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(21)申請案號：098132205 (22)申請日： 中華民國 98 (2009) 年 09 月 24 日

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C07D409/14 (2006.01) *C07D417/10 (2006.01)*
A61K31/4162 (2006.01) *A61K31/407 (2006.01)*
A61K31/4025 (2006.01)

(30)優先權：2008/09/25 日本 2008-245668

(71)申請人：鹽野義製藥股份有限公司 (日本) SHIONOGI & CO., LTD. (JP)
日本

(72)發明人：甲斐浩幸 KAI, HIROYUKI (JP) ；垰田善之 TAODA, YOSHIYUKI (JP) ；遠藤毅 ENDOH, TAKESHI (JP) ；堀口透 HORIGUCHI, TOHRU (JP) ；旭健太郎 ASAHI, KENTARO (JP) ；飛永裕之 TOBINAGA, HIROYUKI (JP)

(74)代理人：何金塗；何秋遠

申請實體審查：無 申請專利範圍項數：13 項 圖式數：0 共 807 頁

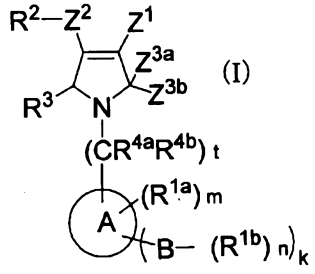
(54)名稱

新穎吡咯啉酮衍生物及含有其之醫藥組成物

NOVEL PYRROLINONE DERIVATIVE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

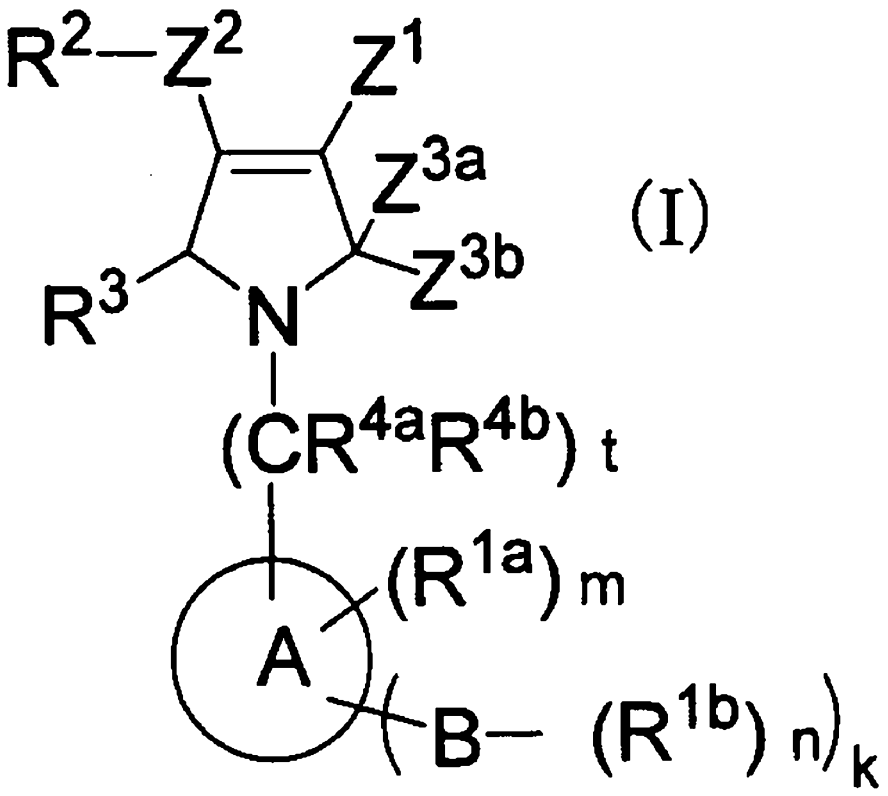
(57)摘要

本發明提供新穎之 $P2X_3$ 及/或 $P2X_{2/3}$ 受體拮抗劑。提供式(I)表示之化合物或其製藥上容許的鹽或彼等之溶劑化物：



(I)

(式中，Z^1 為可經保護之羥基等；Z^2 為-C(=O)-等；Z^{3a} 及 Z^{3b} 一起成為=O 或=S 等；t 為 0~4 之整數；R^{4a} 及 R^{4b} 分別獨立為氫或取代或未取代之低級烷基等；m 及 n 分別獨立為 0~2 之整數；k 為 0 或 1 之整數；環 A 為芳香族碳環或雜環等；B 為芳香族碳環二基或雜環二基等；R^{1a} 及 R^{1b} 分別獨立為鹵素、羥基、取代或未取代之低級烷基等；R^2 取代或未取代之烷基等；R^3 為取代或未取代之烷基、取代或未取代之芳基或取代或未取代之雜環式基等)。



(I)

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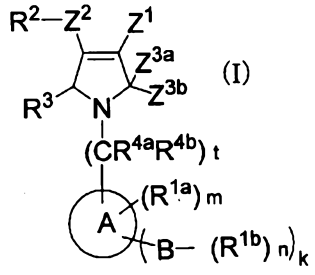
(54)名稱

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(57)摘要

本發明提供新穎之 $P2X_3$ 及/或 $P2X_{2/3}$ 受體拮抗劑。提供式(I)表示之化合物或其製藥上容許的鹽或彼等之溶劑化物：



(式中，Z^1 為可經保護之羥基等；Z^2 為-C(=O)-等；Z^{3a} 及 Z^{3b} 一起成為=O 或=S 等；t 為 0~4 之整數；R^{4a} 及 R^{4b} 分別獨立為氫或取代或未取代之低級烷基等；m 及 n 分別獨立為 0~2 之整數；k 為 0 或 1 之整數；環 A 為芳香族碳環或雜環等；B 為芳香族碳環二基或雜環二基等；R^{1a} 及 R^{1b} 分別獨立為鹵素、羥基、取代或未取代之低級烷基等；R^2 取代或未取代之烷基等；R^3 為取代或未取代之烷基、取代或未取代之芳基或取代或未取代之雜環式基等)。

六、發明說明:

【發明所屬之技術領域】

本發明是關於有用於治療與 P2X 受體(P2X receptor)，特別是與 $P2X_3$ 及/或 $P2X_{2/3}$ 受體有關之疾病或狀態之化合物、及含有該化合物之醫藥組成物。

【先前技術】

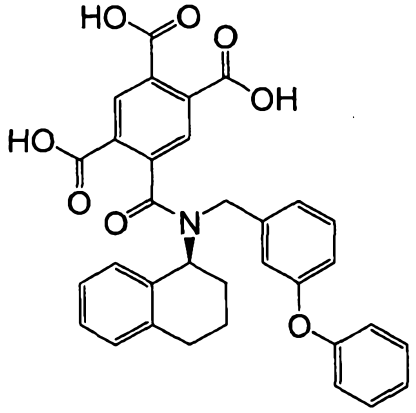
已知 ATP(三磷酸腺苷)一方面在細胞內作爲能量源或磷酸化受質，另一方面也在細胞外作用爲訊息傳導物質。已知 ATP 除了經由細胞的損傷、炎症、侵害刺激、血中氧濃度降低等各種刺激被放出細胞外之外，與其他神經傳導物質一起從初級感覺神經元(primary sensory neuron)終端被放出細胞外。被放出細胞外之 ATP 經由 ATP 受體進行各種細胞外訊息傳導(非專利文獻 6、非專利文獻 7)。

ATP 受體可分類爲離子通道型之 P2X 家族及 G 蛋白連結(G protein-coupled)型之 P2Y 家族。已有報告 P2X 受體家族中有 7 種類的亞型，形成同質 3 聚體或與其他 P2X 亞型形成之異質 3 聚體，作用爲非選擇性之陽離子通道(非專利文獻 8)。

已知 ATP 引起疼痛，再者，經由使用 $P2X_3$ 之剔除(knock out)或減弱(knock down)技術之研究顯示 $P2X_3$ 受體與慢性疼痛的傳達有關。$P2X_3$ 受體專一地表現於末梢感覺神經，形成同質複合物或與 $P2X_2$ 形成異質複合物($P2X_{2/3}$)。(非專利文獻 1)

之後，報告有對 $P2X_3$ 及 $P2X_{2/3}$ 受體專一之拮抗劑

(antagonist)，稱爲 A-317491 之化合物。已報告 A-317491 爲如下式所示之三取代-N-[(1S)-1,2,3,4-四氫-1-萘基]苯甲醯胺衍生物(專利文獻 1)，



顯示對 $P2X_3$ 及 $P2X_{2/3}$ 受體之拮抗劑活性，在大鼠的神經障害性疼痛模式及炎症性疼痛模式中顯示鎮痛作用(非專利文獻 9)。由此顯示經由 $P2X_3$ 或 $P2X_{2/3}$ 受體傳達痛覺，且 $P2X_3$ 或 $P2X_{2/3}$ 受體拮抗劑有用於作爲鎮痛藥。此外，專利文獻 2~7 中也記載顯示 $P2X_3$ 或 $P2X_{2/3}$ 受體拮抗作用之化合物。

再者，近年已有報告 $P2X_3$ 剔除(knock out)小鼠表現顯著的膀胱反射降低(非專利文獻 2)，已教示 $P2X_3$ 拮抗藥也有用於因膀胱過度活動造成之疾病的治療。

非專利文獻 12 中記載具有與本發明化合物類似構造之化合物，但未記載鎮痛作用及 $P2X_3$ 或 $P2X_{2/3}$ 受體拮抗作用。此外，非專利文獻 3、4、10 及 11 中記載具有與本發明化合物類似構造及顯示鎮痛活性之化合物，但未記載 $P2X_3$ 或 $P2X_{2/3}$ 受體拮抗作用。

[專利文獻 1]國際申請公開 WO02/094767 公報

[專利文獻 2]國際申請公開 WO2005/095359 公報

[專利文獻 3]美國申請公開 US20070037974 公報

[專利文獻 4]美國申請公開 US20070049758 公報

[專利文獻 5]美國申請公開 US20070049610 公報

[專利文獻 6]美國申請公開 US20070049609 公報

[專利文獻 7]美國申請公開 US20070049534 公報

[非專利文獻 1]Neuroscientist 11 (2005) pp.345-356

[非專利文獻 2]J. Physiol. 567.2 (2005) pp.621-639

[非專利文獻 3]Pharmaceutical Chemistry Journal Vol.39, No.9, (2005), pp484-487

[非專利文獻 4]Pharmaceutical Chemistry Journal Vol.31, No.5, (1997), pp251-254

[非專利文獻 5]Expert Opin. Ther. Patens (2006) 16(8) 113-1127

[非專利文獻 6]J. Physiology (2003), 554(2), 301-308

[非專利文獻 7]J. Physiology (2003), 553(3), 683-694

[非專利文獻 8]Pflungers Arch Eur J physiol (2006), 452, 513-537

[非專利文獻 9]PNAS (2002), 99(26), 17179-17184

[非專利文獻 10]Khimiko-Farmatsevticheskii Zhurnal, Vol 31, No.11, (1997) 35-36

[非專利文獻 11]Pharmaceutical Chemistry Journal Vol 36, No.4, (2002), 188-191

[非專利文獻 12]Phosphorus, Sulfur and Silicon and the Related Elements (2006), 181(4), 771-777

【發明內容】

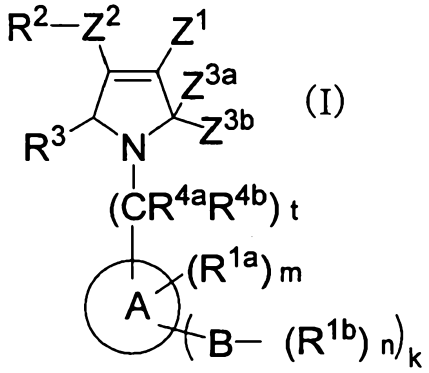
(發明欲解決之課題)

本發明提供新穎的 $P2X_3$ 及/或 $P2X_{2/3}$ 受體拮抗劑。

(解決課題之手段)

本發明者們爲達成上述目的反覆精心研究的結果，發現專一結合 $P2X_3$ 及/或 $P2X_{2/3}$ 受體、顯示拮抗作用之新穎化合物，而完成以下記載之發明。

(1)式(I)表示之化合物或其製藥上容許的鹽或彼等之溶劑化物：

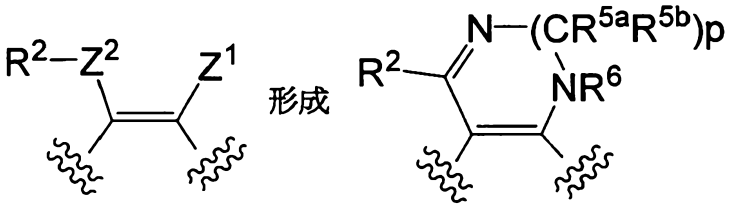


(I)

(式中，

Z^1 爲可經保護之羥基或可經保護之巰基；

Z^2 爲 -C(=O)-、-C(=S)-或 -S(O)v-、或



(式中，R^{5a} 及 R^{5b} 分別獨立爲氫或低級烷基；

R^6 爲氫、取代或未取代之低級烷基、取代或未取代之醯基或取代或未取代之低級烷氧羰基；

p 爲 0~2 之整數)；

v 爲 0~2 之整數；

Z^{3a} 及 Z^{3b} 分別獨立爲氫、取代或未取代之低級烷基、或一起形成=O 或=S；

t 爲 0~4 之整數；

R^{4a} 及 R^{4b} 分別獨立爲氫或取代或未取代之低級烷基；

m 及 n 分別獨立爲 0~2 之整數；

k 爲 0 或 1 之整數；

環 A 爲環烷、環烯、芳香族碳環或雜環；

B 爲環烷二基、環烯二基、芳香族碳環二基或雜環二基；

R^{1a} 及 R^{1b} 分別獨立爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基、取代或未取代之胺磺醯基、氰基、硝基或 $-C(R^{7a})=N-O-R^{7b}$；

R^{7a} 及 R^{7b} 分別獨立爲氫或取代或未取代之低級烷基；

R^{2} 爲取代或未取代之烷基、取代或未取代之烯基、取代或未取代之炔基、取代或未取代之烷氧基、取代或未取代之芳氧基、羥基、取代或未取代之胺基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基；

R^{3} 爲取代或未取代之烷基、取代或未取代之烷氧羰基、取代或未取代之芳氧基羰基、羧基、取代或未取代之胺甲醯基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未

取代之芳基或取代或未取代之雜環式基；)

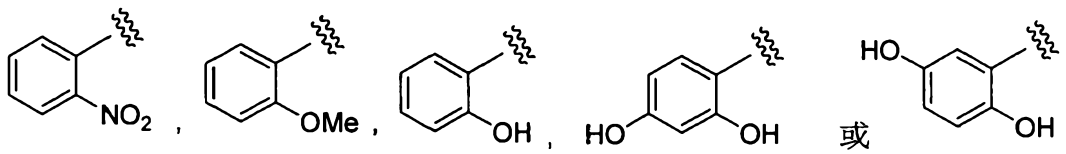
但以下除外：

(i)環 A 爲噻二唑，k 爲 0，且 R^{1a} 爲甲硫基之化合物；

(ii)環 A 爲苯并噻吩，k 爲 0，R^{1a} 爲甲磺醯基，且 R^2 爲取代或未取代之呋喃基或取代或未取代之苯基之化合物；

(iii)環 A 爲噻唑或 7H-嘌呤，且 R^2 爲取代或未取代之呋喃基之化合物；

(iv)R^3 爲下式表示之基：



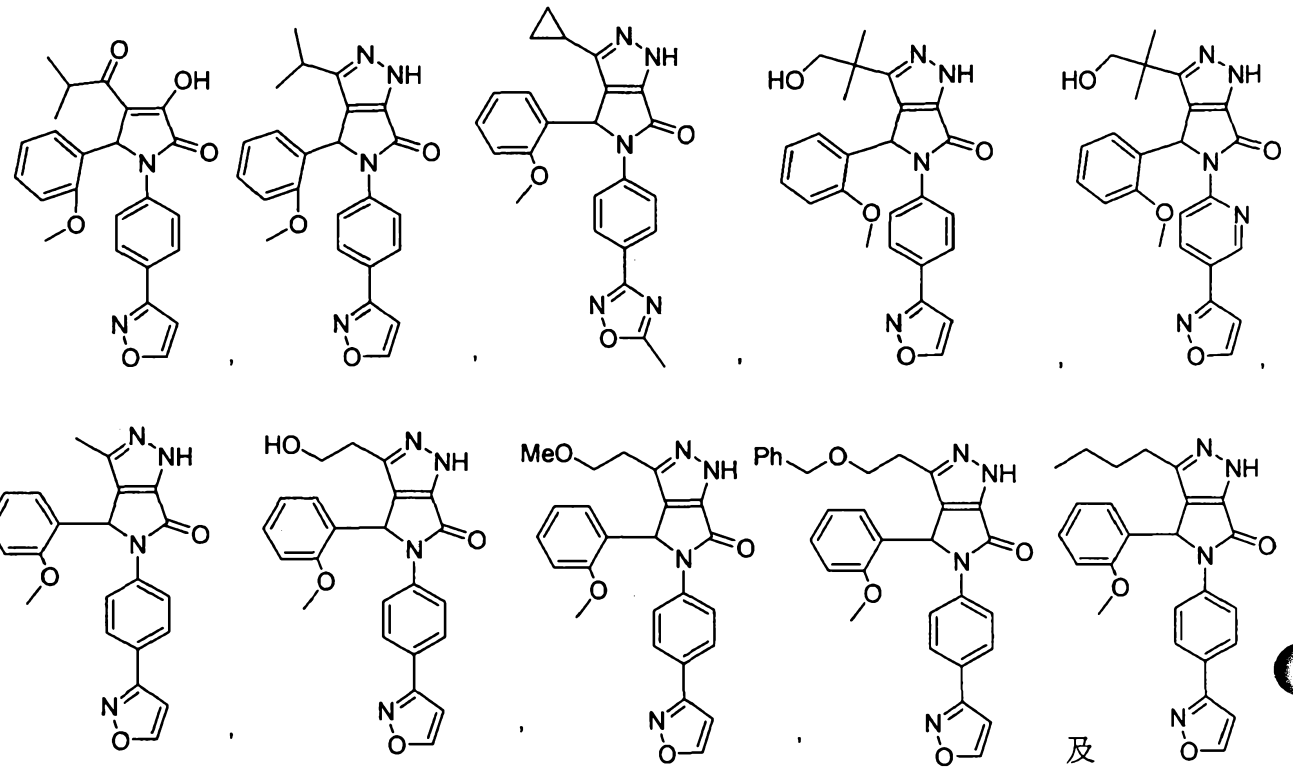
t 爲 1~2 之整数、且環 A 爲呋喃或苯之化合物；

(v)R^2 爲第三丁基或 4-甲基氧基苯基之化合物；

(vi)R^2 爲取代或未取代之烷基(但取代或未取代之異丙基及取代或未取代之異丁基除外)，R^3 爲取代或未取代之碳環或取代或未取代之雜環，且 k 爲 0 之化合物；

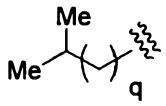
(vii)R^2 爲取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基，且 R^3 爲戊烷-3-基之化合物；以及

(viii)以下式表示之化合物：



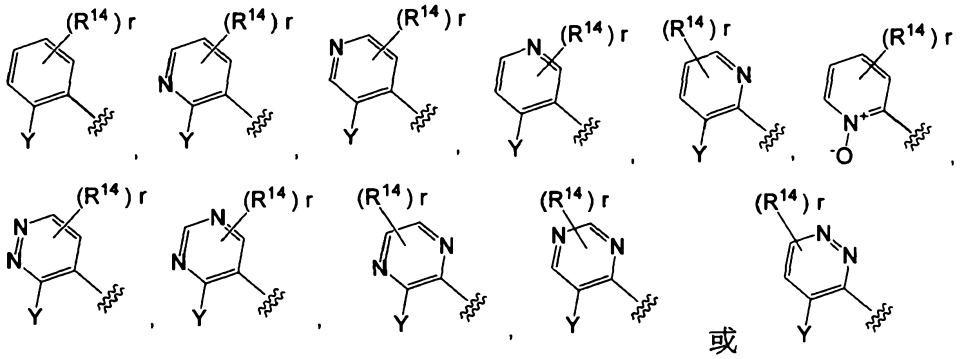
(2)上記(1)記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中

R^2 爲以下式表示之基：



(式中，Me爲甲基，q爲0~4之整數)；

R^3 爲以下式表示之基：

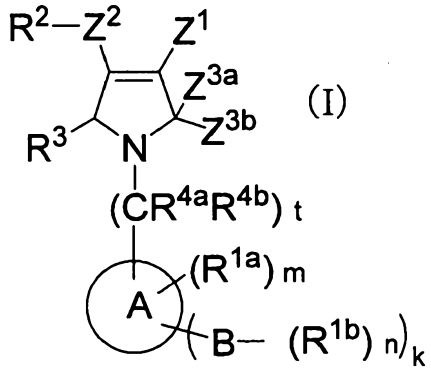


(式中，Y 爲羥基、鹵素、氰基、羧基、取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式基，或 Y 及 R^{14} 亦可結合於鄰接之碳原子形成取代或未取代之雜環式基；

R^{14} 爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基；

r 爲 0~2 之整數)。

(2')式(I)表示之化合物或其製藥上容許的鹽或彼等之溶劑化物：

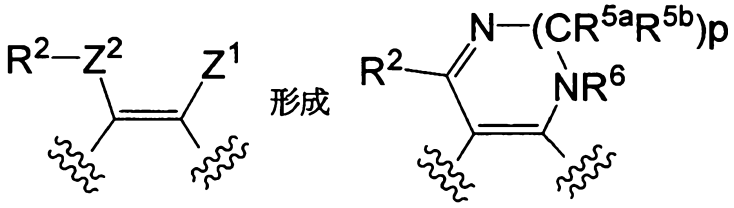


(I)

(式中，

Z^1 爲可經保護之羥基或可經保護之巯基；

Z^2 爲 -C(=O)-、-C(=S)-或 -S(O)v-，或



(式中，R^{5a} 及 R^{5b} 分別獨立爲氫或低級烷基；

R^6 爲氫、取代或未取代之低級烷基、取代或未取代之醯基或取代或未取代之低級烷氧羰基；

p 爲 0~2 之整數)；

v 爲 0~2 之整數；

Z^{3a} 及 Z^{3b} 分別獨立爲氫、取代或未取代之低級烷基，或一起形成 =O 或 =S；

t 爲 0~4 之整數；

R^{4a} 及 R^{4b} 分別獨立爲氫或取代或未取代之低級烷基；

m 及 n 分別獨立爲 0~2 之整數；

k 爲 0 或 1 之整數；

環 A 爲環烷、環烯、芳香族碳環或雜環；

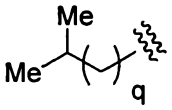
B 爲環烷二基、環烯二基、芳香族碳環二基或雜環二基；

R^{1a} 及 R^{1b} 分別獨立爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取

代或未取代之胺基、取代亞磺醯基、取代磺醯基、取代或未取代之胺磺醯基、氰基、硝基或-C(R^{7a})=N-O-R^{7b}；

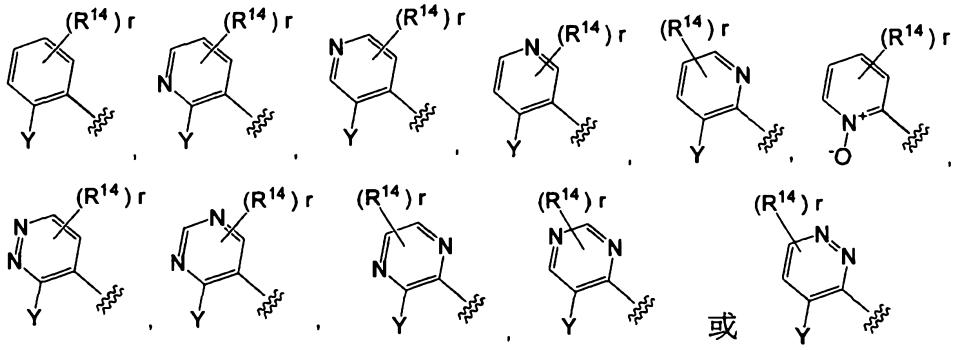
R^{7a}及R^{7b}分別獨立爲氫或取代或未取代之低級烷基；

R^2爲以下式表示之基：



(式中，Me爲甲基，q爲0~4之整數)；

R^3爲以下式表示之基：



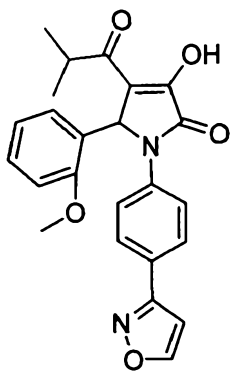
(式中，Y爲羥基、鹵素、氰基、羧基、取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式基，或Y及R^{14}亦可結合於鄰接之碳原子形成取代或未取代之雜環式基；

R^{14}爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之

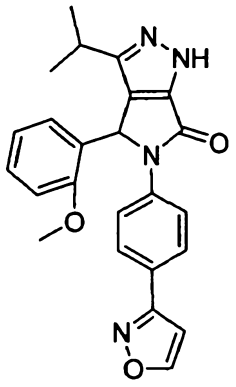
低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基；

r 爲 0~2 之整數)；

(但以下式表示之化合物除外：



及



)。

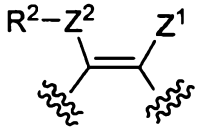
(3)上記(2)或(2')記載知化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 Z^{3a} 及 Z^{3b} 一起成爲=O。

(4)上記(2)、(2')或(3)記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 t 爲 0。

(5)上記(2)~(4)或(2')之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 Z^2 爲 -C(=O)-、-C(=S)-或 $-S(O)_2-$。

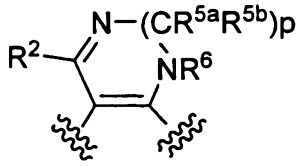
(6)上記(2)~(5)或(2')之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 Z^2 爲 -C(=O)-。

(7)上記(2)~(6)或(2')之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中以下式表示之基：



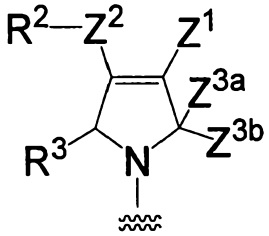
(式中，Z^1、Z^2及R^2與上記(1)同意義。)

爲下式：



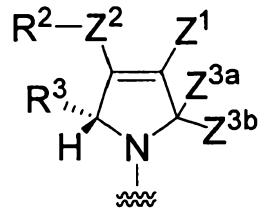
(式中，R^2、R^{5a}、R^{5b}、R^6及p與上記(1)同意義。)。

(8)上記(2)~(7)或(2')之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中以下式表示之基：



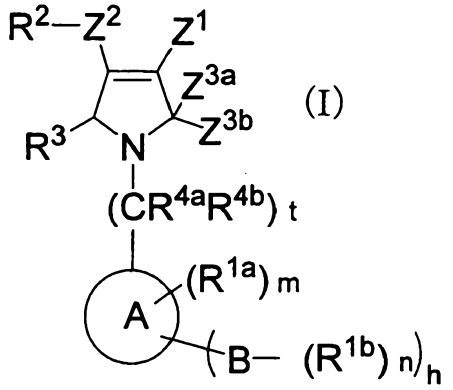
(式中，Z^1、Z^2、Z^{3a}、Z^{3b}、R^2及R^3與上記(1)同意義。)

爲以下式表示之基：



(式中，Z^1、Z^2、Z^{3a}、Z^{3b}、R^2及R^3與上記(1)同意義。)。

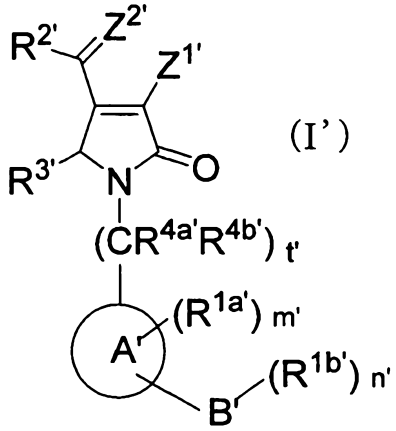
(9)式(I)：



(I)

(式中、Z^1、Z^2、Z^{3a}、Z^{3b}、R^{1a}、R^{1b}、R^2、R^3、R^{4a}、R^{4b}、環A、B、h、m、n、t與上記(1)同意義。)

爲式(I')表示之化合物或其製藥上容許的鹽或彼等之溶劑化物：

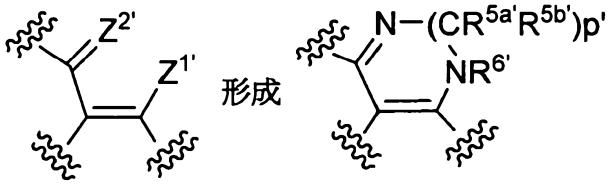


(I')

(式中，

$Z^{1'}$爲可經保護之羥基或可經保護之巯基；

$Z^{2'}$爲O或S，或



($R^{5a'}$及 $R^{5b'}$分別獨立爲氫或低級烷基，$R^{6'}$爲氫、取代或未取代之低級烷基、取代或未取代之醯基或取代或未取代之低級烷氧羰基，p'爲 0~2 之整數)；

t'爲 0~4 之整數；

$R^{4a'}$及 $R^{4b'}$分別獨立爲氫或低級烷基；

m'及 n'分別獨立爲 0~2 之整數；

環 A'爲環烷、環烯、芳香族碳環或雜環；

B'爲環烷二基、環烯二基、芳香族碳環二基或雜環二基；

n'爲 0 時，B'可爲甲硫基、三氟甲硫基或 $-C(R^{7a'})=N-O-R^{7b'}$；

$R^{1a'}$及 $R^{1b'}$分別獨立爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基；

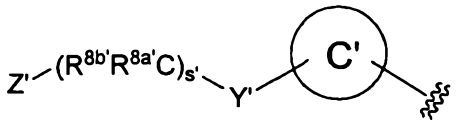
$R^{2'}$及 $R^{3'}$分別獨立爲取代或未取代之烷基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基；

$R^{7a'}$及 $R^{7b'}$分別獨立爲氫或取代或未取代之低級烷基)

(但環 A'爲噻二唑、B'爲甲硫基之化合物除外)。

(10)上記(9)記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中

$R^{3'}$爲以下式表示

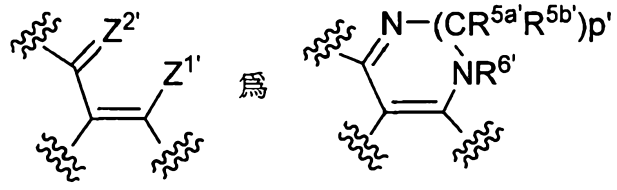


(式中，環 C'爲取代或未取代之芳香族碳環或取代或未取代之芳香族雜環，Y'爲-O-、-S-或-$NR^{9'}$-；$R^{9'}$爲氫或低級烷基；Z'爲羥基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之低級烷基亞磺醯基、取代或未取代之胺磺醯基或氰基；$R^{8a'}$及 $R^{8b'}$分別獨立爲氫或取代或未取代之低級烷基；s'爲 1~4 之整數)。

(11)上記(9)或(10)記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 Y'爲-O-。

(12)上記(9)~(11)之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 t'爲 0。

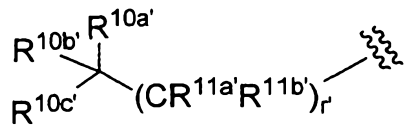
(13)上記(9)~(12)之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中



；

t'及 p'爲 0；

R^2爲以下式表示之基：



(式中，$R^{10a'}$及$R^{10b'}$分別獨立爲羥基、鹵素、取代或未取代之烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、羧基、取代或未取代之胺甲醯基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基、取代或未取代之雜環式基，

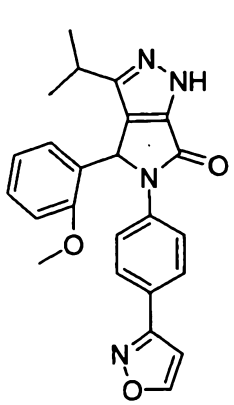
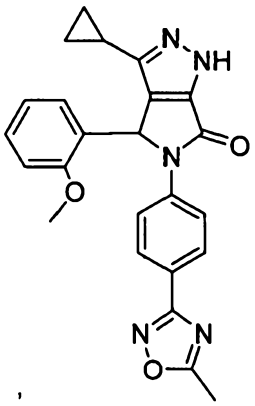
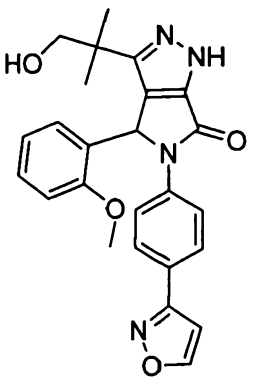
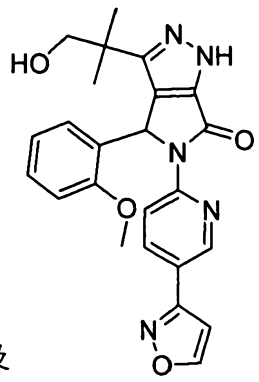
或$R^{10a'}$及$R^{10b'}$與鄰接之碳原子可一起形成取代或未取代之非芳香族碳環或取代或未取代之非芳香族雜環；

$R^{10c'}$爲氫、羥基、鹵素、取代或未取代之烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、羧基、取代或未取代之低級烷基胺甲醯基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基；

$R^{11a'}$及$R^{11b'}$分別獨立爲氫、低級烷基，或可一起成爲=O；

r'爲 0~4 之整數)

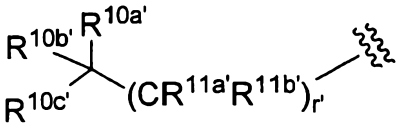
(但$R^{10a'}$、$R^{10b'}$及$R^{10c'}$全部爲甲基之化合物以及以下表示之化合物除外：


，

，

及

。

(14)上記(13)記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中$R^{10a'}$及$R^{10b'}$爲低級烷基；$R^{10c'}$爲羧基、羥烷

基、取代或未取代之芳基、取代或未取代之雜芳基或取代或未取代之低級烷基胺甲醯基。

(15)上記(10)~(12)之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 $Z^{1'}$為可經保護之羥基；$Z^{2'}$為 O；$R^{2'}$為以下式表示之基：



(式中，$R^{10a'}$及 $R^{10b'}$分別獨立為羥基、鹵素、取代或未取代之烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、羧基、取代或未取代之低級烷基胺甲醯基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基、取代或未取代之雜環式基，或 $R^{10a'}$及 $R^{10b'}$亦可與鄰接之碳原子一起形成取代或未取代之非芳香族碳環或取代或未取代之非芳香族雜環；

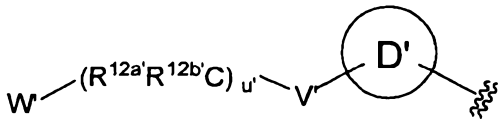
$R^{10c'}$為氫、羥基、鹵素、取代或未取代之烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、羧基、取代或未取代之低級烷基胺甲醯基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基；

$R^{11a'}$及 $R^{11b'}$亦可分別獨立為氫或低級烷基；

r'為 0~4 之整數)。

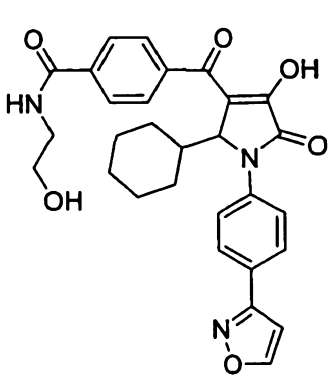
(16)上記(10)~(12)之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 $Z^{1'}$為可經保護之羥基；$Z^{2'}$為 O；

$R^{2'}$為以下式表示之基：

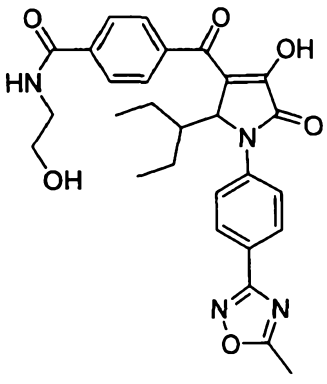


(式中，環 D'為取代或未取代之芳香族碳環或取代或未取代之芳香族雜環；V'為 -C(=O)-、-O-C(=O)-、-C(=O)-O-、$-NR^{13'}-C(=O)-NR^{13'}-$、$-NR^{13'}-C(=O)-$、$-C(=O)-NR^{13'}-$、-O-、-S-或$-NR^{13'}-$；$R^{13'}$為氫或低級烷基；W'為羥基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之低級烷基亞磺醯基、取代或未取代之胺磺醯基或氰基；$R^{12a'}$及$R^{12b'}$分別獨立為氫或取代或未取代之低級烷基；u'為 1~4 之整數)

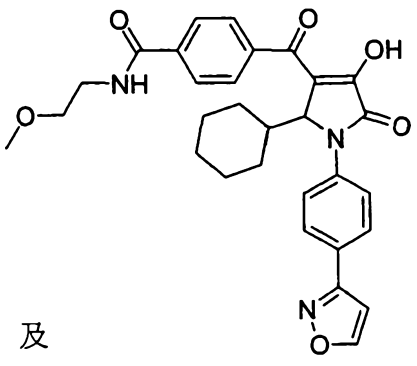
(但以下所示之化合物除外：



，



及



)。

(17)上記(15)或(16)記載之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 t'為 0。

(18)含有上記(1)~(17)或(2')之任一記載之化合物或其製藥

上容許的鹽或彼等之溶劑化物之醫藥組成物。

(19)上記(1)~(17)或(2')之任一記載之醫藥組成物，其爲 $P2X_3$ 及/或 $P2X_{2/3}$ 受體拮抗劑。

(20)與 $P2X_3$ 及/或 $P2X_{2/3}$ 受體有關之疾病之預防或治療方法，其特徵爲投與上記(1)~(17)或(2')之任一記載之化合物其製藥上容許的鹽或彼等之溶劑化物。

(21)上記(1)~(17)或(2')之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物之使用，其係用於與 $P2X_3$ 及/或 $P2X_{2/3}$ 受體有關之疾病的治療及/或預防。

(22)上記(1)~(17)或(2')之任一記載之化合物或其製藥上容許的鹽或彼等之溶劑化物之使用，其係用於製造與 $P2X_3$ 及/或 $P2X_{2/3}$ 受體有關之疾病的治療藥及/或預防藥。

【實施方式】

【實施本發明之最佳態樣】

以下說明本說明書中所用之用語。各用語除非特別記載，否則具有以下之意義。

所謂「烷基」包括碳數 1~10，較佳爲碳數 1~8，更佳爲碳數 1~6 之直鏈或枝鏈之 1 價的烴基。可舉出例如甲基、乙基、正丙基、異丙基、正丁基、異丁基、第二丁基、第三丁基、正戊基、異戊基、新戊基、正己基、異己基、正庚基、異庚基、正辛基、異辛基、正壬基、正癸基等。

R^2 中作爲「烷基」以異丙基、異丁基等爲佳。

所謂「低級烷基」包括碳數 1~6，較佳爲碳數 1~3 之直鏈或枝鏈之 1 價的烴基。可舉出例如甲基、乙基、正丙基、

異丙基、正丁基、異丁基、第二丁基、第三丁基、正戊基、異戊基、新戊基、正己基、異己基等。

R^{1a}中作爲「低級烷基」是碳數 1~4 之烷基，較佳爲例如甲基、乙基、正丙基、異丙基、第三丁基等。

R^{1b}中作爲「低級烷基」是碳數 1~3 之烷基，較佳爲例如甲基、乙基等。

Y 中作爲「低級烷基」是碳數 1~3 之烷基，較佳爲例如甲基、乙基、正丙基、異丙基等。

所謂「醯基」包括 R-CO-(例如 R 爲氫、前記「低級烷基」或後述之「低級烯基」、「芳基」、「雜環式基」、「環烷基」或「環烯基」)所示之基。

R^{1a}中作爲「醯基」是碳數 1~3 之烷基羰基，較佳爲例如乙醯基等。

所謂「環烷」包括碳數爲 3~10 之單環式或多環式飽和碳環。作爲單環式環烷，可舉出例如環丙烷、環丁烷、環戊烷、環己烷、環庚烷、環辛烷、環壬烷、環癸烷等。作爲多環式環烷，可舉出例如降萡烷(norbornane)、四氫萘等。

環 A 中作爲「環烷」是碳數 3~6 之單環式環烷，較佳爲例如環己烷等。

所謂「環烷基」包括衍生自上記「環烷」之 1 價的基。作爲單環式環烷基，可舉出例如環丙基、環丁基、環戊基、環己基、環庚基、環辛基、環壬基、環癸基等。作爲多環式環烷基，可舉出例如降萡基、四氫萘-5-基、四氫萘-6-基等。

R^2中作爲「環烷基」是碳數 3~6 之單環式環烷基，較佳

爲例如環戊基、環己基等。

所謂「環烷二基」包括衍生自上記「環烷」之2價的基。作爲單環式環烷二基，可舉出例如環丙烷二基、環丁烷二基、環戊烷二基、環己烷二基、環庚烷二基、環辛烷二基、環壬烷二基、環癸烷二基等。作爲多環式環烷二基，可舉出降萡烷二基等。

B中作爲「環烷二基」是碳數3~6之單環式環烷二基，較佳爲例如環戊烷二基、環己烷二基等。

所謂「環烯」包括含有至少1個碳-碳雙鍵之碳數3~10之非芳香族單環或多環式環。作爲單環式環烯，可舉出環戊烯、環己烯等。作爲多環式環烯，可舉出降萡烯、茚等。

所謂「環烯基」包括衍生自上記「環烯」之1價的基。作爲單環式環烯基，可舉出環戊烯基、環己烯基等。作爲多環式環烯基，可舉出降萡烯基、茚-1-基、茚-2-基、茚-3-基等。

所謂「環烯二基」包括衍生自上記「環烯」之2價的基。作爲單環式環烯二基，可舉出環戊烯二基、環己烯二基等。作爲多環式環烯二基，可舉出降萡烯二基等。

B中作爲「環烯二基」是碳數3~6之單環式環烯二基，較佳爲例如環戊烯二基、環己烯二基等。

所謂「芳香族碳環」包括單環或稠合環之芳香族烴環。可舉出例如苯環、萘環、蒽環、菲環等。

環A中作爲「芳香族碳環」較佳爲苯環。

所謂「芳基」意指衍生自上記「芳香族碳環」之1價的

基。可舉出例如苯基、1-萘基、2-萘基、蒽基、菲基等。

R^3中作爲「芳基」較佳爲苯基。

所謂「芳香族碳環二基」包括衍生自上記「芳香族碳環」之2價的基。可舉出例如1,2-伸苯基、1,3-伸苯基、1,4-伸苯基、1,2-伸萘基等。

B中作爲「芳香族碳環二基」較佳爲1,2-伸苯基、1,3-伸苯基、1,4-伸苯基等。更佳爲可舉出1,4-伸苯基。

所謂「雜環」包括環內至少含有1個氮原子、氧原子、及/或硫原子之5~7員環，此等2個以上稠合之環，或環內至少含有1個氮原子、氧原子、及/或硫原子之5~7員環與1個以上之上記「芳香族碳環」、上記「環烷」或上記「環烯」稠合之環所衍生之芳香族或非芳香族的單環或稠合環。可舉出例如二氫吡咯、吡咯啶、咪唑、吡唑、哌啶、哌啡、嗎福啉、噻嗎福啉、四氫哌喃、二氫吡啶、二氫嗒啡、二噁烷、氧硫戊環、硫己環(thiane)、四氫呋喃、四氫哌喃、四氫噻唑、四氫異噻唑等之非芳香族雜環，

例如吡咯、吡啡、吡唑、四唑、呋喃、噻吩、吡啶、咪唑、三唑、四唑、三啡、嗒啡、嘧啶、異噁唑、噻唑、異噻唑、噻二唑、噁唑、噁二唑等之單環的芳香族雜環，

吲哚、異吲哚、吲唑、吲啡(indolizine)、吲哚啉、異吲哚啉、喹啉、異喹啉、哢啶啉、呔啡、喹唑啉、嗪啶、喹啶啉、嘌呤、喋啶、苯并哌喃、苯并咪唑、苯并異噁唑、苯并噁唑、苯并噁二唑、苯并呋喃、異苯并呋喃、苯并噻吩、苯并三唑、咪唑并吡啶、三唑

并吡啶、咪唑并噻唑、吡咔并嗒咔、苯并咪唑、苯并二噁烷、四氫喹啉、四氫苯并噻吩等之稠合之雜環。

環A中作爲「雜環」較佳爲哌啶、噻吩、呋喃、吡啶、苯并噻吩、苯并噻唑、苯并噁唑等。

所謂「雜環式基」包括衍生自上記「雜環」之1價的基。可舉出例如吡咯啉基、N-吡咯啶基(pyrrolidino)、吡咯啶基、咪唑啉基、咪唑啶基、吡唑啉基、吡唑啶基、N-六氫吡啶基(piperidino)、哌啶基、N-哌咔基(piperazino)、哌咔基、嗎福啉基(morpholinyl)、N-嗎福啉基(morpholino)、硫嗎福啉基、N-硫嗎福啉基、四氫哌喃基、二氫吡啶基、二氫嗒咔基、二氫吡咔基、二噁烷基、噁硫戊環基(oxathiolanyl)、硫己環基(thianyl)、四氫呋喃基、四氫哌喃基、四氫噻唑啉基、四氫異噻唑啉基等之非芳香族雜環式基，

吡咯基、吡咔基、吡唑基、四唑基、呋喃基、噻吩基、吡啶基、咪唑基、三唑基、四唑基、三咔基、嗒咔基、嘧啶基、吡咔基、異噁唑基、噻唑基、異噻唑基、噻二唑基、噁唑基、噁二唑基等之單環芳香族雜環式基、

吲哚基、異吲哚基、吲唑基、吲咔基、吲哚啉基、異吲哚啉基、喹啉基、異喹啉基、啐啉基、呔咔基、喹唑啉基、嗪啶基、喹噁啉基、嘌呤基、喋啶基、苯并哌喃基、苯并咪唑基、苯并異噁唑基、苯并噁唑基、苯并噁二唑基、苯并異噻唑基、苯并噻唑基、苯并噻二唑基、苯并呋喃基、異苯并呋喃基、苯并噻吩基、苯并三唑基、咪唑吡啶基、三唑吡啶基、咪唑噻唑基、吡咔并嗒咔基、苯并咪唑啉基、苯并二噁烷基、四

氫喹啉、四氫苯并噻吩基等之稠合雜環式基。

Y中作爲「雜環式基」較佳爲N-六氫吡啶基(piperidino)、N-嗎福啉基(morpholino)等。

所謂「雜環式二基」包括衍生自上記「雜環」之2價的基。可舉出例如二氫吡咯二基、吡咯啶二基、咪唑二基、咪唑啶二基、吡唑啉二基、吡唑啶二基、哌啶二基、哌吡二基、嗎福啉二基、硫嗎福啉二基、四氫哌喃二基、二氫吡啶二基、二氫嗒吡二基、二氫吡吡二基、二噁烷二基、氧硫戊環二基、硫己環(thiane)二基、四氫呋喃二基、四氫哌喃二基、四氫噻唑二基、四氫異噻唑二基等之非芳香族雜環式二基，

吡咯二基、吡吡二基、吡唑二基、四唑二基、呋喃二基、噻吩二基、吡啶二基、咪唑二基、三唑二基、四唑二基、三吡二基、嗒吡二基、嘧啶二基、吡吡二基、異噁唑二基、噻唑二基、異噻唑二基、噻二唑二基、噁唑二基、噁二唑二基等之單環芳香族雜環二基，

吲哚二基、異吲哚二基、吲唑二基、吲吡(indolizine)二基、吲喹啉二基、異吲喹啉二基、喹啉二基、異喹啉二基、苯喃啉二基、呔吡二基、喹唑啉二基、嗟啶二基、喹喏啉二基、嘌呤二基、喋啶二基、苯并哌喃二基、苯并咪唑二基、苯并異噁唑二基、苯并噁唑二基、苯并噁二唑二基、苯并呋喃二基、異苯并呋喃二基、苯并噻吩二基、苯并三唑二基、咪唑并吡啶二基、三唑并吡啶二基、咪唑并噻唑二基、吡吡并嗒吡二基、苯并咪唑啉二基、苯并二噁烷二基、四氫喹啉二基、四氫苯

并噻吩二基等之稠合雜環二基。

B中作爲「雜環式二基」較佳爲吡咯二基、吡咔二基、吡唑二基、四唑二基、呋喃二基、噻吩二基、吡啶二基、咪唑二基、三唑二基、四唑二基、三咔二基、嗒咔二基、嘧啶二基、吡咔二基、異噁唑二基、噻唑二基、異噻唑二基、噻二唑二基、噁唑二基、噁二唑二基等。

更佳可舉出二氫噻唑二基、吡咯啶二基、噻唑二基、噻吩二基、吡咯二基、呋喃二基、異噁唑二基、噻二唑二基等。

所謂「非芳香族碳環」包括上記「芳香族碳環」稠合上記「環烷」、「環烯」、上記「環烷」之環，以及上記「芳香族碳環」稠合上記「環烯」之環。作爲稠合環可舉出茚等。

所謂「芳香族雜環」包括上記「雜環」中之芳香環。

包括環內至少含有1個氮原子、氧原子、及/或硫原子之5~7員之芳香環、

稠合此等2個以上之芳香環、

環內至少含有1個氮原子、氧原子、及/或硫原子之5~7員之芳香環與1以上之上記「芳香族碳環」稠合之芳香環。

可舉出例如吡咔、吡唑、四唑、呋喃、噻吩、吡啶、咪唑、三唑、三咔、嗒咔、嘧啶、吡咔、異噁唑、噻唑、異噻唑、噻二唑、噁唑、噁二唑等之單環芳香族雜環，

吲哚、異吲哚、吲唑、吲咔(indolizine)、喹啉、異喹啉、苯并哌啶啉、呔咔、喹唑啉、嗪啶、喹啶啉、嘌呤、喋啶、苯并咪唑、苯并異噁唑、苯并噁唑、苯并噁二唑、苯并異噻唑、苯并噻唑、苯并噻二唑、苯并呋喃、異苯并呋喃、苯并噻吩、

苯并三唑、咪唑并吡啶、三唑并吡啶、咪唑并噻唑、吡咯并噠咯、苯并咪唑啉等之稠合雜芳香環。

所謂「雜芳基」包括衍生自上記「芳香族雜環」之 1 價的基。環內至少含有 1 個氮原子、氧原子、及/或硫原子之 5~7 員之芳香環式基、

稠合此等 2 個以上之芳香環式基、

或環內至少含有 1 個氮原子、氧原子、及/或硫原子之 5~7 員芳香環與 1 以上的上記「芳香族碳環」稠合之芳香環式基。可舉出例如吡咯基、吡咯基、吡唑基、四唑基、呋喃基、噻吩基、吡啶基、咪唑基、三唑基、四唑基、三咯基、噠咯基、嘧啶基、吡咯基、異噁唑基、噻唑基、異噻唑基、噻二唑基、噁唑基、噁二唑基等之單環芳香族雜環式基，

吲哚基、異吲哚基、吲唑基、吲咯基、異吲哚啉基、喹啉基、異喹啉基、啐啉基、呔咯基、喹唑啉基、嗪啶基、喹噁啉基、嘌呤基、喋啶基、苯并咪唑基、苯并異噁唑基、苯并噁唑基、苯并噁二唑基、苯并異噻唑基、苯并噻唑基、苯并噻二唑基、苯并呋喃基、異苯并呋喃基、苯并噻吩基、苯并三唑基、咪唑吡啶基、三唑吡啶基、咪唑噻唑基、吡咯并噠咯基、苯并咪唑啉基等之稠合雜芳香環式基。

所謂「非芳香族雜環」包括上記「雜環」中之非芳香環。包括環內至少含有 1 個氮原子、氧原子、及/或硫原子之 5~7 員之非芳香族環、

稠合此等 2 個以上之非芳香族環、

環內至少含有 1 個氮原子、氧原子、及/或硫原子之 5~7 員

之芳香族環與 1 以上的上記「環烷」或上記「環烯」稠合之環、

或環內至少含有 1 個氮原子、氧原子、及/或硫原子之 5~7 員之非芳香族複素環與 1 以上的上記「芳香族碳環」或「非芳香族碳環」稠合之環。可舉出例如二氫吡咯、吡咯啶、咪唑啉、咪唑啶、吡唑啉、吡唑啶、哌啶、哌哄、嗎福啉、硫嗎福啉、硫嗎福啉、四氫哌喃、二氫吡啶、二氫嗒哄、二氫吡哄、二噁烷、氧硫戊環、硫己環(thiane)、四氫呋喃、四氫哌喃、四氫噻唑啉、四氫異噻唑啉等之非芳香族雜環，吲哚啉、異吲哚啉、苯并哌喃、苯并二噁烷、四氫喹啉、四氫苯并噻吩等之非芳香族稠合雜芳香環。

所謂「鹵素」意指氟、氯、臭及碘。

所謂「低級烷氧基」包括以 RO-表示之基。可舉出例如 R 爲與前記低級烷基同意義之甲氧基、乙氧基、丙氧基、異丙氧基、丁氧基、異丁氧基、第二丁氧基、第三丁氧基、戊氧基、異戊氧基、新戊氧基、己氧基等之低級烷氧基。

Y 中作爲「低級烷氧基」是碳數 1~4 之烷氧基，較佳爲例如甲氧基、乙氧基、丙氧基、異丙氧基、丁氧基等。

所謂「低級烷硫基」包括以 RS-表示之基。可舉出例如 R 爲與前記低級烷基同意義之甲硫基、乙硫基、丙硫基、異丙硫基、丁硫基、異丁硫基、第二丁硫基、第三丁硫基、戊硫基、異戊硫基、新戊硫基、己硫基等之低級烷硫基。

R^{1a} 中作爲「低級烷硫基」是碳數 1~4 之烷硫基，較佳爲例如甲硫基。

所謂「低級烷氧羰基」包括以 R-O-C(=O)-表示之基。可舉出例如 R 爲與前記低級烷基同意義之甲氧基羰基、乙氧基羰基、正丙氧基羰基、異丙氧基羰基、正丁氧基羰基、第三丁氧基羰基、正戊氧基羰基等之低級烷氧羰基。

R^{1a}、R^3及 Y 中作爲「低級烷氧羰基」是碳數 1~4 之烷氧羰基，較佳爲例如甲氧基羰基、乙氧基羰基等。

作爲「低級烷基胺甲醯基」可舉出例如甲基胺甲醯基、乙基胺甲醯基、正丙基胺甲醯基、異丙基胺甲醯基、正丁基胺甲醯基、二甲基胺甲醯基、二乙基胺甲醯基、二丙基胺甲醯基等之烷基部分的碳數爲 1~6 之單或二低級烷基胺甲醯基。

R^{1a}中作爲「低級烷基胺甲醯基」是碳數 1~4 之烷氧基胺甲醯基，較佳爲例如甲基胺甲醯基、二甲基胺甲醯基等。

所謂「硫胺甲醯基」包括以-C(=S)-NR^XR^Y(例如 R^X 及 R^Y分別獨立爲氫、前記「烷基」或「烯基」、或後述之「芳基」、「雜芳基」、「非芳香族碳環基」、「非芳香族複素環基」「芳烷基」或「雜芳基烷基」。此等亦可分別獨立經羥基、羧基、前記或後述之「烷基」、「烯基」、「炔基」、「鹵素」、「烷基氧基」、「烯基氧基」、「炔基氧基」、「烷硫基」、「胺甲醯基」、「烷基氧基羰基」、「芳基氧基羰基」等取代)表示之基。

所謂「亞磺醯基」包括以-S(=O)-R(R 爲前記「烷基」或「烯基」、或後述之「芳基」、「雜芳基」、「非芳香族碳環基」、「非芳香族複素環基」「芳烷基」或「雜芳基烷基」。此等亦可分別獨立經羥基、羧基、前記或後述之「烷基」、「烯基」、

「炔基」、「鹵素」、「烷基氧基」、「烯基氧基」、「炔基氧基」、「烷硫基」、「胺甲醯基」、「烷基氧基羰基」、「芳基氧基羰基」等取代)表示之基。

R^{1a}及Y中作爲「亞磺醯基」是碳數1~4之烷基亞磺醯基，較佳爲例如甲基亞磺醯基等。

所謂「磺醯基」包括以$-S(=O)_2-R$(R爲前記「烷基」或「烯基」、或後述之「芳基」、「雜芳基」、「非芳香族碳環基」、「非芳香族複素環基」「芳烷基」或「雜芳基烷基」。此等亦可分別獨立經羥基、羧基、前記或後述之「烷基」、「烯基」、「炔基」、「鹵素」、「烷基氧基」、「烯基氧基」、「炔基氧基」、「烷硫基」、「胺甲醯基」、「烷基氧基羰基」、「芳基氧基羰基」等取代)表示之基。

R^{1a}及Y中作爲「磺醯基」是碳數1~4之烷基磺醯基、較佳爲例如甲磺醯基等。

所謂「胺磺醯基」包括以$-S(=O)_2-NR^XR^Y$(例如R^X及R^Y分別獨立爲氫、前記「烷基」或「烯基」、或後述之「芳基」、「雜芳基」、「非芳香族碳環基」、「非芳香族複素環基」「芳烷基」或「雜芳基烷基」。此等亦可分別獨立經羥基、羧基、前記或後述之「烷基」、「烯基」、「炔基」、「鹵素」、「烷基氧基」、「烯基氧基」、「炔基氧基」、「烷硫基」、「胺甲醯基」、「烷基氧基羰基」、「芳基氧基羰基」等取代)表示之基。

作爲「取代低級烷基」、「取代第三丁基」、「取代異丙基」、「取代低級烯基」、「取代低級炔基」、「取代低級烷氧基」、「取代低級烷硫基」、「取代低級烷氧羰基」、「取代低級

烷基胺甲醯基」之取代基，可舉出選自由以下所組群組之1個或1個以上之各自相同或不同之取代基，但不限定於此：羥基、羧基、鹵素(F、Cl、Br、I)、鹵低級烷氧基(例如CF_3O)、環烷基(例如環丙基)、環烯基(例如環丙烯基)、低級烷氧基(例如甲氧基、乙氧基、丙氧基、丁氧基等)、低級烯基氧基(例如乙烯基氧基、烯丙基氧基等)、低級烷氧羰基(例如甲氧基羰基、乙氧基羰基、第三丁氧基羰基等)、硝基、亞硝基、胺基、低級烷基胺基(例如甲基胺基、乙基胺基、二甲基胺基等)、醯胺基(例如乙醯基胺基、苄醯基胺基等)、芳烷基胺基(例如苄基胺基、三苯甲基胺基)、羥基胺基、亞胺基、羥基亞胺基、低級烷基亞胺基(例如甲基亞胺基、乙基亞胺基、二甲基亞胺基等)、低級烷氧基亞胺基(例如甲氧基亞胺基、乙氧基亞胺基等)、醯基亞胺基(例如乙醯基亞胺基、苄醯基亞胺基等)、疊氮基、芳基(例如苯基等)、芳烷基(例如苄基等)、芳烷基氧基(例如苄基氧基)、氰基、異氰基、異氰氧基、硫氰氧基、異硫氰氧基、巰基、低級烷硫基(例如甲硫基等)、低級烷基磺醯基(例如甲磺醯基、乙磺醯基)、胺甲醯基、低級烷基胺甲醯基(例如甲基胺甲醯基、乙基胺甲醯基、二甲基胺甲醯基等)、胺磺醯基、低級烷基胺磺醯基、醯基(例如甲醯基、乙醯基等)、甲醯基氧基、硫甲醯基、硫羧基、二硫羧基、硫胺甲醯基、亞磺酸基、磺酸基、肼基、疊氮基、脲基、脒基、胍基、酞醯亞胺基、三低級烷基矽烷基(三甲基矽烷基等)以及酮基。

R^{1a}及R^{1b}中作爲「取代低級烷基」之取代基，較佳爲

羥基、鹵素、硝基、氰基、鹵低級烷氧基、低級烯基氧基等。更佳可舉出羥基、低級烷氧基等。

R^{1a}及R^{1b}中作爲「取代低級烷氧基」及「取代低級烷硫基」之取代基，較佳爲鹵素、羥基等。

Y中作爲「取代低級烷基」之取代基，較佳爲羥基、鹵素、氰基、羧基、胺甲醯基、低級烷氧基、鹵低級烷氧基、低級烷基胺甲醯基、胺基、低級烷基胺基、經低級烷基磺醯基取代之胺基、低級烷氧基羰基甲基氧基等。

更佳爲可舉出羥基、鹵素、氰基、羧基、胺甲醯基、低級烷氧基、低級烷基胺甲醯基、胺基、低級烷基胺基、經低級烷基磺醯基取代之胺基、低級烷氧基羰基甲基氧基等。

Y中作爲「取代低級烷氧基」及「取代低級烷硫基」之取代基，較佳爲鹵素、羧基、氰基、羥基、低級烷基、經羥基取代之低級烷基、低級烷氧基、鹵低級烷氧基、低級烯基氧基、低級烷氧羰基、胺基、低級烷基胺基、經低級烷基磺醯基取代之胺基、低級烷基亞磺醯基、低級烷基磺醯基、胺甲醯基、低級烷基胺甲醯基、經胺基取代之胺甲醯基、經羥基取代之胺甲醯基、低級烷基亞磺醯基、低級烷基磺醯基、環烷基、雜環式基等。

更佳爲可舉出鹵素、羧基、氰基、胺甲醯基、低級烷基胺甲醯基、經羥基取代之亞胺基、低級烷氧基、胺基、低級烷基胺基、低級烷氧羰基、低級烷基亞磺醯基、四唑基等。

「取代醯基」之取代基與上記「取代低級烷基」的取代基相同。特別是醯基(R-C(=O)-)之R爲「芳基」、「雜環式基」、

「環烷基」或「環烯基」時，各自環亦可以低級烷基(例如甲基、乙基、異丙基、第三丁基等)、鹵低級烷基(例如 CF_3、CH_2CF_3、CH_2CCl_3 等)、低級烯基、低級炔基(例如乙炔基)等作爲取代基。

「取代胺甲醯基」、「取代硫胺甲醯基」及「取代胺磺醯基」的取代基可舉出選自由以下所組群組之 1 個或 1 個以上之各自相同或不同之取代基，但不限定於此：

羥基、羧基、鹵素(F、Cl、Br、I)、低級烷基(例如甲基)、低級烯基(例如乙烯基)、低級炔基(例如乙炔基)、環烷基(例如環丙基)、環烯基(例如環丙烯基)、低級烷氧羰基(例如甲氧基羰基、乙氧基羰基、第三丁氧基羰基等)、胺基、低級烷基胺基(例如甲基胺基、乙基胺基、二甲基胺基等)、醯胺基(例如乙醯基胺基、苄醯基胺基等)、芳烷基胺基(例如苄基胺基、三苯甲基胺基)、羥基胺基、芳基(例如苯基等)、氰基、異氰基、異氰氧基、硫氰氧基、異硫氰氧基及醯基(例如甲醯基、乙醯基等)。

R^{1a} 及 R^{1b} 中作爲「取代胺甲醯基」、「取代硫胺甲醯基」及「取代胺磺醯基」之取代基，較佳爲低級烷基、低級烯基、低級炔基、胺基、低級烷基胺基、醯胺基、羥基胺基等。

更佳爲可舉出低級烷基、低級烷基胺基等。

Y 中作爲「取代胺甲醯基」之取代基，較佳爲低級烷基、經羥基取代之低級烷基、經低級烷氧基取代之低級烷基、經氰基取代之低級烷基、低級烯基、低級炔基、低級烷基胺基、醯胺基等。

更佳爲可舉出低級烷基、經羥基取代之低級烷基、經低級烷氧基取代之低級烷基、經氰基取代之低級烷基、低級烷基胺基等。

作爲「取代胺基」之取代基可舉出選自由以下所組群組之1個或1個以上之各自相同或不同之取代基，但不限定於此：

羥基、鹵素(F、Cl、Br、I)、鹵低級烷基(例如 CF_3、CH_2CF_3、CH_2CCl_3等)、羥基低級烷基(例如羥基乙基、$-C(CH_3)_2CH_2OH$等)鹵低級烷氧基(例如 CF_3O)、低級烷基(例如甲基、乙基、異丙基、第三丁基等)、低級烯基(例如乙烯基)、低級炔基(例如乙炔基)、環烷基(例如環丙基)、環烯基(例如環丙烯基)、低級烷氧基(例如甲氧基、乙氧基、丙氧基、丁氧基等)、低級烷氧基羰基(第三丁氧基羰基等)、低級烯基氧基(例如乙烯基氧基、烯丙基氧基等)、胺基、低級烷基胺基(例如甲基胺基、乙基胺基、二甲基胺基等)、醯胺基(例如乙醯基胺基、苄醯基胺基等)、芳烷基胺基(例如苄基胺基、三苯甲基胺基)、羥基胺基、亞胺基、羥基亞胺基、低級烷基亞胺基(例如甲基亞胺基、乙基亞胺基、二甲基亞胺基等)、低級烷氧基亞胺基(例如甲氧基亞胺基、乙氧基亞胺基等)、醯基亞胺基(例如乙醯基亞胺基、苄醯基亞胺基等)、芳基(例如苯基等)、芳烷基(例如苄基等)、氰基及醯基(例如甲醯基、乙醯基等)。

R^{1a}及R^{1b}中作爲「取代胺基」之取代基，較佳爲低級烷基、低級烯基、低級炔基、鹵低級烷基、羥基低級烷基、

低級烷氧基、鹵低級烷氧基、低級烯基氧基、醯基等。

更佳爲可舉出低級烷基、醯基等。

Y中作爲「取代胺基」之取代基，較佳爲低級烷基、乙醯基、低級烷氧基羰基、胺甲醯基、低級烷基磺醯基等。

作爲「取代環烷基」、「取代環烯基」、「取代芳基」、「取代雜環式基」、「取代雜芳基」、「取代苯基」、「取代吡啶基」之取代基可舉出選自由以下所組群組之1個或1個以上之各自相同或不同之取代基，但不限定於此：

羥基、羧基、鹵素(F、Cl、Br、I)、鹵低級烷基(例如CF_3、CH_2CF_3、CH_2CCl_3等)、鹵低級烷氧基(例如CF_3O)、低級烷基(例如甲基、乙基、異丙基、第三丁基等)、低級烯基(例如乙烯基)、低級炔基(例如乙炔基)、環烷基(例如環丙基)、環烯基(例如環丙烯基)、低級烷氧基(例如甲氧基、乙氧基、丙氧基、丁氧基等)、低級烯基氧基(例如乙烯基氧基、烯丙基氧基等)、低級烷氧羰基(例如甲氧基羰基、乙氧基羰基、第三丁氧基羰基等)、硝基、亞硝基、胺基、低級烷基胺基(例如甲基胺基、乙基胺基、二甲基胺基等)、醯胺基(例如乙醯基胺基、苄醯基胺基等)、芳烷基胺基(例如苄基胺基、三苯甲基胺基)、羥基胺基、亞胺基、羥基亞胺基、低級烷基亞胺基(例如甲基亞胺基、乙基亞胺基、二甲基亞胺基等)、低級烷氧基亞胺基(例如甲氧基亞胺基、乙氧基亞胺基等)、醯基亞胺基(例如乙醯基亞胺基、苄醯基亞胺基等)、疊氮基、芳基(例如苯基等)、芳烷基(例如苄基等)、芳烷基氧基(例如苄基氧基等)、氰基、異氰基、異氰氧基、硫氰氧基、異硫

氰氧基、巰基、低級烷硫基(例如甲硫基等)、低級烷基磺醯基(例如甲磺醯基、乙磺醯基)、取代或未取代之胺甲醯基(例如胺甲醯基、N-甲基-N-甲氧基胺甲醯基等)、取代或未取代之低級烷基胺甲醯基(例如甲基胺甲醯基、乙基胺甲醯基、二甲基胺甲醯基、羥基乙基胺甲醯基、三氟甲基胺甲醯基、三氟乙基胺甲醯基等)、胺磺醯基、低級烷基胺磺醯基、醯基(例如甲醯基、乙醯基等)、甲醯基氧基、硫甲醯基、硫羧基、二硫羧基、硫胺甲醯基、亞磺酸基、磺酸基、肼基、疊氮基、脒基、胍基、胲基、酞醯亞胺基及酮基。

作爲「取代環烷基」、「取代環烯基」、「取代芳基」、「取代雜環式基」、「取代雜芳基」、「取代苯基」、「取代吡啶基」之取代基，較佳爲鹵素、低級烷基、鹵低級烷基、低級烷氧基、鹵低級烷氧基等。

此處鹵低級烷基、鹵低級烷氧基之鹵素部分與上記「鹵素」同意義。

「鹵低級烷基」、「低級烷基胺基」、「低級烷基亞胺基」、「低級烷基磺醯基」、「低級烷基胺磺醯基」、「低級烷基胺甲醯基」、「芳烷基」及「芳烷基胺基」之「烷基」或「低級烷基」部分與上記「低級烷基」同意義。

「鹵低級烷氧基」及「低級烷氧基亞胺基」之「低級烷氧基」部分與上記「低級烷氧基」同意義。

「低級烯基」所謂包括在任意位置具有 1 個以上雙鍵之碳數 2~6、較佳爲碳數 2~3 之直鏈或分枝狀的烯基。具體可舉出乙烯基、丙烯基、異丙烯基、丁烯基、異丁烯基、異戊

二烯基、丁二烯基、戊烯基、異戊烯基、戊二烯基、己烯基、異己烯基、己二烯基等。

低級烯基氧基之低級烯基部分與上記「低級烯基」同意義。

所謂「低級炔基」包括碳數2~6、較佳爲碳數2~3之直鏈狀或分枝狀之炔基，具體可舉出乙炔基、丙炔基、丁炔基、戊炔基、己炔基等。此等在任意位置具有1個以上參鍵，亦可更具有雙鍵。

所謂「芳烷基」包括於上記「低級烷基」有上記「芳基」取代之基。具體可舉出苄基、苯乙基等。

「芳烷基胺基」及「芳烷基」之芳基部分與上記「芳基」同意義。

「醯基」、「醯胺基」及「醯基亞胺基」之「醯基」部分與上記「醯基」同意義。

「可經保護之羥基」及「可經保護之巯基」中之保護基爲所屬領域周知，可舉出例如醚及取代醚形成基(例如甲基、甲氧基甲基、第三丁氧基甲基、1-乙氧基乙基及苄基等)；矽烷基醚形成基(例如三甲基矽烷基、三乙基矽烷基、第三丁基二甲基矽烷基及甲基-二異丙基矽烷基等)；酯形成基(例如甲酸酯、乙酸酯及三氯乙酸酯等)；碳酸酯基(例如甲基碳酸酯、2,2,2-三氯乙基碳酸酯、及 p-硝基苯基碳酸酯等)；磺醯基形成基(甲磺醯基、p-甲苯磺醯基)等。

作爲「可經保護之羥基」及「可經保護之巯基」中之保護基，較佳爲醚及取代醚形成基等。特佳爲取代醚形成基等。

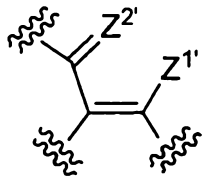
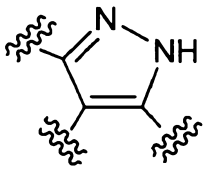
再者，式(I)化合物之一個以上的氫、碳或其他原子可經氫、碳或其他原子的同位素取代。式(I)之化合物包括式(I)化合物之全部的放射性標識體。式(I)化合物之此等「放射性標識化」、「放射性標識體」等各自包括於本發明中，有用於作爲代謝藥物動態研究及結合分析之研究及/或診斷工具。此外，也有用作爲醫藥品。

可併入本發明之式(I)化合物之同位素之例，分別包括 ^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{31}P、^{32}P、^{35}S、^{18}F、及 ^{36}Cl 之類、氫、碳、氮、氧、磷、硫、氟、及氯。本發明之放射性標識化合物可以所屬技術領域周知的方法調製。例如式(I)之氚標識化合物，可使用例如氚之觸媒的脫鹵素化反應，將氚導入式(I)之特定的化合物來調製。該方法亦可包括在適切的觸媒，例如 Pd/C 之存在下、在鹼基之存在或非存在下，使式(I)之化合物經適當鹵素取代之前驅體與氚氣反應。作爲其他調製氚標識化合物之適宜方法，可參照文件 Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A), Chapter 6 (1987 年)。^{14}C-標識化合物可使用具有 ^{14}C 碳之原料來調製。

本發明化合物(I')之較佳態樣如下。各記號與上記記載同意義。

作爲 $Z^{1'}$ 可舉出羥基。

作爲 $Z^{2'}$，可舉出 O。

作爲  可舉出  。

作爲環 A’，可舉出芳香族碳環或雜環。

例如作爲環 A’，可舉出芳香族碳環或芳香族雜環。

例如作爲環 A’，可舉出苯環或吡啶環。

作爲 $R^{2'}$，可舉出取代或未取代之芳基或取代或未取代之芳香族雜環式基(例如噻吩基、吡啶基、咪唑基、嘧啶基、異噁唑基、噻唑基、異噻唑基、噻二唑基、噁唑基、吡唑基、噁二唑基等)。

例如作爲 $R^{2'}$，可舉出取代或未取代之苯基。

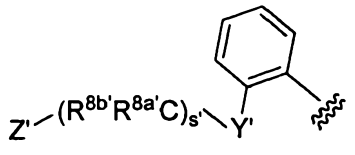
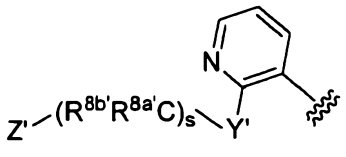
例如作爲 $R^{2'}$，可舉出取代或未取代之吡啶基。

例如作爲 $R^{2'}$，可舉出取代或未取代之第三丁基。

作爲 $R^{3'}$，可舉出取代或未取代之烷基、取代或未取代之環烷基、取代或未取代之苯基。

例如作爲 $R^{3'}$，可舉出取代或未取代之烷基、取代或未取代之環烷基、取代或未取代之芳基或取代或未取代之雜環式基。

例如作爲 $R^{3'}$，可舉出下式：

 或  。

作爲環 D’，可舉出苯環或吡啶環。

V’可舉出 -O-C(=O)-、-C(=O)-O-、$-NR^{13'}$-C(=O)-、-C(=O)-$NR^{13'}$-。

作為 $R^{4a'}$及 $R^{4b'}$，可舉出分別獨立為氫或低級烷基。

例如作為 $R^{4a'}$及 $R^{4b'}$，可舉出氫。

作為 t'，可舉出 0。

作為 m'，可舉出 0~2 之整數。

例如作為 m'，可舉出 1 或 2 之整數。

例如作為 m'，可舉出 0。

作為 $R^{1a'}$，可舉出鹵素、取代或未取代之低級烷基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之芳基或取代或未取代之雜環式基。

例如作為 $R^{1a'}$，可舉出取代或未取代之低級烷氧羰基、取代或未取代之苯基、取代或未取代之芳香族雜環式基(例如噻吩基、吡啶基、咪唑基、嘧啶基、異噁唑基、噻唑基、異噻唑基、噻二唑基、噁唑基、吡唑基、噁二唑基等)。

例如作為 $R^{1a'}$，可舉出取代或未取代之低級烷氧羰基、取代或未取代之芳基或取代或未取代之雜環式基。

例如作為 $R^{1a'}$，可舉出取代或未取代之低級烷氧羰基、取代或未取代之芳基或取代或未取代之雜環式基。

例如作為 $R^{1a'}$，可舉出取代或未取代之低級烷氧羰基、取代或未取代之苯基、取代或未取代之芳香族雜環式基(例如噻吩基、吡啶基、咪唑基、嘧啶基、異噁唑基、噻唑基、異噻唑基、噻二唑基、噁唑基、吡唑基、噁二唑基等)。

作為 $R^{1b'}$，可舉出鹵素、取代或未取代之低級烷基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之芳基或取代或未取代之雜環式基。

例如作爲 $R^{1b'}$，可舉出鹵素、取代或未取代之低級烷基、羧基、取代或未取代之低級烷氧羰基。

進一步上記所示各取代基之選擇的全部組合所示之化合物。

本發明化合物(I')中較佳態樣如下。

Z^2 爲 O；

t 爲 0；

$R^{2'}$ 爲取代或未取代之第三丁基、取代或未取代之異丙基；

$R^{3'}$ 爲下式之化合物：

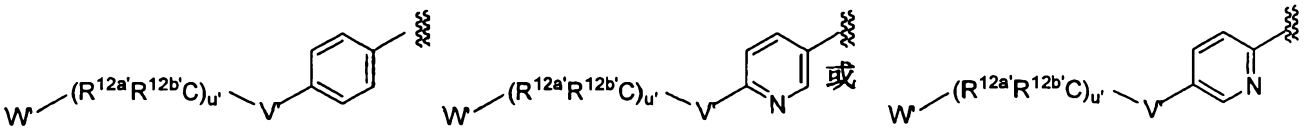


。

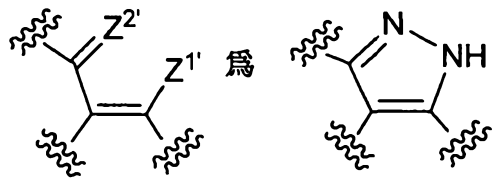
$Z^{2'}$ 爲 O；

t' 爲 0；

R^2 爲



$R^{3'}$ 爲取代或未取代之芳基或取代或未取代之雜環式基之合物。



；

t'爲 0；

$R^{2'}$爲取代或未取代之第三丁基、取代或未取代之異丙基；

$R^{3'}$爲下式之化合物：

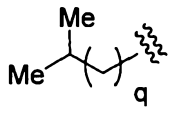


。

進一步上記所示各取代基之選擇的全部組合所示之化合物。

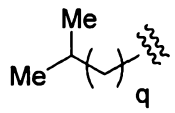
本發明化合物(I)中較佳態樣如下。各記號與上記記載同意義。

作爲 R^2，可舉出以下式表示之基：



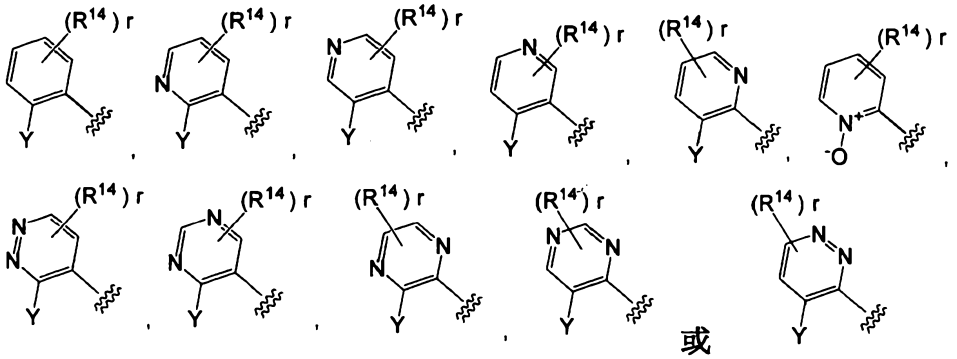
(式中，Me爲甲基，q爲 0~4 之整數)。

例如作爲 R^2，可舉出以下式表示之基：



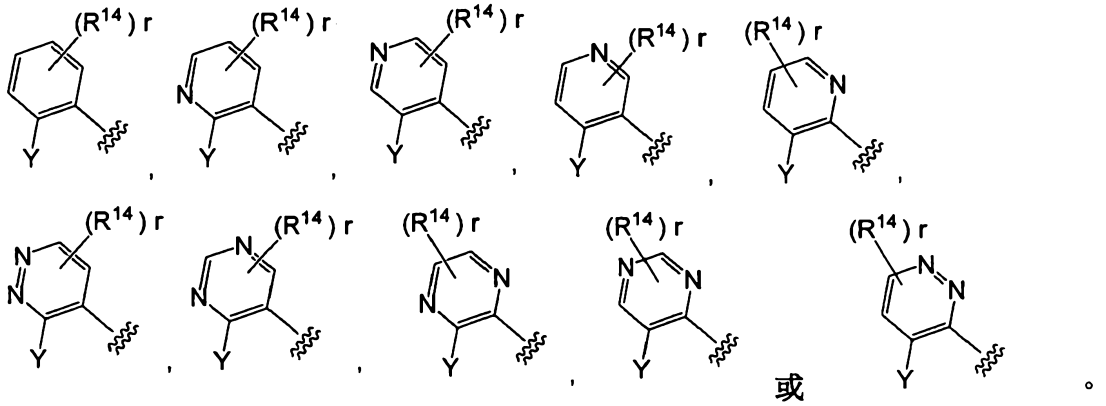
(式中，Me爲甲基，q爲 0~1 之整數)。

作爲 R^3，可舉出以下式表示之基：



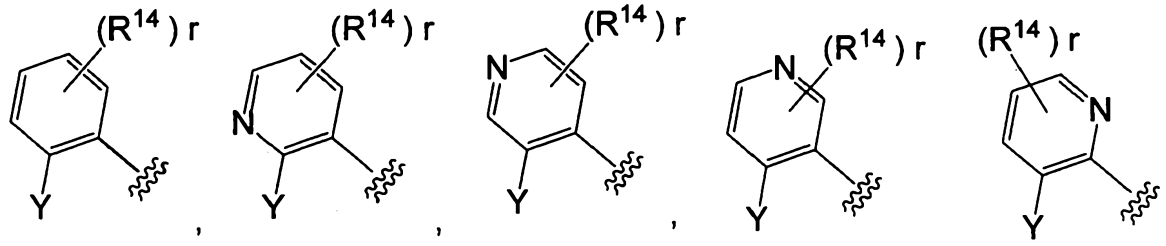
或 。

例如作爲 R^3，可舉出以下式表示之基：



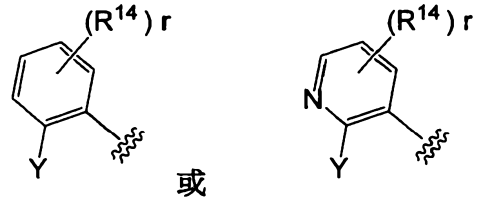
或 。

例如作爲 R^3，可舉出以下式表示之基：



或 。

例如作爲 R^3，可舉出以下式表示之基：



或 。

作爲 Y，可舉出羥基、鹵素、氰基、羧基、取代或未取

代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式基。

例如Y作爲Y，可舉出取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基或取代磺醯基。

例如作爲Y，可舉出取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基或取代磺醯基。

作爲R^{14}，可舉出鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基。

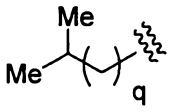
例如作爲 R^{14}，可舉出鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基。

作爲 r，可舉出 0~2 之整數。

進一步上記所示各取代基之選擇的全部組合所示之化合物。

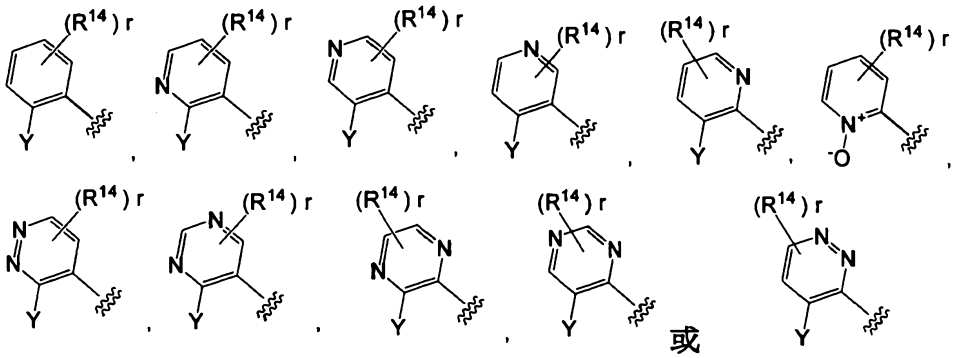
本發明化合物(I)中更佳態樣如下。

(a)以下所示之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 R^2 爲下式表示之基：



(式中，Me 爲甲基，q 爲 0~1 之整數)；

R^3 爲下式表示之基：



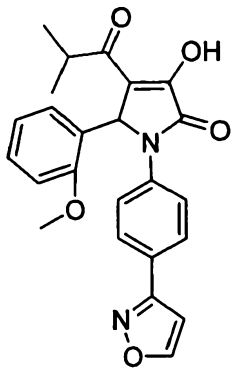
或

(式中，Y 爲羥基、鹵素、氰基、羧基、取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級

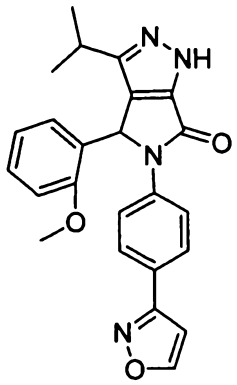
烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式基；或 Y 及 R^{14} 亦可結合於鄰接之碳原子形成取代或未取代之雜環式基；

R^{14} 爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基；r 爲 0~2 之整數)；

(但以下式表示之化合物除外：



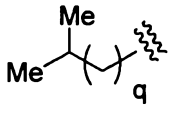
及



)。

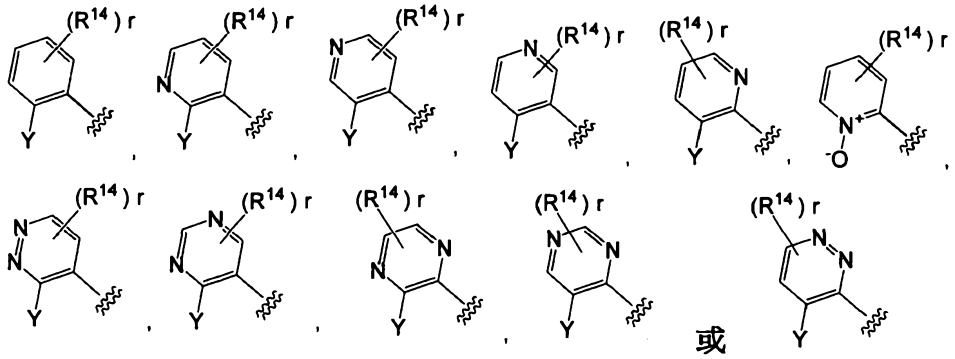
本發明化合物(I)中更佳態樣如下。

(b)以下所示之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 R^2 爲下式表示之基：



(式中，Me為甲基，q為0~1之整數)；

R^3為下式表示之基：

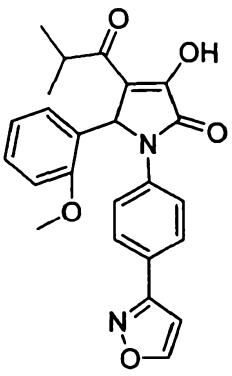
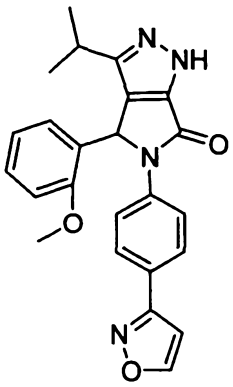


或

(式中，Y為取代或未取代之烷氧基、取代或未取代之烷硫基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、氰基、羧基、取代亞磺醯基、取代磺醯基、取代或未取代之雜環式基；

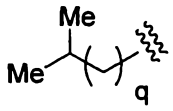
R^{14}為鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基；r為0~2之整數)

(但以下式表示之化合物除外：


及

)。

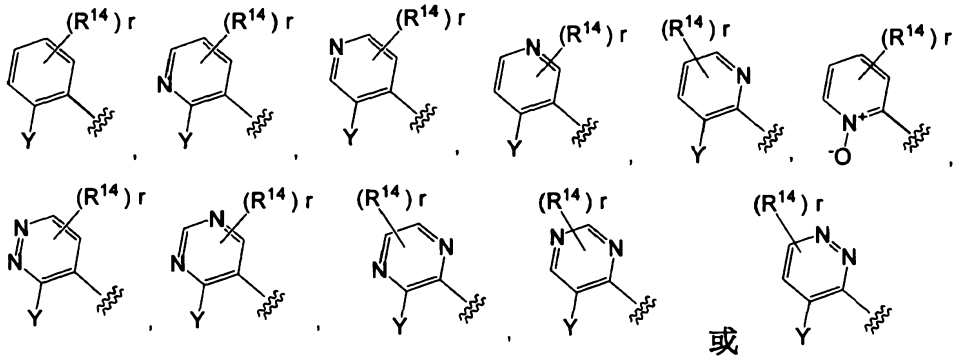
本發明化合物(I)中更佳態樣如下。

(c)以下所示之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中 R^2 爲下式表示之基：



(式中，Me爲甲基，q爲0~1之整數)；

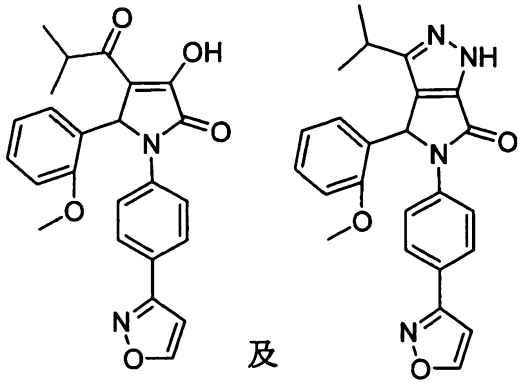
R^3 爲下式表示之基：



(式中，Y爲羥基、鹵素、氰基、羧基、取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式

基；r 爲 0)

(但以下式表示之化合物除外：



及

)。

本發明化合物(I)中更佳態樣如下。

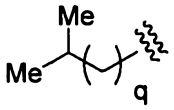
(d)以下所示之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中

Z^1 爲羥基；

Z^2 爲 -C(=O)-；

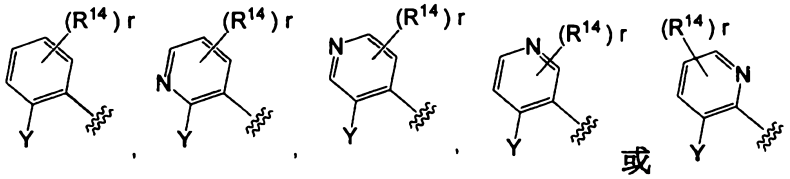
Z^{3a} 及 Z^{3b} 一起成爲 =O；

R^2 爲下式表示之基：



(式中，Me 爲甲基，q 爲 0~1 之整數)；

R^3 爲下式表示之基：



或

(式中，Y 爲羥基、鹵素、氰基、羧基、取代或未取代之低

級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式基；r爲0)；

t爲0；

k爲0或1之整數；

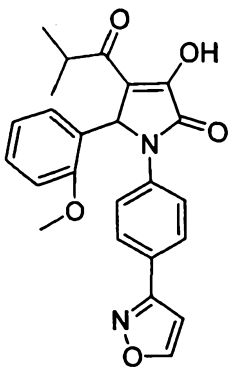
m爲0或1之整數；

n爲0或1之整數；

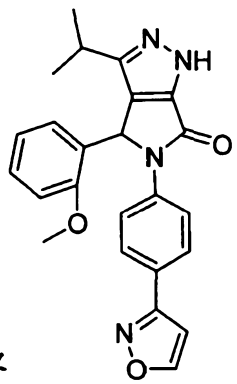
R^{1a}及R^{1b}分別獨立爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基、取代或未取代之胺磺醯基、氰基、硝基或$-C(R^{7a})=N-O-R^{7b}$；

R^{7a}及R^{7b}分別獨立爲氫或取代或未取代之低級烷基；)

(但以下式表示之化合物除外：



及



)。

本發明化合物(I)中更佳態樣如下。

(e)以下所示之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中

Z^1 爲羥基；

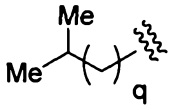
Z^2 爲 -C(=O)-；

Z^{3a} 及 Z^{3b} 一起成爲 =O；

環 A 爲苯或吡啶；

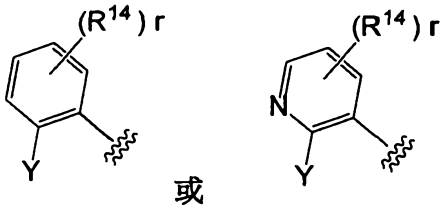
B 爲芳香族碳環二基或芳香族雜環二基；

R^2 爲下式表示之基：



(式中，Me 爲甲基，q 爲 0~1 之整數)；

R^3 爲下式表示之基：



(式中，Y 爲取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、或取代或未取代之胺基；r 爲 0)；

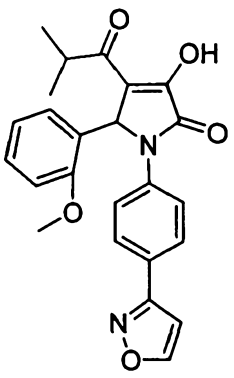
t 爲 0；

k 爲 1 之整數；

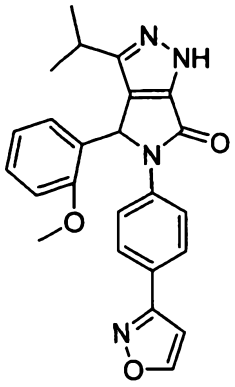
m 爲 0 或 1 之整數；

n 爲 0 或 1 之整數；

R^{1a} 及 R^{1b} 分別獨立爲鹵素、取代或未取代之低級烷基、取代或未取代之低級烷氧基、或取代或未取代之低級烷硫基)(但以下式表示之化合物除外：



及



)。

本發明化合物(I)中更佳態樣如下。

(f)以下所示之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中

Z^1 爲羥基；

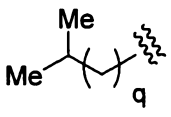
Z^2 爲 -C(=O)-；

Z^{3a} 及 Z^{3b} 一起成爲 =O；

環 A 爲苯或吡啶；

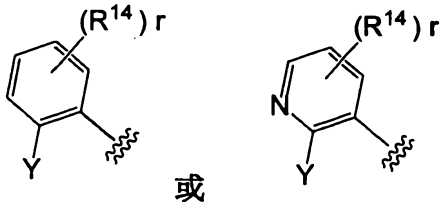
B 爲芳香族碳環二基或芳香族雜環二基；

R^2 爲下式表示之基：



(式中，Me 爲甲基，q 爲 0~1 之整數)；

R^3 爲下式表示之基：



或

(式中，Y 爲取代低級烷氧基、取代低級烷硫基、或取代胺基；r 爲 0)；

t 爲 0；

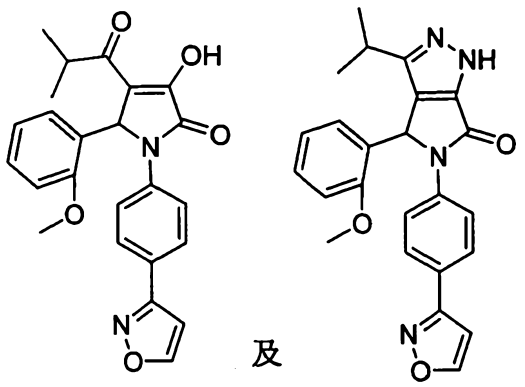
k 爲 1；

m 爲 0 或 1；

n 爲 0 或 1；

R^{1a} 及 R^{1b} 分別獨立爲鹵素、取代或未取代之低級烷基、取代或未取代之低級烷氧基、或取代或未取代之低級烷硫基)

(但以下式表示之化合物除外：



及

)。

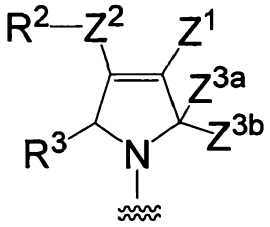
(g)上記(a)~(f)中，

Y 爲經選自取代基群 A(取代基群 A：羥基、胺甲醯基、低級烷基胺甲醯基、經羥基取代之亞胺基、低級烷氧基、胺基、低級烷基胺基、低級烷氧羰基、低級烷基亞磺醯基及低級烷

基磺醯基)之 1 個或 1 個以上的取代基取代之低級烷氧基之化合物或其製藥上容許的鹽或彼等之溶劑化物。

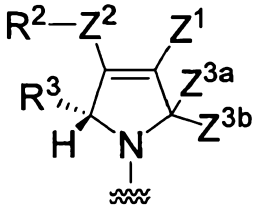
(h)上記(a)~(g)中，

下式表示之基：



爲

下式表示之基：



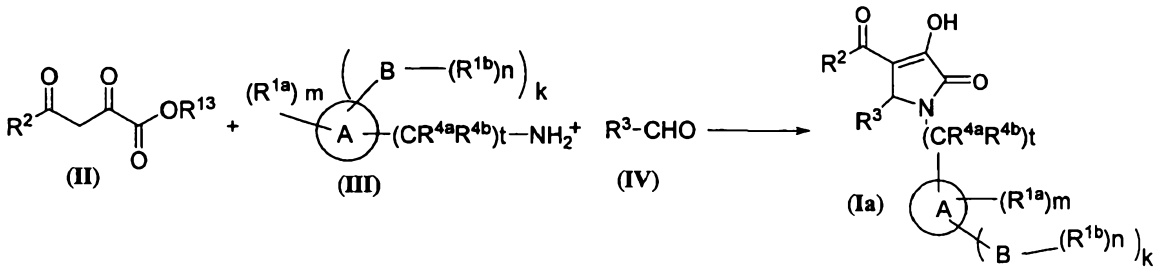
(式中之各取代基與上記(a)~(e)的定義爲同意義)

之化合物或其製藥上容許的鹽或彼等之溶劑化物。

以下顯示本發明化合物之一般的合成方法。用於這些合成的開始物質及反應試藥皆可得自市售商品，或使用市售商品依照所屬領域周知的方法來製造。

本發明之化合物(I)(亦即一般式(I)表示之化合物。以下，其他式表示之化合物也同樣地縮寫)可例如依據以下所示之合成路徑製造。

[路徑 1]



[式中，R^{13}為取代或未取代之低級烷基，其他的記號與前記同意義]

亦即，一般式(Ia)表示之本發明化合物，可在酸的存在下或未存在下、在無溶劑或適當溶劑中使化合物(II)、化合物(III)及化合物(IV)反應來製造。

本反應中，相對於化合物(II)，可使用 1 當量或 1 當量以上之化合物(III)及化合物(IV)，較佳爲 1~3 當量。

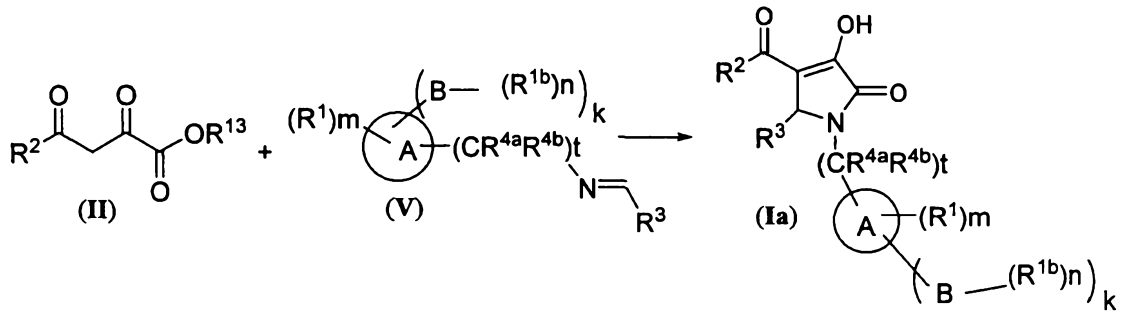
作爲可使用的酸，可舉出乙酸、對甲苯磺酸、鹽酸等。

作爲可使用的溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、醚類(例如四氫呋喃、二乙基醚、二噁烷等)及彼等之混合溶劑等。

反應溫度爲-10~160℃，較佳爲 20~120℃。反應時間視化合物而異，可爲 10 分鐘~80 小時反應。

獲得之所欲化合物(Ia)視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 2]



[式中之記號與前記同意義]

亦即，一般式(Ia)表示之本發明化合物，可在酸的存在下或未存在下、在無溶劑或適當溶劑中使化合物(II)及化合物(V)反應來製造。

本反應中，相對於化合物(II)，可使用1當量或1當量以上之化合物(V)，較佳爲1~3當量。

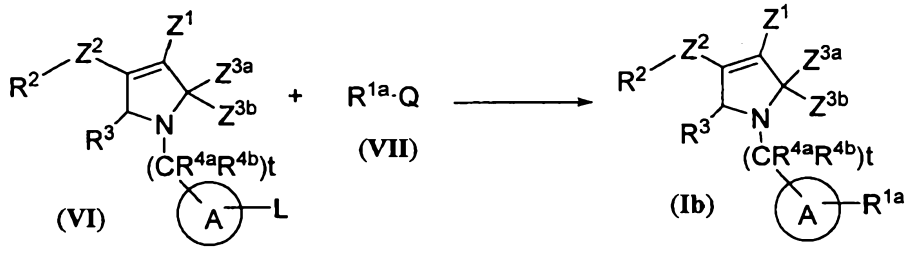
作爲可使用的酸，可舉出乙酸、對甲苯磺酸、鹽酸等。

作爲可使用的溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、醚類(例如四氫呋喃、二乙基醚、二噁烷等)及彼等之混合溶劑等。

反應溫度爲-10~160℃，較佳爲 20~120℃。反應時間視化合物而異，可爲10分鐘~80小時反應。

獲得之所欲化合物(Ia)視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 3]



[式中，L及Q之一方表示二羥基硼烷、二低級烷基硼烷或

二低級烷氧基硼烷，另一方則爲鹵素或-$OSO_2(CiF_2i+1)$(i 爲1~4之整數)，其他的記號與前記同意義。]

亦即，一般式(Ib)表示之本發明化合物，可使用鈴木偶合(Suzuki coupling)反應，在鈀觸媒及鹼基存在下、在適當溶劑中使化合物(VI)及化合物(VII)反應來製造。

本反應中，相對於化合物(VI)，可使用1當量或1當量以上之化合物(VII)，較佳爲1~3當量。

作爲可使用的鹼基，可舉出例如金屬氫氧化物(例如氫氧化鈉、氫氧化鉀、磷酸三鉀等)、金屬氫化物(例如氫化鈉、氫化鋰等)、金屬碳酸鹽(例如碳酸鈉、碳酸鉀、碳酸銫等)等，相對於化合物(VI)，可使用1當量或1當量以上，較佳爲1~5當量。

作爲可使用之鈀觸媒，可舉出例如三(二亞苄基丙酮)二鈀(0)、乙酸鈀(II)、二氯雙三苯膦鈀(II)或肆(三苯膦)鈀(II)等，相對於化合物(VI)，可使用0.001當量或0.001當量以上，較佳爲0.01~1當量。

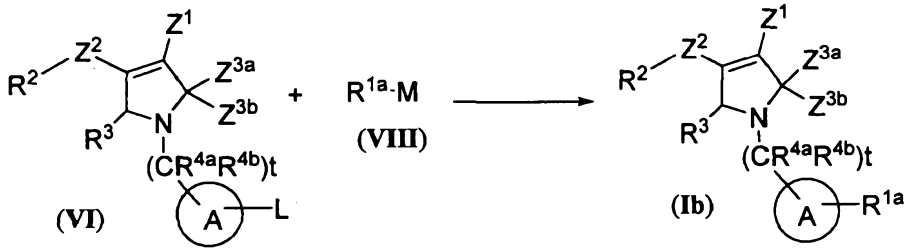
作爲可使用之溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、醚類(例如四氫呋喃、二乙基醚、二噁烷、二甲氧基乙烷等)、N,N-二甲基甲醯胺、水及彼等之混合溶劑等。

反應溫度爲-10~180℃，視情況微波照射下，較佳爲20~120℃。反應時間視化合物而異，可爲10分鐘~80小時反應。

獲得之所欲化合物(Ib)視需要可經由常法(例如管柱色

層分析、再結晶等)純化。

[路徑 4]



[式中，L 及 M 之一方表示三烷基錫(例如-$SnBu_3$等)，另一方則爲鹵素或-$OSO_2(CiF_2i+1)$(i 爲 1~4 之整數)，其他的記號與前記同意義。]

亦即，一般式(Ib)表示之本發明化合物，可使用 Stille 偶合反應，在觸媒存在下、在適當溶劑中使化合物(VI)及化合物(VIII)反應來製造。

本反應中，相對於化合物(VI)，可使用 1 當量或 1 當量以上之化合物(VIII)，較佳爲 1~3 當量。

作爲可使用之觸媒，可舉出例如三(二亞苄基丙酮)二鈀(0)、乙酸鈀(II)、二氯雙三苯膦鈀(II)或肆(三苯膦)鈀(II)等，相對於化合物(VI)，可使用 0.001 當量或 0.001 當量以上，較佳爲 0.01~1 當量。視需要可添加觸媒之 2 倍莫耳的膦配位子、例如三-第三丁基膦、2-(二-第三丁基膦)二苯基、2-(二-環己基膦)二苯基、三苯膦、參-(2-呋喃基)膦等。

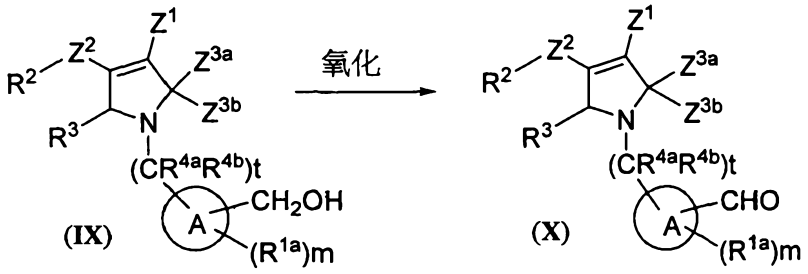
作爲可使用之溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、醚類(例如四氫呋喃、二乙基醚、二噁烷、二甲氧基乙烷等)、N,N-二甲基甲醯胺及彼等之混合溶劑等。

反應溫度爲-10~180℃，視情況微波照射下，較佳爲

20~120℃。反應時間視化合物而異，可爲 10 分鐘~80 小時反應。

獲得之所欲化合物(Ib)視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 5]



[式中之記號與前記同意義]

亦即，一般式(X)表示之本發明化合物，可在氧化劑存在下、在適當溶劑中使化合物(IX)反應來製造。

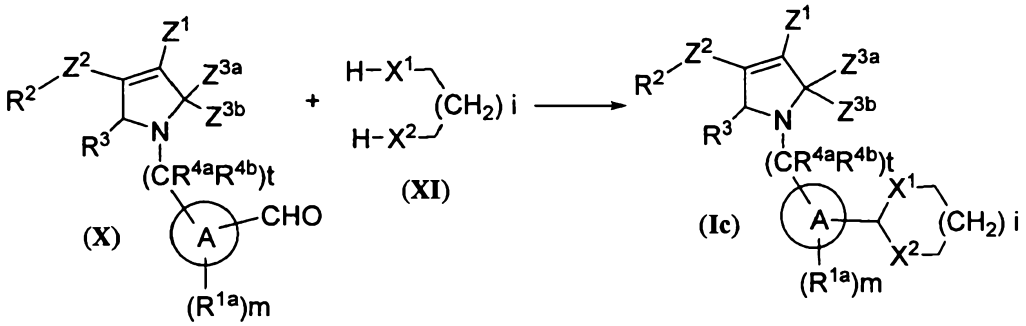
作爲可使用之氧化劑，可舉出例如二氧化錳、2-碘羥基苯甲酸等，相對於化合物(IX)可使用 1 當量或 1 當量以上，較佳爲 1~1.5 當量。

作爲可使用之溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、鹵素化烴類(例如二氯甲烷、1,2-二氯乙烷等)、醚類(例如四氫呋喃、二噁烷等)、酮類(例如丙酮、甲基乙基酮等)、腈類(例如乙腈等)及彼等之混合溶劑等。

反應溫度爲-10~150℃，較佳爲 20~100℃。反應時間視化合物而異，可爲 10 分鐘~80 小時反應。

化合物(IX)爲粗製物，或可使用以下步驟經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 5(繼續)]



[式中，i 爲 0~3 之整數，X^1 及 X^2 分別獨立爲 NR^{14}、O 或 S，R^{14} 爲氫或低級烷基，其他的記號與前記同意義]

亦即，一般式(Ic)表示之本發明化合物，可在酸的存在下或未存在下、在無溶劑或適當溶劑中使化合物(X)及化合物(XI)反應來製造。

本反應中，相對於化合物(X)，可使用 1 當量或 1 當量以上之化合物(XI)，較佳爲 1~3 當量。

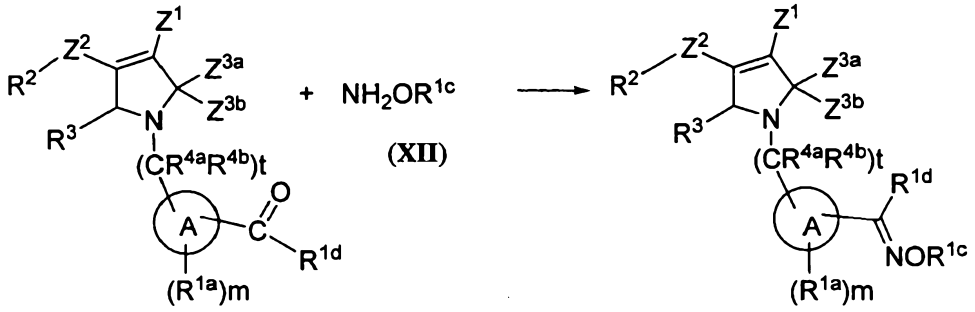
作爲可使用的酸，可舉出對甲苯磺酸、硫酸、對甲苯磺酸吡啶鎓鹽等。

作爲可使用的溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)及彼等之混合溶劑等。

反應溫度爲-10~170℃，較佳爲 20~150℃。反應時間視化合物而異，可爲 10 分鐘~80 小時反應。

獲得之所欲化合物(Ic)，視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 6]



(X) (Id)

[式中之記號與前記同意義]

亦即，一般式(Id)表示之本發明化合物，可在適當溶劑中使化合物(X)及化合物(XII)或其鹽反應來製造。相對於化合物(X)，使用 1~4 當量之化合物(XII)及其鹽，較佳爲 1~2.5 當量。

作爲化合物(XII)的鹽，可舉出例如鹽酸鹽、硫酸鹽等之無機酸鹽等。使用該鹽時，以鹼基中和以反應之。

作爲可使用之鹼基，可舉出例如乙酸鈉、胺類(吡啶等)等；相對於化合物(XI)的鹽，其使用量爲 1~3 當量，較佳爲 1~2 當量。

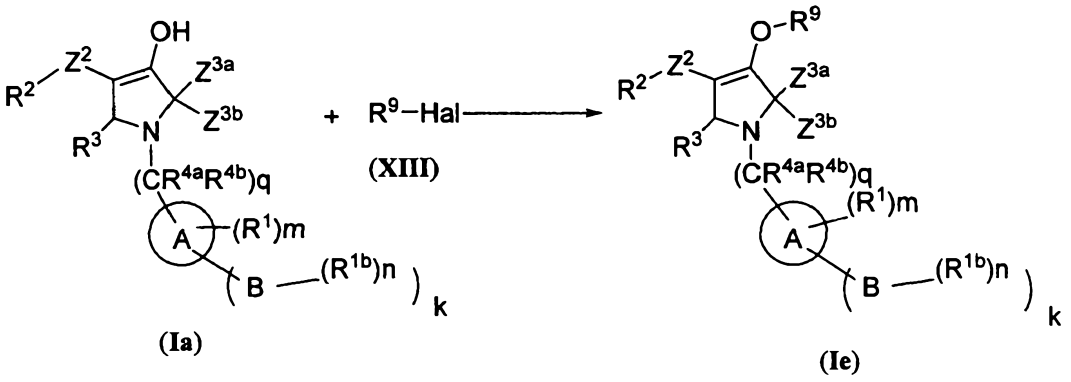
作爲可使用之溶劑，可舉出例如烴類(例如苯、甲苯、二甲苯等)、鹵素化烴類(例如氯仿、1,2-二氯乙烷等)、醚類(例如四氫呋喃、二噁烷等)、醇類(例如甲醇、乙醇、正丙醇、異丙醇等)、水及彼等之混合溶劑等。

反應溫度爲 0~150℃，較佳爲 20~120℃。

反應時間通常爲 10 分鐘~24 小時左右。

獲得之所欲化合物(Id)，視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 7]



[式中，Hal 爲鹵素，R^9 爲羥基的保護基，其他的記號與前記同意義]

亦即，一般式(Ie)表示之本發明化合物，可在鹼基存在下、在適當溶劑中使化合物(Ia)及化合物(XIII)反應來製造。相對於化合物(Ia)，使用 1~4 當量之化合物(XII)，較佳爲 1~2.5 當量。

作爲可使用之鹼基，可舉出例如氫化鈉、甲氧基鈉、胺類(三乙基胺、吡啶等)等，相對於化合物(Ia)，其使用量爲 1~3 當量，較佳爲 1~2 當量。

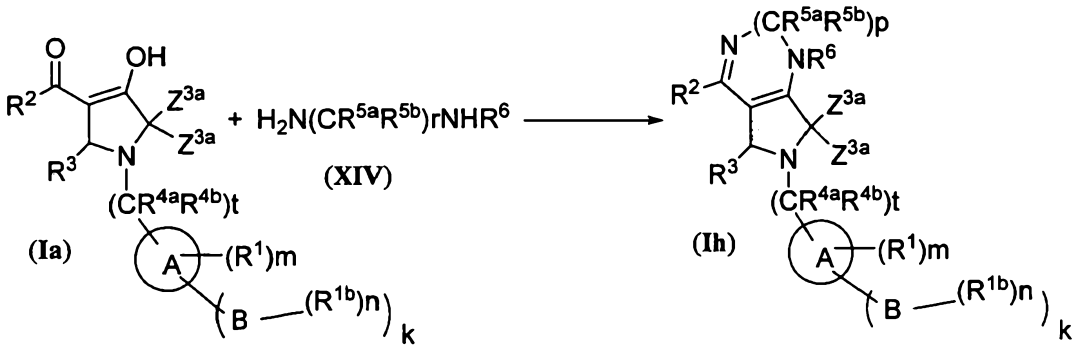
作爲可使用之溶劑，可舉出例如烴類(例如苯、甲苯、二甲苯等)、鹵素化烴類(例如氯仿、1,2-二氯乙烷等)、醚類(例如四氫呋喃、二噁烷等)、N,N-二甲基甲醯胺、二甲亞碸及彼等之混合溶劑等。

反應溫度爲 -20~150℃，較佳爲 0~120℃。

反應時間通常爲 10 分鐘~24 小時左右。

獲得之所欲化合物(Ie)，視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑 8]



[式中之記號與前記同意義]

亦即，一般式(Ih)表示之本發明化合物，可在適當溶劑中使化合物(Ia)及化合物(XIV)反應來製造。相對於化合物(Ia)，使用1~4當量之化合物(XIV)，較佳爲1~2.5當量。

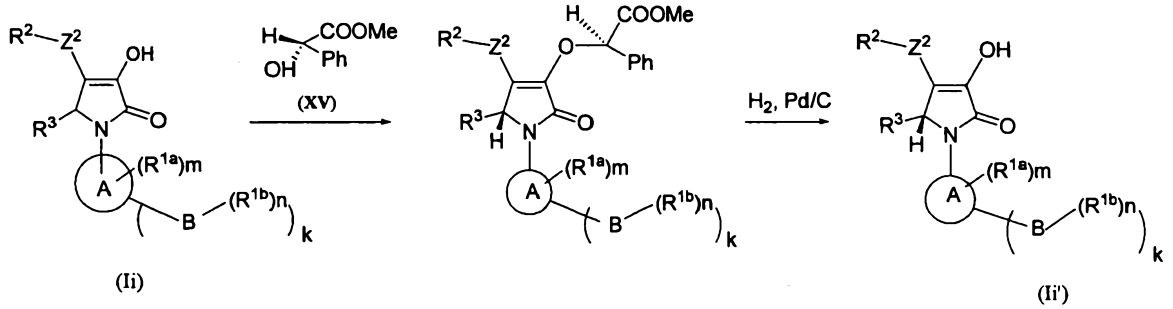
作爲可使用之溶劑，可舉出例如乙酸、烃類(例如苯、甲苯、二甲苯等)、醚類(例如四氫呋喃、二噁烷等)、醇類(例如甲醇、乙醇、正丙醇、異丙醇等)及彼等之混合溶劑等。

反應溫度爲0~150℃，較佳爲50~130℃。

反應時間通常爲10分鐘~24小時左右。

獲得之所欲化合物(Ih)，視需要可經由常法(例如管柱色層分析、再結晶等)純化。

[路徑9]



[式中之記號與前記同意義]

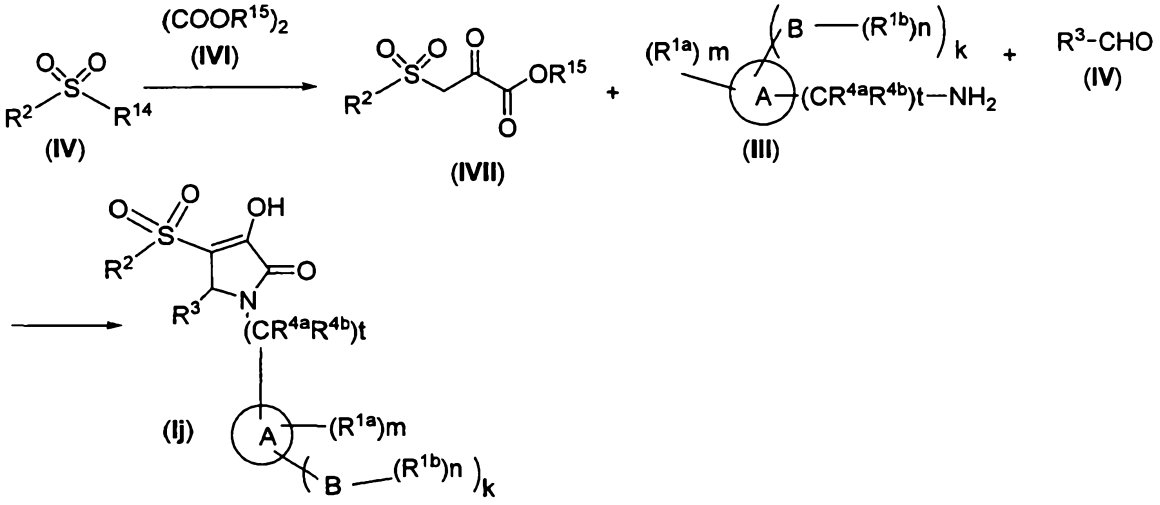
在適當溶劑中使化合物(Ii)及光學分割劑(resolving reagent)(XV)(例如(R)或(S)-甲基2-羥基-2-苯基乙酸鹽)與稠

合劑(例如偶氮二羧酸異丙酯)反應，經由常法(例如管柱色層分析、再結晶等)純化所得之混合物，可單離具有所欲構形之非鏡像異構物(diastereomer)。所得非鏡像異構物經脫保護反應(例如氫化反應，氯化鋰等)可製造目的之鏡像異構物(enantiomer)。相對於化合物(Ii)，使用 1~4 等量之光學分割劑(resolving reagent)，較佳爲 1~2.5 等量。

作爲可使用之溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷、1,3-二甲基-2-咪唑啶酮等)、醚類(例如四氫呋喃、二乙基醚、二噁烷等)醯胺類(例如二甲基甲醯胺、二甲基乙醯胺、N-甲基吡咯啶酮)及彼等之混合溶劑等。

反應溫度爲-10~150℃，較佳爲 0~80℃。反應時間視化合物而異，可爲 10 分鐘~48 小時反應。

[路徑 10]



[式中，R^{14}及R^{15}分別獨立爲取代或未取代之低級烷基，其他的記號與前記同意義]

亦即，一般式(Ij)表示之本發明化合物，可在酸的存在下或未存在下、在無溶劑或適當溶劑中使化合物(III)、化合

物(IV)及化合物(XIX)反應來製造。

在鹼基的存在下、在無溶劑或適當溶劑中使化合物(XVII)及化合物(XVIII)反應可製造化合物(XIX)。

本反應中相對於化合物(XVIII)，可使用 1 當量或 1 當量以上之化合物(XVII)，較佳爲 1~3 當量。

作爲可使用之鹼基，可舉出氫化鈉、甲氧基鈉、第三丁氧基鉀等。

作爲可使用之溶劑，可舉出醇類(例如甲醇、乙醇等)、芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、醚類(例如四氫呋喃、二乙基醚、二噁烷等)及彼等之混合溶劑等。

反應溫度爲-10~150℃，較佳爲 20~100℃。反應時間視化合物而異，可爲 10 分鐘~80 小時反應。

獲得之所欲化合物(XIX)，視需要可經由常法(例如管柱色層分析、再結晶、減壓蒸餾等)純化。

本反應中相對於化合物(XIX)，可使用 1 當量或 1 當量以上之化合物(III)及化合物(IV)，較佳爲 1~3 當量。

作爲可使用的酸，可舉出乙酸、對甲苯磺酸、鹽酸等。

作爲可使用的溶劑，可舉出芳香族烴類(例如甲苯、苯、二甲苯等)、飽和烴類(例如環己烷、己烷等)、醚類(例如四氫呋喃、二乙基醚、二噁烷等)及彼等之混合溶劑等。

反應溫度爲-10~150℃，較佳爲 20~100℃。反應時間視化合物而異，可爲 10 分鐘~80 小時反應。

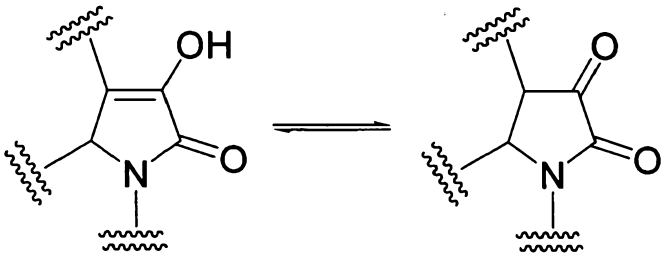
獲得之所欲化合物(Ia)，視需要可經由常法(例如管柱色

層分析、再結晶等)純化。

本發明化合物與製藥上可容許的酸或鹼基可形成的鹽，例如與鹽酸、硫酸、硝酸、磷酸、氫氟酸、氫溴酸等之無機酸的鹽，與甲酸、乙酸、草酸、丁二酸、順丁烯二酸、酒石酸、乳酸、檸檬酸、反丁烯二酸等之有機酸的鹽，與銨、三甲基銨、三乙基銨等之有機鹼基的鹽，與鈉、鉀等之鹼金屬的鹽，鈣、鎂等之鹼土類金屬的鹽。

再者，本發明化合物或上記之製藥上可容許的鹽，亦可與其溶劑化物(較佳爲水合物)成爲溶劑化物。作爲溶劑化物，可舉出與有機溶劑及/或水之溶劑化物。形成溶劑化物時，可與任意數的溶劑分子配位。

本發明化合物(I)不限定於特定的異構物，包括所有可能的異構物或外消旋物。例如含有下記之互變異構物。



本發明之化合物可爲具有特定構形之經單離之鏡像異構物，或彼等鏡像異構物之混合物的任一。例如本發明之化合物可有在吡咯啶酮環的5位具有特定構形之經單離的鏡像異構物或該等鏡像異構物的混合物。具有特定構形之鏡像異構物，所屬領域之技藝者可使用所屬領域慣用的技術例如以結晶化、酵素反應、色層分析、非鏡像異構物鹽等而容易地

單離。

上記一般式(1)表示之本發明化合物，對 $P2X_3$ 及/或 $P2X_{2/3}$ 受體具有拮抗作用，有用於作爲與 $P2X_3$ 及/或 $P2X_{2/3}$ 有關之疾病的治療劑。$P2X_3$ 及/或 $P2X_{2/3}$ 受體已被認爲與疼痛及泌尿系統疾病有關(Nature 407, 26, 1011-1015 (2000), Nature, Vol.407, No.26, 1015-1017 (2000)、非專利文獻 1、非專利文獻 2 等)，對於例如類風濕性關節炎伴隨的疼痛、變形性關節症伴隨的疼痛、頭痛、偏頭痛、口腔顏面痛、尺齒痛、舌痛症、顎關節症伴隨的疼痛、三叉神經痛、肩痛、椎間盤突出伴隨的疼痛、變形性頸椎症伴隨的疼痛、脊椎管狹窄症伴隨的疼痛、胸廓出口症候群伴隨的疼痛、臂神經叢撕裂症候群伴隨的疼痛、肩手症候群、頸部外傷症伴隨的疼痛、胸痛、腹痛、疝痛、膽石症伴隨的疼痛、胰臟炎伴隨的疼痛、尿道結石症、過敏性腸症候群伴隨的疼痛、腰背部痛、坐骨神經痛、骨折伴隨的疼痛、骨質疏鬆症伴隨的疼痛、關節痛、痛風伴隨的疼痛、馬尾症候群(cauda equina syndrome)伴隨的疼痛、僵直性脊椎炎症伴隨的疼痛、肌肉痛、有痛性痙攣、肌筋膜痛症候群、纖維肌痛症候群、閉塞性動脈硬化症伴隨的疼痛、柏格氏症(Buerger's disease)伴隨的疼痛、雷諾氏現象(Raynaud's phenomenon)伴隨的疼痛、帶狀疱疹伴隨的疼痛、灼熱痛(causalgia)、包夾性神經病變(entrapment neuropathy)伴隨的疼痛、腕隧道症候群伴隨的疼痛、糖尿病伴隨的疼痛、吉-巴氏症候群(Guillain-Barre disease)伴隨的疼痛、漢生氏病(Hansen's disease)伴隨的疼

痛、藥物療法伴隨的疼痛、放射線療法伴隨的疼痛、脊髓損傷伴隨的疼痛、脊髓空洞症伴隨的疼痛、腦中風伴隨的疼痛、視丘疼痛、去除傳入神經痛(deafferentation pain)、交感神經依存性疼痛、ABC症候群、多發性硬化症、皮膚疾病伴隨的疼痛、癌性疼痛、手術後疼痛、外傷伴隨的疼痛、壞疽伴隨的疼痛、身體表現性障害伴隨的疼痛、身體化症(somatization disorder)伴隨的疼痛、憂鬱症伴隨的疼痛、帕金森氏症(Parkinson's disease)伴隨的疼痛、膝關節痛、關節炎伴隨的疼痛、生理痛、中間痛、陣痛等之神經障害性疼痛、炎症性疼痛、侵害受容性疼痛、心因性疼痛、以及膀胱過動症、尿失禁、頻尿、尿意逼迫(urinary urgency)、膀胱萎縮、前列腺肥大、前列腺炎、前列腺痛、逼尿肌反射過度(detrusor hyperreflexia)、排尿障害、神經性頻尿、慢性前列腺炎、慢性膀胱炎等之治療、症狀的緩和或預防有效。

本發明之化合物對ATP受體，特別是$P2X_3$受體親和性高，由於對亞型選擇性及其他受體的選擇性高，可成爲減輕副作用(例如對運動機能的影響等)之醫藥。又，本發明之化合物具有安定性高、經口吸收性高、溶解度高、表示良好的生物利用率，清除率低、半衰期長、藥效持續性高、及/或肝酵素阻害活性低等優點。

在其他態樣中，本發明提供含有有效量之本發明化合物與製藥上可容許的載劑組合所構成之醫藥組成物。

使用本發明化合物爲醫藥時，可使用例如賦形劑、結合劑、崩壞劑、潤滑劑、著色劑、矯味劑、矯臭劑、界面活性

劑等所屬領域周知的製藥上可容許的載劑，依照常法製造醫藥組成物。

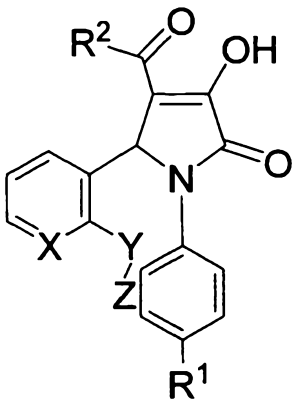
對包括人之哺乳動物的治療，投與本發明有關之醫藥組成物之場合，投與單位劑型可視治療目的及投與路徑適當地選擇。具體可舉出錠劑、被覆錠劑、散劑、顆粒劑、膠囊劑、液劑、丸劑、懸浮劑、乳劑等之經口劑，以及注射劑、栓劑、軟膏、貼附劑、氣溶膠劑等之非經口劑。這些投與單位劑型可經由所屬領域周知之方法製劑化。

上記製劑中應含有之本發明化合物的量，可依據劑型、投與路徑、投與計畫等適宜地變更。

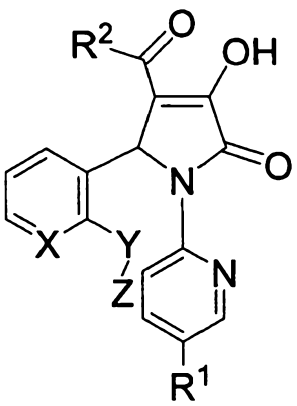
本發明有關之醫藥組成物的投與方法，可依據製劑之劑型、患者的年齡、性別、體重、症狀的程度及其他條件等適宜地決定，可從經口、皮下、經皮、直腸、鼻內、口腔等各種路徑選擇。

本發明之醫藥組成物所含有之本發明化合物的用量，可依據所選擇的投與路徑、患者的年齡、性別、體重、疾病的狀態、所投與之本發明化合物的種類、其他條件等適宜地選擇，但在成人經口投與之場合，通常爲 0.05~1000mg/kg/日，較佳爲 0.1~10mg/kg/日之範圍內。非經口投與之場合雖因投與路徑而差異變大，但通常爲 0.005~100mg/kg/日，較佳爲 0.01~1mg/kg/日之範圍內。這些本發明之醫藥組成物可 1 日投與 1 回或分開複數回。

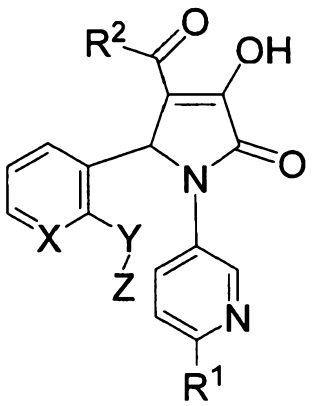
本發明化合物之較佳態樣，在以下式(a)~(f)中具有以下之基者。


R2
O
OH
O
N
X
Y
Z
R1

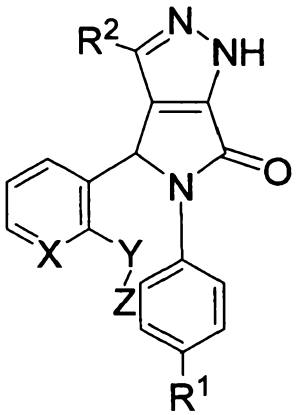
(a)


R2
O
OH
O
N
X
Y
Z
N
R1

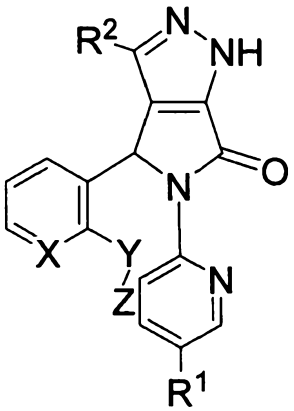
(b)


R2
O
OH
O
N
X
Y
Z
N
R1

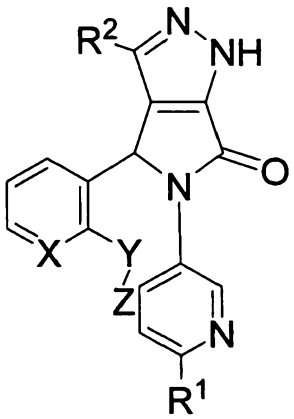
(c)


R2
N
NH
O
N
X
Y
Z
R1

(d)


R2
N
NH
O
N
X
Y
Z
N
R1

(e)


R2
N
NH
O
N
X
Y
Z
N
R1

(f)

【表 1】

	R^1
R1A	COOEt
R1B	CF_3
R1C	SCF_3
R1D	異噁唑-3-基
R1E	3-Me-異噁唑-5-基
R1F	5-Me-異噁唑-3-基
R1G	1,2,4-噁二唑-3-基
R1H	1,3,4-噁二唑-2-基
R1I	5-Me-1,2,4-噁二唑-3-基
R1J	3-Me-1,2,4-噁二唑-5-基
R1K	C(Me)=NOMe
R1L	CH=NOMe
R1M	2-噁唑啉基
R1N	2-噻唑啉基
R1O	2-噻唑基
R1P	2-或 3-噻吩基
R1Q	2-或 3-呋喃基

【表 2】

	R^2
R2A	iPr
R2B	cPr
R2C	tBu
R2D	Ph
R2E	4-Cl 或 F-Ph
R2F	4-CF_3-Ph
R2G	4-Me_2N-Ph
R2H	2-或 3-噻吩基
R2I	3-吡啶基
R2J	6-MeO-3-吡啶基
R2K	2 或 3 或 4-MeO-Ph
R2L	$HOCH_2C(Me)_2$
R2M	$HOCOC(Me)_2$
R2N	$MeC(CH_2OH)_2$
R2O	$Me_2NCOC(Me)_2$
R2P	$Me_2NHCOC(Me)_2$
R2Q	$H_2NCOC(Me)_2$

【表 3】

	Z
ZA	Me
ZB	Et
ZC	iPr
ZD	CHF_2
ZE	CF_3
ZF	$HOCH_2CH_2$
ZG	$MeOCH_2CH_2$
ZH	$NCCH_2$
ZI	$MeSCH_2CH_2$
ZJ	$MeSOCH_2CH_2$
ZK	$Me_2NCH_2CH_2$
ZL	$AcNHCH_2CH_2$
ZM	$MsNHCH_2CH_2$
ZN	$EtOCOCH_2$
ZO	$HOCOCH_2$
ZP	$HOCOCH_2CH_2$
ZQ	HOCOCH(Me)
ZR	$HOCOC(Me)_2$
ZS	Me_2NCOCH_2
ZT	$MeHNCOCH_2$
ZU	H_2NCOCH_2

【表 4】

	X
XA	CH
XB	N

【表 5】

	Y
YA	O
YB	S

(上記表中，Ac表示乙醯基、Ms表示甲磺醯基、Me表示甲基、Et表示乙基、Pr表示丙基、iPr表示異丙基、nBu表示正丁基、tBu表示第三丁基、cPr表示環丙基、cBu表示環丁基、cPent表示環戊基、cHex表示環己基、Ph表示苯基)

R1、R2、Z、X及Y之組合爲(R1,R2,Z,X,Y)之以下之化合物。

(R1,R2,Z,X,Y)=(R1A,R2A,ZA,XA,YA),(R1B,R2A,ZA,XA,YA),(R1C,R2A,ZA,XA,YA),(R1D,R2A,ZA,XA,YA),(R1E,R2A,ZA,XA,YA),(R1F,R2A,ZA,XA,YA),(R1G,R2A,ZA,XA,YA),(R1H,R2A,ZA,XA,YA),(R1I,R2A,ZA,XA,YA),(R1J,R2A,ZA,XA,YA),(R1K,R2A,ZA,XA,YA),(R1L,R2A,ZA,XA,YA),(R1M,R2A,ZA,XA,YA),(R1N,R2A,ZA,XA,YA),(R1O,R2A,ZA,XA,YA),(R1P,R2A,ZA,XA,YA),(R1Q,R2A,ZA,XA,YA),(R1A,R2B,ZA,XA,YA),(R1B,R2B,ZA,XA,YA),(R1C,R2B,ZA,XA,YA),(R1D,R2B,ZA,XA,YA),(R1E,R2B,ZA,XA,YA),(R1F,R2B,ZA,XA,YA),(R1G,R2B,ZA,XA,YA),(R1H,R2B,ZA,XA,YA),(R1I,R2B,ZA,XA,YA),(R1J,R2B,ZA,XA,YA),(R1K,R2B,ZA,XA,YA),(R1L,R2B,ZA,XA,YA),(R1M,R2B,ZA,XA,YA),(R1N,R2B,ZA,XA,YA),(R1O,R2B,ZA,XA,YA),(R1P,R2B,ZA,XA,YA),(R1Q,R2B,ZA,XA,YA),(R1A,R2C,ZA,XA,YA),(R1B,R2C,ZA,XA,YA),(R1C,R2C,ZA,XA,YA),(R1D,R2C,ZA,XA,YA),(R1E,R2C,ZA,XA,YA),(R

1F,R2C,ZA,XA,YA),(R1G,R2C,ZA,XA,YA),(R1H,R2C,ZA,XA
,YA),(R1I,R2C,ZA,XA,YA),(R1J,R2C,ZA,XA,YA),(R1K,R2C,
ZA,XA,YA),(R1L,R2C,ZA,XA,YA),(R1M,R2C,ZA,XA,YA),(R
1N,R2C,ZA,XA,YA),(R1O,R2C,ZA,XA,YA),(R1P,R2C,ZA,XA
,YA),(R1Q,R2C,ZA,XA,YA),(R1A,R2D,ZA,XA,YA),(R1B,R2
D,ZA,XA,YA),(R1C,R2D,ZA,XA,YA),(R1D,R2D,ZA,XA,YA),
(R1E,R2D,ZA,XA,YA),(R1F,R2D,ZA,XA,YA),(R1G,R2D,ZA,
XA,YA),(R1H,R2D,ZA,XA,YA),(R1I,R2D,ZA,XA,YA),(R1J,R
2D,ZA,XA,YA),(R1K,R2D,ZA,XA,YA),(R1L,R2D,ZA,XA,YA)
,(R1M,R2D,ZA,XA,YA),(R1N,R2D,ZA,XA,YA),(R1O,R2D,ZA
,XA,YA),(R1P,R2D,ZA,XA,YA),(R1Q,R2D,ZA,XA,YA),(R1A,
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),(R1D,R2E,ZA,XA,YA),(R1E,R2E,ZA,XA,YA),(R1F,R2E,ZA
,XA,YA),(R1G,R2E,ZA,XA,YA),(R1H,R2E,ZA,XA,YA),(R1I,
R2E,ZA,XA,YA),(R1J,R2E,ZA,XA,YA),(R1K,R2E,ZA,XA,YA
),(R1L,R2E,ZA,XA,YA),(R1M,R2E,ZA,XA,YA),(R1N,R2E,ZA
,XA,YA),(R1O,R2E,ZA,XA,YA),(R1P,R2E,ZA,XA,YA),(R1Q,
R2E,ZA,XA,YA),(R1A,R2F,ZA,XA,YA),(R1B,R2F,ZA,XA,YA
),(R1C,R2F,ZA,XA,YA),(R1D,R2F,ZA,XA,YA),(R1E,R2F,ZA,
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2F,ZA,XA,YA),(R1I,R2F,ZA,XA,YA),(R1J,R2F,ZA,XA,YA),(
R1K,R2F,ZA,XA,YA),(R1L,R2F,ZA,XA,YA),(R1M,R2F,ZA,X
A,YA),(R1N,R2F,ZA,XA,YA),(R1O,R2F,ZA,XA,YA),(R1P,R2
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R1B,R2G,ZA,XA,YA),(R1C,R2G,ZA,XA,YA),(R1D,R2G,ZA,X
A,YA),(R1E,R2G,ZA,XA,YA),(R1F,R2G,ZA,XA,YA),(R1G,R2
G,ZA,XA,YA),(R1H,R2G,ZA,XA,YA),(R1I,R2G,ZA,XA,YA),(
R1J,R2G,ZA,XA,YA),(R1K,R2G,ZA,XA,YA),(R1L,R2G,ZA,X
A,YA),(R1M,R2G,ZA,XA,YA),(R1N,R2G,ZA,XA,YA),(R1O,R
2G,ZA,XA,YA),(R1P,R2G,ZA,XA,YA),(R1Q,R2G,ZA,XA,YA),
(R1A,R2H,ZA,XA,YA),(R1B,R2H,ZA,XA,YA),(R1C,R2H,ZA,
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A),(R1I,R2H,ZA,XA,YA),(R1J,R2H,ZA,XA,YA),(R1K,R2H,Z
A,XA,YA),(R1L,R2H,ZA,XA,YA),(R1M,R2H,ZA,XA,YA),(R1
N,R2H,ZA,XA,YA),(R1O,R2H,ZA,XA,YA),(R1P,R2H,ZA,XA,
YA),(R1Q,R2H,ZA,XA,YA),(R1A,R2I,ZA,XA,YA),(R1B,R2I,
ZA,XA,YA),(R1C,R2I,ZA,XA,YA),(R1D,R2I,ZA,XA,YA),(R1
E,R2I,ZA,XA,YA),(R1F,R2I,ZA,XA,YA),(R1G,R2I,ZA,XA,Y
A),(R1H,R2I,ZA,XA,YA),(R1I,R2I,ZA,XA,YA),(R1J,R2I,ZA,
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2I,ZA,XA,YA),(R1N,R2I,ZA,XA,YA),(R1O,R2I,ZA,XA,YA),(
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,YA),(R1B,R2J,ZA,XA,YA),(R1C,R2J,ZA,XA,YA),(R1D,R2J,
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A),(R1J,R2J,ZA,XA,YA),(R1K,R2J,ZA,XA,YA),(R1L,R2J,ZA
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N,R2K,ZA,XA,YA),(R1O,R2K,ZA,XA,YA),(R1P,R2K,ZA,XA,
YA),(R1Q,R2K,ZA,XA,YA),(R1A,R2L,ZA,XA,YA),(R1B,R2L,
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YA),(R1H,R2L,ZA,XA,YA),(R1I,R2L,ZA,XA,YA),(R1J,R2L,
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,YA),(R1P,R2L,ZA,XA,YA),(R1Q,R2L,ZA,XA,YA),(R1A,R2M
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R1D,R2M,ZA,XA,YA),(R1E,R2M,ZA,XA,YA),(R1F,R2M,ZA,
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YA),(R1B,R2C,ZE,XA,YA),(R1C,R2C,ZE,XA,YA),(R1D,R2C,ZE,XA,YA),(R1E,R2C,ZE,XA,YA),(R1F,R2C,ZE,XA,YA),(R1G,R2C,ZE,XA,YA),(R1H,R2C,ZE,XA,YA),(R1I,R2C,ZE,XA,YA),(R1J,R2C,ZE,XA,YA),(R1K,R2C,ZE,XA,YA),(R1L,R2C,ZE,XA,YA),(R1M,R2C,ZE,XA,YA),(R1N,R2C,ZE,XA,YA),(R1O,R2C,ZE,XA,YA),(R1P,R2C,ZE,XA,YA),(R1Q,R2C,ZE,XA,YA),(R1A,R2D,ZE,XA,YA),(R1B,R2D,ZE,XA,YA),(R1C,R2D,ZE,XA,YA),(R1D,R2D,ZE,XA,YA),(R1E,R2D,ZE,XA,YA),(R1F,R2D,ZE,XA,YA),(R1G,R2D,ZE,XA,YA),(R1H,R2D,ZE,XA,YA),(R1I,R2D,ZE,XA,YA),(R1J,R2D,ZE,XA,YA),(R1K,R2D,ZE,XA,YA),(R1L,R2D,ZE,XA,YA),(R1M,R2D,ZE,XA,YA),(R1N,R2D,ZE,XA,YA),(R1O,R2D,ZE,XA,YA),(R1P,R2D,ZE,XA,YA),(R1Q,R2D,ZE,XA,YA),(R1A,R2E,ZE,XA,YA),(R1B,R2E,ZE,XA,YA),(R1C,R2E,ZE,XA,YA),(R1D,R2E,ZE,XA,YA),(R1E,R2E,ZE,XA,YA),(R1F,R2E,ZE,XA,YA),(R1G,R2E,ZE,XA,YA),(R1H,R2E,ZE,XA,YA),(R1I,R2E,ZE,XA,YA),(R1J,R2E,ZE,XA,YA),(R1K,R2E,ZE,XA,YA),(R1L,R2E,ZE,XA,YA),(R1M,R2E,ZE,XA,YA),(R1N,R2E,ZE,XA,YA),(R1O,R2E,ZE,XA,YA),(R1P,R2E,ZE,XA,YA),(R1Q,R2E,ZE,XA,YA),(R1A,R2F,ZE,XA,YA),(R1B,R2F,ZE,XA,YA),(R1C,R2F,ZE,XA,YA),(R1D,R2F,ZE,XA,YA),(R1E,R2F,ZE,XA,YA),(R1F,R2F,ZE,XA,YA),(R1G,R2F,ZE,XA,YA),(R1H,R2F,ZE,XA,YA),(R1I,R2F,ZE,XA,YA),(R1J,R2F,ZE,XA,YA),(R1K,R2F,ZE,XA,YA),(R1L,R2F,ZE,XA,YA),(R1M,R2F,ZE,XA,YA),(R1N,R2F,ZE,XA,YA),(R1O

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2A,ZF,XA,YA),(R1E,R2A,ZF,XA,YA),(R1F,R2A,ZF,XA,YA),(R1G,R2A,ZF,XA,YA),(R1H,R2A,ZF,XA,YA),(R1I,R2A,ZF,XA,YA),(R1J,R2A,ZF,XA,YA),(R1K,R2A,ZF,XA,YA),(R1L,R2A,ZF,XA,YA),(R1M,R2A,ZF,XA,YA),(R1N,R2A,ZF,XA,YA),(R1O,R2A,ZF,XA,YA),(R1P,R2A,ZF,XA,YA),(R1Q,R2A,ZF,XA,YA),(R1A,R2B,ZF,XA,YA),(R1B,R2B,ZF,XA,YA),(R1C,R2B,ZF,XA,YA),(R1D,R2B,ZF,XA,YA),(R1E,R2B,ZF,XA,YA),(R1F,R2B,ZF,XA,YA),(R1G,R2B,ZF,XA,YA),(R1H,R2B,ZF,XA,YA),(R1I,R2B,ZF,XA,YA),(R1J,R2B,ZF,XA,YA),(R1K,R2B,ZF,XA,YA),(R1L,R2B,ZF,XA,YA),(R1M,R2B,ZF,XA,YA),(R1N,R2B,ZF,XA,YA),(R1O,R2B,ZF,XA,YA),(R1P,R2B,ZF,XA,YA),(R1Q,R2B,ZF,XA,YA),(R1A,R2C,ZF,XA,YA),(R1B,R2C,ZF,XA,YA),(R1C,R2C,ZF,XA,YA),(R1D,R2C,ZF,XA,YA),(R1E,R2C,ZF,XA,YA),(R1F,R2C,ZF,XA,YA),(R1G,R2C,ZF,XA,YA),(R1H,R2C,ZF,XA,YA),(R1I,R2C,ZF,XA,YA),(R1J,R2C,ZF,XA,YA),(R1K,R2C,ZF,XA,YA),(R1L,R2C,ZF,XA,YA),(R1M,R2C,ZF,XA,YA),(R1N,R2C,ZF,XA,YA),(R1O,R2C,ZF,XA,YA),(R1P,R2C,ZF,XA,YA),(R1Q,R2C,ZF,XA,YA),(R1A,R2D,ZF,XA,YA),(R1B,R2D,ZF,XA,YA),(R1C,R2D,ZF,XA,YA),(R1D,R2D,ZF,XA,YA),(R1E,R2D,ZF,XA,YA),(R1F,R2D,ZF,XA,YA),(R1G,R2D,ZF,XA,YA),(R1H,R2D,ZF,XA,YA),(R1I,R2D,ZF,XA,YA),(R1J,R2D,ZF,XA,YA),(R1K,R2D,ZF,XA,YA),(R1L,R2D,ZF,XA,YA),(R1M,R2D,ZF,XA,YA),(R1N,R2D,ZF,XA,YA),(R1O,R2D,ZF,XA,YA),(R1P,R2D,ZF,XA,YA),(R1Q,R2D,ZF,XA,YA),(R1

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,YA),(R1K,R2G,ZF,XA,YA),(R1L,R2G,ZF,XA,YA),(R1M,R2G,
ZF,XA,YA),(R1N,R2G,ZF,XA,YA),(R1O,R2G,ZF,XA,YA),(R1
P,R2G,ZF,XA,YA),(R1Q,R2G,ZF,XA,YA),(R1A,R2H,ZF,XA,Y
A),(R1B,R2H,ZF,XA,YA),(R1C,R2H,ZF,XA,YA),(R1D,R2H,Z
F,XA,YA),(R1E,R2H,ZF,XA,YA),(R1F,R2H,ZF,XA,YA),(R1G,
R2H,ZF,XA,YA),(R1H,R2H,ZF,XA,YA),(R1I,R2H,ZF,XA,YA)
,(R1J,R2H,ZF,XA,YA),(R1K,R2H,ZF,XA,YA),(R1L,R2H,ZF,X
A,YA),(R1M,R2H,ZF,XA,YA),(R1N,R2H,ZF,XA,YA),(R1O,R2

H,ZF,XA,YA),(R1P,R2H,ZF,XA,YA),(R1Q,R2H,ZF,XA,YA),(R1A,R2I,ZF,XA,YA),(R1B,R2I,ZF,XA,YA),(R1C,R2I,ZF,XA,YA),(R1D,R2I,ZF,XA,YA),(R1E,R2I,ZF,XA,YA),(R1F,R2I,ZF,XA,YA),(R1G,R2I,ZF,XA,YA),(R1H,R2I,ZF,XA,YA),(R1I,R2I,ZF,XA,YA),(R1J,R2I,ZF,XA,YA),(R1K,R2I,ZF,XA,YA),(R1L,R2I,ZF,XA,YA),(R1M,R2I,ZF,XA,YA),(R1N,R2I,ZF,XA,YA),(R1O,R2I,ZF,XA,YA),(R1P,R2I,ZF,XA,YA),(R1Q,R2I,ZF,XA,YA),(R1A,R2J,ZF,XA,YA),(R1B,R2J,ZF,XA,YA),(R1C,R2J,ZF,XA,YA),(R1D,R2J,ZF,XA,YA),(R1E,R2J,ZF,XA,YA),(R1F,R2J,ZF,XA,YA),(R1G,R2J,ZF,XA,YA),(R1H,R2J,ZF,XA,YA),(R1I,R2J,ZF,XA,YA),(R1J,R2J,ZF,XA,YA),(R1K,R2J,ZF,XA,YA),(R1L,R2J,ZF,XA,YA),(R1M,R2J,ZF,XA,YA),(R1N,R2J,ZF,XA,YA),(R1O,R2J,ZF,XA,YA),(R1P,R2J,ZF,XA,YA),(R1Q,R2J,ZF,XA,YA),(R1A,R2K,ZF,XA,YA),(R1B,R2K,ZF,XA,YA),(R1C,R2K,ZF,XA,YA),(R1D,R2K,ZF,XA,YA),(R1E,R2K,ZF,XA,YA),(R1F,R2K,ZF,XA,YA),(R1G,R2K,ZF,XA,YA),(R1H,R2K,ZF,XA,YA),(R1I,R2K,ZF,XA,YA),(R1J,R2K,ZF,XA,YA),(R1K,R2K,ZF,XA,YA),(R1L,R2K,ZF,XA,YA),(R1M,R2K,ZF,XA,YA),(R1N,R2K,ZF,XA,YA),(R1O,R2K,ZF,XA,YA),(R1P,R2K,ZF,XA,YA),(R1Q,R2K,ZF,XA,YA),(R1A,R2L,ZF,XA,YA),(R1B,R2L,ZF,XA,YA),(R1C,R2L,ZF,XA,YA),(R1D,R2L,ZF,XA,YA),(R1E,R2L,ZF,XA,YA),(R1F,R2L,ZF,XA,YA),(R1G,R2L,ZF,XA,YA),(R1H,R2L,ZF,XA,YA),(R1I,R2L,ZF,XA,YA),(R1J,R2L,ZF,XA,YA),(R1K,R2L,ZF,XA,YA),(R1L,R2L,ZF,XA,YA

),(R1M,R2L,ZF,XA,YA),(R1N,R2L,ZF,XA,YA),(R1O,R2L,ZF,XA,YA),(R1P,R2L,ZF,XA,YA),(R1Q,R2L,ZF,XA,YA),(R1A,R2M,ZF,XA,YA),(R1B,R2M,ZF,XA,YA),(R1C,R2M,ZF,XA,YA),(R1D,R2M,ZF,XA,YA),(R1E,R2M,ZF,XA,YA),(R1F,R2M,ZF,XA,YA),(R1G,R2M,ZF,XA,YA),(R1H,R2M,ZF,XA,YA),(R1I,R2M,ZF,XA,YA),(R1J,R2M,ZF,XA,YA),(R1K,R2M,ZF,XA,YA),(R1L,R2M,ZF,XA,YA),(R1M,R2M,ZF,XA,YA),(R1N,R2M,ZF,XA,YA),(R1O,R2M,ZF,XA,YA),(R1P,R2M,ZF,XA,YA),(R1Q,R2M,ZF,XA,YA),(R1A,R2N,ZF,XA,YA),(R1B,R2N,ZF,XA,YA),(R1C,R2N,ZF,XA,YA),(R1D,R2N,ZF,XA,YA),(R1E,R2N,ZF,XA,YA),(R1F,R2N,ZF,XA,YA),(R1G,R2N,ZF,XA,YA),(R1H,R2N,ZF,XA,YA),(R1I,R2N,ZF,XA,YA),(R1J,R2N,ZF,XA,YA),(R1K,R2N,ZF,XA,YA),(R1L,R2N,ZF,XA,YA),(R1M,R2N,ZF,XA,YA),(R1N,R2N,ZF,XA,YA),(R1O,R2N,ZF,XA,YA),(R1P,R2N,ZF,XA,YA),(R1Q,R2N,ZF,XA,YA),(R1A,R2O,ZF,XA,YA),(R1B,R2O,ZF,XA,YA),(R1C,R2O,ZF,XA,YA),(R1D,R2O,ZF,XA,YA),(R1E,R2O,ZF,XA,YA),(R1F,R2O,ZF,XA,YA),(R1G,R2O,ZF,XA,YA),(R1H,R2O,ZF,XA,YA),(R1I,R2O,ZF,XA,YA),(R1J,R2O,ZF,XA,YA),(R1K,R2O,ZF,XA,YA),(R1L,R2O,ZF,XA,YA),(R1M,R2O,ZF,XA,YA),(R1N,R2O,ZF,XA,YA),(R1O,R2O,ZF,XA,YA),(R1P,R2O,ZF,XA,YA),(R1Q,R2O,ZF,XA,YA),(R1A,R2P,ZF,XA,YA),(R1B,R2P,ZF,XA,YA),(R1C,R2P,ZF,XA,YA),(R1D,R2P,ZF,XA,YA),(R1E,R2P,ZF,XA,YA),(R1F,R2P,ZF,XA,YA),(R1G,R2P,ZF,XA,YA),(R1H,R2P,ZF,XA,YA),(R1I,R2P,

ZF,XA,YA),(R1J,R2P,ZF,XA,YA),(R1K,R2P,ZF,XA,YA),(R1L,R2P,ZF,XA,YA),(R1M,R2P,ZF,XA,YA),(R1N,R2P,ZF,XA,YA),(R1O,R2P,ZF,XA,YA),(R1P,R2P,ZF,XA,YA),(R1Q,R2P,ZF,XA,YA),(R1A,R2Q,ZF,XA,YA),(R1B,R2Q,ZF,XA,YA),(R1C,R2Q,ZF,XA,YA),(R1D,R2Q,ZF,XA,YA),(R1E,R2Q,ZF,XA,YA),(R1F,R2Q,ZF,XA,YA),(R1G,R2Q,ZF,XA,YA),(R1H,R2Q,ZF,XA,YA),(R1I,R2Q,ZF,XA,YA),(R1J,R2Q,ZF,XA,YA),(R1K,R2Q,ZF,XA,YA),(R1L,R2Q,ZF,XA,YA),(R1M,R2Q,ZF,XA,YA),(R1N,R2Q,ZF,XA,YA),(R1O,R2Q,ZF,XA,YA),(R1P,R2Q,ZF,XA,YA),(R1Q,R2Q,ZF,XA,YA),(R1A,R2A,ZG,XA,YA),(R1B,R2A,ZG,XA,YA),(R1C,R2A,ZG,XA,YA),(R1D,R2A,ZG,XA,YA),(R1E,R2A,ZG,XA,YA),(R1F,R2A,ZG,XA,YA),(R1G,R2A,ZG,XA,YA),(R1H,R2A,ZG,XA,YA),(R1I,R2A,ZG,XA,YA),(R1J,R2A,ZG,XA,YA),(R1K,R2A,ZG,XA,YA),(R1L,R2A,ZG,XA,YA),(R1M,R2A,ZG,XA,YA),(R1N,R2A,ZG,XA,YA),(R1O,R2A,ZG,XA,YA),(R1P,R2A,ZG,XA,YA),(R1Q,R2A,ZG,XA,YA),(R1A,R2B,ZG,XA,YA),(R1B,R2B,ZG,XA,YA),(R1C,R2B,ZG,XA,YA),(R1D,R2B,ZG,XA,YA),(R1E,R2B,ZG,XA,YA),(R1F,R2B,ZG,XA,YA),(R1G,R2B,ZG,XA,YA),(R1H,R2B,ZG,XA,YA),(R1I,R2B,ZG,XA,YA),(R1J,R2B,ZG,XA,YA),(R1K,R2B,ZG,XA,YA),(R1L,R2B,ZG,XA,YA),(R1M,R2B,ZG,XA,YA),(R1N,R2B,ZG,XA,YA),(R1O,R2B,ZG,XA,YA),(R1P,R2B,ZG,XA,YA),(R1Q,R2B,ZG,XA,YA),(R1A,R2C,ZG,XA,YA),(R1B,R2C,ZG,XA,YA),(R1C,R2C,ZG,XA,YA),(R1D,R2C,ZG,XA,YA),(R1E,R2C,ZG,XA,YA

),(R1F,R2C,ZG,XA,YA),(R1G,R2C,ZG,XA,YA),(R1H,R2C,ZG,XA,YA),(R1I,R2C,ZG,XA,YA),(R1J,R2C,ZG,XA,YA),(R1K,R2C,ZG,XA,YA),(R1L,R2C,ZG,XA,YA),(R1M,R2C,ZG,XA,YA),(R1N,R2C,ZG,XA,YA),(R1O,R2C,ZG,XA,YA),(R1P,R2C,ZG,XA,YA),(R1Q,R2C,ZG,XA,YA),(R1A,R2D,ZG,XA,YA),(R1B,R2D,ZG,XA,YA),(R1C,R2D,ZG,XA,YA),(R1D,R2D,ZG,XA,YA),(R1E,R2D,ZG,XA,YA),(R1F,R2D,ZG,XA,YA),(R1G,R2D,ZG,XA,YA),(R1H,R2D,ZG,XA,YA),(R1I,R2D,ZG,XA,YA),(R1J,R2D,ZG,XA,YA),(R1K,R2D,ZG,XA,YA),(R1L,R2D,ZG,XA,YA),(R1M,R2D,ZG,XA,YA),(R1N,R2D,ZG,XA,YA),(R1O,R2D,ZG,XA,YA),(R1P,R2D,ZG,XA,YA),(R1Q,R2D,ZG,XA,YA),(R1A,R2E,ZG,XA,YA),(R1B,R2E,ZG,XA,YA),(R1C,R2E,ZG,XA,YA),(R1D,R2E,ZG,XA,YA),(R1E,R2E,ZG,XA,YA),(R1F,R2E,ZG,XA,YA),(R1G,R2E,ZG,XA,YA),(R1H,R2E,ZG,XA,YA),(R1I,R2E,ZG,XA,YA),(R1J,R2E,ZG,XA,YA),(R1K,R2E,ZG,XA,YA),(R1L,R2E,ZG,XA,YA),(R1M,R2E,ZG,XA,YA),(R1N,R2E,ZG,XA,YA),(R1O,R2E,ZG,XA,YA),(R1P,R2E,ZG,XA,YA),(R1Q,R2E,ZG,XA,YA),(R1A,R2F,ZG,XA,YA),(R1B,R2F,ZG,XA,YA),(R1C,R2F,ZG,XA,YA),(R1D,R2F,ZG,XA,YA),(R1E,R2F,ZG,XA,YA),(R1F,R2F,ZG,XA,YA),(R1G,R2F,ZG,XA,YA),(R1H,R2F,ZG,XA,YA),(R1I,R2F,ZG,XA,YA),(R1J,R2F,ZG,XA,YA),(R1K,R2F,ZG,XA,YA),(R1L,R2F,ZG,XA,YA),(R1M,R2F,ZG,XA,YA),(R1N,R2F,ZG,XA,YA),(R1O,R2F,ZG,XA,YA),(R1P,R2F,ZG,XA,YA),(R1Q,R2F,ZG,XA,YA),(R1A,R2G,ZG,XA,YA),(R1B,R2G,

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,ZG,XA,YA),(R1Q,R2J,ZG,XA,YA),(R1A,R2K,ZG,XA,YA),(R1B,R2K,ZG,XA,YA),(R1C,R2K,ZG,XA,YA),(R1D,R2K,ZG,XA,YA),(R1E,R2K,ZG,XA,YA),(R1F,R2K,ZG,XA,YA),(R1G,R2K,ZG,XA,YA),(R1H,R2K,ZG,XA,YA),(R1I,R2K,ZG,XA,YA),(R1J,R2K,ZG,XA,YA),(R1K,R2K,ZG,XA,YA),(R1L,R2K,ZG,XA,YA),(R1M,R2K,ZG,XA,YA),(R1N,R2K,ZG,XA,YA),(R1O,R2K,ZG,XA,YA),(R1P,R2K,ZG,XA,YA),(R1Q,R2K,ZG,XA,YA),(R1A,R2L,ZG,XA,YA),(R1B,R2L,ZG,XA,YA),(R1C,R2L,ZG,XA,YA),(R1D,R2L,ZG,XA,YA),(R1E,R2L,ZG,XA,YA),(R1F,R2L,ZG,XA,YA),(R1G,R2L,ZG,XA,YA),(R1H,R2L,ZG,XA,YA),(R1I,R2L,ZG,XA,YA),(R1J,R2L,ZG,XA,YA),(R1K,R2L,ZG,XA,YA),(R1L,R2L,ZG,XA,YA),(R1M,R2L,ZG,XA,YA),(R1N,R2L,ZG,XA,YA),(R1O,R2L,ZG,XA,YA),(R1P,R2L,ZG,XA,YA),(R1Q,R2L,ZG,XA,YA),(R1A,R2M,ZG,XA,YA),(R1B,R2M,ZG,XA,YA),(R1C,R2M,ZG,XA,YA),(R1D,R2M,ZG,XA,YA),(R1E,R2M,ZG,XA,YA),(R1F,R2M,ZG,XA,YA),(R1G,R2M,ZG,XA,YA),(R1H,R2M,ZG,XA,YA),(R1I,R2M,ZG,XA,YA),(R1J,R2M,ZG,XA,YA),(R1K,R2M,ZG,XA,YA),(R1L,R2M,ZG,XA,YA),(R1M,R2M,ZG,XA,YA),(R1N,R2M,ZG,XA,YA),(R1O,R2M,ZG,XA,YA),(R1P,R2M,ZG,XA,YA),(R1Q,R2M,ZG,XA,YA),(R1A,R2N,ZG,XA,YA),(R1B,R2N,ZG,XA,YA),(R1C,R2N,ZG,XA,YA),(R1D,R2N,ZG,XA,YA),(R1E,R2N,ZG,XA,YA),(R1F,R2N,ZG,XA,YA),(R1G,R2N,ZG,XA,YA),(R1H,R2N,ZG,XA,YA),(R1I,R2N,ZG,XA,YA),(R1J,R2N,ZG,XA,YA),(R1K,R2N,ZG,XA,YA),(R1L,R

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,(R1O,R2N,ZG,XA,YA),(R1P,R2N,ZG,XA,YA),(R1Q,R2N,ZG,
XA,YA),(R1A,R2O,ZG,XA,YA),(R1B,R2O,ZG,XA,YA),(R1C,
R2O,ZG,XA,YA),(R1D,R2O,ZG,XA,YA),(R1E,R2O,ZG,XA,YA
),(R1F,R2O,ZG,XA,YA),(R1G,R2O,ZG,XA,YA),(R1H,R2O,ZG
,XA,YA),(R1I,R2O,ZG,XA,YA),(R1J,R2O,ZG,XA,YA),(R1K,R
2O,ZG,XA,YA),(R1L,R2O,ZG,XA,YA),(R1M,R2O,ZG,XA,YA)
,(R1N,R2O,ZG,XA,YA),(R1O,R2O,ZG,XA,YA),(R1P,R2O,ZG,
XA,YA),(R1Q,R2O,ZG,XA,YA),(R1A,R2P,ZG,XA,YA),(R1B,R
2P,ZG,XA,YA),(R1C,R2P,ZG,XA,YA),(R1D,R2P,ZG,XA,YA),(
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YA),(R1H,R2P,ZG,XA,YA),(R1I,R2P,ZG,XA,YA),(R1J,R2P,Z
G,XA,YA),(R1K,R2P,ZG,XA,YA),(R1L,R2P,ZG,XA,YA),(R1M
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XA,YA),(R1B,R2Q,ZG,XA,YA),(R1C,R2Q,ZG,XA,YA),(R1D,
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),(R1G,R2Q,ZG,XA,YA),(R1H,R2Q,ZG,XA,YA),(R1I,R2Q,ZG,
XA,YA),(R1J,R2Q,ZG,XA,YA),(R1K,R2Q,ZG,XA,YA),(R1L,R
2Q,ZG,XA,YA),(R1M,R2Q,ZG,XA,YA),(R1N,R2Q,ZG,XA,YA)
,(R1O,R2Q,ZG,XA,YA),(R1P,R2Q,ZG,XA,YA),(R1Q,R2Q,ZG,
XA,YA),(R1A,R2A,ZH,XA,YA),(R1B,R2A,ZH,XA,YA),(R1C,
R2A,ZH,XA,YA),(R1D,R2A,ZH,XA,YA),(R1E,R2A,ZH,XA,Y
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),(R1H,R2E,ZN,XA,YA),(R1I,R2E,ZN,XA,YA),(R1J,R2E,ZN,XA,YA),(R1K,R2E,ZN,XA,YA),(R1L,R2E,ZN,XA,YA),(R1M,R2E,ZN,XA,YA),(R1N,R2E,ZN,XA,YA),(R1O,R2E,ZN,XA,YA),(R1P,R2E,ZN,XA,YA),(R1Q,R2E,ZN,XA,YA),(R1A,R2F,ZN,XA,YA),(R1B,R2F,ZN,XA,YA),(R1C,R2F,ZN,XA,YA),(R1D,R2F,ZN,XA,YA),(R1E,R2F,ZN,XA,YA),(R1F,R2F,ZN,XA,YA),(R1G,R2F,ZN,XA,YA),(R1H,R2F,ZN,XA,YA),(R1I,R2F,ZN,XA,YA),(R1J,R2F,ZN,XA,YA),(R1K,R2F,ZN,XA,YA),(R1L,R2F,ZN,XA,YA),(R1M,R2F,ZN,XA,YA),(R1N,R2F,ZN,XA,YA),(R1O,R2F,ZN,XA,YA),(R1P,R2F,ZN,XA,YA),(R1Q,R2F,ZN,XA,YA),(R1A,R2G,ZN,XA,YA),(R1B,R2G,ZN,XA,YA),(R1C,R2G,ZN,XA,YA),(R1D,R2G,ZN,XA,YA),(R1E,R2G,ZN,XA,YA),(R1F,R2G,ZN,XA,YA),(R1G,R2G,ZN,XA,YA),(R1H,R2G,ZN,XA,YA),(R1I,R2G,ZN,XA,YA),(R1J,R2G,ZN,XA,YA),(R1K,R2G,ZN,XA,YA),(R1L,R2G,ZN,XA,YA),(R1M,R2G,ZN,XA,YA),(R1N,R2G,ZN,XA,YA),(R1O,R2G,ZN,XA,YA),(R1P,R2G,ZN,XA,YA),(R1Q,R2G,ZN,XA,YA),(R1A,R2H,ZN,XA,YA),(R1B,R2H,ZN,XA,YA),(R1C,R2H,ZN,XA,YA),(R1D,R2H,ZN,XA,YA),(R1E,R2H,ZN,XA,YA),(R1F,R2H,ZN,XA,YA),(R1G,R2H,ZN,XA,YA),(R1H,R2H,ZN,XA,YA),(R1I,R2H,ZN,XA,YA),(R1J,R2H,ZN,XA,YA),(R1K,R2H,ZN,XA,YA),(R1L,R2H,ZN,XA,YA),(R1M,R2H,ZN,XA,YA),(R1N,R2H,ZN,XA,YA),(R1O,R2H,ZN,XA,YA),(R1P,R2H,ZN,XA,YA),(R1Q,R2H,ZN,XA,YA),(R1A,R2I,ZN,XA,YA),(R1B,R2I,ZN,XA,YA),(R1C,R2I,ZN,XA,YA)

,(R1D,R2I,ZN,XA,YA),(R1E,R2I,ZN,XA,YA),(R1F,R2I,ZN,X
A,YA),(R1G,R2I,ZN,XA,YA),(R1H,R2I,ZN,XA,YA),(R1I,R2I
,ZN,XA,YA),(R1J,R2I,ZN,XA,YA),(R1K,R2I,ZN,XA,YA),(R1
L,R2I,ZN,XA,YA),(R1M,R2I,ZN,XA,YA),(R1N,R2I,ZN,XA,Y
A),(R1O,R2I,ZN,XA,YA),(R1P,R2I,ZN,XA,YA),(R1Q,R2I,ZN
,XA,YA),(R1A,R2J,ZN,XA,YA),(R1B,R2J,ZN,XA,YA),(R1C,
R2J,ZN,XA,YA),(R1D,R2J,ZN,XA,YA),(R1E,R2J,ZN,XA,YA)
,(R1F,R2J,ZN,XA,YA),(R1G,R2J,ZN,XA,YA),(R1H,R2J,ZN,X
A,YA),(R1I,R2J,ZN,XA,YA),(R1J,R2J,ZN,XA,YA),(R1K,R2J,
ZN,XA,YA),(R1L,R2J,ZN,XA,YA),(R1M,R2J,ZN,XA,YA),(R1
N,R2J,ZN,XA,YA),(R1O,R2J,ZN,XA,YA),(R1P,R2J,ZN,XA,Y
A),(R1Q,R2J,ZN,XA,YA),(R1A,R2K,ZN,XA,YA),(R1B,R2K,Z
N,XA,YA),(R1C,R2K,ZN,XA,YA),(R1D,R2K,ZN,XA,YA),(R1
E,R2K,ZN,XA,YA),(R1F,R2K,ZN,XA,YA),(R1G,R2K,ZN,XA,
YA),(R1H,R2K,ZN,XA,YA),(R1I,R2K,ZN,XA,YA),(R1J,R2K,
ZN,XA,YA),(R1K,R2K,ZN,XA,YA),(R1L,R2K,ZN,XA,YA),(R
1M,R2K,ZN,XA,YA),(R1N,R2K,ZN,XA,YA),(R1O,R2K,ZN,X
A,YA),(R1P,R2K,ZN,XA,YA),(R1Q,R2K,ZN,XA,YA),(R1A,R2
L,ZN,XA,YA),(R1B,R2L,ZN,XA,YA),(R1C,R2L,ZN,XA,YA),(
R1D,R2L,ZN,XA,YA),(R1E,R2L,ZN,XA,YA),(R1F,R2L,ZN,X
A,YA),(R1G,R2L,ZN,XA,YA),(R1H,R2L,ZN,XA,YA),(R1I,R2
L,ZN,XA,YA),(R1J,R2L,ZN,XA,YA),(R1K,R2L,ZN,XA,YA),(
R1L,R2L,ZN,XA,YA),(R1M,R2L,ZN,XA,YA),(R1N,R2L,ZN,X
A,YA),(R1O,R2L,ZN,XA,YA),(R1P,R2L,ZN,XA,YA),(R1Q,R2

L,ZN,XA,YA),(R1A,R2M,ZN,XA,YA),(R1B,R2M,ZN,XA,YA),(R1C,R2M,ZN,XA,YA),(R1D,R2M,ZN,XA,YA),(R1E,R2M,ZN,XA,YA),(R1F,R2M,ZN,XA,YA),(R1G,R2M,ZN,XA,YA),(R1H,R2M,ZN,XA,YA),(R1I,R2M,ZN,XA,YA),(R1J,R2M,ZN,XA,YA),(R1K,R2M,ZN,XA,YA),(R1L,R2M,ZN,XA,YA),(R1M,R2M,ZN,XA,YA),(R1N,R2M,ZN,XA,YA),(R1O,R2M,ZN,XA,YA),(R1P,R2M,ZN,XA,YA),(R1Q,R2M,ZN,XA,YA),(R1A,R2N,ZN,XA,YA),(R1B,R2N,ZN,XA,YA),(R1C,R2N,ZN,XA,YA),(R1D,R2N,ZN,XA,YA),(R1E,R2N,ZN,XA,YA),(R1F,R2N,ZN,XA,YA),(R1G,R2N,ZN,XA,YA),(R1H,R2N,ZN,XA,YA),(R1I,R2N,ZN,XA,YA),(R1J,R2N,ZN,XA,YA),(R1K,R2N,ZN,XA,YA),(R1L,R2N,ZN,XA,YA),(R1M,R2N,ZN,XA,YA),(R1N,R2N,ZN,XA,YA),(R1O,R2N,ZN,XA,YA),(R1P,R2N,ZN,XA,YA),(R1Q,R2N,ZN,XA,YA),(R1A,R2O,ZN,XA,YA),(R1B,R2O,ZN,XA,YA),(R1C,R2O,ZN,XA,YA),(R1D,R2O,ZN,XA,YA),(R1E,R2O,ZN,XA,YA),(R1F,R2O,ZN,XA,YA),(R1G,R2O,ZN,XA,YA),(R1H,R2O,ZN,XA,YA),(R1I,R2O,ZN,XA,YA),(R1J,R2O,ZN,XA,YA),(R1K,R2O,ZN,XA,YA),(R1L,R2O,ZN,XA,YA),(R1M,R2O,ZN,XA,YA),(R1N,R2O,ZN,XA,YA),(R1O,R2O,ZN,XA,YA),(R1P,R2O,ZN,XA,YA),(R1Q,R2O,ZN,XA,YA),(R1A,R2P,ZN,XA,YA),(R1B,R2P,ZN,XA,YA),(R1C,R2P,ZN,XA,YA),(R1D,R2P,ZN,XA,YA),(R1E,R2P,ZN,XA,YA),(R1F,R2P,ZN,XA,YA),(R1G,R2P,ZN,XA,YA),(R1H,R2P,ZN,XA,YA),(R1I,R2P,ZN,XA,YA),(R1J,R2P,ZN,XA,YA),(R1K,R2P,ZN,XA,YA),(R1L,R2P,ZN,XA,YA)

,(R1M,R2P,ZN,XA,YA),(R1N,R2P,ZN,XA,YA),(R1O,R2P,ZN,XA,YA),(R1P,R2P,ZN,XA,YA),(R1Q,R2P,ZN,XA,YA),(R1A,R2Q,ZN,XA,YA),(R1B,R2Q,ZN,XA,YA),(R1C,R2Q,ZN,XA,YA),(R1D,R2Q,ZN,XA,YA),(R1E,R2Q,ZN,XA,YA),(R1F,R2Q,ZN,XA,YA),(R1G,R2Q,ZN,XA,YA),(R1H,R2Q,ZN,XA,YA),(R1I,R2Q,ZN,XA,YA),(R1J,R2Q,ZN,XA,YA),(R1K,R2Q,ZN,XA,YA),(R1L,R2Q,ZN,XA,YA),(R1M,R2Q,ZN,XA,YA),(R1N,R2Q,ZN,XA,YA),(R1O,R2Q,ZN,XA,YA),(R1P,R2Q,ZN,XA,YA),(R1Q,R2Q,ZN,XA,YA),(R1A,R2A,ZO,XA,YA),(R1B,R2A,ZO,XA,YA),(R1C,R2A,ZO,XA,YA),(R1D,R2A,ZO,XA,YA),(R1E,R2A,ZO,XA,YA),(R1F,R2A,ZO,XA,YA),(R1G,R2A,ZO,XA,YA),(R1H,R2A,ZO,XA,YA),(R1I,R2A,ZO,XA,YA),(R1J,R2A,ZO,XA,YA),(R1K,R2A,ZO,XA,YA),(R1L,R2A,ZO,XA,YA),(R1M,R2A,ZO,XA,YA),(R1N,R2A,ZO,XA,YA),(R1O,R2A,ZO,XA,YA),(R1P,R2A,ZO,XA,YA),(R1Q,R2A,ZO,XA,YA),(R1A,R2B,ZO,XA,YA),(R1B,R2B,ZO,XA,YA),(R1C,R2B,ZO,XA,YA),(R1D,R2B,ZO,XA,YA),(R1E,R2B,ZO,XA,YA),(R1F,R2B,ZO,XA,YA),(R1G,R2B,ZO,XA,YA),(R1H,R2B,ZO,XA,YA),(R1I,R2B,ZO,XA,YA),(R1J,R2B,ZO,XA,YA),(R1K,R2B,ZO,XA,YA),(R1L,R2B,ZO,XA,YA),(R1M,R2B,ZO,XA,YA),(R1N,R2B,ZO,XA,YA),(R1O,R2B,ZO,XA,YA),(R1P,R2B,ZO,XA,YA),(R1Q,R2B,ZO,XA,YA),(R1A,R2C,ZO,XA,YA),(R1B,R2C,ZO,XA,YA),(R1C,R2C,ZO,XA,YA),(R1D,R2C,ZO,XA,YA),(R1E,R2C,ZO,XA,YA),(R1F,R2C,ZO,XA,YA),(R1G,R2C,ZO,XA,YA),(R1H,R2C,ZO

,XA,YA),(R1I,R2C,ZO,XA,YA),(R1J,R2C,ZO,XA,YA),(R1K,R2C,ZO,XA,YA),(R1L,R2C,ZO,XA,YA),(R1M,R2C,ZO,XA,YA),(R1N,R2C,ZO,XA,YA),(R1O,R2C,ZO,XA,YA),(R1P,R2C,ZO,XA,YA),(R1Q,R2C,ZO,XA,YA),(R1A,R2D,ZO,XA,YA),(R1B,R2D,ZO,XA,YA),(R1C,R2D,ZO,XA,YA),(R1D,R2D,ZO,XA,YA),(R1E,R2D,ZO,XA,YA),(R1F,R2D,ZO,XA,YA),(R1G,R2D,ZO,XA,YA),(R1H,R2D,ZO,XA,YA),(R1I,R2D,ZO,XA,YA),(R1J,R2D,ZO,XA,YA),(R1K,R2D,ZO,XA,YA),(R1L,R2D,ZO,XA,YA),(R1M,R2D,ZO,XA,YA),(R1N,R2D,ZO,XA,YA),(R1O,R2D,ZO,XA,YA),(R1P,R2D,ZO,XA,YA),(R1Q,R2D,ZO,XA,YA),(R1A,R2E,ZO,XA,YA),(R1B,R2E,ZO,XA,YA),(R1C,R2E,ZO,XA,YA),(R1D,R2E,ZO,XA,YA),(R1E,R2E,ZO,XA,YA),(R1F,R2E,ZO,XA,YA),(R1G,R2E,ZO,XA,YA),(R1H,R2E,ZO,XA,YA),(R1I,R2E,ZO,XA,YA),(R1J,R2E,ZO,XA,YA),(R1K,R2E,ZO,XA,YA),(R1L,R2E,ZO,XA,YA),(R1M,R2E,ZO,XA,YA),(R1N,R2E,ZO,XA,YA),(R1O,R2E,ZO,XA,YA),(R1P,R2E,ZO,XA,YA),(R1Q,R2E,ZO,XA,YA),(R1A,R2F,ZO,XA,YA),(R1B,R2F,ZO,XA,YA),(R1C,R2F,ZO,XA,YA),(R1D,R2F,ZO,XA,YA),(R1E,R2F,ZO,XA,YA),(R1F,R2F,ZO,XA,YA),(R1G,R2F,ZO,XA,YA),(R1H,R2F,ZO,XA,YA),(R1I,R2F,ZO,XA,YA),(R1J,R2F,ZO,XA,YA),(R1K,R2F,ZO,XA,YA),(R1L,R2F,ZO,XA,YA),(R1M,R2F,ZO,XA,YA),(R1N,R2F,ZO,XA,YA),(R1O,R2F,ZO,XA,YA),(R1P,R2F,ZO,XA,YA),(R1Q,R2F,ZO,XA,YA),(R1A,R2G,ZO,XA,YA),(R1B,R2G,ZO,XA,YA),(R1C,R2G,ZO,XA,YA),(R1D,R2G,Z

O,XA,YA),(R1E,R2G,ZO,XA,YA),(R1F,R2G,ZO,XA,YA),(R1G,R2G,ZO,XA,YA),(R1H,R2G,ZO,XA,YA),(R1I,R2G,ZO,XA,YA),(R1J,R2G,ZO,XA,YA),(R1K,R2G,ZO,XA,YA),(R1L,R2G,ZO,XA,YA),(R1M,R2G,ZO,XA,YA),(R1N,R2G,ZO,XA,YA),(R1O,R2G,ZO,XA,YA),(R1P,R2G,ZO,XA,YA),(R1Q,R2G,ZO,XA,YA),(R1A,R2H,ZO,XA,YA),(R1B,R2H,ZO,XA,YA),(R1C,R2H,ZO,XA,YA),(R1D,R2H,ZO,XA,YA),(R1E,R2H,ZO,XA,YA),(R1F,R2H,ZO,XA,YA),(R1G,R2H,ZO,XA,YA),(R1H,R2H,ZO,XA,YA),(R1I,R2H,ZO,XA,YA),(R1J,R2H,ZO,XA,YA),(R1K,R2H,ZO,XA,YA),(R1L,R2H,ZO,XA,YA),(R1M,R2H,ZO,XA,YA),(R1N,R2H,ZO,XA,YA),(R1O,R2H,ZO,XA,YA),(R1P,R2H,ZO,XA,YA),(R1Q,R2H,ZO,XA,YA),(R1A,R2I,ZO,XA,YA),(R1B,R2I,ZO,XA,YA),(R1C,R2I,ZO,XA,YA),(R1D,R2I,ZO,XA,YA),(R1E,R2I,ZO,XA,YA),(R1F,R2I,ZO,XA,YA),(R1G,R2I,ZO,XA,YA),(R1H,R2I,ZO,XA,YA),(R1I,R2I,ZO,XA,YA),(R1J,R2I,ZO,XA,YA),(R1K,R2I,ZO,XA,YA),(R1L,R2I,ZO,XA,YA),(R1M,R2I,ZO,XA,YA),(R1N,R2I,ZO,XA,YA),(R1O,R2I,ZO,XA,YA),(R1P,R2I,ZO,XA,YA),(R1Q,R2I,ZO,XA,YA),(R1A,R2J,ZO,XA,YA),(R1B,R2J,ZO,XA,YA),(R1C,R2J,ZO,XA,YA),(R1D,R2J,ZO,XA,YA),(R1E,R2J,ZO,XA,YA),(R1F,R2J,ZO,XA,YA),(R1G,R2J,ZO,XA,YA),(R1H,R2J,ZO,XA,YA),(R1I,R2J,ZO,XA,YA),(R1J,R2J,ZO,XA,YA),(R1K,R2J,ZO,XA,YA),(R1L,R2J,ZO,XA,YA),(R1M,R2J,ZO,XA,YA),(R1N,R2J,ZO,XA,YA),(R1O,R2J,ZO,XA,YA),(R1P,R2J,ZO,XA,YA),(R1Q,R2J,ZO,XA,YA)

,(R1A,R2K,ZO,XA,YA),(R1B,R2K,ZO,XA,YA),(R1C,R2K,ZO,XA,YA),(R1D,R2K,ZO,XA,YA),(R1E,R2K,ZO,XA,YA),(R1F,R2K,ZO,XA,YA),(R1G,R2K,ZO,XA,YA),(R1H,R2K,ZO,XA,YA),(R1I,R2K,ZO,XA,YA),(R1J,R2K,ZO,XA,YA),(R1K,R2K,ZO,XA,YA),(R1L,R2K,ZO,XA,YA),(R1M,R2K,ZO,XA,YA),(R1N,R2K,ZO,XA,YA),(R1O,R2K,ZO,XA,YA),(R1P,R2K,ZO,XA,YA),(R1Q,R2K,ZO,XA,YA),(R1A,R2L,ZO,XA,YA),(R1B,R2L,ZO,XA,YA),(R1C,R2L,ZO,XA,YA),(R1D,R2L,ZO,XA,YA),(R1E,R2L,ZO,XA,YA),(R1F,R2L,ZO,XA,YA),(R1G,R2L,ZO,XA,YA),(R1H,R2L,ZO,XA,YA),(R1I,R2L,ZO,XA,YA),(R1J,R2L,ZO,XA,YA),(R1K,R2L,ZO,XA,YA),(R1L,R2L,ZO,XA,YA),(R1M,R2L,ZO,XA,YA),(R1N,R2L,ZO,XA,YA),(R1O,R2L,ZO,XA,YA),(R1P,R2L,ZO,XA,YA),(R1Q,R2L,ZO,XA,YA),(R1A,R2M,ZO,XA,YA),(R1B,R2M,ZO,XA,YA),(R1C,R2M,ZO,XA,YA),(R1D,R2M,ZO,XA,YA),(R1E,R2M,ZO,XA,YA),(R1F,R2M,ZO,XA,YA),(R1G,R2M,ZO,XA,YA),(R1H,R2M,ZO,XA,YA),(R1I,R2M,ZO,XA,YA),(R1J,R2M,ZO,XA,YA),(R1K,R2M,ZO,XA,YA),(R1L,R2M,ZO,XA,YA),(R1M,R2M,ZO,XA,YA),(R1N,R2M,ZO,XA,YA),(R1O,R2M,ZO,XA,YA),(R1P,R2M,ZO,XA,YA),(R1Q,R2M,ZO,XA,YA),(R1A,R2N,ZO,XA,YA),(R1B,R2N,ZO,XA,YA),(R1C,R2N,ZO,XA,YA),(R1D,R2N,ZO,XA,YA),(R1E,R2N,ZO,XA,YA),(R1F,R2N,ZO,XA,YA),(R1G,R2N,ZO,XA,YA),(R1H,R2N,ZO,XA,YA),(R1I,R2N,ZO,XA,YA),(R1J,R2N,ZO,XA,YA),(R1K,R2N,ZO,XA,YA),(R1L,R2N,ZO,XA,YA),(R1M,

R2N,ZO,XA,YA),(R1N,R2N,ZO,XA,YA),(R1O,R2N,ZO,XA,Y
A),(R1P,R2N,ZO,XA,YA),(R1Q,R2N,ZO,XA,YA),(R1A,R2O,Z
O,XA,YA),(R1B,R2O,ZO,XA,YA),(R1C,R2O,ZO,XA,YA),(R1
D,R2O,ZO,XA,YA),(R1E,R2O,ZO,XA,YA),(R1F,R2O,ZO,XA,
YA),(R1G,R2O,ZO,XA,YA),(R1H,R2O,ZO,XA,YA),(R1I,R2O,
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1L,R2O,ZO,XA,YA),(R1M,R2O,ZO,XA,YA),(R1N,R2O,ZO,X
A,YA),(R1O,R2O,ZO,XA,YA),(R1P,R2O,ZO,XA,YA),(R1Q,R2
O,ZO,XA,YA),(R1A,R2P,ZO,XA,YA),(R1B,R2P,ZO,XA,YA),(
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A,YA),(R1F,R2P,ZO,XA,YA),(R1G,R2P,ZO,XA,YA),(R1H,R2
P,ZO,XA,YA),(R1I,R2P,ZO,XA,YA),(R1J,R2P,ZO,XA,YA),(R
1K,R2P,ZO,XA,YA),(R1L,R2P,ZO,XA,YA),(R1M,R2P,ZO,XA,
YA),(R1N,R2P,ZO,XA,YA),(R1O,R2P,ZO,XA,YA),(R1P,R2P,Z
O,XA,YA),(R1Q,R2P,ZO,XA,YA),(R1A,R2Q,ZO,XA,YA),(R1
B,R2Q,ZO,XA,YA),(R1C,R2Q,ZO,XA,YA),(R1D,R2Q,ZO,XA,
YA),(R1E,R2Q,ZO,XA,YA),(R1F,R2Q,ZO,XA,YA),(R1G,R2Q,
ZO,XA,YA),(R1H,R2Q,ZO,XA,YA),(R1I,R2Q,ZO,XA,YA),(R
1J,R2Q,ZO,XA,YA),(R1K,R2Q,ZO,XA,YA),(R1L,R2Q,ZO,XA
,YA),(R1M,R2Q,ZO,XA,YA),(R1N,R2Q,ZO,XA,YA),(R1O,R2
Q,ZO,XA,YA),(R1P,R2Q,ZO,XA,YA),(R1Q,R2Q,ZO,XA,YA),(
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A,YA),(R1D,R2A,ZP,XA,YA),(R1E,R2A,ZP,XA,YA),(R1F,R2
A,ZP,XA,YA),(R1G,R2A,ZP,XA,YA),(R1H,R2A,ZP,XA,YA),(

R1I,R2A,ZP,XA,YA),(R1J,R2A,ZP,XA,YA),(R1K,R2A,ZP,XA,YA),(R1L,R2A,ZP,XA,YA),(R1M,R2A,ZP,XA,YA),(R1N,R2A,ZP,XA,YA),(R1O,R2A,ZP,XA,YA),(R1P,R2A,ZP,XA,YA),(R1Q,R2A,ZP,XA,YA),(R1A,R2B,ZP,XA,YA),(R1B,R2B,ZP,XA,YA),(R1C,R2B,ZP,XA,YA),(R1D,R2B,ZP,XA,YA),(R1E,R2B,ZP,XA,YA),(R1F,R2B,ZP,XA,YA),(R1G,R2B,ZP,XA,YA),(R1H,R2B,ZP,XA,YA),(R1I,R2B,ZP,XA,YA),(R1J,R2B,ZP,XA,YA),(R1K,R2B,ZP,XA,YA),(R1L,R2B,ZP,XA,YA),(R1M,R2B,ZP,XA,YA),(R1N,R2B,ZP,XA,YA),(R1O,R2B,ZP,XA,YA),(R1P,R2B,ZP,XA,YA),(R1Q,R2B,ZP,XA,YA),(R1A,R2C,ZP,XA,YA),(R1B,R2C,ZP,XA,YA),(R1C,R2C,ZP,XA,YA),(R1D,R2C,ZP,XA,YA),(R1E,R2C,ZP,XA,YA),(R1F,R2C,ZP,XA,YA),(R1G,R2C,ZP,XA,YA),(R1H,R2C,ZP,XA,YA),(R1I,R2C,ZP,XA,YA),(R1J,R2C,ZP,XA,YA),(R1K,R2C,ZP,XA,YA),(R1L,R2C,ZP,XA,YA),(R1M,R2C,ZP,XA,YA),(R1N,R2C,ZP,XA,YA),(R1O,R2C,ZP,XA,YA),(R1P,R2C,ZP,XA,YA),(R1Q,R2C,ZP,XA,YA),(R1A,R2D,ZP,XA,YA),(R1B,R2D,ZP,XA,YA),(R1C,R2D,ZP,XA,YA),(R1D,R2D,ZP,XA,YA),(R1E,R2D,ZP,XA,YA),(R1F,R2D,ZP,XA,YA),(R1G,R2D,ZP,XA,YA),(R1H,R2D,ZP,XA,YA),(R1I,R2D,ZP,XA,YA),(R1J,R2D,ZP,XA,YA),(R1K,R2D,ZP,XA,YA),(R1L,R2D,ZP,XA,YA),(R1M,R2D,ZP,XA,YA),(R1N,R2D,ZP,XA,YA),(R1O,R2D,ZP,XA,YA),(R1P,R2D,ZP,XA,YA),(R1Q,R2D,ZP,XA,YA),(R1A,R2E,ZP,XA,YA),(R1B,R2E,ZP,XA,YA),(R1C,R2E,ZP,XA,YA),(R1D,R2E,ZP,XA,YA),(R1E,R2E,ZP,XA,Y

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,R2I,ZP,XA,YA),(R1D,R2I,ZP,XA,YA),(R1E,R2I,ZP,XA,YA),(R1F,R2I,ZP,XA,YA),(R1G,R2I,ZP,XA,YA),(R1H,R2I,ZP,XA,YA),(R1I,R2I,ZP,XA,YA),(R1J,R2I,ZP,XA,YA),(R1K,R2I,ZP,XA,YA),(R1L,R2I,ZP,XA,YA),(R1M,R2I,ZP,XA,YA),(R1N,R2I,ZP,XA,YA),(R1O,R2I,ZP,XA,YA),(R1P,R2I,ZP,XA,YA),(R1Q,R2I,ZP,XA,YA),(R1A,R2J,ZP,XA,YA),(R1B,R2J,ZP,XA,YA),(R1C,R2J,ZP,XA,YA),(R1D,R2J,ZP,XA,YA),(R1E,R2J,ZP,XA,YA),(R1F,R2J,ZP,XA,YA),(R1G,R2J,ZP,XA,YA),(R1H,R2J,ZP,XA,YA),(R1I,R2J,ZP,XA,YA),(R1J,R2J,ZP,XA,YA),(R1K,R2J,ZP,XA,YA),(R1L,R2J,ZP,XA,YA),(R1M,R2J,ZP,XA,YA),(R1N,R2J,ZP,XA,YA),(R1O,R2J,ZP,XA,YA),(R1P,R2J,ZP,XA,YA),(R1Q,R2J,ZP,XA,YA),(R1A,R2K,ZP,XA,YA),(R1B,R2K,ZP,XA,YA),(R1C,R2K,ZP,XA,YA),(R1D,R2K,ZP,XA,YA),(R1E,R2K,ZP,XA,YA),(R1F,R2K,ZP,XA,YA),(R1G,R2K,ZP,XA,YA),(R1H,R2K,ZP,XA,YA),(R1I,R2K,ZP,XA,YA),(R1J,R2K,ZP,XA,YA),(R1K,R2K,ZP,XA,YA),(R1L,R2K,ZP,XA,YA),(R1M,R2K,ZP,XA,YA),(R1N,R2K,ZP,XA,YA),(R1O,R2K,ZP,XA,YA),(R1P,R2K,ZP,XA,YA),(R1Q,R2K,ZP,XA,YA),(R1A,R2L,ZP,XA,YA),(R1B,R2L,ZP,XA,YA),(R1C,R2L,ZP,XA,YA),(R1D,R2L,ZP,XA,YA),(R1E,R2L,ZP,XA,YA),(R1F,R2L,ZP,XA,YA),(R1G,R2L,ZP,XA,YA),(R1H,R2L,ZP,XA,YA),(R1I,R2L,ZP,XA,YA),(R1J,R2L,ZP,XA,YA),(R1K,R2L,ZP,XA,YA),(R1L,R2L,ZP,XA,YA),(R1M,R2L,ZP,XA,YA),(R1N,R2L,ZP,XA,YA),(R1O,R2L,ZP,XA,YA),(R1P,R2L,ZP,XA,YA),(R1Q,R2L,ZP,XA,YA),

(R1A,R2M,ZP,XA,YA),(R1B,R2M,ZP,XA,YA),(R1C,R2M,ZP,XA,YA),(R1D,R2M,ZP,XA,YA),(R1E,R2M,ZP,XA,YA),(R1F,R2M,ZP,XA,YA),(R1G,R2M,ZP,XA,YA),(R1H,R2M,ZP,XA,YA),(R1I,R2M,ZP,XA,YA),(R1J,R2M,ZP,XA,YA),(R1K,R2M,ZP,XA,YA),(R1L,R2M,ZP,XA,YA),(R1M,R2M,ZP,XA,YA),(R1N,R2M,ZP,XA,YA),(R1O,R2M,ZP,XA,YA),(R1P,R2M,ZP,XA,YA),(R1Q,R2M,ZP,XA,YA),(R1A,R2N,ZP,XA,YA),(R1B,R2N,ZP,XA,YA),(R1C,R2N,ZP,XA,YA),(R1D,R2N,ZP,XA,YA),(R1E,R2N,ZP,XA,YA),(R1F,R2N,ZP,XA,YA),(R1G,R2N,ZP,XA,YA),(R1H,R2N,ZP,XA,YA),(R1I,R2N,ZP,XA,YA),(R1J,R2N,ZP,XA,YA),(R1K,R2N,ZP,XA,YA),(R1L,R2N,ZP,XA,YA),(R1M,R2N,ZP,XA,YA),(R1N,R2N,ZP,XA,YA),(R1O,R2N,ZP,XA,YA),(R1P,R2N,ZP,XA,YA),(R1Q,R2N,ZP,XA,YA),(R1A,R2O,ZP,XA,YA),(R1B,R2O,ZP,XA,YA),(R1C,R2O,ZP,XA,YA),(R1D,R2O,ZP,XA,YA),(R1E,R2O,ZP,XA,YA),(R1F,R2O,ZP,XA,YA),(R1G,R2O,ZP,XA,YA),(R1H,R2O,ZP,XA,YA),(R1I,R2O,ZP,XA,YA),(R1J,R2O,ZP,XA,YA),(R1K,R2O,ZP,XA,YA),(R1L,R2O,ZP,XA,YA),(R1M,R2O,ZP,XA,YA),(R1N,R2O,ZP,XA,YA),(R1O,R2O,ZP,XA,YA),(R1P,R2O,ZP,XA,YA),(R1Q,R2O,ZP,XA,YA),(R1A,R2P,ZP,XA,YA),(R1B,R2P,ZP,XA,YA),(R1C,R2P,ZP,XA,YA),(R1D,R2P,ZP,XA,YA),(R1E,R2P,ZP,XA,YA),(R1F,R2P,ZP,XA,YA),(R1G,R2P,ZP,XA,YA),(R1H,R2P,ZP,XA,YA),(R1I,R2P,ZP,XA,YA),(R1J,R2P,ZP,XA,YA),(R1K,R2P,ZP,XA,YA),(R1L,R2P,ZP,XA,YA),(R1M,R2P,ZP,XA,YA),(R1N,R2P,ZP,XA,YA)

,(R1O,R2P,ZP,XA,YA),(R1P,R2P,ZP,XA,YA),(R1Q,R2P,ZP,X
A,YA),(R1A,R2Q,ZP,XA,YA),(R1B,R2Q,ZP,XA,YA),(R1C,R2
Q,ZP,XA,YA),(R1D,R2Q,ZP,XA,YA),(R1E,R2Q,ZP,XA,YA),(
R1F,R2Q,ZP,XA,YA),(R1G,R2Q,ZP,XA,YA),(R1H,R2Q,ZP,XA
,YA),(R1I,R2Q,ZP,XA,YA),(R1J,R2Q,ZP,XA,YA),(R1K,R2Q,
ZP,XA,YA),(R1L,R2Q,ZP,XA,YA),(R1M,R2Q,ZP,XA,YA),(R1
N,R2Q,ZP,XA,YA),(R1O,R2Q,ZP,XA,YA),(R1P,R2Q,ZP,XA,Y
A),(R1Q,R2Q,ZP,XA,YA),(R1A,R2A,ZQ,XA,YA),(R1B,R2A,Z
Q,XA,YA),(R1C,R2A,ZQ,XA,YA),(R1D,R2A,ZQ,XA,YA),(R1
E,R2A,ZQ,XA,YA),(R1F,R2A,ZQ,XA,YA),(R1G,R2A,ZQ,XA,
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A,YA),(R1P,R2A,ZQ,XA,YA),(R1Q,R2A,ZQ,XA,YA),(R1A,R2
B,ZQ,XA,YA),(R1B,R2B,ZQ,XA,YA),(R1C,R2B,ZQ,XA,YA),(
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A,YA),(R1G,R2B,ZQ,XA,YA),(R1H,R2B,ZQ,XA,YA),(R1I,R2
B,ZQ,XA,YA),(R1J,R2B,ZQ,XA,YA),(R1K,R2B,ZQ,XA,YA),(
R1L,R2B,ZQ,XA,YA),(R1M,R2B,ZQ,XA,YA),(R1N,R2B,ZQ,X
A,YA),(R1O,R2B,ZQ,XA,YA),(R1P,R2B,ZQ,XA,YA),(R1Q,R2
B,ZQ,XA,YA),(R1A,R2C,ZQ,XA,YA),(R1B,R2C,ZQ,XA,YA),(
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C,ZQ,XA,YA),(R1I,R2C,ZQ,XA,YA),(R1J,R2C,ZQ,XA,YA),(

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A,YA),(R1N,R2C,ZQ,XA,YA),(R1O,R2C,ZQ,XA,YA),(R1P,R2
C,ZQ,XA,YA),(R1Q,R2C,ZQ,XA,YA),(R1A,R2D,ZQ,XA,YA),
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),(R1A,R2E,ZQ,XA,YA),(R1B,R2E,ZQ,XA,YA),(R1C,R2E,ZQ
,XA,YA),(R1D,R2E,ZQ,XA,YA),(R1E,R2E,ZQ,XA,YA),(R1F,
R2E,ZQ,XA,YA),(R1G,R2E,ZQ,XA,YA),(R1H,R2E,ZQ,XA,YA
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),(R1Q,R2E,ZQ,XA,YA),(R1A,R2F,ZQ,XA,YA),(R1B,R2F,ZQ
,XA,YA),(R1C,R2F,ZQ,XA,YA),(R1D,R2F,ZQ,XA,YA),(R1E,
R2F,ZQ,XA,YA),(R1F,R2F,ZQ,XA,YA),(R1G,R2F,ZQ,XA,YA)
,(R1H,R2F,ZQ,XA,YA),(R1I,R2F,ZQ,XA,YA),(R1J,R2F,ZQ,X
A,YA),(R1K,R2F,ZQ,XA,YA),(R1L,R2F,ZQ,XA,YA),(R1M,R2
F,ZQ,XA,YA),(R1N,R2F,ZQ,XA,YA),(R1O,R2F,ZQ,XA,YA),(
R1P,R2F,ZQ,XA,YA),(R1Q,R2F,ZQ,XA,YA),(R1A,R2G,ZQ,X
A,YA),(R1B,R2G,ZQ,XA,YA),(R1C,R2G,ZQ,XA,YA),(R1D,R2
G,ZQ,XA,YA),(R1E,R2G,ZQ,XA,YA),(R1F,R2G,ZQ,XA,YA),(

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A,YA),(R1J,R2G,ZQ,XA,YA),(R1K,R2G,ZQ,XA,YA),(R1L,R2
G,ZQ,XA,YA),(R1M,R2G,ZQ,XA,YA),(R1N,R2G,ZQ,XA,YA),
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A,YA),(R1A,R2H,ZQ,XA,YA),(R1B,R2H,ZQ,XA,YA),(R1C,R
2H,ZQ,XA,YA),(R1D,R2H,ZQ,XA,YA),(R1E,R2H,ZQ,XA,YA)
,(R1F,R2H,ZQ,XA,YA),(R1G,R2H,ZQ,XA,YA),(R1H,R2H,ZQ,
XA,YA),(R1I,R2H,ZQ,XA,YA),(R1J,R2H,ZQ,XA,YA),(R1K,R
2H,ZQ,XA,YA),(R1L,R2H,ZQ,XA,YA),(R1M,R2H,ZQ,XA,YA)
,(R1N,R2H,ZQ,XA,YA),(R1O,R2H,ZQ,XA,YA),(R1P,R2H,ZQ,
XA,YA),(R1Q,R2H,ZQ,XA,YA),(R1A,R2I,ZQ,XA,YA),(R1B,
R2I,ZQ,XA,YA),(R1C,R2I,ZQ,XA,YA),(R1D,R2I,ZQ,XA,YA)
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A,YA),(R1H,R2I,ZQ,XA,YA),(R1I,R2I,ZQ,XA,YA),(R1J,R2I,
ZQ,XA,YA),(R1K,R2I,ZQ,XA,YA),(R1L,R2I,ZQ,XA,YA),(R1
M,R2I,ZQ,XA,YA),(R1N,R2I,ZQ,XA,YA),(R1O,R2I,ZQ,XA,Y
A),(R1P,R2I,ZQ,XA,YA),(R1Q,R2I,ZQ,XA,YA),(R1A,R2J,ZQ
,XA,YA),(R1B,R2J,ZQ,XA,YA),(R1C,R2J,ZQ,XA,YA),(R1D,
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1O,R2J,ZQ,XA,YA),(R1P,R2J,ZQ,XA,YA),(R1Q,R2J,ZQ,XA,
YA),(R1A,R2K,ZQ,XA,YA),(R1B,R2K,ZQ,XA,YA),(R1C,R2K

,ZQ,XA,YA),(R1D,R2K,ZQ,XA,YA),(R1E,R2K,ZQ,XA,YA),(R1F,R2K,ZQ,XA,YA),(R1G,R2K,ZQ,XA,YA),(R1H,R2K,ZQ,XA,YA),(R1I,R2K,ZQ,XA,YA),(R1J,R2K,ZQ,XA,YA),(R1K,R2K,ZQ,XA,YA),(R1L,R2K,ZQ,XA,YA),(R1M,R2K,ZQ,XA,YA),(R1N,R2K,ZQ,XA,YA),(R1O,R2K,ZQ,XA,YA),(R1P,R2K,ZQ,XA,YA),(R1Q,R2K,ZQ,XA,YA),(R1A,R2L,ZQ,XA,YA),(R1B,R2L,ZQ,XA,YA),(R1C,R2L,ZQ,XA,YA),(R1D,R2L,ZQ,XA,YA),(R1E,R2L,ZQ,XA,YA),(R1F,R2L,ZQ,XA,YA),(R1G,R2L,ZQ,XA,YA),(R1H,R2L,ZQ,XA,YA),(R1I,R2L,ZQ,XA,YA),(R1J,R2L,ZQ,XA,YA),(R1K,R2L,ZQ,XA,YA),(R1L,R2L,ZQ,XA,YA),(R1M,R2L,ZQ,XA,YA),(R1N,R2L,ZQ,XA,YA),(R1O,R2L,ZQ,XA,YA),(R1P,R2L,ZQ,XA,YA),(R1Q,R2L,ZQ,XA,YA),(R1A,R2M,ZQ,XA,YA),(R1B,R2M,ZQ,XA,YA),(R1C,R2M,ZQ,XA,YA),(R1D,R2M,ZQ,XA,YA),(R1E,R2M,ZQ,XA,YA),(R1F,R2M,ZQ,XA,YA),(R1G,R2M,ZQ,XA,YA),(R1H,R2M,ZQ,XA,YA),(R1I,R2M,ZQ,XA,YA),(R1J,R2M,ZQ,XA,YA),(R1K,R2M,ZQ,XA,YA),(R1L,R2M,ZQ,XA,YA),(R1M,R2M,ZQ,XA,YA),(R1N,R2M,ZQ,XA,YA),(R1O,R2M,ZQ,XA,YA),(R1P,R2M,ZQ,XA,YA),(R1Q,R2M,ZQ,XA,YA),(R1A,R2N,ZQ,XA,YA),(R1B,R2N,ZQ,XA,YA),(R1C,R2N,ZQ,XA,YA),(R1D,R2N,ZQ,XA,YA),(R1E,R2N,ZQ,XA,YA),(R1F,R2N,ZQ,XA,YA),(R1G,R2N,ZQ,XA,YA),(R1H,R2N,ZQ,XA,YA),(R1I,R2N,ZQ,XA,YA),(R1J,R2N,ZQ,XA,YA),(R1K,R2N,ZQ,XA,YA),(R1L,R2N,ZQ,XA,YA),(R1M,R2N,ZQ,XA,YA),(R1N,R2N,ZQ,XA,YA),(R1O,R2N,ZQ,XA,Y

A),(R1P,R2N,ZQ,XA,YA),(R1Q,R2N,ZQ,XA,YA),(R1A,R2O,Z
Q,XA,YA),(R1B,R2O,ZQ,XA,YA),(R1C,R2O,ZQ,XA,YA),(R1
D,R2O,ZQ,XA,YA),(R1E,R2O,ZQ,XA,YA),(R1F,R2O,ZQ,XA,
YA),(R1G,R2O,ZQ,XA,YA),(R1H,R2O,ZQ,XA,YA),(R1I,R2O,
ZQ,XA,YA),(R1J,R2O,ZQ,XA,YA),(R1K,R2O,ZQ,XA,YA),(R
1L,R2O,ZQ,XA,YA),(R1M,R2O,ZQ,XA,YA),(R1N,R2O,ZQ,X
A,YA),(R1O,R2O,ZQ,XA,YA),(R1P,R2O,ZQ,XA,YA),(R1Q,R2
O,ZQ,XA,YA),(R1A,R2P,ZQ,XA,YA),(R1B,R2P,ZQ,XA,YA),(
R1C,R2P,ZQ,XA,YA),(R1D,R2P,ZQ,XA,YA),(R1E,R2P,ZQ,X
A,YA),(R1F,R2P,ZQ,XA,YA),(R1G,R2P,ZQ,XA,YA),(R1H,R2
P,ZQ,XA,YA),(R1I,R2P,ZQ,XA,YA),(R1J,R2P,ZQ,XA,YA),(R
1K,R2P,ZQ,XA,YA),(R1L,R2P,ZQ,XA,YA),(R1M,R2P,ZQ,XA,
YA),(R1N,R2P,ZQ,XA,YA),(R1O,R2P,ZQ,XA,YA),(R1P,R2P,Z
Q,XA,YA),(R1Q,R2P,ZQ,XA,YA),(R1A,R2Q,ZQ,XA,YA),(R1
B,R2Q,ZQ,XA,YA),(R1C,R2Q,ZQ,XA,YA),(R1D,R2Q,ZQ,XA,
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ZQ,XA,YA),(R1H,R2Q,ZQ,XA,YA),(R1I,R2Q,ZQ,XA,YA),(R
1J,R2Q,ZQ,XA,YA),(R1K,R2Q,ZQ,XA,YA),(R1L,R2Q,ZQ,XA
,YA),(R1M,R2Q,ZQ,XA,YA),(R1N,R2Q,ZQ,XA,YA),(R1O,R2
Q,ZQ,XA,YA),(R1P,R2Q,ZQ,XA,YA),(R1Q,R2Q,ZQ,XA,YA),(
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A,ZR,XA,YA),(R1G,R2A,ZR,XA,YA),(R1H,R2A,ZR,XA,YA),(
R1I,R2A,ZR,XA,YA),(R1J,R2A,ZR,XA,YA),(R1K,R2A,ZR,X

A,YA),(R1L,R2A,ZR,XA,YA),(R1M,R2A,ZR,XA,YA),(R1N,R2A,ZR,XA,YA),(R1O,R2A,ZR,XA,YA),(R1P,R2A,ZR,XA,YA),(R1Q,R2A,ZR,XA,YA),(R1A,R2B,ZR,XA,YA),(R1B,R2B,ZR,XA,YA),(R1C,R2B,ZR,XA,YA),(R1D,R2B,ZR,XA,YA),(R1E,R2B,ZR,XA,YA),(R1F,R2B,ZR,XA,YA),(R1G,R2B,ZR,XA,YA),(R1H,R2B,ZR,XA,YA),(R1I,R2B,ZR,XA,YA),(R1J,R2B,ZR,XA,YA),(R1K,R2B,ZR,XA,YA),(R1L,R2B,ZR,XA,YA),(R1M,R2B,ZR,XA,YA),(R1N,R2B,ZR,XA,YA),(R1O,R2B,ZR,XA,YA),(R1P,R2B,ZR,XA,YA),(R1Q,R2B,ZR,XA,YA),(R1A,R2C,ZR,XA,YA),(R1B,R2C,ZR,XA,YA),(R1C,R2C,ZR,XA,YA),(R1D,R2C,ZR,XA,YA),(R1E,R2C,ZR,XA,YA),(R1F,R2C,ZR,XA,YA),(R1G,R2C,ZR,XA,YA),(R1H,R2C,ZR,XA,YA),(R1I,R2C,ZR,XA,YA),(R1J,R2C,ZR,XA,YA),(R1K,R2C,ZR,XA,YA),(R1L,R2C,ZR,XA,YA),(R1M,R2C,ZR,XA,YA),(R1N,R2C,ZR,XA,YA),(R1O,R2C,ZR,XA,YA),(R1P,R2C,ZR,XA,YA),(R1Q,R2C,ZR,XA,YA),(R1A,R2D,ZR,XA,YA),(R1B,R2D,ZR,XA,YA),(R1C,R2D,ZR,XA,YA),(R1D,R2D,ZR,XA,YA),(R1E,R2D,ZR,XA,YA),(R1F,R2D,ZR,XA,YA),(R1G,R2D,ZR,XA,YA),(R1H,R2D,ZR,XA,YA),(R1I,R2D,ZR,XA,YA),(R1J,R2D,ZR,XA,YA),(R1K,R2D,ZR,XA,YA),(R1L,R2D,ZR,XA,YA),(R1M,R2D,ZR,XA,YA),(R1N,R2D,ZR,XA,YA),(R1O,R2D,ZR,XA,YA),(R1P,R2D,ZR,XA,YA),(R1Q,R2D,ZR,XA,YA),(R1A,R2E,ZR,XA,YA),(R1B,R2E,ZR,XA,YA),(R1C,R2E,ZR,XA,YA),(R1D,R2E,ZR,XA,YA),(R1E,R2E,ZR,XA,YA),(R1F,R2E,ZR,XA,YA),(R1G,R2E,

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YA),(R1D,R2I,ZR,XA,YA),(R1E,R2I,ZR,XA,YA),(R1F,R2I,Z
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,ZR,XA,YA),(R1A,R2J,ZR,XA,YA),(R1B,R2J,ZR,XA,YA),(R
1C,R2J,ZR,XA,YA),(R1D,R2J,ZR,XA,YA),(R1E,R2J,ZR,XA,
YA),(R1F,R2J,ZR,XA,YA),(R1G,R2J,ZR,XA,YA),(R1H,R2J,Z
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2C,ZS,XA,YA),(R1J,R2C,ZS,XA,YA),(R1K,R2C,ZS,XA,YA),(R1L,R2C,ZS,XA,YA),(R1M,R2C,ZS,XA,YA),(R1N,R2C,ZS,XA,YA),(R1O,R2C,ZS,XA,YA),(R1P,R2C,ZS,XA,YA),(R1Q,R2C,ZS,XA,YA),(R1A,R2D,ZS,XA,YA),(R1B,R2D,ZS,XA,YA),(R1C,R2D,ZS,XA,YA),(R1D,R2D,ZS,XA,YA),(R1E,R2D,ZS,XA,YA),(R1F,R2D,ZS,XA,YA),(R1G,R2D,ZS,XA,YA),(R1H,R2D,ZS,XA,YA),(R1I,R2D,ZS,XA,YA),(R1J,R2D,ZS,XA,YA),(R1K,R2D,ZS,XA,YA),(R1L,R2D,ZS,XA,YA),(R1M,R2D,ZS,XA,YA),(R1N,R2D,ZS,XA,YA),(R1O,R2D,ZS,XA,YA),(R1P,R2D,ZS,XA,YA),(R1Q,R2D,ZS,XA,YA),(R1A,R2E,ZS,XA,YA),(R1B,R2E,ZS,XA,YA),(R1C,R2E,ZS,XA,YA),(R1D,R2E,ZS,XA,YA),(R1E,R2E,ZS,XA,YA),(R1F,R2E,ZS,XA,YA),(R1G,R2E,ZS,XA,YA),(R1H,R2E,ZS,XA,YA),(R1I,R2E,ZS,XA,YA),(R1J,R2E,ZS,XA,YA),(R1K,R2E,ZS,XA,YA),(R1L,R2E,ZS,XA,YA),(R1M,R2E,ZS,XA,YA),(R1N,R2E,ZS,XA,YA),(R1O,R2E,ZS,XA,YA),(R1P,R2E,ZS,XA,YA),(R1Q,R2E,ZS,XA,YA),(R1A,R2F,ZS,XA,YA),(R1B,R2F,ZS,XA,YA),(R1C,R2F,ZS,XA,YA),(R1D,R2F,ZS,XA,YA),(R1E,R2F,ZS,XA,YA),(R1F,R2F,ZS,XA,YA),(R1G,R2F,ZS,XA,YA),(R1H,R2F,ZS,XA,YA),(R1I,R2F,ZS,XA,YA),(R1J,R2F,ZS,XA,YA),(R1K,R2F,ZS,XA,YA),(R1L,R2F,ZS,XA,YA),(R1M,R2F,ZS,XA,YA),(R1N,R2F,ZS,XA,YA),(R1O,R2F,ZS,XA,YA),(R1P,R2F,ZS,XA,YA),(R1Q,R2F,ZS,XA,YA),(R1A,R2G,ZS,XA,YA),(R1B,R2G,ZS,XA,YA),(R1C,R2G,ZS,XA,YA),(R1D,R2G,ZS,XA,YA),(R1E,R2G,ZS,XA,YA),(

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A,YA),(R1H,R2L,ZS,XA,YA),(R1I,R2L,ZS,XA,YA),(R1J,R2L
,ZS,XA,YA),(R1K,R2L,ZS,XA,YA),(R1L,R2L,ZS,XA,YA),(R
1M,R2L,ZS,XA,YA),(R1N,R2L,ZS,XA,YA),(R1O,R2L,ZS,XA,
YA),(R1P,R2L,ZS,XA,YA),(R1Q,R2L,ZS,XA,YA),(R1A,R2M,
ZS,XA,YA),(R1B,R2M,ZS,XA,YA),(R1C,R2M,ZS,XA,YA),(R
1D,R2M,ZS,XA,YA),(R1E,R2M,ZS,XA,YA),(R1F,R2M,ZS,XA
,YA),(R1G,R2M,ZS,XA,YA),(R1H,R2M,ZS,XA,YA),(R1I,R2M
,ZS,XA,YA),(R1J,R2M,ZS,XA,YA),(R1K,R2M,ZS,XA,YA),(R
1L,R2M,ZS,XA,YA),(R1M,R2M,ZS,XA,YA),(R1N,R2M,ZS,X
A,YA),(R1O,R2M,ZS,XA,YA),(R1P,R2M,ZS,XA,YA),(R1Q,R2
M,ZS,XA,YA),(R1A,R2N,ZS,XA,YA),(R1B,R2N,ZS,XA,YA),(
R1C,R2N,ZS,XA,YA),(R1D,R2N,ZS,XA,YA),(R1E,R2N,ZS,X
A,YA),(R1F,R2N,ZS,XA,YA),(R1G,R2N,ZS,XA,YA),(R1H,R2
N,ZS,XA,YA),(R1I,R2N,ZS,XA,YA),(R1J,R2N,ZS,XA,YA),(R
1K,R2N,ZS,XA,YA),(R1L,R2N,ZS,XA,YA),(R1M,R2N,ZS,XA
,YA),(R1N,R2N,ZS,XA,YA),(R1O,R2N,ZS,XA,YA),(R1P,R2N

,ZS,XA,YA),(R1Q,R2N,ZS,XA,YA),(R1A,R2O,ZS,XA,YA),(R1B,R2O,ZS,XA,YA),(R1C,R2O,ZS,XA,YA),(R1D,R2O,ZS,XA,YA),(R1E,R2O,ZS,XA,YA),(R1F,R2O,ZS,XA,YA),(R1G,R2O,ZS,XA,YA),(R1H,R2O,ZS,XA,YA),(R1I,R2O,ZS,XA,YA),(R1J,R2O,ZS,XA,YA),(R1K,R2O,ZS,XA,YA),(R1L,R2O,ZS,XA,YA),(R1M,R2O,ZS,XA,YA),(R1N,R2O,ZS,XA,YA),(R1O,R2O,ZS,XA,YA),(R1P,R2O,ZS,XA,YA),(R1Q,R2O,ZS,XA,YA),(R1A,R2P,ZS,XA,YA),(R1B,R2P,ZS,XA,YA),(R1C,R2P,ZS,XA,YA),(R1D,R2P,ZS,XA,YA),(R1E,R2P,ZS,XA,YA),(R1F,R2P,ZS,XA,YA),(R1G,R2P,ZS,XA,YA),(R1H,R2P,ZS,XA,YA),(R1I,R2P,ZS,XA,YA),(R1J,R2P,ZS,XA,YA),(R1K,R2P,ZS,XA,YA),(R1L,R2P,ZS,XA,YA),(R1M,R2P,ZS,XA,YA),(R1N,R2P,ZS,XA,YA),(R1O,R2P,ZS,XA,YA),(R1P,R2P,ZS,XA,YA),(R1Q,R2P,ZS,XA,YA),(R1A,R2Q,ZS,XA,YA),(R1B,R2Q,ZS,XA,YA),(R1C,R2Q,ZS,XA,YA),(R1D,R2Q,ZS,XA,YA),(R1E,R2Q,ZS,XA,YA),(R1F,R2Q,ZS,XA,YA),(R1G,R2Q,ZS,XA,YA),(R1H,R2Q,ZS,XA,YA),(R1I,R2Q,ZS,XA,YA),(R1J,R2Q,ZS,XA,YA),(R1K,R2Q,ZS,XA,YA),(R1L,R2Q,ZS,XA,YA),(R1M,R2Q,ZS,XA,YA),(R1N,R2Q,ZS,XA,YA),(R1O,R2Q,ZS,XA,YA),(R1P,R2Q,ZS,XA,YA),(R1Q,R2Q,ZS,XA,YA),(R1A,R2A,ZT,XA,YA),(R1B,R2A,ZT,XA,YA),(R1C,R2A,ZT,XA,YA),(R1D,R2A,ZT,XA,YA),(R1E,R2A,ZT,XA,YA),(R1F,R2A,ZT,XA,YA),(R1G,R2A,ZT,XA,YA),(R1H,R2A,ZT,XA,YA),(R1I,R2A,ZT,XA,YA),(R1J,R2A,ZT,XA,YA),(R1K,R2A,ZT,XA,YA),(R1L,R2A,ZT,XA,YA),

(R1M,R2A,ZT,XA,YA),(R1N,R2A,ZT,XA,YA),(R1O,R2A,ZT,XA,YA),(R1P,R2A,ZT,XA,YA),(R1Q,R2A,ZT,XA,YA),(R1A,R2B,ZT,XA,YA),(R1B,R2B,ZT,XA,YA),(R1C,R2B,ZT,XA,YA),(R1D,R2B,ZT,XA,YA),(R1E,R2B,ZT,XA,YA),(R1F,R2B,ZT,XA,YA),(R1G,R2B,ZT,XA,YA),(R1H,R2B,ZT,XA,YA),(R1I,R2B,ZT,XA,YA),(R1J,R2B,ZT,XA,YA),(R1K,R2B,ZT,XA,YA),(R1L,R2B,ZT,XA,YA),(R1M,R2B,ZT,XA,YA),(R1N,R2B,ZT,XA,YA),(R1O,R2B,ZT,XA,YA),(R1P,R2B,ZT,XA,YA),(R1Q,R2B,ZT,XA,YA),(R1A,R2C,ZT,XA,YA),(R1B,R2C,ZT,XA,YA),(R1C,R2C,ZT,XA,YA),(R1D,R2C,ZT,XA,YA),(R1E,R2C,ZT,XA,YA),(R1F,R2C,ZT,XA,YA),(R1G,R2C,ZT,XA,YA),(R1H,R2C,ZT,XA,YA),(R1I,R2C,ZT,XA,YA),(R1J,R2C,ZT,XA,YA),(R1K,R2C,ZT,XA,YA),(R1L,R2C,ZT,XA,YA),(R1M,R2C,ZT,XA,YA),(R1N,R2C,ZT,XA,YA),(R1O,R2C,ZT,XA,YA),(R1P,R2C,ZT,XA,YA),(R1Q,R2C,ZT,XA,YA),(R1A,R2D,ZT,XA,YA),(R1B,R2D,ZT,XA,YA),(R1C,R2D,ZT,XA,YA),(R1D,R2D,ZT,XA,YA),(R1E,R2D,ZT,XA,YA),(R1F,R2D,ZT,XA,YA),(R1G,R2D,ZT,XA,YA),(R1H,R2D,ZT,XA,YA),(R1I,R2D,ZT,XA,YA),(R1J,R2D,ZT,XA,YA),(R1K,R2D,ZT,XA,YA),(R1L,R2D,ZT,XA,YA),(R1M,R2D,ZT,XA,YA),(R1N,R2D,ZT,XA,YA),(R1O,R2D,ZT,XA,YA),(R1P,R2D,ZT,XA,YA),(R1Q,R2D,ZT,XA,YA),(R1A,R2E,ZT,XA,YA),(R1B,R2E,ZT,XA,YA),(R1C,R2E,ZT,XA,YA),(R1D,R2E,ZT,XA,YA),(R1E,R2E,ZT,XA,YA),(R1F,R2E,ZT,XA,YA),(R1G,R2E,ZT,XA,YA),(R1H,R2E,ZT,XA,YA),(R1I,R

2E,ZT,XA,YA),(R1J,R2E,ZT,XA,YA),(R1K,R2E,ZT,XA,YA),(R1L,R2E,ZT,XA,YA),(R1M,R2E,ZT,XA,YA),(R1N,R2E,ZT,XA,YA),(R1O,R2E,ZT,XA,YA),(R1P,R2E,ZT,XA,YA),(R1Q,R2E,ZT,XA,YA),(R1A,R2F,ZT,XA,YA),(R1B,R2F,ZT,XA,YA),(R1C,R2F,ZT,XA,YA),(R1D,R2F,ZT,XA,YA),(R1E,R2F,ZT,XA,YA),(R1F,R2F,ZT,XA,YA),(R1G,R2F,ZT,XA,YA),(R1H,R2F,ZT,XA,YA),(R1I,R2F,ZT,XA,YA),(R1J,R2F,ZT,XA,YA),(R1K,R2F,ZT,XA,YA),(R1L,R2F,ZT,XA,YA),(R1M,R2F,ZT,XA,YA),(R1N,R2F,ZT,XA,YA),(R1O,R2F,ZT,XA,YA),(R1P,R2F,ZT,XA,YA),(R1Q,R2F,ZT,XA,YA),(R1A,R2G,ZT,XA,YA),(R1B,R2G,ZT,XA,YA),(R1C,R2G,ZT,XA,YA),(R1D,R2G,ZT,XA,YA),(R1E,R2G,ZT,XA,YA),(R1F,R2G,ZT,XA,YA),(R1G,R2G,ZT,XA,YA),(R1H,R2G,ZT,XA,YA),(R1I,R2G,ZT,XA,YA),(R1J,R2G,ZT,XA,YA),(R1K,R2G,ZT,XA,YA),(R1L,R2G,ZT,XA,YA),(R1M,R2G,ZT,XA,YA),(R1N,R2G,ZT,XA,YA),(R1O,R2G,ZT,XA,YA),(R1P,R2G,ZT,XA,YA),(R1Q,R2G,ZT,XA,YA),(R1A,R2H,ZT,XA,YA),(R1B,R2H,ZT,XA,YA),(R1C,R2H,ZT,XA,YA),(R1D,R2H,ZT,XA,YA),(R1E,R2H,ZT,XA,YA),(R1F,R2H,ZT,XA,YA),(R1G,R2H,ZT,XA,YA),(R1H,R2H,ZT,XA,YA),(R1I,R2H,ZT,XA,YA),(R1J,R2H,ZT,XA,YA),(R1K,R2H,ZT,XA,YA),(R1L,R2H,ZT,XA,YA),(R1M,R2H,ZT,XA,YA),(R1N,R2H,ZT,XA,YA),(R1O,R2H,ZT,XA,YA),(R1P,R2H,ZT,XA,YA),(R1Q,R2H,ZT,XA,YA),(R1A,R2I,ZT,XA,YA),(R1B,R2I,ZT,XA,YA),(R1C,R2I,ZT,XA,YA),(R1D,R2I,ZT,XA,YA),(R1E,R2I,ZT,XA,YA),(R1

F,R2I,ZT,XA,YA),(R1G,R2I,ZT,XA,YA),(R1H,R2I,ZT,XA,YA),(R1I,R2I,ZT,XA,YA),(R1J,R2I,ZT,XA,YA),(R1K,R2I,ZT,XA,YA),(R1L,R2I,ZT,XA,YA),(R1M,R2I,ZT,XA,YA),(R1N,R2I,ZT,XA,YA),(R1O,R2I,ZT,XA,YA),(R1P,R2I,ZT,XA,YA),(R1Q,R2I,ZT,XA,YA),(R1A,R2J,ZT,XA,YA),(R1B,R2J,ZT,XA,YA),(R1C,R2J,ZT,XA,YA),(R1D,R2J,ZT,XA,YA),(R1E,R2J,ZT,XA,YA),(R1F,R2J,ZT,XA,YA),(R1G,R2J,ZT,XA,YA),(R1H,R2J,ZT,XA,YA),(R1I,R2J,ZT,XA,YA),(R1J,R2J,ZT,XA,YA),(R1K,R2J,ZT,XA,YA),(R1L,R2J,ZT,XA,YA),(R1M,R2J,ZT,XA,YA),(R1N,R2J,ZT,XA,YA),(R1O,R2J,ZT,XA,YA),(R1P,R2J,ZT,XA,YA),(R1Q,R2J,ZT,XA,YA),(R1A,R2K,ZT,XA,YA),(R1B,R2K,ZT,XA,YA),(R1C,R2K,ZT,XA,YA),(R1D,R2K,ZT,XA,YA),(R1E,R2K,ZT,XA,YA),(R1F,R2K,ZT,XA,YA),(R1G,R2K,ZT,XA,YA),(R1H,R2K,ZT,XA,YA),(R1I,R2K,ZT,XA,YA),(R1J,R2K,ZT,XA,YA),(R1K,R2K,ZT,XA,YA),(R1L,R2K,ZT,XA,YA),(R1M,R2K,ZT,XA,YA),(R1N,R2K,ZT,XA,YA),(R1O,R2K,ZT,XA,YA),(R1P,R2K,ZT,XA,YA),(R1Q,R2K,ZT,XA,YA),(R1A,R2L,ZT,XA,YA),(R1B,R2L,ZT,XA,YA),(R1C,R2L,ZT,XA,YA),(R1D,R2L,ZT,XA,YA),(R1E,R2L,ZT,XA,YA),(R1F,R2L,ZT,XA,YA),(R1G,R2L,ZT,XA,YA),(R1H,R2L,ZT,XA,YA),(R1I,R2L,ZT,XA,YA),(R1J,R2L,ZT,XA,YA),(R1K,R2L,ZT,XA,YA),(R1L,R2L,ZT,XA,YA),(R1M,R2L,ZT,XA,YA),(R1N,R2L,ZT,XA,YA),(R1O,R2L,ZT,XA,YA),(R1P,R2L,ZT,XA,YA),(R1Q,R2L,ZT,XA,YA),(R1A,R2M,ZT,XA,YA),(R1B,R2M,ZT,XA,YA),(R1

C,R2M,ZT,XA,YA),(R1D,R2M,ZT,XA,YA),(R1E,R2M,ZT,XA,YA),(R1F,R2M,ZT,XA,YA),(R1G,R2M,ZT,XA,YA),(R1H,R2M,ZT,XA,YA),(R1I,R2M,ZT,XA,YA),(R1J,R2M,ZT,XA,YA),(R1K,R2M,ZT,XA,YA),(R1L,R2M,ZT,XA,YA),(R1M,R2M,ZT,XA,YA),(R1N,R2M,ZT,XA,YA),(R1O,R2M,ZT,XA,YA),(R1P,R2M,ZT,XA,YA),(R1Q,R2M,ZT,XA,YA),(R1A,R2N,ZT,XA,YA),(R1B,R2N,ZT,XA,YA),(R1C,R2N,ZT,XA,YA),(R1D,R2N,ZT,XA,YA),(R1E,R2N,ZT,XA,YA),(R1F,R2N,ZT,XA,YA),(R1G,R2N,ZT,XA,YA),(R1H,R2N,ZT,XA,YA),(R1I,R2N,ZT,XA,YA),(R1J,R2N,ZT,XA,YA),(R1K,R2N,ZT,XA,YA),(R1L,R2N,ZT,XA,YA),(R1M,R2N,ZT,XA,YA),(R1N,R2N,ZT,XA,YA),(R1O,R2N,ZT,XA,YA),(R1P,R2N,ZT,XA,YA),(R1Q,R2N,ZT,XA,YA),(R1A,R2O,ZT,XA,YA),(R1B,R2O,ZT,XA,YA),(R1C,R2O,ZT,XA,YA),(R1D,R2O,ZT,XA,YA),(R1E,R2O,ZT,XA,YA),(R1F,R2O,ZT,XA,YA),(R1G,R2O,ZT,XA,YA),(R1H,R2O,ZT,XA,YA),(R1I,R2O,ZT,XA,YA),(R1J,R2O,ZT,XA,YA),(R1K,R2O,ZT,XA,YA),(R1L,R2O,ZT,XA,YA),(R1M,R2O,ZT,XA,YA),(R1N,R2O,ZT,XA,YA),(R1O,R2O,ZT,XA,YA),(R1P,R2O,ZT,XA,YA),(R1Q,R2O,ZT,XA,YA),(R1A,R2P,ZT,XA,YA),(R1B,R2P,ZT,XA,YA),(R1C,R2P,ZT,XA,YA),(R1D,R2P,ZT,XA,YA),(R1E,R2P,ZT,XA,YA),(R1F,R2P,ZT,XA,YA),(R1G,R2P,ZT,XA,YA),(R1H,R2P,ZT,XA,YA),(R1I,R2P,ZT,XA,YA),(R1J,R2P,ZT,XA,YA),(R1K,R2P,ZT,XA,YA),(R1L,R2P,ZT,XA,YA),(R1M,R2P,ZT,XA,YA),(R1N,R2P,ZT,XA,YA),(R1O,R2P,ZT,XA,YA),(R1P,R2P,ZT

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B,YA),(R1N,R2C,ZF,XB,YA),(R1O,R2C,ZF,XB,YA),(R1P,R2C,ZF,XB,YA),(R1Q,R2C,ZF,XB,YA),(R1A,R2D,ZF,XB,YA),(R1B,R2D,ZF,XB,YA),(R1C,R2D,ZF,XB,YA),(R1D,R2D,ZF,XB,YA),(R1E,R2D,ZF,XB,YA),(R1F,R2D,ZF,XB,YA),(R1G,R2D,ZF,XB,YA),(R1H,R2D,ZF,XB,YA),(R1I,R2D,ZF,XB,YA),(R1J,R2D,ZF,XB,YA),(R1K,R2D,ZF,XB,YA),(R1L,R2D,ZF,XB,YA),(R1M,R2D,ZF,XB,YA),(R1N,R2D,ZF,XB,YA),(R1O,R2D,ZF,XB,YA),(R1P,R2D,ZF,XB,YA),(R1Q,R2D,ZF,XB,YA),(R1A,R2E,ZF,XB,YA),(R1B,R2E,ZF,XB,YA),(R1C,R2E,ZF,XB,YA),(R1D,R2E,ZF,XB,YA),(R1E,R2E,ZF,XB,YA),(R1F,R2E,ZF,XB,YA),(R1G,R2E,ZF,XB,YA),(R1H,R2E,ZF,XB,YA),(R1I,R2E,ZF,XB,YA),(R1J,R2E,ZF,XB,YA),(R1K,R2E,ZF,XB,YA),(R1L,R2E,ZF,XB,YA),(R1M,R2E,ZF,XB,YA),(R1N,R2E,ZF,XB,YA),(R1O,R2E,ZF,XB,YA),(R1P,R2E,ZF,XB,YA),(R1Q,R2E,ZF,XB,YA),(R1A,R2F,ZF,XB,YA),(R1B,R2F,ZF,XB,YA),(R1C,R2F,ZF,XB,YA),(R1D,R2F,ZF,XB,YA),(R1E,R2F,ZF,XB,YA),(R1F,R2F,ZF,XB,YA),(R1G,R2F,ZF,XB,YA),(R1H,R2F,ZF,XB,YA),(R1I,R2F,ZF,XB,YA),(R1J,R2F,ZF,XB,YA),(R1K,R2F,ZF,XB,YA),(R1L,R2F,ZF,XB,YA),(R1M,R2F,ZF,XB,YA),(R1N,R2F,ZF,XB,YA),(R1O,R2F,ZF,XB,YA),(R1P,R2F,ZF,XB,YA),(R1Q,R2F,ZF,XB,YA),(R1A,R2G,ZF,XB,YA),(R1B,R2G,ZF,XB,YA),(R1C,R2G,ZF,XB,YA),(R1D,R2G,ZF,XB,YA),(R1E,R2G,ZF,XB,YA),(R1F,R2G,ZF,XB,YA),(R1G,R2G,ZF,XB,YA),(R1H,R2G,ZF,XB,YA),(R1I,R2G,ZF,XB,YA),(R1J,R2G,ZF,XB,

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B,YA),(R1K,R2O,ZF,XB,YA),(R1L,R2O,ZF,XB,YA),(R1M,R2
O,ZF,XB,YA),(R1N,R2O,ZF,XB,YA),(R1O,R2O,ZF,XB,YA),(
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YA),(R1M,R2P,ZF,XB,YA),(R1N,R2P,ZF,XB,YA),(R1O,R2P,Z
F,XB,YA),(R1P,R2P,ZF,XB,YA),(R1Q,R2P,ZF,XB,YA),(R1A,
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B,YA),(R1G,R2Q,ZF,XB,YA),(R1H,R2Q,ZF,XB,YA),(R1I,R2
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G,XB,YA),(R1H,R2B,ZG,XB,YA),(R1I,R2B,ZG,XB,YA),(R1J,
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B,YA),(R1G,R2C,ZG,XB,YA),(R1H,R2C,ZG,XB,YA),(R1I,R2
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1B,R2E,ZG,XB,YA),(R1C,R2E,ZG,XB,YA),(R1D,R2E,ZG,XB,
YA),(R1E,R2E,ZG,XB,YA),(R1F,R2E,ZG,XB,YA),(R1G,R2E,Z
G,XB,YA),(R1H,R2E,ZG,XB,YA),(R1I,R2E,ZG,XB,YA),(R1J,
R2E,ZG,XB,YA),(R1K,R2E,ZG,XB,YA),(R1L,R2E,ZG,XB,YA)
,(R1M,R2E,ZG,XB,YA),(R1N,R2E,ZG,XB,YA),(R1O,R2E,ZG,

XB,YA),(R1P,R2E,ZG,XB,YA),(R1Q,R2E,ZG,XB,YA),(R1A,R2F,ZG,XB,YA),(R1B,R2F,ZG,XB,YA),(R1C,R2F,ZG,XB,YA),(R1D,R2F,ZG,XB,YA),(R1E,R2F,ZG,XB,YA),(R1F,R2F,ZG,XB,YA),(R1G,R2F,ZG,XB,YA),(R1H,R2F,ZG,XB,YA),(R1I,R2F,ZG,XB,YA),(R1J,R2F,ZG,XB,YA),(R1K,R2F,ZG,XB,YA),(R1L,R2F,ZG,XB,YA),(R1M,R2F,ZG,XB,YA),(R1N,R2F,ZG,XB,YA),(R1O,R2F,ZG,XB,YA),(R1P,R2F,ZG,XB,YA),(R1Q,R2F,ZG,XB,YA),(R1A,R2G,ZG,XB,YA),(R1B,R2G,ZG,XB,YA),(R1C,R2G,ZG,XB,YA),(R1D,R2G,ZG,XB,YA),(R1E,R2G,ZG,XB,YA),(R1F,R2G,ZG,XB,YA),(R1G,R2G,ZG,XB,YA),(R1H,R2G,ZG,XB,YA),(R1I,R2G,ZG,XB,YA),(R1J,R2G,ZG,XB,YA),(R1K,R2G,ZG,XB,YA),(R1L,R2G,ZG,XB,YA),(R1M,R2G,ZG,XB,YA),(R1N,R2G,ZG,XB,YA),(R1O,R2G,ZG,XB,YA),(R1P,R2G,ZG,XB,YA),(R1Q,R2G,ZG,XB,YA),(R1A,R2H,ZG,XB,YA),(R1B,R2H,ZG,XB,YA),(R1C,R2H,ZG,XB,YA),(R1D,R2H,ZG,XB,YA),(R1E,R2H,ZG,XB,YA),(R1F,R2H,ZG,XB,YA),(R1G,R2H,ZG,XB,YA),(R1H,R2H,ZG,XB,YA),(R1I,R2H,ZG,XB,YA),(R1J,R2H,ZG,XB,YA),(R1K,R2H,ZG,XB,YA),(R1L,R2H,ZG,XB,YA),(R1M,R2H,ZG,XB,YA),(R1N,R2H,ZG,XB,YA),(R1O,R2H,ZG,XB,YA),(R1P,R2H,ZG,XB,YA),(R1Q,R2H,ZG,XB,YA),(R1A,R2I,ZG,XB,YA),(R1B,R2I,ZG,XB,YA),(R1C,R2I,ZG,XB,YA),(R1D,R2I,ZG,XB,YA),(R1E,R2I,ZG,XB,YA),(R1F,R2I,ZG,XB,YA),(R1G,R2I,ZG,XB,YA),(R1H,R2I,ZG,XB,YA),(R1I,R2I,ZG,XB,YA),(R1J,R2I,ZG,XB,YA),(R1K,R2I,ZG,XB,YA),(R1L,R2I,ZG,X

B,YA),(R1M,R2I,ZG,XB,YA),(R1N,R2I,ZG,XB,YA),(R1O,R2I,ZG,XB,YA),(R1P,R2I,ZG,XB,YA),(R1Q,R2I,ZG,XB,YA),(R1A,R2J,ZG,XB,YA),(R1B,R2J,ZG,XB,YA),(R1C,R2J,ZG,XB,YA),(R1D,R2J,ZG,XB,YA),(R1E,R2J,ZG,XB,YA),(R1F,R2J,ZG,XB,YA),(R1G,R2J,ZG,XB,YA),(R1H,R2J,ZG,XB,YA),(R1I,R2J,ZG,XB,YA),(R1J,R2J,ZG,XB,YA),(R1K,R2J,ZG,XB,YA),(R1L,R2J,ZG,XB,YA),(R1M,R2J,ZG,XB,YA),(R1N,R2J,ZG,XB,YA),(R1O,R2J,ZG,XB,YA),(R1P,R2J,ZG,XB,YA),(R1Q,R2J,ZG,XB,YA),(R1A,R2K,ZG,XB,YA),(R1B,R2K,ZG,XB,YA),(R1C,R2K,ZG,XB,YA),(R1D,R2K,ZG,XB,YA),(R1E,R2K,ZG,XB,YA),(R1F,R2K,ZG,XB,YA),(R1G,R2K,ZG,XB,YA),(R1H,R2K,ZG,XB,YA),(R1I,R2K,ZG,XB,YA),(R1J,R2K,ZG,XB,YA),(R1K,R2K,ZG,XB,YA),(R1L,R2K,ZG,XB,YA),(R1M,R2K,ZG,XB,YA),(R1N,R2K,ZG,XB,YA),(R1O,R2K,ZG,XB,YA),(R1P,R2K,ZG,XB,YA),(R1Q,R2K,ZG,XB,YA),(R1A,R2L,ZG,XB,YA),(R1B,R2L,ZG,XB,YA),(R1C,R2L,ZG,XB,YA),(R1D,R2L,ZG,XB,YA),(R1E,R2L,ZG,XB,YA),(R1F,R2L,ZG,XB,YA),(R1G,R2L,ZG,XB,YA),(R1H,R2L,ZG,XB,YA),(R1I,R2L,ZG,XB,YA),(R1J,R2L,ZG,XB,YA),(R1K,R2L,ZG,XB,YA),(R1L,R2L,ZG,XB,YA),(R1M,R2L,ZG,XB,YA),(R1N,R2L,ZG,XB,YA),(R1O,R2L,ZG,XB,YA),(R1P,R2L,ZG,XB,YA),(R1Q,R2L,ZG,XB,YA),(R1A,R2M,ZG,XB,YA),(R1B,R2M,ZG,XB,YA),(R1C,R2M,ZG,XB,YA),(R1D,R2M,ZG,XB,YA),(R1E,R2M,ZG,XB,YA),(R1F,R2M,ZG,XB,YA),(R1G,R2M,ZG,XB,YA),(R1H,R2M,ZG,XB,YA),(R1I,R2M

,ZG,XB,YA),(R1J,R2M,ZG,XB,YA),(R1K,R2M,ZG,XB,YA),(R1L,R2M,ZG,XB,YA),(R1M,R2M,ZG,XB,YA),(R1N,R2M,ZG,XB,YA),(R1O,R2M,ZG,XB,YA),(R1P,R2M,ZG,XB,YA),(R1Q,R2M,ZG,XB,YA),(R1A,R2N,ZG,XB,YA),(R1B,R2N,ZG,XB,YA),(R1C,R2N,ZG,XB,YA),(R1D,R2N,ZG,XB,YA),(R1E,R2N,ZG,XB,YA),(R1F,R2N,ZG,XB,YA),(R1G,R2N,ZG,XB,YA),(R1H,R2N,ZG,XB,YA),(R1I,R2N,ZG,XB,YA),(R1J,R2N,ZG,XB,YA),(R1K,R2N,ZG,XB,YA),(R1L,R2N,ZG,XB,YA),(R1M,R2N,ZG,XB,YA),(R1N,R2N,ZG,XB,YA),(R1O,R2N,ZG,XB,YA),(R1P,R2N,ZG,XB,YA),(R1Q,R2N,ZG,XB,YA),(R1A,R2O,ZG,XB,YA),(R1B,R2O,ZG,XB,YA),(R1C,R2O,ZG,XB,YA),(R1D,R2O,ZG,XB,YA),(R1E,R2O,ZG,XB,YA),(R1F,R2O,ZG,XB,YA),(R1G,R2O,ZG,XB,YA),(R1H,R2O,ZG,XB,YA),(R1I,R2O,ZG,XB,YA),(R1J,R2O,ZG,XB,YA),(R1K,R2O,ZG,XB,YA),(R1L,R2O,ZG,XB,YA),(R1M,R2O,ZG,XB,YA),(R1N,R2O,ZG,XB,YA),(R1O,R2O,ZG,XB,YA),(R1P,R2O,ZG,XB,YA),(R1Q,R2O,ZG,XB,YA),(R1A,R2P,ZG,XB,YA),(R1B,R2P,ZG,XB,YA),(R1C,R2P,ZG,XB,YA),(R1D,R2P,ZG,XB,YA),(R1E,R2P,ZG,XB,YA),(R1F,R2P,ZG,XB,YA),(R1G,R2P,ZG,XB,YA),(R1H,R2P,ZG,XB,YA),(R1I,R2P,ZG,XB,YA),(R1J,R2P,ZG,XB,YA),(R1K,R2P,ZG,XB,YA),(R1L,R2P,ZG,XB,YA),(R1M,R2P,ZG,XB,YA),(R1N,R2P,ZG,XB,YA),(R1O,R2P,ZG,XB,YA),(R1P,R2P,ZG,XB,YA),(R1Q,R2P,ZG,XB,YA),(R1A,R2Q,ZG,XB,YA),(R1B,R2Q,ZG,XB,YA),(R1C,R2Q,ZG,XB,YA),(R1D,R2Q,ZG,XB,YA),(R1E,R2Q,ZG,XB,

YA),(R1F,R2Q,ZG,XB,YA),(R1G,R2Q,ZG,XB,YA),(R1H,R2Q,ZG,XB,YA),(R1I,R2Q,ZG,XB,YA),(R1J,R2Q,ZG,XB,YA),(R1K,R2Q,ZG,XB,YA),(R1L,R2Q,ZG,XB,YA),(R1M,R2Q,ZG,XB,YA),(R1N,R2Q,ZG,XB,YA),(R1O,R2Q,ZG,XB,YA),(R1P,R2Q,ZG,XB,YA),(R1Q,R2Q,ZG,XB,YA),(R1A,R2A,ZH,XB,YA),(R1B,R2A,ZH,XB,YA),(R1C,R2A,ZH,XB,YA),(R1D,R2A,ZH,XB,YA),(R1E,R2A,ZH,XB,YA),(R1F,R2A,ZH,XB,YA),(R1G,R2A,ZH,XB,YA),(R1H,R2A,ZH,XB,YA),(R1I,R2A,ZH,XB,YA),(R1J,R2A,ZH,XB,YA),(R1K,R2A,ZH,XB,YA),(R1L,R2A,ZH,XB,YA),(R1M,R2A,ZH,XB,YA),(R1N,R2A,ZH,XB,YA),(R1O,R2A,ZH,XB,YA),(R1P,R2A,ZH,XB,YA),(R1Q,R2A,ZH,XB,YA),(R1A,R2B,ZH,XB,YA),(R1B,R2B,ZH,XB,YA),(R1C,R2B,ZH,XB,YA),(R1D,R2B,ZH,XB,YA),(R1E,R2B,ZH,XB,YA),(R1F,R2B,ZH,XB,YA),(R1G,R2B,ZH,XB,YA),(R1H,R2B,ZH,XB,YA),(R1I,R2B,ZH,XB,YA),(R1J,R2B,ZH,XB,YA),(R1K,R2B,ZH,XB,YA),(R1L,R2B,ZH,XB,YA),(R1M,R2B,ZH,XB,YA),(R1N,R2B,ZH,XB,YA),(R1O,R2B,ZH,XB,YA),(R1P,R2B,ZH,XB,YA),(R1Q,R2B,ZH,XB,YA),(R1A,R2C,ZH,XB,YA),(R1B,R2C,ZH,XB,YA),(R1C,R2C,ZH,XB,YA),(R1D,R2C,ZH,XB,YA),(R1E,R2C,ZH,XB,YA),(R1F,R2C,ZH,XB,YA),(R1G,R2C,ZH,XB,YA),(R1H,R2C,ZH,XB,YA),(R1I,R2C,ZH,XB,YA),(R1J,R2C,ZH,XB,YA),(R1K,R2C,ZH,XB,YA),(R1L,R2C,ZH,XB,YA),(R1M,R2C,ZH,XB,YA),(R1N,R2C,ZH,XB,YA),(R1O,R2C,ZH,XB,YA),(R1P,R2C,ZH,XB,YA),(R1Q,R2C,ZH,XB,YA),(R1A,R2D,ZH,XB

,YA),(R1B,R2D,ZH,XB,YA),(R1C,R2D,ZH,XB,YA),(R1D,R2D,ZH,XB,YA),(R1E,R2D,ZH,XB,YA),(R1F,R2D,ZH,XB,YA),(R1G,R2D,ZH,XB,YA),(R1H,R2D,ZH,XB,YA),(R1I,R2D,ZH,XB,YA),(R1J,R2D,ZH,XB,YA),(R1K,R2D,ZH,XB,YA),(R1L,R2D,ZH,XB,YA),(R1M,R2D,ZH,XB,YA),(R1N,R2D,ZH,XB,YA),(R1O,R2D,ZH,XB,YA),(R1P,R2D,ZH,XB,YA),(R1Q,R2D,ZH,XB,YA),(R1A,R2E,ZH,XB,YA),(R1B,R2E,ZH,XB,YA),(R1C,R2E,ZH,XB,YA),(R1D,R2E,ZH,XB,YA),(R1E,R2E,ZH,XB,YA),(R1F,R2E,ZH,XB,YA),(R1G,R2E,ZH,XB,YA),(R1H,R2E,ZH,XB,YA),(R1I,R2E,ZH,XB,YA),(R1J,R2E,ZH,XB,YA),(R1K,R2E,ZH,XB,YA),(R1L,R2E,ZH,XB,YA),(R1M,R2E,ZH,XB,YA),(R1N,R2E,ZH,XB,YA),(R1O,R2E,ZH,XB,YA),(R1P,R2E,ZH,XB,YA),(R1Q,R2E,ZH,XB,YA),(R1A,R2F,ZH,XB,YA),(R1B,R2F,ZH,XB,YA),(R1C,R2F,ZH,XB,YA),(R1D,R2F,ZH,XB,YA),(R1E,R2F,ZH,XB,YA),(R1F,R2F,ZH,XB,YA),(R1G,R2F,ZH,XB,YA),(R1H,R2F,ZH,XB,YA),(R1I,R2F,ZH,XB,YA),(R1J,R2F,ZH,XB,YA),(R1K,R2F,ZH,XB,YA),(R1L,R2F,ZH,XB,YA),(R1M,R2F,ZH,XB,YA),(R1N,R2F,ZH,XB,YA),(R1O,R2F,ZH,XB,YA),(R1P,R2F,ZH,XB,YA),(R1Q,R2F,ZH,XB,YA),(R1A,R2G,ZH,XB,YA),(R1B,R2G,ZH,XB,YA),(R1C,R2G,ZH,XB,YA),(R1D,R2G,ZH,XB,YA),(R1E,R2G,ZH,XB,YA),(R1F,R2G,ZH,XB,YA),(R1G,R2G,ZH,XB,YA),(R1H,R2G,ZH,XB,YA),(R1I,R2G,ZH,XB,YA),(R1J,R2G,ZH,XB,YA),(R1K,R2G,ZH,XB,YA),(R1L,R2G,ZH,XB,YA),(R1M,R2G,ZH,XB,YA),(R1N,R2G,ZH,XB,YA),(

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B,YA),(R1A,R2H,ZH,XB,YA),(R1B,R2H,ZH,XB,YA),(R1C,R2
H,ZH,XB,YA),(R1D,R2H,ZH,XB,YA),(R1E,R2H,ZH,XB,YA),(
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B,YA),(R1I,R2H,ZH,XB,YA),(R1J,R2H,ZH,XB,YA),(R1K,R2
H,ZH,XB,YA),(R1L,R2H,ZH,XB,YA),(R1M,R2H,ZH,XB,YA),
(R1N,R2H,ZH,XB,YA),(R1O,R2H,ZH,XB,YA),(R1P,R2H,ZH,
XB,YA),(R1Q,R2H,ZH,XB,YA),(R1A,R2I,ZH,XB,YA),(R1B,R
2I,ZH,XB,YA),(R1C,R2I,ZH,XB,YA),(R1D,R2I,ZH,XB,YA),(
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YA),(R1H,R2I,ZH,XB,YA),(R1I,R2I,ZH,XB,YA),(R1J,R2I,Z
H,XB,YA),(R1K,R2I,ZH,XB,YA),(R1L,R2I,ZH,XB,YA),(R1M
,R2I,ZH,XB,YA),(R1N,R2I,ZH,XB,YA),(R1O,R2I,ZH,XB,YA)
,(R1P,R2I,ZH,XB,YA),(R1Q,R2I,ZH,XB,YA),(R1A,R2J,ZH,X
B,YA),(R1B,R2J,ZH,XB,YA),(R1C,R2J,ZH,XB,YA),(R1D,R2J
,ZH,XB,YA),(R1E,R2J,ZH,XB,YA),(R1F,R2J,ZH,XB,YA),(R1
G,R2J,ZH,XB,YA),(R1H,R2J,ZH,XB,YA),(R1I,R2J,ZH,XB,Y
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,XB,YA),(R1M,R2J,ZH,XB,YA),(R1N,R2J,ZH,XB,YA),(R1O,
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2K,ZH,XB,YA),(R1G,R2K,ZH,XB,YA),(R1H,R2K,ZH,XB,YA)
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YA),(R1O,R2M,ZI,XB,YA),(R1P,R2M,ZI,XB,YA),(R1Q,R2M,ZI,XB,YA),(R1A,R2N,ZI,XB,YA),(R1B,R2N,ZI,XB,YA),(R1C,R2N,ZI,XB,YA),(R1D,R2N,ZI,XB,YA),(R1E,R2N,ZI,XB,YA),(R1F,R2N,ZI,XB,YA),(R1G,R2N,ZI,XB,YA),(R1H,R2N,ZI,XB,YA),(R1I,R2N,ZI,XB,YA),(R1J,R2N,ZI,XB,YA),(R1K,R2N,ZI,XB,YA),(R1L,R2N,ZI,XB,YA),(R1M,R2N,ZI,XB,YA),(R1N,R2N,ZI,XB,YA),(R1O,R2N,ZI,XB,YA),(R1P,R2N,ZI,XB,YA),(R1Q,R2N,ZI,XB,YA),(R1A,R2O,ZI,XB,YA),(R1B,R2O,ZI,XB,YA),(R1C,R2O,ZI,XB,YA),(R1D,R2O,ZI,XB,YA),(R1E,R2O,ZI,XB,YA),(R1F,R2O,ZI,XB,YA),(R1G,R2O,ZI,XB,YA),(R1H,R2O,ZI,XB,YA),(R1I,R2O,ZI,XB,YA),(R1J,R2O,ZI,XB,YA),(R1K,R2O,ZI,XB,YA),(R1L,R2O,ZI,XB,YA),(R1M,R2O,ZI,XB,YA),(R1N,R2O,ZI,XB,YA),(R1O,R2O,ZI,XB,YA),(R1P,R2O,ZI,XB,YA),(R1Q,R2O,ZI,XB,YA),(R1A,R2P,ZI,XB,YA),(R1B,R2P,ZI,XB,YA),(R1C,R2P,ZI,XB,YA),(R1D,R2P,ZI,XB,YA),(R1E,R2P,ZI,XB,YA),(R1F,R2P,ZI,XB,YA),(R1G,R2P,ZI,XB,YA),(R1H,R2P,ZI,XB,YA),(R1I,R2P,ZI,XB,YA),(R1J,R2P,ZI,XB,YA),(R1K,R2P,ZI,XB,YA),(R1L,R2P,ZI,XB,YA),(R1M,R2P,ZI,XB,YA),(R1N,R2P,ZI,XB,YA),(R1O,R2P,ZI,XB,YA),(R1P,R2P,ZI,XB,YA),(R1Q,R2P,ZI,XB,YA),(R1A,R2Q,ZI,XB,YA),(R1B,R2Q,ZI,XB,YA),(R1C,R2Q,ZI,XB,YA),(R1D,R2Q,ZI,XB,YA),(R1E,R2Q,ZI,XB,YA),(R1F,R2Q,ZI,XB,YA),(R1G,R2Q,ZI,XB,YA),(R1H,R2Q,ZI,XB,YA),(R1I,R2Q,ZI,XB,YA),(R1J,R2Q,ZI,XB,YA),(R1K,R2Q,ZI,XB,YA),(R1L,R2Q,ZI,

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K,R2G,ZJ,XB,YA),(R1L,R2G,ZJ,XB,YA),(R1M,R2G,ZJ,XB,Y
A),(R1N,R2G,ZJ,XB,YA),(R1O,R2G,ZJ,XB,YA),(R1P,R2G,ZJ,
XB,YA),(R1Q,R2G,ZJ,XB,YA),(R1A,R2H,ZJ,XB,YA),(R1B,R
2H,ZJ,XB,YA),(R1C,R2H,ZJ,XB,YA),(R1D,R2H,ZJ,XB,YA),(
R1E,R2H,ZJ,XB,YA),(R1F,R2H,ZJ,XB,YA),(R1G,R2H,ZJ,XB,

YA),(R1H,R2H,ZJ,XB,YA),(R1I,R2H,ZJ,XB,YA),(R1J,R2H,Z
J,XB,YA),(R1K,R2H,ZJ,XB,YA),(R1L,R2H,ZJ,XB,YA),(R1M,
R2H,ZJ,XB,YA),(R1N,R2H,ZJ,XB,YA),(R1O,R2H,ZJ,XB,YA)
,(R1P,R2H,ZJ,XB,YA),(R1Q,R2H,ZJ,XB,YA),(R1A,R2I,ZJ,X
B,YA),(R1B,R2I,ZJ,XB,YA),(R1C,R2I,ZJ,XB,YA),(R1D,R2I,
ZJ,XB,YA),(R1E,R2I,ZJ,XB,YA),(R1F,R2I,ZJ,XB,YA),(R1G,
R2I,ZJ,XB,YA),(R1H,R2I,ZJ,XB,YA),(R1I,R2I,ZJ,XB,YA),(
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,ZJ,XB,YA),(R1B,R2J,ZJ,XB,YA),(R1C,R2J,ZJ,XB,YA),(R1D
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J,ZJ,XB,YA),(R1P,R2J,ZJ,XB,YA),(R1Q,R2J,ZJ,XB,YA),(R1
A,R2K,ZJ,XB,YA),(R1B,R2K,ZJ,XB,YA),(R1C,R2K,ZJ,XB,Y
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,XB,YA),(R1G,R2K,ZJ,XB,YA),(R1H,R2K,ZJ,XB,YA),(R1I,R
2K,ZJ,XB,YA),(R1J,R2K,ZJ,XB,YA),(R1K,R2K,ZJ,XB,YA),(
R1L,R2K,ZJ,XB,YA),(R1M,R2K,ZJ,XB,YA),(R1N,R2K,ZJ,XB
,YA),(R1O,R2K,ZJ,XB,YA),(R1P,R2K,ZJ,XB,YA),(R1Q,R2K,
ZJ,XB,YA),(R1A,R2L,ZJ,XB,YA),(R1B,R2L,ZJ,XB,YA),(R1C
,R2L,ZJ,XB,YA),(R1D,R2L,ZJ,XB,YA),(R1E,R2L,ZJ,XB,YA)

,(R1F,R2L,ZJ,XB,YA),(R1G,R2L,ZJ,XB,YA),(R1H,R2L,ZJ,X
B,YA),(R1I,R2L,ZJ,XB,YA),(R1J,R2L,ZJ,XB,YA),(R1K,R2L,
ZJ,XB,YA),(R1L,R2L,ZJ,XB,YA),(R1M,R2L,ZJ,XB,YA),(R1
N,R2L,ZJ,XB,YA),(R1O,R2L,ZJ,XB,YA),(R1P,R2L,ZJ,XB,YA
),(R1Q,R2L,ZJ,XB,YA),(R1A,R2M,ZJ,XB,YA),(R1B,R2M,ZJ,
XB,YA),(R1C,R2M,ZJ,XB,YA),(R1D,R2M,ZJ,XB,YA),(R1E,R
2M,ZJ,XB,YA),(R1F,R2M,ZJ,XB,YA),(R1G,R2M,ZJ,XB,YA),(
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,YA),(R1K,R2M,ZJ,XB,YA),(R1L,R2M,ZJ,XB,YA),(R1M,R2
M,ZJ,XB,YA),(R1N,R2M,ZJ,XB,YA),(R1O,R2M,ZJ,XB,YA),(
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,YA),(R1B,R2N,ZJ,XB,YA),(R1C,R2N,ZJ,XB,YA),(R1D,R2N,
ZJ,XB,YA),(R1E,R2N,ZJ,XB,YA),(R1F,R2N,ZJ,XB,YA),(R1G
,R2N,ZJ,XB,YA),(R1H,R2N,ZJ,XB,YA),(R1I,R2N,ZJ,XB,YA)
,(R1J,R2N,ZJ,XB,YA),(R1K,R2N,ZJ,XB,YA),(R1L,R2N,ZJ,X
B,YA),(R1M,R2N,ZJ,XB,YA),(R1N,R2N,ZJ,XB,YA),(R1O,R2
N,ZJ,XB,YA),(R1P,R2N,ZJ,XB,YA),(R1Q,R2N,ZJ,XB,YA),(R
1A,R2O,ZJ,XB,YA),(R1B,R2O,ZJ,XB,YA),(R1C,R2O,ZJ,XB,
YA),(R1D,R2O,ZJ,XB,YA),(R1E,R2O,ZJ,XB,YA),(R1F,R2O,Z
J,XB,YA),(R1G,R2O,ZJ,XB,YA),(R1H,R2O,ZJ,XB,YA),(R1I,
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B,YA),(R1O,R2O,ZJ,XB,YA),(R1P,R2O,ZJ,XB,YA),(R1Q,R2
O,ZJ,XB,YA),(R1A,R2P,ZJ,XB,YA),(R1B,R2P,ZJ,XB,YA),(R

1C,R2P,ZJ,XB,YA),(R1D,R2P,ZJ,XB,YA),(R1E,R2P,ZJ,XB,Y
A),(R1F,R2P,ZJ,XB,YA),(R1G,R2P,ZJ,XB,YA),(R1H,R2P,ZJ,
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,(R1Q,R2P,ZJ,XB,YA),(R1A,R2Q,ZJ,XB,YA),(R1B,R2Q,ZJ,X
B,YA),(R1C,R2Q,ZJ,XB,YA),(R1D,R2Q,ZJ,XB,YA),(R1E,R2
Q,ZJ,XB,YA),(R1F,R2Q,ZJ,XB,YA),(R1G,R2Q,ZJ,XB,YA),(R
1H,R2Q,ZJ,XB,YA),(R1I,R2Q,ZJ,XB,YA),(R1J,R2Q,ZJ,XB,Y
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XB,YA),(R1E,R2A,ZK,XB,YA),(R1F,R2A,ZK,XB,YA),(R1G,R
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B,YA),(R1P,R2F,ZK,XB,YA),(R1Q,R2F,ZK,XB,YA),(R1A,R2
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B,YA),(R1G,R2J,ZK,XB,YA),(R1H,R2J,ZK,XB,YA),(R1I,R2J

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B,YA),(R1F,R2H,ZN,XB,YA),(R1G,R2H,ZN,XB,YA),(R1H,R2

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R,XB,YA),(R1M,R2H,ZR,XB,YA),(R1N,R2H,ZR,XB,YA),(R1O,R2H,ZR,XB,YA),(R1P,R2H,ZR,XB,YA),(R1Q,R2H,ZR,XB,YA),(R1A,R2I,ZR,XB,YA),(R1B,R2I,ZR,XB,YA),(R1C,R2I,ZR,XB,YA),(R1D,R2I,ZR,XB,YA),(R1E,R2I,ZR,XB,YA),(R1F,R2I,ZR,XB,YA),(R1G,R2I,ZR,XB,YA),(R1H,R2I,ZR,XB,YA),(R1I,R2I,ZR,XB,YA),(R1J,R2I,ZR,XB,YA),(R1K,R2I,ZR,XB,YA),(R1L,R2I,ZR,XB,YA),(R1M,R2I,ZR,XB,YA),(R1N,R2I,ZR,XB,YA),(R1O,R2I,ZR,XB,YA),(R1P,R2I,ZR,XB,YA),(R1Q,R2I,ZR,XB,YA),(R1A,R2J,ZR,XB,YA),(R1B,R2J,ZR,XB,YA),(R1C,R2J,ZR,XB,YA),(R1D,R2J,ZR,XB,YA),(R1E,R2J,ZR,XB,YA),(R1F,R2J,ZR,XB,YA),(R1G,R2J,ZR,XB,YA),(R1H,R2J,ZR,XB,YA),(R1I,R2J,ZR,XB,YA),(R1J,R2J,ZR,XB,YA),(R1K,R2J,ZR,XB,YA),(R1L,R2J,ZR,XB,YA),(R1M,R2J,ZR,XB,YA),(R1N,R2J,ZR,XB,YA),(R1O,R2J,ZR,XB,YA),(R1P,R2J,ZR,XB,YA),(R1Q,R2J,ZR,XB,YA),(R1A,R2K,ZR,XB,YA),(R1B,R2K,ZR,XB,YA),(R1C,R2K,ZR,XB,YA),(R1D,R2K,ZR,XB,YA),(R1E,R2K,ZR,XB,YA),(R1F,R2K,ZR,XB,YA),(R1G,R2K,ZR,XB,YA),(R1H,R2K,ZR,XB,YA),(R1I,R2K,ZR,XB,YA),(R1J,R2K,ZR,XB,YA),(R1K,R2K,ZR,XB,YA),(R1L,R2K,ZR,XB,YA),(R1M,R2K,ZR,XB,YA),(R1N,R2K,ZR,XB,YA),(R1O,R2K,ZR,XB,YA),(R1P,R2K,ZR,XB,YA),(R1Q,R2K,ZR,XB,YA),(R1A,R2L,ZR,XB,YA),(R1B,R2L,ZR,XB,YA),(R1C,R2L,ZR,XB,YA),(R1D,R2L,ZR,XB,YA),(R1E,R2L,ZR,XB,YA),(R1F,R2L,ZR,XB,YA),(R1G,R2L,ZR,XB,YA),(R1H,R2L,ZR,XB,YA),(R1I,R2

L,ZR,XB,YA),(R1J,R2L,ZR,XB,YA),(R1K,R2L,ZR,XB,YA),(R1L,R2L,ZR,XB,YA),(R1M,R2L,ZR,XB,YA),(R1N,R2L,ZR,XB,YA),(R1O,R2L,ZR,XB,YA),(R1P,R2L,ZR,XB,YA),(R1Q,R2L,ZR,XB,YA),(R1A,R2M,ZR,XB,YA),(R1B,R2M,ZR,XB,YA),(R1C,R2M,ZR,XB,YA),(R1D,R2M,ZR,XB,YA),(R1E,R2M,ZR,XB,YA),(R1F,R2M,ZR,XB,YA),(R1G,R2M,ZR,XB,YA),(R1H,R2M,ZR,XB,YA),(R1I,R2M,ZR,XB,YA),(R1J,R2M,ZR,XB,YA),(R1K,R2M,ZR,XB,YA),(R1L,R2M,ZR,XB,YA),(R1M,R2M,ZR,XB,YA),(R1N,R2M,ZR,XB,YA),(R1O,R2M,ZR,XB,YA),(R1P,R2M,ZR,XB,YA),(R1Q,R2M,ZR,XB,YA),(R1A,R2N,ZR,XB,YA),(R1B,R2N,ZR,XB,YA),(R1C,R2N,ZR,XB,YA),(R1D,R2N,ZR,XB,YA),(R1E,R2N,ZR,XB,YA),(R1F,R2N,ZR,XB,YA),(R1G,R2N,ZR,XB,YA),(R1H,R2N,ZR,XB,YA),(R1I,R2N,ZR,XB,YA),(R1J,R2N,ZR,XB,YA),(R1K,R2N,ZR,XB,YA),(R1L,R2N,ZR,XB,YA),(R1M,R2N,ZR,XB,YA),(R1N,R2N,ZR,XB,YA),(R1O,R2N,ZR,XB,YA),(R1P,R2N,ZR,XB,YA),(R1Q,R2N,ZR,XB,YA),(R1A,R2O,ZR,XB,YA),(R1B,R2O,ZR,XB,YA),(R1C,R2O,ZR,XB,YA),(R1D,R2O,ZR,XB,YA),(R1E,R2O,ZR,XB,YA),(R1F,R2O,ZR,XB,YA),(R1G,R2O,ZR,XB,YA),(R1H,R2O,ZR,XB,YA),(R1I,R2O,ZR,XB,YA),(R1J,R2O,ZR,XB,YA),(R1K,R2O,ZR,XB,YA),(R1L,R2O,ZR,XB,YA),(R1M,R2O,ZR,XB,YA),(R1N,R2O,ZR,XB,YA),(R1O,R2O,ZR,XB,YA),(R1P,R2O,ZR,XB,YA),(R1Q,R2O,ZR,XB,YA),(R1A,R2P,ZR,XB,YA),(R1B,R2P,ZR,XB,YA),(R1C,R2P,ZR,XB,YA),(R1D,R2P,ZR,XB,YA),(R1

E,R2P,ZR,XB,YA),(R1F,R2P,ZR,XB,YA),(R1G,R2P,ZR,XB,Y
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XB,YA),(R1K,R2P,ZR,XB,YA),(R1L,R2P,ZR,XB,YA),(R1M,R
2P,ZR,XB,YA),(R1N,R2P,ZR,XB,YA),(R1O,R2P,ZR,XB,YA),(
R1P,R2P,ZR,XB,YA),(R1Q,R2P,ZR,XB,YA),(R1A,R2Q,ZR,XB
,YA),(R1B,R2Q,ZR,XB,YA),(R1C,R2Q,ZR,XB,YA),(R1D,R2Q
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1G,R2Q,ZR,XB,YA),(R1H,R2Q,ZR,XB,YA),(R1I,R2Q,ZR,XB,
YA),(R1J,R2Q,ZR,XB,YA),(R1K,R2Q,ZR,XB,YA),(R1L,R2Q,
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F,R2A,ZS,XB,YA),(R1G,R2A,ZS,XB,YA),(R1H,R2A,ZS,XB,Y
A),(R1I,R2A,ZS,XB,YA),(R1J,R2A,ZS,XB,YA),(R1K,R2A,ZS
,XB,YA),(R1L,R2A,ZS,XB,YA),(R1M,R2A,ZS,XB,YA),(R1N,
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,(R1Q,R2A,ZS,XB,YA),(R1A,R2B,ZS,XB,YA),(R1B,R2B,ZS,
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YA),(R1K,R2B,ZS,XB,YA),(R1L,R2B,ZS,XB,YA),(R1M,R2B,
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S,XB,YA),(R1E,R2C,ZS,XB,YA),(R1F,R2C,ZS,XB,YA),(R1G,
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B,YA),(R1M,R2C,ZS,XB,YA),(R1N,R2C,ZS,XB,YA),(R1O,R2
C,ZS,XB,YA),(R1P,R2C,ZS,XB,YA),(R1Q,R2C,ZS,XB,YA),(
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D,ZS,XB,YA),(R1G,R2D,ZS,XB,YA),(R1H,R2D,ZS,XB,YA),(
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Q,R2D,ZS,XB,YA),(R1A,R2E,ZS,XB,YA),(R1B,R2E,ZS,XB,Y
A),(R1C,R2E,ZS,XB,YA),(R1D,R2E,ZS,XB,YA),(R1E,R2E,Z
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B,YA),(R1N,R2E,ZS,XB,YA),(R1O,R2E,ZS,XB,YA),(R1P,R2
E,ZS,XB,YA),(R1Q,R2E,ZS,XB,YA),(R1A,R2F,ZS,XB,YA),(R
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F,ZS,XB,YA),(R1K,R2F,ZS,XB,YA),(R1L,R2F,ZS,XB,YA),(R
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YA),(R1P,R2F,ZS,XB,YA),(R1Q,R2F,ZS,XB,YA),(R1A,R2G,Z
S,XB,YA),(R1B,R2G,ZS,XB,YA),(R1C,R2G,ZS,XB,YA),(R1D,
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,ZS,XB,YA),(R1M,R2G,ZS,XB,YA),(R1N,R2G,ZS,XB,YA),(R
1O,R2G,ZS,XB,YA),(R1P,R2G,ZS,XB,YA),(R1Q,R2G,ZS,XB,
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F,R2H,ZS,XB,YA),(R1G,R2H,ZS,XB,YA),(R1H,R2H,ZS,XB,Y
A),(R1I,R2H,ZS,XB,YA),(R1J,R2H,ZS,XB,YA),(R1K,R2H,ZS
,XB,YA),(R1L,R2H,ZS,XB,YA),(R1M,R2H,ZS,XB,YA),(R1N,
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,(R1Q,R2H,ZS,XB,YA),(R1A,R2I,ZS,XB,YA),(R1B,R2I,ZS,X
B,YA),(R1C,R2I,ZS,XB,YA),(R1D,R2I,ZS,XB,YA),(R1E,R2I,
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YA),(R1N,R2I,ZS,XB,YA),(R1O,R2I,ZS,XB,YA),(R1P,R2I,ZS
,XB,YA),(R1Q,R2I,ZS,XB,YA),(R1A,R2J,ZS,XB,YA),(R1B,R
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YA),(R1H,R2J,ZS,XB,YA),(R1I,R2J,ZS,XB,YA),(R1J,R2J,ZS
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2J,ZS,XB,YA),(R1N,R2J,ZS,XB,YA),(R1O,R2J,ZS,XB,YA),(R1P,R2J,ZS,XB,YA),(R1Q,R2J,ZS,XB,YA),(R1A,R2K,ZS,XB,YA),(R1B,R2K,ZS,XB,YA),(R1C,R2K,ZS,XB,YA),(R1D,R2K,ZS,XB,YA),(R1E,R2K,ZS,XB,YA),(R1F,R2K,ZS,XB,YA),(R1G,R2K,ZS,XB,YA),(R1H,R2K,ZS,XB,YA),(R1I,R2K,ZS,XB,YA),(R1J,R2K,ZS,XB,YA),(R1K,R2K,ZS,XB,YA),(R1L,R2K,ZS,XB,YA),(R1M,R2K,ZS,XB,YA),(R1N,R2K,ZS,XB,YA),(R1O,R2K,ZS,XB,YA),(R1P,R2K,ZS,XB,YA),(R1Q,R2K,ZS,XB,YA),(R1A,R2L,ZS,XB,YA),(R1B,R2L,ZS,XB,YA),(R1C,R2L,ZS,XB,YA),(R1D,R2L,ZS,XB,YA),(R1E,R2L,ZS,XB,YA),(R1F,R2L,ZS,XB,YA),(R1G,R2L,ZS,XB,YA),(R1H,R2L,ZS,XB,YA),(R1I,R2L,ZS,XB,YA),(R1J,R2L,ZS,XB,YA),(R1K,R2L,ZS,XB,YA),(R1L,R2L,ZS,XB,YA),(R1M,R2L,ZS,XB,YA),(R1N,R2L,ZS,XB,YA),(R1O,R2L,ZS,XB,YA),(R1P,R2L,ZS,XB,YA),(R1Q,R2L,ZS,XB,YA),(R1A,R2M,ZS,XB,YA),(R1B,R2M,ZS,XB,YA),(R1C,R2M,ZS,XB,YA),(R1D,R2M,ZS,XB,YA),(R1E,R2M,ZS,XB,YA),(R1F,R2M,ZS,XB,YA),(R1G,R2M,ZS,XB,YA),(R1H,R2M,ZS,XB,YA),(R1I,R2M,ZS,XB,YA),(R1J,R2M,ZS,XB,YA),(R1K,R2M,ZS,XB,YA),(R1L,R2M,ZS,XB,YA),(R1M,R2M,ZS,XB,YA),(R1N,R2M,ZS,XB,YA),(R1O,R2M,ZS,XB,YA),(R1P,R2M,ZS,XB,YA),(R1Q,R2M,ZS,XB,YA),(R1A,R2N,ZS,XB,YA),(R1B,R2N,ZS,XB,YA),(R1C,R2N,ZS,XB,YA),(R1D,R2N,ZS,XB,YA),(R1E,R2N,ZS,XB,YA),(R1F,R2N,ZS,XB,YA),(R1G,R2N,ZS,XB,YA),(R1H,R2N,ZS,XB,YA),(R1I,R2N,ZS,XB

,YA),(R1J,R2N,ZS,XB,YA),(R1K,R2N,ZS,XB,YA),(R1L,R2N,ZS,XB,YA),(R1M,R2N,ZS,XB,YA),(R1N,R2N,ZS,XB,YA),(R1O,R2N,ZS,XB,YA),(R1P,R2N,ZS,XB,YA),(R1Q,R2N,ZS,XB,YA),(R1A,R2O,ZS,XB,YA),(R1B,R2O,ZS,XB,YA),(R1C,R2O,ZS,XB,YA),(R1D,R2O,ZS,XB,YA),(R1E,R2O,ZS,XB,YA),(R1F,R2O,ZS,XB,YA),(R1G,R2O,ZS,XB,YA),(R1H,R2O,ZS,XB,YA),(R1I,R2O,ZS,XB,YA),(R1J,R2O,ZS,XB,YA),(R1K,R2O,ZS,XB,YA),(R1L,R2O,ZS,XB,YA),(R1M,R2O,ZS,XB,YA),(R1N,R2O,ZS,XB,YA),(R1O,R2O,ZS,XB,YA),(R1P,R2O,ZS,XB,YA),(R1Q,R2O,ZS,XB,YA),(R1A,R2P,ZS,XB,YA),(R1B,R2P,ZS,XB,YA),(R1C,R2P,ZS,XB,YA),(R1D,R2P,ZS,XB,YA),(R1E,R2P,ZS,XB,YA),(R1F,R2P,ZS,XB,YA),(R1G,R2P,ZS,XB,YA),(R1H,R2P,ZS,XB,YA),(R1I,R2P,ZS,XB,YA),(R1J,R2P,ZS,XB,YA),(R1K,R2P,ZS,XB,YA),(R1L,R2P,ZS,XB,YA),(R1M,R2P,ZS,XB,YA),(R1N,R2P,ZS,XB,YA),(R1O,R2P,ZS,XB,YA),(R1P,R2P,ZS,XB,YA),(R1Q,R2P,ZS,XB,YA),(R1A,R2Q,ZS,XB,YA),(R1B,R2Q,ZS,XB,YA),(R1C,R2Q,ZS,XB,YA),(R1D,R2Q,ZS,XB,YA),(R1E,R2Q,ZS,XB,YA),(R1F,R2Q,ZS,XB,YA),(R1G,R2Q,ZS,XB,YA),(R1H,R2Q,ZS,XB,YA),(R1I,R2Q,ZS,XB,YA),(R1J,R2Q,ZS,XB,YA),(R1K,R2Q,ZS,XB,YA),(R1L,R2Q,ZS,XB,YA),(R1M,R2Q,ZS,XB,YA),(R1N,R2Q,ZS,XB,YA),(R1O,R2Q,ZS,XB,YA),(R1P,R2Q,ZS,XB,YA),(R1Q,R2Q,ZS,XB,YA),(R1A,R2A,ZT,XB,YA),(R1B,R2A,ZT,XB,YA),(R1C,R2A,ZT,XB,YA),(R1D,R2A,ZT,XB,YA),(R1E,R2A,ZT,XB,YA),(R1F,R2A,ZT,

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E,ZT,XB,YA),(R1D,R2E,ZT,XB,YA),(R1E,R2E,ZT,XB,YA),(R1F,R2E,ZT,XB,YA),(R1G,R2E,ZT,XB,YA),(R1H,R2E,ZT,XB,YA),(R1I,R2E,ZT,XB,YA),(R1J,R2E,ZT,XB,YA),(R1K,R2E,ZT,XB,YA),(R1L,R2E,ZT,XB,YA),(R1M,R2E,ZT,XB,YA),(R1N,R2E,ZT,XB,YA),(R1O,R2E,ZT,XB,YA),(R1P,R2E,ZT,XB,YA),(R1Q,R2E,ZT,XB,YA),(R1A,R2F,ZT,XB,YA),(R1B,R2F,ZT,XB,YA),(R1C,R2F,ZT,XB,YA),(R1D,R2F,ZT,XB,YA),(R1E,R2F,ZT,XB,YA),(R1F,R2F,ZT,XB,YA),(R1G,R2F,ZT,XB,YA),(R1H,R2F,ZT,XB,YA),(R1I,R2F,ZT,XB,YA),(R1J,R2F,ZT,XB,YA),(R1K,R2F,ZT,XB,YA),(R1L,R2F,ZT,XB,YA),(R1M,R2F,ZT,XB,YA),(R1N,R2F,ZT,XB,YA),(R1O,R2F,ZT,XB,YA),(R1P,R2F,ZT,XB,YA),(R1Q,R2F,ZT,XB,YA),(R1A,R2G,ZT,XB,YA),(R1B,R2G,ZT,XB,YA),(R1C,R2G,ZT,XB,YA),(R1D,R2G,ZT,XB,YA),(R1E,R2G,ZT,XB,YA),(R1F,R2G,ZT,XB,YA),(R1G,R2G,ZT,XB,YA),(R1H,R2G,ZT,XB,YA),(R1I,R2G,ZT,XB,YA),(R1J,R2G,ZT,XB,YA),(R1K,R2G,ZT,XB,YA),(R1L,R2G,ZT,XB,YA),(R1M,R2G,ZT,XB,YA),(R1N,R2G,ZT,XB,YA),(R1O,R2G,ZT,XB,YA),(R1P,R2G,ZT,XB,YA),(R1Q,R2G,ZT,XB,YA),(R1A,R2H,ZT,XB,YA),(R1B,R2H,ZT,XB,YA),(R1C,R2H,ZT,XB,YA),(R1D,R2H,ZT,XB,YA),(R1E,R2H,ZT,XB,YA),(R1F,R2H,ZT,XB,YA),(R1G,R2H,ZT,XB,YA),(R1H,R2H,ZT,XB,YA),(R1I,R2H,ZT,XB,YA),(R1J,R2H,ZT,XB,YA),(R1K,R2H,ZT,XB,YA),(R1L,R2H,ZT,XB,YA),(R1M,R2H,ZT,XB,YA),(R1N,R2H,ZT,XB,YA),(R1O,R2H,ZT,XB,YA),(R1P,R2H,ZT,XB,YA),(R1Q,R2

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,(R1O,R2L,ZT,XB,YA),(R1P,R2L,ZT,XB,YA),(R1Q,R2L,ZT,X
B,YA),(R1A,R2M,ZT,XB,YA),(R1B,R2M,ZT,XB,YA),(R1C,R2
M,ZT,XB,YA),(R1D,R2M,ZT,XB,YA),(R1E,R2M,ZT,XB,YA),(
R1F,R2M,ZT,XB,YA),(R1G,R2M,ZT,XB,YA),(R1H,R2M,ZT,X
B,YA),(R1I,R2M,ZT,XB,YA),(R1J,R2M,ZT,XB,YA),(R1K,R2
M,ZT,XB,YA),(R1L,R2M,ZT,XB,YA),(R1M,R2M,ZT,XB,YA),
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XB,YA),(R1Q,R2M,ZT,XB,YA),(R1A,R2N,ZT,XB,YA),(R1B,
R2N,ZT,XB,YA),(R1C,R2N,ZT,XB,YA),(R1D,R2N,ZT,XB,YA
),(R1E,R2N,ZT,XB,YA),(R1F,R2N,ZT,XB,YA),(R1G,R2N,ZT,
XB,YA),(R1H,R2N,ZT,XB,YA),(R1I,R2N,ZT,XB,YA),(R1J,R2
N,ZT,XB,YA),(R1K,R2N,ZT,XB,YA),(R1L,R2N,ZT,XB,YA),(
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B,YA),(R1P,R2N,ZT,XB,YA),(R1Q,R2N,ZT,XB,YA),(R1A,R2
O,ZT,XB,YA),(R1B,R2O,ZT,XB,YA),(R1C,R2O,ZT,XB,YA),(
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,YA),(R1G,R2O,ZT,XB,YA),(R1H,R2O,ZT,XB,YA),(R1I,R2O,
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L,R2O,ZT,XB,YA),(R1M,R2O,ZT,XB,YA),(R1N,R2O,ZT,XB,
YA),(R1O,R2O,ZT,XB,YA),(R1P,R2O,ZT,XB,YA),(R1Q,R2O,
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,R2P,ZT,XB,YA),(R1D,R2P,ZT,XB,YA),(R1E,R2P,ZT,XB,YA)
,(R1F,R2P,ZT,XB,YA),(R1G,R2P,ZT,XB,YA),(R1H,R2P,ZT,X
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,R2A,ZC,XA,YB),(R1K,R2A,ZC,XA,YB),(R1L,R2A,ZC,XA,Y
B),(R1M,R2A,ZC,XA,YB),(R1N,R2A,ZC,XA,YB),(R1O,R2A,
ZC,XA,YB),(R1P,R2A,ZC,XA,YB),(R1Q,R2A,ZC,XA,YB),(R
1A,R2B,ZC,XA,YB),(R1B,R2B,ZC,XA,YB),(R1C,R2B,ZC,XA
,YB),(R1D,R2B,ZC,XA,YB),(R1E,R2B,ZC,XA,YB),(R1F,R2B
,ZC,XA,YB),(R1G,R2B,ZC,XA,YB),(R1H,R2B,ZC,XA,YB),(R
1I,R2B,ZC,XA,YB),(R1J,R2B,ZC,XA,YB),(R1K,R2B,ZC,XA,
YB),(R1L,R2B,ZC,XA,YB),(R1M,R2B,ZC,XA,YB),(R1N,R2B
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1Q,R2B,ZC,XA,YB),(R1A,R2C,ZC,XA,YB),(R1B,R2C,ZC,XA
,YB),(R1C,R2C,ZC,XA,YB),(R1D,R2C,ZC,XA,YB),(R1E,R2C
,ZC,XA,YB),(R1F,R2C,ZC,XA,YB),(R1G,R2C,ZC,XA,YB),(R
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,ZC,XA,YB),(R1N,R2C,ZC,XA,YB),(R1O,R2C,ZC,XA,YB),(
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A,YB),(R1B,R2D,ZC,XA,YB),(R1C,R2D,ZC,XA,YB),(R1D,R
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,(R1G,R2D,ZC,XA,YB),(R1H,R2D,ZC,XA,YB),(R1I,R2D,ZC,
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B),(R1O,R2D,ZC,XA,YB),(R1P,R2D,ZC,XA,YB),(R1Q,R2D,Z

C,XA,YB),(R1A,R2E,ZC,XA,YB),(R1B,R2E,ZC,XA,YB),(R1C,R2E,ZC,XA,YB),(R1D,R2E,ZC,XA,YB),(R1E,R2E,ZC,XA,YB),(R1F,R2E,ZC,XA,YB),(R1G,R2E,ZC,XA,YB),(R1H,R2E,ZC,XA,YB),(R1I,R2E,ZC,XA,YB),(R1J,R2E,ZC,XA,YB),(R1K,R2E,ZC,XA,YB),(R1L,R2E,ZC,XA,YB),(R1M,R2E,ZC,XA,YB),(R1N,R2E,ZC,XA,YB),(R1O,R2E,ZC,XA,YB),(R1P,R2E,ZC,XA,YB),(R1Q,R2E,ZC,XA,YB),(R1A,R2F,ZC,XA,YB),(R1B,R2F,ZC,XA,YB),(R1C,R2F,ZC,XA,YB),(R1D,R2F,ZC,XA,YB),(R1E,R2F,ZC,XA,YB),(R1F,R2F,ZC,XA,YB),(R1G,R2F,ZC,XA,YB),(R1H,R2F,ZC,XA,YB),(R1I,R2F,ZC,XA,YB),(R1J,R2F,ZC,XA,YB),(R1K,R2F,ZC,XA,YB),(R1L,R2F,ZC,XA,YB),(R1M,R2F,ZC,XA,YB),(R1N,R2F,ZC,XA,YB),(R1O,R2F,ZC,XA,YB),(R1P,R2F,ZC,XA,YB),(R1Q,R2F,ZC,XA,YB),(R1A,R2G,ZC,XA,YB),(R1B,R2G,ZC,XA,YB),(R1C,R2G,ZC,XA,YB),(R1D,R2G,ZC,XA,YB),(R1E,R2G,ZC,XA,YB),(R1F,R2G,ZC,XA,YB),(R1G,R2G,ZC,XA,YB),(R1H,R2G,ZC,XA,YB),(R1I,R2G,ZC,XA,YB),(R1J,R2G,ZC,XA,YB),(R1K,R2G,ZC,XA,YB),(R1L,R2G,ZC,XA,YB),(R1M,R2G,ZC,XA,YB),(R1N,R2G,ZC,XA,YB),(R1O,R2G,ZC,XA,YB),(R1P,R2G,ZC,XA,YB),(R1Q,R2G,ZC,XA,YB),(R1A,R2H,ZC,XA,YB),(R1B,R2H,ZC,XA,YB),(R1C,R2H,ZC,XA,YB),(R1D,R2H,ZC,XA,YB),(R1E,R2H,ZC,XA,YB),(R1F,R2H,ZC,XA,YB),(R1G,R2H,ZC,XA,YB),(R1H,R2H,ZC,XA,YB),(R1I,R2H,ZC,XA,YB),(R1J,R2H,ZC,XA,YB),(R1K,R2H,ZC,XA,YB),(R1L,R2H,ZC,XA,YB),(R1M,R2H,Z

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A,YB),(R1D,R2C,ZD,XA,YB),(R1E,R2C,ZD,XA,YB),(R1F,R2
C,ZD,XA,YB),(R1G,R2C,ZD,XA,YB),(R1H,R2C,ZD,XA,YB),
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G,XA,YB),(R1Q,R2N,ZG,XA,YB),(R1A,R2O,ZG,XA,YB),(R1
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YB),(R1E,R2O,ZG,XA,YB),(R1F,R2O,ZG,XA,YB),(R1G,R2O,
ZG,XA,YB),(R1H,R2O,ZG,XA,YB),(R1I,R2O,ZG,XA,YB),(R1
J,R2O,ZG,XA,YB),(R1K,R2O,ZG,XA,YB),(R1L,R2O,ZG,XA,
YB),(R1M,R2O,ZG,XA,YB),(R1N,R2O,ZG,XA,YB),(R1O,R2O
,ZG,XA,YB),(R1P,R2O,ZG,XA,YB),(R1Q,R2O,ZG,XA,YB),(R
1A,R2P,ZG,XA,YB),(R1B,R2P,ZG,XA,YB),(R1C,R2P,ZG,XA,

YB),(R1D,R2P,ZG,XA,YB),(R1E,R2P,ZG,XA,YB),(R1F,R2P,Z
G,XA,YB),(R1G,R2P,ZG,XA,YB),(R1H,R2P,ZG,XA,YB),(R1I,
R2P,ZG,XA,YB),(R1J,R2P,ZG,XA,YB),(R1K,R2P,ZG,XA,YB),
(R1L,R2P,ZG,XA,YB),(R1M,R2P,ZG,XA,YB),(R1N,R2P,ZG,X
A,YB),(R1O,R2P,ZG,XA,YB),(R1P,R2P,ZG,XA,YB),(R1Q,R2
P,ZG,XA,YB),(R1A,R2Q,ZG,XA,YB),(R1B,R2Q,ZG,XA,YB),(
R1C,R2Q,ZG,XA,YB),(R1D,R2Q,ZG,XA,YB),(R1E,R2Q,ZG,X
A,YB),(R1F,R2Q,ZG,XA,YB),(R1G,R2Q,ZG,XA,YB),(R1H,R2
Q,ZG,XA,YB),(R1I,R2Q,ZG,XA,YB),(R1J,R2Q,ZG,XA,YB),(
R1K,R2Q,ZG,XA,YB),(R1L,R2Q,ZG,XA,YB),(R1M,R2Q,ZG,X
A,YB),(R1N,R2Q,ZG,XA,YB),(R1O,R2Q,ZG,XA,YB),(R1P,R2
Q,ZG,XA,YB),(R1Q,R2Q,ZG,XA,YB),(R1A,R2A,ZH,XA,YB),
(R1B,R2A,ZH,XA,YB),(R1C,R2A,ZH,XA,YB),(R1D,R2A,ZH,
XA,YB),(R1E,R2A,ZH,XA,YB),(R1F,R2A,ZH,XA,YB),(R1G,
R2A,ZH,XA,YB),(R1H,R2A,ZH,XA,YB),(R1I,R2A,ZH,XA,Y
B),(R1J,R2A,ZH,XA,YB),(R1K,R2A,ZH,XA,YB),(R1L,R2A,Z
H,XA,YB),(R1M,R2A,ZH,XA,YB),(R1N,R2A,ZH,XA,YB),(R1
O,R2A,ZH,XA,YB),(R1P,R2A,ZH,XA,YB),(R1Q,R2A,ZH,XA,
YB),(R1A,R2B,ZH,XA,YB),(R1B,R2B,ZH,XA,YB),(R1C,R2B
,ZH,XA,YB),(R1D,R2B,ZH,XA,YB),(R1E,R2B,ZH,XA,YB),(
R1F,R2B,ZH,XA,YB),(R1G,R2B,ZH,XA,YB),(R1H,R2B,ZH,X
A,YB),(R1I,R2B,ZH,XA,YB),(R1J,R2B,ZH,XA,YB),(R1K,R2
B,ZH,XA,YB),(R1L,R2B,ZH,XA,YB),(R1M,R2B,ZH,XA,YB),
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XA,YB),(R1Q,R2B,ZH,XA,YB),(R1A,R2C,ZH,XA,YB),(R1B,R2C,ZH,XA,YB),(R1C,R2C,ZH,XA,YB),(R1D,R2C,ZH,XA,YB),(R1E,R2C,ZH,XA,YB),(R1F,R2C,ZH,XA,YB),(R1G,R2C,ZH,XA,YB),(R1H,R2C,ZH,XA,YB),(R1I,R2C,ZH,XA,YB),(R1J,R2C,ZH,XA,YB),(R1K,R2C,ZH,XA,YB),(R1L,R2C,ZH,XA,YB),(R1M,R2C,ZH,XA,YB),(R1N,R2C,ZH,XA,YB),(R1O,R2C,ZH,XA,YB),(R1P,R2C,ZH,XA,YB),(R1Q,R2C,ZH,XA,YB),(R1A,R2D,ZH,XA,YB),(R1B,R2D,ZH,XA,YB),(R1C,R2D,ZH,XA,YB),(R1D,R2D,ZH,XA,YB),(R1E,R2D,ZH,XA,YB),(R1F,R2D,ZH,XA,YB),(R1G,R2D,ZH,XA,YB),(R1H,R2D,ZH,XA,YB),(R1I,R2D,ZH,XA,YB),(R1J,R2D,ZH,XA,YB),(R1K,R2D,ZH,XA,YB),(R1L,R2D,ZH,XA,YB),(R1M,R2D,ZH,XA,YB),(R1N,R2D,ZH,XA,YB),(R1O,R2D,ZH,XA,YB),(R1P,R2D,ZH,XA,YB),(R1Q,R2D,ZH,XA,YB),(R1A,R2E,ZH,XA,YB),(R1B,R2E,ZH,XA,YB),(R1C,R2E,ZH,XA,YB),(R1D,R2E,ZH,XA,YB),(R1E,R2E,ZH,XA,YB),(R1F,R2E,ZH,XA,YB),(R1G,R2E,ZH,XA,YB),(R1H,R2E,ZH,XA,YB),(R1I,R2E,ZH,XA,YB),(R1J,R2E,ZH,XA,YB),(R1K,R2E,ZH,XA,YB),(R1L,R2E,ZH,XA,YB),(R1M,R2E,ZH,XA,YB),(R1N,R2E,ZH,XA,YB),(R1O,R2E,ZH,XA,YB),(R1P,R2E,ZH,XA,YB),(R1Q,R2E,ZH,XA,YB),(R1A,R2F,ZH,XA,YB),(R1B,R2F,ZH,XA,YB),(R1C,R2F,ZH,XA,YB),(R1D,R2F,ZH,XA,YB),(R1E,R2F,ZH,XA,YB),(R1F,R2F,ZH,XA,YB),(R1G,R2F,ZH,XA,YB),(R1H,R2F,ZH,XA,YB),(R1I,R2F,ZH,XA,YB),(R1J,R2F,ZH,XA,YB),(R1K,R2F,ZH,XA,YB),(

R1L,R2F,ZH,XA,YB),(R1M,R2F,ZH,XA,YB),(R1N,R2F,ZH,X
A,YB),(R1O,R2F,ZH,XA,YB),(R1P,R2F,ZH,XA,YB),(R1Q,R2
F,ZH,XA,YB),(R1A,R2G,ZH,XA,YB),(R1B,R2G,ZH,XA,YB),(
R1C,R2G,ZH,XA,YB),(R1D,R2G,ZH,XA,YB),(R1E,R2G,ZH,X
A,YB),(R1F,R2G,ZH,XA,YB),(R1G,R2G,ZH,XA,YB),(R1H,R2
G,ZH,XA,YB),(R1I,R2G,ZH,XA,YB),(R1J,R2G,ZH,XA,YB),(
R1K,R2G,ZH,XA,YB),(R1L,R2G,ZH,XA,YB),(R1M,R2G,ZH,X
A,YB),(R1N,R2G,ZH,XA,YB),(R1O,R2G,ZH,XA,YB),(R1P,R2
G,ZH,XA,YB),(R1Q,R2G,ZH,XA,YB),(R1A,R2H,ZH,XA,YB),
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XA,YB),(R1E,R2H,ZH,XA,YB),(R1F,R2H,ZH,XA,YB),(R1G,
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B),(R1J,R2H,ZH,XA,YB),(R1K,R2H,ZH,XA,YB),(R1L,R2H,Z
H,XA,YB),(R1M,R2H,ZH,XA,YB),(R1N,R2H,ZH,XA,YB),(R1
O,R2H,ZH,XA,YB),(R1P,R2H,ZH,XA,YB),(R1Q,R2H,ZH,XA,
YB),(R1A,R2I,ZH,XA,YB),(R1B,R2I,ZH,XA,YB),(R1C,R2I,Z
H,XA,YB),(R1D,R2I,ZH,XA,YB),(R1E,R2I,ZH,XA,YB),(R1F
,R2I,ZH,XA,YB),(R1G,R2I,ZH,XA,YB),(R1H,R2I,ZH,XA,YB
),(R1I,R2I,ZH,XA,YB),(R1J,R2I,ZH,XA,YB),(R1K,R2I,ZH,X
A,YB),(R1L,R2I,ZH,XA,YB),(R1M,R2I,ZH,XA,YB),(R1N,R2
I,ZH,XA,YB),(R1O,R2I,ZH,XA,YB),(R1P,R2I,ZH,XA,YB),(R
1Q,R2I,ZH,XA,YB),(R1A,R2J,ZH,XA,YB),(R1B,R2J,ZH,XA,
YB),(R1C,R2J,ZH,XA,YB),(R1D,R2J,ZH,XA,YB),(R1E,R2J,
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B),(R1K,R2J,ZH,XA,YB),(R1L,R2J,ZH,XA,YB),(R1M,R2J,Z
H,XA,YB),(R1N,R2J,ZH,XA,YB),(R1O,R2J,ZH,XA,YB),(R1P
,R2J,ZH,XA,YB),(R1Q,R2J,ZH,XA,YB),(R1A,R2K,ZH,XA,Y
B),(R1B,R2K,ZH,XA,YB),(R1C,R2K,ZH,XA,YB),(R1D,R2K,
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,ZH,XA,YB),(R1M,R2K,ZH,XA,YB),(R1N,R2K,ZH,XA,YB),(
R1O,R2K,ZH,XA,YB),(R1P,R2K,ZH,XA,YB),(R1Q,R2K,ZH,X
A,YB),(R1A,R2L,ZH,XA,YB),(R1B,R2L,ZH,XA,YB),(R1C,R
2L,ZH,XA,YB),(R1D,R2L,ZH,XA,YB),(R1E,R2L,ZH,XA,YB)
,(R1F,R2L,ZH,XA,YB),(R1G,R2L,ZH,XA,YB),(R1H,R2L,ZH,
XA,YB),(R1I,R2L,ZH,XA,YB),(R1J,R2L,ZH,XA,YB),(R1K,R
2L,ZH,XA,YB),(R1L,R2L,ZH,XA,YB),(R1M,R2L,ZH,XA,YB)
,(R1N,R2L,ZH,XA,YB),(R1O,R2L,ZH,XA,YB),(R1P,R2L,ZH,
XA,YB),(R1Q,R2L,ZH,XA,YB),(R1A,R2M,ZH,XA,YB),(R1B,
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B),(R1E,R2M,ZH,XA,YB),(R1F,R2M,ZH,XA,YB),(R1G,R2M,
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1J,R2M,ZH,XA,YB),(R1K,R2M,ZH,XA,YB),(R1L,R2M,ZH,X
A,YB),(R1M,R2M,ZH,XA,YB),(R1N,R2M,ZH,XA,YB),(R1O,
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B),(R1A,R2N,ZH,XA,YB),(R1B,R2N,ZH,XA,YB),(R1C,R2N,

ZH,XA,YB),(R1D,R2N,ZH,XA,YB),(R1E,R2N,ZH,XA,YB),(R1F,R2N,ZH,XA,YB),(R1G,R2N,ZH,XA,YB),(R1H,R2N,ZH,XA,YB),(R1I,R2N,ZH,XA,YB),(R1J,R2N,ZH,XA,YB),(R1K,R2N,ZH,XA,YB),(R1L,R2N,ZH,XA,YB),(R1M,R2N,ZH,XA,YB),(R1N,R2N,ZH,XA,YB),(R1O,R2N,ZH,XA,YB),(R1P,R2N,ZH,XA,YB),(R1Q,R2N,ZH,XA,YB),(R1A,R2O,ZH,XA,YB),(R1B,R2O,ZH,XA,YB),(R1C,R2O,ZH,XA,YB),(R1D,R2O,ZH,XA,YB),(R1E,R2O,ZH,XA,YB),(R1F,R2O,ZH,XA,YB),(R1G,R2O,ZH,XA,YB),(R1H,R2O,ZH,XA,YB),(R1I,R2O,ZH,XA,YB),(R1J,R2O,ZH,XA,YB),(R1K,R2O,ZH,XA,YB),(R1L,R2O,ZH,XA,YB),(R1M,R2O,ZH,XA,YB),(R1N,R2O,ZH,XA,YB),(R1O,R2O,ZH,XA,YB),(R1P,R2O,ZH,XA,YB),(R1Q,R2O,ZH,XA,YB),(R1A,R2P,ZH,XA,YB),(R1B,R2P,ZH,XA,YB),(R1C,R2P,ZH,XA,YB),(R1D,R2P,ZH,XA,YB),(R1E,R2P,ZH,XA,YB),(R1F,R2P,ZH,XA,YB),(R1G,R2P,ZH,XA,YB),(R1H,R2P,ZH,XA,YB),(R1I,R2P,ZH,XA,YB),(R1J,R2P,ZH,XA,YB),(R1K,R2P,ZH,XA,YB),(R1L,R2P,ZH,XA,YB),(R1M,R2P,ZH,XA,YB),(R1N,R2P,ZH,XA,YB),(R1O,R2P,ZH,XA,YB),(R1P,R2P,ZH,XA,YB),(R1Q,R2P,ZH,XA,YB),(R1A,R2Q,ZH,XA,YB),(R1B,R2Q,ZH,XA,YB),(R1C,R2Q,ZH,XA,YB),(R1D,R2Q,ZH,XA,YB),(R1E,R2Q,ZH,XA,YB),(R1F,R2Q,ZH,XA,YB),(R1G,R2Q,ZH,XA,YB),(R1H,R2Q,ZH,XA,YB),(R1I,R2Q,ZH,XA,YB),(R1J,R2Q,ZH,XA,YB),(R1K,R2Q,ZH,XA,YB),(R1L,R2Q,ZH,XA,YB),(R1M,R2Q,ZH,XA,YB),(R1N,R2Q,ZH,XA,YB),(R1O,R2Q,ZH,XA,YB),(

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A,YB),(R1B,R2A,ZI,XA,YB),(R1C,R2A,ZI,XA,YB),(R1D,R2
A,ZI,XA,YB),(R1E,R2A,ZI,XA,YB),(R1F,R2A,ZI,XA,YB),(R
1G,R2A,ZI,XA,YB),(R1H,R2A,ZI,XA,YB),(R1I,R2A,ZI,XA,Y
B),(R1J,R2A,ZI,XA,YB),(R1K,R2A,ZI,XA,YB),(R1L,R2A,ZI
,XA,YB),(R1M,R2A,ZI,XA,YB),(R1N,R2A,ZI,XA,YB),(R1O,
R2A,ZI,XA,YB),(R1P,R2A,ZI,XA,YB),(R1Q,R2A,ZI,XA,YB)
,(R1A,R2B,ZI,XA,YB),(R1B,R2B,ZI,XA,YB),(R1C,R2B,ZI,X
A,YB),(R1D,R2B,ZI,XA,YB),(R1E,R2B,ZI,XA,YB),(R1F,R2
B,ZI,XA,YB),(R1G,R2B,ZI,XA,YB),(R1H,R2B,ZI,XA,YB),(R
1I,R2B,ZI,XA,YB),(R1J,R2B,ZI,XA,YB),(R1K,R2B,ZI,XA,Y
B),(R1L,R2B,ZI,XA,YB),(R1M,R2B,ZI,XA,YB),(R1N,R2B,ZI
,XA,YB),(R1O,R2B,ZI,XA,YB),(R1P,R2B,ZI,XA,YB),(R1Q,R
2B,ZI,XA,YB),(R1A,R2C,ZI,XA,YB),(R1B,R2C,ZI,XA,YB),(
R1C,R2C,ZI,XA,YB),(R1D,R2C,ZI,XA,YB),(R1E,R2C,ZI,XA
,YB),(R1F,R2C,ZI,XA,YB),(R1G,R2C,ZI,XA,YB),(R1H,R2C,
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,R2C,ZI,XA,YB),(R1L,R2C,ZI,XA,YB),(R1M,R2C,ZI,XA,YB
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I,XA,YB),(R1K,R2D,ZI,XA,YB),(R1L,R2D,ZI,XA,YB),(R1M

,R2D,ZI,XA,YB),(R1N,R2D,ZI,XA,YB),(R1O,R2D,ZI,XA,YB),(R1P,R2D,ZI,XA,YB),(R1Q,R2D,ZI,XA,YB),(R1A,R2E,ZI,XA,YB),(R1B,R2E,ZI,XA,YB),(R1C,R2E,ZI,XA,YB),(R1D,R2E,ZI,XA,YB),(R1E,R2E,ZI,XA,YB),(R1F,R2E,ZI,XA,YB),(R1G,R2E,ZI,XA,YB),(R1H,R2E,ZI,XA,YB),(R1I,R2E,ZI,XA,YB),(R1J,R2E,ZI,XA,YB),(R1K,R2E,ZI,XA,YB),(R1L,R2E,ZI,XA,YB),(R1M,R2E,ZI,XA,YB),(R1N,R2E,ZI,XA,YB),(R1O,R2E,ZI,XA,YB),(R1P,R2E,ZI,XA,YB),(R1Q,R2E,ZI,XA,YB),(R1A,R2F,ZI,XA,YB),(R1B,R2F,ZI,XA,YB),(R1C,R2F,ZI,XA,YB),(R1D,R2F,ZI,XA,YB),(R1E,R2F,ZI,XA,YB),(R1F,R2F,ZI,XA,YB),(R1G,R2F,ZI,XA,YB),(R1H,R2F,ZI,XA,YB),(R1I,R2F,ZI,XA,YB),(R1J,R2F,ZI,XA,YB),(R1K,R2F,ZI,XA,YB),(R1L,R2F,ZI,XA,YB),(R1M,R2F,ZI,XA,YB),(R1N,R2F,ZI,XA,YB),(R1O,R2F,ZI,XA,YB),(R1P,R2F,ZI,XA,YB),(R1Q,R2F,ZI,XA,YB),(R1A,R2G,ZI,XA,YB),(R1B,R2G,ZI,XA,YB),(R1C,R2G,ZI,XA,YB),(R1D,R2G,ZI,XA,YB),(R1E,R2G,ZI,XA,YB),(R1F,R2G,ZI,XA,YB),(R1G,R2G,ZI,XA,YB),(R1H,R2G,ZI,XA,YB),(R1I,R2G,ZI,XA,YB),(R1J,R2G,ZI,XA,YB),(R1K,R2G,ZI,XA,YB),(R1L,R2G,ZI,XA,YB),(R1M,R2G,ZI,XA,YB),(R1N,R2G,ZI,XA,YB),(R1O,R2G,ZI,XA,YB),(R1P,R2G,ZI,XA,YB),(R1Q,R2G,ZI,XA,YB),(R1A,R2H,ZI,XA,YB),(R1B,R2H,ZI,XA,YB),(R1C,R2H,ZI,XA,YB),(R1D,R2H,ZI,XA,YB),(R1E,R2H,ZI,XA,YB),(R1F,R2H,ZI,XA,YB),(R1G,R2H,ZI,XA,YB),(R1H,R2H,ZI,XA,YB),(R1I,R2H,ZI,XA,YB),(R1J,R2H,ZI,XA,Y

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),(R1P,R2I,ZI,XA,YB),(R1Q,R2I,ZI,XA,YB),(R1A,R2J,ZI,X
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),(R1D,R2F,ZO,XA,YB),(R1E,R2F,ZO,XA,YB),(R1F,R2F,ZO,
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A,YB),(R1L,R2B,ZP,XA,YB),(R1M,R2B,ZP,XA,YB),(R1N,R2
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(R1N,R2F,ZP,XA,YB),(R1O,R2F,ZP,XA,YB),(R1P,R2F,ZP,XA
,YB),(R1Q,R2F,ZP,XA,YB),(R1A,R2G,ZP,XA,YB),(R1B,R2G,
ZP,XA,YB),(R1C,R2G,ZP,XA,YB),(R1D,R2G,ZP,XA,YB),(R1
E,R2G,ZP,XA,YB),(R1F,R2G,ZP,XA,YB),(R1G,R2G,ZP,XA,Y
B),(R1H,R2G,ZP,XA,YB),(R1I,R2G,ZP,XA,YB),(R1J,R2G,ZP,
XA,YB),(R1K,R2G,ZP,XA,YB),(R1L,R2G,ZP,XA,YB),(R1M,R
2G,ZP,XA,YB),(R1N,R2G,ZP,XA,YB),(R1O,R2G,ZP,XA,YB),(
R1P,R2G,ZP,XA,YB),(R1Q,R2G,ZP,XA,YB),(R1A,R2H,ZP,XA
,YB),(R1B,R2H,ZP,XA,YB),(R1C,R2H,ZP,XA,YB),(R1D,R2H
,ZP,XA,YB),(R1E,R2H,ZP,XA,YB),(R1F,R2H,ZP,XA,YB),(R1
G,R2H,ZP,XA,YB),(R1H,R2H,ZP,XA,YB),(R1I,R2H,ZP,XA,Y
B),(R1J,R2H,ZP,XA,YB),(R1K,R2H,ZP,XA,YB),(R1L,R2H,ZP
,XA,YB),(R1M,R2H,ZP,XA,YB),(R1N,R2H,ZP,XA,YB),(R1O,
R2H,ZP,XA,YB),(R1P,R2H,ZP,XA,YB),(R1Q,R2H,ZP,XA,YB)
,(R1A,R2I,ZP,XA,YB),(R1B,R2I,ZP,XA,YB),(R1C,R2I,ZP,X
A,YB),(R1D,R2I,ZP,XA,YB),(R1E,R2I,ZP,XA,YB),(R1F,R2I,
ZP,XA,YB),(R1G,R2I,ZP,XA,YB),(R1H,R2I,ZP,XA,YB),(R1I,
R2I,ZP,XA,YB),(R1J,R2I,ZP,XA,YB),(R1K,R2I,ZP,XA,YB),(
R1L,R2I,ZP,XA,YB),(R1M,R2I,ZP,XA,YB),(R1N,R2I,ZP,XA,
YB),(R1O,R2I,ZP,XA,YB),(R1P,R2I,ZP,XA,YB),(R1Q,R2I,ZP
,XA,YB),(R1A,R2J,ZP,XA,YB),(R1B,R2J,ZP,XA,YB),(R1C,R

2J,ZP,XA,YB),(R1D,R2J,ZP,XA,YB),(R1E,R2J,ZP,XA,YB),(R1F,R2J,ZP,XA,YB),(R1G,R2J,ZP,XA,YB),(R1H,R2J,ZP,XA,YB),(R1I,R2J,ZP,XA,YB),(R1J,R2J,ZP,XA,YB),(R1K,R2J,ZP,XA,YB),(R1L,R2J,ZP,XA,YB),(R1M,R2J,ZP,XA,YB),(R1N,R2J,ZP,XA,YB),(R1O,R2J,ZP,XA,YB),(R1P,R2J,ZP,XA,YB),(R1Q,R2J,ZP,XA,YB),(R1A,R2K,ZP,XA,YB),(R1B,R2K,ZP,XA,YB),(R1C,R2K,ZP,XA,YB),(R1D,R2K,ZP,XA,YB),(R1E,R2K,ZP,XA,YB),(R1F,R2K,ZP,XA,YB),(R1G,R2K,ZP,XA,YB),(R1H,R2K,ZP,XA,YB),(R1I,R2K,ZP,XA,YB),(R1J,R2K,ZP,XA,YB),(R1K,R2K,ZP,XA,YB),(R1L,R2K,ZP,XA,YB),(R1M,R2K,ZP,XA,YB),(R1N,R2K,ZP,XA,YB),(R1O,R2K,ZP,XA,YB),(R1P,R2K,ZP,XA,YB),(R1Q,R2K,ZP,XA,YB),(R1A,R2L,ZP,XA,YB),(R1B,R2L,ZP,XA,YB),(R1C,R2L,ZP,XA,YB),(R1D,R2L,ZP,XA,YB),(R1E,R2L,ZP,XA,YB),(R1F,R2L,ZP,XA,YB),(R1G,R2L,ZP,XA,YB),(R1H,R2L,ZP,XA,YB),(R1I,R2L,ZP,XA,YB),(R1J,R2L,ZP,XA,YB),(R1K,R2L,ZP,XA,YB),(R1L,R2L,ZP,XA,YB),(R1M,R2L,ZP,XA,YB),(R1N,R2L,ZP,XA,YB),(R1O,R2L,ZP,XA,YB),(R1P,R2L,ZP,XA,YB),(R1Q,R2L,ZP,XA,YB),(R1A,R2M,ZP,XA,YB),(R1B,R2M,ZP,XA,YB),(R1C,R2M,ZP,XA,YB),(R1D,R2M,ZP,XA,YB),(R1E,R2M,ZP,XA,YB),(R1F,R2M,ZP,XA,YB),(R1G,R2M,ZP,XA,YB),(R1H,R2M,ZP,XA,YB),(R1I,R2M,ZP,XA,YB),(R1J,R2M,ZP,XA,YB),(R1K,R2M,ZP,XA,YB),(R1L,R2M,ZP,XA,YB),(R1M,R2M,ZP,XA,YB),(R1N,R2M,ZP,XA,YB),(R1O,R2M,ZP,XA,YB),(R1P,R2M,ZP,XA,YB),(R

1Q,R2M,ZP,XA,YB),(R1A,R2N,ZP,XA,YB),(R1B,R2N,ZP,XA,YB),(R1C,R2N,ZP,XA,YB),(R1D,R2N,ZP,XA,YB),(R1E,R2N,ZP,XA,YB),(R1F,R2N,ZP,XA,YB),(R1G,R2N,ZP,XA,YB),(R1H,R2N,ZP,XA,YB),(R1I,R2N,ZP,XA,YB),(R1J,R2N,ZP,XA,YB),(R1K,R2N,ZP,XA,YB),(R1L,R2N,ZP,XA,YB),(R1M,R2N,ZP,XA,YB),(R1N,R2N,ZP,XA,YB),(R1O,R2N,ZP,XA,YB),(R1P,R2N,ZP,XA,YB),(R1Q,R2N,ZP,XA,YB),(R1A,R2O,ZP,XA,YB),(R1B,R2O,ZP,XA,YB),(R1C,R2O,ZP,XA,YB),(R1D,R2O,ZP,XA,YB),(R1E,R2O,ZP,XA,YB),(R1F,R2O,ZP,XA,YB),(R1G,R2O,ZP,XA,YB),(R1H,R2O,ZP,XA,YB),(R1I,R2O,ZP,XA,YB),(R1J,R2O,ZP,XA,YB),(R1K,R2O,ZP,XA,YB),(R1L,R2O,ZP,XA,YB),(R1M,R2O,ZP,XA,YB),(R1N,R2O,ZP,XA,YB),(R1O,R2O,ZP,XA,YB),(R1P,R2O,ZP,XA,YB),(R1Q,R2O,ZP,XA,YB),(R1A,R2P,ZP,XA,YB),(R1B,R2P,ZP,XA,YB),(R1C,R2P,ZP,XA,YB),(R1D,R2P,ZP,XA,YB),(R1E,R2P,ZP,XA,YB),(R1F,R2P,ZP,XA,YB),(R1G,R2P,ZP,XA,YB),(R1H,R2P,ZP,XA,YB),(R1I,R2P,ZP,XA,YB),(R1J,R2P,ZP,XA,YB),(R1K,R2P,ZP,XA,YB),(R1L,R2P,ZP,XA,YB),(R1M,R2P,ZP,XA,YB),(R1N,R2P,ZP,XA,YB),(R1O,R2P,ZP,XA,YB),(R1P,R2P,ZP,XA,YB),(R1Q,R2P,ZP,XA,YB),(R1A,R2Q,ZP,XA,YB),(R1B,R2Q,ZP,XA,YB),(R1C,R2Q,ZP,XA,YB),(R1D,R2Q,ZP,XA,YB),(R1E,R2Q,ZP,XA,YB),(R1F,R2Q,ZP,XA,YB),(R1G,R2Q,ZP,XA,YB),(R1H,R2Q,ZP,XA,YB),(R1I,R2Q,ZP,XA,YB),(R1J,R2Q,ZP,XA,YB),(R1K,R2Q,ZP,XA,YB),(R1L,R2Q,ZP,XA,YB),(R1M,R2Q,ZP,XA,Y

B),(R1N,R2Q,ZP,XA,YB),(R1O,R2Q,ZP,XA,YB),(R1P,R2Q,Z
P,XA,YB),(R1Q,R2Q,ZP,XA,YB),(R1A,R2A,ZQ,XA,YB),(R1
B,R2A,ZQ,XA,YB),(R1C,R2A,ZQ,XA,YB),(R1D,R2A,ZQ,XA,
YB),(R1E,R2A,ZQ,XA,YB),(R1F,R2A,ZQ,XA,YB),(R1G,R2A,
ZQ,XA,YB),(R1H,R2A,ZQ,XA,YB),(R1I,R2A,ZQ,XA,YB),(R
1J,R2A,ZQ,XA,YB),(R1K,R2A,ZQ,XA,YB),(R1L,R2A,ZQ,XA
,YB),(R1M,R2A,ZQ,XA,YB),(R1N,R2A,ZQ,XA,YB),(R1O,R2
A,ZQ,XA,YB),(R1P,R2A,ZQ,XA,YB),(R1Q,R2A,ZQ,XA,YB),
(R1A,R2B,ZQ,XA,YB),(R1B,R2B,ZQ,XA,YB),(R1C,R2B,ZQ,
XA,YB),(R1D,R2B,ZQ,XA,YB),(R1E,R2B,ZQ,XA,YB),(R1F,
R2B,ZQ,XA,YB),(R1G,R2B,ZQ,XA,YB),(R1H,R2B,ZQ,XA,Y
B),(R1I,R2B,ZQ,XA,YB),(R1J,R2B,ZQ,XA,YB),(R1K,R2B,Z
Q,XA,YB),(R1L,R2B,ZQ,XA,YB),(R1M,R2B,ZQ,XA,YB),(R1
N,R2B,ZQ,XA,YB),(R1O,R2B,ZQ,XA,YB),(R1P,R2B,ZQ,XA,
YB),(R1Q,R2B,ZQ,XA,YB),(R1A,R2C,ZQ,XA,YB),(R1B,R2C
,ZQ,XA,YB),(R1C,R2C,ZQ,XA,YB),(R1D,R2C,ZQ,XA,YB),(
R1E,R2C,ZQ,XA,YB),(R1F,R2C,ZQ,XA,YB),(R1G,R2C,ZQ,X
A,YB),(R1H,R2C,ZQ,XA,YB),(R1I,R2C,ZQ,XA,YB),(R1J,R2
C,ZQ,XA,YB),(R1K,R2C,ZQ,XA,YB),(R1L,R2C,ZQ,XA,YB),
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XA,YB),(R1P,R2C,ZQ,XA,YB),(R1Q,R2C,ZQ,XA,YB),(R1A,
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B),(R1D,R2D,ZQ,XA,YB),(R1E,R2D,ZQ,XA,YB),(R1F,R2D,Z
Q,XA,YB),(R1G,R2D,ZQ,XA,YB),(R1H,R2D,ZQ,XA,YB),(R1

I,R2D,ZQ,XA,YB),(R1J,R2D,ZQ,XA,YB),(R1K,R2D,ZQ,XA,YB),(R1L,R2D,ZQ,XA,YB),(R1M,R2D,ZQ,XA,YB),(R1N,R2D,ZQ,XA,YB),(R1O,R2D,ZQ,XA,YB),(R1P,R2D,ZQ,XA,YB),(R1Q,R2D,ZQ,XA,YB),(R1A,R2E,ZQ,XA,YB),(R1B,R2E,ZQ,XA,YB),(R1C,R2E,ZQ,XA,YB),(R1D,R2E,ZQ,XA,YB),(R1E,R2E,ZQ,XA,YB),(R1F,R2E,ZQ,XA,YB),(R1G,R2E,ZQ,XA,YB),(R1H,R2E,ZQ,XA,YB),(R1I,R2E,ZQ,XA,YB),(R1J,R2E,ZQ,XA,YB),(R1K,R2E,ZQ,XA,YB),(R1L,R2E,ZQ,XA,YB),(R1M,R2E,ZQ,XA,YB),(R1N,R2E,ZQ,XA,YB),(R1O,R2E,ZQ,XA,YB),(R1P,R2E,ZQ,XA,YB),(R1Q,R2E,ZQ,XA,YB),(R1A,R2F,ZQ,XA,YB),(R1B,R2F,ZQ,XA,YB),(R1C,R2F,ZQ,XA,YB),(R1D,R2F,ZQ,XA,YB),(R1E,R2F,ZQ,XA,YB),(R1F,R2F,ZQ,XA,YB),(R1G,R2F,ZQ,XA,YB),(R1H,R2F,ZQ,XA,YB),(R1I,R2F,ZQ,XA,YB),(R1J,R2F,ZQ,XA,YB),(R1K,R2F,ZQ,XA,YB),(R1L,R2F,ZQ,XA,YB),(R1M,R2F,ZQ,XA,YB),(R1N,R2F,ZQ,XA,YB),(R1O,R2F,ZQ,XA,YB),(R1P,R2F,ZQ,XA,YB),(R1Q,R2F,ZQ,XA,YB),(R1A,R2G,ZQ,XA,YB),(R1B,R2G,ZQ,XA,YB),(R1C,R2G,ZQ,XA,YB),(R1D,R2G,ZQ,XA,YB),(R1E,R2G,ZQ,XA,YB),(R1F,R2G,ZQ,XA,YB),(R1G,R2G,ZQ,XA,YB),(R1H,R2G,ZQ,XA,YB),(R1I,R2G,ZQ,XA,YB),(R1J,R2G,ZQ,XA,YB),(R1K,R2G,ZQ,XA,YB),(R1L,R2G,ZQ,XA,YB),(R1M,R2G,ZQ,XA,YB),(R1N,R2G,ZQ,XA,YB),(R1O,R2G,ZQ,XA,YB),(R1P,R2G,ZQ,XA,YB),(R1Q,R2G,ZQ,XA,YB),(R1A,R2H,ZQ,XA,YB),(R1B,R2H,ZQ,XA,YB),(R1C,R2H,ZQ,XA,YB),(R1D,R2H,ZQ,XA,Y

B),(R1E,R2H,ZQ,XA,YB),(R1F,R2H,ZQ,XA,YB),(R1G,R2H,Z
Q,XA,YB),(R1H,R2H,ZQ,XA,YB),(R1I,R2H,ZQ,XA,YB),(R1J
,R2H,ZQ,XA,YB),(R1K,R2H,ZQ,XA,YB),(R1L,R2H,ZQ,XA,Y
B),(R1M,R2H,ZQ,XA,YB),(R1N,R2H,ZQ,XA,YB),(R1O,R2H,
ZQ,XA,YB),(R1P,R2H,ZQ,XA,YB),(R1Q,R2H,ZQ,XA,YB),(R
1A,R2I,ZQ,XA,YB),(R1B,R2I,ZQ,XA,YB),(R1C,R2I,ZQ,XA,
YB),(R1D,R2I,ZQ,XA,YB),(R1E,R2I,ZQ,XA,YB),(R1F,R2I,Z
Q,XA,YB),(R1G,R2I,ZQ,XA,YB),(R1H,R2I,ZQ,XA,YB),(R1I,
R2I,ZQ,XA,YB),(R1J,R2I,ZQ,XA,YB),(R1K,R2I,ZQ,XA,YB),
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A,YB),(R1O,R2I,ZQ,XA,YB),(R1P,R2I,ZQ,XA,YB),(R1Q,R2I
,ZQ,XA,YB),(R1A,R2J,ZQ,XA,YB),(R1B,R2J,ZQ,XA,YB),(R
1C,R2J,ZQ,XA,YB),(R1D,R2J,ZQ,XA,YB),(R1E,R2J,ZQ,XA,
YB),(R1F,R2J,ZQ,XA,YB),(R1G,R2J,ZQ,XA,YB),(R1H,R2J,Z
Q,XA,YB),(R1I,R2J,ZQ,XA,YB),(R1J,R2J,ZQ,XA,YB),(R1K,
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B),(R1E,R2K,ZQ,XA,YB),(R1F,R2K,ZQ,XA,YB),(R1G,R2K,Z
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B),(R1M,R2K,ZQ,XA,YB),(R1N,R2K,ZQ,XA,YB),(R1O,R2K,
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1A,R2L,ZQ,XA,YB),(R1B,R2L,ZQ,XA,YB),(R1C,R2L,ZQ,XA,YB),(R1D,R2L,ZQ,XA,YB),(R1E,R2L,ZQ,XA,YB),(R1F,R2L,ZQ,XA,YB),(R1G,R2L,ZQ,XA,YB),(R1H,R2L,ZQ,XA,YB),(R1I,R2L,ZQ,XA,YB),(R1J,R2L,ZQ,XA,YB),(R1K,R2L,ZQ,XA,YB),(R1L,R2L,ZQ,XA,YB),(R1M,R2L,ZQ,XA,YB),(R1N,R2L,ZQ,XA,YB),(R1O,R2L,ZQ,XA,YB),(R1P,R2L,ZQ,XA,YB),(R1Q,R2L,ZQ,XA,YB),(R1A,R2M,ZQ,XA,YB),(R1B,R2M,ZQ,XA,YB),(R1C,R2M,ZQ,XA,YB),(R1D,R2M,ZQ,XA,YB),(R1E,R2M,ZQ,XA,YB),(R1F,R2M,ZQ,XA,YB),(R1G,R2M,ZQ,XA,YB),(R1H,R2M,ZQ,XA,YB),(R1I,R2M,ZQ,XA,YB),(R1J,R2M,ZQ,XA,YB),(R1K,R2M,ZQ,XA,YB),(R1L,R2M,ZQ,XA,YB),(R1M,R2M,ZQ,XA,YB),(R1N,R2M,ZQ,XA,YB),(R1O,R2M,ZQ,XA,YB),(R1P,R2M,ZQ,XA,YB),(R1Q,R2M,ZQ,XA,YB),(R1A,R2N,ZQ,XA,YB),(R1B,R2N,ZQ,XA,YB),(R1C,R2N,ZQ,XA,YB),(R1D,R2N,ZQ,XA,YB),(R1E,R2N,ZQ,XA,YB),(R1F,R2N,ZQ,XA,YB),(R1G,R2N,ZQ,XA,YB),(R1H,R2N,ZQ,XA,YB),(R1I,R2N,ZQ,XA,YB),(R1J,R2N,ZQ,XA,YB),(R1K,R2N,ZQ,XA,YB),(R1L,R2N,ZQ,XA,YB),(R1M,R2N,ZQ,XA,YB),(R1N,R2N,ZQ,XA,YB),(R1O,R2N,ZQ,XA,YB),(R1P,R2N,ZQ,XA,YB),(R1Q,R2N,ZQ,XA,YB),(R1A,R2O,ZQ,XA,YB),(R1B,R2O,ZQ,XA,YB),(R1C,R2O,ZQ,XA,YB),(R1D,R2O,ZQ,XA,YB),(R1E,R2O,ZQ,XA,YB),(R1F,R2O,ZQ,XA,YB),(R1G,R2O,ZQ,XA,YB),(R1H,R2O,ZQ,XA,YB),(R1I,R2O,ZQ,XA,YB),(R1J,R2O,ZQ,XA,YB),(R1K,R2O,ZQ,XA,YB),(R1L,R2O,ZQ,XA,YB),(R1M,

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B),(R1P,R2O,ZQ,XA,YB),(R1Q,R2O,ZQ,XA,YB),(R1A,R2P,Z
Q,XA,YB),(R1B,R2P,ZQ,XA,YB),(R1C,R2P,ZQ,XA,YB),(R1
D,R2P,ZQ,XA,YB),(R1E,R2P,ZQ,XA,YB),(R1F,R2P,ZQ,XA,Y
B),(R1G,R2P,ZQ,XA,YB),(R1H,R2P,ZQ,XA,YB),(R1I,R2P,ZQ
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B),(R1F,R2Q,ZQ,XA,YB),(R1G,R2Q,ZQ,XA,YB),(R1H,R2Q,Z
Q,XA,YB),(R1I,R2Q,ZQ,XA,YB),(R1J,R2Q,ZQ,XA,YB),(R1K
,R2Q,ZQ,XA,YB),(R1L,R2Q,ZQ,XA,YB),(R1M,R2Q,ZQ,XA,
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,ZQ,XA,YB),(R1Q,R2Q,ZQ,XA,YB),(R1A,R2A,ZR,XA,YB),(
R1B,R2A,ZR,XA,YB),(R1C,R2A,ZR,XA,YB),(R1D,R2A,ZR,X
A,YB),(R1E,R2A,ZR,XA,YB),(R1F,R2A,ZR,XA,YB),(R1G,R2
A,ZR,XA,YB),(R1H,R2A,ZR,XA,YB),(R1I,R2A,ZR,XA,YB),(
R1J,R2A,ZR,XA,YB),(R1K,R2A,ZR,XA,YB),(R1L,R2A,ZR,X
A,YB),(R1M,R2A,ZR,XA,YB),(R1N,R2A,ZR,XA,YB),(R1O,R
2A,ZR,XA,YB),(R1P,R2A,ZR,XA,YB),(R1Q,R2A,ZR,XA,YB)
,(R1A,R2B,ZR,XA,YB),(R1B,R2B,ZR,XA,YB),(R1C,R2B,ZR,
XA,YB),(R1D,R2B,ZR,XA,YB),(R1E,R2B,ZR,XA,YB),(R1F,
R2B,ZR,XA,YB),(R1G,R2B,ZR,XA,YB),(R1H,R2B,ZR,XA,YB

),(R1I,R2B,ZR,XA,YB),(R1J,R2B,ZR,XA,YB),(R1K,R2B,ZR,XA,YB),(R1L,R2B,ZR,XA,YB),(R1M,R2B,ZR,XA,YB),(R1N,R2B,ZR,XA,YB),(R1O,R2B,ZR,XA,YB),(R1P,R2B,ZR,XA,YB),(R1Q,R2B,ZR,XA,YB),(R1A,R2C,ZR,XA,YB),(R1B,R2C,ZR,XA,YB),(R1C,R2C,ZR,XA,YB),(R1D,R2C,ZR,XA,YB),(R1E,R2C,ZR,XA,YB),(R1F,R2C,ZR,XA,YB),(R1G,R2C,ZR,XA,YB),(R1H,R2C,ZR,XA,YB),(R1I,R2C,ZR,XA,YB),(R1J,R2C,ZR,XA,YB),(R1K,R2C,ZR,XA,YB),(R1L,R2C,ZR,XA,YB),(R1M,R2C,ZR,XA,YB),(R1N,R2C,ZR,XA,YB),(R1O,R2C,ZR,XA,YB),(R1P,R2C,ZR,XA,YB),(R1Q,R2C,ZR,XA,YB),(R1A,R2D,ZR,XA,YB),(R1B,R2D,ZR,XA,YB),(R1C,R2D,ZR,XA,YB),(R1D,R2D,ZR,XA,YB),(R1E,R2D,ZR,XA,YB),(R1F,R2D,ZR,XA,YB),(R1G,R2D,ZR,XA,YB),(R1H,R2D,ZR,XA,YB),(R1I,R2D,ZR,XA,YB),(R1J,R2D,ZR,XA,YB),(R1K,R2D,ZR,XA,YB),(R1L,R2D,ZR,XA,YB),(R1M,R2D,ZR,XA,YB),(R1N,R2D,ZR,XA,YB),(R1O,R2D,ZR,XA,YB),(R1P,R2D,ZR,XA,YB),(R1Q,R2D,ZR,XA,YB),(R1A,R2E,ZR,XA,YB),(R1B,R2E,ZR,XA,YB),(R1C,R2E,ZR,XA,YB),(R1D,R2E,ZR,XA,YB),(R1E,R2E,ZR,XA,YB),(R1F,R2E,ZR,XA,YB),(R1G,R2E,ZR,XA,YB),(R1H,R2E,ZR,XA,YB),(R1I,R2E,ZR,XA,YB),(R1J,R2E,ZR,XA,YB),(R1K,R2E,ZR,XA,YB),(R1L,R2E,ZR,XA,YB),(R1M,R2E,ZR,XA,YB),(R1N,R2E,ZR,XA,YB),(R1O,R2E,ZR,XA,YB),(R1P,R2E,ZR,XA,YB),(R1Q,R2E,ZR,XA,YB),(R1A,R2F,ZR,XA,YB),(R1B,R2F,ZR,XA,YB),(R1C,R2F,ZR,XA,YB),(R1D,R2F,ZR,X

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,R2F,ZB,XB,YB),(R1A,R2G,ZB,XB,YB),(R1B,R2G,ZB,XB,Y
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B),(R1F,R2F,ZF,XB,YB),(R1G,R2F,ZF,XB,YB),(R1H,R2F,ZF,
XB,YB),(R1I,R2F,ZF,XB,YB),(R1J,R2F,ZF,XB,YB),(R1K,R2
F,ZF,XB,YB),(R1L,R2F,ZF,XB,YB),(R1M,R2F,ZF,XB,YB),(R
1N,R2F,ZF,XB,YB),(R1O,R2F,ZF,XB,YB),(R1P,R2F,ZF,XB,Y
B),(R1Q,R2F,ZF,XB,YB),(R1A,R2G,ZF,XB,YB),(R1B,R2G,ZF
,XB,YB),(R1C,R2G,ZF,XB,YB),(R1D,R2G,ZF,XB,YB),(R1E,
R2G,ZF,XB,YB),(R1F,R2G,ZF,XB,YB),(R1G,R2G,ZF,XB,YB),
(R1H,R2G,ZF,XB,YB),(R1I,R2G,ZF,XB,YB),(R1J,R2G,ZF,XB
,YB),(R1K,R2G,ZF,XB,YB),(R1L,R2G,ZF,XB,YB),(R1M,R2G,
ZF,XB,YB),(R1N,R2G,ZF,XB,YB),(R1O,R2G,ZF,XB,YB),(R1

P,R2G,ZF,XB,YB),(R1Q,R2G,ZF,XB,YB),(R1A,R2H,ZF,XB,Y
B),(R1B,R2H,ZF,XB,YB),(R1C,R2H,ZF,XB,YB),(R1D,R2H,Z
F,XB,YB),(R1E,R2H,ZF,XB,YB),(R1F,R2H,ZF,XB,YB),(R1G,
R2H,ZF,XB,YB),(R1H,R2H,ZF,XB,YB),(R1I,R2H,ZF,XB,YB)
,(R1J,R2H,ZF,XB,YB),(R1K,R2H,ZF,XB,YB),(R1L,R2H,ZF,X
B,YB),(R1M,R2H,ZF,XB,YB),(R1N,R2H,ZF,XB,YB),(R1O,R2
H,ZF,XB,YB),(R1P,R2H,ZF,XB,YB),(R1Q,R2H,ZF,XB,YB),(
R1A,R2I,ZF,XB,YB),(R1B,R2I,ZF,XB,YB),(R1C,R2I,ZF,XB,
YB),(R1D,R2I,ZF,XB,YB),(R1E,R2I,ZF,XB,YB),(R1F,R2I,ZF
,XB,YB),(R1G,R2I,ZF,XB,YB),(R1H,R2I,ZF,XB,YB),(R1I,R2
I,ZF,XB,YB),(R1J,R2I,ZF,XB,YB),(R1K,R2I,ZF,XB,YB),(R1
L,R2I,ZF,XB,YB),(R1M,R2I,ZF,XB,YB),(R1N,R2I,ZF,XB,YB
),(R1O,R2I,ZF,XB,YB),(R1P,R2I,ZF,XB,YB),(R1Q,R2I,ZF,X
B,YB),(R1A,R2J,ZF,XB,YB),(R1B,R2J,ZF,XB,YB),(R1C,R2J
,ZF,XB,YB),(R1D,R2J,ZF,XB,YB),(R1E,R2J,ZF,XB,YB),(R1
F,R2J,ZF,XB,YB),(R1G,R2J,ZF,XB,YB),(R1H,R2J,ZF,XB,YB
),(R1I,R2J,ZF,XB,YB),(R1J,R2J,ZF,XB,YB),(R1K,R2J,ZF,X
B,YB),(R1L,R2J,ZF,XB,YB),(R1M,R2J,ZF,XB,YB),(R1N,R2J
,ZF,XB,YB),(R1O,R2J,ZF,XB,YB),(R1P,R2J,ZF,XB,YB),(R1
Q,R2J,ZF,XB,YB),(R1A,R2K,ZF,XB,YB),(R1B,R2K,ZF,XB,Y
B),(R1C,R2K,ZF,XB,YB),(R1D,R2K,ZF,XB,YB),(R1E,R2K,Z
F,XB,YB),(R1F,R2K,ZF,XB,YB),(R1G,R2K,ZF,XB,YB),(R1H,
R2K,ZF,XB,YB),(R1I,R2K,ZF,XB,YB),(R1J,R2K,ZF,XB,YB),
(R1K,R2K,ZF,XB,YB),(R1L,R2K,ZF,XB,YB),(R1M,R2K,ZF,X

B,YB),(R1N,R2K,ZF,XB,YB),(R1O,R2K,ZF,XB,YB),(R1P,R2K,ZF,XB,YB),(R1Q,R2K,ZF,XB,YB),(R1A,R2L,ZF,XB,YB),(R1B,R2L,ZF,XB,YB),(R1C,R2L,ZF,XB,YB),(R1D,R2L,ZF,XB,YB),(R1E,R2L,ZF,XB,YB),(R1F,R2L,ZF,XB,YB),(R1G,R2L,ZF,XB,YB),(R1H,R2L,ZF,XB,YB),(R1I,R2L,ZF,XB,YB),(R1J,R2L,ZF,XB,YB),(R1K,R2L,ZF,XB,YB),(R1L,R2L,ZF,XB,YB),(R1M,R2L,ZF,XB,YB),(R1N,R2L,ZF,XB,YB),(R1O,R2L,ZF,XB,YB),(R1P,R2L,ZF,XB,YB),(R1Q,R2L,ZF,XB,YB),(R1A,R2M,ZF,XB,YB),(R1B,R2M,ZF,XB,YB),(R1C,R2M,ZF,XB,YB),(R1D,R2M,ZF,XB,YB),(R1E,R2M,ZF,XB,YB),(R1F,R2M,ZF,XB,YB),(R1G,R2M,ZF,XB,YB),(R1H,R2M,ZF,XB,YB),(R1I,R2M,ZF,XB,YB),(R1J,R2M,ZF,XB,YB),(R1K,R2M,ZF,XB,YB),(R1L,R2M,ZF,XB,YB),(R1M,R2M,ZF,XB,YB),(R1N,R2M,ZF,XB,YB),(R1O,R2M,ZF,XB,YB),(R1P,R2M,ZF,XB,YB),(R1Q,R2M,ZF,XB,YB),(R1A,R2N,ZF,XB,YB),(R1B,R2N,ZF,XB,YB),(R1C,R2N,ZF,XB,YB),(R1D,R2N,ZF,XB,YB),(R1E,R2N,ZF,XB,YB),(R1F,R2N,ZF,XB,YB),(R1G,R2N,ZF,XB,YB),(R1H,R2N,ZF,XB,YB),(R1I,R2N,ZF,XB,YB),(R1J,R2N,ZF,XB,YB),(R1K,R2N,ZF,XB,YB),(R1L,R2N,ZF,XB,YB),(R1M,R2N,ZF,XB,YB),(R1N,R2N,ZF,XB,YB),(R1O,R2N,ZF,XB,YB),(R1P,R2N,ZF,XB,YB),(R1Q,R2N,ZF,XB,YB),(R1A,R2O,ZF,XB,YB),(R1B,R2O,ZF,XB,YB),(R1C,R2O,ZF,XB,YB),(R1D,R2O,ZF,XB,YB),(R1E,R2O,ZF,XB,YB),(R1F,R2O,ZF,XB,YB),(R1G,R2O,ZF,XB,YB),(R1H,R2O,ZF,XB,YB),(R1I,R2O,ZF,XB,YB),(R

1J,R2O,ZF,XB,YB),(R1K,R2O,ZF,XB,YB),(R1L,R2O,ZF,XB,YB),(R1M,R2O,ZF,XB,YB),(R1N,R2O,ZF,XB,YB),(R1O,R2O,ZF,XB,YB),(R1P,R2O,ZF,XB,YB),(R1Q,R2O,ZF,XB,YB),(R1A,R2P,ZF,XB,YB),(R1B,R2P,ZF,XB,YB),(R1C,R2P,ZF,XB,YB),(R1D,R2P,ZF,XB,YB),(R1E,R2P,ZF,XB,YB),(R1F,R2P,ZF,XB,YB),(R1G,R2P,ZF,XB,YB),(R1H,R2P,ZF,XB,YB),(R1I,R2P,ZF,XB,YB),(R1J,R2P,ZF,XB,YB),(R1K,R2P,ZF,XB,YB),(R1L,R2P,ZF,XB,YB),(R1M,R2P,ZF,XB,YB),(R1N,R2P,ZF,XB,YB),(R1O,R2P,ZF,XB,YB),(R1P,R2P,ZF,XB,YB),(R1Q,R2P,ZF,XB,YB),(R1A,R2Q,ZF,XB,YB),(R1B,R2Q,ZF,XB,YB),(R1C,R2Q,ZF,XB,YB),(R1D,R2Q,ZF,XB,YB),(R1E,R2Q,ZF,XB,YB),(R1F,R2Q,ZF,XB,YB),(R1G,R2Q,ZF,XB,YB),(R1H,R2Q,ZF,XB,YB),(R1I,R2Q,ZF,XB,YB),(R1J,R2Q,ZF,XB,YB),(R1K,R2Q,ZF,XB,YB),(R1L,R2Q,ZF,XB,YB),(R1M,R2Q,ZF,XB,YB),(R1N,R2Q,ZF,XB,YB),(R1O,R2Q,ZF,XB,YB),(R1P,R2Q,ZF,XB,YB),(R1Q,R2Q,ZF,XB,YB),(R1A,R2A,ZG,XB,YB),(R1B,R2A,ZG,XB,YB),(R1C,R2A,ZG,XB,YB),(R1D,R2A,ZG,XB,YB),(R1E,R2A,ZG,XB,YB),(R1F,R2A,ZG,XB,YB),(R1G,R2A,ZG,XB,YB),(R1H,R2A,ZG,XB,YB),(R1I,R2A,ZG,XB,YB),(R1J,R2A,ZG,XB,YB),(R1K,R2A,ZG,XB,YB),(R1L,R2A,ZG,XB,YB),(R1M,R2A,ZG,XB,YB),(R1N,R2A,ZG,XB,YB),(R1O,R2A,ZG,XB,YB),(R1P,R2A,ZG,XB,YB),(R1Q,R2A,ZG,XB,YB),(R1A,R2B,ZG,XB,YB),(R1B,R2B,ZG,XB,YB),(R1C,R2B,ZG,XB,YB),(R1D,R2B,ZG,XB,YB),(R1E,R2B,ZG,XB,YB),(R1F,R2B,ZG,XB,YB)

,(R1G,R2B,ZG,XB,YB),(R1H,R2B,ZG,XB,YB),(R1I,R2B,ZG,XB,YB),(R1J,R2B,ZG,XB,YB),(R1K,R2B,ZG,XB,YB),(R1L,R2B,ZG,XB,YB),(R1M,R2B,ZG,XB,YB),(R1N,R2B,ZG,XB,YB),(R1O,R2B,ZG,XB,YB),(R1P,R2B,ZG,XB,YB),(R1Q,R2B,ZG,XB,YB),(R1A,R2C,ZG,XB,YB),(R1B,R2C,ZG,XB,YB),(R1C,R2C,ZG,XB,YB),(R1D,R2C,ZG,XB,YB),(R1E,R2C,ZG,XB,YB),(R1F,R2C,ZG,XB,YB),(R1G,R2C,ZG,XB,YB),(R1H,R2C,ZG,XB,YB),(R1I,R2C,ZG,XB,YB),(R1J,R2C,ZG,XB,YB),(R1K,R2C,ZG,XB,YB),(R1L,R2C,ZG,XB,YB),(R1M,R2C,ZG,XB,YB),(R1N,R2C,ZG,XB,YB),(R1O,R2C,ZG,XB,YB),(R1P,R2C,ZG,XB,YB),(R1Q,R2C,ZG,XB,YB),(R1A,R2D,ZG,XB,YB),(R1B,R2D,ZG,XB,YB),(R1C,R2D,ZG,XB,YB),(R1D,R2D,ZG,XB,YB),(R1E,R2D,ZG,XB,YB),(R1F,R2D,ZG,XB,YB),(R1G,R2D,ZG,XB,YB),(R1H,R2D,ZG,XB,YB),(R1I,R2D,ZG,XB,YB),(R1J,R2D,ZG,XB,YB),(R1K,R2D,ZG,XB,YB),(R1L,R2D,ZG,XB,YB),(R1M,R2D,ZG,XB,YB),(R1N,R2D,ZG,XB,YB),(R1O,R2D,ZG,XB,YB),(R1P,R2D,ZG,XB,YB),(R1Q,R2D,ZG,XB,YB),(R1A,R2E,ZG,XB,YB),(R1B,R2E,ZG,XB,YB),(R1C,R2E,ZG,XB,YB),(R1D,R2E,ZG,XB,YB),(R1E,R2E,ZG,XB,YB),(R1F,R2E,ZG,XB,YB),(R1G,R2E,ZG,XB,YB),(R1H,R2E,ZG,XB,YB),(R1I,R2E,ZG,XB,YB),(R1J,R2E,ZG,XB,YB),(R1K,R2E,ZG,XB,YB),(R1L,R2E,ZG,XB,YB),(R1M,R2E,ZG,XB,YB),(R1N,R2E,ZG,XB,YB),(R1O,R2E,ZG,XB,YB),(R1P,R2E,ZG,XB,YB),(R1Q,R2E,ZG,XB,YB),(R1A,R2F,ZG,XB,YB),(R1B,R2F,ZG,XB,YB),(R1

C,R2F,ZG,XB,YB),(R1D,R2F,ZG,XB,YB),(R1E,R2F,ZG,XB,Y
B),(R1F,R2F,ZG,XB,YB),(R1G,R2F,ZG,XB,YB),(R1H,R2F,ZG
,XB,YB),(R1I,R2F,ZG,XB,YB),(R1J,R2F,ZG,XB,YB),(R1K,R
2F,ZG,XB,YB),(R1L,R2F,ZG,XB,YB),(R1M,R2F,ZG,XB,YB),(
R1N,R2F,ZG,XB,YB),(R1O,R2F,ZG,XB,YB),(R1P,R2F,ZG,XB
,YB),(R1Q,R2F,ZG,XB,YB),(R1A,R2G,ZG,XB,YB),(R1B,R2G
,ZG,XB,YB),(R1C,R2G,ZG,XB,YB),(R1D,R2G,ZG,XB,YB),(R
1E,R2G,ZG,XB,YB),(R1F,R2G,ZG,XB,YB),(R1G,R2G,ZG,XB,
YB),(R1H,R2G,ZG,XB,YB),(R1I,R2G,ZG,XB,YB),(R1J,R2G,Z
G,XB,YB),(R1K,R2G,ZG,XB,YB),(R1L,R2G,ZG,XB,YB),(R1M
,R2G,ZG,XB,YB),(R1N,R2G,ZG,XB,YB),(R1O,R2G,ZG,XB,YB
),(R1P,R2G,ZG,XB,YB),(R1Q,R2G,ZG,XB,YB),(R1A,R2H,ZG,
XB,YB),(R1B,R2H,ZG,XB,YB),(R1C,R2H,ZG,XB,YB),(R1D,
R2H,ZG,XB,YB),(R1E,R2H,ZG,XB,YB),(R1F,R2H,ZG,XB,YB
),(R1G,R2H,ZG,XB,YB),(R1H,R2H,ZG,XB,YB),(R1I,R2H,ZG,
XB,YB),(R1J,R2H,ZG,XB,YB),(R1K,R2H,ZG,XB,YB),(R1L,R
2H,ZG,XB,YB),(R1M,R2H,ZG,XB,YB),(R1N,R2H,ZG,XB,YB)
,(R1O,R2H,ZG,XB,YB),(R1P,R2H,ZG,XB,YB),(R1Q,R2H,ZG,
XB,YB),(R1A,R2I,ZG,XB,YB),(R1B,R2I,ZG,XB,YB),(R1C,R
2I,ZG,XB,YB),(R1D,R2I,ZG,XB,YB),(R1E,R2I,ZG,XB,YB),(
R1F,R2I,ZG,XB,YB),(R1G,R2I,ZG,XB,YB),(R1H,R2I,ZG,XB,
YB),(R1I,R2I,ZG,XB,YB),(R1J,R2I,ZG,XB,YB),(R1K,R2I,ZG
,XB,YB),(R1L,R2I,ZG,XB,YB),(R1M,R2I,ZG,XB,YB),(R1N,R
2I,ZG,XB,YB),(R1O,R2I,ZG,XB,YB),(R1P,R2I,ZG,XB,YB),(

R1Q,R2I,ZG,XB,YB),(R1A,R2J,ZG,XB,YB),(R1B,R2J,ZG,XB,YB),(R1C,R2J,ZG,XB,YB),(R1D,R2J,ZG,XB,YB),(R1E,R2J,ZG,XB,YB),(R1F,R2J,ZG,XB,YB),(R1G,R2J,ZG,XB,YB),(R1H,R2J,ZG,XB,YB),(R1I,R2J,ZG,XB,YB),(R1J,R2J,ZG,XB,YB),(R1K,R2J,ZG,XB,YB),(R1L,R2J,ZG,XB,YB),(R1M,R2J,ZG,XB,YB),(R1N,R2J,ZG,XB,YB),(R1O,R2J,ZG,XB,YB),(R1P,R2J,ZG,XB,YB),(R1Q,R2J,ZG,XB,YB),(R1A,R2K,ZG,XB,YB),(R1B,R2K,ZG,XB,YB),(R1C,R2K,ZG,XB,YB),(R1D,R2K,ZG,XB,YB),(R1E,R2K,ZG,XB,YB),(R1F,R2K,ZG,XB,YB),(R1G,R2K,ZG,XB,YB),(R1H,R2K,ZG,XB,YB),(R1I,R2K,ZG,XB,YB),(R1J,R2K,ZG,XB,YB),(R1K,R2K,ZG,XB,YB),(R1L,R2K,ZG,XB,YB),(R1M,R2K,ZG,XB,YB),(R1N,R2K,ZG,XB,YB),(R1O,R2K,ZG,XB,YB),(R1P,R2K,ZG,XB,YB),(R1Q,R2K,ZG,XB,YB),(R1A,R2L,ZG,XB,YB),(R1B,R2L,ZG,XB,YB),(R1C,R2L,ZG,XB,YB),(R1D,R2L,ZG,XB,YB),(R1E,R2L,ZG,XB,YB),(R1F,R2L,ZG,XB,YB),(R1G,R2L,ZG,XB,YB),(R1H,R2L,ZG,XB,YB),(R1I,R2L,ZG,XB,YB),(R1J,R2L,ZG,XB,YB),(R1K,R2L,ZG,XB,YB),(R1L,R2L,ZG,XB,YB),(R1M,R2L,ZG,XB,YB),(R1N,R2L,ZG,XB,YB),(R1O,R2L,ZG,XB,YB),(R1P,R2L,ZG,XB,YB),(R1Q,R2L,ZG,XB,YB),(R1A,R2M,ZG,XB,YB),(R1B,R2M,ZG,XB,YB),(R1C,R2M,ZG,XB,YB),(R1D,R2M,ZG,XB,YB),(R1E,R2M,ZG,XB,YB),(R1F,R2M,ZG,XB,YB),(R1G,R2M,ZG,XB,YB),(R1H,R2M,ZG,XB,YB),(R1I,R2M,ZG,XB,YB),(R1J,R2M,ZG,XB,YB),(R1K,R2M,ZG,XB,YB),(R1L,R2M,ZG,XB,YB),(R1M,R2M,Z

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H,ZJ,XB,YB),(R1O,R2H,ZJ,XB,YB),(R1P,R2H,ZJ,XB,YB),(R
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B,YB),(R1P,R2O,ZM,XB,YB),(R1Q,R2O,ZM,XB,YB),(R1A,R
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(R1D,R2P,ZM,XB,YB),(R1E,R2P,ZM,XB,YB),(R1F,R2P,ZM,X
B,YB),(R1G,R2P,ZM,XB,YB),(R1H,R2P,ZM,XB,YB),(R1I,R2
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B,YB),(R1O,R2P,ZM,XB,YB),(R1P,R2P,ZM,XB,YB),(R1Q,R2
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,XB,YB),(R1F,R2Q,ZM,XB,YB),(R1G,R2Q,ZM,XB,YB),(R1H
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,YB),(R1B,R2J,ZO,XB,YB),(R1C,R2J,ZO,XB,YB),(R1D,R2J,ZO,XB,YB),(R1E,R2J,ZO,XB,YB),(R1F,R2J,ZO,XB,YB),(R1G,R2J,ZO,XB,YB),(R1H,R2J,ZO,XB,YB),(R1I,R2J,ZO,XB,YB),(R1J,R2J,ZO,XB,YB),(R1K,R2J,ZO,XB,YB),(R1L,R2J,ZO,XB,YB),(R1M,R2J,ZO,XB,YB),(R1N,R2J,ZO,XB,YB),(R1O,R2J,ZO,XB,YB),(R1P,R2J,ZO,XB,YB),(R1Q,R2J,ZO,XB,YB),(R1A,R2K,ZO,XB,YB),(R1B,R2K,ZO,XB,YB),(R1C,R2K,ZO,XB,YB),(R1D,R2K,ZO,XB,YB),(R1E,R2K,ZO,XB,YB),(R1F,R2K,ZO,XB,YB),(R1G,R2K,ZO,XB,YB),(R1H,R2K,ZO,XB,YB),(R1I,R2K,ZO,XB,YB),(R1J,R2K,ZO,XB,YB),(R1K,R2K,ZO,XB,YB),(R1L,R2K,ZO,XB,YB),(R1M,R2K,ZO,XB,YB),(R1N,R2K,ZO,XB,YB),(R1O,R2K,ZO,XB,YB),(R1P,R2K,ZO,XB,YB),(R1Q,R2K,ZO,XB,YB),(R1A,R2L,ZO,XB,YB),(R1B,R2L,ZO,XB,YB),(R1C,R2L,ZO,XB,YB),(R1D,R2L,ZO,XB,YB),(R1E,R2L,ZO,XB,YB),(R1F,R2L,ZO,XB,YB),(R1G,R2L,ZO,XB,YB),(R1H,R2L,ZO,XB,YB),(R1I,R2L,ZO,XB,YB),(R1J,R2L,ZO,XB,YB),(R1K,R2L,ZO,XB,YB),(R1L,R2L,ZO,XB,YB),(R1M,R2L,ZO,XB,YB),(R1N,R2L,ZO,XB,YB),(R1O,R2L,ZO,XB,YB),(R1P,R2L,ZO,XB,YB),(R1Q,R2L,ZO,XB,YB),(R1A,R2M,ZO,XB,YB),(R1B,R2M,ZO,XB,YB),(R1C,R2M,ZO,XB,YB),(R1D,R2M,ZO,XB,YB),(R1E,R2M,ZO,XB,YB),(R1F,R2M,ZO,XB,YB),(R1G,R2M,ZO,XB,YB),(R1H,R2M,ZO,XB,YB),(R1I,R2M,ZO,XB,YB),(R1J,R2M,ZO,XB,YB),(R1K,R2M,ZO,XB,YB),(R1L,R2M,ZO,XB,YB),(R1M,R2M,ZO,XB,YB),(R1N,R2M,

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B,YB),(R1D,R2A,ZP,XB,YB),(R1E,R2A,ZP,XB,YB),(R1F,R2
A,ZP,XB,YB),(R1G,R2A,ZP,XB,YB),(R1H,R2A,ZP,XB,YB),(
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ZP,XB,YB),(R1O,R2A,ZP,XB,YB),(R1P,R2A,ZP,XB,YB),(R1
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B),(R1C,R2B,ZP,XB,YB),(R1D,R2B,ZP,XB,YB),(R1E,R2B,ZP
,XB,YB),(R1F,R2B,ZP,XB,YB),(R1G,R2B,ZP,XB,YB),(R1H,R
2B,ZP,XB,YB),(R1I,R2B,ZP,XB,YB),(R1J,R2B,ZP,XB,YB),(
R1K,R2B,ZP,XB,YB),(R1L,R2B,ZP,XB,YB),(R1M,R2B,ZP,X
B,YB),(R1N,R2B,ZP,XB,YB),(R1O,R2B,ZP,XB,YB),(R1P,R2
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,YB),(R1E,R2C,ZP,XB,YB),(R1F,R2C,ZP,XB,YB),(R1G,R2C,
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,R2C,ZP,XB,YB),(R1K,R2C,ZP,XB,YB),(R1L,R2C,ZP,XB,YB
),(R1M,R2C,ZP,XB,YB),(R1N,R2C,ZP,XB,YB),(R1O,R2C,ZP,
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B,YB),(R1G,R2D,ZP,XB,YB),(R1H,R2D,ZP,XB,YB),(R1I,R2D,ZP,XB,YB),(R1J,R2D,ZP,XB,YB),(R1K,R2D,ZP,XB,YB),(R1L,R2D,ZP,XB,YB),(R1M,R2D,ZP,XB,YB),(R1N,R2D,ZP,XB,YB),(R1O,R2D,ZP,XB,YB),(R1P,R2D,ZP,XB,YB),(R1Q,R2D,ZP,XB,YB),(R1A,R2E,ZP,XB,YB),(R1B,R2E,ZP,XB,YB),(R1C,R2E,ZP,XB,YB),(R1D,R2E,ZP,XB,YB),(R1E,R2E,ZP,XB,YB),(R1F,R2E,ZP,XB,YB),(R1G,R2E,ZP,XB,YB),(R1H,R2E,ZP,XB,YB),(R1I,R2E,ZP,XB,YB),(R1J,R2E,ZP,XB,YB),(R1K,R2E,ZP,XB,YB),(R1L,R2E,ZP,XB,YB),(R1M,R2E,ZP,XB,YB),(R1N,R2E,ZP,XB,YB),(R1O,R2E,ZP,XB,YB),(R1P,R2E,ZP,XB,YB),(R1Q,R2E,ZP,XB,YB),(R1A,R2F,ZP,XB,YB),(R1B,R2F,ZP,XB,YB),(R1C,R2F,ZP,XB,YB),(R1D,R2F,ZP,XB,YB),(R1E,R2F,ZP,XB,YB),(R1F,R2F,ZP,XB,YB),(R1G,R2F,ZP,XB,YB),(R1H,R2F,ZP,XB,YB),(R1I,R2F,ZP,XB,YB),(R1J,R2F,ZP,XB,YB),(R1K,R2F,ZP,XB,YB),(R1L,R2F,ZP,XB,YB),(R1M,R2F,ZP,XB,YB),(R1N,R2F,ZP,XB,YB),(R1O,R2F,ZP,XB,YB),(R1P,R2F,ZP,XB,YB),(R1Q,R2F,ZP,XB,YB),(R1A,R2G,ZP,XB,YB),(R1B,R2G,ZP,XB,YB),(R1C,R2G,ZP,XB,YB),(R1D,R2G,ZP,XB,YB),(R1E,R2G,ZP,XB,YB),(R1F,R2G,ZP,XB,YB),(R1G,R2G,ZP,XB,YB),(R1H,R2G,ZP,XB,YB),(R1I,R2G,ZP,XB,YB),(R1J,R2G,ZP,XB,YB),(R1K,R2G,ZP,XB,YB),(R1L,R2G,ZP,XB,YB),(R1M,R2G,ZP,XB,YB),(R1N,R2G,ZP,XB,YB),(R1O,R2G,ZP,XB,YB),(R1P,R2G,ZP,XB,YB),(R1Q,R2G,ZP,XB,YB),(R1A,R2H,ZP,XB,YB),(R1B,R2H,ZP,XB,YB),(R1C,R2H,ZP,XB,YB)

,(R1D,R2H,ZP,XB,YB),(R1E,R2H,ZP,XB,YB),(R1F,R2H,ZP,X
B,YB),(R1G,R2H,ZP,XB,YB),(R1H,R2H,ZP,XB,YB),(R1I,R2
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,R2I,ZP,XB,YB),(R1D,R2I,ZP,XB,YB),(R1E,R2I,ZP,XB,YB),
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YB),(R1I,R2I,ZP,XB,YB),(R1J,R2I,ZP,XB,YB),(R1K,R2I,ZP,
XB,YB),(R1L,R2I,ZP,XB,YB),(R1M,R2I,ZP,XB,YB),(R1N,R2
I,ZP,XB,YB),(R1O,R2I,ZP,XB,YB),(R1P,R2I,ZP,XB,YB),(R1
Q,R2I,ZP,XB,YB),(R1A,R2J,ZP,XB,YB),(R1B,R2J,ZP,XB,YB
),(R1C,R2J,ZP,XB,YB),(R1D,R2J,ZP,XB,YB),(R1E,R2J,ZP,X
B,YB),(R1F,R2J,ZP,XB,YB),(R1G,R2J,ZP,XB,YB),(R1H,R2J,
ZP,XB,YB),(R1I,R2J,ZP,XB,YB),(R1J,R2J,ZP,XB,YB),(R1K,
R2J,ZP,XB,YB),(R1L,R2J,ZP,XB,YB),(R1M,R2J,ZP,XB,YB),
(R1N,R2J,ZP,XB,YB),(R1O,R2J,ZP,XB,YB),(R1P,R2J,ZP,XB,
YB),(R1Q,R2J,ZP,XB,YB),(R1A,R2K,ZP,XB,YB),(R1B,R2K,
ZP,XB,YB),(R1C,R2K,ZP,XB,YB),(R1D,R2K,ZP,XB,YB),(R1
E,R2K,ZP,XB,YB),(R1F,R2K,ZP,XB,YB),(R1G,R2K,ZP,XB,Y
B),(R1H,R2K,ZP,XB,YB),(R1I,R2K,ZP,XB,YB),(R1J,R2K,ZP
,XB,YB),(R1K,R2K,ZP,XB,YB),(R1L,R2K,ZP,XB,YB),(R1M,
R2K,ZP,XB,YB),(R1N,R2K,ZP,XB,YB),(R1O,R2K,ZP,XB,YB)
,(R1P,R2K,ZP,XB,YB),(R1Q,R2K,ZP,XB,YB),(R1A,R2L,ZP,X

B,YB),(R1B,R2L,ZP,XB,YB),(R1C,R2L,ZP,XB,YB),(R1D,R2L,ZP,XB,YB),(R1E,R2L,ZP,XB,YB),(R1F,R2L,ZP,XB,YB),(R1G,R2L,ZP,XB,YB),(R1H,R2L,ZP,XB,YB),(R1I,R2L,ZP,XB,YB),(R1J,R2L,ZP,XB,YB),(R1K,R2L,ZP,XB,YB),(R1L,R2L,ZP,XB,YB),(R1M,R2L,ZP,XB,YB),(R1N,R2L,ZP,XB,YB),(R1O,R2L,ZP,XB,YB),(R1P,R2L,ZP,XB,YB),(R1Q,R2L,ZP,XB,YB),(R1A,R2M,ZP,XB,YB),(R1B,R2M,ZP,XB,YB),(R1C,R2M,ZP,XB,YB),(R1D,R2M,ZP,XB,YB),(R1E,R2M,ZP,XB,YB),(R1F,R2M,ZP,XB,YB),(R1G,R2M,ZP,XB,YB),(R1H,R2M,ZP,XB,YB),(R1I,R2M,ZP,XB,YB),(R1J,R2M,ZP,XB,YB),(R1K,R2M,ZP,XB,YB),(R1L,R2M,ZP,XB,YB),(R1M,R2M,ZP,XB,YB),(R1N,R2M,ZP,XB,YB),(R1O,R2M,ZP,XB,YB),(R1P,R2M,ZP,XB,YB),(R1Q,R2M,ZP,XB,YB),(R1A,R2N,ZP,XB,YB),(R1B,R2N,ZP,XB,YB),(R1C,R2N,ZP,XB,YB),(R1D,R2N,ZP,XB,YB),(R1E,R2N,ZP,XB,YB),(R1F,R2N,ZP,XB,YB),(R1G,R2N,ZP,XB,YB),(R1H,R2N,ZP,XB,YB),(R1I,R2N,ZP,XB,YB),(R1J,R2N,ZP,XB,YB),(R1K,R2N,ZP,XB,YB),(R1L,R2N,ZP,XB,YB),(R1M,R2N,ZP,XB,YB),(R1N,R2N,ZP,XB,YB),(R1O,R2N,ZP,XB,YB),(R1P,R2N,ZP,XB,YB),(R1Q,R2N,ZP,XB,YB),(R1A,R2O,ZP,XB,YB),(R1B,R2O,ZP,XB,YB),(R1C,R2O,ZP,XB,YB),(R1D,R2O,ZP,XB,YB),(R1E,R2O,ZP,XB,YB),(R1F,R2O,ZP,XB,YB),(R1G,R2O,ZP,XB,YB),(R1H,R2O,ZP,XB,YB),(R1I,R2O,ZP,XB,YB),(R1J,R2O,ZP,XB,YB),(R1K,R2O,ZP,XB,YB),(R1L,R2O,ZP,XB,YB),(R1M,R2O,ZP,XB,YB),(R1N,R2O,ZP,XB,YB),(R1O,R2O

,ZP,XB,YB),(R1P,R2O,ZP,XB,YB),(R1Q,R2O,ZP,XB,YB),(R1A,R2P,ZP,XB,YB),(R1B,R2P,ZP,XB,YB),(R1C,R2P,ZP,XB,YB),(R1D,R2P,ZP,XB,YB),(R1E,R2P,ZP,XB,YB),(R1F,R2P,ZP,XB,YB),(R1G,R2P,ZP,XB,YB),(R1H,R2P,ZP,XB,YB),(R1I,R2P,ZP,XB,YB),(R1J,R2P,ZP,XB,YB),(R1K,R2P,ZP,XB,YB),(R1L,R2P,ZP,XB,YB),(R1M,R2P,ZP,XB,YB),(R1N,R2P,ZP,XB,YB),(R1O,R2P,ZP,XB,YB),(R1P,R2P,ZP,XB,YB),(R1Q,R2P,ZP,XB,YB),(R1A,R2Q,ZP,XB,YB),(R1B,R2Q,ZP,XB,YB),(R1C,R2Q,ZP,XB,YB),(R1D,R2Q,ZP,XB,YB),(R1E,R2Q,ZP,XB,YB),(R1F,R2Q,ZP,XB,YB),(R1G,R2Q,ZP,XB,YB),(R1H,R2Q,ZP,XB,YB),(R1I,R2Q,ZP,XB,YB),(R1J,R2Q,ZP,XB,YB),(R1K,R2Q,ZP,XB,YB),(R1L,R2Q,ZP,XB,YB),(R1M,R2Q,ZP,XB,YB),(R1N,R2Q,ZP,XB,YB),(R1O,R2Q,ZP,XB,YB),(R1P,R2Q,ZP,XB,YB),(R1Q,R2Q,ZP,XB,YB),(R1A,R2A,ZQ,XB,YB),(R1B,R2A,ZQ,XB,YB),(R1C,R2A,ZQ,XB,YB),(R1D,R2A,ZQ,XB,YB),(R1E,R2A,ZQ,XB,YB),(R1F,R2A,ZQ,XB,YB),(R1G,R2A,ZQ,XB,YB),(R1H,R2A,ZQ,XB,YB),(R1I,R2A,ZQ,XB,YB),(R1J,R2A,ZQ,XB,YB),(R1K,R2A,ZQ,XB,YB),(R1L,R2A,ZQ,XB,YB),(R1M,R2A,ZQ,XB,YB),(R1N,R2A,ZQ,XB,YB),(R1O,R2A,ZQ,XB,YB),(R1P,R2A,ZQ,XB,YB),(R1Q,R2A,ZQ,XB,YB),(R1A,R2B,ZQ,XB,YB),(R1B,R2B,ZQ,XB,YB),(R1C,R2B,ZQ,XB,YB),(R1D,R2B,ZQ,XB,YB),(R1E,R2B,ZQ,XB,YB),(R1F,R2B,ZQ,XB,YB),(R1G,R2B,ZQ,XB,YB),(R1H,R2B,ZQ,XB,YB),(R1I,R2B,ZQ,XB,YB),(R1J,R2B,ZQ,XB,YB),(R1K,R2B,ZQ,XB,YB),(

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B,YB),(R1O,R2B,ZQ,XB,YB),(R1P,R2B,ZQ,XB,YB),(R1Q,R2
B,ZQ,XB,YB),(R1A,R2C,ZQ,XB,YB),(R1B,R2C,ZQ,XB,YB),(
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B,YB),(R1F,R2C,ZQ,XB,YB),(R1G,R2C,ZQ,XB,YB),(R1H,R2
C,ZQ,XB,YB),(R1I,R2C,ZQ,XB,YB),(R1J,R2C,ZQ,XB,YB),(
R1K,R2C,ZQ,XB,YB),(R1L,R2C,ZQ,XB,YB),(R1M,R2C,ZQ,X
B,YB),(R1N,R2C,ZQ,XB,YB),(R1O,R2C,ZQ,XB,YB),(R1P,R2
C,ZQ,XB,YB),(R1Q,R2C,ZQ,XB,YB),(R1A,R2D,ZQ,XB,YB),
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XB,YB),(R1E,R2D,ZQ,XB,YB),(R1F,R2D,ZQ,XB,YB),(R1G,R
2D,ZQ,XB,YB),(R1H,R2D,ZQ,XB,YB),(R1I,R2D,ZQ,XB,YB),
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),(R1A,R2E,ZQ,XB,YB),(R1B,R2E,ZQ,XB,YB),(R1C,R2E,ZQ
,XB,YB),(R1D,R2E,ZQ,XB,YB),(R1E,R2E,ZQ,XB,YB),(R1F,
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),(R1I,R2E,ZQ,XB,YB),(R1J,R2E,ZQ,XB,YB),(R1K,R2E,ZQ,
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),(R1Q,R2E,ZQ,XB,YB),(R1A,R2F,ZQ,XB,YB),(R1B,R2F,ZQ
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B,YB),(R1K,R2F,ZQ,XB,YB),(R1L,R2F,ZQ,XB,YB),(R1M,R2
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B,YB),(R1B,R2G,ZQ,XB,YB),(R1C,R2G,ZQ,XB,YB),(R1D,R2
G,ZQ,XB,YB),(R1E,R2G,ZQ,XB,YB),(R1F,R2G,ZQ,XB,YB),(
R1G,R2G,ZQ,XB,YB),(R1H,R2G,ZQ,XB,YB),(R1I,R2G,ZQ,X
B,YB),(R1J,R2G,ZQ,XB,YB),(R1K,R2G,ZQ,XB,YB),(R1L,R2
G,ZQ,XB,YB),(R1M,R2G,ZQ,XB,YB),(R1N,R2G,ZQ,XB,YB),
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B,YB),(R1A,R2H,ZQ,XB,YB),(R1B,R2H,ZQ,XB,YB),(R1C,R
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,XB,YB),(R1B,R2J,ZQ,XB,YB),(R1C,R2J,ZQ,XB,YB),(R1D,

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B,YB),(R1F,R2D,ZS,XB,YB),(R1G,R2D,ZS,XB,YB),(R1H,R2
D,ZS,XB,YB),(R1I,R2D,ZS,XB,YB),(R1J,R2D,ZS,XB,YB),(R
1K,R2D,ZS,XB,YB),(R1L,R2D,ZS,XB,YB),(R1M,R2D,ZS,XB
,YB),(R1N,R2D,ZS,XB,YB),(R1O,R2D,ZS,XB,YB),(R1P,R2D
,ZS,XB,YB),(R1Q,R2D,ZS,XB,YB),(R1A,R2E,ZS,XB,YB),(R
1B,R2E,ZS,XB,YB),(R1C,R2E,ZS,XB,YB),(R1D,R2E,ZS,XB,
YB),(R1E,R2E,ZS,XB,YB),(R1F,R2E,ZS,XB,YB),(R1G,R2E,
ZS,XB,YB),(R1H,R2E,ZS,XB,YB),(R1I,R2E,ZS,XB,YB),(R1J
,R2E,ZS,XB,YB),(R1K,R2E,ZS,XB,YB),(R1L,R2E,ZS,XB,YB
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,XB,YB),(R1P,R2E,ZS,XB,YB),(R1Q,R2E,ZS,XB,YB),(R1A,
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,YB),(R1G,R2F,ZS,XB,YB),(R1H,R2F,ZS,XB,YB),(R1I,R2F,ZS,XB,YB),(R1J,R2F,ZS,XB,YB),(R1K,R2F,ZS,XB,YB),(R1L,R2F,ZS,XB,YB),(R1M,R2F,ZS,XB,YB),(R1N,R2F,ZS,XB,YB),(R1O,R2F,ZS,XB,YB),(R1P,R2F,ZS,XB,YB),(R1Q,R2F,ZS,XB,YB),(R1A,R2G,ZS,XB,YB),(R1B,R2G,ZS,XB,YB),(R1C,R2G,ZS,XB,YB),(R1D,R2G,ZS,XB,YB),(R1E,R2G,ZS,XB,YB),(R1F,R2G,ZS,XB,YB),(R1G,R2G,ZS,XB,YB),(R1H,R2G,ZS,XB,YB),(R1I,R2G,ZS,XB,YB),(R1J,R2G,ZS,XB,YB),(R1K,R2G,ZS,XB,YB),(R1L,R2G,ZS,XB,YB),(R1M,R2G,ZS,XB,YB),(R1N,R2G,ZS,XB,YB),(R1O,R2G,ZS,XB,YB),(R1P,R2G,ZS,XB,YB),(R1Q,R2G,ZS,XB,YB),(R1A,R2H,ZS,XB,YB),(R1B,R2H,ZS,XB,YB),(R1C,R2H,ZS,XB,YB),(R1D,R2H,ZS,XB,YB),(R1E,R2H,ZS,XB,YB),(R1F,R2H,ZS,XB,YB),(R1G,R2H,ZS,XB,YB),(R1H,R2H,ZS,XB,YB),(R1I,R2H,ZS,XB,YB),(R1J,R2H,ZS,XB,YB),(R1K,R2H,ZS,XB,YB),(R1L,R2H,ZS,XB,YB),(R1M,R2H,ZS,XB,YB),(R1N,R2H,ZS,XB,YB),(R1O,R2H,ZS,XB,YB),(R1P,R2H,ZS,XB,YB),(R1Q,R2H,ZS,XB,YB),(R1A,R2I,ZS,XB,YB),(R1B,R2I,ZS,XB,YB),(R1C,R2I,ZS,XB,YB),(R1D,R2I,ZS,XB,YB),(R1E,R2I,ZS,XB,YB),(R1F,R2I,ZS,XB,YB),(R1G,R2I,ZS,XB,YB),(R1H,R2I,ZS,XB,YB),(R1I,R2I,ZS,XB,YB),(R1J,R2I,ZS,XB,YB),(R1K,R2I,ZS,XB,YB),(R1L,R2I,ZS,XB,YB),(R1M,R2I,ZS,XB,YB),(R1N,R2I,ZS,XB,YB),(R1O,R2I,ZS,XB,YB),(R1P,R2I,ZS,XB,YB),(R1Q,R2I,ZS,XB,YB),(R1A,R2J,ZS,XB,YB),(R1B,R2J,ZS,XB,YB),(R1C,R2J,ZS,XB,Y

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B),(R1M,R2N,ZT,XB,YB),(R1N,R2N,ZT,XB,YB),(R1O,R2N,Z
T,XB,YB),(R1P,R2N,ZT,XB,YB),(R1Q,R2N,ZT,XB,YB),(R1A
,R2O,ZT,XB,YB),(R1B,R2O,ZT,XB,YB),(R1C,R2O,ZT,XB,Y
B),(R1D,R2O,ZT,XB,YB),(R1E,R2O,ZT,XB,YB),(R1F,R2O,Z
T,XB,YB),(R1G,R2O,ZT,XB,YB),(R1H,R2O,ZT,XB,YB),(R1I,
R2O,ZT,XB,YB),(R1J,R2O,ZT,XB,YB),(R1K,R2O,ZT,XB,YB)
,(R1L,R2O,ZT,XB,YB),(R1M,R2O,ZT,XB,YB),(R1N,R2O,ZT,
XB,YB),(R1O,R2O,ZT,XB,YB),(R1P,R2O,ZT,XB,YB),(R1Q,R

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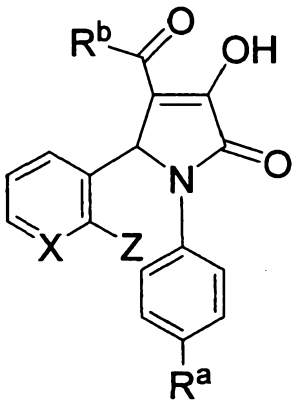
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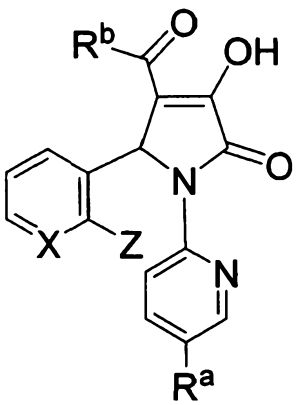
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,XB,YB),(R1O,R2N,ZU,XB,YB),(R1P,R2N,ZU,XB,YB),(R1Q,
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,ZU,XB,YB),(R1L,R2Q,ZU,XB,YB),(R1M,R2Q,ZU,XB,YB),(

R1N,R2Q,ZU,XB,YB),(R1O,R2Q,ZU,XB,YB),(R1P,R2Q,ZU,XB,YB)及(R1Q,R2Q,ZU,XB,YB)。

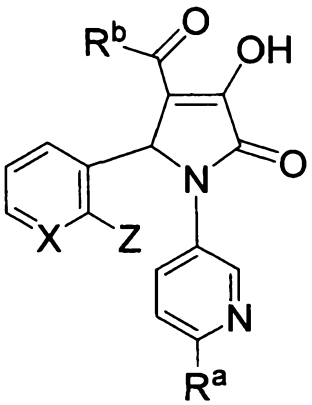
本發明化合物之較佳態樣，在以下式(a')~(f')中具有以下之基者。



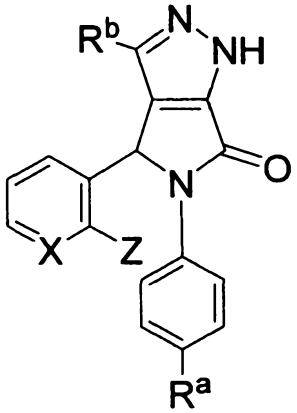
(a')



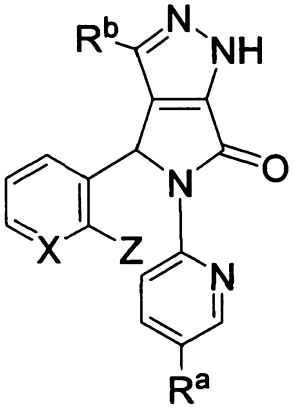
(b')



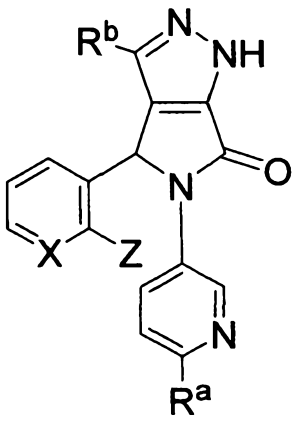
(c')



(d')



(e')



(f')

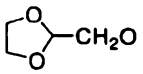
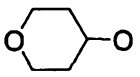
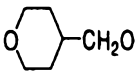
【表 6】

R^a1	R^a
R^a2	COOEt
R^a3	異噁唑-3-基
R^a4	3-Me-異噁唑-5-基
R^a5	5-Me-1,2,4-噁二唑-3-基
R^a6	3-Me-1,2,4-噁二唑-5-基
R^a7	2-噻唑啉基
R^a8	2-噻唑基
R^a9	2-或 3-噻吩基
R^a10	2-或 3-呋喃基
R^a11	5-Me-2-或 3-噻吩基
R^a12	5-Me-2-或 3-呋喃基
R^a13	SMe
R^a14	1-吡咯啶基
R^a15	1-環戊基
R^a16	1-環戊烯基

【表 7】

	R^b
R^b 1	iPr
R^b 2	iBu
R^b 3	tBu
R^b 4	$HOCH_2C(Me)_2$
R^b 5	$MeC(CH_2OH)_2$
R^b 6	$Me_2NCOC(Me)_2$
R^b 7	$MeNHCOC(Me)_2$
R^b 8	$H_2NCOC(Me)_2$

【表 8】

	Z		Z
Z 1	$(HOCH_2)_2CHCH_2O$	Z 21	$MeNHCOCH_2O$
Z 2	c-戊基 O	Z 22	MeO
Z 3	Et(Me)NCO	Z 23	$MeO(CH_2)_2$
Z 4	EtHNCO	Z 24	$MeO(CH_2)_2(Me)NCO$
Z 5	EtO	Z 25	$MeO(CH_2)_2O$
Z 6	$EtOCH_2O$	Z 26	$MeO(CH_2)_2OCH_2$
Z 7	$H_2NCO(CH_2)_2$	Z 27	$MeO(CH_2)_3O$
Z 8	H_2NCOCH_2O	Z 28	$MeOCH_2$
Z 9	$HO(CH_2)_2O$	Z 29	$MeOCH_2O$
Z 10	$HO(CH_2)_3O$	Z 30	MeS
Z 11	i-BuO	Z 31	$MeSO(CH_2)_2O$
Z 12	$i\text{-}PrHNCO(CH_2)_2$	Z 32	$MeSO_2$
Z 13	i-PrO	Z 33	N-嗎福啉基
Z 14	$i\text{-}PrOCH_2$	Z 34	NC
Z 15	$Me_2N(CH_2)_2O$	Z 35	$NC(CH_2)_2O$
Z 16	Me_2NCO	Z 36	$NCCH_2O$
Z 17	$Me_2NCO(CH_2)_2$	Z 37	
Z 18	Me_2NCOCH_2	Z 38	
Z 19	Me_2NCOCH_2O	Z 39	
Z 20	$MeHNCO(CH_2)_2$		

【表 9】

	X
X 1	CH
X 2	N

Ra、Rb、X 及 Z 之組合爲(Ra,Rb,X,Z)之以下之化合物。

(Ra,Rb,X,Z)=(Ra1,Rb1,X1,Z1),(Ra1,Rb1,X1,Z2),(Ra1,Rb1,X1,Z3),(Ra1,Rb1,X1,Z4),(Ra1,Rb1,X1,Z5),(Ra1,Rb1,X1,Z6),(

Ra1,Rb1,X1,Z7),(Ra1,Rb1,X1,Z8),(Ra1,Rb1,X1,Z9),(Ra1,Rb1,X1,Z10),(Ra1,Rb1,X1,Z11),(Ra1,Rb1,X1,Z12),(Ra1,Rb1,X1,Z13),(Ra1,Rb1,X1,Z14),(Ra1,Rb1,X1,Z15),(Ra1,Rb1,X1,Z16),(Ra1,Rb1,X1,Z17),(Ra1,Rb1,X1,Z18),(Ra1,Rb1,X1,Z19),(Ra1,Rb1,X1,Z20),(Ra1,Rb1,X1,Z21),(Ra1,Rb1,X1,Z22),(Ra1,Rb1,X1,Z23),(Ra1,Rb1,X1,Z24),(Ra1,Rb1,X1,Z25),(Ra1,Rb1,X1,Z26),(Ra1,Rb1,X1,Z27),(Ra1,Rb1,X1,Z28),(Ra1,Rb1,X1,Z29),(Ra1,Rb1,X1,Z30),(Ra1,Rb1,X1,Z31),(Ra1,Rb1,X1,Z32),(Ra1,Rb1,X1,Z33),(Ra1,Rb1,X1,Z34),(Ra1,Rb1,X1,Z35),(Ra1,Rb1,X1,Z36),(Ra1,Rb1,X1,Z37),(Ra1,Rb1,X1,Z38),(Ra1,Rb1,X1,Z39),(Ra1,Rb1,X2,Z1),(Ra1,Rb1,X2,Z2),(Ra1,Rb1,X2,Z3),(Ra1,Rb1,X2,Z4),(Ra1,Rb1,X2,Z5),(Ra1,Rb1,X2,Z6),(Ra1,Rb1,X2,Z7),(Ra1,Rb1,X2,Z8),(Ra1,Rb1,X2,Z9),(Ra1,Rb1,X2,Z10),(Ra1,Rb1,X2,Z11),(Ra1,Rb1,X2,Z12),(Ra1,Rb1,X2,Z13),(Ra1,Rb1,X2,Z14),(Ra1,Rb1,X2,Z15),(Ra1,Rb1,X2,Z16),(Ra1,Rb1,X2,Z17),(Ra1,Rb1,X2,Z18),(Ra1,Rb1,X2,Z19),(Ra1,Rb1,X2,Z20),(Ra1,Rb1,X2,Z21),(Ra1,Rb1,X2,Z22),(Ra1,Rb1,X2,Z23),(Ra1,Rb1,X2,Z24),(Ra1,Rb1,X2,Z25),(Ra1,Rb1,X2,Z26),(Ra1,Rb1,X2,Z27),(Ra1,Rb1,X2,Z28),(Ra1,Rb1,X2,Z29),(Ra1,Rb1,X2,Z30),(Ra1,Rb1,X2,Z31),(Ra1,Rb1,X2,Z32),(Ra1,Rb1,X2,Z33),(Ra1,Rb1,X2,Z34),(Ra1,Rb1,X2,Z35),(Ra1,Rb1,X2,Z36),(Ra1,Rb1,X2,Z37),(Ra1,Rb1,X2,Z38),(Ra1,Rb1,X2,Z39),(Ra1,Rb2,X1,Z1),(Ra1,Rb2,X1,Z2),(Ra1,Rb2,X1,Z3),(Ra1,Rb2,X1,Z4),(Ra1,Rb2,X1,Z5),(Ra1,Rb2,X

1,Z6),(Ra1,Rb2,X1,Z7),(Ra1,Rb2,X1,Z8),(Ra1,Rb2,X1,Z9),(Ra1,Rb2,X1,Z10),(Ra1,Rb2,X1,Z11),(Ra1,Rb2,X1,Z12),(Ra1,Rb2,X1,Z13),(Ra1,Rb2,X1,Z14),(Ra1,Rb2,X1,Z15),(Ra1,Rb2,X1,Z16),(Ra1,Rb2,X1,Z17),(Ra1,Rb2,X1,Z18),(Ra1,Rb2,X1,Z19),(Ra1,Rb2,X1,Z20),(Ra1,Rb2,X1,Z21),(Ra1,Rb2,X1,Z22),(Ra1,Rb2,X1,Z23),(Ra1,Rb2,X1,Z24),(Ra1,Rb2,X1,Z25),(Ra1,Rb2,X1,Z26),(Ra1,Rb2,X1,Z27),(Ra1,Rb2,X1,Z28),(Ra1,Rb2,X1,Z29),(Ra1,Rb2,X1,Z30),(Ra1,Rb2,X1,Z31),(Ra1,Rb2,X1,Z32),(Ra1,Rb2,X1,Z33),(Ra1,Rb2,X1,Z34),(Ra1,Rb2,X1,Z35),(Ra1,Rb2,X1,Z36),(Ra1,Rb2,X1,Z37),(Ra1,Rb2,X1,Z38),(Ra1,Rb2,X1,Z39),(Ra1,Rb2,X2,Z1),(Ra1,Rb2,X2,Z2),(Ra1,Rb2,X2,Z3),(Ra1,Rb2,X2,Z4),(Ra1,Rb2,X2,Z5),(Ra1,Rb2,X2,Z6),(Ra1,Rb2,X2,Z7),(Ra1,Rb2,X2,Z8),(Ra1,Rb2,X2,Z9),(Ra1,Rb2,X2,Z10),(Ra1,Rb2,X2,Z11),(Ra1,Rb2,X2,Z12),(Ra1,Rb2,X2,Z13),(Ra1,Rb2,X2,Z14),(Ra1,Rb2,X2,Z15),(Ra1,Rb2,X2,Z16),(Ra1,Rb2,X2,Z17),(Ra1,Rb2,X2,Z18),(Ra1,Rb2,X2,Z19),(Ra1,Rb2,X2,Z20),(Ra1,Rb2,X2,Z21),(Ra1,Rb2,X2,Z22),(Ra1,Rb2,X2,Z23),(Ra1,Rb2,X2,Z24),(Ra1,Rb2,X2,Z25),(Ra1,Rb2,X2,Z26),(Ra1,Rb2,X2,Z27),(Ra1,Rb2,X2,Z28),(Ra1,Rb2,X2,Z29),(Ra1,Rb2,X2,Z30),(Ra1,Rb2,X2,Z31),(Ra1,Rb2,X2,Z32),(Ra1,Rb2,X2,Z33),(Ra1,Rb2,X2,Z34),(Ra1,Rb2,X2,Z35),(Ra1,Rb2,X2,Z36),(Ra1,Rb2,X2,Z37),(Ra1,Rb2,X2,Z38),(Ra1,Rb2,X2,Z39),(Ra1,Rb3,X1,Z1),(Ra1,Rb3,X1,Z2),(Ra1,Rb3,X1,Z3),(Ra1,Rb3,X1,Z4),(Ra1,Rb3,X1,Z5),(Ra1

,Rb3,X1,Z6),(Ra1,Rb3,X1,Z7),(Ra1,Rb3,X1,Z8),(Ra1,Rb3,X1,Z9),(Ra1,Rb3,X1,Z10),(Ra1,Rb3,X1,Z11),(Ra1,Rb3,X1,Z12),(Ra1,Rb3,X1,Z13),(Ra1,Rb3,X1,Z14),(Ra1,Rb3,X1,Z15),(Ra1,Rb3,X1,Z16),(Ra1,Rb3,X1,Z17),(Ra1,Rb3,X1,Z18),(Ra1,Rb3,X1,Z19),(Ra1,Rb3,X1,Z20),(Ra1,Rb3,X1,Z21),(Ra1,Rb3,X1,Z22),(Ra1,Rb3,X1,Z23),(Ra1,Rb3,X1,Z24),(Ra1,Rb3,X1,Z25),(Ra1,Rb3,X1,Z26),(Ra1,Rb3,X1,Z27),(Ra1,Rb3,X1,Z28),(Ra1,Rb3,X1,Z29),(Ra1,Rb3,X1,Z30),(Ra1,Rb3,X1,Z31),(Ra1,Rb3,X1,Z32),(Ra1,Rb3,X1,Z33),(Ra1,Rb3,X1,Z34),(Ra1,Rb3,X1,Z35),(Ra1,Rb3,X1,Z36),(Ra1,Rb3,X1,Z37),(Ra1,Rb3,X1,Z38),(Ra1,Rb3,X1,Z39),(Ra1,Rb3,X2,Z1),(Ra1,Rb3,X2,Z2),(Ra1,Rb3,X2,Z3),(Ra1,Rb3,X2,Z4),(Ra1,Rb3,X2,Z5),(Ra1,Rb3,X2,Z6),(Ra1,Rb3,X2,Z7),(Ra1,Rb3,X2,Z8),(Ra1,Rb3,X2,Z9),(Ra1,Rb3,X2,Z10),(Ra1,Rb3,X2,Z11),(Ra1,Rb3,X2,Z12),(Ra1,Rb3,X2,Z13),(Ra1,Rb3,X2,Z14),(Ra1,Rb3,X2,Z15),(Ra1,Rb3,X2,Z16),(Ra1,Rb3,X2,Z17),(Ra1,Rb3,X2,Z18),(Ra1,Rb3,X2,Z19),(Ra1,Rb3,X2,Z20),(Ra1,Rb3,X2,Z21),(Ra1,Rb3,X2,Z22),(Ra1,Rb3,X2,Z23),(Ra1,Rb3,X2,Z24),(Ra1,Rb3,X2,Z25),(Ra1,Rb3,X2,Z26),(Ra1,Rb3,X2,Z27),(Ra1,Rb3,X2,Z28),(Ra1,Rb3,X2,Z29),(Ra1,Rb3,X2,Z30),(Ra1,Rb3,X2,Z31),(Ra1,Rb3,X2,Z32),(Ra1,Rb3,X2,Z33),(Ra1,Rb3,X2,Z34),(Ra1,Rb3,X2,Z35),(Ra1,Rb3,X2,Z36),(Ra1,Rb3,X2,Z37),(Ra1,Rb3,X2,Z38),(Ra1,Rb3,X2,Z39),(Ra1,Rb4,X1,Z1),(Ra1,Rb4,X1,Z2),(Ra1,Rb4,X1,Z3),(Ra1,Rb4,X1,Z4),(Ra1,Rb4,X1,Z

5),(Ra1,Rb4,X1,Z6),(Ra1,Rb4,X1,Z7),(Ra1,Rb4,X1,Z8),(Ra1,Rb4,X1,Z9),(Ra1,Rb4,X1,Z10),(Ra1,Rb4,X1,Z11),(Ra1,Rb4,X1,Z12),(Ra1,Rb4,X1,Z13),(Ra1,Rb4,X1,Z14),(Ra1,Rb4,X1,Z15),(Ra1,Rb4,X1,Z16),(Ra1,Rb4,X1,Z17),(Ra1,Rb4,X1,Z18),(Ra1,Rb4,X1,Z19),(Ra1,Rb4,X1,Z20),(Ra1,Rb4,X1,Z21),(Ra1,Rb4,X1,Z22),(Ra1,Rb4,X1,Z23),(Ra1,Rb4,X1,Z24),(Ra1,Rb4,X1,Z25),(Ra1,Rb4,X1,Z26),(Ra1,Rb4,X1,Z27),(Ra1,Rb4,X1,Z28),(Ra1,Rb4,X1,Z29),(Ra1,Rb4,X1,Z30),(Ra1,Rb4,X1,Z31),(Ra1,Rb4,X1,Z32),(Ra1,Rb4,X1,Z33),(Ra1,Rb4,X1,Z34),(Ra1,Rb4,X1,Z35),(Ra1,Rb4,X1,Z36),(Ra1,Rb4,X1,Z37),(Ra1,Rb4,X1,Z38),(Ra1,Rb4,X1,Z39),(Ra1,Rb4,X2,Z1),(Ra1,Rb4,X2,Z2),(Ra1,Rb4,X2,Z3),(Ra1,Rb4,X2,Z4),(Ra1,Rb4,X2,Z5),(Ra1,Rb4,X2,Z6),(Ra1,Rb4,X2,Z7),(Ra1,Rb4,X2,Z8),(Ra1,Rb4,X2,Z9),(Ra1,Rb4,X2,Z10),(Ra1,Rb4,X2,Z11),(Ra1,Rb4,X2,Z12),(Ra1,Rb4,X2,Z13),(Ra1,Rb4,X2,Z14),(Ra1,Rb4,X2,Z15),(Ra1,Rb4,X2,Z16),(Ra1,Rb4,X2,Z17),(Ra1,Rb4,X2,Z18),(Ra1,Rb4,X2,Z19),(Ra1,Rb4,X2,Z20),(Ra1,Rb4,X2,Z21),(Ra1,Rb4,X2,Z22),(Ra1,Rb4,X2,Z23),(Ra1,Rb4,X2,Z24),(Ra1,Rb4,X2,Z25),(Ra1,Rb4,X2,Z26),(Ra1,Rb4,X2,Z27),(Ra1,Rb4,X2,Z28),(Ra1,Rb4,X2,Z29),(Ra1,Rb4,X2,Z30),(Ra1,Rb4,X2,Z31),(Ra1,Rb4,X2,Z32),(Ra1,Rb4,X2,Z33),(Ra1,Rb4,X2,Z34),(Ra1,Rb4,X2,Z35),(Ra1,Rb4,X2,Z36),(Ra1,Rb4,X2,Z37),(Ra1,Rb4,X2,Z38),(Ra1,Rb4,X2,Z39),(Ra1,Rb5,X1,Z1),(Ra1,Rb5,X1,Z2),(Ra1,Rb5,X1,Z3),(Ra1,Rb5,X1,Z4),(Ra1,Rb

5,X1,Z5),(Ra1,Rb5,X1,Z6),(Ra1,Rb5,X1,Z7),(Ra1,Rb5,X1,Z8),(Ra1,Rb5,X1,Z9),(Ra1,Rb5,X1,Z10),(Ra1,Rb5,X1,Z11),(Ra1,Rb5,X1,Z12),(Ra1,Rb5,X1,Z13),(Ra1,Rb5,X1,Z14),(Ra1,Rb5,X1,Z15),(Ra1,Rb5,X1,Z16),(Ra1,Rb5,X1,Z17),(Ra1,Rb5,X1,Z18),(Ra1,Rb5,X1,Z19),(Ra1,Rb5,X1,Z20),(Ra1,Rb5,X1,Z21),(Ra1,Rb5,X1,Z22),(Ra1,Rb5,X1,Z23),(Ra1,Rb5,X1,Z24),(Ra1,Rb5,X1,Z25),(Ra1,Rb5,X1,Z26),(Ra1,Rb5,X1,Z27),(Ra1,Rb5,X1,Z28),(Ra1,Rb5,X1,Z29),(Ra1,Rb5,X1,Z30),(Ra1,Rb5,X1,Z31),(Ra1,Rb5,X1,Z32),(Ra1,Rb5,X1,Z33),(Ra1,Rb5,X1,Z34),(Ra1,Rb5,X1,Z35),(Ra1,Rb5,X1,Z36),(Ra1,Rb5,X1,Z37),(Ra1,Rb5,X1,Z38),(Ra1,Rb5,X1,Z39),(Ra1,Rb5,X2,Z1),(Ra1,Rb5,X2,Z2),(Ra1,Rb5,X2,Z3),(Ra1,Rb5,X2,Z4),(Ra1,Rb5,X2,Z5),(Ra1,Rb5,X2,Z6),(Ra1,Rb5,X2,Z7),(Ra1,Rb5,X2,Z8),(Ra1,Rb5,X2,Z9),(Ra1,Rb5,X2,Z10),(Ra1,Rb5,X2,Z11),(Ra1,Rb5,X2,Z12),(Ra1,Rb5,X2,Z13),(Ra1,Rb5,X2,Z14),(Ra1,Rb5,X2,Z15),(Ra1,Rb5,X2,Z16),(Ra1,Rb5,X2,Z17),(Ra1,Rb5,X2,Z18),(Ra1,Rb5,X2,Z19),(Ra1,Rb5,X2,Z20),(Ra1,Rb5,X2,Z21),(Ra1,Rb5,X2,Z22),(Ra1,Rb5,X2,Z23),(Ra1,Rb5,X2,Z24),(Ra1,Rb5,X2,Z25),(Ra1,Rb5,X2,Z26),(Ra1,Rb5,X2,Z27),(Ra1,Rb5,X2,Z28),(Ra1,Rb5,X2,Z29),(Ra1,Rb5,X2,Z30),(Ra1,Rb5,X2,Z31),(Ra1,Rb5,X2,Z32),(Ra1,Rb5,X2,Z33),(Ra1,Rb5,X2,Z34),(Ra1,Rb5,X2,Z35),(Ra1,Rb5,X2,Z36),(Ra1,Rb5,X2,Z37),(Ra1,Rb5,X2,Z38),(Ra1,Rb5,X2,Z39),(Ra1,Rb6,X1,Z1),(Ra1,Rb6,X1,Z2),(Ra1,Rb6,X1,Z3),(Ra1,Rb6,X1,Z4),(

Ra1,Rb6,X1,Z5),(Ra1,Rb6,X1,Z6),(Ra1,Rb6,X1,Z7),(Ra1,Rb6,X1,Z8),(Ra1,Rb6,X1,Z9),(Ra1,Rb6,X1,Z10),(Ra1,Rb6,X1,Z11),(Ra1,Rb6,X1,Z12),(Ra1,Rb6,X1,Z13),(Ra1,Rb6,X1,Z14),(Ra1,Rb6,X1,Z15),(Ra1,Rb6,X1,Z16),(Ra1,Rb6,X1,Z17),(Ra1,Rb6,X1,Z18),(Ra1,Rb6,X1,Z19),(Ra1,Rb6,X1,Z20),(Ra1,Rb6,X1,Z21),(Ra1,Rb6,X1,Z22),(Ra1,Rb6,X1,Z23),(Ra1,Rb6,X1,Z24),(Ra1,Rb6,X1,Z25),(Ra1,Rb6,X1,Z26),(Ra1,Rb6,X1,Z27),(Ra1,Rb6,X1,Z28),(Ra1,Rb6,X1,Z29),(Ra1,Rb6,X1,Z30),(Ra1,Rb6,X1,Z31),(Ra1,Rb6,X1,Z32),(Ra1,Rb6,X1,Z33),(Ra1,Rb6,X1,Z34),(Ra1,Rb6,X1,Z35),(Ra1,Rb6,X1,Z36),(Ra1,Rb6,X1,Z37),(Ra1,Rb6,X1,Z38),(Ra1,Rb6,X1,Z39),(Ra1,Rb6,X2,Z1),(Ra1,Rb6,X2,Z2),(Ra1,Rb6,X2,Z3),(Ra1,Rb6,X2,Z4),(Ra1,Rb6,X2,Z5),(Ra1,Rb6,X2,Z6),(Ra1,Rb6,X2,Z7),(Ra1,Rb6,X2,Z8),(Ra1,Rb6,X2,Z9),(Ra1,Rb6,X2,Z10),(Ra1,Rb6,X2,Z11),(Ra1,Rb6,X2,Z12),(Ra1,Rb6,X2,Z13),(Ra1,Rb6,X2,Z14),(Ra1,Rb6,X2,Z15),(Ra1,Rb6,X2,Z16),(Ra1,Rb6,X2,Z17),(Ra1,Rb6,X2,Z18),(Ra1,Rb6,X2,Z19),(Ra1,Rb6,X2,Z20),(Ra1,Rb6,X2,Z21),(Ra1,Rb6,X2,Z22),(Ra1,Rb6,X2,Z23),(Ra1,Rb6,X2,Z24),(Ra1,Rb6,X2,Z25),(Ra1,Rb6,X2,Z26),(Ra1,Rb6,X2,Z27),(Ra1,Rb6,X2,Z28),(Ra1,Rb6,X2,Z29),(Ra1,Rb6,X2,Z30),(Ra1,Rb6,X2,Z31),(Ra1,Rb6,X2,Z32),(Ra1,Rb6,X2,Z33),(Ra1,Rb6,X2,Z34),(Ra1,Rb6,X2,Z35),(Ra1,Rb6,X2,Z36),(Ra1,Rb6,X2,Z37),(Ra1,Rb6,X2,Z38),(Ra1,Rb6,X2,Z39),(Ra1,Rb7,X1,Z1),(Ra1,Rb7,X1,Z2),(Ra1,Rb7,X1,Z3),(Ra1,Rb7,X

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【實施例】

以下顯示實施例來具體地說明本發明，但本發明不被限定於此。再者，各縮寫符號具有以下所示意義。

Me：甲基

Et：乙基

Bu：丁基

Ac:乙醯基

TMS：四甲基矽烷

TMS-Cl：三甲基矽烷基氯

DMSO：二甲亞碸

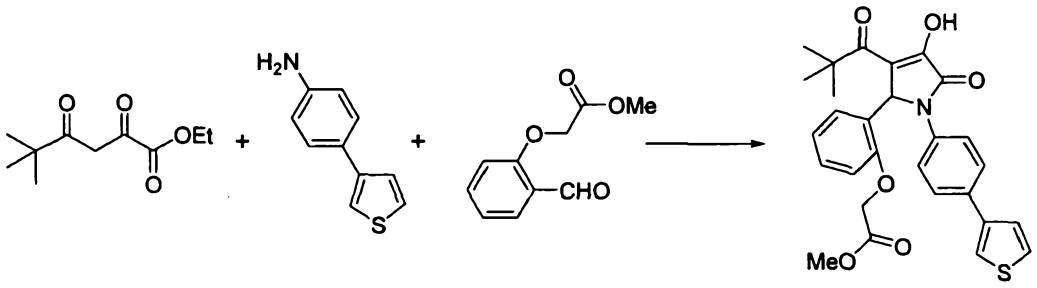
DMF：二甲基甲醯胺

THF：四氫呋喃

rt：室溫

實施例 1

4-(2,2-二甲基丙醯基)-3-羥基-5-(2-甲氧基羰基甲基氧基苯基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮之製造

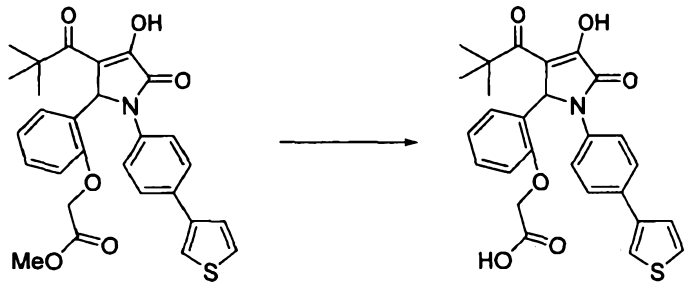


將三甲基乙醯丙酮酸乙酯(0.40 g, 2 mmol)、4-噻吩-3-基苯胺(0.35 g, 2 mmol)、2-(甲氧基羰基甲基氧基)苯甲醛(0.39, 2 mmol)、乙酸(0.057 mL, 1 mmol)及二噁烷(4 mL)之混合液在加熱回流下攪拌一夜。反應後添加飽和碳酸氫鈉水及飽和食鹽水於反應液，以乙酸乙酯萃取。以無水硫酸鈉乾燥萃取液後，減壓濃縮。以矽膠管柱色層分析(甲醇/氯仿)純化所得殘渣，以乙酸乙酯及二異丙基醚粉末化所得目的物，得到淡褐色固體之 4-(2,2-二甲基丙醯基)-3-羥基-5-(2-甲氧基羰基甲基氧基苯基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.42 g，產率 41%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.10 (9H, s), 3.78 (3H, s), 4.50-4.90 (2H, m), 6.00-6.45 (1H, m), 6.60-7.11 (11H, m).

實施例 2

5-(2-羥基羰基甲基氧基苯基)-4-(2,2-二甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮之製造

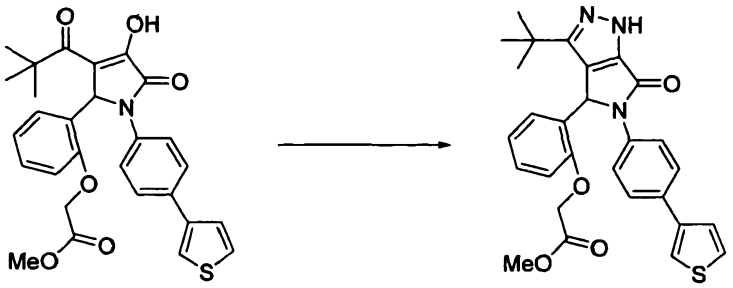


於 4-(2,2-二甲基丙醯基)-3-羥基-5-(2-甲氧基羰基甲基氧基苯基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.172 g, 0.34 mmol)、THF(1.72 mL)及甲醇(1.72 mL)之混合液添加1mol/L氫氧化鋰水溶液(1.02 mL)，在室溫攪拌1小時。反應後添加2mol/L鹽酸(0.52 mL)及水(14 mL)於反應液，濾取析出之目的物。將所得目的物溶解於乙酸乙酯，以無水硫酸鈉乾燥後，減壓濃縮。以乙基醚及二異丙基醚粉末化所得殘渣，得到淡橙色固體之 5-(2-羥基羰基甲基氧基苯基)-4-(2,2-二甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.137 g，產率 82%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.10 (9H, s), 4.85 (2H, s), 6.46 (1H, brs), 6.76-7.75 (11H, m).

實施例 3

3-第三丁基-5-(4-噻吩-3-基苯基)-4-(2-甲氧基羰基甲基氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造

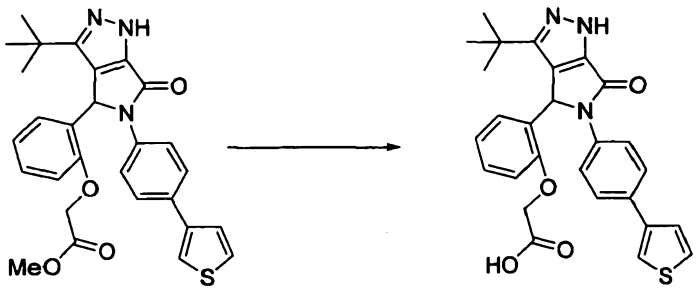


將 4-(2,2-二甲基丙醯基)-3-羥基-5-(2-甲氧基羰基甲基氧基苯基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.207 g, 0.41 mmol)、肼 1 水合物(0.022 mL, 0.45 mmol)及乙酸(3.1 mL)之混合液在 95℃攪拌 1 小時。反應後，添加飽和碳酸氫鈉水於反應液，以氯仿萃取。以飽和食鹽水清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。以乙基醚及二異丙基醚粉末化所得殘渣，得到淡褐色固體之 3-第三丁基-5-(4-噻吩-3-基苯基)-4-(2-甲氧基羰基甲基氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.191 g，產率 93%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.05 (9H, s), 3.78 (3H, s), 4.94 (2H, s), 6.70-7.77 (12H, m), 13.4 (1H, brs).

實施例 4

3-第三丁基-5-(4-噻吩-3-基苯基)-4-(2-羥基羰基甲基氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造

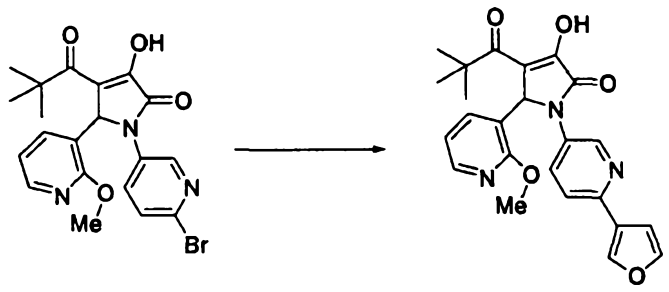


於 3-第三丁基-5-(4-噻吩-3-基苯基)-4-(2-甲氧基羰基甲基氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.124 g, 0.25 mmol)、THF(1.24 mL)及甲醇(1.24 mL)之混合液添加1mol/L氫氧化鋰水溶液(0.74 mL)，在室溫攪拌 1.5 小時。反應後，添加 2mol/L 鹽酸(0.38 mL)及水(10 mL)於反應液，濾取析出之目的物。將所得目的物溶解於乙酸乙酯，以無水硫酸鈉乾燥後，減壓濃縮。以乙基醚及二異丙基醚粉末化所得殘渣，得到微褐色固體之 5-(2-羥基羰基甲基氧基苯基)-4-(2,2-二甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.104 g，產率 87%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.05 (9H, s), 4.78 (2H, s), 6.70-7.80 (12H, m), 13.33 (1H, brs).

實施例 5

1-(6-呋喃-3-基-3-吡啶基)-4-(2,2-二甲基丙醯基)-3-羥基-5-(2-甲氧基-3-吡啶基)-1,5-二氫吡咯-2-酮之製造



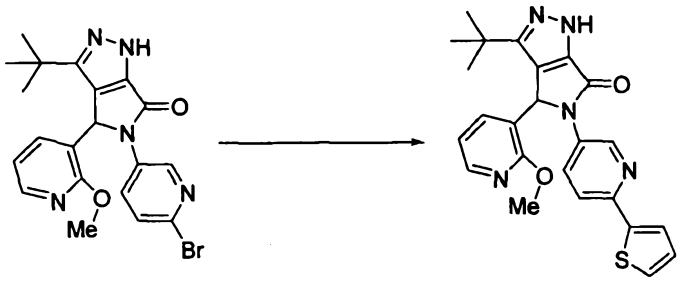
1-(6-溴-3-吡啶基)-4-(2,2-二甲基丙醯基)-3-羥基-5-(2-甲氧基-3-吡啶基)-1,5-二氫吡咯-2-酮(0.10 g, 0.22 mmol)、呋喃-3-基硼酸(0.038 g, 0.34 mmol)、磷酸三鉀(0.14 mg, 0.67 mmol)、乙二醇二甲基醚(3 mL)及水(0.6 mL)之混合液經氮取

代後，添加[1,1'-雙(二苯基膦)二茂鐵]二氯鈀(II) 二氯甲烷加合物(adduct)(0.018 g, 0.022 mmol)，在加熱回流下攪拌4小時。反應後，添加飽和氯化銨水溶液於反應液，以乙酸乙酯萃取。以飽和食鹽水清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣，以乙酸乙酯及正己烷粉末化所得目的物，得到無色固體之 1-(6-呋喃-3-基-3-吡啶基)-4-(2,2-二甲基丙醯基)-3-羥基-1-5-(2-甲氧基-3-吡啶基)-1,5-二氫吡咯-2-酮(0.045 g，產率 46%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.11 (9H, s), 3.79 (3H, brs), 6.24 (1H, brs), 6.86 (1H, m), 6.96 (1H, m), 7.64-7.95 (4H, m), 8.23 (1H, s), 8.71 (1H, s), 12.31 (1H, brs).

實施例 6

3-第三丁基-5-(6-噻吩-2-基-3-吡啶基)-4-(2-甲氧基-3-吡啶基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造



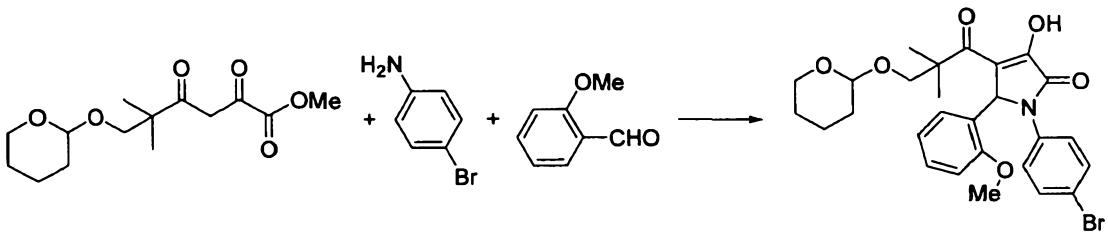
5-(6-溴-3-吡啶基)-3-第三丁基-4-(2-甲氧基-3-吡啶基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.10 g, 0.23 mmol)、噻吩-2-基硼酸(0.043 g, 0.34 mmol)、磷酸三鉀(0.14 mg, 0.67 mmol)、乙二醇二甲基醚(3 mL)及水(0.6 mL)之混合

液經氮取代後，添加[1,1'-雙(二苯基膦)二茂鐵]二氯鈀(II)二氯甲烷加合物(0.018 g, 0.022 mmol)，在加熱回流下攪拌3小時。反應後，添加水於反應液，以乙酸乙酯萃取。以無水硫酸鈉乾燥萃取液後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣，以乙酸乙酯及正己烷粉末化所得目的物，得到無色固體之 1-(6-呋喃-3-基-3-吡啶基)-4-(2,2-二甲基丙醯基)-3-羥基-1-5-(2-甲氧基-3-吡啶基)-1,5-二氫吡咯-2-酮(0.089 g，產率 88%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.07 (9H, s), 3.97 (3.55) (3H, s), 6.56-7.28 (4H, m), 7.58 (1H, d, J=5.0), 7.69 (1H, d, J=3.7), 7.87-8.10 (3H, m), 8.64 (1H, s), 13.36 (1H, m).

實施例 7

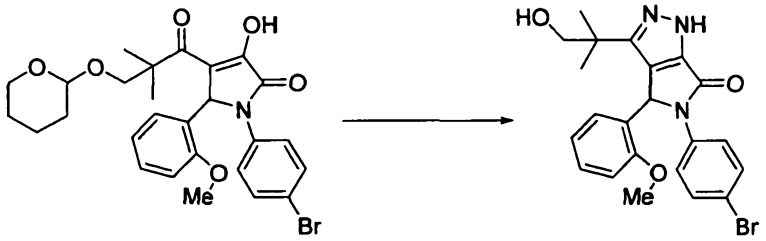
3-(1-羥基甲基-1-甲基乙基)-4-(2-甲氧基苯基)-5-(4-噻吩-3-基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造



將 5,5-二甲基-2,4-二酮基-6-(四氫-2H-哌喃-2-基氧基)己酸甲酯(4.29 g, 15 mmol)、4-溴苯胺(2.58 g, 15 mmol)、2-甲氧基苯甲醛(1.812 mL, 15 mmol)、乙酸(0.343 mL, 6 mmol)及二噁烷(15 ml)之混合液在加熱回流下攪拌一夜。反應後，減壓濃縮，以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣。以乙酸乙酯及正己烷粉末化所得目的物，得到無色固

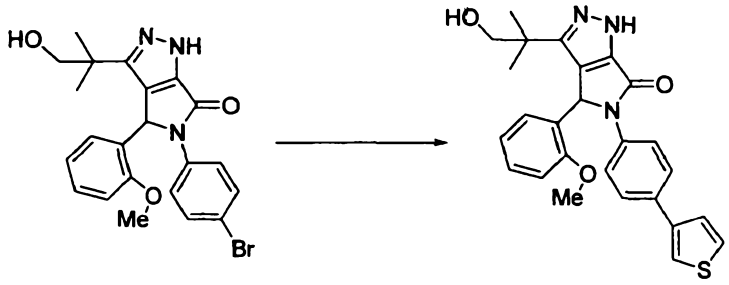
體之 1-(4-溴苯基)-4-(2,2-二甲基-3-四氫-2H-哌喃-2-基氧基丙醯基)-3-羥基-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(2.69 g，產率 33%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.08 (3H, s), 1.13 (3H, s), 1.20-1.40 (6H, m), 3.50-3.90 (7H, m), 4.37 (1H, m), 6.31 (1H, brs), 6.70-7.44 (8H, m), 12.23 (1H, brs).



將 1-(4-溴苯基)-4-(2,2-二甲基-3-四氫-2H-哌喃-2-基氧基丙醯基)-3-羥基-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(1.51 g, 2.77 mmol)、肼水合物(0.204 mL, 4.16 mmol)及乙酸(3 mL)之混合液在 95℃攪拌 2 小時。反應後，添加飽和碳酸氫鈉水(150 mL)於反應液，以乙酸乙酯萃取。以飽和碳酸氫鈉水清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。以乙酸乙酯粉末化所得殘渣，得到無色固體之 5-(4-溴苯基)-3-(1-羥基甲基-1-甲基乙基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(1.02 g，產率 81%)。

1H-NMR (δ ppm TMS / DMSO-d6): 0.88 (3H, s), 1.00 (3H, s), 3.11 (2H, m), 3.87 (3H, s), 4.73 (1H, brs), 6.30-7.50 (9H, m), 13.21 (1H, m).

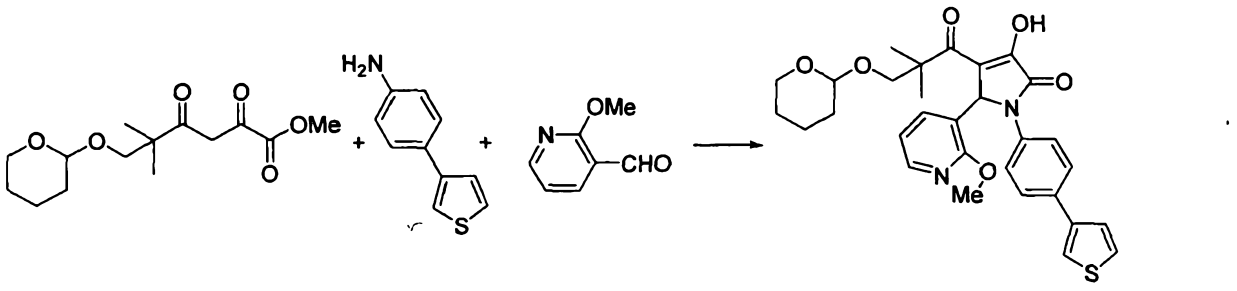


5-(4-溴苯基)-3-(1-羥基甲基-1-甲基乙基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.15 g, 0.33 mmol)、噻吩-3-基硼酸(0.063.g, 0.49 mmol)、磷酸三鉀(0.21 mg, 0.99 mmol)、乙二醇二甲基醚(3 mL)及水(0.6 mL)之混合液經氮取代後，添加[1,1'-雙(二苯基膦)二茂鐵]二氯鈀(II)二氯甲烷加合物(0.027 mg, 0.033 mmol)，在加熱回流下攪拌5小時。反應後，以矽膠管柱色層分析(乙酸乙酯/正己烷)純化反應液。以乙酸乙酯及正己烷粉末化所得目的物，得到無色固體之 3-(1-羥基甲基-1-甲基乙基)-4-(2-甲氧基苯基)-5-(4-噻吩-3-基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.038 g，產率 25%)。

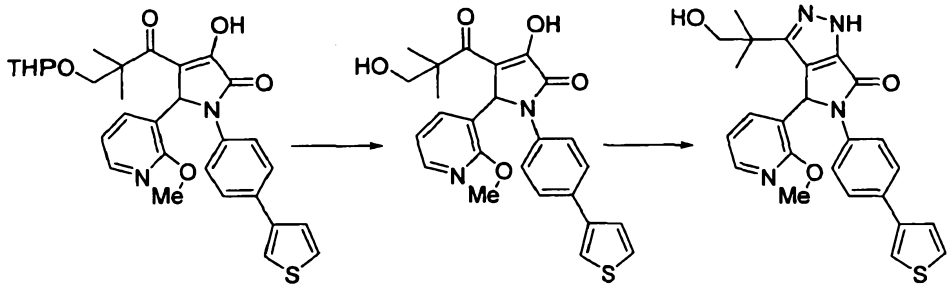
1H-NMR (δ ppm TMS / DMSO-d6): 0.91 (3H, s), 1.04 (3H, s), 3.25 (2H, m), 3.91 (3H, s), 4.74 (1H, s), 6.33-7.78 (9H, m), 13.21 (1H, m)

實施例 8

3-(1-羥基甲基-1-甲基乙基)-4-(2-甲氧基-3-吡啶基)-5-(4-噻吩-3-基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造



將 5,5-二甲基-2,4-二酮基-6-(四氫-2H-哌喃-2-基氧基)己酸甲酯(0.29 mg, 1.0 mmol)、4-(3-噻吩基)苯胺(0.18 g, 1.0 mmol)、2-甲氧基菸鹼醛(0.14 g, 1.0 mmol)、乙酸(0.043 mL, 0.75 mmol)及二噁烷(2 ml)之混合液在加熱回流下攪拌一夜。反應後，減壓濃縮反應液，以矽膠管柱色層分析(甲醇/氯仿)純化所得殘渣，得到淡黃色固體之 4-(2,2-二甲基-3-四氫-2H-哌喃-2-基氧基丙醯基)-3-羥基-5-(2-甲氧基-3-吡啶基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.30 g，產率55%)。



於 4-(2,2-二甲基-3-四氫-2H-哌喃-2-基氧基丙醯基)-3-羥基-5-(2-甲氧基-3-吡啶基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.30 g, 0.55 mmol)、甲醇(3 mL)及氯仿(3 mL)之混合液添加對甲苯磺酸水合物(0.158 g, 0.8mmol)，在室溫攪拌 3 小時。反應後，添加飽和碳酸氫鈉水及飽和食鹽水於反應液，以氯仿萃取。以無水硫酸鈉乾燥萃取液後，減壓濃縮。

於所得 4-(2,2-二甲基-3-羥基丙醯基)-3-羥基-5-(2-甲氧基-3-吡啶基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.233 g)之粗製物添加乙酸(2 mL)及肼水合物(0.074 mL, 1.5 mmol)，在 50℃攪拌 1 小時。反應後，添加飽和碳酸氫鈉水於反應液，以氯仿萃取。以無水硫酸鈉乾燥萃取液後，減壓濃縮。以乙酸乙酯粉末化所得殘渣，得到無色固體之 3-(1-羥基甲基-1-甲基乙基)-4-(2-甲氧基-3-吡啶基)-5-(4-噻吩-3-基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.061 g，產率 26%)。

1H-NMR (δ ppm TMS / DMSO-d6): 0.95 (3H, s), 1.06 (3H, s), 3.23 (2H, m), 4.06 (2H, s), 4.78 (1H, brs), 6.43-8.10 (10H, m), 13.40 (1H, m).

實施例 9

3-(1,1-二羥基甲基乙基)-4-(2-甲氧基苯基)-5-(4-噻吩-3-基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造



於 3-羥基-2-羥基甲基-2-甲基丙酸(6.71 g, 50mmol)、二甲氧基丙烷(7.99 mL, 65mmol)及丙酮(50 mL)之混合液添加對甲苯磺酸水合物(0.048 g, 0.25mmol)，在室溫攪拌 2.5 小時。反應後，添加碳酸氫鈉(0.1 g)於反應液，在室溫攪拌 5 分鐘後，減壓濃縮，添加水於所得殘渣，以乙基醚萃取。以無水硫酸鈉乾燥萃取液後，減壓濃縮，得到無色油狀物之 2,2,5-三甲基-1,3-二噁烷-5-羧酸(7.87 g，產率 90%)。

1H-NMR (δ ppm TMS / CDCl3): 1.20 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 3.70 (2H, d, J=11.7), 4.16 (2H, d, J=11.7).



在氮氣氛圍氣下，於 2,2,5-三甲基-1,3-二噁烷-5-羧酸(1.0 g, 5.74 mmol)及 DMF(10 mL)之混合液添加 N,O-二甲基羥基胺鹽酸鹽(0.84 g, 8.6 mmol)、1-羥基苯并三唑水合物(1.32 g, 8.6 mmol)、鹽酸 1-乙基-3-(3-二甲基胺基丙基)碳二醯亞胺(1.651 g, 8.61 mmol)及三乙基胺(2.39 mL, 17.2 mmol)，在室溫攪拌 3 小時。反應後、添加水於反應液，以乙酸乙酯萃取。以飽和食鹽水清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮，得到無色油狀物之 N-甲氧基-N,2,2,5-四甲基-1,3-二噁烷-5-羧酸醯胺(1.08 g，產率 86%)。

1H-NMR (δ ppm TMS / CDCl3): 1.38 (3H, s), 1.41 (3H, s), 1.42 (3H, s), 3.18 (3H, s), 3.69 (3H, s), 3.76 (2H, d, J=11.7), 4.19 (2H, d, J=11.7).

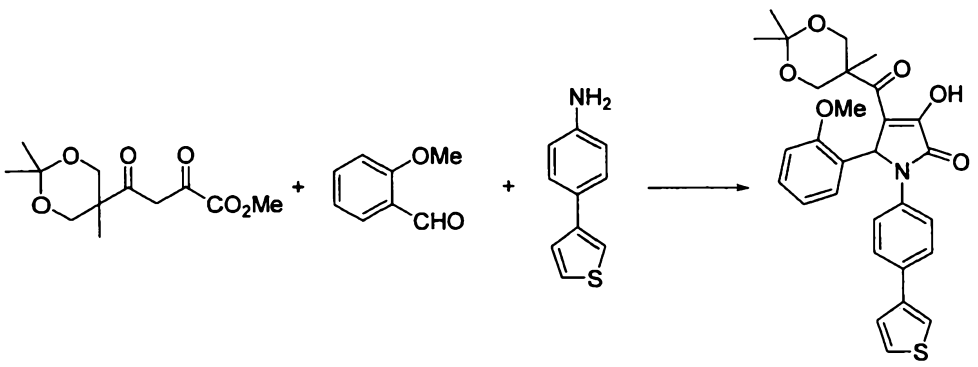


在氮氣氛圍氣下，在 0℃緩慢添加 3mol/L 溴化甲基鎂 THF 溶液(2.46 mL, 7.4 mmol)於 N-甲氧基-N,2,2,5-四甲基-1,3-二噁烷-5-羧酸醯胺(1.07 g, 4.92 mmol)及 THF(10 mL)之混合液，在 0℃攪拌 4 小時。反應後，添加飽和氯化銨水溶液於反應液，以乙酸乙酯萃取。以飽和食鹽水清洗萃取

液，以無水硫酸鈉乾燥後，減壓濃縮，得到無色油狀物之1-(2,2,5-三甲基-1,3-二噁烷-5-基)乙烷(0.76 g，產率 90%)。1H-NMR (δ ppm TMS / CDCl3): 1.03 (3H, s), 1.37 (3H, d, J=0.5), 1.45 (3H, d, J=0.5), 2.28 (3H, s), 3.68 (2H, d, J=12.2), 4.16 (2H, d, J=12.2).



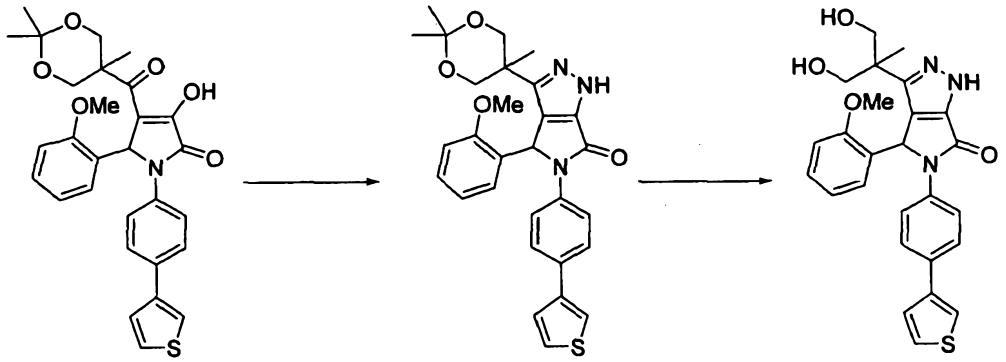
在氮氣氛圍氣下添加氫化鈉(0.16 g, 6.6 mmol)於1-(2,2,5-三甲基-1,3-二噁烷-5-基)乙烷(0.76g, 4.4 mmol)及THF(7.6 mL)之混合液，在室溫攪拌 0.5 小時。之後於反應液添加草酸二甲酯(0.78 g, 6.6 mmol)，在加熱回流下攪拌 2 小時。反應後，添加飽和氯化銨水溶液，以乙酸乙酯萃取。以飽和食鹽水清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣，得到無色油狀物之 2,4-二酮基-4-(2,2,5-三甲基-1,3-二噁烷-5-基)丁酸甲酯(1.0 g，產率 88%)。



將 2,4-二酮基-4-(2,2,5-三甲基-1,3-二噁烷-5-基)丁酸甲酯(0.26 mg, 1.0 mmol)、4-(3-噻吩基)苯胺(0.18 g, 1.0 mmol)、

2-甲氧基苯甲醛(0.12 mL, 1.0 mmol)、乙酸(0.023 mL, 0.40 mmol)及二噁烷(2 ml)之混合液，在加熱回流下攪拌一夜。反應後，減壓濃縮。於所得殘渣添加二異丙基醚，冷卻之。濾取析出之目的物，得到微黃色固體之 3-羥基-4-(2,2,5-三甲基-1,3-二噁烷-5-基)羰基-5-(2-甲氧基苯基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.29g，產率 56%)。

1H-NMR (δ ppm TMS / CDCl3): 0.99 (3H, s), 1.12 (3H, s), 1.40 (3H, s), 3.63-3.76 (2H, m), 3.89 (3H, brs), 4.20-4.37 (2H, m), 6.50-7.58 (12H, m), 9.00 (1H, brs).



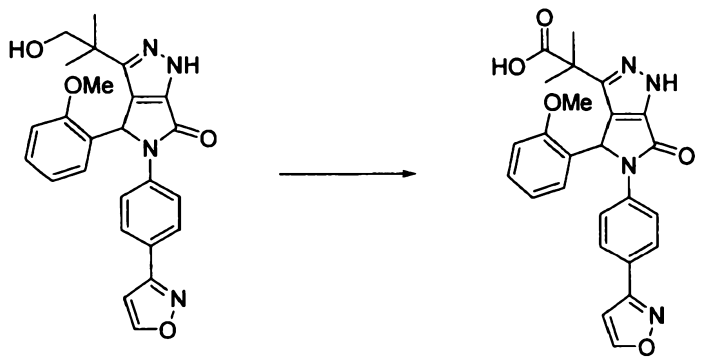
將 3-羥基-4-(2,2,5-三甲基-1,3-二噁烷-5-基)羰基-5-(2-甲氧基苯基)-1-(4-噻吩-3-基苯基)-1,5-二氫吡咯-2-酮(0.15 g, 0.3 mmol)、肼水合物(0.07 mL, 1.4 mmol)及乙酸(1 mL)之混合液，在加熱回流下攪拌一夜。減壓濃縮反應液後，於所得殘渣添加 2mol/L 鹽酸/甲醇溶液(2.89 mL, 5.8 mmol)，在加熱回流下攪拌 6 小時。減壓濃縮反應液後，添加飽和碳酸氫鈉水，以氯仿萃取。以無水硫酸鎂乾燥萃取液後，減壓濃縮。以矽膠管柱色層分析(甲醇/氯仿)純化所得殘渣。以乙酸乙酯及正己烷粉末化所得目的物，得到無色固體之 3-(1,1-

二羥基甲基乙基)-4-(2-甲氧基苯基)-5-(4-噻吩-3-基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.105 g，產率77%)。

1H-NMR (δ ppm TMS / DMSO-d6): 0.95 (3H, s), 3.91 (2H, m), 4.57 (2H, m), 6.29-7.78 (12H, m), 12.97 (1H, m).

實施例 10

3-(1-羥基羰基-1-甲基乙基)-5-(4-異噁唑基-3-基苯基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造

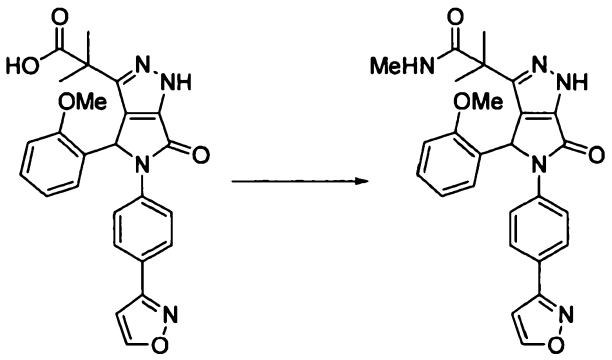


於過碘酸(0.32 mg, 1.4 mmol)之乙腈(15 mL)溶液添加3-(1-羥基甲基-1-甲基乙基)-5-(4-異噁唑基-3-基苯基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.206 g, 0.463 mmol)之二氯甲烷溶液(15 mL)及氯鉻酸吡啶鹽(0.01 g, 0.046 mmol)，在室溫攪拌 4 小時。反應後，添加水於反應液，以乙酸乙酯萃取。以飽和食鹽水清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。於所得殘渣添加二氯甲烷，濾取析出之目的物，得到微黃色固體之 3-(1-羥基羰基-1-甲基乙基)-5-(4-異噁唑基-3-基苯基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.11g，產率 49%)。

1H-NMR (δ ppm TMS / DMSO-d6): 1.19 (3H, s), 1.30 (3H, s), 3.91 (3H, brs), 6.40-7.19 (6H, m), 7.66-7.80 (4H, m), 8.94 (1H, d, J=1.7), 12.50 (1H, brs), 13.55 (1H, brs).

實施例 11

5-(4-異噁唑基-3-基苯基)-4-(2-甲氧基苯基)-3-[1-(N-甲基胺甲醯基)-1-甲基乙基]-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮之製造



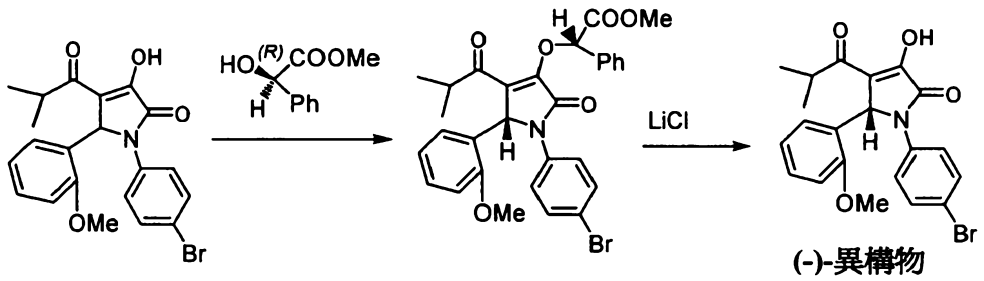
於 3-(1-羥基羰基-1-甲基乙基)-5-(4-異噁唑基-3-基苯基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.05 g, 0.11 mmol)及 DMF(2 mL)之混合液，添加甲基胺鹽酸鹽(0.013 g, 0.19 mmol)、1-羥基苯并三唑(0.039 g, 0.29 mmol)、4-二甲基胺基吡啶(0.005 g, 0.04 mmol)、鹽酸 1-乙基-3-(3-二甲基胺基丙基)碳二醯亞胺(0.058 g, 0.3 mmol)及三乙基胺(0.040 mL, 0.29 mmol)，在室溫攪拌 2 小時。反應後，冰冷下添加水(2 mL)於反應液，些微攪拌。濾取析出之目的物後，以矽膠管柱色層分析(乙酸乙酯/正己烷)純化，得到微褐色固體之 5-(4-異噁唑基-3-基苯基)-4-(2-甲氧基苯基)-3-[1-(N-甲基胺甲醯基)-1-甲基乙基]-4,5-二氫-1H-吡咯

并[3,4-c]吡唑-6-酮(0.036 g，產率 40%)。

1H-NMR (δ ppm TMS / DMSO-d6) 1.12 (3H, s), 1.29 (3H, s), 2.43 (3H, brs), 3.91 (3H, brs), 6.63-7.20 (7H, m), 7.67-7.82 (4H, m), 8.95 (1H, d, J=1.7), 13.43 (1H, brs).

實施例 12

(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-溴苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮之製造



在室溫下於1分鐘添加偶氮二羧酸二甲氧基乙酯(1.29 g, 5.5 mmol)於 4-(2-甲基丙醯基)-3-羥基-1-(4-溴苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(2.15 g, 5 mmol)、2-羥基-2-苯基乙酸(R)-甲酯(1.00 g, 6.0 mmol)、三苯膦(1.44 g, 5.5 mmol)及二噁烷(15 mL)之混合液，在室溫攪拌6小時。於反應液添加水(200 mL)，以乙酸乙酯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鎂乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣。再結晶(乙酸乙酯/正己烷)所得之非鏡像異構物混合物，得到淡黃色結晶之非鏡像異構物(0.80 g，產率 28%)。

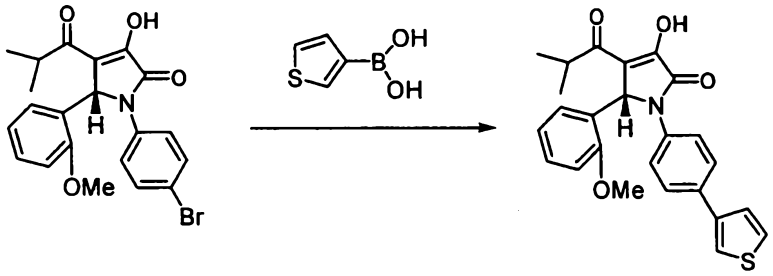
所得之非鏡像異構物(0.59 g, 1 mmol)、氯化鋰(0.127 g, 3 mmol)及1,3-二甲基-2-咪唑啶酮(3 mL)之混合液，在80℃攪拌6小時。於反應液添加水(200 mL)及1mol/L鹽酸(3 mL)，

以甲苯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鎂乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣。再結晶(乙酸乙酯/正己烷)所得之目的物，得到淡黃色結晶之(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-溴苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(0.40 g，產率 93%)。

$[\alpha]_D$: -142.2±3.6°.(in CHCl3), 1H-NMR (δ ppm TMS / DMSO-d6) 0.88 (3H, d, J=6.9), 0.91 (3H, d, J=6.9), 3.33 (1H, sept, J=6.9), 3.81 (3H, brs), 6.23 (1H, brs), 6.75-7.15 (4H, m), 7.45-7.53 (4H, m), 12.00 (1H, brs).

實施例 13

(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮之製造



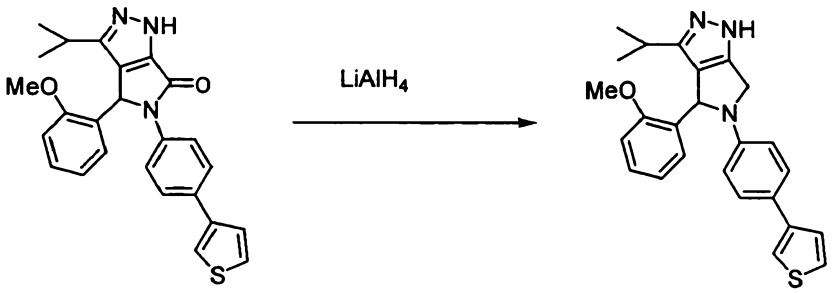
(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-溴苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(0.10 g, 0.23 mmol)、3-噻吩硼酸(0.045 g, 0.35 mmol)、磷酸三鉀(0.148 g, 0.7 mmol)、乙二醇二甲基醚(3 mL)及水(3 mL)之混合液經氮取代後，添加[1,1'-雙(二苯基膦)二茂鐵]二氯鈀(II)二氯甲烷加合物(0.019 g, 0.023 mmol)，回流下攪拌 3 小時。於反應液添加

水(50 mL)，以二氯甲烷(50 mL)萃取。以飽和食鹽水(50 mL)清洗萃取液，以無水硫酸鎂乾燥後，減壓濃縮。以矽膠管柱色層分析(甲醇/氯仿)純化所得殘渣。以乙酸乙酯/正己烷粉末化所得之目的物，得到淡褐色粉末之(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(0.029 g，產率 29%)。

$[\alpha]_D$: -57.4±1.9°.(in CHCl3), 1H-NMR (δ ppm TMS / DMSO-d6) 0.89 (3H, d, J=6.9), 0.92 (3H, d, J=6.9), 3.34 (1H, sept, J=6.9), 3.87 (3H, brs), 6.32 (1H, brs), 6.75-7.15 (5H, m), 7.51 (1H, d, J=1.1), 7.58-7.63 (4H, m), 7.81 (1H, m), 12.00 (1H, brs).

實施例 14

3-異丙基-5-(4-噻吩-3-基苯基)-4-(2-甲氧基苯基)-1,4,5,6-四氫-1H-吡咯并[3,4-c]吡唑之製造



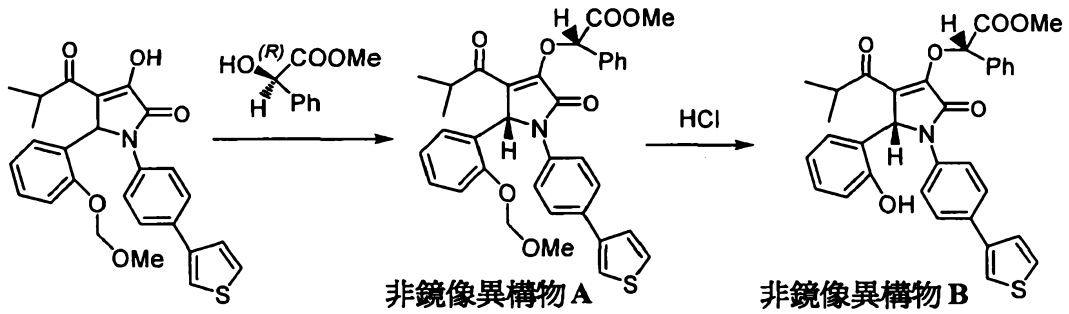
於 3-異丙基-5-(4-噻吩-3-基苯基)-4-(2-甲氧基苯基)-4,5-二氫-1H-吡咯并[3,4-c]吡唑-6-酮(0.72 g, 1.65 mmol)及二噁烷(40 mL)之混合液添加氫化鋁鋰(0.19 g, 5 mmol)，在加熱回流下攪拌 2 小時。添加反應液於冰水(100 mL)及2mol/L 鹽酸(10 mL)之混合液，以氯仿(100 mL)萃取。以飽

和食鹽水(100 mL)清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。以矽膠管柱色層分析(甲醇/氯仿)純化所得殘渣。以醚粉末化所得之目的物，得到淡褐色粉末之 3-異丙基-5-(4-噻吩-3-基苯基)-4-(2-甲氧基苯基)-1,4,5,6-四氫-1H-吡咯并[3,4-c]吡唑(0.029 g，產率 29%)。

1H-NMR (δ ppm TMS / DMSO-d6) 0.86 (3H, d, J=7.0), 0.97 (3H, d, J=7.0), 2.78 (1H, sept, J=7.0), 3.94 (3H, s), 4.42 (1H, d, J=12.6), 4.77 (1H, d, J=12.6), 6.11 (1H, d, J=2.0), 6.55-7.53 (11H, m), 12.32 (1H, s).

實施例 15

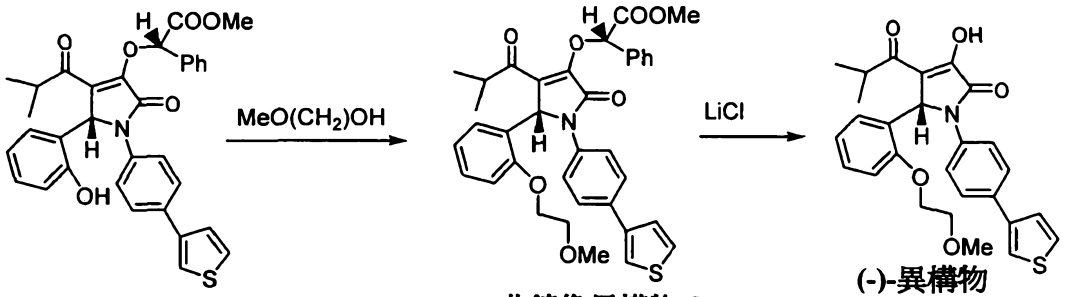
(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-5-(2-甲氧基乙氧基苯基)-1,5-二氫吡咯-2-酮之製造



在室溫下於2分鐘添加偶氮二羧酸二甲氧基乙酯(6.67 g, 28.5 mmol)於 4-(2-甲基丙醯基)-3-羥基-1-(4-溴苯基)-5-(2-甲氧基甲基苯基)-1,5-二氫吡咯-2-酮(11.0 g, 23.7 mmol)、(R)-甲基 2-羥基-2-苯基乙酸鹽(4.73 g, 28.5 mmol)、三苯膦(7.47 g, 28.5 mmol)及 THF(150 mL)之混合液，在室溫攪拌一夜。於反應液添加水(200 mL)，以甲苯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鎂乾燥後，減

壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣。以乙酸乙酯/正己烷再結晶所得之非鏡像異構物混合物，得到淡黃色結晶之非鏡像異構物 A(4.98 g，產率 34%)。1H-NMR (δ ppm TMS / CDCl3) 0.85 (3H, d, J=7.0), 1.15 (3H, d, J=7.0), 3.49 (1H, sept, J=7.0), 3.57 (3H, brs), 3.73 (3H, s), 5.25 (2H, brs), 6.40-6.80 (2H, m), 7.05-7.63 (16H, m).

於非鏡像異構物 A(4.0 g, 6.5 mmol)之乙酸乙酯(33 mL)溶液添加 2mol/l 鹽酸/甲醇溶液(32.7 mL)，在 60℃攪拌 1 小時。於反應液添加水(200 mL)，以乙酸乙酯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鎂乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣。以乙酸乙酯/正己烷粉末化所得之非鏡像異構物混合物，得到黃色粉末之非鏡像異構物 B(2.93 g，產率 79%)。1H-NMR (δ ppm TMS / CDCl3) 0.90 (3H, d, J=6.9), 1.24 (3H, d, J=6.9), 3.52 (1H, sept, J=6.9), 3.75 (3H, s), 6.22 (1H, s), 6.68-6.75 (2H, m), 6.97-7.56 (15H, m), 7.95 (1H, s).



非鏡像異構物 B　　非鏡像異構物 C　　(-)-異構物

在室溫下於 2 分鐘添加偶氮二羧酸二甲氧基乙酯(1.64 g, 7.0 mmol)於非鏡像異構物 B(2.65 g, 4.7 mmol)、2-甲氧基乙醇(0.71 g, 9.3 mmol)、三苯膦(1.84 g, 7.0 mmol)及 THF(50

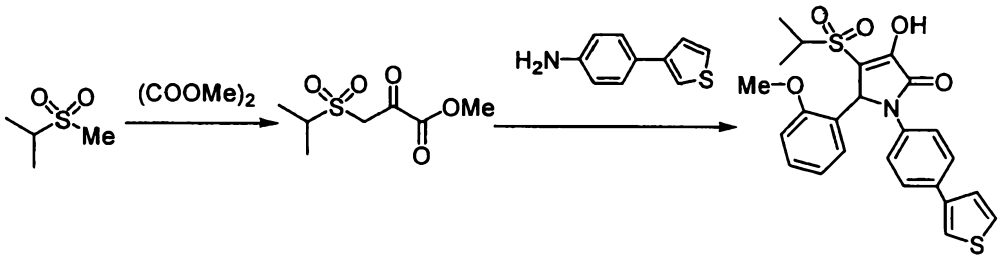
mL)之混合液，在室溫攪拌一夜。於反應液添加水(200 mL)，以甲苯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鎂乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣，得到黃色非晶形之非鏡像異構物 C(2.44 g，產率 84%)。

將所得之非鏡像異構物 C(2.25 g, 3.6 mmol)、氯化鋰(0.46 g, 10.8 mmol)及 1,3-二甲基-2-咪唑啶酮(45 mL)之混合液，在 100℃攪拌 16 小時。於反應液添加水(200 mL)及 2mol/L 鹽酸(15 mL)，以甲苯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鎂乾燥後，減壓濃縮。以矽膠管柱色層分析(甲醇/氯仿)純化所得殘渣。以乙酸乙酯/正己烷粉末化所得之目的物，得到淡黃色粉末之(-)-4-(2-甲基丙醯基)-3-羥基-1-(4-噻吩-3-基苯基)-5-(2-甲氧基乙氧基苯基)-1,5-二氫吡咯-2-酮(1.01 g，產率 59%)。

$[\alpha]_D$: -39.3±1.6°.(in CHCl3), 1H-NMR (δ ppm TMS / DMSO-d6) 0.89 (3H, d, J=7.0), 0.93 (3H, d, J=7.0), 3.44 (3H, s), 3.57 (2H, brs), 3.83 (3H, s), 4.15 (1H, m), 4.29 (1H, m), 6.01 (1H, s), 6.38 (1H, s), 6.63-7.13 (4H, m), 7.40-7.76 (7H, m), 7.78 (1H, m), 12.5 (1H, brs)

實施例 16

4-(異丙基磺醯基)-3-羥基-1-(4-噻吩-3-基苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮之製造



在室溫下添加28%甲氧基鈉甲醇溶液(8.58 g, 44.5 mmol)於異丙基甲基碸(5.17 g, 42.3 mmol)與THF(20 mL)之混合液後，在室溫緩慢添加草酸甲酯(5.0 g, 42.3 mmol)，在室溫攪拌一夜。於反應液添加冰水(200 mL)，以2mol/L鹽酸調整至pH3以下，以乙酸乙酯(200 mL)萃取。以飽和食鹽水(200 mL)清洗萃取液，以無水硫酸鈉乾燥後，減壓濃縮。以矽膠管柱色層分析(乙酸乙酯/正己烷)純化所得殘渣，得到無色油狀物之3-(異丙基磺醯基)-2-酮基丙酸甲酯(2.7 g，產率28%)。

1H-NMR (δ ppm TMS / DMSO-d6) 1.26 (6H, d, J=6.7), 3.46 (1H, sept, J=6.7), 3.81 (3H, s), 4.74 (2H, s).

將3-(異丙基磺醯基)-2-酮基丙酸甲酯(0.23 g, 1 mmol)、4-噻吩-3-基苯胺(0.18 g, 1 mmol)、2-甲氧基苯甲醛(0.14, 1 mmol)、乙酸(0.023 mL, 0.4 mmol)與甲苯(3 mL)之混合液，在加熱回流下攪拌一夜。反應後，冷却至室溫，添加醚，濾取析出之目的物。以醚/正己烷溶液洗淨所得之目的物，得到淡褐色固體之 4-(異丙基磺醯基)-3-羥基-1-(4-噻吩-3-基苯基)-5-(2-甲氧基苯基)-1,5-二氫吡咯-2-酮(0.37 g，產率79%)。

1H-NMR (δ ppm TMS / DMSO-d6):0.97-1.15 (6H, m), 3.62 (3.87) (3H, s), 6.13 (6.50) (1H, s), 6.82-7.27 (3H, m), 7.48-7.81 (8H, m), 12.20 (1H, brs).

依照上記合成路徑、一般的製造法及實施例記載之方法，得到以下之化合物。以下示出構造及物性。

(化合物之鑑定方法)

本發明之化合物的 LC/MS 數據，是分別以以下的 2 個條件(方法 1~3)測定，顯示保持時間及$[M+H]^+$。

(方法 1)

管柱：Xbridge C18(5μm、i.d.4.6x50mm)(Waters)

流速：3 mL/分鐘

UV 偵測波長：254nm

移動相：[A]爲含有 0.1%甲酸之水溶液，[B]爲含有 0.1%甲酸之乙腈溶液

梯度：以 3 分鐘進行 10%-100%溶劑[B]之線性梯度，以 1 分鐘維持 100%溶劑[B]。

(方法 2)

管柱：Shim-pack XR-ODS (2.2μm、i.d.50x3.0mm) (Shimadzu)

流速：1.6 mL/分鐘

UV 偵測波長：254nm

移動相：[A]爲含有 0.1%甲酸之水溶液，[B]爲含有 0.1%甲酸之乙腈溶液

梯度：以 3 分鐘進行 10%-100%溶劑[B]之線性梯度，以 1 分鐘維持 100%溶劑[B]。

(方法 3)

管柱：Gemini-NX (5μm、i.d.4.6x50mm)(Phenomenex)

流速：3 mL/分鐘

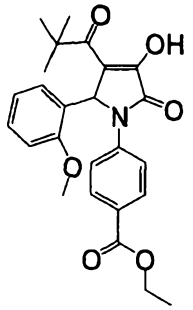
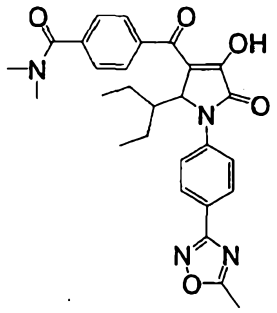
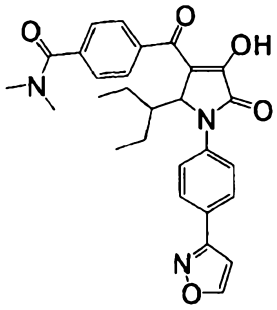
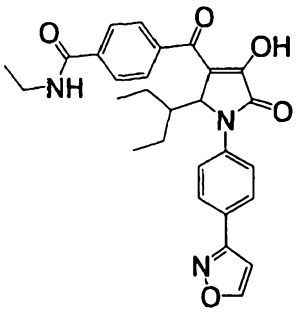
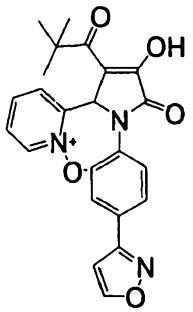
UV 偵測波長：254nm

移動相：[A]爲含有 0.1%甲酸之水溶液，[B]爲含有 0.1%甲酸之甲醇溶液

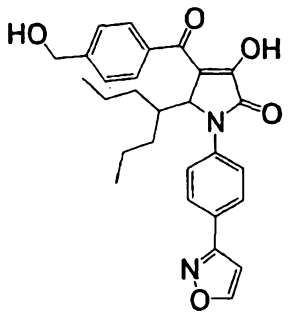
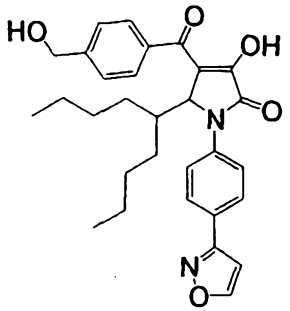
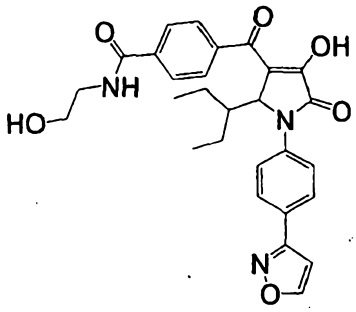
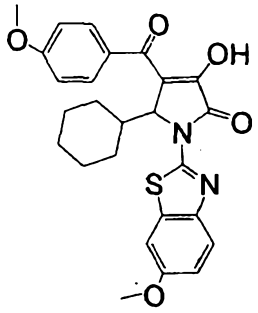
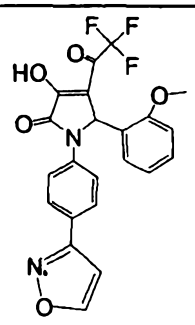
梯度：以 3.5 分鐘進行 5%-100%溶劑[B]之線性梯度，以 0.5 分鐘維持 100%溶劑[B]。

(註：以下【表 11】至【表 186】的第 1 列標題與【表 10】所示相同，其中『化合物番号』意指『化合物編號』;『LC メソッド』意指『LC 方法』)

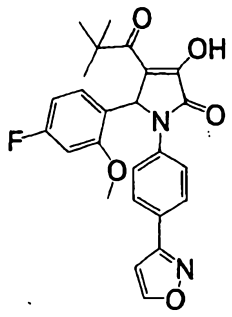
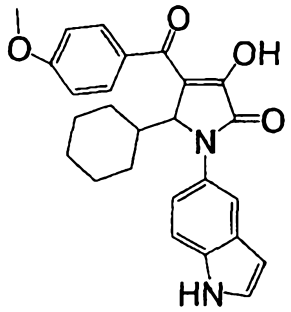
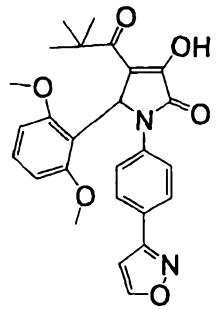
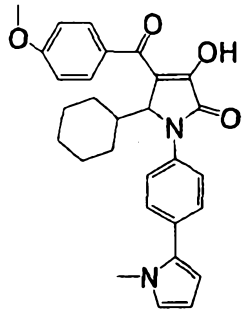
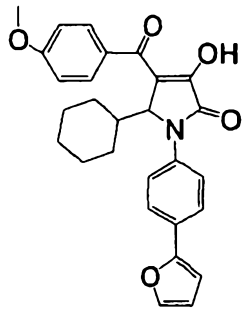
【表 10】

構造式	化合物編號	MS $[M+H]^+$	LC 方法	LC/MS 保持時間(分)
	I-001	438	2	2.49
	I-002	503	2	2.30
	I-003	488	2	2.17
	I-004	488	2	2.20
	I-005	420	2	1.60

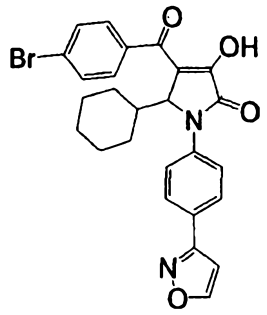
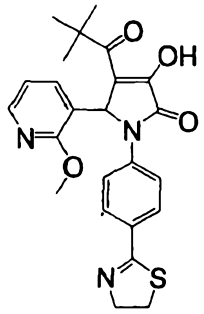
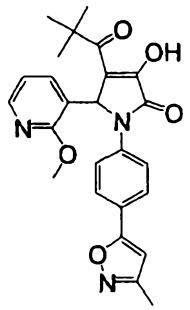
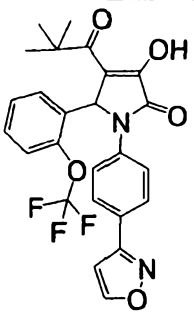
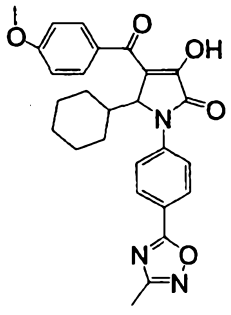
【表 11】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-006	475	2	2.36
	I-007	503	2	2.61
	I-008	504	2	1.90
	I-009	479	2	2.80
	I-010	445	2	2.09

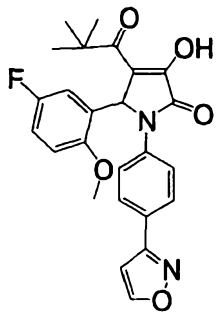
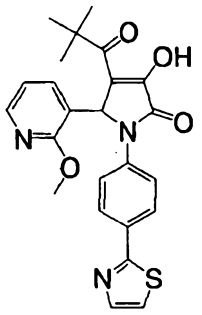
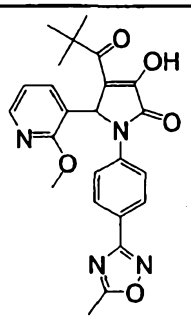
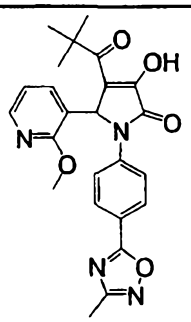
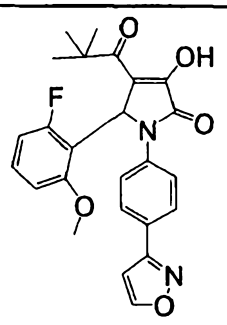
【表 12】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-011	451	2	2.34
	I-012	431	2	2.26
	I-013	463	2	2.26
	I-014	471	2	2.70
	I-015	458	2	2.80

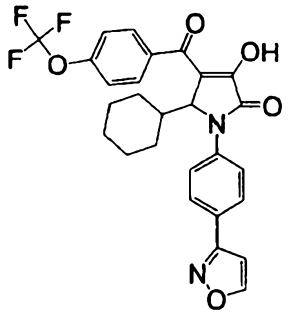
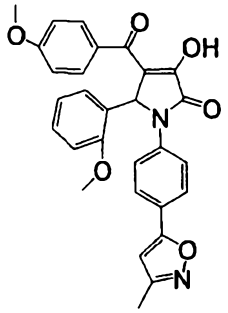
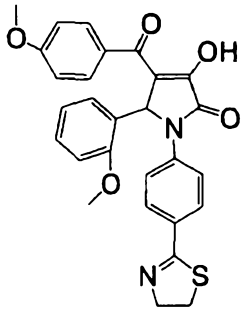
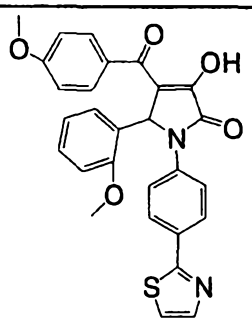
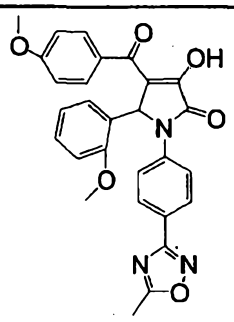
【表 13】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-016	507	2	2.77
	I-017	452	2	2.03
	I-018	448	2	2.23
	I-019	487	2	2.47
	I-020	474	2	2.55

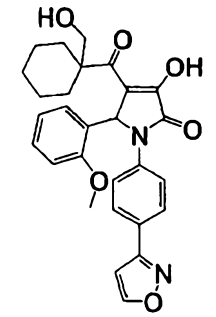
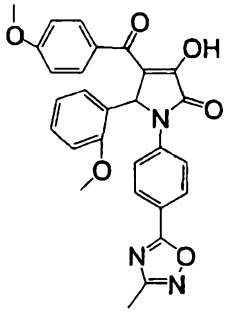
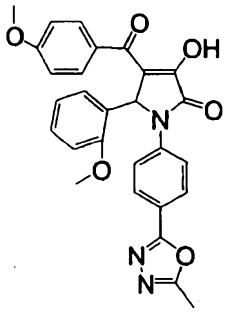
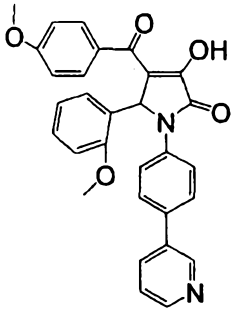
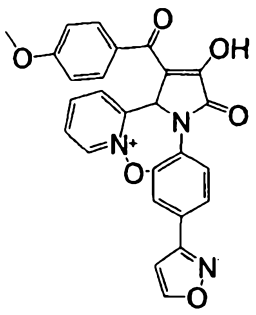
【表 14】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-021	451	2	2.31
	I-022	450	2	2.22
	I-023	449	2	2.19
	I-024	449	2	2.23
	I-025	451	2	2.25

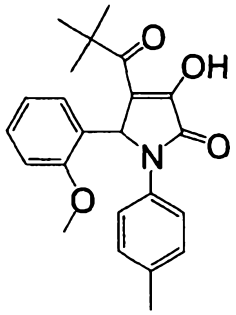
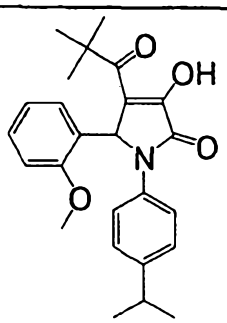
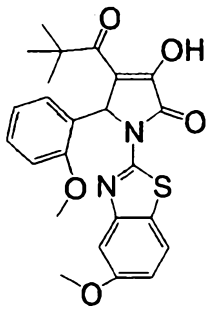
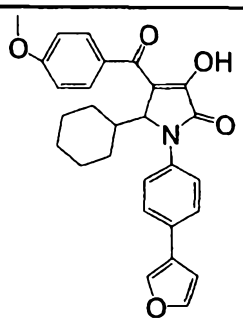
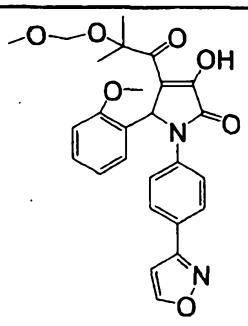
【表 15】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-026	513	2	2.73
	I-027	497	2	2.10
	I-028	501	2	2.00
	I-029	499	2	2.20
	I-030	498	2	2.10

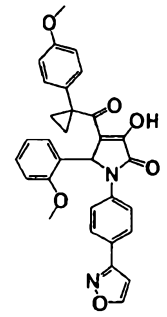
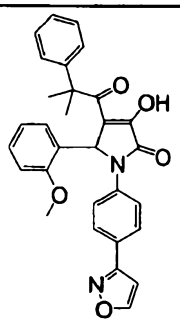
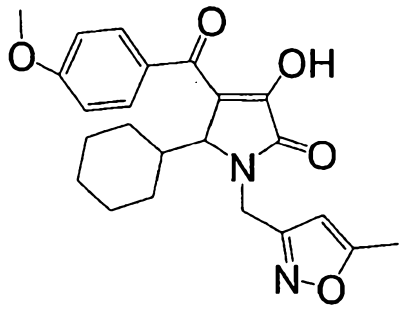
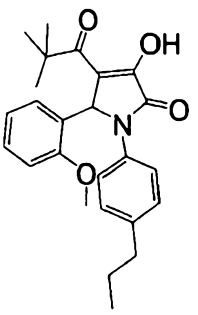
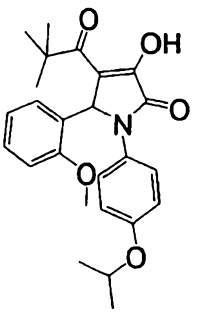
【表 16】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-031	489	2	2.08
	I-032	498	2	2.10
	I-033	498	2	1.90
	I-034	493	2	1.60
	I-035	470	2	1.52

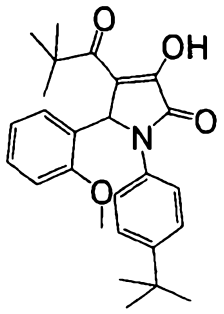
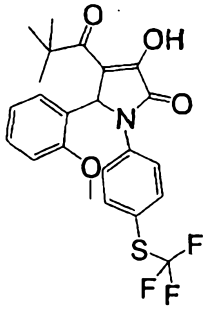
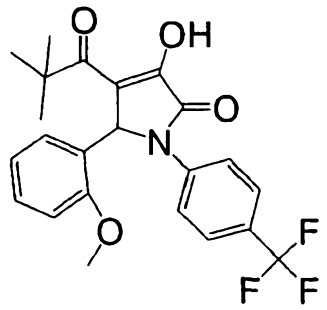
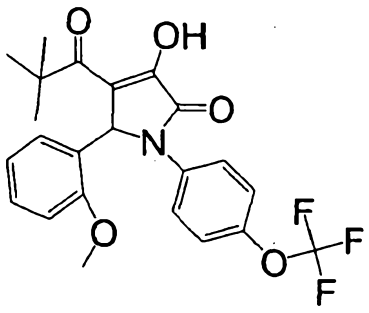
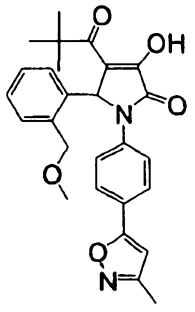
【表 17】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS保持時間(分)
	I-036	380	2	2.46
	I-037	408	2	2.69
	I-038	453	2	2.50
	I-039	458	2	2.60
	I-040	478	2	2.11

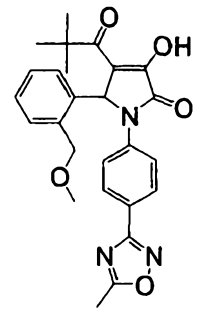
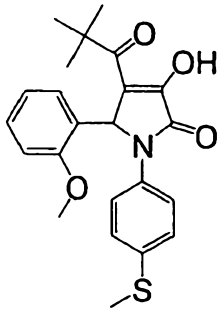
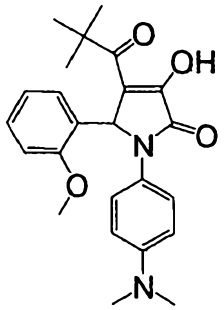
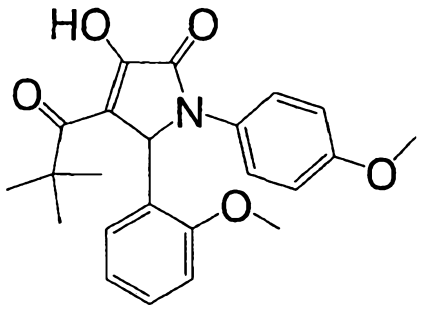
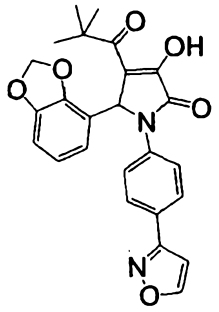
【表 18】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-041	523	2	2.41
	I-042	495	2	2.52
	I-043	411	2	2.28
	I-044	408	1	2.50
	I-045	424	1	2.30

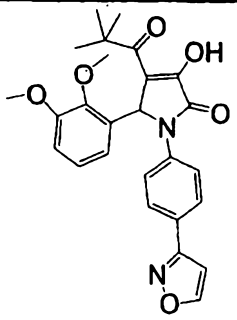
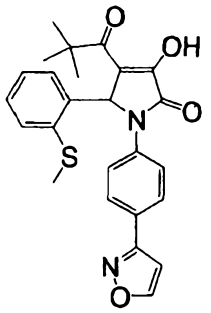
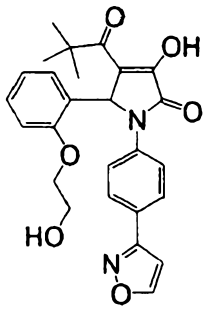
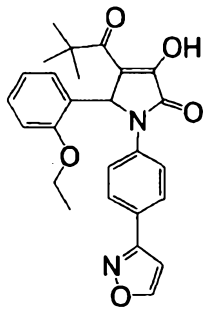
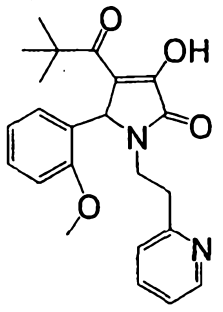
【表 19】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-046	422	1	2.50
	I-047	466	1	2.50
	I-048	433	1	2.40
	I-049	449	1	2.40
	I-050	461	2	2.53

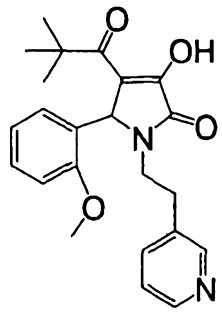
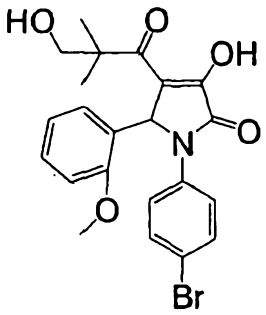
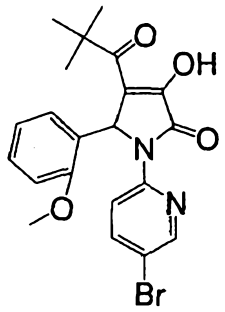
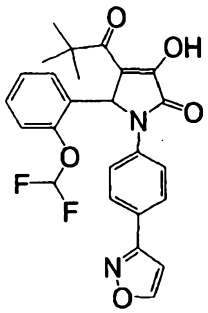
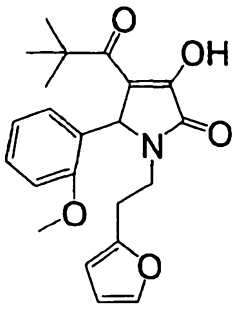
【表 20】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-051	462	2	2.49
	I-052	412	1	2.26
	I-053	409	2	2.23
	I-054	396	1	2.10
	I-055	447	1	2.00

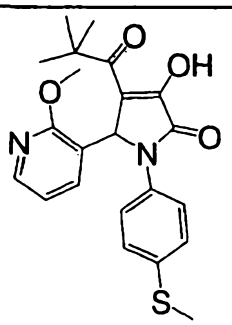
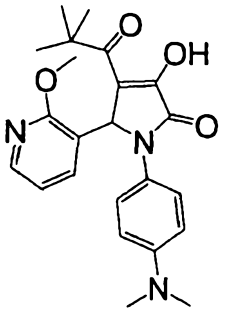
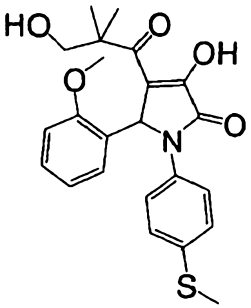
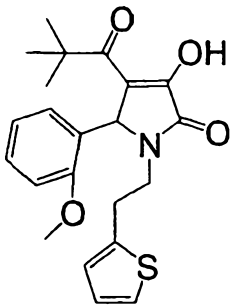
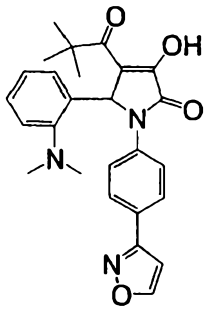
【表 21】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-056	463	1	2.10
	I-057	449	1	2.20
	I-058	463	1	1.80
	I-059	447	1	2.20
	I-060	395	2	1.51

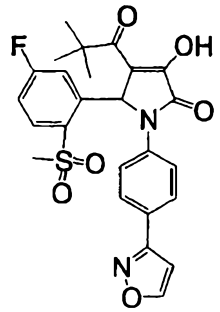
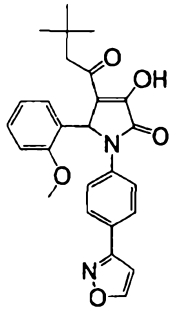
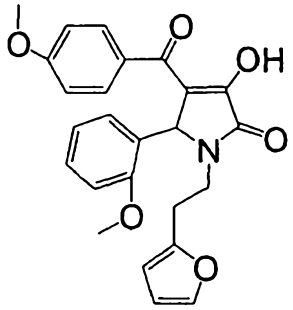
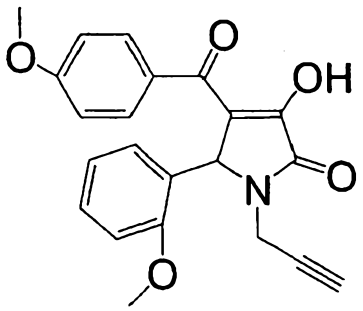
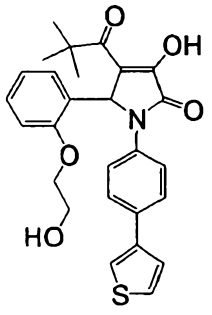
【表 22】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-061	395	2	1.43
	I-062	461	1	1.90
	I-063	445	2	2.52
	I-064	469	1	2.20
	I-065	384	2	2.40

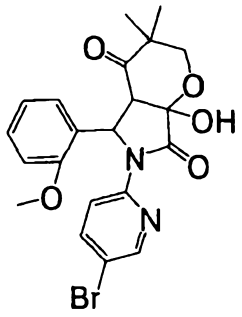
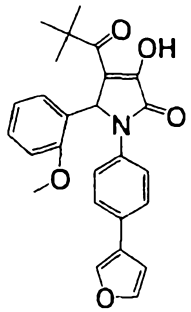
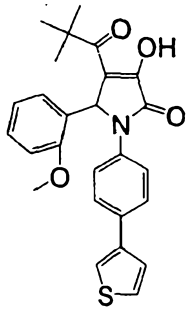
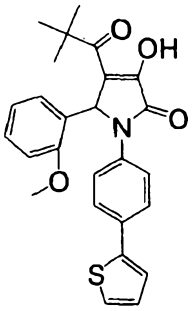
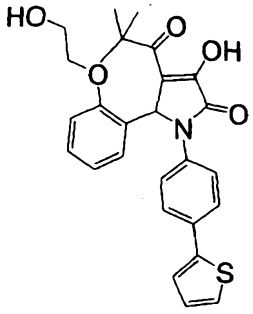
【表 23】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-066	413	1	2.10
	I-067	410	1	1.80
	I-068	428	1	1.80
	I-069	400	2	2.50
	I-070	446	1	2.00

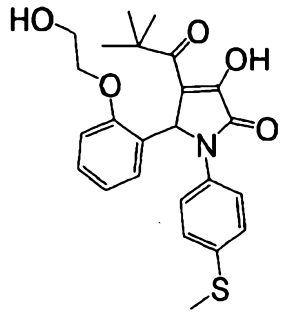
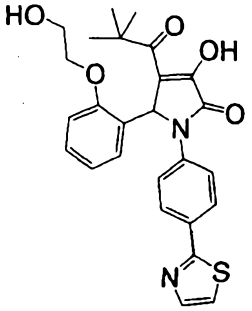
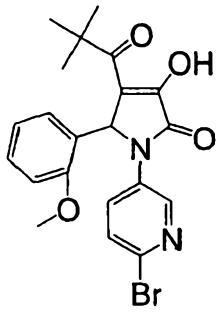
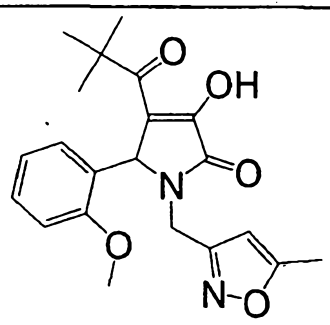
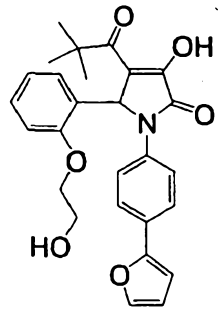
【表 24】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-071	499	1	1.90
	I-072	447	1	2.20
	I-073	434	2	2.20
	I-074	378	2	2.00
	I-075	478	1	2.10

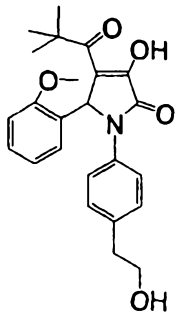
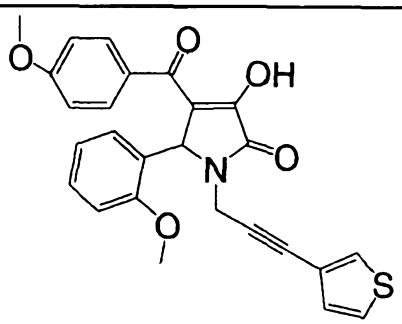
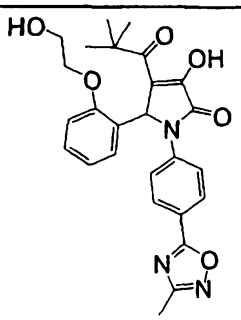
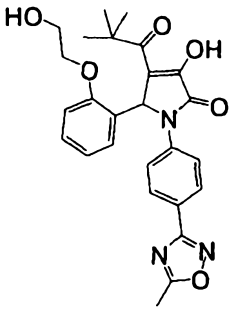
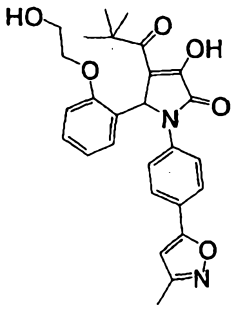
【表 25】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-076	461	2	2.27
	I-077	432	2	2.54
	I-078	448	2	2.65
	I-079	448	2	2.69
	I-080	478	1	2.10

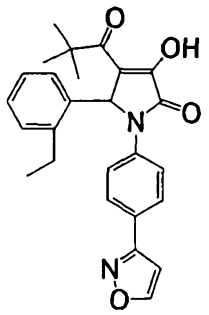
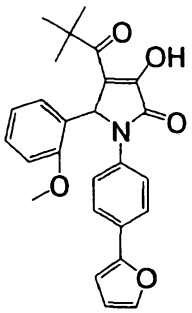
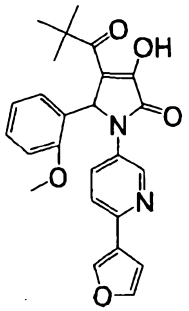
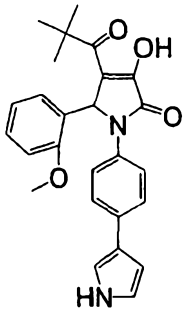
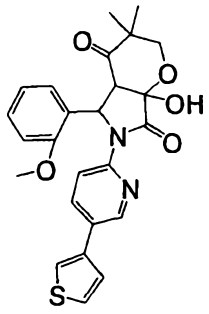
【表 26】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-081	442	1	2.00
	I-082	479	1	1.90
	I-083	445	2	2.36
	I-084	385	1	1.91
	I-085	462	1	2.10

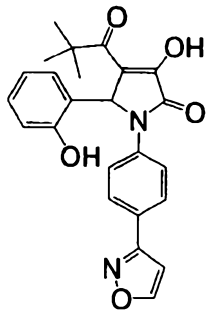
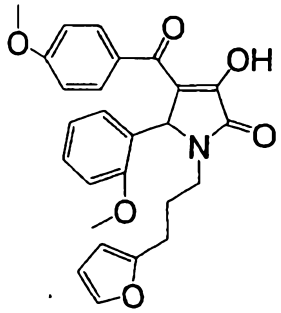
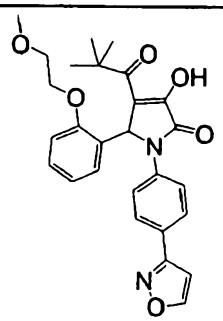
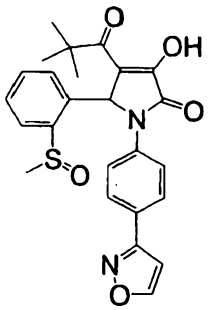
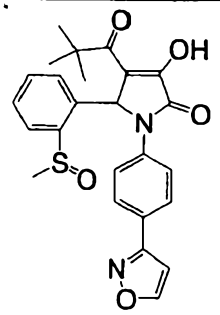
【表 27】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-086		2	2.05
	I-087	460	2	2.40
	I-088	478	1	1.90
	I-089	478	1	1.80
	I-090	477	1	1.90

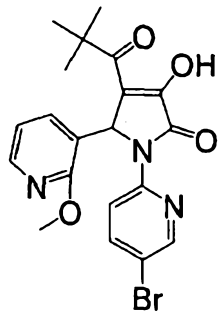
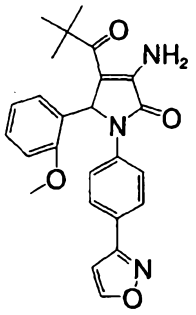
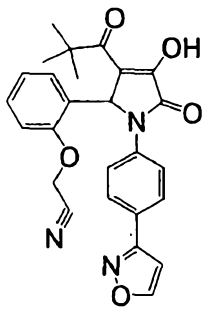
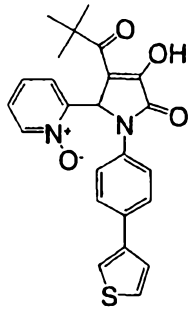
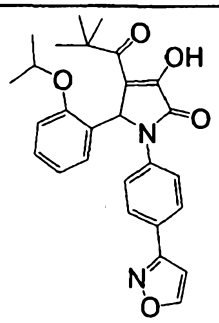
【表 28】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-091	431	1	2.30
	I-092	432	2	2.61
	I-093	433	2	1.19
	I-094	431	2	1.17
	I-095	465	2	2.14

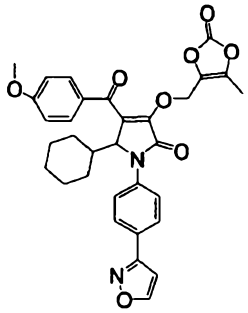
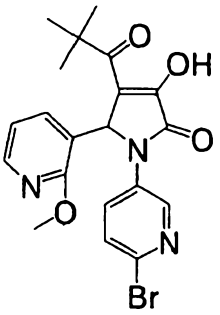
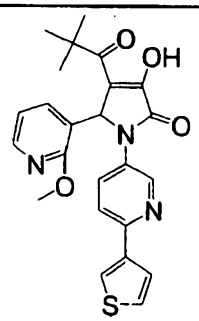
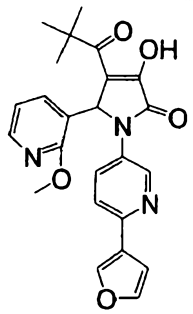
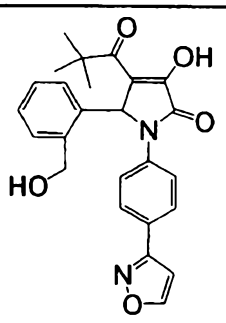
【表 29】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-096	419	1	1.90
	I-097	448	2	2.20
	I-098	477	1	2.10
	I-099	465	2	1.80
	I-100	465	2	1.90

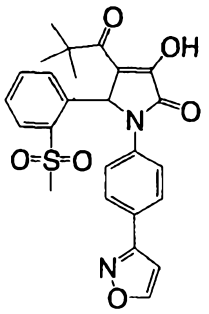
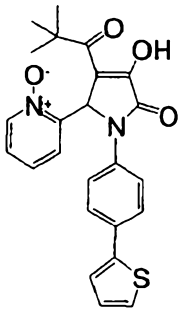
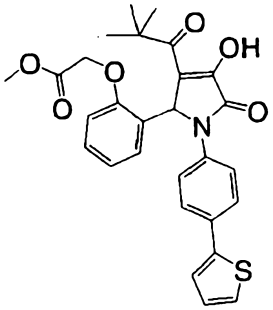
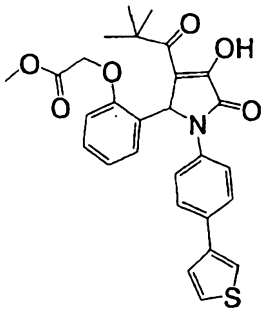
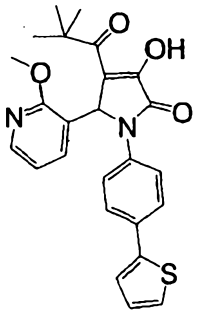
【表 30】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-101	446	2	2.42
	I-102	432	2	1.98
	I-103	458	1	1.90
	I-104	435	2	1.96
	I-105	461	1	2.30

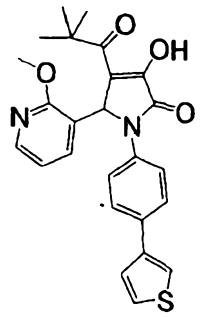
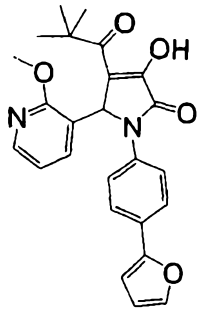
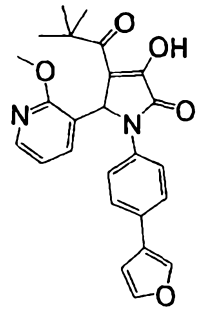
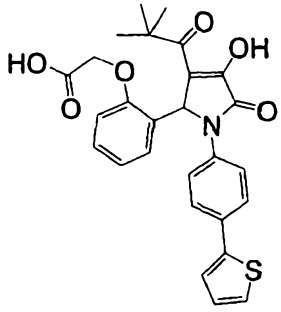
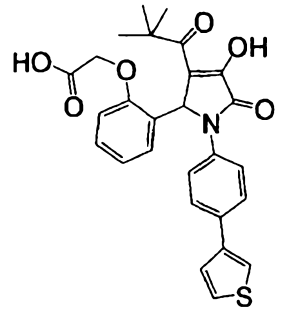
【表 31】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-106	459	2	2.70
	I-107	446	2	2.21
	I-108	450	2	2.30
	I-109	434	2	2.16
	I-110	433	1	1.80

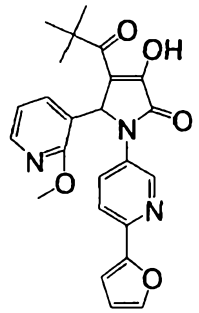
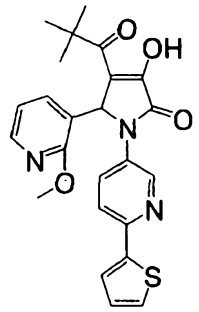
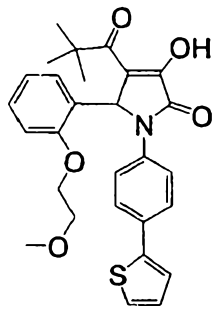
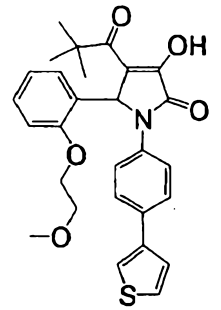
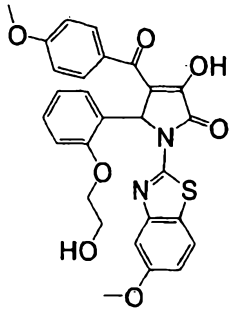
【表 32】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-111	481	1	1.90
	I-112	435	2	2.00
	I-113	506	1	2.30
	I-114	506	1	2.30
	I-115	449	1	2.30

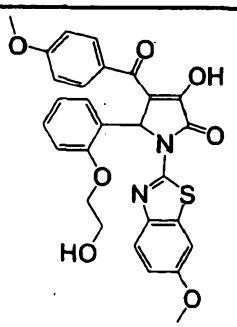
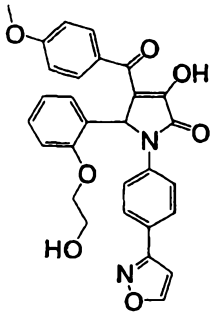
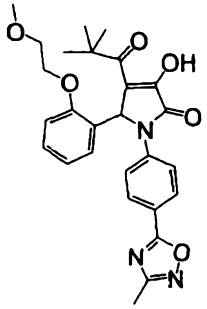
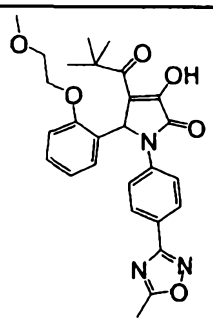
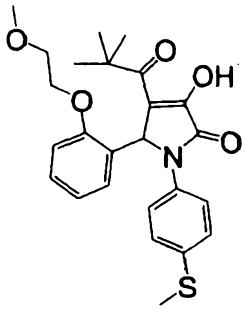
【表 33】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-116	449	1	2.20
	I-117	433	1	2.20
	I-118	433	1	2.10
	I-119	492	1	2.10
	I-120	492	1	2.00

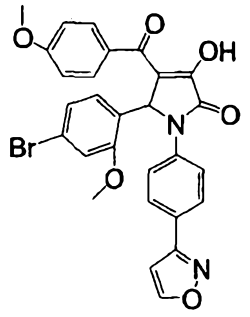
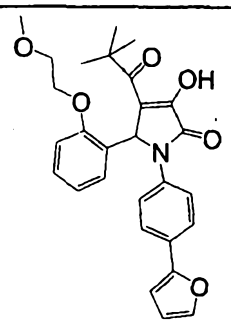
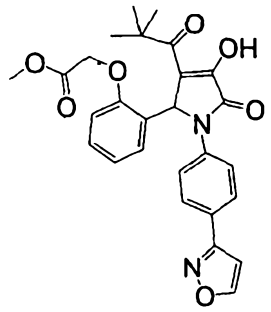
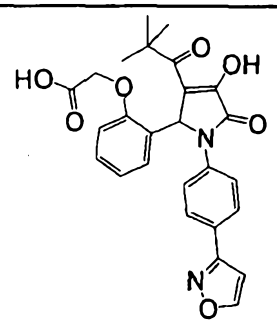
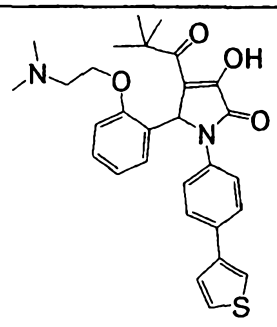
【表 34】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-121	434	2	2.19
	I-122	450	2	2.36
	I-123	492	1	2.40
	I-124	492	1	2.30
	I-125	533	1	1.90

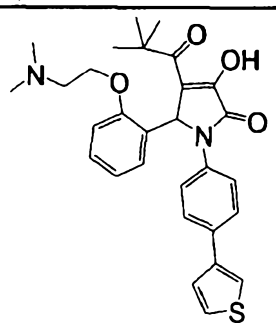
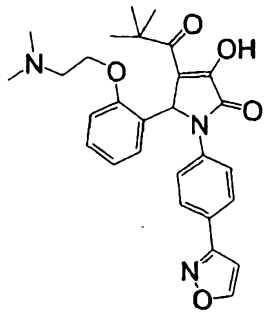
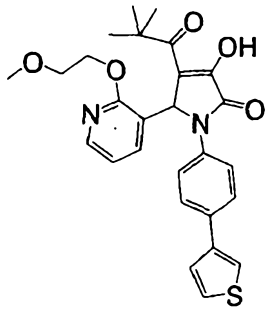
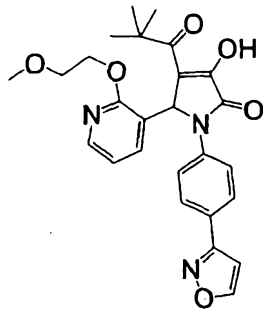
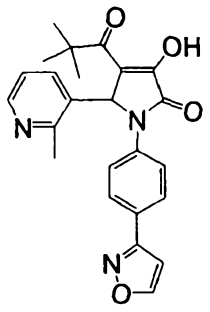
【表 35】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-126	533	1	1.90
	I-127	513	1	1.70
	I-128	492	1	2.10
	I-129	492	1	2.10
	I-130	456	1	2.20

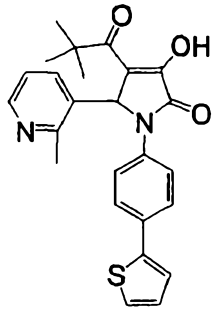
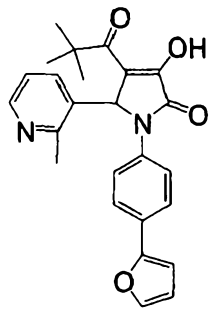
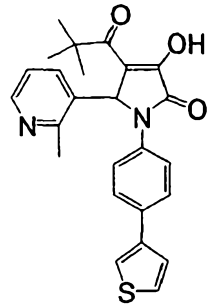
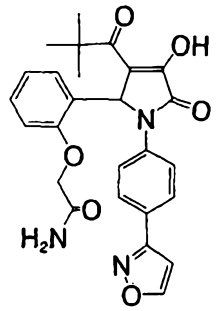
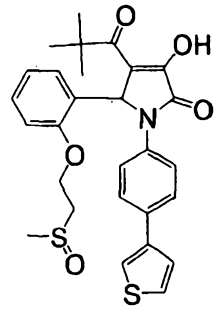
【表 36】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-131	561	2	2.40
	I-132	476	1	2.30
	I-133	491	1	2.00
	I-134	477	1	1.80
	I-135	505	1	1.50

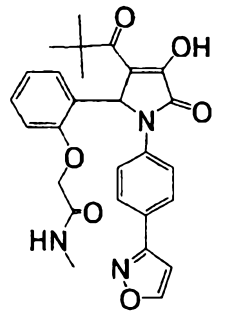
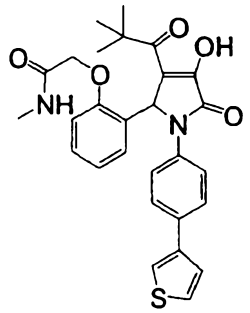
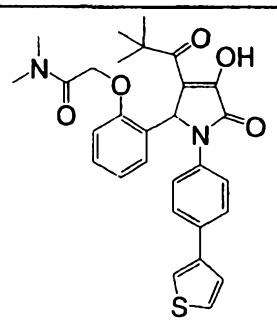
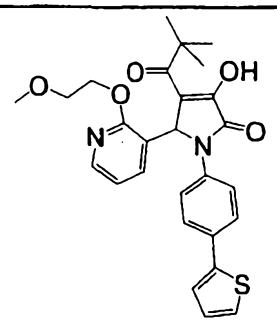
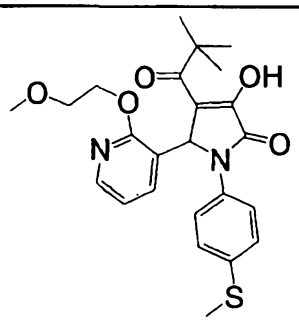
【表 37】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS保持時間(分)
	I-136	505	1	1.90
	I-137	490	1	1.30
	I-138	493	1	2.20
	I-139	478	1	1.90
	I-140	418	1	1.20

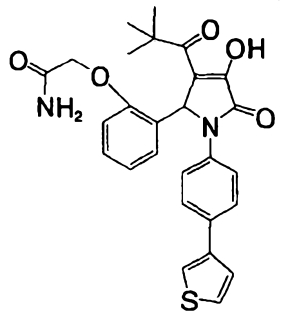
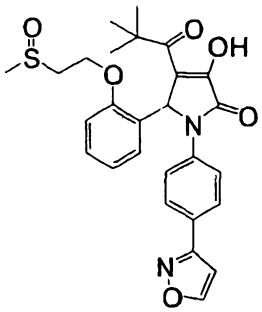
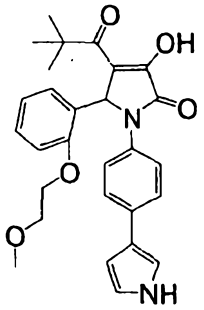
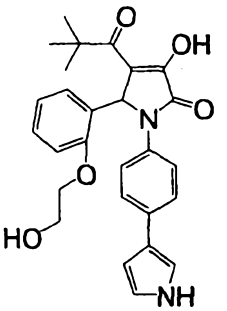
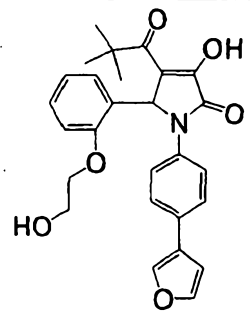
【表 38】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-141	433	1	1.50
	I-142	417	1	1.40
	I-143	433	1	1.40
	I-144	476	1	1.67
	I-145	524	1	1.91

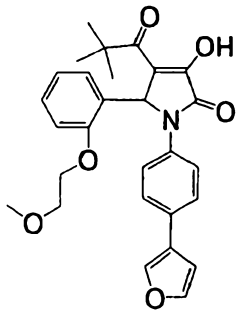
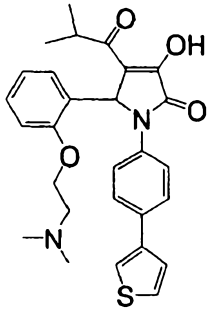
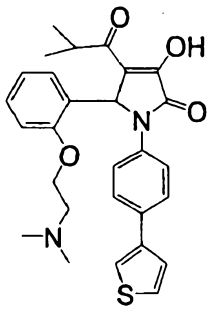
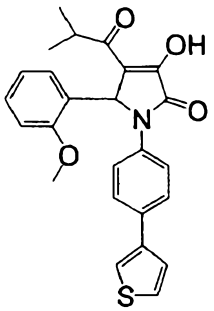
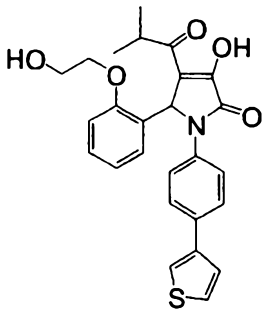
【表 39】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-146	490	1	1.81
	I-147	505	2	2.36
	I-148	519	2	2.39
	I-149	493	1	2.30
	I-150	457	1	2.10

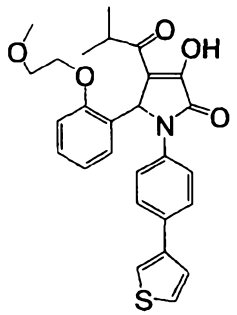
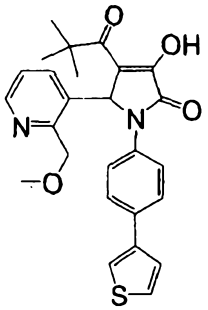
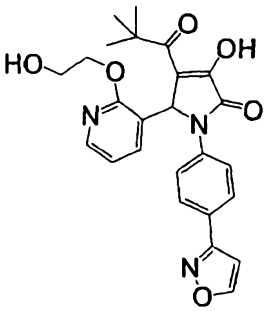
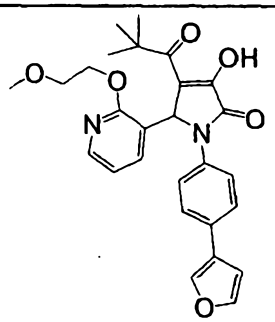
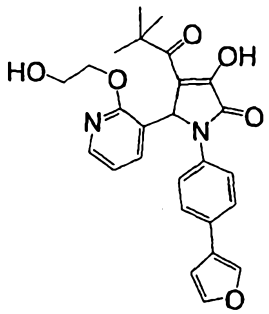
【表 40】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-151	491	2	2.22
	I-152	509	2	1.94
	I-153	475	2	1.76
	I-154	461	2	2.10
	I-155	462	1	1.90

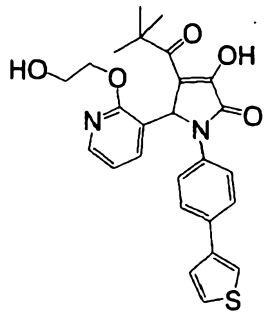
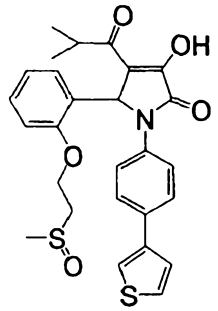
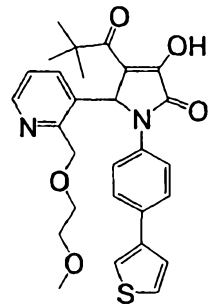
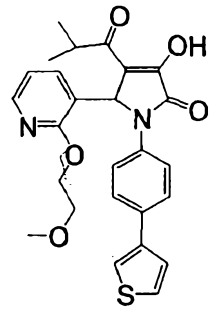
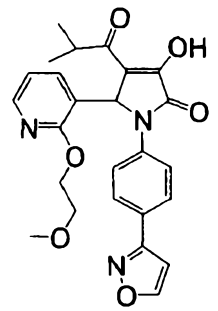
【表 41】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-156	476	1	2.20
	I-157	491	1	1.50
	I-158	491	1	1.55
	I-159	434	1	2.20
	I-160	464	2	2.27

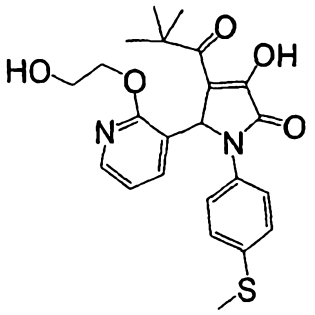
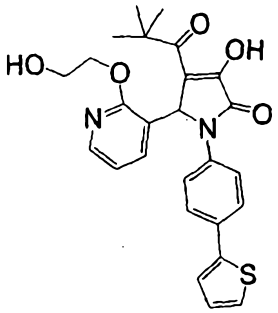
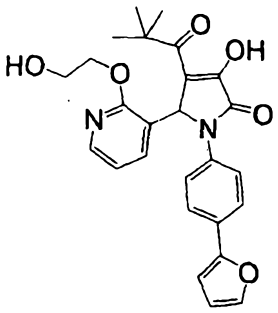
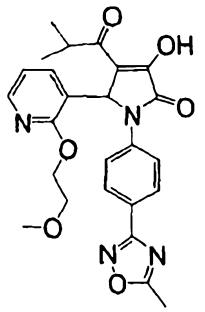
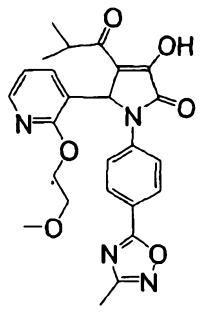
【表 42】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-161	478	2	2.56
	I-162	463	1	1.70
	I-163	464	1	1.60
	I-164	477	1	2.10
	I-165	463	1	1.80

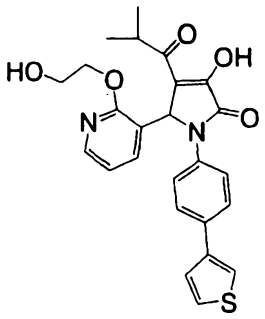
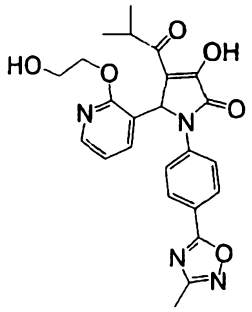
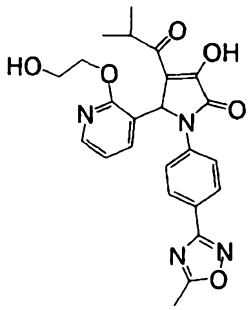
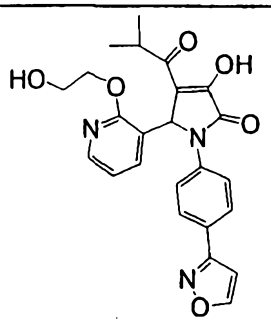
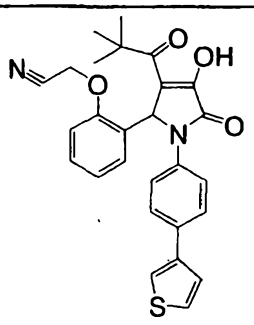
【表 43】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-166	479	1	2.00
	I-167	510	1	1.79
	I-168	507	1	1.65
	I-169	479	2	2.45
	I-170	464	2	2.11

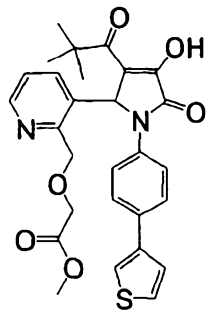
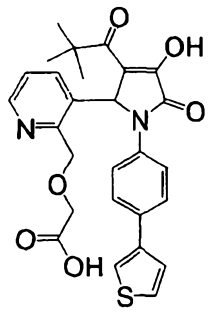
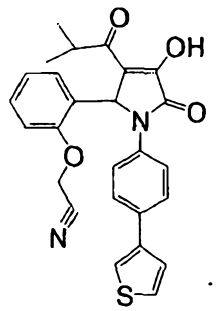
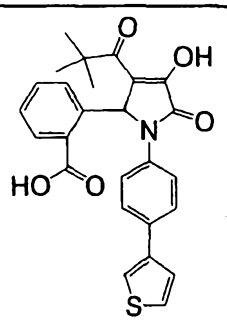
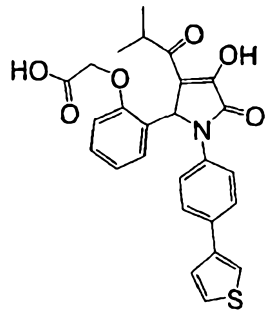
【表 44】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-171	443	1	1.80
	I-172	479	1	2.00
	I-173	463	1	1.90
	I-174	479	2	2.15
	I-175	479	2	2.18

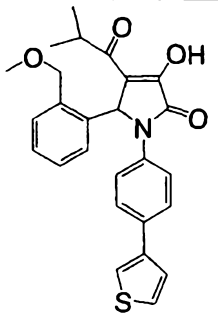
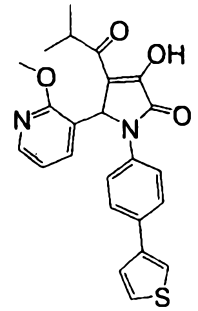
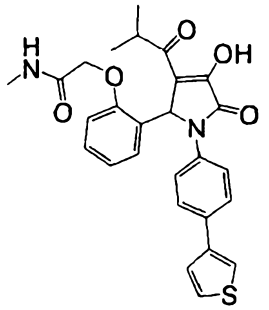
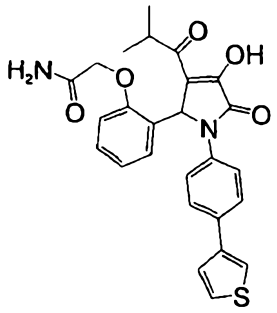
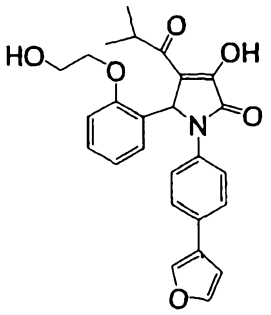
【表 45】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-176	465	1	1.80
	I-177	465	1	1.60
	I-178	465	1	1.50
	I-179	450	1	1.50
	I-180	473	2	2.52

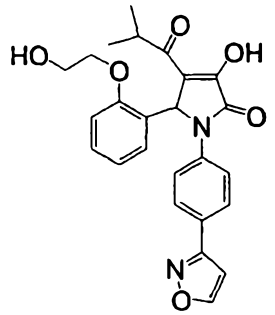
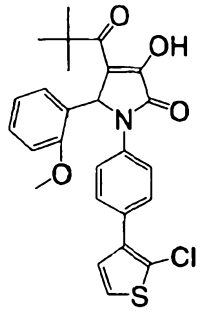
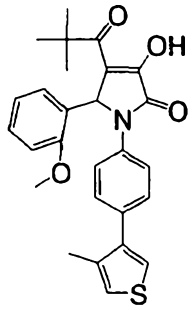
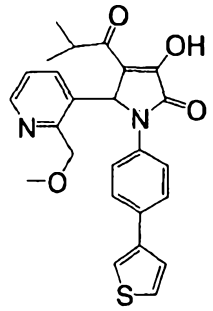
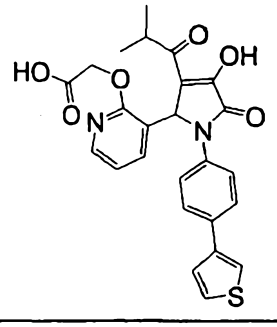
【表 46】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-181	521	1	1.79
	I-182	507	1	1.51
	I-183	459	1	2.11
	I-184	462	1	2.05
	I-185	478	1	1.90

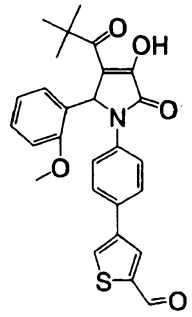
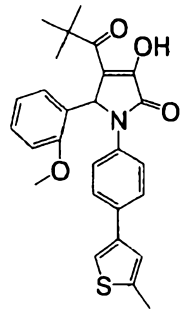
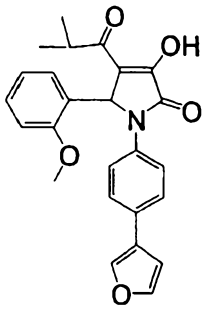
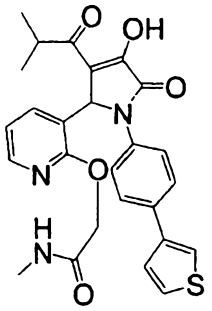
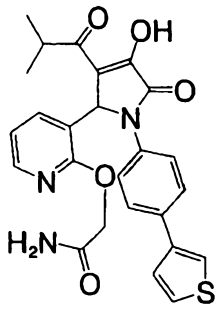
【表 47】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-186	448	2	2.56
	I-187	435	1	2.10
	I-188	491	1	2.00
	I-189	477	1	1.80
	I-190	448	2	2.15

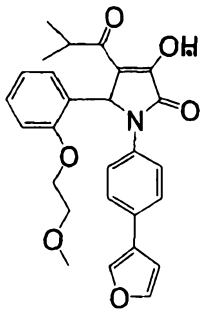
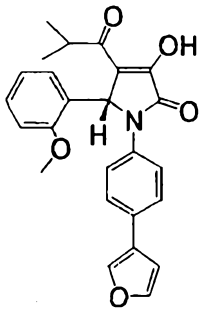
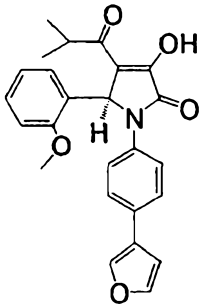
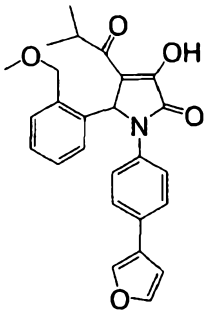
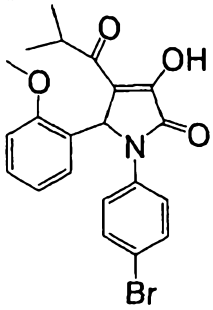
【表 48】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-191	449	2	1.87
	I-192	482	2	2.84
	I-193	462	2	2.80
	I-194	449	1	1.53
	I-195	479	1	1.80

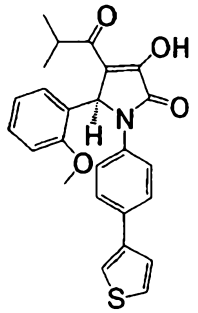
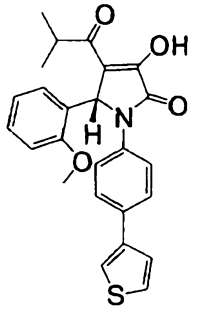
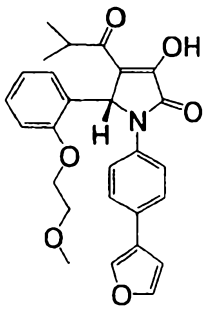
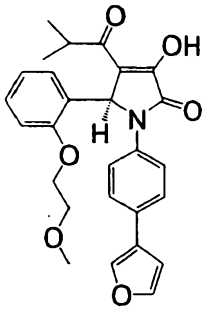
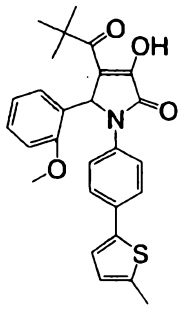
【表 49】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-196	476	2	2.52
	I-197	462	2	2.83
	I-198	418	1	2.16
	I-199	492	1	1.90
	I-200	478	1	1.80

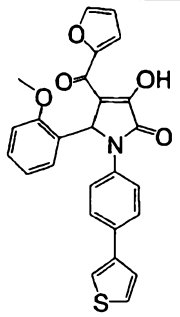
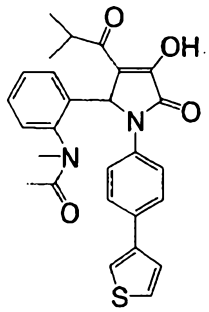
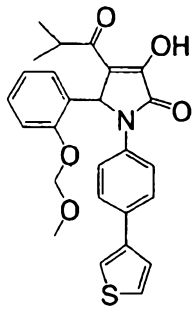
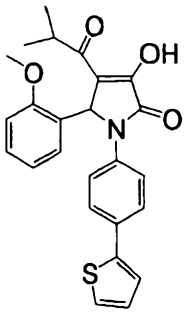
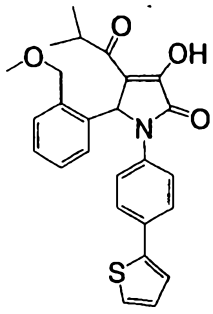
【表 50】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-201	462	1	2.14
	I-202	418	1	2.17
	I-203	418	1	2.17
	I-204	432	2	2.45
	I-205	431	2	2.48

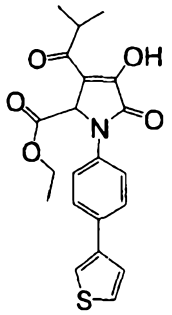
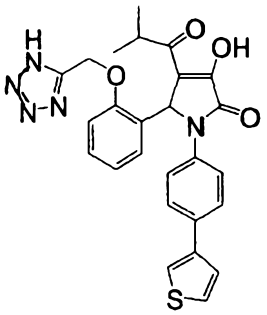
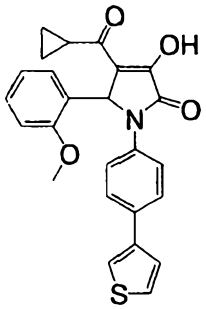
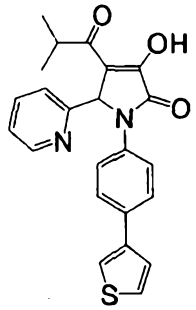
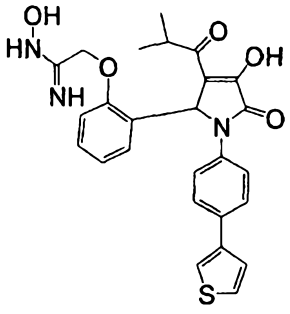
【表 51】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-206	434	2	2.58
	I-207	434	2	2.58
	I-208	462	1	2.14
	I-209	462	1	2.14
	I-210	462	2	2.87

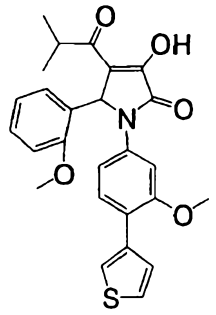
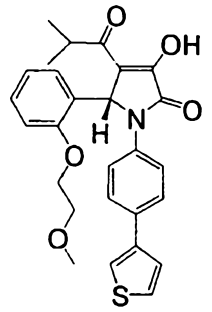
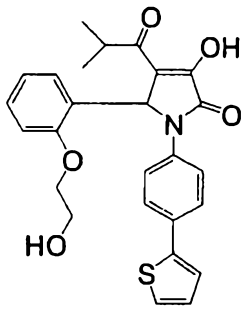
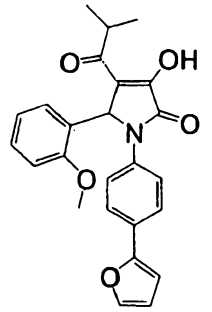
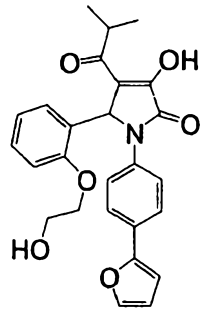
【表 52】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-211	458	2	2.38
	I-212	475	1	1.90
	I-213	464	1	2.29
	I-214	434	2	2.57
	I-215	448	2	2.59

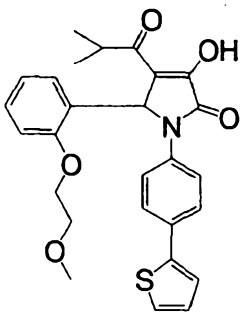
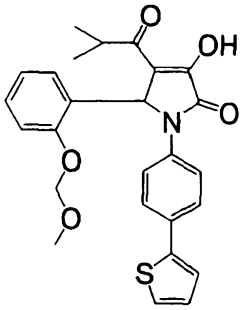
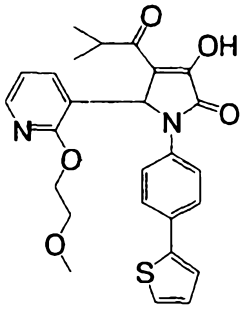
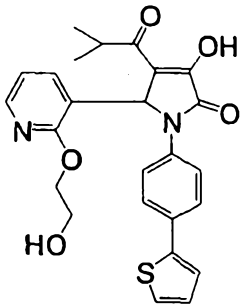
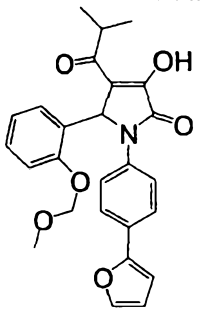
【表 53】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-216	400	2	2.47
	I-217	502	2	2.22
	I-218	432	1	2.20
	I-219	405	2	2.28
	I-220	492	2	1.84

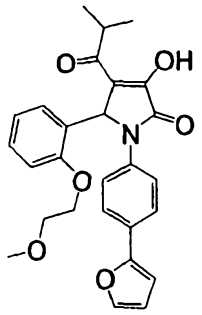
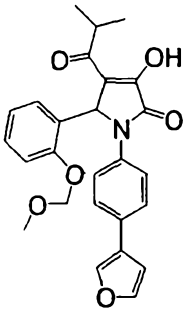
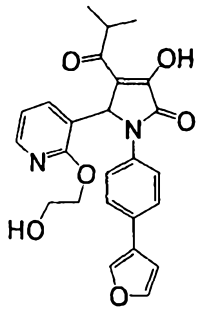
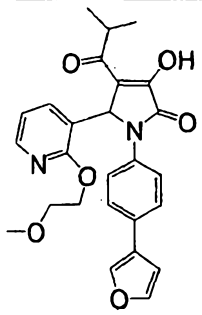
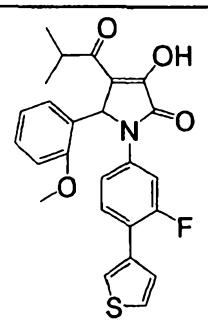
【表 54】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-221	464	2	2.61
	I-222	478	1	2.26
	I-223	464	1	2.04
	I-224	418	2	2.51
	I-225	448	2	2.21

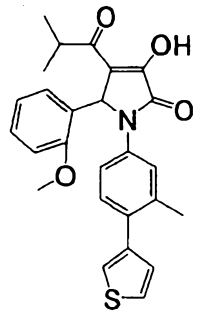
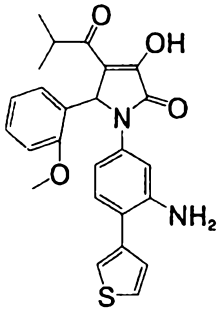
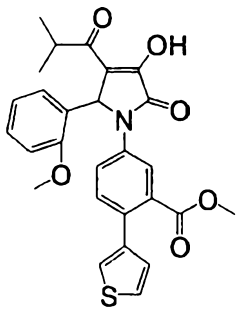
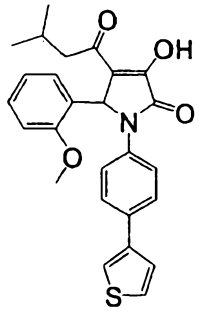
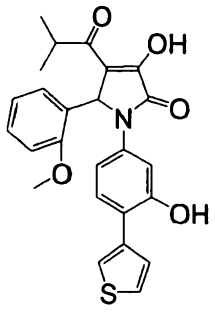
【表 55】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-226	478	1	2.29
	I-227	464	1	2.32
	I-228	479	1	2.15
	I-229	465	1	1.87
	I-230	448	2	2.51

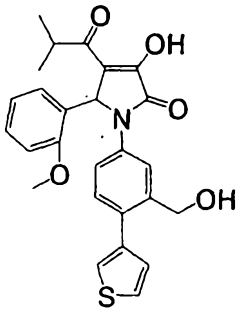
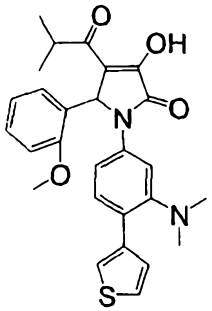
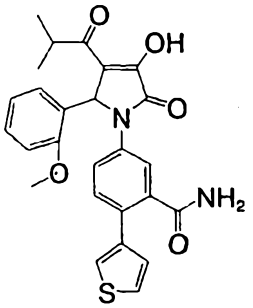
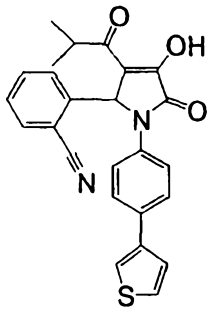
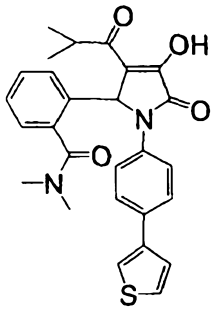
【表 56】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-231	462	2	2.47
	I-232	448	1	2.18
	I-233	449	2	2.00
	I-234	462	1	1.99
	I-235	452	2	2.67

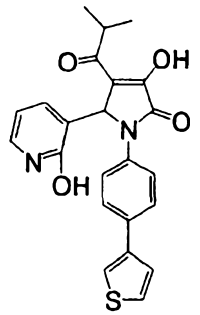
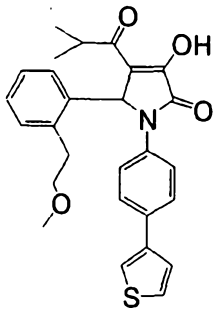
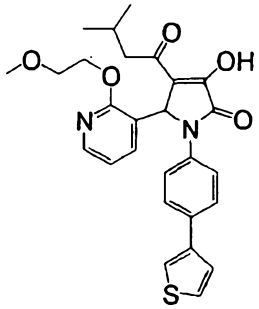
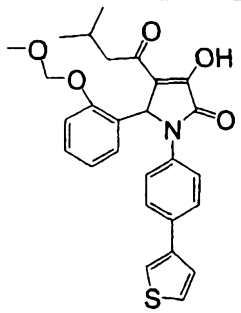
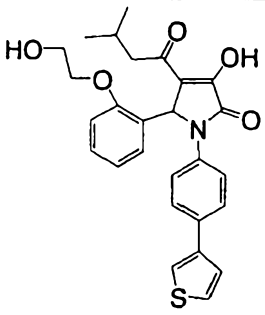
【表 57】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-236	448	2	2.66
	I-237	449	2	2.38
	I-238	492	2	2.51
	I-239	448	1	2.37
	I-240	450	1	2.09

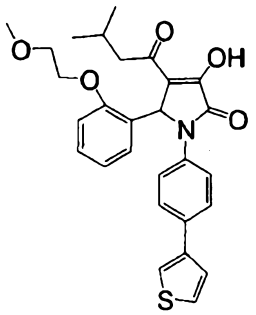
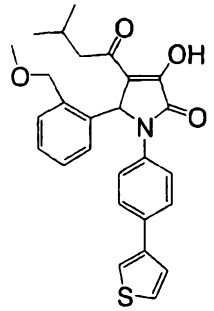
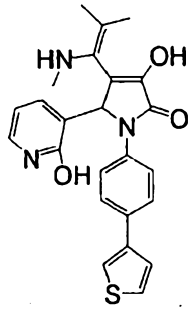
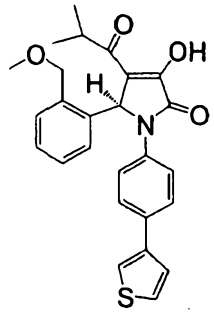
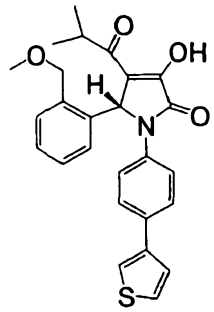
【表 58】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-241	464	1	2.03
	I-242	477	1	2.39
	I-243	477	2	2.05
	I-244	428	1	2.12
	I-245	475	1	2.10

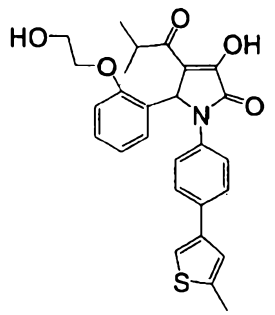
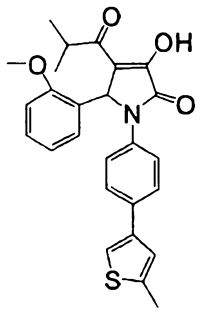
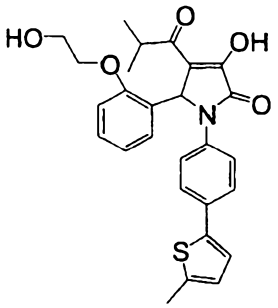
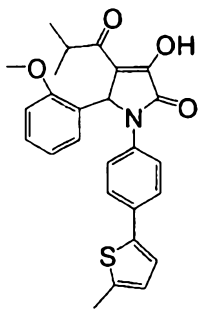
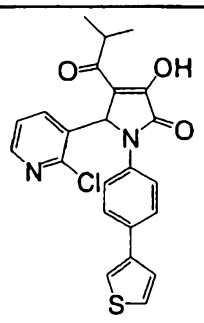
【表 59】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-246	421	2	1.87
	I-247	462	1	2.28
	I-248	493	1	2.19
	I-249	478	1	2.38
	I-250	478	1	2.09

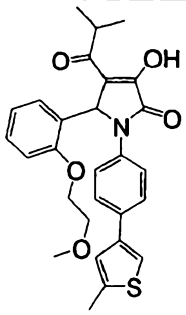
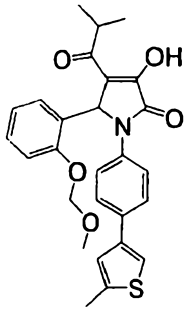
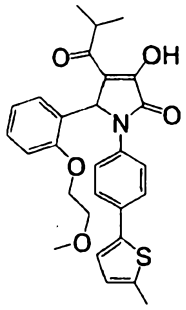
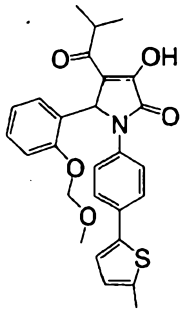
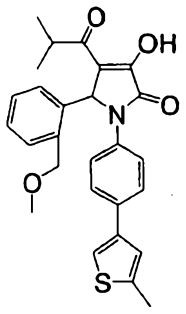
【表 60】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-251	492	1	2.37
	I-252	462	1	2.39
	I-253	434	1	1.41
	I-254	448	2	2.59
	I-255	448	2	2.59

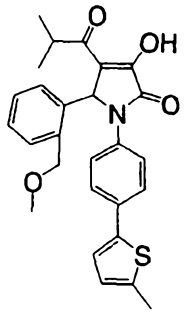
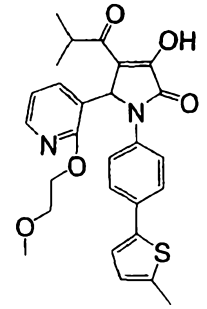
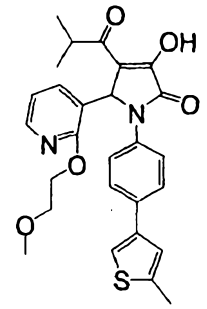
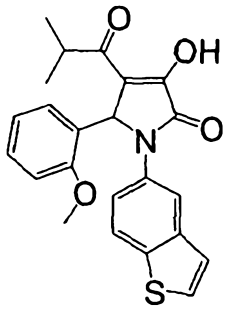
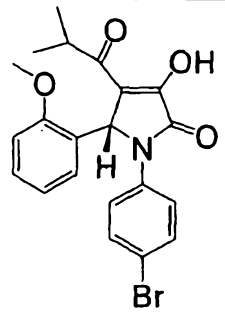
【表 61】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-256	478	1	2.14
	I-257	448	1	2.39
	I-258	478	1	2.16
	I-259	448	1	2.42
	I-260	438	2	2.33

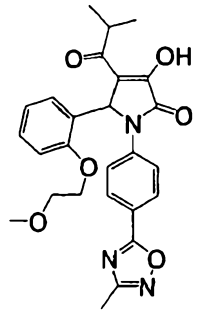
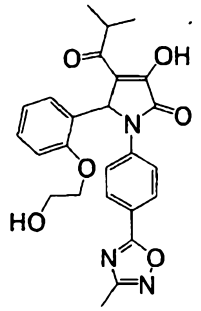
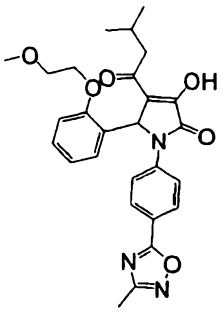
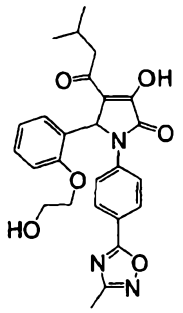
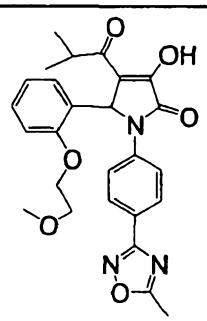
【表 62】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-261	492	2	2.70
	I-262	478	2	2.71
	I-263	492	2	2.73
	I-264	478	2	2.75
	I-265	462	2	2.73

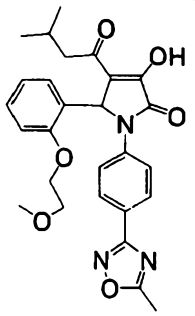
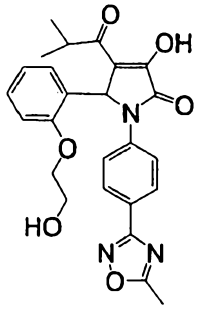
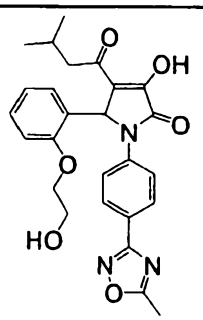
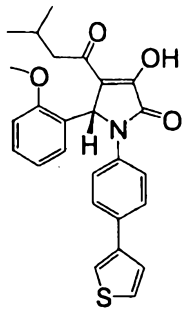
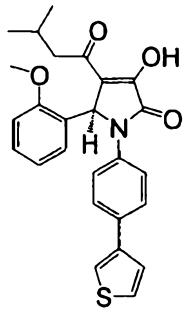
【表 63】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-266	462	2	2.76
	I-267	493	2	2.60
	I-268	493	2	2.56
	I-269	408	2	2.42
	I-270	431	2	2.49

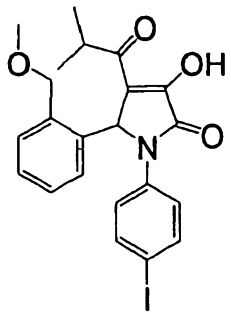
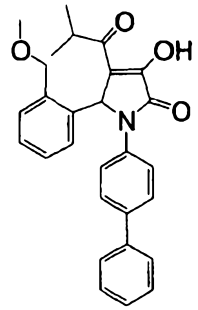
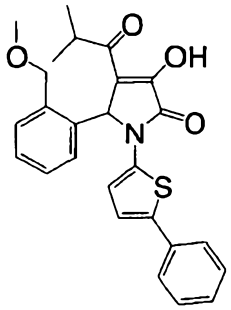
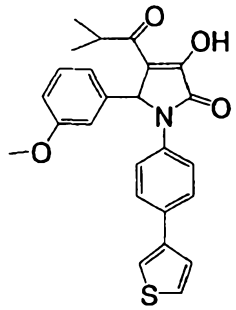
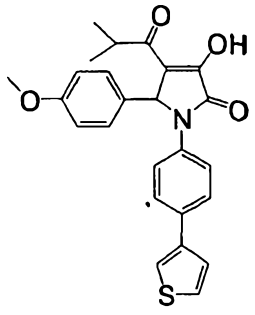
【表 64】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-271	478	1	2.02
	I-272	464	1	1.73
	I-273	492	1	2.15
	I-274	478	1	1.85
	I-275	478	1	1.97

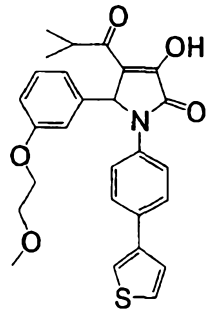
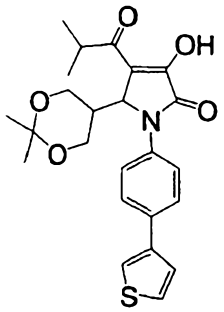
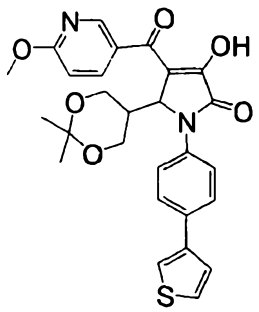
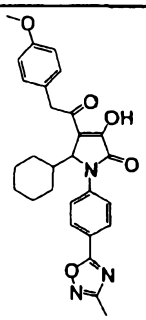
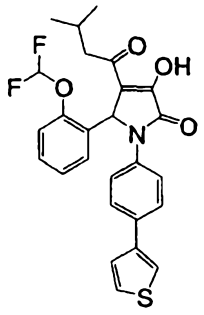
【表 65】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-276	492	1	2.12
	I-277	464	1	1.72
	I-278	478	1	1.86
	I-279	448	2	2.68
	I-280	448	2	2.67

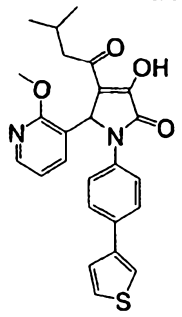
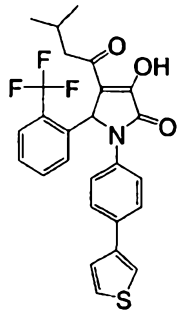
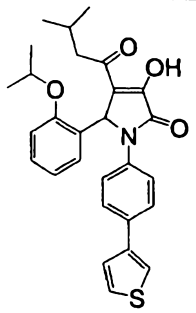
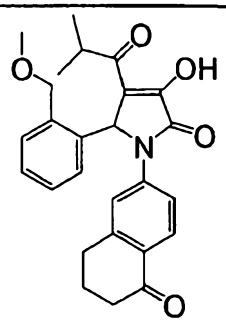
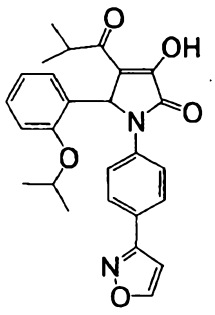
【表 66】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-281	492	1	2.30
	I-282	442	1	2.37
	I-283	448	1	2.40
	I-284	434	2	2.50
	I-285	434	2	2.50

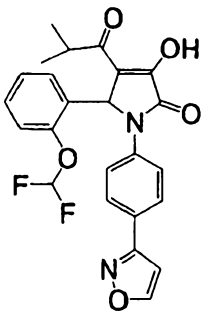
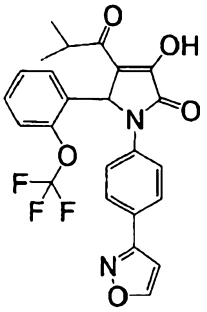
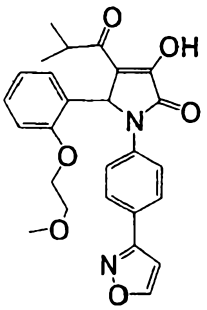
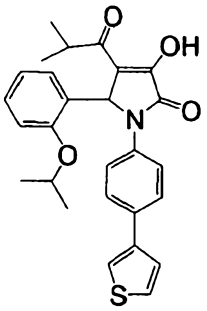
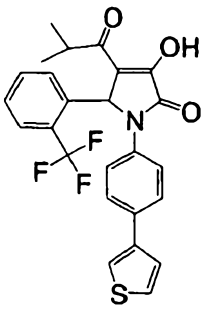
【表 67】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-286	478	2	2.45
	I-287	442	1	2.10
	I-288	507	1	2.04
	I-289	488	2	2.63
	I-290	484	1	2.44

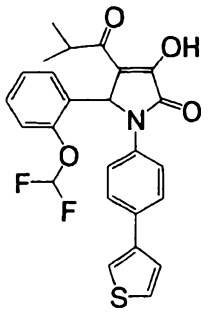
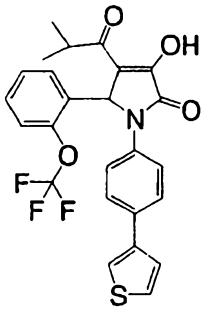
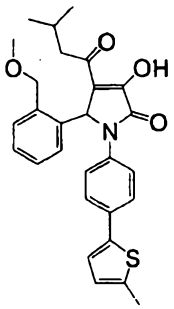
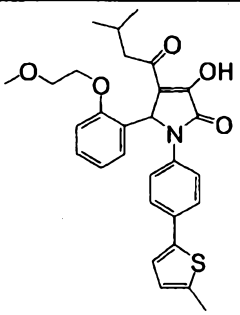
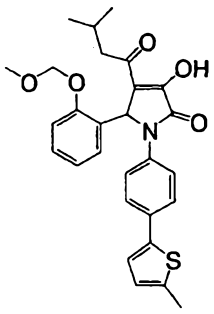
【表 68】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-291	449	2	2.51
	I-292	486	2	2.72
	I-293	476	2	2.87
	I-294	434	1	1.99
	I-295	477	1	2.18

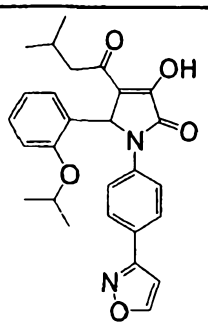
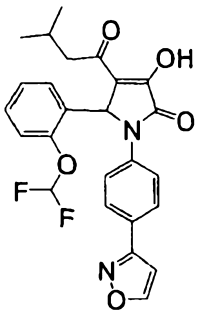
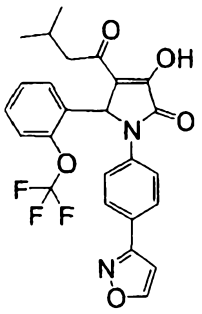
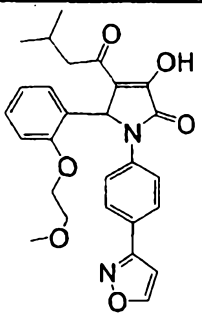
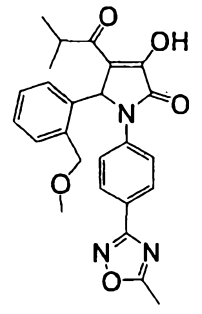
【表 69】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-296	430	1	2.07
	I-297	473	1	2.11
	I-298	463	1	1.96
	I-299	462	1	2.48
	I-300	472	1	2.33

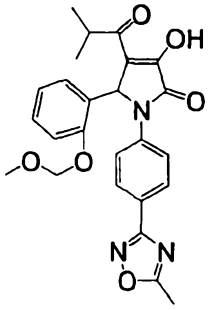
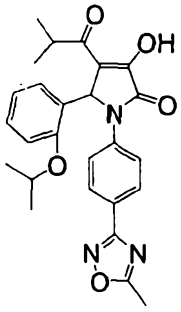
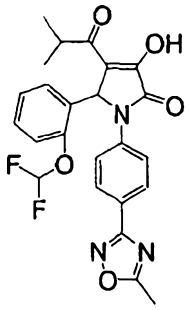
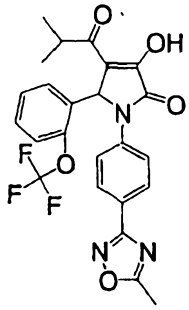
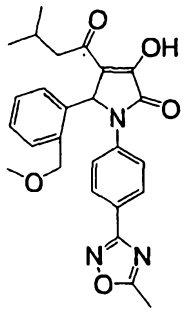
【表 70】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-301	470	1	2.35
	I-302	488	1	2.39
	I-303	476	1	2.54
	I-304	506	1	2.53
	I-305	492	1	2.51

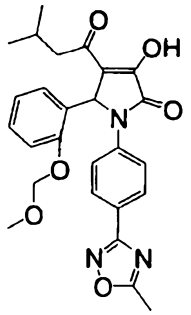
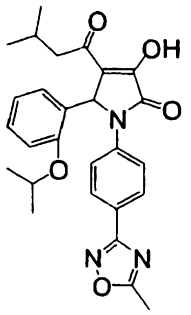
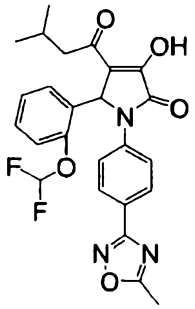
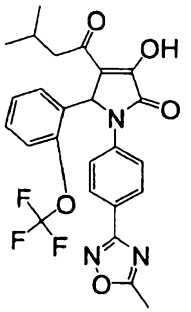
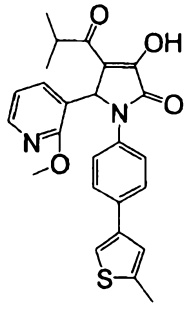
【表 71】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-306	461	1	2.27
	I-307	469	1	2.17
	I-308	487	1	2.21
	I-309	477	1	2.09
	I-310	448	2	2.29

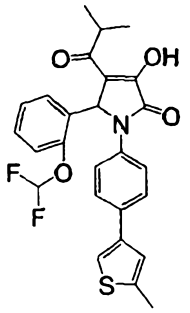
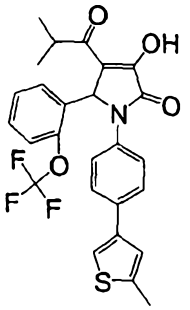
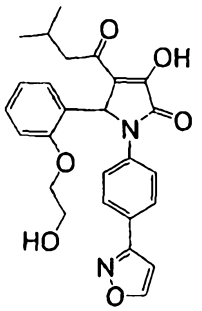
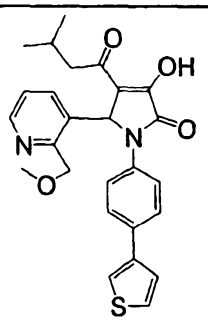
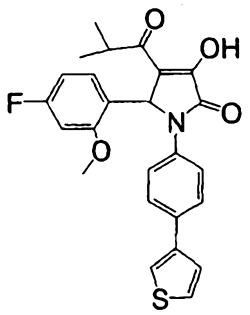
【表 72】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-311	464	2	2.28
	I-312	462	2	2.49
	I-313	470	2	2.34
	I-314	488	2	2.43
	I-315	462	2	2.42

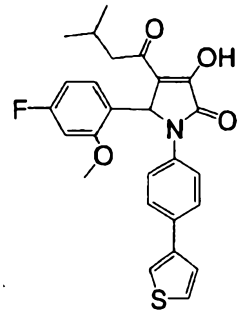
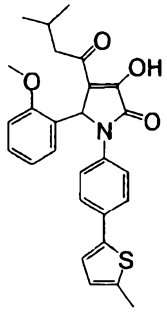
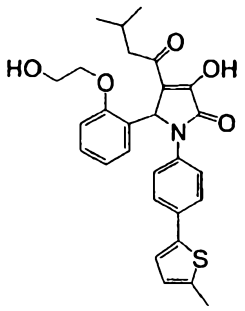
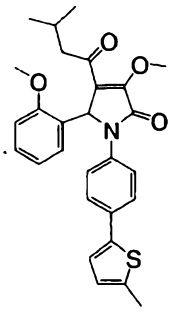
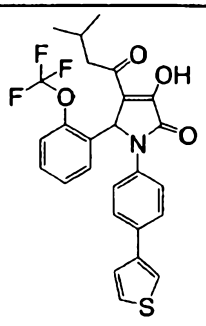
【表 73】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS保持時間(分)
	I-316	478	2	2.40
	I-317	476	2	2.61
	I-318	484	2	2.45
	I-319	502	2	2.54
	I-320	449	2	2.53

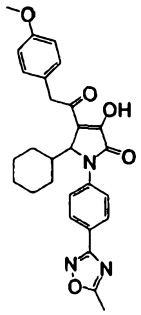
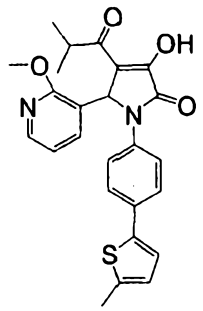
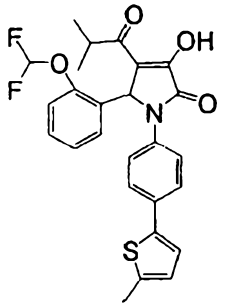
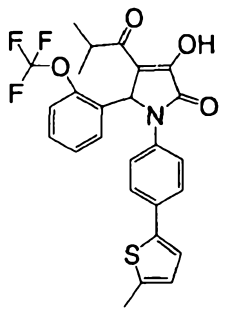
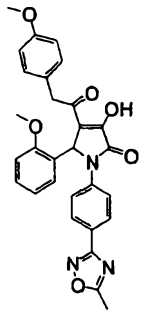
【表 74】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-321	484	2	2.73
	I-322	502	2	2.80
	I-323	463	1	1.83
	I-324	463	1	1.69
	I-325	452	1	2.27

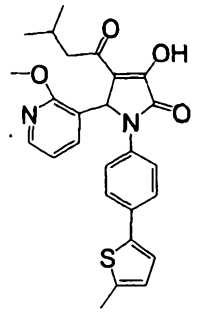
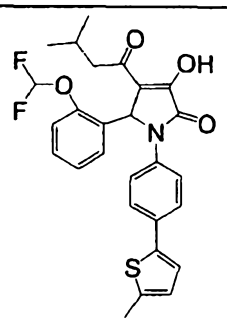
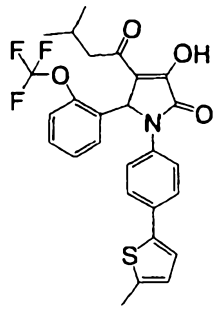
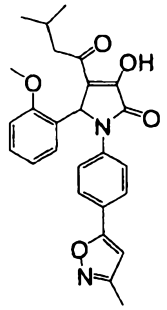
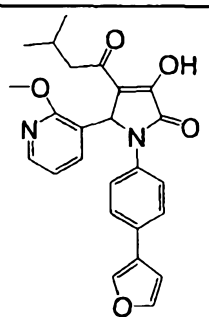
【表 75】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-326	466	1	2.40
	I-327	462	1	2.52
	I-328	492	1	2.27
	I-329	476	1	2.74
	I-330	502	1	2.51

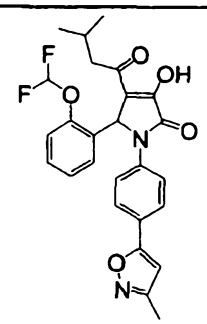
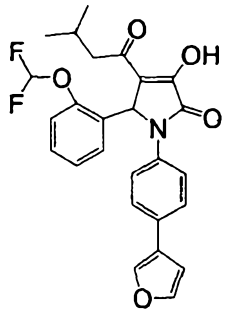
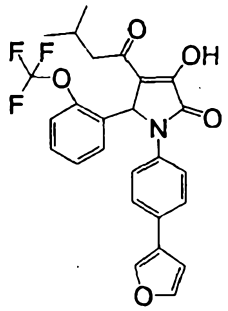
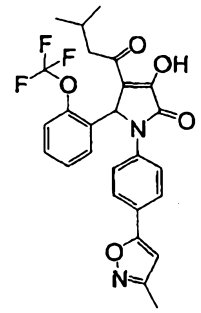
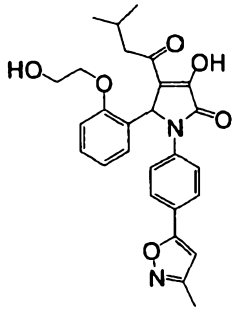
【表 76】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-331	488	2	2.61
	I-332	449	1	2.26
	I-333	484	1	2.50
	I-334	502	1	2.55
	I-335	512	2	2.36

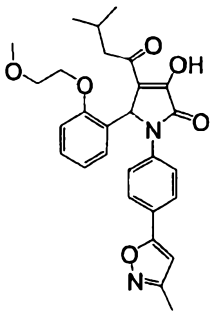
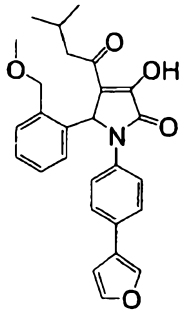
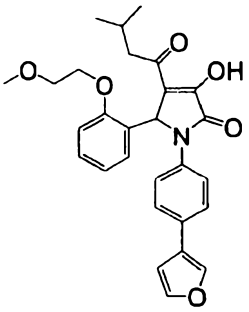
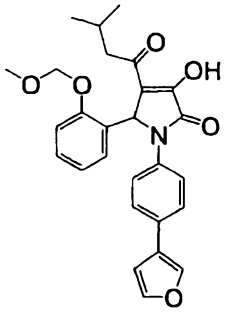
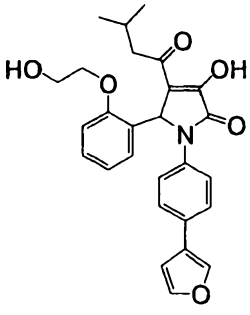
【表 77】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-336	463	1	2.40
	I-337	498	1	2.56
	I-338	516	1	2.67
	I-339	447	2	2.47
	I-340	433	1	2.10

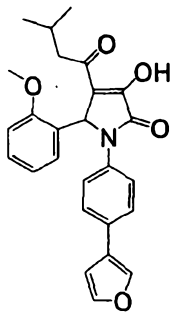
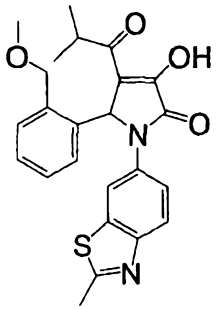
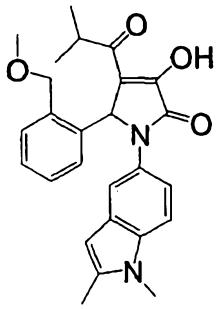
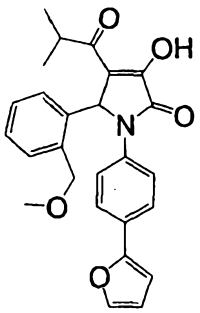
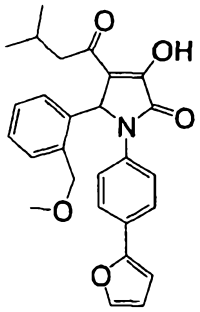
【表 78】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-341	483	2	2.53
	I-342	468	1	2.30
	I-343	486	1	2.40
	I-344	501	2	2.59
	I-345	477	2	2.19

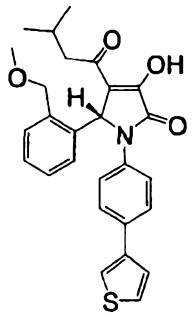
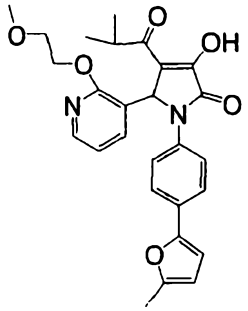
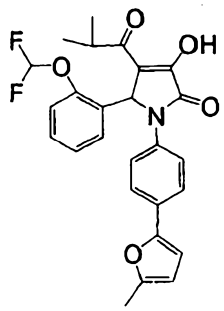
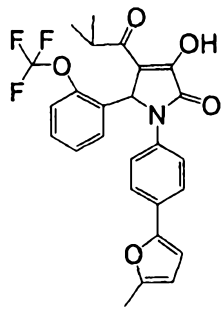
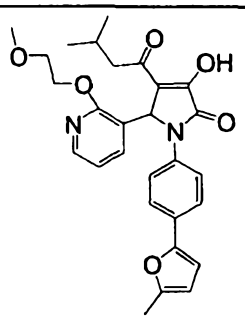
【表 79】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-346	491	2	2.46
	I-347	446	1	2.25
	I-348	476	1	2.21
	I-349	462	1	2.26
	I-350	462	1	1.98

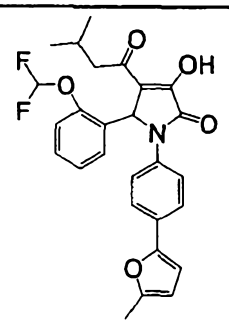
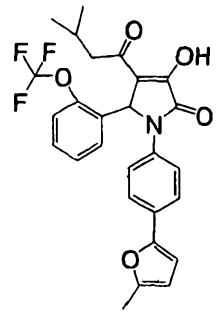
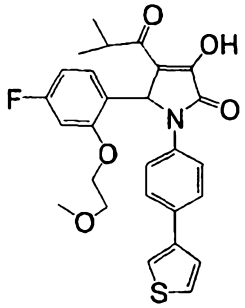
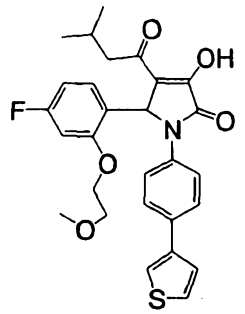
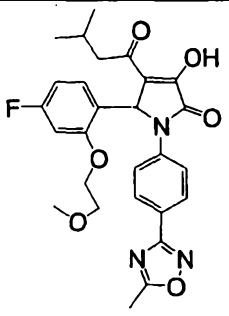
【表 80】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-351	432	1	2.27
	I-352	437	1	1.92
	I-353	433	1	2.09
	I-354	432	2	2.53
	I-355	446	2	2.64

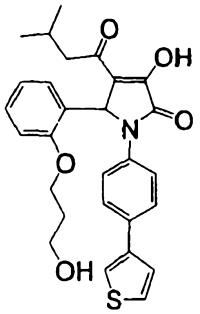
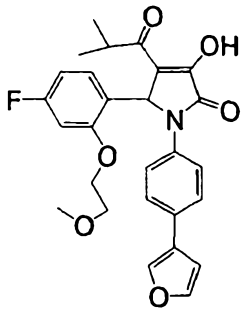
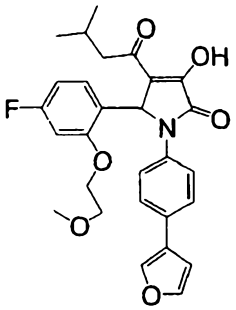
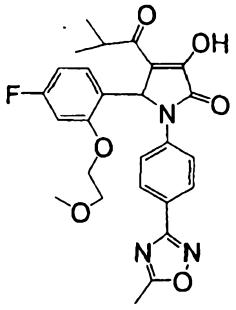
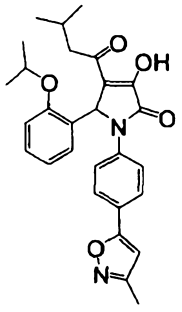
【表 81】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-356	462	2	2.67
	I-357	477	1	2.16
	I-358	468	1	2.41
	I-359	486	1	2.46
	I-360	491	1	2.29

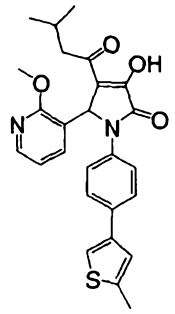
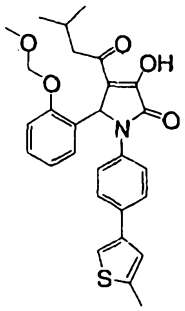
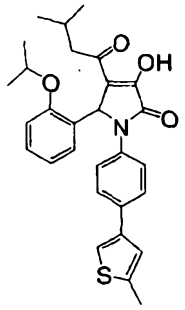
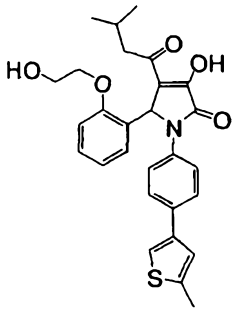
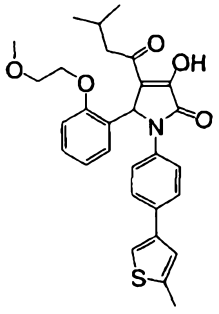
【表 82】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-361	482	1	2.47
	I-362	500	1	2.56
	I-363	496	1	2.26
	I-364	510	1	2.39
	I-365	510	1	2.11

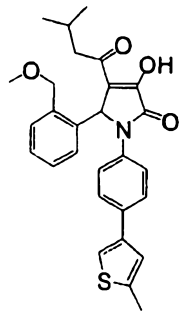
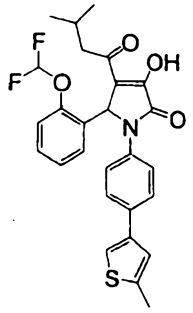
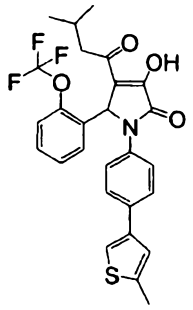
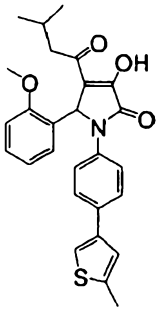
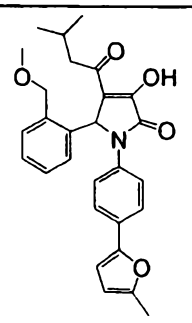
【表 83】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-366	492	1	2.12
	I-367	480	1	2.15
	I-368	494	1	2.27
	I-369	496	1	2.00
	I-370	475	1	2.38

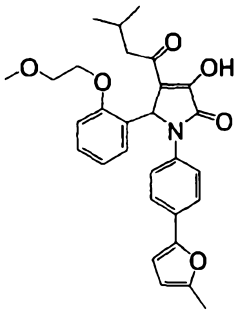
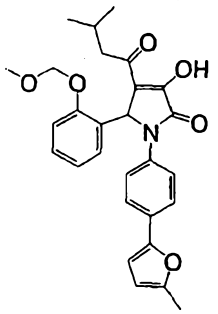
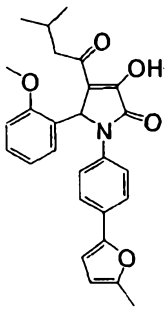
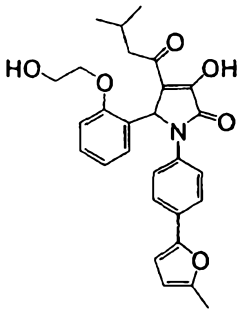
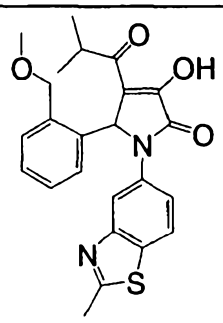
【表 84】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-371	463	2	2.67
	I-372	492	2	2.81
	I-373	490	2	2.97
	I-374	492	2	2.51
	I-375	506	2	2.79

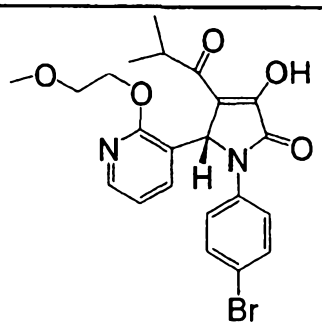
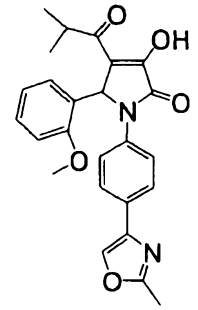
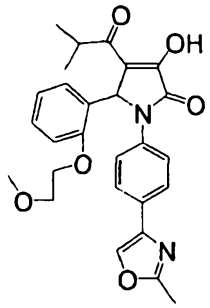
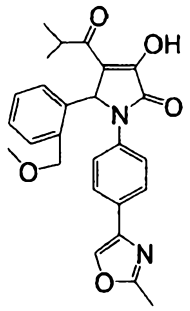
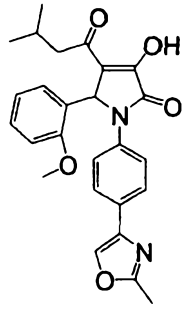
【表 85】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-376	476	2	2.83
	I-377	498	1	2.52
	I-378	516	1	2.61
	I-379	462	1	2.52
	I-380	460	1	2.48

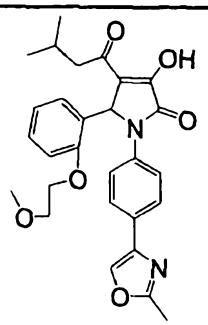
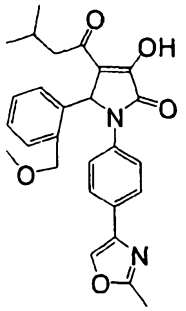
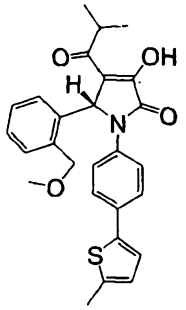
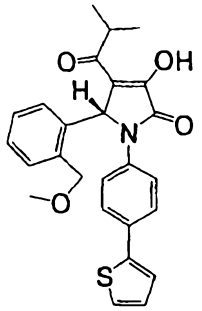
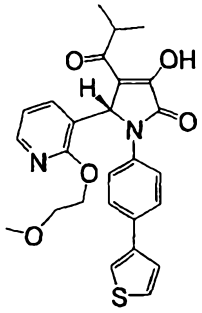
【表 86】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-381	490	1	2.40
	I-382	476	1	2.45
	I-383	446	1	2.43
	I-384	476	1	2.18
	I-385	437	1	1.91

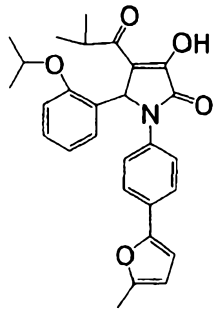
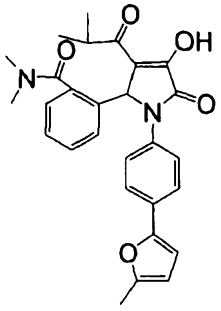
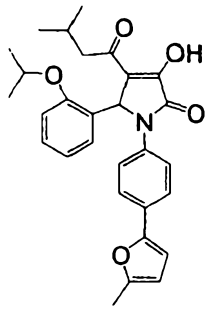
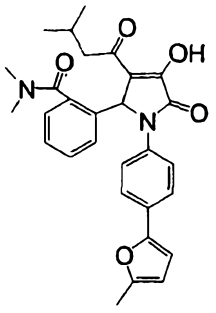
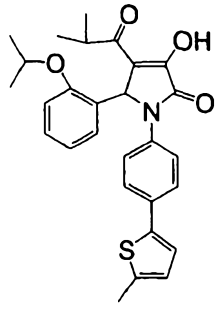
【表 87】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-386	476	2	2.32
	I-387	433	2	2.18
	I-388	477	2	2.17
	I-389	447	2	2.19
	I-390	447	2	2.30

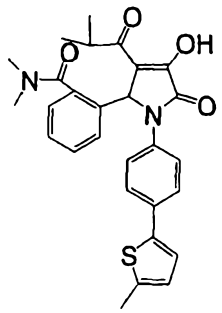
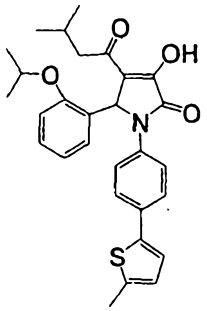
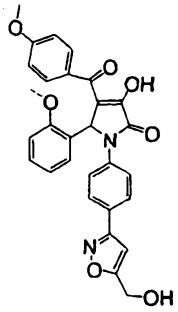
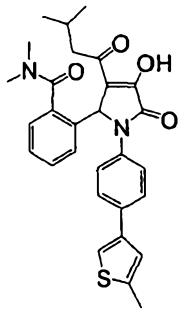
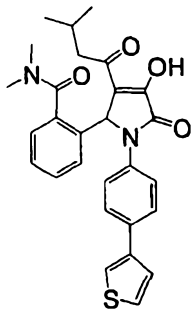
【表 88】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-391	491	2	2.32
	I-392	461	2	2.35
	I-393	462	1	2.47
	I-394	448	1	2.29
	I-395	479	1	2.11

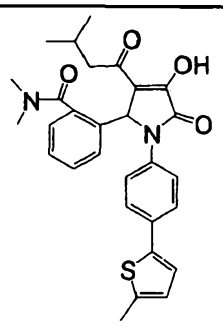
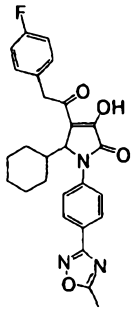
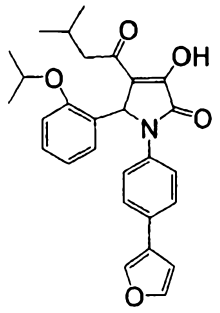
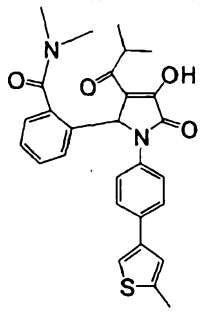
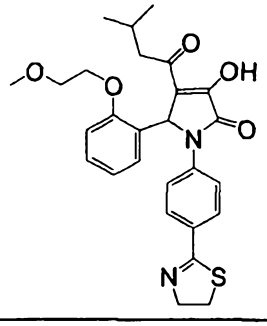
【表 89】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-396	460	1	2.52
	I-397	473	1	2.17
	I-398	474	1	2.65
	I-399	487	1	2.25
	I-400	476	1	2.61

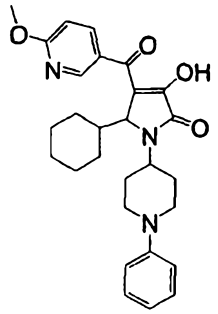
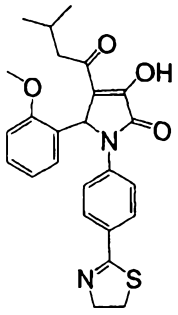
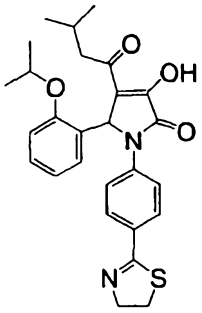
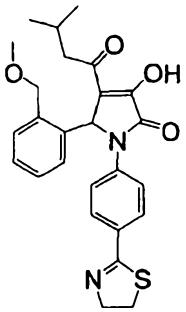
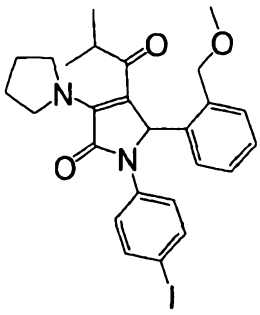
【表 90】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS保持時間(分)
	I-401	489	1	2.27
	I-402	490	1	2.70
	I-403	513	2	2.00
	I-404	503	2	2.64
	I-405	489	2	2.51

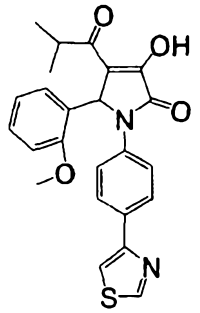
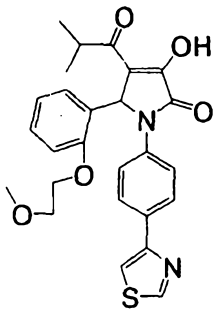
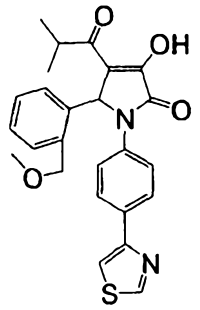
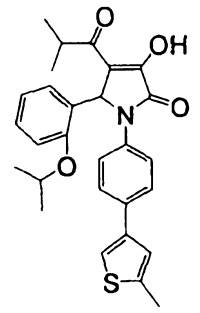
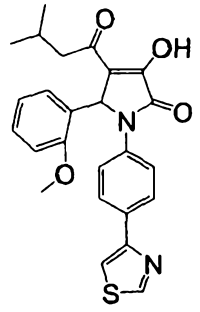
【表 91】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-406	503	1	2.38
	I-407	476	2	2.67
	I-408	460	1	2.44
	I-409	489	2	2.53
	I-410	495	1	1.97

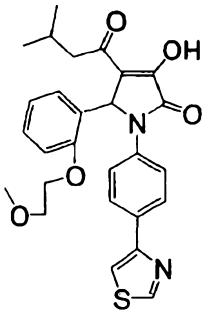
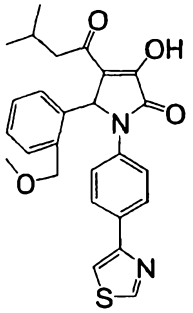
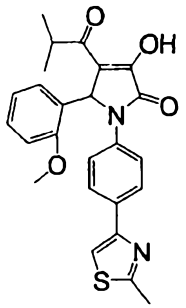
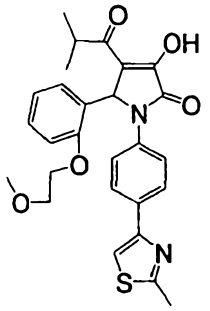
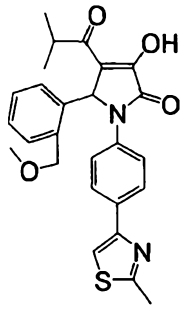
【表 92】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-411	476	1	2.09
	I-412	451	1	2.00
	I-413	479	1	2.21
	I-414	465	1	2.02
	I-415	545	1	2.58

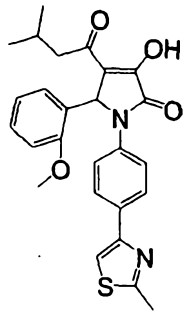
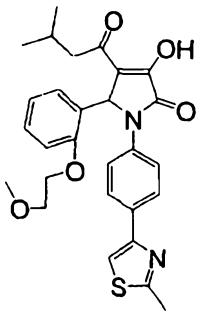
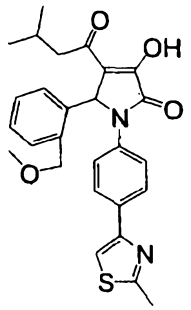
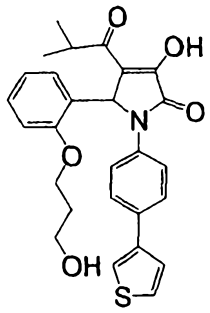
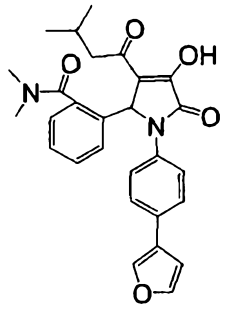
【表 93】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-416	435	2	2.27
	I-417	479	2	2.27
	I-418	449	2	2.28
	I-419	476	2	2.89
	I-420	449	2	2.39

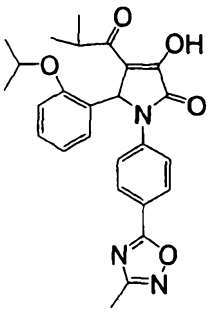
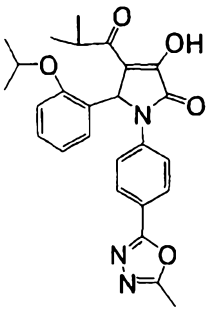
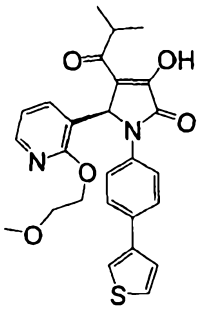
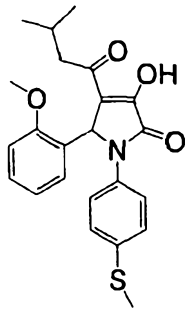
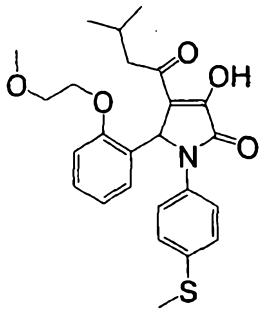
【表 94】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-421	493	2	2.40
	I-422	463	2	2.41
	I-423	449	2	2.41
	I-424	493	2	2.39
	I-425	463	2	2.42

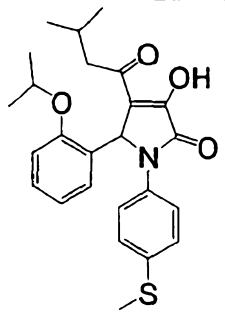
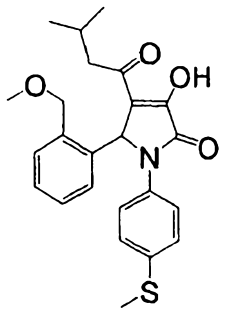
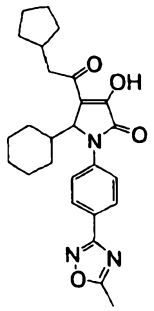
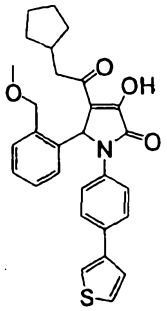
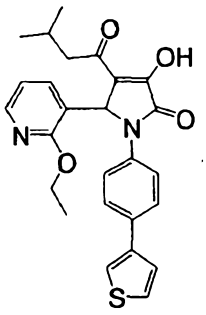
【表 95】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-426	463	2	2.53
	I-427	507	2	2.52
	I-428	477	2	2.55
	I-429	478	1	2.00
	I-430	473	1	2.08

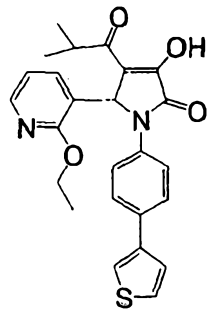
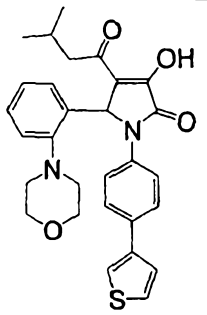
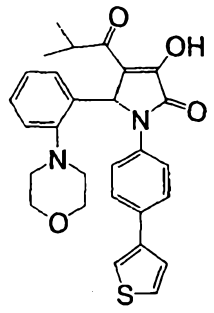
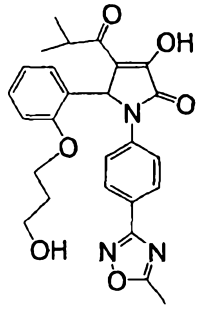
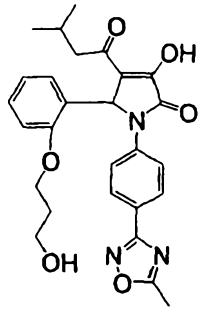
【表 96】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-431	462	1	2.26
	I-432	462	1	1.97
	I-433	479	1	2.08
	I-434	413	2	2.52
	I-435	456	2	2.48

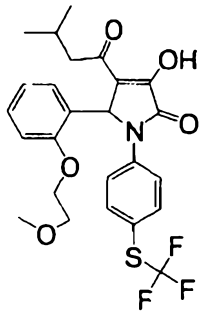
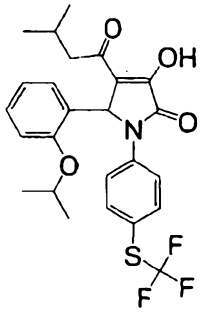
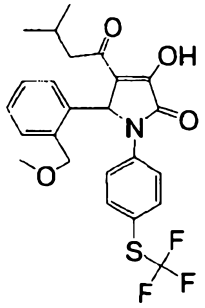
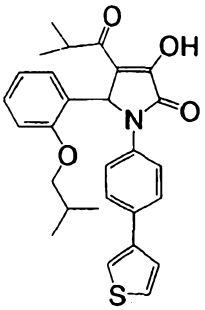
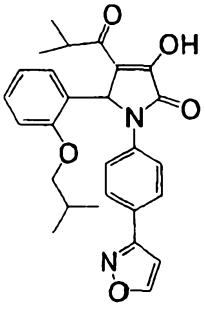
【表 97】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-436	440	2	2.71
	I-437	426	2	2.55
	I-438	450	2	2.91
	I-439	488	2	2.85
	I-440	463	1	2.32

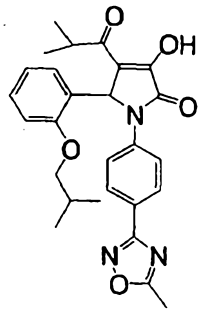
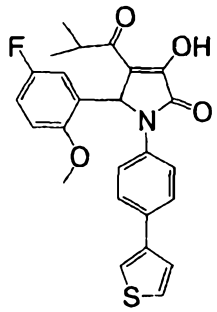
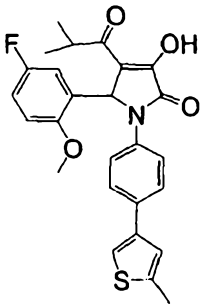
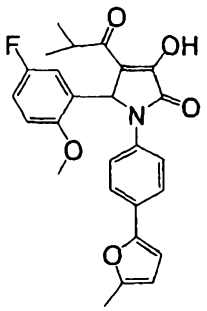
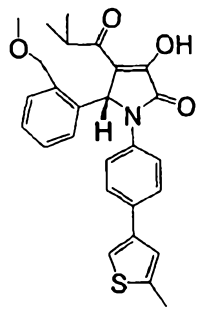
【表 98】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-441	449	1	2.18
	I-442	503	1	2.37
	I-443	489	1	2.26
	I-444	478	1	1.75
	I-445	492	1	1.84

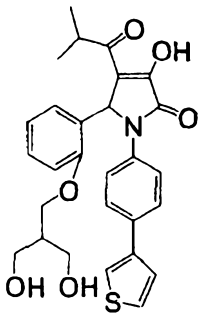
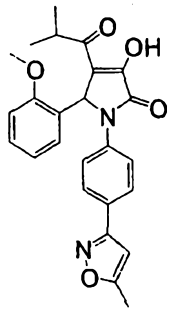
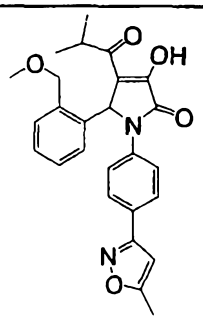
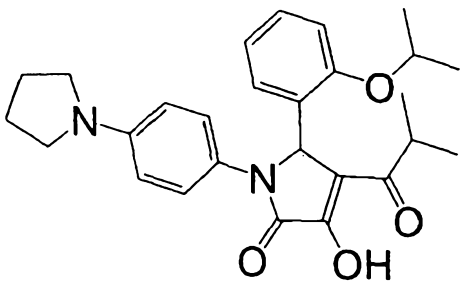
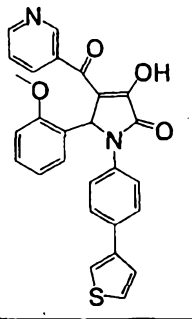
【表 99】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-446	510	1	2.50
	I-447	494	1	2.69
	I-448	480	1	2.51
	I-449	476	1	2.62
	I-450	461	1	2.31

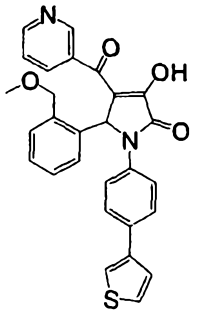
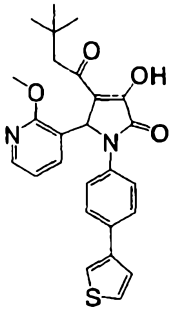
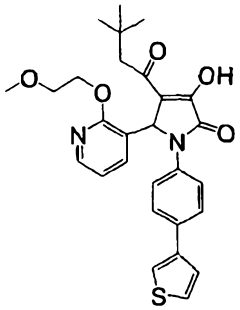
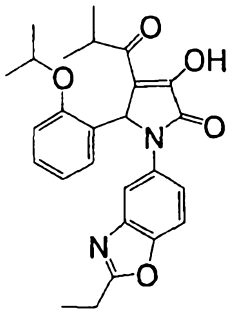
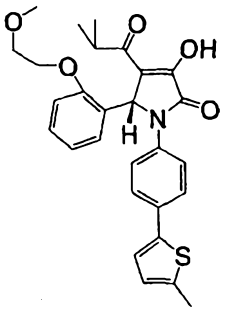
【表 100】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-451	476	1	2.38
	I-452	452	1	2.23
	I-453	466	1	2.41
	I-454	450	1	2.30
	I-455	462	2	2.72

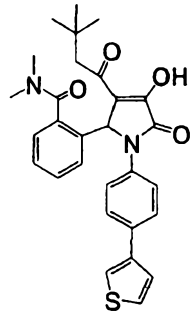
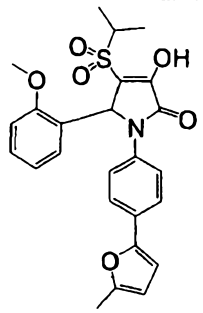
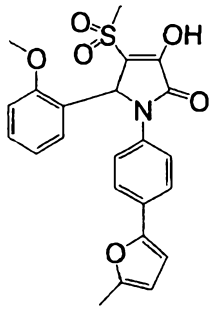
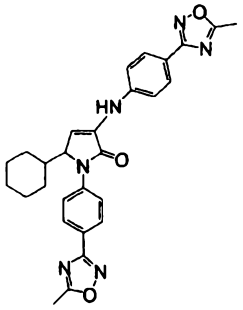
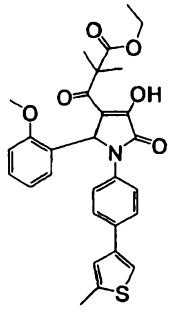
【表 101】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-456	508	2	2.12
	I-457	433	2	2.36
	I-458	447	2	2.39
	I-459	449	1	2.44
	I-460	469	2	2.04

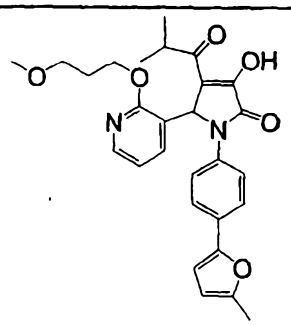
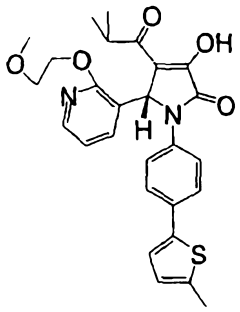
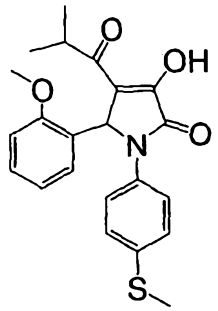
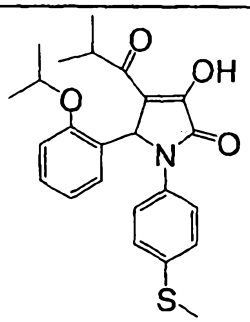
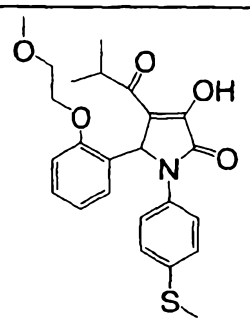
【表 102】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-461	483	2	2.04
	I-462	463	2	2.61
	I-463	507	2	2.64
	I-464	449	1	2.19
	I-465	492	2	2.73

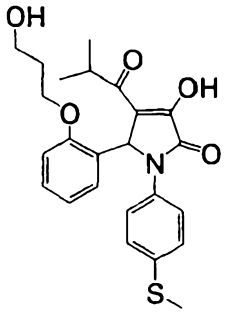
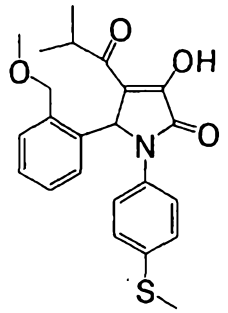
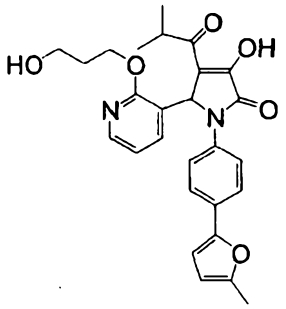
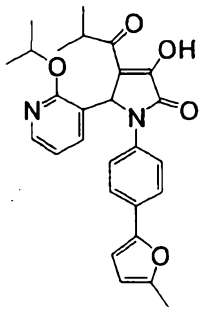
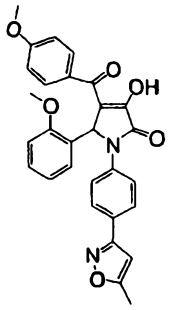
【表 103】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-466	503	2	2.61
	I-467	468	2	2.38
	I-468	440	2	2.23
	I-469	497	2	2.88
	I-470	520	2	2.70

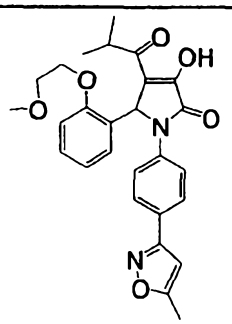
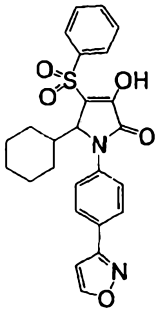
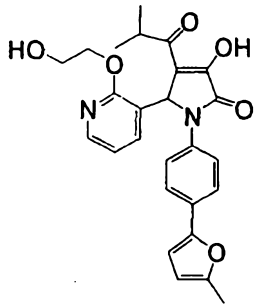
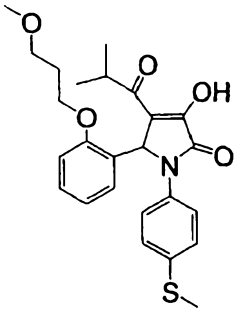
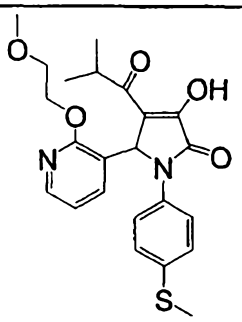
【表 104】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-471	491	1	2.24
	I-472	493	2	2.60
	I-473	398	2	2.38
	I-474	426	2	2.61
	I-475	442	2	2.36

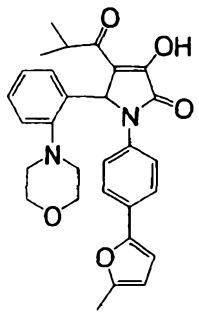
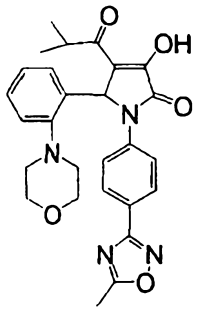
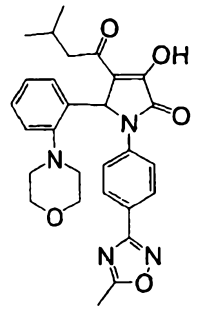
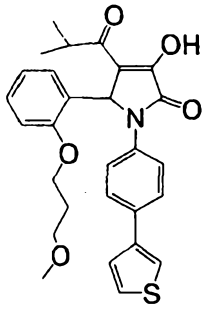
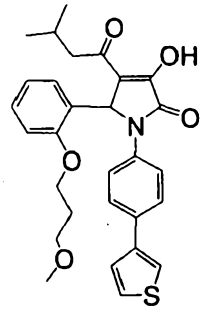
【表 105】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-476	442	2	2.12
	I-477	412	2	2.39
	I-478	477	1	1.89
	I-479	461	1	2.39
	I-480	497	2	2.32

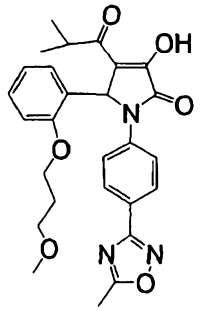
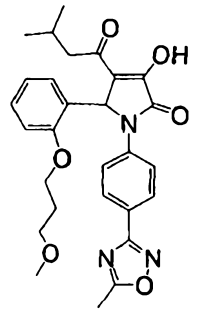
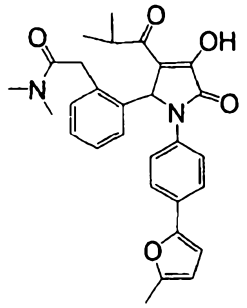
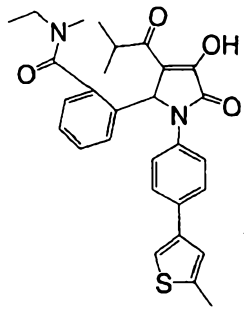
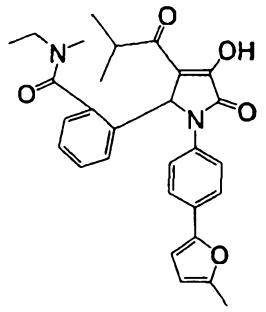
【表 106】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-481	477	2	2.35
	I-482	465	2	2.41
	I-483	463	1	1.89
	I-484	456	2	2.47
	I-485	443	2	2.24

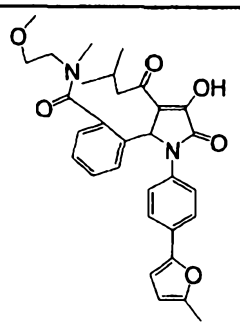
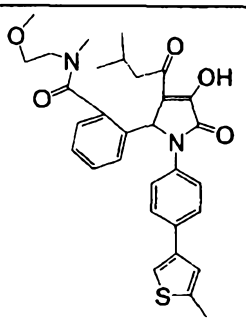
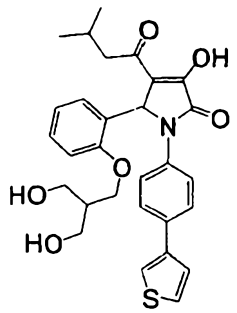
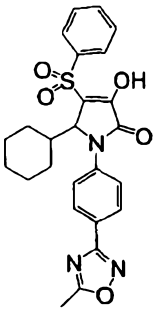
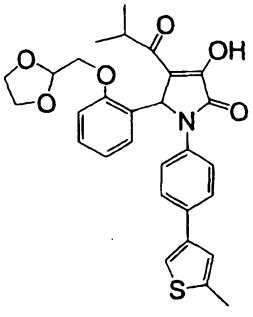
【表 107】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-486	487	1	2.28
	I-487	489	1	1.97
	I-488	503	1	2.07
	I-489	492	1	2.32
	I-490	506	1	2.39

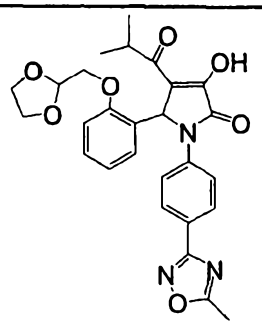
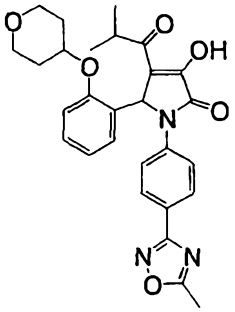
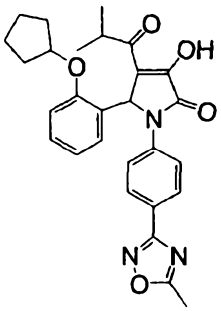
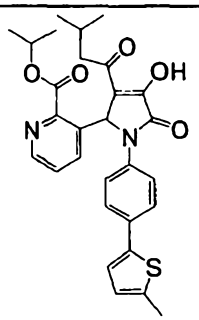
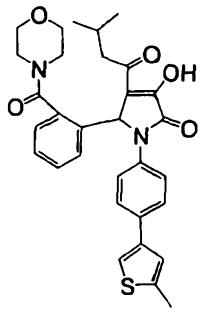
【表 108】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-491	492	1	2.06
	I-492	506	1	2.15
	I-493	487	1	1.98
	I-494	503	2	2.65
	I-495	487	2	2.59

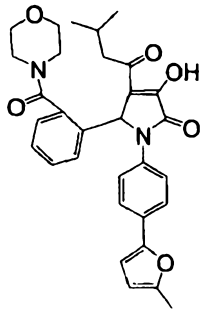
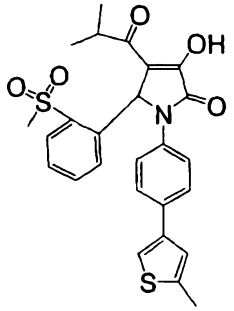
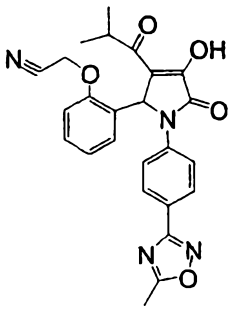
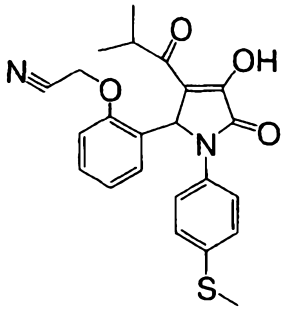
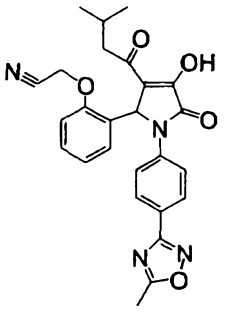
【表 109】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-496	531	2	2.63
	I-497	547	2	2.70
	I-498	522	2	2.23
	I-499	480	2	2.44
	I-500	520	2	2.63

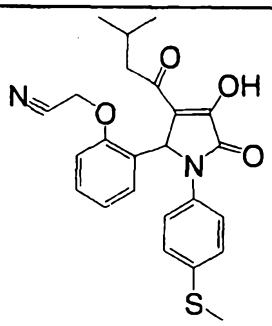
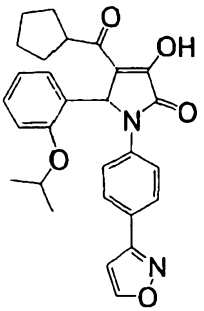
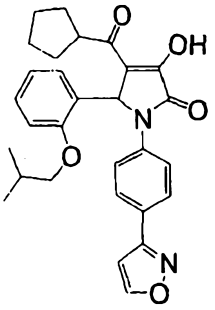
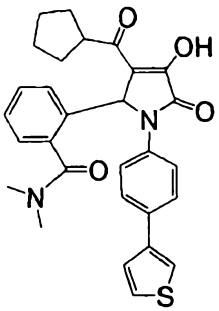
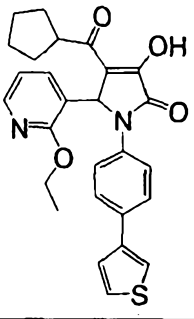
【表 110】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-501	506	2	2.24
	I-502	504	1	1.96
	I-503	487	1	2.34
	I-504	519	1	2.39
	I-505	545	2	2.61

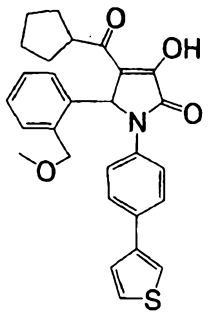
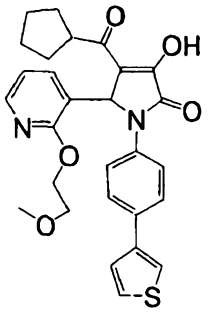
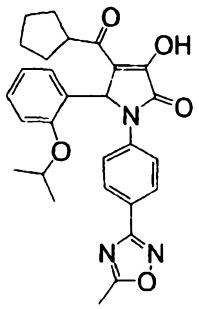
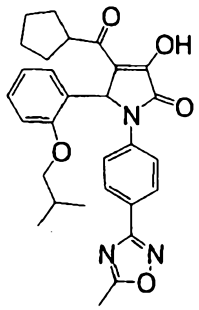
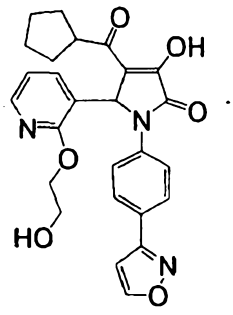
【表 111】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-506	529	2	2.55
	I-507	496	2	2.45
	I-508	459	2	2.11
	I-509	423	2	2.20
	I-510	474	2	2.21

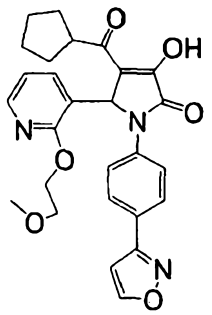
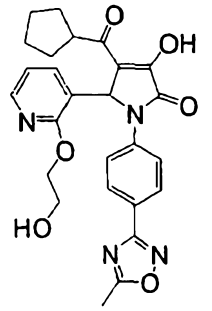
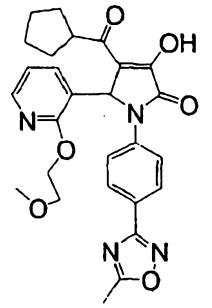
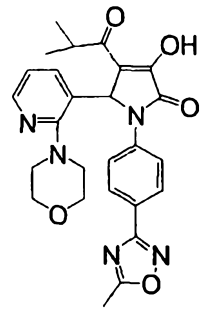
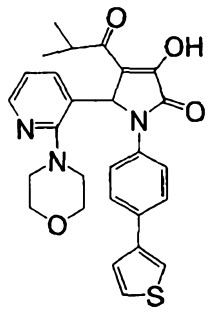
【表 112】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-511	437	2	2.29
	I-512	473	1	2.36
	I-513	487	1	2.49
	I-514	501	1	2.24
	I-515	475	1	2.38

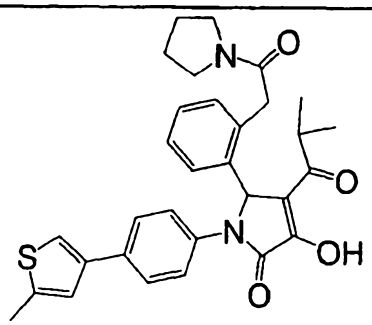
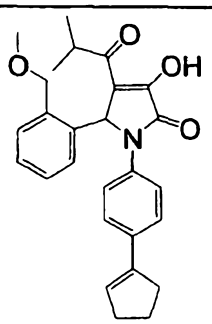
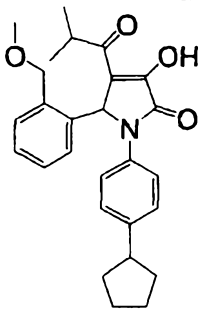
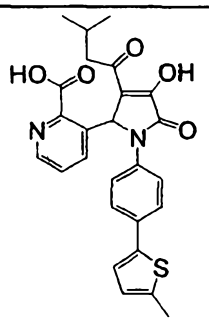
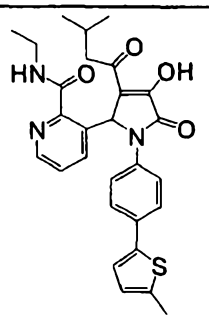
【表 113】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-516	474	1	2.43
	I-517	505	1	2.26
	I-518	488	1	2.39
	I-519	502	1	2.55
	I-520	476	1	1.70

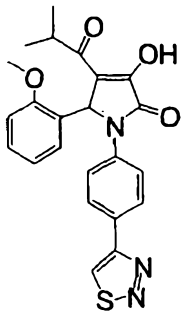
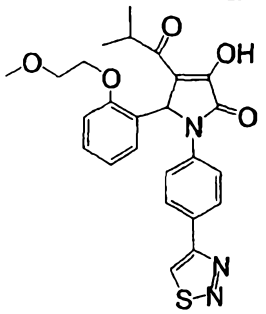
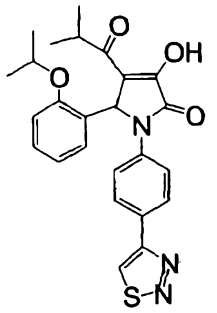
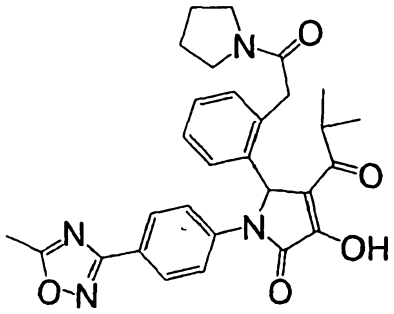
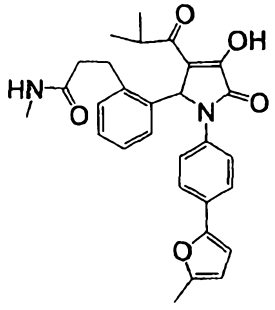
【表 114】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-521	490	1	1.96
	I-522	491	1	1.71
	I-523	505	1	1.98
	I-524	490	1	1.65
	I-525	490	1	1.91

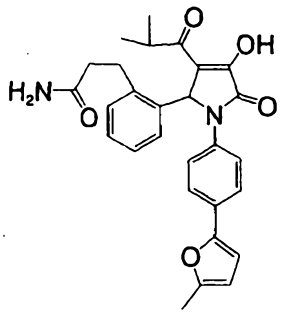
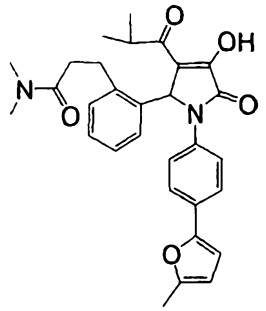
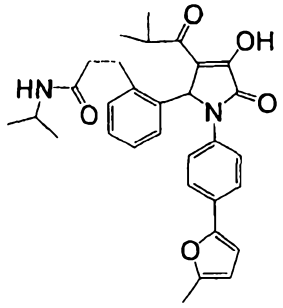
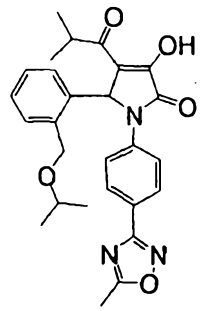
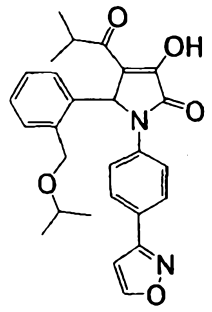
【表 115】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-526	529	2	2.43
	I-527	432	1	2.46
	I-528	434	1	2.50
	I-529	477	1	1.76
	I-530	504	1	2.30

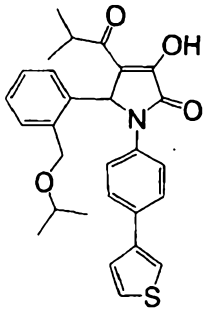
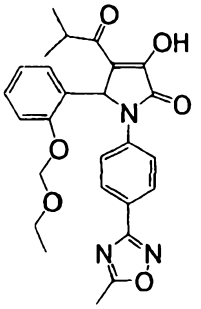
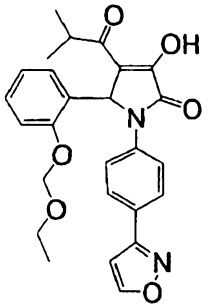
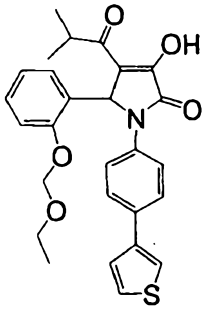
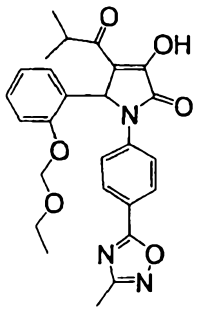
【表 116】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-531	436	2	2.28
	I-532	480	2	2.25
	I-533	464	2	2.51
	I-534	515	1	1.75
	I-535	487	1	1.89

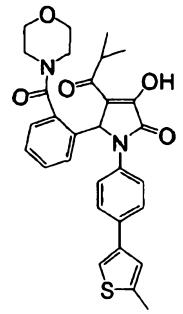
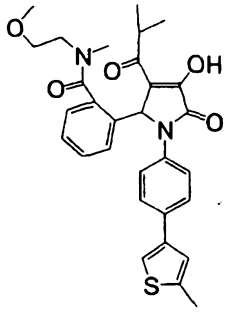
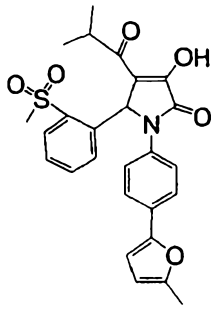
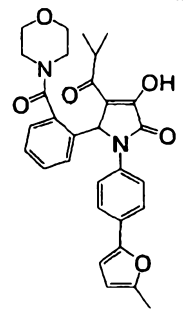
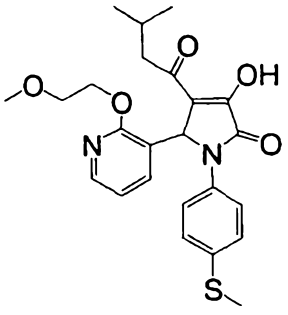
【表 117】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-536	473	1	1.80
	I-537	501	2	2.25
	I-538	515	2	2.31
	I-539	476	1	2.27
	I-540	461	1	2.23

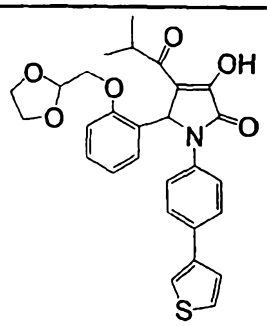
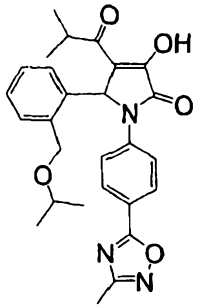
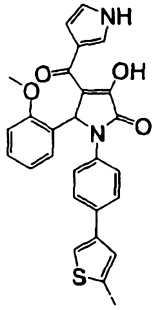
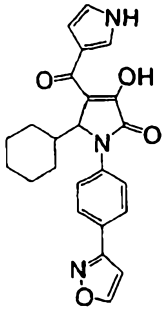
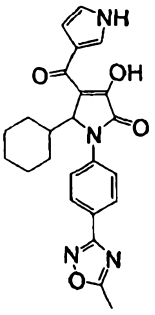
【表 118】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-541	476	1	2.51
	I-542	478	1	2.12
	I-543	463	1	2.09
	I-544	478	1	2.37
	I-545	478	1	2.14

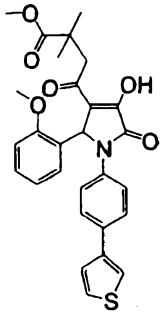
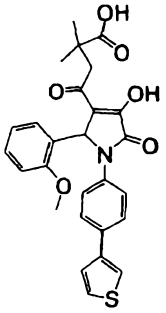
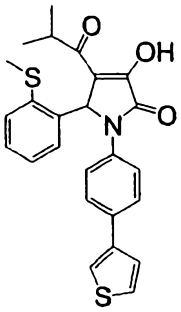
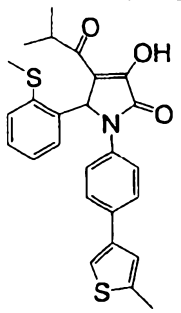
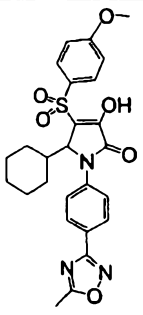
【表 119】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-546	531	2	2.52
	I-547	533	2	2.53
	I-548	480	2	2.38
	I-549	515	2	2.44
	I-550	457	2	2.22

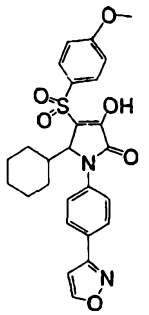
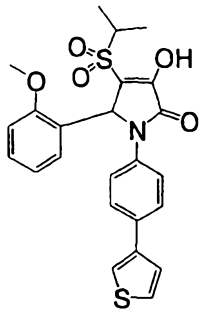
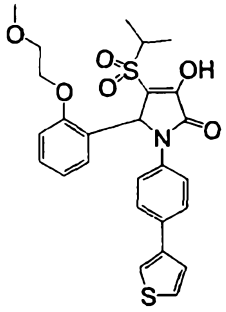
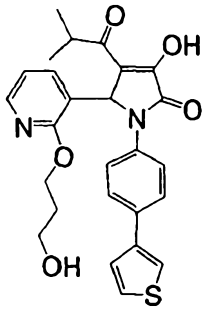
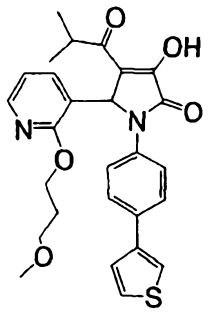
【表 120】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-551	506	2	2.39
	I-552	476	1	2.32
	I-553	471	2	2.37
	I-554	418	2	2.08
	I-555	433	2	2.11

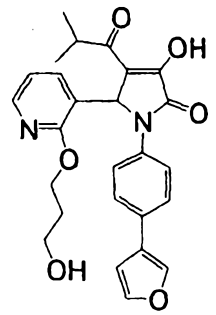
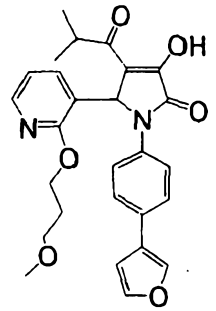
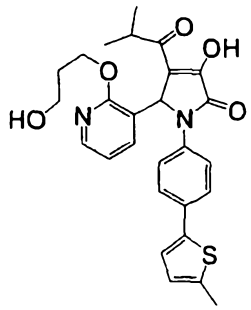
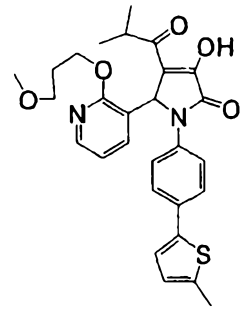
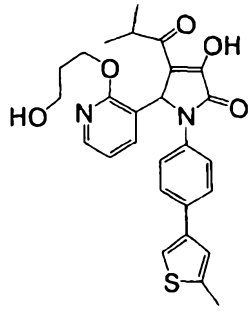
【表 121】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-556	506	2	2.43
	I-557	492	2	2.19
	I-558	450	2	2.53
	I-559	464	2	2.65
	I-560	510	2	2.35

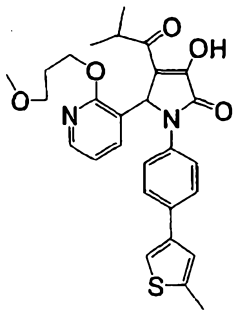
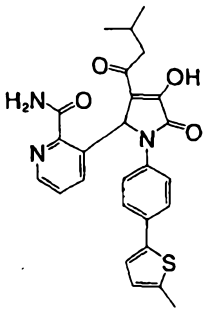
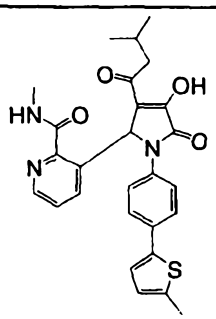
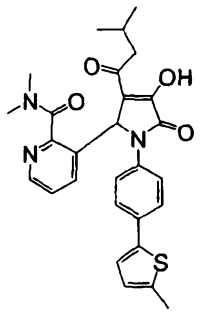
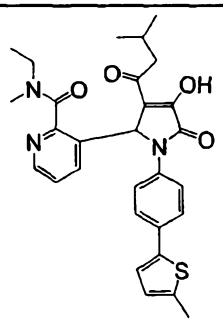
【表 122】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-561	495	2	2.31
	I-562	479	2	2.19
	I-563	514	2	2.20
	I-564	479	1	1.83
	I-565	493	1	2.14

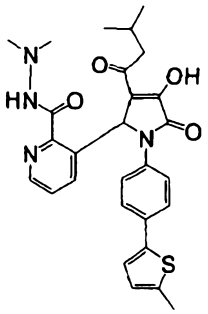
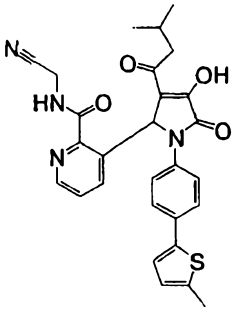
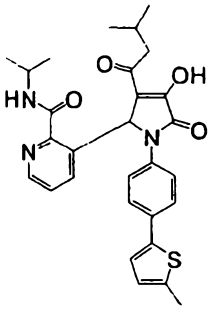
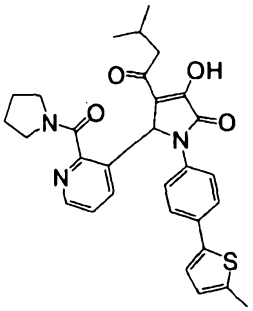
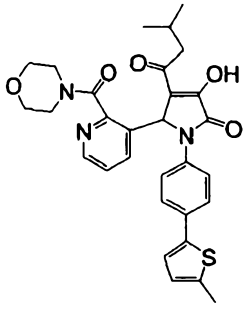
【表 123】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-566	463	1	1.72
	I-567	477	1	2.02
	I-568	493	2	2.21
	I-569	507	2	2.54
	I-570	493	2	2.19

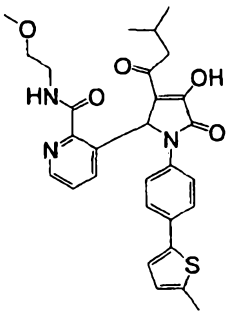
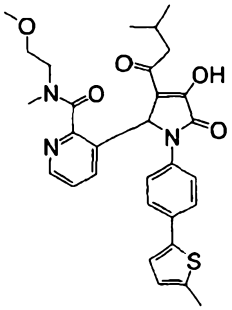
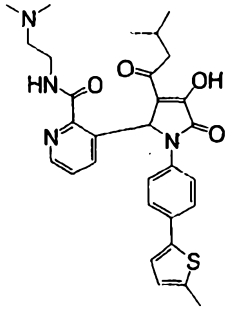
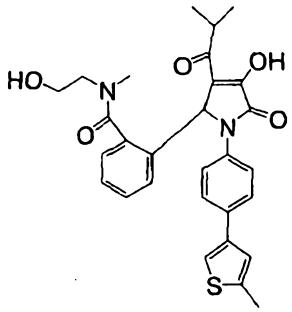
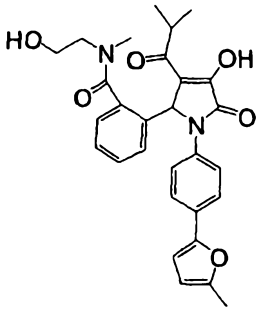
【表 124】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-571	507	2	2.51
	I-572	476	3	3.28
	I-573	490	3	3.35
	I-574	504	3	3.32
	I-575	518	3	3.41

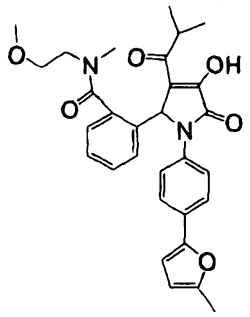
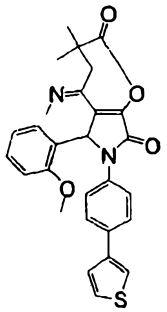
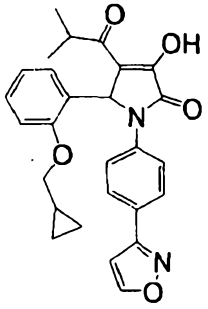
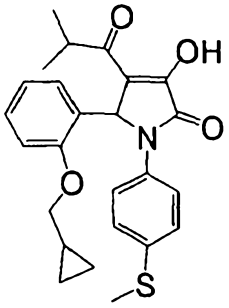
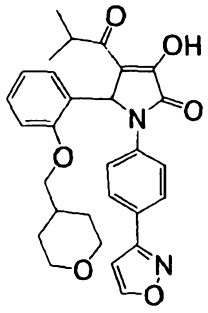
【表 125】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS保持時間(分)
	I-576	519	3	3.40
	I-577	515	3	3.24
	I-578	518	3	3.68
	I-579	530	3	3.45
	I-580	546	3	3.40

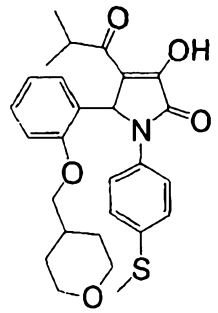
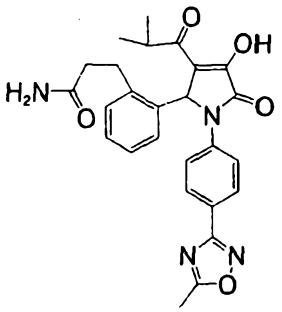
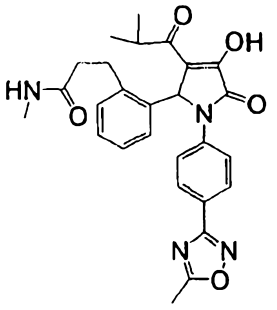
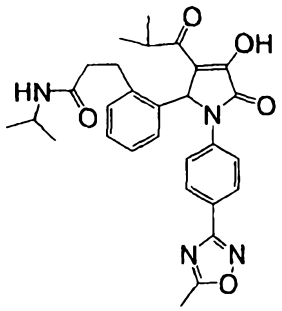
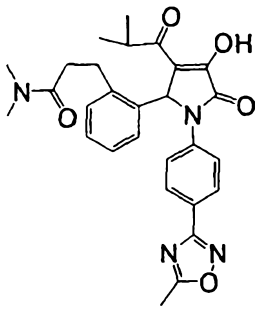
【表 126】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-581	534	3	3.50
	I-582	548	3	3.37
	I-583	547	3	2.43
	I-584	519	2	2.17
	I-585	503	2	2.10

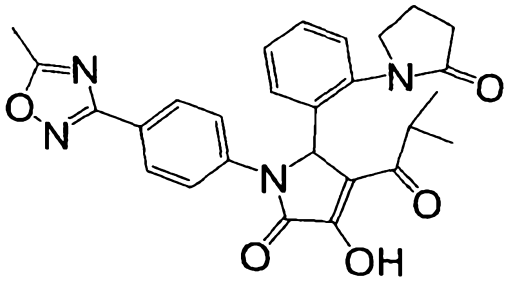
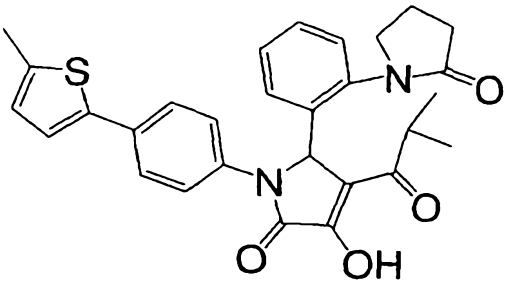
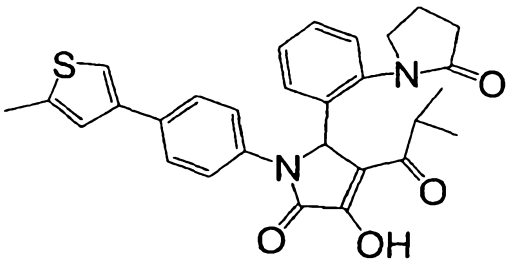
【表 127】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-586	517	2	2.39
	I-587	487	2	2.24
	I-588	459	1	2.20
	I-589	438	1	2.34
	I-590	503	1	2.01

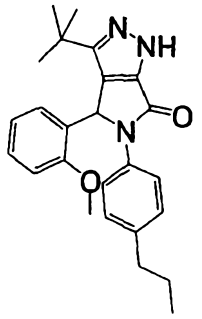
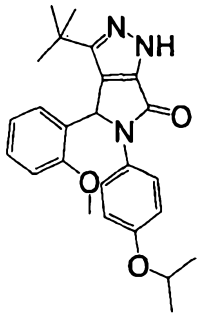
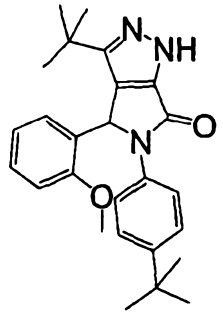
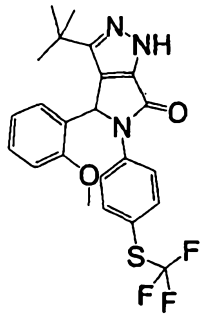
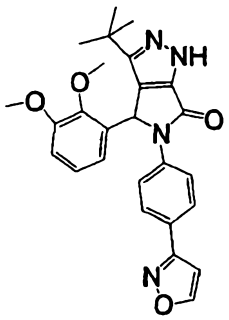
【表 128】

構造式	化合物番号	MS $[M+H]^+$	LCメソッド	LC/MS 保持時間(分)
	I-591	482	1	2.15
	I-592	475	1	1.52
	I-593	489	1	1.60
	I-594	517	1	1.83
	I-595	503	1	1.75

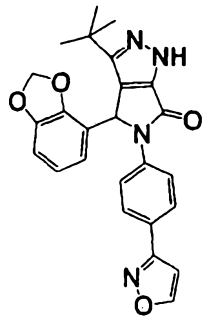
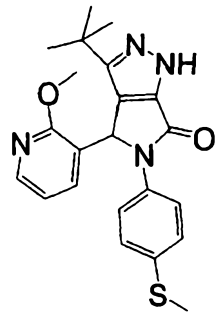
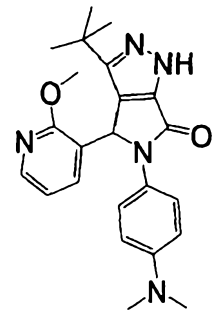
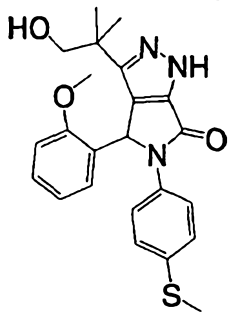
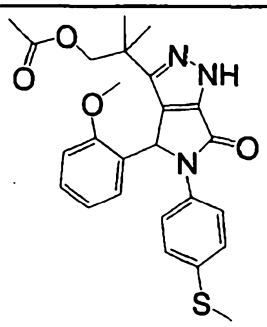
【表 129】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-596	487	2	1.82
	I-597	501	2	2.29
	I-598	501	2	2.27

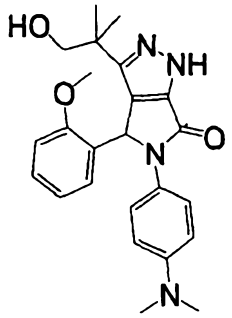
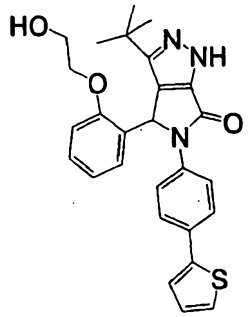
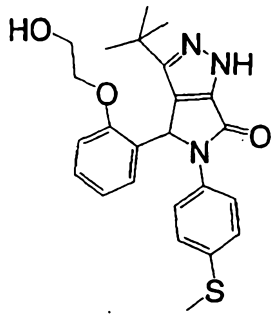
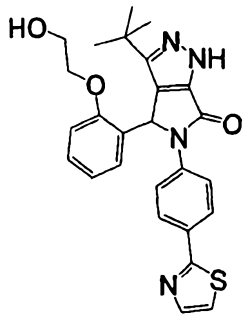
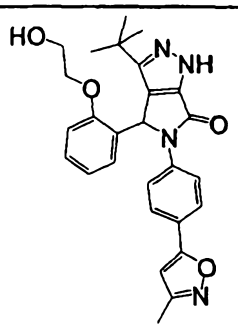
【表 130】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-001	404	1	2.30
	II-002	420	1	2.10
	II-003	418	1	2.40
	II-004	462	1	2.40
	II-005	459	1	1.90

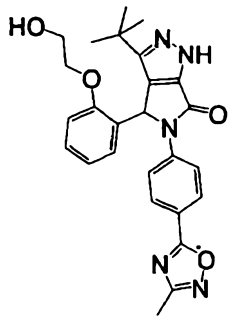
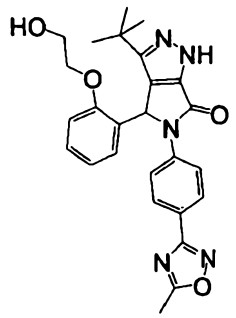
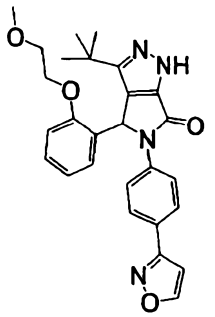
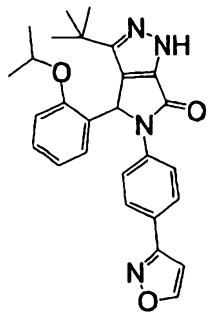
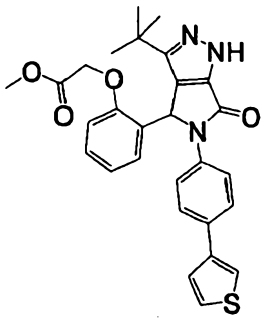
【表 131】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-006	443	1	1.80
	II-007	409	1	1.90
	II-008	406	1	1.50
	II-009	424	1	1.70
	II-010	466	1	1.90

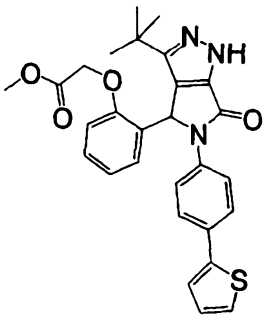
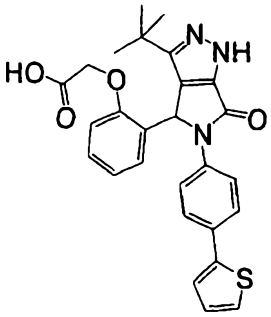
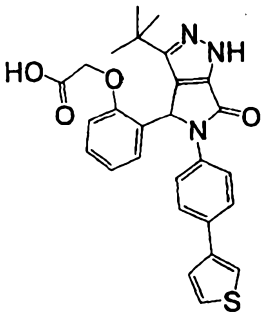
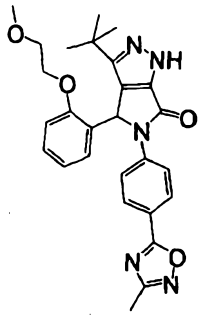
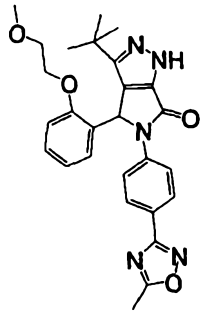
【表 132】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-011	421	1	1.30
	II-012	474	1	2.00
	II-013	438	1	1.80
	II-014	475	1	1.70
	II-015	473	1	1.70

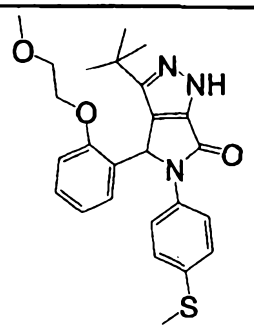
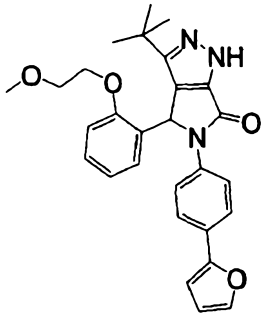
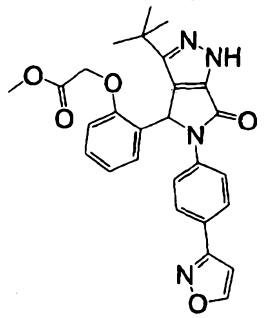
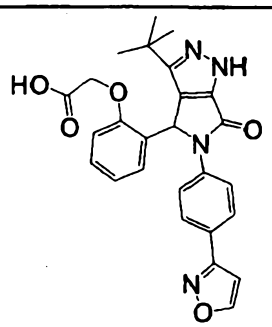
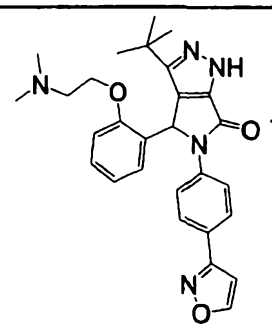
【表 133】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-016	474	1	1.70
	II-017	474	1	1.70
	II-018	473	1	1.90
	II-019	457	1	2.10
	II-020	502	1	2.10

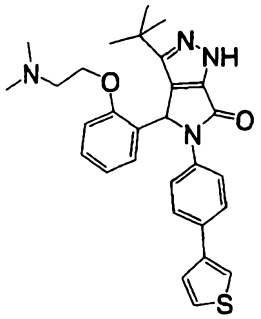
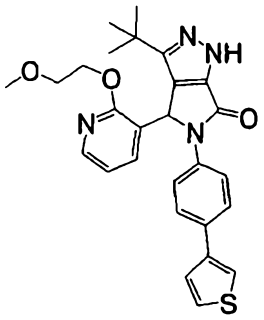
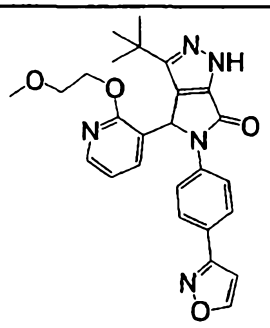
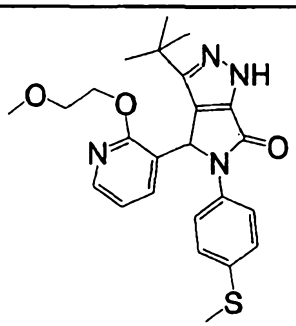
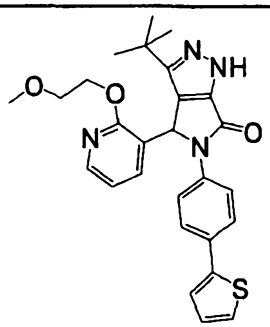
【表 134】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-021	502	1	2.10
	II-022	488	1	1.80
	II-023	488	1	1.80
	II-024	488	1	1.90
	II-025	488	1	1.90

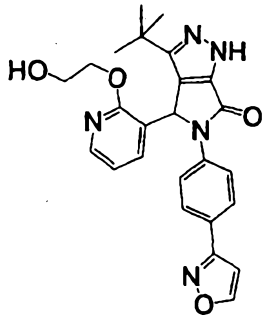
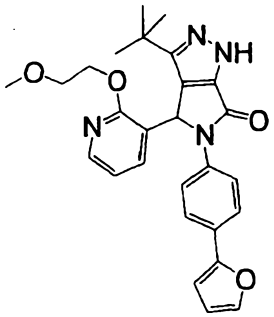
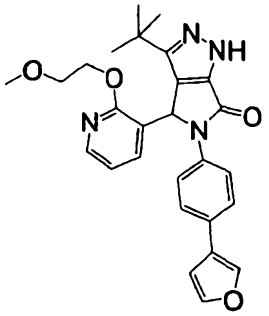
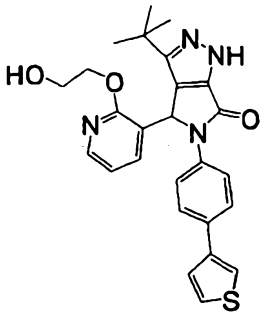
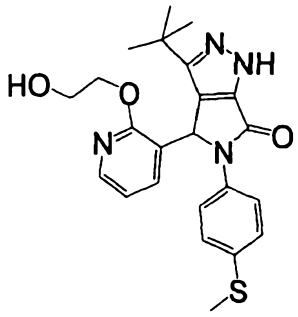
【表 135】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-026	452	1	2.00
	II-027	472	1	2.10
	II-028	487	1	1.80
	II-029	473	1	1.60
	II-030	486	1	1.20

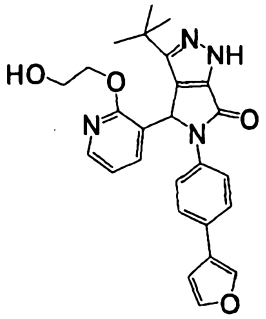
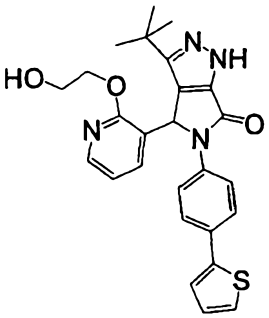
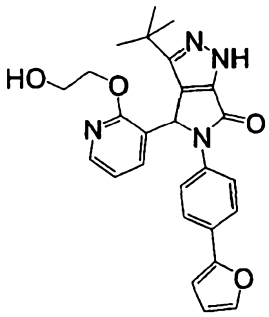
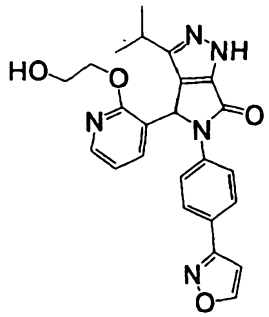
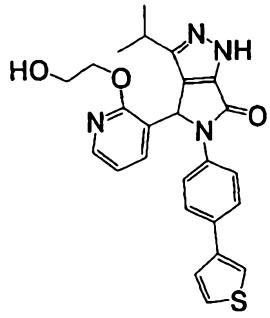
【表 136】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-031	501	1	1.50
	II-032	489	1	2.00
	II-033	474	1	1.70
	II-034	453	1	1.80
	II-035	489	1	2.10

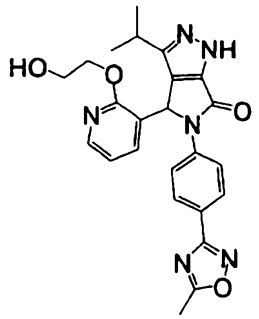
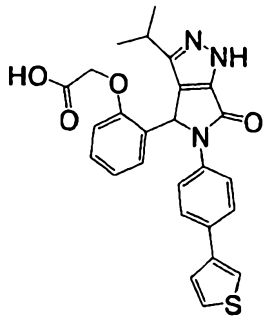
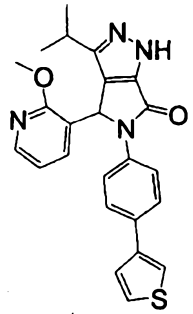
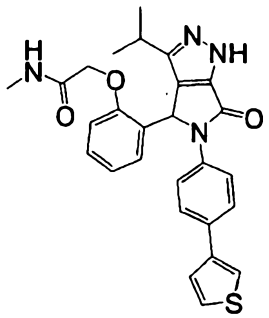
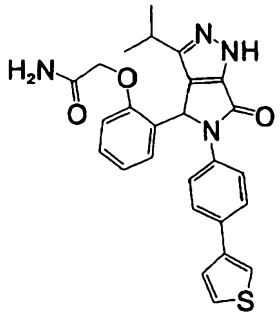
【表 137】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-036	460	1	1.50
	II-037	473	1	2.00
	II-038	473	1	1.90
	II-039	475	1	1.80
	II-040	439	1	1.60

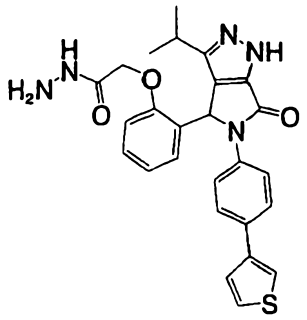
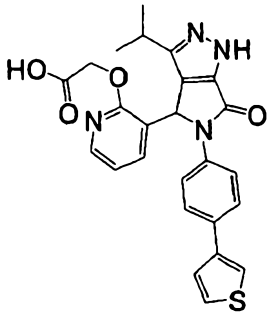
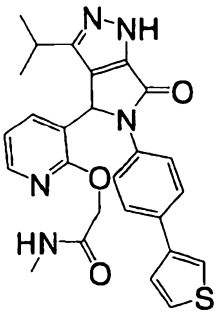
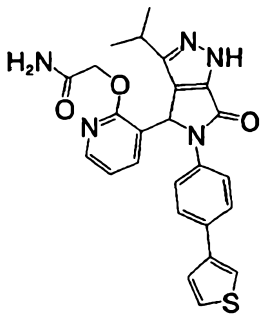
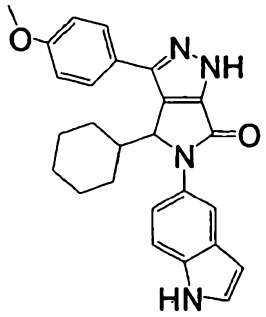
【表 138】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-041	459	1	1.70
	II-042	475	1	1.80
	II-043	459	1	1.70
	II-044	446	1	1.40
	II-045	461	1	1.70

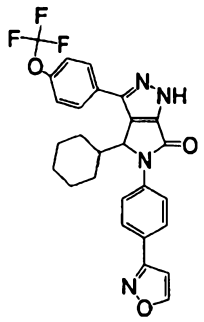
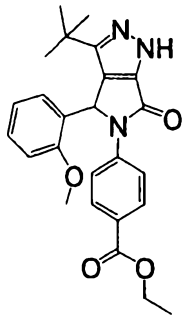
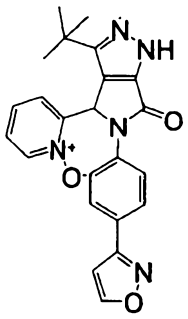
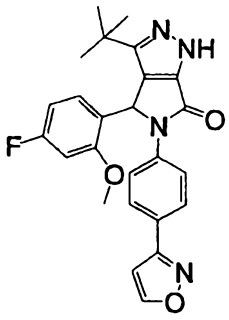
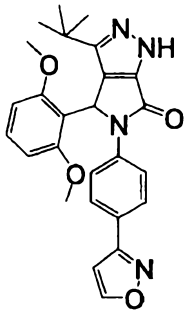
【表 139】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-046	461	1	1.40
	II-047	474	1	1.80
	II-048	431	1	2.00
	II-049	487	1	1.80
	II-050	473	1	1.70

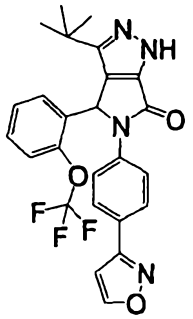
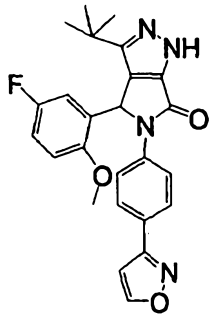
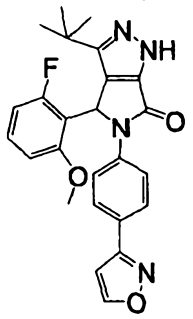
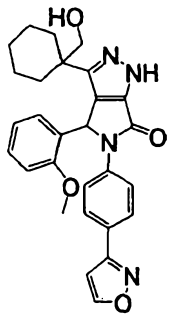
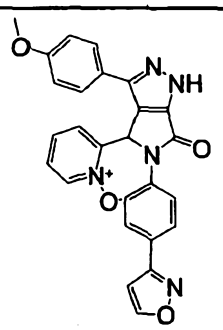
【表 140】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-051	488	1	1.60
	II-052	475	1	1.70
	II-053	488	1	1.70
	II-054	474	1	1.60
	II-055	427	2	2.13

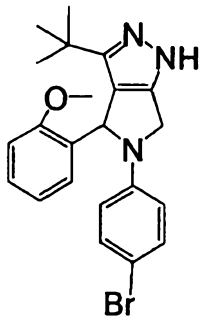
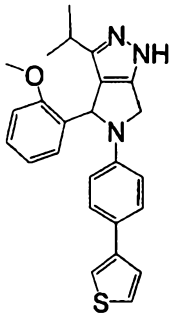
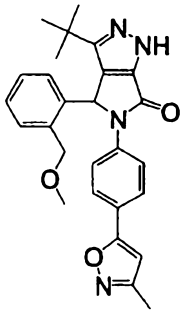
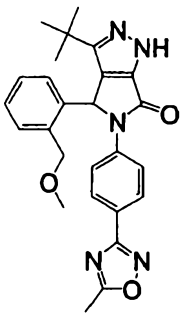
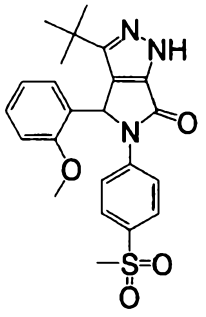
【表 141】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-056	509	1	2.43
	II-057	434	1	2.09
	II-058	416	1	1.23
	II-059	447	1	1.93
	II-060	459	2	2.07

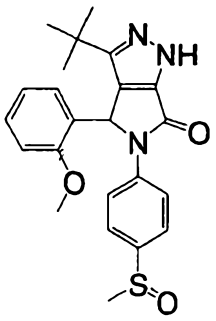
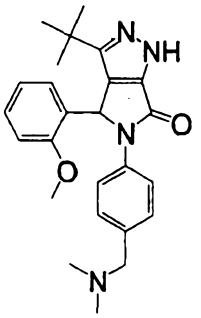
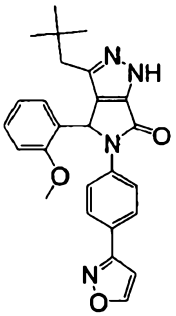
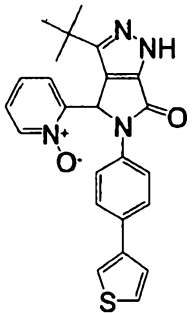
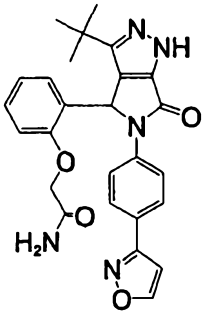
【表 142】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-061	483	2	2.23
	II-062	447	2	2.08
	II-063	447	1	1.9
	II-064	485	1	1.76
	II-065	466	1	1.36

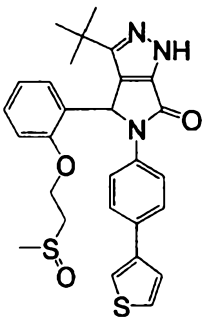
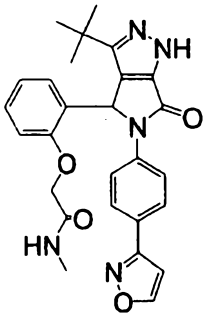
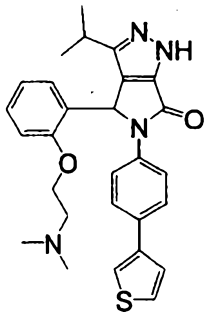
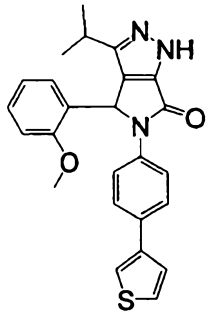
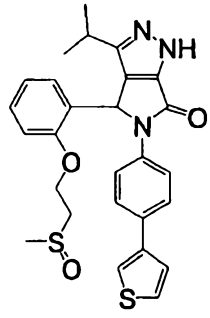
【表 143】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-066	426	1	2.47
	II-067	416	1	2.43
	II-068	457	1	1.93
	II-069	458	1	1.88
	II-070	440	1	1.68

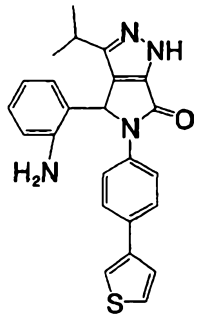
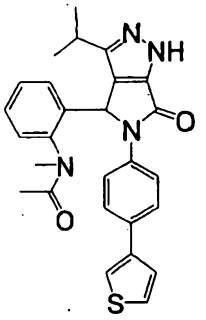
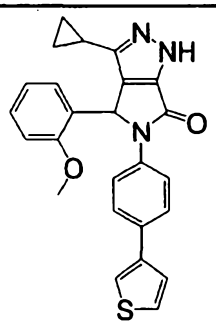
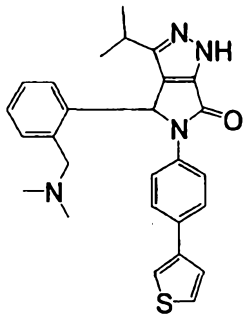
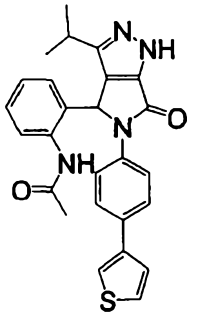
【表 144】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-071	424	1	1.49
	II-072	419	1	1.25
	II-073	443	1	2.03
	II-074	431	1	1.55
	II-075	472	1	1.48

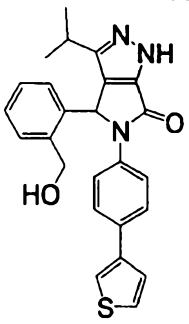
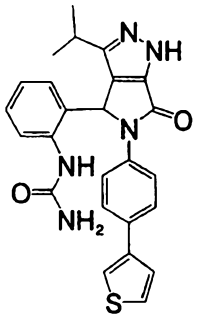
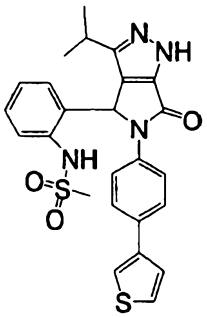
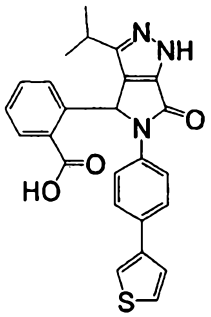
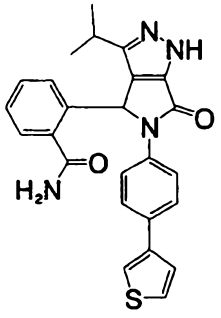
【表 145】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-076	520	1	1.76
	II-077	486	1	1.55
	II-078	487	1	1.39
	II-079	430	1	1.91
	II-080	506	1	1.69

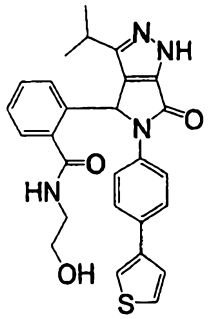
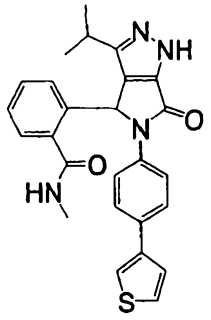
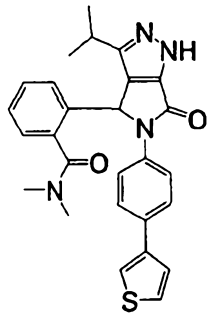
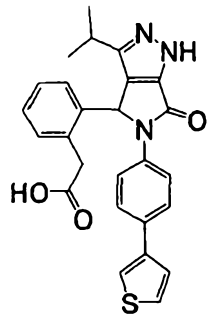
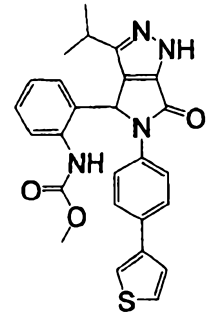
【表 146】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-081	415	1	1.96
	II-082	471	1	1.78
	II-083	428	1	2.09
	II-084	457	1	1.23
	II-085	457	1	1.72

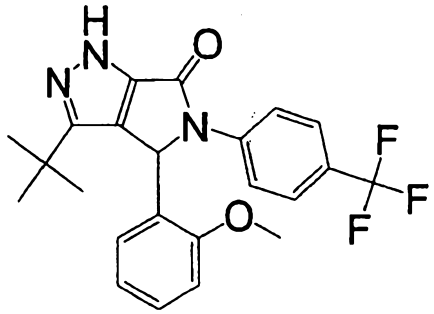
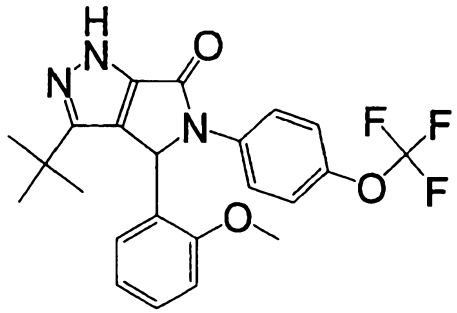
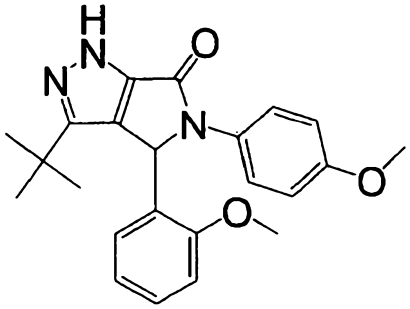
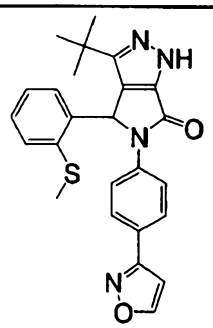
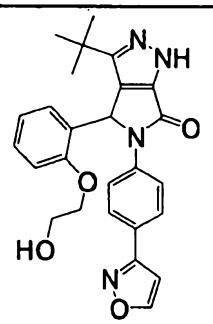
【表 147】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-086	430	1	1.79
	II-087	458	1	1.58
	II-088	493	1	1.76
	II-089	444	1	1.77
	II-090	443	1	1.62

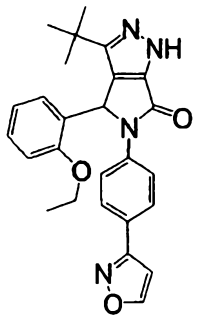
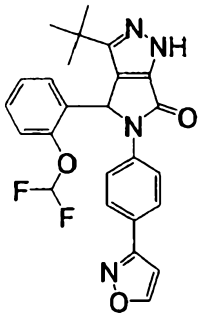
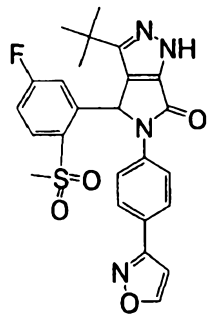
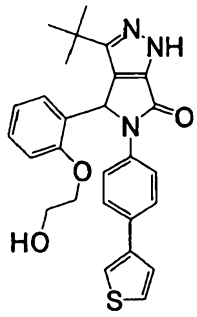
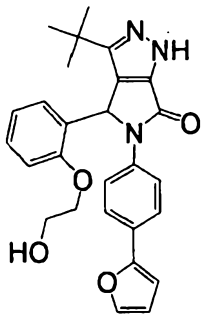
【表 148】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-091	487	1	1.55
	II-092	457	1	1.74
	II-093	471	1	1.86
	II-094	458	1	1.75
	II-095	473	1	1.87

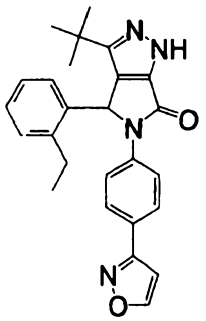
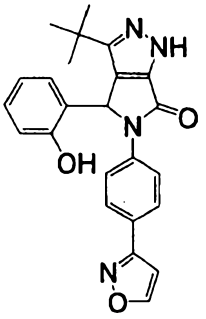
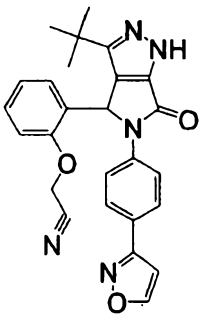
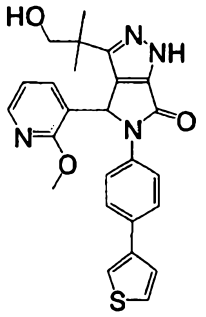
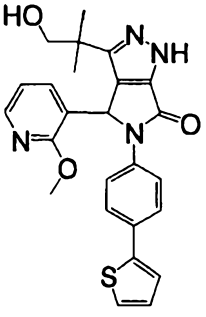
【表 149】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-096	425	1	2.30
	II-097	446	1	2.20
	II-098	392	1	1.90
	II-099	445	1	2.00
	II-100	459	1	1.60

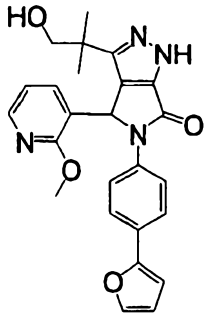
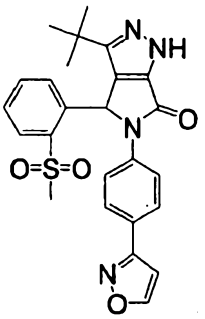
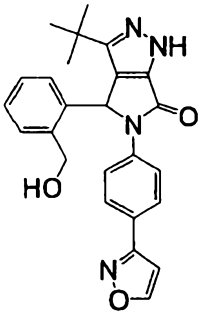
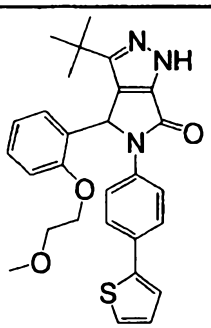
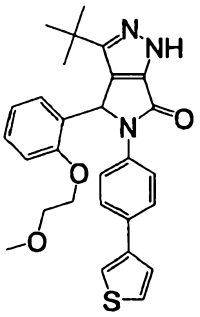
【表 150】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-101	443	1	2.00
	II-102	465	1	1.90
	II-103	495	1	1.60
	II-104	474	1	1.90
	II-105	458	1	1.90

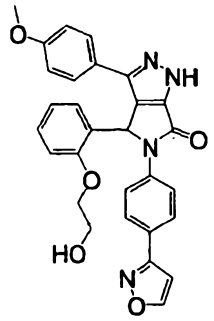
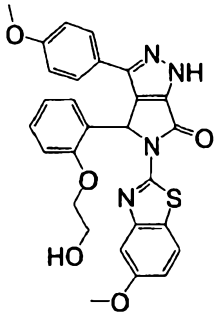
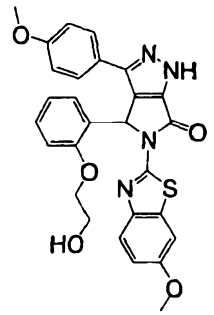
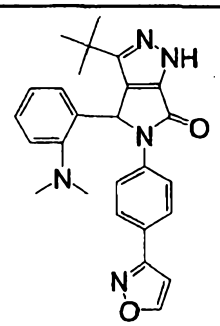
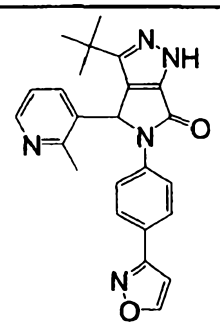
【表 151】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-106	427	1	2.40
	II-107	415	1	1.60
	II-108	454	1	1.70
	II-109	461	1	1.70
	II-110	461	1	1.80

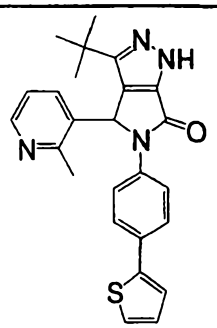
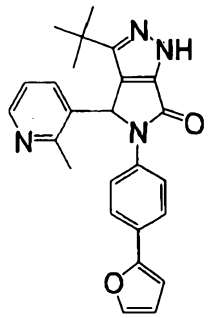
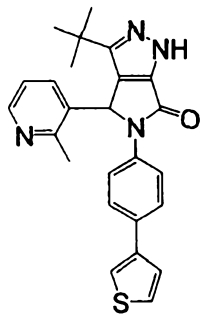
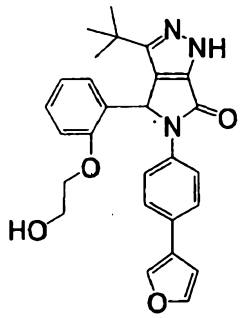
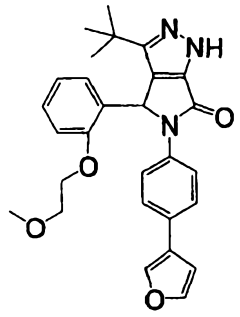
【表 152】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-111	445	1	1.70
	II-112	477	1	1.60
	II-113	429	1	1.60
	II-114	488	1	2.20
	II-115	488	1	2.20

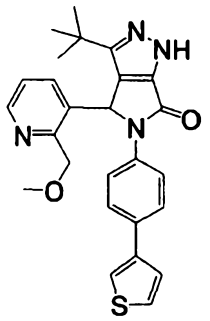
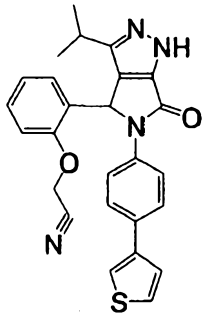
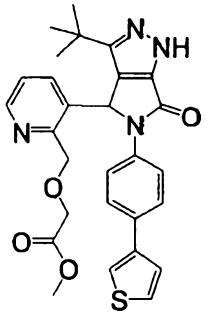
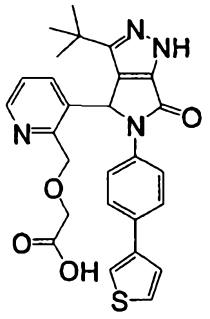
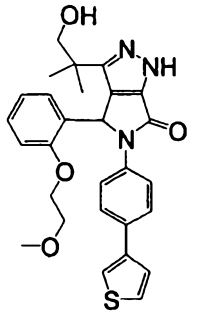
【表 153】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-116	509	1	1.70
	II-117	529	1	1.90
	II-118	529	1	2.00
	II-119	442	1	2.00
	II-120	414	1	1.10

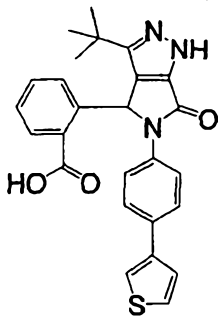
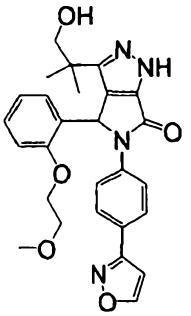
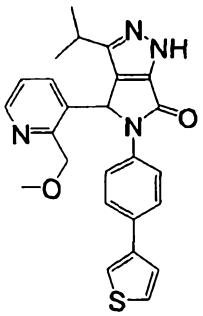
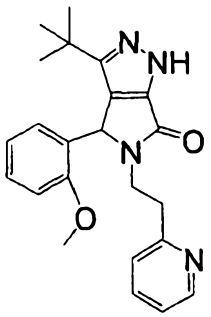
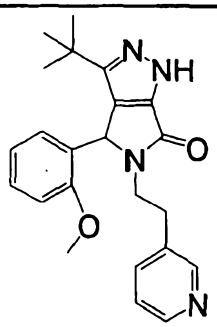
【表 154】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-121	429	1	1.50
	II-122	413	1	1.40
	II-123	429	1	1.50
	II-124	458	1	1.60
	II-125	472	1	1.80

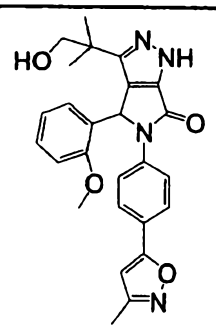
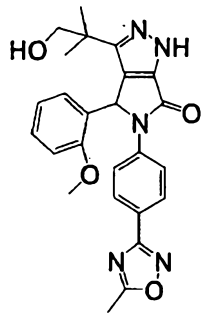
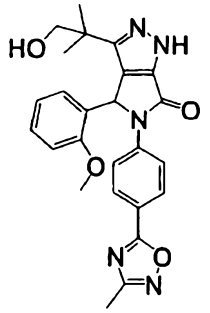
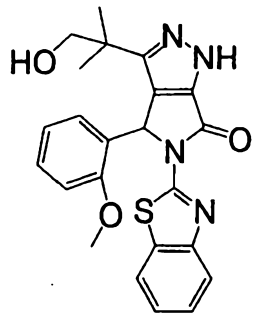
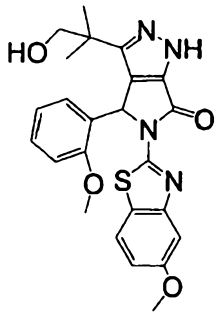
【表 155】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-126	459	1	1.70
	II-127	455	1	1.95
	II-128	517	1	1.72
	II-129	503	1	1.48
	II-130	504	1	1.88

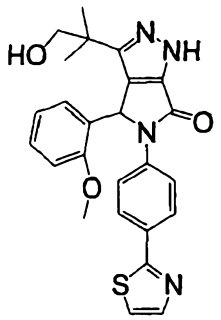
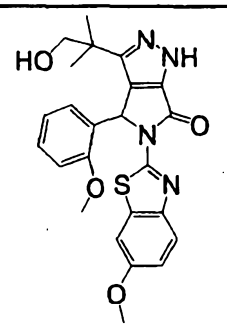
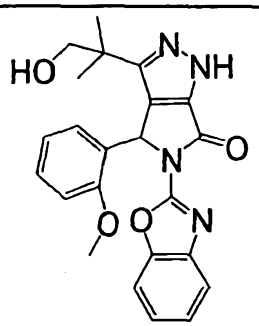
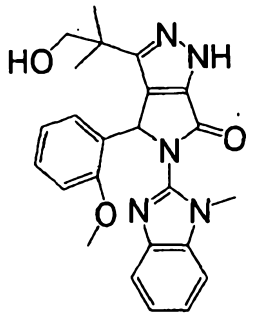
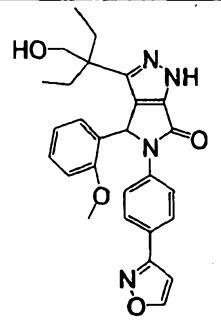
【表 156】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-131	458	1	1.81
	II-132	489	1	1.56
	II-133	445	1	1.67
	II-134	391	2	1.37
	II-135	391	2	1.31

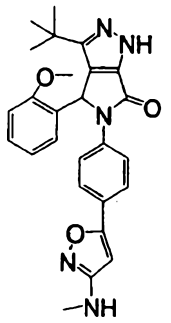
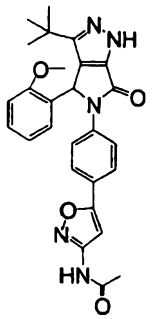
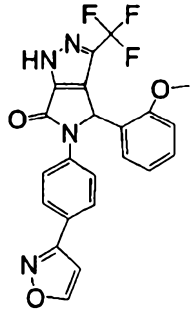
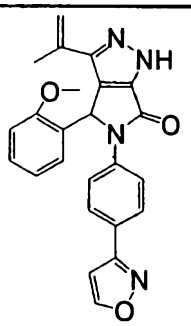
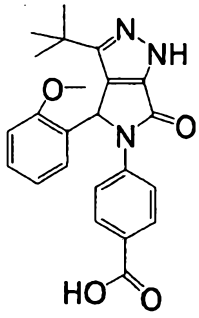
【表 157】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-136	459	2	1.90
	II-137	460	2	1.90
	II-138	460	2	1.90
	II-139	435	2	2.20
	II-140	465	2	2.10

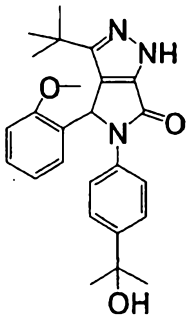
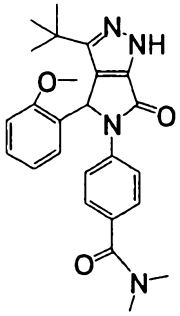
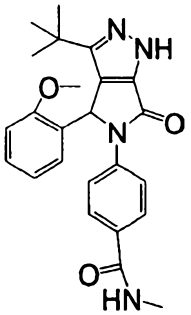
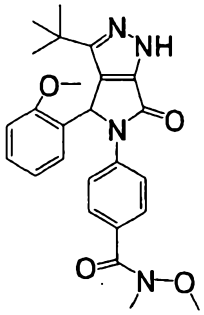
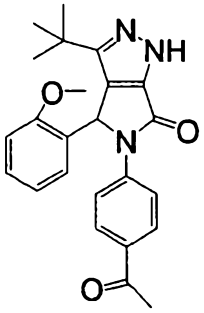
【表 158】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-141	461	2	1.90
	II-142	465	2	2.20
	II-143	419	2	2.10
	II-144	432	2	1.90
	II-145	473	2	1.70

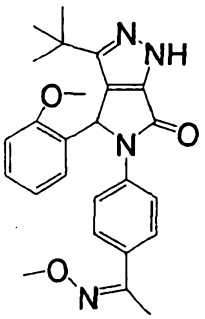
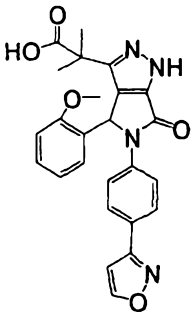
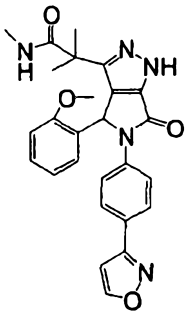
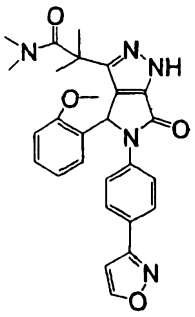
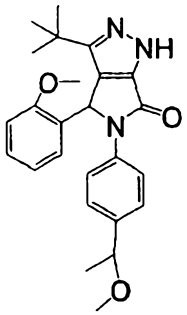
【表 159】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-146	458	2	1.98
	II-147	486	2	1.96
	II-148	441	2	2.07
	II-149	413	2	1.85
	II-150	406	2	1.88

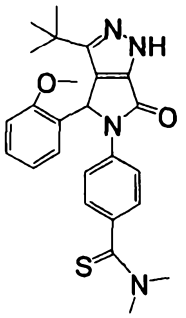
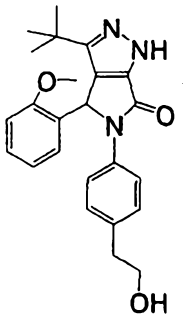
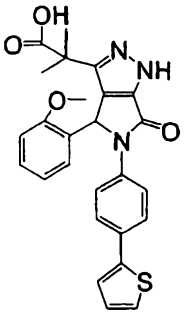
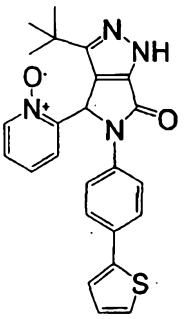
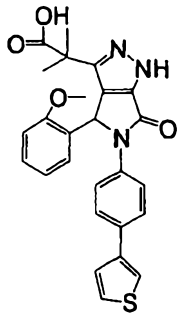
【表 160】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-151	420	2	2.03
	II-152	433	2	1.97
	II-153	419	2	1.79
	II-154	449	2	1.97
	II-155	404	2	2.07

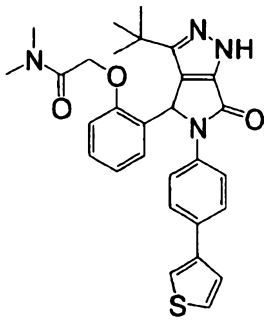
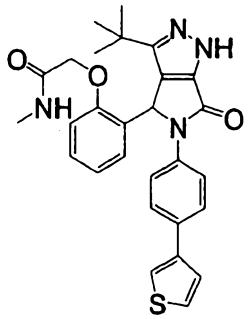
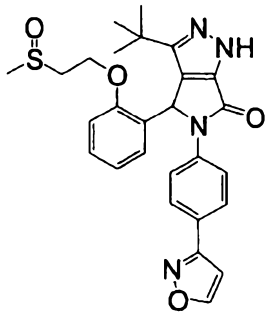
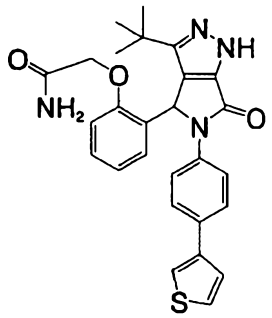
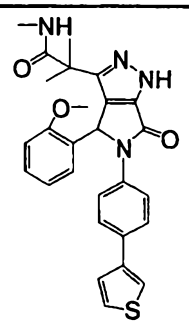
【表 161】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-156	433	2	2.40
	II-157	458	2	1.77
	II-158	486	2	1.21
	II-159	472	2	1.20
	II-160	420	2	2.41

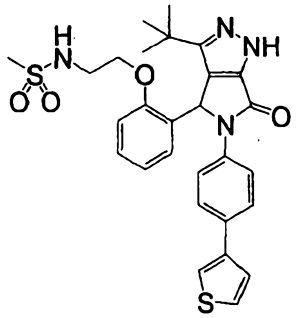
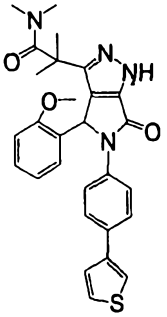
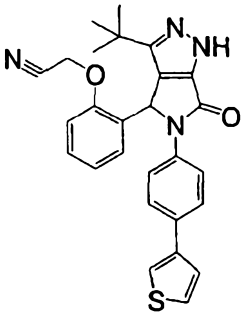
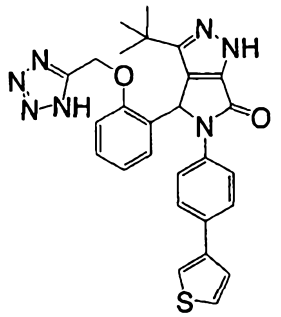
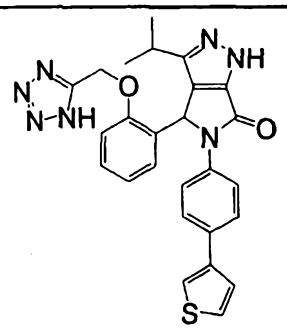
【表 162】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-161	449	2	1.88
	II-162	406	2	1.57
	II-163	474	2	2.16
	II-164	431	2	1.86
	II-165	474	2	2.13

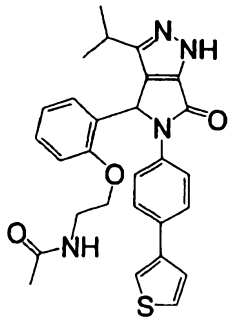
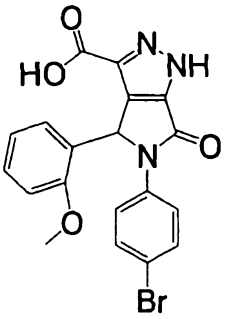
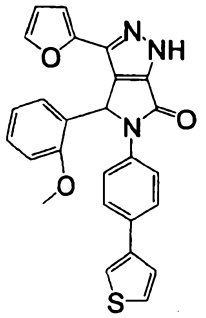
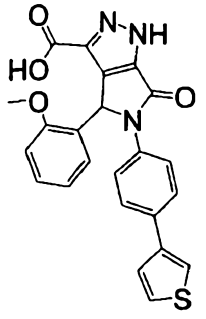
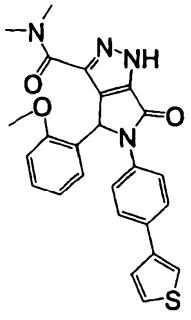
【表 163】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	I-166	515	2	2.19
	I-167	501	2	2.12
	I-168	505	2	1.76
	I-169	487	2	2.03
	I-170	487	2	2.06

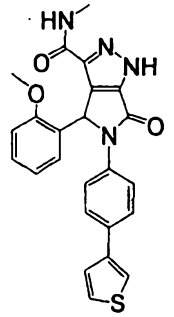
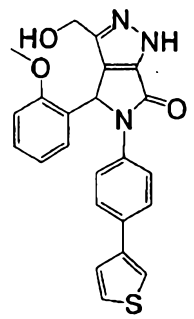
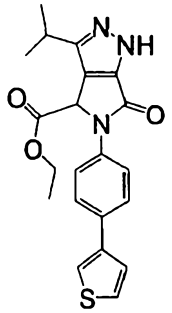
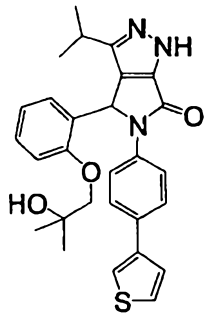
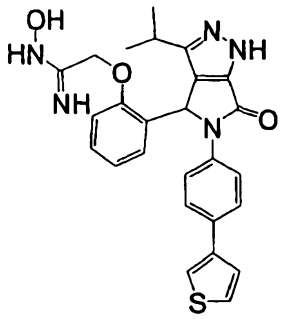
【表 164】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-171	551	2	2.23
	II-172	501	2	2.19
	II-173	469	2	2.39
	II-174	512	2	2.40
	II-175	498	2	2.05

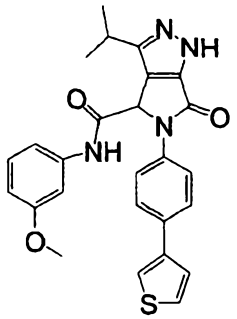
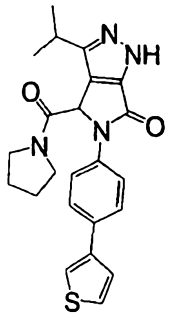
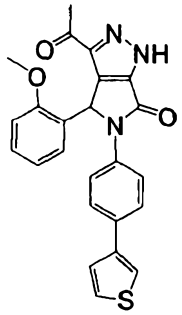
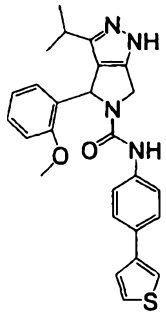
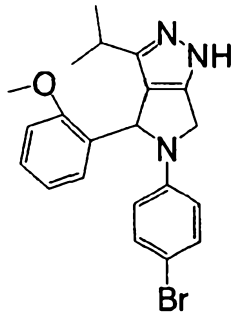
【表 165】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-176	501	2	2.10
	II-177	428	2	1.97
	II-178	454	2	2.42
	II-179	432	2	2.10
	II-180	459	2	2.15

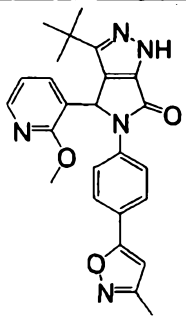
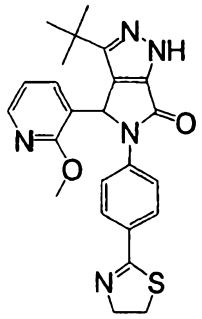
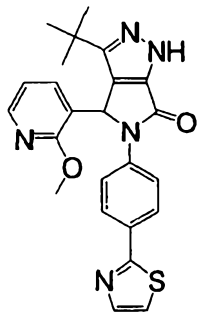
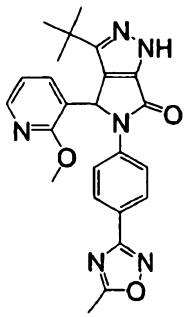
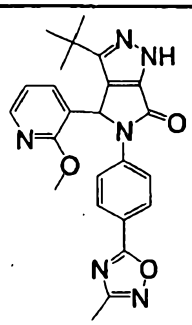
【表 166】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-181	445	2	2.14
	II-182	418	2	2.13
	II-183	396	2	2.30
	II-184	488	2	2.27
	II-185	488	2	1.79

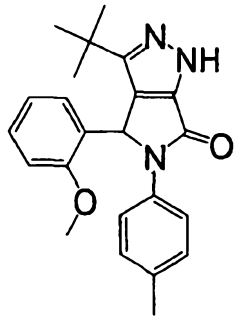
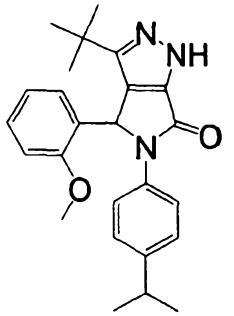
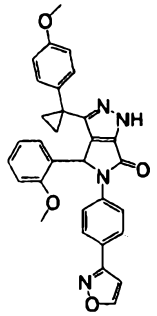
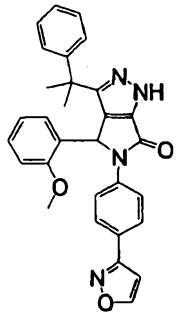
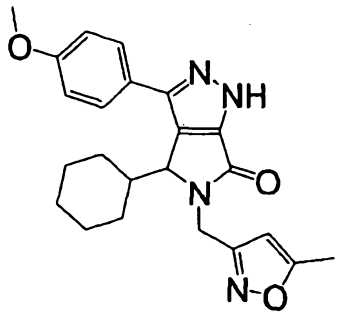
【表 167】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-186	473	2	2.23
	II-187	421	2	1.92
	II-188	430	2	2.25
	II-189	459	2	2.40
	II-190	413	2	2.70

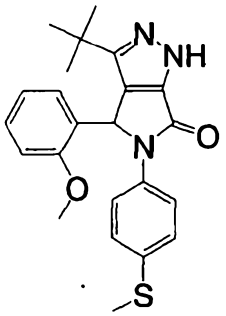
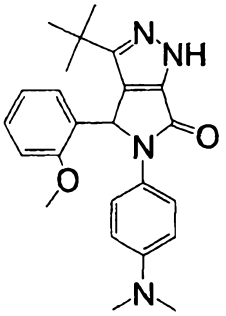
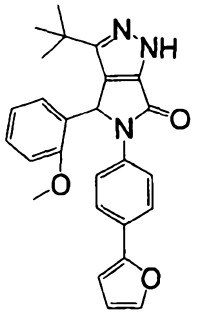
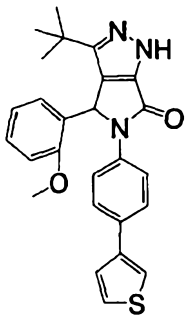
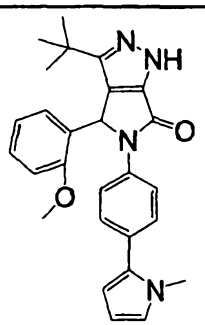
【表 168】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-191	444	2	2.06
	II-192	448	2	1.83
	II-193	446	2	2.06
	II-194	445	2	2.04
	II-195	445	2	2.08

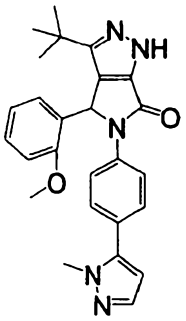
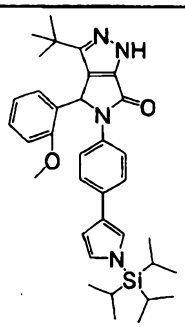
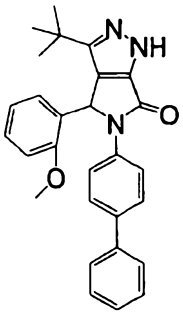
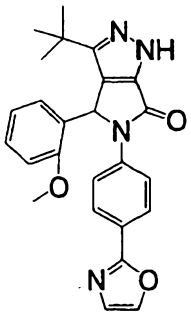
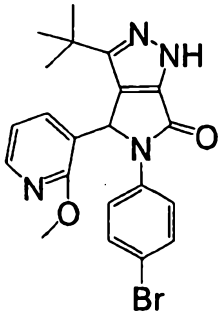
【表 169】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-196	376	2	2.17
	II-197	404	2	2.43
	II-198	519	2	2.34
	II-199	491	2	2.37
	II-200	407	2	2.22

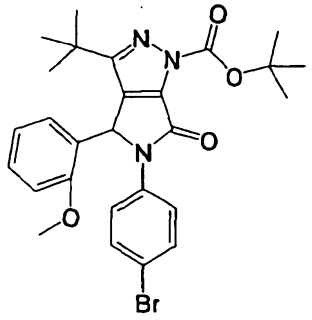
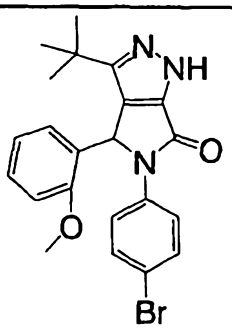
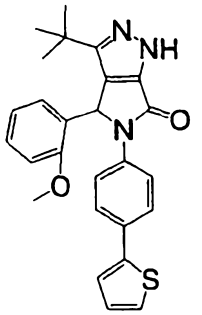
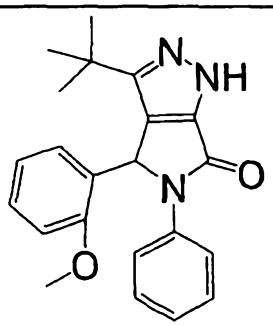
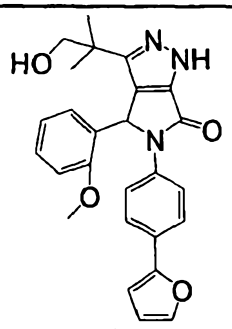
【表 170】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-201	408	2	2.35
	II-202	405	2	1.94
	II-203	428	2	2.40
	II-204	444	2	2.50
	II-205	441	2	2.40

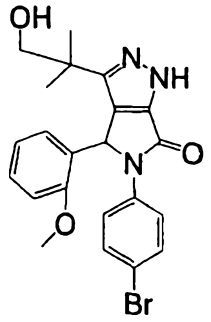
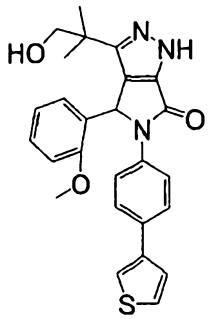
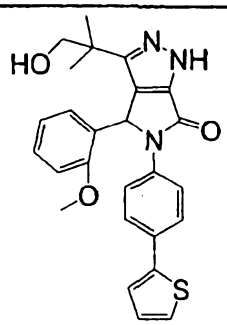
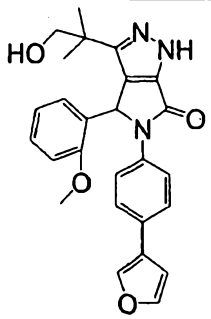
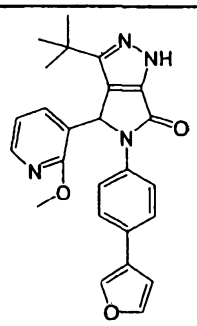
【表 171】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-206	442	2	2.00
	II-207	583	2	3.30
	II-208	438	2	2.50
	II-209	429	2	2.10
	II-210	442	2	2.30

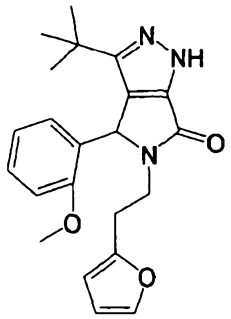
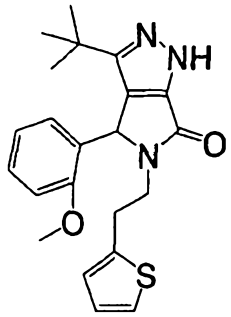
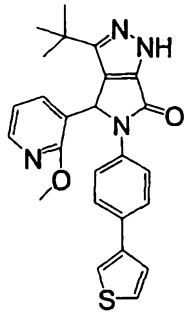
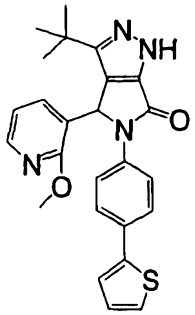
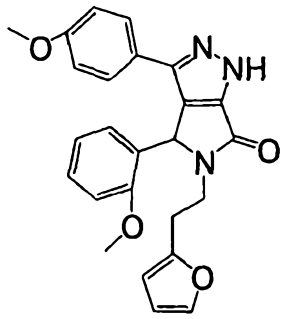
【表 172】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-211	540	2	3.10
	II-212	441	2	2.40
	II-213	444	2	2.60
	II-214	362	2	2.20
	II-215	444	2	2.10

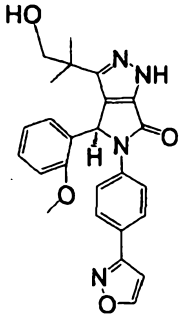
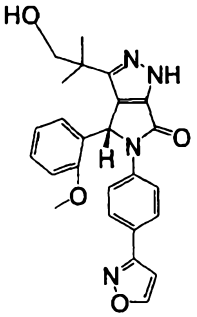
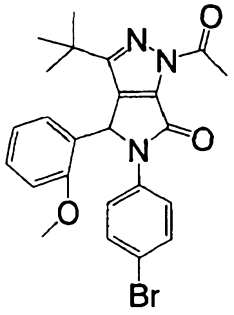
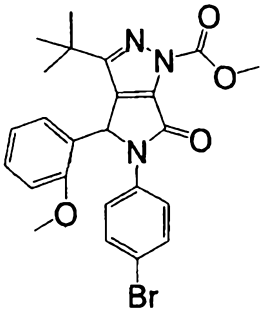
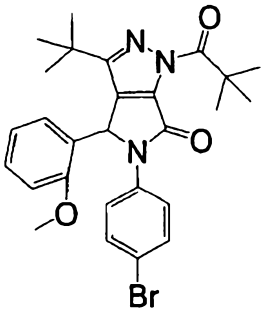
【表 173】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-216	457	2	2.10
	II-217	460	2	2.20
	II-218	460	2	2.20
	II-219	444	2	2.00
	II-220	429	2	2.20

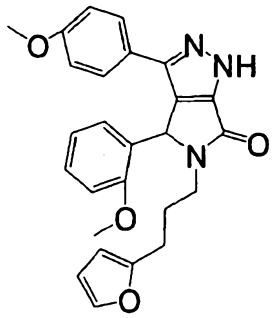
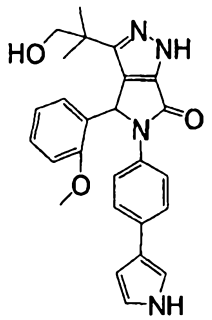
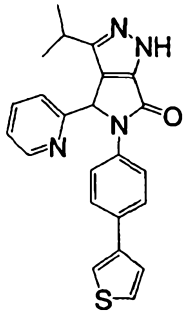
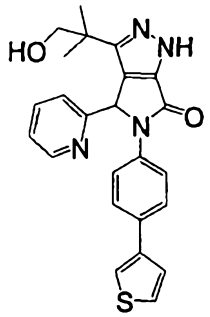
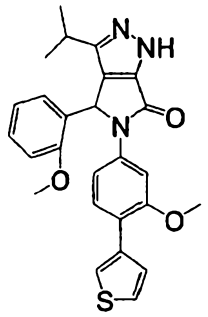
【表 174】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-221	380	2	2.20
	II-222	396	2	2.30
	II-223	445	2	2.40
	II-224	445	2	2.40
	II-225	430	2	2.20

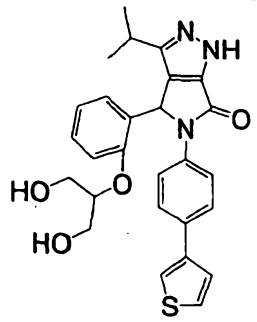
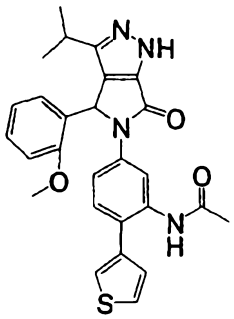
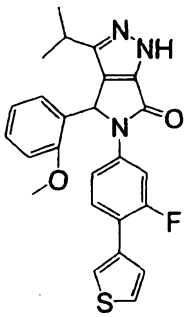
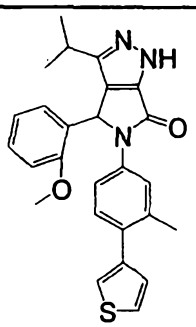
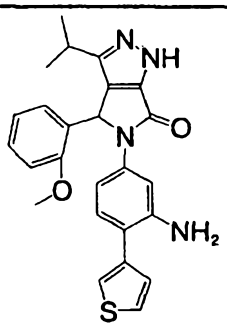
【表 175】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-226	445	2	1.80
	II-227	445	2	1.80
	II-228	483	2	2.40
	II-229	498	2	2.20
	II-230	524	2	1.40

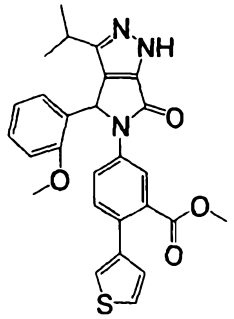
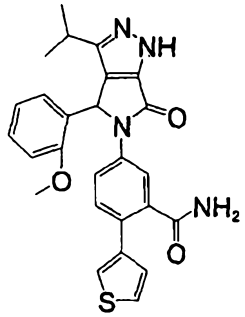
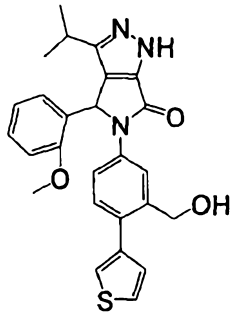
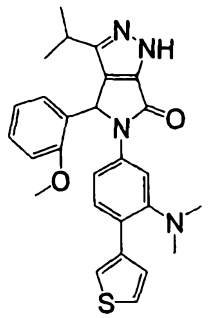
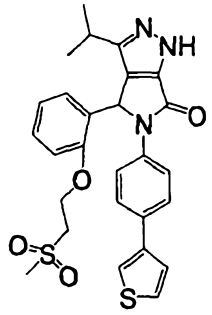
【表 176】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-231	444	2	2.00
	II-232	443	2	1.70
	II-233	401	2	2.12
	II-234	431	2	1.85
	II-235	460	2	2.50

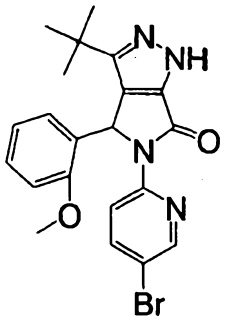
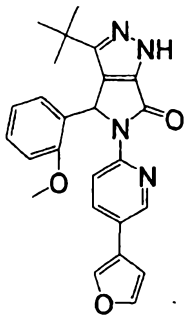
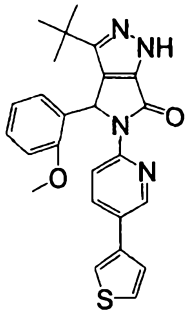
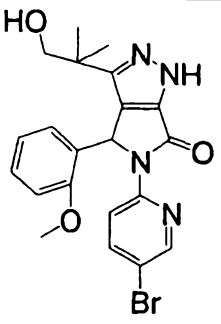
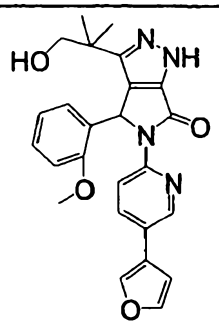
【表 177】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-236	490	2	1.88
	II-237	487	2	2.07
	II-238	448	2	2.56
	II-239	444	2	2.55
	II-240	445	2	2.24

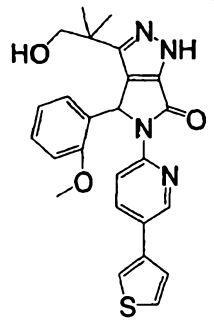
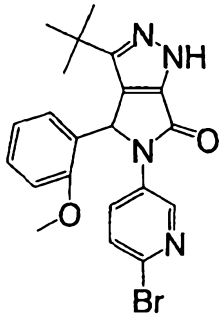
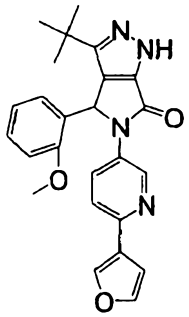
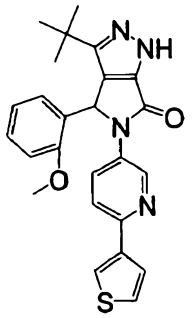
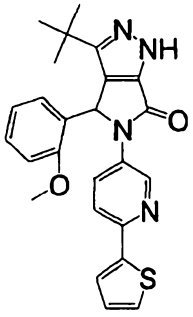
【表 178】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-241	488	2	2.39
	II-242	473	2	1.93
	II-243	460	2	2.18
	II-244	473	2	2.51
	II-245	522	2	2.12

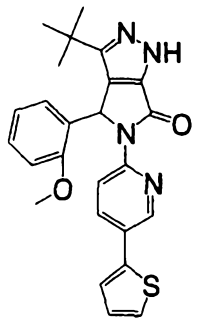
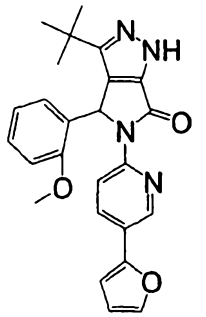
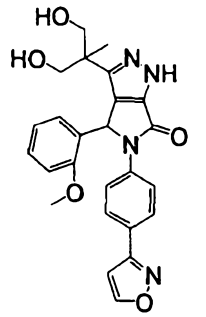
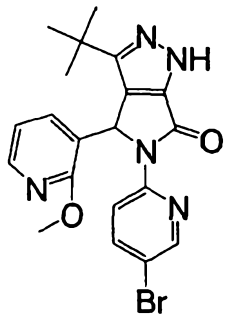
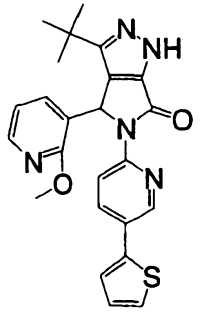
【表 179】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-246	441	2	2.46
	II-247	429	2	2.37
	II-248	445	2	2.52
	II-249	457	2	2.09
	II-250	445	2	1.98

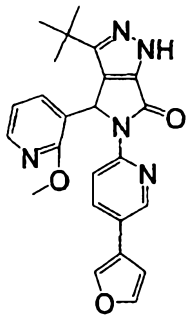
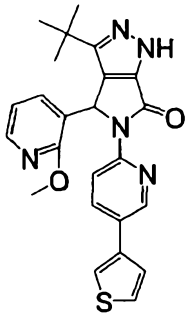
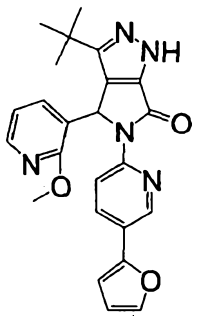
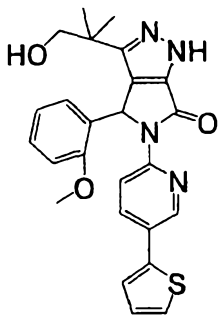
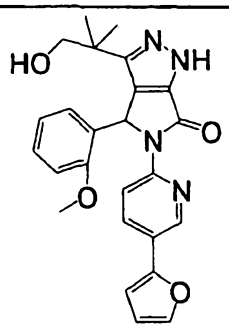
【表 180】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-251	461	2	1.18
	II-252	441	2	2.20
	II-253	429	2	1.90
	II-254	445	2	2.06
	II-255	445	2	2.13

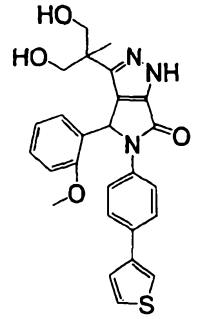
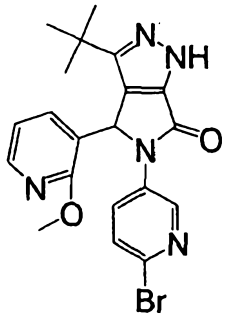
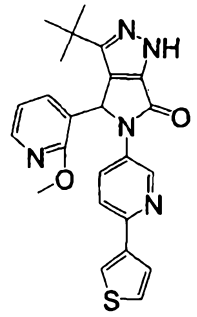
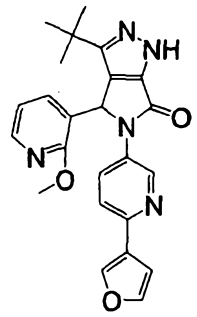
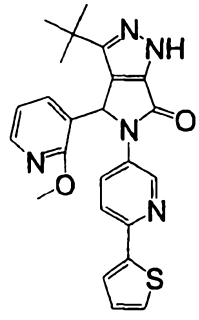
【表 181】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-256	445	2	2.55
	II-257	429	2	2.44
	II-258	461	2	1.56
	II-259	442	2	2.39
	II-260	446	2	2.47

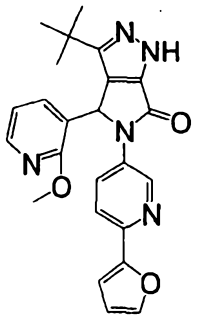
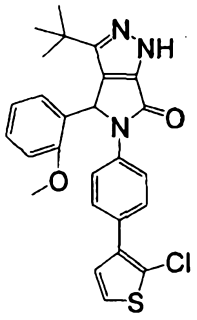
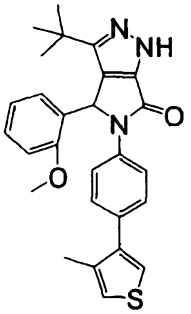
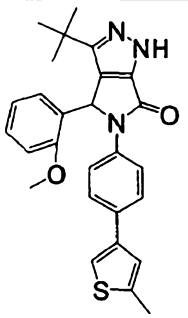
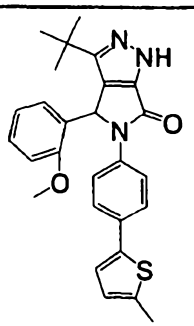
【表 182】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-261	430	2	2.25
	II-262	446	2	2.41
	II-263	430	2	2.36
	II-264	461	2	2.20
	II-265	445	2	2.09

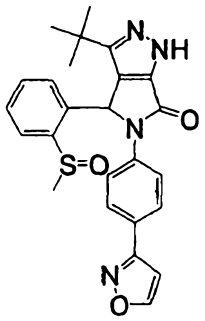
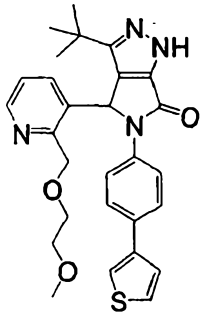
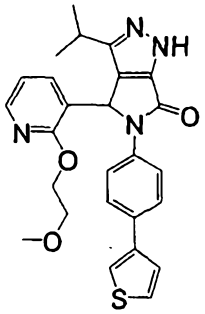
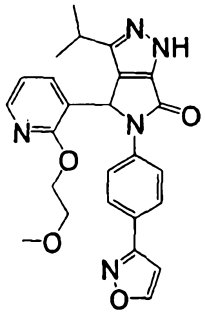
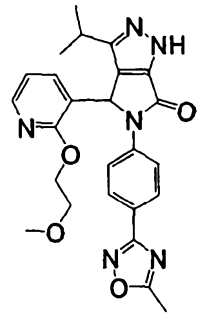
【表 183】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-266	476	2	1.93
	II-267	442	2	2.05
	II-268	446	2	2.09
	II-269	430	2	1.94
	II-270	446	2	2.20

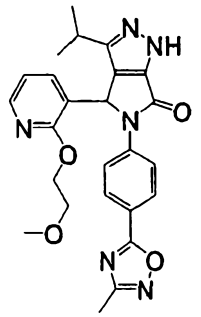
【表 184】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-271	430	2	2.03
	II-272	478	2	2.70
	II-273	458	2	2.65
	II-274	458	2	2.68
	II-275	458	2	2.74

【表 185】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-276	461	2	1.60
	II-277	503	2	1.98
	II-278	475	2	2.29
	II-279	460	2	1.94
	II-280	475	2	1.98

【表 186】

構造式	化合物番号	MS [M+H]+	LCメソッド	LC/MS 保持時間(分)
	II-281	475	2	2.03

試驗例

將導入人 $P2X_3$ 受體基因(GenBank 登錄序列 Y07683)於 C6BU-1 細胞之安定表現細胞株，以每 1 井 8000 個播種於塗覆 PDL 之 96 井微平板，於培養基(含有 8.3%胎牛血清、8.3%馬血清、1%抗生素抗真菌劑混合溶液之 DMEM)中，在 37℃、5%二氧化碳下培養 1 日。以含有 4μM Fluo-3-AM 的添加液(20mM HEPES、137mM NaCl、2.7mM KCl、0.9mM $MgCl_2$、5.0mM$CaCl_2$、5.6mM D-葡萄糖、2.5mM Probenecid、10%BSA、0.08% Pluronic F-127、pH7.5)取代培養基，在 37℃、5%二氧化碳下培育 1 小時。經由洗淨用緩衝液(20mM HEPES、137mM NaCl、2.7mM KCl、0.9mM $MgCl_2$、5.0mM $CaCl_2$、5.6mM D-葡萄糖、2.5mM Probenecid、pH7.5)洗淨，每 1 井填入 40μl 的洗淨用緩衝液。將微平板設置於高速篩選系統(High Throughput Screening system)FDSS 3000(HAMAMATSU Japan)。經由 FDSS 3000 開始螢光強度的測定，以 FDSS 3000 內藏的自動分注裝置將經由稀釋用緩衝液(20mM HEPES、137mM NaCl、2.7mM KCl、0.9mM

$MgCl_2$、5.0mM $CaCl_2$、5.6mM D-葡萄糖、2.5mM Probenecid、0.1%Pluronic F-127、pH7.5)稀釋爲不同濃度的被檢驗化合物DMSO溶液分注於每1井各40μl。5分鐘後，以FDSS 3000內藏的自動分注裝置分注經稀釋用緩衝液稀釋之40nM ATP溶液50μl，之後3分鐘繼續螢光強度的測定。從測定之螢光強度的值，算出微平板的每一井中以ATP溶液添加後之螢光強度的最大值相對於測定開始時之螢光強度的比所表示之比最大螢光強度。以不含被檢驗化合物時的比最大螢光強度的值爲阻害0%，以添加稀釋用緩衝液取代ATP時之比最大螢光強度的值爲阻害100%，算出阻害爲50%的濃度(IC_{50})來評價被檢驗化合物的阻害活性。使用FDSS軟體(濱松赫德尼古斯公司)進行比最大螢光強度的計算。使用微軟Excel(Microsoft公司)及XLfit(idbs公司)的軟體進行IC_{50}的計算。

本發明化合物之試驗結果示於以下表中。

【表 187】

化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)
I-001	0.032	I-225	0.065	I-416	0.322
I-002	0.024	I-226	0.012	I-417	0.181
I-003	0.040	I-227	0.008	I-418	0.593
I-004	0.012	I-228	0.015	I-419	0.032
I-005	0.247	I-229	0.029	I-420	0.257
I-006	0.027	I-230	0.018	I-421	0.191
I-007	0.100	I-231	0.023	I-422	0.361
I-008	0.014	I-232	0.024	I-424	0.519
I-009	0.014	I-233	0.124	I-425	0.697
I-010	0.595	I-234	0.056	I-427	0.331
I-011	0.270	I-235	0.035	I-428	0.399
I-012	0.340	I-236	0.431	I-429	0.007
I-014	0.134	I-237	0.705	I-430	0.153
I-015	0.012	I-239	0.035	I-431	0.232
I-016	0.079	I-240	0.185	I-433	0.425
I-019	0.132	I-241	0.822	I-434	0.125
I-020	0.021	I-242	0.357	I-435	0.082
I-021	0.382	I-244	0.027	I-436	0.042
I-026	0.339	I-245	0.047	I-437	0.111
I-027	0.040	I-247	0.015	I-438	0.490
I-028	0.075	I-248	0.030	I-439	0.116
I-029	0.160	I-249	0.010	I-440	0.035
I-030	0.053	I-250	0.029	I-441	0.013
I-031	0.700	I-251	0.017	I-442	0.005
I-032	0.160	I-252	0.010	I-443	0.006
I-033	0.053	I-253	0.193	I-444	0.172
I-034	0.700	I-254	0.511	I-445	0.152
I-037	0.954	I-255	0.008	I-446	0.338
I-038	0.926	I-256	0.023	I-447	0.128
I-039	0.012	I-257	0.037	I-448	0.246
I-044	0.468	I-258	0.024	I-449	0.013
I-046	0.580	I-259	0.030	I-450	0.036
I-047	0.221	I-260	0.331	I-451	0.019
I-048	0.752	I-261	0.019	I-452	0.026
I-050	0.642	I-262	0.016	I-453	0.041
I-051	0.277	I-263	0.008	I-454	0.036
I-052	0.187	I-264	0.014	I-455	0.014
I-055	0.596	I-265	0.028	I-456	0.006
I-057	0.159	I-266	0.025	I-457	0.488
I-058	0.082	I-267	0.014	I-458	0.699
I-059	0.260	I-268	0.032	I-459	0.026
I-064	0.137	I-269	0.347	I-460	0.103
I-066	0.434	I-271	0.542	I-461	0.036
I-068	0.305	I-273	0.491	I-462	0.427
I-070	0.519	I-275	0.172	I-463	0.127
I-072	0.352	I-276	0.117	I-464	0.453
I-075	0.013	I-277	0.342	I-465	0.007
I-077	0.048	I-278	0.366	I-466	0.260
I-078	0.016	I-279	0.016	I-467	0.286

【表 188】

化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)
I-079	0.023	I-280	0.477	I-468	0.467
I-080	0.016	I-281	0.637	I-469	0.646
I-081	0.151	I-282	0.472	I-470	0.972
I-082	0.650	I-283	0.144	I-471	0.019
I-085	0.048	I-284	0.300	I-472	0.007
I-089	0.700	I-285	0.648	I-473	0.182
I-090	0.555	I-286	0.669	I-474	0.071
I-091	0.341	I-288	0.036	I-475	0.181
I-092	0.092	I-290	0.051	I-476	0.051
I-093	0.756	I-291	0.130	I-477	0.477
I-094	0.301	I-292	0.127	I-478	0.034
I-095	0.195	I-293	0.012	I-479	0.010
I-098	0.370	I-295	0.054	I-480	0.042
I-102	0.134	I-296	0.244	I-481	0.378
I-103	0.355	I-297	0.220	I-482	0.333
I-104	0.424	I-298	0.269	I-483	0.089
I-105	0.097	I-299	0.008	I-484	0.091
I-108	0.192	I-300	0.114	I-485	0.218
I-111	0.624	I-301	0.018	I-486	0.004
I-112	0.388	I-302	0.034	I-487	0.167
I-113	0.012	I-303	0.031	I-488	0.067
I-114	0.012	I-304	0.021	I-489	0.006
I-115	0.108	I-305	0.020	I-490	0.017
I-116	0.077	I-306	0.054	I-491	0.155
I-117	0.383	I-307	0.158	I-492	0.104
I-118	0.282	I-308	0.193	I-493	0.105
I-119	0.098	I-309	0.182	I-494	0.053
I-120	0.074	I-310	0.337	I-495	0.059
I-122	0.342	I-311	0.121	I-496	0.055
I-123	0.013	I-312	0.054	I-497	0.036
I-124	0.011	I-313	0.320	I-498	0.008
I-125	0.110	I-314	0.329	I-499	0.398
I-126	0.015	I-315	0.252	I-500	0.012
I-127	0.049	I-316	0.130	I-501	0.052
I-128	0.155	I-317	0.073	I-502	0.067
I-129	0.091	I-318	0.328	I-503	0.017
I-130	0.476	I-319	0.222	I-504	0.238
I-131	0.251	I-320	0.274	I-505	0.168
I-132	0.043	I-321	0.070	I-506	0.112
I-133	0.367	I-322	0.102	I-507	0.101
I-134	0.776	I-323	0.310	I-508	0.133
I-135	0.015	I-324	0.109	I-509	0.247
I-136	0.015	I-325	0.018	I-510	0.174
I-137	0.615	I-326	0.027	I-511	0.117
I-138	0.016	I-327	0.093	I-512	0.062
I-139	0.930	I-328	0.065	I-513	0.065
I-141	0.346	I-329	0.578	I-514	0.138
I-142	0.315	I-330	0.070	I-515	0.037
I-143	0.331	I-331	0.722	I-516	0.033

【表 189】

化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)
I-144	0.365	I-332	0.281	I-517	0.026
I-145	0.016	I-333	0.058	I-518	0.087
I-146	0.727	I-334	0.078	I-519	0.033
I-147	0.017	I-336	0.351	I-521	0.554
I-148	0.073	I-337	0.103	I-523	0.351
I-149	0.015	I-338	0.147	I-524	0.696
I-150	0.415	I-339	0.892	I-525	0.018
I-151	0.008	I-340	0.336	I-526	0.219
I-152	0.219	I-341	0.508	I-527	0.039
I-153	0.216	I-342	0.067	I-528	0.070
I-154	0.192	I-343	0.078	I-530	0.237
I-155	0.035	I-344	0.594	I-531	0.286
I-156	0.032	I-345	0.999	I-532	0.204
I-157	0.025	I-346	0.677	I-533	0.033
I-158	0.023	I-347	0.047	I-535	0.049
I-159	0.016	I-348	0.055	I-536	0.032
I-160	0.013	I-349	0.037	I-537	0.083
I-161	0.007	I-350	0.066	I-538	0.119
I-162	0.041	I-351	0.101	I-539	0.062
I-164	0.074	I-353	0.210	I-540	0.496
I-165	0.095	I-354	0.057	I-541	0.010
I-166	0.019	I-355	0.044	I-542	0.058
I-167	0.013	I-356	0.007	I-543	0.240
I-168	0.120	I-357	0.020	I-544	0.008
I-169	0.019	I-358	0.025	I-545	0.142
I-171	0.610	I-359	0.024	I-546	0.395
I-172	0.024	I-360	0.021	I-547	0.217
I-173	0.137	I-361	0.048	I-548	0.077
I-174	0.572	I-362	0.040	I-549	0.213
I-176	0.046	I-363	0.007	I-550	0.254
I-178	0.374	I-364	0.009	I-551	0.005
I-179	0.659	I-365	0.082	I-552	0.186
I-180	0.005	I-366	0.013	I-553	0.337
I-181	0.114	I-367	0.019	I-555	0.579
I-183	0.004	I-368	0.016	I-556	0.032
I-184	0.163	I-369	0.091	I-557	0.444
I-185	0.111	I-370	0.194	I-558	0.008
I-186	0.013	I-371	0.447	I-559	0.040
I-187	0.086	I-372	0.035	I-560	0.275
I-188	0.022	I-373	0.051	I-562	0.101
I-189	0.014	I-374	0.040	I-563	0.042
I-190	0.040	I-375	0.030	I-564	0.018
I-191	0.279	I-376	0.025	I-565	0.013
I-192	0.612	I-377	0.148	I-566	0.061
I-193	0.994	I-378	0.192	I-567	0.057
I-194	0.063	I-379	0.118	I-568	0.066
I-195	0.235	I-380	0.007	I-569	0.035
I-197	0.036	I-381	0.007	I-570	0.070
I-198	0.064	I-382	0.006	I-571	0.060

【表 190】

化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)	化合物編號	P2X3 IC50(μM)
I-199	0.019	I-383	0.036	I-572	0.171
I-200	0.014	I-384	0.019	I-573	0.123
I-201	0.039	I-385	0.227	I-574	0.280
I-202	0.040	I-391	0.684	I-575	0.252
I-204	0.043	I-392	0.946	I-576	0.237
I-206	0.630	I-393	0.015	I-577	0.047
I-207	0.008	I-394	0.011	I-578	0.386
I-208	0.014	I-395	0.006	I-579	0.429
I-209	0.234	I-396	0.007	I-581	0.466
I-210	0.047	I-397	0.122	I-582	0.359
I-211	0.157	I-398	0.014	I-583	0.010
I-212	0.092	I-399	0.044	I-584	0.167
I-213	0.006	I-400	0.022	I-585	0.157
I-214	0.022	I-401	0.079	I-586	0.254
I-215	0.013	I-402	0.080	I-587	0.374
I-216	0.679	I-404	0.071	I-588	0.029
I-217	0.012	I-405	0.031	I-589	0.032
I-218	0.073	I-406	0.029	I-590	0.028
I-219	0.324	I-408	0.018	I-591	0.031
I-220	0.005	I-409	0.177	I-592	0.827
I-221	0.081	I-410	0.151	I-593	0.811
I-222	0.006	I-412	0.310	I-594	0.715
I-223	0.012	I-413	0.042	I-597	0.668
I-224	0.073	I-414	0.268	I-598	0.785

【表 191】

化合物編號	P2X3 IC50 (μM)	化合物編號	P2X3 IC50 (μM)	化合物編號	P2X3 IC50 (μM)
II-001	0.104	II-088	0.004	II-189	0.897
II-002	0.217	II-089	0.107	II-191	0.322
II-003	0.140	II-090	0.002	II-192	0.222
II-004	0.378	II-091	0.002	II-193	0.195
II-006	0.245	II-092	0.002	II-194	0.392
II-007	0.062	II-093	0.002	II-195	0.944
II-008	0.505	II-094	0.065	II-196	0.783
II-009	0.054	II-095	0.012	II-197	0.106
II-010	0.134	II-096	0.223	II-198	0.123
II-011	0.319	II-097	0.358	II-199	0.113
II-012	0.004	II-098	0.761	II-200	0.448
II-013	0.019	II-099	0.046	II-201	0.033
II-014	0.017	II-100	0.031	II-202	0.076
II-015	0.087	II-101	0.027	II-203	0.028
II-016	0.158	II-102	0.076	II-204	0.017
II-017	0.054	II-104	0.003	II-205	0.811
II-018	0.022	II-105	0.013	II-208	0.112
II-019	0.021	II-106	0.226	II-209	0.087
II-020	0.008	II-107	0.114	II-210	0.811
II-021	0.009	II-108	0.015	II-211	0.135
II-022	0.004	II-109	0.021	II-212	0.238
II-023	0.004	II-110	0.024	II-213	0.011
II-024	0.062	II-111	0.091	II-215	0.015
II-025	0.015	II-112	0.389	II-216	0.473
II-026	0.023	II-113	0.838	II-217	0.003
II-027	0.008	II-114	0.012	II-218	0.005
II-028	0.014	II-115	0.011	II-219	0.014
II-029	0.090	II-117	0.348	II-220	0.069
II-030	0.128	II-118	0.429	II-223	0.023
II-031	0.018	II-119	0.137	II-224	0.031
II-032	0.006	II-121	0.464	II-225	0.979
II-033	0.117	II-123	0.431	II-227	0.034
II-034	0.046	II-124	0.008	II-229	0.082
II-035	0.006	II-125	0.010	II-231	0.344
II-036	0.231	II-126	0.221	II-232	0.016
II-037	0.008	II-127	0.004	II-233	0.092
II-038	0.014	II-128	0.216	II-234	0.130
II-039	0.005	II-130	0.004	II-235	0.017
II-040	0.070	II-131	0.088	II-236	0.005
II-041	0.027	II-132	0.141	II-237	0.853
II-042	0.010	II-133	0.116	II-238	0.019
II-043	0.017	II-136	0.055	II-239	0.205
II-044	0.582	II-137	0.148	II-240	0.116
II-045	0.016	II-138	0.044	II-241	0.213
II-046	0.861	II-139	0.332	II-242	0.152
II-047	0.011	II-141	0.022	II-243	0.138
II-048	0.057	II-142	0.104	II-244	0.144
II-049	0.011	II-145	0.033	II-245	0.006
II-050	0.007	II-146	0.416	II-246	0.871

【表 192】

化合物編號	P2X3 IC50 (μM)	化合物編號	P2X3 IC50 (μM)	化合物編號	P2X3 IC50 (μM)
II-051	0.005	II-147	0.977	II-247	0.033
II-052	0.033	II-148	0.311	II-248	0.013
II-053	0.035	II-149	0.377	II-250	0.043
II-054	0.026	II-151	0.650	II-251	0.008
II-055	0.548	II-155	0.322	II-253	0.020
II-057	0.017	II-156	0.412	II-254	0.002
II-058	0.494	II-157	0.524	II-255	0.003
II-059	0.046	II-158	0.650	II-256	0.018
II-060	0.538	II-159	0.360	II-257	0.033
II-061	0.166	II-163	0.034	II-258	0.304
II-062	0.112	II-164	0.036	II-259	0.410
II-064	0.075	II-165	0.041	II-260	0.036
II-067	0.153	II-166	0.007	II-261	0.140
II-068	0.508	II-167	0.005	II-262	0.039
II-069	0.414	II-168	0.101	II-263	0.108
II-072	0.739	II-169	0.004	II-264	0.011
II-073	0.105	II-170	0.034	II-265	0.031
II-074	0.032	II-171	0.007	II-266	0.007
II-075	0.153	II-172	0.011	II-268	0.024
II-076	0.012	II-173	0.004	II-269	0.363
II-077	0.237	II-174	0.003	II-270	0.025
II-078	0.016	II-175	0.003	II-271	0.153
II-079	0.011	II-176	0.010	II-272	0.392
II-080	0.011	II-178	0.149	II-274	0.019
II-081	0.189	II-180	0.262	II-275	0.027
II-082	0.044	II-181	0.301	II-277	0.274
II-083	0.024	II-182	0.060	II-278	0.013
II-084	0.018	II-183	0.460	II-279	0.378
II-085	0.023	II-184	0.012	II-280	0.244
II-086	0.032	II-185	0.011	II-281	0.664
II-087	0.009	II-188	0.156		

本發明之化合物顯示對 $P2X_3$ 受體有阻害活性。此外，本發明之化合物因作用於 $P2X_3$ 亞型，因此同樣地被認爲對於含 $P2X_2$ 亞型所構成之 $P2X_{2/3}$ 受體也顯示阻害活性。

(CYP3A4 螢光 MBI 試驗)

CYP3A4 螢光 MBI 試驗是經由代謝反應，研究化合物的 CYP3A4 阻害增強的試驗，其係使用大腸菌表現的酵素 CYP3A4，經由 CYP3A4 酵素將 7-苄基氧基三氟甲基香豆素

(BFC)脫苄基化，生成發出螢光的代謝物 7-羥基三氟甲基香豆素(HFC)之反應爲指標來進行。

反應條件如下所示：基質爲 5.6μmol/L 7-BFC；預反應時間爲 0 或 30 分鐘；反應時間爲 15 分鐘；反應溫度爲 25℃(室溫)；CYP3A4 含量(大腸菌表現酵素)在預反應時爲 62.5pmol/mL，反應時爲 6.25pmol/mL(10 倍稀釋時)；被檢驗藥物濃度爲 0.625、1.25、2.5、5、10、20μmol/L(6 點)。

於 96 井平板，以上記預反應之組成添加酵素、被檢驗藥物溶液於 K-Pi 緩衝液(pH7.4)作爲預反應液，將其經 K-Pi 緩衝液稀釋 1/10 的一部分與基質移行到另一 96 井平板，添加輔酵素 NADPH 爲指標，開始反應(無預反應)，經所定的時間反應後，經由添加乙腈/0.5mol/L Tris(三羥基胺基甲烷)=4/1 來停止反應。此外，於剩餘的預反應液也添加 NADPH，開始預反應(有預反應)，經所定時間預反應後，將基質與經 K-Pi 緩衝液稀釋 1/10 的一部分移行另一平板爲指標，開始反應。經所定的時間反應後，經由添加乙腈/0.5mol/L Tris(三羥基胺基甲烷)=4/1 來停止反應。以螢光平板讀取儀測定平板中所進行之各個指標反應之代謝物 7-HFC 的螢光值。(Ex=420nm、Em=535nm)

以只添加溶解藥物用溶劑 DMSO 於反應系者作爲對照組(100%)，算出添加被檢驗藥物溶液之各個濃度下的殘存活性(%)，使用濃度及抑制率，經由邏輯模式以逆推定算出 IC50。IC50 值的差爲 5μM 以上之情形爲(+)，3μM 以下之情形爲(-)。

(CYP 阻害試驗)

使用市售之合集的人肝臟微粒體(pooled human liver microsomes)作爲人主要 CYP5 分子種類(CYP1A2、2C9、2C19、2D6、3A4)的典型基質代謝反應，以 7-乙氧基試鹵靈(Resorufin)的 O-脫乙基化(CYP1A2)、氨磺(Tolbutamide)的甲基-氫氧化(CYP2C9)、美芬妥英(Mephenytoin)的 4'-氫氧化(CYP2C19)、右旋美蘇仿(Dextromethorphan)的 O 脫甲基化(CYP2D6)、特芬那定(Terfenadine)的氫氧化(CYP3A4)爲指標，評價各個代謝物生成量經由被檢驗化合物阻害的程度。

反應條件如下所示：基質爲 0.5 μmol/L 乙氧基試鹵靈(CYP1A2)、100 μmol/L 氨磺(CYP2C9)、50 μmol/L S-美芬妥英(CYP2C19)、5μmol/L 右旋美蘇仿(CYP2D6)、1 μmol/L 特芬那定(CYP3A4)；反應時間爲 15 分鐘；反應溫度爲 37℃；酵素爲合集的人肝臟微粒體 0.2mg 蛋白質/mL；被檢驗藥物濃度爲 1、5、10、20 μmol/L(4 點)。

在 96 井平板，以上記組成添加各 5 種基質、人肝臟微粒體、被檢驗藥物於 50mM Hepes 緩衝液中作爲反應溶液，添加輔酵素 NADPH 爲指標，開始代謝反應，在 37℃反應 15 分鐘後，添加甲醇/乙腈=1/1(v/v)溶液來停止反應。3000rpm、15 分鐘的離心操作後，以螢光多標記計數器定量離心上清中的試鹵靈(CYP1A2 代謝物)，以 LC/MS/MS 定量氨磺氫氧化體(CYP2C9 代謝物)、美芬妥英 4'氫氧化體(CYP2C19 代謝物)、右旋蘇仿(dextrophan)(CYP2D6 代謝物)、特芬那定醇體(CYP3A4 代謝物)。

以只添加溶解藥物用溶劑 DMSO 於反應系者作爲對照組(100%)，算出添加被檢驗藥物溶液之各個濃度下的殘存活性(%)，使用濃度及抑制率，經由邏輯模式以逆推定算出 IC_{50}。

(FAT 試驗)

將 20μL 冷凍保存之鼠傷寒熱菌(*Salmonella typhimurium* TA98 株、TA100 株)接種於 10 mL 液體營養培養基(2.5% Oxoid 營養素肉汁 No.2)，在 37℃振盪前培養 10 小時。離心(2000×g、10 分鐘)9mL 的 TA98 株菌液，除去培養液，將菌懸浮於 9mL 的 Micro F 緩衝液(K2HPO4:3.5 g/L、KH2PO4:1 g/L、(NH4)2SO4:1g/L、檸檬酸三鈉二水合物：0.25 g/L、MgSO4·7H20：0.1g/L)，添加於 110 mL 的 Exposure 培養基(含有生物素：8 μg/mL、組胺酸：0.2 μg/mL、葡萄糖：8 mg/mL 之 MicroF 緩衝液)；相對於 TA100 株則是 3.16mL 菌液添加於 120mL 的 Exposure 培養基來調製試驗菌液。被驗物質 DMSO 溶液(從最高用量 50mg/mL 以 2 倍公比做 8 階段稀釋)、作爲陰性對照之 DMSO、作爲陽性對照之非代謝活性化條件下 TA98 株爲 50 μg/mL 的 4-硝基喹啉-1-氧化物 DMSO 溶液、而 TA100 株爲 0.25 μg/mL 的 2-(2-呋喃基)-3-(5-硝基-2-呋喃基)丙烯酸醯胺 DMSO 溶液、代謝活性化條件下 TA98 株爲 40μg/mL 的 2-胺基蒽 DMSO 溶液、而 TA100 株爲 20 μg/mL 的 2-胺基蒽 DMSO 溶液各 12 μL，與 588μL 的試驗菌液(代謝活性化條件之試驗菌液 498 μL 與 S9 mix 90 μL 的混合液)混合，在 37℃振盪培養 90 分鐘。接觸被驗物質之菌

液 460 μL 與指示培養基(含有生物素：8 μg/mL、組胺酸：0.2 μg/mL、葡萄糖：8 mg/mL、溴甲酚紫(Bromocresol Purple)：37.5 μg/mL 之 MicroF 緩衝液)2300μL 混合，以每一 50 μL 用量分注於微平板 48 井，在 37℃靜置培養 3 日。含有經由胺基酸(組胺酸)合成酵素基因的突變而獲得增殖能力之菌的井，因經由 pH 變化從紫色到黃色的變色，計數每 1 用量之 48 井中變色爲黃色的菌增殖井，與陰性對照組比較來評價。

(溶解性試驗)

化合物的溶解度是在 1%DMSO 添加條件下決定。以 DMSO 調製 10mM 化合物溶液，添加 6 μL 的化合物溶液於 594μL 之 pH 6.8 人工腸液(於 0.2 mol/L 磷酸二氫鉀試液 250 mL 添加 0.2 mol/L NaOH 試液 118 mL、水成爲 1000 mL)。在 25℃靜置 16 小時後，吸引過濾混液。以甲醇/水= 1/1 2 倍稀釋濾液，使用 HPLC 或 LC/MS/MS，經由絕對校正法測定濾液中濃度。

(代謝安定性試驗)

使用市售之合集的人肝臟微粒體，與對象化合物反應一定時間，經由反應樣品與未反應樣品的比較算出殘存率，評價肝的代謝程度。

在含有人肝臟微粒體 0.5mg 蛋白質/mL 之 0.2mL 緩衝液(50mmol/L tris-HCl pH7.4、150mmol/L 氯化鉀、10 mmol/L 氯化鎂)中，於 1mmol/L NADPH 存在下，在 37℃反應 0 分鐘或 30 分鐘(氧化的反應)。反應後，於 100μL 的甲醇/乙腈

=1/1(v/v)溶液添加反應液 50μL、混合，以 3000rpm 離心 15 分鐘。以 LC/MS/MS 定量其離心上清中之試驗化合物，0 分鐘反應時的化合物量爲 100%，計算反應後之試驗化合物的殘存量。又，氫化反應在 NADPH 未存在下進行反應，而葡萄醣醛酸抱合反應是在 5mM UDP-葡萄醣醛酸存在下置換爲 NADPH 來進行反應，之後實施相同的操作。

(hERG 試驗)

以心電圖 QT 間隔延長的風險評價作爲目的，使用表現 hERG(human ether-a-go-go related gene)通道的 HEK293 細胞，檢討對在心室再極化過程扮演重要角色之遲延整流 K+ 電流(IKr)的作用。

使用全自動膜片箝制系統(patch-clamp system)(PatchXpress 7000A, Axon Instruments Inc.)，經由整個細胞膜片箝制法，保持細胞於-80 mV 的膜電位後，記錄給予+50 mV 的去極化刺激 2 秒，再給予-50 mV 的再極化刺激 2 秒時誘發的 IKr。產生之電流安定後，在室溫條件下將以目的濃度溶解被檢驗物質之細胞外液(NaCl: 137 mmol/L、KCl: 4 mmol/L、$CaCl_2 \cdot 2H_2O$：1.8 mmol/L、$MgCl_2 \cdot 6H_2O$：1 mmol/L、葡萄糖：10 mmol/L、HEPES(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid；4-(2-羥基乙基)-1-哌啉乙烷磺酸)：10 mmol/L、pH = 7.4)，適用於細胞 10 分鐘。使用解析軟體(DataXpress ver. 1、Molecular Devices Corporation)，從所得 IKr，以保持膜電位中電流值爲基準，計測最大尾端電流的絕對值。再者，算出對被檢驗物質適用前之最大尾端電流的阻害率，與介質適

用組(0.1%二甲亞碸溶液)比較，評價被檢驗物質對IKr的影響。

(BA試驗)

經口吸收性之檢討實驗材料及方法

(1)使用動物：購買自日本Charles River的6週齡雄性Crl:CD(SD)大鼠，1週之預備飼育之後，在投與前的3日以上施予頸靜脈引流導管(cannulation)，在8週齡時用於實驗。

(2)飼育條件：大鼠之飼育環境，溫度設定爲20-26℃，濕度爲30-70%，照明設定爲8:00~20:00點燈、20:00~8:00熄燈之循環。預備飼育中、實驗期間自由攝取固形飼料(CRF-1、日本Charles River)及滅菌的自來水。

(3)個體及鼠籠的識別：以油性墨在大鼠的尾或背中記上個體編號進行識別。在鼠籠附上記在試驗負責人名、到達日、系統、性別、供給來源之標識，預備飼育中以5匹/鼠籠來飼育。實驗開始後以1匹/鼠籠來飼育。

(4)投與量、分組的設定：以經口投與、靜脈內投與的投與量，設定如以下之組。

經口投與　1mg/kg(n=2)

靜脈內投與　0.5mg/kg(n=2)

(5)投與液之調製：使用0.5%甲基纖維素(400cP)調整懸浮液作爲經口投與介質。使用N,N-二甲基乙醯胺/丙二醇(=1/1)調整可溶化溶液作爲靜脈內投與介質。

(6)投與方法：經口投與是以5mL/kg的比例以經口探針(sonde)強制地投與胃內。靜脈內投與是以1mL/kg的比例經

由附有注射針的針筒從尾靜脈投與。

(7)評價項目：採血是從頸靜脈導管的採血，使用LC/MS/MS測定血漿中藥物濃度。

(8)統計解析：關於血漿中濃度轉變，使用非線形最小二乘法程式WinNonlin(登錄商標)，算出血漿中濃度-時間曲線下面積(AUC)，從經口投與組與靜脈內投與組的AUC算出生物利用率(BA)。

製劑例 1

製造含有以下成分的顆粒劑。

成分	式(I)表示之合物	10 mg
	乳糖	700 mg
	玉米澱粉	274 mg
	HPC-L	16 mg

將式(I)表示之合物與乳糖通過60篩孔的篩。將玉米澱粉通過120篩孔的篩。以V型混合機混合這些。於混合粉末添加HPC-L(低粘度羥基丙基纖維素)水溶液，混合、造粒(押出造粒，孔徑0.5~1mm)、乾燥步驟。以振動篩(12/60篩孔)通過所得乾燥顆粒得到顆粒劑。

製劑例 2

製造含有以下成分之膠囊充填用顆粒劑。

成分	式(I)表示之合物	15 mg
	乳糖	90 mg
	玉米澱粉	42 mg
	HPC-L	3 mg

將式(I)表示之合物與乳糖通過 60 篩孔的篩。將玉米澱粉通過 120 篩孔的篩。混合這些，於混合粉末添加 HPC-L 溶液，混合、造粒、乾燥。整粒所得乾燥顆粒後，將其 150mg 填充於 4 號硬明膠膠囊。

製劑例 3

製造含有以下成分的錠劑。

成分	式(I)表示之合物	10 mg
	乳糖	90 mg
	微結晶纖維素	30 mg
	CMC-Na	15 mg
	硬脂酸鎂	5 mg

將式(I)表示之合物、乳糖、微結晶纖維素、CMC-Na(羧基甲基纖維素鈉鹽)通過 60 篩孔的篩、混合。於混合粉末混合硬脂酸鎂，得到製錠用混合粉末。直打(直接粉末壓縮)本混合粉末，得到 150mg 錠劑。

製劑例 4

加溫混合以下的成分後，滅菌成爲注射劑。

成分	式(I)表示之合物	3 mg
	非離子性界面活性劑	15 mg
	注射用純化水	1 ml

製劑例 5

製造含有以下成分的泥敷劑(cataplasm)。

成分	式(I)表示之合物	50 mg
	水性基劑(5%乙醇/5%丁二醇/90%純化水)	950mg
	甘油	
	高嶺土	
	聚乙烯基醇水溶液	

於水性基劑添加式(I)表示之化合物，超音波照射15分鐘左右後，充分地攪拌成爲溶液。均一地混合甘油5份、高嶺土1份、聚乙烯基醇水溶液5份，添加經調製之溶液1份。進一步混合這些成爲糊狀物，塗布於不織布上，以聚酯膜覆蓋成爲泥敷劑。

(產業上之可利用性)

本發明之化合物對 $P2X_3$ 及/或 $P2X_{2/3}$ 受體據有拮抗作用，有用於與 $P2X_3$ 及/或 $P2X_{2/3}$ 受體有關之疾病或狀態，例如慢性疼痛、膀胱過度活動。

【圖式簡單說明】

無。

【主要元件符號說明】

無。

201016702

C07D	487/04	2006.01
C07D	413/10	2006.01
C07D	413/14	2006.01
C07D	401/04	2006.01
C07D	405/10	2006.01
C07D	409/10	2006.01
C07D	409/14	2006.01
C07D	417/10	2006.01
A61K	31/4162	2006.01
A61K	31/407	2006.01
A61K	31/4025	2006.01

發明專利說明書

PD10

(本說明書格式、順序,請勿任意更動,※記號部分請勿填寫)

※ 申請案號: 98132205

※ 申請日: 98 9 24 ※IPC 分類:

一、發明名稱:(中文/英文)

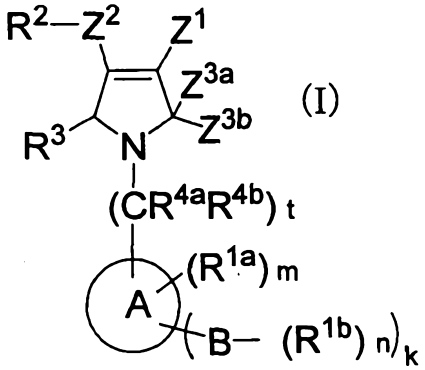
新穎吡咯啉酮衍生物及含有其之醫藥組成物

NOVEL PYRROLINONE DERIVATIVE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

二、中文發明摘要:

本發明提供新穎之 $P2X_3$ 及/或 $P2X_{2/3}$ 受體拮抗劑。

提供式(I)表示之化合物或其製藥上容許的鹽或彼等之溶劑化物:



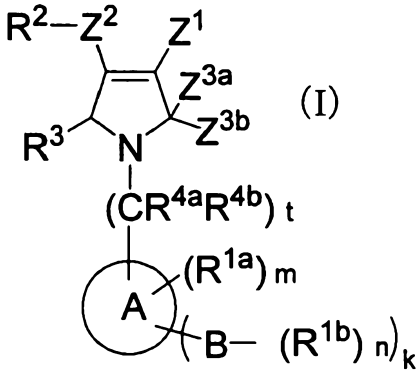
(I)

(式中,Z^1 爲可經保護之羥基等;Z^2 爲 -C(=O)- 等;Z^{3a} 及 Z^{3b} 一起成爲 =O 或 =S 等;t 爲 0~4 之整數;R^{4a} 及 R^{4b} 分別獨立爲氫或取代或未取代之低級烷基等;m 及 n 分別獨立爲 0~2 之整數;k 爲 0 或 1 之整數;環 A 爲芳香族碳環或雜環等;B 爲芳香族碳環二基或雜環二基等;R^{1a} 及 R^{1b} 分別獨立爲鹵素、羥基、取代或未取代之低級烷基等;R^2 取代或未取代之烷基等;R^3 爲取代或未取代之烷基、取代或未取代之芳基或取代或未取代之雜環式基等)。

三、英文發明摘要:

This invention provides a novel $P2X_3$ and/or $P2X_{2/3}$ receptor antagonist.

Provided is a compound of formula (I):



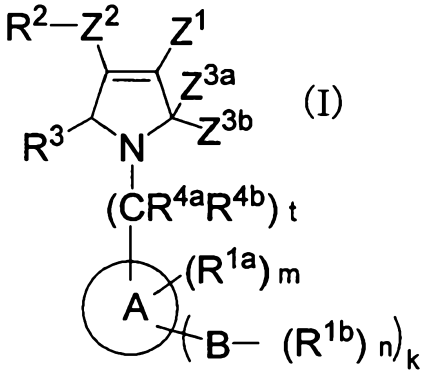
(I)

(wherein Z^1 is an optionally protected hydroxyl and the like; Z^2 is -C(=O)- and the like; Z^{3a} and Z^{3b} together form =O or =S and the like; t is an integral of 0~4; R^{4a} and R^{4b} are independently hydrogen, or substituted or unsubstituted lower alkyl and the like; m and n are independently an integral of 0~2; k is an integral of 0 or 1; ring A is an aromatic carboncycle or a heterocycle and the like; ring B is an aromatic carboncycle diyl or a heterocycle diyl and the like; R^{1a} and R^{1b} are independently halogen, hydroxyl, substituted or unsubstituted lower alkyl and the like; R^2 is a substituted or unsubstituted alkyl and the like; R^3 is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic groupe and the like);

or a pharmaceutically acceptable salt thereof or a solvate thereof.

七、申請專利範圍:

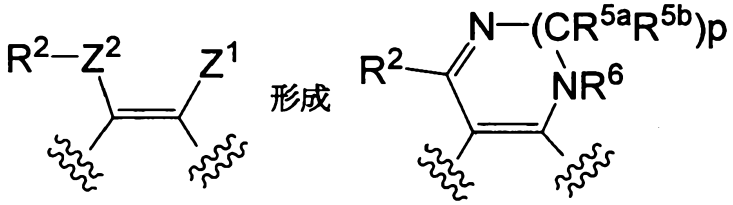
1.一種式(I)表示之化合物或其製藥上容許的鹽或彼等之溶劑化物，



(式中，

Z^1為可經保護之羥基或可經保護之巰基；

Z^2為-C(=O)-、-C(=S)-或-S(O)v-、或



(式中，R^{5a}及R^{5b}分別獨立為氫或低級烷基；

R^6為氫、取代或未取代之低級烷基、取代或未取代之醯基或取代或未取代之低級烷氧羰基；

p為0~2之整數)；

v為0~2之整數；

Z^{3a}及Z^{3b}分別獨立為氫、取代或未取代之低級烷基、或一起形成=O或=S；

t為0~4之整數；

R^{4a}及R^{4b}分別獨立爲氫或取代或未取代之低級烷基；

m及n分別獨立爲0~2之整數；

k爲0或1之整數；

環A爲環烷、環烯、芳香族碳環或雜環；

B爲環烷二基、環烯二基、芳香族碳環二基或雜環二基；

R^{1a}及R^{1b}分別獨立爲鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基、取代或未取代之胺磺醯基、氰基、硝基或$-C(R^{7a})=N-O-R^{7b}$；

R^{7a}及R^{7b}分別獨立爲氫或取代或未取代之低級烷基；

R^{2}爲取代或未取代之烷基、取代或未取代之烯基、取代或未取代之炔基、取代或未取代之烷氧基、取代或未取代之芳氧基、羥基、取代或未取代之胺基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基；

R^{3}爲取代或未取代之烷基、取代或未取代之烷氧羰基、取代或未取代之芳氧基羰基、羧基、取代或未取代之胺甲醯基、取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基；)

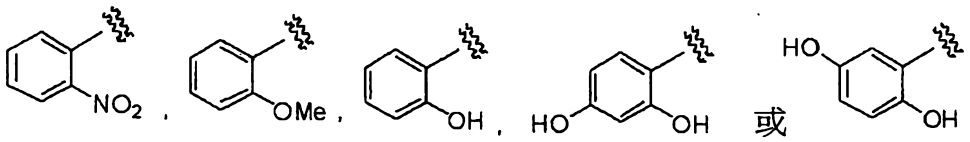
但以下除外：

(i)環A爲噻二唑，k爲0，且R^{1a}爲甲硫基之化合物；

(ii)環 A 爲苯并噻吩，k 爲 0，R^{1a}爲甲磺醯基，且 R^2爲取代或未取代之呋喃基或取代或未取代之苯基之化合物；

(iii)環 A 爲噻唑或 7H-嘌呤，且 R^2爲取代或未取代之呋喃基之化合物；

(iv)R^3爲下式表示之基：



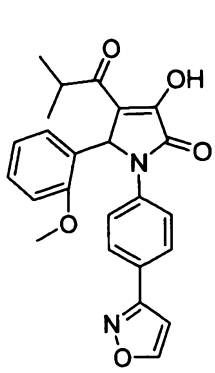
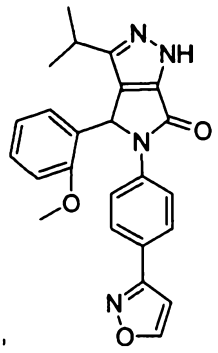
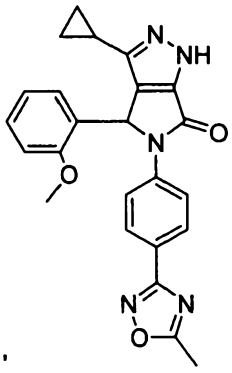
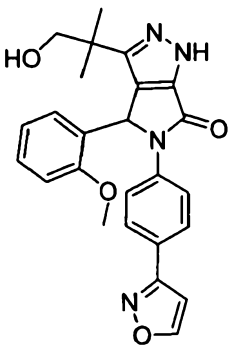
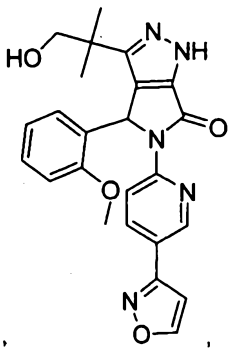
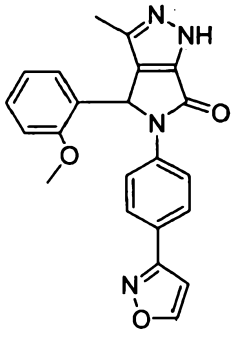
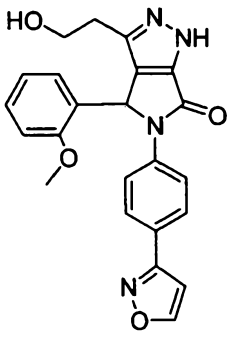
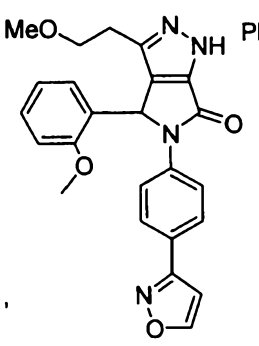
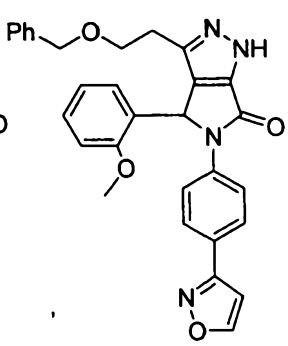
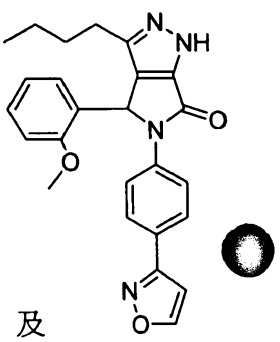
t 爲 1~2 之整數、且環 A 爲呋喃或苯之化合物；

(v)R^2爲第三丁基或 4-甲基氧基苯基之化合物；

(vi)R^2爲取代或未取代之烷基(但取代或未取代之異丙基及取代或未取代之異丁基除外)，R^3爲取代或未取代之碳環或取代或未取代之雜環，且 k 爲 0 之化合物；

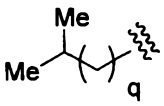
(vii)R^2爲取代或未取代之環烷基、取代或未取代之環烯基、取代或未取代之芳基或取代或未取代之雜環式基，且 R^3爲戊烷-3-基之化合物；以及

(viii)以下式表示之化合物：


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及

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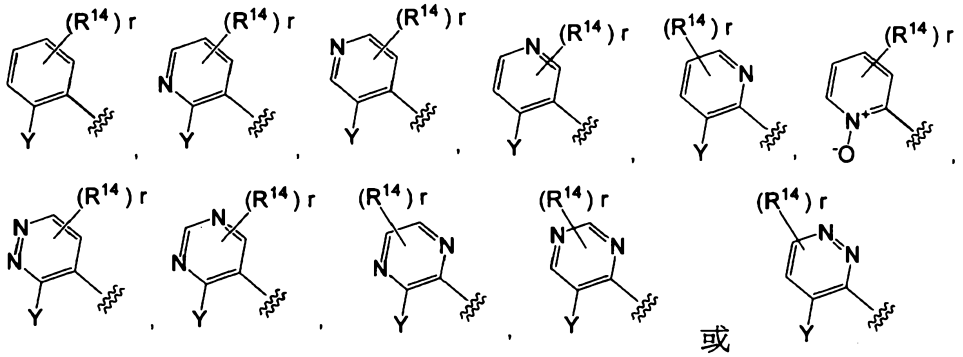
2.如申請專利範圍第 1 項之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中

R^2 爲以下式表示之基：



(式中，Me 爲甲基，q 爲 0~4 之整數)；

R^3 爲以下式表示之基：



(式中，Y為羥基、鹵素、氰基、羧基、取代或未取代之低級烷基、取代或未取代之低級烷氧基、取代或未取代之低級烷氧羰基、取代或未取代之醯基、取代或未取代之胺甲醯基、取代或未取代之硫胺甲醯基、取代或未取代之低級烷硫基、取代或未取代之低級烷基胺磺醯基、取代或未取代之胺基、取代亞磺醯基、取代磺醯基或取代或未取代之雜環式基，或Y及R^{14}亦可結合於鄰接之碳原子形成取代或未取代之雜環式基；

R^{14}為鹵素、羥基、取代或未取代之低級烷基、取代或未取代之低級烯基、取代或未取代之低級炔基、取代或未取代之低級烷氧基、取代或未取代之低級烷硫基、取代或未取代之醯基、羧基、取代或未取代之低級烷氧羰基、取代或未取代之胺甲醯基、取代或未取代之胺基、取代或未取代之胺磺醯基、氰基或硝基；

r為0~2之整數)。

3.如申請專利範圍第2項之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中Z^{3a}及Z^{3b}一起成為=O。

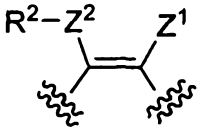
4.如申請專利範圍第2項之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中t為0。

5.如申請專利範圍第2項之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中Z^2為-C(=O)-、-C(=S)-或-S(O)$_2$-。

6.如申請專利範圍第2項之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中Z^2為-C(=O)-。

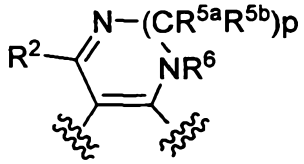
7.如申請專利範圍第2項之化合物或其製藥上容許的鹽或彼

等之溶劑化物，其中以下式表示之基：



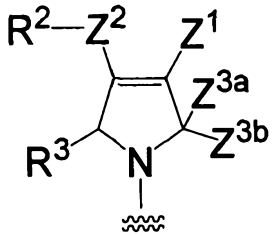
(式中，Z^1、Z^2及R^2與如申請專利範圍第1項同意義)

爲下式：



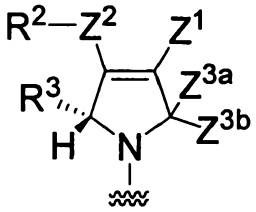
(式中，R^2、R^{5a}、R^{5b}、R^6及p與如申請專利範圍第1項同意義)。

8.如申請專利範圍第2項之化合物或其製藥上容許的鹽或彼等之溶劑化物，其中以下式表示之基：



(式中，Z^1、Z^2、Z^{3a}、Z^{3b}、R^2及R^3與如申請專利範圍第1項同意義)

爲以下式表示之基：



(式中，Z^1、Z^2、Z^{3a}、Z^{3b}、R^2及R^3與如申請專利範圍第1項同意義)。

9.一種醫藥組成物，含有如申請專利範圍第1至8項中任一之化合物或其製藥上容許的鹽或彼等之溶劑化物。

10.如申請專利範圍第1至8項之醫藥組成物，其爲$P2X_3$及/或$P2X_{2/3}$受體拮抗劑。

11.一種與$P2X_3$及/或$P2X_{2/3}$受體有關之疾病之預防或治療方法，其特徵爲投與如申請專利範圍第1至8項中任一之化合物或其製藥上容許的鹽或彼等之溶劑化物。

12.一種如申請專利範圍第1至8項中任一之化合物或其製藥上容許的鹽或彼等之溶劑化物之使用，其係用於與$P2X_3$及/或$P2X_{2/3}$受體有關之疾病的治療及/或預防。

13.一種如申請專利範圍第1至8項中任一之化合物或其製藥上容許的鹽或彼等之溶劑化物之使用，其係用於製造與$P2X_3$及/或$P2X_{2/3}$受體有關之疾病的治療藥及/或預防藥。

四、指定代表圖:

(一)本案指定代表圖為: 無 。

(二)本代表圖之元件符號簡單說明:無

無。

五、本案若有化學式時,請揭示最能顯示發明特徵的化學式:

