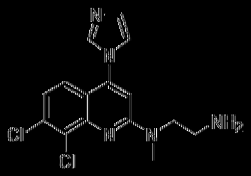
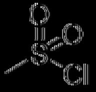
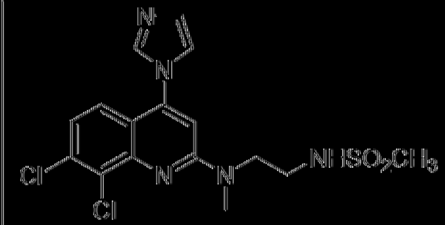
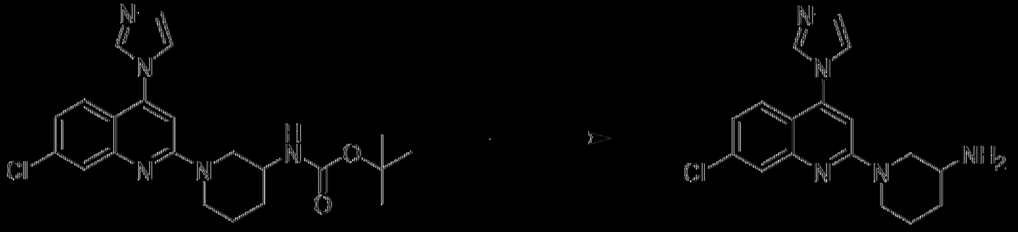
I-231				443
I-236				344
I-237				406
I-234				380
I-235				414
I-225				414

實例35：合成(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-胺) (I-108)

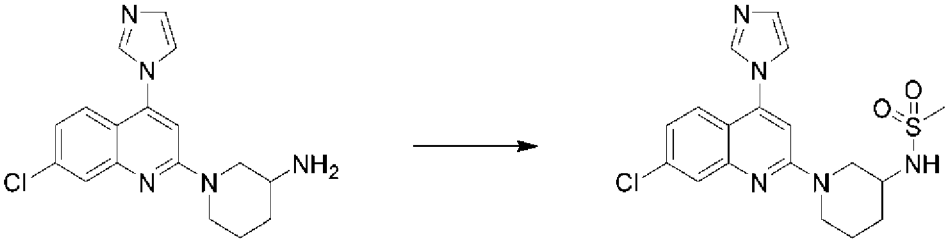


I-108

【0607】 向小瓶中添加(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-

3-基)胺基甲酸三級丁酯(90 mg，0.21 mmol)及二氯甲烷(5 mL)。添加三氟甲烷磺酸(0.5 mL)並在室溫下攪拌反應16小時。藉由旋轉蒸發移除揮發性物質並將粗產物(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-胺) (二-三氟乙酸鹽)直接用於下一步驟(MS: $[M+1]^+$ 328)。

實例36：合成N-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲烷磺醯胺(**I-105**)



I-105

【0608】 向1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-胺(二-三氟乙酸鹽) (55 mg，0.10 mmol)於二氯甲烷(3 mL)及DMF (0.3 mL)中之溶液中添加三乙胺(0.3mL)，隨後添加甲烷磺醯氯(23 mg，0.20 mmol)。在室溫下將混合物攪拌3小時。添加水(5mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。藉由二氧化矽層析法純化，得到N-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲烷磺醯胺(33 mg) (MS: $[M+1]^+$ 406)。

【0609】 以下化合物基本上藉由與以上關於製備**I-105**所描述相同的方法製備。

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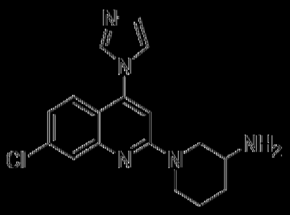
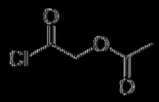
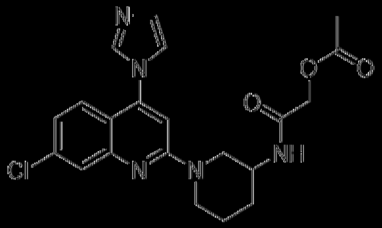
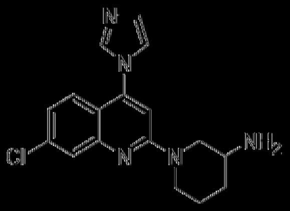
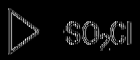
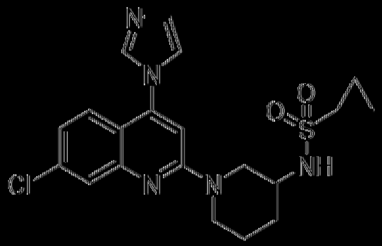
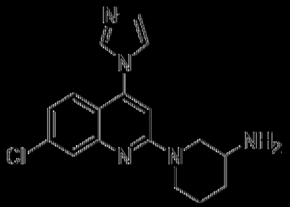
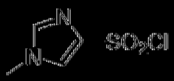
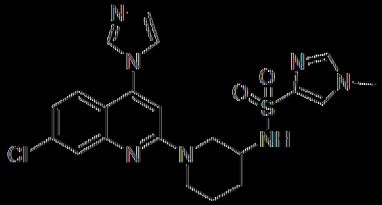
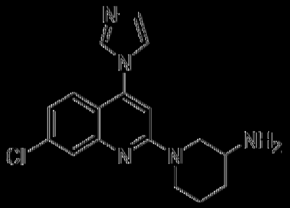
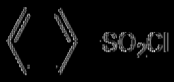
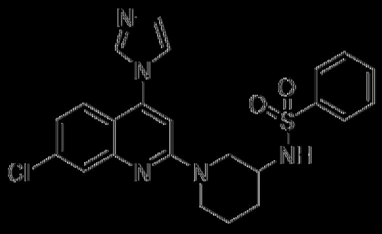
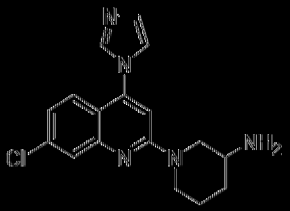
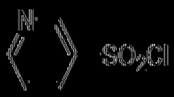
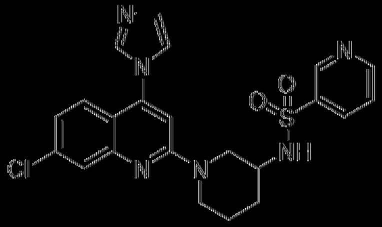
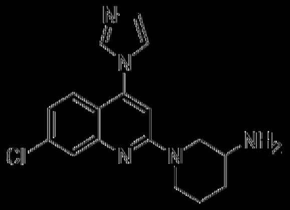
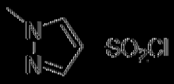
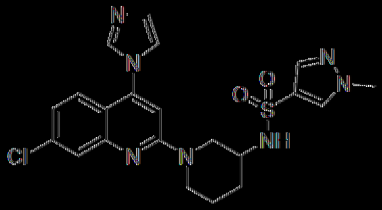
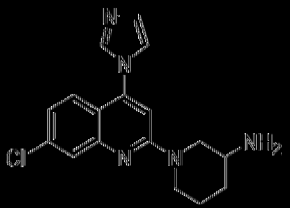
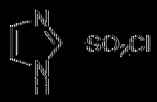
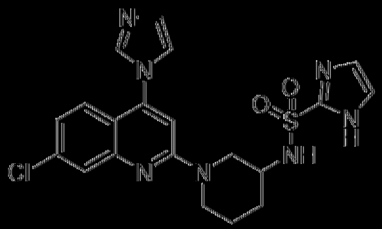
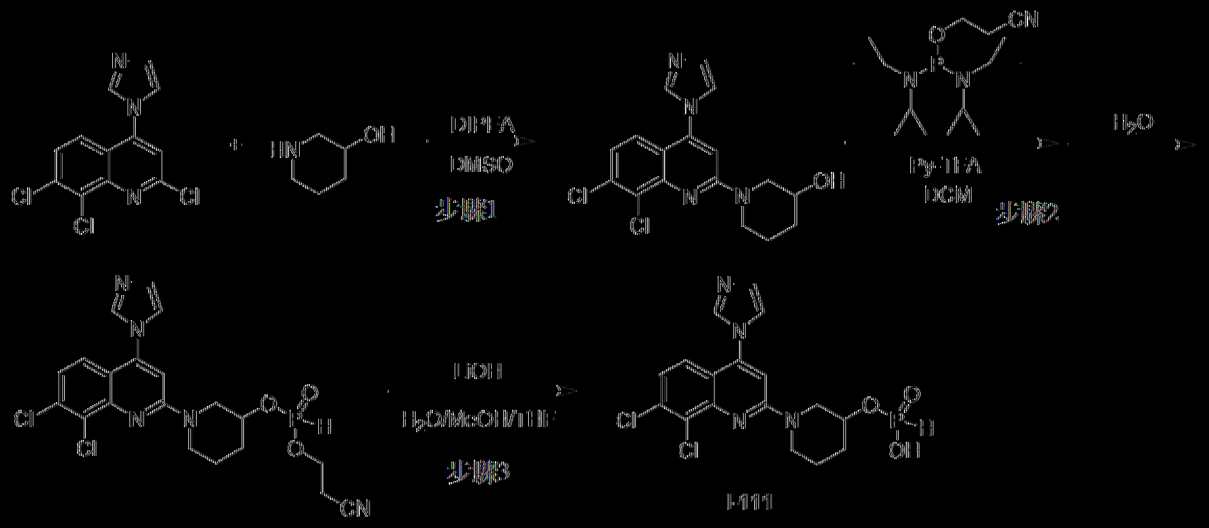
I-395				428
I-100				432
I-103				472
I-107				468
I-102				469
I-109				472
I-101				458

實例37：合成二氟膦酸1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基酯(I-111)



【0610】 步驟1：1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-醇係根據以上關於製備化合物I-353所描述之程序製備。

【0611】 步驟2：膦酸2-氰基乙酯1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基酯. 向小瓶中添加1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-醇(20 mg，0.0551 mmol)、DCM (1.0 mL)、三氟乙酸吡錠(10.6 mg，0.0551 mmol)。接著，添加3-(雙(二異丙基胺基)膦氧基)丙腈(26 µl，0.0826 mmol)。在室溫下將所得反應混合物攪拌隔夜。藉由LC-MS監測反應。添加H_2O (0.1 mL)並將反應混合物攪拌1小時。減壓移除所有揮發性物質。將粗品用於下一步驟。

【0612】 步驟3：氫膦酸1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基酯。向含有步驟2中之粗產物膦酸2-氰基乙酯1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基酯的小瓶中添加MeOH (0. 5 mL)、THF (1.0 mL)及$LiOH·H_2O$於H_2O中之溶液(4.63 mg/0.5 mL，0.110 mmol)。將所得反應混合物攪拌隔夜，酸化至pH 5，並濃縮。將粗品藉由HPLC純化，得到呈白色固體狀之標題產物(8 mg) (MS: $[M+1]^+$ 427)。

【0613】 以下化合物基本上藉由與以上關於製備I-111所描述相同的方法製備。

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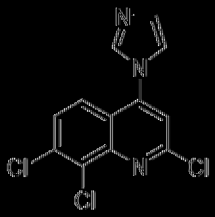
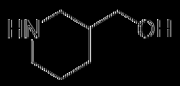
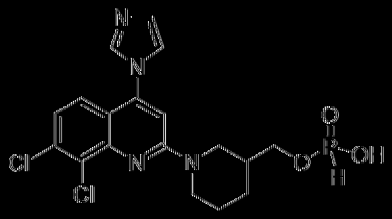
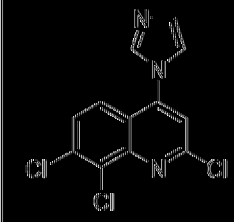
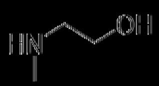
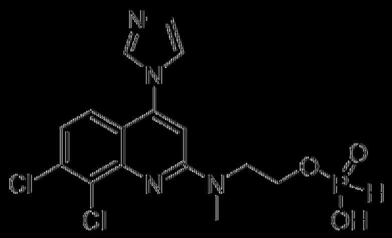
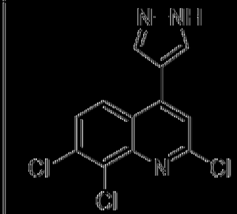
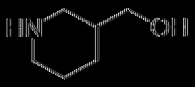
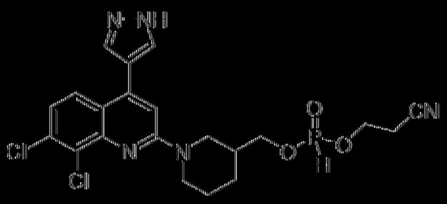
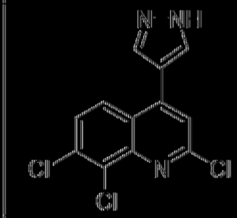
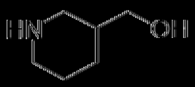
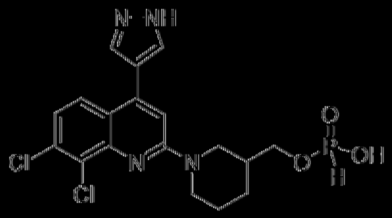
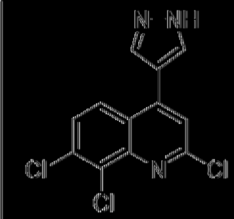
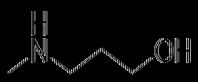
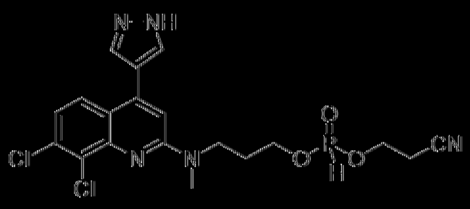
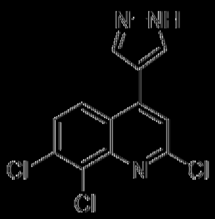
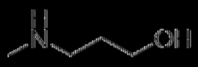
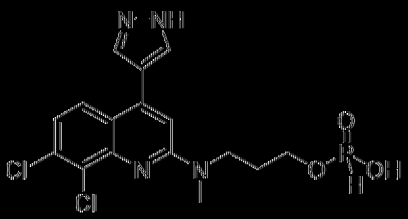
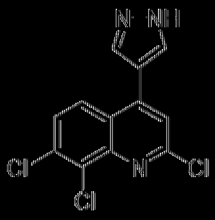
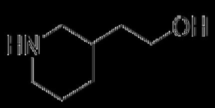
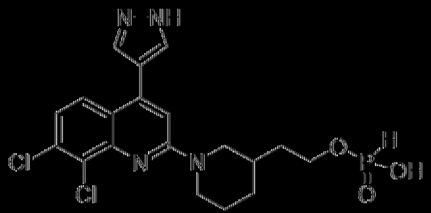
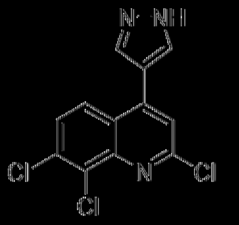
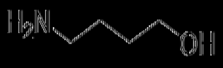
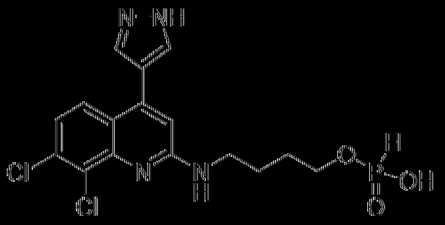
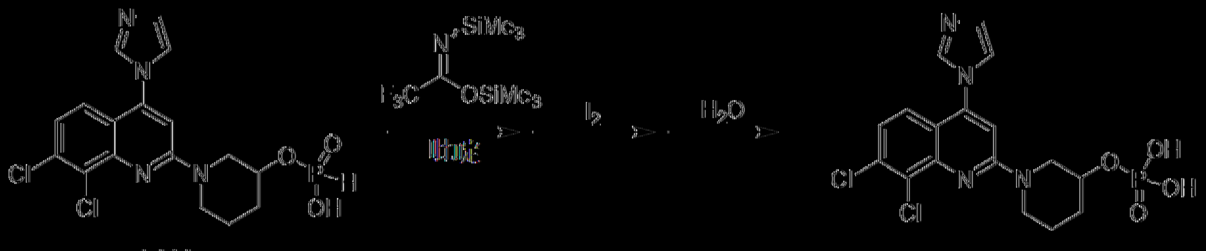
I-110				441
I-255				401
I-396				494
I-329				441
I-257				468
I-256				415
I-330				455

I-#	起始材料		結構	MS [M+1]+
I-268				415

實例38：合成二氫磷酸1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基酯(I-112)

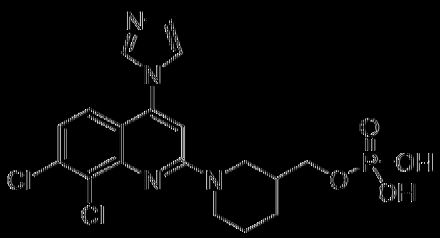


I-111

I-112

【0614】 向小瓶中添加產物I-111 (6.2 mg，0.0145 mmol)及吡啶(0.3 mL)。接著，添加2,2,2-三氟-N-(三甲基矽基)乙醯亞胺酸三甲基矽基酯(0.019 mL，0.0726 mmol)。將所得反應混合物攪拌5分鐘。接著逐滴添加I_2於吡啶中之溶液(4.4 mg/0.1 mL)並將反應混合物攪拌5分鐘。減壓移除揮發性物質。將粗品藉由製備型HPLC純化，得到呈白色固體狀之標題產物(2.6 mg) (MS: $[M+1]^+$ 443)。

實例39：合成二氫磷酸(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲酯(I-113)

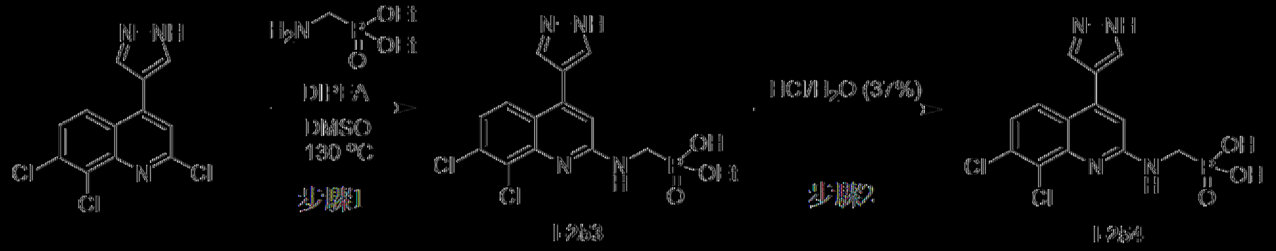


I-113

【0615】 二氫磷酸(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲酯係根據以上關於製備化合物I-112所描述之程序製備(MS: $[M+1]^+$

457)。

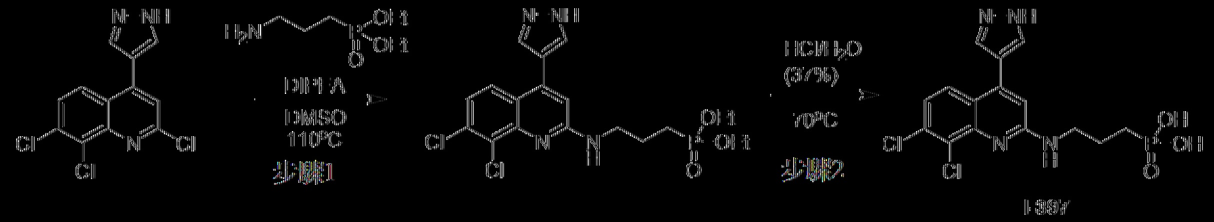
實例40：合成氫(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)甲基膦酸乙酯(I-253)及(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)甲基膦酸(I-254)



【0616】 步驟1：氫(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)甲基膦酸乙酯. 向小瓶中添加2,7,8-三氯-4-(1H-吡唑-4-基)喹啉(30 mg，0.10 mmol)、DMSO (0.3 mL)、胺基甲基膦酸二乙酯(50 mg，0.3 mmol)及DIPEA (52 µl，0.3 mmol)。在130℃下將所得反應混合物攪拌20小時。將粗品藉由製備型HPLC純化，得到呈白色固體狀之產物2157 (5.2 mg) (MS: $[M+1]^+$ 401)。

【0617】 步驟2：(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)甲基膦酸. 向小瓶中添加氫(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)甲基膦酸乙酯(3.7 mg，0.0092 mmol)及鹽酸(37%，0.5 mL)。在70℃下將所得反應混合物攪拌隔夜。所有起始材料均轉化成所需產物。濃縮後，獲得呈白色固體狀之標題產物(3.5 mg) (MS: $[M+1]^+$ 373)。

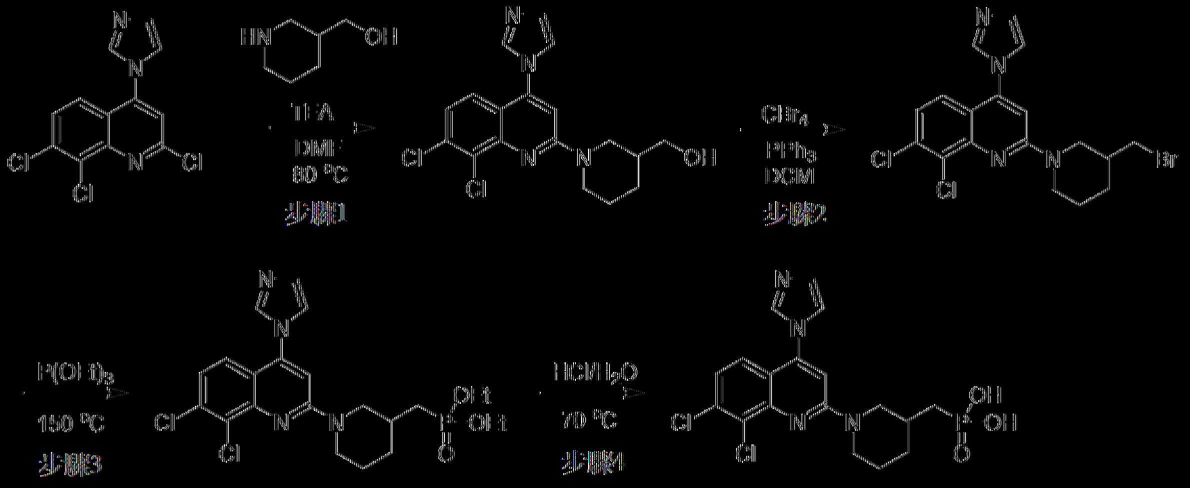
實例41：合成(3-((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)胺基)丙基)膦酸(I-397)



【0618】 步驟1：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)丙基膦酸二乙酯. 向小瓶中添加2,7,8-三氯-4-(1H-吡唑-4-基)喹啉(30 mg，0.10 mmol)、DMSO (0.3 mL)、3-胺基丙基膦酸二乙酯(58.6 mg，0.30 mmol)及DIPEA (52 µl，0.30 mmol)。在110℃下將所得反應混合物攪拌5小時，隨後添加H_2O (4 mL)。藉由離心機收集沈澱之白色固體，並將粗品藉由矽膠層析法(藉由5% MeOH/DCM溶離)純化，得到呈白色固體狀之所需產物(9 mg) (MS: $[M+1]^+$ 457)。

【0619】 步驟2：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)丙基膦酸. 向小瓶中添加3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基胺基)丙基膦酸二乙酯(4.5 mg，0.0098 mmol)及鹽酸(37%，0.5 mL)。在70℃下將所得反應混合物攪拌隔夜。所有起始材料均轉化成所需產物。濃縮後，獲得呈白色固體狀之標題產物(4.0 mg) (MS: $[M+1]^+$ 401)。

實例42：合成(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲基膦酸二乙酯(I-114)



I-114

【0620】 步驟1：(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲醇係根據以上關於製備化合物I-353所描述之程序製備。(MS:

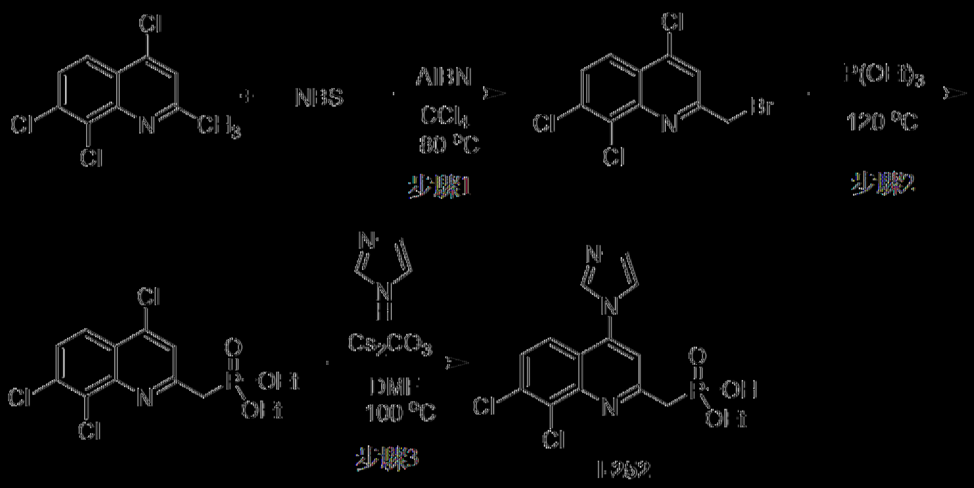
[M+1]$^+$ 377)。

【0621】 步驟2：2-(3-(溴甲基)哌啶-1-基)-7,8-二氯-4-(1H-咪唑-1-基)喹啉. 向小瓶中添加(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲醇(100 mg，0.265 mmol)、CBr_4 (176 mg，0.53 mmol)及DCM (5 mL)。將混合物在冰-水浴中冷卻20分鐘，隨後添加Ph_3P於DCM中之溶液(105 mg/1 mL，0.398 mmol)。在0℃下將所得混合物攪拌1小時。將混合物濃縮，藉由矽膠層析法，用50%至60%乙酸乙酯/己烷溶離來純化，得到呈灰白色固體狀之所需產物(85 mg) (MS: [M+1]$^+$ 439)。

【0622】 步驟3：(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲基膦酸二乙酯. 向小瓶中添加2-(3-(溴甲基)哌啶-1-基)-7,8-二氯-4-(1H-咪唑-1-基)喹啉(20 mg，0.0455 mmol)及膦酸三乙酯(0.5 mL)。在150℃下將所得混合物攪拌10小時。將反應混合物(30%)藉由PTLC純化，得到呈白色固體狀之所需產物(2.0 mg) (MS: [M+1]$^+$ 497)。

【0623】 步驟4：(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)甲基膦酸係根據以上關於製備化合物**I-397** (步驟2)所描述之程序製備(MS: [M+1]$^+$ 441)。

實例43：合成氫(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲基膦酸乙酯(**I-252**)



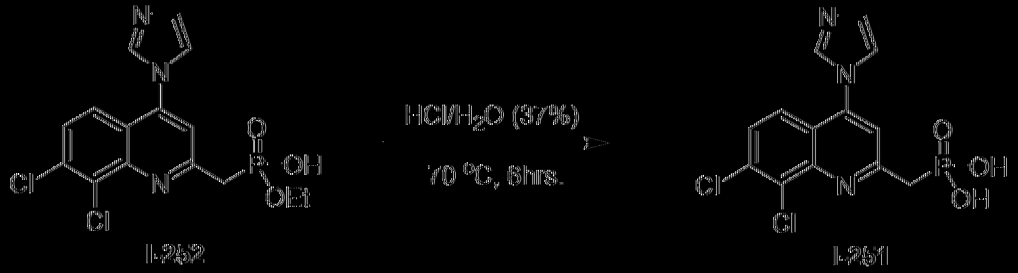
I-252

【0624】 步驟1：2-(溴甲基)-4,7,8-三氯喹啉. 向燒瓶中添加4,7,8-三氯-2-甲基喹啉(493 mg，2.0 mmol)、NBS (356 mg，2.0 mmol)、AIBN (66 mg，0.40 mmol)及CCl_4 (6 mL)。藉由使氮氣流鼓泡20分鐘來使反應混合物脫氣並在N_2下，在65℃下攪拌16小時。冷卻至室溫後，將混合物用乙酸乙酯(50 mL)稀釋，用H_2O (20 mL)及鹽水(20 mL)洗滌，經Na_2SO_4乾燥。濃縮後，將粗品用於下一步驟。

【0625】 步驟2：(4,7,8-三氯喹啉-2-基)甲基膦酸二乙酯係根據以上關於製備實例42之步驟3之化合物所描述之程序製備(MS: $[M+1]^+$ 382)。

【0626】 步驟3：氫(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲基膦酸乙酯係根據以上關於製備化合物I-56 (步驟3)所描述之程序製備(MS: $[M+1]^+$ 386)。

實例44：合成((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲基)膦酸(I-251)

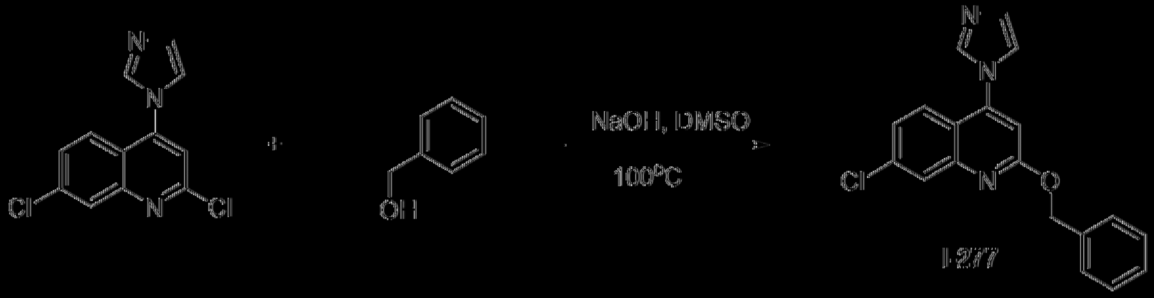


I-252 I-251

【0627】 ((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)甲基)膦酸係根據

以上關於製備化合物I-397 (步驟2)所描述之程序製備(MS: $[M+1]^+$ 358)。

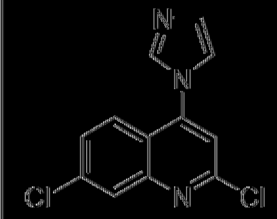
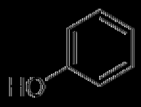
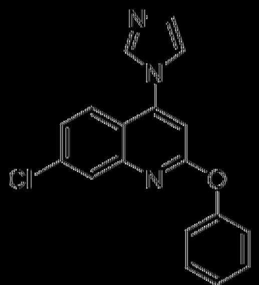
實例45：合成2-(苯甲氧基)-7-氯-4-(1H-咪唑-1-基)喹啉(I-277)

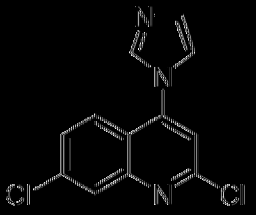
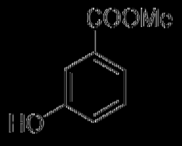
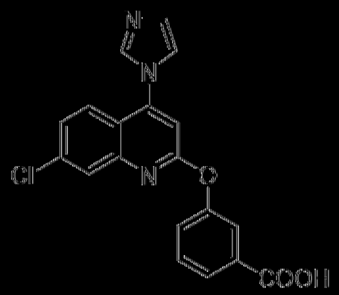
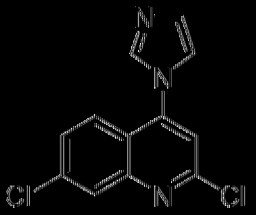
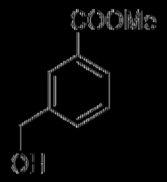
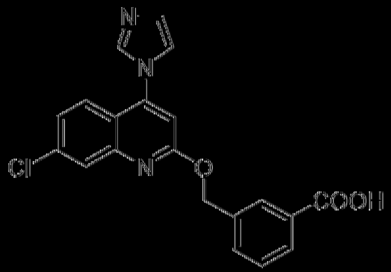
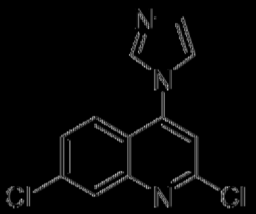
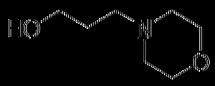
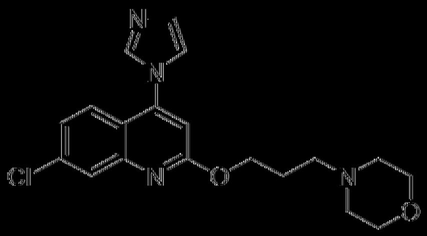
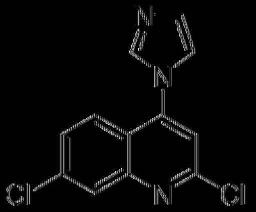
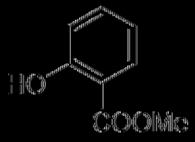
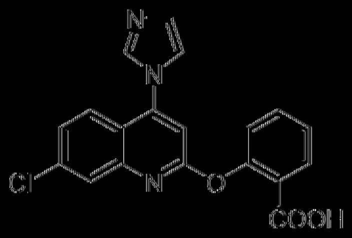
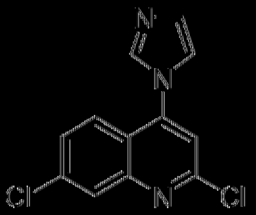
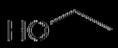
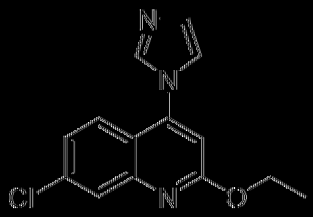
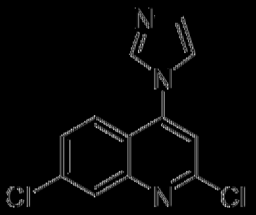
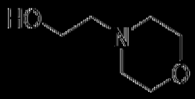
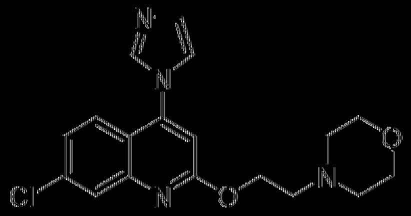


I-277

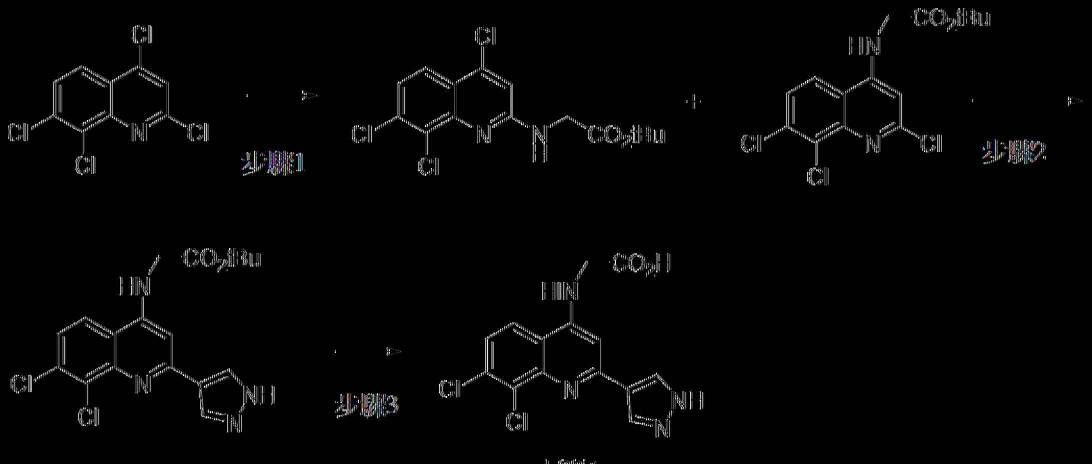
【0628】 向小瓶中添加2,7-二氯-4-(1H-咪唑-1-基)喹啉(132 mg，0.5 mmol)、DMSO (1 mL)、苯甲醇(62 μl，0.6 mmol)及NaOH (24 mg，0.6 mmol)。在100℃下將混合物攪拌隔夜。將10%反應混合物藉由PTLC，藉由7.5% MeOH/DCM溶離來純化，得到呈白色固體狀之標題產物(4.5 mg，27%產率) (MS: $[M+1]^+$ 336.1)。

【0629】 以下化合物基本上藉由與以上關於製備I-277所描述相同的方法製備。

I#	起始材料		結構	MS [M+1]+
I-278				322

I-#	起始材料		結構	MS [M+1]+
I-282				366
I-281				380
I-284				373
I-283				366
I-280				274
I-279				359

實例46：合成(7,8-二氯-2-(1H-吡唑-3-基)喹啉-4-基)甘胺酸(I-287)



I-287

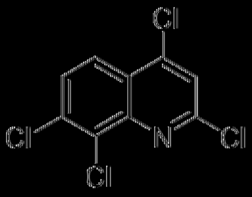
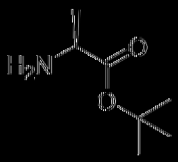
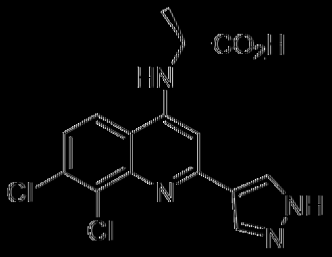
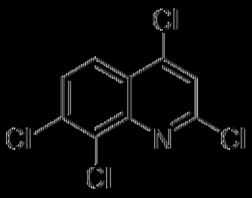
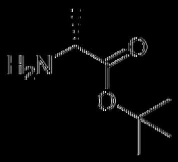
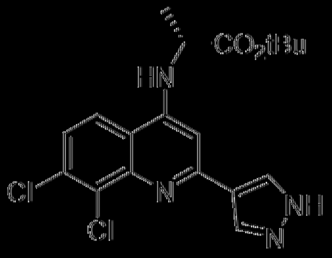
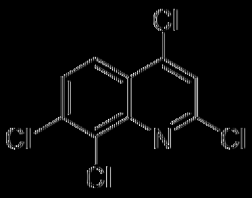
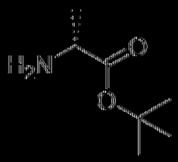
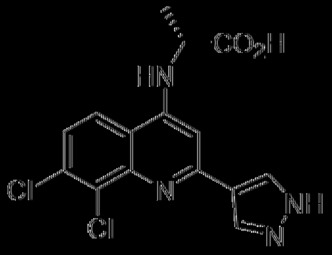
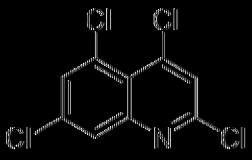
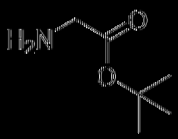
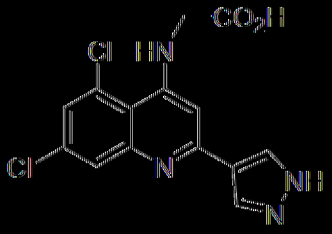
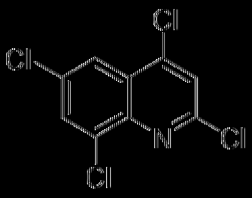
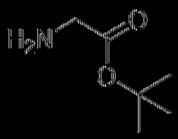
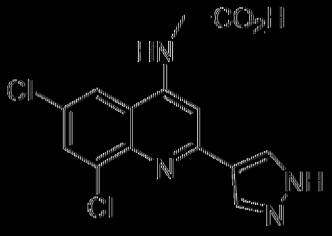
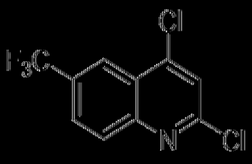
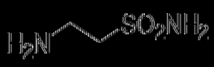
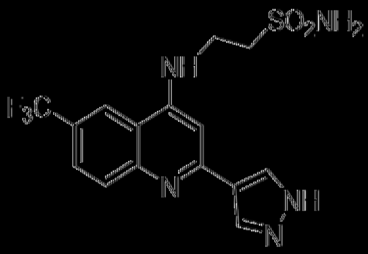
【0630】 步驟1：(4,7,8-三氯喹啉-2-基)甘胺酸三級丁酯及(2,7,8-三氯喹啉-4-基)甘胺酸三級丁酯. 向2,4,7,8-四氯喹啉(270 mg)及甘胺酸三級丁酯HCl (270 mg)於DMSO (0.8 mL)中之溶液中添加K_2CO_3 (276 mg)。在85℃下將所得反應混合物加熱4小時。用EtOAc (30 mL)進行水性處理並進行管柱層析，用0至50% DCM/己烷梯度溶離，得到兩種無色化合物。較早溶離出的部分係4-經取代之產物(120 mg) (MS: $[M+1]^+$ 361)且較晚溶離之部分含2-經取代之產物(62mg) (MS: $[M+1]^+$ 361)。

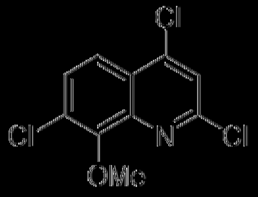
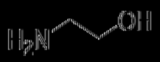
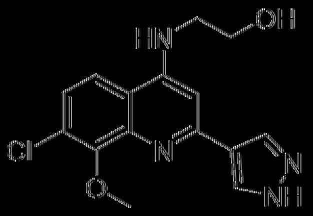
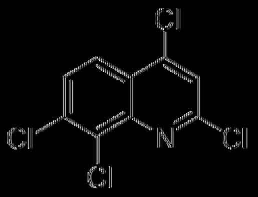
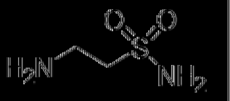
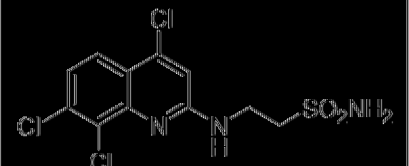
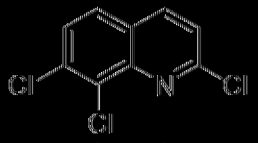
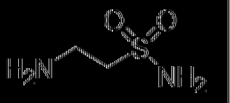
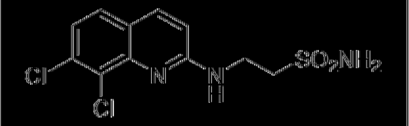
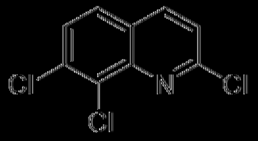
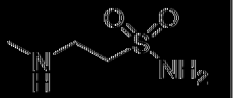
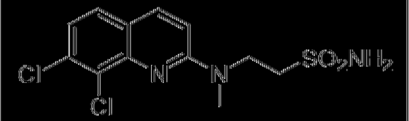
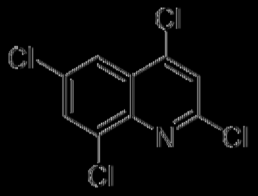
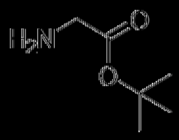
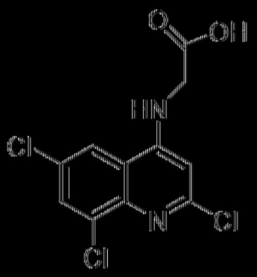
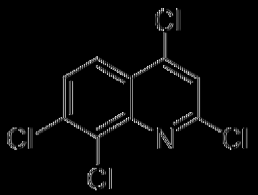
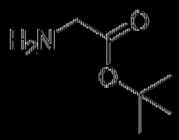
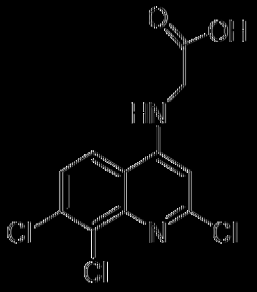
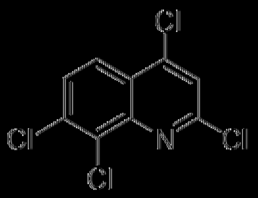
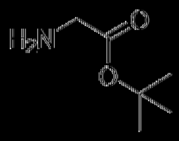
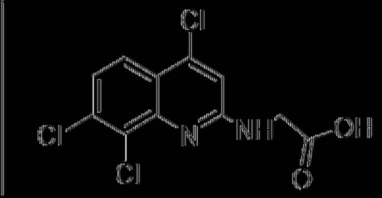
【0631】 步驟2：(7,8-二氯-2-(1H-吡唑-4-基)喹啉-4-基)甘胺酸三級丁酯. 向(2,7,8-三氯喹啉-4-基)甘胺酸三級丁酯(52 mg)、4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(50 mg)、K_2CO_3 (48 mg)及$Pd(PPh_3)_4$ (16 mg)之混合物中添加二噁烷(2 mL)及水(0.5 mL)。將所得懸浮溶液抽真空且用氬氣反覆吹掃三次，接著攪拌並在氬氣下，在85℃下加熱4小時。用EtOAc進行水性處理並進行管柱層析，得到所需無色產物(27 mg) (MS: $[M+1]^+$ 393)。

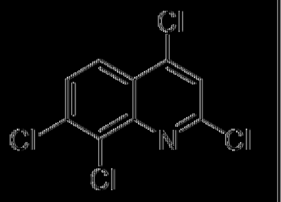
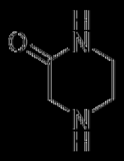
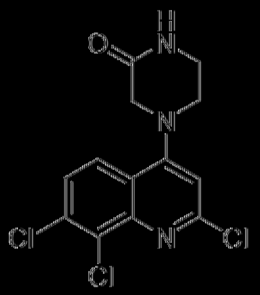
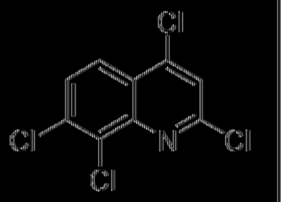
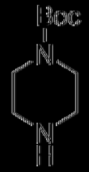
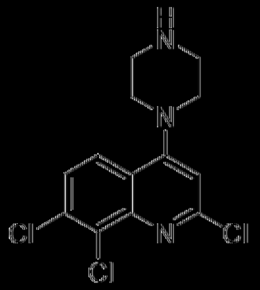
【0632】 步驟3：(7,8-二氯-2-(1H-吡唑-3-基)喹啉-4-基)甘胺酸. 向(7,8-二氯-2-(1H-吡唑-3-基)喹啉-4-基)甘胺酸三級丁酯(27 mg)於DCM (0.5 mL)中之溶液中添加TFA (0.2 mL)。將所得溶液攪拌隔夜。減壓移除

DCM及TFA後，將所得物與0.4 mL水混合並凍乾，得到標題產物(MS: $[M+1]^+$ 337)。

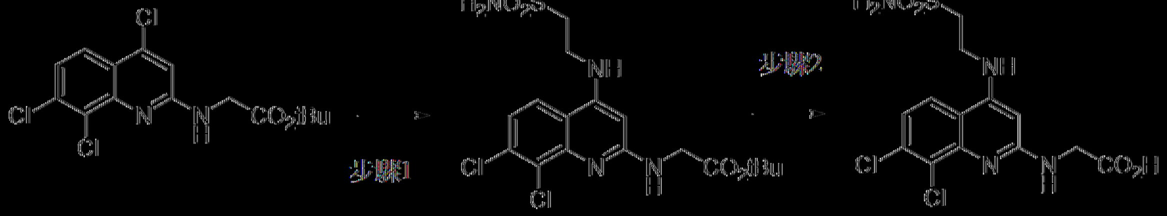
【0633】 以下化合物基本上藉由與以上關於製備I-287所描述相同的方法製備且一些類似物係由中間體，藉由額外脫保護製備。

I#	起始材料		結構	MS $[M+1]^+$
I-285				351
I-290				407
I-286				351
I-300				337
I-288				337
I-301				386

I-#	起始材料		結構	MS [M+1]$^+$
I-401				319
I-295				354
I-296				320
I-161				334
I-306				305
I-294				305
I-171				305

I#	起始材料		結構	MS [M+1]$^+$
I-307				330
I-312				316

實例47：合成(7,8-二氯-4-((2-胺磺醯基乙基)胺基)喹啉-2-基)甘胺酸(I-319)

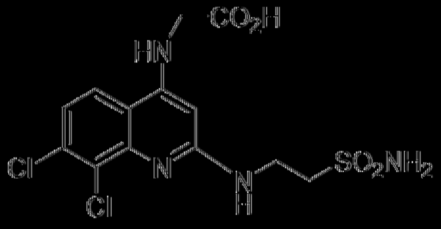


I-319

【0634】 步驟1：(7,8-二氯-4-((2-胺磺醯基乙基)胺基)喹啉-2-基)甘胺酸三級丁酯. 向(4,7,8-三氯喹啉-2-基)甘胺酸三級丁酯(28 mg)、2-胺基乙烷-1-磺醯胺(20 mg)及K_2CO_3 (22 mg)之混合物中添加DMSO (0.4 mL)。在130℃下攪拌隔夜後，將反應混合物用水稀釋並用EtOAc (15 mL)萃取。進行管柱層析，得到所需產物(6 mg) (MS: [M+1]$^+$ 449)。

【0635】 步驟2：(7,8-二氯-4-((2-胺磺醯基乙基)胺基)喹啉-2-基)甘胺酸. 對DCM (0.4 mL)及TFA (0.1 mL)中之(7,8-二氯-4-((2-胺磺醯基乙基)胺基)喹啉-2-基)甘胺酸三級丁酯(6 mg)進行酸性脫保護，得到所需產物(5 mg) (MS: [M+1]$^+$ 393)。

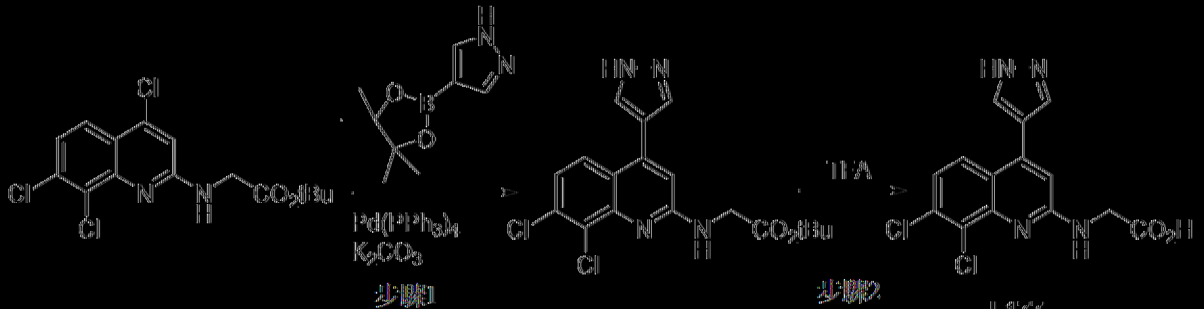
實例48：合成(7,8-二氯-2-((2-胺磺醯基乙基)胺基)喹啉-4-基)甘胺酸(I-318)



I-318

【0636】 遵循與I-319類似之製備程序，用在DMSO中之2-胺基乙烷-1-磺醯胺(18.5 mg)處理(4,7,8-三氯喹啉-2-基)甘胺酸三級丁酯(27.8 mg)且隨後脫保護，得到所需產物(5.9 mg) (MS: [M+1]$^+$ 393)。

實例49：合成(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)甘胺酸(I-177)



I-177

【0637】 (7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)甘胺酸基本上藉由與以上關於製備I-287所描述相同的方法製備。

【0638】 以下化合物基本上藉由與以上關於製備I-177所描述相同的方法製備。

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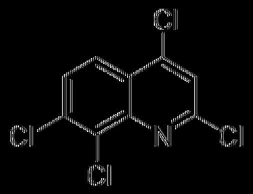
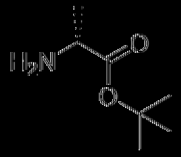
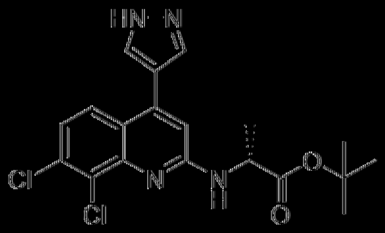
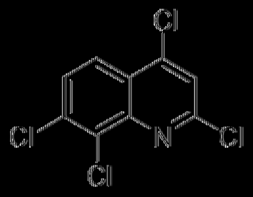
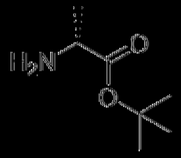
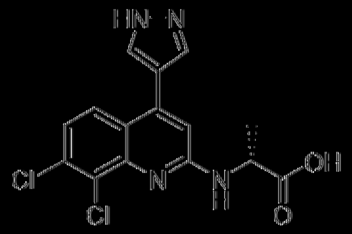
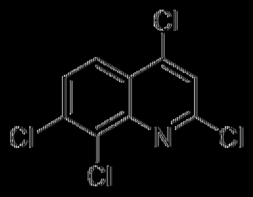
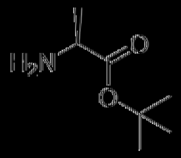
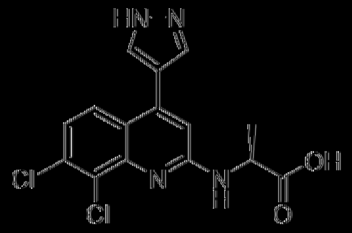
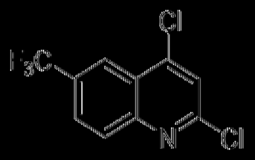
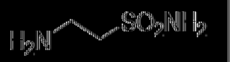
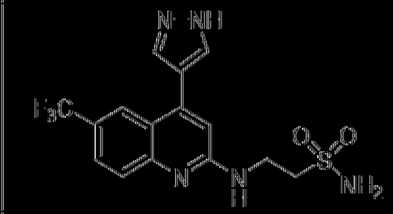
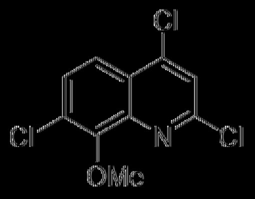
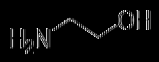
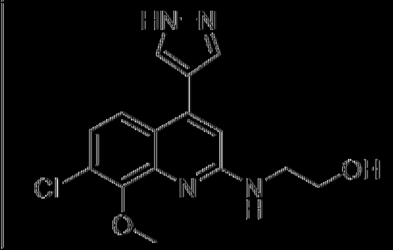
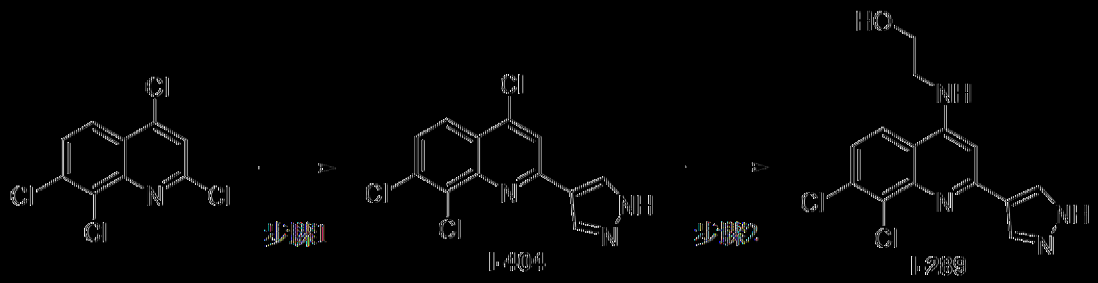
I-402				407
I-180				351
I-181				351
I-265				386
I-403				319

實例50：合成4,7,8-三氯-2-(1H-吡唑-4-基)喹啉(I-404)及2-((7,8-二氯-2-(1H-吡唑-4-基)喹啉-4-基)胺基)乙-1-醇(I-289)

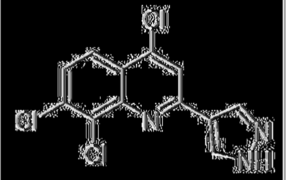
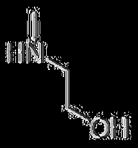
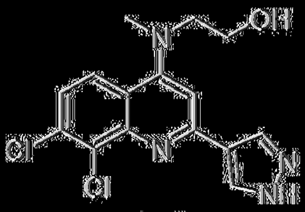
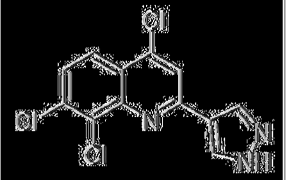
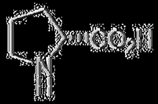
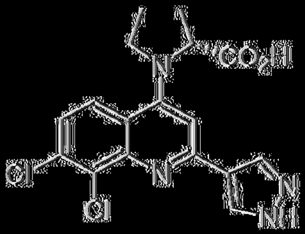
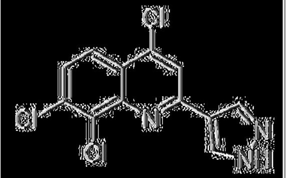
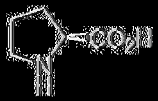
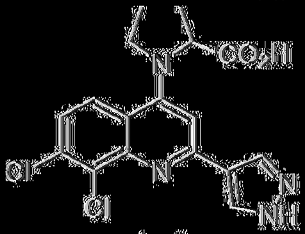
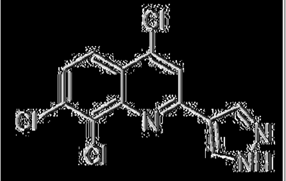
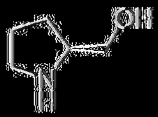
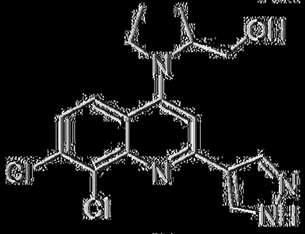
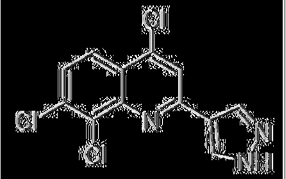
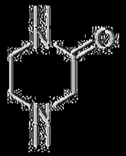
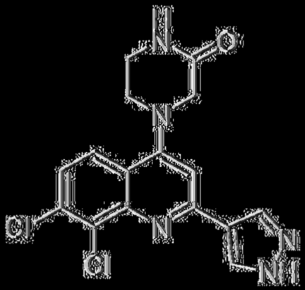


[0639] 步驟1：4,7,8-三氯-2-(1H-吡唑-4-基)喹啉. 向2,4,7,8-四氯喹啉(430 mg)、4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡

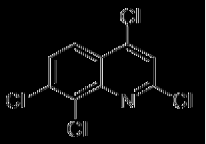
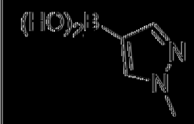
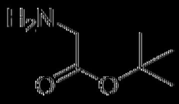
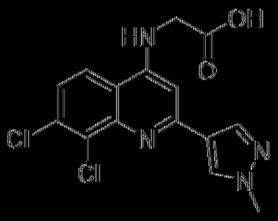
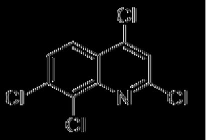
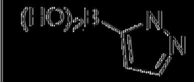
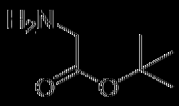
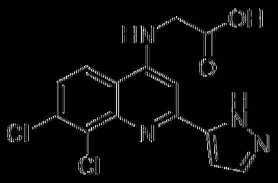
唑(345 mg)、Na_2CO_3 (513 mg)及$Pd(PPh_3)_4$ (186 mg)之混合物中添加二噁烷(6 mL)及水(3 mL)。將所得混合物抽真空且用N_2反覆吹掃三次，接著攪拌並在90℃下加熱2小時。將4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(300 mg)於二噁烷(2 mL)中之溶液添加至反應混合物中。1.5小時後，添加第二份於二噁烷(2 mL)中之4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(300 mg)。1.5小時後，起始材料2,4,7,8-四氯喹啉完全消耗且LC-MS僅觀察到一種主要產物。將反應混合物用水(4 mL)稀釋，沈澱析出所需產物。藉由過濾分離後，將分離之固體用水(4 mL)及EtOAc/己烷(1:1，6 mL)洗滌，得到所需產物**I-404** (350 mg) (MS: $[M+1]^+$ 298)。

【0640】 步驟2：2-((7,8-二氯-2-(1H-吡唑-4-基)喹啉-4-基)胺基)乙-1-醇. 向4,7,8-三氯-2-(1H-吡唑-4-基)喹啉(45 mg)及2-胺基乙-1-醇(46 mg)之混合物中添加Na_2CO_3 (32 mg)及DMSO (0.4 mL)。在110℃下將所得懸浮液攪拌隔夜，直至起始材料消耗。用水(3 mL)稀釋以使所需產物沈澱。藉由離心機分離，用水冲洗並真空乾燥，得到標題產物(27.2 mg) (MS: $[M+1]^+$ 323)。

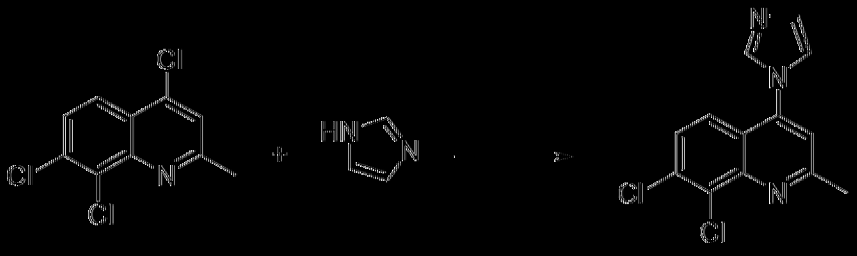
【0641】 以下化合物基本上藉由與以上關於製備**I-289**所描述相同的方法製備。

I-#	起始材料		結構	MS [M+H]+
I-297				337
I-292				377
I-291				377
I-298				363
I-299				362

【0642】以下化合物基本上藉由與以上關於製備I-289所描述相同的方法製備(鈴木偶合(Suzuki coupling)、親核取代及脫保護)。

實例	起始材料			結構	MS [M+1]+
I-425					351
I-426					337

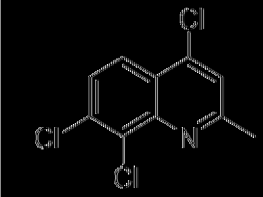
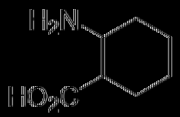
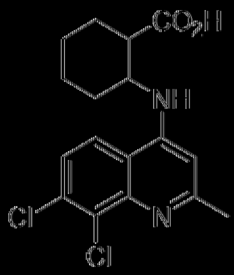
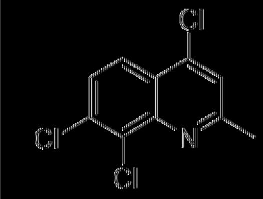
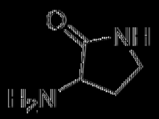
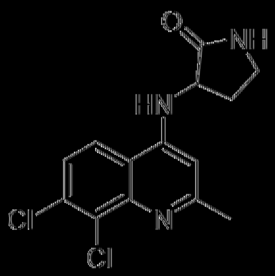
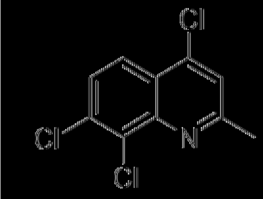
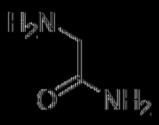
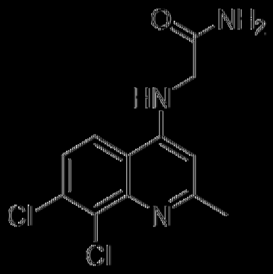
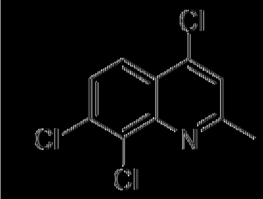
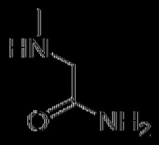
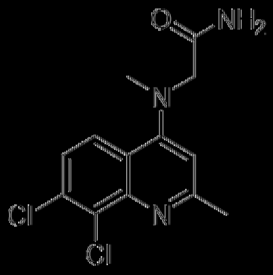
實例51：合成2-(苯甲氧基)-7-氯-4-(1H-咪唑-1-基)喹啉(I-405)

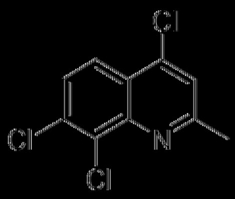
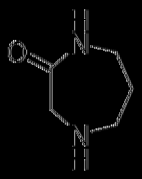
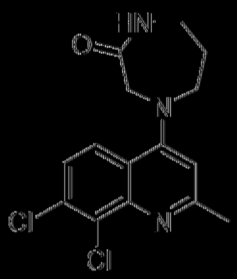
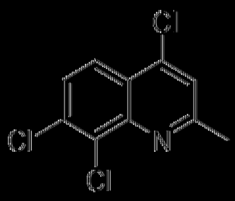
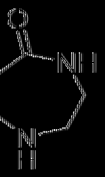
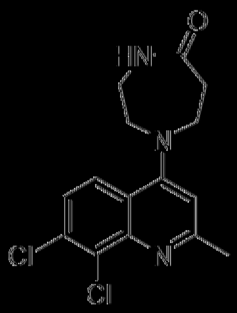
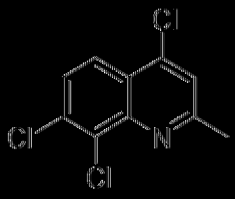
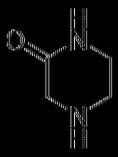
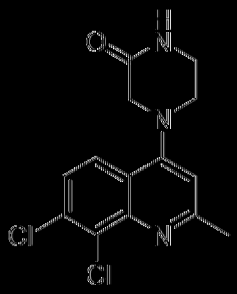
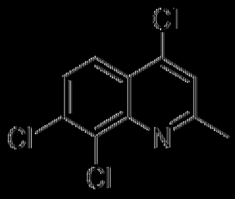
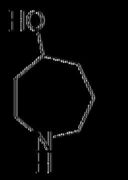
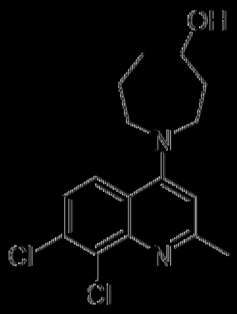
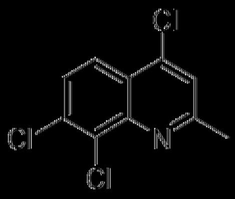
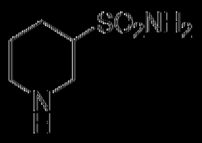
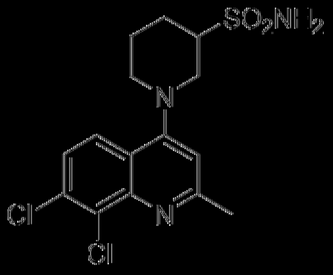


I-405

【0643】 向4,7,8-三氯-2-甲基喹啉(0.5 g)於DMF (4 mL)中之溶液中添加K_2CO_3 (0.2 g)及咪唑(0.54 g)。在120℃下將所得懸浮液加熱2小時。將反應混合物用水(8 mL)稀釋以沈澱析出標題化合物。過濾並用水沖洗，得到標題化合物(0.55 g)，即7,8-二氯-4-(1H-咪唑-1-基)-2-甲基喹啉(MS: $[M+1]^+$ 278)。

【0644】 以下化合物基本上藉由與以上關於製備I-405所描述相同的方法製備。一些類似物係藉由自水沈澱而以純形式分離且其他類似物係藉由管柱層析法純化。

I-#	起始材料		結構	MS [M+1]$^+$
I-316				353
I-315				310
I-313				284
I-314				298

I-#	起始材料		結構	MS [M+1]+
I-305				324
I-310				324
I-302				310
I-311				325
I-317				374.0

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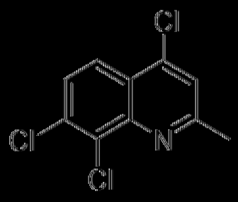
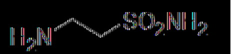
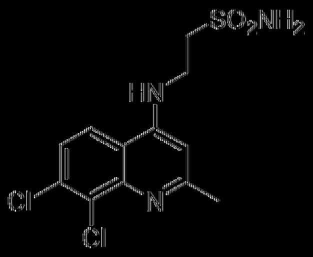
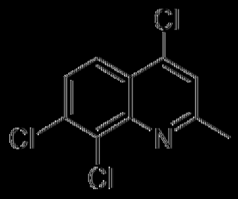
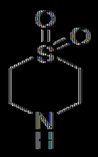
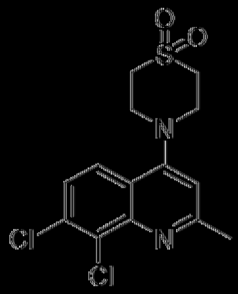
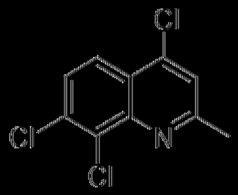
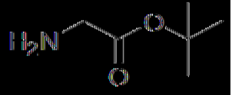
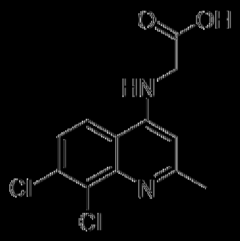
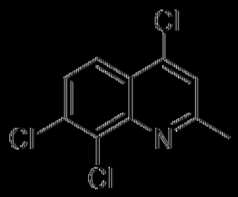
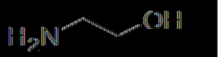
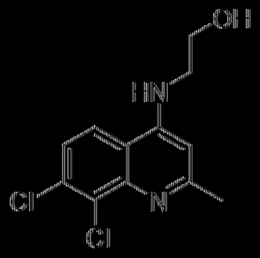
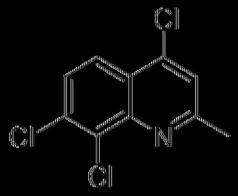
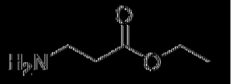
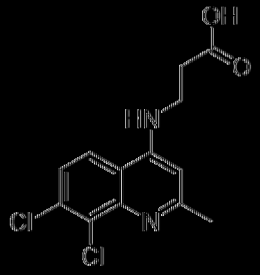
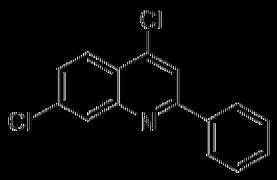
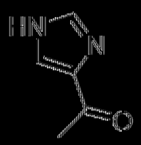
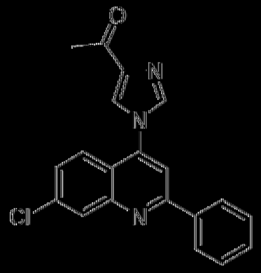
I-308				334.0
I-303				345.0
I-293				285.0
I-304				271.0
I-309				299.0
I-66				348

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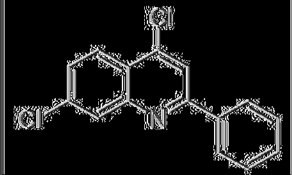
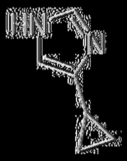
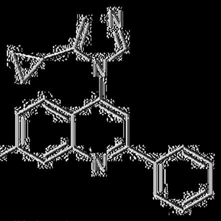
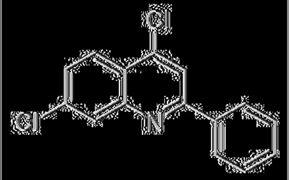
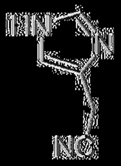
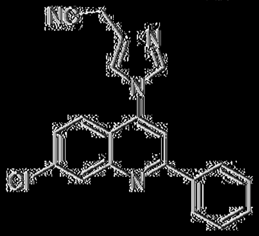
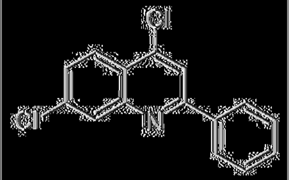
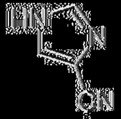
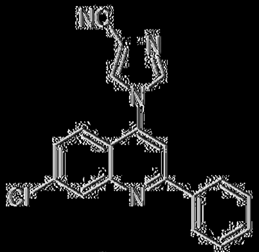
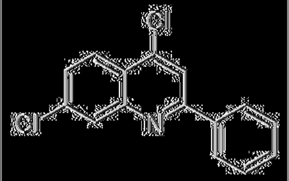
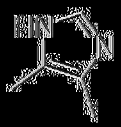
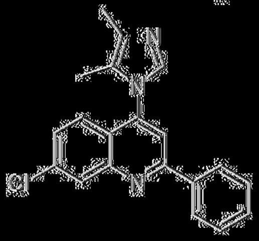
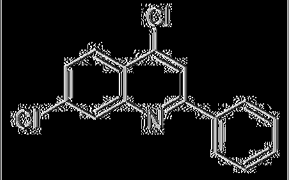
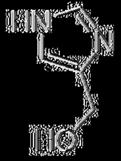
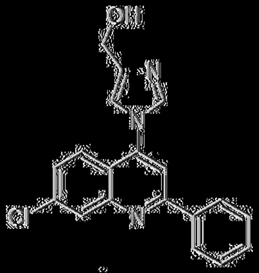
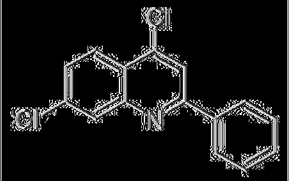
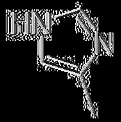
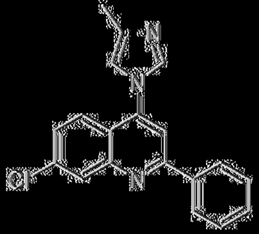
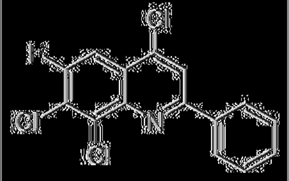
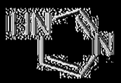
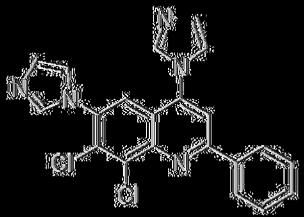
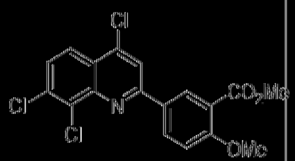
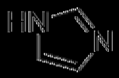
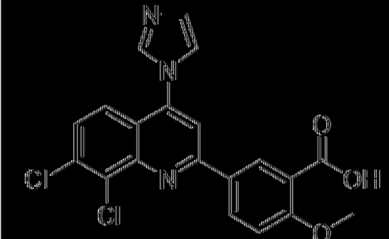
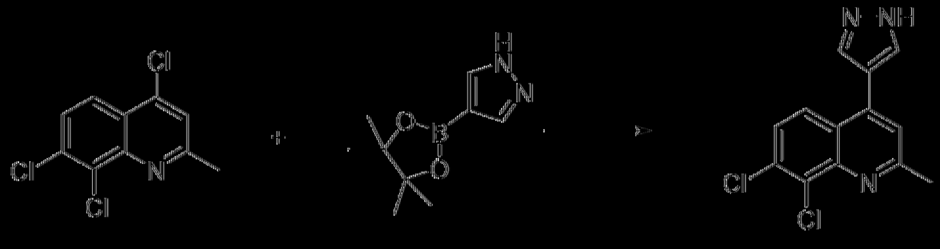
I-65				346
I-64				345
I-62				331
I-61				334
I-63				336
I-60				320
I-52				406

I-#	起始材料		結構	MS $[M+1]^+$
I-39	 	 	 	414

實例52：合成7,8-二氯-2-甲基-4-(1H-吡唑-4-基)喹啉(I-406)



I-406

【0645】 向4,7,8-三氯-2-甲基喹啉(0.2 g)、4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(281 mg)、K_2CO_3 (278 mg)及$Pd(PPh_3)_4$ (85 mg)之混合物中添加二噁烷(4 mL)及水(2 mL)。將所得混合物抽真空且用N_2反覆吹掃三次，接著攪拌並在90℃下加熱2小時。使4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(150 mg)於二噁烷(2 mL)中之溶液脫氣並將其添加至反應混合物中。2小時後，添加第二份於二噁烷(2 mL)中之4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(150 mg)。攪拌隔夜後，2,4,7,8-四氯喹啉完全消耗。水性處理並進行管柱純化，用己烷/EtOAc溶離，得到標題化合物(108 mg)，即7,8-二氯-2-甲基-4-(1H-吡唑-4-基)喹啉。MS: $[M+1]^+$ 278。

【0646】 以下化合物基本上藉由與以上關於製備I-406及I-42中之鈴木偶合所描述相同的方法製備。

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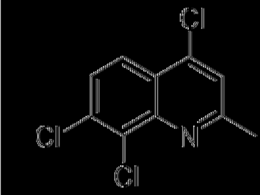
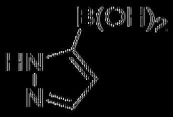
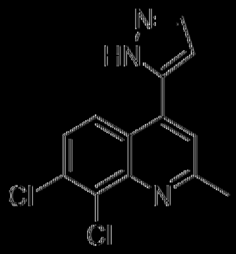
I-407	 	 	 	278

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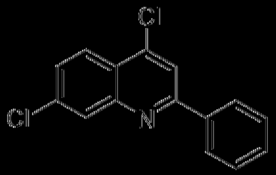
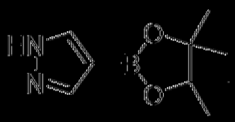
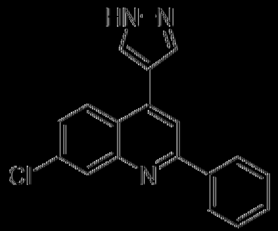
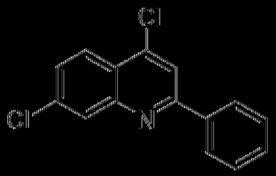
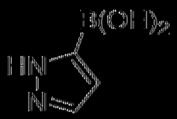
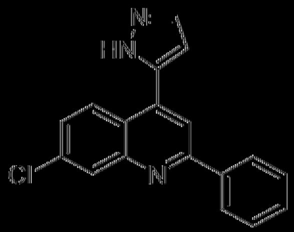
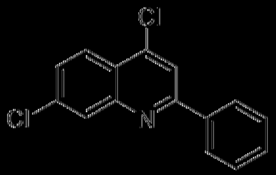
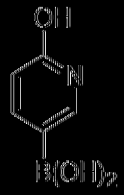
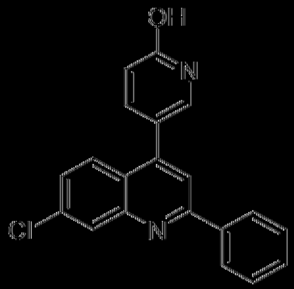
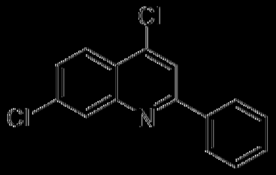
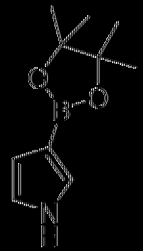
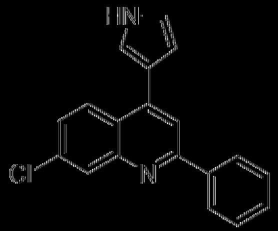
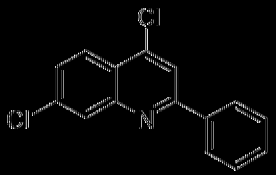
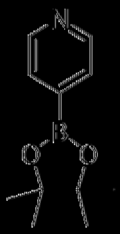
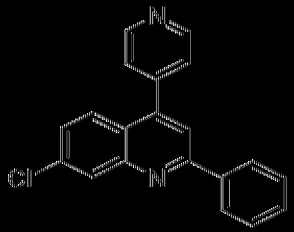
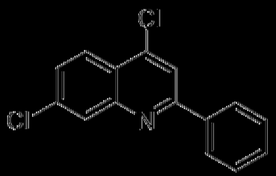
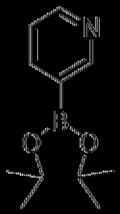
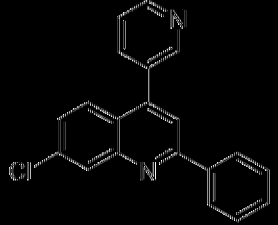
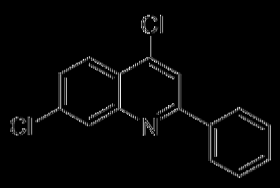
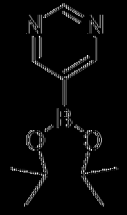
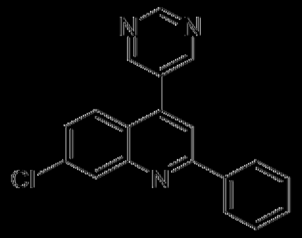
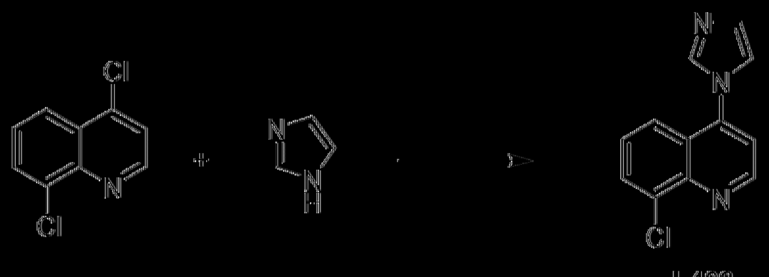
I-67				306
I-68				306
I-73				333
I-72				305
I-70				317
I-69				317

I-#	起始材料		結構	MS [M+1]+
I-71				318

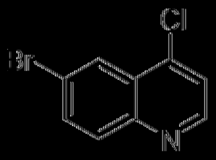
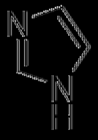
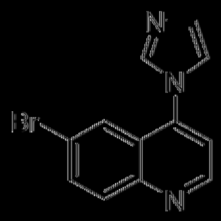
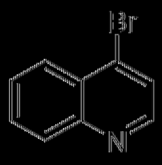
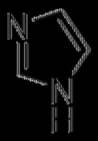
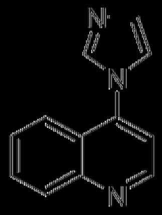
實例53：合成8-氯-4-(1H-咪唑-1-基)喹啉(I-408)

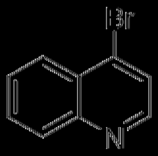
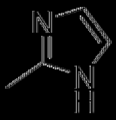
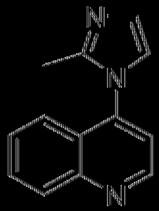
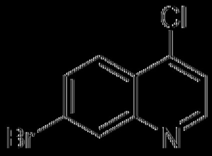
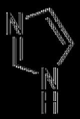
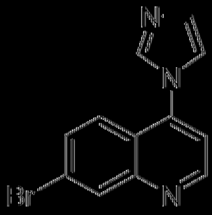
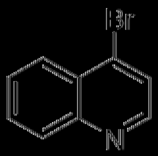
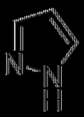
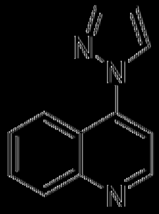
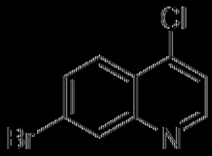
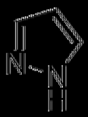
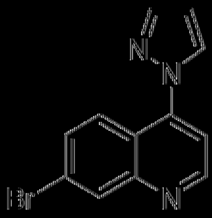
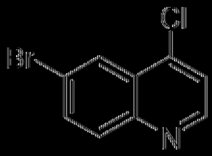
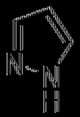
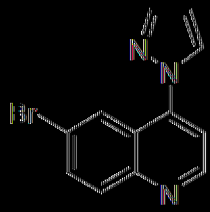
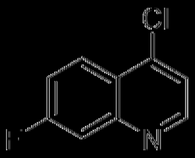
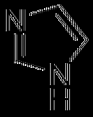
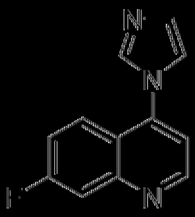
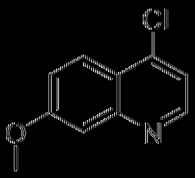
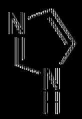
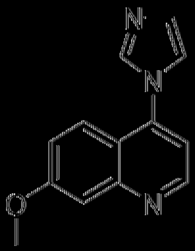


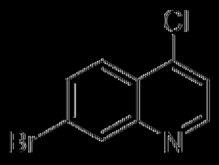
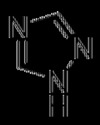
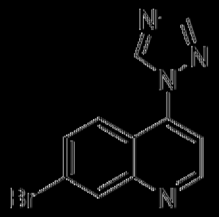
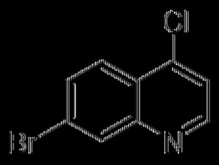
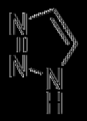
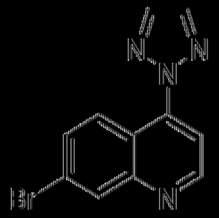
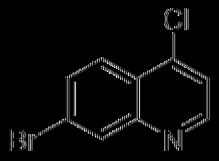
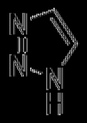
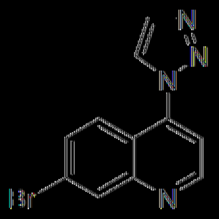
I-408

【0647】 將4,8-二氯喹啉(50 mg，0.25 mmol)放入含二噁烷(2 mL)之小瓶中。添加咪唑(68 mg，1.0 mmol)並將反應物加熱至130℃，保持16小時。將水(10 mL)添加至反應物中，且接著，將有機相萃取至乙酸乙酯(2 × 5 mL)中。將有機相乾燥(Na_2SO_4)並濃縮。將殘餘物藉由二氧化矽層析法，使用30-100% (EtOAc/己烷)純化，得到呈固體狀之8-氯-4-(1H-咪唑-1-基)喹啉(MS: $[M+1]^+$ 230)。

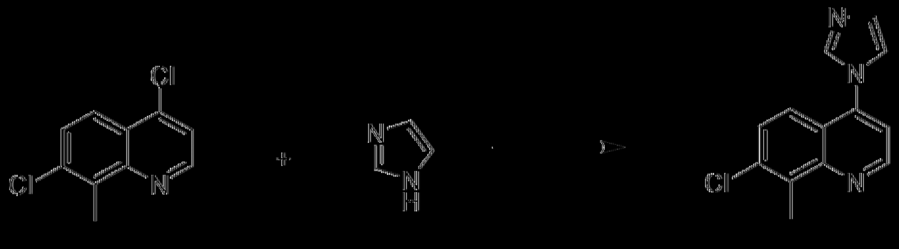
【0648】 以下化合物基本上藉由與以上關於製備I-408所描述相同的方法製備。

I-#	起始材料		結構	MS [M+1]+
I-409				274
I-410				196

I-#	起始材料		結構	MS [M+1]$^+$
I-411				210
I-412				274
I-413				196
I-414				274
I-415				274
I-416				214
I-417				226.1

I-#	起始材料		結構	MS $[M+1]^+$
I-418				275.0
I-419				275.0
I-420				274.9

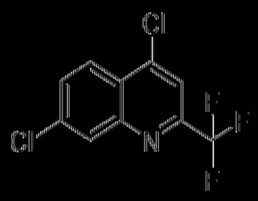
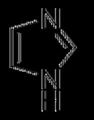
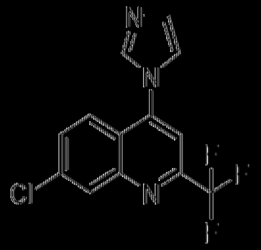
實例54：合成7-氯-4-(1H-咪唑-1-基)-8-甲基喹啉(I-421)



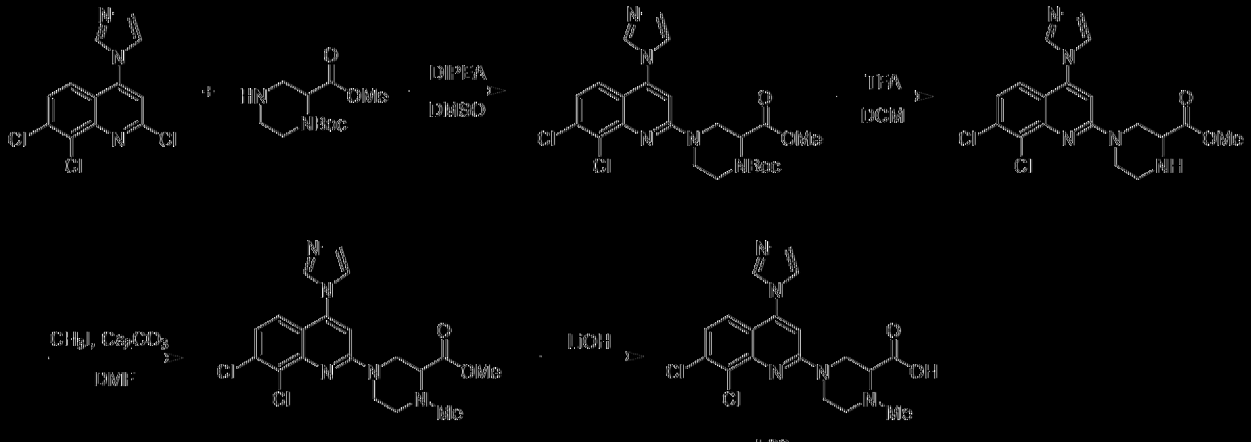
I-421

【0649】 在N_2下，將4,7-二氯-8-甲基喹啉(53 mg，0.25 mmol)、咪唑(43 mg，0.63 mmol)、三級丁醇鉀(42 mg，0.38 mmol)、二氯化雙(三苯基膦)鈀(II)(9 mg，0.013 mmol)及DMF (3 mL)放入小瓶中。在110℃下將混合物加熱2小時。冷卻至室溫後，將粗品用EtOAc (20 mL)稀釋並用水(5 mL × 2)及鹽水(5 mL × 2)洗滌。將有機相濃縮並在矽膠上藉由管柱層析法純化，得到呈固體狀之7-氯-4-(1H-咪唑-1-基)-8-甲基喹啉。(MS: $[M+1]^+$ 244.0)

【0650】 以下化合物基本上藉由與以上關於製備I-421所描述相同的方法製備。

I-#	起始材料		結構	MS $[M+1]^+$
I-422				298

實例55：合成7-氯-4-(1H-咪唑-1-基)-8-甲基喹啉(I-82)



I-82

[0651] 步驟1：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1,2-二甲酸1-三級丁酯2-甲酯基本上藉由與以上關於製備I-79所描述相同的方法製備。

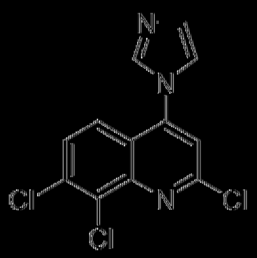
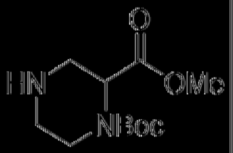
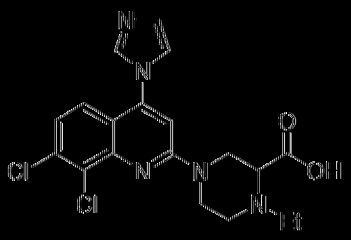
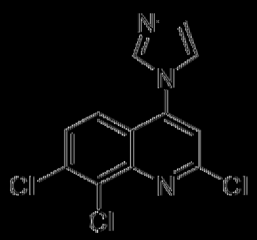
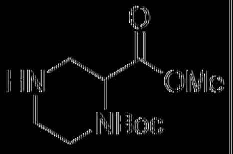
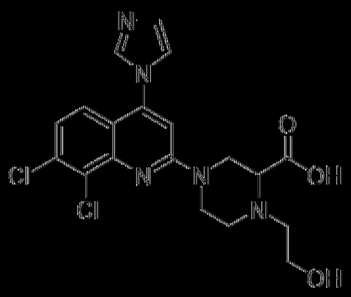
[0652] 步驟2：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸甲酯. 向小瓶中添加4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1,2-二甲酸1-三級丁酯2-甲酯(276 mg)、DCM (1.0 mL)及TFA (1.0 mL)。在室溫下將所得反應混合物攪拌2小時。減壓移除所有溶劑。在高真空下乾燥殘餘物並將粗品用於下一步驟(MS: [M+1]+ 506)。

[0653] 步驟3：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-1-甲基哌𠯤-2-甲酸甲酯. 向小瓶中添加4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸甲酯(0.025 mmol)、DMF (0.5 mL)、Cs_2CO_3 (16 mg，0.05 mmol)、CH_3I於DMF中之溶液(1.87 µl/0.5 mL，0.03 mmol)。在室溫下將

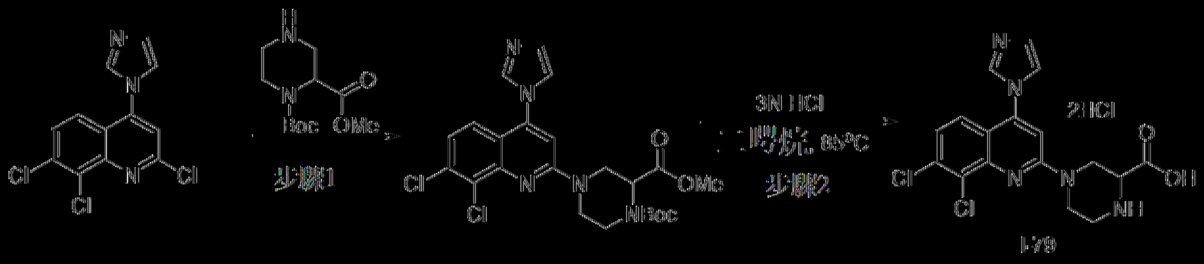
所得反應混合物攪拌3小時。將反應混合物用乙酸乙酯(20 mL)稀釋，用水(5 mL × 2)及鹽水(5 mL)洗滌並經Na_2SO_4乾燥。將粗品藉由矽膠層析法純化，得到4 mg標題化合物(MS: $[M+1]^+$ 420)。

【0654】 步驟4：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-1-甲基哌𠯤-2-甲酸. 向小瓶中添加4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-1-甲基哌𠯤-2-甲酸甲酯(4.4 mg，0.0105 mmol)、MeOH (0.25 mL)、THF (0.5 mL)、$LiOH \cdot H_2O$於H_2O中之溶液(2.2 mg/0.25 mL，0.0523 mmol)。在室溫下將所得反應混合物攪拌隔夜，酸化至pH 4。將渾濁混合物離心並在高真空下乾燥殘餘物，得到4 mg呈白色固體狀之標題產物(MS: $[M+1]^+$ 406)。

【0655】 以下化合物基本上藉由與以上關於製備I-82所描述相同之方法製備。

I-#	起始材料		結構	MS $[M+1]^+$
I-80				420
I-81				436

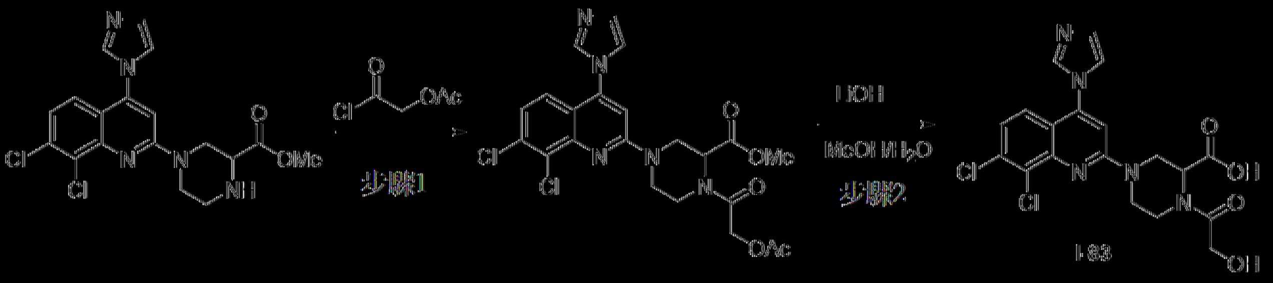
實例56：合成4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸(I-79)



【0656】 步驟1：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1,2-二甲酸1-(三級丁基)酯2-甲酯. 在90℃下，將2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(120 mg)、哌𠯤-1,2-二甲酸1-(三級丁基)酯2-甲酯(230 mg)及DIPEA (0.1 mL)於DMF (0.6 mL)中之溶液加熱隔夜，直至起始材料消耗。用EtOAc (25 mL)/水(10 mL)進行水性處理並進行管柱層析，用己烷及EtOAc梯度溶離，得到標題化合物(85 mg) (MS: [M+1]$^+$ 506)。

【0657】 步驟2：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸. 向4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1,2-二甲酸1-(三級丁基)酯2-甲酯(85 mg)於二噁烷(2 mL)中之溶液中添加12 N HCl (2 mL)。在80℃下將所得混合物加熱4小時，直至移除Boc保護基及該甲酯。減壓蒸發並凍乾，得到呈二鹽酸鹽形式之標題化合物(80 mg) (MS: [M+1]$^+$ 392)。

實例57：合成4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-1-(2-羥基乙醯基)哌𠯤-2-甲酸(I-83)

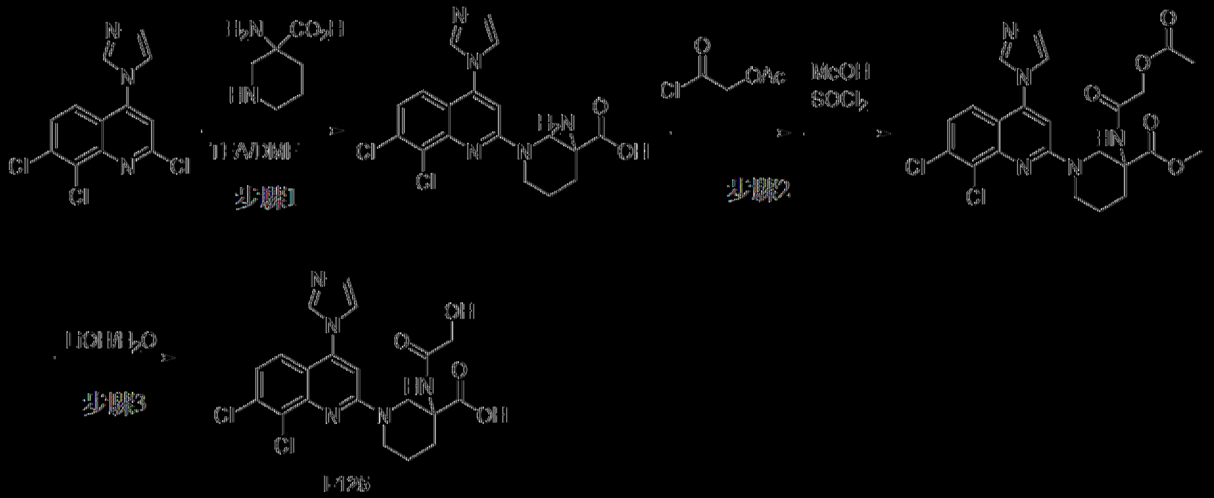


【0658】 步驟1：1-(2-乙醯氧基乙醯基)-4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸甲酯. 用乙酸2-氯-2-側氧基乙酯(20 mg)處理於

DMF (0.5 mL)及TEA (0.1 mL)中之4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸甲酯三氟乙酸鹽(20 mg) 4小時。用EtOAc/水/飽和$NaHCO_3$/鹽水進行水性處理並藉由管柱層析法純化，得到1-(2-乙醯氧基乙醯基)-4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-2-甲酸甲酯(12 mg) (MS: $[M+1]^+$ 506)。

【0659】 步驟2：4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-1-(2-羥基乙醯基)哌𠯤-2-甲酸. 將中間體溶解於MeOH (0.8 mL)及水(0.2 mL)中並用$LiOH \cdot H_2O$ (20 mg)處理隔夜。將反應混合物用水(2 mL)稀釋並用HOAc (0.02 mL)酸化以沈澱得到4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-1-(2-羥基乙醯基)哌𠯤-2-甲酸(7 mg) (MS: $[M+1]^+$ 450)。

實例58：合成1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(2-羥基乙醯胺基)哌啶-3-甲酸(I-125)



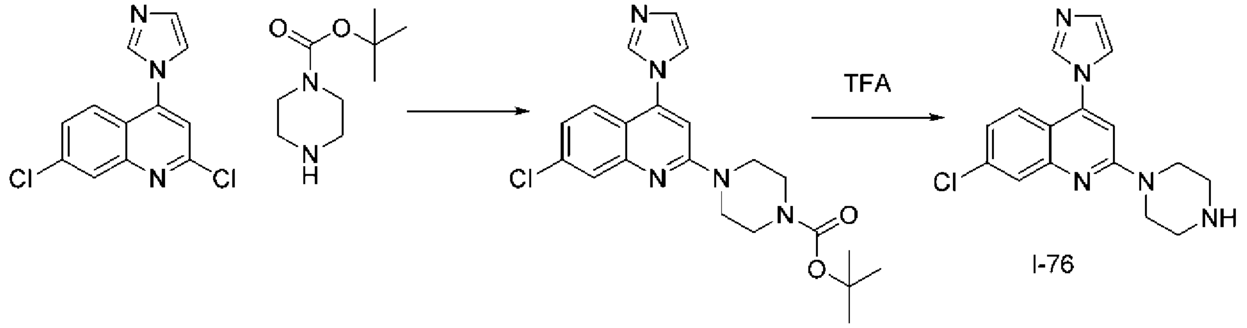
【0660】 步驟1：3-胺基-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-甲酸. 在90°C下，將2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg)與3-胺基哌啶-3-甲酸(65 mg)及三乙胺(0.2 mL)於DMF (0.5 mL)中之溶液加熱5小時，直至起始材料消耗。將所得混合物用水(2 mL)稀釋，冷凍並凍乾，得到含有標題化合物之混合物，將其直接用於下一步驟中(MS:

[M+1]$^+$ 406)。

【0661】 步驟2：1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(2-羥基乙醯胺基)哌啶-3-甲酸甲酯. 將來自上一步驟之混合物懸浮於無水DCM (2 mL)中並與乙酸2-氯-2-側氧基乙酯(0.06 mL)及TEA (0.1 mL)混合。在室溫下將所得混合物攪拌3小時，直至起始材料完全消耗。將反應混合物減壓濃縮至乾。將所得混合物溶解於無水MeOH (5 mL)中並用數滴$SOCl_2$處理。攪拌隔夜後，酸轉化成甲酯。減壓蒸發溶劑並用EtOAc進行水性處理後，進行管柱層析，得到所需甲酯(12 mg)。(MS: [M+1]$^+$ 478)

【0662】 步驟3：1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(2-羥基乙醯胺基)哌啶-3-甲酸. 用MeOH (2 mL)及水(0.5 mL)中之$LiOH\text{-}H_2O$ (8 mg)處理1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(2-羥基乙醯胺基)哌啶-3-甲酸甲酯(12 mg) 4小時。減壓蒸發有機溶劑後，將所得固體混合物小心地懸浮於水(1 mL)中並用HOAc (0.020 mL)中和。藉由離心機分離固體並用水(1 mL)沖洗。將所得濕餅凍乾，得到呈無色粉末狀之標題化合物(7 mg) (MS: [M+1]$^+$ 464)。

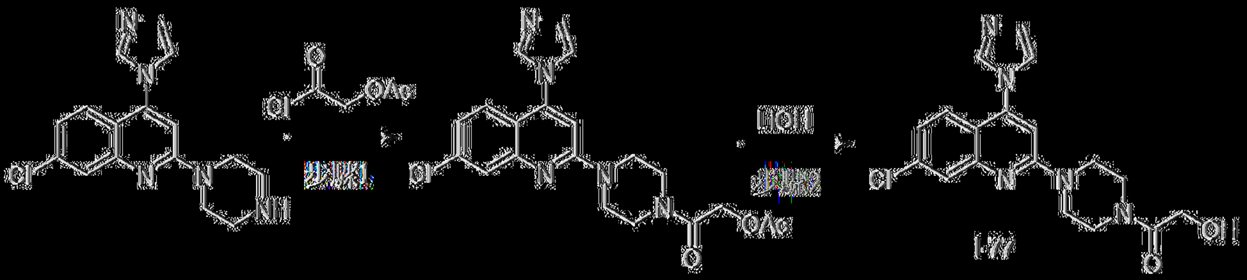
實例59：合成7-氯-4-(1H-咪唑-1-基)-2-(哌哢-1-基)喹啉(**I-76**)



【0663】 在80℃下，在K_2CO_3 (48 mg)存在下用哌哢-1-甲酸三級丁酯(60 mg)處理2,7-二氯-4-(1H-咪唑-1-基)喹啉(46 mg)於EtOH (5 mL)中之溶液隔夜。用EtOAc及水進行水性處理以移除無機鹼。分離有機層並蒸發

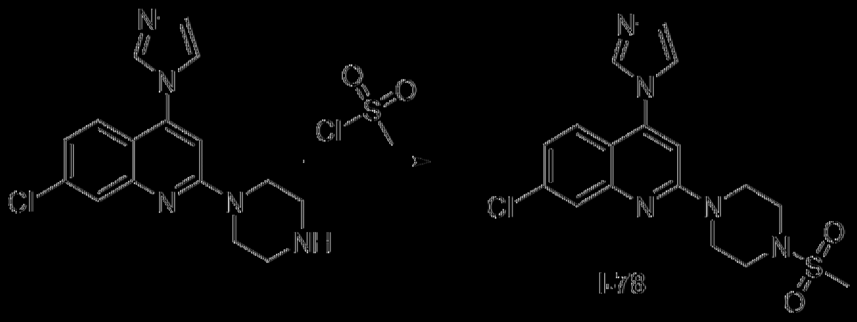
有機溶劑，得到所需4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1-甲酸三級丁酯中間體。在室溫下，經4小時用DCM (3 mL)及TFA (1 mL)脫保護，得到所需產物之三氟乙酸鹽。將三氟乙酸鹽溶解於DMF (1 mL)中並在添加$NaHCO_3$水溶液後沈澱析出中性產物(40 mg)，得到標題化合物(30 mg) (MS: $[M+1]^+$ 314)。

實例60：合成1-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1-基)-2-羥基乙-1-酮(I-77)



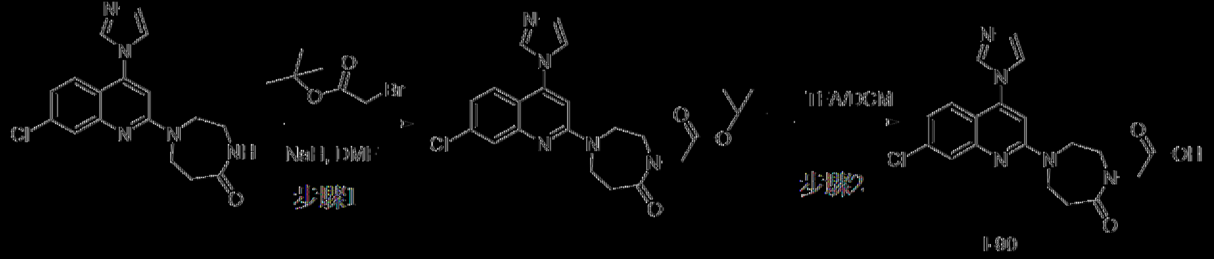
【0664】 將7-氯-4-(1H-咪唑-1-基)-2-(哌𠯤-1-基)喹啉(10 mg，1981)於DMF (1mL)中之溶液添加至乙酸2-氯-2-側氧基乙酯(56 mg)及TEA (0.1 mL)之混合物中。攪拌2小時後，用EtOAc (10 mL)水性處理並減壓蒸發，得到含所需中間體乙酸2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌𠯤-1-基)-2-側氧基乙酯的殘餘物(20 mg)。(MS: $[M+1]^+$ 414)。用MeOH (4 mL)及水(1 mL)中之LiOH (60 mg)處理此殘餘物4小時。用EtOAc進行水性處理並進行管柱層析，得到所需產物(7 mg) (MS: $[M+1]^+$ 372)。

實例61：合成7-氯-4-(1H-咪唑-1-基)-2-(4-(甲基磺醯基)哌𠯤-1-基)喹啉(I-78)



[0665] 向7-氯-4-(1H-咪唑-1-基)-2-(哌𠯤-1-基)喹啉(10 mg)於DMF (1mL)中之溶液中添加甲烷磺醯氯(30 mg)及TEA (0.1 mL)。攪拌隔夜後，用EtOAc/水進行水性處理並進行管柱層析，得到標題產物(8 mg) (MS: [M+1]+ 392)。

實例62：合成2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-側氧基-1,4-二氮雜環庚烷-1-基)乙酸(I-90)

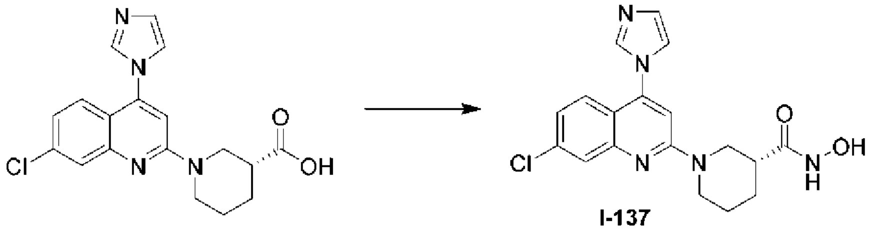


[0666] 步驟1：2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-側氧基-1,4-二氮雜環庚烷-1-基)乙酸三級丁酯. 向4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-1,4-二氮雜環庚烷-2-酮(20 mg)及2-溴乙酸三級丁酯(30 mg)於無水DMF中之溶液中添加NaH (10 mg，65%於礦物油中)。攪拌3小時後，將反應混合物用EtOAc (10 mL)稀釋並小心地用水(5 mL)淬滅。分離有機層並進行管柱層析，用己烷及EtOAc梯度溶離，得到所需中間體2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-側氧基-1,4-二氮雜環庚烷-1-基)乙酸三級丁酯(20 mg) (MS: [M+1]+ 456)。

[0667] 步驟2：2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-側氧基-1,4-二氮雜環庚烷-1-基)乙酸. 再用DCM (0.8 mL)中之TFA (0.4 mL)處理

2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-側氧基-1,4-二氮雜環庚烷-1-基)乙酸三級丁酯。減壓移除DCM及TFA並凍乾，得到所需產物(10 mg)，即2-(4-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-側氧基-1,4-二氮雜環庚烷-1-基)乙酸(MS: $[M+1]^+$ 400)。

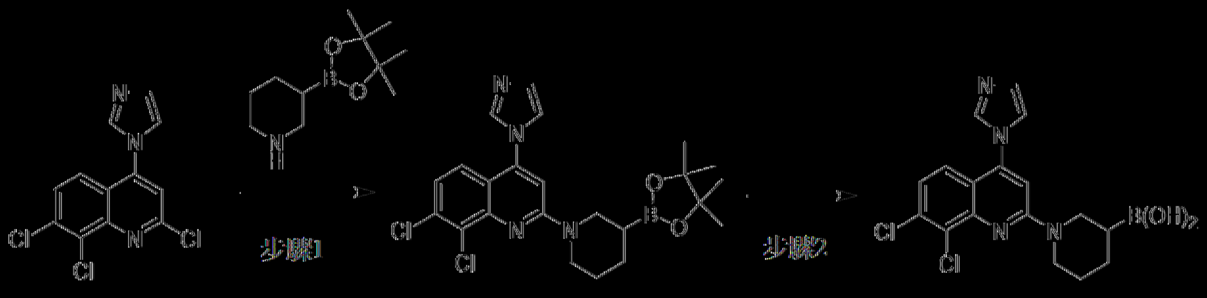
實例63：合成(R)-1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-羥基哌啶-3-甲醯胺(**I-137**)



【0668】 在0℃下，向(R)-1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-甲酸(25 mg，0.05 mmol，TEA鹽)於DMF (2 mL)中之溶液中添加$(COCl)_2$ (0.017 mL，0.2 mmol)。在室溫下將溶液攪拌1小時。蒸發混合物，得到呈白色固體狀之粗品。

【0669】 在0℃下，將羥胺鹽酸鹽(35 mg，0.5 mmol)及TEA (0.1 mL)溶解於THF (0.5 mL)及水(0.1 mL)中。添加來自第一步之粗品於DCM (1 mL)中之溶液。在室溫下將混合物攪拌隔夜。將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之(R)-1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)-N-羥基哌啶-3-甲醯胺。(11 mg，59%產率) (MS: $[M+1]^+$ 372)。

實例64：合成(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)硼酸(**I-120**)

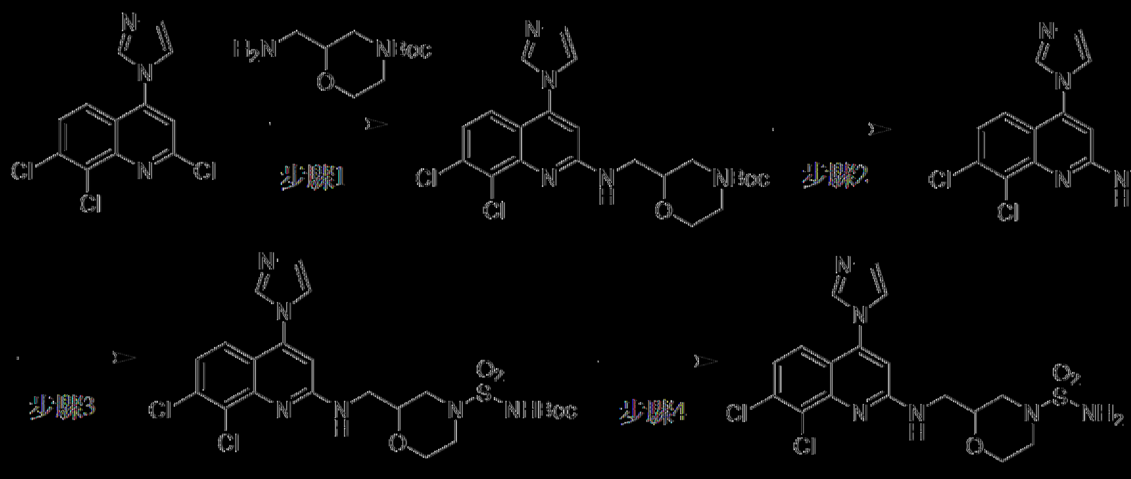


I-120

【0670】 步驟1：7,8-二氯-4-(1H-咪唑-1-基)-2-(3-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)哌啶-1-基)喹啉. 向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)及3-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)哌啶(38 mg，0.15 mmol)於DMF (1 mL)中之溶液中添加$NaHCO_3$ (42 mg，0.5 mmol)。在100℃下將溶液劇烈攪拌2小時。冷卻至室溫後，添加水(2 mL)。藉由過濾收集粗品(50 mg)，將其不經進一步純化即用於下一步驟(MS: $[M+1]^+$ 472)。

【0671】 步驟2：(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)硼酸. 向7,8-二氯-4-(1H-咪唑-1-基)-2-(3-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)哌啶-1-基)喹啉(50 mg，0.1 mmol)、$NaIO_4$ (43 mg，0.2 mmol)及NH_4OAc (15 mg，0.2 mmol)之混合物中添加水(1 mL)及丙酮(1 mL)。在室溫下將混合物攪拌隔夜。蒸發後，將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(35 mg) (MS: $[M+1]^+$ 391)。

實例65：合成((2-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)(N-味啉基))磺醯基)胺基甲酸三級丁酯(I-398)及2-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)味啉-4-磺醯胺(I-219)



I-398　　I-219

【0672】 步驟1：2-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)𠰌啉-4-甲酸三級丁酯. 向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(300 mg，1 mmol)於DMF (2 mL)中之溶液中添加2-(胺基甲基)𠰌啉-4-甲酸三級丁酯(320 mg，1.5 mmol)及$NaHCO_3$ (336 mg，4 mmol)。在120℃下將混合物劇烈攪拌2小時。冷卻至室溫後，藉由蒸發移除DMF。將殘餘物溶解於DCM (20 mL)中並用H_2O (10 mL)及鹽水(10 mL × 2)洗滌。收集有機相並濃縮，得到白色固體(500 mg)，將其不經純化即直接使用(MS: [M+1]$^+$ 478)。

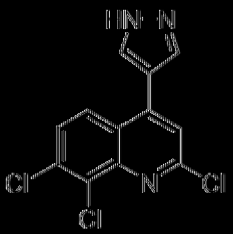
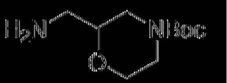
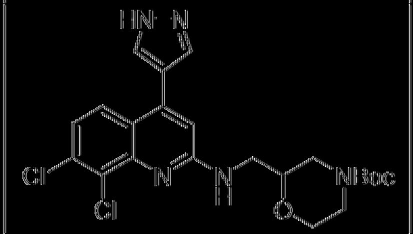
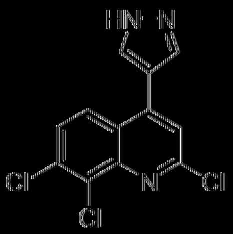
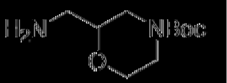
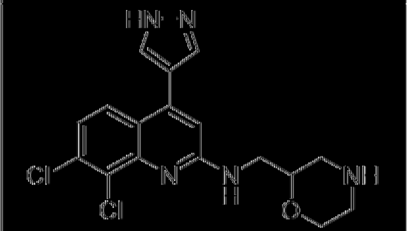
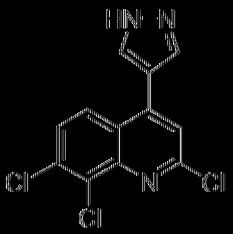
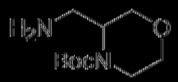
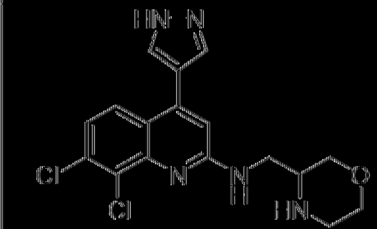
【0673】 步驟2：7,8-二氯-4-(1H-咪唑-1-基)-N-(𠰌啉-2-基甲基)喹啉-2-胺. 在室溫下，將2-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)𠰌啉-4-甲酸三級丁酯(500 mg來自步驟1之粗品)於含50% TFA之DCM (5 mL)中之溶液攪拌1小時。蒸發後，將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(110 mg)。(MS: [M+1]$^+$ 378)。

【0674】 步驟3：((2-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)(N-𠰌啉基))磺醯基)胺基甲酸三級丁酯. 在0℃下，向氯磺醯基異氰酸酯(0.1 mL，1.15 mmol)於DCM (1 mL)中之溶液中添加*t*-BuOH (0.085 mL，1.15 mmol)，保持30分鐘。在0℃下，向7,8-二氯-4-(1H-咪唑-1-基)-

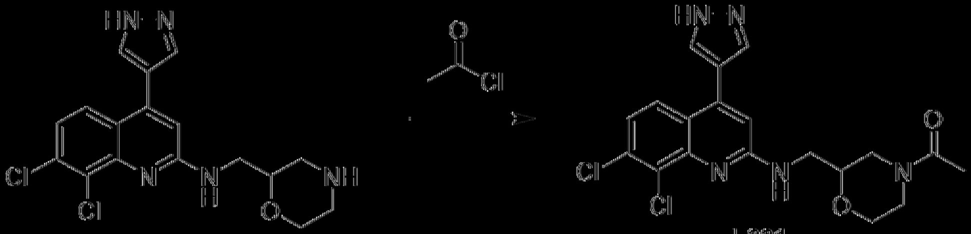
N-(𠰌啉-2-基甲基)喹啉-2-胺(48 mg，0.1 mmol)及三乙胺(0.04 mL，0.3 mmol)於DCM (1 mL)中之溶液中添加上述N-氯磺醯基胺基甲酸酯溶液(0.1 mL，0.115 mmol)。2小時後，蒸發混合物並在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(25 mg) (MS: [M+1]$^+$ 557)。

【0675】 步驟4：2-((((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)𠰌啉-4-磺醯胺. 在室溫下，將((2-((((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)(N-𠰌啉基))磺醯基)胺基甲酸三級丁酯(11 mg，0.02 mmol)於含50% TFA之DCM (1 mL)中之溶液攪拌1小時。蒸發後，將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之標題產物(3 mg) (MS: [M+1]$^+$ 457.0)。

【0676】 以下化合物基本上藉由與以上關於製備I-398及I-219所描述相同的方法製備。

I-#	起始材料		結構	MS [M+1]+
I-399				478.2
I-220				378.1
I-217				378.1

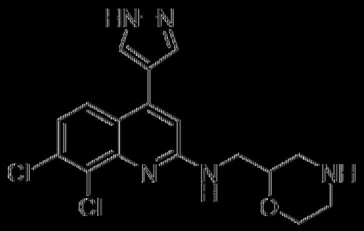
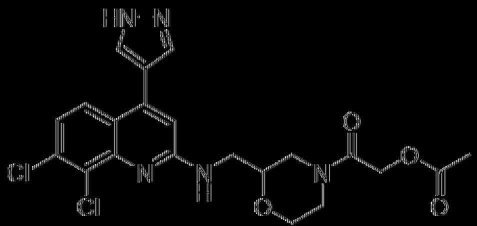
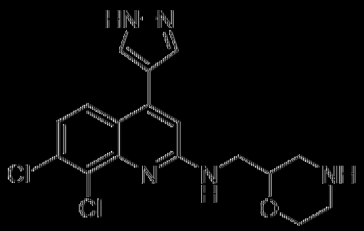
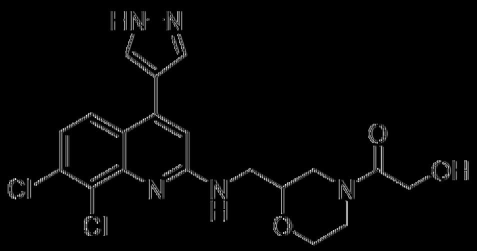
實例66：合成7-氯-4-(1H-咪唑-1-基)-8-甲基喹啉(I-221)



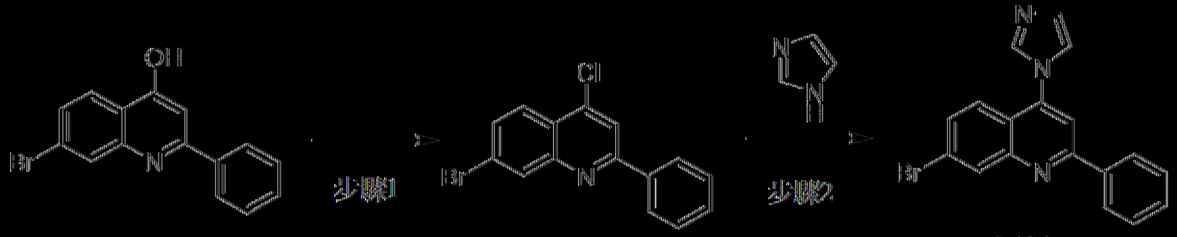
I-221

【0677】 在0℃下，向7,8-二氯-N-(味啉-2-基甲基)-4-(1H-吡唑-4-基)喹啉-2-胺(20 mg，0.053 mmol)於THF (1 mL)中之溶液中添加三乙胺(0.074 mL，0.53 mmol)及乙醯氯(0.0057 mL，0.08 mmol)。在室溫下1小時後，藉由MeOH (0.1 mL)淬滅反應。蒸發後，將粗品直接在矽膠上藉由管柱層析法純化，得到呈固體狀之1-(2-(((7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)胺基)甲基)(N-味啉基))乙-1-酮(7 mg) (MS: [M+1]$^+$ 420.0)。

【0678】 以下化合物基本上藉由與以上關於製備I-221所描述相同的方法製備。

I-#	起始材料	結構	MS [M+1]+
I-400			478.1
I-222			436.1

實例67：合成7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉(I-424)

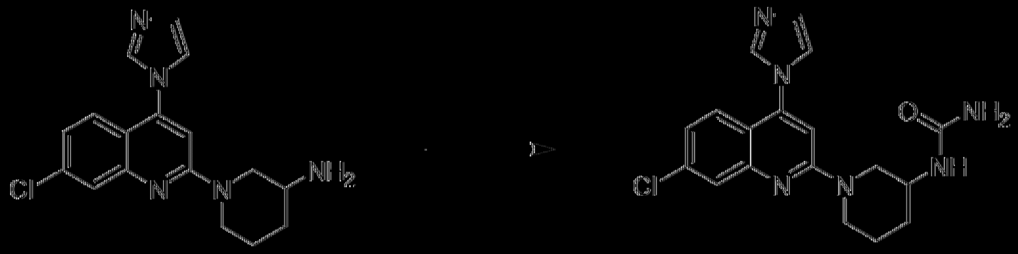


I-424

【0679】 步驟1：將7-溴-2-苯基喹啉-4-醇(250 mg，0.83 mmol)放入含氧氯化磷(8 mL)之燒瓶中並加熱至100℃，保持4小時。減壓移除揮發性物質後，真空乾燥殘餘物。將粗品7-溴-4-氯-2-苯基喹啉不經進一步純化即用於下一步。

【0680】 步驟2：在N_2下，將7-溴-4-氯-2-苯基喹啉(50 mg，0.16 mmol)、咪唑(27 mg，0.39 mmol)、三級丁醇鉀(26 mg，0.23 mmol)、二氯化雙(三苯基膦)鈀(II)(6 mg，0.008 mmol)及DMA (5 mL)放入小瓶中。在110℃下將混合物加熱2小時。冷卻至室溫後，添加冰且接著，將水層用EtOAc (2 × 10 mL)萃取並用水(5 mL × 2)及鹽水(5 mL × 2)洗滌。將有機相濃縮並在矽膠上藉由管柱層析法純化，得到呈固體狀之7-溴-4-(1H-咪唑-1-基)-2-苯基喹啉(37 mg) (MS: $[M+1]^+$ 350)。

實例68：合成1-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)脲(I-104)

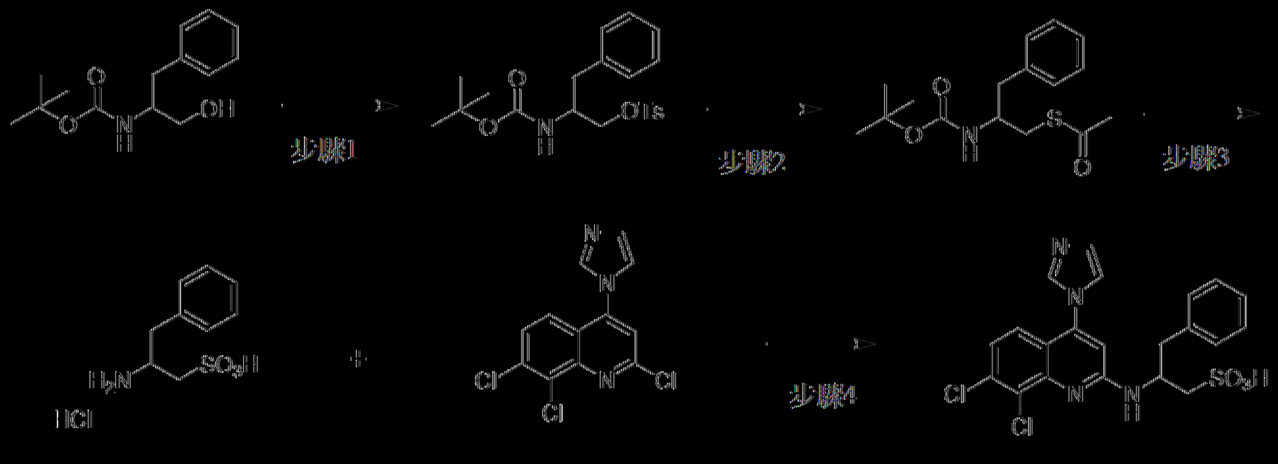


I-104

【0681】 向1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-胺(三-三氟乙酸鹽) (I-108，23 mg，0.041 mmol)於THF (3 mL)及三乙胺(0.03 mL，0.212 mmol)中之溶液中添加(三甲基矽基)異氰酸酯(8 mg，0.071 mmol)。在室溫下將溶液攪拌3小時。添加甲醇(1 mL)且接著，藉由旋轉

蒸發移除揮發性物質。將水(3 mL)添加至殘餘物中且將所得固體過濾並乾燥，得到1-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)脲(12 mg)(MS: $[M+1]^+$ 371)。

實例69：合成2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-3-苯基丙烷-1-磺酸(I-162)



I-162

【0682】 步驟1：4-甲基苯磺酸2-((三級丁氧基羰基)胺基)-3-苯基丙酯. 將(1-羥基-3-苯基丙-2-基)胺基甲酸三級丁酯(1.25 g，5.0 mmol)於吡啶(2 mL)中之溶液冷卻至-10℃。逐滴添加於吡啶(2 mL)中之甲苯磺醯氯(0.95 g，5.0 mmol)。在0℃下攪拌反應1小時，接著使其升溫至室溫並攪拌16小時。將反應物倒至冰上，接著用(4:1)己烷/乙酸乙酯(2 × 10 mL)萃取。將合併之有機層乾燥(Na_2SO_4)並濃縮。將粗4-甲基苯磺酸2-((三級丁氧基羰基)胺基)-3-苯基丙酯(MS: $[M+1-Boc]^+$ 306)直接用於下一步。

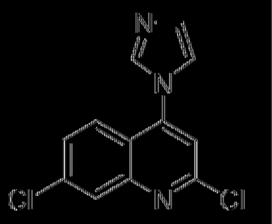
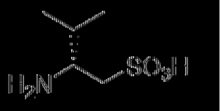
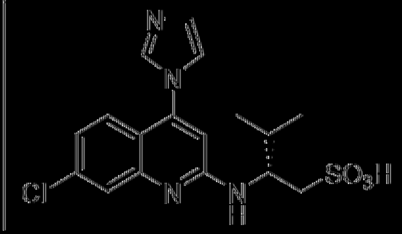
【0683】 步驟2：硫代乙酸S-(2-((三級丁氧基羰基)胺基)-3-苯基丙基)酯. 將4-甲基苯磺酸2-((三級丁氧基羰基)胺基)-3-苯基丙酯(1.6 g，3.95 mmol)放入含DMF (10 mL)之燒瓶中。將於DMF (5 mL)中之硫代乙酸鉀(677 mg，5.93 mmol)添加至燒瓶中，接著在室溫下將其攪拌16小時。添加水(25 mL)並將有機物萃取至(4:1)己烷/EtOAc (2 × 20 mL)中。將合併

之有機層乾燥(Na_2SO_4)並濃縮，得到硫代乙酸S-(2-((三級丁氧基羰基)胺基)-3-苯基丙基)酯(MS: $[M+1-Boc]^+$ 210)。

[0684] 步驟3：2-胺基-3-苯基丙烷-1-磺酸鹽酸鹽. 將硫代乙酸S-(2-((三級丁氧基羰基)胺基)-3-苯基丙基)酯(309 mg，1.0 mmol)溶解於甲酸(1.0 mL)中並在0℃下逐滴添加至過氧化氫(1 mL，30%水溶液)於甲酸中之溶液中。在室溫下攪拌反應16小時。濃縮去除揮發性物質，得到2-胺基-3-苯基丙烷-1-磺酸鹽酸鹽(MS: $[M+1]^+$ 216)。

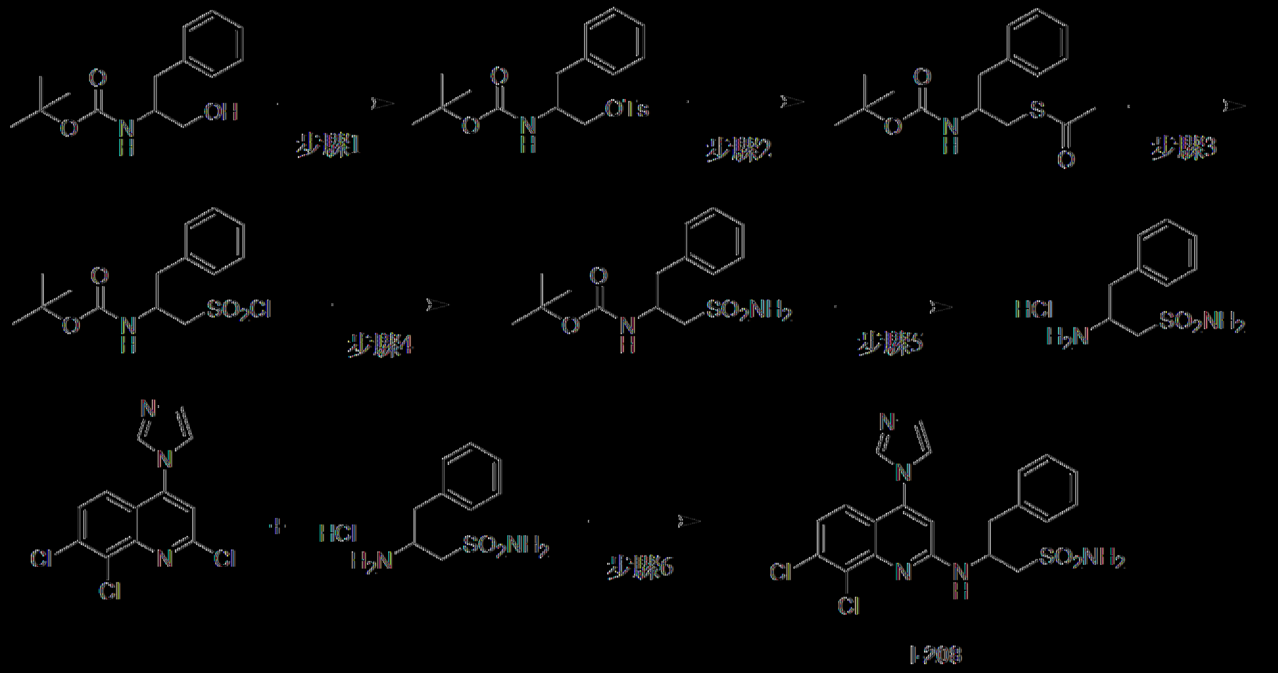
[0685] 步驟4：2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-3-苯基丙烷-1-磺酸. 將2-胺基-3-苯基丙烷-1-磺酸鹽酸鹽(62 mg，0.25 mmol)放入含於DMSO (0.2 mL)及N,N-二異丙基乙胺(0.1 mL)中之2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)的小瓶中。在95℃下將溶液攪拌16小時。冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由二氧化矽層析法，使用0-25%甲醇/二氯甲烷純化，得到2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-3-苯基丙烷-1-磺酸(MS: $[M+1]^+$ 477)。

[0686] 以下化合物基本上藉由與以上關於製備I-162所描述相同的方法製備：

I-#	起始材料		結構	MS [M+1]+
I-163				395

實例70：合成2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-3-苯基丙烷

-1-磺醯胺(I-208)



【0687】 步驟1：4-甲基苯磺酸2-((三級丁氧基羰基)胺基)-3-苯基丙酯. 將(1-羥基-3-苯基丙-2-基)胺基甲酸三級丁酯(1.25 g，5.0 mmol)於吡啶(2 mL)中之溶液冷卻至-10℃。逐滴添加於吡啶(2 mL)中之甲苯磺醯氯(0.95 g，5.0 mmol)。在0℃下攪拌反應1小時，接著使其升溫至室溫並攪拌16小時。將反應物倒至冰上，接著用(4:1)己烷/乙酸乙酯(2 × 10 mL)萃取。將合併之有機層乾燥(Na_2SO_4)並濃縮。將粗4-甲基苯磺酸2-((三級丁氧基羰基)胺基)-3-苯基丙酯(MS: $[M+1 - \text{Boc}]^+$ 306)直接用於下一步。

【0688】 步驟2：硫代乙酸S-(2-((三級丁氧基羰基)胺基)-3-苯基丙基)酯. 將4-甲基苯磺酸2-((三級丁氧基羰基)胺基)-3-苯基丙酯(1.6 g，3.95 mmol)放入含DMF (10 mL)之燒瓶中。將於DMF (5 mL)中之硫代乙酸鉀(677 mg，5.93 mmol)添加至燒瓶中，接著在室溫下將其攪拌16小時。添加水(25 mL)並將有機物萃取至(4:1)己烷/EtOAc (2 × 20 mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮，得到硫代乙酸S-(2-((三級丁氧基羰基)胺基)-3-苯基丙基)酯(MS: $[M+1 - \text{Boc}]^+$ 210)。

【0689】 步驟3：(1-(氯磺醯基)-3-苯基丙-2-基)胺基甲酸三級丁酯. 將S-(2-((三級丁氧基羰基)胺基)-3-苯基丙基)硫代乙酸酯(300 mg，0.97 mmol)放入含乙腈(3 mL)及水(52 μL)之小瓶中，接著冷卻至0℃。添加次氯酸三級丁酯(0.33 mL，2.9 mmol)並在0℃下攪拌反應20分鐘。藉由旋轉蒸發移除揮發性物質並將粗(1-(氯磺醯基)-3-苯基丙-2-基)胺基甲酸三級丁酯不經進一步純化即用於下一步。

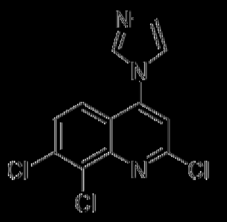
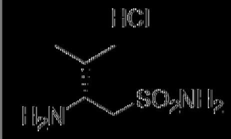
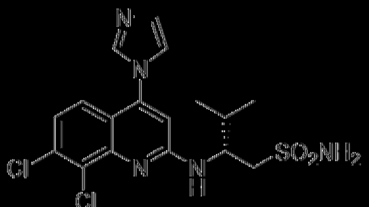
【0690】 步驟4：(1-苯基-3-胺磺醯基丙-2-基)胺基甲酸三級丁酯. 將(1-(氯磺醯基)-3-苯基丙-2-基)胺基甲酸三級丁酯放入含乙腈(5 mL)之小瓶中並冷卻至0℃。添加氫氧化銨(2 mL)並在0℃下攪拌反應10分鐘，接著使其升溫至室溫並攪拌1小時。添加二氯甲烷(25 mL)，隨後添加水(10 mL)並將混合物劇烈攪拌5分鐘。將有機層分離，乾燥(Na_2SO_4)並濃縮，得到(1-苯基-3-胺磺醯基丙-2-基)胺基甲酸三級丁酯(MS: $[M+1 - Boc]^+$ 215)。

【0691】 步驟5：2-胺基-3-苯基丙烷-1-磺醯胺鹽酸鹽. 將(1-苯基-3-胺磺醯基丙-2-基)胺基甲酸三級丁酯(100 mg，0.32 mmol)放入含二氯甲烷(2 mL)之小瓶中。添加鹽酸(4.0M於二噚烷中) (0.5 mL)並在室溫下攪拌反應1小時。添加乙腈並過濾出所得固體且真空乾燥，得到2-胺基-3-苯基丙烷-1-磺醯胺鹽酸鹽(MS: $[M+1]^+$ 215)。

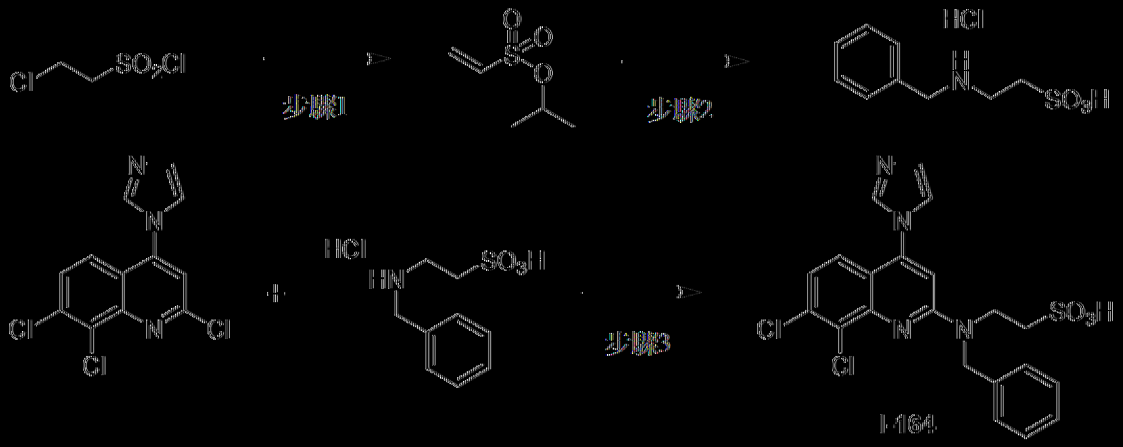
【0692】 步驟6：2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-3-苯基丙烷-1-磺醯胺. 將2-胺基-3-苯基丙烷-1-磺醯胺鹽酸鹽(55 mg，0.23 mmol)放入含於DMSO (0.2 mL)及N,N-二異丙基乙胺(0.1 mL)中之2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)的小瓶中。在95℃下將溶液攪拌16小時。冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所

得殘餘物藉由Combiflash，使用0-10%甲醇/二氯甲烷純化，得到2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)-3-苯基丙烷-1-磺醯胺(MS: $[M+1]^+$ 476)

【0693】 以下化合物基本上藉由與以上關於製備I-208所描述相同的方法製備：

I#	起始材料		結構	MS $[M+1]^+$
I-209				428.0

實例71：合成2-(苯甲基(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙烷-1-磺酸(I-164)

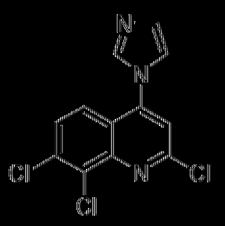
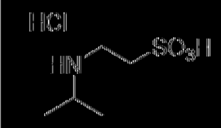
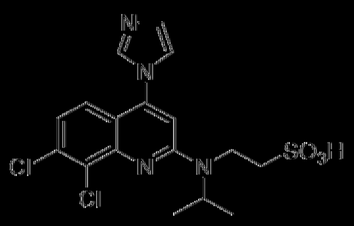


【0694】 步驟1：乙烯磺酸異丙酯. 將2-氯乙烷-1-磺醯氯(0.65 mL，6.1 mmol)放入含二氯甲烷(3.0 mL)及異丙醇(0.47 mL，6.1 mmol)之燒瓶中並將其冷卻至-10℃。逐滴添加吡啶(0.98 mL，6.1 mmol)於二氯甲烷(1.4 mL)中之溶液並在-10℃下攪拌反應2小時並經30分鐘使其升溫至室溫。藉由添加1M HCl (20 mL)淬滅混合物。用乙酸乙酯(2 × 10 mL)萃取水層。將合併之萃取物乾燥(Na_2SO_4)並濃縮，得到呈油狀之乙烯磺酸異丙酯且其不經進一步純化即用於下一步。

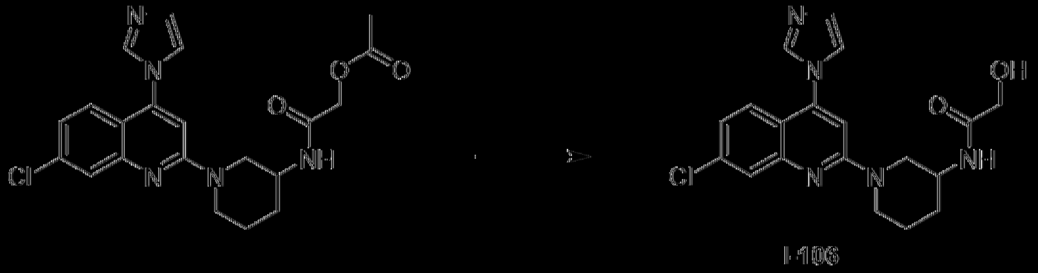
【0695】 步驟2：2-(苯甲胺基)乙烷-1-磺酸鹽酸鹽. 在0℃下，將乙烯磺酸異丙酯(440 mg，0.2 mmol)於甲醇(1.5 mL)中之溶液添加至苯甲胺(0.31g, 2.9 mmol)於甲醇(1.0 mL)中之溶液中。在0℃下攪拌反應1.5小時，接著使其升溫至室溫。藉由添加HCl (1.0M於MeOH中)酸化該溶液，接著在90℃下加熱16小時。過濾出所得沈澱並乾燥，得到2-(苯甲胺基)乙烷-1-磺酸鹽酸鹽(MS: $[M+1]^+$ 216)。

【0696】 步驟3：2-(苯甲基(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙烷-1-磺酸. 將2-(苯甲胺基)乙烷-1-磺酸鹽酸鹽(50 mg，0.2 mmol)放入含於DMSO (0.2 mL)及N,N-二異丙基乙胺(0.1 mL)中之2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)的小瓶中。在95℃下將溶液攪拌16小時。冷卻至室溫後，添加水(5 mL)並將有機物萃取至含10%甲醇之二氯甲烷(2 × 5mL)中。將合併之有機層乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由Combiflash ，使用0-10%甲醇/二氯甲烷純化，得到2-(苯甲基(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙烷-1-磺酸(33 mg) (MS: $[M+1]^+$ 477)。

【0697】 以下化合物基本上藉由與以上關於製備I-164所描述相同的方法製備：

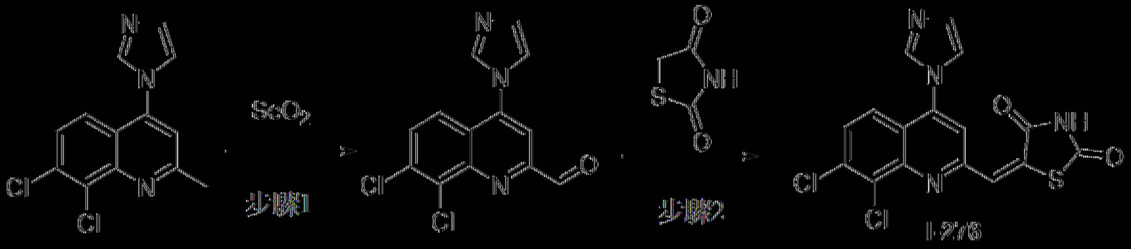
I#	起始材料		結構	MS $[M+1]^+$
I-165				429

實例72：合成N-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)-2-羥基乙醯胺(I-106)



【0698】 向乙酸2-((1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)胺基)-2-側氧基乙酯(I-395) (17 mg，0.04mmol)於THF (2 mL)及水(0.5 mL)中之溶液中添加單水合氫氧化鋰(5 mg，0.12 mmol)。在室溫下將溶液攪拌16小時。移除揮發性物質，並用1M HCl (水溶液)將殘餘物中和至約pH 7。將有機層萃取至乙酸乙酯(2 × 5mL)中。將合併之有機層乾燥並濃縮，得到N-(1-(7-氯-4-(1H-咪唑-1-基)喹啉-2-基)哌啶-3-基)-2-羥基乙醯胺(9 mg) (MS: [M+1]$^+$ 386)。

實例73：合成(E)-5-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)亞甲基)噻唑啶-2,4-二酮(I-276)

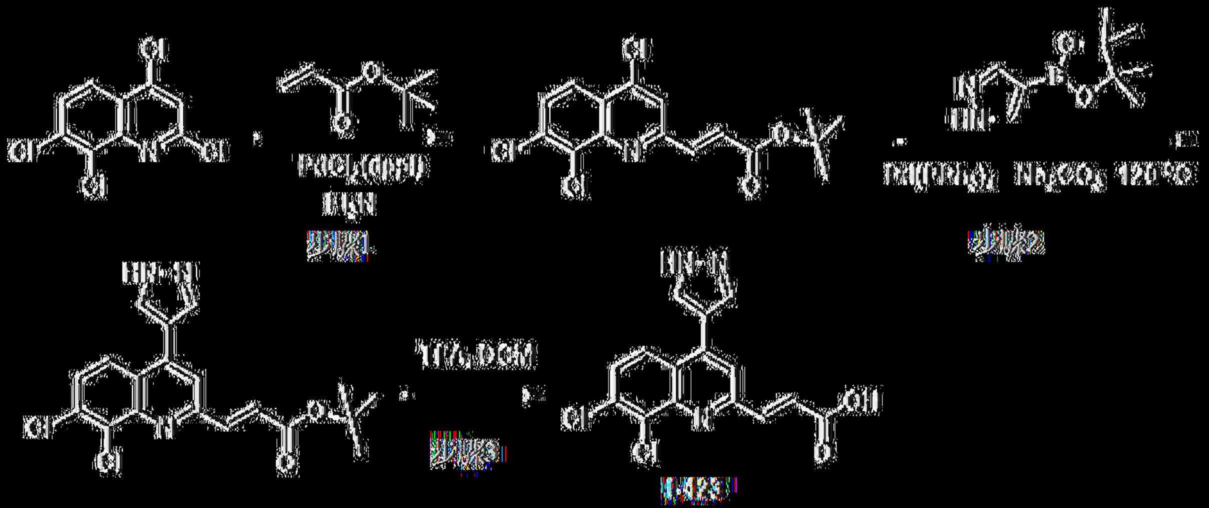


【0699】 步驟1：7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-甲醛. 向7,8-二氯-4-(1H-咪唑-1-基)-2-甲基喹啉(104 mg)於二噁烷(5 mL)中之溶液中添加二氧化硒(82 mg)。在85℃下將反應混合物攪拌2小時後，經由矽藻土墊過濾並減壓蒸發，得到呈褐色固體狀之所需7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-甲醛(90 mg)。

【0700】 步驟2：(E)-5-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)亞甲基)噻唑啶-2,4-二酮. 將該醛(20 mg)懸浮於HOAc (1 mL)中並在100℃下用

噻唑啶-2,4-二酮(65 mg)及β-苯胺(33 mg)處理4小時。減壓移除HOAc後，將殘餘物用水(1 mL)及飽和$NaHCO_3$溶液(1 mL)稀釋。藉由離心機分離固體並用水及50%乙腈/水沖洗。真空乾燥，得到呈褐色固體狀之所需產物(24 mg)，即(E)-5-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)亞甲基)噻唑啶-2,4-二酮(MS: $[M+1]^+$ 391)。

實例74：合成3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙烯酸(I-423)



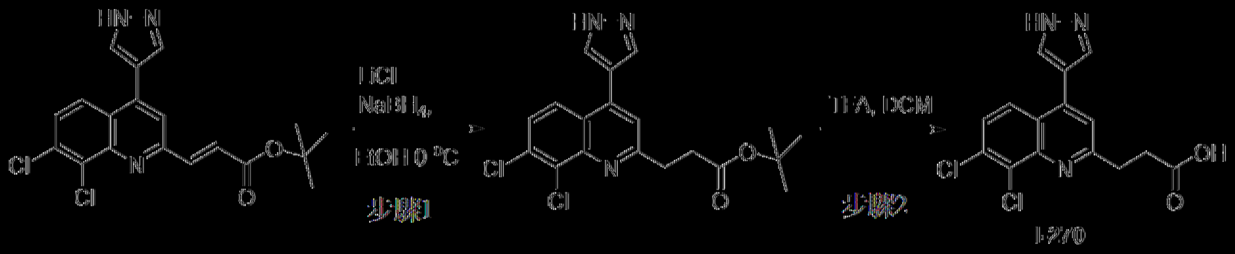
[0701] 步驟1：3-(4,7,8-三氯喹啉-2-基)丙烯酸三級丁酯. 向2,4,7,8-四氯喹啉(1.3 g)於無水DMF (1 mL)中之溶液中添加丙烯酸三級丁酯(3.4 g)、TEA (1.96 g)及$PdCl_2(PPh_3)_4$ (0.34 g)。在110℃下將所得混合物攪拌隔夜並用水稀釋。用EtOAc (80 mL)萃取水層，並將分離之有機層用飽和NH_4Cl沖洗且經無水Na_2SO_4乾燥。進行矽膠管柱層析(用石油醚及EtOAc梯度溶離)，得到所需產物(1.4 g) (MS: $[M+1]^+$ 358)。

[0702] 步驟2：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙烯酸三級丁酯. 向3-(4,7,8-三氯喹啉-2-基)丙烯酸三級丁酯(358 mg)於二噁烷(5 mL)及水(2 mL)中之溶液中添加4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(580 mg)、Na_2CO_3 (650 mg)及$Pd(PPh_3)_4$ (115 mg)。將所得混合物用N_2吹掃(經由3個真空及吹掃循環)並在N_2下，在120℃下攪拌

4小時。用水(20 mL)稀釋後，將水層用EtOAc (30 mL)萃取。將分離之有機層用鹽水洗滌且經無水Na_2SO_4乾燥。進行管柱層析，得到所需產物(130 mg) (MS: $[M+1]^+$ 390)。

【0703】 步驟3：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙烯酸. 向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙烯酸三級丁酯(15 mg)於DCM (0.4 mL)中之溶液中添加TFA (0.2 mL)。將所得溶液攪拌1小時並濃縮至乾。將殘餘物藉由製備型薄層層析法純化，得到標題化合物(1.4 mg) (MS: $[M+1]^+$ 334)。

實例75：合成3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸(I-270)

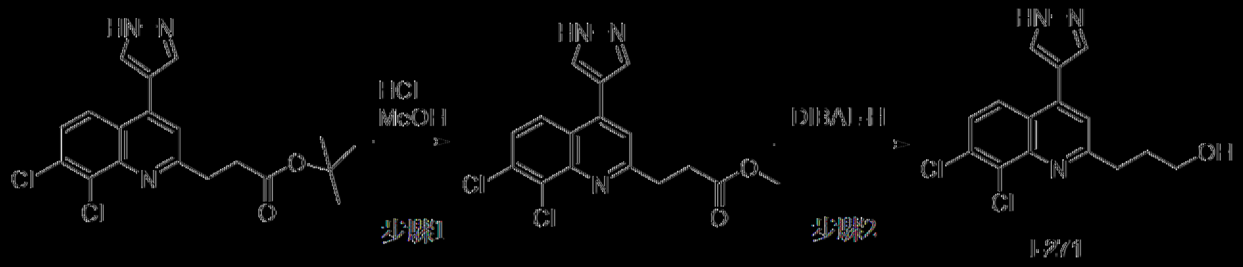


【0704】 步驟1：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸三級丁酯. 在0℃下，向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙烯酸三級丁酯(60 mg)於EtOH (5 mL)中之溶液中添加LiCl (23 mg)及$NaBH_4$ (9 mg)。在0℃下攪拌1小時後，用0.5 N HCl (0.5 mL)淬滅反應混合物。將混合物濃縮至乾，得到粗3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸三級丁酯。

【0705】 步驟2：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸. 向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸三級丁酯殘餘物於DCM (2 mL)中之溶液中添加TFA (0.8 mL)並在室溫下攪拌反應4小時。將粗產物藉由製備型HPLC純化，得到所需3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸(19 mg)。MS: $[M+1]^+$ 336。^1H NMR (400 MHz, DMSO-D6): δ

8.193-8.171 (m, 3H), 7.735-7.712 (d, *J* = 8.8 Hz, 1H), 7.626 (s, 1H), 3.216-3.252 (t, *J* = 7.2 Hz, 2H), 2.863-2.899 (t, *J* = 7.2 Hz, 2H) ppm。

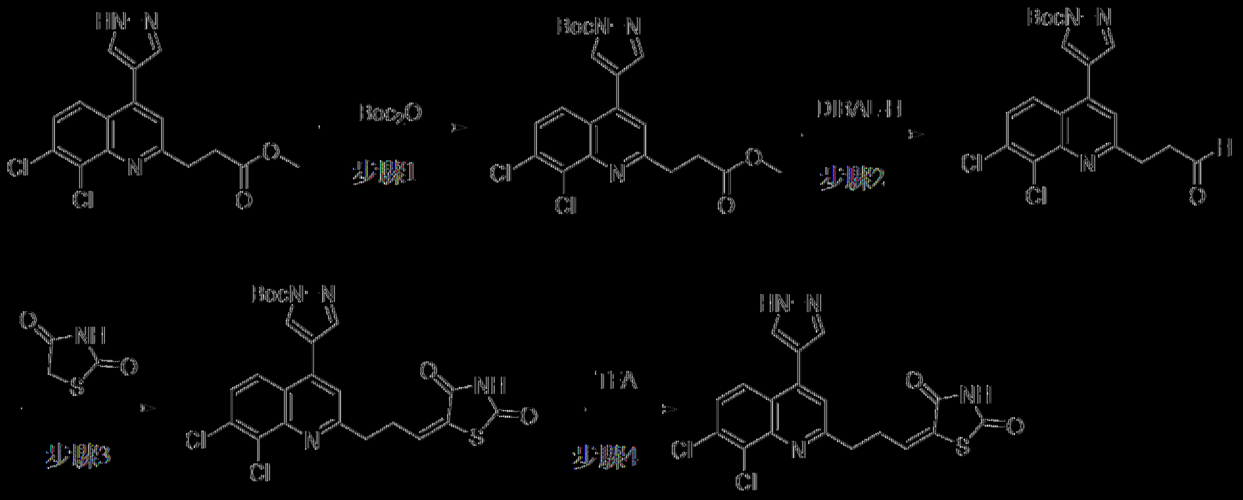
實例76：合成3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙-1-醇(I-271)



【0706】 步驟1：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸甲酯. 向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸三級丁酯(235 mg)於MeOH中之溶液加入HCl (5 mL)。在室溫下將所得溶液攪拌隔夜。減壓濃縮後，將殘餘物藉由製備型薄層層析法純化，得到呈粉末狀之標題化合物(150 mg) (MS: $[M+1]^+$ 322)。

【0707】 步驟2：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙-1-醇. 在-60℃下，向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸甲酯(100 mg)於無水THF (4 mL)中之溶液中添加DIABL-H (1.1 mL，1M於THF中)。在60℃下攪拌一小時後，將反應混合物緩慢升溫至室溫，藉由添加MeOH (1 mL)淬滅並用EtOAc (25 mL)稀釋。將合併之有機層用鹽水洗滌且經無水Na_2SO_4乾燥。減壓濃縮並藉由製備型HPLC純化，得到標題化合物(6 mg)。MS: $[M+1]^+$ 322。^{1}H NMR (400 MHz, DMSO-D6): δ 8.195-8.173 (m, 3H), 7.735-7.712 (d, *J* = 8.8 Hz, 1H), 7.594 (s, 1H), 3.520-3.536 (m, 2H), 2.996-3.034 (t, *J* = 7.6 Hz, 2H), 1.965-2.002 (m, 2H) ppm。

實例77：合成7-氯-4-(1H-咪唑-1-基)-8-甲基喹啉(I-274)



I-274

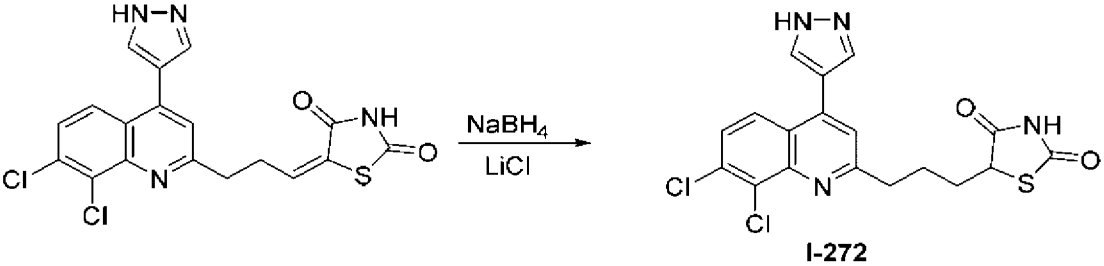
【0708】 步驟1：4-(7,8-二氯-2-(3-甲氧基-3-側氧基丙基)喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯. 在N_2下，向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙酸甲酯(30 mg)於DMF (1 mL)中之溶液中添加DMAP (12 mg)、$(BOC)_2O$ (28 mg)及TEA (35 mg)。在室溫下攪拌2小時後，將反應混合物用水(10 mL)稀釋並用EtOAc (25 mL)萃取。將分離之有機層用飽和NH_4Cl洗滌並濃縮至乾。將殘餘物藉由製備型薄層層析法純化，得到呈固體狀之標題化合物(33 mg)。(MS: $[M+1]^+$ 450)

【0709】 步驟2：4-(7,8-二氯-2-(3-側氧基丙基)喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯. 在-60℃下，向4-(7,8-二氯-2-(3-甲氧基-3-側氧基丙基)喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯(190 mg)於DCM (2 mL)中之溶液中添加DIBAL-H (0.56 mL)。攪拌反應混合物並使其在2小時內緩慢升溫至室溫。用MeOH (1 mL)及水(100 mL)淬滅反應。用EtOAc萃取，用鹽水洗滌並藉由製備型薄層層析法純化，得到呈固體狀之標題化合物(57 mg)。(MS: $[M+1]^+$ 420)

【0710】 步驟3及步驟4：(E)-5-(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)亞丙基)噻唑啶-2,4-二酮. 向4-(7,8-二氯-2-(3-側氧基丙基)喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯(30 mg)於EtOH中之溶液中添加噻唑啶-2,4-

二酮(18 mg)及哌啶(8 mg)。在85℃下將反應混合物攪拌1小時。減壓濃縮後，將殘餘物用EtOAc (10 mL)稀釋並用水(10 mL)洗滌移除有機溶劑後，用DCM (0.9 mL)中之TFA (0.3 mL)處理粗中間體2小時。減壓濃縮後，將粗產物藉由製備型HPLC純化，得到呈粉末狀之標題化合物(7.3 mg)。MS: $[M+1]^+$ 419.1。^{1}H NMR (400 MHz, DMSO-D6): δ 8.186-8.209 (d, *J* = 9.2 Hz, 1H), 8.168 (s, 1H), 7.733-7.756 (d, *J* = 9.2 Hz, 1H), 7.636 (s, 1H), 7.073-7.111 (t, *J* = 7.6 Hz, 1H), 3.3 (m, 2H), 2.768-2.822 (dd, *J* = 14.4及7.2 Hz, 2H) ppm。

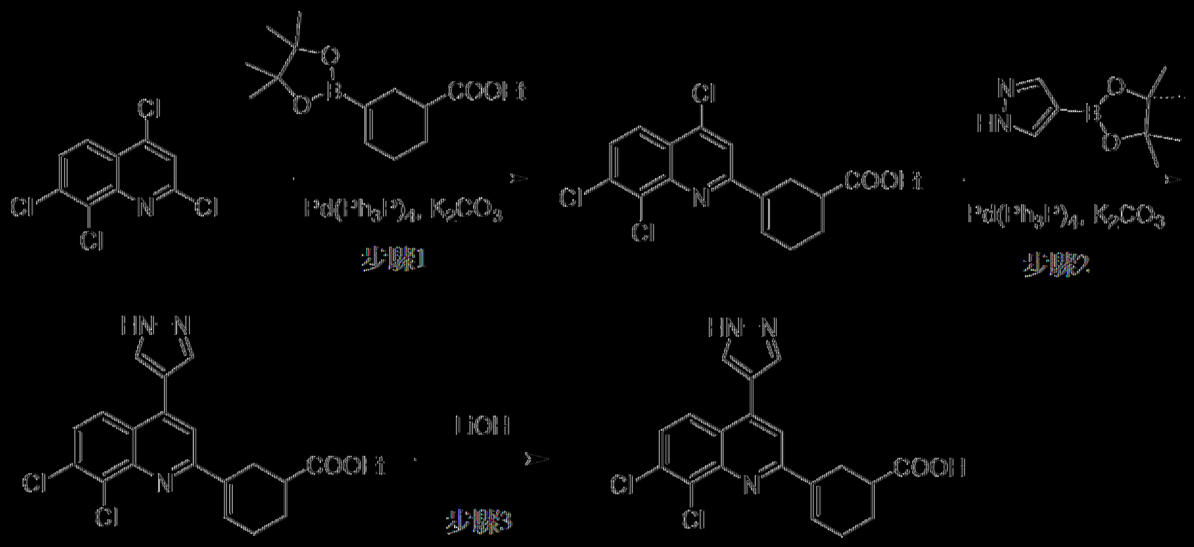
實例78：合成5-(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙基)噻唑啶-2,4-二酮(**I-272**)



I-272

【0711】在0℃下，用$NaBH_4$ (7 mg)及LiCl (5 mg)處理於DMF (1 mL)中之粗(E)-5-(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)亞丙基)噻唑啶-2,4-二酮(40 mg) 3小時。將產物藉由製備型HPLC純化，得到標題產物(4.5 mg)。MS: $[M+1]^+$ 421.0。^{1}H NMR (400 MHz, CD_3OD): δ 8.202-8.224 (d, *J* = 9.2 Hz, 1H), 8.143 (s, 1H), 7.733-7.710 (d, *J* = 9.2 Hz, 1H), 7.643-7.650 (d, *J* = 2.8 Hz, 1H), 4.532-7.552 (d, *J* = 8 Hz, 1H), 3.154-3.171 (m, 2H), 2.259-2.291 (m, 2H)及2.014-2.062 (m, 2H) ppm。

實例79：合成3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)環己-3-烯-1-甲酸(**I-273**)



I-273

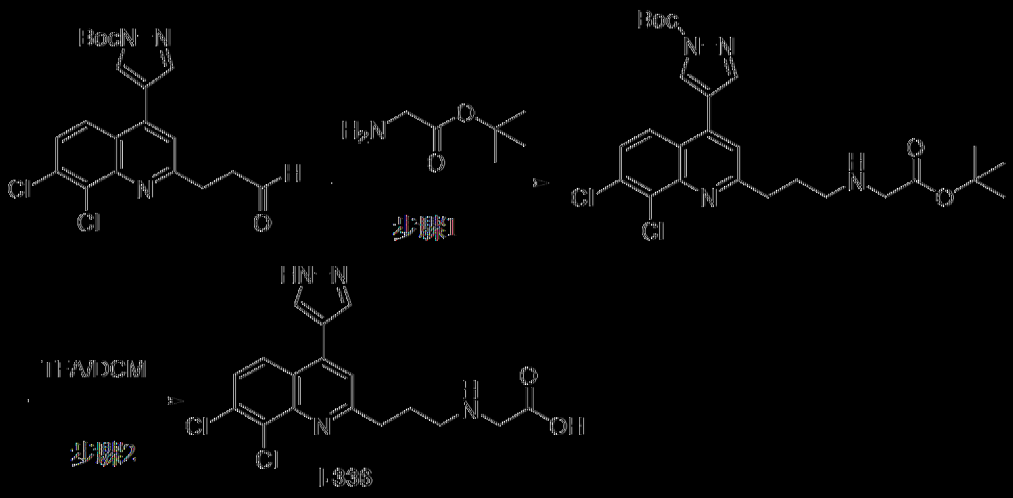
【0712】 步驟1：3-(4,7,8-三氯喹啉-2-基)環己-3-烯-1-甲酸乙酯. 3-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)環己-3-烯-1-甲酸乙酯係根據WO2020/112706合成。經由3個真空/吹掃循環，用N_2吹掃2,4,7,8-四氯喹啉、3-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)環己-3-烯-1-甲酸乙酯(50 mg，0.19mmol)、Na_2CO_3 (53 mg，0.38 mmol)、$Pd(Ph_3P)_4$ (23 mg，0.02 mmol)於二噁烷/H_2O (5/1, 5 mL)中之混合物。接著，在100℃下將反應混合物攪拌隔夜。冷卻至室溫後，用EtOAc溶解反應混合物，用鹽水洗滌，並減壓濃縮。將粗品藉由製備型TLC，用石油醚/DCM (1/1)純化，得到呈淺褐色半固體狀之所需產物3-(4,7,8-三氯喹啉-2-基)環己-3-烯-1-甲酸乙酯(36 mg)。MS (ES^+): $[M+1]^+$, m/z 384.1, 386.1

【0713】 步驟2：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)環己-3-烯-1-甲酸乙酯. 經由3個真空/吹掃循環，用N_2吹掃3-(4,7,8-三氯喹啉-2-基)環己-3-烯-1-甲酸乙酯、4-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)-1H-吡唑(36 mg，0.093 mmol)、Na_2CO_3 (38.6 mg，0.28 mmol)、$Pd(Ph_3P)_4$ (10.7 mg，0.009mmol)、二噁烷/H_2O (2/1，15 mL)之混合物。接著，在100℃下攪拌反應隔夜。冷卻至室溫後，將其用EtOAc溶解，用鹽水洗滌，濃縮。將粗品藉由製備型TLC，用石油醚/DCM (1/1)純化，得

到呈灰白色固體狀之所需產物3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)環己-3-烯-1-甲酸乙酯(5.1 mg)。MS: (ES$^+$): [M+1]$^+$ m/z 416.1, 418.1

【0714】 步驟3：3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)環己-3-烯-1-甲酸. 向3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)環己-3-烯-1-甲酸乙酯(10 mg，0.024mmol)於CH_3OH/ H_2O/THF (1/1/1，3 mL)中之混合物中添加LiOH (6 mg)。在室溫下將反應混合物攪拌隔夜。用HCl水溶液淬滅後，將其用DCM/iPrOH溶解，用鹽水洗滌，並濃縮。將粗品藉由製備型HPLC純化，得到呈灰白色固體狀之所需產物3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)環己-3-烯-1-甲酸(3.4 mg) (MS: (ES$^+$): m/z 388.1 [M+1]$^+$)。^{1}H NMR (400 MHz, CD_3OD, ppm): δ 8.38 (s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.70 (s, 1H), 7.56 (d, *J* = 9.2 Hz, 1H), 5.89 (s, 1H), 2.90 (s, 1H), 2.71-2.63 (m, 2H), 2.42 (s, 2H), 2.01-1.94(s, 2H)。

實例80：合成(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙基)甘胺酸(I-336)

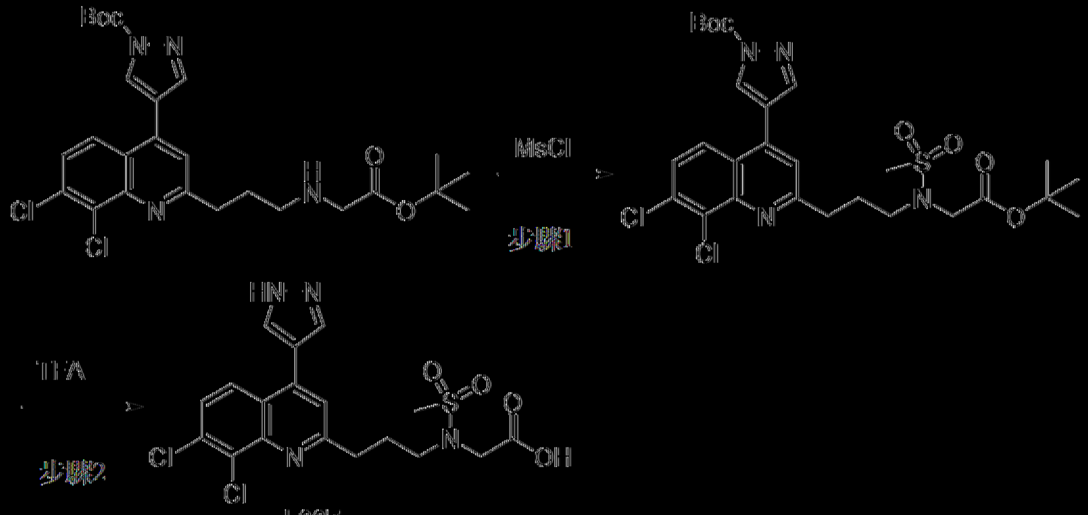


【0715】 步驟1：4-(2-(3-((2-(三級丁氧基)-2-側氧基乙基)胺基)丙基)-7,8-二氯喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯. 向4-(7,8-二氯-2-(3-側氧基丙基)喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯(100 mg)及甘胺酸三級丁酯(62 mg)於DCM (0.5 mL)及EtOH (2.5 mL)中之溶液中添加

NaBH$_3$CN(100 mg)及乙酸(1滴)。攪拌隔夜，用水淬滅，用DCM萃取並減壓濃縮後，將殘餘物藉由製備型薄層層析法(用15% MeOH/DCM溶離)純化，得到標題化合物(58 mg)。MS: $[M+1]^+$479。

【0716】 步驟2：(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙基)甘胺酸. 向4-(2-(3-((2-(三級丁氧基)-2-側氧基乙基)胺基)丙基)-7,8-二氯喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯(15 mg)於DCM (3 mL)中之溶液中添加TFA (0.5 mL)。在室溫下將所得溶液攪拌6小時。減壓蒸發後，將殘餘物藉由製備型HPLC純化，得到標題化合物(6.4 mg) (MS: $[M+1]^+$ 379.1)。^{1}H NMR (400 MHz, CD3OD): δ 8.179-8.202 (d, J = 9.2 Hz, 1H), 8.140 (s, 1H), 7.690-7.713 (d, J = 9.2 Hz, 1H), 7.596 (s, 1H), 4.019 (S, 2H), 3.324-3.365 (m, 4H), 2.338-2.391 (m, 2H) ppm

實例81：合成N-(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙基)-N-(甲基磺醯基)甘胺酸(I-337)



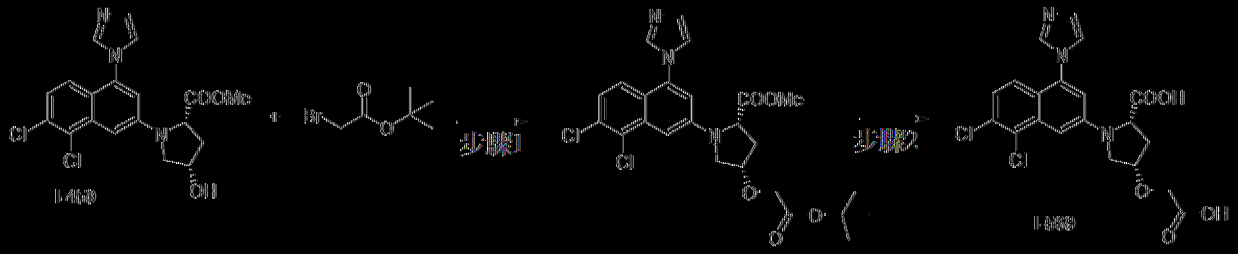
I-337

【0717】 步驟1：4-(2-(3-(N-(2-(三級丁氧基)-2-側氧基乙基)甲基磺醯胺基)丙基)-7,8-二氯喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯. 向4-(2-(3-((2-(三級丁氧基)-2-側氧基乙基)胺基)丙基)-7,8-二氯喹啉-4-基)-1H-吡唑-1-甲酸三級丁酯(15 mg)於DCM (0.5 mL)中之溶液中添加MsCl (6.4 mg)及

TEA (14.8 mg)。在室溫下攪拌1小時後，用DCM進行水性處理，用鹽水洗滌，減壓濃縮，並藉由製備型薄層層析法純化，得到標題化合物(8 mg)。MS: $[M+1]^+$ 613。

【0718】 步驟2：N-(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙基)-N-(甲基磺醯基)甘胺酸. 向N-(3-(7,8-二氯-4-(1H-吡唑-4-基)喹啉-2-基)丙基)-N-(甲基磺醯基)甘胺酸(8 mg)於DCM (5 mL)中之溶液中添加TFA (1 mL)。在室溫下將反應混合物攪拌5小時。減壓蒸發並藉由製備型HPLC純化，得到呈粉末狀之標題化合物(3 mg) (MS: $[M+1]^+$ 457.1)。^{1}H NMR (400 MHz, DMSO-D6): δ 8.192-8.215 (d, *J* = 9.2 Hz, 1H), 8.140 (s, 1H), 7.697-7.720 (d, *J* = 9.2 Hz, 1H), 7.664 (s, 1H), 4.149 (S, 2H), 3.468-3.503 (t, *J* = 7.2 Hz, 2H), 3.160-3.196 (t, *J* = 7.2 Hz, 2H), 3.011 (S, 3H), 2.202-2.237 (m, 2H) ppm。

實例82：合成(2S,4S)-4-(羧基甲氧基)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸(I-569)

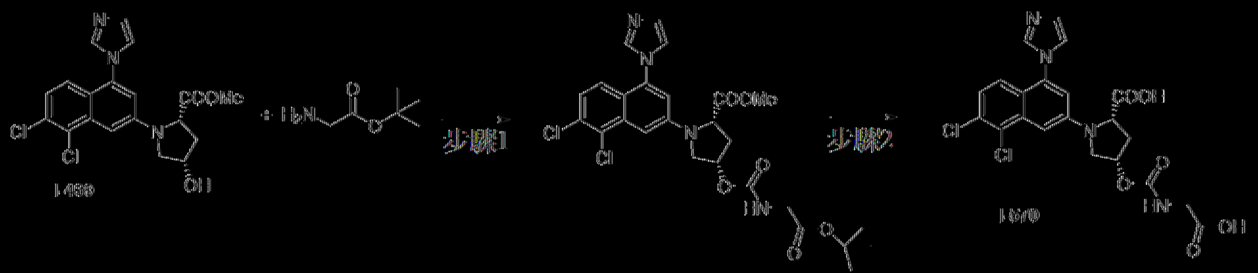


【0719】 步驟1：在0℃下，向NaH (6 mg，0.15 mmol)、2-溴乙酸三級丁酯(80 uL，0.4 mmol)及TBAI (5 mg，0.01 mmol)以及THF (1 mL)之混合物中添加(2S,4S)-1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)-4-羥基吡咯啶-2-甲酸甲酯(41 mg，0.1 mmol)於THF (1 mL)中之溶液。在室溫下將所得混合物攪拌2小時並藉由NH4Cl (飽和水溶液，1 mL)淬滅。用EtOAc稀釋粗品並將有機相用水、鹽水洗滌且經無水Na_2SO_4乾燥。進行管柱層析，用己烷及EtOAc梯度溶離，得到呈白色固體狀之所需產物(25 mg)

(MS: [M+1]$^+$ 520.1)。

【0720】 步驟2：將(2S,4S)-4-(2-(三級丁氧基)-2-側氧基乙氧基)-1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)吡咯啶-2-甲酸甲酯(25 mg，0.05 mmol)放入含THF (1.2 mL)、甲醇(0.4 mL)及水(0.4 mL)之小瓶中。添加單水合氫氧化鋰(8 mg，0.18 mmol)並在室溫下攪拌反應16小時。濃縮去除揮發性物質並藉由添加1 N鹽酸中和所得殘餘物。將所得溶液凍乾，得到標題化合物(MS: [M+1]$^+$ 450.1)。

【0721】 合成(2S,4S)-4-(((羧基甲基)胺甲醯基)氧基)-1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)吡咯啶-2-甲酸(I-570)

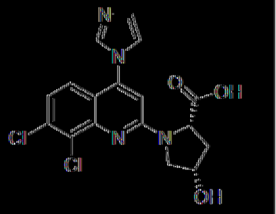
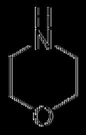
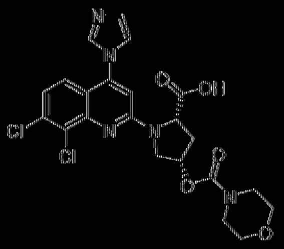


【0722】 步驟1：向(2S,4S)-1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)-4-羥基吡咯啶-2-甲酸甲酯(40 mg，0.1 mmol)於THF (1 mL)中之溶液中添加CDI (32 mg，0.2 mmol)。1小時後，添加甘胺酸三級丁酯(25 mg，0.15 mmol)及DIPEA (52 μL，0.3 mmol)於THF (1 mL)中之溶液。在60℃下將混合物攪拌隔夜。冷卻至室溫後，蒸發溶劑。將粗品溶解於EtOAc (5 mL)中並用水、鹽水洗滌且經無水Na_2SO_4乾燥。進行管柱層析，用己烷及EtOAc梯度溶離，得到呈白色固體狀之所需產物(40 mg) (MS: [M+1]$^+$ 563.1)。

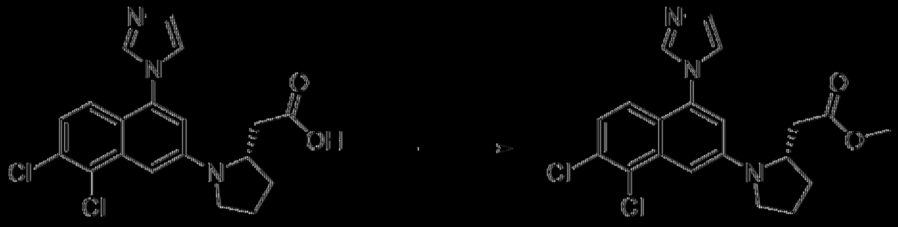
【0723】 步驟2：將(2S,4S)-4-(((2-(三級丁氧基)-2-側氧基乙基)胺甲醯基)氧基)-1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)吡咯啶-2-甲酸甲酯(40 mg，0.07 mmol)放入含THF (1.2 mL)、甲醇(0.4 mL)及水(0.4 mL)之

小瓶中。添加單水合氫氧化鋰(8 mg，0.18 mmol)，並在室溫下攪拌反應16小時。濃縮去除揮發性物質並藉由添加1 N鹽酸中和所得殘餘物。將所得溶液凍乾，得到標題化合物(MS: $[M+1]^+$ 493.1)。

【0724】 以下化合物基本上藉由與以上關於製備I-570所描述相同之方法製備。

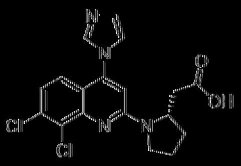
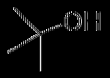
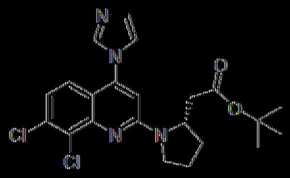
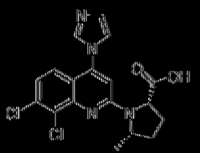
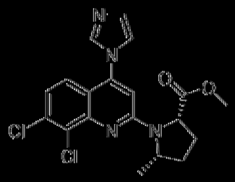
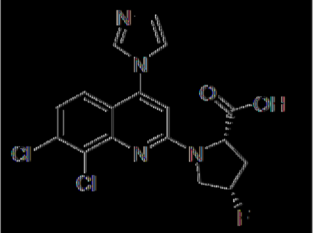
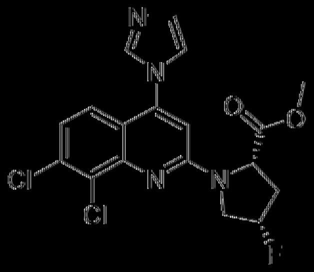
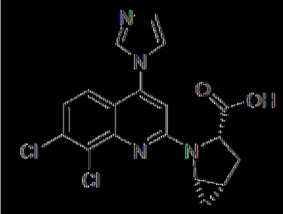
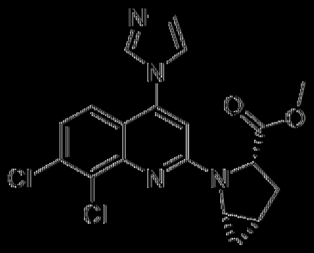
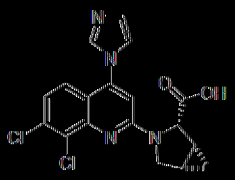
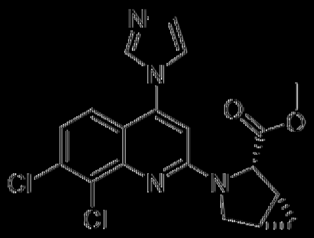
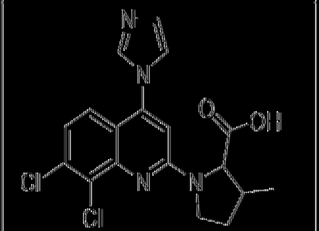
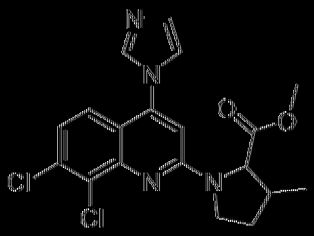
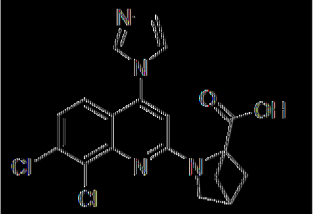
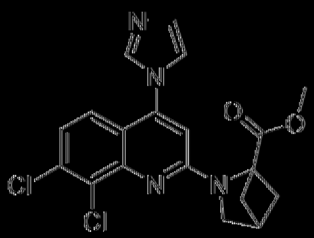
I#	起始材料		結構	MS $[M+1]^+$
I-571				506

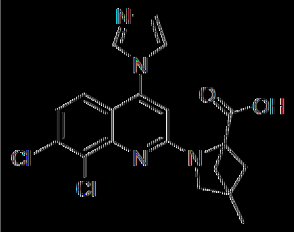
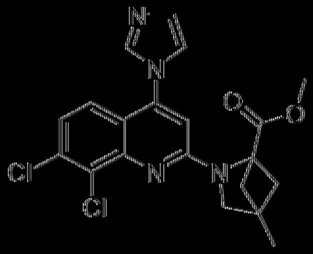
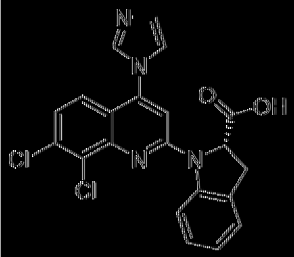
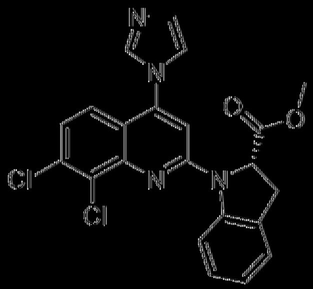
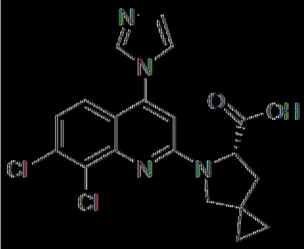
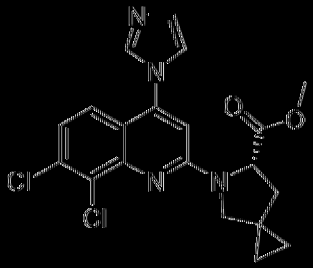
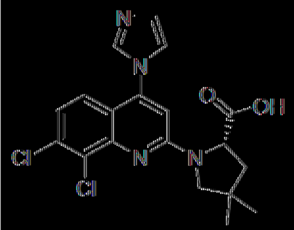
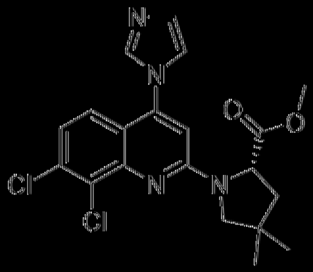
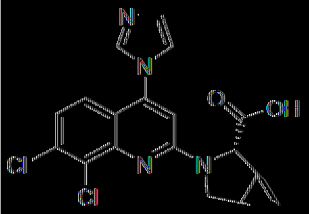
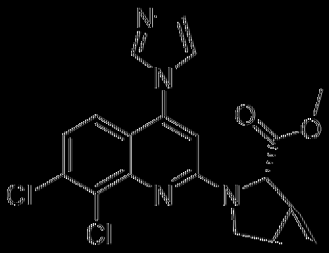
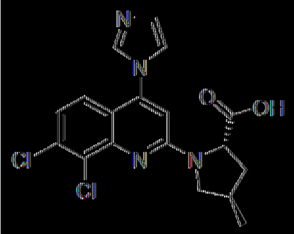
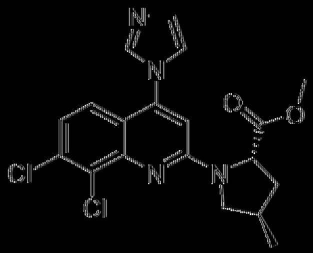
實例83：合成(S)-2-(1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)吡咯啶-2-基)乙酸甲酯(I-572)

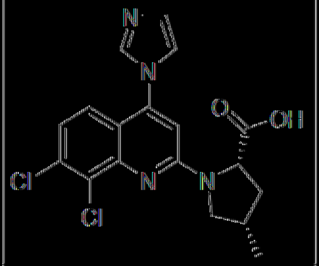
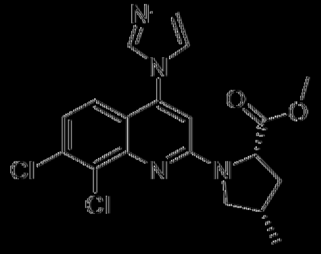
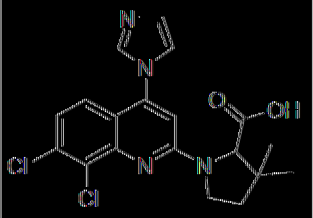
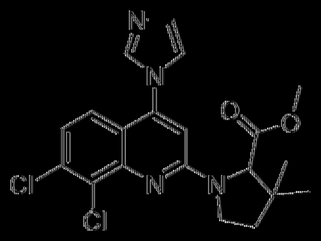
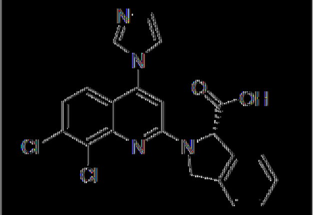
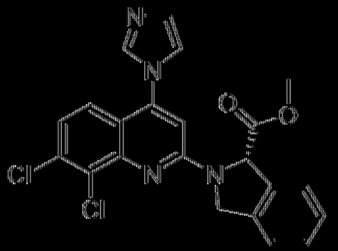
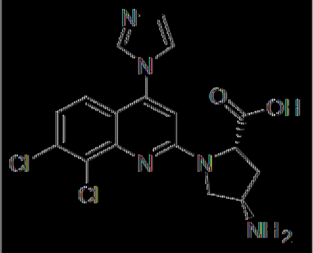
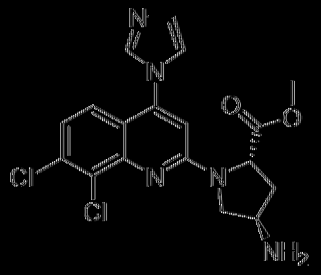
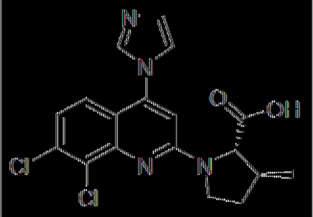
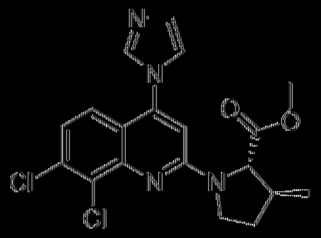
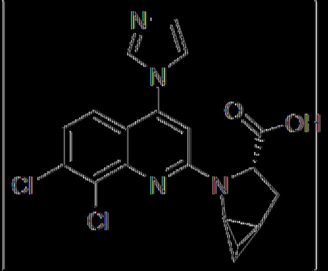
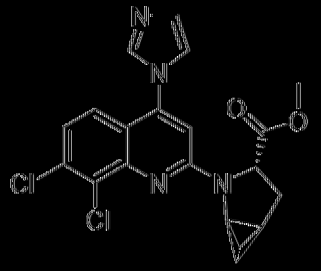


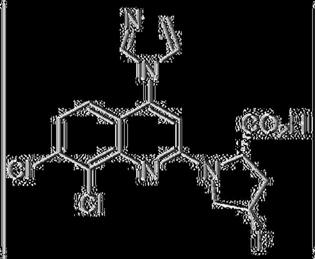
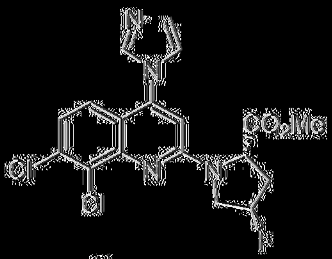
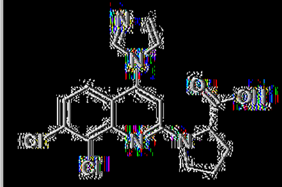
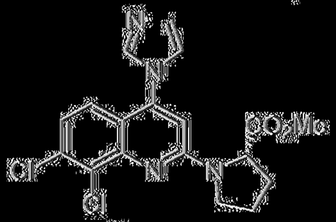
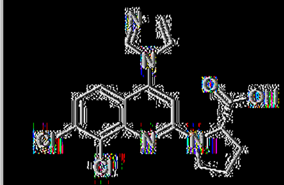
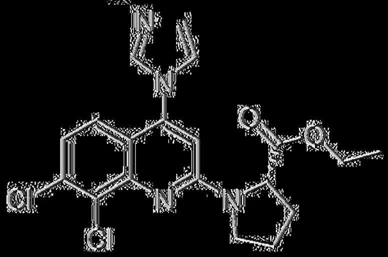
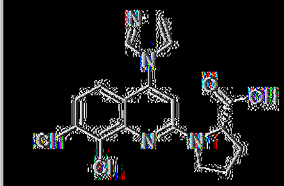
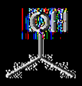
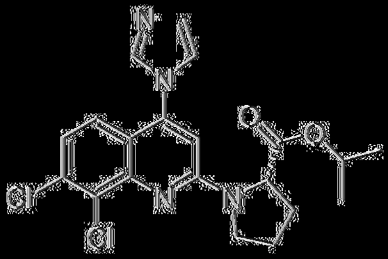
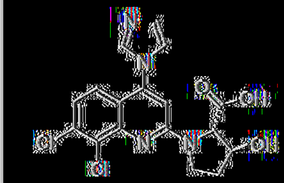
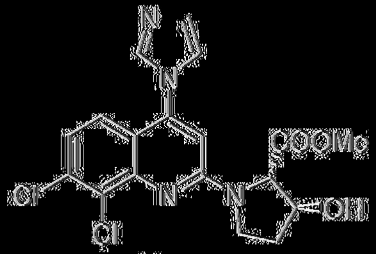
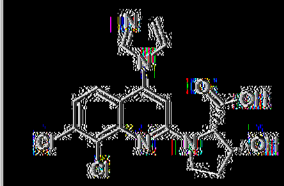
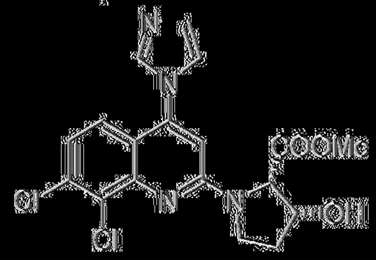
【0725】 在0℃下，將草醯氯(60 μL，0.5 mmol)或亞硫醯氯逐滴添加至MeOH (1 mL)中。30分鐘後，添加(S)-2-(1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)吡咯啶-2-基)乙酸(40 mg，0.1 mmol)於MeOH (0.1 mL)中之溶液。在室溫下將溶液攪拌隔夜。蒸發後，將粗品溶解於EtOAc (5 mL)中並用飽和$NaHCO_3$ (水溶液)、水、鹽水洗滌且經無水Na_2SO_4乾燥。進行管柱層析，用己烷及EtOAc梯度溶離，得到呈白色固體狀之所需產物(40 mg) (MS: $[M+1]^+$ 404.1)。

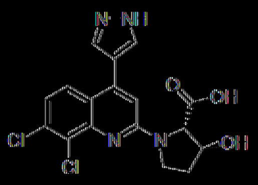
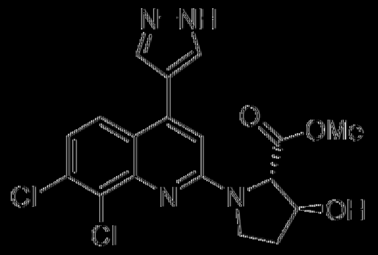
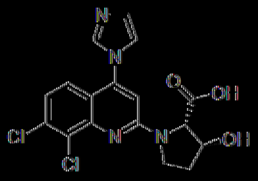
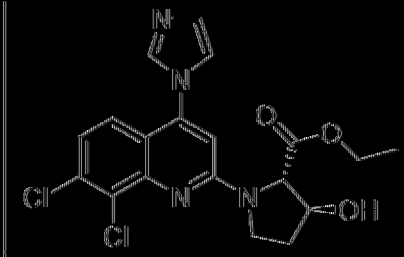
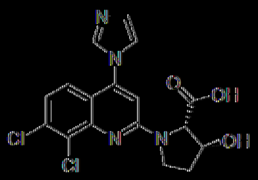
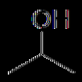
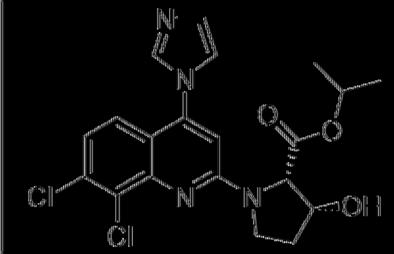
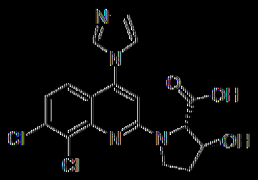
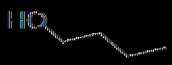
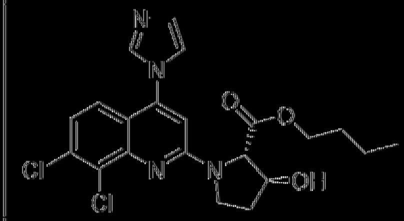
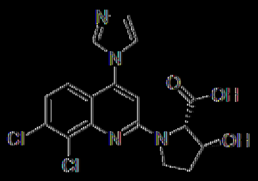
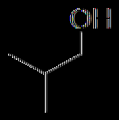
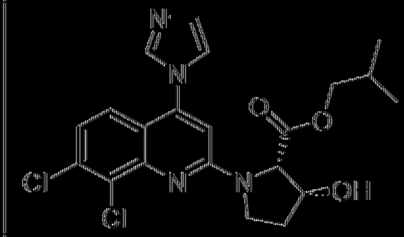
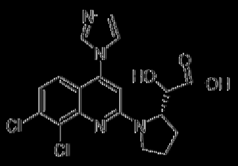
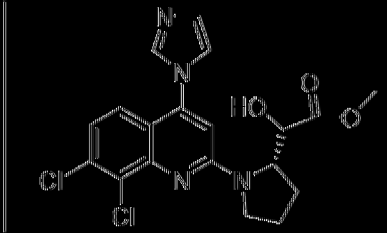
【0726】 以下化合物基本上藉由與以上關於製備I-572所描述相同之方法製備。

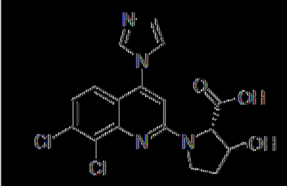
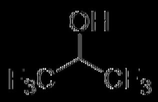
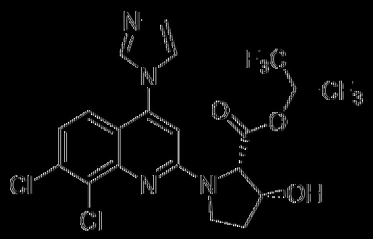
I-#	起始材料		結構	MS [M+1]+
I-573				447
I-574		MeOH		405
I-575		MeOH		409
I-576		MeOH		403
I-577		MeOH		403
I-578		MeOH		405
I-579		MeOH		403

I-#	起始材料		結構	MS [M+1]+
I-580		MeOH		417
I-581		MeOH		439
I-582		MeOH		417
I-583		MeOH		419
I-584		MeOH		403
I-585		MeOH		405

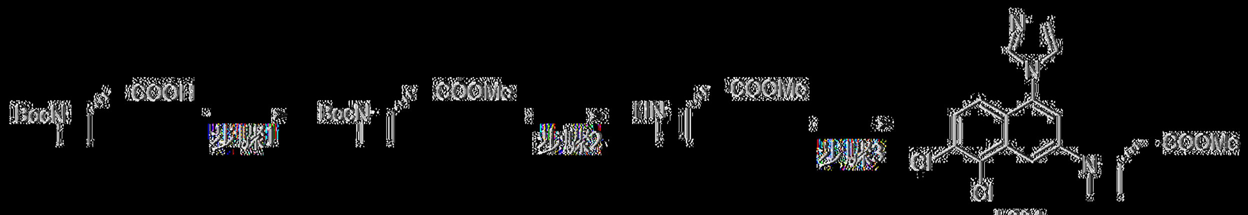
I-#	起始材料		結構	MS [M+1]+
I-586		MeOH		405
I-587		MeOH		419
I-588		MeOH		439
I-589		MeOH		406
I-590		MeOH		405
I-591		MeOH		403

I-#	起始材料		結構	MS [M+1]+
I-592		MeOH		409
I-593		MeOH		391
I-594		CH$_3$CH$_2$OH		405
I-595				419
I-596		CH$_3$OH		407
I-597		CH$_3$OH		407

I-#	起始材料		結構	MS $[M+1]^+$
I-598		CH_3OH		407
I-599		CH_3CH_2OH		421
I-600				435
I-601				449
I-602				449
I-662		MeOH		421

I#	起始材料		結構	MS [M+1]+
I-663				543

實例84：合成(S)-2-(1-(7,8-二氯-4-(1H-咪唑-1-基)萘-2-基)氮雜環丁烷-2-基)乙酸甲酯(I-604)



I-604

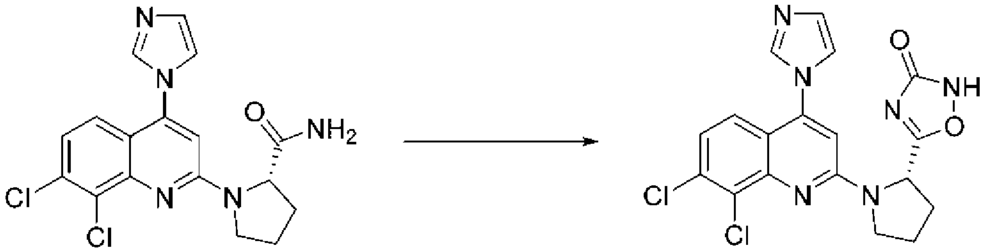
【0727】 步驟1：在0℃下，將草醯氯(0.1 mL)逐滴添加至MeOH (1 mL)中。30分鐘後，添加(S)-2-(1-(三級丁氧基羰基)氮雜環丁烷-2-基)乙酸(43 mg，0.2 mmol)於MeOH (0.1 mL)中之溶液。在室溫下將溶液攪拌隔夜。蒸發後，將粗品溶解於EtOAc (5 mL)中並用飽和$NaHCO_3$ (水溶液)、水、鹽水洗滌且經無水Na_2SO_4乾燥。粗品不經進一步純化即用於下一步驟中。(MS: $[M+1]^+$ 230.1)。

【0728】 步驟2：在室溫下，將(S)-2-(2-甲氧基-2-側氧基乙基)氮雜環丁烷-1-甲酸三級丁酯(50 mg粗品，0.2 mmol)於50% TFA/DCM中之溶液攪拌30分鐘。蒸發後，將粗品溶解於DCM (2 mL)中。藉由蒸發移除溶劑。將該程序重複兩次。將粗產物不經進一步純化即用於下一步驟中。(MS: $[M+1]^+$ 130.1)。

【0729】 步驟3：I-604基本上藉由與I-353相同之方法製備。(MS: $[M+1]^+$ 390.1)。

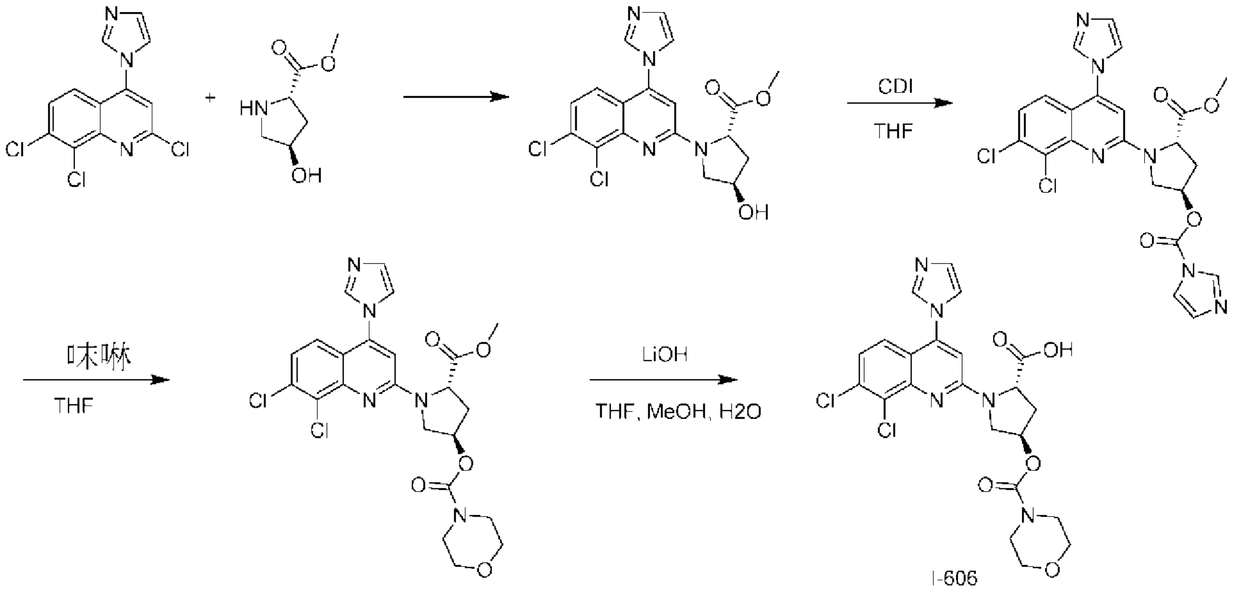
實例85：合成(S)-5-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-

基)-1,2,4-噁二唑-3(2H)-酮(**I-605**)



【0730】 在室溫下，向(S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲醯胺(100 mg，0.27 mmol)及DCE (2 mL)之混合物中添加$(COCl)_2$ (35 μL，0.4 mmol)。在70℃下將混合物攪拌隔夜且接著，添加$TMSN_3$ (1 mL)。在80℃下將溶液攪拌2天。冷卻至室溫後，將粗品在矽膠上直接藉由管柱層析法純化，得到呈固體狀之標題產物(MS: $[M+1]^+$ 417.1)。

實例86：合成(2S,4R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-4-((味啉-4-羰基)氧基)吡咯啶-2-甲酸(**I-606**)



【0731】 步驟1：(2S,4R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-4-羥基吡咯啶-2-甲酸甲酯. 向小瓶中添加2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(90 mg，0.302 mmol)、(2S,4R)-4-羥基吡咯啶-2-甲酸甲酯(146 mg，0.603 mmol)、DMSO (0.20 mL)及N,N-二異丙基乙胺(0.10 mL)。在90℃

下將所得反應混合物攪拌16小時並冷卻至室溫，隨後添加H_2O (20 mL)。將渾濁混合物離心並用10% MeOH/DCM (2 × 10 mL)萃取殘餘物。將有機相用H_2O (10 mL)、鹽水(10 mL)洗滌，經Na_2SO_4乾燥，並濃縮。將粗殘餘物藉由二氧化矽層析法純化，得到(104 mg) (MS: $[M+1]^+$ 407)。

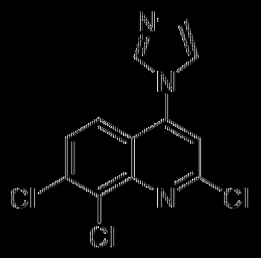
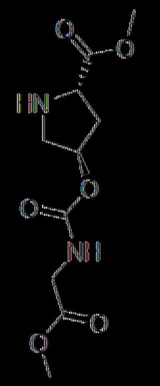
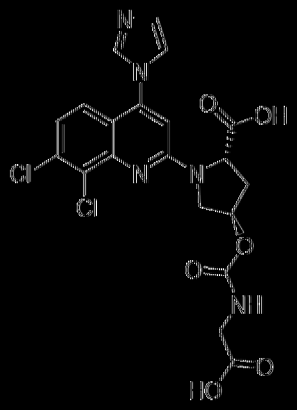
【0732】 步驟2：1H-咪唑-1-甲酸(3R,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(甲氧基羰基)吡咯啶-3-基酯. 向小瓶中添加(2S,4R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-4-羥基吡咯啶-2-甲酸甲酯(100 mg，0.246 mmol)、THF (5 mL)及羰基二咪唑(CDI) (80 mg，0.493mmol)。在室溫下將所得混合物攪拌4小時。接著，減壓移除所有揮發性溶劑並在高真空下乾燥殘餘物，得到標題產物。將粗品用於下一步驟。

【0733】 步驟3：味啉-4-甲酸(3R,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(甲氧基羰基)吡咯啶-3-基酯. 向小瓶中添加1H-咪唑-1-甲酸(3R,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(甲氧基羰基)吡咯啶-3-基酯(125 mg，0.250 mmol)、THF (2 mL)及味啉(44 mg，0.505 mmol)。在室溫下將所得反應混合物攪拌3小時。濃縮去除揮發性物質。用乙酸乙酯(15 mL)稀釋反應混合物。將有機相用H_2O (3 × 5 mL)、鹽水(5 mL)洗滌並經Na_2SO_4乾燥。濃縮後，將粗品藉由矽膠層析法純化，得到呈灰白色固體狀之標題產物(60 mg) (MS: $[M+1]^+$ 520)。

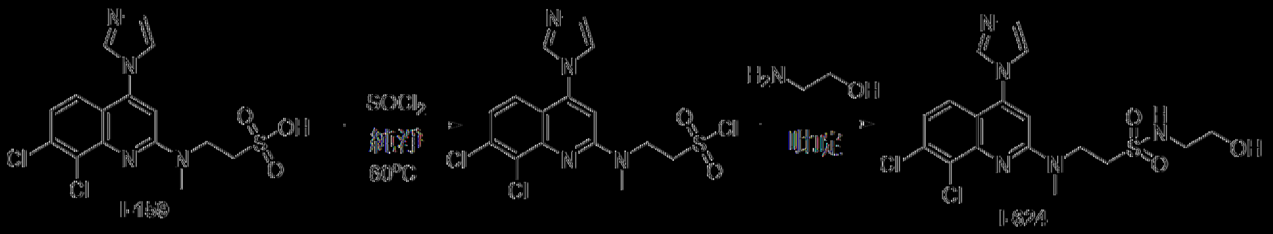
【0734】 步驟4：(2S,4R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-4-((味啉-4-羰基)氧基)吡咯啶-2-甲酸. 向小瓶中添加味啉-4-甲酸(3R,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(甲氧基羰基)吡咯啶-3-基酯(50 mg，0.096 mmol)、THF (0.8 mL)、甲醇(0.2 mL)、水(0.2 mL)及味

啉。添加單水合氫氧化鋰(12 mg，0.288 mmol)並在室溫下將所得反應混合物攪拌16小時。濃縮去除揮發性物質。將反應混合物用水(2 mL)稀釋，接著用1M HCl酸化，得到呈灰白色固體狀之標題產物(38 mg) (MS: [M+1]$^+$ 506)。

【0735】 以下化合物係與I-606類似之方式合成：

I-#	起始材料		結構	MS [M+1]+
I-607				494

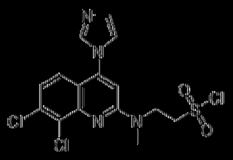
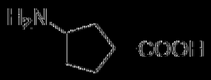
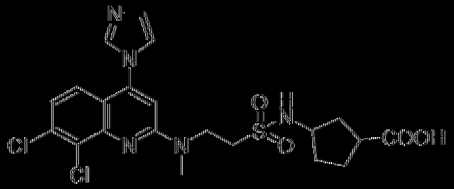
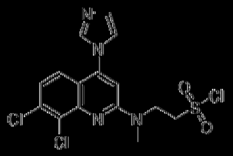
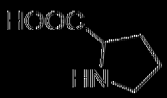
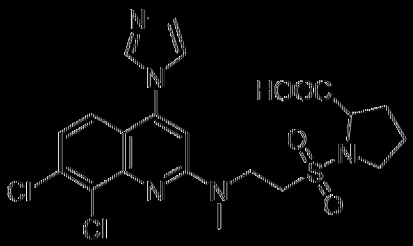
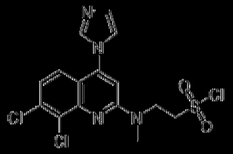
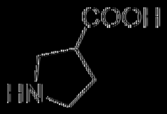
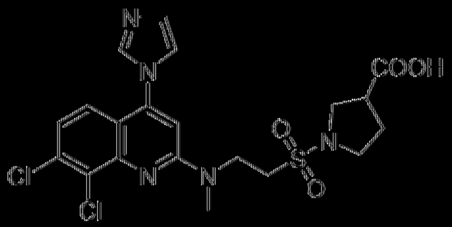
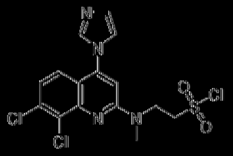
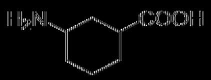
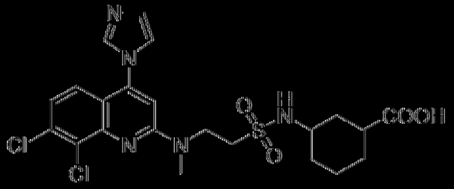
實例87：合成2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)-N-(2-羥基乙基)乙烷-1-磺醯胺(I-624)

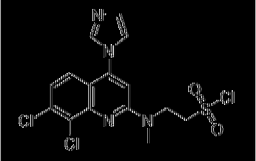
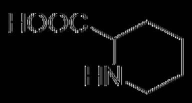
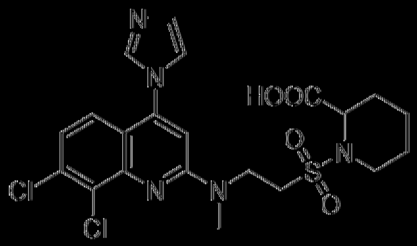
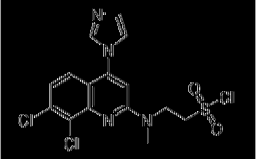
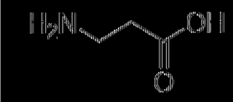
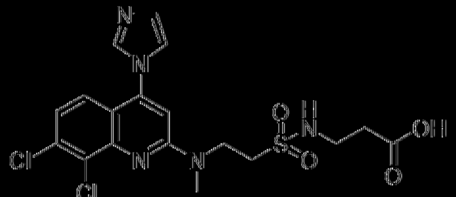
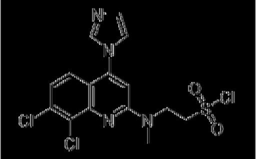
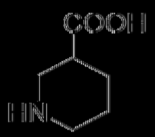
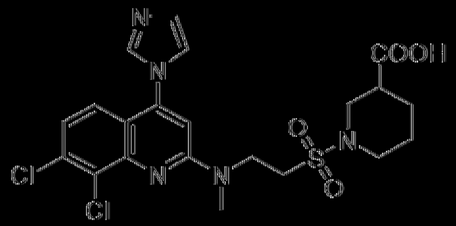
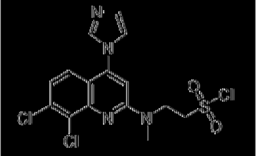
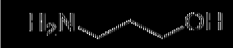
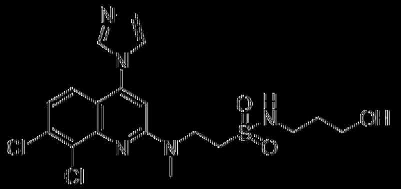
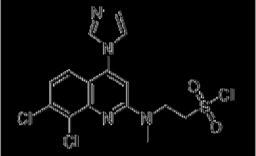
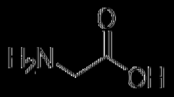
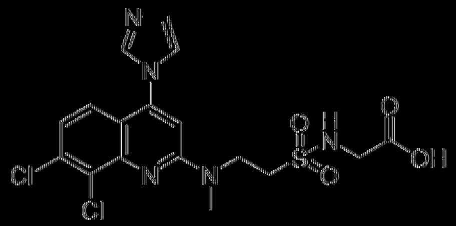


【0736】 步驟1：在60℃下，將I-159在過量亞硫醯氯中加熱4小時。真空濃縮所得溶液，得到2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙烷-1-磺醯氯，將其不經進一步純化即用於下一步驟中。

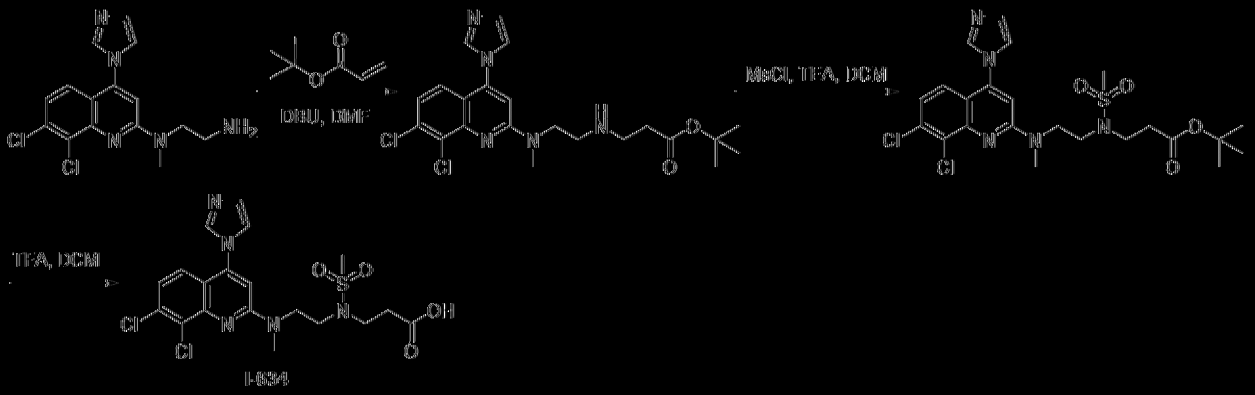
【0737】 步驟2：將2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙烷-1-磺醯氯與2-胺基乙-1-醇混合於吡啶中。進行水性處理且藉由製備型HPLC純化，得到標題化合物(I-624)。MS [M+1]$^+$ 444。

【0738】 遵循以上描述的I-624之製備，製備以下化合物。

I-#	起始材料		結構	MS [M+1]+
I-625				512
I-626				498
I-627				498
I-628				526

I-#	起始材料		結構	MS [M+1]$^+$
I-629				512
I-630				472
I-631				512
I-632				458
I-633				458

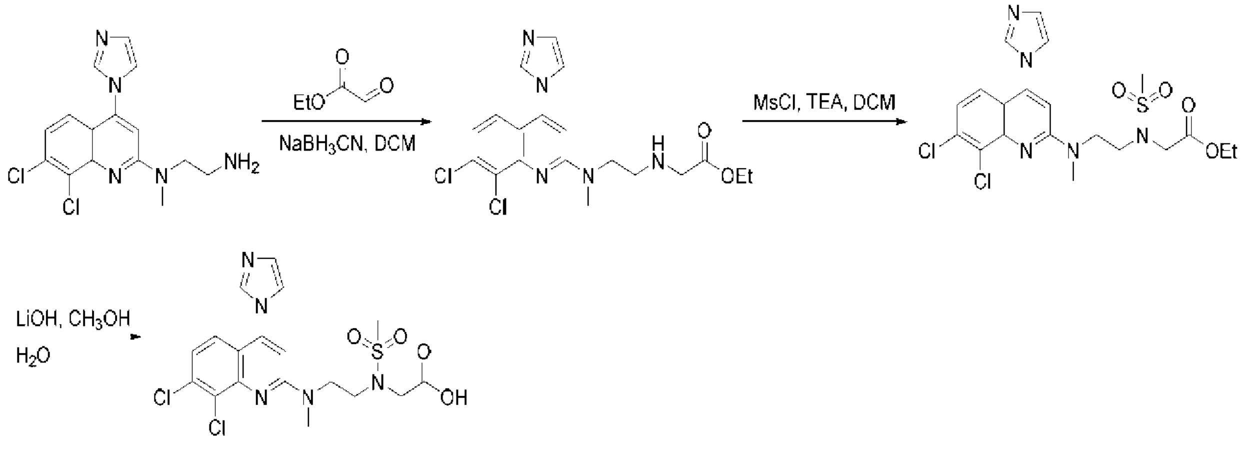
實例88：合成3-(N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)甲基磺醯胺基)丙酸(I-634)



【0739】在40℃下，攪拌N-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N1-甲基乙-1,2-二胺(100 mg，0.3 mmol)、丙烯酸三級丁酯(41.9

mg，0.33 mmol)及DBU (135 mg，0.9 mmol)於DMF中之混合物，直至LCMS確定完成。冷卻至0℃後，添加MsCl (103 mg，0.9 mmol)並將混合物再攪拌3小時，藉由TLC監測。接著，用$NaHCO_3$水溶液淬滅混合物，用DCM溶解，用鹽水洗滌，乾燥，濃縮並藉由製備型TLC純化，得到3-(N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)甲基磺醯胺基)丙酸三級丁酯，將其溶解於DCM/TFA (1/1, 2 mL)中並攪拌2小時，藉由TLC監測。接著，在真空下移除溶劑並將殘餘物藉由製備型HPLC純化，得到呈淺黃色固體狀之標題產物(**I-634**)。^1H NMR (400 MHz, CD_3OH, ppm): δ 9.22 (s, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 7.41-7.33 (m, 3H), 4.05(s, 2H), 3.59-3.58(m, 4H), 3.31(s, 3H), 2.92 (s, 3H), 2.65 (s, 2H)。LCMS: (ES^+): m/z 486.1 $[M+1]^+$。

實例89：合成N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)-N-(甲基磺醯基)甘胺酸(**I-635**)

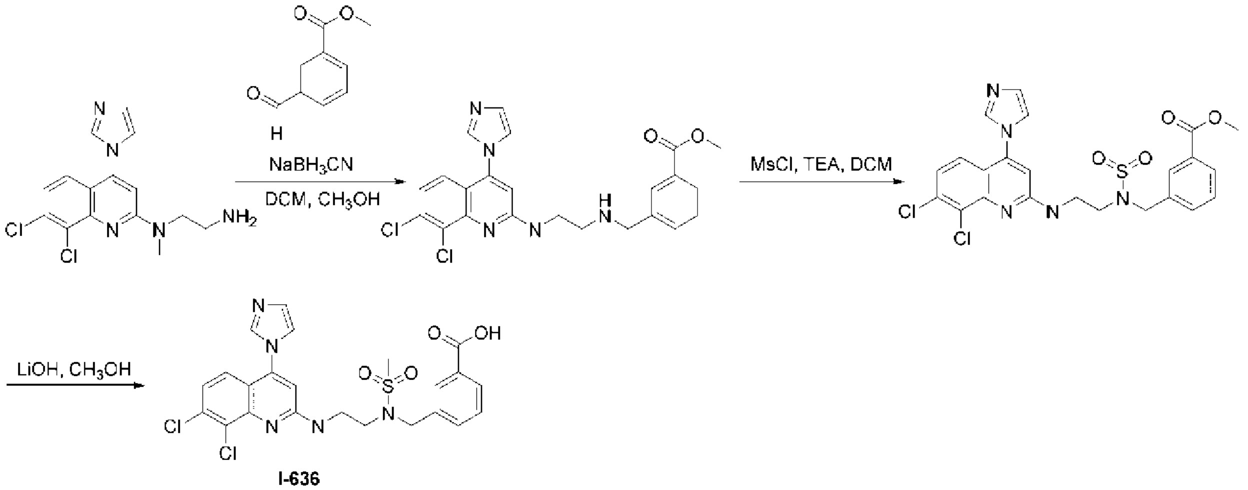


I-635

【0740】 在室溫下，向N-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-N1-甲基乙-1,2-二胺(100 mg，0.3 mmol)及2-側氧基乙酸乙酯(74 mg，約50%於甲苯中，0.36 mmol)於DCM/DCM/CH_3OH (2/1, 3 mL)及催化量之AcOH (2滴)中之混合物中添加$NaBH_3CN$ (38 mg，0.6 mmol)，並攪拌10

小時，直至LCMS確定完成。接著，用$NaHCO_3$水溶液淬滅混合物，用DCM溶解，用鹽水洗滌，乾燥，並濃縮，得到粗所需產物2-側氧基乙酸乙酯，將其不經進一步純化即用於下一步驟中。將殘餘物溶解於DCM/TEA (5/1，5 mL)中，接著在室溫下將MsCl (150 μL)添加至混合物中，並再攪拌2小時，藉由TLC監測。接著，用NH_4Cl水溶液淬滅混合物，用DCM溶解，用鹽水洗滌，乾燥，並濃縮。將殘餘物藉由製備型TLC純化，得到N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)-N-(甲基磺醯基)甘胺酸乙酯，將其溶解於CH_3OH/H_2O (2/1, 3 mL)中，添加LiOH並攪拌1小時，藉由TLC監測。接著，用TFA淬滅反應，濃縮並藉由製備型TLC (DCM/CH_3OH = 8/1)純化，得到呈淺黃色固體狀之標題產物(**I-635**)。^1H NMR (400 MHz, CD_3OD, ppm): δ 8.09 (s, 1H), 7.56 (s, 1H), 7.36-7.20 (m, 4H), 4.02-3.97 (m, 4H), 3.65(br, 2H), 3.31(s, 3H), 3.02 (s, 3H)。LCMS: (ES^+): m/z 473.1 $[M+1]^+$。

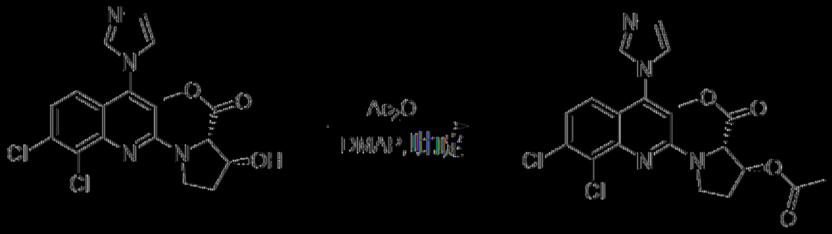
實例90：合成3-((N-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(甲基)胺基)乙基)甲基磺醯胺基)甲基)苯甲酸(**I-636**)

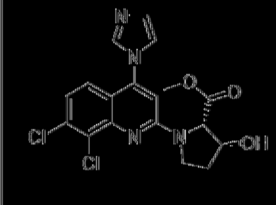
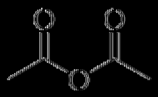
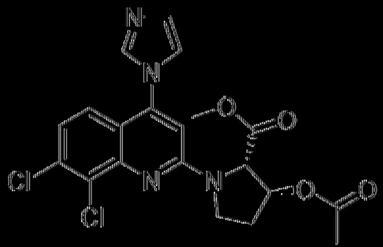
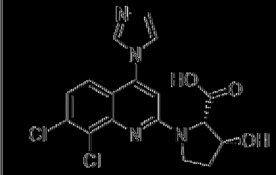
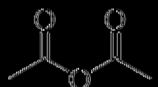
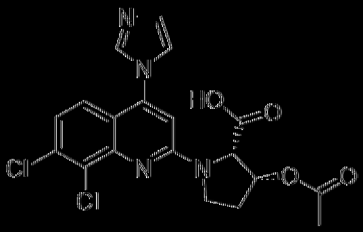


【0741】 **I-636**係根據與製備**I-635**相同之方法製備。^1H NMR (400 MHz, CD_3OD, ppm): δ 9.20 (s, 1H), 8.00 (s, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.57-7.47 (m, 2H), 7.34(d, J = 8.8Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 4.33 (s, 2H), 3.84-3.72(m, 4H), 3.06(m, 3H), 3.02(s, 3H)。LCMS: (ES$^+$): m/z 548.1 [M+1]$^+$。

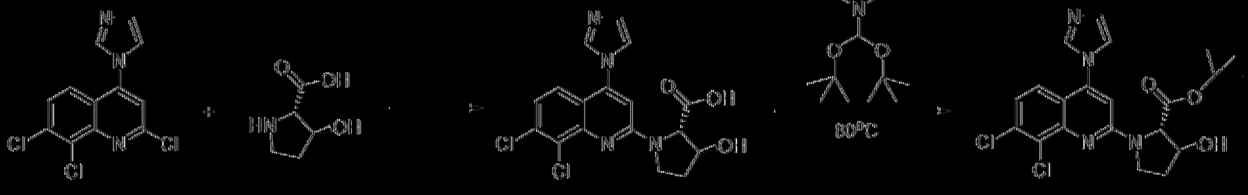
實例91：合成(2S,3S)-3-乙醯氧基-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸甲酯(I-642)及(2S,3S)-3-乙醯氧基-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸(I-643)

【0742】 I-642及I-643係根據以下合成方案製備：



I-#	起始材料		結構	MS [M+1]+
I-642				449
I-643				435

實例92：合成(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲酸三級丁酯(I-645)



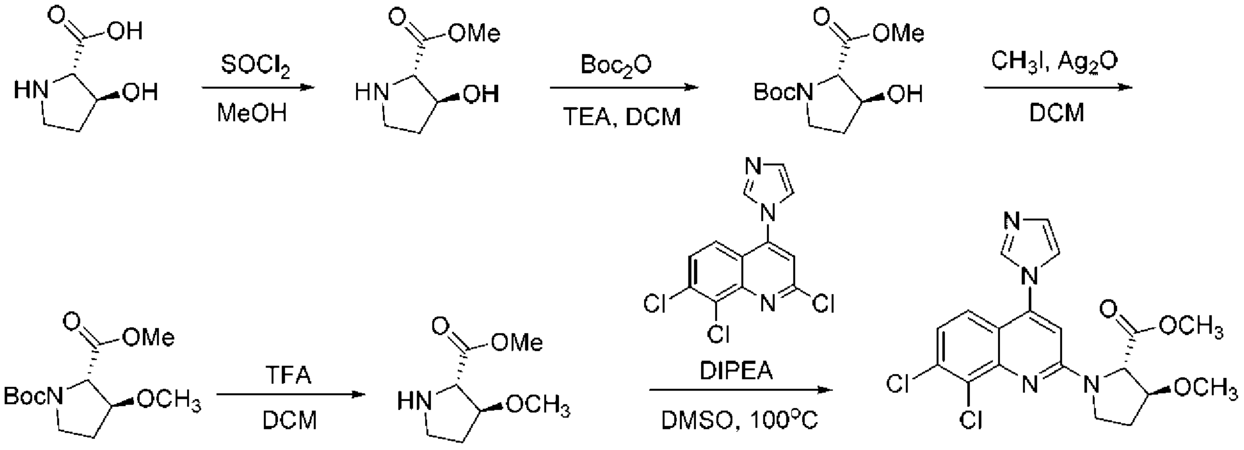
I-645

【0743】 步驟1：(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-

3-羥基吡咯啶-2-甲酸係根據與製備**I-123**步驟1類似之方式製備。

【0744】 步驟2：在80℃下，將(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲酸(380 mg，0.083 mmol)及1,1-二-三級丁氧基-N,N-二甲基甲胺(200 mg，0.983 mmol)之混合物攪拌隔夜。將粗品藉由矽膠層析法純化，得到**I-645** (MS: $[M+1]^+$ 449)

實例93：合成(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-甲氧基吡咯啶-2-甲酸甲酯(**I-646**)



I-646

【0745】 步驟1：(2S,3S)-3-羥基吡咯啶-2-甲酸甲酯鹽酸鹽係根據與製備**I-593**類似之方式製備。

【0746】 步驟2：向(2S,3S)-3-羥基吡咯啶-2-甲酸鹽酸鹽(268 mg，1.47 mmol)於DCN (6 mL)中之溶液中添加Boc_2O (385 mg，1.76 mmol)及TEA (0.612 mL，4.39 mmol)。將所得反應溶液攪拌隔夜。將混合物用DCM (20 mL)稀釋，用H_2O (2 × 10 mL)、鹽水(10 mL)洗滌並經Na_2SO_4乾燥。濃縮後，將粗(2S,3S)-3-羥基吡咯啶-1,2-二甲酸1-三級丁酯2-甲酯用於下一步驟。

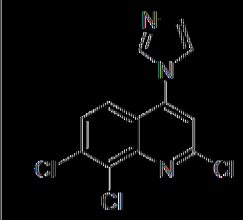
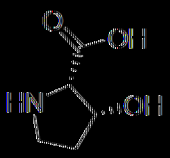
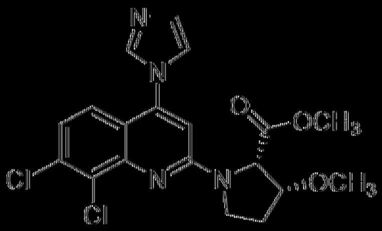
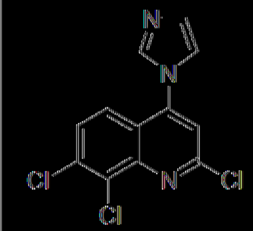
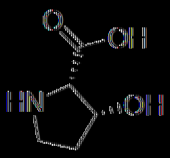
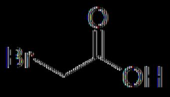
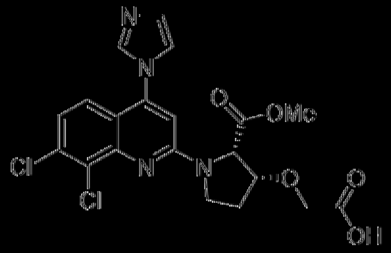
【0747】 步驟3：向(2S,3S)-3-羥基吡咯啶-1,2-二甲酸1-三級丁酯2-甲酯(0.5 mmol)及碘甲烷(0.093 mL，1.5 mmol)於DCM (1.5 mL)中之溶液

中添加700 mg Ag_2O (700 mg，3.02 mmol)。攪拌隔夜後，經由矽藻土墊過濾混合物並藉由矽膠層析法純化，得到呈油狀之(2S,3S)-3-甲氧基吡咯啶-1,2-二甲酸1-三級丁酯2-甲酯。

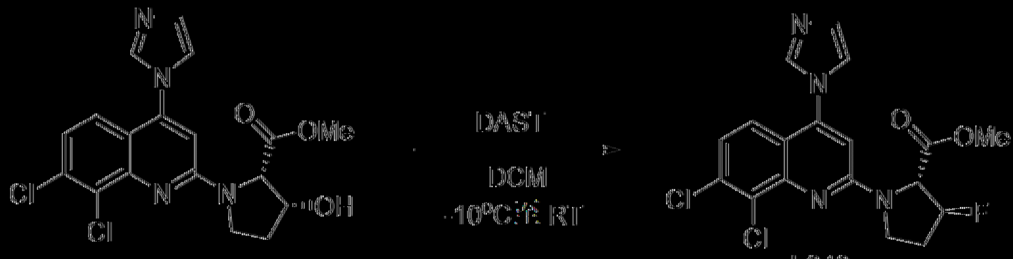
【0748】 步驟4：向(2S,3S)-3-甲氧基吡咯啶-1,2-二甲酸1-三級丁酯2-甲酯(56.5 mg，0.218 mmol)於DCM (0.5 mL)中之溶液中添加TFA (0.25 mL)。攪拌4小時後，濃縮混合物以移除所有揮發性物質。將殘餘物(2S,3S)-3-甲氧基吡咯啶-2-甲酸甲酯用於下一步驟。

【0749】 步驟5：(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-甲氧基吡咯啶-2-甲酸甲酯係藉由與製備I-123步驟1之程序類似的程序。(MS: $[M+1]^+$ 421)。

【0750】 以下化合物基本上藉由與製備I-646相同之方法製備。

I#	起始材料		結構	MS $[M+1]^+$
I-647		 CH_3I		421
I-648		 		465

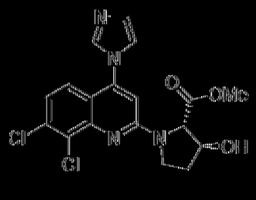
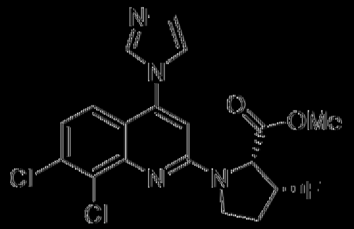
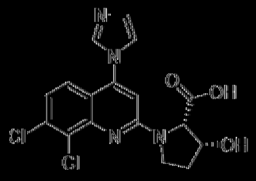
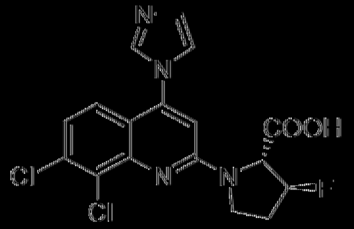
實例94：合成(2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-氟吡咯啶-2-甲酸甲酯(I-649)



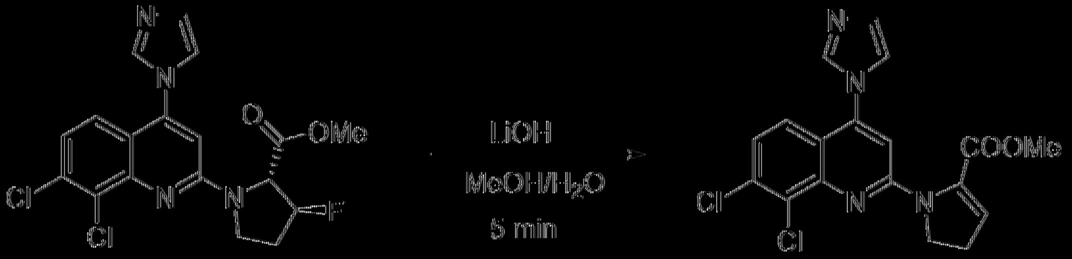
I-649

【0751】 在-10℃下，向(2S,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲酸甲酯(40.7 mg，0.1 mmol)於DCM (0.5 mL)中之混合物中添加DAST (0.040 mL，0.30 mmol)於DCM (0.2 mL)中之溶液。在-10℃下將混合物攪拌2小時。水性處理後，將粗品藉由PTLC純化，得到呈白色固體狀之標題產物(MS: [M+1]$^+$ 409)。

【0752】 以下化合物基本上藉由與製備I-649相同之方法製備。

I #	起始材料		結構	MS [M+1]$^+$
I-650		DAST		409
I-651		DAST		395

實例95：合成1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-4,5-二氫-1H-吡咯-2-甲酸甲酯(I-652)

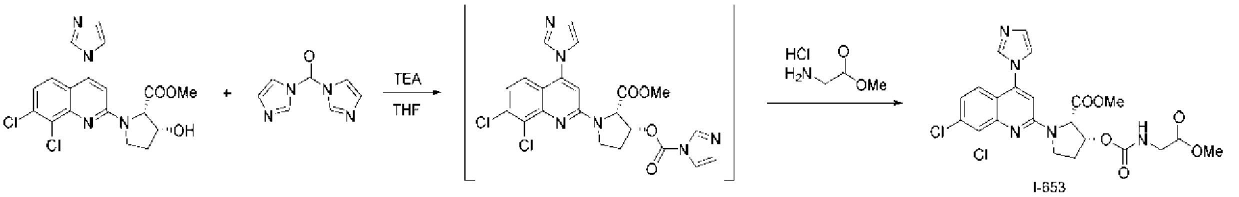


I-652

【0753】 在攪拌下，向(2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-

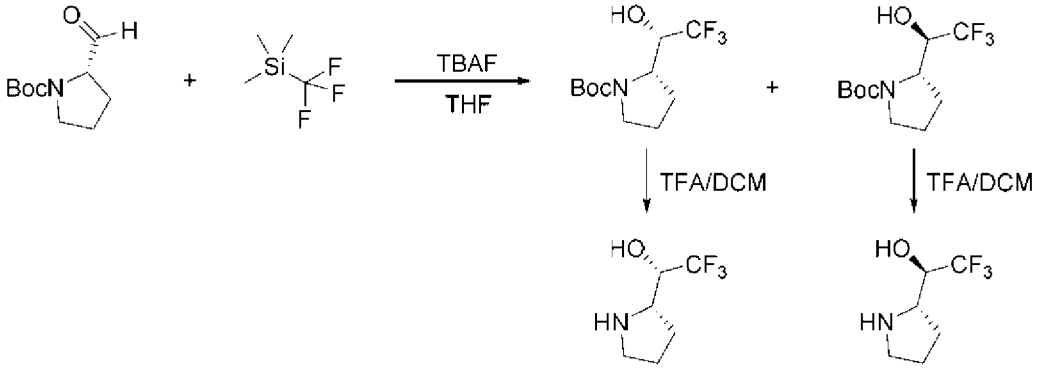
2-基)-3-氟吡咯啶-2-甲酸甲酯(10 mg，0.0244 mmol)於甲醇(0.5 mL)中之溶液中添加LiOH-H_2O (1.57 mg，0.0366 mmol)於H_2O (0.10 mL)中之溶液。5分鐘後，用H_2O (0.10 mL)中之HOAc (0.00209 mL，0.0366 mmol)淬滅反應。將所得混合物藉由HPLC純化，得到呈白色固體狀之標題產物。(MS: $[M+1]^+$ 389)。

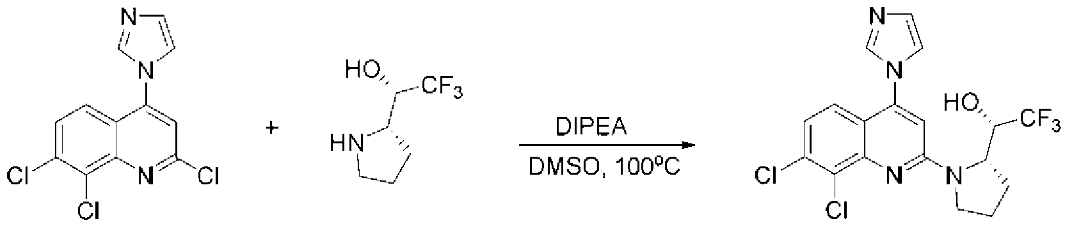
實例96：合成(2S,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(((2-甲氧基-2-側氧基乙基)胺甲醯基)氧基)吡咯啶-2-甲酸甲酯(**I-653**)



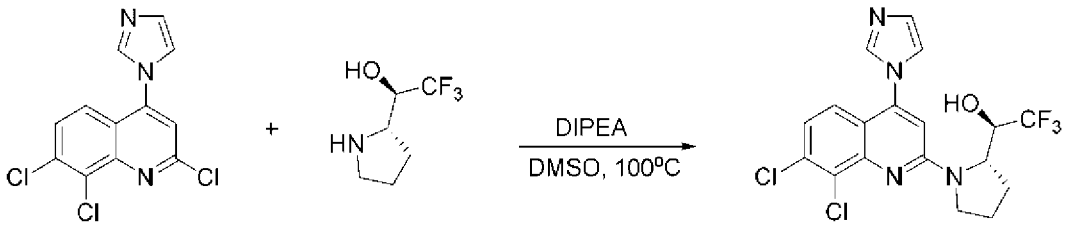
【0754】 向(2S,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲酸甲酯(30 mg，0.0737 mmol)於THF (0.5 mL)中之溶液中添加TEA (0.051 mL，0.369 mmol)及CDI (40 mg，0.247 mmol)。將所得混合物攪拌2小時。接著，添加甘胺酸甲酯鹽酸鹽(18.5 mg，0.147 mmol)。攪拌2小時後，將混合物用DCM (20 mL)稀釋，用H_2O (2 × 10 mL)、鹽水(10 mL)洗滌並經Na_2SO_4乾燥。將粗品藉由矽膠層析法純化，得到呈白色固體狀之標題產物。(MS: $[M+1]^+$ 522)。

實例97：合成(S)-1-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2,2,2-三氟乙-1-醇(**I-654**)及(R)-1-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2,2,2-三氟乙-1-醇(**I-655**)





I-654



I-655

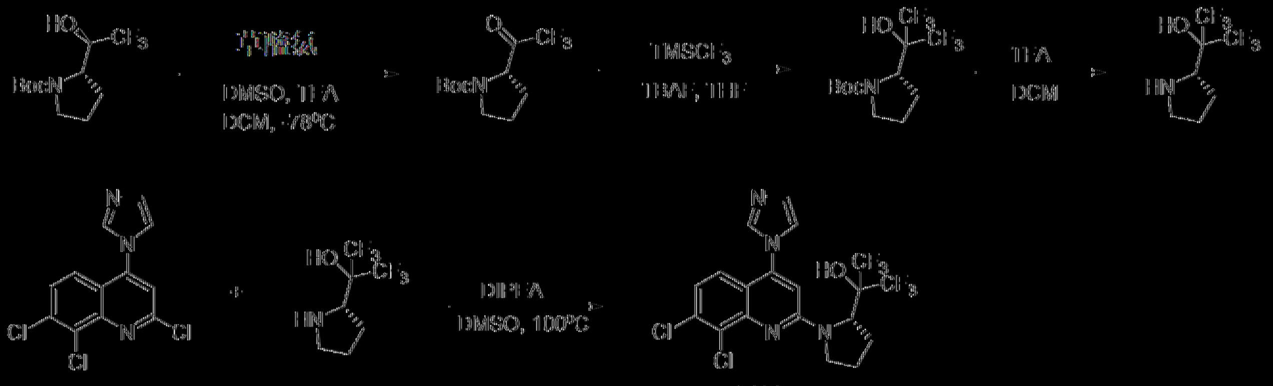
【0755】 步驟1：向燒瓶中添加(S)-2-甲醯基吡咯啶-1-甲酸三級丁酯(1.992 g，10 mmol)及THF (25 mL)。在冰浴中將溶液冷卻20分鐘。在0℃下，緩慢添加三甲基(三氟甲基)矽烷於THF中之溶液(2.0 M，7.5 mL，15 mmol)後，逐滴添加TBAF於THF中之溶液(1.0 M，0.5 mL，0.5 mmol)。在相同溫度下，將所得混合物攪拌2小時。再添加TBAF於THF中之溶液(1.0 M，2.0 mL，2.0 mmol)並在室溫下將混合物再攪拌2小時。用飽和NH_4Cl淬滅並濃縮後，將所得混合物用DCM (150 mL)稀釋，用H_2O、鹽水洗滌，經Na_2SO_4乾燥且接著濃縮。將粗產物藉由矽膠層析法純化，得到(S)-2-((S)-2,2,2-三氟-1-羥基乙基)吡咯啶-1-甲酸三級丁酯及(S)-2-((R)-2,2,2-三氟-1-羥基乙基)吡咯啶-1-甲酸三級丁酯。

【0756】 步驟2：向小瓶中添加(S)-2-((S)-2,2,2-三氟-1-羥基乙基)吡咯啶-1-甲酸三級丁酯(50 mg，0.186 mmol)、DCM (0.5 mL)及TFA

(0.25 mL)。將所得溶液攪拌2小時。在真空下移除所有揮發性物質後，將粗(S)-2,2,2-三氟-1-((S)-吡咯啶-2-基)乙-1-醇直接用於下一步驟中。使用相同程序製備(R, S)-異構體。

【0757】 步驟3：(S)-1-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2,2,2-三氟乙-1-醇I-654 (MS: $[M+1]^+$ 431)及(R)-1-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2,2,2-三氟乙-1-醇I-655 (MS: $[M+1]^+$ 431)均遵循製備I-123步驟1之合成程序製備。

實例98：合成(S)-2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-1,1,1,3,3,3-六氟丙-2-醇(I-656)



I-656

【0758】 步驟1：向小瓶中添加DCM (3 mL)及草醯氯(0.220 mL，2.6 mmol)，隨後在乾冰/丙酮浴中冷卻。逐滴添加DMSO (0.383 mL，5.4 mmol)於DCM (2.5 mL)中之溶液。在-78℃下將混合物攪拌30分鐘。接著，在相同溫度下逐滴添加(S)-2-((R)-2,2,2-三氟-1-羥基乙基)吡咯啶-1-甲酸三級丁酯(582 mg，2.16 mmol)於DCM (2.5 mL)中之溶液。30分鐘後，逐滴添加TEA (1.5 mL，10.8 mmol)並在-78℃下將混合物攪拌30分鐘。在室溫下將所得混合物攪拌1小時，接著藉由添加H_2O (10 mL)淬滅。藉由DCM (2 × 15 mL)萃取水相。將合併之有機相濃縮，藉由矽膠層析法純化，得到(S)-2-(2,2,2-三氟乙醯基)吡咯啶-1-甲酸三級丁酯。

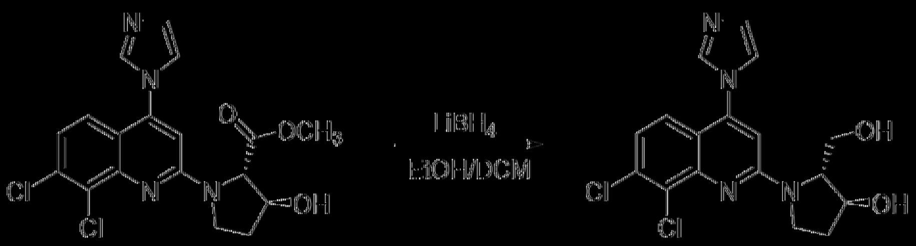
【0759】 步驟2：(S)-2-(1,1,1,3,3,3-六氟-2-羥基丙-2-基)吡咯啶-1-

甲酸三級丁酯係根據與製備I-654步驟1類似之程序製備。

【0760】 步驟3：(S)-1,1,1,3,3,3-六氟-2-(吡咯啶-2-基)丙-2-醇係根據與製備I-654步驟2類似之程序製備。

【0761】 步驟4：(S)-2-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-1,1,1,3,3,3-六氟丙-2-醇係根據與製備I-123步驟1類似之程序製備。(MS: $[M+1]^+$ 499)

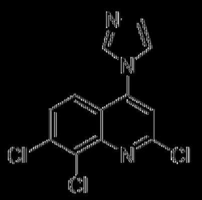
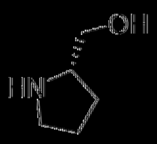
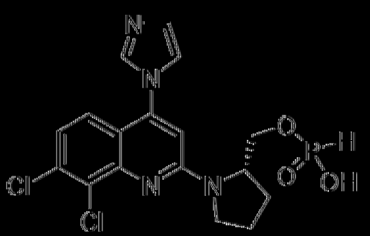
實例99：合成(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲酸甲酯(I-657)



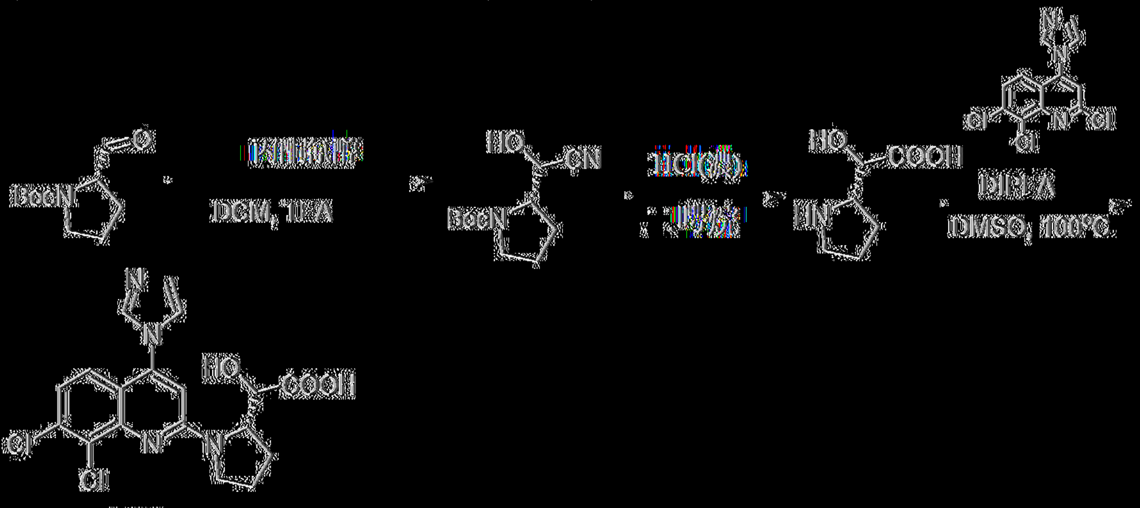
【0762】 向小瓶中添加(2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲酸甲酯(20 mg，0.0491 mmol)、THF(0.5 mL)及乙醇(1.0 mL)。在0℃下，添加$LiBH_4$ (9.5 mg，0.436 mmol)並將所得混合物攪拌隔夜。將混合物用DCM (20 mL)稀釋，用飽和NH_4Cl (5 mL)、H_2O (5 mL)、鹽水(5 mL)洗滌並經Na_2SO_4乾燥。將粗品藉由矽膠層析法純化，得到呈白色固體狀之標題化合物(MS: $[M+1]^+$ 379)。

實例100：合成二氫膦酸((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲酯(I-658)

【0763】 I-658基本上藉由與製備I-111相同之方法製備。

I#	起始材料		結構	MS $[M+1]^+$
I-658				427

實例101：合成(R)-2-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基乙酸. 六氟丙-2-醇(I-661)



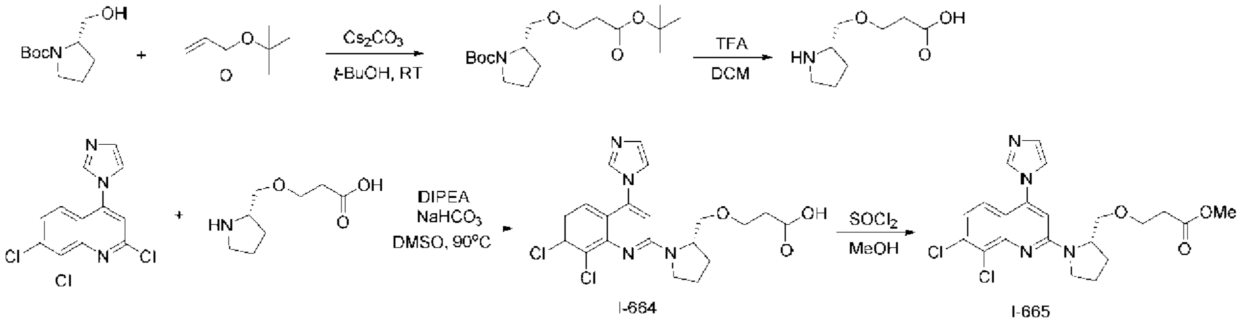
I-661

【0764】 步驟1：向小瓶中添加DCM (10 mL)、TEA (1 mmol，0.1 mL)及(S)-2-甲醯基吡咯啶-1-甲酸三級丁酯(1 g，5 mmol)並在室溫下將混合物攪拌隔夜。蒸發後，將粗(S)-2-((R)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯不經進一步純化即用於下一步驟中。(MS: [M+1]+ 227.1)。

【0765】 步驟2：使(S)-2-((R)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯(230 mg，1 mmol)、HCl (濃，1 mL)及1,4-二噁烷(1 mL)之混合物回流2小時。蒸發後，將粗(R)-2-羥基-2-((S)-吡咯啶-2-基)乙酸不經進一步純化即用於下一步驟中。(MS: [M+1]+ 146.1)。

【0766】 步驟3：(R)-2-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基乙酸(I-661)係以與製備I-123之步驟1類似之方式製備。(MS: [M+1]+ 407.1)。

實例102：合成(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯(I-665)及(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(I-664)



I-664

I-665

【0767】 步驟1：(S)-2-((3-(三級丁氧基)-3-側氧基丙氧基)甲基)吡咯啶-1-甲酸三級丁酯. 向小瓶中添加(S)-2-(羥基甲基)吡咯啶-1-甲酸三級丁酯(805 mg，4.1 mmol，1.0 eq.)、Cs_2CO_3 (1.3 g，4.1 mmol，1.0 eq.)、t-BuOH (5 mL)及丙烯酸三級丁酯(1.8 mL，20 mmol，5 eq.)。將所得反應混合物攪拌隔夜。接著，將混合物用乙酸乙酯(50 mL)稀釋，用H_2O (3 × 15 mL)、鹽水(15 mL)洗滌且經Na_2SO_4乾燥。濃縮後，將粗品藉由矽膠層析法純化，得到標題產物(1.22 g)。

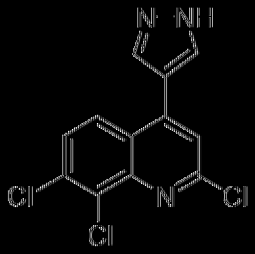
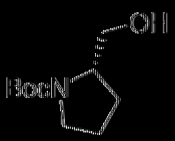
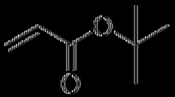
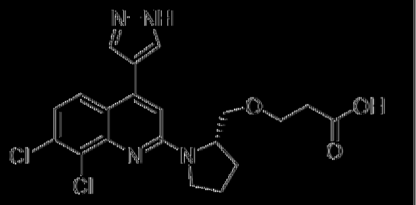
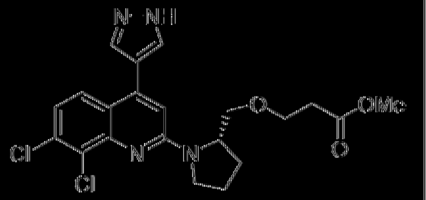
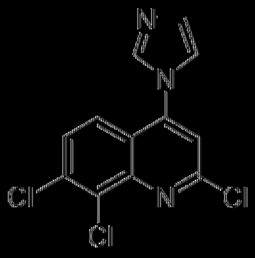
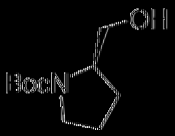
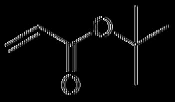
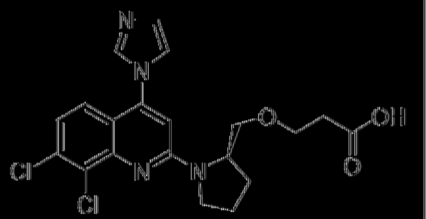
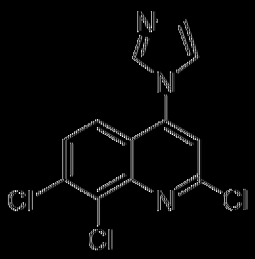
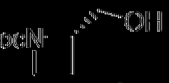
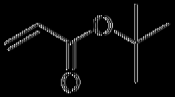
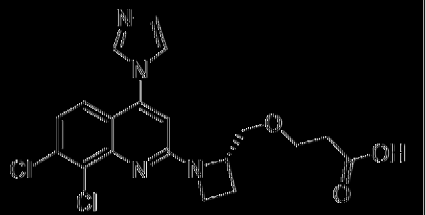
【0768】 步驟2：(S)-3-(吡咯啶-2-基甲氧基)丙酸. 在室溫下，將(S)-2-((3-(三級丁氧基)-3-側氧基丙氧基)甲基)吡咯啶-1-甲酸三級丁酯(400 mg，1.21 mmol)、TFA (2 mL)及DCM (2 mL)之混合物攪拌隔夜。濃縮混合物以移除所有揮發性物質。將粗品用於下一步驟中。

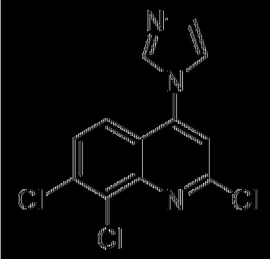
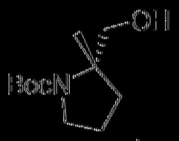
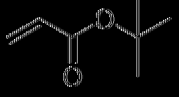
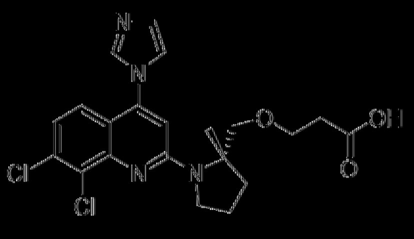
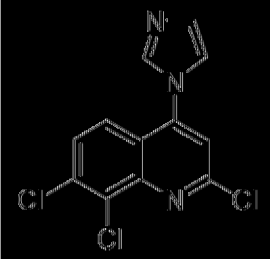
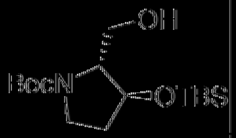
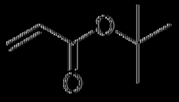
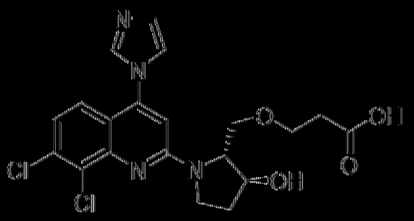
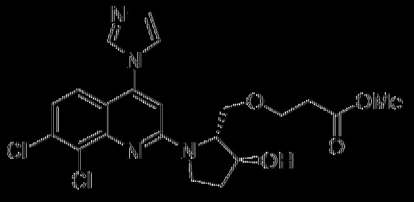
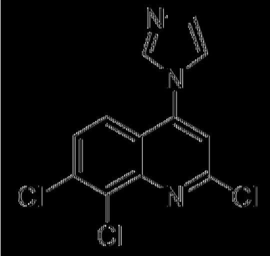
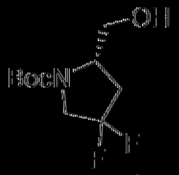
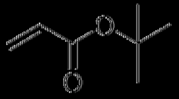
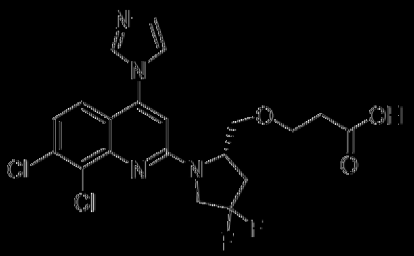
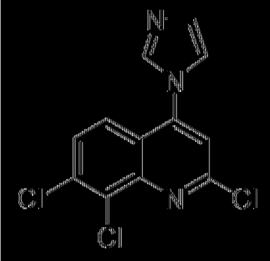
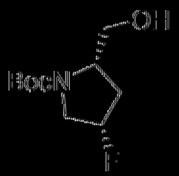
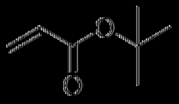
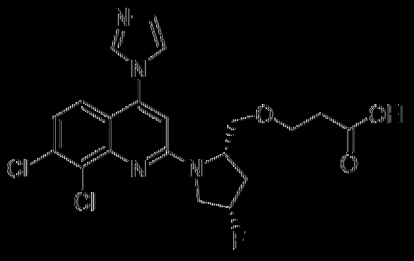
【0769】 步驟3：(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(**I-664**). 向小瓶中添加2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(227 mg，0.759 mmol，1.0 eq.)、步驟2中之粗產物(0.911 mmol)、DMSO (4.0 mL)、DIPEA (0.66 mL，3.8 mmol，5.0 eq.)及$NaHCO_3$。在90℃下將反應混合物攪拌隔夜。接著，將混合物用乙酸乙酯(30 mL)稀釋並藉由HOAc (1 M，5 mL)酸化，用H_2O (3 × 10 mL)、鹽水(10 mL)洗滌且經Na_2SO_4乾燥。濃縮後，將粗品用於下一步驟中。將酸產物藉由矽膠層析法純化。MS: $[M+1]^+$ 435。

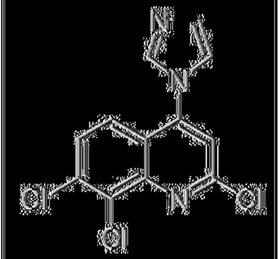
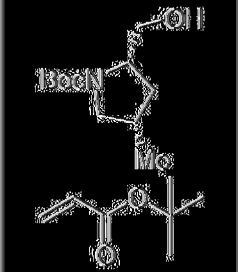
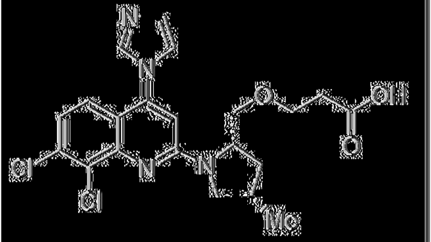
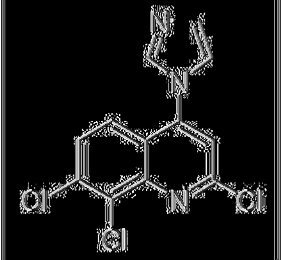
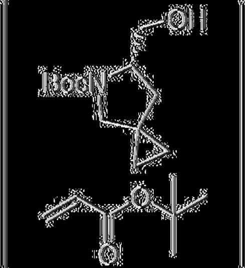
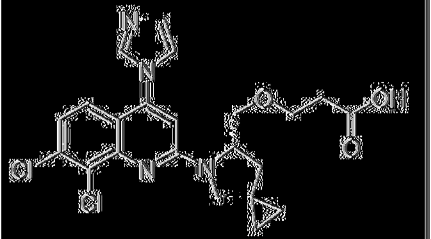
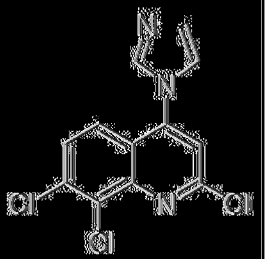
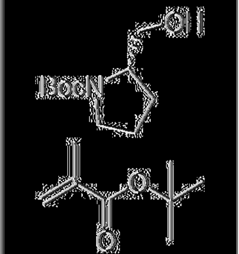
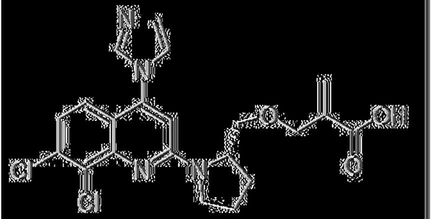
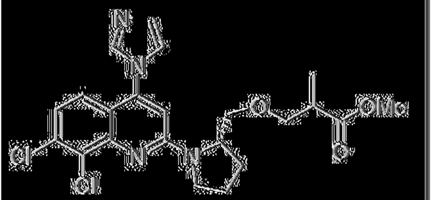
【0770】 步驟4：(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯(**I-665**). 向小瓶中添加步驟3中之粗產物(0.345 mmol)及無水甲醇(2.0 mL)。將反應溶液冷卻至0℃並在0℃下用

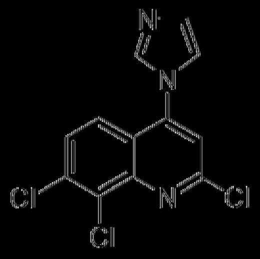
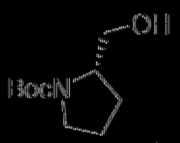
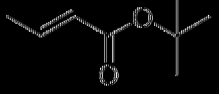
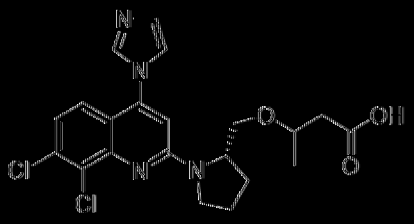
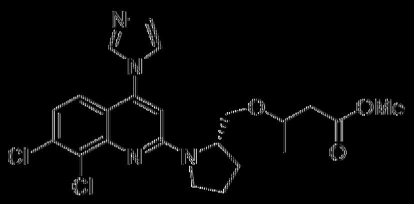
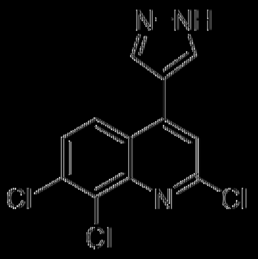
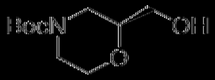
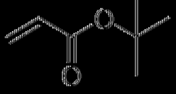
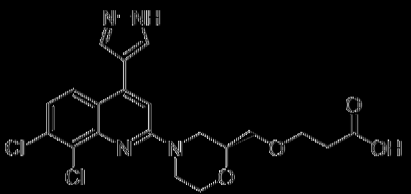
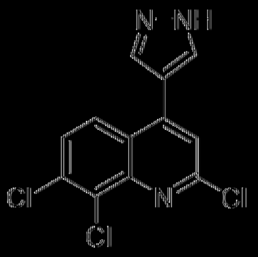
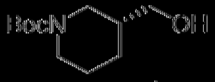
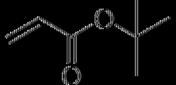
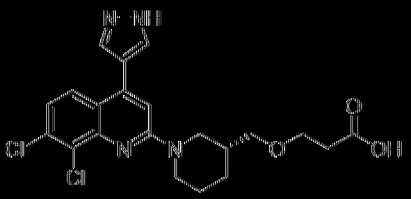
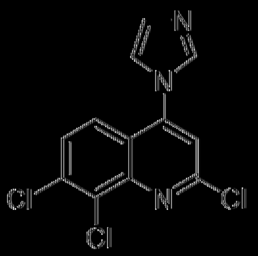
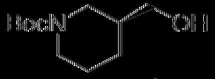
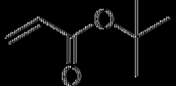
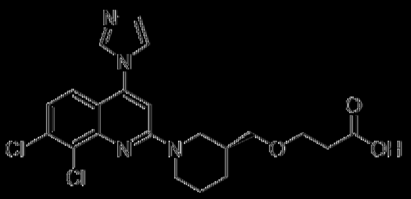
$SOCl_2$ (0.100 mL，1.38 mmol，4.0 eq.)處理。在室溫下攪拌2小時後，將反應混合物用乙酸乙酯(30 mL)稀釋，用$NaHCO_3/H_2O$ (5%，10 mL)、H_2O (3 × 10 mL)、鹽水(10 mL)洗滌且經Na_2SO_4乾燥。濃縮後，將粗品藉由矽膠管柱純化，得到標題產物(135 mg)。MS: $[M+1]^+$ 449。

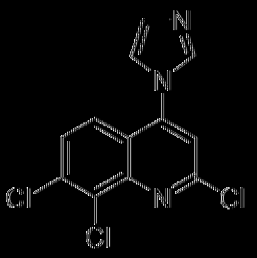
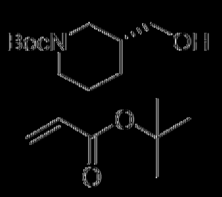
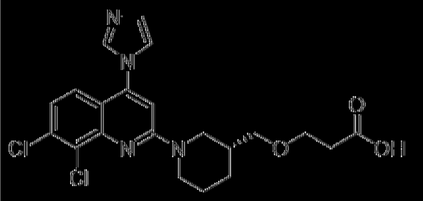
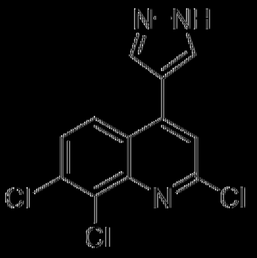
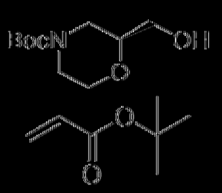
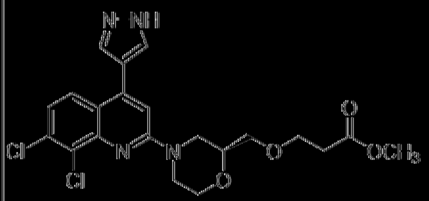
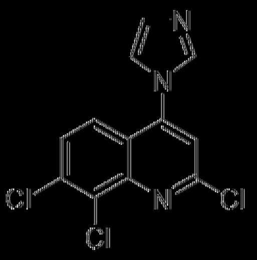
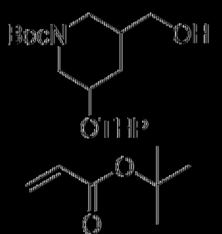
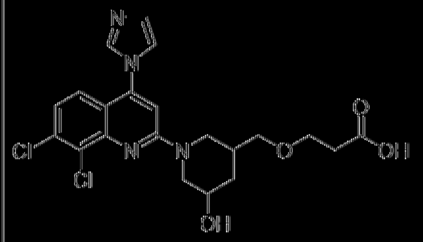
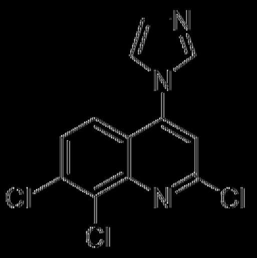
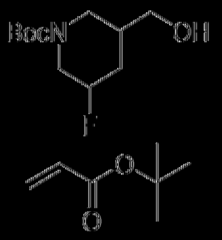
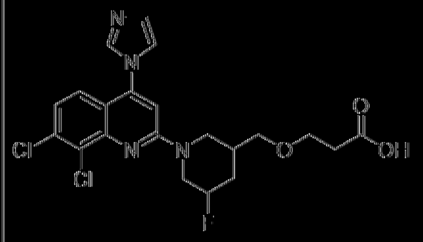
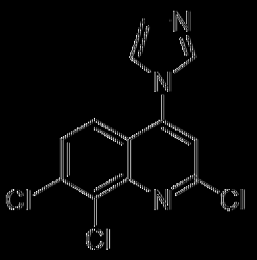
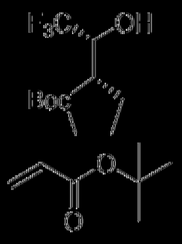
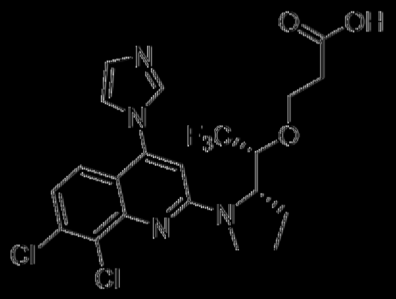
【0771】 以下化合物基本上藉由與以上關於I-664及665所描述相同之方法製備。

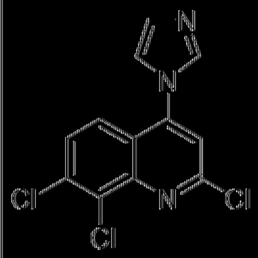
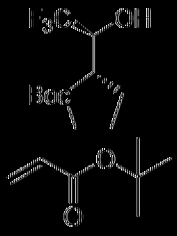
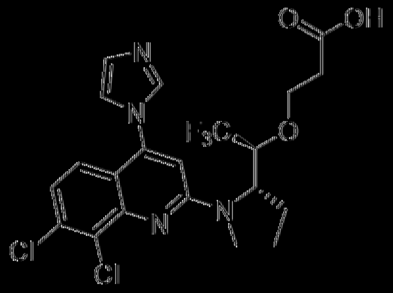
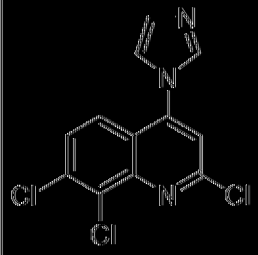
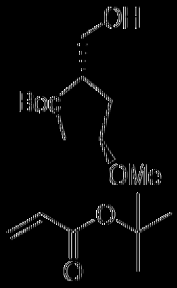
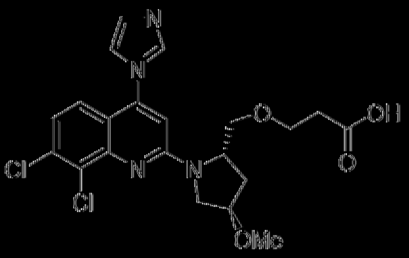
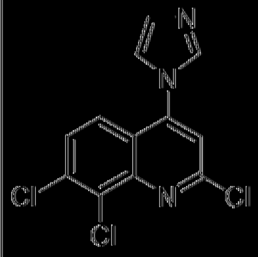
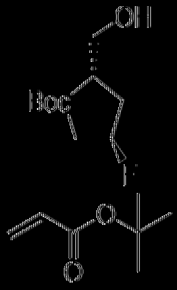
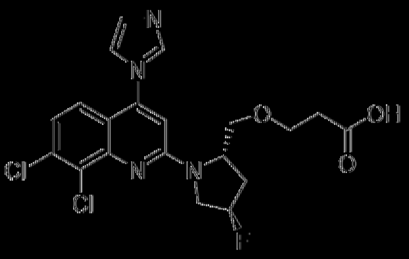
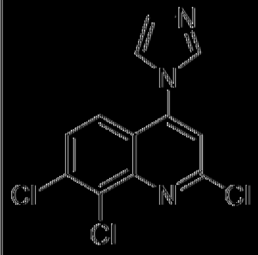
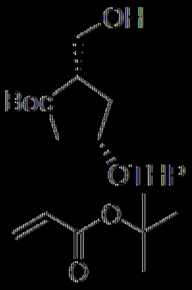
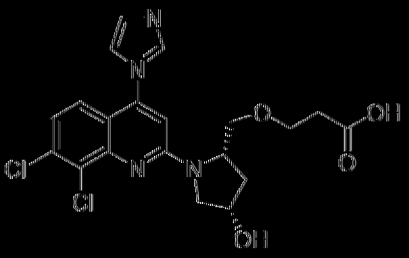
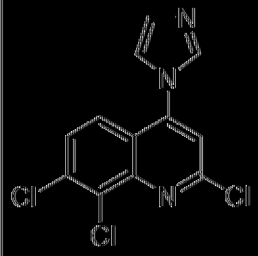
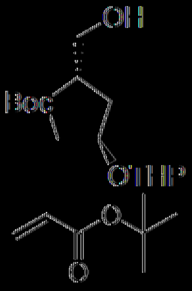
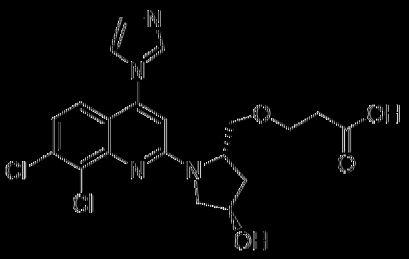
實例	起始材料		結構	MS $[M+1]^+$
I-670		 		435
I-671				449
I-674		 		435
I-688		 		421

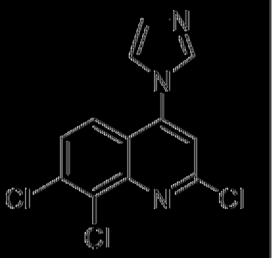
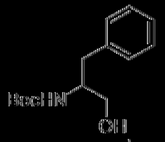
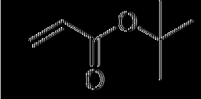
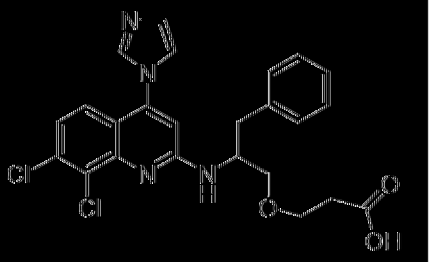
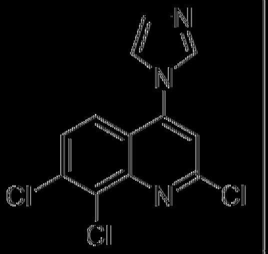
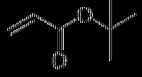
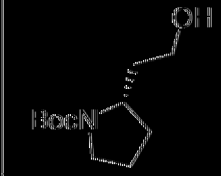
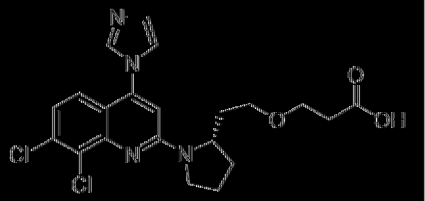
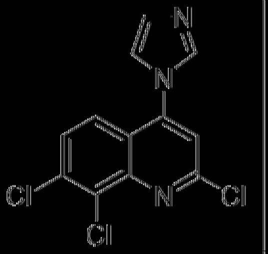
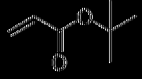
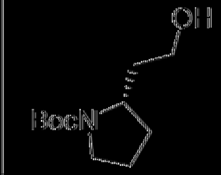
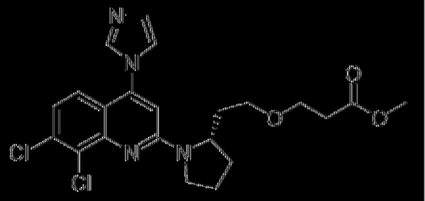
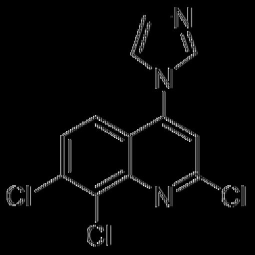
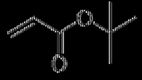
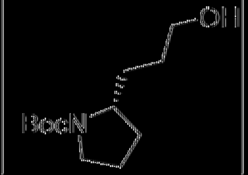
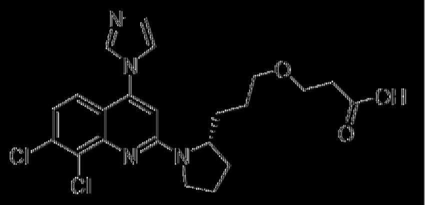
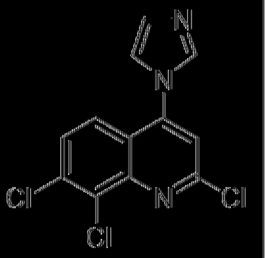
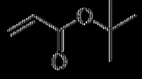
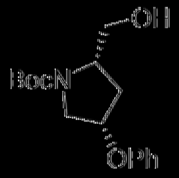
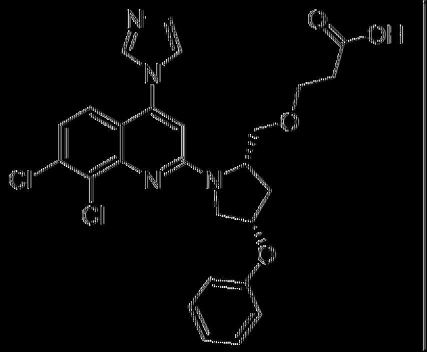
實例	起始材料		結構	MS [M+1]$^+$
I-696		 		449
I-698		 		451
I-701				465
I-699		 		471
I-705		 		453

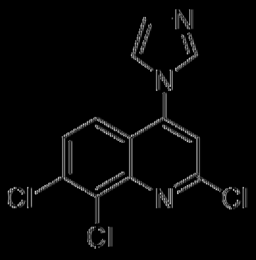
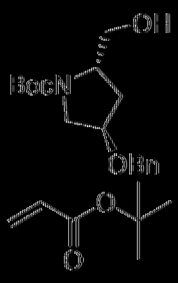
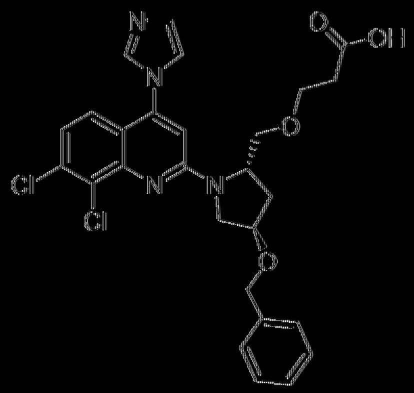
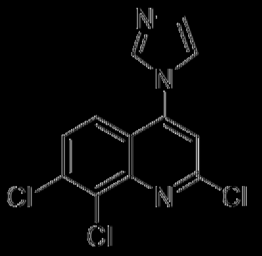
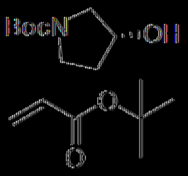
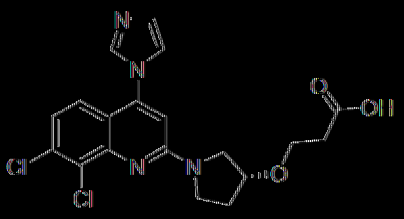
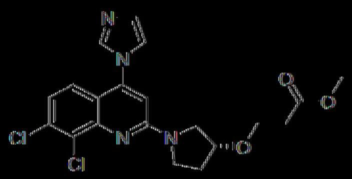
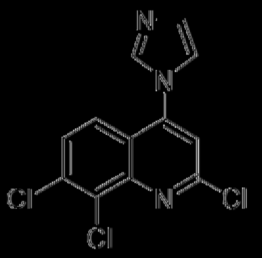
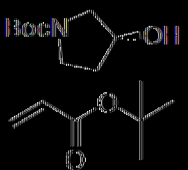
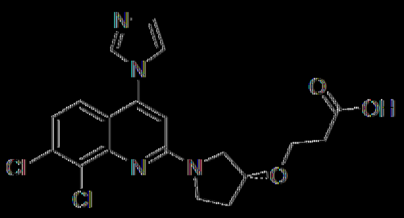
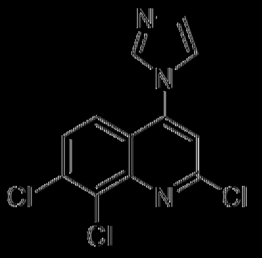
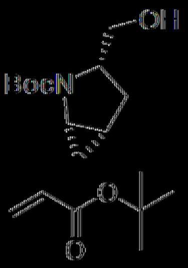
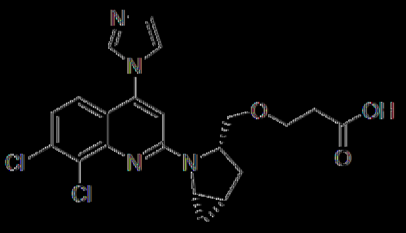
實例	起始材料		結構	MS [M+1]+
I-708				449
I-709				461
I-719				449
I-720				463

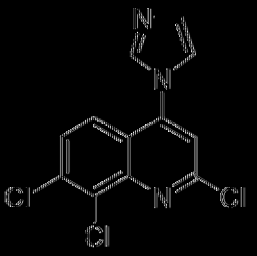
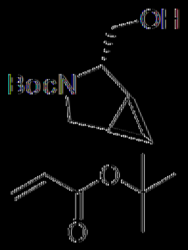
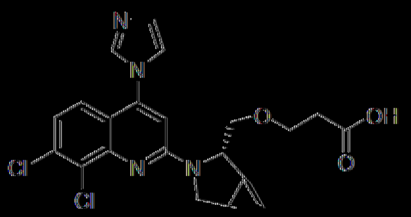
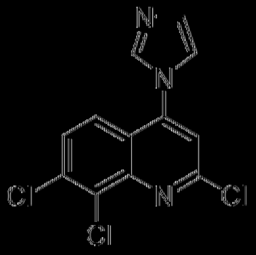
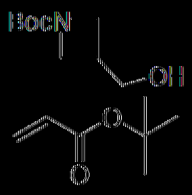
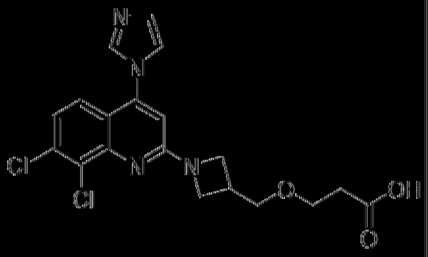
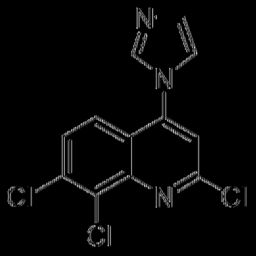
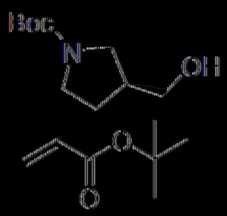
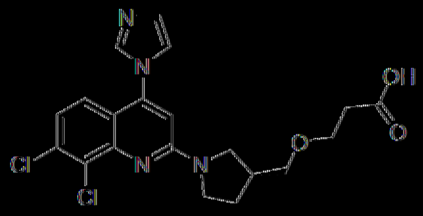
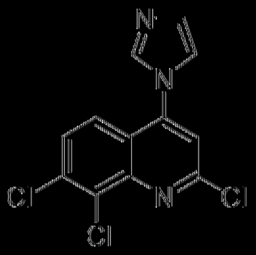
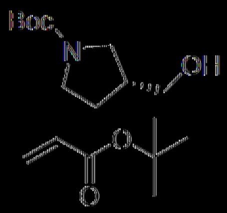
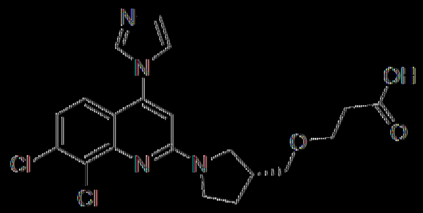
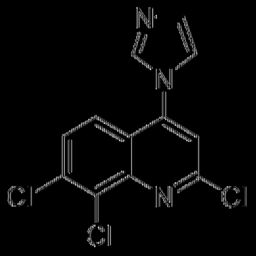
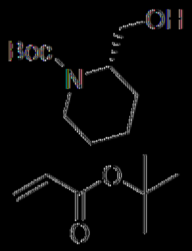
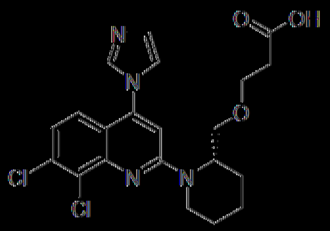
實例	起始材料		結構	MS [M+1]+
E717		 		449
E718				463
E741		 		451
E747		 		449
E745		 		449

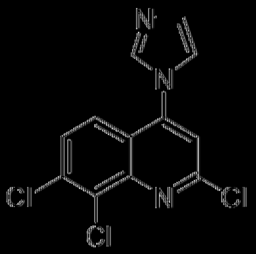
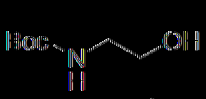
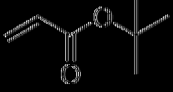
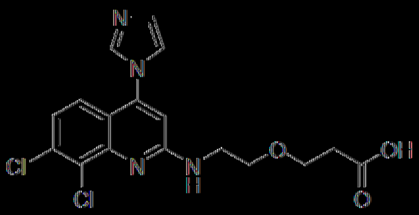
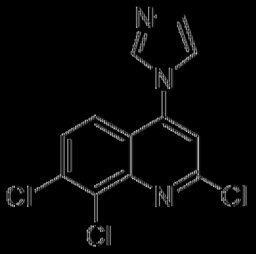
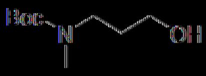
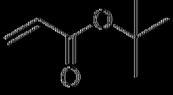
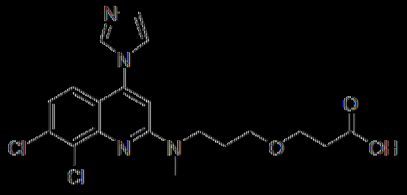
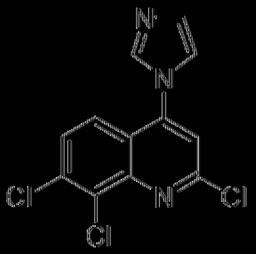
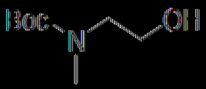
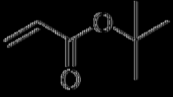
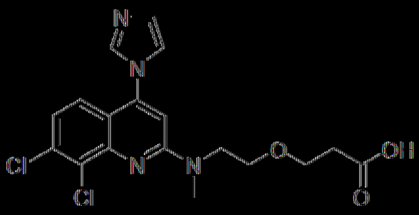
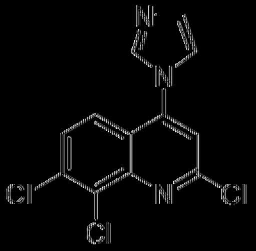
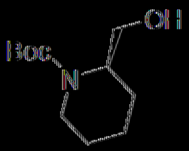
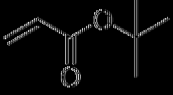
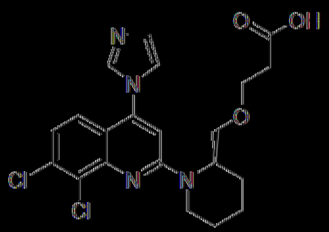
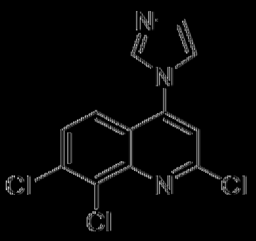
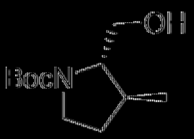
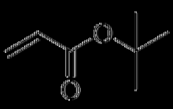
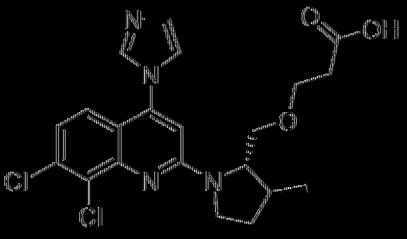
實例	起始材料		結構	MS [M+1]+
E750				449
E752				465
E748				465
E749				467
E721				503

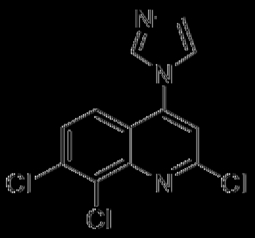
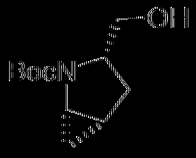
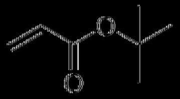
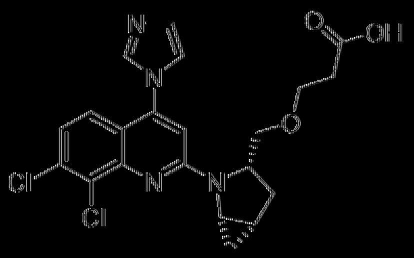
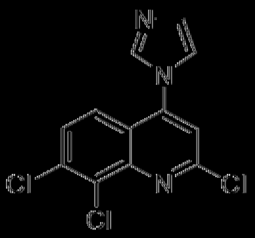
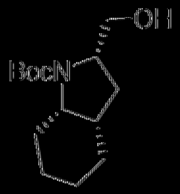
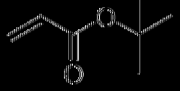
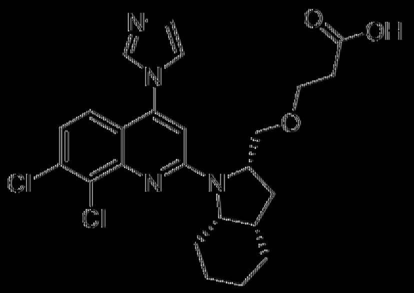
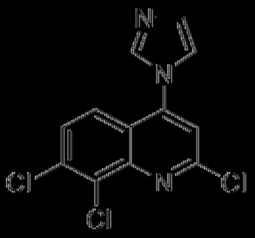
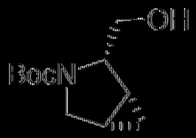
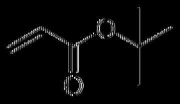
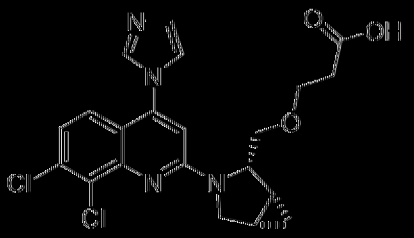
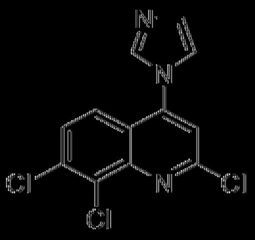
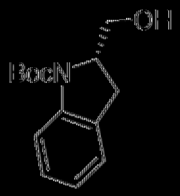
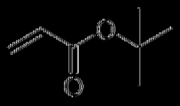
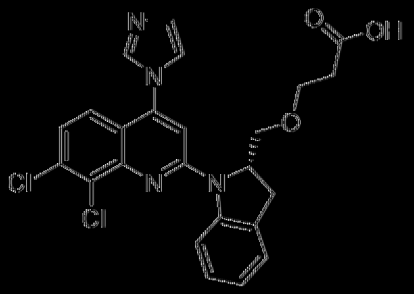
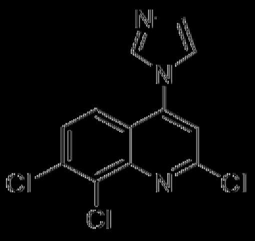
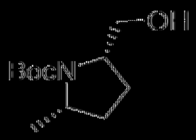
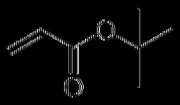
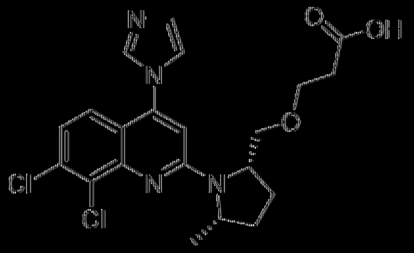
實例	起始材料		結構	MS [M+1]$^+$
E722				503
E711				465
E704				453
E702				451
E703				451

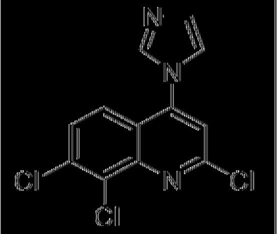
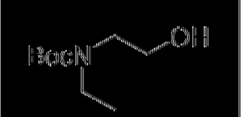
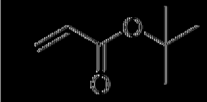
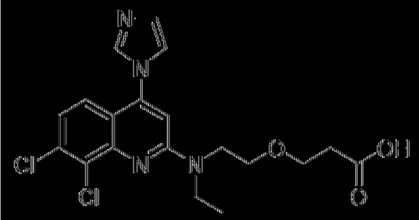
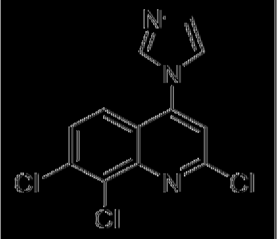
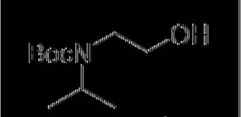
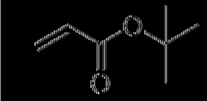
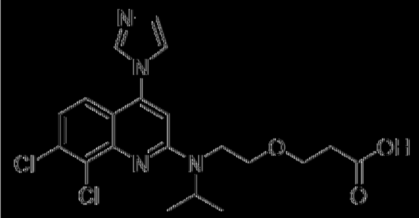
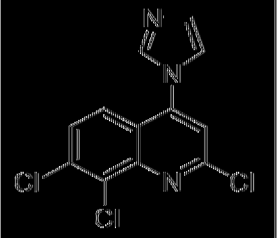
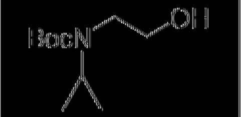
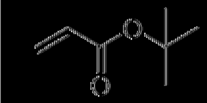
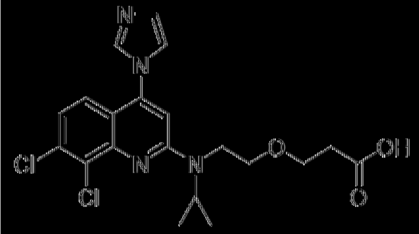
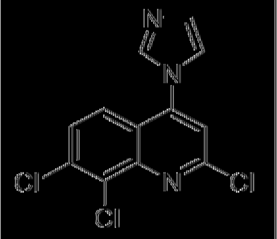
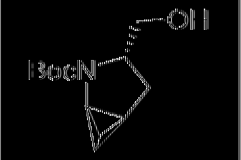
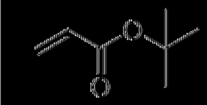
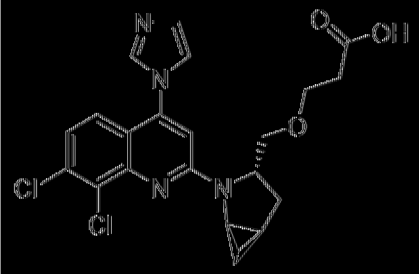
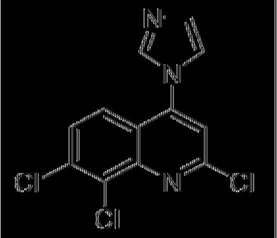
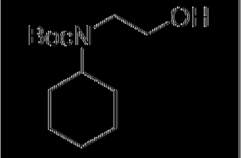
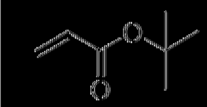
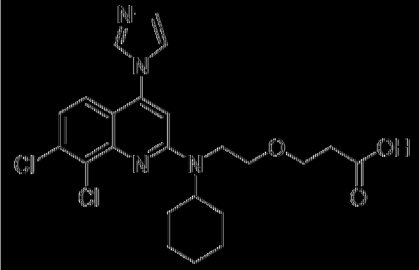
實例	起始材料		結構	MS [M+1]$^+$
I-695		 		485
I-672		 		449
I-673		 		463
I-677		 		463
I-713		 		527

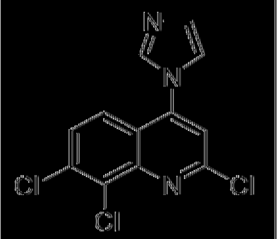
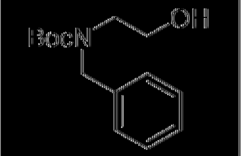
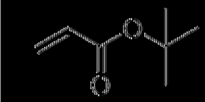
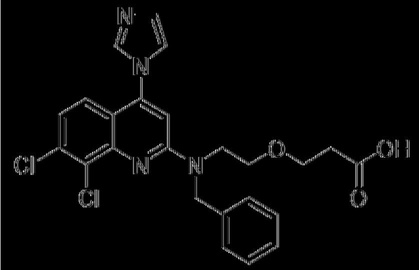
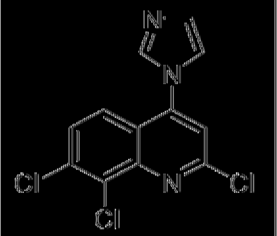
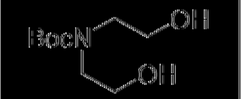
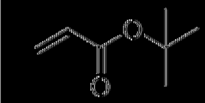
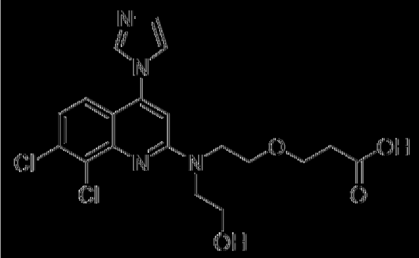
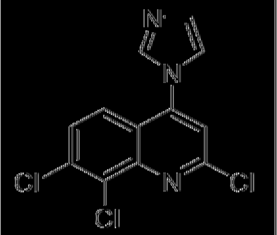
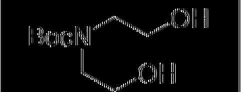
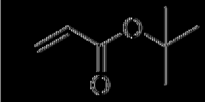
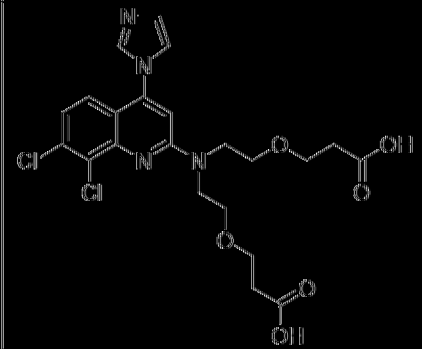
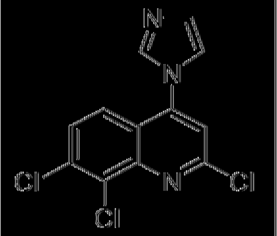
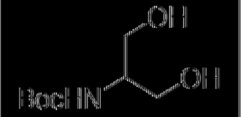
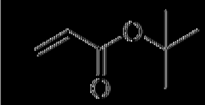
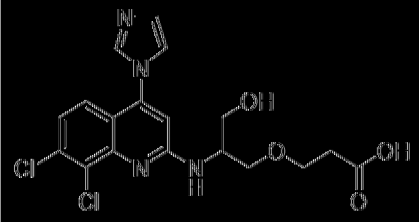
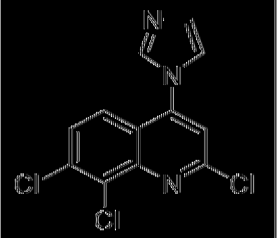
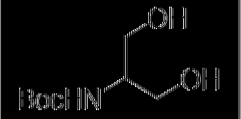
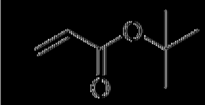
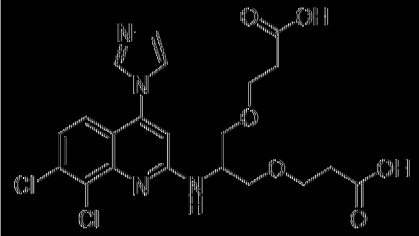
實例	起始材料		結構	MS [M+1]$^+$
E712				541
E767				421
E769				435
E771				421
E707				447

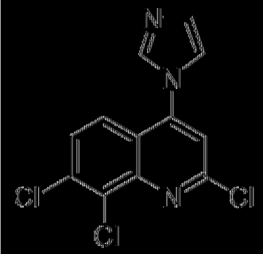
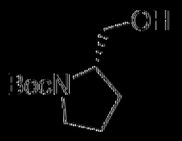
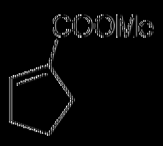
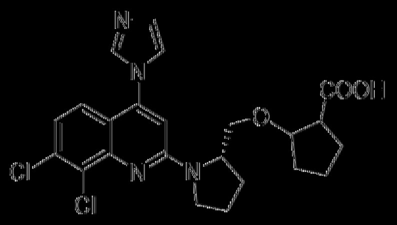
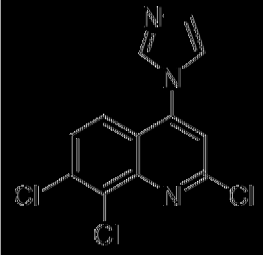
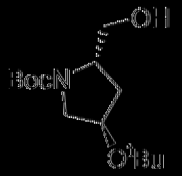
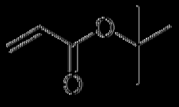
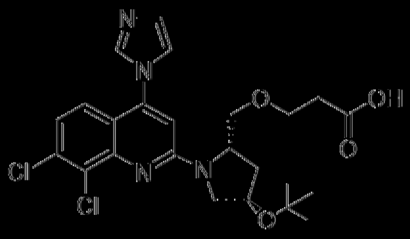
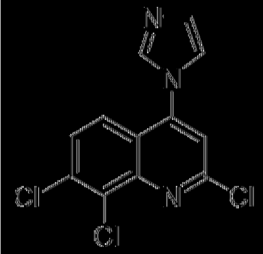
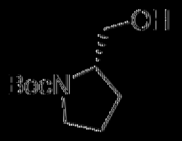
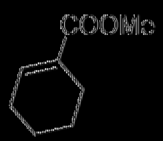
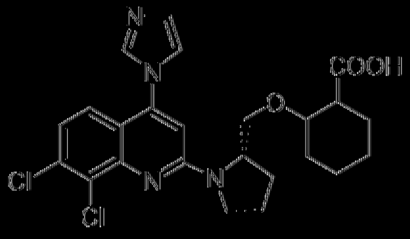
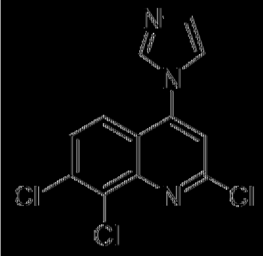
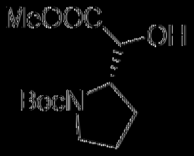
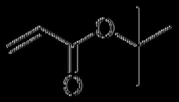
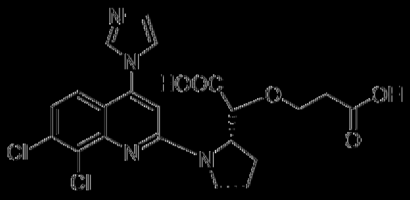
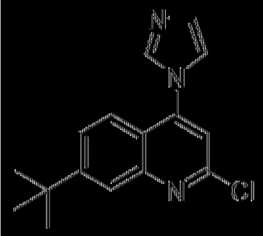
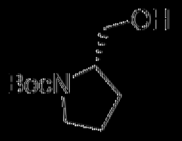
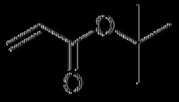
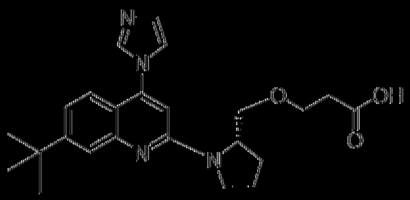
實例	起始材料		結構	MS [M+1]+
I-710				447
I-689				421
I-772				435
I-773				435
I-789				449

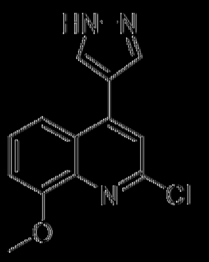
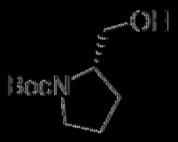
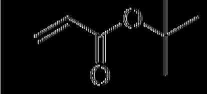
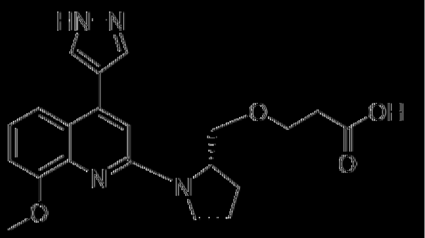
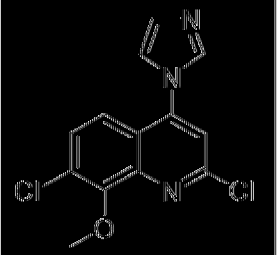
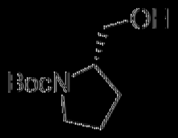
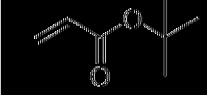
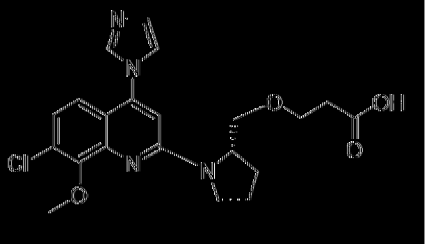
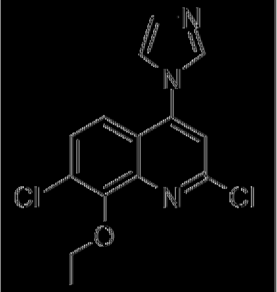
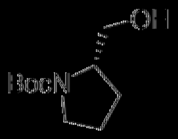
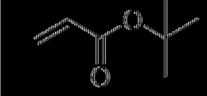
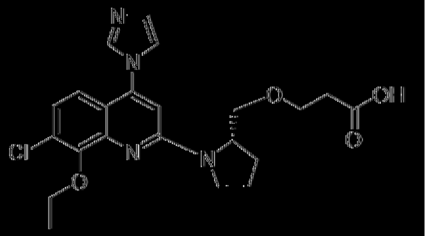
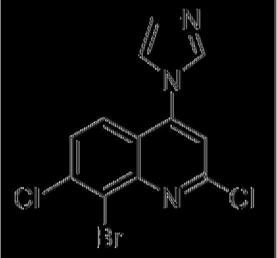
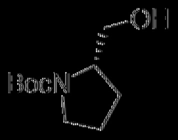
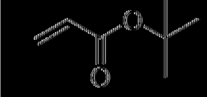
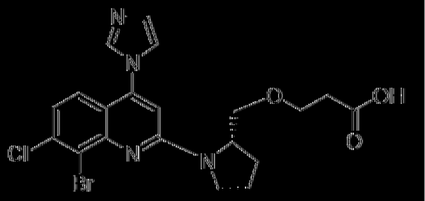
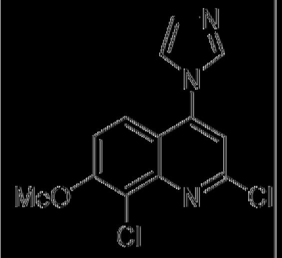
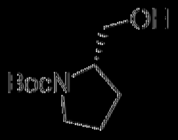
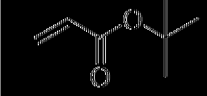
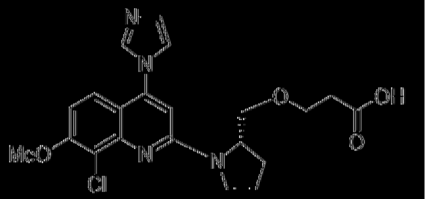
實例	起始材料		結構	MS [M+1]+
I-693		 		395
I-692		 		423
I-694		 		409
I-790		 		449
I-792		 		449

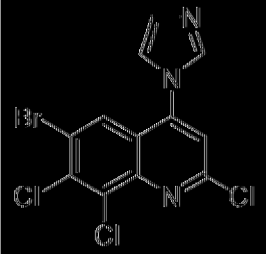
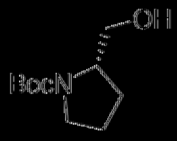
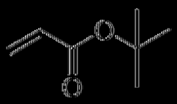
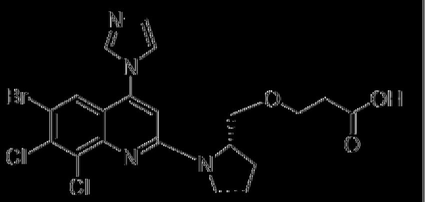
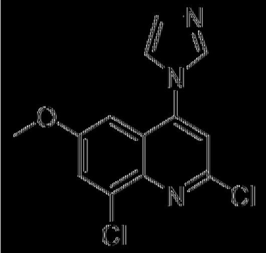
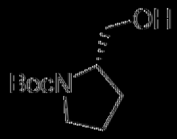
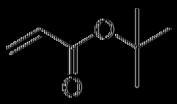
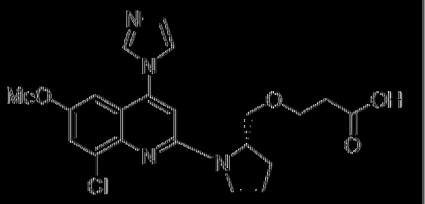
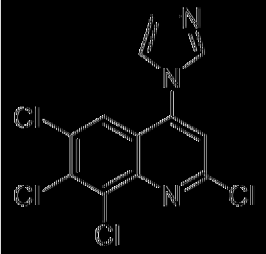
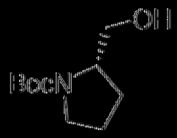
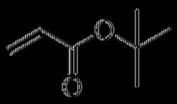
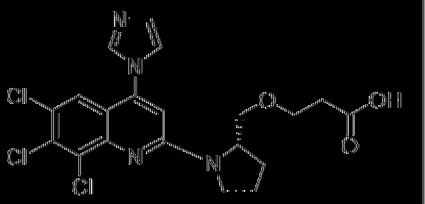
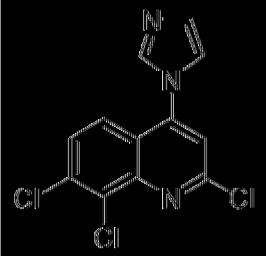
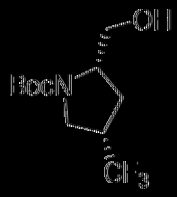
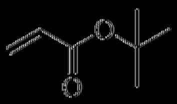
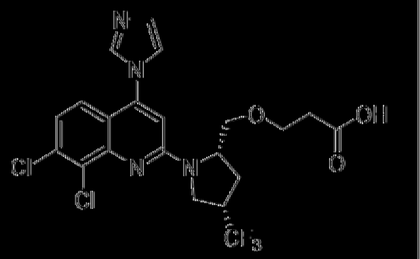
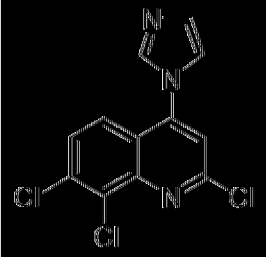
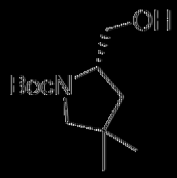
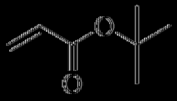
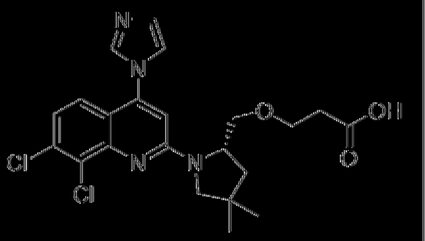
實例	起始材料		結構	MS [M+1]+
I-804		 		447
I-808		 		489
I-809		 		447
I-806		 		483
I-810		 		449

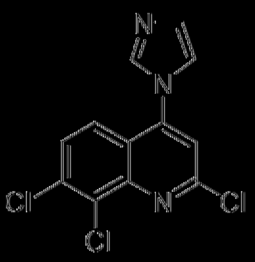
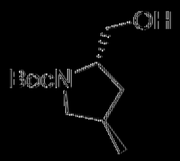
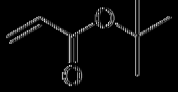
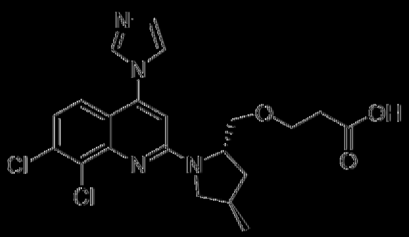
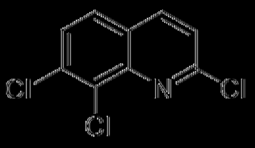
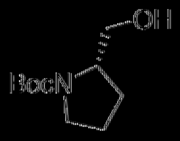
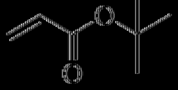
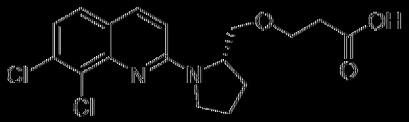
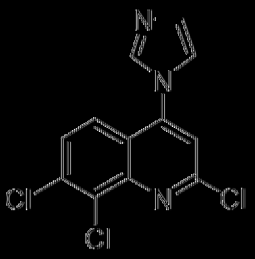
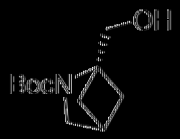
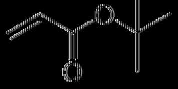
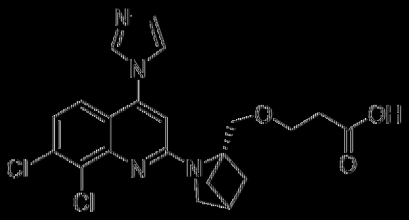
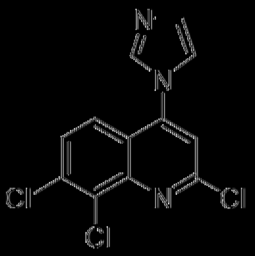
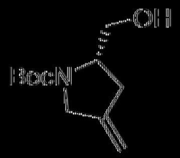
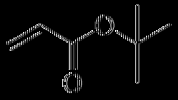
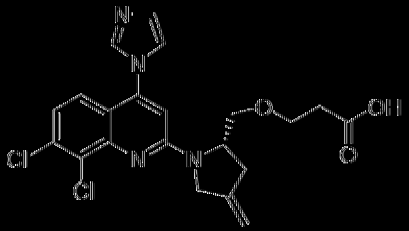
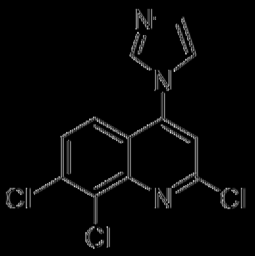
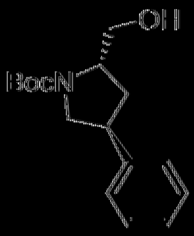
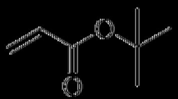
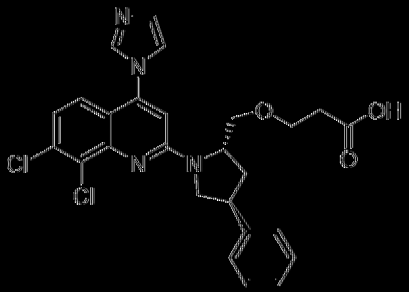
實例	起始材料		結構	MS [M+1]$^+$
I-832		 		423
I-833		 		437
I-834		 		435
I-805		 		447
I-836		 		477

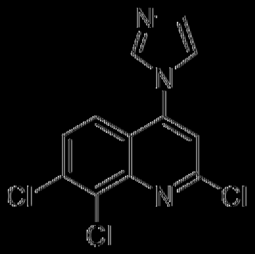
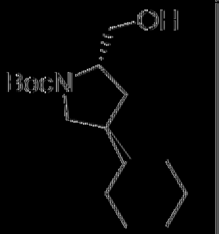
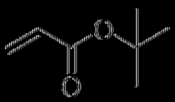
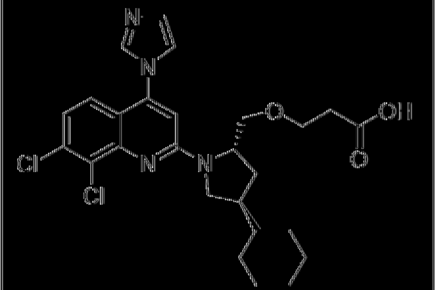
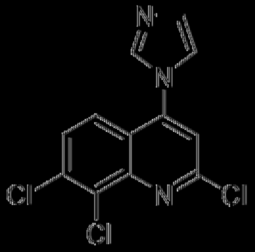
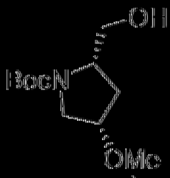
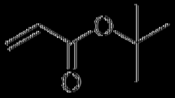
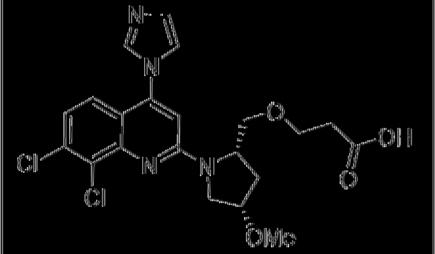
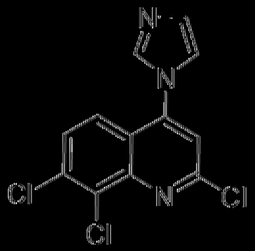
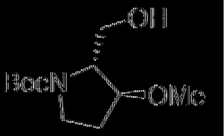
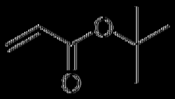
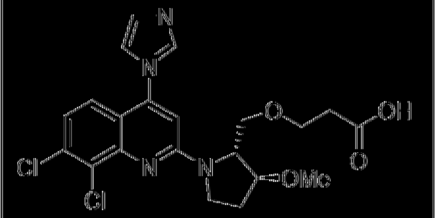
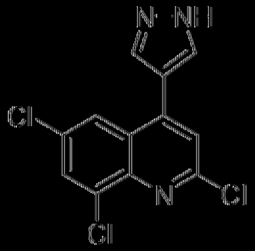
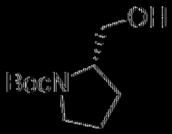
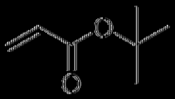
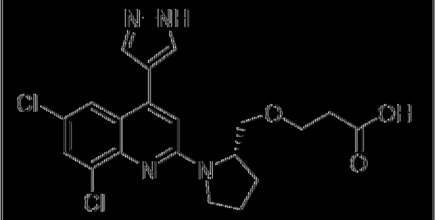
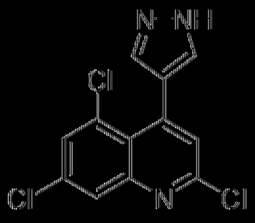
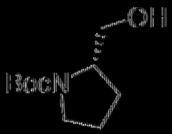
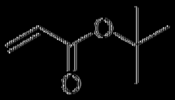
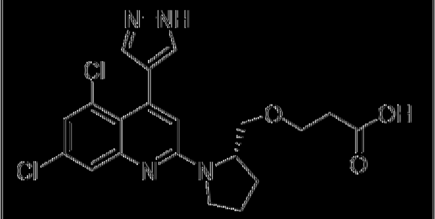
實例	起始材料		結構	MS $[M+1]^+$
I-837		 		485
I-838		 		439
I-839		 		511
I-873		 		425
I-874		 		497

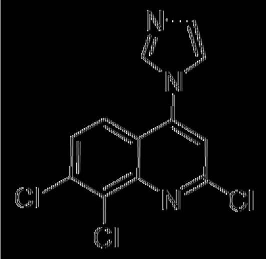
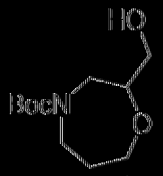
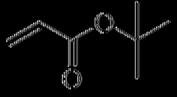
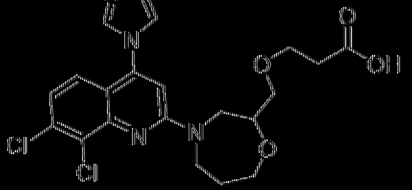
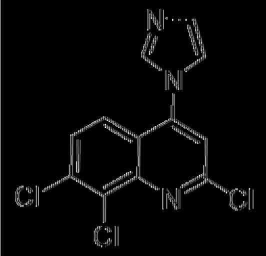
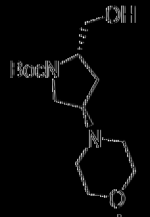
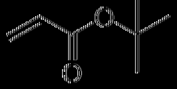
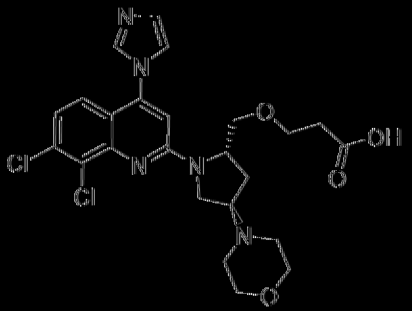
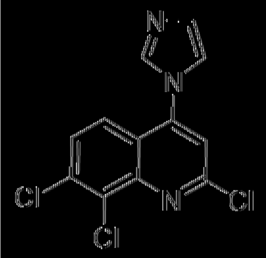
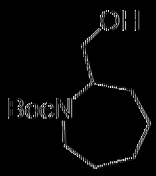
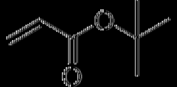
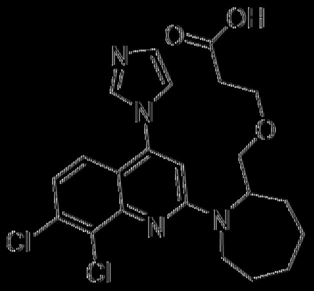
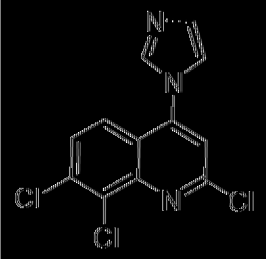
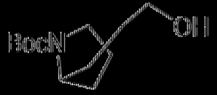
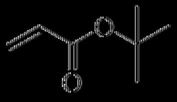
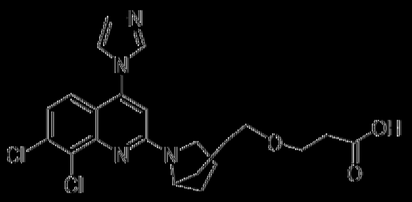
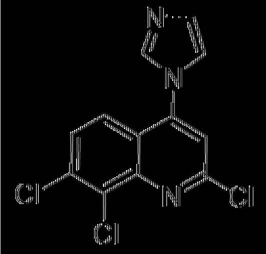
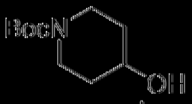
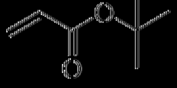
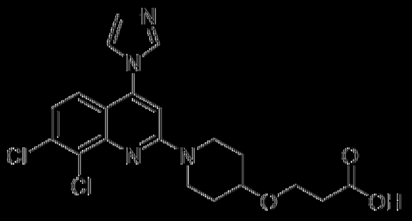
實例	起始材料		結構	MS [M+1]$^+$
I-816		 		475
I-796		 		507
I-815		 		489
I-818		 		479
I-858		 		423

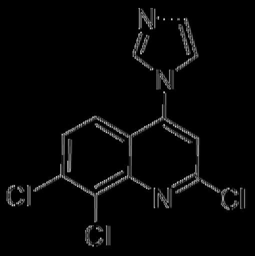
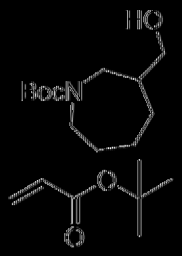
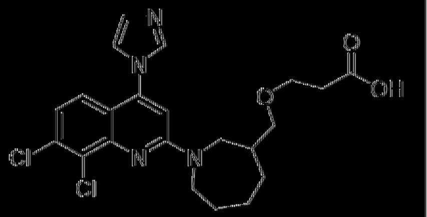
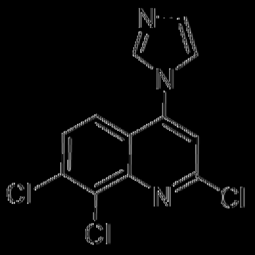
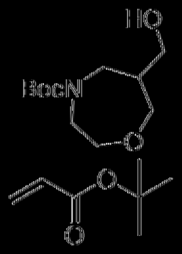
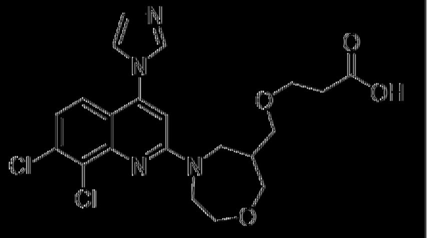
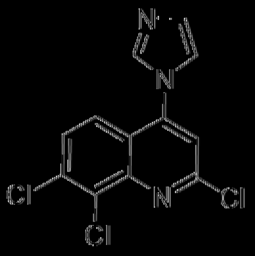
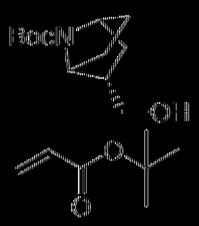
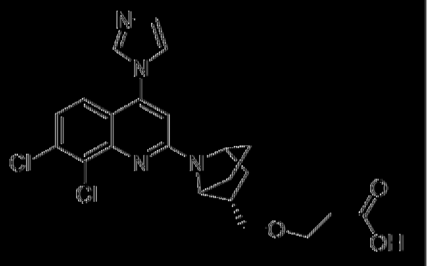
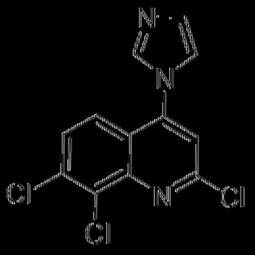
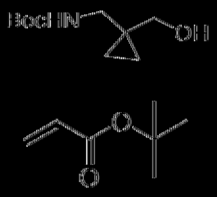
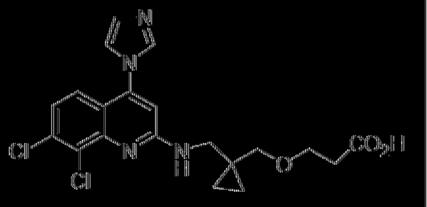
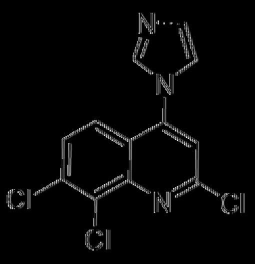
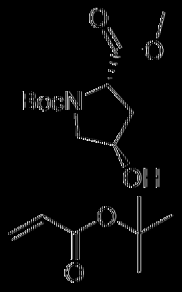
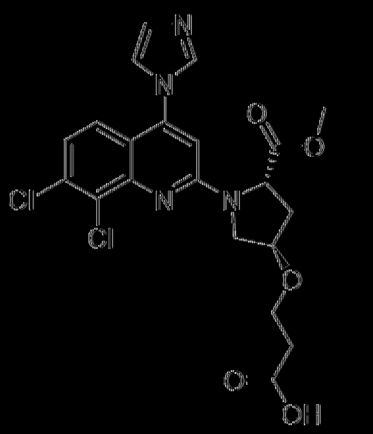
實例	起始材料		結構	MS [M+1]$^+$
I-859		 		397
I-860		 		431
I-861		 		445
I-862		 		479
I-856		 		431

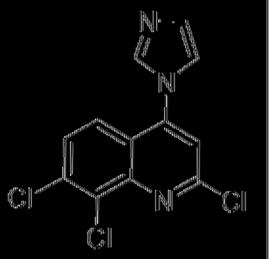
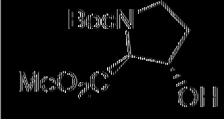
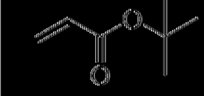
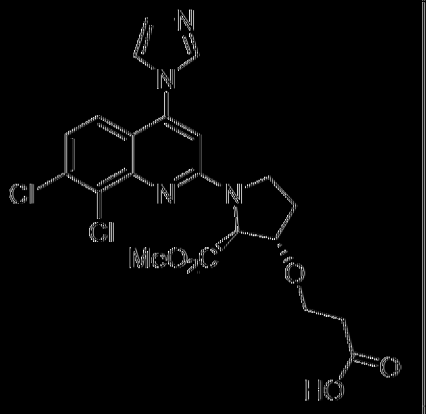
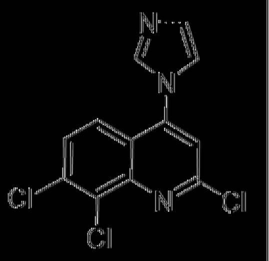
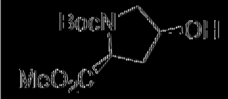
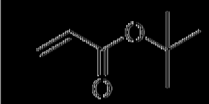
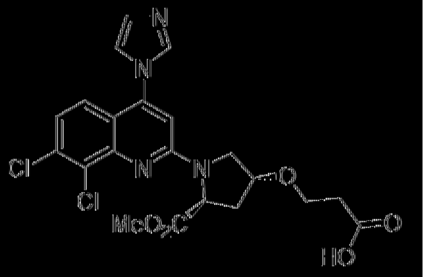
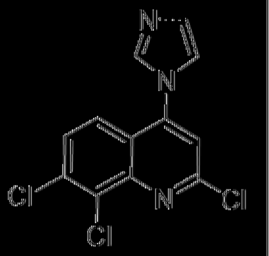
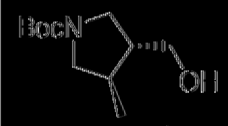
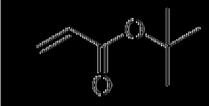
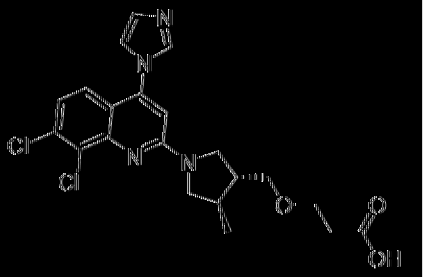
實例	起始材料		結構	MS [M+1]$^+$
I-857		 		513
I-875		 		431
I-876		 		469
I-793		 		503
I-794		 		463

實例	起始材料		結構	MS [M+1]+
I-795		 		449
I-827		 		369
I-800		 		447
I-801		 		447
I-802		 		511

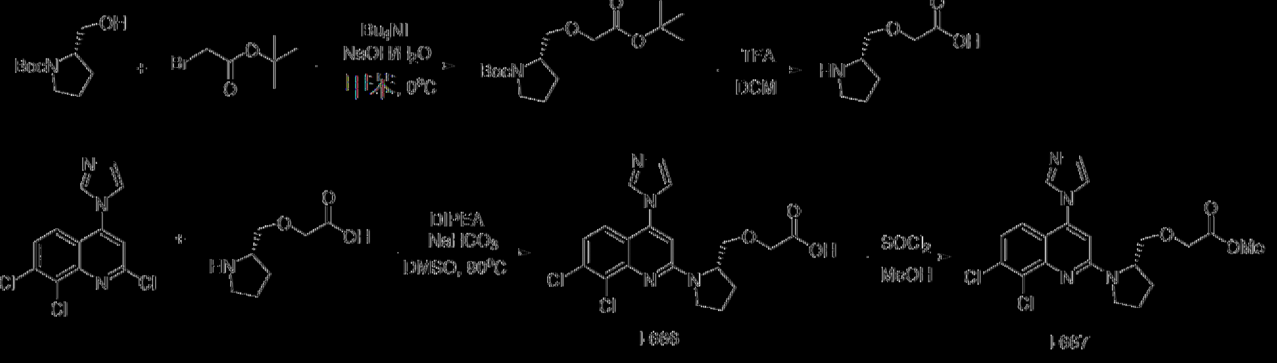
實例	起始材料		結構	MS $[M+1]^+$
I-803		 		517
I-797		 		465
I-798		 		465
I-853		 		435
I-855		 		435

實例	起始材料		結構	MS $[M+1]^+$
I-867		 		465
I-799		 		520
I-865		 		463
I-807		 		461
I-864		 		435

實例	起始材料		結構	MS [M+1]$^+$
I-866				463
I-868				465
I-811				461
I-829				435
I-869				479

實例	起始材料		結構	MS [M+1]+
I-870		 		479
I-871		 		479
I-814		 		449

實例103：合成(S)-2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙酸甲酯(I-667)及(S)-2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙酸(I-666)



【0772】 步驟1：(S)-2-((2-(三級丁氧基)-2-側氧基乙氧基)甲基)吡咯啶-1-甲酸三級丁酯. 向燒瓶中添加(S)-2-(羥基甲基)吡咯啶-1-甲酸三級丁酯(1.0 g，4.98 mmol，1.0 eq.)、Bu_4NI (920 mg，2.49 mmol，0.50

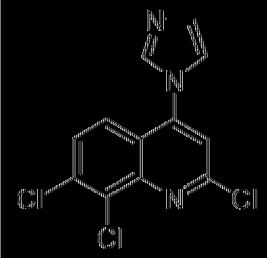
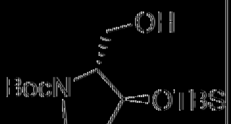
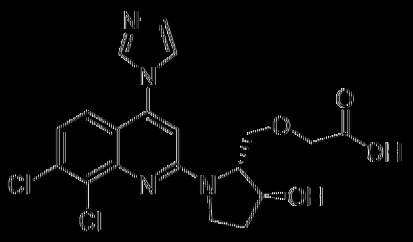
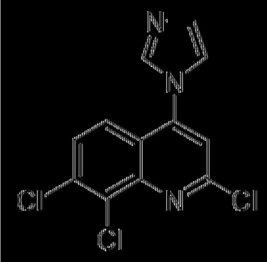
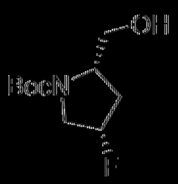
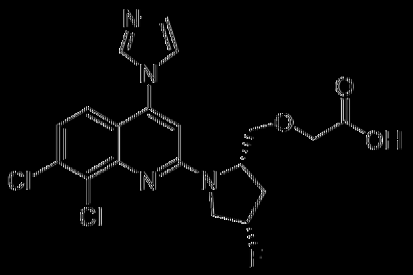
eq.)、甲苯(20 mL)及2-溴乙酸三級丁酯(1.94 g，9.95 mmol，2.0 eq.)。在冰浴中冷卻反應混合物。在0℃下，緩慢添加NaOH/H_2O溶液(30%，12 mL)。在0℃下將所得反應混合物攪拌3小時。接著，將混合物用乙酸乙酯(50 mL)稀釋，用H_2O (3 × 15 mL)、鹽水(15 mL)洗滌並經Na_2SO_4乾燥。濃縮後，將粗品藉由矽膠層析法純化，得到標題產物(1.14 g)。

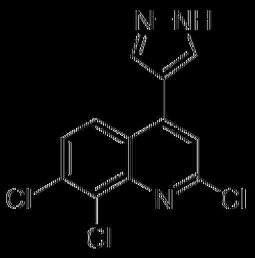
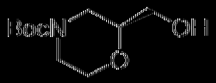
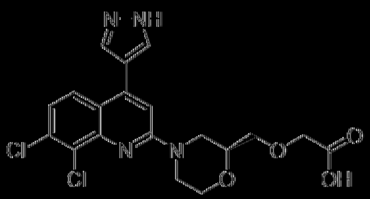
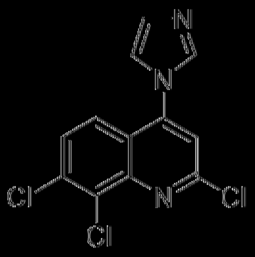
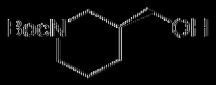
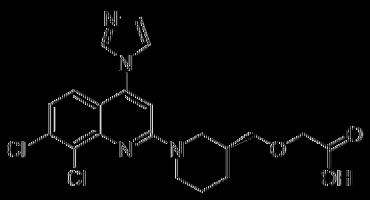
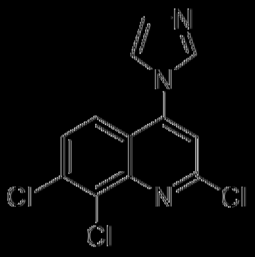
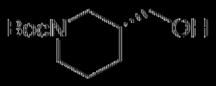
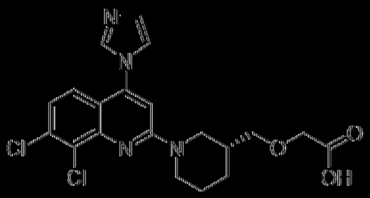
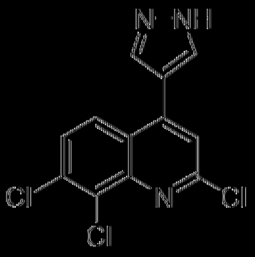
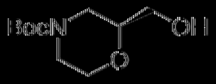
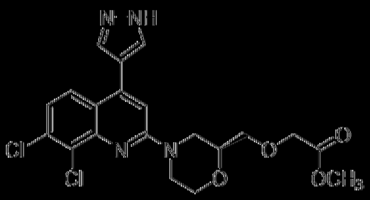
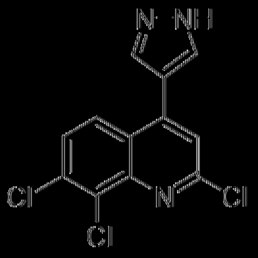
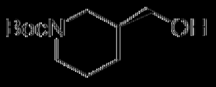
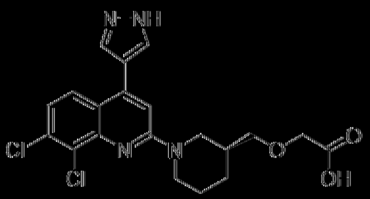
【0773】 步驟2：(S)-2-(吡咯啶-2-基甲氧基)乙酸. 在室溫下，將(S)-2-((2-(三級丁氧基)-2-側氧基乙氧基)甲基)吡咯啶-1-甲酸三級丁酯(300 mg，0.951 mmol)、TFA (1.5 mL)及DCM (1.5 mL)之混合物攪拌隔夜。濃縮混合物以移除所有揮發性物質。將粗品用於下一步驟中。

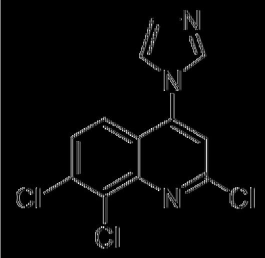
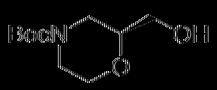
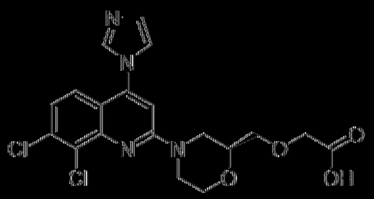
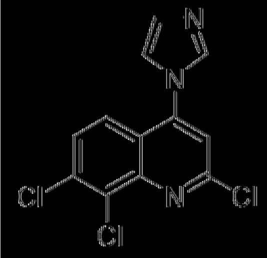
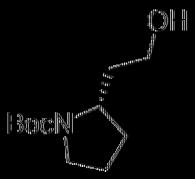
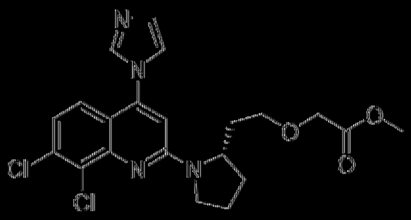
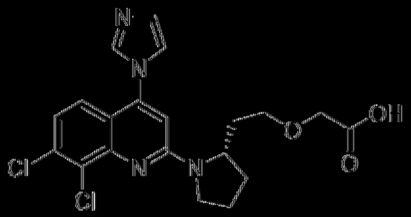
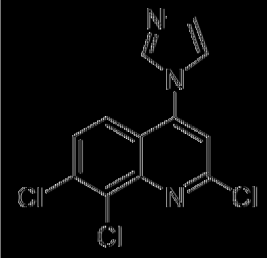
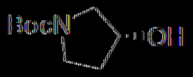
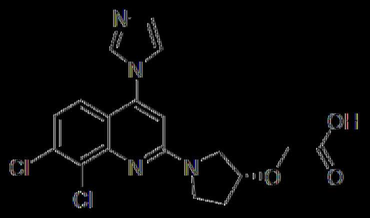
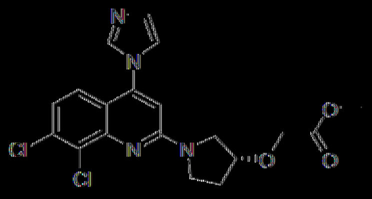
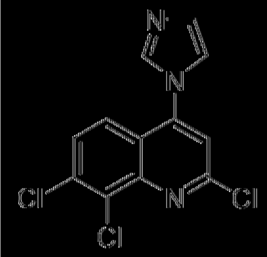
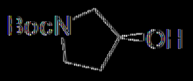
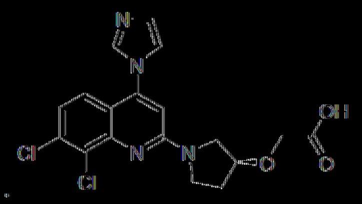
【0774】 步驟3：(S)-2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙酸(I-666). 該程序與合成I-665中之程序相同。MS: $[M+1]^+$ 421。

【0775】 步驟4：(S)-2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙酸甲酯. 該程序與合成I-665中之程序相同。MS: $[M+1]^+$ 435。

【0776】 以下化合物基本上藉由以上關於I-666所描述相同之方法製備。

實例	起始材料		結構	MS $[M+1]^+$
I-697				437
I-706				439

實例	起始材料		結構	MS $[M+1]^+$
E740				437
E743				435
E744				435
E751				451
E746				435

實例	起始材料		結構	MS [M+1]+
I-742				437
I-669				449
I-668				435
I-766				407
I-768				421
I-770				407

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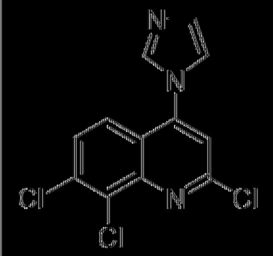
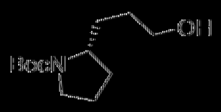
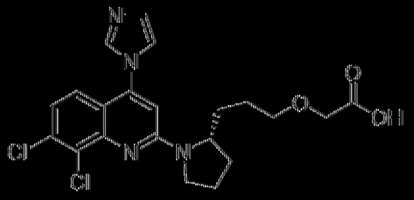
<tr><td>I-820</td><td></td><td></td><td></td><td>449</td></tr>
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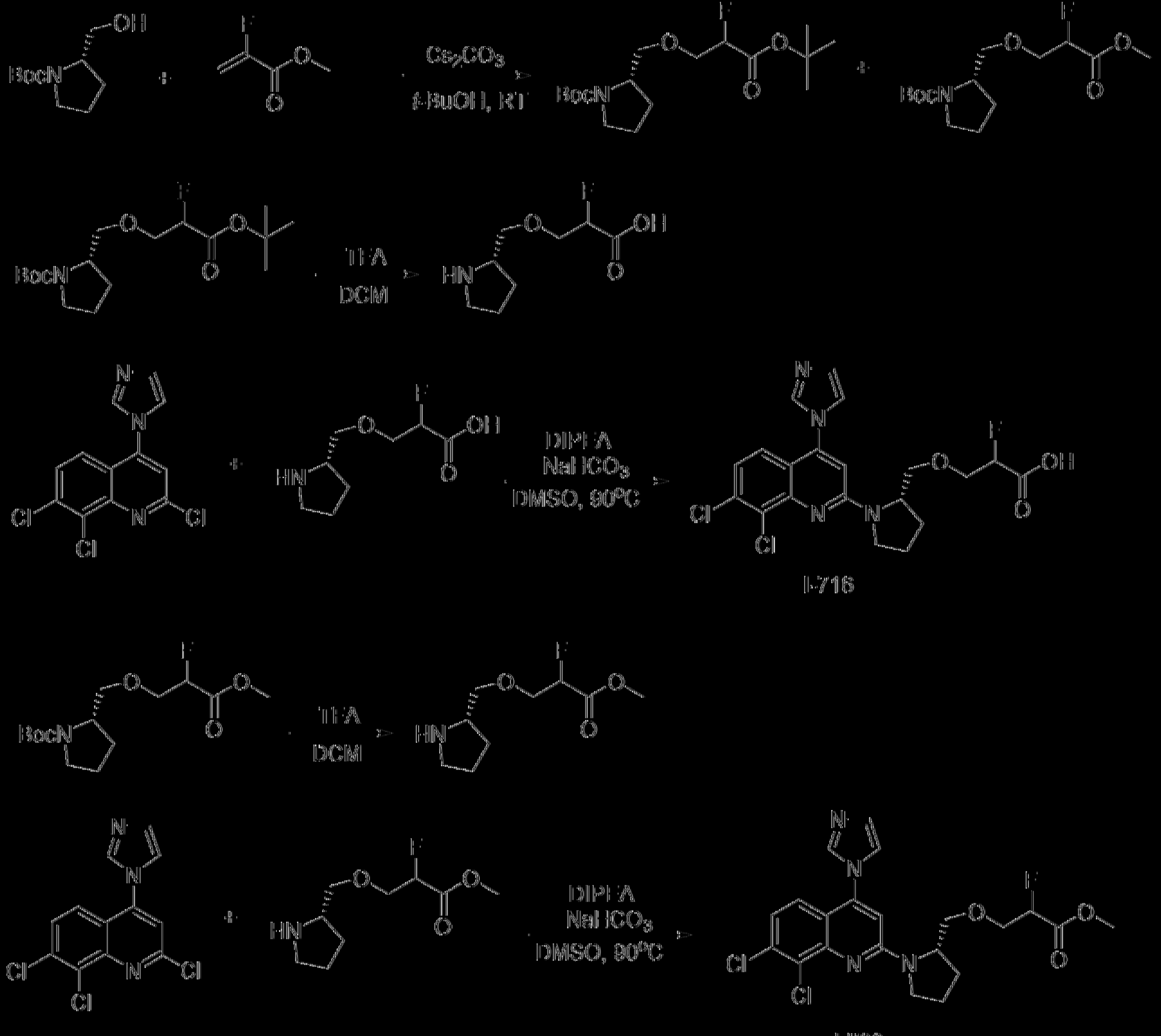
實例104：合成3-(((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)-2-氟丙酸(I-716)及3-(((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)-2-氟丙酸甲酯(I-700)



【0777】 步驟1：(2S)-2-((3-(三級丁氧基)-2-氟-3-側氧基丙氧基)甲

基)吡咯啶-1-甲酸三級丁酯及(2S)-2-((2-氟-3-甲氧基-3-側氧基丙氧基)甲基)吡咯啶-1-甲酸三級丁酯. 該程序與合成I-665中之程序相同。獲得兩種標題化合物。

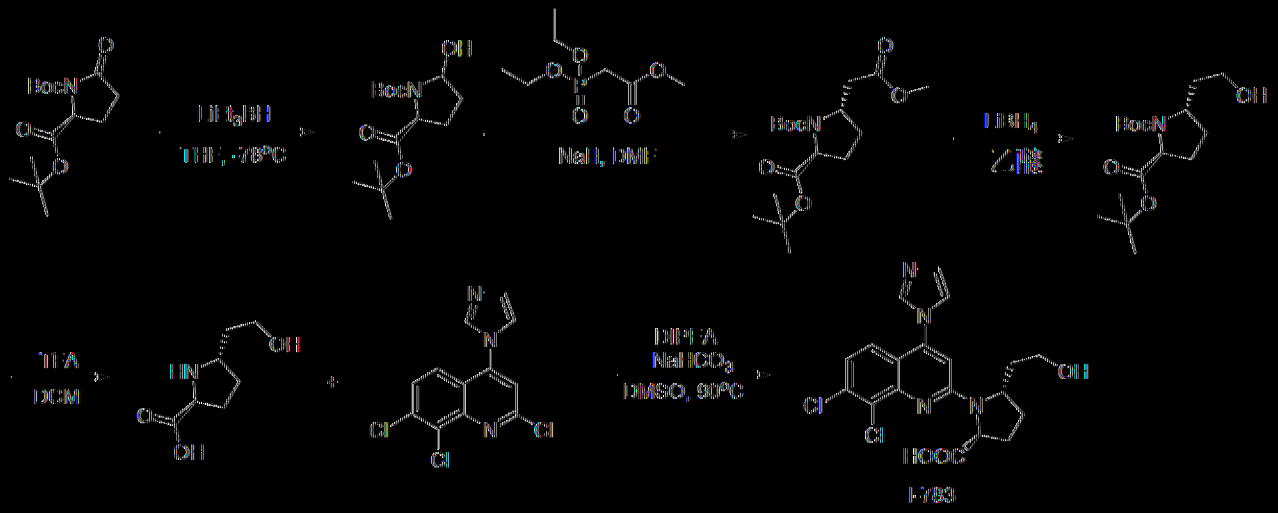
【0778】 步驟2：2-氟-3-(((S)-吡咯啶-2-基)甲氧基)丙酸. 該程序與合成I-665中之程序相同。

【0779】 步驟3：3-(((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)-2-氟丙酸. 該程序與合成I-665中之程序相同。(MS: [M+1]$^+$ 453)

【0780】 步驟4：2-氟-3-(((S)-吡咯啶-2-基)甲氧基)丙酸甲酯. 該程序與合成I-665中之程序相同。

【0781】 步驟5：3-(((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)-2-氟丙酸甲酯. 該程序與合成I-665中之程序相同。MS: [M+1]$^+$ 467。

實例105：合成(2S,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-羥基乙基)吡咯啶-2-甲酸(I-783)



【0782】 步驟1：(2S)-5-羥基吡咯啶-1,2-二甲酸二-三級丁酯. 向小瓶中添加(S)-5-側氧基吡咯啶-1,2-二甲酸二-三級丁酯(1.14 g，4.0

mmol，1.0 eq.)及無水THF (20 mL)。在乾冰/丙酮浴中將溶液冷卻20分鐘。接著，在-78℃下逐滴添加$LiEt_3BH$溶液(1 M，4.8 mL，4.8 mmol)。添加後，在-78℃下將所得反應混合物攪拌30分鐘。添加飽和$NaHCO_3$之水溶液(6 mL)以淬滅反應並將反應混合物緩慢升溫至0℃，隨後添加H_2O_2/H_2O (30%，0.050 mL)。在室溫下攪拌20分鐘後，將反應混合物濃縮，用H_2O (20 mL)稀釋，用DCM (3 × 20 mL)萃取並經Na_2SO_4乾燥。濃縮後，將粗品用於下一步驟中。

【0783】 步驟2：(2S,5S)-5-(2-甲氧基-2-側氧基乙基)吡咯啶-1,2-二甲酸二-三級丁酯. 向氫化鈉(60%，100 mg，2.5 mmol，1.2 eq.)於無水DMF (5 mL)中經攪拌之懸浮液中添加2-(二乙氧基磷氧基)乙酸甲酯(529 mg，2.5 mmol，1.2 eq.)。在室溫下將混合物攪拌1小時且接著添加步驟1中之粗品(602 mg，2.09 mmol)於DMF (5 mL)中之溶液。在室溫下攪拌反應隔夜，用飽和NH_4Cl水溶液淬滅，用乙酸乙酯(3 × 25 mL)萃取並經Na_2SO_4乾燥。濃縮後，將殘餘物藉由矽膠層析法純化，得到標題產物(150 mg)。

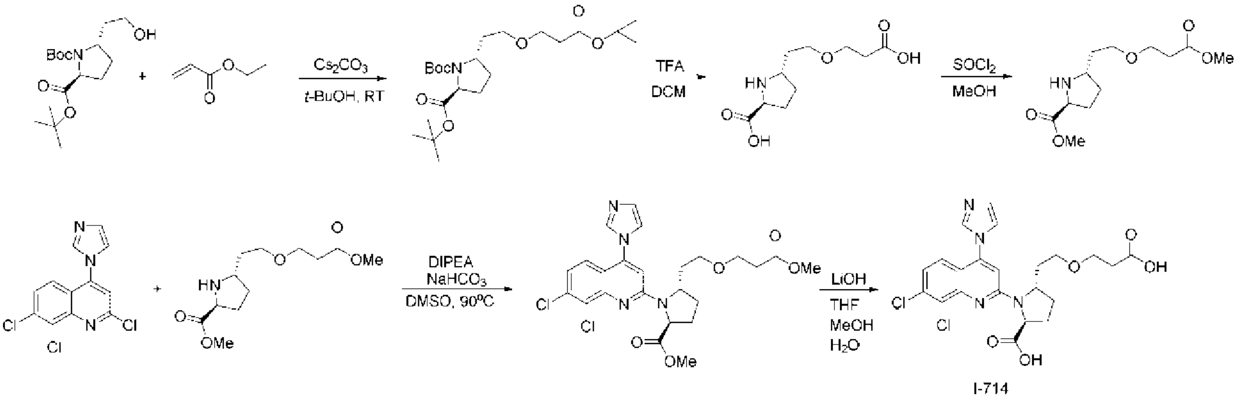
【0784】 步驟3：(2S,5S)-5-(2-羥基乙基)吡咯啶-1,2-二甲酸二-三級丁酯. 向小瓶中添加(2S,5S)-5-(2-甲氧基-2-側氧基乙基)吡咯啶-1,2-二甲酸二-三級丁酯(150 mg，0.437 mmol，1.0 eq.)及乙醚(2.5 mL)。接著，添加$LiBH_4$ (19 mg，0.874 mmol，2 eq.)並在室溫下將所得反應混合物攪拌隔夜。添加HOAc/H_2O (1 M，2 mL)及H_2O (10 mL)後，將反應混合物用乙酸乙酯(2 × 20 mL)萃取且經Na_2SO_4乾燥。濃縮後，將殘餘物藉由矽膠層析法純化，得到標題產物(103 mg)。

【0785】 步驟4：(2S,5S)-5-(2-羥基乙基)吡咯啶-2-甲酸. 該程序與

合成**I-665**中之程序相同。

【0786】 步驟5：(2S,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-羥基乙基)吡咯啶-2-甲酸. 該程序與以上關於**I-665**所描述之合成中的程序相同。MS: $[M+1]^+$ 421。

實例106：合成(2S,5S)-5-(2-(2-羧基乙氧基)乙基)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸(**I-714**)



【0787】 步驟1：(2S,5S)-5-(2-(3-(三級丁氧基)-3-側氧基丙氧基)乙基)吡咯啶-1,2-二甲酸二-三級丁酯. 該程序與以上關於**I-665**所描述之合成中的程序相同。

【0788】 步驟2：(2S,5S)-5-(2-(2-羧基乙氧基)乙基)吡咯啶-2-甲酸. 該程序與合成**I-665**中之程序相同。

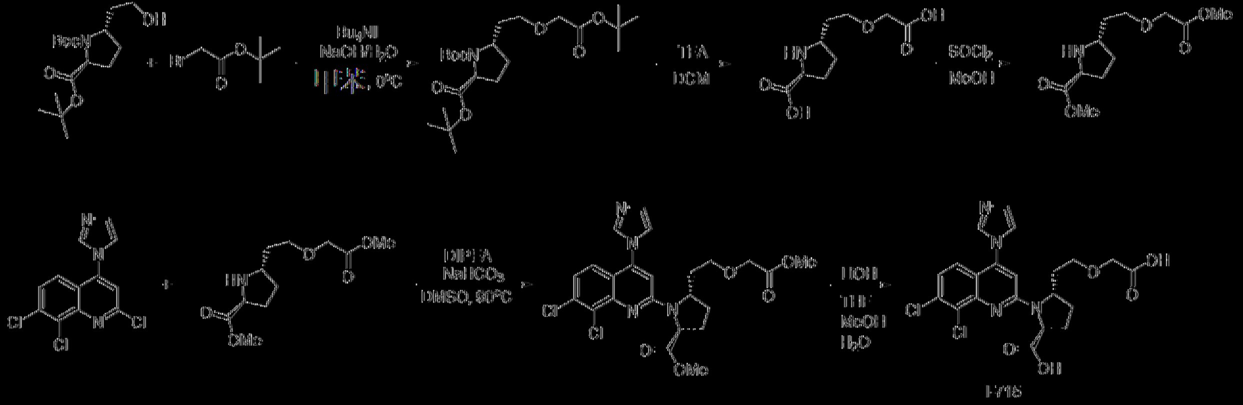
【0789】 步驟3：(2S,5S)-5-(2-(3-甲氧基-3-側氧基丙氧基)乙基)吡咯啶-2-甲酸甲酯. 該程序與以上關於**I-665**所描述之合成中的程序相同。

【0790】 步驟4：(2S,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-(3-甲氧基-3-側氧基丙氧基)乙基)吡咯啶-2-甲酸甲酯. 該程序與以上關於**I-665**所描述之合成中的程序相同。

【0791】 步驟5：(2S,5S)-5-(2-(2-羧基乙氧基)乙基)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸(**I-714**). 向小瓶中添加(2S,5S)-1-

(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-(3-甲氧基-3-側氧基丙氧基)乙基)吡咯啶-2-甲酸甲酯(3.7 mg，0.0071 mmol，1.0 eq.)、THF (0.5 mL)、MeOH (0.3 mL)及LiOH·H$_2$O溶液(1.5 mg，0.0355 mmol，5.0 eq.)/H$_2$O (0.1 mL)。在40℃下將所得溶液攪拌6小時並藉由HOAc水溶液(1 M，0.040 mL)酸化。濃縮後，獲得標題產物。MS: [M+1]$^+$ 493。

實例107：合成(2S,5S)-5-(2-(羧基甲氧基)乙基)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸(I-715)



[0792] 步驟1：(2S,5S)-5-(2-(2-(三級丁氧基)-2-側氧基乙氧基)乙基)吡咯啶-1,2-二甲酸二-三級丁酯. 該程序與以上關於I-667所描述之合成中的程序相同。

[0793] 步驟2：(2S,5S)-5-(2-(羧基甲氧基)乙基)吡咯啶-2-甲酸. 該程序與以上關於I-665所描述之合成中的程序相同。

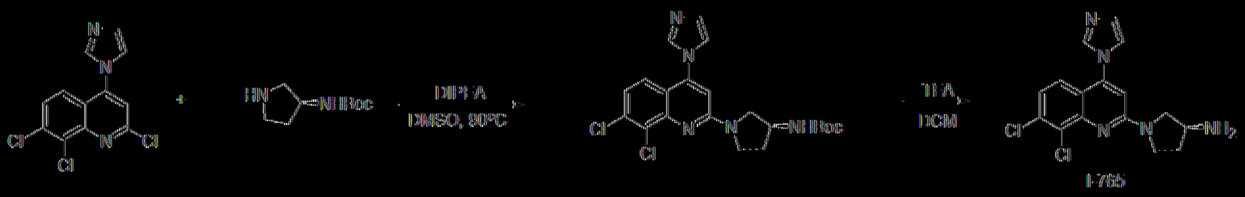
[0794] 步驟3：(2S,5S)-5-(2-(2-甲氧基-2-側氧基乙氧基)乙基)吡咯啶-2-甲酸甲酯. 該程序與以上關於I-665所描述之合成中的程序相同。

[0795] 步驟4：(2S,5S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(2-(2-甲氧基-2-側氧基乙氧基)乙基)吡咯啶-2-甲酸甲酯. 該程序與以上關於I-665所描述之合成中的程序相同。

[0796] 步驟5：(2S,5S)-5-(2-(羧基甲氧基)乙基)-1-(7,8-二氯-4-

(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸. 該程序與以上關於I-714所描述之合成中的程序相同。MS: $[M+1]^+$ 479。

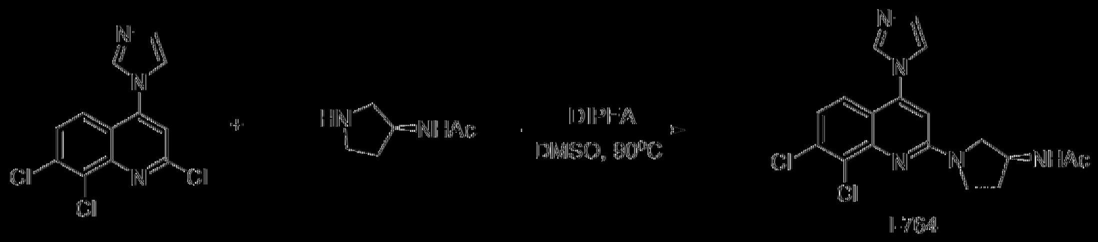
實例108：合成(S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-3-胺(I-765)



【0797】 步驟1：(S)-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-3-基)胺基甲酸三級丁酯. 該程序與合成I-665中之程序相同。

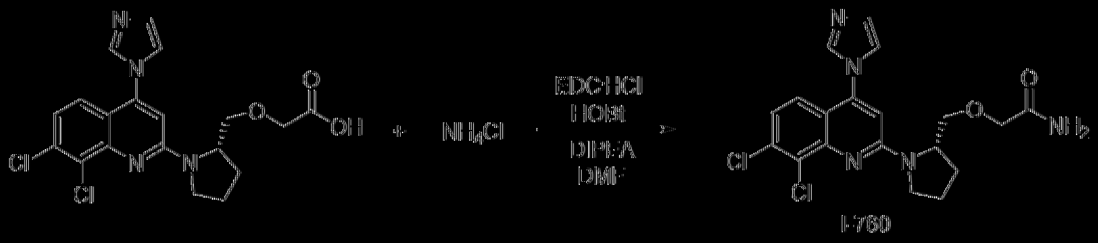
【0798】 步驟2：(S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-3-胺. 該程序與以上關於I-665所描述之合成中的程序相同。MS: $[M+1]^+$ 348。

實例109：合成(S)-N-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-3-基)乙醯胺(I-764)



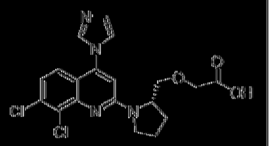
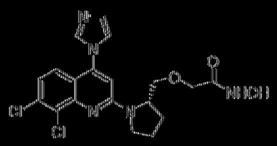
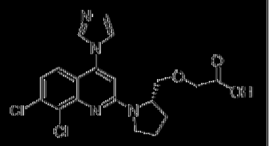
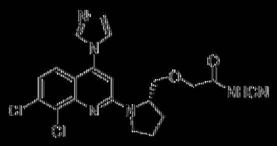
【0799】 用於製備I-764之程序與以上關於製備I-665所描述之程序相同。MS: $[M+1]^+$ 390。

實例110：合成(S)-2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙醯胺(I-760)

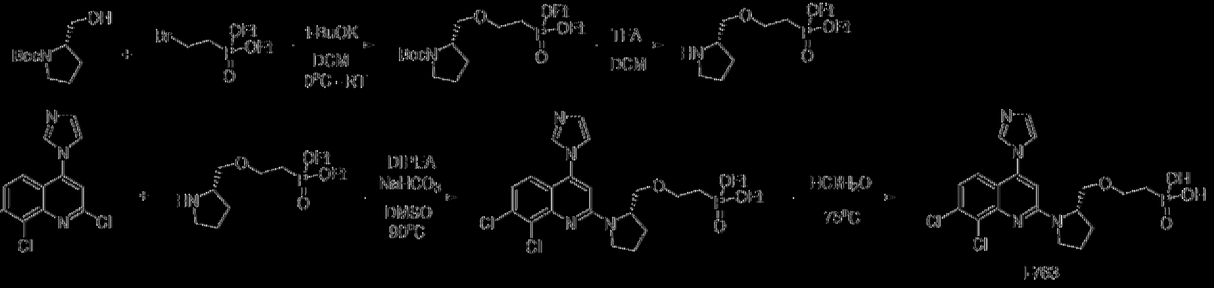


【0800】 向小瓶中添加(S)-2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙酸(30 mg，0.0712 mmol，1.0 eq.)、NH_4Cl (19 mg，0.356 mmol，5.0 eq.)、EDC·HCl (27 mg，0.142 mmol，2.0 eq.)、HOBt (9.6 mg，0.0712 mmol，1.0 eq)、DMF (0.5 mL)。在攪拌下，添加DIPEA (0.062 mL，0.356 mmol，5.0 eq.)並在室溫下將反應混合物攪拌隔夜。將反應混合物用乙酸乙酯(20 mL)稀釋，用H_2O (3 × 10 mL)、鹽水(10 mL)洗滌，經Na_2SO_4乾燥。濃縮後，將殘餘物藉由矽膠層析法純化，得到標題產物。MS: $[M+1]^+$ 420。

【0801】 以下化合物基本上藉由與以上關於I-760所描述相同之方法製備。

實例	起始材料		結構	MS $[M+1]^+$
I-761		$NH_2OH \cdot HCl$		436
I-762		NH_2CN		445

實例111：合成(S)-(2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙基)膦酸(I-763)



【0802】 步驟1：(S)-2-((2-(二乙氧基磷氧基)乙氧基)甲基)吡咯啶-1-甲酸三級丁酯. 向小瓶中添加t-BuOK (247 mg，2.2 mmol，2.2 eq.)及無

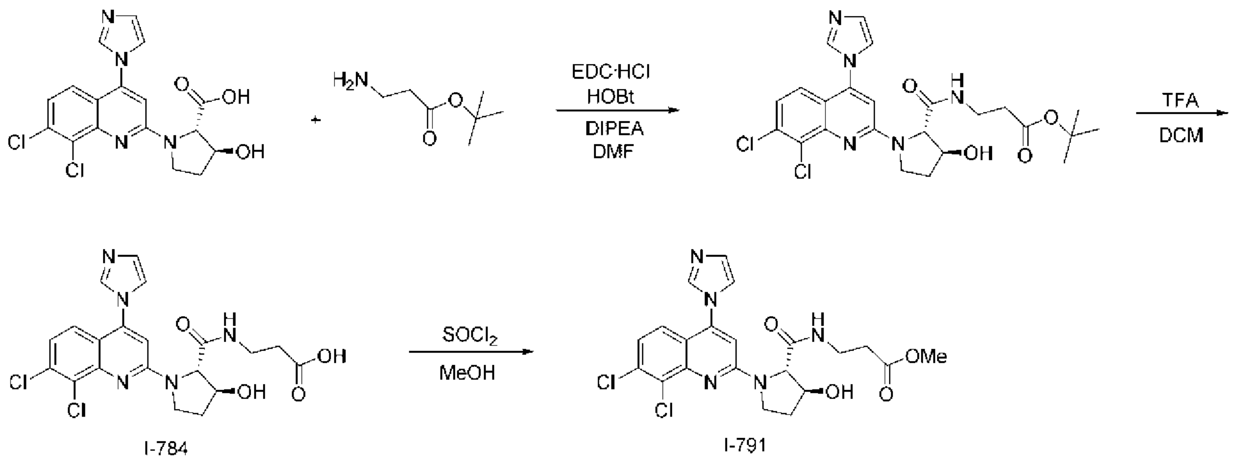
水DCM (2.0 mL)。在冰浴中將混合物冷卻20分鐘，隨後添加(S)-2-(羥基甲基)吡咯啶-1-甲酸三級丁酯(201 mg，1.0 mmol，1.0 eq.)。在0℃下將混合物攪拌30分鐘後，添加(2-溴乙基)膦酸二乙酯(294 mg，1.2 mmol，1.2 eq.)並在室溫下將所得反應混合物攪拌隔夜。藉由添加冰(5 g)淬滅後，將混合物用乙酸乙酯(30 mL)稀釋，用H_2O (2 × 10 mL)、鹽水(10 mL)洗滌並經Na_2SO_4乾燥。濃縮後，將殘餘物藉由矽膠層析法純化，得到標題產物(155 mg)。

【0803】 步驟2：(S)-(2-(吡咯啶-2-基甲氧基)乙基)膦酸二乙酯. 該程序與以上關於**I-665**所描述之合成中的程序相同。

【0804】 步驟3：(S)-(2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙基)膦酸二乙酯. 該程序與以上關於**I-665**所描述之合成中的程序相同。

【0805】 步驟4：(S)-(2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙基)膦酸. 在75℃下，將(S)-(2-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)乙基)膦酸二乙酯(9.5 mg，0.018 mmol)及HCl/H_2O溶液(37%，1.0 mL)之混合物攪拌兩天。濃縮混合物，得到標題產物。(MS: $[M+1]^+$ 471)

實例112：合成3-((2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲醯胺基)丙酸(**I-784**)及3-((2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲醯胺基)丙酸甲酯(**I-791**)

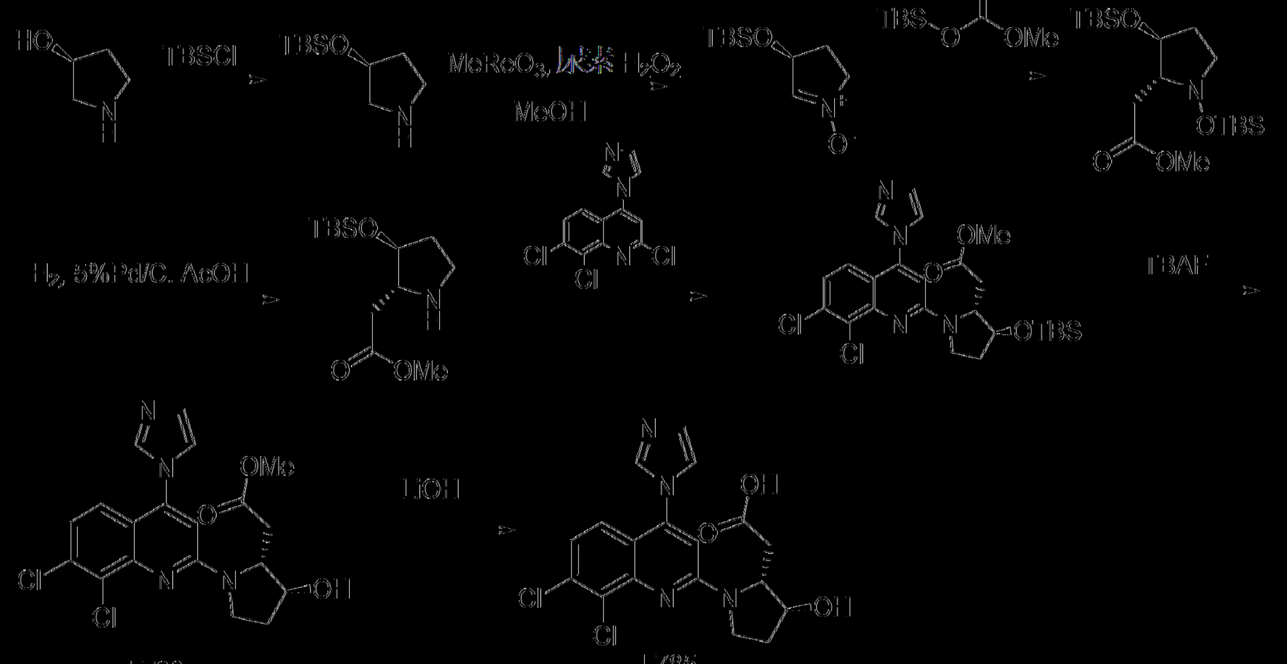


【0806】 步驟1：3-((2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲醯胺基)丙酸三級丁酯. 該程序與以上關於**I-760**所描述之合成中的程序相同。

【0807】 步驟2：3-((2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲醯胺基)丙酸. 該程序與以上關於**I-665**所描述之合成中的程序相同。MS: [M+1]$^+$ 464。

【0808】 步驟3：3-((2S,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-甲醯胺基)丙酸甲酯. 該程序與以上關於**I-665**所描述之合成中的程序相同。MS: [M+1]$^+$ 478。

實例113：合成2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙酸(**I-785**)及2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙酸甲酯(**I-786**)



E786

E785

【0809】 步驟1：(S)-4-((三級丁基二甲基矽基)氧基)-3,4-二氫-2H-吡咯1-氧化物. 用DCM (25 mL)中之TBSCl (3.37 g，22.3 mol)及咪唑(3.51 g)處理(S)-吡咯啶-3-醇(1.5 g，17.2 mmol)隔夜。用DCM (50 mL)稀釋後，用水(15 mL)、飽和$NaHCO_3$ (15 mL)及鹽水洗滌有機層。將分離之有機層經無水Na_2SO_4乾燥。減壓濃縮，得到所需粗(S)-3-((三級丁基二甲基矽基)氧基)吡咯啶(4.3 g)，將其不經進一步純化即用於下一步驟中。向(S)-3-((三級丁基二甲基矽基)氧基)吡咯啶(3.5 g)於MeOH (40 mL)中之冰-水冷卻之溶液中添加尿素-過氧化氫(4.94 g)。接著，經3小時將CH_3ReO_3 (21.8 mg)於MeOH (3 mL)中之溶液逐步添加至以上反應混合物中。在室溫下攪拌4小時後，用$Na_2S_2O_3$ (4 g，27 mmol)小心地淬滅反應混合物。用EtOAc (80 mL)進行水性處理後，將反應混合物藉由矽膠管柱層析法純化，得到兩種產物，極性較低之溶離份係標題產物(0.72 g)，用在DCM與EtOAc之間之梯度溶離。MASS: m/z: $[M+1]^+$: 216。

【0810】 步驟2：2-((2R,3S)-1,3-雙((三級丁基二甲基矽基)氧基)吡

咯啶-2-基)乙酸甲酯. 向(S)-4-((三級丁基二甲基矽基)氧基)-3,4-二氫-2H-吡咯1-氧化物(0.72 g)於DCM中之溶液中添加4 Å篩(1.1 g)及ZnI_2 (0.26 g)。在N_2下，用乾冰-丙酮浴冷卻懸浮之溶液後，經由注射器逐步添加三級丁基((1-甲氧基乙烯基)氧基)二甲基矽烷(640 mg)。將反應混合物攪拌隔夜，同時溫度緩慢升回至室溫。用DCM水性處理並減壓濃縮後，將所得混合物藉由矽膠管柱層析法，用5% EtOAc/己烷溶離來純化，得到呈無色固體狀之標題產物(245 mg)。MASS: m/z: $[M+1]^+$: 404。

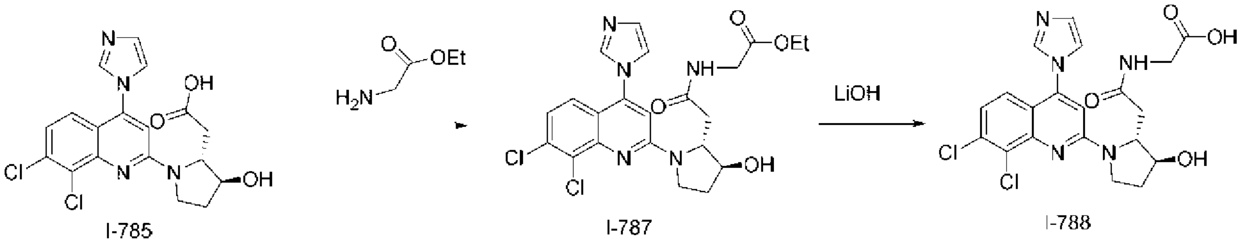
【0811】 步驟3：2-((2R,3S)-3-((三級丁基二甲基矽基)氧基)吡咯啶-2-基)乙酸甲酯. 用氫氣將2-((2R,3S)-1,3-雙((三級丁基二甲基矽基)氧基)吡咯啶-2-基)乙酸甲酯(109 mg)及含5% Pd/C之AcOH (3.5 mL)之溶液脫氣(真空/吹掃)三次並在氫氣下攪拌隔夜。過濾後，用EtOAc沖洗，並減壓濃縮，將所得混合物溶解於EtOAc (15 mL)中。將有機層用飽和$NaHCO_3$、鹽水洗滌並經無水Na_2SO_4乾燥。減壓濃縮，得到標題產物(I-786-4，76.8 mg)。MASS: m/z: $[M+1]^+$: 274。

【0812】 步驟4：2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙酸酯(**I-786**). 向2-((2R,3S)-3-((三級丁基二甲基矽基)氧基)吡咯啶-2-基)乙酸甲酯(76.8 mg)及DIPEA (0.12 mL)於DMSO (0.4 mL)中之溶液中添加2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(50 mg)。在90℃下將所得混合物攪拌3小時並用EtOAc (15 mL)稀釋。用1 M TBAF之THF溶液(0.4 mL)處理有機溶液30分鐘。將有機溶液用水及鹽水洗滌，接著經無水Na_2SO_4乾燥。減壓濃縮並藉由矽膠管柱層析法純化，得到呈淺棕色固體狀之標題產物(**I-786**，18 mg)。MASS: m/z: $[M+1]^+$: 421。

【0813】 步驟5：2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-

基)-3-羥基吡咯啶-2-基)乙酸(**I-785**). 向**I-786** (44.8 mg)於MeOH (0.8 mL)、THF (0.6 mL)及水(0.2 mL)中之溶液中添加LiOH.H_2O (18 mg)。在室溫下將溶液攪拌3小時。減壓移除有機溶劑後，將所得漿液與AcOH (0.025 mL)及水(1.5 mL)混合，得到懸浮溶液。經由離心機分離固體並用水(0.5 mL × 2)沖洗。將濕餅凍乾，得到呈棕色固體狀之標題產物(30 mg)。MASS: m/z: $[M+1]^+$: 407。

實例114：合成(2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙醯基)甘胺酸乙酯(**I-787**)及(2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙醯基)甘胺酸(**I-788**)

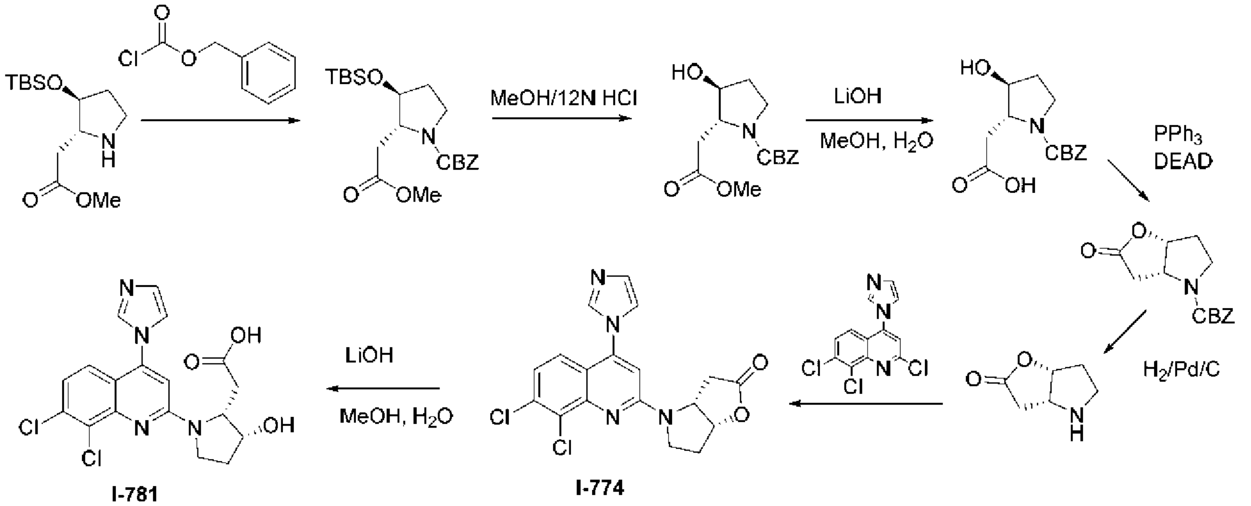


【0814】 步驟1：(2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙醯基)甘胺酸乙酯(**I-787**). 向2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙酸(**I-785**，20 mg)於DMF (0.7 mL)中之溶液中添加EDC HCl (19 mg)、HOBt (13 mg)及TEA (20 mg)。在室溫下將所得溶液攪拌24小時。用EtOAc (15 mL)稀釋後，將有機層用飽和$NaHCO_3$、鹽水洗滌且經無水Na_2SO_4乾燥。減壓濃縮並進行矽膠管柱層析，用在己烷與EtOAc之間之梯度溶離，得到標題產物(16 mg)。MASS: m/z: $[M+1]^+$: 492。

【0815】 步驟2：(2-((2R,3S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙醯基)甘胺酸(**I-788**). 向**I-787** (8 mg)於MeOH (0.6 mL)及水(0.2 mL)中之溶液中添加LiOH.H_2O (8 mg)。在室溫下將所

得溶液攪拌2小時。移除MeOH並用1M HOAc (0.08 mL)酸化水性部分後，經由離心機分離所形成之固體並凍乾，得到呈棕色固體狀之標題產物(6 mg)。MASS: m/z: [M+1]$^+$: 464。

實例115：合成(3aR,6aR)-4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)六氫-2H-呋喃并[3,2-b]吡咯-2-酮(**I-774**)及2-((2R,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙酸(**I-781**)



【0816】 步驟1：(2R,3S)-3-((三級丁基二甲基矽基)氧基)-2-(2-甲氧基-2-側氧基乙基)吡咯啶-1-甲酸苯甲酯. 向2-((2R,3S)-3-((三級丁基二甲基矽基)氧基)吡咯啶-2-基)乙酸甲酯(280 mg)於EtOAc (8 mL)及水(3 mL)中之溶液中添加氯甲酸苯甲酯(CBZ-Cl，0.2 mL)及K_2CO_3 (200 mg)。在室溫下將反應混合物攪拌4小時。用EtOAc (25 mL)稀釋反應混合物後，將有機層用水及鹽水洗滌，接著經無水Na_2SO_4乾燥。移除有機溶劑，得到呈油狀之標題產物(300 mg)。MASS: m/z: [M+1]$^+$: 408。

【0817】 步驟2：(2R,3S)-3-羥基-2-(2-甲氧基-2-側氧基乙基)吡咯啶-1-甲酸苯甲酯. 向(2R,3S)-3-((三級丁基二甲基矽基)氧基)-2-(2-甲氧基-2-側氧基乙基)吡咯啶-1-甲酸苯甲酯(300 mg)於MeOH (5 mL)中之溶液中添加水(0.2 mL)及濃HCl (0.2 mL)。將所得溶液攪拌隔夜後，用EtOAc

(40 mL)對其進行稀釋。將有機層用水及鹽水洗滌，接著經無水Na_2SO_4乾燥。移除有機溶劑並藉由矽膠管柱純化，得到呈油狀之標題產物(143 mg)。MASS: m/z: $[M+1]^+$ 294。

【0818】 步驟3：2-((2R,3S)-1-((苯甲氧基)羰基)-3-羥基吡咯啶-2-基)乙酸. 向(2R,3S)-3-羥基-2-(2-甲氧基-2-側氧基乙基)吡咯啶-1-甲酸苯甲酯(143 mg)於MeOH (5 mL)及水(2 mL)中之溶液中添加$LiOH.H_2O$ (62 mg)。將所得溶液攪拌3小時後，添加12 M HCl (0.014 mL)以將pH值調至2。用EtOAc (15 mL × 3)萃取反應混合物後，用鹽水洗滌合併之有機層且經無水Na_2SO_4乾燥。移除有機溶劑，得到呈無色固體狀之標題產物(98 mg)。MASS: m/z: $[M+1]^+$ 280。

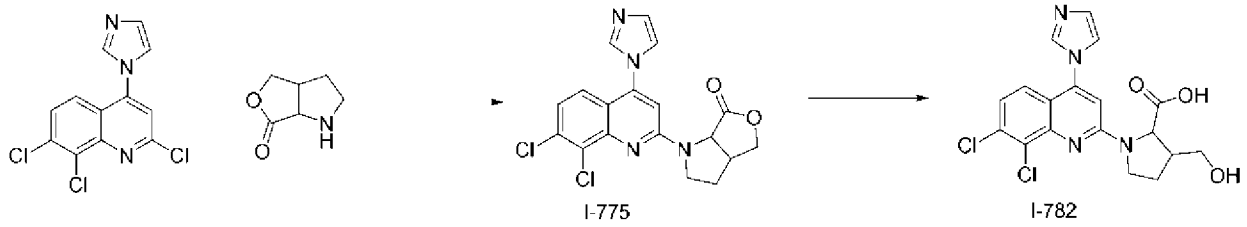
【0819】 步驟4：(3aR,6aR)-2-側氧基六氫-4H-呋喃并[3,2-b]吡咯-4-甲酸苯甲酯. 向2-((2R,3S)-1-((苯甲氧基)羰基)-3-羥基吡咯啶-2-基)乙酸(97 mg)於THF (8 mL)中之溶液中添加PPh_3 (137 mg)及DEAD (0.24 mL，40wt%於甲苯中)。攪拌4小時後，用EtOAc稀釋反應混合物。將有機層用水及鹽水洗滌，接著經無水Na_2SO_4乾燥。移除有機溶劑後，將殘餘物藉由矽膠管柱，用EtOAc/Hex溶離來純化，得到標題產物(75 mg)。

【0820】 步驟5：(3aR,6aR)-六氫-2H-呋喃并[3,2-b]吡咯-2-酮. 向(3aR,6aR)-2-側氧基六氫-4H-呋喃并[3,2-b]吡咯-4-甲酸苯甲酯(75 mg)於MeOH (4 mL)中之溶液中添加AcOH (0.1 mL)及5% Pd/C (20 mg)。用氫氣將所得懸浮液脫氣(真空-吹掃)三次並在氫氣下攪拌隔夜。過濾並濃縮，得到標題產物。MASS: m/z: $[M+1]^+$ 128。

【0821】 步驟6：(3aR,6aR)-4-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)六氫-2H-呋喃并[3,2-b]吡咯-2-酮(**I-774**)及2-((2R,3R)-1-(7,8-二氯-4-

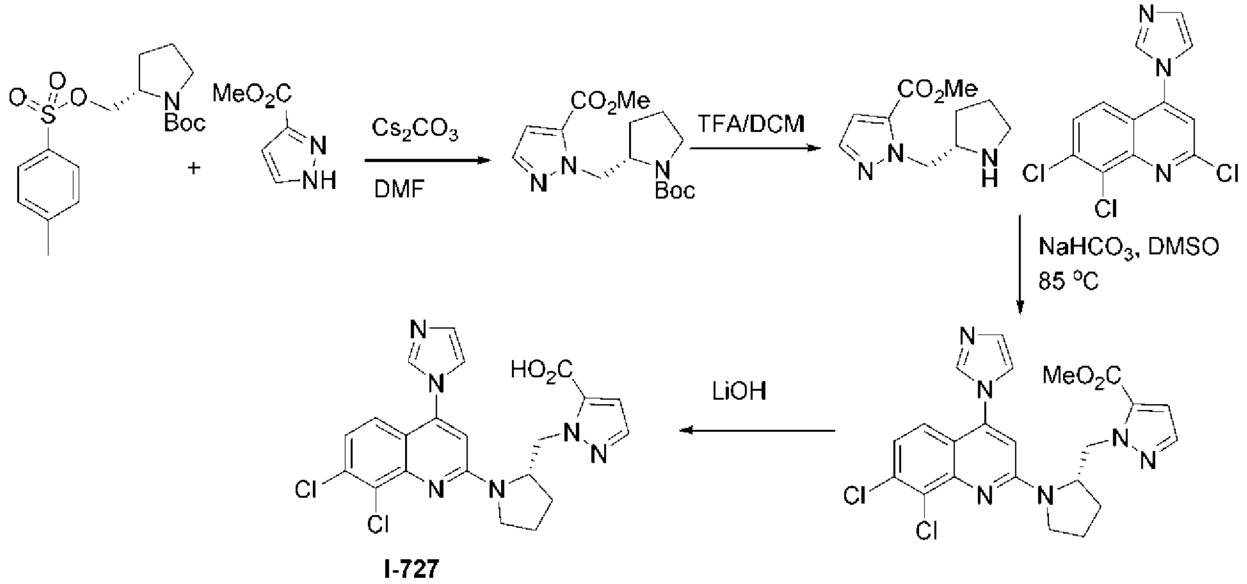
(1H-咪唑-1-基)喹啉-2-基)-3-羥基吡咯啶-2-基)乙酸(**I-781**). 遵循**I-786**及**I-785**之製備程序的最後兩個步驟，製備兩種標題化合物。**I-774**，MASS: m/z: $[M+1]^+$ 389。**I-781**，MASS: m/z: $[M+1]^+$ 407。

實例116：合成1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)六氫-6H-呋喃并[3,4-b]吡咯-6-酮(**I-775**)及1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(羥基甲基)吡咯啶-2-甲酸(**I-782**)



【0822】 遵循**I-786**及**I-785**之製備程序的最後兩個步驟，由六氫-6H-呋喃并[3,4-b]吡咯-6-酮製備**I-775**並在水解後，得到**I-782**。**I-775**，MASS: m/z: $[M+1]^+$ 389。**I-782**，MASS: m/z: $[M+1]^+$ 407。

實例117：合成(S)-1-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)-1H-吡唑-5-甲酸(**I-727**)

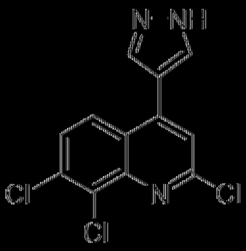
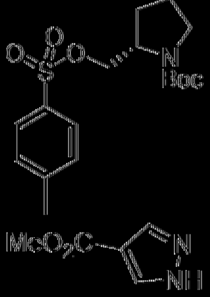
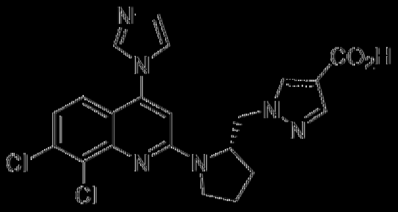
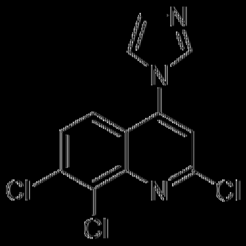
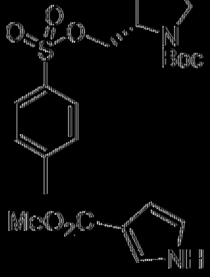
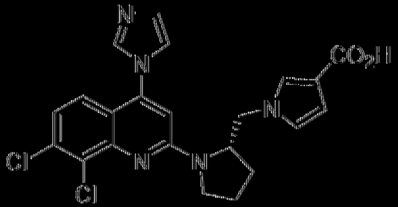
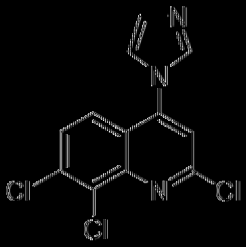
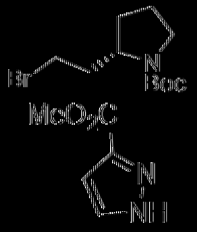
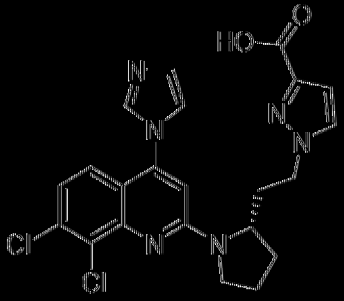
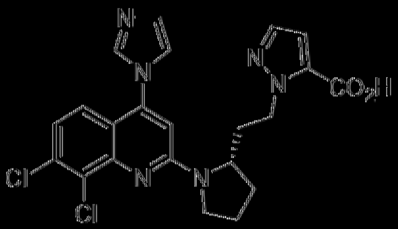
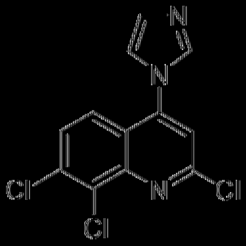
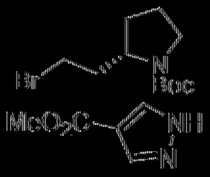
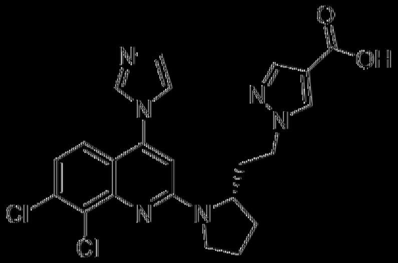


【0823】 步驟1：(S)-1-((1-(三級丁氧基羰基)吡咯啶-2-基)甲基)-1H-吡唑-5-甲酸甲酯. 向(S)-2-((甲苯磺醯氧基)甲基)吡咯啶-1-甲酸三級丁

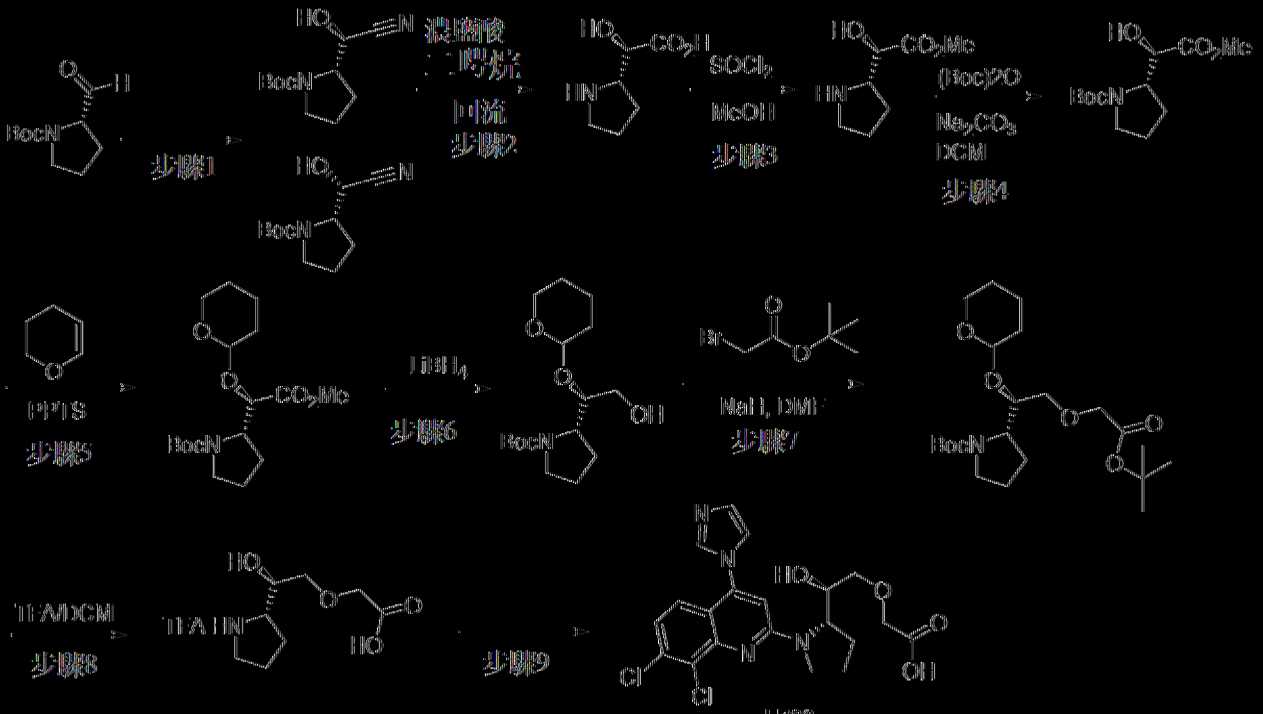
酯(274 mg)於DMF (1.5 mL)中之溶液中添加1H-吡唑-3-甲酸甲酯(145.8 mg)及Cs_2CO_3 (377 mg)。將所得混合物攪拌隔夜後，用EtOAC對其進行稀釋。將有機層用水及鹽水洗滌，經無水Na_2SO_4乾燥。減壓移除溶劑並進行矽膠管柱純化，用在己烷與EtOAc/DCM (1:3)之間之梯度溶離，得到標題產物。

【0824】 步驟2：(S)-1-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)-1H-吡唑-5-甲酸(**I-727**). 標題產物係藉由用TFA/DCM使(S)-1-((1-(三級丁氧基羰基)吡咯啶-2-基)甲基)-1H-吡唑-5-甲酸甲酯脫保護，使其與2,7,8-三氯-4-(1H-咪唑-1-基)喹啉偶合並用LiOH水解來製備，該等步驟與以上關於製備**I-664**所描述的最後三個步驟相同。MASS: m/z: $[M+1]^+$ 457。

【0825】 以下化合物基本上藉由以上關於**I-727**所描述相同之方法製備。

實例	起始材料		結構	MS [M+1]+
E728				457
E732				456
E731				471
E729				471
E730				471

實例118：合成2-((R)-2-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基乙氧基)乙酸(I-726)



I-726

【0826】 步驟1：(S)-2-((R)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯及(S)-2-((S)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯. 向(S)-2-甲醯基吡咯啶-1-甲酸三級丁酯(1.92 g)於DCM (20 mL)中之溶液中添加TEA (2 mL)及丙酮氰醇(0.98 g)。在室溫下將所得溶液攪拌40小時。減壓移除DCM後，用EtOAc (30 mL)稀釋殘餘物。將有機層用稀HCl (0.5 N)及鹽水洗滌，接著經無水Na_2SO_4乾燥。將反應混合物用矽膠管柱，用己烷及Hex/EtOAc/DCM (3/1/6)梯度溶離來純化，得到呈油狀之(S)-2-((R)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯(1.4 g)及呈固體狀之(S)-2-((S)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯(0.98 g)。

【0827】 步驟2-4：(S)-2-((R)-1-羥基-2-甲氧基-2-側氧基乙基)吡咯啶-1-甲酸三級丁酯. 向(S)-2-((R)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯(0.68 g)於二噁烷(8 mL)中之溶液中添加濃HCl (8 mL)。在回流下將所得

溶液加熱4小時。將溶液減壓濃縮至乾。將殘餘物溶解於MeOH (10 mL)中並用$SOCl_2$ (0.1 mL)處理隔夜。減壓移除MeOH後，在$(Boc)_2O$ (1.29 g)及Na_2CO_3 (954 mg)存在下將殘餘物懸浮於DCM (10 mL)及水(4 mL)中隔夜。添加DCM (15 mL)後，將合併之DCM層分離並用鹽水洗滌，接著經無水Na_2SO_4乾燥。進行矽膠管柱純化，得到呈油狀之標題化合物(0.64 g)。MASS: m/z: $[M+Na]^+$ 282。

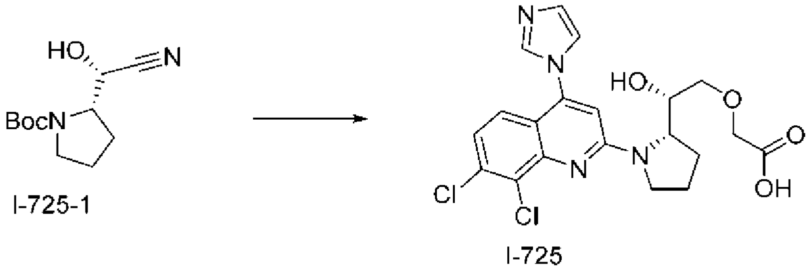
【0828】 步驟5-6：(2S)-2-((1R)-2-羥基-1-((四氫-2H-哌喃-2-基)氧基)乙基)吡咯啶-1-甲酸三級丁酯. 向(S)-2-((R)-1-羥基-2-甲氧基-2-側氧基乙基)吡咯啶-1-甲酸三級丁酯(440 mg)於DCM (6 mL)中之溶液中添加3,4-二氫-2H-哌喃(336 mg)及PPTS (100 mg)。將溶液攪拌6小時。減壓移除溶劑後，將殘餘物懸浮於THF (6 mL)中並用$LiBH_4$ (96 mg)處理。將所得懸浮液攪拌隔夜後，藉由添加水緩慢將其淬滅。用EtOAc (25 mL)水性處理後，將分離之有機層用鹽水洗滌且經無水Na_2SO_4乾燥。進行矽膠管柱純化，得到標題產物(224 mg)。MASS: m/z: $[M+Na]^+$ 338。

【0829】 步驟7：(2S)-2-((1R)-2-(2-(三級丁氧基)-2-側氧基乙氧基)-1-((四氫-2H-哌喃-2-基)氧基)乙基)吡咯啶-1-甲酸三級丁酯. 向(2S)-2-((1R)-2-羥基-1-((四氫-2H-哌喃-2-基)氧基)乙基)吡咯啶-1-甲酸三級丁酯(101 mg)於DMF (3 mL)中之冰冷的溶液中緩慢添加NaH (40 mg，60% wt於礦物油中之懸浮液)。在0℃下將所得溶液攪拌20分鐘後，添加2-溴乙酸三級丁酯(187 mg)。在室溫下將反應混合物攪拌隔夜且接著，用水(0.5 mL)淬滅。用EtOAc水性處理並進行矽膠管柱純化，得到呈油狀之標題產物(86 mg)。MASS: m/z: $[M+Na]^+$ 452。

【0830】 步驟8-9：2-((R)-2-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹

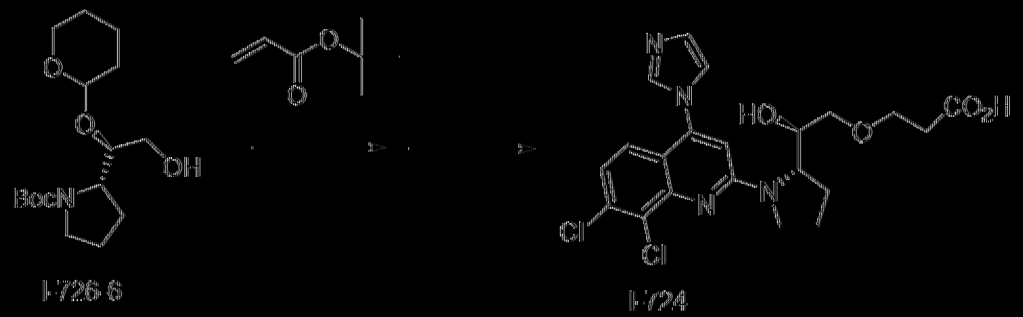
啉-2-基)吡咯啶-2-基)-2-羥基乙氧基)乙酸(**I-726**). 用TFA (0.2 mL)處理於DCM (0.2 mL)中之(2S)-2-((1R)-2-(2-(三級丁氧基)-2-側氧基乙氧基)-1-((四氫-2H-哌喃-2-基)氧基)乙基)吡咯啶-1-甲酸三級丁酯(86 mg)隔夜後，減壓移除有機溶劑。再與甲苯/ACN共蒸發有助於移除過量的TFA。將DMSO (0.4 mL)中之殘餘物與2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(48 mg)及Na_2CO_3 (32 mg)混合物。在90℃下，將所得懸浮液加熱5小時。用AcOH (0.03 mL)處理反應混合物並使其懸浮於水中。用EtOAc進行水性處理並藉由在EtOAc與DCM/MeOH/AcOH (9/1/0.1)之間梯度溶離進行矽膠管柱純化，得到呈棕色固體狀之所需產物(14.2 mg)。MASS: m/z: $[M+1]^+$: 451。

實例119：合成2-((S)-2-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基乙氧基)乙酸(**I-725**)



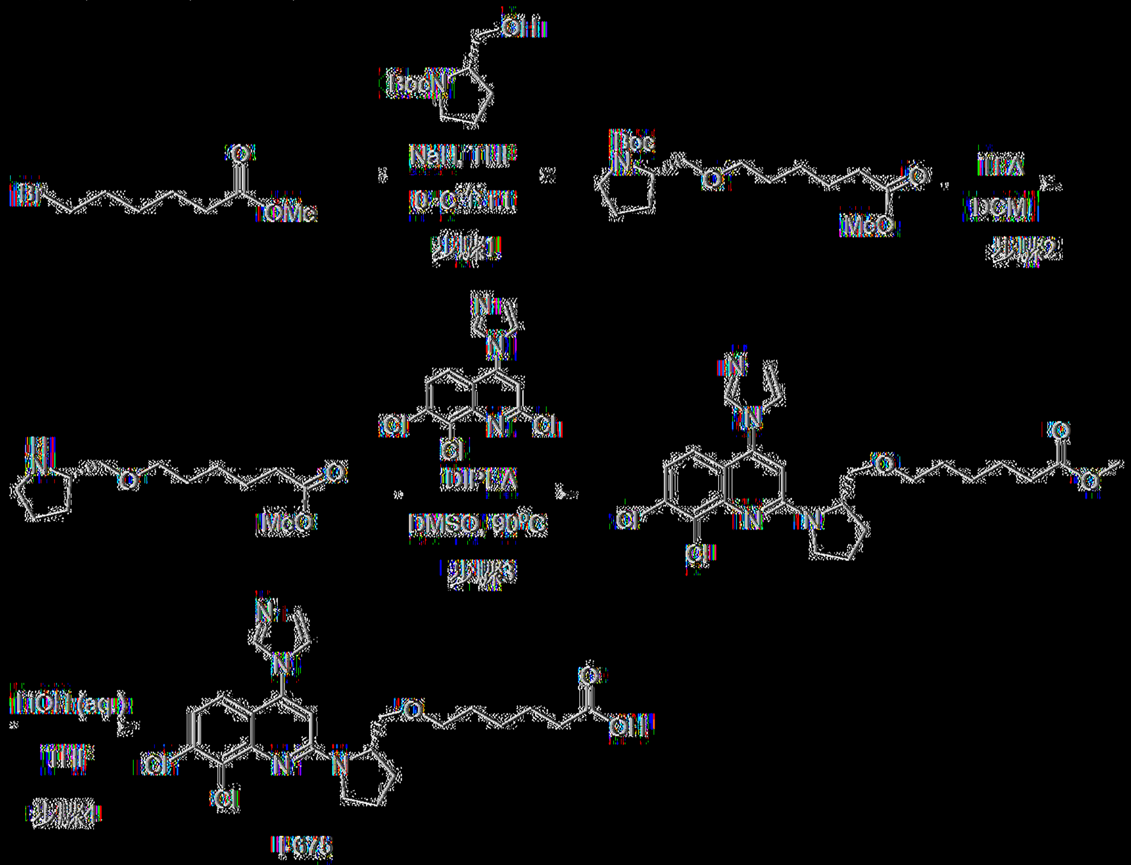
【0831】 遵循以上關於製備**I-726**所描述相同之方法，由(S)-2-((S)-氰基(羥基)甲基)吡咯啶-1-甲酸三級丁酯製備**I-725**。**I-725**：MASS: m/z: $[M+1]^+$: 451。

實例120：合成3-((R)-2-((S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基乙氧基)丙酸(**I-724**)



【0832】 遵循以上關於製備I-664所描述相同之方法，由(2S)-2-((1R)-2-羥基-1-((四氫-2H-哌喃-2-基)氧基)乙基)吡咯啶-1-甲酸三級丁酯製備I-724。I-724：MASS: m/z: [M+1]$^+$: 465。

實例121：合成(*S*)-6-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)己酸(I-675)



【0833】 步驟1：(*S*)-2-((3-(三級丁氧基)-3-側氧基丙氧基)甲基)吡咯啶-1-甲酸三級丁酯. 在0℃下，將NaH (80 mg，60%於礦物油中，2.0 mmol)添加至(*S*)-2-(羥基甲基)吡咯啶-1-甲酸三級丁酯(201 mg，1 mmol)於THF (5 mL)中之溶液中。在室溫下攪拌30分鐘後，在0℃下添加6-溴己

酸甲酯(0.6 mL)於THF (1 mL)中之溶液。在室溫下將混合物攪拌2小時，隨後在0℃下藉由H_2O (1 mL)淬滅。將有機相濃縮並藉由矽膠管柱純化，得到呈無色油狀之標題產物(75 mg)。MS: $[M+1]^+$ 330。

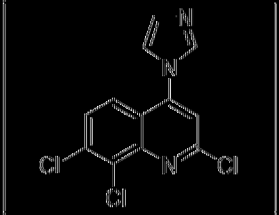
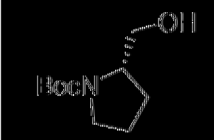
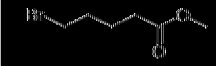
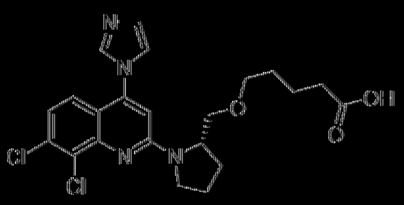
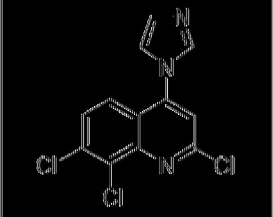
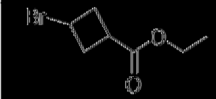
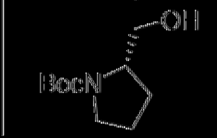
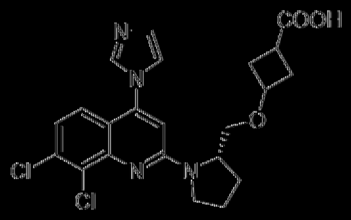
【0834】 步驟2：(*S*)-6-(吡咯啶-2-基甲氧基)己酸甲酯. 在0℃下，向(*S*)-2-((3-(三級丁氧基)-3-側氧基丙氧基)甲基)吡咯啶-1-甲酸三級丁酯(75 mg，0.23 mmol)於DCM (0.8 mL)中之溶液中添加TFA (0.8 mL)。在室溫下攪拌1小時後，減壓濃縮反應混合物以得到無色油狀物(75 mg)。粗品不經進一步純化即用於下一步驟中。MS: $[M+1]^+$: 230。

【0835】 步驟3：(*S*)-6-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)己酸甲酯. 向(*S*)-6-(吡咯啶-2-基甲氧基)己酸甲酯(75 mg，來自上一個步驟之粗品，約0.2 mmol)及2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(100 mg，0.33 mmol)於DMSO (1 mL)中之溶液中添加DIPEA (0.1 mL)。在80℃下將混合物攪拌隔夜。冷卻至室溫後，添加H_2O (10 mL)。利用1 N HCl將混合物酸化至pH. = 1並藉由過濾收集沈澱。藉由矽膠管柱純化，得到呈無色油狀之標題產物(100 mg)。MS: $[M+1]^+$ 491。

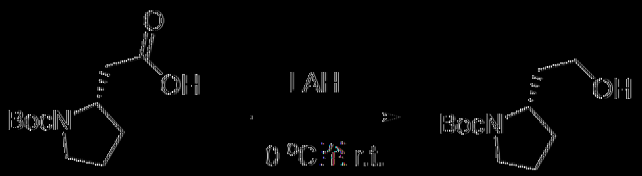
【0836】 步驟4：(*S*)-6-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)己酸. 在0℃下，向(*S*)-6-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)己酸甲酯(100 mg，0.2 mmol)於THF (2 mL)中之溶液中添加LiOH (水溶液，1 M. 0.4 mL)。在50℃下將混合物攪拌隔夜。冷卻至室溫後，添加H_2O (3 mL)及1 N HCl (0.35 mL)。藉由過濾收集沈澱，得到呈白色固體狀之標題產物(80 mg)。MS: $[M+1]^+$ 477。

【0837】 以下化合物基本上藉由與以上關於製備**I-675**所描述相同的

方法製備。

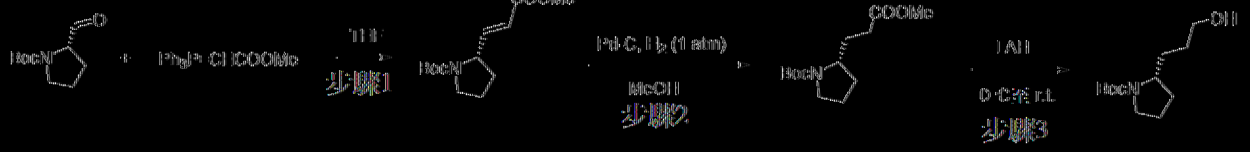
實例	起始材料		結構	MS [M+1]$^+$
I-676		 		463
I-723		 		461

實例122：合成(*S*)-2-(2-羥基乙基)吡咯啶-1-甲酸三級丁酯



【0838】 在0℃下，將LAH (1.2 eq.)添加至(*S*)-2-(1-(三級丁氧基羰基)吡咯啶-2-基)乙酸(4 g，17 mmol)於THF (75 mL)中之溶液中。在室溫下將混合物攪拌1小時。在0℃下，分別藉由H_2O (3 mL)、15% NaOH (3 mL)及H_2O (9 mL)淬滅反應。過濾後，將濾液藉由矽膠管柱純化，得到呈無色油狀之標題產物(2.3 g)。MS: [M+1]$^+$ 216。

實例123：合成(*S*)-2-(3-羥基丙基)吡咯啶-1-甲酸三級丁酯



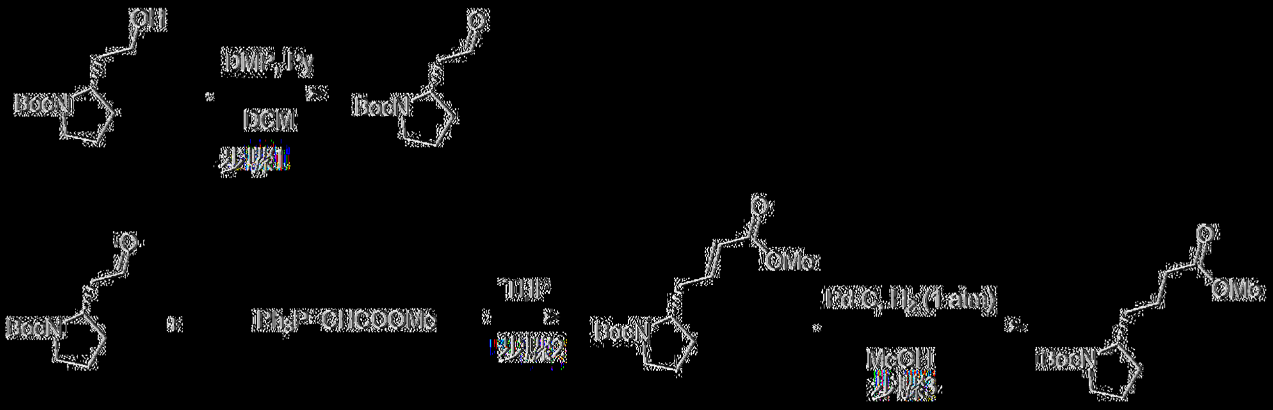
【0839】 步驟1：(*S,E*)-2-(3-甲氧基-3-側氧基丙-1-烯-1-基)吡咯啶-1-甲酸三級丁酯. 向(*S*)-2-(羥基甲基)吡咯啶-1-甲酸三級丁酯(398 mg，2 mmol)於THF (8 mL)中之溶液中添加$Ph_3P=CHCOOMe$ (700 mg，2.2 mmol)。在50℃下將混合物攪拌隔夜。冷卻至室溫後，將混合物真空濃縮

並藉由矽膠層析法純化，得到呈無色油狀之標題產物(430 mg)。MS: $[M+1]^+$ 256。

【0840】 步驟2：(*S*)-2-(3-甲氧基-3-側氧基丙基)吡咯啶-1-甲酸三級丁酯. 向(*S*,*E*)-2-(3-甲氧基-3-側氧基丙-1-烯-1-基)吡咯啶-1-甲酸三級丁酯(800 mg，3.1 mmol)於MeOH (10 mL)中之溶液中添加Pd/C (10%，40 mg)。在H_2 (1 atm)下將混合物攪拌隔夜。過濾後，濃縮濾液並得到呈無色油狀之標題產物(800 mg)，將其不經純化即直接使用。MS: $[M+1]^+$ 258。

【0841】 步驟3：(*S*)-2-(3-羥基丙基)吡咯啶-1-甲酸三級丁酯. 該程序與以上關於製備(*S*)-2-(2-羥基乙基)吡咯啶-1-甲酸三級丁酯所描述基本上相同。MS: $[M+1]^+$ 230。

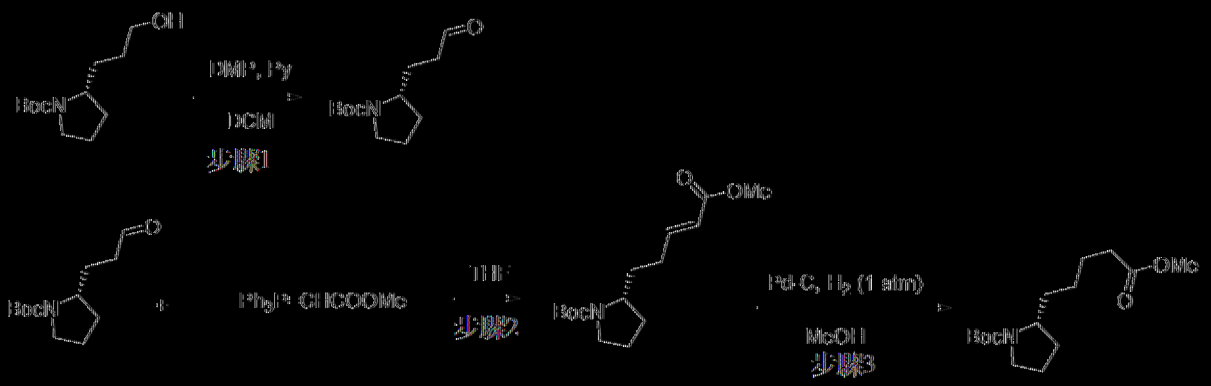
實例124：合成(*R*)-2-(4-甲氧基-4-側氧基丁基)吡咯啶-1-甲酸三級丁酯



【0842】 步驟1：(*S*)-2-(2-側氧基乙基)吡咯啶-1-甲酸三級丁酯. 在0℃下，向(*S*)-2-(2-羥基乙基)吡咯啶-1-甲酸三級丁酯(340 mg，1.5 mmol)於DCM (6 mL)及吡啶(1 mL)中之溶液中添加DMP (800 mg)。在室溫下將混合物攪拌2小時並藉由$Na_2S_2O_3/NaHCO_3$ (飽和，10 mL)淬滅。將有機相真空濃縮並藉由矽膠層析法純化，得到呈無色油狀之標題產物(280 mg)。MS: $[M+1]^+$ 214。

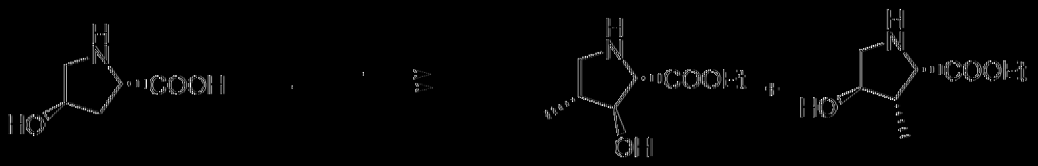
【0843】步驟2及步驟3與以上關於製備(*S*)-2-(3-羥基丙基)吡咯啶-1-甲酸三級丁酯製備(步驟1及步驟2)所描述之程序基本上相同。

實例125：合成(*R*)-2-(5-甲氧基-5-側氧基戊基)吡咯啶-1-甲酸三級丁酯



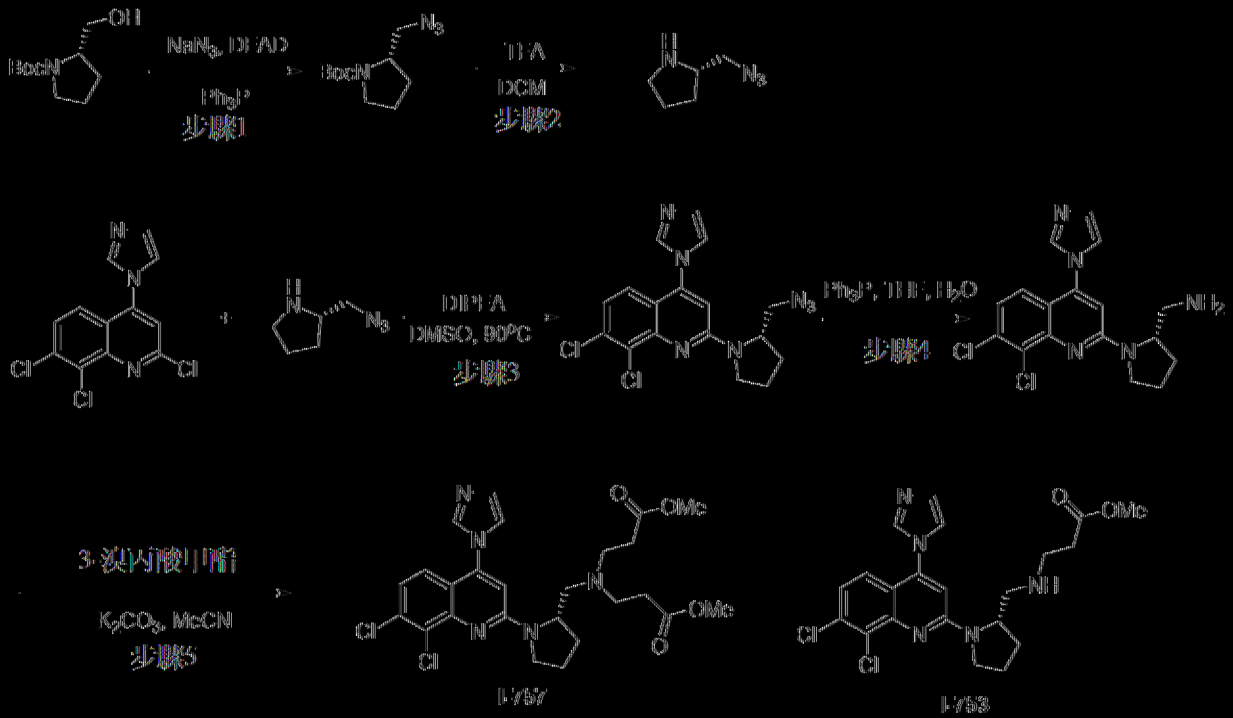
【0844】(*R*)-2-(5-甲氧基-5-側氧基戊基)吡咯啶-1-甲酸三級丁酯基本上藉由與以上關於製備(*R*)-2-(4-甲氧基-4-側氧基丁基)吡咯啶-1-甲酸三級丁酯所描述相同的方法製備。

實例126：合成(*2S,3S,4R*)-3-羥基-4-甲基吡咯啶-2-甲酸乙酯及(*2S,3S,4R*)-4-羥基-3-甲基吡咯啶-2-甲酸乙酯



【0845】根據WO 2011/091407中所描述之方法製備出兩種中間體，該案內容以引用之方式併入本文中。

實例127：合成(*S*)-3-(((1-(7,8-二氟-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)胺基)丙酸甲酯(I-753)及3,3'-(((1-(7,8-二氟-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)氮二基)(*S*)-二丙酸二甲酯(I-757)



【0846】 步驟1：(*S*)-2-(疊氮基甲基)吡咯啶-1-甲酸三級丁酯. 向(*S*)-2-(羥基甲基)吡咯啶-1-甲酸三級丁酯(400 mg，2 mmol)、Ph_3P (800 mg，3 mmol)及NaN_3 (200 mg，3 mmol)於THF (10 mL)中之溶液中添加DEAD (0.47 mL，3 mmol)。在室溫下攪拌反應隔夜。蒸發後，將粗品藉由矽膠層析法純化，得到呈無色油狀之標題產物(280 mg)。MS: $[M+1]^+$ 227。

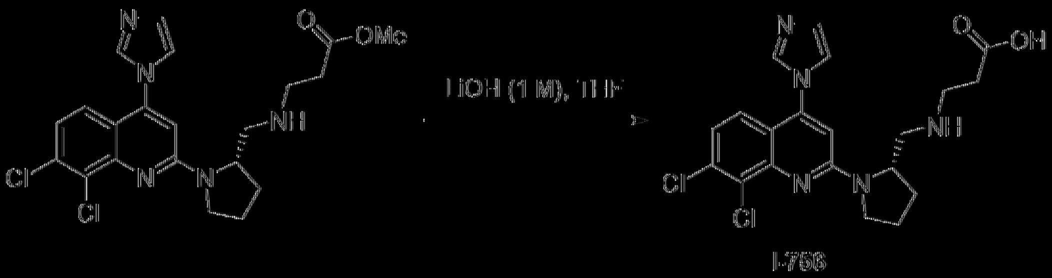
【0847】 步驟2及步驟3與以上關於製備I-675 (步驟2及步驟3)所描述之程序基本上相同。

【0848】 步驟4：(*S*)-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲胺. 向(*S*)-2-(2-(疊氮基甲基)吡咯啶-1-基)-7,8-二氯-4-(1H-咪唑-1-基)喹啉(190 mg，0.5 mmol)於THF (3 mL)及H_2O (1 mL)中之溶液中添加Ph_3P (262 mg，1 mmol)。在室溫下將混合物攪拌隔夜。蒸發後，將粗品藉由矽膠層析法純化，得到呈白色固體狀之標題產物(160 mg)。MS: $[M+1]^+$ 362。

【0849】 步驟5：(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)胺基)丙酸甲酯(I-753)及3,3'-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)氮二基)(*S*)-二丙酸二甲酯(I-757). 向(*S*)-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲胺(160 mg)

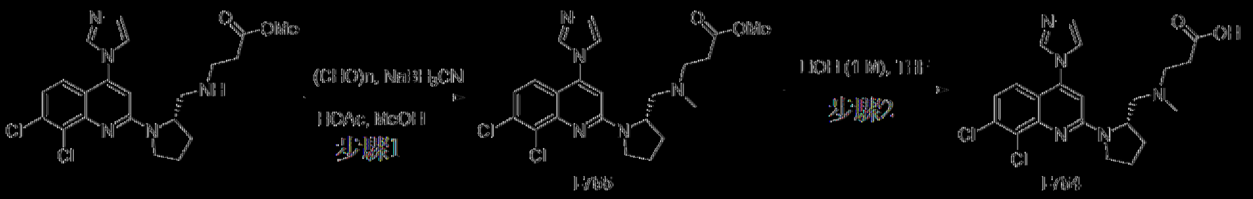
及3-溴丙酸甲酯(50 mg，0.44 mmol)之溶液中添加K_2CO_3 (60 mg)。在50℃下將混合物攪拌隔夜。過濾後，將粗品藉由矽膠層析法純化，得到呈白色固體狀之標題混合物I-753 (45 mg，MS: $[M+1]^+$ 448)及I-757 (2.5 mg，MS: $[M+1]^+$ 534)。

實例128：合成(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)胺基)丙酸(I-756)



【0850】 該程序與以上關於I-675 (步驟4)所描述之製備方法基本上相同。MS: $[M+1]^+$ 434。

實例129：合成(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)(甲基)胺基)丙酸甲酯(I-755)及(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)(甲基)胺基)丙酸(I-754)

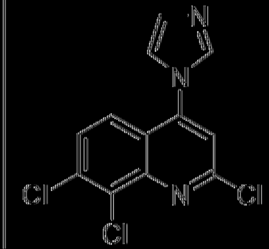
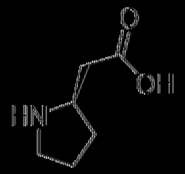
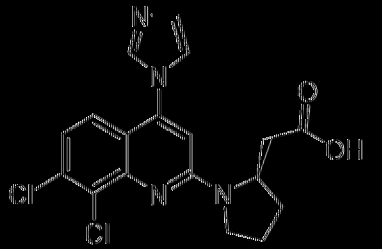
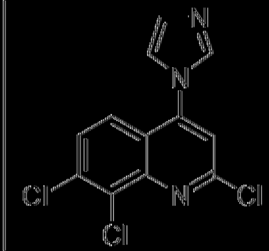
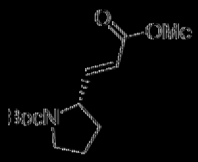
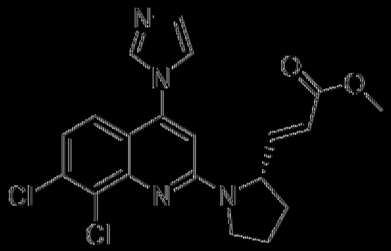
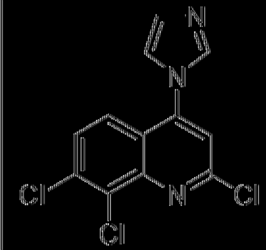
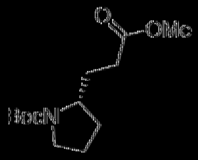
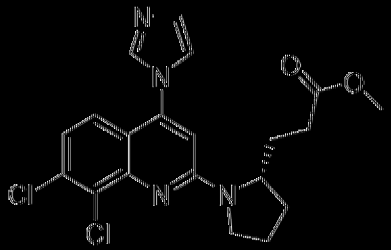
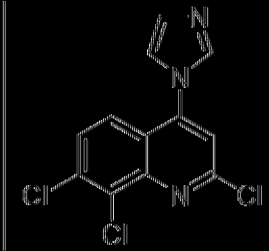
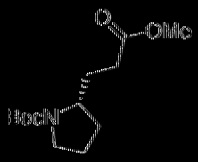
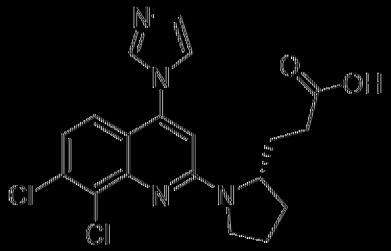
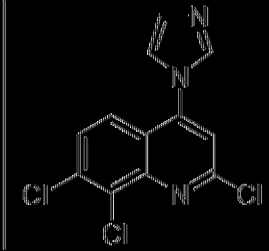
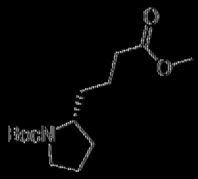
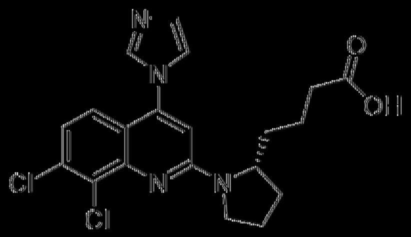
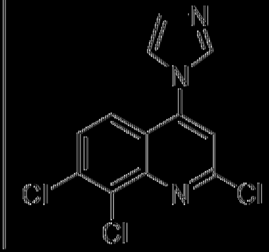
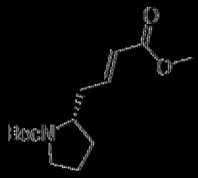
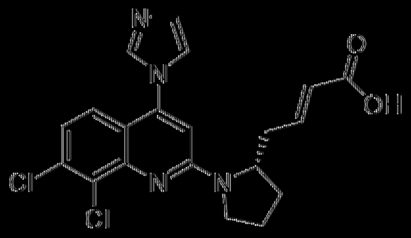


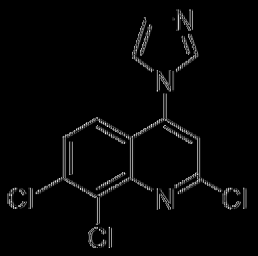
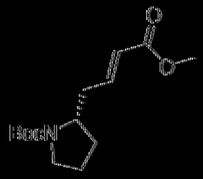
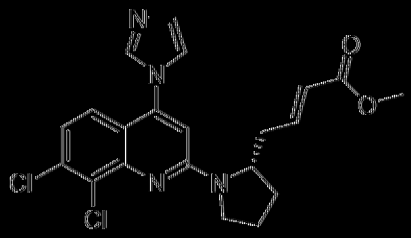
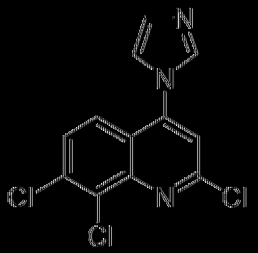
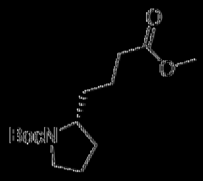
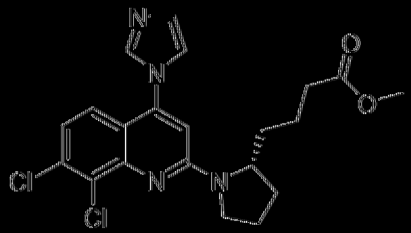
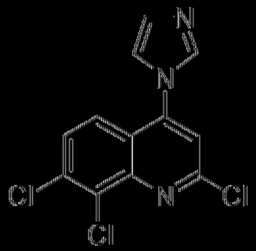
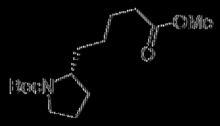
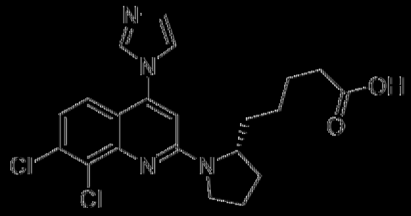
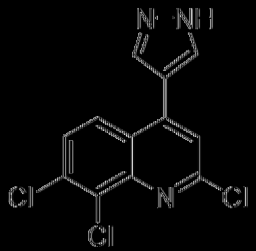
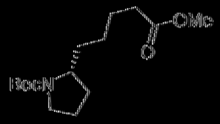
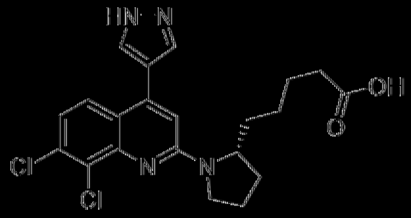
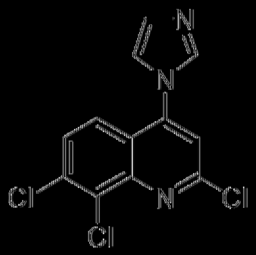
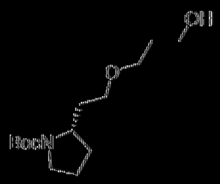
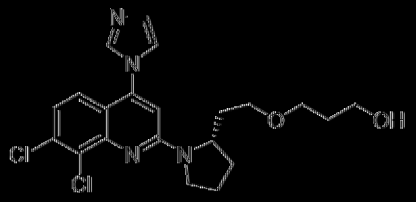
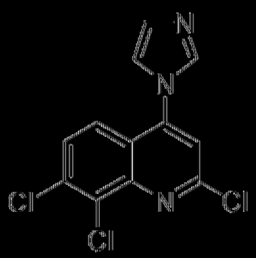
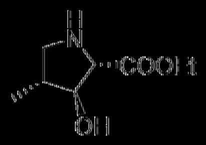
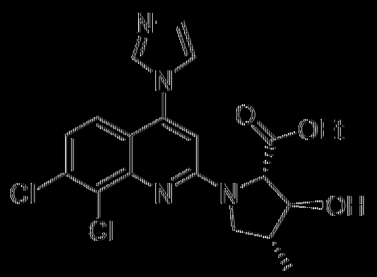
【0851】 步驟1：(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)(甲基)胺基)丙酸甲酯(I-755). 向(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)胺基)丙酸甲酯(19 mg，0.05 mmol)、三聚甲醛(6 mg，0.2 mmol)、HOAc (0.025 mL)於MeOH (1 mL)中之溶液中添加$NaBH_3CN$ (13 mg，0.2 mmol)。在室溫下將混合物攪拌隔夜。蒸發後，將粗品藉由矽膠層析法純化，得到標題產物(15 mg)。MS: $[M+1]^+$ 462。

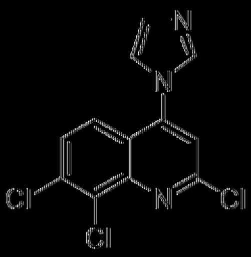
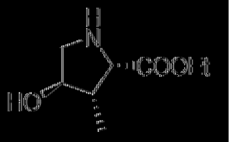
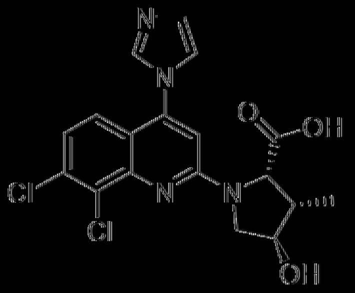
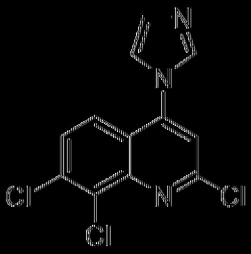
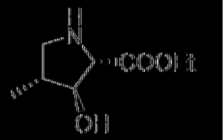
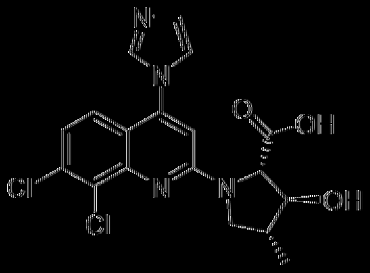
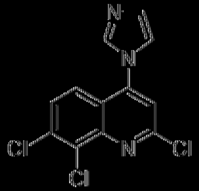
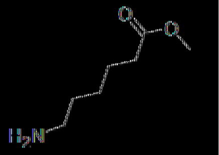
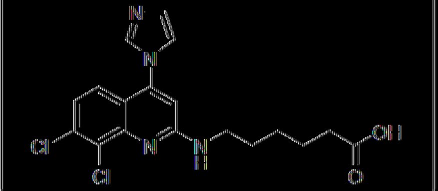
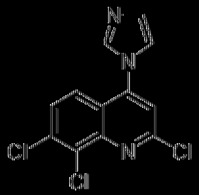
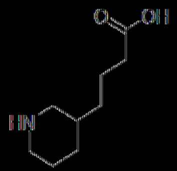
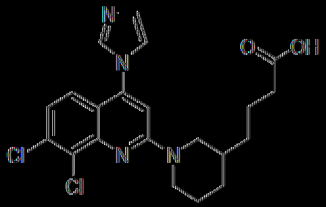
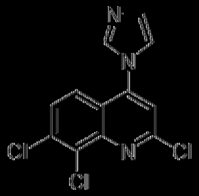
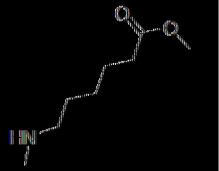
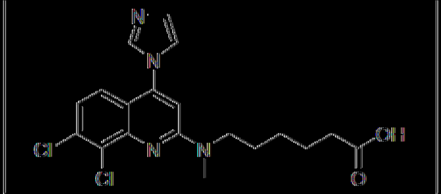
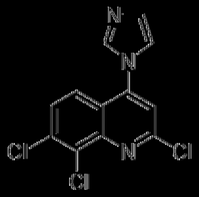
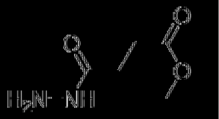
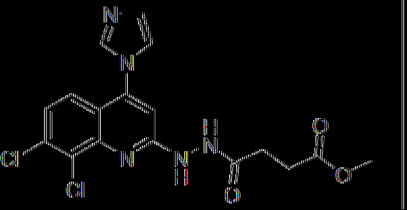
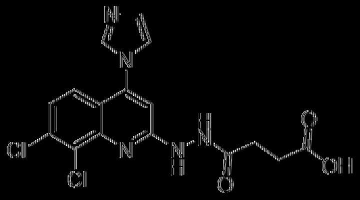
【0852】 步驟2：(*S*)-3-(((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲基)(甲基)胺基)丙酸(I-754). 該程序與以上關於製備I-675

(步驟4)所描述之程序基本上相同。MS: $[M+1]^+$ 448。

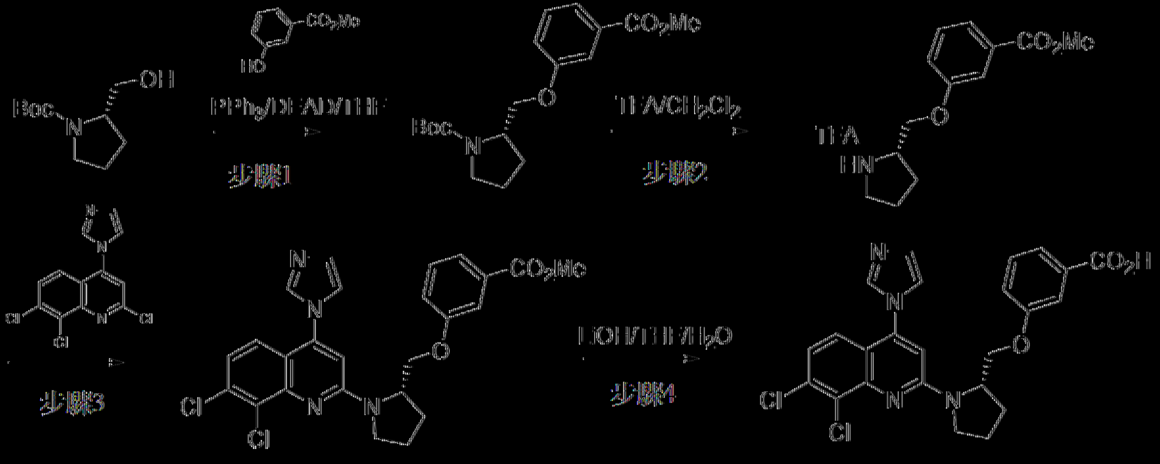
【0853】 以下化合物基本上藉由與以上關於製備I-123所描述相同的方法製備。

實例	起始材料		結構	MS $[M+1]^+$
I-776				391
I-687				417
I-680				419
I-679				405
I-682				419
I-685				417

實例	起始材料		結構	MS [M+1]$^+$
I-686				431
I-681				433
I-683				433
I-684				433
I-678				435
I-779				435

實例	起始材料		結構	MS [M+1]$^+$
I-780				407
I-778				407
I-690				393
I-739				433
I-691				407
I-758				408
I-759				394

實例130：合成(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)苯甲酸(I-735)



I-735

【0854】 步驟1：(S)-2-((3-(甲氧基羰基)苯氧基)甲基)吡咯啶-1-甲酸三級丁酯. 向Boc-脯胺醇(300 mg，1.49 mmol)、3-羥基苯甲酸甲酯(240 mg，1.45 mmol)及三苯基膦(391 mg，1.49 mmol)於THF (10 mL)中之經攪拌混合物中逐滴添加偶氮二甲酸二乙酯(261 mg，0.65 mL，1.49 mmol (40%於甲苯中))。在75℃下將所得混合物加熱3小時。在冷卻之後，真空濃縮混合物。將殘餘物溶解於EtOAc中並依序用1N NaOH、水且接著鹽水洗滌。將有機層乾燥(Na_2SO_4) ，接著濃縮。將殘餘物藉由矽膠層析法，使用0-40%乙酸乙酯/己烷作為溶離劑純化，得到標題化合物。MS: $[M+1]^+$ 280.1 (-t-Bu)。

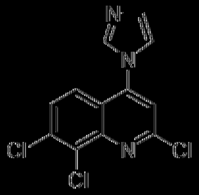
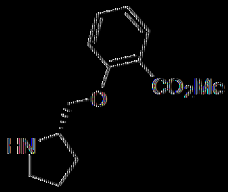
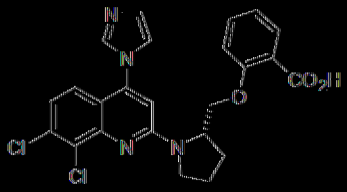
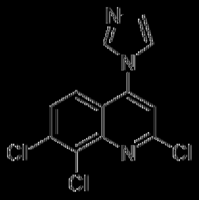
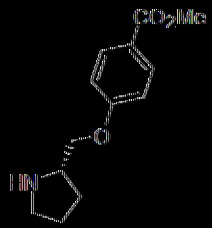
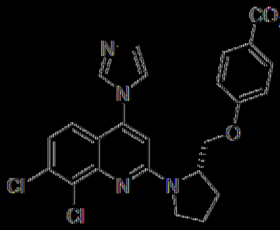
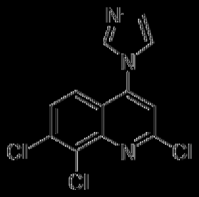
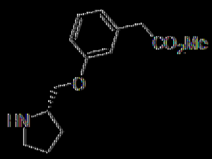
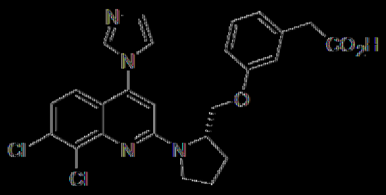
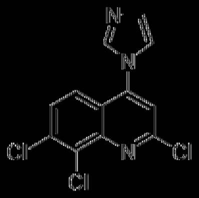
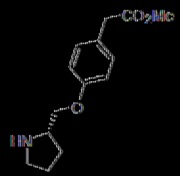
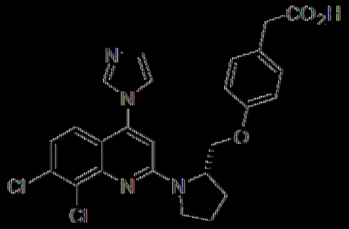
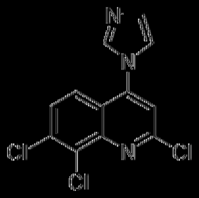
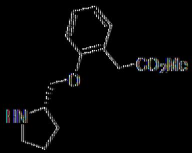
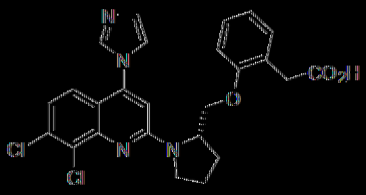
【0855】 步驟2：(S)-3-(吡咯啶-2-基甲氧基)苯甲酸甲酯. 向含有(S)-2-((3-(甲氧基羰基)苯氧基)甲基)吡咯啶-1-甲酸三級丁酯(200 mg，0.546 mmol)之燒瓶中添加二氯甲烷(5 mL)。添加三氟乙酸(1 mL)並在室溫下攪拌反應16小時。移除揮發性物質，得到標題化合物，將其不經進一步純化即用於下一步。MS: $[M+1]^+$ 236.1。

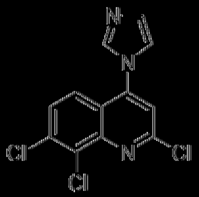
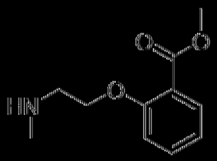
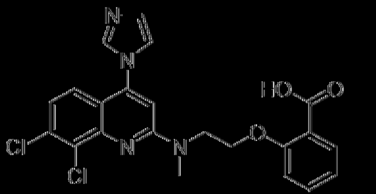
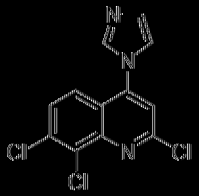
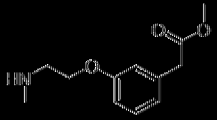
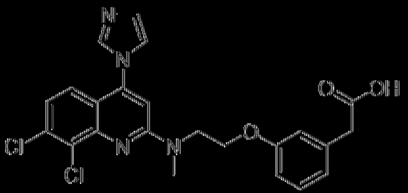
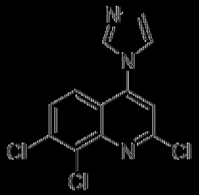
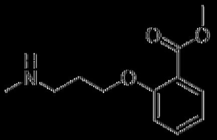
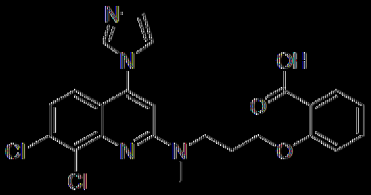
【0856】 步驟3：(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)

吡咯啶-2-基)甲氧基)苯甲酸甲酯. 向含有(S)-3-(吡咯啶-2-基甲氧基)苯甲酸甲酯(70 mg，0.3 mmol)之小瓶中添加DMSO (0.15 mL)及DIPEA (0.10 mL)。接下來，添加2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)並將混合物加熱至90℃，保持16小時。將反應物冷卻至室溫，接著添加水並將有機層萃取至10% $MeOH/CH_2Cl_2$中。將合併之有機層乾燥(Na_2SO_4)，接著濃縮。將殘餘物藉由矽膠層析法，使用含0.5% HOAc之0-5% $MeOH/CH_2Cl_2$作為溶離劑純化，得到標題化合物。MS: $[M+1]^+$ 497.1。

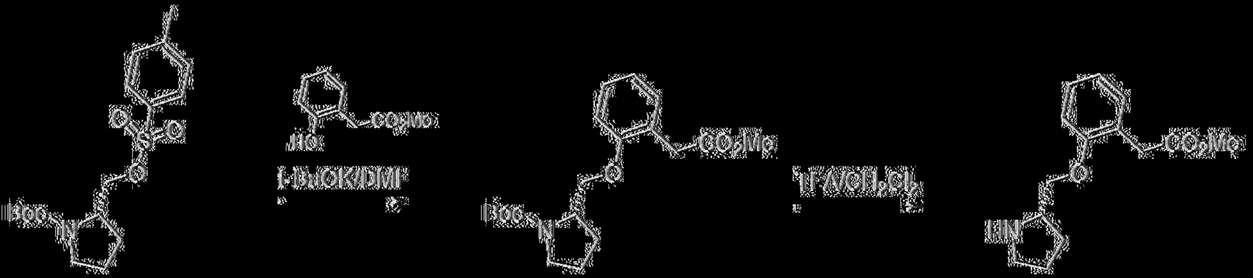
【0857】 步驟4：(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)苯甲酸. 向含有(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)苯甲酸甲酯(20 mg，0.040 mmol)、THF (2 mL)及水(0.5 mL)之小瓶中添加單水合氫氧化鋰(5 mg，0.12 mmol)並在室溫下攪拌反應16小時。移除揮發性物質並將殘餘物溶解於水中，接著用1M HCl酸化直至約pH 7。過濾出所得固體並真空乾燥，得到標題化合物。MS: $[M+1]^+$ 483.1。

【0858】 以下化合物基本上藉由與以上關於製備**I-735**所描述相同之方法製備：

實例	起始材料		結構	MS [M+1]$^+$
E733				483.1
E737				483.1
E736				497.1
E738				497.1
E734				497.1

實例	起始材料		結構	MS [M+1]$^+$
I-842				457
I-843				471
I-846				471

實例131：合成(S)-2-(2-(吡咯啶-2-基甲氧基)苯基)乙酸甲酯

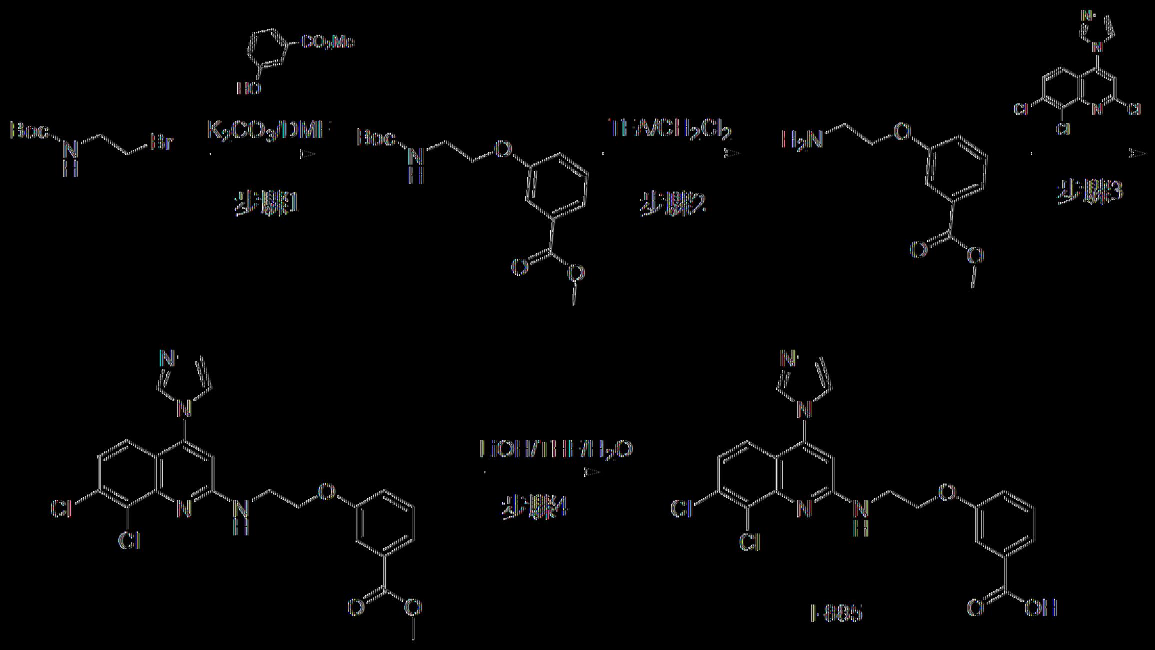


【0859】 步驟1：(S)-2-((2-(2-甲氧基-2-側氧基乙基)苯氧基)甲基)吡咯啶-1-甲酸三級丁酯. 向含有(S)-2-((甲苯磺醯氧基)甲基)吡咯啶-1-甲酸三級丁酯(355 mg，1.00 mmol)、2-(2-羥基苯基)乙酸甲酯(166 mg，1.00 mmol)及DMF (10 mL)之燒瓶中添加三級丁醇鉀(112 mg，1.00 mmol)並在55℃下加熱反應16小時。將反應物冷卻至室溫，藉由緩慢添加水淬滅，接著用乙酸乙酯稀釋。分離有機層且再用5% NaOH、水及鹽水洗滌，接著乾燥(Na_2SO_4)並濃縮。將所得殘餘物藉由矽膠層析法，使用0-35% EtOAc/己烷作為溶離劑純化，得到標題化合物。(MS: [M+1]$^+$ 250.1 (-Boc)。

【0860】 步驟2：(S)-2-(2-(吡咯啶-2-基甲氧基)苯基)乙酸甲酯. 向含有(S)-2-((2-(2-甲氧基-2-側氧基乙基)苯氧基)甲基)吡咯啶-1-甲酸三級丁

酯(25 mg，0.061 mmol)之小瓶中添加二氯甲烷(2 mL)及三氟乙酸(0.5 mL)。在室溫下攪拌反應16小時。移除揮發性物質，得到標題化合物，將其用於製備I-735。MS: $[M+1]^+$ 250.1。

實例132：合成3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙氧基)苯甲酸(I-885)



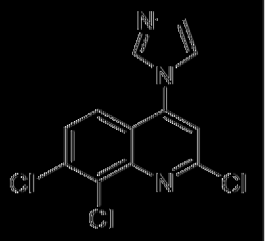
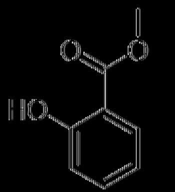
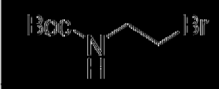
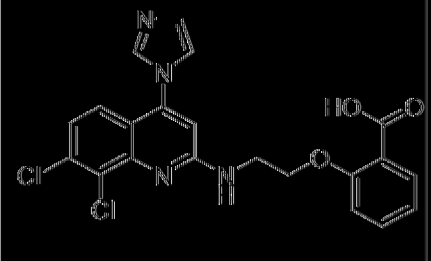
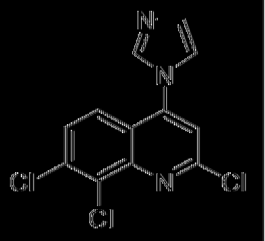
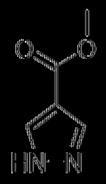
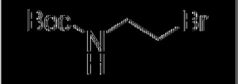
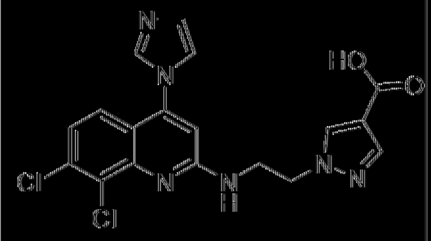
【0861】 步驟1：3-(2-((三級丁氧基羰基)胺基)乙氧基)苯甲酸甲酯：向含有3-羥基苯甲酸甲酯(152 mg，1.0 mmol)及DMF (5 mL)之燒瓶中添加碳酸鉀(152 mg，1.1 mol)。在室溫下將內含物攪拌10分鐘，接著添加(2-溴乙基)胺基甲酸三級丁酯(246 mg，1.1 mmol)。將反應物加熱至65℃，保持16小時。冷卻後，添加水(10 mL)並將有機物萃取至乙酸乙酯(2 × 10 mL)中，乾燥(Na2SO4)並濃縮。將殘餘物藉由矽膠層析法純化，得到175 mg標題化合物。

【0862】 步驟2：3-(2-胺基乙氧基)苯甲酸甲酯三氟乙酸鹽：向含有3-(2-((三級丁氧基羰基)胺基)乙氧基)苯甲酸甲酯(120 mg，0.4 mmol)及二氯甲烷(5 mL)之燒瓶中添加三氟乙酸(1 mL)。在室溫下攪拌反應16小時。濃縮去除揮發性物質，得到粗標題化合物，將其直接用於下一步驟。

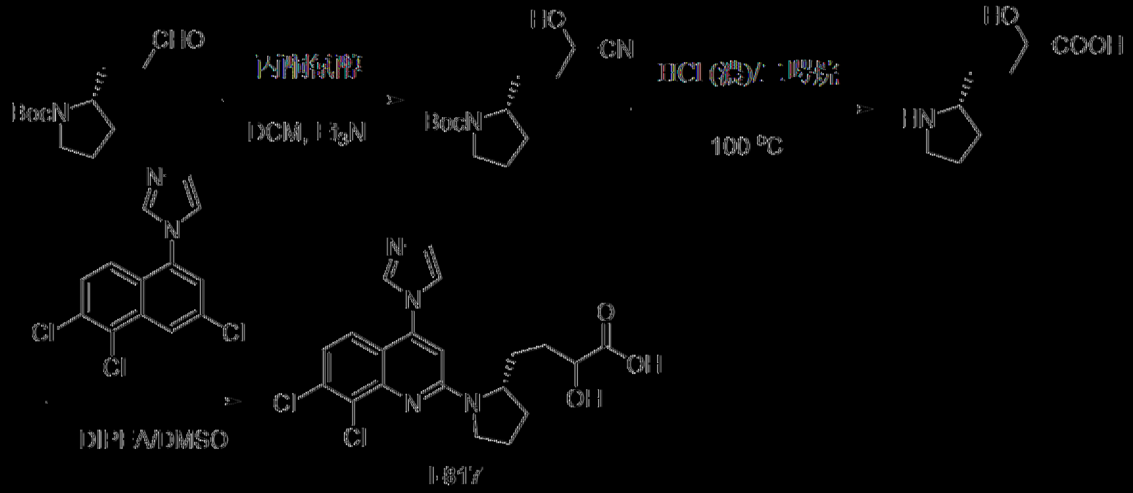
【0863】 步驟3：3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙氧基)苯甲酸甲酯：向含有2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(30 mg，0.1 mmol)及DMSO之小瓶中添加3-(2-胺基乙氧基)苯甲酸甲酯三氟乙酸鹽(0.4 mmol)及DIPEA。將反應物加熱至90℃，保持16小時，接著冷卻至室溫。添加水(5 mL)並將有機層萃取至乙酸乙酯(2 × 5 mL)中，乾燥(Na2SO4)並濃縮。將殘餘物藉由矽膠層析法純化，得到27 mg標題化合物。

【0864】 步驟4：3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙氧基)苯甲酸：向含有3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)乙氧基)苯甲酸甲酯(20 mg，0.44 mmol)於THF/H_2O (4 mL/1 mL)之小瓶中添加單水合氫氧化鋰(7 mg，0.175 mmol)並在室溫下攪拌反應16小時。移除揮發性物質且接著，用1M HCl酸化殘餘物。將所得固體過濾並乾燥，得到標題化合物。

【0865】 以下化合物基本上藉由與以上關於製備I-885所描述相同的方法製備。

實例	起始材料		結構	MS $[M+1]^+$
I-886		 		443
I-889		 		417

實例133：合成4-((*S*)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基丁酸(I-817)

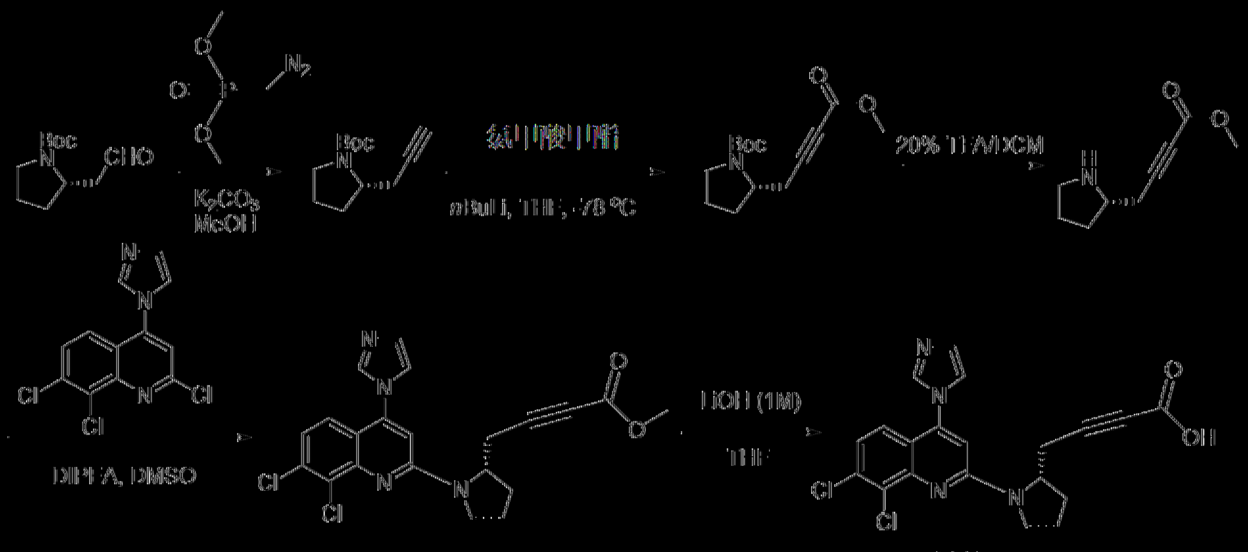


【0866】 步驟1：(2*S*)-2-(3-氰基-3-羥基丙基)吡咯啶-1-甲酸三級丁酯. 向(*S*)-2-(3-側氧基丙基)吡咯啶-1-甲酸三級丁酯(114 mg，0.5 mmol)於DCM (1 mL)中之溶液中添加Et_3N (0.1 mL)及丙酮氰醇(0.1 mL，1.2 mmol)。在室溫下將混合物攪拌隔夜。真空濃縮溶液並藉由矽膠管柱純化，得到呈無色油狀之標題產物(120 mg)。MS: $[M+1]^+$ 255。

【0867】 步驟2：2-羥基-4-((*S*)-吡咯啶-2-基)丁酸. 向(2*S*)-2-(3-氰基-3-羥基丙基)吡咯啶-1-甲酸三級丁酯(60 mg，0.23 mmol)於二噁烷(0.8 mL)中之溶液中添加HCl (濃，0.8 mL)。在100℃下將混合物攪拌隔夜。冷卻至室溫後，藉由蒸發移除二噁烷。用EtOAc (0.5 mL × 2)洗滌殘餘物。收集水相並蒸發，得到粗產物，將其不經純化直接用於下一步驟。MS: $[M+1]^+$ 174。

【0868】 步驟3：4-((*S*)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)-2-羥基丁酸(I-817). 標題化合物基本上藉由與I-664相同之方法製備。MS: $[M+1]^+$ 435。

【0869】 合成(*S*)-4-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)丁-2-炔酸(I-819)



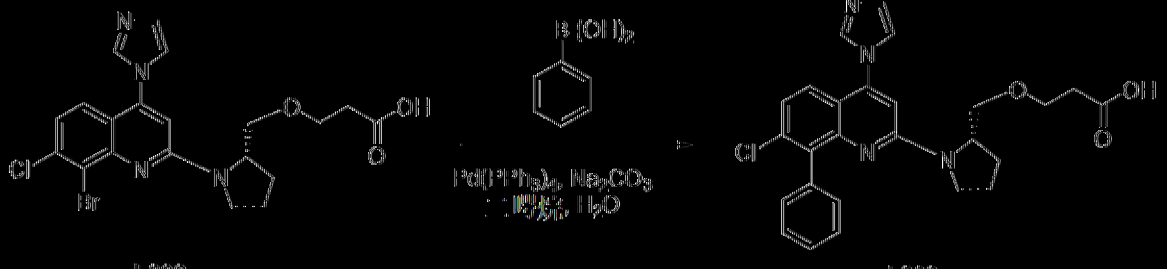
I-819

【0870】 步驟1：(*S*)-2-(丙-2-炔-1-基)吡咯啶-1-甲酸三級丁酯. 向(*S*)-2-(2-側氧基乙基)吡咯啶-1-甲酸三級丁酯(457 mg，2.15 mmol)於MeOH (4.5 mL)中之溶液中添加K_2CO_3 (594 mg，4.3 mmol)及二唑(480 mg，3.22 mmol)。在室溫下將混合物攪拌隔夜。真空濃縮混合物並藉由矽膠管柱純化，得到呈無色油狀之標題產物(330 mg)。MS: $[M+1]^+$ 210。

【0871】 步驟2：(*S*)-2-(4-甲氧基-4-側氧基丁-2-炔-1-基)吡咯啶-1-甲酸三級丁酯. 在-78℃下，向(*S*)-2-(丙-2-炔-1-基)吡咯啶-1-甲酸三級丁酯(330 mg，1.58 mmol)於THF (3.5 mL)中之溶液中添加*n*-BuLi (1.1 mL，1.6 M於己烷中)。30分鐘後，逐滴添加氯甲酸甲酯(0.15 mL)於THF (1 mL)中之溶液。使混合物升溫至室溫並攪拌隔夜。接著，藉由NH_4Cl (飽和，0.5 mL)淬滅反應。真空濃縮混合物並藉由矽膠管柱純化，得到呈無色油狀之標題產物(200 mg)。MS: $[M+1]^+$ 268。

【0872】 (*S*)-4-(1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)丁-2-炔酸(I-819)係基本上藉由與I-664相同之方法，由(*S*)-2-(4-甲氧基-4-側氧基丁-2-炔-1-基)吡咯啶-1-甲酸三級丁酯製備。MS: $[M+1]^+$ 415 。

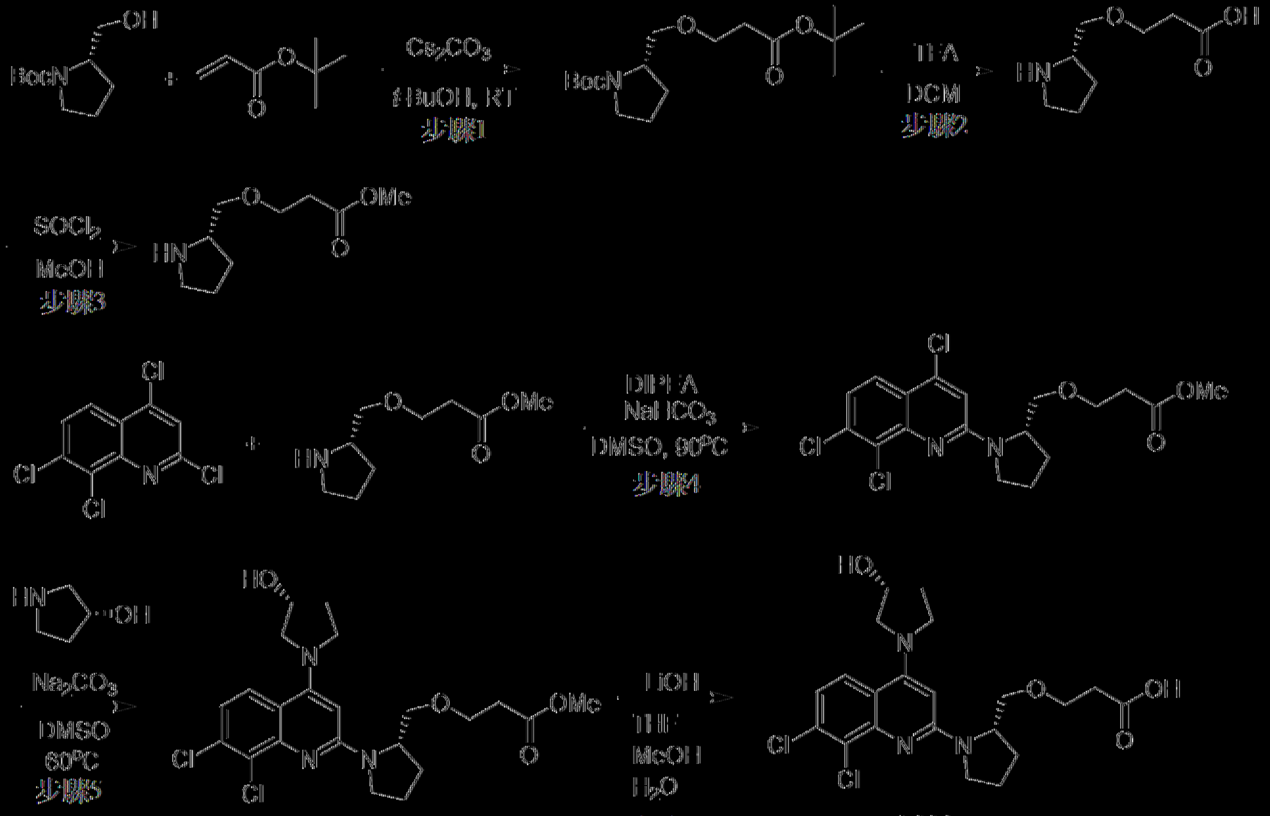
實例134：合成(*S*)-3-((1-(7-氯-4-(1H-咪唑-1-基)-8-苯基喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(I-863)



I-862　　I-863

【0873】 藉由N_2將(*S*)-3-((1-(8-溴-7-氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(14 mg，0.03 mmol)、Na_2CO_3 (10 mg，0.14 mmol)、二噁烷(1mL)及H_2O (0.5 mL)之混合物吹掃10分鐘。添加Tetrakis (1 mg，0.001 mmol)。在80℃下將混合物攪拌3小時。真空濃縮混合物並藉由矽膠管柱純化，得到呈白色固體狀之I-863 (6 mg)。MS: $[M+1]^+$ 477。

實例135：合成3-(((S)-1-(7,8-二氯-4-((R)-3-羥基吡咯啶-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(I-821)



I-821

【0874】 步驟1：(S)-2-((3-(三級丁氧基)-3-側氧基丙氧基)甲基)吡

咯啶-1-甲酸三級丁酯. 該程序與合成**I-665**中之程序相同。

【0875】 步驟2：(S)-3-(吡咯啶-2-基甲氧基)丙酸. 該程序與合成**I-665**中之程序相同。

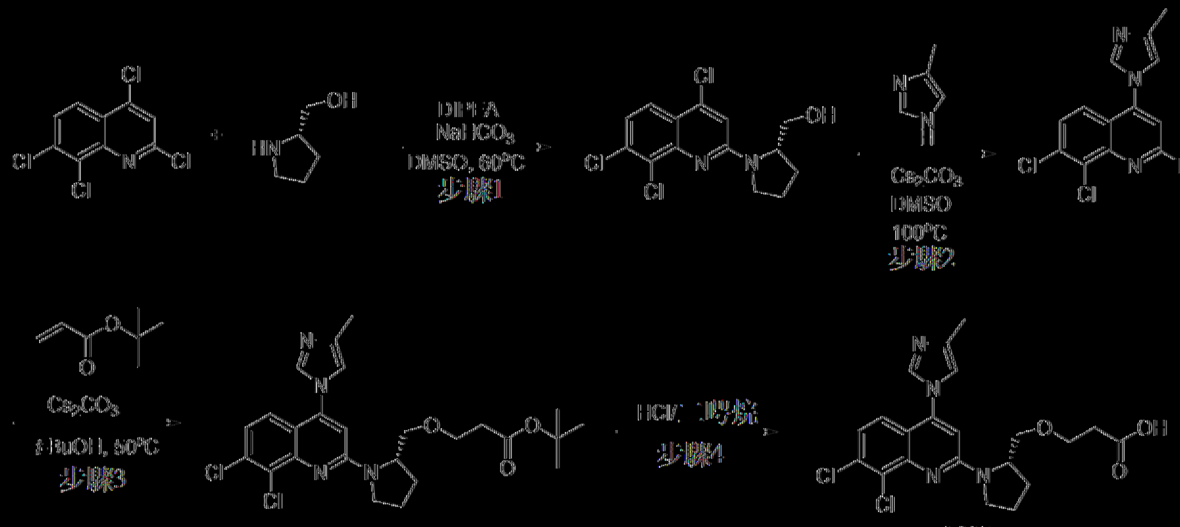
【0876】 步驟3：(S)-3-(吡咯啶-2-基甲氧基)丙酸甲酯. 該程序與合成**I-665**中之程序相同。

【0877】 步驟4：(S)-3-((1-(4,7,8-三氯喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯. 該程序與合成**I-665**中之程序相同。

【0878】 步驟5：3-(((S)-1-(7,8-二氯-4-((R)-3-羥基吡咯啶-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯. 向小瓶中添加(S)-3-((1-(4,7,8-三氯喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯(21 mg，0.050 mmol)、(R)-吡咯啶-3-醇(22 mg，0.25 mmol)、Na_2CO_3 (5.3 mg，0.050 mmol)及DMSO (0.5 ml)。在60℃下將反應混合物攪拌隔夜。簡單處理後，將粗品藉由矽膠層析法純化，得到標題產物(9.2 mg)。(MS: $[M+1]^+$ 454)

【0879】 步驟6：3-(((S)-1-(7,8-二氯-4-((R)-3-羥基吡咯啶-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸. 該程序與合成**I-665**中之程序相同。(MS: $[M+1]^+$ 454)

實例136：合成(S)-3-((1-(7,8-二氯-4-(4-甲基-1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(**I-825**)



I-825

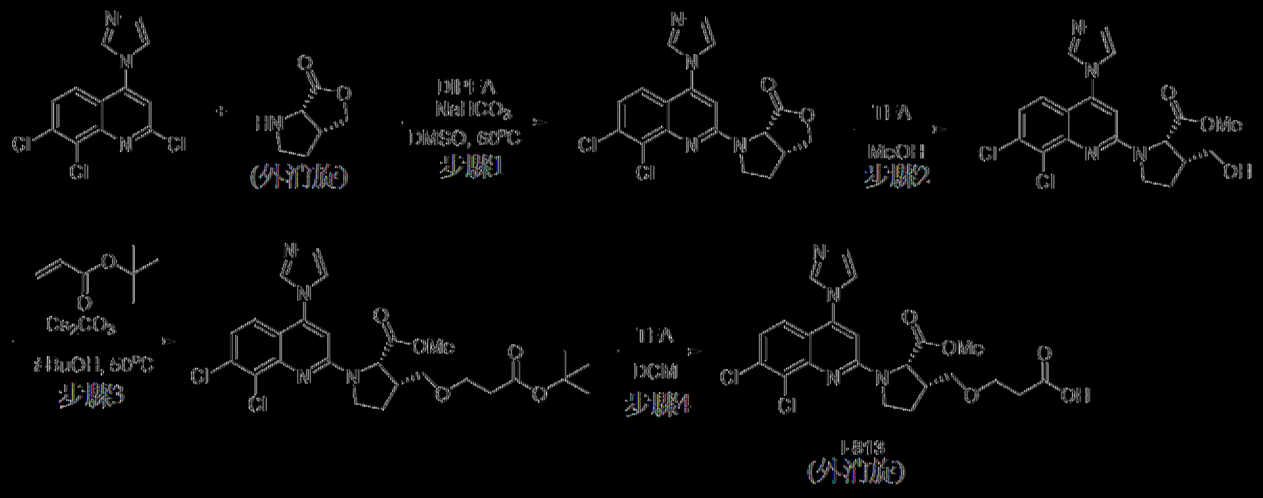
【0880】 步驟1：(S)-(1-(4,7,8-三氯喹啉-2-基)吡咯啶-2-基)甲醇. 該程序與合成I-287中之程序相同。

【0881】 步驟2：(S)-(1-(7,8-二氯-4-(4-甲基-1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲醇. 該程序與合成I-821中之程序相同。

【0882】 步驟3：(S)-3-((1-(7,8-二氯-4-(4-甲基-1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸三級丁酯. 該程序與合成I-665中之程序相同。

【0883】 步驟4：(S)-3-((1-(7,8-二氯-4-(4-甲基-1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(I-825). 向小瓶中添加(S)-3-((1-(7,8-二氯-4-(4-甲基-1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸三級丁酯(13 mg，0.0257 mmol)及HCl之1,4-二噁烷溶液(4 N，0.3 ml)。在室溫下將混合物攪拌3小時。減壓移除所有揮發性物質。凍乾後，獲得呈鹽酸鹽形式之標題化合物(11 mg)。(MS: [M+1]$^+$ 449)

實例137：合成(±)3-(((2S,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-(甲氧基羰基)吡咯啶-3-基)甲氧基)丙酸(I-813)。



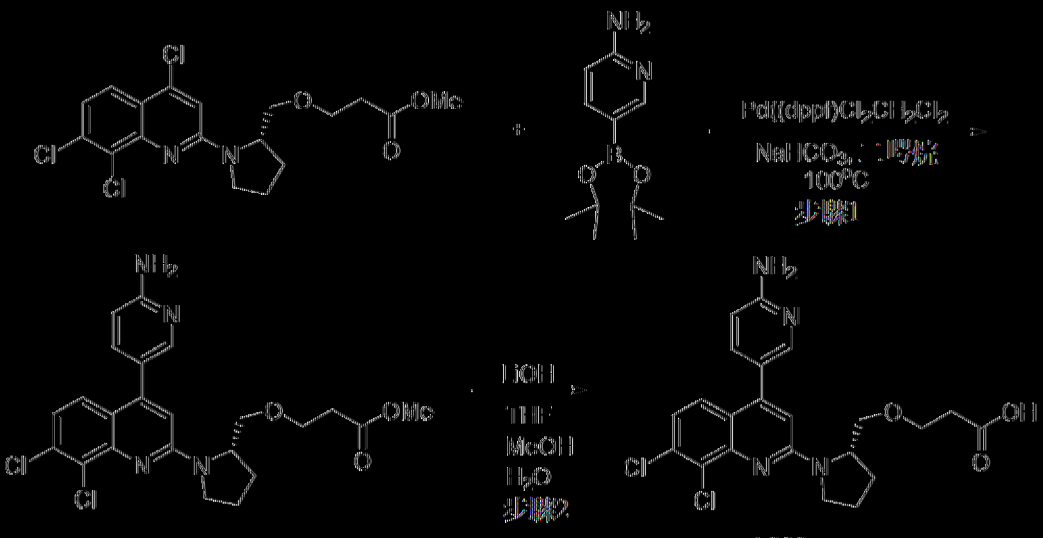
[0884] 步驟1：(±)(3aR,6aS)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)六氫-6H-呋喃并[3,4-b]吡咯-6-酮. 該程序與合成I-665中之程序相同。

[0885] 步驟2：(±)(2S,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-3-(羥基甲基)吡咯啶-2-甲酸甲酯. 用TEA (20 μl，0.143 mmol)及甲醇(0.5 ml)處理步驟1中之粗產物18小時。移除所有揮發性物質後，將粗品用於下一步驟。

[0886] 步驟3：(±)(2S,3R)-3-((3-(三級丁氧基)-3-側氧基丙氧基)甲基)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)吡咯啶-2-甲酸甲酯. 該程序與合成I-665中之程序相同。

[0887] 步驟4：(±)3-(((2S,3R)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-2-(甲氧基羰基)吡咯啶-3-基)甲氧基)丙酸. 該程序與合成I-665中之程序相同。獲得呈三氟乙酸鹽形式之標題化合物(17 mg)。(MS: $[M+1]^+$ 493)

實例138：合成(S)-3-((1-(4-(6-胺基吡啶-3-基)-7,8-二氯喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸(I-822)

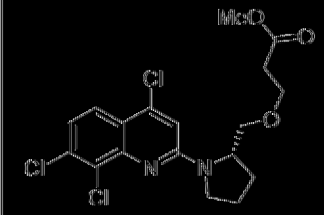
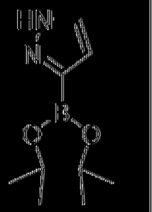
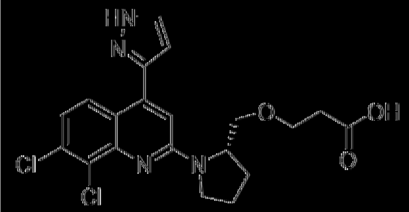
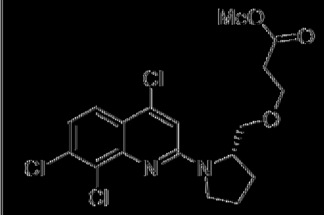
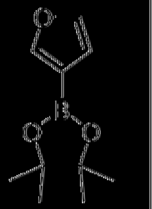
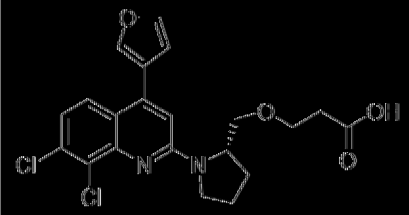
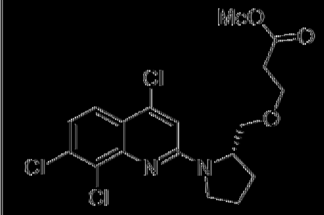
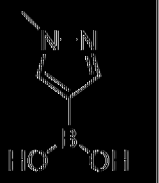
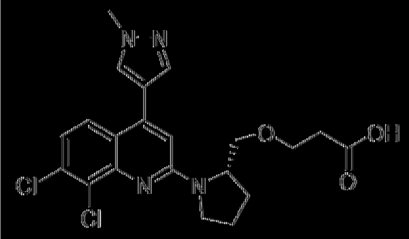


I-822

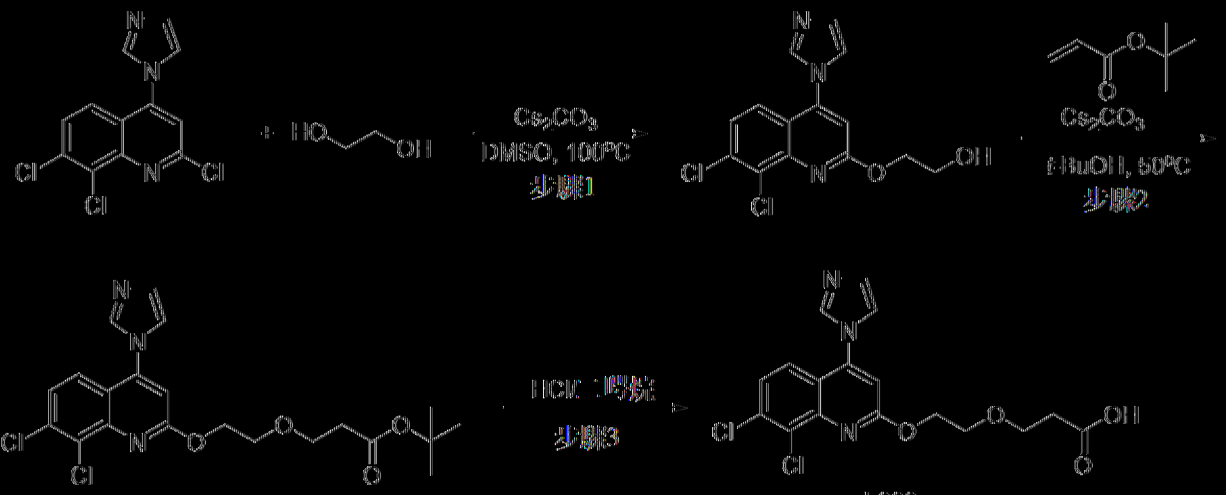
【0888】 步驟1：(S)-3-((1-(4-(6-胺基吡啶-3-基)-7,8-二氯喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯. 向燒瓶中添加(S)-3-((1-(4,7,8-三氯喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸甲酯(104 mg，0.25 mmol)、1,4-二噁烷(8.0 ml)、5-(4,4,5,5-四甲基-1,3,2-二氧雜硼雜環戊烷-2-基)吡啶-2-胺(110 mg，0.50 mmol)、$NaHCO_3$ (62 mg，0.75 mmol)、$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (41 mg，0.050 mmol)及H_2O (1.0 ml)。用N_2脫氣4次後，在100℃下將反應混合物攪拌6小時。將反應混合物用乙酸乙酯稀釋，用H_2O、鹽水洗滌且經Na_2SO_4乾燥。濃縮後，將粗品藉由矽膠管柱純化，得到標題產物(90 mg)。

【0889】 步驟2：(S)-3-((1-(4-(6-胺基吡啶-3-基)-7,8-二氯喹啉-2-基)吡咯啶-2-基)甲氧基)丙酸. 該程序與合成I-636中之程序相同。獲得呈游離酸形式之標題化合物。(MS: $[M+1]^+$ 461)

【0890】 以下化合物基本上藉由與I-822相同之方法製備。

實例	起始材料		結構	MS $[M+1]^+$
I-823				435
I-824				435
I-826				449

實例139：合成3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)氧基)乙氧基)丙酸(I-828)



I-828

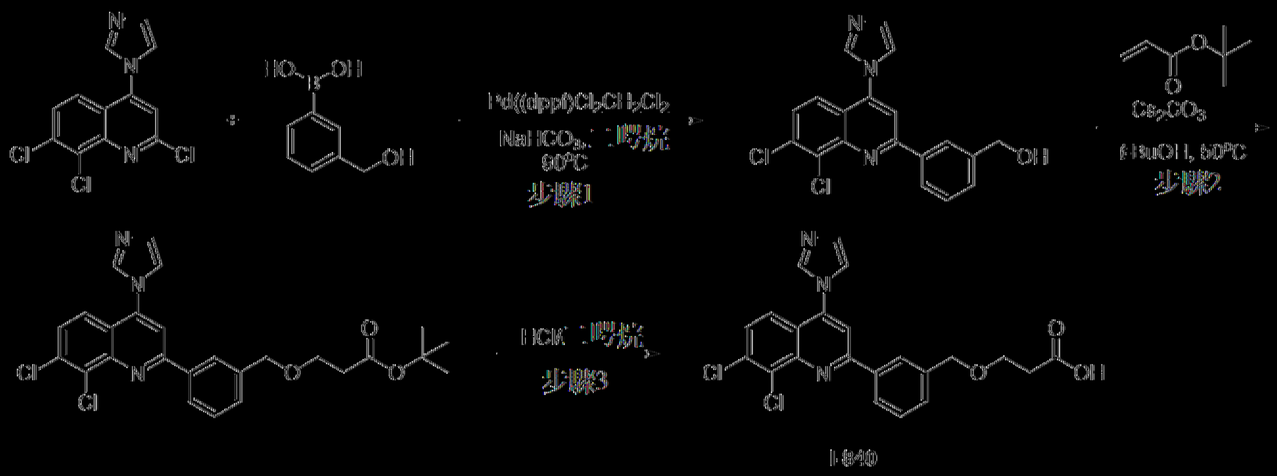
【0891】步驟1：2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)氧基)乙-1-醇. 該程序與合成I-277中之程序相同。

【0892】步驟2：3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)氧基)

乙氧基)丙酸三級丁酯. 該程序與合成I-665中之程序相同。

[0893] 步驟3：3-(2-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)氧基)乙氧基)丙酸. 該程序與合成I-825中之程序相同。獲得呈鹽酸鹽形式之標題化合物。(MS: $[M+1]^+$ 396)

實例140：合成3-((3-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲基)氧基)丙酸(I-840)

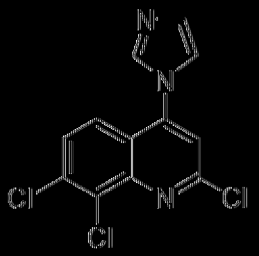
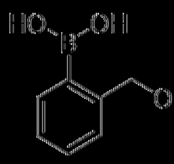
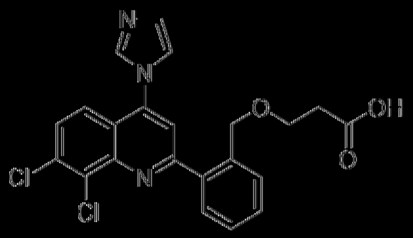


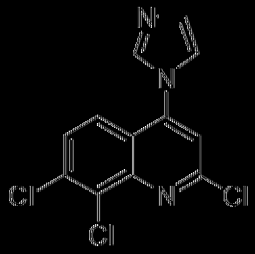
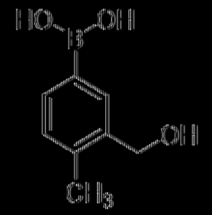
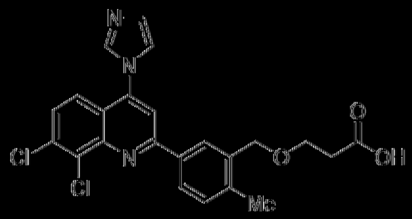
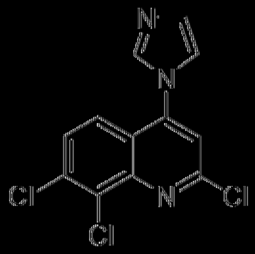
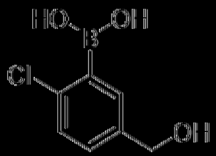
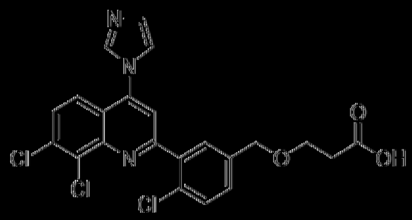
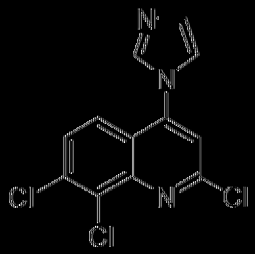
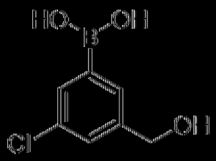
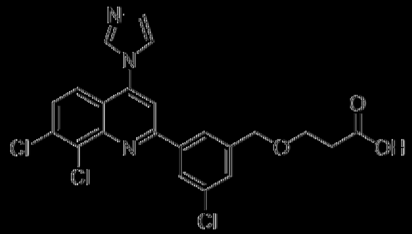
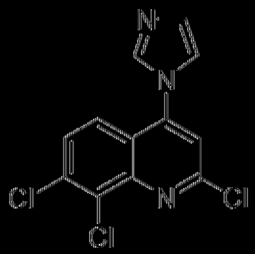
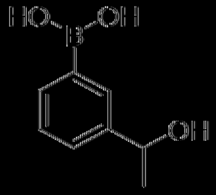
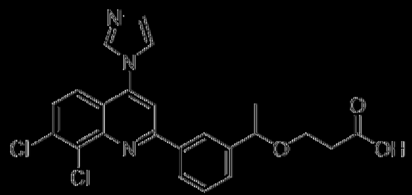
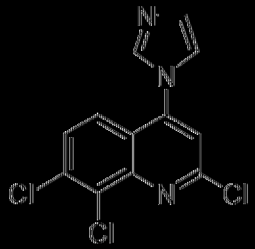
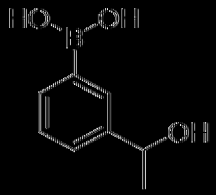
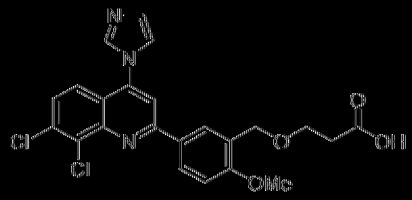
[0894] 步驟1：(3-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)苯基)甲醇. 該程序與合成I-822中之程序相同。

[0895] 步驟2：3-((3-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲基)氧基)丙酸三級丁酯. 該程序與合成I-665中之程序相同。

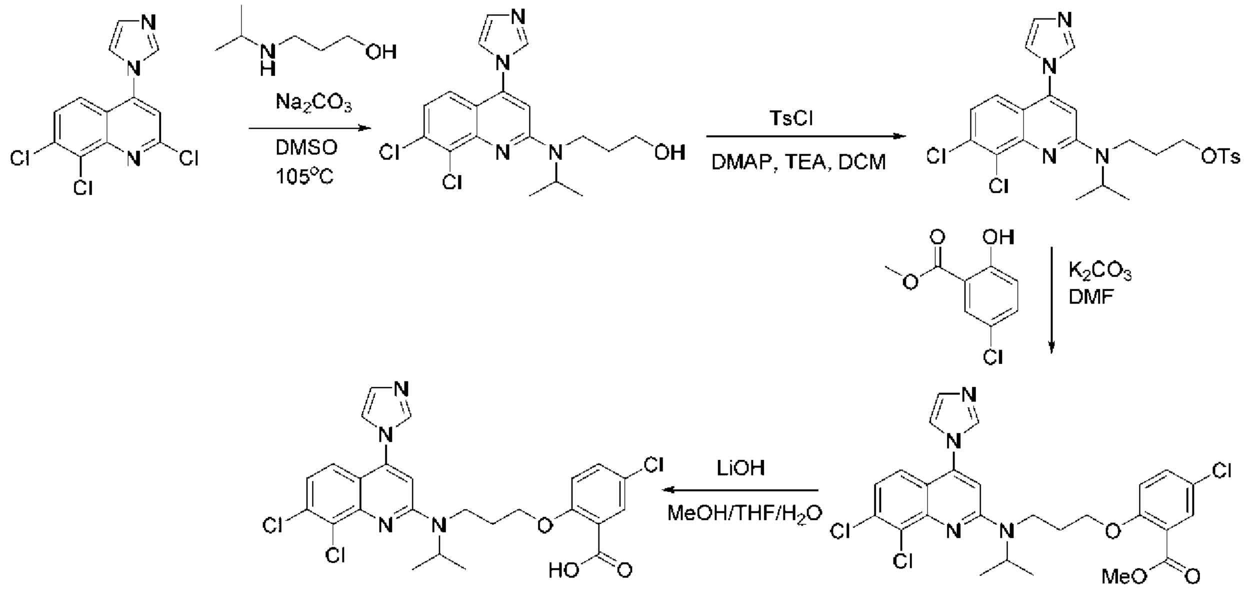
[0896] 步驟3：3-((3-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)苯甲基)氧基)丙酸. 該程序與合成I-825中之程序相同。獲得呈鹽酸鹽形式之標題化合物。(MS: $[M+1]^+$ 442)

[0897] 以下化合物基本上藉由與I-840相同之方法製備。

實例	起始材料		結構	MS $[M+1]^+$
I-841				442

實例	起始材料		結構	MS [M+1]$^+$
I-877				456
I-878				476
I-879				476
I-880				456
I-884				472

實例141：合成5-氯-2-(3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(異丙基)胺基)丙氧基)苯甲酸(I-848)



I-848

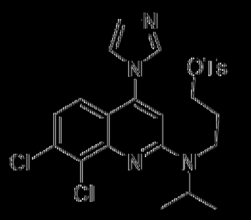
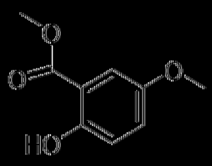
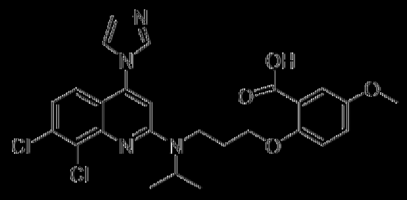
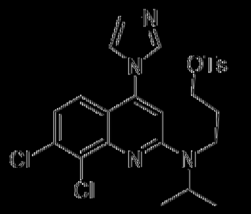
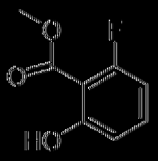
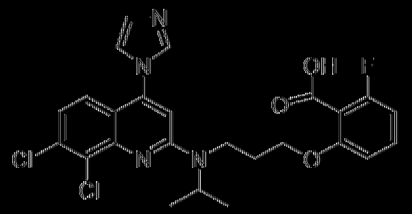
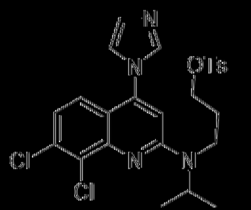
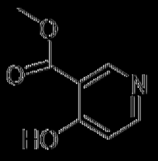
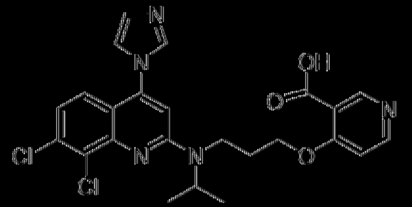
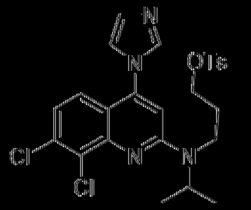
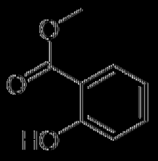
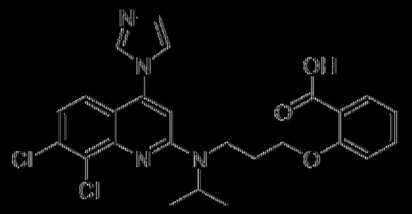
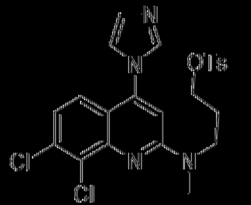
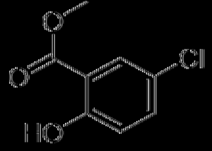
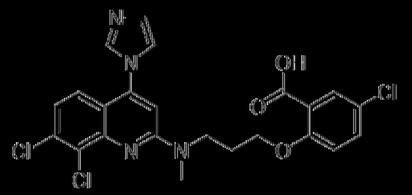
【0898】 步驟1：3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(異丙基)胺基)丙-1-醇. 向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(1.074 g)、3-(異丙基胺基)丙-1-醇(0.53 g)及Na_2CO_3 (0.96 g)之混合物中添加DMSO (3.4 mL)。在105℃下將所得懸浮溶液加熱隔夜。冷卻至室溫後，將反應混合物用水(5 mL)稀釋並用EtOAc (20 mL)萃取。將分離之有機層用鹽水洗滌且經無水Na_2SO_4乾燥。減壓濃縮後，將殘餘物藉由矽膠管柱層析法，用己烷及EtOAc (5% MeOH)梯度溶離來純化，得到呈淺褐色固體狀之標題化合物(654 mg)。MS: $[M+1]^+$ 379。

【0899】 步驟2：4-甲基苯磺酸3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基(異丙基)胺基)丙酯. 向3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(異丙基)胺基)丙-1-醇(654 mg)、DMAP (45 mg)及TsCl (228 mg)於DCM (10 mL)中之懸浮液中添加TEA (0.3 mL)。將反應混合物攪拌3小時後，用DCM (20 mL)對其進行稀釋。將所得有機溶液用水(10 mL)及鹽水(10 mL)洗滌且經無水Na_2SO_4乾燥。減壓濃縮，得到將粗標題化合物(610 mg)，將其不經進一步純化即用於下一步驟中。MS: $[M+1]^+$ 533。

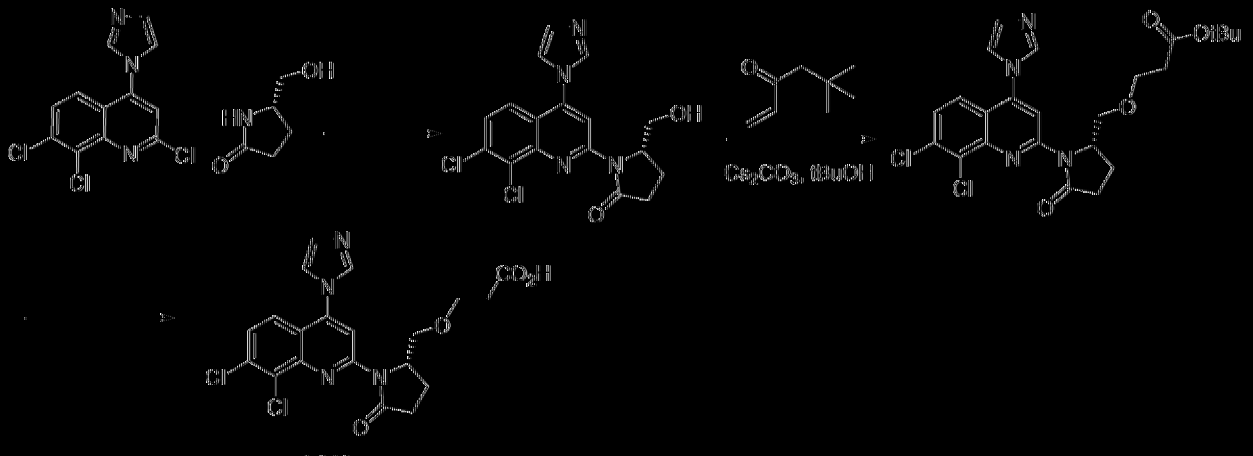
【0900】 步驟3：5-氯-2-(3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(異丙基)胺基)丙氧基)苯甲酸甲酯. 向4-甲基苯磺酸3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基(異丙基)胺基)丙酯(32 mg)及5-氯-2-羥基苯甲酸甲酯(13.5 mg)於無水DMF (0.5 mL)中之溶液中添加無水K_2CO_3 (10 mg)。在55℃下將反應混合物攪拌3小時後，用水(4 mL)及EtOAc (15 mL)對其進行稀釋。將有機層分離，用鹽水(10 mL)洗滌且經無水Na_2SO_4乾燥。減壓濃縮且藉由矽膠管柱層析法，用己烷及EtOAc (5% MeOH)梯度溶離來純化，得到標題化合物(24 mg)。MS: $[M+1]^+$ 547。

【0901】 步驟4：5-氯-2-(3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(異丙基)胺基) 丙氧基)苯甲酸(**I-848**). 向5-氯-2-(3-((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)(異丙基)胺基)丙氧基)苯甲酸甲酯(24 mg)於MeOH (0.4 mL)及水(0.1 mL)中之懸浮液中添加LiOH.H_2O (10.2 mg)。攪拌1小時後，添加THF (0.2 mL)。將反應混合物攪拌隔夜後，得到澄清溶液。藉由LC/MS監測反應進展。減壓濃縮移除揮發性物質後，將殘餘物懸浮於水(0.2 mL)中並用HOAc (0.015 mL)處理。音波處理5分鐘後，藉由離心機收集固體並凍乾，得到標題化合物(13 mg)。MS: $[M+1]^+$ 533。

【0902】 以下化合物基本上藉由與以上關於**I-848**所描述相同之方法製備。

實例	起始材料		結構	MS [M+1]+
I-849				529
I-850				517
I-851				500
I-852				499
I-847				505

實例142：合成(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-側氧基吡咯啶-2-基)甲氧基)丙酸(I-812)



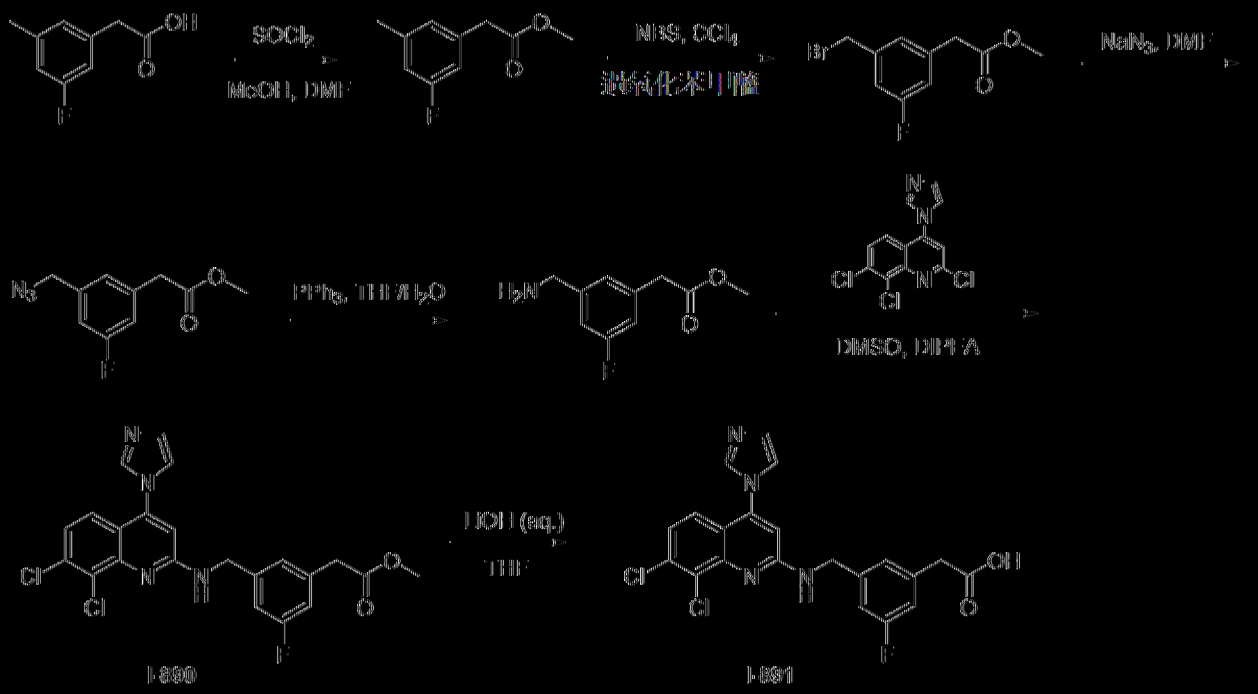
I-812

【0903】 步驟1：(S)-1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-(羥基甲基)吡咯啶-2-酮. 在N_2下，向2,7,8-三氯-4-(1H-咪唑-1-基)喹啉(200 mg)、雙(二苯亞甲基丙酮)鈀(0) (20 mg)、Rac-BINAP (14 mg)、(S)-5-(羥基甲基)吡咯啶-2-酮(92 mg)及Cs_2CO_3 (441 mg)之混合物中添加無水二噁烷(6 mL)。經由真空及用N2吹掃將所得混合物脫氣三個循環。將所得混合物加熱並在N_2下，在100℃下攪拌隔夜。用EtOAc水性處理後，將分離之有機層經無水Na_2SO_4乾燥。減壓濃縮後，將殘餘物藉由矽膠管柱層析法，用己烷及EtOAc (5% MeOH)梯度溶離來純化，得到標題化合物(28 mg)。MS: $[M+1]^+$ 377。

【0904】 步驟2：(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-側氧基吡咯啶-2-基)甲氧基)丙酸三級丁酯. 遵循與**I-825**之步驟3中所描述相同之製備程序，製備出標題化合物。MS: $[M+1]^+$ 505。

【0905】 步驟3：(S)-3-((1-(7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)-5-側氧基吡咯啶-2-基)甲氧基)丙酸(**I-812**). 遵循與**I-825**之步驟4中所描述相同之製備程序，製備出標題化合物。MS: $[M+1]^+$ 449。

實例143：合成2-(3-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)-5-氟苯基)乙酸甲酯(**I-890**)及2-(3-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)-5-氟苯基)乙酸(**I-891**)



【0906】 步驟1：2-(3-氟-5-甲基苯基)乙酸甲酯. 在0℃下，向2-(3-氟-5-甲基苯基)乙酸(336 mg，2 mmol)於MeOH (4 mL)及DMF (0.01 mL)中之溶液中逐滴添加$SOCl_2$ (0.22 mL，3 mmol)。將溶液升溫至室溫並攪拌2小時。蒸發後，藉由$NaHCO_3$ (飽和，2 mL)淬滅反應並藉由EtOAc (5 mL × 2)萃取。收集有機相並蒸發，得到粗產物，將其不經純化即直接用於下一步驟。

【0907】 步驟2：2-(3-(溴甲基)-5-氟苯基)乙酸甲酯. 向來自步驟1之粗品於CCl_4 (5 mL)中之溶液中添加NBS (392 mg，2.2 mmol)及過氧化苯甲醯(10 mg)。在75℃下將混合物攪拌隔夜。冷卻至室溫後，濃縮溶液並藉由矽膠管柱純化，得到呈無色油狀之標題產物(150 mg)。

【0908】 步驟3：2-(3-(疊氮基甲基)-5-氟苯基)乙酸甲酯. 向2-(3-(溴甲基)-5-氟苯基)乙酸甲酯(50 mg，0.19 mmol)於DMF (1 mL)中之溶液中添加NaN_3 (19 mg，0.29 mmol)。在75℃下將混合物攪拌隔夜。冷卻至室溫後，將混合物用H_2O (2 mL)稀釋並藉由EtOAc (3 mL × 2)萃取。收集有機相並蒸發，得到粗產物，將其不經純化即直接用於下一步驟。

【0909】 步驟4：2-(3-(胺基甲基)-5-氟苯基)乙酸甲酯. 施陶丁格反應(Staudinger reaction)係以與**I-757**基本上相同之方式執行。

【0910】 步驟5：2-(3-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)-5-氟苯基)乙酸甲酯(**I-890**). **I-890**係基本上藉由與**I-664**相同之方法製備。MS: $[M-1]^-$ 457。

【0911】 步驟6：2-(3-(((7,8-二氯-4-(1H-咪唑-1-基)喹啉-2-基)胺基)甲基)-5-氟苯基)乙酸(**I-891**). **I-891**係基本上藉由與**I-714**相同之方法製備。MS: $[M-1]^-$ 443。

實例144：生物學

【0912】 重組cGAS蛋白質之表現及純化：將編碼人類cGAS之全長或胺基酸147-520的cDNA插入含有框內His6-SUMO標籤之經修飾pET28a載體中。在18℃下，用0.5 mM IPTG誘導含有該質體之大腸桿菌菌株BL21/pLys隔夜。如先前所描述(Sun等人, 2013, *Science* 339,786)，在純化His6-SUMO-cGAS之後，藉由SUMO蛋白酶消化來移除His6-SUMO標籤。

【0913】 cGAS活性之活體外抑制分析：將60 μL含有20 mM Tirs-Cl pH 7.5、5 mM $MgCl_2$、0.2 mg/mL BSA、0.01 mg/mL鯡魚睪丸DNA、6.6 μM ATP、0.1 mM GTP、1.5 μg/mL重組人類cGAS (aa147-522)以及測試化合物於DMSO中之連續稀釋液的混合物添加至96孔盤中並在37℃下培育20分鐘。在反應結束時，添加40 μL KinaseGlo Max (Promega)並用光度計量測化學發光。藉由將ATP消耗百分比對化合物濃度之對數作圖來評估化合物之抑制作用。使用GraphPad Prism 8(GraphPad Software, Inc.)計算IC_{50}值。

【0914】 本發明化合物之cGAS抑制分析的結果呈現於**表2**及**表3**中。cGAS IC$_{50}$之字母代碼包括：A(<2 μM)；B(2-30 μM)；C(>30 μM)。

表2. cGAS抑制結果

I-#	**IC$_{50}$**
I-1	B
I-2	B
I-3	C
I-4	B
I-5	B
I-6	A
I-7	B
I-8	B
I-9	C
I-10	B
I-11	B
I-12	C
I-13	C
I-14	C
I-15	A
I-16	C
I-17	B
I-18	B
I-19	A
I-20	A
I-21	A
I-22	A
I-23	A
I-24	A
I-25	C
I-26	A
I-27	C
I-28	A
I-29	A
I-30	B
I-31	C
I-32	A
I-33	B
I-34	C
I-35	B
I-36	C
I-37	C
I-38	C
I-39	A
I-40	C
I-41	A
I-42	A
I-43	A
I-44	C
I-45	B
I-46	A
I-47	A
I-48	A
I-49	C
I-50	A
I-51	C
I-52	C
I-53	B
I-54	B
I-55	A
I-56	B
I-57	B
I-58	C
I-59	C
I-60	C
I-61	C
I-62	C
I-63	C
I-64	C
I-65	C
I-66	C
I-67	B
I-68	C
I-69	C
I-70	C
I-71	C
I-72	C
I-73	C
I-74	C
I-75	C
I-76	B
I-77	C
I-78	C
I-79	A
I-80	A
I-81	A
I-82	A
I-83	B
I-84	B
I-85	A
I-86	A
I-87	B
I-88	B
I-89	B
I-90	C
I-91	A
I-92	A
I-93	A
I-94	A
I-95	B
I-96	A
I-97	B
I-98	B
I-99	B
I-100	A
I-101	A
I-102	B
I-103	B
I-104	B
I-105	B
I-106	B
I-107	C
I-108	C
I-109	C
I-110	A
I-111	A
I-112	A
I-113	A
I-114	B
I-115	A
I-116	A
I-117	B
I-118	A
I-119	B
I-120	A
I-121	B
I-122	B
I-123	B
I-124	A
I-125	A
I-126	B

I-#	IC$_{50}$
I-127	B
I-128	B
I-130	B
I-131	B
I-132	B
I-133	A
I-134	B
I-135	C
I-136	B
I-137	B
I-138	A
I-139	A
I-140	B
I-141	A
I-142	A
I-143	A
I-144	A
I-145	A
I-147	A
I-148	A
I-149	A
I-150	A
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I-161	C
I-162	C
I-163	C
I-164	B
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I-166	B
I-167	A
I-168	A
I-169	A
I-170	A
I-171	C
I-172	B
I-173	B
I-174	A
I-175	A
I-176	B
I-177	B

I-#	IC$_{50}$
I-178	B
I-179	B
I-180	B
I-181	C
I-182	B
I-183	A
I-184	A
I-185	B
I-186	A
I-187	B
I-188	B
I-189	B
I-190	A
I-191	A
I-192	A
I-193	B
I-194	A
I-195	A
I-196	A
I-197	A
I-198	A
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I-200	A
I-201	A
I-202	A
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I-205	A
I-206	B
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I-209	C
I-210	B
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I-212	B
I-213	B
I-214	B
I-215	B
I-216	B
I-217	C
I-218	A
I-219	A
I-220	B
I-221	A
I-222	A
I-223	A
I-224	A
I-225	A
I-226	B

I-#	IC$_{50}$
I-227	C
I-228	C
I-229	C
I-230	B
I-231	B
I-232	B
I-234	A
I-235	A
I-236	B
I-237	B
I-238	A
I-239	A
I-240	A
I-241	A
I-242	A
I-243	A
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I-245	A
I-246	B
I-247	B
I-248	A
I-249	A
I-250	A
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I-262	A
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I-264	A
I-265	C
I-266	C
I-267	C
I-268	C
I-269	C
I-270	A
I-271	B
I-272	B
I-273	B
I-274	B
I-275	C
I-276	A

I-#	IC_{50}
I-277	B
I-278	B
I-279	C
I-280	C
I-281	B
I-282	B
I-283	C
I-284	C
I-285	A
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I-291	B
I-292	B
I-293	B
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I-296	C
I-297	C
I-298	C
I-299	C
I-300	C
I-301	C
I-302	C
I-303	C
I-304	C
I-305	C
I-306	C
I-307	C
I-308	C
I-309	C
I-310	C
I-311	C
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I-318	C
I-319	C
I-320	A
I-321	A
I-322	A
I-323	A
I-324	A
I-325	A
I-326	A
I-327	A
I-328	A
I-329	A
I-330	A
I-331	B
I-332	A
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I-334	C
I-335	A
I-336	B
I-337	A
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I-339	A
I-340	A
I-341	A
I-342	A
I-343	B
I-344	A
I-345	A
I-346	A
I-347	A
I-348	C
I-349	A
I-350	A
I-351	A
I-352	B
I-353	C
I-354	C
I-355	B
I-356	C
I-357	B
I-358	B
I-359	B
I-360	A
I-361	B
I-362	C
I-363	B
I-364	B
I-365	C
I-366	B
I-367	C
I-368	B
I-369	A
I-370	A
I-371	A
I-372	A
I-373	A
I-374	A
I-375	B
I-376	C
I-377	C
I-378	A
I-379	B
I-380	B
I-381	C
I-382	B
I-383	C
I-384	B
I-385	B
I-386	A
I-387	A
I-388	B
I-389	A
I-390	B
I-391	A
I-392	B
I-393	C
I-394	C
I-395	B
I-396	A
I-397	A
I-398	B
I-399	B
I-400	B
I-401	C
I-402	B
I-403	C
I-404	C
I-405	B
I-406	B
I-407	C
I-408	C
I-409	C
I-410	C
I-411	C
I-412	B
I-413	C
I-414	C
I-415	C
I-416	C
I-417	C
I-418	C
I-419	C
I-420	C
I-421	B
I-422	C
I-423	A

I-#	IC$_{50}$
I-424	B
I-425	C
I-426	C
I-427	A
I-428	A
I-429	A
I-430	A
I-431	A
I-432	B
I-433	A

I-#	IC$_{50}$
I-434	B
I-435	A
I-436	B
I-437	A
I-438	B
I-439	B
I-443	A
I-444	A
I-445	B
I-446	B

I-#	IC$_{50}$
I-447	C
I-448	A
I-449	A
I-450	B
I-451	B
I-452	B
I-453	C
I-454	A

表3. cGAS抑制結果

I-#	IC$_{50}$
I-455	A
I-456	C
I-457	B
I-458	B
I-459	B
I-460	B
I-461	A
I-462	B
I-463	B
I-464	A
I-465	A
I-466	A
I-467	B
I-468	B
I-469	A
I-470	A
I-471	B
I-472	B
I-473	A
I-474	B
I-475	B
I-476	B
I-477	A
I-478	A
I-479	A
I-480	A
I-481	A
I-482	A
I-483	B
I-484	B
I-485	A
I-486	A
I-487	A
I-488	A
I-489	A

I-#	IC$_{50}$
I-490	A
I-491	A
I-492	B
I-493	A
I-494	A
I-495	A
I-496	B
I-497	B
I-498	B
I-499	A
I-500	B
I-501	A
I-502	B
I-503	A
I-504	A
I-505	B
I-506	B
I-507	A
I-508	A
I-509	A
I-510	A
I-511	A
I-512	A
I-513	A
I-514	A
I-515	A
I-516	A
I-517	A
I-518	A
I-519	A
I-520	A
I-521	A
I-522	B
I-524	A
I-525	A

I-#	IC$_{50}$
I-526	A
I-527	A
I-528	C
I-529	A
I-530	A
I-531	A
I-532	B
I-533	A
I-534	B
I-535	B
I-536	A
I-537	B
I-538	A
I-539	A
I-540	A
I-541	A
I-542	B
I-543	B
I-544	B
I-545	A
I-546	B
I-547	B
I-548	A
I-549	A
I-550	B
I-551	C
I-552	A
I-553	A
I-554	B
I-555	A
I-556	A
I-557	A
I-558	A
I-559	A
I-560	A

I-#	IC$_{50}$
I-561	A
I-562	A
I-563	A
I-564	A
I-565	A
I-566	A
I-567	A
I-568	B
I-569	A
I-570	B
I-571	A
I-572	A
I-573	B
I-574	B
I-575	B
I-576	A
I-577	B
I-578	B
I-579	C
I-580	C
I-581	B
I-582	A
I-583	B
I-584	B
I-585	B
I-586	B
I-587	B
I-588	A
I-589	B
I-590	B
I-591	B
I-592	B
I-593	B
I-594	B
I-595	B
I-596	B
I-597	B
I-598	B
I-599	B
I-600	B
I-601	B
I-602	B
I-603	A
I-604	B
I-605	C
I-606	B
I-607	A
I-608	B
I-609	C

I-#	IC$_{50}$
I-610	A
I-611	C
I-612	B
I-613	A
I-614	B
I-615	B
I-616	A
I-617	A
I-618	A
I-619	B
I-620	B
I-621	B
I-622	A
I-623	B
I-624	A
I-625	A
I-626	A
I-627	A
I-628	A
I-629	A
I-630	A
I-631	A
I-632	A
I-633	A
I-634	A
I-635	A
I-636	A
I-637	A
I-638	B
I-639	A
I-640	A
I-641	A
I-642	B
I-643	A
I-644	B
I-645	B
I-646	B
I-647	B
I-648	B
I-649	B
I-650	B
I-651	A
I-652	B
I-653	A
I-654	A
I-655	A
I-656	C
I-657	A
I-658	A

I-#	IC$_{50}$
I-659	A
I-660	B
I-661	A
I-662	B
I-663	A
I-664	A
I-665	A
I-666	A
I-667	A
I-668	A
I-669	B
I-670	A
I-671	A
I-672	A
I-673	B
I-674	A
I-675	A
I-676	A
I-677	A
I-678	A
I-679	A
I-680	B
I-681	B
I-682	A
I-683	A
I-684	A
I-685	A
I-686	B
I-687	B
I-688	A
I-689	A
I-690	A
I-691	A
I-692	A
I-693	A
I-694	A
I-695	B
I-696	A
I-697	A
I-698	A
I-699	A
I-700	A
I-701	A
I-702	A
I-703	A
I-704	A
I-705	A
I-706	A
I-707	A

I-#	IC$_{50}$
I-708	A
I-709	A
I-710	A
I-711	A
I-712	A
I-713	A
I-714	A
I-715	A
I-716	A
I-717	A
I-718	B
I-719	A
I-720	B
I-721	B
I-722	A
I-723	A
I-724	A
I-725	A
I-726	A
I-727	A
I-728	A
I-729	A
I-730	A
I-731	A
I-732	A
I-733	A
I-734	A
I-735	A
I-736	A
I-737	A
I-738	A
I-739	A
I-740	A
I-741	A
I-742	A
I-743	A
I-744	A
I-745	A
I-746	A
I-747	A
I-748	A
I-749	A
I-750	A
I-751	A
I-752	A
I-753	C
I-754	B
I-755	C
I-756	B

I-#	IC$_{50}$
I-757	B
I-758	B
I-759	A
I-760	A
I-761	A
I-762	A
I-763	A
I-764	A
I-765	B
I-766	A
I-767	B
I-768	B
I-769	B
I-770	A
I-771	B
I-772	B
I-773	A
I-774	A
I-775	A
I-776	A
I-778	B
I-779	B
I-780	B
I-781	A
I-782	A
I-783	A
I-784	A
I-785	A
I-786	A
I-787	A
I-788	A
I-789	A
I-790	B
I-791	B
I-792	A
I-793	A
I-794	A
I-795	A
I-796	A
I-797	A
I-798	A
I-799	A
I-800	A
I-801	A
I-802	A
I-803	A
I-804	A
I-805	A
I-806	A

I-#	IC$_{50}$
I-807	A
I-808	A
I-809	A
I-810	A
I-811	A
I-812	A
I-813	A
I-814	A
I-815	A
I-816	A
I-817	A
I-818	B
I-819	A
I-820	A
I-821	C
I-822	C
I-823	C
I-824	C
I-825	C
I-826	C
I-827	C
I-828	B
I-829	A
I-830	A
I-831	A
I-832	A
I-833	A
I-834	A
I-835	A
I-836	A
I-837	A
I-838	A
I-839	A
I-840	A
I-841	A
I-842	A
I-843	A
I-844	A
I-845	A
I-846	A
I-847	B
I-848	B
I-849	B
I-850	B
I-851	B
I-852	B
I-853	A
I-854	A
I-855	B

I-#	IC$_{50}$
I-856	A
I-857	A
I-858	C
I-859	B
I-860	A
I-861	C
I-862	A
I-863	C
I-864	A
I-865	A
I-866	A
I-867	A

I-#	IC$_{50}$
I-868	A
I-869	B
I-870	B
I-871	B
I-872	B
I-873	A
I-874	A
I-875	A
I-876	A
I-877	A
I-878	A
I-879	A

I-#	IC$_{50}$
I-880	A
I-881	A
I-882	A
I-883	A
I-884	A
I-885	A
I-886	A
I-887	A
I-888	A
I-889	A
I-890	B
I-891	A

【0915】 量測cGAS活性之細胞分析：使用報導體THP1細胞株測試合成化合物對人類細胞中cGAS活性之抑制作用，該細胞株含有編碼長腹水蚤螢光素酶之基因，該基因處於與ISG54最小啟動子融合的干擾素刺激反應元件(ISRE)之5個串聯重複序列控制下。此等細胞以每孔0.3×10^{6}個塗鋪於96孔盤上並與化合物之連續稀釋液或DMSO一起培育5分鐘，隨後利用2 μg/mL ISD(干擾素刺激DNA，45 bp DNA寡聚物)轉染，或根據製造商說明書，使用lipofectamine 2000(Life Technology)方法進行模擬轉染。16小時後，將15 μL來自各孔之培養基轉移至新盤中，向各孔中添加50 μL含有50 mM Hepes-NaOH pH 6.5、50 mM NaCl、10 mM EDTA、1 μM腔腸素之溶液並立即量測發光。將相較於模擬轉染之發光增加倍數針對各化合物之濃度作圖，並使用Graphpad計算IC$_{50}$。為評估化合物之特異性，執行相同程序，但用2 μg/mL聚(I:C)轉染或用50個單位/毫升已知可活化RIG-I MAVS路徑之仙台病毒(Sendai Virus，SeV)感染細胞。特異性抑制性化合物應抑制DNA之干擾素誘導，而且對聚(I:C)或仙台病毒誘導之干擾素報導體基因表現具有最小作用。

【0916】 本發明化合物之細胞分析的結果呈現於**表4**中。cGAS IC$_{50}$之字母代碼包括：A (<2 μM)；B (2 - 10 μM)；C (>10 μM)。

表4. 細胞分析結果

I-#	IC$_{50}$
I-15	C
I-24	B
I-39	B
I-86	B
I-92	C
I-116	B
I-139	B
I-149	C
I-200	A
I-322	C
I-428	B
I-429	C
I-435	B
I-443	B
I-448	C
I-461	C
I-467	B
I-469	A
I-470	B
I-471	B
I-473	A
I-477	B
I-478	B
I-487	B
I-507	B
I-516	C
I-532	B
I-539	B
I-556	A
I-575	B
I-576	A
I-577	B
I-578	B
I-582	A
I-583	A
I-584	B
I-585	A
I-586	A
I-591	B
I-592	B
I-593	B
I-594	B
I-595	B
I-596	A
I-597	C
I-598	A
I-599	A
I-600	A
I-601	A
I-642	A
I-645	A
I-649	B
I-650	B
I-663	A
I-664	A
I-665	A
I-666	A
I-667	A
I-668	A
I-669	A
I-670	A
I-671	A
I-672	A
I-673	A
I-674	B
I-676	A
I-677	A
I-678	B
I-679	B
I-680	B
I-681	A
I-682	A
I-683	A
I-684	A
I-685	A
I-686	A
I-687	C
I-688	A
I-689	C
I-690	A
I-691	A
I-692	A
I-693	C
I-694	A
I-695	B
I-696	A
I-698	C
I-699	A
I-700	B
I-701	B
I-702	B
I-703	C
I-704	A
I-705	A
I-706	A
I-707	A
I-708	A
I-709	A
I-710	B
I-711	A
I-712	A
I-713	A
I-714	B
I-715	C
I-716	C
I-717	A
I-718	A
I-719	A
I-720	A
I-722	B
I-723	B
I-724	B
I-725	C
I-726	C
I-728	B
I-730	B
I-732	A
I-733	A
I-734	A
I-735	B
I-736	A
I-739	A
I-740	C
I-741	B
I-742	C
I-743	A
I-744	A
I-745	A
I-747	A
I-748	C
I-749	A
I-750	A
I-751	B
I-752	C
I-753	C
I-755	C
I-756	C
I-758	C

I-#	IC$_{50}$
I-759	C
I-760	C
I-761	C
I-762	C
I-764	C
I-765	B
I-773	A
I-774	B
I-775	B
I-776	C
I-778	C
I-779	C
I-780	C
I-781	C
I-782	C
I-784	C
I-785	C
I-786	B
I-787	B
I-788	C
I-789	A
I-791	C
I-792	A
I-793	A
I-794	A
I-795	A
I-796	A
I-797	A
I-798	A
I-799	C
I-800	A
I-801	A

I-#	IC$_{50}$
I-802	A
I-803	A
I-804	A
I-805	A
I-806	B
I-807	A
I-808	A
I-809	A
I-810	A
I-811	A
I-813	C
I-814	A
I-815	B
I-816	A
I-817	C
I-820	A
I-828	C
I-829	B
I-830	A
I-831	B
I-832	A
I-833	A
I-834	A
I-835	B
I-836	A
I-837	A
I-838	C
I-839	C
I-840	A
I-841	C
I-842	B
I-843	B

I-#	IC$_{50}$
I-844	A
I-845	A
I-846	A
I-853	A
I-854	C
I-855	C
I-856	B
I-857	A
I-860	C
I-862	A
I-864	C
I-865	A
I-866	B
I-867	A
I-868	B
I-872	A
I-875	A
I-876	A
I-877	A
I-878	A
I-879	A
I-880	B
I-882	C
I-883	B
I-884	A
I-885	B
I-886	A
I-887	B
I-888	B
I-889	C
I-890	A
I-891	A

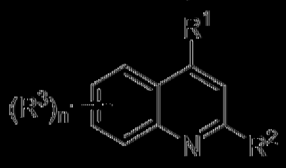
【0917】本申請案中引用的所有出版物、專利、專利申請案及其他文獻，包括美國臨時申請案第63/074,446號、第63/124,713號及第63/196,146號在內，均以全文引用的方式併入本文中用於所有目的，其引用程度就如同個別地指示每一個別出版物、專利、專利申請案或其他文獻係以引用之方式併入用於所有目的。

【0918】雖然已說明且描述各種具體實施例，但應瞭解，可在不偏離所主張之發明之精神及範圍的情況下作出各種改變。

【發明申請專利範圍】

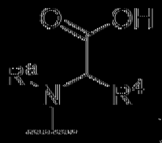
【請求項1】

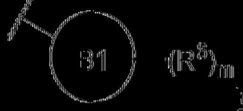
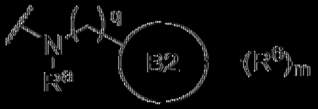
一種化合物，其中該化合物具有式I*：



I*

或其醫藥學上可接受之鹽，其中：

R^{1}係  或具有1至4個獨立地選自氮、氧及硫之雜原子的視情況經取代之5至6員雜芳基環；

R^{2}係-NR^{a}R^5、 或 ；

每個R^{3}獨立地係鹵素、-OR、-NR$_2$、-SR或R^C；

環B1係苯基，較佳地為經取代之苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；或具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

環B2係苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；或具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

每個R獨立地係氫或視情況經取代的選自以下之基團：C$_{1-6}$脂族基；苯甲基；苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環；及具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

R^{4}係氫或視情況經取代之C$_{1-6}$脂族基；

R^5係$-(CR_2)_{0-4}OR$、$-(CR_2)_{0-5}CO_2R$、$-(CR_2)_{0-5}CONR_2$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CO_2R$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-4}SO_3R$、$-(CR_2)_{0-4}SO_2NR_2$、$-(CR_2)_{0-4}OSO_2NR_2$、$-(CR_2)_{0-4}NRSO_2R$、$-(CR_2)_{0-4}NRSO_2OR$、$-(CR_2)_{0-4}OP(OR)_2$、$-(CR_2)_{0-4}OP(O)(OR)_2$、$-(CR_2)_{0-4}P(O)(OR)_2$、$-(CR_2)_{0-4}OP(O)(H)OR$或$R^B$；

每個R^6獨立地係鹵素、$-COR$、$-(CR_2)_{0-4}CO_2R$、$-(CR_2)_{0-4}CONR_2$、$-OR$、$-(CR_2)_{1-4}OR$、$-NR_2$、$-(CR_2)_{1-4}NR_2$、$-NRC(O)OR$、$-NRC(O)R$、$-NRC(O)NR_2$、$-SR$、$-SO_2R$、$-S(O)R$、$-(CR_2)_{0-4}SO_3R$、$-(CR_2)_{0-4}SO_2NR_2$、$-(CR_2)_{0-4}OSO_2NR_2$、$-(CR_2)_{0-4}NRSO_2R$、$-(CR_2)_{0-4}NRSO_2OR$、$-(CR_2)_{0-4}OP(OR)_2$、$-(CR_2)_{0-4}OP(O)(OR)_2$、$-(CR_2)_{0-4}P(O)(OR)_2$、$-(CR_2)_{0-4}OP(O)(H)OR$、$-B(OR)_2$或R^B；

R^B及R^C獨立地係視情況經取代的選自以下之基團：C_{1-6}脂族基；苯基；具有1至3個獨立地選自氮、氧及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環；及具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環；

每個R^a獨立地係H或C_{1-6}烷基；

每個m係0、1、2、3或4；

n係1、2、3或4；

q係0、1或2。

【請求項2】

如請求項1之化合物，其中R^1係具有1至4個獨立地選自氮、氧及硫之雜原子的視情況經取代之5至6員雜芳基環。

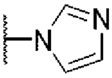
【請求項3】

如請求項1之化合物，其中R^1係咪唑。

【請求項4】

如請求項3之化合物，其中該咪唑未經取代。

【請求項5】

如請求項4之化合物，其中R^1係。

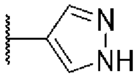
【請求項6】

如請求項1之化合物，其中R^1係吡唑。

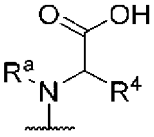
【請求項7】

如請求項6之化合物，其中該吡唑未經取代。

【請求項8】

如請求項7之化合物，其中R^1係。

【請求項9】

如請求項1之化合物，其中R^1係。

【請求項10】

如請求項9之化合物，其中R^4係C_{1-6}烷基。

【請求項11】

如請求項1至10中任一項之化合物，其中至少一個出現之R^3係鹵素。

【請求項12】

如請求項11之化合物，其中至少一個出現之R^3係氯。

【請求項13】

如請求項11之化合物，其中n係2且兩個R^3均為氯。

【請求項14】

如請求項11之化合物，其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【請求項15】

如請求項1至14中任一項之化合物，其中R^2係$-NR^aR^5$。

【請求項16】

如請求項15之化合物，其中R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{0-5}CO_2R$、$-(CR_2)_{0-5}CONR_2$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CO_2R$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-4}SO_3R$、$-(CR_2)_{0-4}SO_2NR_2$、$-(CR_2)_{0-4}OSO_2NR_2$、$-(CR_2)_{0-4}NRSO_2R$、$-(CR_2)_{0-4}NRSO_2OR$、$-(CR_2)_{0-4}OP(OR)_2$、$-(CR_2)_{0-4}OP(O)(OR)_2$、$-(CR_2)_{0-4}P(O)(OR)_2$或$-(CR_2)_{0-4}OP(O)(H)OR$。

【請求項17】

如請求項15之化合物，其中R^5係$-(CR_2)_{2-4}OR$、$-(CR_2)_{1-4}CO_2R$、$-(CR_2)_{1-4}CONR_2$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CO_2R$、$-(CR_2)_{0-4}C(O)NR(CR_2)_{0-4}CONR_2$、$-(CR_2)_{0-4}NRC(O)R$、$-(CR_2)_{0-4}SO_3R$、$-(CR_2)_{0-4}SO_2NR_2$、$-(CR_2)_{0-4}OSO_2NR_2$、$-(CR_2)_{0-4}NRSO_2R$、$-(CR_2)_{0-4}NRSO_2OR$、$-(CR_2)_{0-4}OP(OR)_2$、$-(CR_2)_{0-4}OP(O)(OR)_2$、$-(CR_2)_{0-4}P(O)(OR)_2$或$-(CR_2)_{0-4}OP(O)(H)OR$。

【請求項18】

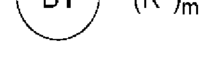
如請求項15之化合物，其中R^5係$-(CH_2)_{2-4}OH$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{2-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-3}CH(CH_2OH)_2$、$-(CH_2)_{2-4}OC_{1-4}$烷基、$-(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CONH_2$、$-(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{1-}$

$_{4}C(O)NR^{a}(CH_{2})_{1-4}CO_{2}H$、$-(CH_{2})_{1-4}C(O)NR^{a}(CH_{2})_{1-4}CONH_{2}$、$-(CH_{2})_{1-4}C(O)NR^{a}(CH_{2})_{1-4}CONHC_{1-4}$烷基、$-(CH_{2})_{1-4}C(O)NR^{a}(CH_{2})_{1-4}CON(C_{1-4}$烷基$)_{2}$、$-(CH_{2})_{0-4}NR^{a}C(O)(CH_{2})_{1-5}CO_{2}H$、$-(CH_{2})_{0-4}NR^{a}C(O)(CH_{2})_{1-5}CO_{2}C_{1-4}$烷基、$-(CH_{2})_{2-4}SO_{3}H$、$-(CH_{2})_{2-4}SO_{3}C_{1-4}$烷基、$-(CH_{2})_{2-4}SO_{2}NH_{2}$、$-(CH_{2})_{2-4}SO_{2}NHC_{1-4}$烷基、$-(CH_{2})_{2-4}SO_{2}N(C_{1-4}$烷基$)_{2}$、$-(CH_{2})_{2-4}OSO_{2}NH_{2}$、$-(CH_{2})_{2-4}NR^{a}SO_{2}C_{1-4}$烷基、$-(CH_{2})_{2-4}NR^{a}SO_{3}H$、$-(CH_{2})_{1-4}OP(OH)_{2}$、$-(CH_{2})_{1-4}P(O)(OH)_{2}$、$-(CH_{2})_{1-4}P(O)(OH)(OC_{1-4}$烷基$)$或$-(CH_{2})_{2-4}OP(O)(H)OH$，其中R^{a}在每次出現時獨立地係H或C$_{1-6}$烷基。

【請求項19】

如請求項15之化合物，其中R^{5}係$-(CH_{2})_{2-4}OH$、$-(CH_{2})_{2-4}O(CH_{2})_{1-5}CO_{2}H$、$-(CH_{2})_{2-4}O(CH_{2})_{1-5}CO_{2}C_{1-4}$烷基、$-(CH_{2})_{0-3}CH(CH_{2}OH)_{2}$、$-(CH_{2})_{1-4}CO_{2}H$、$-(CH_{2})_{1-4}CONH_{2}$、$-(CH_{2})_{1-4}C(O)NR^{a}(CH_{2})_{1-4}CO_{2}H$、$-(CH_{2})_{1-4}C(O)NR^{a}(CH_{2})_{1-4}CONH_{2}$、$-(CH_{2})_{0-4}NR^{a}C(O)(CH_{2})_{1-5}CO_{2}H$、$-(CH_{2})_{0-4}NR^{a}C(O)(CH_{2})_{1-5}CO_{2}C_{1-4}$烷基、$-(CH_{2})_{2-4}SO_{3}H$、$-(CH_{2})_{2-4}SO_{2}NH_{2}$、$-(CH_{2})_{2-4}SO_{2}NR^{a}C_{1-4}$烷基、$-(CH_{2})_{2-4}NR^{a}SO_{2}C_{1-4}$烷基、$-(CH_{2})_{1-4}P(O)(OH)_{2}$或$-(CH_{2})_{2-4}OP(O)(H)OH$，其中R^{a}在每次出現時獨立地係H或C$_{1-4}$烷基。

【請求項20】

如請求項1至14中任一項之化合物，其中R^{2}係 

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【請求項21】

如請求項20之化合物，其中環B1係經取代之苯基。

【請求項22】

如請求項21之化合物，其中該苯基經一或多個羧基取代。

【請求項23】

如請求項21之化合物，其中環B1係3-羧基苯基，其視情況經一或多個R^6基團取代。

【請求項24】

如請求項21之化合物，其中環B1係3,5-二羧基苯基，其視情況經一或多個R^6基團取代。

【請求項25】

如請求項20之化合物，其中環B1係具有1至3個獨立地選自氮、氧及硫之雜原子的4至10員飽和或部分不飽和單環或雙環碳環或雜環。

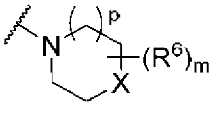
【請求項26】

如請求項20之化合物，其中環B1係具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環。

【請求項27】

如請求項20至26中任一項之化合物，其中m係1、2、3或4。

【請求項28】

如請求項20之化合物，其中R^2係  ，其中

X係不存在(亦即，為環中的鍵)、$-CR_2-$、-NR-、-O-、-S-或$-SO_2-$；且

p係0、1或2。

【請求項29】

如請求項28之化合物，其中X係$-CR_2-$、-NR-或-O-。

【請求項30】

如請求項28或29之化合物，其中p係1。

【請求項31】

如請求項28至30中任一項之化合物，其中m係1、2、3或4。

【請求項32】

如請求項20至30中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}\text{烷基})_2$、$-(CH_2)_{0-4}CO(N\text{-脯胺酸})$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}\text{烷基})_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}\text{烷基})_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}\text{烷基})$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項33】

如請求項20至30中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO(N\text{-脯胺酸})$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-2}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$。

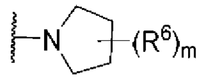
【請求項34】

如請求項20至30中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-(CH_2)_{0-2}CO_2H$、$-(CH_2)_{0-2}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}CO($*N*-脯胺酸)、$-(CH_2)_{0-2}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-(CH_2)_{1-2}OH$、$-(CH_2)_{0-2}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-2}OC(O)C_{1-4}$烷基、$-(CH_2)_{0-2}SO_3H$、$-(CH_2)_{0-2}SO_2NH_2$、$-(CH_2)_{0-2}NR^aSO_2C_{0-2}$烷基、$-(CH_2)_{0-2}OP(OH)_2$或$-(CR_2)_{0-2}OP(O)(H)OH$。

【請求項35】

如請求項20至30中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-CO_2H$、$-CO_2C_{1-4}$烷基、-CO(N-脯胺酸)、$-CH_2CO_2H$、$-OH$、$-OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-OC(O)C_{1-4}$烷基、$-SO_3H$、$-SO_2NH_2$、$-NR^aSO_2C_{1-4}$烷基、$-OP(OH)_2$或$-OP(O)(H)OH$。

【請求項36】

如請求項20之化合物，其中R^2係。

【請求項37】

如請求項36之化合物，其中m係1、2、3或4。

【請求項38】

如請求項36之化合物，其中m係1或2。

【請求項39】

如請求項36至38中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$

烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}CO(N$-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OC(O)C_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NR^aC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基$)$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-6}$烷基。

【請求項40】

如請求項36至38中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-CO_2H$、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}CO(N$-吡咯啶-3-羧酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aC(O)Ph$、$-(CH_2)_{0-4}NR^aCO(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2Ph$、-

$(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項41】

如請求項36至38中任一項之化合物，其中每個R^6獨立地係鹵素、$=CH_2$、$=O$、$-C_{1-4}$烷基、$-C_{1-4}$鹵烷基、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基、-CO(*N*-脯胺酸)、-CO(*N*-吡咯啶-3-羧酸)、$-C(O)NR^a(CH_2)_{1-4}CO_2H$、$-C(O)NR^a-CH(C_{1-4}$烷基$)-CO_2H$、-OH、$-OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-NR^aC(O)C_{1-4}$烷基、$-NR^aC(O)Ph$、$-NR^aCO(CH_2)_{1-4}OH$、$-SO_3H$、$-SO_2NH_2$、$-NR^aSO_2C_{1-4}$烷基、$-NR^aSO_2Ph$、$-NR^aSO_2(CH_2)_{1-4}CO_2H$、$-OP(OH)_2$或$-OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項42】

如請求項20之化合物，其中環B1係具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環，其中該5至6員雜芳基環之碳原子直接鍵接至在喹諾酮環2-位置之碳。

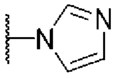
【請求項43】

如請求項20之化合物，其中環B1係咪唑或吡唑。

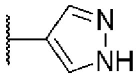
【請求項44】

如請求項43之化合物，其中該咪唑或吡唑未經取代。

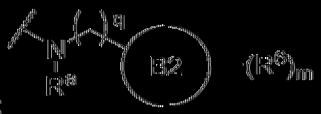
【請求項45】

如請求項43之化合物，其中R^2係。

【請求項46】

如請求項43之化合物，其中R^2係。

【請求項47】

如請求項1至14中任一項之化合物，其中R^{2}係

。

【請求項48】

如請求項47之化合物，其中環B2係苯基。

【請求項49】

如請求項47之化合物，其中環B2係具有1至3個獨立地選自氮、氧及硫之雜原子的4至7員飽和或部分不飽和碳環或雜環。

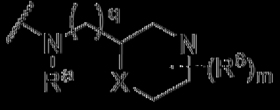
【請求項50】

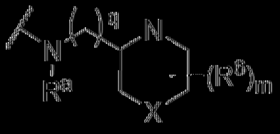
如請求項47之化合物，其中環B2係具有1至4個獨立地選自氮、氧及硫之雜原子的5至6員雜芳基環。

【請求項51】

如請求項47至50中任一項之化合物，其中m係1、2、3或4。

【請求項52】

如請求項47之化合物，其中R^{2}係

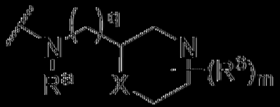
或

，其中

X係不存在(亦即，為環中的鍵)、$-CR_2-$、$-NR-$、$-O-$、$-S-$或$-SO_2-$；且

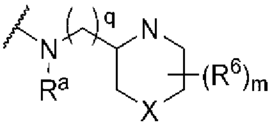
m係1、2、3或4。

【請求項53】

如請求項52之化合物，其中R^{2}係

。

【請求項54】

如請求項52之化合物，其中R^2係  。

【請求項55】

如請求項52至54中任一項之化合物，其中X係$-CR_2-$、-NR-或-O-。

【請求項56】

如請求項52至55中任一項之化合物，其中q係1或2。

【請求項57】

如請求項52至56中任一項之化合物，其中q係1。

【請求項58】

如請求項52至57中任一項之化合物，其中m係1或2。

【請求項59】

如請求項47至58中任一項之化合物，其中每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CONH_2$、$-(CH_2)_{0-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}CON(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONHC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CON(C_{1-4}$烷基$)_2$、-OH、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}OC_{1-4}$烷基、$-NH_2$、$-(CH_2)_{1-4}NH_2$、$-(CH_2)_{0-4}NHC_{1-4}$烷基、$-(CH_2)_{0-4}N(C_{1-4}$烷基$)_2$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}SO_2NHC_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$、$-(CH_2)_{0-4}OP(OH)(OC_{1-4}$烷基)或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項60】

如請求項47至58中任一項之化合物，其中每個R^6獨立地係鹵素、$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO(N$-脯胺酸)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-}$

$_{4}CO_2H$、$-OH$、$-(CH_2)_{1-4}OH$、$-(CH_2)_{0-4}SO_3H$、$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}NR^aSO_2C_{1-4}$烷基、$-(CH_2)_{0-4}OP(OH)_2$或$-(CR_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項61】

如請求項47至58中任一項之化合物，其中每個R^6獨立地係鹵素、$-CO_2H$、-CO(*N*-脯胺酸)、$-C(O)NR^a(CH_2)_{1-4}CO_2H$、$-OH$、$-SO_3H$、$-SO_2NH_2$、$-NR^aSO_2C_{1-4}$烷基、$-OP(OH)_2$或$-OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項62】

如請求項1至61中任一項之化合物，其中R^6不為R^B。

【請求項63】

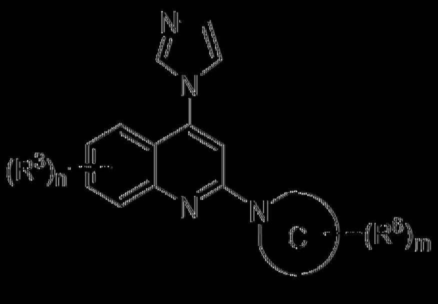
如請求項1至62中任一項之化合物，其中m係至少1，且至少一個R^6包括末端$-CO_2H$或$-CO_2C_{1-4}$烷基。

【請求項64】

如請求項63之化合物，其中至少一個R^6係$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO_2H$或$-(CH_2)_{0-4}CO_2C_{1-4}$烷基。

【請求項65】

如請求項1之化合物，其中該化合物係式I-d-10之化合物：



I-d-10

或其醫藥學上可接受之鹽，其中：

環C係吡咯基或具有0至3個獨立地選自氮、氧及硫之雜原子(除環C中已描繪之氮外)的4至10員飽和或部分不飽和單環、雙環、橋連雙環或螺環雜環；

每個R^6獨立地係鹵素、=O、-COR、-$(CR_2)_{0-6}CO_2R$、-$(CR_2)_{0-6}CONR_2$、-OR、-$(CR_2)_{1-4}OR$、-NR_2、-$(CR_2)_{1-4}NR_2$、-NRC(O)OR、-NRC(O)R、-NRC(O)NR_2、-SR、-SO_2R、-S(O)R、-$(CR_2)_{0-6}SO_3R$、-$(CR_2)_{0-6}SO_2NR_2$、-$(CR_2)_{0-6}OSO_2NR_2$、-$(CR_2)_{0-6}NRSO_2R$、-$(CR_2)_{0-6}NRSO_2OR$、-$(CR_2)_{0-6}OP(OR)_2$、-$(CR_2)_{0-6}OP(O)(OR)_2$、-$(CR_2)_{0-6}P(O)(OR)_2$、-$(CR_2)_{0-6}OP(O)(H)OR$、-$B(OR)_2$或R^B；且

m係1、2、3或4。

【請求項66】

如請求項65之化合物，其中環C係氮雜環丁烷基、吡咯基、2,3-二氫-1H-吡咯基、吡咯啶基、哌啶基、味啉基、噻唑啶基、吲哚啉基、異吲哚啉基、八氫吲哚基、氮雜環庚烷基、氧氮雜環庚烷、氮雜雙環己烷、氮雜雙環庚烷、氮雜雙環辛烷、氮雜雙環壬烷、氮雜螺庚烷或八氫環戊并吡咯。

【請求項67】

如請求項65或66之化合物，其中環C係吡咯基、2-氮雜雙環[3.1.0]己基、3-氮雜雙環[3.1.0]己烷、5-氮雜螺[2.4]庚基或八氫環戊并[b]吡咯基。

【請求項68】

如請求項65至67中任一項之化合物，其中每個R^6獨立地係氟、-

CN、甲基、$-CF_3$、$-CO_2H$、$-NH_2$、-OH、$-OC_{1-4}$烷基、$-C_{3-6}$環烷基、$=CH_2$、=O、四唑基、咪唑基、噻吩基、1,2,4-噁二唑-3(2H)-酮基、味啉基、苯基、$-(CH_2)_{1-4}OC_{1-4}$烷基、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{0-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CHFCO_2C_{1-4}$烷基、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2H$、$-(CH_2)_{1-4}OCH(CH_3)(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-4}CH(CH_3)CO_2C_{1-4}$烷基、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHOH(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-CHCF_3(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-CHCF_3(CH_2)_{1-4}O-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^a{}_2$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aOH$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CONR^aCN$、$-(CH_2)_{1-4}O(CH_2)_{1-5}P(O)OH_2$、$-CH(OH)CF_3$、$-COH(CF_3)_2$、$-(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-5}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CHCHCO_2H$、$-(CH_2)_{0-4}CHCHCO_2C_{1-4}$烷基、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基、$-OCOC_{1-4}$烷基、$-O(CH_2)_{1-4}CO_2H$、$-O(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-OCONR^a(CH_2)_{0-4}CO_2H$、$-OCONR^a(CH_2)_{0-4}CO_2C_{1-4}$烷基、-OCO-(*N*-味啉)、$-CONH_2$、-CONHOH、$-CONHOC_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}$(吡咯啶-2-酮)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}$(哌啶-2-酮)、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}C(OH)(CF_3)_2$、$-(CH_2)_{0-4}C(O)NR^a(CH_2)_{1-4}CONH_2$、$-(CH_2)_{0-4}CONR^aSO_2C_{1-4}$鹵烷基、$-(CH_2)_{0-4}CO$(*N*-吡咯啶)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-吡咯啶)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}$(*N*-吡唑)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-吡唑)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}$(*N*-吡咯)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-吡咯)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O$(苯基)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O$(苯基)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}-O$(環

烷烴)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}-O$(環烷烴)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO$(*N*-吡咯啶)$-(CH_2)_{0-4}SO_2NH_2$、$-(CH_2)_{0-4}CO$(*N*-吡咯啶)-(四唑)、$-(CH_2)_{0-4}CO$(*N*-哌啶)$-(CH_2)_{0-4}CO_2H$、$-(CH_2)_{0-4}CO$(*N*-哌啶)$-(CH_2)_{0-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}CO$(*N*-味啉)$-(CH_2)_{0-4}CO_2H$、$-CONR^a$(雙環[1.1.1]戊烷)$-(CH_2)_{0-4}CO_2H$、$-NH_2$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^a(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}N[(CH_2)_{1-4}CO_2C_{1-4}$烷基$]_2$、$-(CH_2)_{0-4}NR^aCO$(異噚唑)-OH、$-(CH_2)_{0-4}NR^aSO_2$(苯)$-CO_2H$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2H$、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}CO_2C_{1-4}$烷基、$-(CH_2)_{0-4}NR^aSO_2(CH_2)_{1-4}$(咪唑啶-2,4-二酮)或$-(CH_2)_{0-4}OP(O)(H)OH$，其中$R^a$在每次出現時獨立地係H或$C_{1-4}$烷基。

【請求項69】

如請求項65至68中任一項之化合物，其中每個R^6獨立地係氟、=O、$=CH_2$、甲基、環己基、味啉基、苯基、$-CF_3$、-OMe、-OtBu、$-CO_2H$、$-CO_2C_{1-4}$烷基、$-CO_2C_{1-4}$鹵烷基、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2H$、$-(CH_2)_{1-4}O(CH_2)_{1-5}CO_2C_{1-4}$烷基或-OH。

【請求項70】

如請求項65至69中任一項之化合物，其中m係1、2或3。

【請求項71】

如請求項65至70中任一項之化合物，其中m係1或2。

【請求項72】

如請求項65至71中任一項之化合物，其中至少一個出現之R^3係鹵素。

【請求項73】

如請求項72之化合物，其中至少一個出現之R^3係氯。

【請求項74】

如請求項72之化合物，其中n係2且兩個R^3均為氯。

【請求項75】

如請求項72之化合物，其中n係2且相對於喹啉環位在7-或8-位置之R^3係氯。

【請求項76】

如請求項65至75中任一項之化合物，其中環C係3-羥基脯胺酸、C_{1-6}烷基3-羥基脯胺酸酯或C_{1-6}鹵烷基3-羥基脯胺酸酯。

【請求項77】

一種醫藥組合物，其包含如請求項1至76中任一項之化合物。

【請求項78】

一種拮抗有需要患者體內之環狀GMP-AMP合成酶(cGAS)的方法，其包含投與有效量的如請求項1至76中任一項之化合物或如請求項77之醫藥組合物。

【請求項79】

一種治療有需要患者之發炎性疾病、過敏性疾病、自體免疫疾病或神經退化性疾病的方法，其包含投與有效量的如請求項1至76中任一項之化合物或如請求項77之醫藥組合物。

【請求項80】

一種如請求項1至76中任一項之化合物或如請求項77之醫藥組合物在製造用於拮抗有需要患者體內之環狀GMP-AMP合成酶(cGAS)之藥劑中的用途。

【請求項81】

一種如請求項1至76中任一項之化合物或如請求項77之醫藥組合物在製造用於治療有需要患者之發炎性疾病、過敏性疾病、自體免疫疾病或神經退化性疾病之藥劑中的用途。

【請求項82】

如請求項1至76中任一項之化合物，其用於療法中，諸如用於治療患者之發炎性疾病、過敏性疾病、自體免疫疾病或神經退化性疾病，及/或用於拮抗患者體內之環狀GMP-AMP合成酶(cGAS)。