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(56)參考文獻：
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(54)名稱

雜芳基衍生化合物及其用途

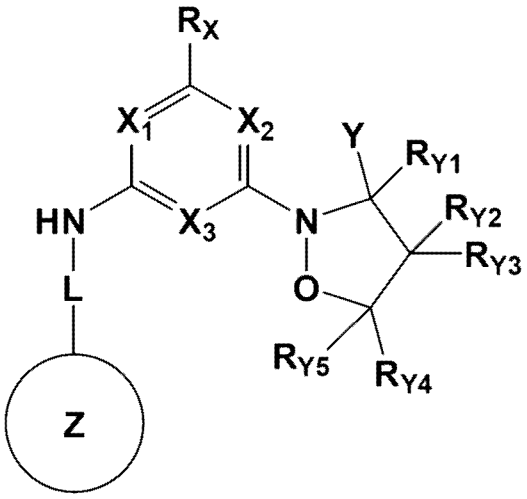
(57)摘要

本發明係關於一種雜芳基衍生物及其用途。本發明之雜芳基衍生物展現出對 EGFR 及/或 HER2 之極佳抑制活性，且因此可有效地用作 EGFR 相關疾病及/或 HER2 相關疾病之治療劑。

The present disclosure relates to a heteroaryl derivative and uses thereof. The heteroaryl derivative of the present disclosure exhibits excellent inhibitory activity against EGFR and/or HER2, and thus may be usefully employed as a therapeutic agent for EGFR- and/or HER2-related diseases.

特徵化學式：

[化學式1]



公告本

I869674

【發明摘要】

【中文發明名稱】

雜芳基衍生化合物及其用途

【英文發明名稱】

HETEROARYL DERIVATIVE COMPOUNDS, AND USES THEREOF

【中文】

本發明係關於一種雜芳基衍生物及其用途。本發明之雜芳基衍生物展現出對EGFR及/或HER2之極佳抑制活性，且因此可有效地用作EGFR相關疾病及/或HER2相關疾病之治療劑。

【英文】

The present disclosure relates to a heteroaryl derivative and uses thereof. The heteroaryl derivative of the present disclosure exhibits excellent inhibitory activity against EGFR and/or HER2, and thus may be usefully employed as a therapeutic agent for EGFR- and/or HER2-related diseases.

【指定代表圖】

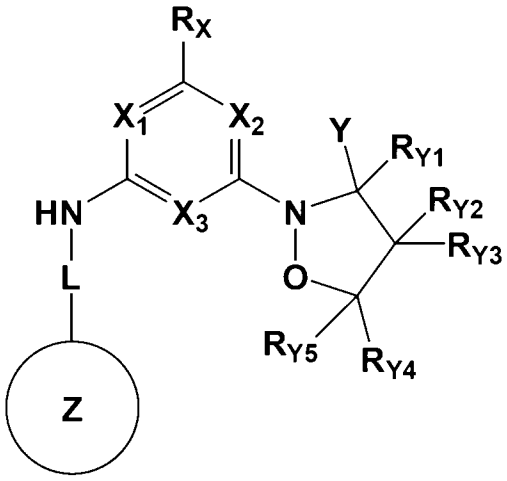
無

【代表圖之符號簡單說明】

無

【特徵化學式】

[化學式1]



【發明說明書】

【中文發明名稱】

雜芳基衍生化合物及其用途

【英文發明名稱】

HETEROARYL DERIVATIVE COMPOUNDS, AND USES THEREOF

【技術領域】

【0001】 本發明係關於一種雜芳基衍生化合物及其藥用用途。特定言之，本發明係關於具有EGFR及/或HER2抑制活性之雜芳基衍生化合物。

【先前技術】

【0002】 蛋白激酶藉由充當分子開關而參與信號傳導路徑，且細胞中激酶對目標蛋白的活性與非活性之間的轉變必須得到平穩調節。若活性與非活性狀態之間的轉變受調節異常，則細胞內信號傳遞就會被過度活化或失活，導致細胞分裂及增殖不可控。特定言之，因蛋白激酶基因之突變、擴增及/或過度表現之異常活化引起各種腫瘤之發展及惡化，或在諸如發炎性疾病、退行性腦病及自體免疫疾病及其類似者之各種疾病的發病中起決定性作用。

【0003】 表皮生長因子受體(EGFR) (ErbB家族中之一種受體酪胺酸激酶)在許多上皮細胞腫瘤中異常活躍，包括非小細胞肺癌(NSCLC)、乳癌、神經膠質瘤、頭頸部鱗狀細胞癌、大腸直腸癌、直腸腺癌、頭頸癌、胃癌及前列腺癌。已知EGFR酪胺酸激酶活化引起連續細胞增殖、侵入周圍組織、遠端癌轉移及血管生成，且增加細胞存活率。

【0004】另外，已知EGFR Del19或EGFR L858R (一種EGFR突變)為非小細胞肺癌及頭頸癌之主要病因，且已研發出Iressa及Tarceva (其為此等突變之治療劑)，並在目前正用於臨床實踐中。然而，當此等藥物用於患者中時，觀測到基於藥物結構引起EGFR二級突變之獲得性耐藥性，且亦發現此為抗藥性之真正主要原因。在使用第一代EGFR抑制劑平均約10個月時，產生位於EGFR激酶之守門因子處之稱為T790M突變的獲得性耐藥性，且因此使第一代EGFR抑制劑失去作用。換言之，出現EGFR Del19/T790M或EGFR L858R/T790M雙重突變，其阻止現有治療劑展現出藥物功效。已研發一種第三代EGFR-TKI靶向藥物奧希替尼(Osimertinib)，其對根據EGFR T790M突變之耐藥性展現出較高反應性，但亦有報告稱其引起耐藥性(Niederst MJ.等人, Clin Cancer Res, 2015, 17(21):3924-3933)。已表明EGFR C797S突變為引起對奧希替尼之耐藥性的主要機制中之一者，且有報告稱約40%之臨床試驗患者具有EGFR C797S突變(Thress KS.等人, Nature Medicine, 2015, 21:560-562)。因此，EGFR Del19/C797S (EGFR DC)或EGFR L858R/C797S (EGFR LC)可為主要目標。

【0005】此外，表現EGFR罕見(或不常見)突變及耐藥性突變之L861Q、G719A、S768I、L718Q、G724S或類似者亦可為潛在目標。

【0006】同時，HER2 (人類表皮生長因子受體2；亦稱為ErbB2)，作為ErbB家族之一種受體酪胺酸激酶，與其他EGFR受體，即HER1 (EGFR, ErbB1)、HER3 (ErbB3)或HER4 (ErbB4)形成均二聚體或雜二聚體，且藉由細胞內酪胺酸殘基處之自體磷酸化來活化，其在正常細胞與癌細胞之細胞增殖、分化及存活方面發揮重要作用(Di Fiore PP.等人,

Science. 1987, 237(481):178-182)。已知HER2在諸如乳癌、胃癌及卵巢癌之若干癌瘤中過度表現(Hardwick RH.等人, Eur. J Surg Oncol. 1997, 23(1):30-35; Korkaya H.等人, Oncogene. 2008, 27(47):6120-6130;)。

【0007】 如上文所描述，對能夠藉由調節EGFR活性(尤其C797S突變，諸如EGFR Del19/C797S及EGFR L858R/C797S、EGFR罕見突變、耐藥性突變或其類似者)及/或HER2，而有效地用於治療EGFR及/或HER2相關疾病的新穎化合物的逐漸增加之需求未得到滿足。

【發明內容】

[技術問題]

【0008】 本發明之目標為提供一種具有新穎結構之雜芳基衍生物、其光學異構體或其醫藥學上可接受之鹽。

【0009】 本發明之另一目標為提供一種用於製備該雜芳基衍生化合物之方法。

【0010】 本發明之又另一目標係提供雜芳基衍生化合物之醫藥用途，且特定言之，係關於一種用於治療或預防EGFR及/或HER2相關疾病，包含雜芳基衍生化合物作為活性成分的醫藥組合物、該化合物用於治療或預防EGFR病及/或HER2相關疾病之用途，或一種用於治療或預防EGFR及/或HER2相關疾病之方法，其包含投與該化合物。

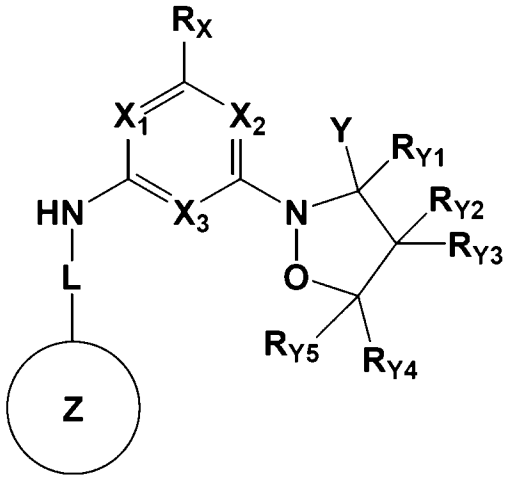
[技術解決方案]

【0011】 為實現上述目標，本發明人努力研究，且因此發現以下由化學式1表示之雜芳基衍生化合物，其抑制EGFR及/或HER2活化細胞之增殖，且完成本發明。

雜芳基衍生化合物

【0012】本發明提供一種由以下化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽：

[化學式1]



在化學式1中，

X_1至X_3各自獨立地為CH或N；

R_X為-H、-C_{1-6}烷基、-C_{1-6}胺烷基、-NH_2、-NH(-C_{1-6}烷基)或-N(-C_{1-6}烷基)(-C_{1-6}烷基)；

Y為-C_{1-6}烷基、-$(CH_2)_n$芳基、-$(CH_2)_n$氫芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基，其中該-$(CH_2)_n$芳基、-$(CH_2)_n$氫芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}羥烷基、-C_{1-6}鹵烷基、-C_{1-6}烷基-O-C_{1-6}烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-(C=O)NR_1R_2、-(C=O)OR_3、-NR_4R_5、-OR_6、-鹵基、=O、環烷基、雜環烷基、芳基或雜芳基取代，其中該環烷基、雜環烷基、芳基或雜芳基中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基或-鹵基取代；

n為0、1、2、3或4；

R_1至R_3各自獨立地為-H、-C_{1-6}烷基或環烷基；

R_4及R_5各自獨立地為-H或-C_{1-6}烷基；

R_6為-H、-C_{1-6}烷基或苯基，其中該苯基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基或鹵基取代；

R_{Y1}至R_{Y5}各自獨立地為-H或-C_{1-6}烷基，或R_{Y2}及R_{Y3}可彼此鍵聯以形成環烷基或雜環烷基，R_{Y4}及R_{Y5}可彼此鍵聯以形成環烷基或雜環烷基，且R_{Y3}及R_{Y4}可彼此鍵聯以形成芳基或雜芳基；

L為-(CH_2)m-、-C(=O)-或不存在；

m為0、1、2、3或4；

環Z為芳基、雜芳基、氫芳基、氫雜芳基、環烷基或雜環烷基，其中該芳基、雜芳基、氫芳基、氫雜芳基、環烷基或雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}氰烷基、-C_{1-6}羥烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-NR_7R_8、-OH、-O-C_{1-6}烷基、-O-C_{1-6}鹵烷基、-S-C_{1-6}烷基、-S-C_{1-6}鹵烷基、-C(=O)-C_{1-6}烷基、-C(=O)-C_{1-6}鹵烷基、-C(=O)O-C_{1-6}烷基、-$S(=O)_2$-C_{1-6}烷基、-C(=N-O-C_{1-6}烷基)(C_{1-6}烷基)、=O、-鹵基或Z_1取代，或該芳基、雜芳基、氫芳基、氫雜芳基、環烷基或雜環烷基環之兩個或更多個取代基可彼此鍵聯以形成稠環或螺環，其中該稠環或螺環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基、-O-C_{1-6}烷基、-鹵基或Z_1取代；

R_7及R_8各自獨立地為-H、-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}烷基-NH-C_{1-6}烷基、-C_{1-6}烷基-N(C_{1-6}烷基)(C_{1-6}烷基)、-(C=O)-C_{1-6}烷基或-(C=O)-C_{1-6}鹵烷基；

Z_1為環烷基、雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基、芳基或雜芳基，其中該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-

NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基、芳基或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烷基-NH-C_{1-6}烷基、-C_{1-6}烷基-N(C_{1-6}烷基)(C_{1-6}烷基)、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-C(=O)-C_{1-6}烷基、-$S(=O)_2$-C_{1-6}烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-NR_9R_{10}、-鹵基、環烷基或Z_2取代；

R_9及R_{10}各自獨立地為-H或-C_{1-6}烷基；

Z_2為雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基、芳基或雜芳基，其中該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基、芳基或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}羥烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-$NR_{11}R_{12}$、環烷基或Z_3取代；

R_{11}及R_{12}各自獨立地為-H或-C_{1-6}烷基；及

Z_3為雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-NH-雜環烷基，其中該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-NH-雜

環烷基環中之至少一個H可經-C_{1-6}烷基或環烷基取代。

【0013】 根據本發明之一個實施例，以上化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽可包括於以下範圍中：

X_1至X_3各自獨立地為CH或N；

R_X為-H、-NH_2、-NH(-C_{1-6}烷基)或-N(-C_{1-6}烷基)(-C_{1-6}烷基)；

Y為-C_{1-6}烷基、-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基，其中該-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-(C=O)NR_1R_2、-(C=O)OR_3、-NR_4R_5、-OR_6、-鹵基、=O、雜環烷基、芳基或雜芳基取代，其中該雜環烷基、芳基或雜芳基中之至少一個H可經-鹵基取代；

n為0、1或2；

R_1至R_3各自獨立地為-H、-C_{1-6}烷基或環烷基；

R_4及R_5各自獨立地為-H或-C_{1-6}烷基；

R_6為-C_{1-6}烷基或苯基，其中該苯基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基或鹵基取代；

R_{Y1}至R_{Y5}各自獨立地為-H或-C_{1-6}烷基，或R_{Y2}及R_{Y3}可彼此鍵聯以形成環烷基，且R_{Y3}及R_{Y4}可彼此鍵聯以形成芳基；

L為-(CH_2)m-、-C(=O)-或不存在；

m為0、1或2；

環Z為芳基、雜芳基、氫雜芳基、環烷基或雜環烷基，其中該芳基、雜芳基、氫雜芳基、環烷基或雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}氰烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-NR_7R_8、-O-C_{1-6}烷基、-O-C_{1-6}鹵烷基、-S-C_{1-6}烷基、-C(=O)-C_{1-6}烷基、-C(=O)-C_{1-6}鹵烷

基、-C(=O)O-C_{1-6}烷基、-S(=O)$_2$-C_{1-6}烷基、-C(=N-O-C_{1-6}烷基)(C_{1-6}烷基)、=O、-鹵基或Z_1取代，或該芳基、雜芳基、氫雜芳基、環烷基或雜環烷基環之兩個或更多個取代基可彼此鍵聯以形成稠環或螺環，其中該稠環或螺環中之至少一個H可經-C_{1-6}烷基或Z_1取代；

R_7及R_8各自獨立地為-H、-C_{1-6}烷基、-C_{1-6}烷基-NH-C_{1-6}烷基、-C_{1-6}烷基-N(C_{1-6}烷基)(C_{1-6}烷基)、-(C=O)-C_{1-6}烷基或-(C=O)-C_{1-6}鹵烷基；

Z_1為環烷基、雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基或雜芳基，其中該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-S(=O)$_2$-C_{1-6}烷基、=O、-NR_9R_{10}、-鹵基、環烷基或Z_2取代；

R_9及R_{10}各自獨立地為-H或-C_{1-6}烷基；

Z_2為雜環烷基、雜雙環烷基或-NH-雜環烷基，其中該雜環烷基、雜雙環烷基或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基或-NH-雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}羥烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-S(=O)$_2$-C_{1-6}烷基、=O、-$NR_{11}R_{12}$、環烷基或Z_3取代；

R_{11}及R_{12}各自獨立地為-H或-C_{1-6}烷基；及

Z_3為雜環烷基、雜雙環烷基或-C_{1-6}烷基-雜環烷基，其中該雜環烷

基、雜雙環烷基或-C_{1-6}烷基-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基或-C_{1-6}烷基-雜環烷基環中之至少一個H可經-C_{1-6}烷基或環烷基取代。

【0014】 根據本發明之一個實施例，以上化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽可包括於以下範圍中：

X_1為N；

X_2及X_3各自獨立地為CH或N；及

R_X為-H、-NH_2或-NH(-C_{1-6}烷基)。

【0015】 根據本發明之一個實施例，以上化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽可包括於以下範圍中：

Y為-C_{1-6}烷基、-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基，其中該-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基、-C_{1-6}炔基、-CN、-(C=O)NH-環烷基、-(C=O)O-C_{1-6}烷基、-N(C_{1-6}烷基)(C_{1-6}烷基)、-O(C_{1-6}烷基)、-O-苯基、-鹵基、=O、雜環烷基、芳基或雜芳基取代，其中該雜環烷基、芳基或雜芳基中之至少一個H可經-鹵基取代；

n為0或1；及

R_{Y1}至R_{Y5}各自獨立地為-H或-C_{1-6}烷基，或R_{Y2}及R_{Y3}可彼此鍵聯以形成3員至6員環烷基，且R_{Y3}及R_{Y4}可彼此鍵聯以形成苯基。

【0016】 根據本發明之一個實施例，以上化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽可包括於以下範圍中：

L為-(CH_2)m-、-C(=O)-或不存在；

m為0或1；

環Z為芳基、雜芳基、氫雜芳基、3員至7員環烷基或5員至7員雜環烷基，其中該芳基、雜芳基、氫雜芳基、3員至7員環烷基或5員至7員雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}氘烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-NR_7R_8、-O-C_{1-6}烷基、-O-C_{1-6}鹵烷基、-S-C_{1-6}烷基、-C(=O)-C_{1-6}烷基、-C(=O)-C_{1-6}鹵烷基、-C(=O)O-C_{1-6}烷基、-$S(=O)_2$-C_{1-6}烷基、-C(=N-O-C_{1-6}烷基)(C_{1-6}烷基)、=O、-鹵基或Z_1取代，其中該芳基、雜芳基、氫雜芳基、3員至7員環烷基或5員至7員雜環烷基環中之至少一個H可經-C_{1-6}烷基或-鹵基取代，或該芳基、雜芳基、氫雜芳基、3員至7員環烷基或5員至7員雜環烷基環之兩個或更多個取代基可彼此鍵聯以形成稠環或螺環，其中該稠環或螺環中之至少一個H可經-C_{1-6}烷基或Z_1取代；

R_7及R_8各自獨立地為-H、-C_{1-6}烷基、-C_{1-6}烷基-N(C_{1-6}烷基)(C_{1-6}烷基)、-(C=O)-C_{1-6}烷基或-(C=O)-C_{1-6}鹵烷基；

Z_1為3員至7員環烷基、5員至7員雜環烷基、6員至10員雜雙環烷基、6員至10員雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基或雜芳基，其中該5員至7員雜環烷基、6員至10員雜雙環烷基、6員至10員雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該5員至7員雜環烷基、6員至10員雜雙環烷基、6員至10員雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、-NH-雜環烷基或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-N(C_{1-6}烷基)(C_{1-6}烷基)、-鹵基、環烷基或Z_2取代；

Z_2為5員至7員雜環烷基、6員至10員雜雙環烷基或-NH-雜環烷基，其中該5員至7員雜環烷基、6員至10員雜雙環烷基或-NH-雜環烷基在該環中含有選自由N、O及S組成之群中之至少一者，且該5員至7員雜環烷基、6員至10員雜雙環烷基或-NH-雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}羥烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-N(C_{1-6}烷基)(C_{1-6}烷基)、3員至7員環烷基或Z_3取代；及

Z_3為5員至7員雜環烷基、6員至10員雜雙環烷基或-C_{1-6}烷基-雜環烷基，其中該5員至7員雜環烷基、6員至10員雜雙環烷基或-C_{1-6}烷基-雜環烷基在該環中含有選自由N、O及S組成之群中之至少一者，且該5員至7員雜環烷基、6員至10員雜雙環烷基或-C_{1-6}烷基-雜環烷基環中之至少一個H可經-C_{1-6}烷基或3員至7員環烷基取代。

【0017】 根據本發明之一個實施例，由以上化學式1表示之化合物可選自由以下表1中所列之化合物組成之群。

【0018】 在本發明中，除非另外規定，否則術語「烷基」可指直鏈或分支鏈非環狀、環狀或其結合之飽和烴。舉例而言，「C_{1-6}烷基」可指示含有1至6個碳原子之烷基。舉例而言，非環狀烷基可包括但不限於甲基、乙基、正丙基、正丁基、異丙基、二級丁基、異丁基、三級丁基或類似者。如本文所用，環狀烷基(cyclic alkyl)可與「環烷基(cycloalkyl)」互換使用，且作為一個實例，可包括但不限於環丙基、環丁基、環戊基、環己基、環庚基、環辛基或類似者。

【0019】 在本發明中，「烷氧基」可指示-(O-烷基)為烷基醚基，其中烷基與上文所定義相同。舉例而言，「C_{1-6}烷氧基」可意謂含C_{1-6}烷基，

即-(O-C_{1-6}烷基)之烷氧基，且作為一個實例，可包括但不限於甲氧基、乙氧基、正丙氧基、異丙氧基、正丁氧基、異丁氧基、二級丁氧基、三級丁氧基或類似者。

【0020】 在本發明中，「鹵基」可為F、Cl、Br或I。

【0021】 如本文所用，「鹵烷基」可意謂具有一或多個如本文所定義之經鹵素取代之碳原子的直鏈或分支鏈烷基(烴)。鹵烷基之實例可包括但不限於獨立地經一或多個鹵素(諸如F、Cl、Br或I)取代之甲基、乙基、丙基、異丙基、異丁基或正丁基。

【0022】 如本文所用，「羥烷基」可指示具有經羥基(OH)取代之碳原子的直鏈或分支鏈烷基(烴)。羥烷基之實例可包括但不限於獨立地經一或多個-OH取代之甲基、乙基、丙基、異丙基、異丁基或正丁基。

【0023】 如本文中所使用，「胺烷基」可意謂具有經胺基(NR'R")取代之碳原子的直鏈或分支鏈烷基(烴)。在此，R'及R"可各自獨立地選自由氫及C_{1-6}烷基組成之群，且所選R'及R"可各自獨立地經取代或未經取代。

【0024】 如本文中所使用，「氰烷基」可指示具有經氰基(CN)取代之碳原子的直鏈或分支鏈烷基(烴)。

【0025】 在本發明中，「雜環烷基」可意謂在環中含有選自N、O、P、P(=O)及S中之至少一者，且可為飽和或部分不飽和的。此處，當不飽和時，其可被稱為雜環烯。除非另有說明，否則雜環烷基可為單環或多環，諸如螺環、橋接環或稠環。另外，「3員至12員雜環烷基」可指示含有3至12個原子形成環之雜環烷基。作為一個實例，雜環烷基可包括但不限於吡咯啶、哌啶、咪唑啶、吡唑啶、丁內醯胺、戊內醯胺、咪唑啶酮、乙內醯脲、二氧雜戊環、鄰苯二甲醯亞胺、哌啶、嘧啶-2,4(1H,3H)-二酮、

1,4-二噁烷、嗎啉、硫代嗎啉、硫代嗎啉-S-氧化物、硫代嗎啉-S,S-氧化物、哌呯、哌喃、吡啶酮、3-吡咯啉、硫代哌喃、哌喃酮、四氫呋喃、四氫噻吩、奎寧環、葸烷、2-氮雜螺[3.3]庚烷、(1R,5S)-3-氮雜雙環[3.2.1]辛烷、(1s,4s)-2-氮雜雙環[2.2.2]辛烷，或(1R,4R)-2-氧雜-5-氮雜雙環[2.2.2]辛烷及其類似者。

【0026】在本發明中，「芳烴」可意謂芳族烴環。芳烴可為單環芳烴或多環芳烴。芳烴中之成環碳之數目可為5或更多且30或更少、5或更多且20或更少、或5或更多且15或更少。芳烴之實例可包括但不限於苯、萘、茀、蒽、菲、雙苯、三苯、四苯、五苯、六苯、聯伸三苯、芘、苯并丙二烯合茀、薁及其類似者。在本說明書中，藉由自「芳烴」移除一個氫原子而獲得的殘基稱為「芳基」。

【0027】在本發明中，「雜芳烴」可為含有O、N、P、Si及S中之至少一者作為異質元素之環。雜芳烴中之成環碳之數目可為2或更多且30或更少，或2或更多且20或更少。雜芳烴可為單環雜芳烴或多環雜芳烴。多環雜芳烴可具有例如雙環或三環結構。雜芳烴之實例可包括噻吩、嘌呤、吡咯、吡唑、咪唑、噻唑、噁唑、異噻唑、噁二唑、三唑、吡啶、二吡啶基、三呯、吖啶基、嗒呯、吡呯、喹啉、喹唑啉、喹噁啉、啡噁 呯、呔呯、嘧啶、吡啶并嘧啶、吡啶并吡呯、吡呯并吡呯、異喹啉、吲哚、咔唑、咪唑并嗒呯、咪唑吡啶、咪唑并嘧啶、吡唑并嘧啶、咪唑并吡呯或吡唑并吡啶、N-芳基咔唑、N-雜芳基咔唑、N-烷基咔唑、苯并噁唑、苯并咪唑、苯并噻唑、苯并咔唑、苯并噻吩、二苯并噻吩、噻吩并噻吩、苯并呋喃、啡啉、異噁唑、噁二唑、噻二唑、苯并噻唑、四唑、啡噻呯、二苯并噻咯、二苯并呋喃及其類似者，但不限於此。在本發明之一個實施例

中，雜芳烴亦可包括雙環雜環芳烴，其含有稠合至雜環烷基環的芳烴環或稠合至環烷基環的雜芳烴。在本說明書中，藉由自「雜芳烴」移除一個氫原子而獲得的殘基稱為「雜芳基」。

【0028】 在本發明中，「氫芳基」意謂「芳基」中存在之一或多個雙鍵經單鍵取代。

【0029】 在本發明中，「氫雜芳基」意謂「雜芳基」中存在之一或多個雙鍵經單鍵取代。

【0030】 在本發明中，術語「光學異構體(鏡像異構體)」意謂本發明之化合物或其鹽，其具有相同化學式或分子式但具有不同立體結構。此等鏡像異構體及其混合物中之各者亦包括在本發明之範疇內。除非另外規定，否則連接不對稱碳原子之直線實線鍵(-)可包括楔形實線鍵 ，或楔形虛線鍵 指示立體中心之絕對組態。

【0031】 在本發明中，術語「順式」係指一個環中的兩個取代基之結合方向相同的情況，且術語「反式」係指一個環中的兩個取代基之結合方向不同的情況。

【0032】 本發明之化學式1之化合物可以「醫藥學上可接受之鹽」形式存在。作為鹽，由醫藥學上可接受之游離酸形成之酸加成鹽係有用的。如本文中所使用，術語「醫藥學上可接受之鹽」意謂由化學式1表示之化合物的任何及所有有機或無機酸加成鹽，其中由該鹽引起的副作用在具有有效作用的濃度下(對患者而言相對無毒且無害)，不降低化合物的有益功效。

【0033】 藉由習知方法製備酸加成鹽，例如藉由將化合物溶解於過量水性酸溶液中且使用可與水混溶之有機溶劑(諸如甲醇、乙醇、丙酮或

乙腈)沈澱鹽。可加熱等莫耳量之化合物及水中的酸或醇，隨後可將混合物蒸發至乾，或可藉由抽吸過濾出沈澱鹽。

【0034】 此處，有機酸及無機酸可用作游離酸，其中無機酸可為鹽酸、磷酸、硫酸、硝酸或類似酸，且有機酸可為甲磺酸、對甲苯磺酸、乙酸、三氟乙酸、順丁烯二酸、琥珀酸、草酸、苯甲酸、酒石酸、反丁烯二酸、杏仁酸、丙酸、檸檬酸、乳酸、乙醇酸、葡萄糖酸、半乳糖醛酸、麩胺酸、戊二酸、葡糖醛酸、天冬胺酸、抗壞血酸、碳酸、香草酸、氫碘酸或其類似者。然而，本發明不限於此。

【0035】 另外，有可能使用鹼製備醫藥學上可接受之金屬鹽。例如藉由將化合物溶解於過量鹼金屬氫氧化物或鹼土金屬氫氧化物溶液中，過濾未溶解的化合物鹽且接著蒸發及脫水濾液，獲得鹼金屬鹽或鹼土金屬鹽。此處，製備鈉、鉀或鈣鹽作為金屬鹽為醫藥學上適合的，但本發明不限於此。此外，可藉由使鹼金屬或鹼土金屬鹽與適合銀鹽(例如硝酸銀)反應獲得對應銀鹽。

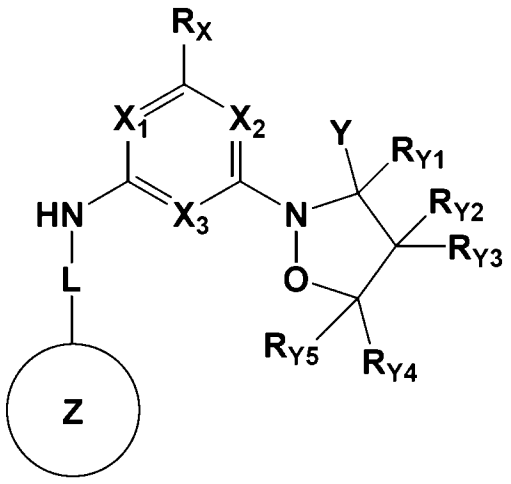
【0036】 除非另外指明，否則本發明之醫藥學上可接受之鹽包括可存在於化學式1之化合物中的酸性或鹼性基團之鹽。舉例而言，醫藥學上可接受之鹽可包括羥基之鈉鹽、鈣鹽及鉀鹽及其類似者，以及作為胺基之其他醫藥學上可接受之鹽，可包括氫溴酸鹽、硫酸鹽、硫酸氫鹽、磷酸鹽、磷酸氫鹽、磷酸二氫鹽、乙酸鹽、琥珀酸鹽、檸檬酸鹽、酒石酸鹽、乳酸鹽、杏仁酸鹽、甲磺酸鹽(methanesulfonate/mesylate)及對甲苯磺酸鹽(甲苯磺酸鹽)及類似鹽，且可藉由此項技術中已知之製備方法製備。

雜芳基衍生化合物之用途

【0037】 本發明提供一種由以下化學式1表示之化合物、其光學異

構體、或其醫藥學上可接受之鹽的用途：

[化學式1]



。

【0038】本發明之由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽展現出對各種激酶之抑制活性。

【0039】根據本發明之一個實施例，由化學式1表示之雜芳基衍生物展現出極佳的對EGFR及/或HER2激酶之抑制活性，且由此可有效地用於治療或預防EGFR及/或HER2相關疾病，尤其癌症。特定言之，化學式1之化合物能夠抑制EGFR及/或HER2野生型或突變型激酶，其藉由下文描述的實驗實例支援。EGFR突變可為C797S突變，諸如EGFR Del19/C797S (EGFR DC)或EGFR L858R/C797S (EGFR LC)，但不限於此。此外，EGFR突變可為EGFR L861Q、EGFR G719A、EGFR S768I、EGFR L718Q或EGFR G724S，但不限於此。此外，EGFR突變可為EGFR d746-750、EGFR d746-750/C797A、EGFR d746-750/C797S、EGFR d746-750/T790M/C797S、EGFR D761Y、EGFR G719C、EGFR G719D、EGFR G719S、EGFR L747S、EGFR L792F、EGFR L858R或EGFR L792F/L858R，但不限於此。

【0040】在本發明中，癌症包括由於EGFR及/或HER2激酶活性之

抑制而能夠展現出治療或預防功效之任何癌症，且可為實體癌症或血液癌。列舉一個非限制性實例，癌症可為選自由以下組成之群的一或多者：假黏液瘤、肝內膽道癌、肝母細胞瘤、肝癌、甲狀腺癌、大腸癌、睪丸癌、骨髓發育不良症候群、神經膠母細胞瘤、口腔癌、唇癌、蕈樣黴菌病、急性骨髓白血病、急性淋巴球性白血病、基細胞癌、卵巢上皮癌、卵巢生殖細胞癌、男性乳癌、腦癌、垂體腺瘤、多發性骨髓瘤、膽囊癌、膽道癌、大腸直腸癌、慢性骨髓性白血病、慢性淋巴球性白血病、視網膜母細胞瘤、脈絡膜黑色素瘤、壺腹癌、膀胱癌、腹膜癌、副甲狀腺癌、腎上腺癌、鼻竇癌、非小細胞肺癌、舌癌、星形細胞瘤、小細胞肺癌、小兒腦癌、小兒淋巴瘤、小兒白血病、小腸癌、腦膜瘤、食道癌、神經膠質瘤、腎盂癌、腎癌、心臟癌、十二指腸癌、惡性軟組織癌、惡性骨癌、惡性淋巴瘤、惡性間皮瘤、惡性黑色素瘤、眼癌、外陰癌、尿管癌、尿道癌、原發部位不明之癌症、胃淋巴瘤、胃癌、胃癌瘤、胃腸基質癌、威爾姆斯癌(Wilms cancer)、乳癌、肉瘤、陰莖癌、咽癌、妊娠期絨毛膜癌、子宮頸癌、子宮內膜癌、子宮肉瘤、前列腺癌、轉移性骨癌、轉移性腦癌、縱隔癌、直腸癌、直腸癌瘤、陰道癌、脊髓癌、聽神經瘤、胰臟癌、唾液腺癌、卡波西氏肉瘤(Kaposi's sarcoma)、佩吉特氏病(Paget's disease)、扁桃體癌、鱗狀細胞癌、肺腺癌、肺癌、肺鱗狀細胞癌、皮膚癌、肛門癌、橫紋肌肉瘤、喉癌、胸膜癌、血液癌及胸腺癌。癌症不僅包括原發癌且亦包括轉移癌。

【0041】 根據本發明之一個實施例，本發明提供一種用於治療或預防EGFR及/或HER2相關疾病的醫藥組合物，其含有由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽作為活性成分。特定言之，

EGFR及/或HER2相關疾病可為癌症。癌症類型與上文所描述相同。

【0042】 本發明之醫藥組合物可進一步包括一或多種活性成分，除由以上化學式1表示之化合物、其光學異構體或其醫藥學上可接受之鹽之外，其亦展現出相同或類似藥物功效。

【0043】 本發明之醫藥組合物可用於臨床投與，且可經製備而以各種經口及非經腸調配物投與。

【0044】 此外，根據本發明之一個實施例，提供一種用於治療或預防EGFR及/或HER2相關疾病之方法，其包含：向有需要之個體投與治療有效量之由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽。個體可為哺乳動物，包括人類。

【0045】 如本文所用，術語「治療有效量」係指對治療或預防EGFR相關及/或HER2相關疾病有效的由化學式1表示之化合物的量。特定言之，「治療有效量」指示具有適用於醫學治療之合理效益/風險比的足以治療疾病之量，且有效劑量水準可視包括以下因素而確定：個體類型及嚴重程度、年齡、性別、疾病類型、藥物活性、藥物敏感性、投與時間、投與途徑及排泄率、治療期、同時使用之藥物及醫學領域中熟知之其他因素。本發明之醫藥組合物可作為個別治療劑投與或可與其他治療劑組合投與，且可與市售治療劑依序或同時投與。另外，本發明之醫藥組合物可以單次劑量或多次劑量投與。重要的是考慮到所有上述因素，投與能夠獲得最大功效而無副作用的最小量，且該量可容易地由熟習此項技術者確定。本發明之醫藥組合物之劑量可由醫療專家根據各種因素(諸如患者之病狀、年齡、性別、併發症及類似因素)來確定。因為本發明之醫藥組合物之活性成分具有極佳安全性，所以其可以高於所確定劑量之劑量使用。

【0046】 此外，根據本發明之一個實施例，本發明提供一種由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽的用途，其用於製備用於治療或預防EGFR及/或HER2相關疾病之藥物。用於製備藥物之由化學式1表示之化合物可與可接受佐劑、稀釋劑、載劑及其類似者混合，且可藉由與其他活性劑製備為複合調配物而具有活性成分之協同效應。

【0047】 本發明之用途、組合物及治療方法中提及之物質同樣適用，但彼此不一致之情況除外。

[有利效應]

【0048】 本發明之雜芳基衍生化合物展現出對EGFR及/或HER2之極佳抑制活性，且因此可有效地用於治療或預防EGFR相關疾病及/或HER2相關疾病。

【實施方式】

【0049】

[最佳模式]

在下文中，將經由實例及實驗實例更詳細地描述本發明。然而，呈現以下實例及實驗實例僅為說明本發明，且本發明之內容不限於此。

【0050】

<分析及純化條件>

本發明之實例中所合成之化合物藉由以下HPLC條件純化或進行結構分析。

【0051】

1. HPLC條件

分析型HPLC條件(ACQUITY UPLC H級核心系統)

使用配備有由Waters公司製造之質量QDa偵測器的Waters UPLC系統(ACQUITY UPLC PDA偵測器)。所使用之管柱為Waters ACQUITY UPLC® BEH C18 (1.7 μm, 2.1×50 mm)，且在30℃下進行。

【0052】 含有0.1%甲酸之水用作流動相A，且含有0.1%甲酸之乙腈用作流動相B。

【0053】 梯度條件(歷經3分鐘10%至100% B且流動速率=0.6 ml/min)

【0054】

用於純化之Prep-LCMS (製備型-液相層析質譜法)

使用配備有由Waters公司製造之質量QDa偵測器的Waters自動純化HPLC系統(2767樣品管理器，2545二元梯度模組，2998光電二極體陣列偵測器)。所用管柱為Waters SunFire®Prep C18 OBDTM (5 μm, 19×50mm)，且在室溫下進行。

【0055】 含有0.035%三氟乙酸之水用作流動相A，且含有0.035%三氟乙酸之甲醇用作流動相B。

【0056】 梯度條件(歷經10分鐘15%至100% B且流動速率=25 ml/min)

【0057】

用於純化之Prep-150 LC系統(製備型-液相層析UV光譜測定法)

使用Waters Prep 150 LC系統(2545四級梯度模組，2998光電二極體陣列偵測器，溶離份收集器III)。所用管柱為Waters XTERRA®Prep RP18 OBD™ (10 μm, 30×300 mm)，且在室溫下進行。

【0058】 梯度條件(歷經120分鐘3%至100% B且流動速率=40 ml/min)

【0059】

用於純化之製備型HPLC系統(製備型-液相層析UV光譜測定法)

使用Teledyne ACCQPrep HP150。所用管柱為Waters XTERRA®Prep RP18 OBD™ (10 μm, 30×300 mm)，且在室溫下進行。

【0060】 梯度條件(歷經120分鐘10%至100% B且流動速率=42 ml/min)

【0061】

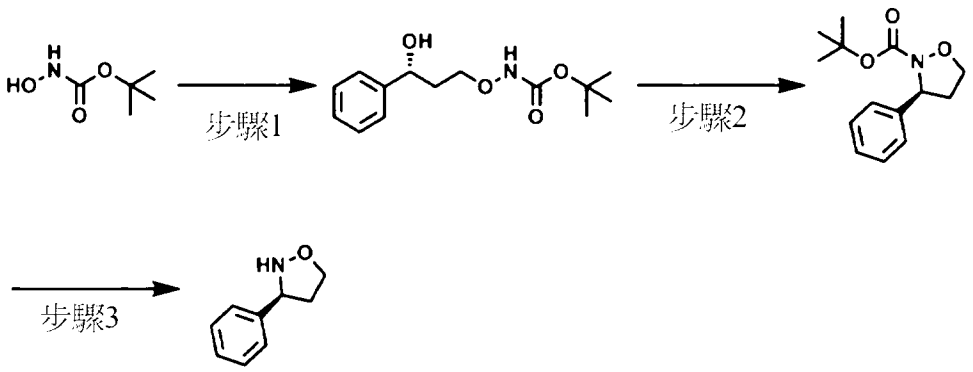
2. NMR分析

使用由Bruker製造之AVANCE III 400或AVANCE III 400 HD進行NMR分析，且資料以百萬分率(δ) (ppm)表示。

【0062】 市售試劑未經進一步純化即使用。在本發明中，室溫或常溫(一般溫度)係指約5℃至40℃之溫度，例如10℃至30℃，作為另一實例20℃至27℃，其不嚴格地受限於以上範圍。使用旋轉式汽化器進行減壓濃縮或溶劑蒸餾。

【0063】

<製備實例1>製備(S)-3-苯基異噁唑啶



步驟1：製備(R)-(3-羥基-3-苯基丙氧基)胺基甲酸三級丁酯

將羥胺基甲酸三級丁酯(7.8 g，58.6 mmol)溶解於二甲基甲醯胺(140 ml)中，接著在0℃下添加氫化鈉(2.58 g，64.5 mmol)且使反應混合物反應30 min。接下來，在0℃下緩慢逐滴添加溶解於二甲基甲醯胺(DMF；10 ml)中之(R)-3-氯-1-苯基丙-1-醇(5 g，29.3 mmol) 10 min，且在室溫下攪拌

72小時。藉由添加氯化銨水溶液至反應混合物中來終止反應，接著用乙酸乙酯及鹽水萃取，合併有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮。藉由使用中壓液相層析(乙酸乙酯/正己烷)純化獲得標題化合物(2.8 g，68%)。

【0064】 MS (m/z): 150.17 $[M+1]^+$, UPLC r.t. (min): 1.51

【0065】

步驟2：製備(S)-3-苯基異噁唑啶-2-甲酸三級丁酯

將在以上步驟1中獲得之(R)-(3-羥基-3-苯基丙氧基)胺基甲酸三級丁酯(2.55 g，9.54 mmol)及三乙胺(3.13 ml，22.44 mmol)溶解於二氯甲烷(250 ml)中，接著冷卻至0℃。接下來，逐滴添加甲磺醯氯(1 ml，13 mmol)且使反應混合物在0℃下反應2小時。用鹽水及二氯甲烷萃取反應混合物，且合併有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得標題化合物，其不經純化即用於下一反應中。

【0066】 MS (m/z): 194.13 $[M+1]^+$, UPLC r.t. (min): 1.69

【0067】

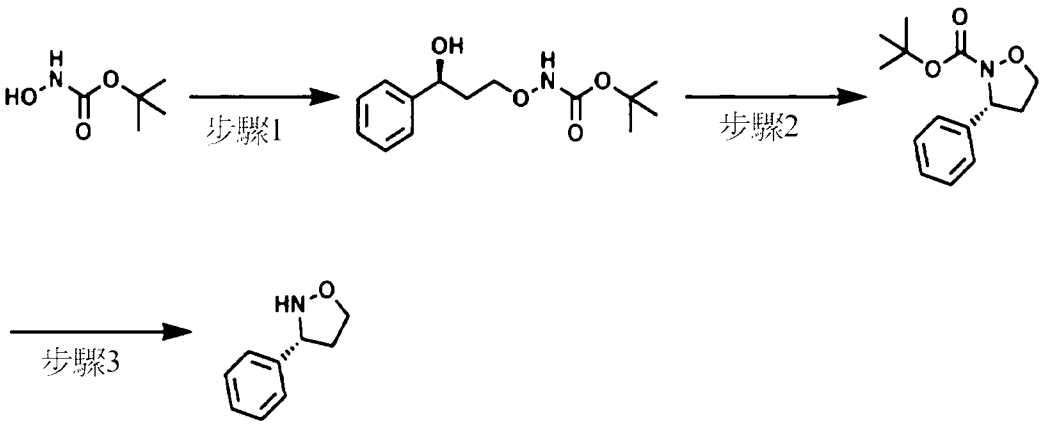
步驟3：製備(S)-3-苯基異噁唑啶

將在步驟2中獲得之(S)-3-苯基異噁唑啶-2-甲酸三級丁酯(2.3 g)溶解於二氯甲烷(90 ml)中，接著添加三氟乙酸(14 ml)且在室溫下使反應混合物反應1小時。用碳酸氫鈉水溶液中和反應混合物，且隨後合併有機層。有機層經硫酸鈉乾燥，接著在減壓下濃縮。藉由使用中壓液相層析(四氫呋喃/正己烷)純化獲得標題化合物(1.3 g，94%)。

【0068】 MS (m/z): 150.08 $[M+1]^+$, UPLC r.t. (min): 0.72

【0069】

<製備實例2>製備(R)-3-苯基異噁唑啶

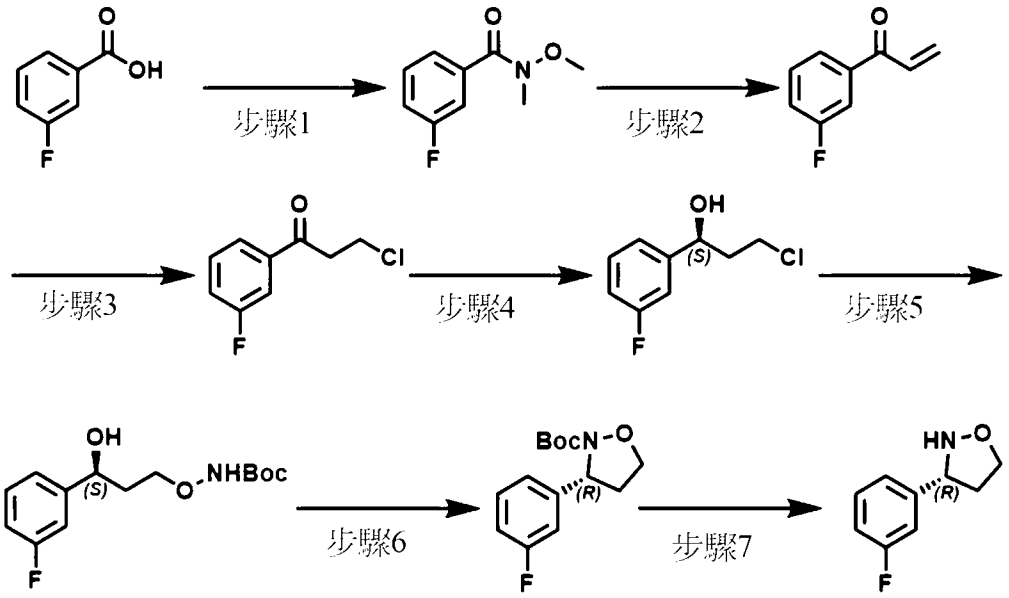


以與製備實例1類似之方式製備製備實例2之化合物，且用於下表1中所示的實例化合物之合成。

【0070】 MS (m/z): 150.08 $[M+1]^+$, UPLC r.t. (min): 0.72

【0071】

<製備實例3>製備(R)-3-(3-氟苯基)異噁唑啶



步驟1：製備3-氟-N-甲氧基-N-甲基苯甲醯胺

將3-氟苯甲酸(90 g，642.35 mmol，1 eq.)溶解於吡啶(150 mL)中，且向其中添加N-甲氧基甲胺(75.19 g，770.81 mmol，1.2 eq，HCl)。隨後，在15℃下添加1-乙基-3-(3-二甲胺基丙基)碳化二亞胺(EDCI；147.77

g，770.81 mmol，1.2 eq.)。在50℃下攪拌反應混合物30 min。作為TLC分析(石油醚(PE):乙酸乙酯(EA)=3:1)之結果，所有起始物質消失，且偵測到具有低極性之新斑點。藉由在減壓下濃縮移除吡啶溶劑，且使用二氯甲烷(DCM；500 mL)、鹽酸(500 mL，2N)及鹽水(200 mL)萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈黃色油狀物的標題化合物(110 g，600.50 mmol，產率93.49%)。

【0072】 ^{1}H NMR (400 MHz, 氯仿-d) δ 7.47-7.40 (m, 1H), 7.39-7.38 (m, 2H), 7.14-7.13 (m, 1H), 3.54 (s, 3H), 3.45 (s, 3H).

【0073】

步驟2：製備1-(3-氟苯基)丙-2-烯-1-酮

將在以上步驟1中獲得之3-氟-N-甲氧基-N-甲基-苯甲醯胺(110 g，600.50 mmol，1 eq.)溶解於四氫呋喃(THF；1 L)中，接著在0℃逐滴添加溴化(乙烯基)鎂(1M，630.53 mL，1.05 eq.)。接下來，在0℃下攪拌反應混合物30 min。作為TLC分析(石油醚(PE):乙酸乙酯(EA)=4:1)之結果，所有起始物質消失，且偵測到具有低極性之新斑點。藉由添加鹽酸(4N，500 mL)終止反應，且使用甲基三級丁基醚(MTBE；2000 mL)及鹽水(500 mL)萃取有機層。有機層經硫酸鈉乾燥，接著在減壓下濃縮。藉由層析(石油醚/乙酸乙酯=30/1)純化經濃縮之化合物，獲得呈黃色油狀物的標題化合物(80 g，532.80 mmol，88.73%產率)。

【0074】 ^{1}H NMR (400 MHz, 氯仿-d) δ 7.65 (m, 1H), 7.58-7.52 (m, 1H), 7.39 (m, 1H), 7.24-7.17 (m, 1H), 7.04 (dd, J = 17.2, 10.4 Hz, 1H), 6.39 (dd, J = 17.2, 1.6 Hz, 1H), 5.90 (dd, J = 10.4, 1.6 Hz, 1H).

【0075】

步驟3：製備3-氯-1-(3-氟苯基)丙-1-酮

將在以上步驟2中獲得之1-(3-氟苯基)丙-2-烯-1-酮(71 g，472.86 mmol，1.0 eq.)溶解於二氯甲烷(DCM；71 mL)中，且在0℃下添加HCl/二噁烷(4 M，295.54 mL，2.5 eq.)。接下來，在15℃下攪拌反應混合物1.5小時。作為TLC分析(石油醚(PE):乙酸乙酯(EA)=10:1)之結果，所有起始物質消失，且偵測到標題化合物。在減壓下濃縮反應混合物，且添加二氯甲烷(DCM；450 mL)及水(200 mL×5)以萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈黃色固體狀之標題化合物(73 g，391.19 mmol，產率82.73%)。

【0076】 ^{1}H NMR (400MHz, 氯仿-d) δ 7.78-7.72 (m, 1H), 7.69-7.60 (m, 1H), 7.53-7.44 (m, 1H), 7.37-7.24 (m, 1H), 3.93 (t, *J* =6.8 Hz, 2H), 3.46 (t, *J* =6.8 Hz, 2H).

【0077】

步驟4：製備(S)-3-氯-1-(3-氟苯基)丙-1-醇

將(3aR)-1-甲基-3,3-二苯基-3a,4,5,6-四氫吡咯并[1,2-c][1,3,2]噁氮硼雜環戊醇(1 M，32.15 mL，0.1 eq.)溶解於四氫呋喃(THF；1.2 L)中，接著在氮氣氛圍下在0℃下逐滴添加硼烷四氫呋喃(BH_3·THF；1 M，186.48 mL，0.6 eq.)。在0℃下攪拌反應混合物30 min。隨後，在0℃下將稀釋於四氫呋喃中之步驟3中所獲得之3-氯-1-(3-氟苯基)丙-1-酮(60 g，309.02 mmol，1 eq.)逐滴添加至反應混合物中。在0℃下攪拌反應混合物30 min。作為TLC分析(石油醚(PE):乙酸乙酯(EA)=5:1)之結果，所有起始物質消失，且偵測到標題化合物之斑點。藉由在0℃下添加甲醇(100 mL)終止反應，且隨後在減壓下蒸餾掉溶劑。使用二氯甲烷(DCM；100 mL×3)

及氯化銨(NH_4Cl)溶液(300 mL)自經濃縮之化合物萃取有機層。有機層經硫酸鈉乾燥，接著在減壓下濃縮。使用矽膠層析(石油醚(PE):乙酸乙酯(EA)=50:1至5:1)純化經濃縮之化合物，得到呈無色油狀之標題化合物(140 g，664.2 mmol，71.65%產率，89.49%純度，65.5% e.e)。

【0078】 ^1H NMR (400 MHz, 氯仿-d) δ 7.33 (m, 1H), 7.16-7.07 (m, 2H), 7.02-6.96 (m, 1H), 4.96 (m, 1H), 3.75 (m, 1H), 3.57 (m, 1H), 2.26-2.15(m, 2H).

【0079】

步驟5：製備(S)-(3-(3-氟苯基)-3-羥丙氧基)胺基甲酸三級丁酯

將羥胺基甲酸三級丁酯(50.4 g，378.52 mmol，1.05 eq.)溶解於二甲基甲醯胺(DMF；500 mL)中，接著在0℃下在氮氣氛圍下添加氫化鈉(NaH；15.86 g，396.55 mmol，60%純度，1.1 eq.)。在10℃下攪拌反應混合物1小時，且在0℃下逐滴添加稀釋於二甲基甲醯胺(DMF；180 mL)中之步驟4中所獲得的(S)-3-氯-1-(3-氟苯基)丙-1-醇(68 g，360.5 mmol，1 eq.)且在10℃下攪拌16小時。作為TLC分析(石油醚(PE):乙酸乙酯(EA)=2:1)之結果，所有起始物質消失，且偵測到標題化合物。在藉由添加氯化銨水溶液(3 L)終止反應之後，使用乙酸乙酯(2000 mL)及鹽水(2000 mL)萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈淡黃色固體狀之標題化合物(176 g，616.87 mmol，85.56%產率)。

【0080】 ^1H NMR (400 MHz, 氯仿-d) δ 7.67-7.64 (m, 1H), 7.23-7.17 (m, 1H), 7.08-7.03 (m, 2H), 6.88-6.81 (m, 1H), 4.99-4.84 (m, 1H), 4.02-3.97 (m, 1H), 3.96-3.89 (m, 1H), 1.95-1.89 (m, 1H), 1.88-1.78 (m, 1H), 1.42-1.39 (m, 9H).

【0081】

步驟6：製備(R)-3-(3-氟苯基)異噁唑啶-2-甲酸三級丁酯

將以上步驟5中獲得之(S)-(3-(3-氟苯基)-3-羥丙氧基)胺基甲酸三級丁酯(88 g，308.44 mmol，1 eq.)及三乙胺(93.63 g，925.31 mmol，128.79 mL，3 eq.)溶解於二氯甲烷(DCM；1 L)中，且接著在0℃下緩慢添加甲磺酸酐(80.59 g，462.65 mmol，1.5 eq.)。在20℃下攪拌反應混合物12小時。作為TLC分析(石油醚(PE):乙酸乙酯(EA)=3:1)之結果，所有起始物質消失，且偵測到新斑點。在藉由添加水(2000 mL)終止反應之後，使用二氯甲烷(DCM；200 mL×3)萃取有機層。有機層經硫酸鈉乾燥，接著在減壓下濃縮。藉由層析(石油醚(PE):乙酸乙酯(EA)=50:1至5:1)純化經濃縮之化合物以萃取88 g具有82.5% e.e值之標題化合物。標題化合物經由SFC(管柱：DAICEL CHIRALPAK AD (250 mm×50 mm, 10 μm)；移動相：[Neu-MeOH]；B%：15%至15%，3.4 min；380 min)純化，獲得呈白色固體狀之標題化合物(51 g，189.66 mmol，30.74%產率，99.4%純度)。

【0082】 在如下SFC條件下分析上述步驟6中所獲得之(R)-3-(3-氟苯基)異噁唑啶-2-甲酸三級丁酯之光學異構體的純度。

儀器：CAS-WH-ANA-SFC-C(SHIMADZU LC-30ADsf)

管柱：Amycoat 50 × 4.6 mm I.D., 3 μm

移動相：針對CO_2，相A且針對MeOH(0.05 % DEA)，相B；

梯度溶離：MeOH(0.05 % DEA)/CO_2，5%至40%

流動速率：3 mL/min；偵測器：PDA；

管柱溫度：35℃；背壓：100巴

【0083】 當在步驟6中獲得之(R)-3-(3-氟苯基)異噁唑啶-2-甲酸三級

丁酯之光學異構體的純度較低時，藉由在如下SFC條件下進行純化獲得呈黃色液體狀之所需光學異構體。

管柱：DAICEL CHIRALPAK AD-H(250 mm×30 mm, 5 μm)；

移動相：[0.1% NH_3H_2O MeOH]; B%: 15%-15%, 3.8 min; 600 min

【0084】

步驟7：製備(R)-3-(3-氟苯基)異噁唑啶

將在以上步驟6中獲得之(R)-3-(3-氟苯基)異噁唑啶-2-甲酸三級丁酯(50 g，185.94 mmol，1 eq.)溶解於乙酸乙酯(EA；200 mL)中，且接著在0℃下添加HCl/EtOAc (4 M，300 mL，6.45 eq.)。接下來，在10℃下攪拌反應混合物1小時。作為LCMS分析之結果，所有起始物質消失且在減壓下濃縮反應混合物以獲得固體，從而得到呈白色固體狀之標題化合物(32 g，150.26 mmol，80.81%產率，95.62%純度，100 % e.e. HCl)。

【0085】 MS: m/z 168.2 $[M+H]^+$

【0086】 ^1H NMR (400 MHz, DMSO-d_6) δ 7.53-7.43 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.30-7.23 (m, 1H), 5.01 (t, J = 8.0 Hz, 1H), 4.47 (m, 1H), 4.27 (m, 1H), 2.87 (m, 1H), 2.62-2.52 (m, 1H).

【0087】 以下條件用於純化或分析以上步驟7中之化合物的光學異構體。

儀器：CAS-WH-ANA-SFC-C(SHIMADZU LC-30ADsf)

管柱：Chiralpak AY-3 50 × 4.6 mm I.D., 3 μm；

移動相：針對CO_2，相A且針對IPA(0.05 % DEA)，相B；

梯度溶離： B in A，5%至40%；

流動速率：3 mL/min；偵測器：PDA；

管柱溫度：35℃；背壓：100巴

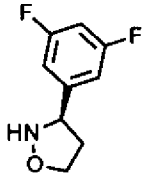
【0088】

<製備實例4至44>

以下製備實例4至44之化合物以類似於以上製備實例1至3之方式製備，且採用製備實例1至44之化合物以製備本發明之實例化合物。

【0089】

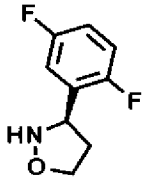
<製備實例4>製備(R)-3-(3,5-二氟苯基)異噁唑啶



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36-7.27 (m, 3H), 5.04-4.98 (t, *J* = 7.6 Hz, 1H), 4.46-4.36 (m, 1H), 4.25-4.19 (dd, *J* = 7.6, 15.2 Hz, 1H), 2.90-2.78 (m, 1H), 2.56-2.51 (m, 1H).

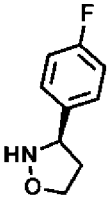
【0090】

<製備實例5>製備(R)-3-(2,5-二氟苯基)異噁唑啶



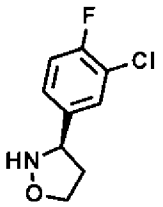
【0091】

<製備實例6>製備(R)-3-(4-氟苯基)異噁唑啶



【0092】

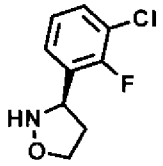
<製備實例7>製備(R)-3-(3-氯-4-氟苯基)異噁唑啶



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82-7.89 (dd, J = 2, 7.2, 1H), 7.56-7.51 (s, J = 15.6, 2H), 5.00-4.96 (m, 1H), 4.46-4.40 (m, 1H), 4.24-4.20 (m, 1H), 2.85-2.82 (m, 1H), 2.54-2.52 (m, 1H).

【0093】

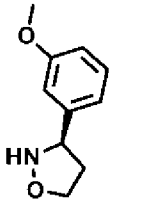
<製備實例8>製備(R)-3-(3-氯-2-氟苯基)異噁唑啶



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49-7.42 (m, 2H), 7.20-7.16 (m, 1H), 6.56 (s, 1H), 4.66-4.65 (m, 1H), 3.96-3.91 (m, 1H), 3.67-3.65 (m, 1H), 2.66-2.61 (m, 1H), 2.08-2.01 (m, 1H).

【0094】

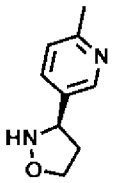
<製備實例9>製備(R)-3-(3-甲氧苯基)異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 7.25-7.20 (m, 2H), 7.11-7.09 (m, 1H), 6.88-6.86 (m, 1H), 4.80-4.76 (m, 1H), 4.46-4.44 (m, 1H), 4.17-4.15 (m, 1H), 3.76 (s, 3H), 2.69-2.66 (m, 2H).

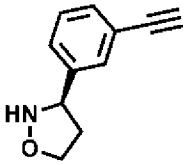
【0095】

<製備實例10>製備(R)-3-(6-甲基吡啶-3-基)異噁唑啶



【0096】

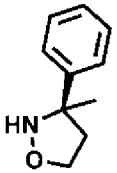
<製備實例11>製備(R)-3-(3-乙炔基苯基)異噁唑啶



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.43-7.37 (m, 1H), 7.36-7.29 (m, 2H), 6.41 (s, 1H), 4.38 (s, 1H), 4.15 (s, 1H), 3.90 (m, 1H), 3.71 (s, 1H), 2.65-2.53 (m, 1H), 2.11-2.00 (m, 1H).

【0097】

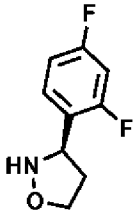
<製備實例12>製備(R)-3-甲基-3-苯基異噁唑啶



^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 7.56-7.46 (m, 2H), 7.44-7.36 (m, 2H), 7.34-7.26 (m, 1H), 3.74-3.62 (m, 1H), 3.46-3.28 (m, 1H), 2.72-2.54 (m, 2H), 1.64 (s, 3H).

【0098】

<製備實例13>製備(R)-3-(2,4-二氟苯基)異噁唑啶

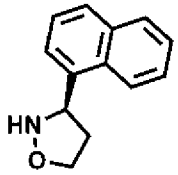


^{1}H NMR (400 MHz, 氯仿-d) δ 7.52-7.47(m, 1H), 6.87-6.75 (m, 2H), 5.30 (s, 1H), 4.71-4.68 (m, 1H), 4.09-4.04 (m, 1H), 3.91-3.85 (m, 1H),

2.73-2.64 (3, 1H), 2.24-2.20 (m, 1H).

【0099】

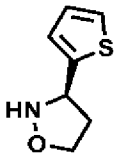
<製備實例14>製備(R)-3-(萘-1-基)異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 8.13 (br s, 1H), 7.89-7.88 (m, 1H), 7.87-7.78 (m, 2H), 7.55-7.48 (m, 3H), 5.54 (br s, 1H), 5.23-5.20 (m, 1H, *J* = 6.4 Hz), 4.15-4.03 (m, 2H), 2.90-2.81 (m, 1H), 2.44-2.41 (m, 1H).

【0100】

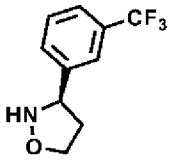
<製備實例15>製備(R)-3-(噻吩-2-基)異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 7.23 (d, *J* = 5.0 Hz, 1H), 7.04-6.94 (m, 2H), 4.97-4.58 (m, 2H), 4.11-3.96 (m, 2H), 2.75-2.58 (m, 1H), 2.44-2.33 (m, 1H).

【0101】

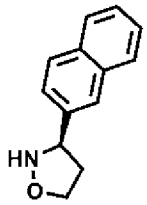
<製備實例16>製備(R)-3-(3-(三氟甲基)苯基)異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 7.65 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 5.64-5.19 (m, 1H), 4.58 (t, *J* = 7.2 Hz, 1H), 4.11 (td, *J* = 8.2, 5.2 Hz, 1H), 3.94 (s, 1H), 2.80-2.67 (m, 1H), 2.36-2.23 (m, 1H).

【0102】

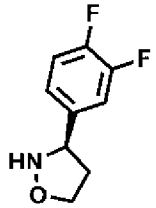
<製備實例17>製備(R)-3-(萘-2-基)異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 7.91-7.81 (m, 4H), 7.56-7.46 (m, 3H), 5.80-5.00 (m, 1H), 4.68 (t, *J* = 7.2 Hz, 1H), 4.19-3.99 (m, 2H), 2.80-2.72 (m, 1H), 2.45-2.37 (m, 1H).

【0103】

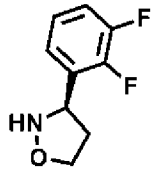
<製備實例18>製備(R)-3-(3,4-二氟苯基)異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 7.24-7.19 (m, 1H), 7.12-7.06 (m, 2H), 5.24 (s, 1H), 4.46 (dd, J1 = 8.4 Hz, J2 = 5.6 Hz, 1H), 4.05 (dt, J1 = 8.0 Hz, J2 = 5.2 Hz, 1H), 3.91-3.85 (m, 1H), 2.70-2.61 (m, 1H), 2.25-2.17 (m, 1H).

【0104】

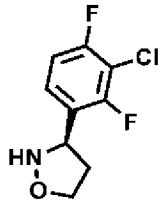
<製備實例19>製備(R)-3-(2,3-二氟苯基)異噁唑啶



^{1}H NMR (氯仿-d, 400 MHz) δ 7.29-7.27 (m, 1H), 7.06-7.02 (m, 2H), 5.44 (br s, 1H), 4.75 (dd, J1 = 4.4 Hz, J2 = 8.4 Hz, 1H), 4.08 (dt, J1 = 5.2 Hz, J2 = 8.0 Hz, 1H), 3.86 (q, J=8.0 Hz, 1H), 2.76-2.66 (m, 1H), 2.27-2.19 (m, 1H).

【0105】

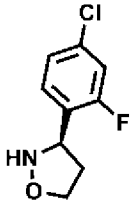
<製備實例20>製備(R)-3-(3-氯-2,4-二氟苯基)異噁唑啶



^{1}H NMR (DMSO-d6, 400 MHz) δ 7.51 (dt, *J* = 6.8, 8.4 Hz, 1H), 7.28 (dt, *J* = 2.0, 8.8 Hz, 1H), 6.60 (br s, 1H), 4.64 (br s, 1H), 3.94 (dt, *J* = 5.2, 8.0 Hz, 1H), 3.76-3.57 (m, 1H), 2.68-2.61 (m, 1H), 2.10-2.01 (m, 1H).

【0106】

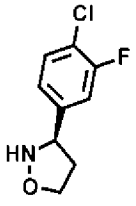
<製備實例21>製備(R)-3-(4-氯-2-氟苯基)異噁唑啶



^{1}H NMR (400 MHz,氧化氘) δ 7.48-7.38 (m, 1H), 7.34-7.22 (m, 2H), 5.29-5.20 (m, 1H), 4.58-4.50 (m, 1H), 4.36-4.27 (m, 1H), 2.96-2.84 (m, 1H), 2.79-2.66 (m, 1H).

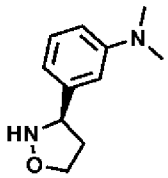
【0107】

<製備實例22>製備(R)-3-(4-氯-3-氟苯基)異噁唑啶



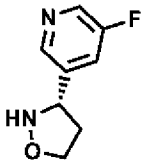
【0108】

<製備實例23>製備(R)-3-(異噁唑啶-3-基)-N, N-二甲基苯胺



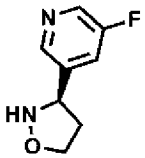
【0109】

<製備實例24>製備(S)-3-(5-氟吡啶-3-基)異噁唑啶



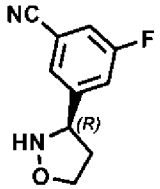
【0110】

<製備實例25>製備(R)-3-(5-氟吡啶-3-基)異噁唑啶



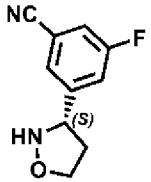
【0111】

<製備實例26>製備(R)-3-氟基-5-(異噁唑啶-3-基)苯甲腈



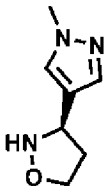
【0112】

<製備實例27>製備(S)-3-氟-5-(異噁唑啶-3-基)苯甲腈



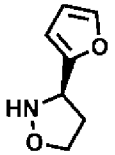
【0113】

<製備實例28>製備(R)-3-(1-甲基-1H-吡唑-4-基)異噁唑啶



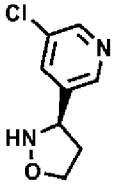
【0114】

<製備實例29>製備(R)-3-(呋喃-2-基)異噁唑啶



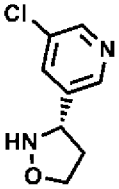
【0115】

<製備實例30>製備(R)-3-(5-氯吡啶-3-基)異噁唑啶



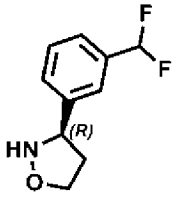
【0116】

<製備實例31>製備(S)-3-(5-氯吡啶-3-基)異噁唑啶



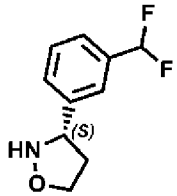
【0117】

<製備實例32>製備(R)-3-(3-二氟甲基)苯基)異噁唑啶



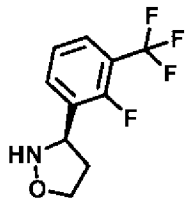
【0118】

<製備實例33>製備(S)-3-(3-(二氟甲基)苯基)異噁唑啶



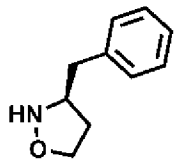
【0119】

<製備實例34>製備(R)-3-(2-氟-3-(三氟甲基)苯基)異噁唑啶



【0120】

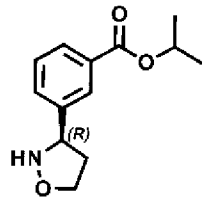
<製備實例35>製備(S)-3-苯甲基異噁唑啶



^{1}H NMR (400 MHz, 氯仿-d) δ 12.7-12.4 (m, 1H), 7.28-7.18 (m, 5H), 4.42-4.32 (m, 1H), 4.25-4.10 (m, 2H), 3.50 (dd, *J* = 4.8, 13.6 Hz, 1H), 3.03 (dd, *J* = 10.4, 13.2 Hz, 1H), 2.44-2.33 (m, 1H), 2.32-2.20 (m, 1H).

【0121】

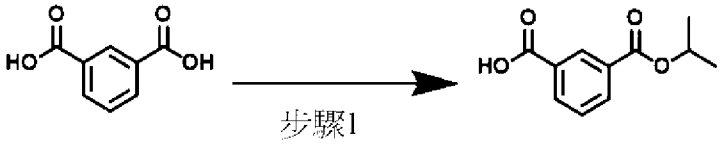
<製備實例36>製備(R)-3-(異噁唑啶-3-基)苯甲酸異丙酯



以與<製備實例3>類似之方式，使用下文<製備實例36-1>中製備之3-(異丙氧基羰基)苯甲酸作為中間物製備所需標題化合物。

【0122】

<製備實例36-1>製備3-(異丙氧基羰基)苯甲酸



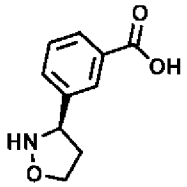
步驟1：製備3-(異丙氧基羰基)苯甲酸

將間苯二甲酸(40 g，1 eq.)溶解於異丙醇(150 mL)及四氫呋喃(THF；450 mL)中，且接著添加硫酸(濃H_2SO_4；38.5 mL，3 eq.)。在75

℃下攪拌反應混合物48小時。反應完成後，在減壓下使有機溶劑經濃縮，且使用乙酸乙酯(EA；500 mL)及水(200 mL)萃取有機層。有機層經硫酸鈉乾燥，接著在減壓下濃縮。藉由層析(二氯甲烷/甲醇=8/1)純化經濃縮之化合物，獲得呈透明油狀物的標題化合物(23.25 g，46.5%產率)。

【0123】

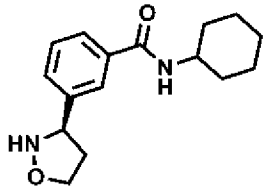
<製備實例37>製備(R)-3-(異噁唑啶-3-基)苯甲酸



藉由用鹼水溶液水解<製備實例36>中獲得之(R)-3-(異噁唑啶-3-基)苯甲酸異丙酯來製備所需標題化合物。

【0124】

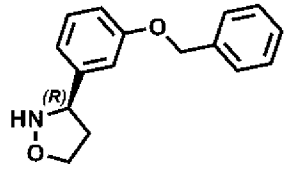
<製備實例38>製備(R)-N-環己基-3-(異噁唑啶-3-基)苯甲醯胺



藉由HATU之方法，採用在<製備實例37>中獲得之(R)-3-(異噁唑啶-3-基)苯甲酸，引入醯胺官能基來製備所需標題化合物。

【0125】

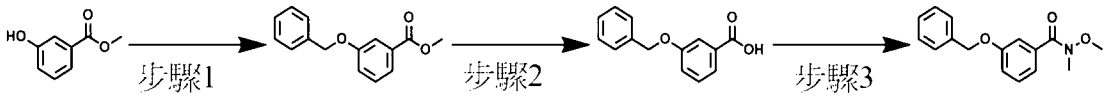
<製備實例39>製備(R)-3-(3-(苯甲氧基)苯基)異噁唑啶



以與<製備實例3>類似之方式，使用下文<製備實例39-1>中製備之3-(苯甲氧基)-N-甲氧基-N-甲基苯甲醯胺作為中間物製備所需標題化合物。

【0126】

<製備實例39-1>製備3-(苯甲氧基)-N-甲氧基-N-甲基苯甲醯胺



步驟1：製備3-(苯甲氧基)苯甲酸甲酯

將3-羥基苯甲酸甲酯(20 g，1.0 eq.)溶解於丙酮(260 mL)中，且接著添加(溴甲基)苯(18.76 ml 1.2 eq.)及碳酸鉀(54.5 g，3 eq.)。在60℃下攪拌反應混合物16小時。作為TLC分析(己烷:乙酸乙酯=3:2)之結果，所有起始物質消失，且偵測到標題化合物。在減壓下濃縮反應混合物，添加二氯甲烷(DCM；300 mL×2)及水(200 mL)以萃取有機層。有機層經硫酸鈉乾燥，且隨後在減壓下濃縮。使用己烷再結晶經濃縮之化合物，獲得呈白色固體狀之標題化合物(29.27 g，92%產率)。

【0127】

步驟2：製備3-(苯甲氧基)苯甲酸

將在步驟1中獲得之3-(苯甲氧基)苯甲酸甲酯(29 g，1.0 eq.)溶解於甲醇(MeOH；300 ml)中，且添加氫氧化鉀(KOH；6M，4.5 eq.)。接下來，在80℃下攪拌反應混合物3小時。作為TLC分析(己烷:乙酸乙酯=7:3)之結果，所有起始物質消失，且偵測到具有低極性之新斑點。在減壓下濃縮反應混合物，添加水(100 ml)且逐滴添加鹽酸(3N)以酸化反應溶液至pH 1。所得沈澱物在減壓下過濾且乾燥，得到呈白色固體狀之標題化合物(27 g，99%產率)。

【0128】

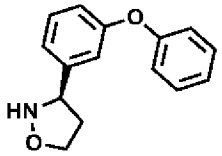
步驟3：製備3-(苯甲氧基)-N-甲氧基-N-甲基苯甲醯胺

將在步驟2中獲得之3-(苯甲氧基)苯甲酸(20 g，1.0 eq.)溶解於二氯甲

烷(DCM；700 ml)中，且緩慢添加1,1-羰基二咪唑(9.40 g，1.1 eq.)。在室溫下攪拌反應混合物2小時，接著添加N,O-二甲基羥胺鹽酸鹽(15.63 g，1.1 eq.)且在40℃下攪拌所得混合物18小時。進行UPLC/MS分析，及其結果為所有起始物質消失，且偵測到標題化合物。用鹽酸(1N，500 ml)及碳酸氫鈉飽和水溶液(500 ml)洗滌反應混合物，經硫酸鈉乾燥，且接著在減壓下濃縮，獲得呈淡黃色油狀之標題化合物(90 g，85%產率)。

【0129】

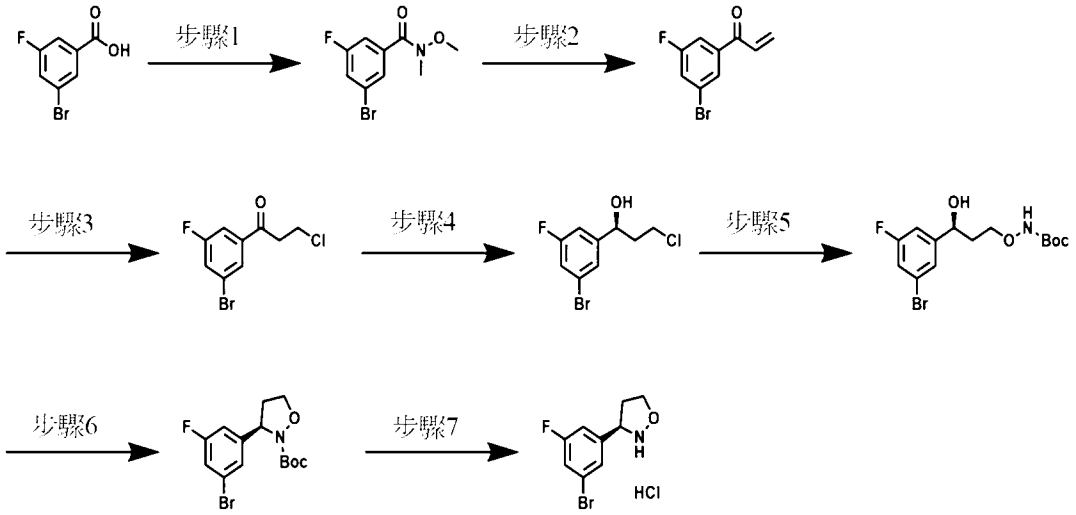
<製備實例40>製備(R)-3-(3-苯氧基苯基)異噁唑啶



以與<製備實例39>類似之方式製備所需標題化合物。

【0130】

<製備實例41>製備(R)-3-(3-溴-5-氟苯基)異噁唑啶鹽酸鹽



步驟1：製備3-溴-5-氟-N-甲氧基-N-甲基苯甲醯胺

將3-溴-5-氟苯甲酸(10 g，1 eq.)溶解於二氯甲烷(110 mL)中，且接著在室溫下依序添加N,O-二甲基羥胺鹽酸鹽(5.4 g，1.2 eq.)、三乙胺(TEA；5.7 mL，0.9 eq.)及1-乙基-3-(3-二甲胺基丙基)碳化二亞胺

(EDCI；11.5 g，1.2 eq.)。在室溫下攪拌反應混合物3小時。作為TLC分析(二氯甲烷)之結果，所有起始物質消失，且偵測到具有低極性之新斑點。使用乙酸乙酯(EA；300 mL)及碳酸氫鈉飽和水溶液(400 mL×2)萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈黃色油狀物之標題化合物(11.2 g，94.0%產率)。

【0131】

步驟2：製備1-(3-溴-5-氟苯基)丙-2-烯-1-酮

將步驟1中獲得的3-溴-5-氟-N-甲氧基-N-甲基苯甲醯胺(11.2 g，1 eq.)溶解於四氫呋喃(THF；220 mL)中，且接著在0℃下逐滴添加溴(乙烯基)鎂(0.7 M，93 mL，1.5 eq.)。接下來，在0℃下攪拌反應混合物1小時。作為TLC分析(己烷:二氯甲烷=1:1)之結果，所有起始物質消失，且偵測到具有低極性之新斑點。藉由添加鹽酸(1 N，50 mL)終止反應，且接著使用乙酸乙酯(EA；300 mL)及鹽酸(1 N，400 mL×2)萃取有機層。有機層經硫酸鈉乾燥，且隨後在減壓下濃縮。藉由層析(二氯甲烷/甲醇=1:1)純化經濃縮之化合物，獲得呈無色油狀物的標題化合物(7.9 g，76%產率)。

【0132】

步驟3：製備1-(3-溴-5-氟苯基)-3-氯丙-1-酮

將步驟2中獲得之1-(3-溴-5-氟苯基)丙-2-烯-1-酮(7.9 g，1.0 eq.)溶解於二氯甲烷(DCM；13 mL)中，且隨後在0℃下添加HCl/二噁烷(4 M，13 mL，1.2 eq.)。隨後，在室溫下攪拌反應混合物12小時。作為TLC分析(己烷:二氯甲烷=1:1)之結果，所有起始物質消失，且偵測到標題化合物。在減壓下濃縮反應混合物，且添加乙酸乙酯(EA；300 mL)及碳酸氫鈉飽和水溶液(400 mL×2)以萃取有機層。有機層經硫酸鈉乾燥且在減壓下濃

縮，獲得呈黃色油狀物之標題化合物(8.9 g，97%產率)。

【0133】

步驟4：製備(S)-1-(3-溴-5-氟苯基)-3-氯丙-1-醇

將(3aR)-1-甲基-3,3-二苯基-3a,4,5,6-四氫吡咯并[1,2-c][1,3,2]噁氮硼雜環戊醇(1 M，6.7 mL，0.2 eq.)溶解於四氫呋喃(THF；84 mL)中，接著在氮氣氛圍下在0℃下逐滴添加硼烷二甲基硫醚($BH_3 \cdot Me_2S$；1 M，21.8 mL，1.3 eq.)。在0℃下攪拌反應混合物30 min，且隨後在0℃下逐滴添加稀釋於四氫呋喃中且在步驟3中所獲得之1-(3-溴-5-氟苯基)-3-氯丙-1-酮(8.9 g，1 eq.)。在0℃下攪拌反應混合物2小時。作為TLC分析(己烷:二氯甲烷=1:1)之結果，所有起始物質消失，且偵測到標題化合物之斑點。藉由在20℃下添加甲醇(20 mL)終止反應，且隨後在減壓下蒸餾掉溶劑。經濃縮之化合物用乙酸乙酯(EA；300 mL)及鹽酸(1N，400 mL×2)處理以萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈黃色油狀物的標題化合物(8.5 g，95%產率)。

【0134】

步驟5：製備(S)-(3-(3-溴-5-氟苯基)-3-羥丙氧基)胺基甲酸三級丁酯

將羥胺基甲酸三級丁酯(9.3 g，2.2 eq.)溶解於二甲基甲醯胺(DMF；80 mL)中，且接著在0℃下在氮氣氛圍下添加氫化鈉(NaH；3.1 g，60%純度，2.4 eq.)。在0℃下攪拌反應混合物30 min。在0℃下逐滴添加稀釋於二甲基甲醯胺(DMF；10 mL)中且在步驟4中所獲得之(S)-1-(3-溴-5-氟苯基)-3-氯丙-1-醇(8.5 g，1 eq.)，且在室溫下攪拌12小時。作為TLC分析(二氯甲烷:EA=9:1)之結果，所有起始物質消失，且偵測到標題化合物。藉由添加鹽水(50 mL)終止反應，且隨後使用乙酸乙酯(EA；300 mL)及碳

酸氫鈉飽和水溶液(400 mL×3)萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈黃色油狀物之標題化合物(9.2 g，79%產率)。

【0135】

步驟6：製備(R)-3-(3-溴-5-氟苯基)異噁唑啶-2-甲酸三級丁酯

將在步驟5中獲得之(S)-(3-(3-溴-5-氟苯基)-3-羥丙氧基)胺基甲酸三級丁酯(9.2 g，1 eq.)及三苯膦(Ph_3P；8.6 g，1.3 eq.)溶解於二氯甲烷(DCM；110 mL)中，且接著在0℃下緩慢添加稀釋於二氯甲烷(DCM；20 mL)中之偶氮二甲酸二異丙酯(DIAD；6.6 g，1.3 eq.)。在0℃下攪拌反應混合物2小時。作為TLC分析(二氯甲烷(DCM):乙酸乙酯(EA)=9:1)之結果，所有起始物質消失，且偵測到新斑點。減壓濃縮反應混合物，且藉由層析(二氯甲烷:乙酸乙酯=10:0至9:1)純化經濃縮化合物，獲得呈黃色油狀物之標題化合物(7.7 g，88%產率)。

【0136】

步驟7：製備(R)-3-(3-溴-5-氟苯基)異噁唑啶鹽酸鹽

將在步驟6中獲得之(R)-3-(3-溴-5-氟苯基)異噁唑啶-2-甲酸三級丁酯(7.7 g，1 eq.)溶解於二氯甲烷(DCM；40 mL)中，且接著在室溫下添加HCl/二噁烷(4 M，28 mL，5 eq.)。隨後，在室溫下攪拌反應混合物2小時。作為LCMS分析之結果，所有起始物質消失，添加乙醚(200 mL)以獲得固體，且過濾所得沈澱並乾燥，獲得呈白色固體狀之標題化合物(5.3 g，84%產率)。

【0137】 以下條件用於純化或分析以上步驟7中之化合物的光學異構體。

儀器：CAS-WH-ANA-SFC-C(SHIMADZU LC-30ADsf)

管柱：Chiralpak AY-3 50 × 4.6mm I.D.，3 μm；

移動相：針對CO_2，相A且針對IPA(0.05 % DEA)，相B；

梯度溶離： B in A，5%至40%；

流動速率：3 mL/min；偵測器：PDA；

管柱溫度：35℃；背壓：100巴

【0138】 在如下SFC條件下純化步驟7中獲得之(R)-3-(3-溴-5-氟苯基)異噁唑啶鹽酸鹽(5.3 g)以獲得所需光學異構體(100%純度，100% e.e.)。

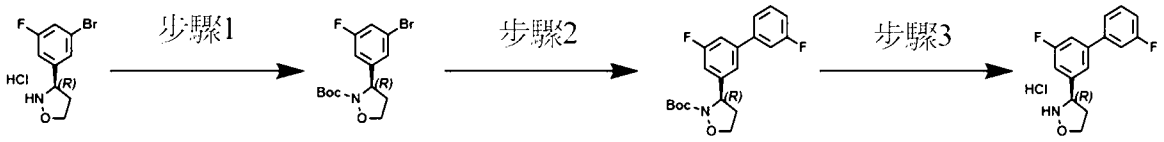
管柱：DAICEL CHIRALPAK AD-H(250 mm×30 mm, 5 μm)；

移動相：[0.1% NH_3H_2O MeOH]; B%: 15%-15%, 3.8 min; 600 min

【0139】 ^{1}H NMR (400 MHz, DMSO-d6) δ 7.62-7.58 (m, 2H), 7.43 (dt, *J* = 9.8, 2.0 Hz, 1H), 4.93 (t, *J* = 7.4 Hz, 1H), 4.36 (td, *J* = 8.1, 4.4 Hz, 1H), 4.12 (q, *J* = 7.8 Hz, 1H), 2.81 (dtd, *J* = 12.4, 7.9, 4.4 Hz, 1H), 2.49-2.41 (m, 1H).

【0140】

<製備實例42>製備(R)-3-(3',5-二氟-[1,1'-聯苯]-3-基)異噁唑啶鹽酸鹽



步驟1：製備(R)-3-(3-溴-5-氟苯基)異噁唑啶-2-甲酸三級丁酯

將在<製備實例41>中獲得之(R)-3-(3-溴-5-氟苯基)異噁唑啶鹽酸鹽(1 g，1 eq.)及三乙胺(TEA；1.5 mL，3 eq.)溶解於四氫呋喃(7 mL)中，且接著在0℃下緩慢添加二-二碳酸三級丁酯(Boc_2O；1.0 mL，1.2 eq.)。接下來，將反應混合物在50℃下攪拌2小時。作為TLC分析(DCM)之結果，所有起始物質消失，且偵測到具有不同極性之新斑點。使用乙酸乙酯(EA；

70 mL)及碳酸氫鈉飽和水溶液(100 mL×2)萃取有機層。有機層經硫酸鈉乾燥，且在減壓下濃縮，獲得呈淡黃色油狀之標題化合物(1.1 g，95%產率)。

【0141】

步驟2：製備(R)-3-(3',5-二氟-[1,1'-聯苯]-3-基)異噁唑啶-2-甲酸三級丁酯

在室溫下在氮氣氛圍下，將在步驟1中獲得之(R)-3-(3-溴-5-氟苯基)異噁唑啶-2-甲酸三級丁酯(350 mg，1 eq.)、(3-氟苯基)硼酸(170 mg，1.2 eq.)及K_2CO_3 (280 mg，2 eq.)溶解於1,4-二噁烷(5 mL)中。接著，在80℃下將肆(三苯膦)鈀(0) (110 mg，0.1 eq.)添加至反應混合物中且攪拌3小時。作為TLC分析(DCM)之結果，所有起始物質消失，且偵測到具有不同極性之新斑點。使用乙酸乙酯(EA；70 mL)及碳酸氫鈉飽和水溶液(100 mL×2)萃取有機層。有機層經硫酸鈉乾燥，且隨後在減壓下濃縮。藉由層析(己烷/二氯甲烷=5:5至0:10)純化經濃縮之化合物，獲得呈無色油狀物的標題化合物(320 mg，88%產率)。

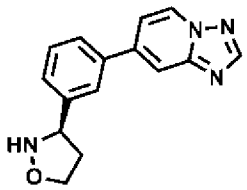
【0142】

步驟3：製備(R)-3-(3',5-二氟-[1,1'-聯苯]-3-基)異噁唑啶鹽酸鹽

將在步驟2中獲得之(R)-3-(3',5-二氟-[1,1'-聯苯]-3-基)異噁唑啶-2-甲酸三級丁酯(320 mg，1 eq.)溶解於二氯甲烷(DCM；40 mL)中，且接著在室溫下添加HCl/二噁烷(4 M，1 mL，5 eq.)。隨後，在室溫下攪拌反應混合物2小時。作為LCMS分析之結果，所有起始物質消失，添加乙醚(10 mL)以獲得固體，且過濾所得沈澱並乾燥，獲得呈白色固體狀之標題化合物(240mg，91%產率)。

【0143】

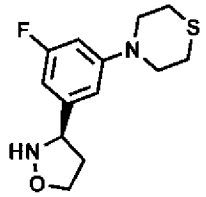
<製備實例43>製備(R)-3-(3-([1,2,4]三唑并[1,5-a]吡啶-7-基)苯基)異噁唑啶



以與<製備實例42>類似之方式製備所需標題化合物。

【0144】

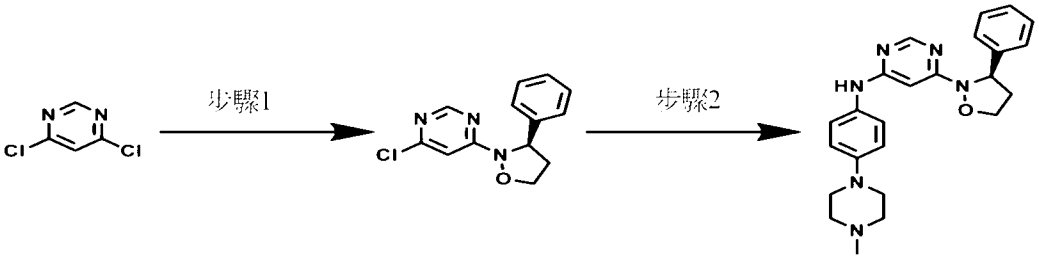
<製備實例44>製備(R)-3-(3-氟-5-硫代嗎啉基苯基)異噁唑啶



化合物藉由諸如S_NAr或類似方法，使用<製備實例41>之化合物製備。

【0145】

<實例1>製備(R)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺



步驟1：製備(R)-2-(6-氯嘧啶-4-基)-3-苯基異噁唑啶

將4,6-二氯嘧啶(600 mg，1 eq.)及(R)-3-苯基異噁唑啶(631 mg，1.05 eq.)溶解於二甲亞碸(DMSO，7 ml)中，且接著添加N,N-二異丙基乙胺(DIPEA；1.41 mL，2 eq.)。在60℃下攪拌反應溶液30 min。反應完成之後，使用乙酸乙酯及水萃取反應溶液。用鹽水洗滌合併之有機層，經無

水硫酸鈉乾燥，在減壓下濃縮，且藉由MPLC (乙酸乙酯/己烷)純化，獲得呈透明液體狀之標題化合物(810 mg，77%產率)。

【0146】

步驟2：製備(R)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺

將在步驟1中獲得的(R)-2-(6-氯嘧啶-4-基)-3-苯基異噁唑啶(139 mg，1 eq.)、4-(4-甲基哌啡-1-基)苯胺(152 mg，1.5 eq.)及碳酸鉀(220 mg，3 eq.)添加至且溶解於二級丁醇(1.8 ml)中，接著在氮氣下音波處理5 min以脫氣。向反應混合物中添加三(二苯亞甲基丙酮)二鈀(0) ($Pd_2(dba)_3$；47 mg，0.1 eq.)及Xphos (51 mg，0.2 eq.)且在100℃下攪拌1小時。反應完成之後，混合物經由矽藻土過濾且用二氯甲烷洗滌。濃縮所得濾液且藉由Prep-HPLC純化，獲得標題化合物(71 mg，32%)。

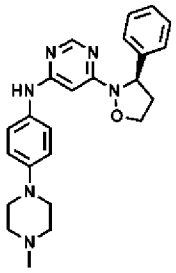
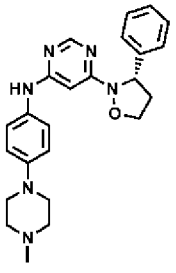
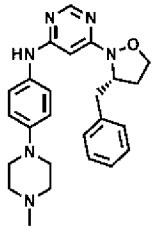
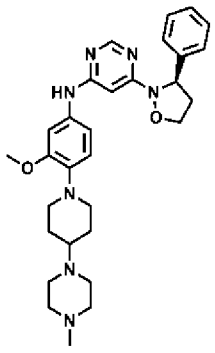
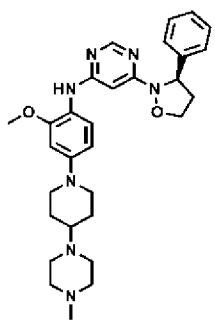
【0147】 ^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.23 (s, 1H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 6.7 Hz, 2H), 7.20-7.16 (m, 2H), 6.97-6.91 (m, 2H), 6.38 (s, 1H), 5.64 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.10 (td, *J* = 7.8, 4.5 Hz, 1H), 3.85 (q, *J* = 7.8 Hz, 1H), 3.23 (t, *J* = 5.1 Hz, 4H), 2.71 (dtd, *J* = 12.2, 7.9, 4.4 Hz, 1H), 2.64 (t, *J* = 5.0 Hz, 4H), 2.38 (s, 3H), 2.37-2.32 (m, 1H), 2.04 (s, 1H).

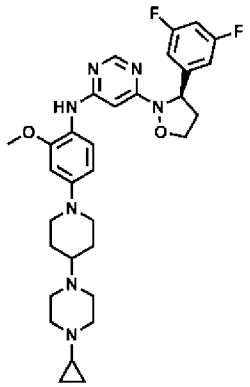
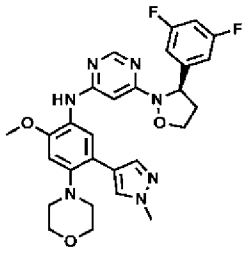
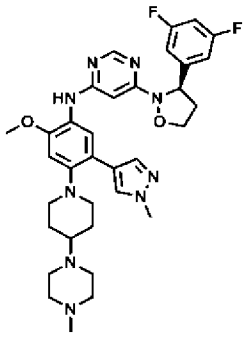
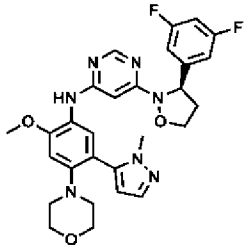
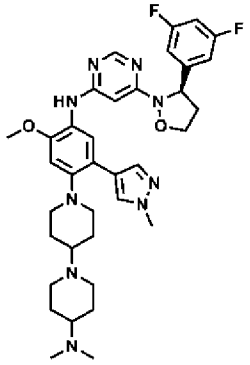
【0148】

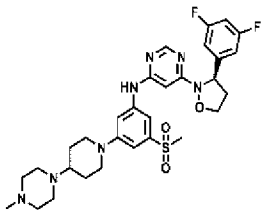
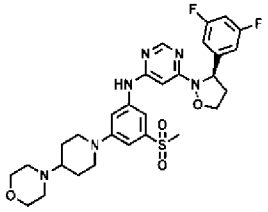
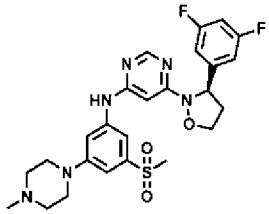
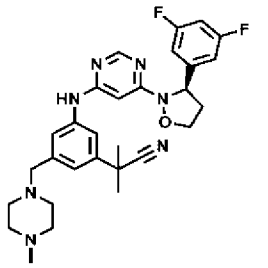
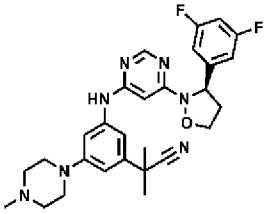
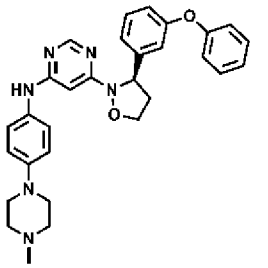
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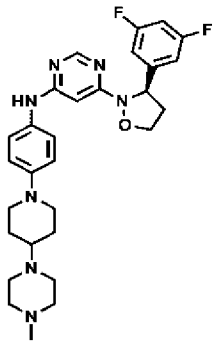
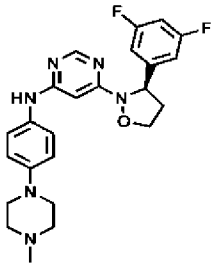
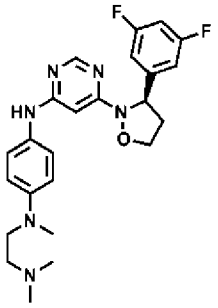
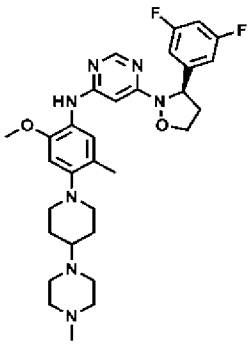
本發明之所有實例化合物(實例化合物編號1至237)係以與實例1類似之方式製備。各別實例化合物之化合物名稱、化學結構及NMR及LCMS分析結果概述及展示於下表1中。

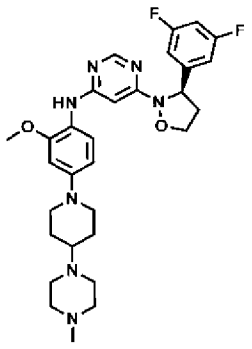
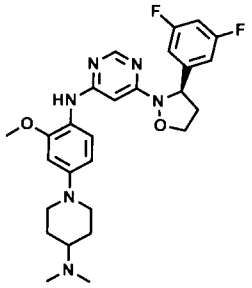
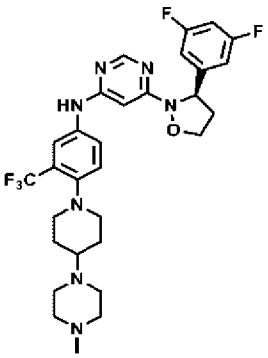
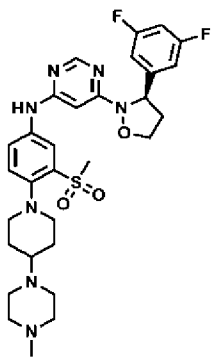
[表1]

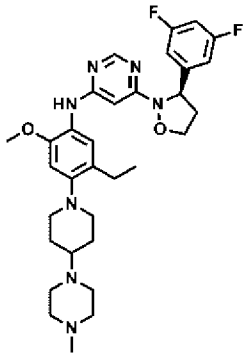
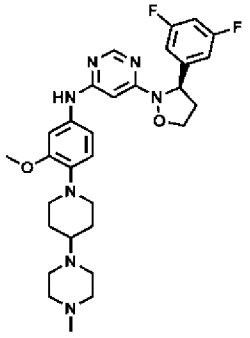
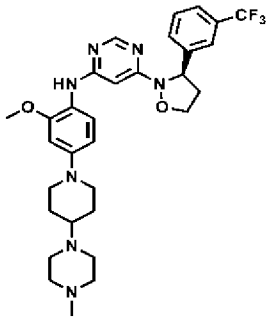
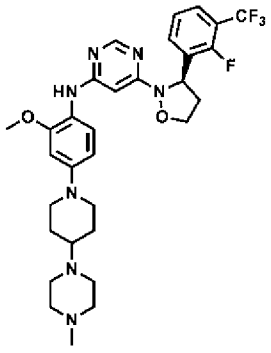
實例化合物	結構	化合物名稱	^{1}H NMR; MS[M+H]$^+$
1		(R)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.23 (s, 1H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 6.7 Hz, 2H), 7.20-7.16 (m, 2H), 6.97-6.91 (m, 2H), 6.38 (s, 1H), 5.64 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.10 (td, *J* = 7.8, 4.5 Hz, 1H), 3.85 (q, *J* = 7.8 Hz, 1H), 3.23 (t, *J* = 5.1 Hz, 4H), 2.71 (dtd, *J* = 12.2, 7.9, 4.4 Hz, 1H), 2.64 (t, *J* = 5.0 Hz, 4H), 2.38 (s, 3H), 2.37-2.32 (m, 1H), 2.04 (s, 1H); 417.4[M+H]$^+$
2		(S)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.23 (s, 1H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 6.7 Hz, 2H), 7.20-7.16 (m, 2H), 6.97-6.91 (m, 2H), 6.38 (s, 1H), 5.64 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.10 (td, *J* = 7.8, 4.5 Hz, 1H), 3.85 (q, *J* = 7.8 Hz, 1H), 3.23 (t, *J* = 5.1 Hz, 4H), 2.71 (dtd, *J* = 12.2, 7.9, 4.4 Hz, 1H), 2.64 (t, *J* = 5.0 Hz, 4H), 2.38 (s, 3H), 2.37-2.32 (m, 1H), 2.04 (s, 1H); 417.3[M+H]$^+$
3		(S)-6-(3-苯甲基噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	431.4[M+H]$^+$
4		(R)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30-8.26 (m, 1H), 7.46-7.41 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.26-7.22 (m, 1H), 6.96-6.90 (m, 2H), 6.85-6.80 (m, 2H), 6.47-6.43 (m, 1H), 5.66 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.11 (td, *J* = 7.8, 4.4 Hz, 1H), 3.89-3.82 (m, 4H), 3.54 (d, *J* = 11.2 Hz, 2H), 2.76-2.65 (m, 4H), 2.63-2.33 (m, 9H), 2.30 (s, 3H), 1.92 (d, *J* = 12.3 Hz, 2H), 1.85-1.75 (m, 2H); 530.4[M+H]$^+$
5		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.26-7.23 (m, 1H), 6.70 (s, 1H), 6.57-6.51 (m, 2H), 6.41 (s, 1H), 5.68 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.11 (td, *J* = 7.8, 4.3 Hz, 1H), 3.92-3.87 (m, 1H), 3.84 (s, 3H), 3.71 (d, *J* = 12.0 Hz, 2H), 2.78-2.64 (m, 7H), 2.58-2.47 (m, 3H),

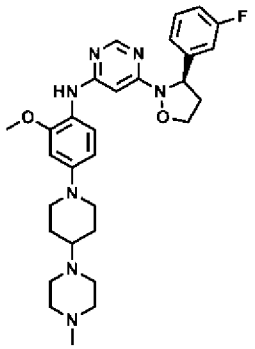
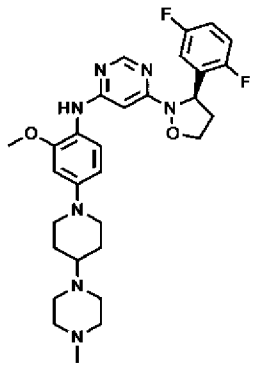
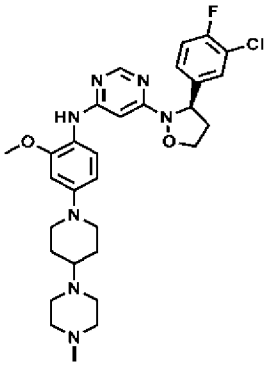
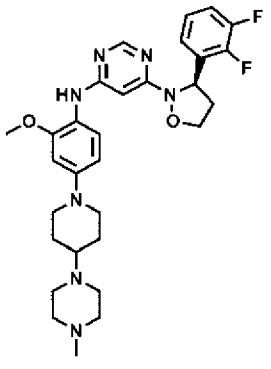
			2.44-2.35 (m, 3H), 2.32 (s, 3H), 1.96 (d, *J* = 12.0 Hz, 2H), 1.74-1.67 (m, 2H); 530.4[M+H]$^+$
6		(R)-N-(4-(4-(4-環丙基哌啡咁-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	592.3[M+H]$^+$
7		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-嗎啉基苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 甲醇-d4) δ 8.47 (s, 1H), 8.39 (s, 1H), 8.22 (s, 1H), 7.47 (s, 1H), 7.06-6.99 (m, 3H), 6.94 (s, 1H), 5.56 (s, 1H), 4.44 (dt, *J* = 7.6, 3.8 Hz, 1H), 4.21 (s, 1H), 4.14 (s, 3H), 3.94 (s, 3H), 3.88-3.82 (m, 4H), 3.56-3.51 (m, 1H), 3.11-3.00 (m, 5H), 2.54-2.44 (m, 1H); 550.4[M+H]$^+$
8		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌啡咁-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 甲醇-d4) δ 8.50 (s, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 7.45 (s, 1H), 7.01 (dt, *J* =6.8, 2.1 Hz, 2H), 6.96-6.88 (m, 1H), 6.00 (s, 1H), 5.52 (d, *J* = 10.1 Hz, 1H), 4.42 (d, *J* = 4.4 Hz, 1H), 4.17 (s, 4H), 4.06 (s, 1H), 3.91 (s, 5H), 3.81-3.47 (m, 7H), 3.37 (s, 2H), 3.07 (s, 4H), 2.84 (t, *J* = 11.8 Hz, 2H), 2.48 (d, *J* = 5.9 Hz, 1H), 2.32 (d, *J* = 11.7 Hz, 2H), 2.13 (d, *J* = 9.4 Hz, 2H); 646.5[M+H]$^+$
9		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-5-基)-4-嗎啉基苯基)嘧啶-4-胺	550.4[M+H]$^+$
10		(R)-1'-(4-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-甲氧基-2-(1-甲基-1H-吡唑-4-基)苯基)-N,N-二甲基-[1,4'-聯哌啶]-4-胺	674.6[M+H]$^+$

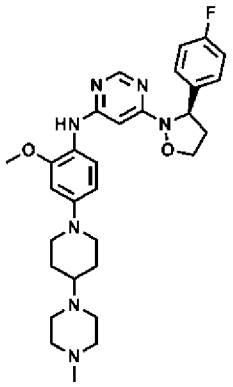
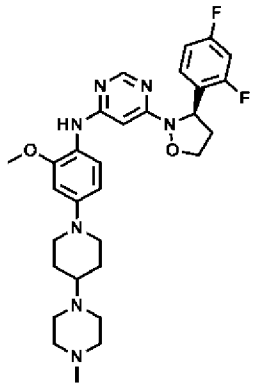
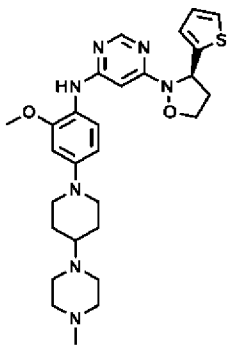
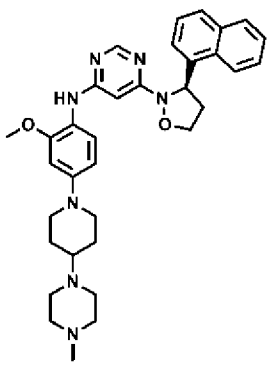
11		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-(4-(4-甲基哌啡-1-基)哌啶-1-基)-5-(甲磺醯基)苯基)嘧啶-4-胺	614.3 $[M+H]^+$
12		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-(甲磺醯基)-5-(4-嗎啉基哌啶-1-基)苯基)嘧啶-4-胺	601.3 $[M+H]^+$
13		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-(4-甲基哌啡-1-基)-5-(甲磺醯基)苯基)嘧啶-4-胺	531.3 $[M+H]^+$
14		(R)-2-(3-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-((4-甲基哌啡-1-基)甲基)苯基)-2-甲基丙腈	534.3 $[M+H]^+$
15		(R)-2-(3-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-(4-甲基哌啡-1-基)苯基)-2-甲基丙腈	520.3 $[M+H]^+$
16		(R)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(3-(3-苯氧基苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.25 (d, J = 1.1 Hz, 1H), 7.12 (dt, J = 4.1, 2.0 Hz, 2H), 7.11-7.05 (m, 3H), 7.01 (dt, J = 5.3, 1.8 Hz, 3H), 7.00-6.98 (m, 1H), 6.96-6.92 (m, 3H), 6.90-6.85 (m, 2H), 5.63 (dt, J = 8.6, 5.6 Hz, 2H), 4.22 (td, J = 7.8, 4.2 Hz, 1H), 3.93-3.79 (m, 2H), 3.24-3.20 (m, 4H), 2.61 (t, J = 5.0 Hz, 4H), 2.48-2.41 (m, 1H), 2.37 (s, 3H), 2.33 (dd, J = 7.8, 4.4 Hz, 1H); 509.4$[M+H]^+$

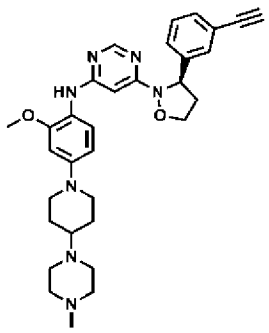
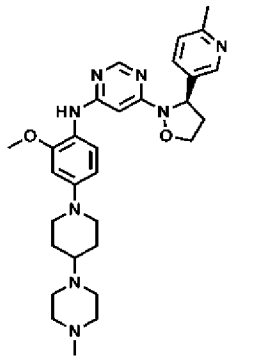
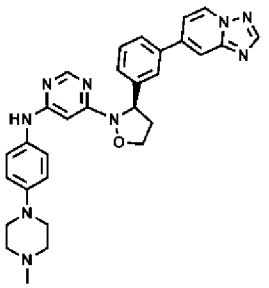
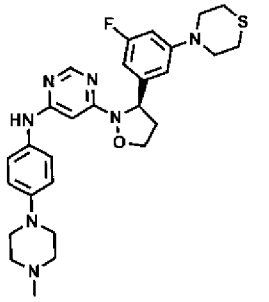
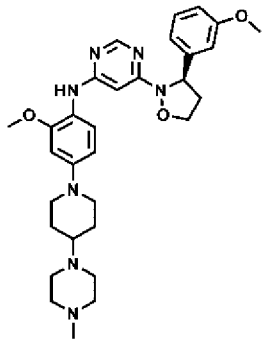
17		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.20 (s, 1H), 8.17 (d, *J* = 1.0 Hz, 1H), 7.20-7.14 (m, 2H), 6.99-6.92 (m, 4H), 6.69 (tt, *J* = 8.8, 2.4 Hz, 1H), 6.38 (d, *J* = 1.0 Hz, 1H), 5.61 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.83 (q, *J* = 8.0 Hz, 1H), 3.77-3.69 (m, 2H), 2.82 (s, 7H), 2.77-2.69 (m, 4H), 2.54 (tt, *J* = 11.5, 3.6 Hz, 1H), 2.45 (s, 3H), 2.36-2.27 (m, 1H), 2.01-1.94 (m, 2H), 1.76-1.64 (m, 2H); 536.4[M+H]$^+$
18		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.18 (s, 1H), 8.11 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.99-6.92 (m, 4H), 6.69 (tt, *J* = 8.9, 2.4 Hz, 1H), 6.39 (d, *J* = 1.0 Hz, 1H), 5.62 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.83 (q, *J* = 7.9 Hz, 1H), 3.31-3.23 (m, 4H), 2.75 (t, *J* = 5.2 Hz, 5H), 2.43 (s, 3H), 2.33 (ddd, *J* = 12.4, 8.3, 4.7 Hz, 1H); 453.3[M+H]$^+$
19		(R)-N^1-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-N^4-(2-(二甲胺基)乙基)-N^4-甲基-1,4-二胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.20 (s, 1H), 7.52 (s, 1H), 7.17-7.10 (m, 2H), 7.00-6.92 (m, 2H), 6.75-6.66 (m, 3H), 6.33-6.31 (m, 1H), 5.63 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.08 (td, *J* = 7.9, 4.2 Hz, 1H), 3.83 (q, *J* = 7.9 Hz, 1H), 3.57-3.52 (m, 2H), 2.98 (s, 3H), 2.78-2.62 (m, 3H), 2.40 (s, 6H), 2.36-2.27 (m, 1H); 455.3[M+H]$^+$
20		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-甲基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.51 (s, 1H), 8.26 (d, *J* = 1.0 Hz, 1H), 7.42 (s, 1H), 7.01-6.95 (m, 2H), 6.69 (tt, *J* = 8.9, 2.4 Hz, 1H), 6.62 (s, 1H), 6.40-6.37 (m, 1H), 5.64 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.11 (td, *J* = 7.9, 4.2 Hz, 1H), 3.90-3.84 (m, 1H), 3.83 (s, 3H), 3.19 (d, *J* = 11.3 Hz, 2H), 2.86 (s, 7H), 2.78-2.62 (m, 4H), 2.61-2.52 (m, 1H), 2.45 (s, 3H), 2.39-2.28 (m, 1H), 2.24 (s, 3H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.74 (qd, *J* = 11.9, 3.8 Hz, 2H); 580.4[M+H]$^+$

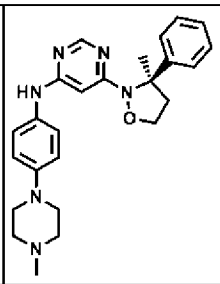
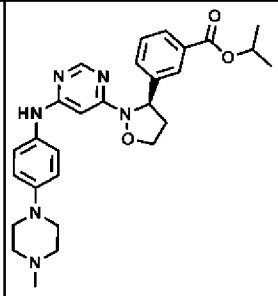
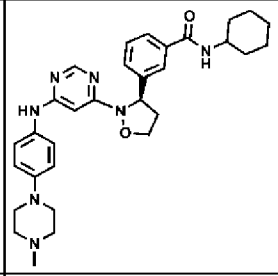
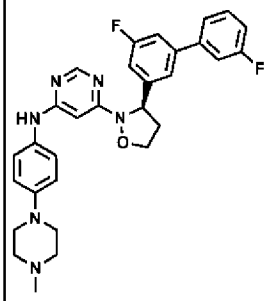
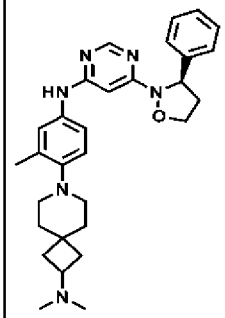
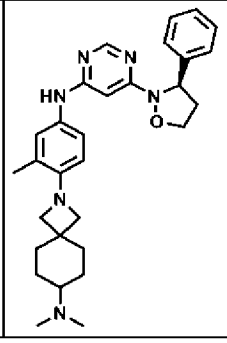
21		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.01-6.95 (m, 2H), 6.93 (s, 1H), 6.73-6.65 (m, 1H), 6.57-6.52 (m, 2H), 6.39 (s, 1H), 5.65 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.13-4.06 (m, 1H), 3.90-3.81 (m, 4H), 3.74-3.68 (m, 2H), 2.78-2.67 (m, 8H), 2.66-2.57 (m, 3H), 2.49-2.40 (m, 1H), 2.38-2.28 (m, 4H), 2.01-1.93 (m, 2H), 1.77-1.65 (m, 2H); 566.5[M+H]$^+$
22		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(二甲胺基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.52 (d, *J* = 9.3 Hz, 1H), 7.02-6.96 (m, 2H), 6.81 (s, 1H), 6.72-6.66 (m, 1H), 6.58-6.53 (m, 2H), 6.41 (s, 1H), 5.65 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.14-4.07 (m, 1H), 3.90-3.82 (m, 4H), 3.74-3.68 (m, 2H), 2.79-2.68 (m, 3H), 2.48-2.28 (m, 8H), 2.02-1.96 (m, 2H), 1.77-1.65 (m, 2H); 511.5[M+H]$^+$
23		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-甲基哌啡-1-基)哌啶-1-基)-3-(三氟甲基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.57 (s, 1H), 8.25-8.22 (m, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.00-6.92 (m, 2H), 6.70 (tt, *J* = 8.8, 2.3 Hz, 1H), 6.50-6.48 (m, 1H), 5.62 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.19-4.13 (m, 1H), 3.88 (q, *J* = 8.0 Hz, 1H), 3.48 (s, 3H), 3.16-3.08 (m, 2H), 2.88 (s, 5H), 2.81-2.71 (m, 3H), 2.66-2.55 (m, 1H), 2.48 (s, 3H), 2.40-2.30 (m, 1H), 1.96-1.88 (m, 2H), 1.75 (tt, *J* = 11.9, 6.0 Hz, 2H); 604.4[M+H]$^+$
24		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-甲基哌啡-1-基)哌啶-1-基)-3-(甲磺醯基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30-8.26 (m, 1H), 8.02 (s, 1H), 7.98 (d, *J* = 2.7 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.00-6.94 (m, 2H), 6.70 (tt, *J* = 8.8, 2.4 Hz, 1H), 6.53-6.51 (m, 1H), 5.63 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.17 (td, *J* = 7.9, 4.2 Hz, 1H), 3.93 (q, *J* = 8.0 Hz, 1H), 3.35-3.28 (m, 4H), 2.82-2.70 (m, 9H), 2.53-2.44 (m, 1H), 2.41 (s, 3H), 2.40-2.32 (m, 1H), 2.05 (s, 3H), 2.00 (d, *J* = 12.7 Hz, 2H), 1.75 (q, *J* = 11.9 Hz, 2H); 614.4[M+H]$^+$

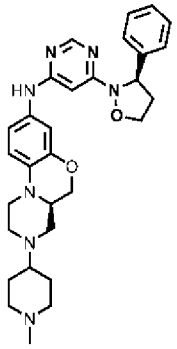
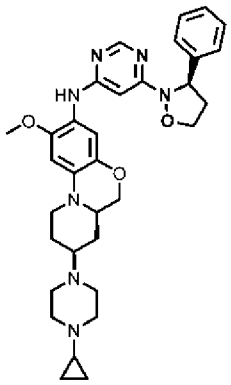
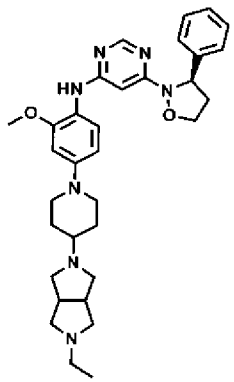
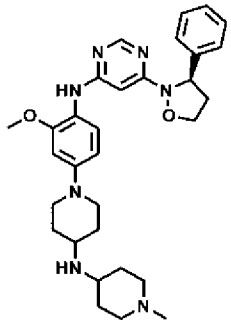
25		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (s, 1H), 7.49 (s, 1H), 7.12 (s, 1H), 7.02-6.95 (m, 2H), 6.72-6.67 (m, 2H), 6.49 (s, 1H), 5.65 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.11 (td, *J* = 7.9, 4.1 Hz, 1H), 3.90-3.79 (m, 7H), 3.13 (d, *J* = 11.4 Hz, 2H), 2.79-2.62 (m, 12H), 2.51-2.44 (m, 1H), 2.39 (s, 3H), 2.36-2.30 (m, 1H), 2.17 (s, 1H), 1.96 (d, *J* = 12.2 Hz, 2H), 1.73 (qd, *J* = 11.5, 3.2 Hz, 2H); 594.4[M+H]$^+$
26		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1)-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.25-8.20 (m, 1H), 7.65-7.60 (m, 1H), 7.00-6.89 (m, 3H), 6.86-6.78 (m, 2H), 6.69 (tt, *J* = 8.7, 2.4 Hz, 1H), 6.46 (d, *J* = 0.9 Hz, 1H), 5.62 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.87 (s, 3H), 3.86-3.82 (m, 1H), 3.55 (d, *J* = 11.4 Hz, 2H), 2.82-2.65 (m, 8H), 2.64-2.47 (m, 4H), 2.38 (s, 3H), 2.37-2.31 (m, 1H), 1.94 (d, *J* = 12.2 Hz, 2H), 1.82 (tt, *J* = 12.0, 6.0 Hz, 2H); 566.4[M+H]$^+$
27		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(3-(三氟甲基)苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.71 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.48 (dt, *J* = 15.8, 7.7 Hz, 3H), 6.95 (s, 1H), 6.59-6.49 (m, 2H), 6.41 (s, 1H), 5.74 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.11 (q, *J* = 8.0 Hz, 1H), 3.93-3.80 (m, 4H), 3.71 (d, *J* = 12.5 Hz, 2H), 2.81-2.67 (m, 7H), 2.62 (s, 4H), 2.48-2.31 (m, 5H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.74-1.66 (m, 2H); 598.44[M+H]$^+$
28		(R)-6-(3-(2-氟-3-(三氟甲基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 9.5 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 6.55 (d, *J* = 7.5 Hz, 2H), 6.42 (s, 1H), 5.93 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.12-4.05 (m, 1H), 3.92-3.81 (m, 4H), 3.72 (d, *J* = 12.2 Hz, 2H), 2.84 (d, *J* = 8.7 Hz, 1H), 2.80-2.51 (m, 10H), 2.50-2.41 (m, 1H), 2.36 (s, 3H), 2.32-2.25 (m, 1H), 1.97 (d, *J* = 12.6 Hz, 2H), 1.71 (q, *J* = 11.4, 10.9 Hz, 2H); 616.35[M+H]$^+$

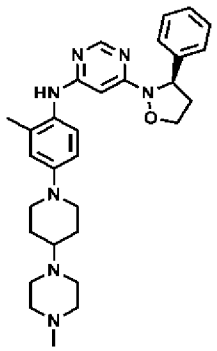
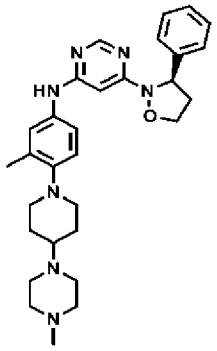
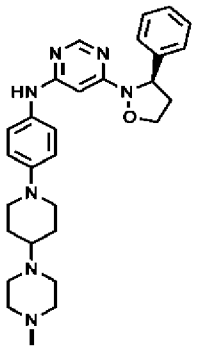
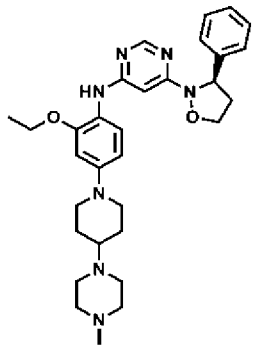
29		(R)-6-(3-(3-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.34-7.28 (m, 1H), 7.19 (dd, *J* = 13.5, 8.8 Hz, 2H), 6.94 (td, *J* = 8.4, 1.9 Hz, 1H), 6.80 (s, 1H), 6.57-6.51 (m, 2H), 6.40 (d, *J* = 1.1 Hz, 1H), 5.67 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.10 (td, *J* = 7.8, 4.2 Hz, 1H), 3.91-3.82 (m, 4H), 3.71 (d, *J* = 12.2 Hz, 2H), 2.78-2.53 (m, 11H), 2.41-2.38 (m, 1H), 2.37-2.34 (m, 1H), 2.32 (d, *J* = 1.3 Hz, 3H), 1.96 (d, *J* = 12.7 Hz, 2H), 1.70 (dt, *J* = 11.5, 7.9 Hz, 2H); 548.39[M+H]$^+$
30		(R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.30 (d, *J* = 3.3 Hz, 1H), 7.00 (td, *J* = 9.0, 4.0 Hz, 1H), 6.94-6.86 (m, 1H), 6.83 (s, 1H), 6.58-6.52 (m, 2H), 6.43 (s, 1H), 5.87 (dd, *J* = 8.7, 4.4 Hz, 1H), 4.10-4.05 (m, 1H), 3.85 (s, 4H), 3.71 (d, *J* = 12.3 Hz, 2H), 2.80-2.66 (m, 7H), 2.56 (s, 4H), 2.42 (t, *J* = 11.6 Hz, 1H), 2.33 (s, 3H), 2.31-2.23 (m, 1H), 2.05-2.01 (m, 2H), 1.70 (dd, *J* = 20.7, 11.3 Hz, 2H); 566.36 [M+H]$^+$
31		(R)-6-(3-(3-氯-4-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.33-7.28 (m, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 6.87 (s, 1H), 6.54 (d, *J* = 7.8 Hz, 2H), 6.39 (s, 1H), 5.63 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.15-4.06 (m, 1H), 3.86 (d, *J* = 11.0 Hz, 4H), 3.71 (d, *J* = 12.0 Hz, 2H), 2.78-2.68 (m, 5H), 2.58 (s, 6H), 2.46-2.40 (m, 1H), 2.37-2.26 (m, 4H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.70 (dd, *J* = 22.3, 10.3 Hz, 2H); 582.36[M+H]$^+$
32		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.31 (t, *J* = 7.0 Hz, 1H), 7.12-7.01 (m, 3H), 6.54 (d, *J* = 7.3 Hz, 2H), 6.39 (d, *J* = 1.0 Hz, 1H), 5.90 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.09 (dt, *J* = 7.8, 3.8 Hz, 1H), 3.90-3.85 (m, 1H), 3.84 (s, 3H), 3.71 (d, *J* = 12.3 Hz, 2H), 2.86-2.60 (m, 11H), 2.51-2.44 (m, 1H), 2.38 (s, 3H), 2.34-2.28 (m, 1H), 1.97 (d, *J* = 12.6 Hz, 2H), 1.76-1.65 (m, 2H); 566.31[M+H]$^+$

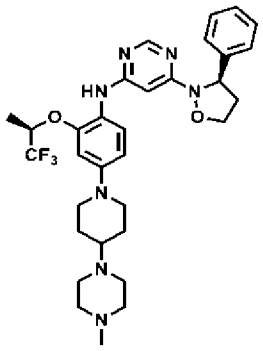
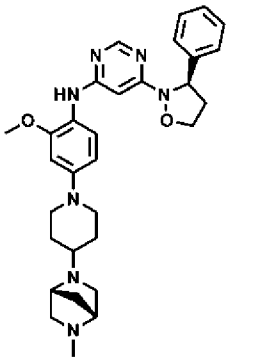
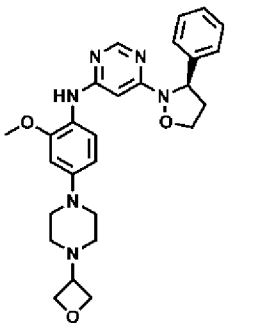
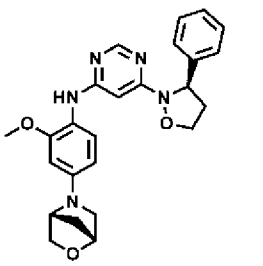
33		(R)-6-(3-(4-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (d, *J* = 1.0 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.43-7.37 (m, 2H), 7.06 (s, 1H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.53 (d, *J* = 8.1 Hz, 2H), 6.36 (d, *J* = 1.0 Hz, 1H), 5.64 (dd, *J* = 8.5, 4.6 Hz, 1H), 4.11 (dt, *J* = 7.9, 4.0 Hz, 1H), 3.91-3.83 (m, 4H), 3.71 (d, *J* = 12.3 Hz, 2H), 2.88-2.55 (m, 11H), 2.50-2.43 (m, 1H), 2.42-2.29 (m, 4H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.76-1.65 (m, 2H); 548.31[M+H]$^+$
34		(R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.44 (s, 1H), 8.11 (d, *J* = 1.0 Hz, 1H), 7.49 (q, *J* = 8.6, 8.1 Hz, 1H), 7.34-7.22 (m, 2H), 7.07 (t, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 2.7 Hz, 1H), 6.49 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.17 (s, 1H), 5.68 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.16-4.10 (m, 1H), 3.83-3.75 (m, 4H), 3.72 (d, *J* = 12.1 Hz, 2H), 3.43-3.36 (m, 5H), 2.80-2.72 (m, 1H), 2.67 (t, *J* = 12.1 Hz, 2H), 2.38-2.25 (m, 4H), 2.21-2.09 (m, 4H), 1.83 (d, 2H), 1.51 (q, *J* = 11.4 Hz, 2H); 566.27[M+H]$^+$
35		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(噻吩-2-基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (d, *J* = 1.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.20 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.08-7.04 (m, 1H), 7.02-6.94 (m, 2H), 6.55-6.49 (m, 2H), 6.38 (d, *J* = 1.1 Hz, 1H), 5.98 (dd, *J* = 8.3, 3.5 Hz, 1H), 4.17 (td, *J* = 7.9, 5.2 Hz, 1H), 3.93 (q, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.75-3.67 (m, 2H), 2.93 (s, 6H), 2.75 (td, *J* = 12.2, 2.3 Hz, 3H), 2.69-2.62 (m, 2H), 2.60 (s, 3H), 2.55-2.44 (m, 2H), 1.98 (d, *J* = 12.4 Hz, 2H), 1.79-1.66 (m, 2H); 536.4[M+H]$^+$
36		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(萘-1-基)異噁唑啶-2-基)嘧啶-4-胺	1H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.58-7.43 (m, 4H), 6.54 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 6.39 (dd, J = 8.7, 4.0 Hz, 1H), 4.16-4.09 (m, 1H), 4.00 (q, J = 7.8 Hz, 1H), 3.86 (s, 3H), 3.71 (d, J = 12.3 Hz, 2H), 2.97-2.87 (m, 4H), 2.76 (t, J = 12.0 Hz, 3H), 2.63 (s, 4H), 2.45-2.35 (m, 2H), 2.08 (s, 3H), 1.97 (d, 2H), 1.75 (ddd, 2H); 580.39[M+H]$^+$

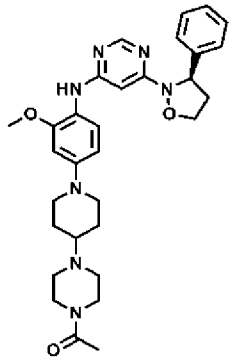
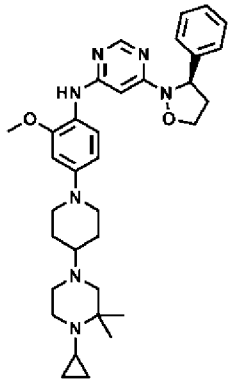
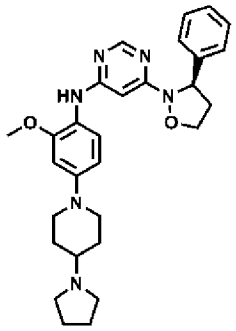
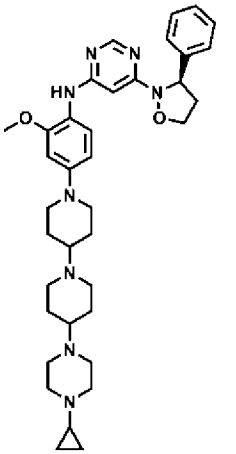
37		(R)-6-(3-(3-乙炔基苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	554.3 $[M+H]^+$
38		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(6-甲基吡啶-3-基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75-8.49 (m, 2H), 8.22-8.12 (m, 1H), 8.08-7.94 (m, 1H), 7.57-7.27 (m, 2H), 6.68 (s, 1H), 6.61-6.50 (m, 1H), 6.25-6.12 (m, 1H), 5.65-5.53 (m, 1H), 4.20-4.13 (m, 1H), 3.99-3.93 (m, 1H), 3.91-3.67 (m, 6H), 3.50-3.27 (m, 4H), 3.19-3.14 (m, 2H), 2.83-2.66 (m, 6H), 2.60-2.55 (m, 2H), 2.38-2.19 (m, 2H), 2.04-1.92 (m, 2H), 1.92-1.79 (m, 2H), 1.68-1.50 (m, 2H); 545.4$[M+H]^+$
39		(R)-6-(3-(3-([1,2,4]三唑并[1,5-a]吡啶-7-基)苯基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	534.3 $[M+H]^+$
40		(R)-6-(3-(3-氟-5-硫代嗎啉基苯基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	536.3 $[M+H]^+$
41		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(3-甲氧苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.83 (s, 1H), 8.04 (s, 1H), 7.31-7.26 (m, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.89-6.79 (m, 3H), 6.62-6.52 (m, 2H), 5.75 (s, 1H), 5.54 (dd, J = 8.6, 4.5 Hz, 1H), 4.24 (td, J = 7.5, 5.5 Hz, 1H), 4.03 (q, J = 7.5 Hz, 1H), 3.89-3.77 (m, 8H), 3.66 (s, 8H), 3.34-3.22 (m, 1H), 2.94-2.81 (m, 6H), 2.49-2.37 (m, 1H), 2.26-2.15 (m, 2H), 2.05-1.93 (m, 2H); 560.4 $[M+H]^+$

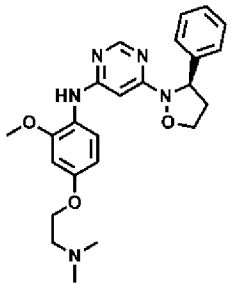
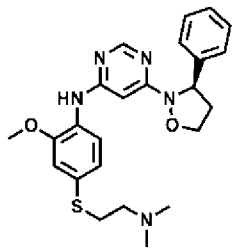
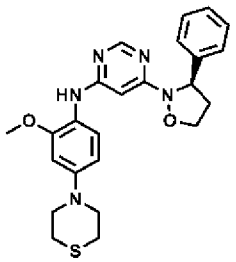
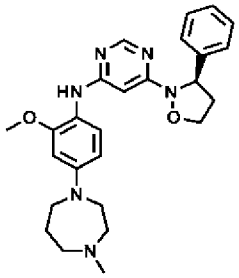
42		(R)-6-(3-甲基-3-苯基異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	431.3 $[M+H]^+$
43		(R)-3-(2-(6-((4-(4-甲基哌啡-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲酸異丙酯	503.3 $[M+H]^+$
44		(R)-N-環己基-3-(2-(6-((4-(4-甲基哌啡-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲醯胺；	542.3 $[M+H]^+$
45		(R)-6-(3-(3',5-二氟-[1,1'-聯苯]-3-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (d, *J* = 1.0 Hz, 1H), 7.45--7.10 (m, 9H), 7.09-6.90 (m, 3H), 6.40 (d, *J* = 1.0 Hz, 1H), 5.71 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.11 (td, J = 7.9, 4.1 Hz, 1H), 3.85 (q, *J* = 7.9 Hz, 1H), 3.26-3.19 (m, 4H), 2.76 (dtt, *J* = 12.2, 7.6, 4.2 Hz, 1H), 2.63-2.54 (m, 4H), 2.44-2.31 (m, 4H); 529.4$[M+H]^+$
46		(R)-N,N-二甲基-7-(2-甲基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-7-氮雜螺[3.5]壬-2-胺	499.3 $[M+H]^+$
47		(R)-N,N-二甲基-2-(2-甲基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-2-氮雜螺[3.5]壬-7-胺	499.3 $[M+H]^+$

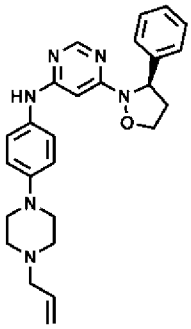
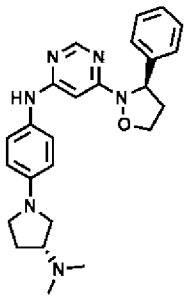
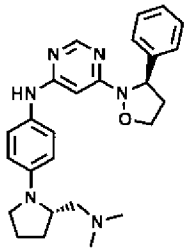
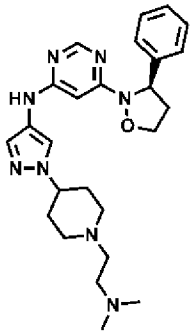
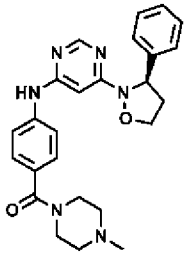
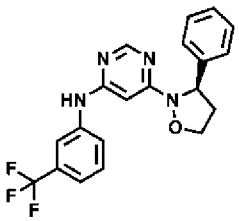
48		(R)-3-(1-甲基哌啶-4-基)-N-(6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-基)-1,2,3,4,4a,5-六氫苯并[b]吡咯并[1,2-d][1,4]噁咯-8-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.17 (d, *J* = 1.0 Hz, 1H), 8.07 (s, 1H), 7.44-7.40 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.26-7.22 (m, 1H), 6.79-6.69 (m, 3H), 6.42 (d, *J* = 1.0 Hz, 1H), 5.64 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.20 (dd, *J* = 10.6, 2.7 Hz, 1H), 4.12 (td, *J* = 7.8, 4.5 Hz, 1H), 4.01 (dd, *J* = 10.6, 8.9 Hz, 1H), 3.88 (q, *J* = 7.8 Hz, 1H), 3.68 (dt, *J* = 11.6, 2.8 Hz, 1H), 3.30 (d, *J* = 11.5 Hz, 2H), 3.16 (ddt, *J* = 11.5, 9.4, 2.9 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.88 (dt, *J* = 10.5, 2.6 Hz, 1H), 2.80 (td, *J* = 11.8, 3.4 Hz, 1H), 2.73 (ddt, *J* = 8.8, 7.6, 4.5 Hz, 1H), 2.54 (s, 3H), 2.47 (ddt, *J* = 11.6, 8.9, 3.8 Hz, 3H), 2.38 (dtd, *J* = 12.4, 7.9, 4.7 Hz, 1H), 2.07 (s, 1H), 2.02 (s, 1H), 1.98-1.86 (m, 4H); 528.37[M+H]$^+$
49		(6aR,8S)-8-(4-環丙基哌咯-1-基)-2-甲氧基-N-(6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-基)-6,6a,7,8,9,10-六氫苯并[b]吡啶并[1,2-d][1,4]噁咯-3-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 1.1 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.20 (s, 1H), 6.80 (s, 1H), 6.45 (s, 1H), 6.41 (d, *J* = 1.1 Hz, 1H), 5.68 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.20-4.07 (m, 2H), 3.98 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.90 (q, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 3.02 (dd, *J* = 11.4, 8.4 Hz, 1H), 2.79-2.47 (m, 10H), 2.43-2.34 (m, 1H), 2.07-1.99 (m, 2H), 1.88-1.83 (m, 1H), 1.69-1.61 (m, 7H); 584.45[M+H]$^+$
50		N-(4-(4-(5-乙基六氫吡咯并[3,4-c]吡咯-2(1H)-基)哌啶-1-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	570.3 [M+H]$^+$
51		(R)-N-(2-甲氧基-4-(4-((1-甲基哌啶-4-基)胺基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	544.3 [M+H]$^+$

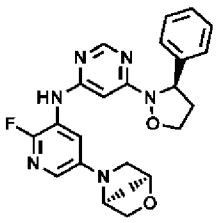
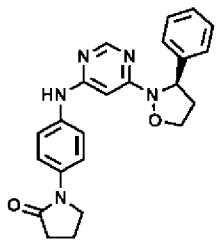
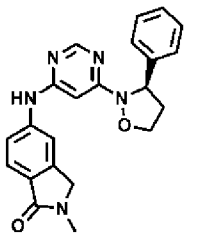
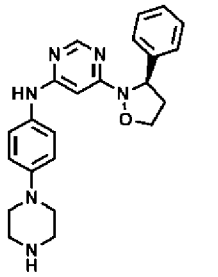
52		(R)-N-(2-甲基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.40 (s, 1H), 8.14 (s, 1H), 7.40-7.31 (m, 4H), 7.24 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.85-6.73 (m, 2H), 5.97 (s, 1H), 5.62 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.10 (td, *J* = 7.8, 4.5 Hz, 1H), 3.85 (q, *J* = 7.8 Hz, 1H), 3.76 (d, *J* = 12.2 Hz, 2H), 3.02 (d, *J* = 30.2 Hz, 8H), 2.81-2.66 (m, 4H), 2.63 (s, 3H), 2.42-2.31 (m, 1H), 2.22 (s, 3H), 1.98 (d, *J* = 12.4 Hz, 2H), 1.72 (qd, *J* = 12.1, 4.0 Hz, 2H); 514.34[M+H]$^+$
53		(R)-N-(3-甲基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29-8.26 (m, 1H), 7.46-7.42 (m, 2H), 7.37-7.31 (m, 2H), 7.26-7.23 (m, 1H), 7.12-7.06 (m, 2H), 7.02-6.98 (m, 1H), 6.63 (s, 1H), 6.45-6.43 (m, 1H), 5.67 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.11 (td, *J* = 7.9, 4.5 Hz, 1H), 3.91-3.83 (m, 1H), 3.21-3.13 (m, 2H), 2.83-2.61 (m, 8H), 2.60-2.45 (m, 3H), 2.43-2.36 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 1.97 (d, *J* = 12.2 Hz, 2H), 1.75-1.69 (m, 2H); 514.3[M+H]$^+$
54		(R)-N-(4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.20 (s, 1H), 7.61 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.26-7.22 (m, 1H), 7.19-7.12 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.37 (s, 1H), 5.65 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.10 (td, *J* = 7.8, 4.4 Hz, 1H), 3.86 (q, *J* = 7.8 Hz, 1H), 3.73 (d, *J* = 12.2 Hz, 2H), 2.79-2.63 (m, 11H), 2.48-2.39 (m, 2H), 2.37 (s, 3H), 1.97 (d, *J* = 12.5 Hz, 2H), 1.69 (qd, *J* = 12.1, 4.0 Hz, 2H); 500.3[M+H]$^+$
55		(R)-N-(2-乙氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	544.3 [M+H]$^+$

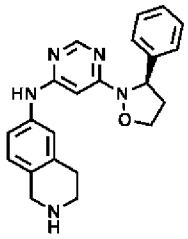
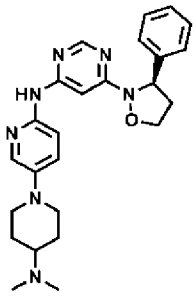
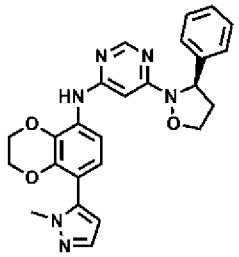
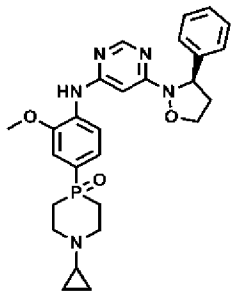
56		N-(4-(4-(4-甲基哌啡-1-基)哌 啶-1-基)-2-(((R)-1,1,1-三氟丙-2-基)氧基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (d, *J* = 1.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.47-7.42 (m, 2H), 7.35 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.26-7.23 (m, 1H), 6.70 (s, 1H), 6.67 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.37 (d, *J* = 1.0 Hz, 1H), 5.67 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.56 (p, *J* = 6.3 Hz, 1H), 4.13 (td, *J* = 7.8, 4.4 Hz, 1H), 3.68 (d, *J* = 12.1 Hz, 2H), 2.84-2.46 (m, 11H), 2.40 (ddd, *J* = 12.5, 8.3, 4.5 Hz, 2H), 2.32 (s, 3H), 1.96 (s, 2H), 1.68 (qd, *J* = 12.2, 4.0 Hz, 2H), 1.49-1.46 (m, 3H), 1.33-1.27 (m, 1H); 612.38[M+H]$^+$
57		N-(2-甲氧基-4-(4-((1R,4R)-5-甲基-2,5-二氮雜雙環[2.2.1]庚-2-基)哌啶-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.95 (s, 1H), 8.01 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 3H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.62 (s, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 5.75 (s, 1H), 5.57 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.32 (s, 1H), 4.25 (q, *J* = 7.0 Hz, 1H), 4.09 (s, 1H), 4.03 (q, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 3.77-3.69 (m, 2H), 3.59 (s, 2H), 3.16 (s, 2H), 2.95-2.81 (m, 7H), 2.45-2.39 (m, 2H), 2.31 (d, *J* = 11.9 Hz, 1H), 2.05 (s, 1H), 1.94 (s, 3H); 542.40[M+H]$^+$
58		(R)-N-(2-甲氧基-4-(4-(氧 咀-3-基)哌 啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	489.3 [M+H]$^+$
59		N-(4-((1R,4R)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (d, *J* = 1.0 Hz, 1H), 7.47-7.37 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.25-7.21 (m, 2H), 6.58 (s, 1H), 6.35 (d, *J* = 1.0 Hz, 1H), 6.20 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.68 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.67 (s, 1H), 4.40 (s, 1H), 4.14-4.07 (m, 1H), 3.97 (d, *J* = 7.4 Hz, 1H), 3.92-3.85 (m, 2H), 3.83 (s, 3H), 3.58 (dd, *J* = 9.0, 1.6 Hz, 1H), 3.20 (d, *J* = 9.1 Hz, 1H), 2.76-2.66 (m, 1H), 2.43-2.33 (m, 1H), 2.07-1.96 (m, 2H); 446.3[M+H]$^+$

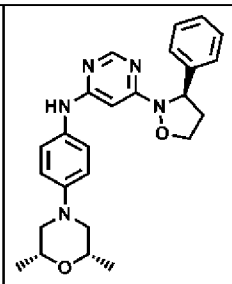
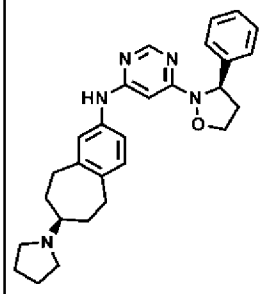
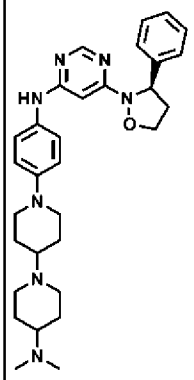
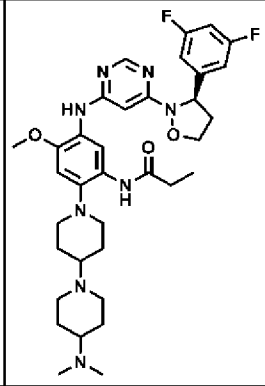
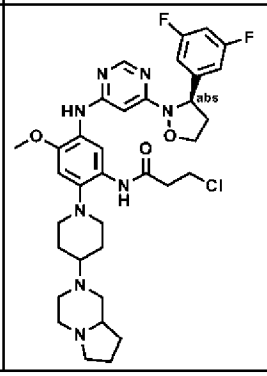
60		(R)-1-(4-(1-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧 啶-4-基)胺 基)苯基)哌 啶-4-基)哌 啡-1-基)乙-1-酮	558.3 $[M+H]^+$
61		(R)-N-(4-(4-(4-環 丙 基-3,3-二甲基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.23 (s, 1H), 7.71 (s, 1H), 7.47-7.39 (m, 3H), 7.38-7.31 (m, 2H), 7.29-7.25 (m, 1H), 6.55-6.48 (m, 2H), 6.27 (s, 1H), 5.65 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.13 (td, *J* = 7.7, 4.6 Hz, 1H), 3.91 (q, *J* = 7.8 Hz, 1H), 3.83 (s, 3H), 3.70 (d, *J* = 12.4 Hz, 2H), 3.20 (s, 3H), 3.08-2.86 (m, 3H), 2.82-2.63 (m, 6H), 2.46-2.32 (m, 2H), 2.14 (s, 1H), 2.06 (s, 1H), 2.03-1.94 (m, 2H), 1.73 (d, *J* = 12.3 Hz, 2H), 1.44 (s, 6H); 584.5 $[M+H]^+$
62		(R)-N-(2-甲 氧 基-4-(4-(吡 咯 啶-1-基)哌 啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 12.12 (s, 1H), 10.75 (s, 1H), 8.02 (s, 1H), 7.39-7.27 (m, 4H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.67-6.54 (m, 2H), 5.75 (s, 1H), 5.57 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.71 (s, 1H), 4.29-4.21 (m, 1H), 4.04 (q, *J* = 7.5 Hz, 1H), 3.93-3.35 (m, 7H), 3.28-3.13 (m, 1H), 3.00-2.80 (m, 4H), 2.48-2.39 (m, 1H), 2.25-1.89 (m, 8H); 501.3 $[M+H]^+$
63		(R)-N-(4-(4-(4-環丙基哌啡-1-基)-[1,4'-聯 哌 啶]-1'-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.22 (s, 1H), 7.71 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.24 (s, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 2H), 6.46 (s, 1H), 5.64 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.12 (td, *J* = 7.8, 4.3 Hz, 1H), 3.86 (s, 4H), 3.55 (d, *J* = 11.2 Hz, 2H), 3.17 (d, *J* = 11.0 Hz, 2H), 2.75-2.55 (m, 12H), 2.49-2.35 (m, 5H), 1.98-1.63 (m, 12H); 639.56 $[M+H]^+$

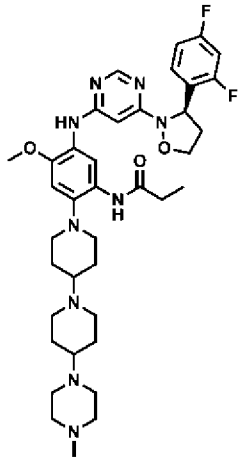
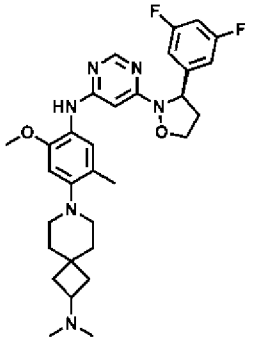
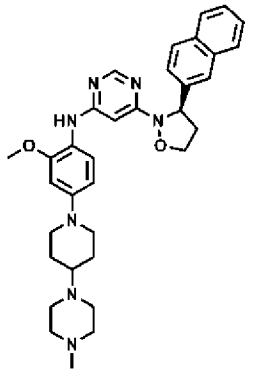
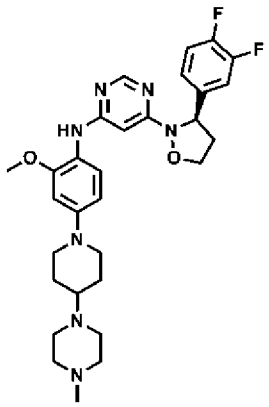
64		(R)-N-(4-(2-(二甲胺基)乙氧基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (d, *J* = 1.0 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.47-7.40 (m, 2H), 7.35 (t, *J* = 8.4, 6.9 Hz, 2H), 7.26-7.23 (m, 1H), 6.90 (s, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.51 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.38 (d, *J* = 1.0 Hz, 1H), 5.67 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.17-4.07 (m, 3H), 3.89 (q, *J* = 7.9 Hz, 1H), 3.83 (s, 3H), 2.81 (t, *J* = 5.6 Hz, 2H), 2.72 (tdd, *J* = 8.7, 7.9, 4.4 Hz, 1H), 2.43-2.32 (m, 7H); 436.24[M+H]$^+$
65		(R)-N-(4-((2-(二甲胺基)乙基)硫基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.36 (d, *J* = 1.0 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.29-7.25 (m, 1H), 7.10 (s, 1H), 7.02 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.52 (d, *J* = 1.0 Hz, 1H), 5.68 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.16 (td, *J* = 7.8, 4.4 Hz, 1H), 3.96-3.87 (m, 4H), 3.06-2.98 (m, 2H), 2.81-2.70 (m, 1H), 2.62-2.55 (m, 2H), 2.46-2.36 (m, 1H), 2.29 (s, 6H); 452.21 [M+H]$^+$
66		(R)-N-(2-甲氧基-4-硫代嗎啉基苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (d, *J* = 1.0 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.26-7.23 (m, 1H), 6.89 (s, 1H), 6.56-6.48 (m, 2H), 6.42 (d, *J* = 1.0 Hz, 1H), 5.68 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.12 (td, *J* = 7.8, 4.4 Hz, 1H), 3.89 (q, *J* = 7.8 Hz, 1H), 3.85 (s, 3H), 3.53-3.49 (m, 4H), 2.81-2.67 (m, 5H), 2.44-2.34 (m, 1H); 450.22[M+H]$^+$
67		(R)-N-(2-甲氧基-4-(4-甲基-1,4-二氮雜環庚烷-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (d, *J* = 1.0 Hz, 1H), 7.47-7.42 (m, 2H), 7.34 (td, *J* = 6.9, 6.3, 3.0 Hz, 3H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.88 (s, 1H), 6.32 (d, *J* = 1.0 Hz, 1H), 6.31-6.23 (m, 2H), 5.68 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.10 (td, *J* = 7.8, 4.4 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 3.83 (s, 3H), 3.67-3.62 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.91-2.86 (m, 2H), 2.78-2.68 (m, 4H), 2.48 (s, 3H), 2.42-2.33 (m, 1H), 2.13 (p, *J* = 6.2 Hz, 1H); 461.21[M+H]$^+$

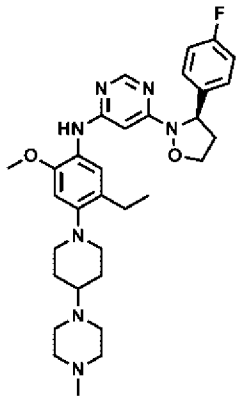
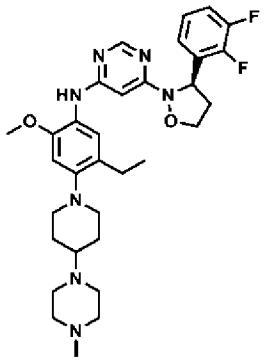
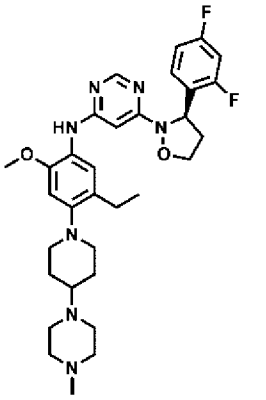
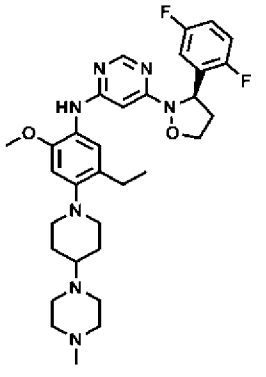
68		(R)-N-(4-(4-烯丙基哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.81 (s, 1H), 8.15 (s, 1H), 7.44-7.31 (m, 4H), 7.29-7.17 (m, 3H), 6.97-6.91 (m, 2H), 6.26 (s, 1H), 6.03-5.91 (m, 1H), 5.62 (dd, *J* = 8.6, 4.6 Hz, 1H), 5.47-5.36 (m, 2H), 4.17 (td, *J* = 7.7, 4.9 Hz, 1H), 3.94 (q, *J* = 7.7 Hz, 1H), 3.45 (d, *J* = 7.0 Hz, 2H), 3.39 (t, *J* = 5.1 Hz, 4H), 3.04 (t, *J* = 5.0 Hz, 4H), 2.83-2.73 (m, 1H), 2.45-2.35 (m, 1H); 443.3[M+H]$^+$
69		N-(4-((R)-3-(二甲胺基)吡咯啶-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.89 (s, 1H), 8.01 (s, 1H), 7.39-7.27 (m, 6H), 7.18-7.13 (m, 2H), 6.60 (d, *J* = 8.7 Hz, 1H), 6.02 (s, 1H), 5.58 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.29-4.20 (m, 1H), 4.04 (q, *J* = 7.5 Hz, 1H), 3.90-3.83 (m, 1H), 3.75-3.55 (m, 3H), 3.38 (q, *J* = 8.3 Hz, 1H), 2.86 (s, 3H), 2.68 (s, 3H), 2.50-2.34 (m, 4H); 431.3 [M+H]$^+$
70		N-(4-((S)-2-((二甲胺基)甲基)吡咯啶-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	445.3 [M+H]$^+$
71		(R)-N-(1-(1-(2-(二甲胺基)乙基)哌啶-4-基)-1H-吡唑-4-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	463.3 [M+H]$^+$
72		(R)-(4-甲基哌啡-1-基)(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)甲酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.66 (s, 1H), 8.24 (s, 1H), 7.47-7.40 (m, 4H), 7.39-7.33 (m, 4H), 7.31-7.27 (m, 1H), 6.57 (s, 1H), 5.63 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.20 (td, *J* = 7.7, 4.5 Hz, 1H), 3.93 (q, *J* = 7.8 Hz, 1H), 3.74 (s, 4H), 2.83-2.74 (m, 1H), 2.63 (s, 4H), 2.48-2.37 (m, 4H); 445.24[M+H]$^+$
73		(R)-6-(3-苯基異噁唑啶-2-基)-N-(3-(三氟甲基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.36 (s, 1H), 7.65 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.48 (t, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 3H), 7.28 (d, *J* = 7.7 Hz, 1H), 6.94 (s, 1H), 6.52 (d, *J* = 1.0 Hz, 1H), 5.67 (dd, *J* =

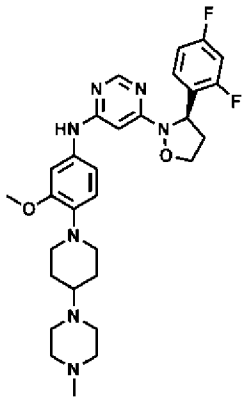
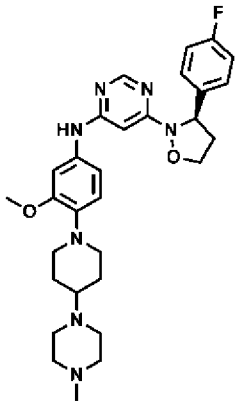
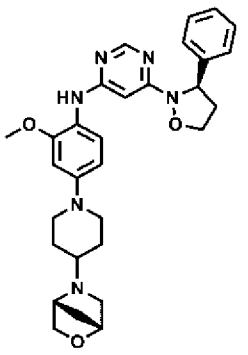
			8.7, 4.8 Hz, 1H), 4.18 (td, *J* = 7.8, 4.4 Hz, 1H), 3.91 (q, *J* = 7.9 Hz, 1H), 2.77 (dtd, *J* = 12.2, 8.0, 4.4 Hz, 1H), 2.46-2.36 (m, 1H); 387.17 $[M+H]^+$
74		N-(5-((1S,4S)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基)-2-氟吡啶-3-基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.37 (d, *J* = 1.0 Hz, 1H), 7.92 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.48-7.41 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30-7.27 (m, 1H), 7.17-7.09 (m, 1H), 6.90 (s, 1H), 6.46 (d, *J* = 0.8 Hz, 1H), 5.66 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.67 (d, *J* = 2.2 Hz, 1H), 4.38 (s, 1H), 4.19 (td, *J* = 7.8, 4.4 Hz, 1H), 3.97-3.86 (m, 3H), 3.59 (dd, *J* = 9.1, 1.6 Hz, 1H), 3.18 (d, *J* = 9.2 Hz, 1H), 2.78 (dddd, *J* = 12.0, 8.6, 7.5, 4.4 Hz, 1H), 2.43 (dtd, *J* = 12.5, 7.9, 4.7 Hz, 1H), 2.02 (ddd, *J* = 22.7, 9.8, 2.4 Hz, 2H); 435.27 $[M+H]^+$
75		(R)-1-(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)吡咯啶-2-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (s, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.50 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.39-7.27 (m, 5H), 6.49 (d, *J* = 1.1 Hz, 1H), 5.65 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.14 (td, *J* = 7.8, 4.4 Hz, 1H), 3.88 (q, *J* = 7.2 Hz, 3H), 2.75 (dtd, *J* = 12.5, 8.0, 4.3 Hz, 1H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.44-2.35 (m, 1H), 2.20 (dd, *J* = 13.7, 6.3 Hz, 2H); 402.21 $[M+H]^+$
76		(R)-2-甲基-5-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)異吲哚啉-1-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (d, *J* = 1.0 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.47-7.41 (m, 2H), 7.37 (td, *J* = 6.9, 1.6 Hz, 2H), 7.33-7.27 (m, 2H), 6.58 (d, *J* = 1.0 Hz, 1H), 5.65 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.38 (s, 2H), 4.18 (td, *J* = 7.8, 4.5 Hz, 1H), 3.91 (q, *J* = 7.9 Hz, 1H), 3.20 (s, 3H), 2.83-2.74 (m, 1H), 2.42 (dtd, *J* = 12.5, 7.9, 4.8 Hz, 1H); 388.23 $[M+H]^+$
77		(R)-6-(3-苯基異噁唑啶-2-基)-N-(4-(哌啡-1-基)苯基)嘧啶-4-胺	1H NMR (400 MHz, 氯仿-*d*) δ 8.19 (d, *J* = 1.0 Hz, 1H), 7.97 (s, 1H), 7.44-7.40 (m, 2H), 7.35 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.28-7.24 (m, 1H), 7.22-7.17 (m, 2H), 6.98-6.90 (m, 2H), 6.39 (d, *J* = 1.1 Hz, 1H), 5.64 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.12 (td, *J* = 7.7, 4.4 Hz, 1H), 3.87 (q, *J* = 7.9 Hz, 1H), 3.25 (dd, *J* = 6.5, 3.5 Hz, 4H), 3.17 (dd, *J* = 6.5, 3.5 Hz, 4H), 2.74 (dddd, *J* = 12.1, 8.7, 7.6, 4.5 Hz, 1H), 2.38 (dtd, *J* = 12.4, 7.9, 4.7 Hz, 1H);

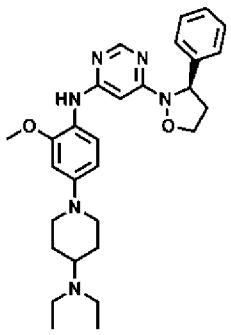
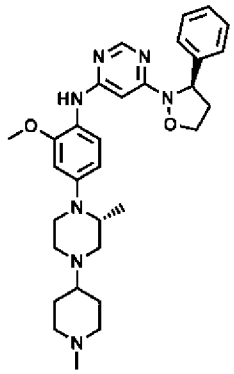
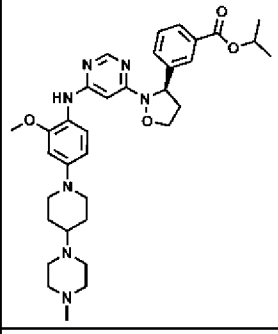
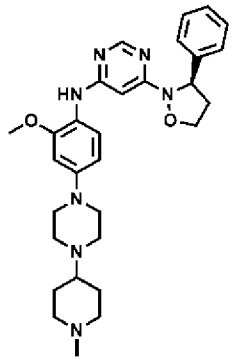
			403.23[M+H]$^+$
78		(R)-N-(6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)-1,2,3,4-四氫異喹啉-6-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.23 (s, 1H), 7.81 (s, 1H), 7.46-7.30 (m, 4H), 7.26-7.22 (m, 1H), 7.20-7.12 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.46 (s, 1H), 5.61 (dd, *J* = 8.6, 4.8 Hz, 1H), 5.13 (s, 1H), 4.23 (s, 2H), 4.14 (td, *J* = 7.8, 4.4 Hz, 1H), 3.88 (q, *J* = 7.8 Hz, 1H), 3.43-3.33 (m, 2H), 3.09-2.98 (m, 2H), 2.80-2.67 (m, 1H), 2.43-2.33 (m, 1H); 374.2 [M+H]$^+$
79		(R)-N-(5-(4-(二甲胺基)哌啶-1-基)吡啶-2-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.76 (s, 1H), 8.30 (d, *J* = 1.0 Hz, 1H), 7.96 (d, *J* = 3.0 Hz, 1H), 7.47 (dd, *J* = 9.0, 7.1 Hz, 3H), 7.36 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.32-7.28 (m, 1H), 7.26-7.24 (m, 2H), 5.67 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.21 (td, *J* = 7.9, 4.6 Hz, 1H), 3.99 (q, *J* = 7.8 Hz, 2H), 3.66 (d, *J* = 12.1 Hz, 2H), 2.87-2.71 (m, 4H), 2.55 (s, 6H), 2.42 (ddt, *J* = 11.5, 7.5, 3.8 Hz, 1H), 2.07 (s, 2H), 1.80 (qd, *J* = 12.1, 4.1 Hz, 1H); 446.30[M+H]$^+$
80		(R)-N-(8-(1-甲基-1H-吡唑-5-基)-2,3-二氫苯并[b][1,4]戴奧辛-5-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.39 (d, *J* = 1.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.48-7.44 (m, 2H), 7.39-7.33 (m, 2H), 7.30-7.27 (m, 1H), 7.01 (s, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 1.0 Hz, 1H), 6.27 (d, *J* = 1.9 Hz, 1H), 5.69 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.40-4.29 (m, 4H), 4.24-4.15 (m, 1H), 3.95 (q, *J* = 7.8 Hz, 1H), 3.79 (s, 3H), 2.84-2.71 (m, 1H), 2.48-2.37 (m, 1H); 457.2 [M+H]$^+$
81		(R)-1-環丙基-4-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-1,4-氮磷雜環己烷4-氧化物	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.67 (s, 1H), 8.13 (s, 1H), 7.68-7.60 (m, 1H), 7.53-7.43 (m, 2H), 7.41-7.25 (m, 5H), 6.03 (s, 1H), 5.61 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.32-4.25 (m, 1H), 4.08 (q, *J* = 7.5 Hz, 1H), 4.03-3.79 (m, 7H), 3.03 (td, *J* = 14.7, 4.9 Hz, 2H), 2.94-2.82 (m, 1H), 2.64-2.57 (m, 1H), 2.50-2.40 (m, 1H), 2.18 (t, *J* = 17.1 Hz, 2H), 1.42-1.34 (m, 2H), 1.00-0.91 (m, 2H); 506.3 [M+H]$^+$

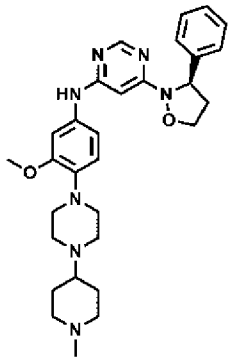
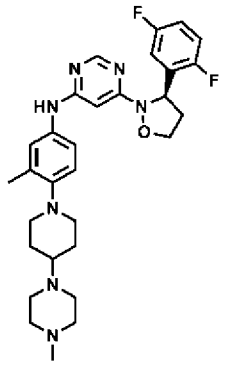
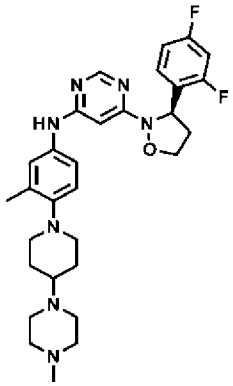
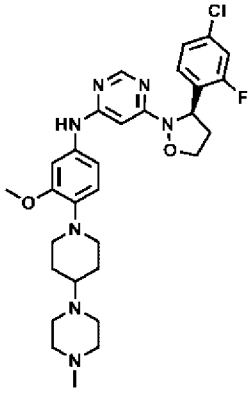
82		N-(4-((2R,6S)-2,6-二甲基嗎啉基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	432.3 $[M+H]^+$
83		6-((R)-3-苯基異噁唑啶-2-基)-N-((R)-7-(吡咯啶-1-基)-6,7,8,9-四氫-5H-苯并[7]輪烯-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 12.65 (s, 1H), 11.67 (s, 1H), 8.01 (s, 1H), 7.40-7.29 (m, 4H), 7.20-7.04 (m, 3H), 6.15 (s, 1H), 5.59 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 1H), 4.11 (q, *J* = 7.4 Hz, 1H), 3.83-3.70 (m, 2H), 3.41 (t, *J* = 11.7 Hz, 1H), 2.98-2.87 (m, 5H), 2.78 (t, *J* = 13.1 Hz, 2H), 2.51-2.36 (m, 3H), 2.22-2.10 (m, 2H), 2.05-1.95 (m, 2H), 1.70-1.56 (m, 2H); 456.3 $[M+H]^+$
84		(R)-N,N-二甲基-1'-(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-[1,4'-聯哌啶]-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (d, *J* = 1.0 Hz, 1H), 7.46-7.40 (m, 2H), 7.38-7.31 (m, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.19-7.15 (m, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.53 (s, 1H), 6.36 (d, *J* = 1.1 Hz, 1H), 5.67 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.14-4.06 (m, 1H), 3.86 (q, *J* = 7.9 Hz, 1H), 3.74 (d, *J* = 12.1 Hz, 2H), 3.05 (d, *J* = 11.3 Hz, 2H), 2.78-2.67 (m, 3H), 2.52-2.35 (m, 3H), 2.33 (s, 6H), 2.29-2.19 (m, 3H), 1.98-1.83 (m, 5H), 1.72 (d, *J* = 3.7 Hz, 2H); 528.3 $[M+H]^+$
85		(R)-N-(5-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-2-(4-(二甲胺基)-[1,4'-聯哌啶]-1'-基)-4-甲氧苯基)丙醯胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.77 (s, 1H), 8.35 (s, 1H), 8.30 (s, 1H), 7.04-6.96 (m, 2H), 6.94 (s, 1H), 6.75-6.64 (m, 3H), 5.71-5.61 (m, 1H), 4.19-4.11 (m, 1H), 4.05 (q, *J* = 8.1 Hz, 1H), 3.83 (s, 3H), 3.17-3.01 (m, 4H), 2.82-2.66 (m, 3H), 2.46-2.29 (m, 11H), 2.24-2.16 (m, 3H), 1.94-1.86 (m, 2H), 1.75-1.54 (m, 5H), 1.31-1.23 (m, 3H); 665.6$[M+H]^+$
86		3-氯-N-(5-((6-((R)-3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-2-(4-(六氫吡咯并[1,2-a]吡咔-2(1H)-基)哌啶-1-基)-4-甲氧苯基)丙醯胺	698.3 $[M+H]^+$

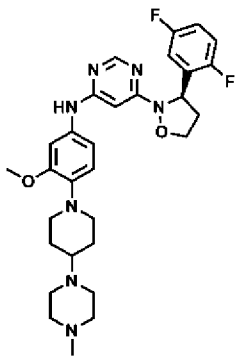
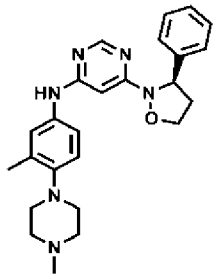
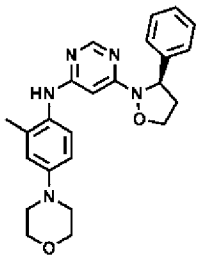
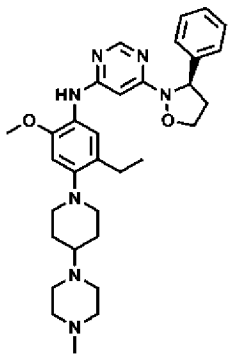
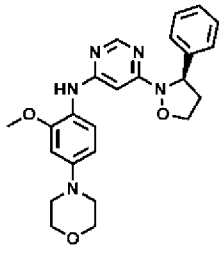
87		(R)-N-(5-((6-(3-(2,4-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-4-甲氧基-2-(4-(4-甲基哌啡-1-基)-[1,4'-聯哌啶]-1'-基)苯基)丙醯胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.72 (s, 1H), 8.36-8.24 (m, 2H), 7.55 (q, *J* = 7.9 Hz, 1H), 6.85-6.77 (m, 2H), 6.71 (d, *J* = 10.1 Hz, 2H), 5.86 (dd, *J* = 8.8, 4.4 Hz, 1H), 4.14-4.00 (m, 3H), 3.85-3.80 (m, 3H), 3.21 (d, *J* = 11.1 Hz, 2H), 3.11-2.99 (m, 3H), 2.82-2.66 (m, 11H), 2.63-2.53 (m, 2H), 2.48-2.41 (m, 3H), 2.39 (s, 3H), 2.35-2.22 (m, 4H), 1.96-1.88 (m, 3H), 1.81-1.63 (m, 5H); 720.7[M+H]$^+$
88		(R)-7-(5-甲氧基-2-甲基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-N,N-二甲基-7-氮雜螺[3.5]壬-2-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29-8.27 (m, 1H), 7.44 (s, 1H), 7.11 (s, 1H), 7.03-6.96 (m, 2H), 6.73-6.65 (m, 1H), 6.61 (s, 1H), 6.43-6.39 (m, 1H), 5.65 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.11 (td, *J* = 7.9, 4.1 Hz, 1H), 3.90-3.84 (m, 1H), 3.83 (s, 3H), 3.43-3.34 (m, 5H), 3.02-2.92 (m, 1H), 2.83-2.70 (m, 5H), 2.35 (s, 6H), 2.24 (s, 3H), 2.15-2.10 (m, 2H), 2.03-1.98 (m, 2H); 565.3[M+H]$^+$
89		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(萘-2-基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.86-7.78 (m, 3H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.49-7.41 (m, 3H), 7.08 (s, 1H), 6.57-6.48 (m, 2H), 6.40 (s, 1H), 5.82 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.15 (td, *J* = 7.8, 4.5 Hz, 1H), 3.93 (q, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 3.71 (d, *J* = 12.2 Hz, 2H), 2.76 (dt, *J* = 19.9, 12.4 Hz, 11H), 2.51-2.42 (m, 2H), 2.39 (s, 3H), 1.97 (d, *J* = 12.5 Hz, 2H), 1.71 (ddd, *J* = 24.0, 12.1, 3.8 Hz, 2H); 580.44[M+H]$^+$
90		(R)-6-(3-(3,4-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.32-7.27 (m, 1H), 7.18-7.08 (m, 2H), 6.84 (s, 1H), 6.54 (d, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 1.1 Hz, 1H), 5.63 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.10 (td, *J* = 7.9, 4.3 Hz, 1H), 3.92-3.80 (m, 4H), 3.71 (d, *J* = 12.3 Hz, 2H), 2.84-2.47 (m, 11H), 2.42 (dq, *J* = 11.5, 3.4 Hz, 1H), 2.34 (s, 4H), 1.97 (d, *J* = 14.1 Hz, 2H), 1.75-1.65 (m, 2H); 566.31[M+H]$^+$

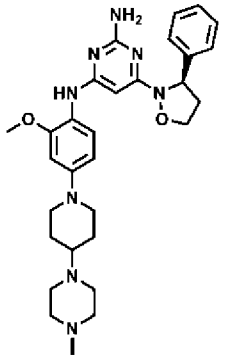
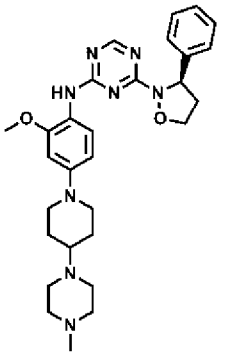
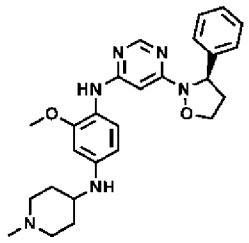
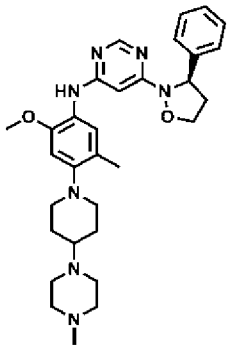
91		(R)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(4-氟苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 2.9 Hz, 1H), 7.48 (d, *J* = 2.9 Hz, 1H), 7.42 (ddd, *J* = 8.5, 5.3, 2.8 Hz, 2H), 7.16 (s, 1H), 7.03 (td, *J* = 8.7, 2.9 Hz, 2H), 6.67 (d, *J* = 3.0 Hz, 1H), 6.48 (d, *J* = 2.9 Hz, 1H), 5.65 (dd, *J* = 8.4, 4.5 Hz, 1H), 4.11 (td, *J* = 7.8, 4.1 Hz, 1H), 3.92-3.86 (m, 1H), 3.83 (d, *J* = 2.9 Hz, 3H), 3.13 (d, *J* = 11.3 Hz, 2H), 2.84-2.59 (m, 13H), 2.50 (d, *J* = 12.7 Hz, 1H), 2.40 (d, *J* = 2.9 Hz, 3H), 2.35 (dt, *J* = 8.0, 4.3 Hz, 1H), 1.96 (d, *J* = 12.1 Hz, 2H), 1.78-1.68 (m, 2H), 1.22 (t, *J* = 7.5 Hz, 3H); 576.42 [M+H]$^+$
92		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.52 (s, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 6.2 Hz, 2H), 6.91 (s, 1H), 6.67 (s, 1H), 6.53 (s, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.10 (dq, *J* = 7.6, 4.2 Hz, 1H), 3.89 (q, *J* = 8.2, 7.8 Hz, 1H), 3.84 (s, 3H), 3.13 (d, *J* = 11.4 Hz, 2H), 2.88-2.49 (m, 13H), 2.43-2.36 (m, 1H), 2.33 (s, 3H), 2.32-2.27 (m, 1H), 1.95 (d, *J* = 13.0 Hz, 2H), 1.78-1.68 (m, 2H), 1.25-1.21 (m, 3H); 594.33[M+H]$^+$
93		(R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (d, *J* = 1.0 Hz, 1H), 7.58-7.50 (m, 2H), 6.88-6.78 (m, 3H), 6.67 (s, 1H), 6.54 (d, *J* = 1.0 Hz, 1H), 5.85 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.08 (td, *J* = 7.9, 4.4 Hz, 1H), 3.90 (q, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 3.13 (d, *J* = 11.5 Hz, 2H), 2.82-2.50 (m, 12H), 2.40-2.24 (m, 5H), 1.96 (d, *J* = 12.1 Hz, 2H), 1.72 (qd, *J* = 12.0, 3.8 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); 594.33[M+H]$^+$
94		(R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (d, *J* = 1.0 Hz, 1H), 7.49 (s, 1H), 7.29 (td, *J* = 6.0, 3.0 Hz, 1H), 7.17 (s, 1H), 7.00 (td, *J* = 9.1, 4.3 Hz, 1H), 6.96-6.85 (m, 1H), 6.67 (s, 1H), 6.51 (d, *J* = 1.1 Hz, 1H), 5.87 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.08 (td, *J* = 7.9, 4.2 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 3.13 (d, *J* = 11.6 Hz, 2H), 2.90-2.59 (m, 13H), 2.54-2.44 (m, 1H), 2.40 (s, 3H), 2.34-2.24 (m, 1H), 1.96 (d, *J* = 12.1 Hz, 2H), 1.73 (qd, *J* = 11.8, 3.7 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); 594.28 [M+H]$^+$

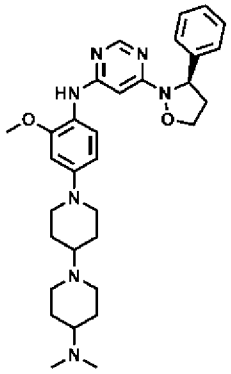
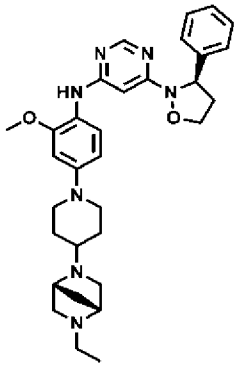
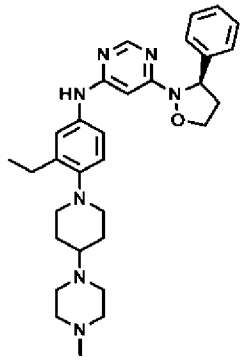
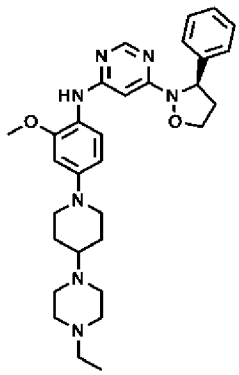
95		(R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.24 (s, 1H), 7.50 (dd, J = 8.8, 6.6 Hz, 1H), 7.27 (ddd, J = 11.2, 9.2, 2.6 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.07 (ddt, J = 11.0, 5.5, 2.4 Hz, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 1.0 Hz, 1H), 5.70 (dd, J = 8.7, 4.9 Hz, 1H), 4.18 (td, J = 7.9, 3.9 Hz, 1H), 3.89 (t, J = 8.1 Hz, 1H), 3.76 (s, 3H), 2.77 (dq, J = 8.1, 4.1 Hz, 1H), 2.38-2.18 (m, 6H), 2.15 (s, 3H), 1.80 (d, J = 12.1 Hz, 2H), 1.76-1.64 (m, 1H), 1.54 (dt, J = 12.1, 5.9 Hz, 2H), 1.32-1.21 (m, 2H), 1.19-0.98 (m, 1H), 0.95-0.80 (m, 2H); 566.4[M+H]$^+$
96		(R)-6-(3-(4-氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.23 (d, J = 1.0 Hz, 1H), 7.44 (ddd, J = 8.8, 5.6, 2.6 Hz, 2H), 7.21-7.12 (m, 3H), 7.05 (dd, J = 8.5, 2.3 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.40 (d, J = 1.1 Hz, 1H), 5.53 (dd, J = 8.6, 5.0 Hz, 1H), 4.16 (td, J = 7.9, 4.0 Hz, 1H), 3.85 (d, J = 8.1 Hz, 1H), 3.76 (s, 3H), 2.75 (dq, J = 8.3, 4.3 Hz, 1H), 2.46 (s, 2H), 2.37-2.22 (m, 6H), 2.15 (s, 3H), 2.09 (d, J = 1.0 Hz, 1H), 1.80 (d, J = 12.0 Hz, 2H), 1.54 (dt, J = 11.6, 5.9 Hz, 2H), 1.25 (d, J = 3.4 Hz, 2H), 1.05-0.80 (m, 2H); 548.3[M+H]$^+$
97		N-(4-(4-((1R,4R)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基)哌啶-1-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.24 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 7.3 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 1.2 Hz, 1H), 7.24 (t, J = 1.4 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 6.51 (dd, J = 8.6, 2.5 Hz, 1H), 6.29 (s, 1H), 5.65 (dd, J = 8.7, 4.6 Hz, 1H), 4.61 (s, 1H), 4.45 (s, 1H), 4.22-4.09 (m, 2H), 3.90 (q, J = 7.8 Hz, 1H), 3.84 (s, 4H), 3.72 (d, J = 12.3 Hz, 3H), 2.98 (s, 2H), 2.74 (ddd, J = 11.9, 7.9, 3.9 Hz, 4H), 2.39 (ddt, J = 11.7, 7.7, 3.9 Hz, 2H), 2.29 (d, J = 11.1 Hz, 1H), 2.16-2.10 (m, 2H), 1.99 (d, J = 12.8 Hz, 1H); 529.39 [M+H]$^+$

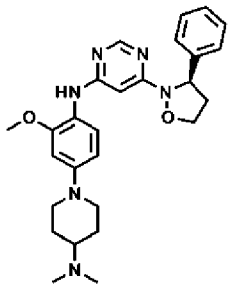
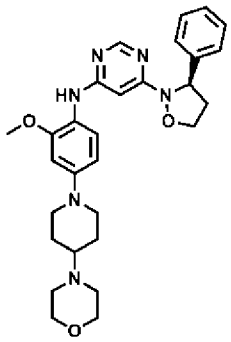
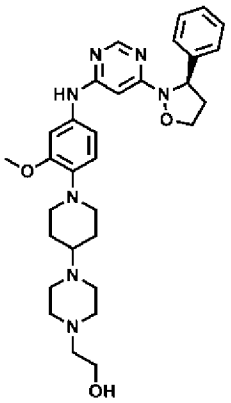
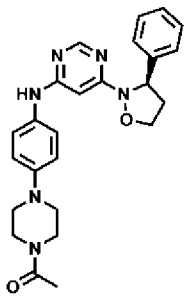
98		(R)-N-(4-(4-(二乙胺基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (d, *J* = 1.0 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.45-7.41 (m, 2H), 7.35 (dd, *J* = 8.4, 6.7 Hz, 3H), 7.27-7.22 (m, 1H), 6.52 (d, *J* = 8.6 Hz, 2H), 6.35 (d, *J* = 1.0 Hz, 1H), 5.66 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.12 (td, *J* = 7.8, 4.5 Hz, 1H), 3.89 (q, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.76 (d, *J* = 13.3 Hz, 2H), 3.39 (tt, *J* = 12.2, 3.7 Hz, 1H), 3.16 (q, *J* = 7.3 Hz, 4H), 2.80 (t, *J* = 11.3 Hz, 2H), 2.72 (tt, *J* = 8.0, 4.4 Hz, 1H), 2.43-2.32 (m, 1H), 2.16 (d, *J* = 9.3 Hz, 2H), 1.98 (qd, *J* = 12.4, 4.1 Hz, 2H), 1.39 (t, *J* = 7.3 Hz, 6H); 503.40 $[M+H]^+$
99		N-(2-甲氧基-4-((R)-2-甲基-4-(1-甲基哌啶-4-基)哌咔-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	1H NMR (400 MHz, 氯仿-*d*) δ 8.27 (s, 1H), 7.54 (d, *J* = 6.6 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28-7.24 (m, 1H), 6.56 (d, *J* = 6.1 Hz, 2H), 6.34 (s, 1H), 5.66 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.14 (td, *J* = 7.8, 4.5 Hz, 1H), 3.91 (q, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 1H), 3.25-3.10 (m, 3H), 2.89-2.84 (m, 1H), 2.80-2.70 (m, 5H), 2.67-2.61 (m, 2H), 2.44-2.35 (m, 2H), 2.24-2.19 (m, 1H), 2.08 (s, 3H), 2.03-1.98 (m, 2H), 1.31 (s, 1H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.87-0.80 (m, 1H); 544.39 $[M+H]^+$
100		(R)-3-(2-(6-((2-甲氧基-4-(4-(4-甲基哌咔-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲酸異丙酯	616.4 $[M+H]^+$
101		(R)-N-(2-甲氧基-4-(4-(1-甲基哌啶-4-基)哌咔-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.21 (s, 1H), 8.00 (s, 1H), 7.44-7.31 (m, 5H), 7.29-7.26 (m, 1H), 6.55-6.49 (m, 2H), 6.24 (s, 1H), 5.64 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.18-4.09 (m, 1H), 3.90 (q, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.50 (s, 2H), 3.24 (t, *J* = 4.8 Hz, 4H), 2.89-2.76 (m, 5H), 2.75 (s, 3H), 2.74-2.61 (m, 2H), 2.44-2.34 (m, 1H), 2.18-2.06 (m, 5H); 530.4 $[M+H]^+$

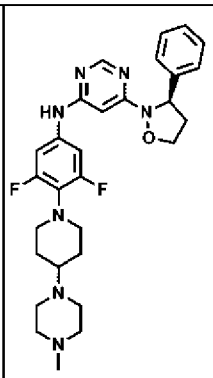
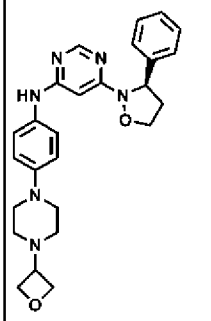
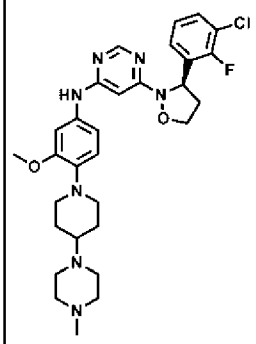
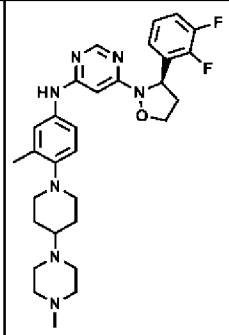
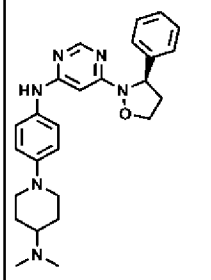
102		(R)-N-(3-甲氧基-4-(4-(1-甲基哌啶-4-基)哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 1.0 Hz, 1H), 7.46-7.41 (m, 2H), 7.38-7.31 (m, 2H), 7.26-7.22 (m, 1H), 6.95-6.90 (m, 1H), 6.86-6.80 (m, 2H), 6.60 (s, 1H), 6.45 (d, *J* = 1.0 Hz, 1H), 5.66 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.16-4.07 (m, 1H), 3.91-3.82 (m, 4H), 3.11 (s, 4H), 2.98 (d, *J* = 11.2 Hz, 2H), 2.82-2.76 (m, 4H), 2.71 (s, 1H), 2.44-2.34 (m, 2H), 2.32 (s, 3H), 2.11-1.96 (m, 2H), 1.88 (d, *J* = 12.4 Hz, 2H), 1.76-1.68 (m, 2H); 530.3 $[M+H]^+$
103		(R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	550.44 $[M+H]^+$
104		(R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.23 (d, *J* = 1.0 Hz, 1H), 7.51 (q, *J* = 8.3 Hz, 1H), 7.41 (s, 1H), 7.12-7.06 (m, 2H), 7.00 (d, *J* = 9.2 Hz, 1H), 6.88-6.77 (m, 2H), 6.47 (d, *J* = 1.0 Hz, 1H), 5.83 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.08 (td, *J* = 7.9, 4.4 Hz, 1H), 3.86 (q, *J* = 7.9 Hz, 1H), 3.18 (d, *J* = 11.7 Hz, 2H), 2.78-2.69 (m, 11H), 2.44 (dtd, *J* = 11.7, 7.6, 3.8 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 2.28-2.23 (m, 1H), 1.96 (d, *J* = 12.2 Hz, 2H), 1.72 (qd, *J* = 12.2, 3.3 Hz, 2H); 550.44$[M+H]^+$
105		(R)-6-(3-(4-氯-2-氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (s, 1H), 7.73 (s, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.13-7.04 (m, 2H), 6.92 (d, *J* = 8.9 Hz, 1H), 6.86-6.79 (m, 2H), 6.48 (s, 1H), 5.82 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.06 (td, *J* = 7.9, 4.3Hz, 1H), 3.86 (s, 3H), 3.85-3.79 (m, 1H), 3.55 (d, *J* = 11.1 Hz, 2H), 2.83-2.75 (m, 1H), 2.72-2.39 (m, 11H), 2.31 (s, 3H), 2.29-2.18 (m, 1H), 1.96-1.88 (m, 2H), 1.80 (qd, *J* = 12.0, 3.7 Hz, 2H); 582.3$[M+H]^+$

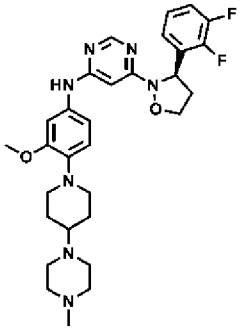
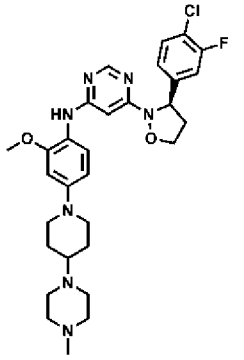
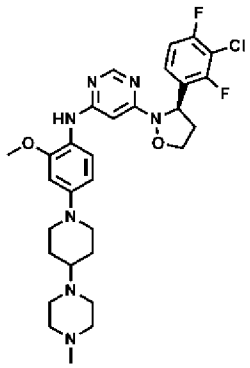
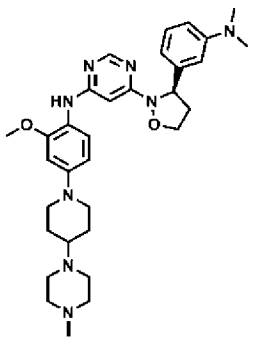
106		(R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (d, *J* = 1.1 Hz, 1H), 7.29 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.05-6.80 (m, 6H), 6.48 (d, *J* = 1.1 Hz, 1H), 5.85 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.07 (td, *J* = 7.8, 4.2 Hz, 1H), 3.87 (s, 3H), 3.85-3.81 (m, 1H), 3.55 (d, *J* = 11.6 Hz, 2H), 2.86-2.76 (m, 1H), 2.73-2.55 (m, 7H), 2.54-2.39 (m, 4H), 2.31 (s, 3H), 2.30-2.21 (m, 1H), 1.92 (d, *J* = 12.3 Hz, 2H), 1.81 (qd, *J* = 11.9, 3.8 Hz, 2H); 566.4[M+H]$^+$
107		(R)-N-(3-甲基-4-(4-甲基哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 1.1 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.25-7.22 (m, 1H), 7.14-7.02 (m, 3H), 6.59 (s, 1H), 6.45 (d, *J* = 1.1 Hz, 1H), 5.67 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.12 (td, *J* = 7.8, 4.4 Hz, 1H), 3.88 (q, *J* = 7.8 Hz, 1H), 3.06-2.95 (m, 4H), 2.80-2.59 (m, 5H), 2.43 (s, 3H), 2.42-2.37 (m, 1H), 2.31 (s, 3H); 431.3 [M+H]$^+$
108		(R)-N-(2-甲基-4-嗎啉基苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (s, 1H), 7.46-7.30 (m, 4H), 7.25-7.22 (m, 2H), 6.84-6.76 (m, 2H), 6.36 (s, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 5.66 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.07 (td, *J* = 7.9, 4.4 Hz, 1H), 3.87 (q, *J* = 7.0, 5.9 Hz, 4H), 3.84-3.79 (m, 1H), 3.18 (t, *J* = 4.9 Hz, 4H), 2.78-2.65 (m, 1H), 2.42-2.30 (m, 1H), 2.23 (s, 3H); 418.3 [M+H]$^+$
109		(R)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.93 (s, 1H), 8.07-8.02 (m, 1H), 7.41-7.27 (m, 5H), 7.11 (s, 1H), 6.65 (s, 1H), 5.88-5.80 (m, 1H), 5.59 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.24 (td, *J* = 7.6, 5.3 Hz, 1H), 4.02 (q, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.40 (s, 7H), 3.22 (d, *J* = 11.7 Hz, 2H), 3.10-2.98 (m, 1H), 2.91-2.82 (m, 1H), 2.79 (s, 3H), 2.77-2.69 (m, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.49-2.39 (m, 1H), 2.13-2.05 (m, 3H), 1.95-1.83 (m, 2H), 1.20 (t, *J* = 7.5 Hz, 3H); 558.4 [M+H]$^+$
110		(R)-N-(2-甲氧基-4-嗎啉基苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 1.0 Hz, 1H), 7.54 (d, *J* = 9.3 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.35 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.27-7.24 (m, 1H), 6.98 (s, 1H), 6.53 (dd, *J* = 6.3, 2.6 Hz, 2H), 6.40 (d, *J* = 1.0 Hz, 1H), 5.67 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.12 (td, *J* = 7.8,

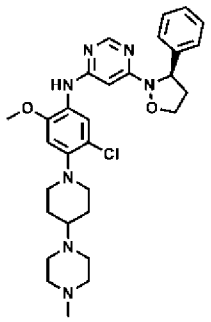
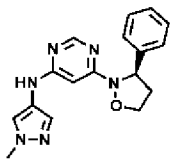
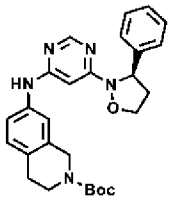
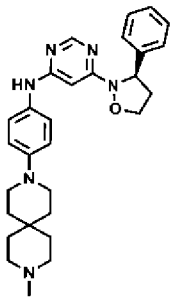
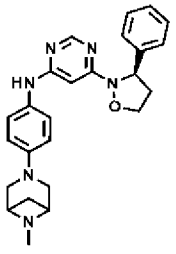
			4.4 Hz, 1H), 3.93-3.86 (m, 5H), 3.85 (s, 3H), 3.20-3.11 (m, 4H), 2.72 (dtd, *J* = 12.3, 8.0, 4.4 Hz, 1H), 2.39 (ddt, *J* = 11.7, 7.7, 3.9 Hz, 1H); 434.25 $[M+H]^+$
111		(R)-N4-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-2,4-二胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 7.44-7.39 (m, 3H), 7.34 (dd, *J* = 8.4, 6.7 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.15 (s, 1H), 6.55-6.47 (m, 2H), 5.61 (dd, *J* = 8.6, 4.4 Hz, 1H), 5.07 (s, 2H), 4.06 (td, *J* = 7.8, 4.6 Hz, 1H), 3.86 (q, *J* = 7.9 Hz, 1H), 3.83 (s, 3H), 3.70 (d, *J* = 12.2 Hz, 2H), 2.80-2.61 (m, 11H), 2.38 (s, 3H), 2.33-2.30 (m, 2H), 1.97 (d, *J* = 12.5 Hz, 2H), 1.72 (q, *J* = 13.1, 9.2 Hz, 2H); 545.40 $[M+H]^+$
112		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-4-(3-苯基異噁唑啶-2-基)-1,3,5-三啡-2-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.33 (s, 1H), 7.59-7.28 (m, 7H), 6.55-6.45 (m, 1H), 6.26 (s, 1H), 5.69-5.45 (m, 1H), 4.31 (s, 1H), 4.07 (q, *J* = 7.7 Hz, 1H), 3.83 (s, 3H), 3.64 (d, *J* = 11.9 Hz, 2H), 2.91-2.83 (m, 1H), 2.69 (t, *J* = 11.4 Hz, 6H), 2.58 (s, 3H), 2.47-2.37 (m, 3H), 2.34 (s, 3H), 1.95 (d, *J* = 12.5 Hz, 2H), 1.78-1.68 (m, 2H); 531.3 $[M+H]^+$
113		(R)-2-甲氧基-N4-(1-甲基哌啶-4-基)-N1-(6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)苯-1,4-二胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 12.30 (s, 1H), 10.70-10.51 (m, 1H), 8.02-7.96 (m, 1H), 7.40-7.26 (m, 5H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.32-6.18 (m, 1H), 5.71 (s, 1H), 5.56 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 1H), 4.03 (q, *J* = 7.5 Hz, 1H), 3.79-3.68 (m, 3H), 3.67-3.49 (m, 3H), 3.36 (d, *J* = 12.3 Hz, 1H), 3.25-3.12 (m, 1H), 2.95-2.75 (m, 5H), 2.48-2.37 (m, 1H), 2.24 (d, *J* = 14.3 Hz, 2H), 1.99 (q, *J* = 13.8, 11.8 Hz, 2H); 461.3 $[M+H]^+$
114		(R)-N-(2-甲氧基-5-甲基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 9.13 (s, 1H), 8.15 (s, 1H), 7.39-7.17 (m, 6H), 6.61 (s, 1H), 6.08 (s, 1H), 5.62 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.21-4.12 (m, 1H), 3.95 (q, *J* = 7.7 Hz, 1H), 3.81 (s, 3H), 3.42-3.19 (m, 3H), 3.09 (s, 5H), 2.86-2.57 (m, 7H), 2.46-2.36 (m, 1H), 2.21 (s, 3H), 2.09-1.97 (m, 4H), 1.85-1.72 (m, 2H); 544.4 $[M+H]^+$

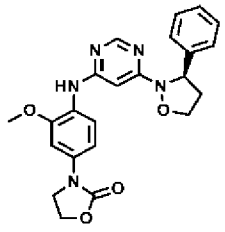
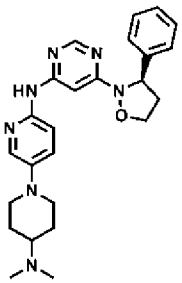
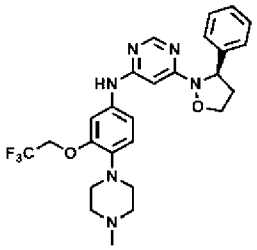
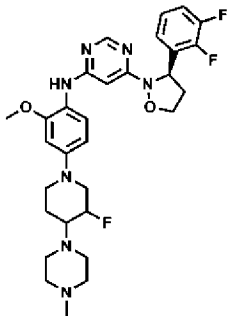
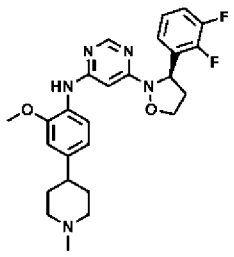
115		(R)-1'-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-N,N-二甲基-[1,4'-聯哌啶]-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.83 (s, 1H), 9.07 (s, 1H), 8.19 (d, J = 0.9 Hz, 1H), 7.38-7.35 (m, 3H), 7.29-7.26 (m, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.57 (dd, J = 8.8, 2.5 Hz, 1H), 6.05 (s, 1H), 5.51 (dd, J = 8.6, 5.2 Hz, 1H), 4.20 (td, J = 7.7, 4.2 Hz, 1H), 3.97-3.87 (m, 3H), 3.79 (s, 3H), 3.69 (d, J = 12.0 Hz, 2H), 3.48-3.35 (m, 2H), 3.11-2.99 (m, 2H), 2.88-2.70 (m, 8H), 2.50 (s, 6H), 2.32-2.24 (m, 2H), 2.14-2.08 (m, 2H); 558.5 $[M+H]^+$
116		N-(4-(4-((1R,4R)-5-乙基-2,5-二氮雜雙環[2.2.1]庚-2-基)哌啶-1-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 7.98 (s, 1H), 7.37-6.98 (m, 7H), 6.64-6.44 (m, 2H), 5.73 (s, 1H), 5.56-5.40 (m, 1H), 4.65-4.54 (m, 1H), 4.44-4.30 (m, 1H), 4.23 (q, J = 7.1 Hz, 1H), 4.13-3.93 (m, 2H), 3.91-3.56 (m, 6H), 3.54-3.04 (m, 5H), 2.95-2.69 (m, 3H), 2.57-2.25 (m, 3H), 2.19-1.74 (m, 5H), 1.34-1.23 (m, 2H); 556.4 $[M+H]^+$
117		(R)-N-(3-乙基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.20 (d, J = 1.0 Hz, 1H), 8.10 (s, 1H), 7.45-7.39 (m, 2H), 7.35 (dd, J = 8.5, 6.8 Hz, 2H), 7.26-7.22 (m, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.10-7.02 (m, 2H), 6.49 (d, J = 1.0 Hz, 1H), 5.65 (dd, J = 8.6, 4.7 Hz, 1H), 4.13 (td, J = 7.8, 4.4 Hz, 1H), 3.88 (q, J = 7.9 Hz, 1H), 3.12 (d, J = 12.0 Hz, 2H), 2.87 (s, 6H), 2.71 (dqd, J = 26.2, 8.1, 7.3, 4.3 Hz, 7H), 2.60-2.52 (m, 1H), 2.48 (s, 3H), 2.39 (dtd, J = 12.5, 7.9, 4.7 Hz, 1H), 1.99-1.92 (m, 2H), 1.74 (qd, J = 11.7, 3.7 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H); 528.42$[M+H]^+$
118		(R)-N-(4-(4-(4-乙基哌啉-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.30 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.25-7.22 (m, 1H), 6.70 (s, 1H), 6.57-6.52 (m, 2H), 6.41 (s, 1H), 5.68 (dd, J = 8.7, 4.5 Hz, 1H), 4.16-4.07 (m, 1H), 3.92-3.86 (m, 1H), 3.84 (s, 3H), 3.71 (d, J = 12.2 Hz, 2H), 2.78-2.65 (m, 6H), 2.54 (s, 2H), 2.51-2.35 (m, 5H), 1.97 (d, J = 12.6 Hz, 2H), 1.75-1.68 (m, 4H), 1.11 (t, J = 7.2 Hz, 3H); 544.3 $[M+H]^+$

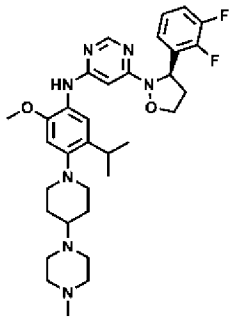
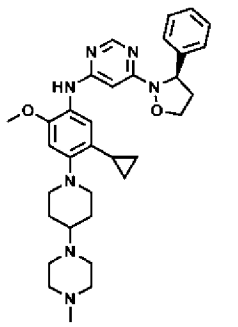
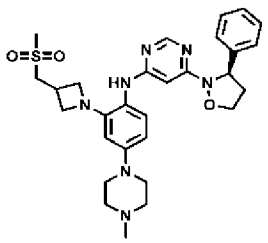
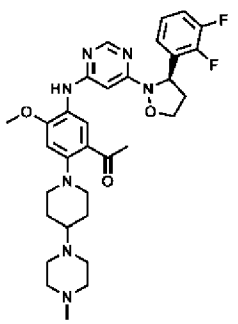
119		(R)-N-(4-(4-(二甲胺基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.23 (s, 1H), 7.83 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.43-7.38 (m, 2H), 7.34 (td, *J* = 8.4, 7.9, 2.8 Hz, 2H), 7.27-7.23 (m, 1H), 6.55-6.47 (m, 2H), 6.26 (d, *J* = 2.8 Hz, 1H), 5.64 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.14 (td, *J* = 7.7, 4.5 Hz, 1H), 3.95-3.88 (m, 1H), 3.83 (s, 3H), 3.80-3.73 (m, 2H), 3.30-3.18 (m, 1H), 2.86-2.71 (m, 9H), 2.45-2.34 (m, 1H), 2.19-2.12 (m, 2H), 1.90 (qd, *J* = 12.2, 3.8 Hz, 2H); 475.3 $[M+H]^+$
120		(R)-N-(2-甲氧基-4-(4-嗎啉基哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.50-7.41 (m, 3H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.26-7.22 (m, 1H), 6.98 (s, 1H), 6.57-6.51 (m, 2H), 6.40-6.36 (m, 1H), 5.67 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.11 (td, *J* = 7.8, 4.5 Hz, 1H), 3.92-3.86 (m, 1H), 3.84 (s, 3H), 3.76 (t, *J* = 4.6 Hz, 3H), 3.71 (d, *J* = 12.1 Hz, 2H), 2.79-2.70 (m, 3H), 2.63 (t, *J* = 4.7 Hz, 3H), 2.43-2.34 (m, 3H), 2.07 (s, 1H), 1.98 (d, *J* = 12.4 Hz, 2H), 1.70 (qd, *J* = 12.1, 3.9 Hz, 2H); 517.3 $[M+H]^+$
121		(R)-2-(4-(1-(2-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)哌啶-4-基)哌啡-1-基)乙-1-醇	560.4 $[M+H]^+$
122		(R)-1-(4-(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)哌啡-1-基)乙-1-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.21-8.10 (m, 2H), 7.45-7.38 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.26-7.17 (m, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 1.1 Hz, 1H), 5.64 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.16-4.07 (m, 1H), 3.87 (q, *J* = 7.8 Hz, 1H), 3.79 (t, *J* = 5.3 Hz, 2H), 3.64 (t, *J* = 5.2 Hz, 2H), 3.22-3.11 (m, 4H), 2.80-2.67 (m, 1H), 2.44-2.32 (m, 1H), 2.15 (s, 3H); 445.3 $[M+H]^+$

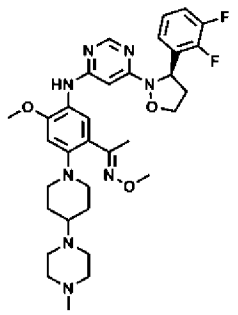
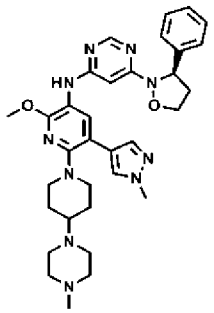
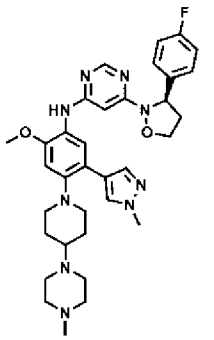
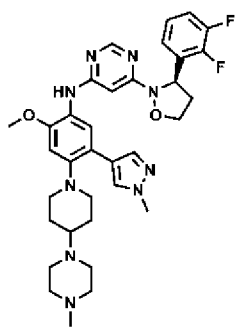
123		(R)-N-(3,5-二氟-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (s, 1H), 7.66 (s, 1H), 7.46-7.33 (m, 4H), 7.31-7.26 (m, 1H), 6.92 (d, *J* = 9.9 Hz, 2H), 6.40 (s, 1H), 5.65 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.25-4.17 (m, 1H), 3.97 (q, *J* = 7.7 Hz, 1H), 3.27 (d, *J* = 11.9 Hz, 3H), 3.12 (t, *J* = 11.8 Hz, 4H), 2.90 (s, 3H), 2.85-2.75 (m, 3H), 2.66 (s, 3H), 2.48-2.38 (m, 2H), 1.99-1.84 (m, 4H); 536.3 $[M+H]^+$
124		(R)-N-(4-(4-(氧 咀-3-基)哌啡-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.52 (s, 1H), 8.48 (s, 1H), 8.04 (s, 1H), 7.36-7.27 (m, 4H), 7.22-7.13 (m, 2H), 6.97-6.87 (m, 2H), 6.14 (s, 1H), 5.58 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.74-4.64 (m, 4H), 4.25-4.15 (m, 1H), 4.04-3.95 (m, 1H), 3.66-3.56 (m, 1H), 3.27 (t, *J* = 5.1 Hz, 4H), 2.88-2.77 (m, 1H), 2.57 (t, *J* = 5.0 Hz, 4H), 2.45-2.35 (m, 1H); 459.3 $[M+H]^+$
125		(R)-6-(3-(3-氯-2-氟 苯基)異 噁 唑 啶-2-基)-N-(3-甲 氧 基-4-(4-(4-甲 基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (s, 1H), 7.50-7.41 (m, 1H), 7.34-7.25 (m, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.87-6.79 (m, 2H), 6.48 (d, *J* = 1.1 Hz, 1H), 5.87 (dd, *J* = 8.9, 4.8 Hz, 1H), 4.07 (tt, *J* = 9.3, 4.6 Hz, 1H), 3.86 -3.81 (m, 4H), 3.55 (d, *J* = 11.1 Hz, 2H), 2.87-2.77 (m, 1H), 2.74-2.54 (m, 7H), 2.43 (ddt, *J* = 11.1, 7.3, 3.8 Hz, 4H), 2.31 (s, 3H), 2.29-2.23 (m, 1H), 1.92 (d, *J* = 12.2 Hz, 2H), 1.81 (qd, *J* = 12.0, 3.8 Hz, 2H); 582.3$[M+H]^+$
126		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-4-(4-(4-甲 基 哌 啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	550.39 $[M+H]^+$
127		(R)-N-(4-(4-(二 甲 胺 基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (d, *J* = 1.1 Hz, 1H), 7.46-7.41 (m, 2H), 7.35 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.28 (t, *J* = 1.5 Hz, 1H), 7.23-7.19 (m, 2H), 6.97-6.92 (m, 2H), 6.37 (d, *J* = 1.1 Hz, 1H), 5.67 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.12 (td, *J* = 7.8, 4.5 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 3.79 (d, *J* = 12.6 Hz, 2H),

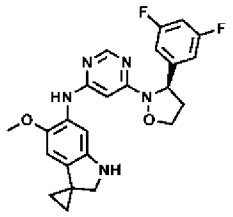
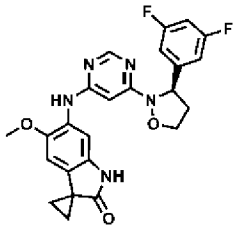
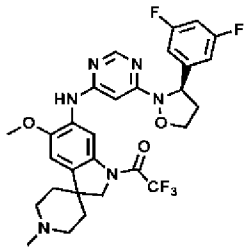
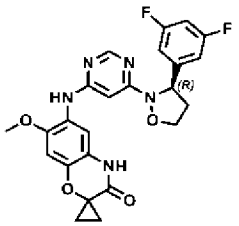
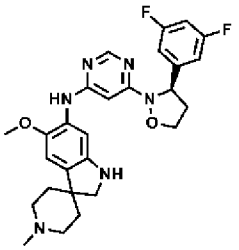
			3.23-3.09 (m, 1H), 2.85-2.67 (m, 9H), 2.44-2.33 (m, 1H), 2.15 (d, *J* = 11.6 Hz, 2H), 1.89 (qd, *J* = 12.1, 4.1 Hz, 3H); 445.24[M+H]$^+$
128		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (d, *J* = 1.0 Hz, 1H), 7.35-7.28 (m, 1H), 7.13-7.01 (m, 2H), 7.00-6.90 (m, 1H), 6.89-6.79 (m, 3H), 6.47 (d, *J* = 1.1 Hz, 1H), 5.89 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.09 (td, *J* = 7.9, 4.2 Hz, 1H), 3.87 (s, 3H), 3.86-3.81 (m, 1H), 3.55 (d, *J* = 11.3 Hz, 2H), 2.86-2.77 (m, 1H), 2.75-2.51 (m, 9H), 2.49-2.40 (m, 2H), 2.33 (s, 3H), 2.30-2.27 (m, 1H), 1.93 (d, *J* = 12.3 Hz, 2H), 1.81 (qd, *J* = 11.9, 3.8 Hz, 2H); 566.4 [M+H]$^+$
129		(R)-6-(3-(4-氯-3-氟 苯基)異 噁 唑 啶-2-基)-N-(2-甲 氧 基-4-(4-(4-甲 基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.27 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.16 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.95 (s, 1H), 6.54 (d, *J* = 7.3 Hz, 2H), 6.37 (s, 1H), 5.63 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.09 (td, *J* = 7.9, 4.2 Hz, 1H), 3.90-3.80 (m, 4H), 3.71 (d, *J* = 12.2 Hz, 2H), 2.78-2.65 (m, 10H), 2.48-2.40 (m, 2H), 2.37-2.25 (m, 4H), 1.97 (d, *J* = 12.5 Hz, 2H), 1.70 (ddd, *J* = 24.4, 12.4, 3.3 Hz, 2H); 582.28[M+H]$^+$
130		(R)-6-(3-(3-氯-2,4-二 氟苯基)異噁唑啶-2-基)-N-(2-甲 氧 基-4-(4-(4-甲 基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (s, 1H), 7.45 (td, *J* = 8.8, 5.6 Hz, 2H), 7.14 (s, 1H), 6.95 (td, *J* = 8.6, 1.8 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 2H), 6.38 (s, 1H), 5.83 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.08 (td, *J* = 8.0, 4.1 Hz, 1H), 3.84 (s, 4H), 3.73 (s, 2H), 2.77 (td, *J* = 16.1, 12.7, 6.9 Hz, 11H), 2.49 (ddt, *J* = 11.5, 7.5, 3.6 Hz, 1H), 2.40 (s, 3H), 2.25 (dtd, *J* = 12.7, 8.0, 4.8 Hz, 1H), 1.98 (d, *J* = 12.7 Hz, 2H), 1.71 (qd, *J* = 12.1, 3.9 Hz, 2H); 600.28 [M+H]$^+$
131		(R)-6-(3-(3-(二 甲 胺 基)苯基)異噁唑啶-2-基)-N-(2-甲 氧 基-4-(4-(4-甲 基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.26 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 6.82 (t, *J* = 2.1 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.55-6.48 (m, 2H), 6.35 (s, 1H), 5.59 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.11 (td, *J* = 7.8, 4.5 Hz, 1H), 3.89-3.81 (m, 4H), 3.70 (d, *J* = 11.9 Hz, 2H), 2.95 (s, 6H), 2.83-2.65 (m, 11H), 2.52-2.45 (m, 1H), 2.40 (s,

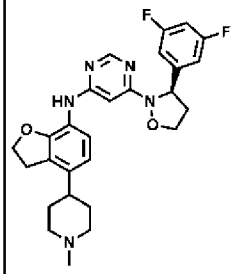
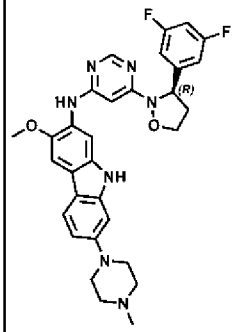
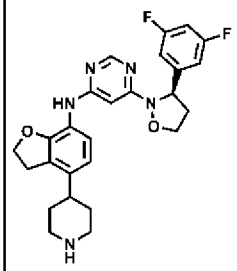
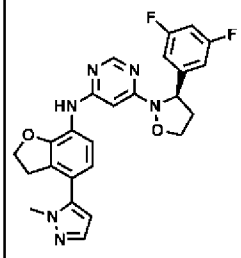
			4H), 1.97 (d, *J* = 12.7 Hz, 2H), 1.71 (qd, *J* = 12.0, 4.0 Hz, 2H); 573.42 $[M+H]^+$
132		(R)-N-(5-氯-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.36 (d, *J* = 1.0 Hz, 1H), 7.98 (s, 1H), 7.47-7.43 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.24 (s, 1H), 6.80 (s, 1H), 6.62 (s, 1H), 6.43 (d, *J* = 1.0 Hz, 1H), 5.68 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.16 (td, *J* = 7.9, 4.5 Hz, 1H), 3.92 (q, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.44 (d, *J* = 11.4 Hz, 2H), 2.80-2.61 (m, 7H), 2.51 (s, 3H), 2.46-2.35 (m, 3H), 2.31 (s, 3H), 1.94 (d, *J* = 12.2 Hz, 2H), 1.85-1.74 (m, 2H); 564.3 $[M+H]^+$
133		(R)-N-(1-甲基-1H-吡唑-4-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 11.36 (s, 1H), 7.98 (s, 1H), 7.49 (d, *J* = 26.4 Hz, 2H), 7.41-7.26 (m, 5H), 6.03 (s, 1H), 5.59 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.30 (q, *J* = 6.8 Hz, 1H), 4.10 (q, *J* = 7.4 Hz, 1H), 3.92 (s, 3H), 2.96-2.85 (m, 1H), 2.52-2.41 (m, 1H); 323.2 $[M+H]^+$
134		(R)-7-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)-3,4-二氫異喹啉-2(1H)-甲酸三級丁酯	^{1}H NMR (400 MHz, 氯仿-*d*) δ 11.65 (s, 1H), 8.04-7.97 (m, 1H), 7.37 (dt, *J* = 7.9, 4.5 Hz, 2H), 7.34-7.27 (m, 3H), 7.25-6.98 (m, 3H), 6.19-6.09 (m, 1H), 5.63-5.54 (m, 1H), 4.59 (s, 1H), 4.32-4.25 (m, 1H), 4.16-4.07 (m, 1H), 3.75-3.54 (m, 2H), 3.18-3.00 (m, 1H), 2.97-2.76 (m, 3H), 2.50-2.40 (m, 1H), 1.67-1.20 (m, 9H); 474.3 $[M+H]^+$
135		(R)-N-(4-(9-甲基-3,9-二氮雜螺[5.5]十一烷-3-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.23 (d, *J* = 1.1 Hz, 1H), 7.46-7.41 (m, 2H), 7.37-7.32 (m, 2H), 7.26-7.21 (m, 2H), 7.20-7.13 (m, 2H), 6.98-6.92 (m, 2H), 6.36 (d, *J* = 1.1 Hz, 1H), 5.65 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.09 (td, *J* = 7.8, 4.5 Hz, 1H), 3.85 (q, *J* = 7.8 Hz, 1H), 3.20-3.13 (m, 4H), 3.05 (s, 2H), 2.77-2.68 (m, 1H), 2.64 (s, 3H), 2.42 (s, 3H), 2.40-2.33 (m, 1H), 1.72-1.65 (m, 7H); 485.4 $[M+H]^+$
136		N-(4-(6-甲基-3,6-二氮雜雙環[3.1.1]庚-3-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.21 (d, *J* = 1.0 Hz, 1H), 7.54 (s, 1H), 7.46-7.30 (m, 4H), 7.27-7.18 (m, 3H), 6.79-6.72 (m, 2H), 6.33 (d, *J* = 1.1 Hz, 1H), 5.67 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.14-4.04 (m, 1H), 3.95 (d, *J* = 6.0 Hz, 2H), 3.90-3.81 (m, 2H), 3.62 (d, *J* = 11.4 Hz, 2H), 3.47

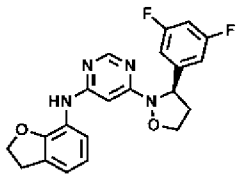
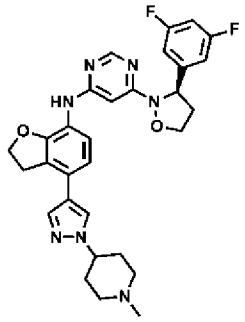
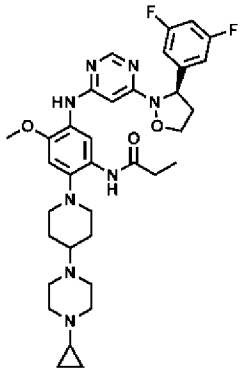
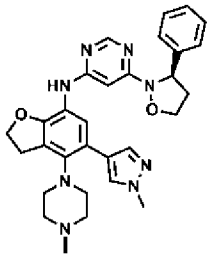
			(d, *J* = 11.3 Hz, 2H), 2.80 (q, *J* = 6.5 Hz, 1H), 2.78-2.66 (m, 1H), 2.37 (dt, *J* = 7.9, 4.5 Hz, 1H), 2.25 (s, 2H), 1.71 (d, *J* = 9.0 Hz, 1H); 429.3 $[M+H]^+$
137		(R)-3-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)噁唑啶-2-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.36 (d, *J* = 1.0 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 2.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.38-7.32 (m, 2H), 7.25-7.21 (m, 1H), 6.97 (s, 1H), 6.73 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.50 (d, *J* = 1.0 Hz, 1H), 5.68 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.56-4.46 (m, 2H), 4.20-4.05 (m, 3H), 3.96-3.87 (m, 4H), 2.80-2.69 (m, 1H), 2.47-2.35 (m, 1H); 434.2 $[M+H]^+$
138		(R)-N-(5-(4-(二甲胺基)哌啶-1-基)吡啶-2-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	
139		(R)-N-(4-(4-甲基哌咔-1-基)-3-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 13.44 (s, 1H), 11.75 (s, 1H), 8.01 (d, *J* = 0.8 Hz, 1H), 7.41-7.26 (m, 4H), 7.07-6.94 (m, 2H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.11-6.03 (m, 1H), 5.59 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.40 (q, *J* = 8.0 Hz, 2H), 4.36-4.29 (m, 1H), 4.17-4.10 (m, 1H), 3.67 (d, *J* = 11.5 Hz, 2H), 3.57-3.46 (m, 2H), 3.39-3.25 (m, 2H), 3.06 (t, *J* = 11.4 Hz, 2H), 2.96-2.85 (m, 4H), 2.52-2.42 (m, 1H); 515.3 $[M+H]^+$
140		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(3-氟-4-(4-甲基哌咔-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.84 (s, 1H), 8.05 (s, 1H), 7.18-6.98 (m, 4H), 6.56-6.47 (m, 2H), 5.83-5.75 (m, 2H), 4.28-4.19 (m, 1H), 4.11-3.96 (m, 2H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.81 (s, 3H), 3.75-3.28 (m, 8H), 3.17-2.99 (m, 2H), 2.98-2.89 (m, 2H), 2.85 (s, 3H), 2.46-2.34 (m, 1H), 2.32-2.19 (m, 1H), 2.05 (s, 1H), 2.00 (d, *J* = 12.5 Hz, 1H); 584.4 $[M+H]^+$
141		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(1-甲基哌啶-4-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 11.01 (s, 1H), 8.07 (s, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.17-6.98 (m, 3H), 6.89-6.82 (m, 2H), 5.86 (s, 1H), 5.80 (dd, *J* = 8.7, 5.0 Hz, 1H), 4.27 (td, *J* = 7.6, 5.0 Hz, 1H), 4.06 (q, *J* = 7.6 Hz, 1H), 3.84 (s, 3H), 3.74-3.66 (m, 2H), 3.01-2.83 (m, 6H),

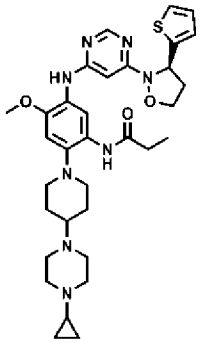
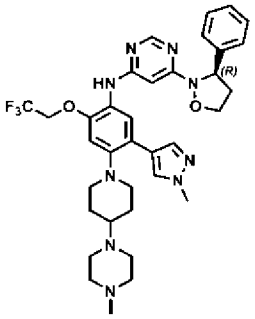
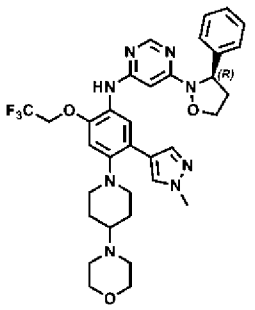
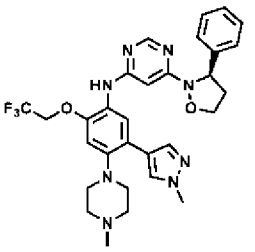
			2.81-2.72 (m, 1H), 2.47-2.37 (m, 1H), 2.28 (q, *J* = 12.3 Hz, 2H), 2.12-2.03 (m, 2H); 482.3 $[M+H]^+$
142		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(5-異丙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 11.18 (s, 1H), 8.07 (s, 1H), 7.17-7.01 (m, 4H), 6.67 (s, 1H), 5.93 (s, 1H), 5.81 (dd, *J* = 8.7, 5.0 Hz, 1H), 4.23 (td, *J* = 7.6, 4.7 Hz, 1H), 4.01 (q, *J* = 7.6 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 7H), 3.34-3.18 (m, 4H), 3.01-2.91 (m, 1H), 2.89 (s, 3H), 2.81 (t, *J* = 11.8 Hz, 2H), 2.40 (td, *J* = 12.7, 7.4 Hz, 1H), 2.18 (d, *J* = 11.9 Hz, 2H), 2.09 (s, 1H), 2.06-1.92 (m, 2H), 1.18 (dd, *J* = 6.9, 2.2 Hz, 6H); 608.4 $[M+H]^+$
143		(R)-N-(5-環丙基-2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 10.86 (s, 1H), 8.04 (s, 1H), 7.41-7.26 (m, 5H), 6.68 (s, 1H), 6.59 (s, 1H), 5.74 (s, 1H), 5.58 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.25 (td, *J* = 7.6, 5.5 Hz, 1H), 4.03 (q, *J* = 7.5 Hz, 1H), 3.97-3.91 (m, 1H), 3.79 (s, 3H), 3.78-3.64 (m, 7H), 3.56 (d, *J* = 11.6 Hz, 2H), 3.30 (t, *J* = 12.2 Hz, 1H), 2.91 (s, 3H), 2.89-2.85 (m, 1H), 2.84-2.75 (m, 2H), 2.50-2.40 (m, 1H), 2.22 (d, *J* = 11.4 Hz, 2H), 2.09-1.97 (m, 3H), 1.03-0.97 (m, 2H), 0.66-0.60 (m, 2H); 570.5 $[M+H]^+$
144		(R)-N-(4-(4-甲基哌啡-1-基)-2-(3-((甲磺醯基)甲基)氮雜環丁-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.18 (d, *J* = 1.0 Hz, 1H), 7.45-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.25-7.22 (m, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.95 (s, 1H), 6.42 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 6.03 (d, *J* = 1.1 Hz, 1H), 5.63 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.14-4.08 (m, 3H), 3.84 (q, *J* = 7.9 Hz, 1H), 3.73-3.65 (m, 2H), 3.29 (d, *J* = 7.4 Hz, 2H), 3.24 (t, *J* = 5.1 Hz, 3H), 3.19-3.10 (m, 1H), 2.88 (s, 3H), 2.77-2.70 (m, 2H), 2.65 (t, *J* = 5.0 Hz, 4H), 2.39 (s, 3H), 2.38-2.33 (m, 1H); 564.4 $[M+H]^+$
145		(R)-1-(5-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-4-甲氧基-2-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)乙-1-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.34 (s, 1H), 8.04 (s, 1H), 7.36-7.30 (m, 1H), 7.11-7.02 (m, 2H), 6.76 (s, 1H), 6.62 (s, 1H), 6.48 (s, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.13 (td, *J* = 7.9, 4.2 Hz, 1H), 3.98-3.93 (m, 1H), 3.91 (s, 3H), 3.33-3.24 (m, 2H), 2.89-2.73 (m, 4H), 2.67 (s, 6H), 2.58-2.40 (m, 4H), 2.37-2.25 (m, 5H), 2.00 (d, *J* = 12.4 Hz, 2H),

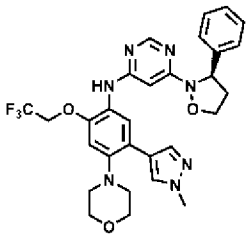
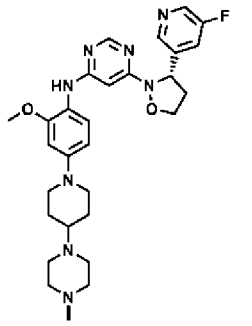
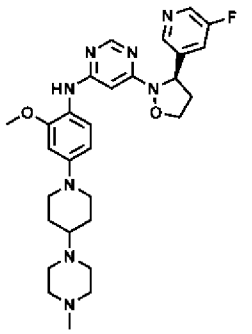
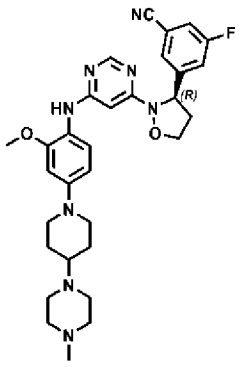
			1.81-1.68 (m, 2H); 608.4 $[M+H]^+$
146		(R,E)-1-(5-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-4-甲氧基-2-(4-(4-甲基哌啡-1-基)哌 啶-1-基)苯 基)乙-1-酮O-甲基肟	^{1}H NMR (400 MHz, 氯仿-*d*) δ 9.46-9.18 (m, 1H), 8.11 (s, 1H), 7.33 (s, 1H), 7.18-6.98 (m, 3H), 6.61 (s, 1H), 5.99 (s, 1H), 5.89-5.74 (m, 1H), 4.31-4.22 (m, 1H), 4.12-4.02 (m, 1H), 3.96 (s, 3H), 3.91-3.71 (m, 6H), 3.61-3.34 (m, 6H), 3.01-2.69 (m, 7H), 2.50-2.37 (m, 2H), 2.36-2.24 (m, 2H), 2.23-2.14 (m, 3H), 2.04-1.87 (m, 2H); 637.4 $[M+H]^+$
147		(R)-N-(2-甲氧基-5-(1-甲基-1H-吡 唑-4-基)-6-(4-(4-甲基哌啡-1-基)哌啶-1-基)吡 啶-3-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (d, *J* = 1.0 Hz, 1H), 8.07 (s, 1H), 7.82 (d, *J* = 0.7 Hz, 1H), 7.75 (s, 1H), 7.47-7.42 (m, 2H), 7.38-7.31 (m, 2H), 7.25-7.20 (m, 1H), 6.85 (s, 1H), 6.37 (d, *J* = 1.1 Hz, 1H), 5.68 (dd, *J* = 8.7, 4.6 Hz, 1H), 4.15 (td, *J* = 7.9, 4.6 Hz, 1H), 3.99-3.88 (m, 6H), 3.55 (d, *J* = 12.4 Hz, 2H), 2.78-2.62 (m, 9H), 2.46-2.38 (m, 1H), 2.35 (s, 4H), 2.06 (s, 3H), 1.92 (d, *J* = 12.4 Hz, 2H), 1.64-1.54 (m, 2H); 611.5 $[M+H]^+$
148		(R)-6-(3-(4-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲 基-1H-吡 唑-4-基)-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.33 (d, *J* = 1.0 Hz, 1H), 7.90-7.84 (m, 2H), 7.78 (s, 1H), 7.46-7.37 (m, 2H), 7.08-6.97 (m, 2H), 6.84 (s, 1H), 6.70 (s, 1H), 6.51 (d, *J* = 1.1 Hz, 1H), 5.66 (dd, *J* = 8.6, 4.6 Hz, 1H), 4.13 (td, *J* = 7.8, 4.3 Hz, 1H), 3.95 (s, 3H), 3.94-3.89 (m, 1H), 3.87 (s, 3H), 3.23 (d, *J* = 10.9 Hz, 2H), 2.84-2.42 (m, 11H), 2.40-2.34 (m, 1H), 2.31 (s, 3H), 2.28-2.20 (m, 1H), 1.99-1.92 (m, 2H), 1.61 (dt, *J* = 11.9, 3.8 Hz, 2H); 628.4 $[M+H]^+$
149		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌啡-1-基)哌 啶-1-基)苯 基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.33 (d, *J* = 1.0 Hz, 1H), 7.88 (s, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.38-7.29 (m, 1H), 7.13-6.99 (m, 2H), 6.90 (s, 1H), 6.71 (s, 1H), 6.53 (d, *J* = 1.1 Hz, 1H), 5.92 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.11 (td, *J* = 7.9, 4.2 Hz, 1H), 3.95 (s, 3H), 3.93-3.89 (m, 1H), 3.88 (s, 3H), 3.24 (dt, *J* = 11.0, 3.5 Hz, 2H), 2.87-2.36 (m, 11H), 2.32 (s, 3H), 2.30-2.20 (m, 2H), 2.00-1.92 (m, 2H), 1.68-1.53 (m, 2H); 646.3 $[M+H]^+$

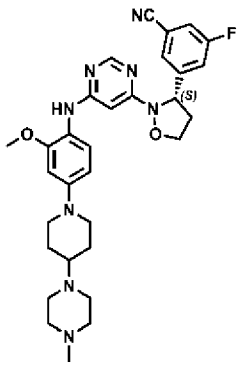
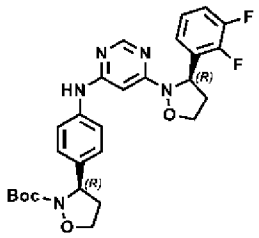
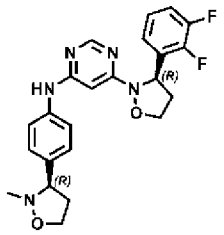
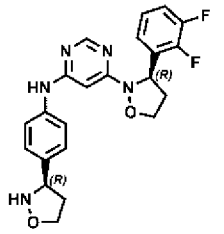
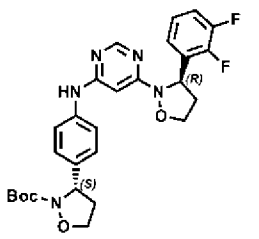
150		(R)-N-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-5'-甲氧基螺[環丙烷-1,3'-吲哚啉]-6'-胺	452.1 $[M+H]^+$
151		(R)-6'-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5'-甲氧基螺[環丙烷-1,3'-吲哚啉]-2'-酮	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.68 (s, 1H), 8.27-8.20 (m, 1H), 7.57 (s, 1H), 7.13 (ddd, J = 6.7, 5.3, 2.9 Hz, 2H), 6.81 (s, 1H), 6.54 (s, 1H), 5.55 (dd, J = 8.7, 5.0 Hz, 1H), 4.16 (td, J = 7.9, 3.9 Hz, 1H), 3.76 (s, 3H), 3.39 (dt, J = 10.9, 6.4 Hz, 2H), 2.76 (ddd, J = 12.2, 8.3, 4.4 Hz, 1H), 2.26 (ddt, J = 11.8, 7.7, 4.0 Hz, 1H), 1.55 (q, J = 3.6, 3.2 Hz, 2H), 1.42 (q, J = 3.5 Hz, 2H); 466.3 $[M+H]^+$
152		(R)-1-(6-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-甲氧基-1'-甲基螺[吲哚啉-3,4'-六氫吡啶]-1-基)-2,2,2-三氟乙-1-酮	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.56 (s, 1H), 8.21 (d, J = 1.0 Hz, 1H), 7.13 (dtd, J = 9.6, 5.2, 2.1 Hz, 3H), 6.53 (s, 1H), 4.18-4.13 (m, 2H), 3.86 (s, 3H), 3.84-3.78 (m, 2H), 2.93 (s, 2H), 2.82-2.74 (m, 2H), 2.40-2.32 (m, 4H), 2.30-2.22 (m, 2H), 2.02 (d, J = 12.3 Hz, 3H), 1.71 (s, 2H); 605.4 $[M+H]^+$
153		(R)-6-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-7-甲氧基螺[苯并[b][1,4]噁 咻-2,1'-環丙烷]-3(4H)-酮	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.64 (s, 1H), 7.31 (s, 1H), 7.16-7.08 (m, 3H), 6.69 (s, 1H), 6.38 (s, 1H), 5.55 (dd, J = 8.8, 5.1 Hz, 1H), 4.15 (td, J = 7.9, 3.9 Hz, 1H), 3.83 (q, J = 7.9 Hz, 1H), 3.73 (s, 3H), 2.78-2.71 (m, 2H), 2.26 (ddd, J = 12.7, 8.4, 5.0 Hz, 1H), 1.25 (q, J = 4.1, 3.2 Hz, 2H), 1.16-1.12 (m, 2H); 482.3 $[M+H]^+$
154		(R)-N-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-5-甲氧基-1'-甲基螺[吲哚啉-3,4'-六氫吡啶]-6-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.18 (d, J = 1.0 Hz, 1H), 7.13 (td, J = 7.4, 2.9 Hz, 3H), 7.01 (s, 1H), 6.79 (s, 1H), 6.43 (s, 1H), 4.14 (td, J = 7.8, 3.8 Hz, 1H), 3.72 (s, 3H), 3.28 (s, 3H), 2.88-2.69 (m, 4H), 2.30 (s, 3H), 2.24 (ddd, J = 12.9, 8.4, 5.1 Hz, 2H), 2.17 (d, J = 6.9 Hz, 2H), 1.91-1.80 (m, 2H), 1.60 (d, J = 12.9 Hz, 2H); 509.3 $[M+H]^+$

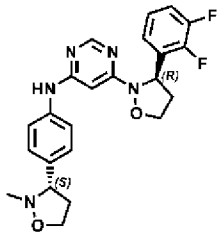
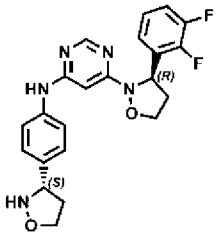
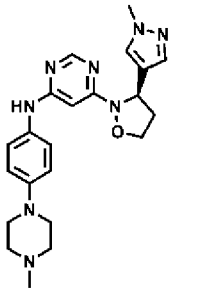
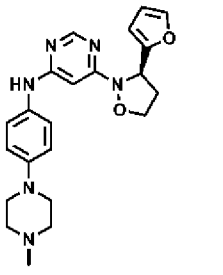
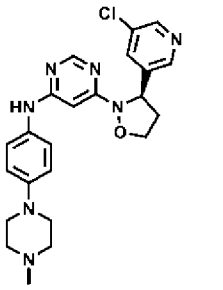
155		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(1-甲基哌啶-4-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.16 (d, J = 1.0 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.11 (dd, J = 7.6, 2.9 Hz, 3H), 6.70 (d, J = 8.3 Hz, 1H), 6.28 (s, 1H), 4.55 (t, J = 9.0 Hz, 2H), 4.14 (td, J = 7.9, 3.8 Hz, 2H), 3.81 (q, J = 7.9 Hz, 2H), 3.22 (t, J = 8.7 Hz, 2H), 2.87 (dt, J = 11.7, 3.2 Hz, 2H), 2.76 (dt, J = 8.4, 4.5 Hz, 2H), 2.47-2.37 (m, 1H), 2.30-2.21 (m, 1H), 2.19 (s, 3H), 1.96 (td, J = 11.0, 4.4 Hz, 2H), 1.68 (td, J = 9.5, 3.1 Hz, 2H); 494.4 $[M+H]^+$
156		(R)-N-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-3-甲氧基-7-(4-甲基哌啡-1-基)-9H-咔唑-2-胺	572.3 $[M+H]^+$
157		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(哌啶-4-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.17 (d, J = 0.9 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.12 (qd, J = 6.9, 3.0 Hz, 3H), 6.69 (d, J = 8.3 Hz, 1H), 6.28 (s, 1H), 4.55 (t, J = 9.1 Hz, 2H), 4.14 (td, J = 7.8, 3.8 Hz, 2H), 3.81 (q, J = 7.9 Hz, 2H), 3.22 (t, J = 8.7 Hz, 2H), 3.06 (d, J = 11.8 Hz, 2H), 2.76 (ddp, J = 12.1, 7.6, 3.8 Hz, 1H), 2.68-2.54 (m, 3H), 2.24 (dtd, J = 16.2, 8.2, 4.1 Hz, 1H), 1.68 (d, J = 12.3 Hz, 2H), 1.63-1.49 (m, 2H); 480.4 $[M+H]^+$
158		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(1-甲基-1H-吡唑-5-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.25 (d, J = 0.9 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.13 (dtd, J = 7.6, 4.2, 2.2 Hz, 3H), 6.91 (d, J = 8.3 Hz, 1H), 6.53 (s, 1H), 6.39 (d, J = 1.9 Hz, 1H), 5.57 (dd, J = 8.7, 5.0 Hz, 1H), 4.61 (t, J = 8.7 Hz, 2H), 4.18 (td, J = 7.9, 3.9 Hz, 1H), 3.85 (q, J = 7.9 Hz, 1H), 3.79 (s, 3H), 3.21 (t, J = 8.7 Hz, 2H), 2.78 (dq, J = 8.2, 4.2, 3.6 Hz, 1H), 2.27 (dt, J = 12.6, 3.9 Hz, 1H); 477.3 $[M+H]^+$

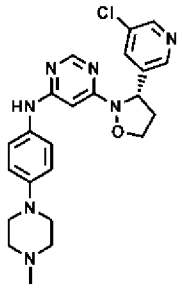
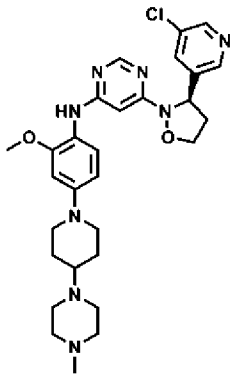
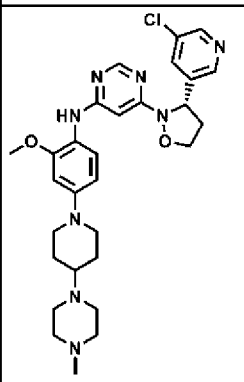
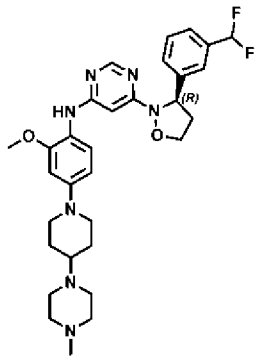
159		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2,3-二氫苯并呋喃-7-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.20 (d, J = 0.9 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.12 (dq, J = 9.5, 3.2 Hz, 3H), 7.03 (dd, J = 7.4, 1.2 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.35 (s, 1H), 5.56 (dd, J = 8.7, 5.0 Hz, 1H), 4.56 (t, J = 8.8 Hz, 2H), 4.15 (td, J = 7.9, 3.8 Hz, 1H), 3.86-3.76 (m, 1H), 3.24 (t, J = 8.7 Hz, 2H), 2.81-2.72 (m, 1H), 2.25 (ddt, J = 11.8, 7.8, 4.0 Hz, 1H); 397.2 [M+H]$^+$
160		(R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(1-(1-甲基哌啶-4-基)-1H-吡唑-4-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.22 (d, J = 1.0 Hz, 1H), 8.14 (s, 1H), 7.88 (s, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.18-7.04 (m, 4H), 6.37 (s, 1H), 5.57 (dd, J = 8.7, 5.0 Hz, 1H), 4.63 (t, J = 8.8 Hz, 2H), 4.48 (t, J = 7.5 Hz, 1H), 4.20-4.09 (m, 1H), 3.83 (d, J = 8.1 Hz, 1H), 3.48-3.36 (m, 4H), 3.11-3.00 (m, 2H), 2.76 (s, 2H), 2.26 (dt, J = 9.1, 4.7 Hz, 4H), 1.92 (s, 3H); 560.4 [M+H]$^+$
161		(R)-N-(2-(4-(4-環丙基哌啡啉-1-基)哌　啶-1-基)-5-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-4-甲氧基苯基)丙醯胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.62 (s, 1H), 8.04 (s, 1H), 7.15-7.07 (m, 3H), 6.81 (s, 1H), 6.33 (s, 1H), 5.55 (dd, J = 8.7, 5.0 Hz, 1H), 4.13 (dt, J = 8.6, 4.2 Hz, 1H), 3.82 (q, J = 6.9, 5.7 Hz, 1H), 3.78 (s, 3H), 3.08 (s, 2H), 2.77 (ddd, J = 12.3, 8.2, 4.1 Hz, 2H), 2.70 (d, J = 13.7 Hz, 4H), 2.50 (d, J = 1.9 Hz, 6H), 2.38 (q, J = 7.6 Hz, 2H), 2.30-2.17 (m, 2H), 1.99 (q, J = 6.0, 5.5 Hz, 1H), 1.89 (d, J = 17.8 Hz, 2H), 1.70 (s, 2H), 1.10 (t, J = 7.5 Hz, 3H), 0.45 (s, 2H), 0.32 (s, 2H); 663.4 [M+H]$^+$
162		(R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-甲基哌啡啉-1-基)-2,3-二氫苯并呋喃-7-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.17 (s, 1H), 7.97 (d, J = 6.5 Hz, 1H), 7.73 (s, 1H), 7.40 (d, J = 7.1 Hz, 3H), 7.35 (t, J = 7.5 Hz, 3H), 7.29-7.22 (m, 1H), 6.31 (s, 1H), 5.53 (dd, J = 8.6, 5.0 Hz, 1H), 4.56 (t, J = 8.9 Hz, 2H), 4.15 (td, J = 7.8, 3.9 Hz, 1H), 3.88 (s, 3H), 3.82 (q, J = 7.9 Hz, 1H), 3.40 (t, J = 8.6 Hz, 2H), 3.10 (d, J = 11.1 Hz, 7H), 2.74 (s, 4H), 2.24 (dtd, J = 12.8, 8.1, 5.0 Hz, 1H); 539.4 [M+H]$^+$

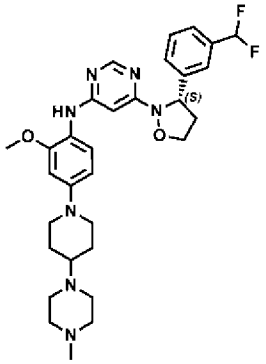
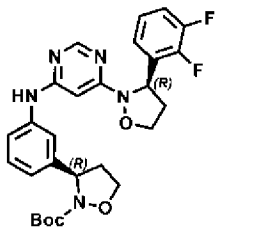
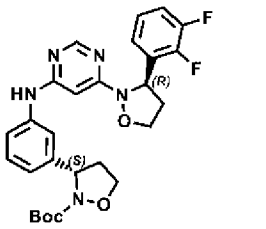
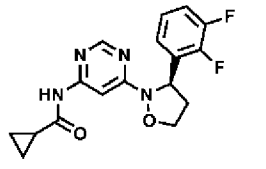
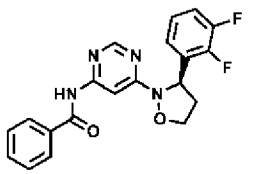
163		(R)-N-(2-(4-(4-環丙基哌啡-1-基)哌啶-1-基)-4-甲氧基-5-((6-(3-(噻吩-2-基)異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)丙醯胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.61 (s, 1H), 8.04 (s, 1H), 7.40 (dd, J = 5.1, 1.3 Hz, 1H), 7.08 (dt, J = 3.5, 1.2 Hz, 1H), 6.98 (dd, J = 5.1, 3.5 Hz, 1H), 6.81 (s, 1H), 6.28 (s, 1H), 5.81 (dd, J = 8.3, 3.9 Hz, 1H), 4.14 (td, J = 7.9, 4.7 Hz, 1H), 3.86 (q, J = 7.9 Hz, 1H), 3.77 (s, 3H), 3.04 (s, 2H), 2.65 (dd, J = 12.2, 3.6 Hz, 4H), 2.53 (d, J = 6.6 Hz, 8H), 2.43-2.32 (m, 4H), 1.85 (s, 2H), 1.67 (s, 2H), 1.58 (s, 1H), 1.10 (t, J = 7.6 Hz, 3H), 0.40 (s, 2H), 0.28 (s, 2H); 633.4 $[M+H]^+$
164		(R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.08 (s, 1H), 7.87 (s, 1H), 7.48 (s, 1H), 7.43-7.37 (m, 2H), 7.34 (dd, J = 8.5, 6.7 Hz, 2H), 7.28-7.23 (m, 1H), 6.90 (s, 1H), 6.23 (s, 1H), 5.53 (dd, J = 8.6, 4.9 Hz, 1H), 4.74 (q, J = 8.9 Hz, 2H), 4.12 (td, J = 7.9, 4.1 Hz, 1H), 3.87 (s, 3H), 3.80 (q, J = 7.9 Hz, 1H), 3.12 (d, J = 11.2 Hz, 2H), 2.73 (qt, J = 7.9, 4.1 Hz, 2H), 2.64-2.50 (m, 9H), 2.24 (hept, J = 7.9 Hz, 5H), 1.84 (dd, J = 13.2, 7.5 Hz, 2H), 1.61-1.43 (m, 3H); 678.5 $[M+H]^+$
165		(R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-嗎啉基哌啶-1-基)-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.08 (s, 1H), 7.87 (s, 1H), 7.48 (s, 1H), 7.44-7.38 (m, 2H), 7.34 (dd, J = 8.5, 6.8 Hz, 2H), 7.30-7.23 (m, 1H), 6.91 (s, 1H), 6.24 (s, 1H), 5.53 (dd, J = 8.6, 4.9 Hz, 1H), 4.75 (q, J = 9.0 Hz, 2H), 4.11 (tt, J = 9.1, 4.6 Hz, 1H), 3.87 (s, 3H), 3.80 (q, J = 7.9 Hz, 1H), 3.60 (s, 3H), 3.12 (s, 2H), 2.73 (dtd, J = 12.1, 7.9, 4.1 Hz, 1H), 2.57 (t, J = 12.6 Hz, 8H), 2.29-2.13 (m, 2H), 1.85 (s, 2H), 1.53 (s, 2H); 665.4 $[M+H]^+$
166		(R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-甲基哌啡-1-基)-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.15 (t, J = 1.1 Hz, 2H), 7.92 (s, 1H), 7.56 (s, 1H), 7.42-7.38 (m, 2H), 7.37-7.32 (m, 2H), 7.28-7.22 (m, 1H), 6.92 (s, 1H), 6.29 (s, 1H), 5.54 (dd, J = 8.6, 4.9 Hz, 1H), 4.79 (q, J = 9.0 Hz, 2H), 4.13 (d, J = 4.1 Hz, 1H), 3.89 (s, 3H), 3.81 (d, J = 8.0 Hz, 1H), 3.26 (s, 4H), 3.05 (s, 4H), 2.81 (s, 3H), 2.73 (dd, J = 8.2, 4.1 Hz, 1H), 2.25 (dt, J = 8.6, 4.7 Hz, 1H); 595.4 $[M+H]^+$

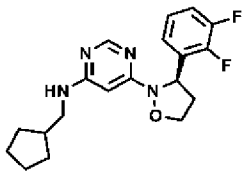
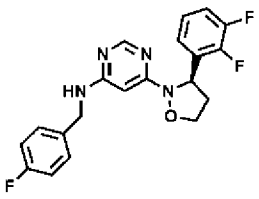
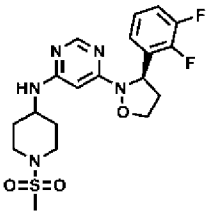
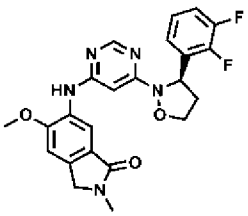
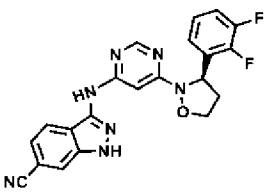
167		(R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-嗎啉基-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.22 (s, 1H), 8.16 (s, 1H), 7.46 (s, 1H), 7.38-7.33 (m, 4H), 7.27 (tt, J = 5.3, 2.4 Hz, 1H), 6.96 (s, 1H), 6.12 (s, 1H), 5.54 (dd, J = 8.5, 5.1 Hz, 1H), 4.79 (dt, J = 8.7, 4.4 Hz, 2H), 4.24-4.18 (m, 1H), 3.93 (d, J = 7.8 Hz, 1H), 3.88 (s, 3H), 3.74 (t, J = 4.5 Hz, 4H), 2.89-2.84 (m, 4H), 2.82 (t, J = 4.6 Hz, 1H), 2.28 (dt, J = 8.0, 4.8 Hz, 1H); 582.4 [M+H]$^+$
168		(S)-6-(3-(5-氟吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.50 (s, 1H), 8.37 (s, 1H), 8.29 (s, 1H), 7.55 (d, J = 9.4 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 6.96 (s, 1H), 6.58-6.51 (m, 2H), 6.41 (s, 1H), 5.76 (dd, J = 8.8, 4.6 Hz, 1H), 4.12 (q, J = 6.9 Hz, 1H), 3.94-3.86 (m, 1H), 3.84 (s, 3H), 3.72 (d, J = 12.0 Hz, 2H), 3.21 (s, 3H), 2.75 (t, J = 12.1 Hz, 4H), 2.68-2.61 (m, 3H), 2.57-2.42 (m, 4H), 2.39-2.34 (m, 2H), 1.96 (d, J = 12.4 Hz, 2H), 1.70 (q, J = 13.0, 12.5 Hz, 2H); 549.3 [M+H]$^+$
169		(R)-6-(3-(5-氟吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.50 (d, J = 1.8 Hz, 1H), 8.37 (d, J = 2.8 Hz, 1H), 8.29 (s, 1H), 7.55 (dt, J = 9.4, 2.3 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.85 (s, 1H), 6.58-6.51 (m, 2H), 6.44-6.39 (m, 1H), 5.76 (dd, J = 8.8, 4.6 Hz, 1H), 4.14-4.10 (m, 1H), 3.93-3.86 (m, 1H), 3.84 (s, 3H), 3.72 (dt, J = 12.1, 3.4 Hz, 2H), 2.84-2.34 (m, 13H), 2.31 (s, 3H), 1.96 (d, J = 11.6 Hz, 2H), 1.70 (qd, J = 12.1, 3.9 Hz, 2H); 549.3 [M+H]$^+$
170		(R)-3-氟基-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲腈	^{1}H NMR (400 MHz, 氯仿-d) δ 8.29 (s, 1H), 7.56 (s, 1H), 7.50 (d, J = 9.1 Hz, 1H), 7.44 (dt, J = 9.4, 2.1 Hz, 1H), 7.26-7.23 (m, 1H), 6.79 (s, 1H), 6.58-6.51 (m, 2H), 6.41 (d, J = 0.9 Hz, 1H), 5.70 (dd, J = 8.8, 4.8 Hz, 1H), 4.12 (td, J = 8.0, 3.9 Hz, 1H), 3.90-3.85 (m, 4H), 3.73 (dd, J = 9.5, 6.3 Hz, 2H), 2.84-2.33 (m, 12H), 2.31 (s, 3H), 2.30-2.23 (m, 1H), 1.97 (d, J = 11.5 Hz, 2H), 1.70 (qd, J = 12.0, 3.8 Hz, 2H); 573.3 [M+H]$^+$

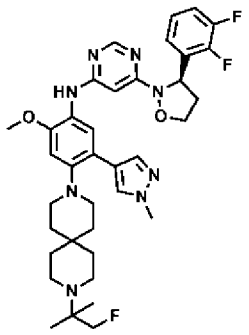
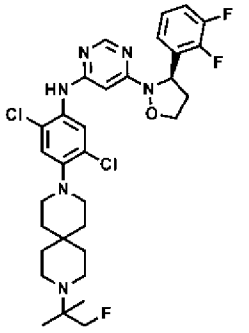
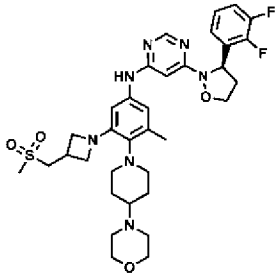
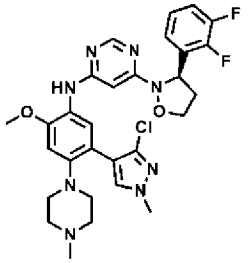
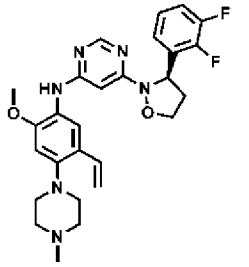
171		(S)-3-氟-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲腈	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (s, 1H), 7.56 (s, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 7.44 (dt, *J* = 9.4, 2.0 Hz, 1H), 7.26-7.23 (m, 1H), 6.77 (s, 1H), 6.58-6.51 (m, 2H), 6.41 (s, 1H), 5.70 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.12 (td, *J* = 8.1, 3.9 Hz, 1H), 3.92-3.85 (m, 4H), 3.72 (d, *J* = 12.5 Hz, 2H), 2.84-2.32 (m, 13H), 2.31 (s, 3H), 1.96 (d, *J* = 11.0 Hz, 2H), 1.70 (qd, *J* = 12.2, 4.1 Hz, 2H); 573.3 [M+H]$^+$
172		(R)-3-(4-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧 啶-4-基)胺 基)苯基)異噁唑啶-2-甲酸三級丁酯	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (d, *J* = 1.0 Hz, 1H), 7.40-7.36 (m, 2H), 7.34-7.27 (m, 3H), 7.10-7.03 (m, 2H), 6.73 (s, 1H), 6.55 (d, *J* = 1.1 Hz, 1H), 5.91 (dd, *J* = 8.7, 4.8 Hz, 1H), 5.22 (dd, *J* = 8.7, 5.5 Hz, 1H), 4.20 (qd, *J* = 8.1, 3.8 Hz, 1H), 4.12 (td, *J* = 8.0, 4.2 Hz, 1H), 3.94-3.84 (m, 2H), 2.88-2.73 (m, 2H), 2.37-2.26 (m, 2H), 1.48 (s, 9H); 526.25 [M+H]$^+$
173		6-((R)-3-(2,3-二氟苯基)異 噁 唑 啶-2-基)-N-(4-((R)-2-甲基異噁唑啶-3-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.32 (d, *J* = 1.1 Hz, 1H), 7.43-7.37 (m, 2H), 7.34-7.28 (m, 3H), 7.11-7.02 (m, 2H), 6.85 (s, 1H), 6.56 (d, *J* = 1.0 Hz, 1H), 5.91 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.16-4.06 (m, 3H), 3.89 (q, *J* = 8.0 Hz, 1H), 3.55 (s, 1H), 2.89-2.79 (m, 1H), 2.76-2.67 (m, 1H), 2.64 (s, 3H), 2.37-2.26 (m, 2H); 440.16 [M+H]$^+$
174		6-((R)-3-(2,3-二氟苯基)異 噁 唑 啶-2-基)-N-(4-((R)-異 噁 唑 啶-3-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (d, *J* = 1.1 Hz, 1H), 7.43-7.39 (m, 2H), 7.33-7.29 (m, 3H), 7.10-7.01 (m, 4H), 6.55 (d, *J* = 1.1 Hz, 1H), 5.90 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.50 (t, *J* = 10.0 Hz, 1H), 4.16-4.09 (m, 2H), 3.88 (q, *J* = 8.2 Hz, 1H), 3.35 (t, *J* = 10.1 Hz, 1H), 2.88-2.80 (m, 1H), 2.74-2.64 (m, 1H), 2.36-2.27 (m, 2H); 426.22 [M+H]$^+$
175		(S)-3-(4-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧 啶-4-基)胺 基)苯基)異噁唑啶-2-甲酸三級丁酯	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (d, *J* = 1.1 Hz, 1H), 7.40-7.27 (m, 5H), 7.09-7.03 (m, 2H), 6.78 (s, 1H), 6.55 (d, *J* = 1.1 Hz, 1H), 5.91 (dd, *J* = 8.9, 4.8 Hz, 1H), 5.22 (dd, *J* = 8.7, 5.4 Hz, 1H), 4.23-4.16 (m, 1H), 4.12 (td, *J* = 7.8, 5.6 Hz, 1H), 3.94-3.84 (m, 2H), 2.88-2.75 (m, 2H), 2.37-2.26 (m, 2H), 1.48 (s, 9H); 526.20 [M+H]$^+$

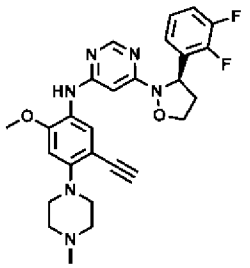
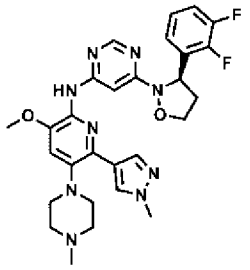
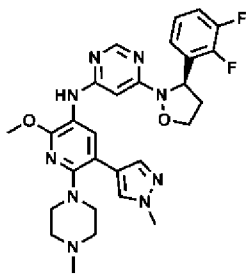
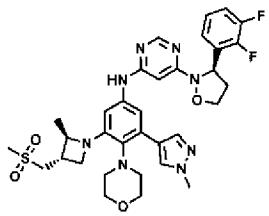
176		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-((S)-2-甲基異噁唑啶-3-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (d, *J* = 1.0 Hz, 1H), 7.42-7.36 (m, 2H), 7.35-7.27 (m, 3H), 7.12-6.99 (m, 2H), 6.94 (s, 1H), 6.57 (d, *J* = 1.1 Hz, 1H), 5.91 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.17-4.04 (m, 3H), 3.89 (q, *J* = 8.0 Hz, 1H), 3.56 (s, 1H), 2.84 (dtd, *J* = 12.3, 8.1, 4.1 Hz, 1H), 2.77-2.66 (m, 1H), 2.64 (s, 3H), 2.37-2.26 (m, 2H); 440.16 [M+H]$^+$
177		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-((S)-異噁唑啶-3-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (d, *J* = 1.1 Hz, 1H), 7.44-7.39 (m, 2H), 7.34-7.29 (m, 3H), 7.13-7.02 (m, 3H), 6.87 (s, 1H), 6.55 (d, *J* = 1.1 Hz, 1H), 5.90 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.50 (t, *J* = 10.1 Hz, 1H), 4.17-4.09 (m, 2H), 3.88 (q, *J* = 8.2 Hz, 1H), 3.35 (t, *J* = 10.1 Hz, 1H), 2.88-2.79 (m, 1H), 2.69 (ddd, *J* = 14.1, 12.3, 8.1 Hz, 1H), 2.33 (ddd, *J* = 12.7, 8.4, 5.4 Hz, 2H); 426.22 [M+H]$^+$
178		(R)-6-(3-(1-甲基-1H-吡唑-4-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.09-6.97 (m, 2H), 6.34 (d, *J* = 0.6 Hz, 1H), 5.54 (dd, *J* = 8.1, 3.3 Hz, 1H), 4.14 (tt, *J* = 8.8, 4.4 Hz, 1H), 4.05-3.95 (m, 1H), 3.86 (d, *J* = 5.6 Hz, 3H), 3.35 (dd, *J* = 8.5, 3.7 Hz, 4H), 3.13-3.03 (m, 4H), 2.69 (s, 3H), 2.60 (dtd, *J* = 12.2, 8.4, 5.8 Hz, 1H), 2.38 (tdd, *J* = 7.9, 6.7, 3.4 Hz, 1H); 421.19 [M+H]$^+$
179		(R)-6-(3-(呋喃-2-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.19 (s, 1H), 7.47 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.42-6.31 (m, 3H), 5.64 (t, *J* = 6.1 Hz, 1H), 4.19 (dt, *J* = 13.6, 6.7 Hz, 1H), 3.96 (q, *J* = 7.8 Hz, 1H), 3.32 (d, *J* = 1.6 Hz, 4H), 3.08-2.99 (m, 4H), 2.65 (s, 3H), 2.57 (dt, *J* = 12.9, 6.5 Hz, 2H); 407.20 [M+H]$^+$
180		(R)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.20 (s, 1H), 8.60 (d, *J* = 1.9 Hz, 1H), 8.55 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 0.9 Hz, 1H), 7.91-7.90 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.94-6.89 (m, 2H), 6.36 (d, *J* = 1.1 Hz, 1H), 3.87 (q, *J* = 7.9 Hz, 1H), 3.11 (t, *J* = 5.1 Hz, 4H), 2.79 (dtt, *J* = 12.2, 7.8, 4.0 Hz, 1H), 2.53 (t, *J* = 5.5 Hz, 4H), 2.33 (ddd, *J* = 12.6, 8.5, 4.8

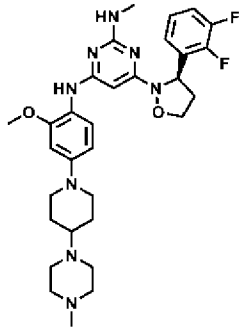
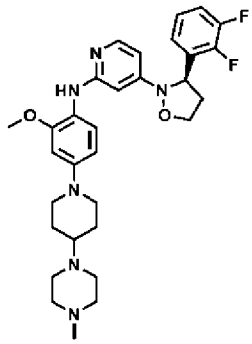
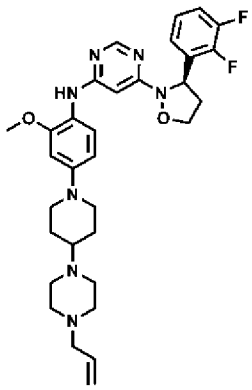
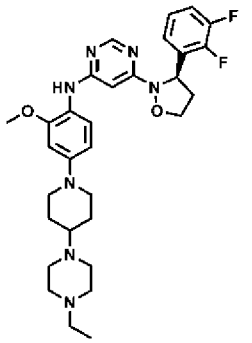
			Hz, 2H), 2.27 (s, 2H), 1.91 (s, 3H); 452.1[M+H]$^+$
181		(S)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 1.9 Hz, 1H), 8.55 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 7.90 (t, J = 2.2 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 6.93-6.89 (m, 2H), 6.36 (s, 1H), 5.63-5.59 (m, 1H), 3.87 (q, J = 8.0 Hz, 2H), 3.08 (t, J = 5.0 Hz, 4H), 2.78 (dtd, J = 12.2, 7.9, 3.9 Hz, 2H), 2.45 (t, J = 5.0 Hz, 4H), 2.37-2.28 (m, 2H), 2.22 (s, 3H), 1.90 (s, 2H); 452.1[M+H]$^+$
182		(R)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 2.3 Hz, 1H), 8.47 (s, 1H), 8.13 (d, J = 1.0 Hz, 1H), 7.89-7.88 (m, 1H), 7.30 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 6.49 (dd, J = 8.8, 2.5 Hz, 1H), 5.59 (dd, J = 8.7, 5.0 Hz, 1H), 4.15 (td, J = 7.8, 3.9 Hz, 1H), 3.82 (t, J = 8.0 Hz, 1H), 3.77 (s, 3H), 3.72 (d, J = 12.4 Hz, 2H), 2.77 (qt, J = 7.9, 3.9 Hz, 2H), 2.67 (td, J = 12.2, 2.4 Hz, 3H), 2.53 (s, 2H), 2.35-2.25 (m, 4H), 2.17 (s, 3H), 1.91 (s, 5H), 1.85 (d, J = 12.5 Hz, 2H), 1.51 (qd, J = 12.1, 3.9 Hz, 3H); 565.2 [M+H]$^+$
183		(S)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	565.3 [M+H]$^+$
184		(R)-6-(3-(3-(二氟甲基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.11 (d, J = 0.6 Hz, 1H), 7.66-7.55 (m, 2H), 7.50-7.43 (m, 2H), 7.32 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 3.1 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.63-6.58 (m, 1H), 6.24 (s, 1H), 5.58 (dd, J = 8.5, 4.8 Hz, 1H), 4.13 (tt, J = 10.5, 5.3 Hz, 1H), 3.97-3.88 (m, 1H), 3.83 (d, J = 6.4 Hz, 3H), 3.80 (d, J = 12.7 Hz, 2H), 2.98 (d, J = 22.3 Hz, 7H), 2.87-2.71 (m, 4H), 2.68-2.65 (m, 4H), 2.39-2.29 (m, 1H), 2.05 (d, J = 11.9 Hz, 2H), 1.78-1.65 (m, 2H); 580.25 [M+H]$^+$

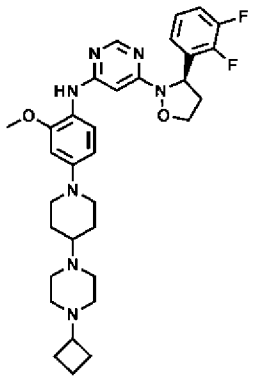
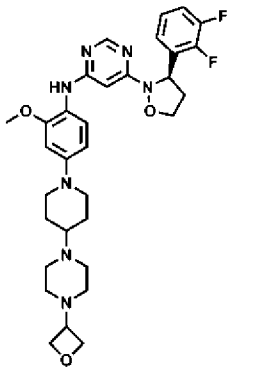
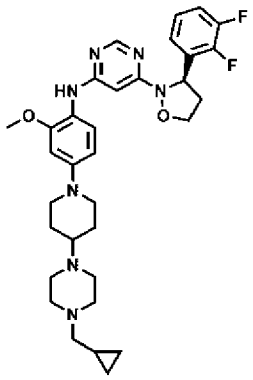
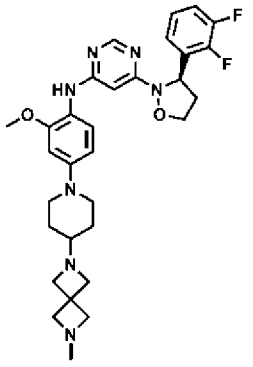
185		(S)-6-(3-(3-(二氟甲基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.65-7.56 (m, 2H), 7.51-7.43 (m, 2H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 3.2 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 6.66-6.57 (m, 1H), 6.24 (s, 1H), 5.58 (dd, *J* = 8.5, 4.8 Hz, 1H), 4.13 (td, *J* = 7.8, 4.3 Hz, 1H), 3.91 (q, *J* = 7.9 Hz, 1H), 3.85 (d, *J* = 6.4 Hz, 3H), 3.80 (d, *J* = 12.6 Hz, 2H), 2.99 (d, *J* = 29.1 Hz, 7H), 2.79 (dqd, *J* = 10.1, 7.5, 4.4 Hz, 4H), 2.68-2.63 (m, 4H), 2.40-2.26 (m, 1H), 2.04 (d, *J* = 12.2 Hz, 2H), 1.73 (tt, *J* = 11.9, 6.1 Hz, 2H); 580.30 $[M+H]^+$
186		(R)-3-(3-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧 啶-4-基)胺 基)苯基)異噁唑啶-2-甲酸三級丁酯	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 1.1 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.33-7.29 (m, 2H), 7.26-7.20 (m, 2H), 7.16-7.12 (m, 1H), 7.09-7.03 (m, 2H), 6.59 (d, *J* = 1.0 Hz, 1H), 5.90 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.23 (dd, *J* = 8.7, 5.4 Hz, 1H), 4.19 (td, *J* = 7.9, 3.7 Hz, 1H), 4.12 (td, *J* = 8.0, 4.3 Hz, 1H), 3.89 (qd, *J* = 8.1, 7.7, 1.9 Hz, 2H), 2.89-2.74 (m, 2H), 2.37-2.25 (m, 2H), 1.48 (s, 9H); 526.25 $[M+H]^+$
187		(S)-3-(3-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧 啶-4-基)胺 基)苯基)異噁唑啶-2-甲酸三級丁酯	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.29 (d, *J* = 1.0 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.32 (p, *J* = 2.7 Hz, 2H), 7.26-7.22 (m, 2H), 7.16-7.12 (m, 1H), 7.06 (qt, *J* = 8.4, 5.8 Hz, 2H), 6.60 (d, *J* = 1.0 Hz, 1H), 5.91 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.24 (dd, *J* = 8.7, 5.3 Hz, 1H), 4.18 (dt, *J* = 7.9, 4.0 Hz, 1H), 4.12 (td, *J* = 8.0, 4.2 Hz, 1H), 3.95-3.85 (m, 2H), 2.89-2.75 (m, 2H), 2.38-2.26 (m, 2H), 1.47 (s, 9H); 526.20 $[M+H]^+$
188		(R)-N-(6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)環丙烷甲醯胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.38 (d, *J* = 1.1 Hz, 1H), 8.26 (s, 1H), 7.91 (d, *J* = 1.1 Hz, 1H), 7.31-7.27 (m, 1H), 7.12-6.98 (m, 2H), 5.86 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.18 (td, *J* = 7.9, 3.9 Hz, 1H), 3.93 (td, *J* = 8.4, 7.3 Hz, 1H), 2.92-2.83 (m, 1H), 2.38-2.28 (m, 1H), 1.55 (dt, *J* = 7.8, 4.7 Hz, 1H), 1.18-1.10 (m, 2H), 0.97-0.90 (m, 2H); 347.19 $[M+H]^+$
189		(R)-N-(6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)苯甲醯胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.51 (s, 1H), 8.42 (d, *J* = 1.1 Hz, 1H), 8.12 (d, *J* = 1.1 Hz, 1H), 7.95-7.90 (m, 2H), 7.64-7.59 (m, 1H), 7.56-7.50 (m, 2H), 7.34-7.29 (m, 1H), 7.13-7.03 (m, 2H),

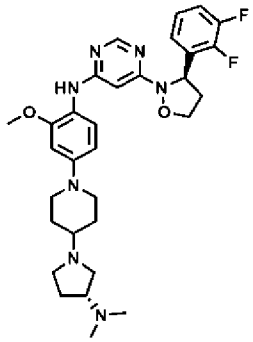
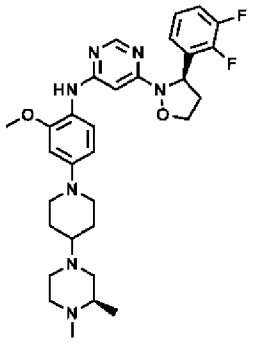
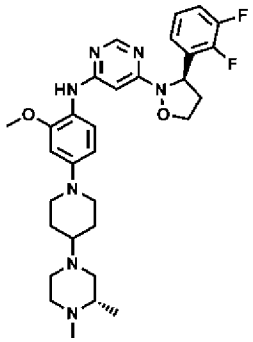
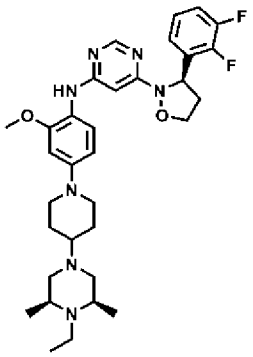
			5.91 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.24 (td, *J* = 8.0, 4.0 Hz, 1H), 3.99 (td, *J* = 8.4, 7.4 Hz, 1H), 2.96-2.85 (m, 1H), 2.43-2.32 (m, 1H); 383.20 $[M+H]^+$
190		(R)-N-(環戊基甲基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.19 (s, 1H), 7.34 (qd, *J* = 4.8, 1.9 Hz, 1H), 7.12-6.97 (m, 2H), 6.13 (d, *J* = 1.0 Hz, 1H), 5.92 (dd, *J* = 8.8, 4.7 Hz, 1H), 5.00-4.84 (m, 1H), 4.14 (ddd, *J* = 8.3, 7.5, 4.3 Hz, 1H), 3.93 (q, *J* = 8.0 Hz, 1H), 3.19 (s, 2H), 2.88-2.79 (m, 1H), 2.32 (tdd, *J* = 12.5, 6.5, 3.0 Hz, 1H), 2.16 (hept, *J* = 7.6 Hz, 1H), 1.89-1.77 (m, 2H), 1.71-1.59 (m, 3H), 1.32-1.20 (m, 3H); 361.22 $[M+H]^+$
191		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-氟苯甲基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.24 (d, *J* = 1.0 Hz, 1H), 7.35-7.28 (m, 3H), 7.08-7.00 (m, 4H), 6.14 (d, *J* = 1.1 Hz, 1H), 5.89 (dd, *J* = 8.8, 4.7 Hz, 1H), 5.21 (s, 1H), 4.50 (d, *J* = 5.9 Hz, 2H), 4.10 (tt, *J* = 7.8, 3.5 Hz, 1H), 3.84 (q, *J* = 7.9 Hz, 1H), 2.87-2.76 (m, 1H), 2.36-2.24 (m, 1H); 387.17 $[M+H]^+$
192		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(1-(甲磺醯基)哌啶-4-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.22 (s, 1H), 7.36-7.27 (m, 1H), 7.12-6.99 (m, 3H), 6.13 (d, *J* = 1.0 Hz, 1H), 5.89 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.14 (td, *J* = 7.9, 4.4 Hz, 1H), 3.92 (q, *J* = 7.9 Hz, 1H), 3.77 (d, *J* = 12.8 Hz, 2H), 2.94 (t, *J* = 12.0 Hz, 2H), 2.88-2.78 (m, 5H), 2.37-2.27 (m, 1H), 2.21-2.11 (m, 2H), 1.68-1.61 (m, 2H); 440.21 $[M+H]^+$
193		(R)-6-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-甲氧基-2-甲基異吲哚啉-1-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.38 (d, *J* = 1.0 Hz, 1H), 8.37 (s, 1H), 7.35-7.27 (m, 2H), 7.12-7.02 (m, 2H), 6.97 (s, 1H), 6.58 (d, *J* = 1.0 Hz, 1H), 5.92 (dd, *J* = 8.9, 4.8 Hz, 1H), 4.33 (s, 2H), 4.13 (ddd, *J* = 8.3, 7.5, 4.2 Hz, 1H), 3.96 (s, 3H), 3.92 (q, *J* = 8.0 Hz, 1H), 3.20 (s, 3H), 2.89-2.79 (m, 1H), 2.37-2.26 (m, 1H); 454.13 $[M+H]^+$
194		(R)-3-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-1H-吲哚-6-甲腈	^{1}H NMR (400 MHz, 氯仿-*d*) δ 9.26 (t, *J* = 1.1 Hz, 1H), 8.59 (d, *J* = 1.0 Hz, 1H), 7.65 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.49 (d, *J* = 1.1 Hz, 1H), 7.46 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.33 (td, *J* = 7.0, 6.2, 3.7 Hz, 1H), 7.15-6.98 (m, 2H), 5.95 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.48 (s, 2H), 4.25 (td, *J* = 7.9, 4.0 Hz, 1H), 4.00 (q, *J* =

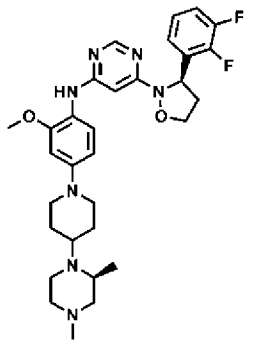
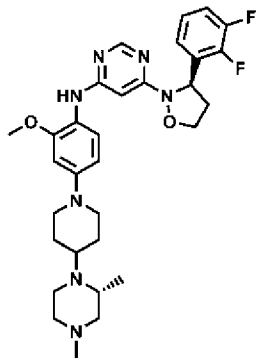
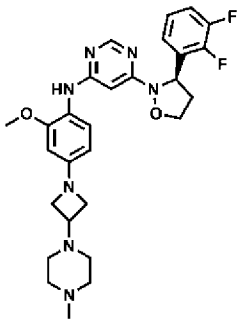
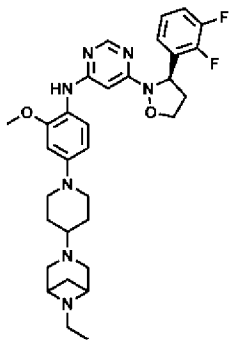
			8.2 Hz, 1H), 2.97-2.87 (m, 1H), 2.45-2.33 (m, 1H); 420.15 $[M+H]^+$
195		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(9-(1-氟基-2-甲基丙-2-基)-3,9-二氮雜螺[5.5]十一烷-3-基)-2-甲氧基-5-(1-甲基-1H-吡唑-4-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.60 (s, 1H), 8.15 (d, *J* = 1.0 Hz, 1H), 8.05 (s, 1H), 7.85 (s, 1H), 7.57 (s, 1H), 7.35 (q, *J* = 8.7 Hz, 2H), 7.27 (q, *J* = 6.8, 6.2 Hz, 2H), 7.20 (dd, *J* = 8.3, 5.2 Hz, 1H), 6.84 (s, 1H), 6.28 (s, 1H), 4.16 (td, *J* = 8.0, 3.8 Hz, 1H), 3.94 (q, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.80 (t, *J* = 5.7 Hz, 4H), 2.45 (d, *J* = 6.5 Hz, 4H), 2.38 (s, 1H), 2.21 (tt, *J* = 8.7, 4.3 Hz, 2H), 1.91 (s, 2H), 1.53 (s, 8H), 1.32 (s, 3H), 1.27 (s, 3H); 691.3 $[M+H]^+$
196		(R)-N-(2,5-二氯-4-(9-(1-氟基-2-甲基丙-2-基)-3,9-二氮雜螺[5.5]十一烷-3-基)苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	649.3 $[M+H]^+$
197		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-5-(3-((甲磺醯基)甲基)氮雜環丁-1-基)-4-(4-嗎啉基哌啶-1-基)苯基)嘧啶-4-胺	684.3 $[M+H]^+$
198		(R)-N-(5-(3-氯-1-甲基-1H-吡唑-4-基)-2-甲氧基-4-(4-甲基哌啡-1-基)苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	597.3 $[M+H]^+$
199		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-甲基哌啡-1-基)-5-乙烯基苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.62 (s, 1H), 8.17 (d, *J* = 1.0 Hz, 1H), 7.76 (s, 1H), 7.39-7.30 (m, 2H), 6.90 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.73 (s, 1H), 6.32 (s, 1H), 5.75 (dd, *J* = 8.9, 5.1 Hz, 1H), 5.57 (dd, *J* = 17.7, 1.6 Hz, 1H), 5.15 (dd, *J* = 10.9, 1.5 Hz, 1H), 4.17 (td, *J* = 8.0, 3.8 Hz, 2H), 3.82 (s, 3H), 2.94 (s, 4H), 2.86-2.76 (m, 2H), 2.59 (s, 2H), 2.32 (s, 3H), 2.26-2.16 (m, 3H), 1.91 (s, 2H); 509.3 $[M+H]^+$

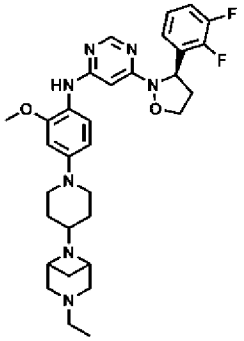
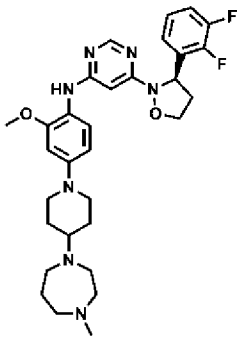
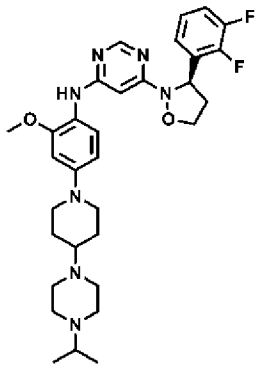
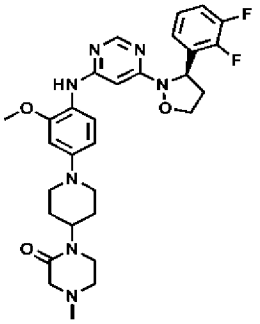
200		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(5-乙炔基-2-甲氧基-4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.64 (d, *J* = 1.2 Hz, 1H), 7.38 (dtd, *J* = 10.3, 8.0, 1.9 Hz, 2H), 7.28 (t, *J* = 6.9 Hz, 1H), 7.23 (dd, *J* = 8.1, 5.1 Hz, 1H), 7.14 (d, *J* = 1.2 Hz, 1H), 6.80 (s, 1H), 6.56 (s, 1H), 5.74 (dd, *J* = 8.8, 5.8 Hz, 1H), 4.31 (td, *J* = 7.8, 3.2 Hz, 1H), 3.94 (q, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.06 (s, 4H), 2.98-2.89 (m, 2H), 2.53 (d, *J* = 5.5 Hz, 2H), 2.25 (s, 3H), 1.91 (s, 4H); 507.3 [M+H]$^+$
201		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-6-(1-甲基-1H-吡唑-4-基)-5-(4-甲基哌啡-1-基)吡啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.31 (t, *J* = 1.3 Hz, 2H), 8.29 (d, *J* = 1.1 Hz, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 7.41-7.35 (m, 1H), 7.34-7.31 (m, 1H), 7.25-7.19 (m, 1H), 5.80 (dd, *J* = 8.7, 5.4 Hz, 1H), 4.01 (q, *J* = 7.9 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 2.97-2.93 (m, 4H), 2.89 (dd, *J* = 12.3, 3.9 Hz, 2H), 2.74 (s, 2H), 2.42 (s, 3H), 2.35-2.26 (m, 2H), 1.91 (s, 2H); 564.3 [M+H]$^+$
202		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-6-(4-甲基哌啡-1-基)吡啶-3-基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.76 (s, 1H), 8.18 (d, *J* = 1.0 Hz, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.39-7.31 (m, 2H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.23-7.19 (m, 1H), 6.42 (s, 1H), 5.75 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.20 (td, *J* = 7.9, 3.7 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.15 (s, 5H), 2.81 (dtd, *J* = 12.0, 8.1, 3.7 Hz, 4H), 2.27-2.16 (m, 2H), 1.91 (s, 3H); 564.3 [M+H]$^+$
203		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-(1-甲基-1H-吡唑-4-基)-5-((2R,3S)-2-甲基-3-((甲磺醯基)甲基)氮雜環丁-1-基)-4-嗎啉基苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.30 (s, 1H), 8.23 (d, *J* = 0.9 Hz, 1H), 7.72 (s, 1H), 7.40 (s, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.23-7.19 (m, 2H), 6.87 (s, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 6.49 (d, *J* = 1.0 Hz, 1H), 4.60 (t, *J* = 7.8 Hz, 1H), 4.22 (d, *J* = 3.8 Hz, 1H), 3.89 (s, 3H), 2.99 (s, 4H), 2.74-2.70 (m, 2H), 2.68-2.66 (m, 1H), 2.33 (t, *J* = 1.9 Hz, 1H), 2.26-2.19 (m, 3H), 1.78 (s, 6H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.24 (s, 3H); 681.3 [M+H]$^+$

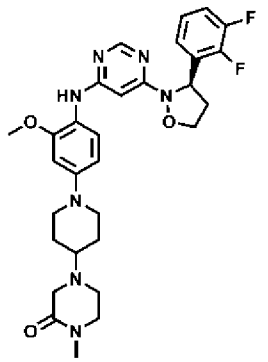
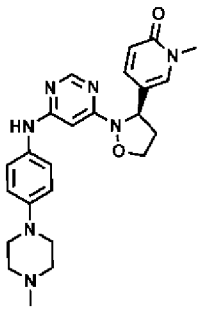
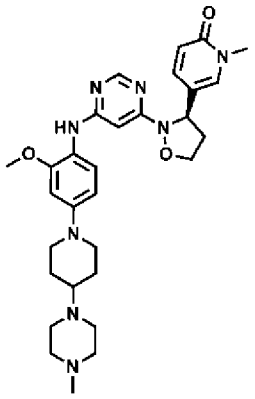
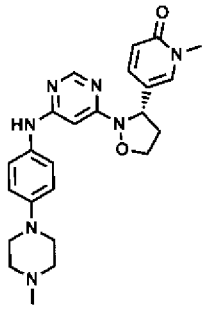
204		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N4-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌　啶-1-基)苯基)-N2-甲基嘧啶-2,4-二胺	595.3 $[M+H]^+$
205		(R)-4-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)吡啶-2-胺	565.3 $[M+H]^+$
206		(R)-N-(4-(4-(4-烯丙基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.36-7.29 (m, 1H), 7.11-6.98 (m, 2H), 6.79 (s, 1H), 6.59-6.48 (m, 2H), 6.44 (d, *J* = 1.0 Hz, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 5.30 (d, *J* = 12.9 Hz, 2H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.92-3.82 (m, 4H), 3.73 (d, *J* = 12.2 Hz, 2H), 3.32-2.69 (m, 13H), 2.35-2.25 (m, 1H), 2.22-1.63 (m, 6H); 592.4$[M+H]^+$
207		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-乙基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.56 (d, *J* = 9.1 Hz, 1H), 7.36-7.29 (m, 1H), 7.11-6.99 (m, 2H), 6.76 (s, 1H), 6.54 (dq, *J* = 5.9, 2.6 Hz, 2H), 6.43 (d, *J* = 1.0 Hz, 1H), 5.91 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.91-3.82 (m, 4H), 3.71 (d, *J* = 12.3 Hz, 2H), 2.99 (s, 6H), 2.89-2.69 (m, 6H), 2.62-2.49 (m, 1H), 2.30 (dtd, *J* = 12.7, 8.2, 4.6 Hz, 1H), 2.06-1.93 (m, 2H), 1.79-1.66 (m, 2H), 1.44-1.23 (m, 4H); 580.43$[M+H]^+$

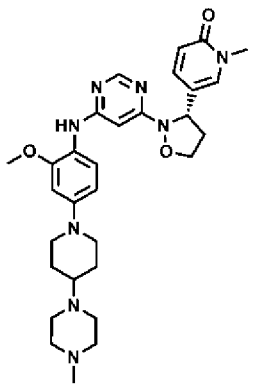
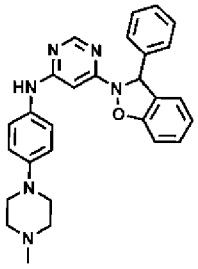
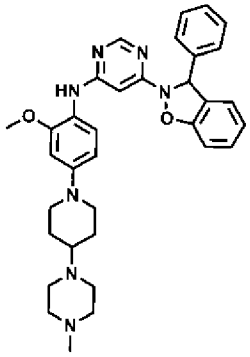
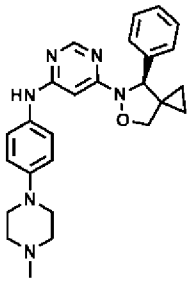
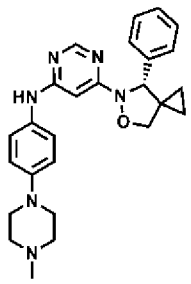
208		(R)-N-(4-(4-(4-環丁基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.11 (d, J = 1.0 Hz, 1H), 7.36-7.30 (m, 2H), 7.16 (dddd, J = 16.0, 12.9, 8.6, 7.1 Hz, 2H), 6.71 (d, J = 2.6 Hz, 1H), 6.62 (dd, J = 8.7, 2.5 Hz, 1H), 6.27 (d, J = 1.1 Hz, 1H), 5.79 (dd, J = 8.8, 4.8 Hz, 1H), 4.14 (td, J = 7.9, 4.1 Hz, 1H), 3.92 (q, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.81 (d, J = 12.3 Hz, 2H), 3.02 (p, J = 8.2 Hz, 1H), 2.92-2.74 (m, 7H), 2.64 (s, 2H), 2.59-2.51 (m, 2H), 2.33-2.22 (m, 1H), 2.20-2.09 (m, 2H), 2.08-1.97 (m, 4H), 1.83-1.64 (m, 5H); 606.42[M+H]$^+$
209		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-(氧咀-3-基)哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.30 (s, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.35-7.31 (m, 1H), 7.11-6.99 (m, 2H), 6.76 (s, 1H), 6.58-6.52 (m, 2H), 6.46-6.40 (m, 1H), 5.91 (dd, J = 8.8, 4.7 Hz, 1H), 4.68 (t, J = 6.6 Hz, 2H), 4.62 (t, J = 6.1 Hz, 2H), 4.09 (td, J = 7.9, 4.2 Hz, 1H), 3.91-3.83 (m, 4H), 3.72 (d, J = 12.2 Hz, 2H), 3.53 (t, J = 6.5 Hz, 1H), 2.87-2.63 (m, 7H), 2.45 (s, 4H), 2.30 (dtd, J = 12.6, 8.0, 4.7 Hz, 2H), 2.03-1.92 (m, 2H), 1.80-1.69 (m, 2H); 608.37[M+H]$^+$
210		(R)-N-(4-(4-(4-(環丙基甲基)哌啡-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.30 (s, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.35-7.30 (m, 1H), 7.10-6.99 (m, 2H), 6.80 (s, 1H), 6.57-6.51 (m, 2H), 6.43 (s, 1H), 5.91 (dd, J = 8.9, 4.7 Hz, 1H), 4.10 (td, J = 7.9, 4.2 Hz, 1H), 3.92-3.80 (m, 4H), 3.71 (d, J = 12.0 Hz, 2H), 3.01 (s, 6H), 2.86-2.49 (m, 8H), 2.31 (ddd, J = 15.3, 8.0, 4.2 Hz, 1H), 2.07-1.95 (m, 2H), 1.80-1.68 (m, 2H), 1.14 (s, 1H), 0.68 (s, 2H), 0.30 (s, 2H); 606.33[M+H]$^+$
211		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(6-甲基-2,6-二氮雜螺[3.3]庚-2-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-d) δ 8.28 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.12-6.99 (m, 2H), 6.93 (s, 1H), 6.57-6.48 (m, 2H), 6.44-6.37 (m, 1H), 5.90 (dd, J = 8.8, 4.7 Hz, 1H), 4.09 (td, J = 7.9, 4.1 Hz, 1H), 3.92-3.86 (m, 1H), 3.84 (s, 3H), 3.68-3.64 (m, 2H), 3.07-2.88 (m, 5H), 2.84-2.67 (m, 4H), 2.31 (tt, J = 12.3, 8.0 Hz, 2H), 2.21-2.10 (m, 2H), 2.05 (s, 3H), 1.79 (d, J = 13.0 Hz, 2H), 1.52-1.41 (m, 2H); 578.4 [M+H]$^+$

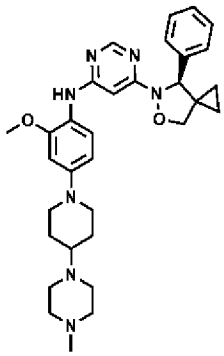
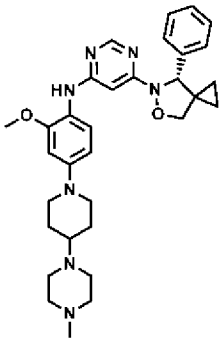
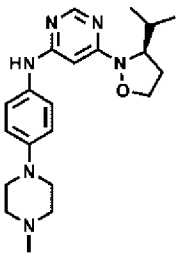
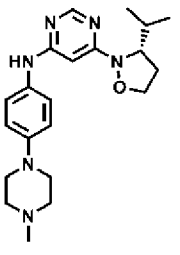
212		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((R)-3-(二甲胺基)吡咯啶-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.34-7.30 (m, 1H), 7.12-7.01 (m, 2H), 6.84 (s, 1H), 6.57-6.50 (m, 2H), 6.43 (s, 1H), 5.91 (dd, *J* = 8.5, 4.5 Hz, 1H), 4.11 (td, *J* = 7.9, 4.1 Hz, 1H), 3.93-3.83 (m, 4H), 3.64 (d, *J* = 10.9 Hz, 2H), 3.15 (s, 2H), 2.86-2.74 (m, 4H), 2.63 (s, 6H), 2.30 (ddd, *J* = 16.3, 7.7, 4.0 Hz, 2H), 2.17-1.99 (m, 4H), 1.97-1.70 (m, 4H); 580.33[M+H]$^+$
213		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((R)-3,4-二甲基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 甲醇-d_4) δ 8.12 (s, 1H), 7.34-7.11 (m, 4H), 6.74 (s, 1H), 6.67 (s, 1H), 6.16 (s, 1H), 5.83-5.75 (m, 1H), 4.29 (td, *J* = 7.7, 4.0 Hz, 1H), 4.06 (q, *J* = 7.8 Hz, 1H), 3.85 (s, 4H), 3.46 (d, *J* = 15.1 Hz, 1H), 3.32-3.22 (m, 3H), 3.17-3.03 (m, 2H), 3.02-2.66 (m, 8H), 2.55-2.44 (m, 1H), 2.37 (td, *J* = 13.2, 7.6 Hz, 1H), 2.10-1.99 (m, 2H), 1.82-1.70 (m, 2H), 1.37 (d, *J* = 6.5 Hz, 3H); 580.38[M+H]$^+$
214		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((S)-3,4-二甲基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 甲醇-d_4) δ 7.99 (d, *J* = 1.0 Hz, 1H), 7.24-7.18 (m, 2H), 7.11-6.97 (m, 2H), 6.59 (d, *J* = 2.5 Hz, 1H), 6.49 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.15 (d, *J* = 1.0 Hz, 1H), 5.67 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.02 (td, *J* = 7.9, 4.1 Hz, 1H), 3.80 (q, *J* = 8.0 Hz, 1H), 3.73 (s, 3H), 3.69 (d, *J* = 12.3 Hz, 2H), 2.98 (t, *J* = 12.9 Hz, 3H), 2.75 (dtd, *J* = 12.1, 8.0, 4.1 Hz, 1H), 2.71-2.61 (m, 2H), 2.60-2.38 (m, 7H), 2.21-2.10 (m, 2H), 1.92 (d, *J* = 12.4 Hz, 2H), 1.58 (q, *J* = 12.1, 11.4 Hz, 2H), 1.11 (d, *J* = 6.3 Hz, 3H); 580.38[M+H]$^+$
215		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((3S,5R)-4-乙基-3,5-二甲基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.35-7.30 (m, 1H), 7.10-7.01 (m, 2H), 6.72 (s, 1H), 6.54 (dd, *J* = 4.6, 2.3 Hz, 2H), 6.44 (s, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.92-3.80 (m, 4H), 3.70 (d, *J* = 11.9 Hz, 2H), 3.44-3.33 (m, 1H), 3.28-3.20 (m, 1H), 3.11-3.03 (m, 1H), 2.98-2.89 (m, 2H), 2.86-2.77 (m, 2H), 2.74 (t, *J* = 12.4 Hz, 2H), 2.54-2.43 (m, 1H), 2.37-2.25 (m, 2H), 1.97-1.89 (m, 2H), 1.71-1.64 (m, 2H), 1.61-1.44 (m, 10H); 608.41[M+H]$^+$

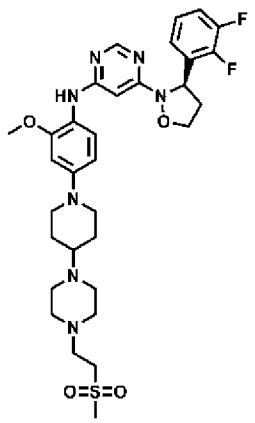
216		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((S)-2,4-二甲基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.59 (s, 1H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.11-7.01 (m, 2H), 6.89 (s, 1H), 6.58-6.50 (m, 2H), 6.42 (s, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.11 (td, *J* = 7.9, 4.2 Hz, 1H), 3.90 (t, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 3.74 (d, *J* = 6.3 Hz, 2H), 3.46-3.36 (m, 1H), 3.11-2.94 (m, 3H), 2.91-2.65 (m, 6H), 2.36-2.26 (m, 1H), 1.99-1.79 (m, 3H), 1.75-1.46 (m, 6H), 1.31-1.12 (m, 2H); 580.43[M+H]$^+$
217		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((R)-2,4-二甲基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.59 (s, 1H), 7.36-7.29 (m, 1H), 7.12-7.01 (m, 2H), 6.75 (s, 1H), 6.58-6.50 (m, 2H), 6.44 (s, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.14-4.05 (m, 1H), 3.89 (q, 1H), 3.86 (s, 3H), 3.73 (d, *J* = 14.1 Hz, 2H), 3.38-3.31 (m, 1H), 3.07-2.90 (m, 3H), 2.86-2.70 (m, 6H), 2.31 (ddt, *J* = 16.1, 7.7, 4.2 Hz, 1H), 1.93-1.81 (m, 3H), 1.73-1.50 (m, 6H), 1.32-1.26 (m, 1H), 1.18-1.12 (m, 1H); 580.38[M+H]$^+$
218		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(3-(4-甲基哌啡-1-基)氮雜環丁-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.28 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.36-7.30 (m, 1H), 7.12-6.99 (m, 2H), 6.62 (s, 1H), 6.33 (s, 1H), 6.07 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.04 (d, *J* = 2.4 Hz, 1H), 5.90 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.08 (td, *J* = 8.0, 4.2 Hz, 1H), 4.01 (t, *J* = 7.0 Hz, 2H), 3.91-3.84 (m, 1H), 3.82 (s, 3H), 3.72 (dd, *J* = 7.1, 5.4 Hz, 2H), 3.41 (p, *J* = 6.1 Hz, 1H), 2.89-2.55 (m, 9H), 2.46 (s, 3H), 2.29 (dtd, *J* = 12.6, 8.1, 4.8 Hz, 1H); 502.3 [M+H]$^+$
219		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(6-乙基-3,6-二氮雜雙環[3.1.1]庚-3-基)哌　啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (d, *J* = 3.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.12-6.99 (m, 2H), 6.86 (s, 1H), 6.55 (d, J = 5.0 Hz, 1H), 6.49 (d, *J* = 8.9 Hz, 1H), 6.44 (s, 1H), 5.94-5.87 (m, 1H), 4.10 (tt, *J* = 16.2, 12.4, 5.5 Hz, 2H), 3.94-3.87 (m, 2H), 3.85 (s, 3H), 3.76-3.53 (m, 4H), 3.44-3.32 (m, 1H), 3.30-3.16 (m, 1H), 2.97-2.77 (m, 4H), 2.74 (d, *J* = 11.2 Hz, 1H), 2.69-2.53 (m, 1H), 2.48 (d, *J* = 12.0 Hz, 1H), 2.30 (dtd, *J* = 20.7, 14.5, 12.9, 6.0 Hz, 2H), 2.19 (d, *J* = 13.2 Hz, 1H), 2.09-1.95 (m, 2H), 1.85-1.71 (m, 1H), 1.38 (t, *J* = 7.3 Hz, 3H); 592.4

			[M+H]+
220		6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(3-乙基-3,6-二氮雜雙環[3.1.1]庚-6-基)哌 啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.25 (s, 1H), 7.52 (s, 1H), 7.32 (t, *J* = 10.5 Hz, 1H), 7.07 (d, *J* = 6.3 Hz, 2H), 6.53 (s, 2H), 6.50 (d, *J* = 8.3 Hz, 1H), 6.32 (s, 1H), 5.89-5.84 (m, 1H), 4.30-4.10 (m, 4H), 3.94 (p, *J* = 8.0 Hz, 3H), 3.86-3.83 (m, 3H), 3.75-3.73 (m, 1H), 3.35-3.31 (m, 1H), 3.14-3.10 (m, 1H), 2.96-2.80 (m, 6H), 2.68-2.59 (m, 1H), 2.39-2.30 (m, 3H), 2.18 (d, *J* = 2.8 Hz, 1H), 2.05-1.95 (m, 2H), 1.41 (t, *J* = 8.5 Hz, 3H); 592.4 [M+H]+
221		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧 基-4-(4-(4-甲 基-1,4)-苯二氮酌-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.34 - 7.29 (m, 1H), 7.11 - 6.99 (m, 2H), 6.83 (s, 1H), 6.54 (d, *J* = 7.1 Hz, 2H), 6.43 (s, 1H), 5.91 (dd, *J* = 8.6, 4.3 Hz, 1H), 4.11 (td, *J* = 7.9, 4.2 Hz, 1H), 3.93 - 3.83 (m, 4H), 3.72 (d, *J* = 12.5 Hz, 2H), 3.30 (s, 2H), 3.07 (s, 2H), 2.87 - 2.71 (m, 7H), 2.32 (ddd, *J* = 15.2, 7.8, 3.9 Hz, 2H), 2.05 - 1.96 (m, 2H), 1.81 - 1.69 (m, 2H), 1.34 - 1.23 (m, 3H), 0.91 - 0.83 (m, 2H) ;580.43[M+H]+
222		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-異丙基哌啡-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.31 (s, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.36-7.30 (m, 1H), 7.11-6.99 (m, 2H), 6.74 (s, 1H), 6.54 (dq, *J* = 5.9, 2.6 Hz, 2H), 6.45-6.41 (m, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.10 (td, *J* = 7.9, 4.2 Hz, 1H), 3.92-3.83 (m, 4H), 3.71 (d, *J* = 12.3 Hz, 2H), 3.10-2.71 (m, 9H), 2.55-2.45 (m, 1H), 2.30 (ddt, *J* = 16.5, 8.2, 4.8 Hz, 1H), 1.97 (s, 2H), 1.91-1.82 (m, 1H), 1.78-1.64 (m, 3H), 1.56-1.47 (m, 1H), 1.45-1.23 (m, 6H); 594.44[M+H]+
223		(R)-1-(1-(4-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧 啶-4-基)胺 基)-3-甲氧苯基)哌啶-4-基)-4-甲基哌啡-2-酮	580.3 [M+H]+

224		(R)-4-(1-(4-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-3-甲氧苯基)哌啶-4-基)-1-甲基哌啡-2-酮	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.36-7.29 (m, 1H), 7.12-7.00 (m, 2H), 6.85 (s, 1H), 6.59-6.50 (m, 2H), 6.42 (d, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.10 (td, *J* = 8.4, 7.9, 4.6 Hz, 1H), 3.89 (q, 1H), 3.85 (s, 3H), 3.69 (d, *J* = 11.2 Hz, 2H), 3.34 (t, *J* = 5.4 Hz, 2H), 3.31 (s, 2H), 2.97 (s, 3H), 2.78 (ddd, *J* = 23.8, 11.4, 3.9 Hz, 5H), 2.43 (tt, *J* = 11.1, 3.7 Hz, 1H), 2.30 (dtd, *J* = 12.6, 8.1, 4.7 Hz, 1H), 1.96 (d, *J* = 12.5 Hz, 2H), 1.70 (qd, *J* = 11.9, 4.0 Hz, 2H); 580.33[M+H]$^+$
225		(R)-1-甲基-5-(2-(6-((4-(4-甲基哌啡-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)吡啶-2(1H)-酮	448.19 [M+H]$^+$
226		(R)-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)-1-甲基吡啶-2(1H)-酮	561.33 [M+H]$^+$
227		(S)-1-甲基-5-(2-(6-((4-(4-甲基哌啡-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)吡啶-2(1H)-酮	448.19 [M+H]$^+$

228		(S)-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)-1-甲基吡啶-2(1H)-酮	561.33 $[M+H]^+$
229		N-(4-(4-甲基哌啡-1-基)苯基)-6-(3-苯基苯并[d]異噁唑-2(3H)-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.36 (s, 1H), 8.01 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.39 (p, *J* = 4.4 Hz, 5H), 6.98-6.75 (m, 9H), 5.64 (s, 1H), 3.22 (d, *J* = 4.3 Hz, 4H), 2.63 (t, *J* = 5.0 Hz, 4H), 2.39 (s, 3H); 465.2$[M+H]^+$
230		N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-苯基苯并[d]異噁唑-2(3H)-基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.38 (s, 1H), 8.01 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.46-7.37 (m, 5H), 6.99-6.86 (m, 4H), 6.79 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.60 (s, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.70 (s, 1H), 3.75 (s, 3H), 3.71 (d, *J* = 12.0 Hz, 2H), 2.80-2.64 (m, 6H), 2.59-2.37 (m, 5H), 2.32 (s, 3H), 1.98 (d, *J* = 12.4 Hz, 2H), 1.73 (tt, *J* = 13.0, 6.6 Hz, 2H); 578.3$[M+H]^+$
231		(S)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.13 (d, *J* = 0.8 Hz, 1H), 7.43-7.25 (m, 7H), 7.07-7.00 (m, 2H), 6.37 (d, *J* = 0.8 Hz, 1H), 5.13 (s, 1H), 4.07-3.97 (m, 2H), 3.37-3.33 (m, 4H), 3.10-2.99 (m, 4H), 2.67 (s, 3H), 0.85 (ddd, *J* = 9.9, 5.8, 4.5 Hz, 1H), 0.72 (dtd, *J* = 15.7, 9.8, 6.1 Hz, 2H), 0.38 (dt, *J* = 10.7, 5.4 Hz, 1H); 443.25 $[M+H]^+$
232		(R)-N-(4-(4-甲基哌啡-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.13 (d, *J* = 0.9 Hz, 1H), 7.46-7.21 (m, 7H), 7.08-6.95 (m, 2H), 6.37 (d, *J* = 0.8 Hz, 1H), 5.13 (s, 1H), 4.09-3.96 (m, 2H), 3.35 (dd, *J* = 9.6, 4.2 Hz, 4H), 3.14-3.02 (m, 4H), 2.69 (s, 3H), 0.88-0.81 (m, 1H), 0.72 (dtd, *J* = 15.8, 9.8, 6.1 Hz, 2H), 0.38 (dt, *J* = 10.7, 5.4 Hz, 1H); 443.21 $[M+H]^+$

233		(S)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.10 (d, J = 0.6 Hz, 1H), 7.37-7.28 (m, 6H), 6.68 (d, J = 2.3 Hz, 1H), 6.58 (dd, J = 8.7, 2.5 Hz, 1H), 6.23 (s, 1H), 5.12 (s, 1H), 4.02-3.97 (m, 2H), 3.85-3.75 (m, 5H), 2.72 (dd, J = 29.9, 19.2 Hz, 10H), 2.49-2.42 (m, 1H), 2.39 (s, 3H), 2.02 (d, J = 12.0 Hz, 2H), 1.69-1.64 (m, 2H), 0.86-0.80 (m, 1H), 0.70 (ddd, J = 14.7, 9.6, 3.9 Hz, 2H), 0.36 (dt, J = 10.7, 5.4 Hz, 1H); 556.30 [M+H]$^+$
234		(R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.09 (d, J = 0.9 Hz, 1H), 7.43-7.24 (m, 6H), 6.68 (d, J = 2.5 Hz, 1H), 6.59 (dd, J = 8.7, 2.5 Hz, 1H), 6.23 (d, J = 0.5 Hz, 1H), 5.12 (s, 1H), 4.05-3.94 (m, 2H), 3.85-3.73 (m, 5H), 2.95-2.58 (m, 10H), 2.48 (ddd, J = 11.5, 7.9, 3.7 Hz, 1H), 2.43 (d, J = 9.3 Hz, 3H), 2.08-1.98 (m, 2H), 1.72-1.62 (m, 2H), 0.87-0.80 (m, 1H), 0.70 (dtd, J = 15.7, 9.8, 6.1 Hz, 2H), 0.36 (dt, J = 10.7, 5.4 Hz, 1H); 556.30 [M+H]$^+$
235		(R)-6-(3-異丙基異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.04 (s, 1H), 7.23-7.17 (m, 2H), 6.95-6.88 (m, 2H), 6.19 (d, J = 0.4 Hz, 1H), 4.12 (td, J = 7.9, 4.7 Hz, 1H), 3.93 (td, J = 8.1, 3.5 Hz, 1H), 3.59 (dt, J = 15.4, 7.7 Hz, 1H), 2.96-2.90 (m, 4H), 2.56-2.51 (m, 7H), 2.19-2.00 (m, 2H), 1.77 (dq, J = 13.6, 6.8 Hz, 1H), 0.90 (dd, J = 11.4, 6.7 Hz, 6H); 383.30 [M+H]$^+$
236		(S)-6-(3-異丙基異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, MeOD) δ 8.16 (s, 1H), 7.36-7.29 (m, 2H), 7.07-7.00 (m, 2H), 6.31 (s, 1H), 4.24 (td, J = 7.9, 4.7 Hz, 1H), 4.05 (td, J = 8.1, 3.4 Hz, 1H), 3.70 (dt, J = 15.6, 7.8 Hz, 1H), 3.09-3.02 (m, 4H), 2.66 (d, J = 7.1 Hz, 7H), 2.31-2.10 (m, 2H), 1.89 (dq, J = 13.6, 6.8 Hz, 1H), 1.01 (dd, J = 11.4, 6.7 Hz, 6H); 383.30 [M+H]$^+$

237		(R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-(2-(甲磺醯基)乙基)哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺	^{1}H NMR (400 MHz, 氯仿-*d*) δ 8.30 (s, 1H), 7.55-7.49 (m, 1H), 7.36-7.28 (m, 1H), 7.10-7.01 (m, 2H), 6.82 (s, 1H), 6.58-6.51 (m, 2H), 6.42 (s, 1H), 5.91 (dd, *J* = 8.8, 4.7 Hz, 1H), 4.09 (td, *J* = 7.9, 4.3 Hz, 1H), 3.88 (q, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.71 (d, *J* = 12.1 Hz, 2H), 3.15 (t, *J* = 6.4 Hz, 2H), 3.04 (s, 3H), 2.89 (t, *J* = 6.5 Hz, 2H), 2.86-2.70 (m, 3H), 2.64 (s, 3H), 2.58 (s, 3H), 2.43-2.36 (m, 1H), 2.34-2.26 (m, 1H), 1.95 (d, *J* = 12.5 Hz, 3H), 1.69 (ddd, *J* = 23.8, 11.7, 3.3 Hz, 3H); 658.35[M+H]$^+$

【0149】

<實驗實例1>評估EGFR突變過度表現Ba/F3細胞之增殖抑制活性

進行以下實驗以評估本發明之化合物對表現EGFR C797S、L861Q、G719A、S768I、L718Q及/或G724S突變之Ba/F3增殖的抑制活性。

【0150】 對於Ba/F3細胞，使用含有10% FBS及5 ng/ml IL-3 (R&D Systems)之RPMI-1640。在添加1 μg/ml嘌呤黴素(Invitrogen)至同一培養基之後，培養經轉導Ba/F3細胞。

【0151】 在用化合物處理之前24小時，將3000至5000個細胞等分至白色透明底96孔盤(Corning)之各孔中。將化合物稀釋於二甲亞碸中(3次稀釋，總計12個濃度)，且以1 μl之量注射以使得最終濃度為0.2 nM至5 μM。為了量測活細胞，在72小時化合物處理之後，使用CellTiter-Glo發光細胞存活試劑(Promega)將細胞儲存在室溫下10 min，且接著使用讀取器(SynergyNeo, Biotek)量測發光強度。各測試重複三次。所得值根據細胞生長速率(%)與對照組相比來計算。使用GraphPad Prism版本8.3.0程式創建圖表且計算GI_{50}值。

【0152】 下表2展示表現EGFR Del19/C797S (EGFR DC)及EGFR L858R/C797S (EGFR LC)突變之Ba/F3細胞之增殖抑制活性的評估結果。

[表2]

實例化合物	Ba/F3 (EGFR DC)	Ba/F3 (EGFR LC)	實例化合物	Ba/F3 (EGFR DC)	Ba/F3 (EGFR LC)	實例化合物	Ba/F3 (EGFR DC)	Ba/F3 (EGFR LC)
1	A	A	**79**	A	-	**141**	A	-
2	B	-	**80**	B	-	**142**	A	-
3	A	-	**81**	B	-	**143**	A	-
4	A	A	**83**	A	-	**145**	A	-
5	A	A	**84**	A	A	**146**	A	-
6	B	B	**85**	A	-	**147**	A	-
7	B	B	**86**	A	-	**152**	A	-
8	A	A	**87**	A	-	**154**	A	-
10	B	B	**88**	A	-	**155**	A	-
11	B	B	**89**	B	-	**157**	A	-
12	B	B	**90**	A	-	**159**	B	-
13	B	B	**91**	A	-	**160**	B	-
14	B	-	**92**	A	-	**161**	A	-
15	A	A	**93**	A	-	**162**	A	-
17	B	-	**94**	A	-	**163**	A	-
18	B	-	**95**	A	-	**164**	A	-
19	B	-	**96**	A	-	**165**	A	-
20	A	-	**97**	A	-	**166**	A	-
21	A	-	**98**	A	-	**167**	A	-
22	A	-	**99**	A	-	**169**	B	-
23	B	-	**100**	B	-	**170**	B	-
24	B	-	**101**	A	-	**174**	B	-
25	A	-	**102**	A	A	**176**	B	-
26	A	-	**103**	A	-	**177**	B	-
27	B	-	**104**	A	A	**180**	B	-
28	B	-	**105**	A	-	**182**	A	-
29	A	-	**106**	A	-	**184**	B	-
30	A	-	**107**	A	-	**193**	B	-
31	A	-	**108**	A	-	**195**	A	-
32	A	-	**109**	A	-	**199**	A	-
33	A	-	**110**	A	-	**200**	A	-
34	A	-	**111**	B	-	**201**	A	-
35	A	-	**112**	B	-	**202**	A	-
36	B	-	**113**	A	-	**203**	A	-
38	B	-	**114**	A	-	**206**	A	-
41	B	-	**115**	A	-	**207**	A	-
48	A	-	**116**	A	-	**208**	A	-
49	A	-	**117**	A	-	**209**	A	-
52	A	-	**118**	A	-	**210**	A	-
53	A	-	**119**	A	-	**211**	A	-
54	A	-	**120**	A	-	**212**	A	-

56	A	-	**121**	A	-	**213**	A	-
57	A		**122**	A	-	**214**	A	-
59	A		**123**	A	-	**215**	A	-
61	A		**124**	A	-	**216**	A	-
62	A		**125**	A	-	**217**	A	-
63	A		**126**	A	-	**218**	A	-
64	A		**127**	A	-	**219**	A	-
65	A		**128**	A	A	**220**	A	-
66	A		**129**	A	A	**221**	A	-
67	A	-	**130**	B	-	**222**	A	-
68	A	-	**131**	B	-	**224**	A	-
69	A	-	**132**	A	A	**229**	B	-
72	B	-	**133**	B	-	**230**	B	-
73	B	-	**134**	A	-	**231**	B	-
74	A	-	**135**	A	-	**233**	A	-
75	A	-	**136**	A	-	**234**	B	-
76	A	-	**138**	A	-	**235**	A	-
77	A	-	**139**	A	-	**237**	A	-
78	A	-	**140**	A	-			

A: GI_{50} < 50 nM；B: 50 nM ≤ GI_{50} < 500 nM；C: 500 nM ≤ GI_{50} < 5000 nM；D: 5000 nM ≤ GI_{50}；

【0153】下表3展示表現EGFR罕見(或不常見)突變及耐藥性突變之Ba/F3細胞(諸如L861Q、G719A、S768I、L718Q、G724S及其類似者)之增殖抑制活性之評估結果。

[表3]

實例化合物	Ba/F3 G719A	Ba/F3 L861Q	Ba/F3 S768I	Ba/F3 L718Q	Ba/F3 G724S
4	A	A	B	-	-
34	A	B	B	B	A

A: GI_{50} < 50 nM；B: 50 nM ≤ GI_{50} < 500 nM；C: 500 nM ≤ GI_{50} < 5000 nM；D: 5000 nM ≤ GI_{50}；

【0154】下表4展示藉由請求外部委託組織，Reaction Biology (https://www.reactionbiology.com/)獲得之EGFR家族突變酶的活性值。

[表4]

EGFR突變酶	化合物**34** (IC_{50}; nM)
EGFR (d746-750)	8.0

EGFR (d746-750/C797A)	3.5
EGFR (d746-750/C797S)	<0.5
EGFR (d746-750/T790M/C797S)	60.5
EGFR (D761Y)	<0.5
EGFR (G719C)	0.5
EGFR (G719D)	<0.5
EGFR (G719S)	2.7
EGFR (L718Q)	49.8
EGFR (L747S)	<0.5
EGFR (L792F)	8.7
EGFR (L792F/L858R)	78.1
EGFR (L861Q)	<0.5
ERBB2/HER2	5.3
ERBB4/HER4	41.7

【0155】 如上表2至表4中所展示，可瞭解，本發明之實例化合物展現出對包括EGFR C797S突變、罕見突變及其類似者之過度表現細胞株或酶具有高抑制能力。

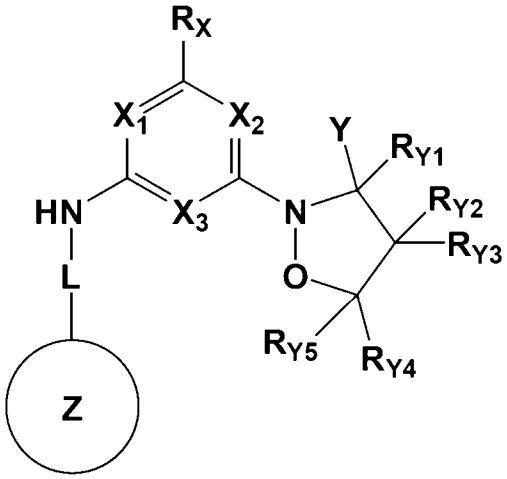
【0156】 如上文所描述，儘管本發明已經以較佳製備實例、實例及實驗實例詳細描述，但本發明之範疇不限於特定實例化合物，且應由隨附申請專利範圍解釋。另外，熟習此項技術者應理解，在不脫離本發明之範疇的情況下可進行許多修改及變化。

【發明申請專利範圍】

【請求項1】

一種由以下化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽，

[化學式1]



在該化學式1中，

X_1至X_3各自獨立地為CH或N；

R_X為-H、$-NH_2$或$-NH(-C_{1-6}$烷基)；

Y為$-C_{1-6}$烷基、$-(CH_2)_n$芳基、$-(CH_2)_n$雜芳基或$-(CH_2)_n$氫雜芳基，其中該$-(CH_2)_n$芳基、$-(CH_2)_n$雜芳基或$-(CH_2)_n$氫雜芳基環中之至少一個H可經$-C_{1-6}$烷基、$-C_{1-6}$胺烷基、$-C_{1-6}$羥烷基、$-C_{1-6}$鹵烷基、$-C_{1-6}$烷基-O-C_{1-6}烷基、$-C_{1-6}$烯基、$-C_{1-6}$炔基、-CN、$-(C=O)NR_1R_2$、$-(C=O)OR_3$、$-NR_4R_5$、$-OR_6$、-鹵基、=O、環烷基、雜環烷基、芳基或雜芳基取代，其中該環烷基、雜環烷基、芳基或雜芳基中之至少一個H可經$-C_{1-6}$烷基、$-C_{1-6}$鹵烷基或-鹵基取代；

n為0、1、2、3或4；

R_1至R_3各自獨立地為-H、$-C_{1-6}$烷基或環烷基；

R_4及R_5各自獨立地為-H或-C_{1-6}烷基；

R_6為-H、-C_{1-6}烷基或苯基，其中該苯基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基或鹵基取代；

R_{Y1}至R_{Y5}各自獨立地為-H或-C_{1-6}烷基，或R_{Y2}及R_{Y3}可彼此鍵聯以形成環烷基且R_{Y3}及R_{Y4}可彼此鍵聯以形成芳基；

L為-(CH_2)m-或-C(=O)-；

m為0、1、2、3或4；

環Z為苯基、5至6員雜芳基、9至10員氫雜芳基、3至5員環烷基或6員雜環烷基，其中該苯基、5至6員雜芳基、9至10員氫雜芳基、3至5員環烷基或6員雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}氘烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-OH、-O-C_{1-6}烷基、-O-C_{1-6}鹵烷基、-S-C_{1-6}烷基、-C(=O)-C_{1-6}烷基、-C(=O)-C_{1-6}鹵烷基、-C(=O)O-C_{1-6}烷基、-S(=O)$_2$-C_{1-6}烷基、-C(=N-O-C_{1-6}烷基)(C_{1-6}烷基)、=O、-鹵基或Z_1取代；或該苯基、5至6員雜芳基、9至10員氫雜芳基、3至5員環烷基或6員雜環烷基環之兩個或更多個取代基可彼此鍵聯以形成稠環或螺環，其中該稠環或螺環中之至少一個H可經-C_{1-6}烷基或Z_1取代；

Z_1為環烷基、雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、芳基或雜芳基，其中該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、或-(C=O)-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、芳基或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烷基-N(C_{1-6}烷基)(C_{1-6}烷基)、-C_{1-6}烷基-S(=O)$_2$-C_{1-6}烷基、=O、-NR_9R_{10}、-鹵

基、環烷基或Z_2取代；

R_9及R_{10}各自獨立地為-C_{1-6}烷基；

Z_2為雜環烷基、雜雙環烷基、雜螺烷基、-NH-雜環烷基、或雜芳基，其中該雜環烷基、雜雙環烷基、雜螺烷基、或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-NH-雜環烷基、或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}羥烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-$NR_{11}R_{12}$、環烷基或Z_3取代；

R_{11}及R_{12}各自獨立地為-C_{1-6}烷基；及

Z_3為雜環烷基、雜雙環烷基、雜螺烷基、或-NH-雜環烷基，其中該雜環烷基、雜雙環烷基、雜螺烷基、或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、或-NH-雜環烷基環中之至少一個H可經-C_{1-6}烷基或環烷基取代。

【請求項2】

如請求項1之由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽，其中

X_1至X_3各自獨立地為CH或N；

R_X為-H、-NH_2、或-NH(-C_{1-6}烷基)；

Y為-C_{1-6}烷基、-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基，其中該-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-$(C=O)NR_1R_2$、

-(C=O)OR_3、-NR_4R_5、-OR_6、-鹵基、=O、雜環烷基、芳基或雜芳基取代，其中該雜環烷基、芳基或雜芳基中之至少一個H可經-鹵基取代；

n為0、1或2；

R_1至R_3各自獨立地為-H、-C_{1-6}烷基或環烷基；

R_4及R_5各自獨立地為-H或-C_{1-6}烷基；

R_6為-C_{1-6}烷基或苯基，其中該苯基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基或鹵基取代；

R_{Y1}至R_{Y5}各自獨立地為-H或-C_{1-6}烷基，或R_{Y2}及R_{Y3}可彼此鍵聯以形成環烷基，且R_{Y3}及R_{Y4}可彼此鍵聯以形成芳基；

L為-(CH_2)m-或-C(=O)-；

m為0、1或2；

Z_1為環烷基、雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基或雜芳基，其中該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、或-(C=O)-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基、雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-NR_9R_{10}、-鹵基、環烷基或Z_2取代；

R_9及R_{10}各自獨立地為-C_{1-6}烷基；

Z_2為雜環烷基、雜雙環烷基或-NH-雜環烷基，其中該雜環烷基、雜雙環烷基或-NH-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基、雜雙環烷基或-NH-雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}羥烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-

C_{1-6}烷基、-C_{1-6}烷基-S(=O)$_2$-C_{1-6}烷基、=O、-$NR_{11}R_{12}$、環烷基或Z_3取代；

R_{11}及R_{12}各自獨立地為-C_{1-6}烷基；及

Z_3為雜環烷基或雜雙環烷基，其中該雜環烷基、或雜雙環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該雜環烷基或雜雙環烷基中之至少一個H可經-C_{1-6}烷基或環烷基取代。

【請求項3】

如請求項1之由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽，其中

X_1為N；

X_2及X_3各自獨立地為CH或N；及

R_X為-H、-NH_2或-NH(-C_{1-6}烷基)。

【請求項4】

如請求項1之由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽，其中

Y為-C_{1-6}烷基、-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基，其中該-$(CH_2)_n$芳基、-$(CH_2)_n$雜芳基或-$(CH_2)_n$氫雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}鹵烷基、-C_{1-6}炔基、-CN、-(C=O)NH-環烷基、-(C=O)O-C_{1-6}烷基、-N(C_{1-6}烷基)(C_{1-6}烷基)、-O(C_{1-6}烷基)、-O-苯基、-鹵基、=O、雜環烷基、芳基或雜芳基取代，其中該雜環烷基、芳基或雜芳基中之至少一個H可經-鹵基取代；

n為0或1；及

R_{Y1}至R_{Y5}各自獨立地為-H或-C_{1-6}烷基，或R_{Y2}及R_{Y3}可彼此鍵聯以形

成3員至6員環烷基，且R_{Y3}及R_{Y4}可彼此鍵聯以形成苯基。

【請求項5】

如請求項1之由化學式1表示之化合物、其光學異構體、或其醫藥學上可接受之鹽，其中

L為-(CH_2)m-或-C(=O)-；

m為0或1；

環Z為苯基、5至6員雜芳基、9至10員氫雜芳基、3員至5員環烷基或6員雜環烷基，其中該苯基、5至6員雜芳基、9至10員氫雜芳基、3員至5員環烷基或6員雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}氟烷基、-C_{1-6}鹵烷基、-C_{1-6}烯基、-C_{1-6}炔基、-CN、-O-C_{1-6}烷基、-O-C_{1-6}鹵烷基、-S-C_{1-6}烷基、-C(=O)-C_{1-6}烷基、-C(=O)-C_{1-6}鹵烷基、-C(=O)O-C_{1-6}烷基、-S(=O)$_2$-C_{1-6}烷基、-C(=N-O-C_{1-6}烷基)(C_{1-6}烷基)、=O、-鹵基或Z_1取代；或該苯基、5至6員雜芳基、9至10員氫雜芳基、3員至5員環烷基或6員雜環烷基環之兩個或更多個取代基可彼此鍵聯以形成稠環或螺環，其中該稠環或螺環中之至少一個H可經-C_{1-6}烷基或Z_1取代；

Z_1為3員至7員環烷基、5員至7員雜環烷基、6員至10員雜雙環烷基、6員至10員雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、或雜芳基，其中該5員至7員雜環烷基、6員至10員雜雙環烷基、6員至10員雜螺烷基、-C_{1-6}烷基-雜環烷基、或-(C=O)-雜環烷基在該環中含有選自由N、O、P、P(=O)及S組成之群中之至少一者，且該5員至7員雜環烷基、6員至10員雜雙環烷基、6員至10員雜螺烷基、-C_{1-6}烷基-雜環烷基、-(C=O)-雜環烷基、或雜芳基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}胺烷基、-C_{1-6}鹵烷基、-C_{1-6}烷基-S(=O)$_2$-C_{1-6}烷基、=O、-N(C_{1-6}烷基)(C_{1-6}烷基)、-鹵

基、環烷基或Z_2取代；

Z_2為5員至7員雜環烷基、6員至10員雜雙環烷基或-NH-雜環烷基，其中該5員至7員雜環烷基、6員至10員雜雙環烷基或-NH-雜環烷基在該環中含有選自由N、O及S組成之群中之至少一者，且該5員至7員雜環烷基、6員至10員雜雙環烷基或-NH-雜環烷基環中之至少一個H可經-C_{1-6}烷基、-C_{1-6}羥烷基、-C_{1-6}烯基、-C_{1-6}炔基、-C(=O)-C_{1-6}烷基、-C_{1-6}烷基-$S(=O)_2$-C_{1-6}烷基、=O、-N(C_{1-6}烷基)(C_{1-6}烷基)、3員至7員環烷基或Z_3取代；及

Z_3為5員至7員雜環烷基、或6員至10員雜雙環烷基，其中該5員至7員雜環烷基或6員至10員雜雙環烷基在該環中含有選自由N、O及S組成之群中之至少一者，且該5員至7員雜環烷基、或6員至10員雜雙環烷基中之至少一個H可經-C_{1-6}烷基或3員至7員環烷基取代。

【請求項6】

一種化合物、其光學異構體、或其醫藥學上可接受之鹽，其選自由以下化合物組成之群：

(1) (R)-N-(4-(4-甲基哌呾-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(2) (S)-N-(4-(4-甲基哌呾-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(3) (S)-6-(3-苯甲基噁唑啶-2-基)-N-(4-(4-甲基哌呾-1-基)苯基)嘧啶-4-胺；

(4) (R)-N-(3-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(5) (R)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(6) (R)-N-(4-(4-(4-環丙基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(7) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-嗎啉基苯基)嘧啶-4-胺；

(8) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(9) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-5-基)-4-嗎啉基苯基)嘧啶-4-胺；

(10) (R)-1'-(4-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-甲氧基-2-(1-甲基-1H-吡唑-4-基)苯基)-N,N-二甲基-[1,4'-聯哌啶]-4-胺；

(11) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-(4-(4-甲基哌呾-1-基)哌啶-1-基)-5-(甲磺醯基)苯基)嘧啶-4-胺；

(12) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-(甲磺醯基)-5-(4-嗎啉基哌啶-1-基)苯基)嘧啶-4-胺；

(13) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-(4-甲基哌呾-1-基)-5-(甲磺醯基)苯基)嘧啶-4-胺；

(14) (R)-2-(3-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-((4-甲基哌呾-1-基)甲基)苯基)-2-甲基丙腈；

(15) (R)-2-(3-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-(4-甲基哌呾-1-基)苯基)-2-甲基丙腈；

(16) (R)-N-(4-(4-甲基哌呾-1-基)苯基)-6-(3-(3-苯氧基苯基)異噁唑啶-2-基)嘧啶-4-胺；

(17) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(18) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-甲基哌呾-1-基)苯基)嘧啶-4-胺；

(19) (R)-N^1-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-N^4-(2-(二甲胺基)乙基)-N^4-甲苯-1,4-二胺；

(20) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-甲基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(21) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(22) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(二甲胺基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(23) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-甲基哌呾-1-基)哌啶-1-基)-3-(三氟甲基)苯基)嘧啶-4-胺；

(24) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-甲基哌呾-1-基)哌啶-1-基)-3-(甲磺醯基)苯基)嘧啶-4-胺；

(25) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(26) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌呾-1)-基)哌啶-1-基)苯基)嘧啶-4-胺；

(27) (R)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-

(3-(3-(三氟甲基)苯基)異噁唑啶-2-基)嘧啶-4-胺；

(28) (R)-6-(3-(2-氟-3-(三氟甲基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(29) (R)-6-(3-(3-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(30) (R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(31) (R)-6-(3-(3-氯-4-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(32) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(33) (R)-6-(3-(4-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(34) (R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(35) (R)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-(噻吩-2-基)異噁唑啶-2-基)嘧啶-4-胺；

(36) (R)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-(萘-1-基)異噁唑啶-2-基)嘧啶-4-胺；

(37) (R)-6-(3-(3-乙炔基苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(38) (R)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-(6-甲基吡啶-3-基)異噁唑啶-2-基)嘧啶-4-胺；

(39) (R)-6-(3-(3-([1,2,4]三唑并[1,5-a]吡啶-7-基)苯基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(40) (R)-6-(3-(3-氟-5-硫代嗎啉基苯基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(41) (R)-N-(2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)-6-(3-(3-甲氧苯基)異噁唑啶-2-基)嘧啶-4-胺；

(42) (R)-6-(3-甲基-3-苯基異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(43) (R)-3-(2-(6-((4-(4-甲基哌啡-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲酸異丙酯；

(44) (R)-N-環己基-3-(2-(6-((4-(4-甲基哌啡-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲醯胺；

(45) (R)-6-(3-(3',5-二氟-[1,1'-聯苯]-3-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(46) (R)-N,N-二甲基-7-(2-甲基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-7-氮雜螺[3.5]壬-2-胺；

(47) (R)-N,N-二甲基-2-(2-甲基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-2-氮雜螺[3.5]壬-7-胺；

(48) (R)-3-(1-甲基哌啶-4-基)-N-(6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-基)-1,2,3,4,4a,5-六氫苯并[b]吡啡并[1,2-d][1,4]噁 啡-8-胺；

(49) (6aR,8S)-8-(4-環丙基哌啡-1-基)-2-甲氧基-N-(6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-基)-6,6a,7,8,9,10-六氫苯并[b]吡啶并[1,2-d][1,4]噁啡-3-胺；

(50) N-(4-(4-(5-乙基六氫吡咯并[3,4-c]吡咯-2(1H)-基)哌啶-1-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(51) (R)-N-(2-甲氧基-4-(4-((1-甲基哌啶-4-基)胺基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(52) (R)-N-(2-甲基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(53) (R)-N-(3-甲基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(54) (R)-N-(4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(55) (R)-N-(2-乙氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(56) N-(4-(4-(4-甲基哌啉-1-基)哌啶-1-基)-2-(((R)-1,1,1-三氟丙-2-基)氧基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(57) N-(2-甲氧基-4-(4-((1R,4R)-5-甲基-2,5-二氮雜雙環[2.2.1]庚-2-基)哌啶-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(58) (R)-N-(2-甲氧基-4-(4-(氧呾-3-基)哌啉-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(59) N-(4-((1R,4R)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(60) (R)-1-(4-(1-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)哌啶-4-基)哌啉-1-基)乙-1-酮；

(61) (R)-N-(4-(4-(4-環丙基-3,3-二甲基哌啉-1-基)哌啶-1-基)-2-甲

氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(62) (R)-N-(2-甲氧基-4-(4-(吡咯啶-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(63) (R)-N-(4-(4-(4-環丙基哌呄-1-基)-[1,4'-聯哌啶]-1'-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(64) (R)-N-(4-(2-(二甲胺基)乙氧基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(65) (R)-N-(4-((2-(二甲胺基)乙基)硫基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(66) (R)-N-(2-甲氧基-4-硫代嗎啉基苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(67) (R)-N-(2-甲氧基-4-(4-甲基-1,4-二氮雜環庚烷-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(68) (R)-N-(4-(4-烯丙基哌呄-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(69) N-(4-((R)-3-(二甲胺基)吡咯啶-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(70) N-(4-((S)-2-((二甲胺基)甲基)吡咯啶-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(71) (R)-N-(1-(1-(2-(二甲胺基)乙基)哌啶-4-基)-1H-吡唑-4-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(72) (R)-(4-甲基哌呄-1-基)(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)甲酮；

(73) (R)-6-(3-苯基異噁唑啶-2-基)-N-(3-(三氟甲基)苯基)嘧啶-4-胺；

(74) N-(5-((1S,4S)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基)-2-氟吡啶-3-基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(75) (R)-1-(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)吡咯啶-2-酮；

(76) (R)-2-甲基-5-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)異吲哚啉-1-酮；

(77) (R)-6-(3-苯基異噁唑啶-2-基)-N-(4-(哌啡-1-基)苯基)嘧啶-4-胺；

(78) (R)-N-(6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)-1,2,3,4-四氫異喹啉-6-胺；

(79) (R)-N-(5-(4-(二甲胺基)哌啶-1-基)吡啶-2-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(80) (R)-N-(8-(1-甲基-1H-吡唑-5-基)-2,3-二氫苯并[b][1,4]戴奧辛-5-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(81) (R)-1-環丙基-4-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-1,4-氮磷雜環己烷4-氧化物；

(82) N-(4-((2R,6S)-2,6-二甲基嗎啉基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(83) 6-((R)-3-苯基異噁唑啶-2-基)-N-((R)-7-(吡咯啶-1-基)-6,7,8,9-四氫-5H-苯并[7]輪烯-2-基)嘧啶-4-胺；

(84) (R)-N,N-二甲基-1'-(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺

基)苯基)-[1,4'-聯哌啶]-4-胺；

(88) (R)-7-(5-甲氧基-2-甲基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-N,N-二甲基-7-氮雜螺[3.5]壬-2-胺；

(89) (R)-N-(2-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)-6-(3-(萘-2-基)異噁唑啶-2-基)嘧啶-4-胺；

(90) (R)-6-(3-(3,4-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(91) (R)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)-6-(3-(4-氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(92) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(93) (R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(94) (R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(95) (R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(96) (R)-6-(3-(4-氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌吡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(97) N-(4-(4-((1R,4R)-2-氧雜-5-氮雜雙環[2.2.1]庚-5-基)哌啶-1-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(98) (R)-N-(4-(4-(二乙胺基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(99) N-(2-甲氧基-4-((R)-2-甲基-4-(1-甲基哌啶-4-基)哌呾-1-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(100) (R)-3-(2-(6-((2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲酸異丙酯；

(101) (R)-N-(2-甲氧基-4-(4-(1-甲基哌啶-4-基)哌呾-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(102) (R)-N-(3-甲氧基-4-(4-(1-甲基哌啶-4-基)哌呾-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(103) (R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(104) (R)-6-(3-(2,4-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(105) (R)-6-(3-(4-氯-2-氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(106) (R)-6-(3-(2,5-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(107) (R)-N-(3-甲基-4-(4-甲基哌呾-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(108) (R)-N-(2-甲基-4-嗎啉基苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(109) (R)-N-(5-乙基-2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(110) (R)-N-(2-甲氧基-4-嗎啉基苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶

-4-胺；

(111) (R)-N4-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-2,4-二胺；

(112) (R)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-4-(3-苯基異噁唑啶-2-基)-1,3,5-三呾-2-胺；

(113) (R)-2-甲氧基-N4-(1-甲基哌啶-4-基)-N1-(6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)苯-1,4-二胺；

(114) (R)-N-(2-甲氧基-5-甲基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(115) (R)-1'-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)-N,N-二甲基-[1,4'-聯哌啶]-4-胺；

(116) N-(4-(4-((1R,4R)-5-乙基-2,5-二氮雜雙環[2.2.1]庚-2-基)哌啶-1-基)-2-甲氧苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(117) (R)-N-(3-乙基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(118) (R)-N-(4-(4-(4-乙基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(119) (R)-N-(4-(4-(二甲胺基)哌啶-1-基)-2-甲氧苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(120) (R)-N-(2-甲氧基-4-(4-嗎啉基哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(121) (R)-2-(4-(1-(2-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)哌啶-4-基)哌呾-1-基)乙-1-醇；

(122) (R)-1-(4-(4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)哌呾-1-基)乙-1-酮；

(123) (R)-N-(3,5-二氟-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(124) (R)-N-(4-(4-(氧呾-3-基)哌呾-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(125) (R)-6-(3-(3-氯-2-氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(126) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(127) (R)-N-(4-(4-(二甲胺基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(128) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(129) (R)-6-(3-(4-氯-3-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(130) (R)-6-(3-(3-氯-2,4-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(131) (R)-6-(3-(3-(二甲胺基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(132) (R)-N-(5-氯-2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(133) (R)-N-(1-甲基-1H-吡唑-4-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-

4-胺；

(134) (R)-7-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)-3,4-二氫異喹啉-2(1H)-甲酸三級丁酯；

(135) (R)-N-(4-(9-甲基-3,9-二氮雜螺[5.5]十一烷-3-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(136) N-(4-(6-甲基-3,6-二氮雜雙環[3.1.1]庚-3-基)苯基)-6-((R)-3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(137) (R)-3-(3-甲氧基-4-((6-(3-苯基異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)噁唑啶-2-酮；

(139) (R)-N-(4-(4-甲基哌呾-1-基)-3-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(140) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(3-氟-4-(4-甲基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(141) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(1-甲基哌啶-4-基)苯基)嘧啶-4-胺；

(142) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(5-異丙基-2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(143) (R)-N-(5-環丙基-2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(144) (R)-N-(4-(4-甲基哌呾-1-基)-2-(3-((甲磺醯基)甲基)氮雜環丁-1-基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(145) (R)-1-(5-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-4-甲氧基-2-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)乙-1-酮；

(146) (R,E)-1-(5-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-4-甲氧基-2-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)乙-1-酮O-甲基肟；

(147) (R)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-6-(4-(4-甲基哌啡-1-基)哌啶-1-基)吡啶-3-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(148) (R)-6-(3-(4-氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(149) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(150) (R)-N-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-5'-甲氧基螺[環丙烷-1,3'-吲哚啉]-6'-胺；

(151) (R)-6'-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5'-甲氧基螺[環丙烷-1,3'-吲哚啉]-2'-酮；

(152) (R)-1-(6-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-5-甲氧基-1'-甲基螺[吲哚啉-3,4'-六氫吡啶]-1-基)-2,2,2-三氟乙-1-酮；

(153) (R)-6-((6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-7-甲氧基螺[苯并[b][1,4]噁 哌-2,1'-環丙烷]-3(4H)-酮；

(154) (R)-N-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-5-甲氧基-1'-甲基螺[吲哚啉-3,4'-六氫吡啶]-6-胺；

(155) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(1-甲基哌啶-4-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺；

(156) (R)-N-(6-(3-(3,5-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)-3-甲氧基-7-(4-甲基哌啡-1-基)-9H-咔唑-2-胺；

(157) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(哌啶-4-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺；

(158) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(1-甲基-1H-吡唑-5-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺；

(159) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(2,3-二氫苯并呋喃-7-基)嘧啶-4-胺；

(160) (R)-6-(3-(3,5-二氟苯基)異噁唑啶-2-基)-N-(4-(1-(1-甲基哌啶-4-基)-1H-吡唑-4-基)-2,3-二氫苯并呋喃-7-基)嘧啶-4-胺；

(162) (R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-甲基哌咔-1-基)-2,3-二氫苯并呋喃-7-基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(164) (R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-(4-甲基哌咔-1-基)哌啶-1-基)-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(165) (R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-嗎啉基哌啶-1-基)-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(166) (R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-(4-甲基哌咔-1-基)-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(167) (R)-N-(5-(1-甲基-1H-吡唑-4-基)-4-嗎啉基-2-(2,2,2-三氟乙氧基)苯基)-6-(3-苯基異噁唑啶-2-基)嘧啶-4-胺；

(168) (S)-6-(3-(5-氟吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌咔-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(169) (R)-6-(3-(5-氟吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌咔-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(170) (R)-3-氟基-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌咔-1-基)哌啶-

1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲腈；

(171) (S)-3-氟-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌啡-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)苯甲腈；

(172) (R)-3-(4-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)異噁唑啶-2-甲酸三級丁酯；

(173) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-((R)-2-甲基異噁唑啶-3-基)苯基)嘧啶-4-胺；

(174) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-((R)-異噁唑啶-3-基)苯基)嘧啶-4-胺；

(175) (S)-3-(4-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)異噁唑啶-2-甲酸三級丁酯；

(176) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-((S)-2-甲基異噁唑啶-3-基)苯基)嘧啶-4-胺；

(177) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-((S)-異噁唑啶-3-基)苯基)嘧啶-4-胺；

(178) (R)-6-(3-(1-甲基-1H-吡唑-4-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(179) (R)-6-(3-(呋喃-2-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(180) (R)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(181) (S)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(4-(4-甲基哌啡-1-基)苯基)嘧啶-4-胺；

(182) (R)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(183) (S)-6-(3-(5-氯吡啶-3-基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(184) (R)-6-(3-(3-(二氟甲基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(185) (S)-6-(3-(3-(二氟甲基)苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(186) (R)-3-(3-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)異噁唑啶-2-甲酸三級丁酯；

(187) (S)-3-(3-((6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)苯基)異噁唑啶-2-甲酸三級丁酯；

(188) (R)-N-(6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)環丙烷甲醯胺；

(189) (R)-N-(6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)苯甲醯胺；

(190) (R)-N-(環戊基甲基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(191) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-氟苯甲基)嘧啶-4-胺；

(192) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(1-(甲磺醯基)哌啶-4-基)嘧啶-4-胺；

(193) (R)-6-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-

5-甲氧基-2-甲基異吲哚啉-1-酮；

(194) (R)-3-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-1H-吲唑-6-甲腈；

(195) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(9-(1-氟基-2-甲基丙-2-基)-3,9-二氮雜螺[5.5]十一烷-3-基)-2-甲氧基-5-(1-甲基-1H-吡唑-4-基)苯基)嘧啶-4-胺；

(196) (R)-N-(2,5-二氯-4-(9-(1-氟基-2-甲基丙-2-基)-3,9-二氮雜螺[5.5]十一烷-3-基)苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(197) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲基-5-(3-((甲磺醯基)甲基)氮雜環丁-1-基)-4-(4-嗎啉基哌啶-1-基)苯基)嘧啶-4-胺；

(198) (R)-N-(5-(3-氯-1-甲基-1H-吡唑-4-基)-2-甲氧基-4-(4-甲基哌呯-1-基)苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(199) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-甲基哌呯-1-基)-5-乙烯基苯基)嘧啶-4-胺；

(200) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(5-乙炔基-2-甲氧基-4-(4-甲基哌呯-1-基)苯基)嘧啶-4-胺；

(201) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-甲氧基-6-(1-甲基-1H-吡唑-4-基)-5-(4-甲基哌呯-1-基)吡啶-2-基)嘧啶-4-胺；

(202) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-5-(1-甲基-1H-吡唑-4-基)-6-(4-甲基哌呯-1-基)吡啶-3-基)嘧啶-4-胺；

(203) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(3-(1-甲基-1H-吡唑-4-基)-5-((2R,3S)-2-甲基-3-((甲磺醯基)甲基)氮雜環丁-1-基)-4-嗎啉基苯基)嘧啶-4-胺；

(204) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N4-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-N2-甲基嘧啶-2,4-二胺；

(205) (R)-4-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)吡啶-2-胺；

(206) (R)-N-(4-(4-(4-烯丙基哌啉-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(207) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-乙基哌啉-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(208) (R)-N-(4-(4-(4-環丁基哌啉-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(209) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-(氧呾-3-基)哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(210) (R)-N-(4-(4-(4-(環丙基甲基)哌啉-1-基)哌啶-1-基)-2-甲氧苯基)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-胺；

(211) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(6-甲基-2,6-二氮雜螺[3.3]庚-2-基)哌啶-1-基)苯基)嘧啶-4-胺；

(212) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((R)-3-(二甲胺基)吡咯啶-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(213) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((R)-3,4-二甲基哌啉-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(214) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((S)-3,4-二甲基哌啉-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(215) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((3S,5R)-4-

乙基-3,5-二甲基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(216) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((S)-2,4-二甲基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(217) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-((R)-2,4-二甲基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(218) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(3-(4-甲基哌呾-1-基)氮雜環丁-1-基)苯基)嘧啶-4-胺；

(219) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(6-乙基-3,6-二氮雜雙環[3.1.1]庚-3-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(220) 6-((R)-3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(3-乙基-3,6-二氮雜雙環[3.1.1]庚-6-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(221) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-甲基-1,4)-苯二氮酌-1-基)哌啶-1-基)苯基)嘧啶-4-胺；

(222) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(4-(4-(4-異丙基哌呾-1-基)哌啶-1-基)-2-甲氧苯基)嘧啶-4-胺；

(223) (R)-1-(1-(4-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-3-甲氧苯基)哌啶-4-基)-4-甲基哌呾-2-酮；

(224) (R)-4-(1-(4-((6-(3-(2,3-二氟苯基)異噁唑啶-2-基)嘧啶-4-基)胺基)-3-甲氧苯基)哌啶-4-基)-1-甲基哌呾-2-酮；

(225) (R)-1-甲基-5-(2-(6-((4-(4-甲基哌呾-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)吡啶-2(1H)-酮；

(226) (R)-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌呾-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)-1-甲基吡啶-2(1H)-酮；

(227) (S)-1-甲基-5-(2-(6-((4-(4-甲基哌啉-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)吡啶-2(1H)-酮；

(228) (S)-5-(2-(6-((2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)胺基)嘧啶-4-基)異噁唑啶-3-基)-1-甲基吡啶-2(1H)-酮；

(229) N-(4-(4-甲基哌啉-1-基)苯基)-6-(3-苯基苯并[d]異噁唑-2(3H)-基)嘧啶-4-胺；

(230) N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(3-苯基苯并[d]異噁唑-2(3H)-基)嘧啶-4-胺；

(231) (S)-N-(4-(4-甲基哌啉-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺；

(232) (R)-N-(4-(4-甲基哌啉-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺；

(233) (S)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺；

(234) (R)-N-(2-甲氧基-4-(4-(4-甲基哌啉-1-基)哌啶-1-基)苯基)-6-(7-苯基-5-氧雜-6-氮雜螺[2.4]庚-6-基)嘧啶-4-胺；

(235) (R)-6-(3-異丙基異噁唑啶-2-基)-N-(4-(4-甲基哌啉-1-基)苯基)嘧啶-4-胺；

(236) (S)-6-(3-異丙基異噁唑啶-2-基)-N-(4-(4-甲基哌啉-1-基)苯基)嘧啶-4-胺；及

(237) (R)-6-(3-(2,3-二氟苯基)異噁唑啶-2-基)-N-(2-甲氧基-4-(4-(4-(2-(甲磺醯基)乙基)哌啉-1-基)哌啶-1-基)苯基)嘧啶-4-胺。

【請求項7】

一種如請求項1至6中任一項之化合物、其光學異構體、或其醫藥學上可接受之鹽之用途，其係用於製備用以治療或預防癌症之醫藥組合物。

【請求項8】

如請求項7之用途，其中該組合物抑制EGFR及/或HER2。

【請求項9】

如請求項8之用途，其中該組合物抑制選自由以下組成之群中之任一或多者：

EGFR Del19/C797S、EGFR L858R/C797S、EGFR L861Q、EGFR G719A、EGFR S768I、EGFR L718Q、EGFR G724S、EGFR d746-750、EGFR d746-750/C797A、EGFR d746-750/C797S、EGFR d746-750/T790M/C797S、EGFR D761Y、EGFR G719C、EGFR G719D、EGFR G719S、EGFR L747S、EGFR L792F、EGFR L858R、EGFR L792F/L858R、ERBB2/HER2及ERBB4/HER4。

【請求項10】

如請求項7之用途，其中該癌症為選自由以下組成之群的一或多者：膽道癌、大腸直腸癌、血液癌、腦癌、神經膠質瘤、乳癌、肺癌、眼癌、小腸癌、惡性軟組織癌、皮膚癌、腎癌、胃癌、及肉瘤。

【請求項11】

如請求項7之用途，其中該癌症為選自由以下組成之群的一或多者：假黏液瘤、肝內膽道癌、肝母細胞瘤、肝癌、甲狀腺癌、大腸癌、睪丸癌、骨髓發育不良症候群、神經膠母細胞瘤、口腔癌、唇癌、蕈樣黴菌病、急性骨髓白血病、急性淋巴球性白血病、基細胞癌、卵巢上皮癌、卵巢生殖細胞癌、男性乳癌、垂體腺瘤、多發性骨髓瘤、膽囊癌、慢性骨髓

性白血病、慢性淋巴球性白血病、視網膜母細胞瘤、脈絡膜黑色素瘤、壺腹癌、膀胱癌、腹膜癌、副甲狀腺癌、腎上腺癌、鼻竇癌、非小細胞肺癌、舌癌、星形細胞瘤、小細胞肺癌、小兒腦癌、小兒淋巴瘤、小兒白血病、腦膜瘤、食道癌、腎盂癌、心臟癌、十二指腸癌、惡性骨癌、惡性淋巴瘤、惡性間皮瘤、惡性黑色素瘤、外陰癌、尿管癌、尿道癌、原發部位不明之癌症、胃淋巴瘤、胃癌瘤、胃腸基質癌、威爾姆斯癌(Wilms cancer)、陰莖癌、咽癌、妊娠期絨毛膜癌、子宮頸癌、子宮內膜癌、子宮肉瘤、前列腺癌、轉移性骨癌、轉移性腦癌、縱隔癌、直腸癌、直腸癌瘤、陰道癌、脊髓癌、聽神經瘤、胰臟癌、唾液腺癌、卡波西氏肉瘤(Kaposi's sarcoma)、佩吉特氏病(Paget's disease)、扁桃體癌、鱗狀細胞癌、肺腺癌、肺鱗狀細胞癌、肛門癌、橫紋肌肉瘤、喉癌、胸膜癌、及胸腺癌。