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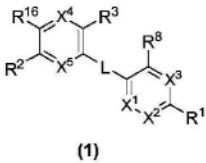
(54) 发明名称

KIF18A抑制剂

(57) 摘要

公开了一类KIF18A抑制剂,具体公开了一种
通式(1)所示的化合物及其制备方法,及通式(1)
化合物及其各异构体、各晶型、药学上可接受的
盐、水合物或溶剂合物作为KIF18A抑制剂在抗肿

瘤药物制备中的用途。004式1



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根据细则 4.17 的声明:

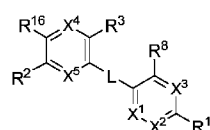
- 关于申请人有权申请并被授予专利(细则 4.17(ii))
- 发明人资格(细则 4.17(iv))

本国际公布:

- 包括国际检索报告(条约第 21 条(3))。

(54) Title: KIF18A INHIBITOR

(54) 发明名称: KIF18A 抑制剂



(1)

(57) Abstract: Disclosed are a class of KIF18A inhibitors, and specifically disclosed are a compound represented by general formula (1) and a preparation method therefor, and a use of a compound represented by general formula (1) and an isomer, crystal forms, pharmaceutically acceptable salt, hydrate or solvate thereof as KIF18A inhibitors in the preparation of anti-tumor drugs. 00 4 Formula 1

(57) 摘要: 公开了一类 KIF18A 抑制剂, 具体公开了一种通式(1)所示的化合物及其制备方法, 及通式(1)化合物及其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物作为 KIF18A 抑制剂在抗肿瘤药物制备中的用途。 00 4 式 1



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KIF18A 抑制剂

本申请要求申请日为 2022 年 11 月 19 日的中国专利申请 202111399876.4、申请日为 2022 年 3 月 9 日的中国专利申请 202210225663.8 和申请日为 2022 年 6 月 13 日的中国专利申请 202210667619.2 的优先权。本申请引用上述中国专利申请的全文。

技术领域

本发明属于药物化学领域，更具体而言，涉及一类及具有 KIF18A 蛋白抑制作用的化合物，及其制备方法和该类化合物用于制备抗肿瘤药物中的应用。

背景技术

基因组的不稳定性是绝大多数肿瘤细胞的一个共同特点。大部分的肿瘤细胞具有染色体的异常获得或缺失。肿瘤细胞的染色体不稳定性(chromosome instability)会导致异常的染色体与有丝分裂纺锤体微管(spindle microtubules)的相互作用，进而造成染色体分离错误。与具有正常染色体的细胞相比，具有染色体不稳定性的细胞会产生增多的纺锤体微管聚合以及减少的纺锤体微管与着丝粒的接触转换。因此，针对微管骨架的抗有丝分裂疗法可能对于具有染色体不稳定性的细胞尤为有效。

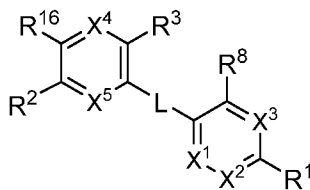
驱动蛋白是一类分子马达，其在细胞分裂和细胞内囊泡和细胞器运输中起到重要作用。在纺锤体组件、染色体分离、中心体分离和动力学等多个方面，有丝分裂驱动蛋白都起到重要作用。基于马达域(motor domain)氨基酸序列的不同，人的驱动蛋白被分类为 14 个亚型，位于马达域的 ATP 酶活性驱动该蛋白沿着微管单向运动。这些蛋白质的非马达结构域负责与底物相互作用，各种不同的膜状细胞器、信号转导支架系统和染色体作为底物都可以与非马达结构域相互作用。驱动蛋白通过 ATP 水解来获得能量，从而沿着极化微管移动底物。因此，驱动蛋白通常被称为“正端”或“负端”定向马达。

KIF18A 蛋白属于驱动蛋白-8 亚型。KIF18A 蛋白在多种类型的癌症中过表达，例如肺癌、卵巢癌、子宫颈癌、乳腺癌、胰腺癌、前列腺癌、结肠癌和膀胱癌。研究认为 KIF18A 影响丝粒微管正端的运动从而控制正确的染色体定位和纺锤体张力。在具有染色体不稳定性的肿瘤细胞中，异常的微管运动使这类细胞尤为依赖 KIF18A 蛋白来减少纺锤体微管与着丝粒的接触转换以及限制微管生长(Nat Commun. 2021, 12, 1213)。当具有染色体不稳定性的肿瘤细胞中缺失 KIF18A 蛋白时，细胞的中心体会发生碎片化，并且有丝分裂进程会变慢或者终止。但这些现象并不会发生在具有正常染色体的细胞中。因此 KIF18A 蛋白的活性对于正常细胞的增殖并不会有很大影响，但对于染色体不稳定的肿瘤的生长非常关键。

因此，开发 KIF18A 抑制剂是一种对抗具有染色体不稳定性的肿瘤的新的有潜力的方法。

发明内容

本发明提供了一种通式(1)所示的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物：



(1)

通式(1)中:

X¹ 为 -CR⁵= 或 N;

X² 为 -CR⁶= 或 N;

X³ 为 -CR⁷= 或 N;

X⁴ 为 -CR⁴= 或 N;

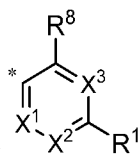
X⁵ 为 -CR¹⁵= 或 N;

当 X⁵ 为 -CR¹⁵= 且 X⁴ 为 -CR⁴= 时, R¹⁶ 为 -C₃₋₈ 环烷基、-OR¹⁷、-SR¹⁸、-NR¹⁸R¹⁹ 或 -NO₂;

当 X⁵ 为 -CR¹⁵= 且 X⁴ 为 N 时, R¹⁶ 为 -O-C₁₋₈ 烃基、-C₃₋₈ 环烷基、-OR¹⁷、-SR¹⁸、-NR²⁰R²¹ 或 -NO₂;

当 X⁵ 为 N 时, R¹⁶ 为 -O-C₁₋₈ 烃基、-C₃₋₈ 环烷基、-OR¹⁷、-SR¹⁸、-NR²⁰R²¹ 或 -NO₂;

L 为 -(C=O)-NR⁹-* 或 -NR⁹-(C=O)-*; 和 X¹、X²、X³、X⁴ 和 X⁵ 中, 不超过 4 个为 N;



*代表连接的是

R¹⁷ 为 H、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基, 其中所述 -C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基可任选被 0、1、2 或 3 个下列基团取代: H、卤素或 -C₁₋₄ 烃基。

R¹⁸ 和 R¹⁹ 各自独立地为 H、-C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基, 其中所述 -C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基可任选被 0、1、2 或 3 个下列基团取代: H、卤素或 -C₁₋₄ 烃基。

R²⁰ 和 R²¹ 各自独立地为 H、-C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基, 其中所述 -C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基可任选被 0、1、2 或 3 个下列基团取代: H、卤素或 -C₁₋₄ 烃基; 或 R²⁰ 和 R²¹ 可以与它们各自连接的氮原子组合以形成含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子的饱和的或部分饱和的 3 元、4 元、5 元或 6 元单环或 4 元、5 元、6 元、7 元、8 元、9 元、10 元、11 元或 12 元双环;

R¹ 为 -CN 或 -Z-R¹⁰, 其中 Z 为化学键、-C₀₋₄ 烃基、-NR¹¹、-NR¹¹SO₂、-SO₂NR¹¹、-NR¹¹-S(=O)(=NH)-、-S(=O)(=NH)-、-S-、-S(=O)-、-SO₂、-C₀₋₄ 烃基-O-、-(C=O)-、-(C=O)NR¹¹、-C(=N-OH)-或 -NR¹¹(C=O)-; 或所述基团 -Z-R¹⁰ 为 -N=S(=O)-(R¹⁰)₂, 其中所述两个 R¹⁰ 可以与它们各自连接的硫原子组合以形成含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子的饱和的或部分饱和的 3 元、4 元、5 元或 6 元单环;

R² 为卤素或基团 -Y-R¹², 其中 Y 为化学键、-C₀₋₄ 烃基、-N(C₀₋₁ 烃基)-C₀₋₄ 烃基、-C(=O)NR^aR^a (C₁₋₄ 烃基)-、-O-C₀₋₄ 烃基、-S-、-S(=O)-、-SO₂、-SO₂NR¹² 或 -S(=O)(=NH)-;

R³ 为 H、卤素、C₁₋₈ 烷基或 C₁₋₄ 卤代烷基;

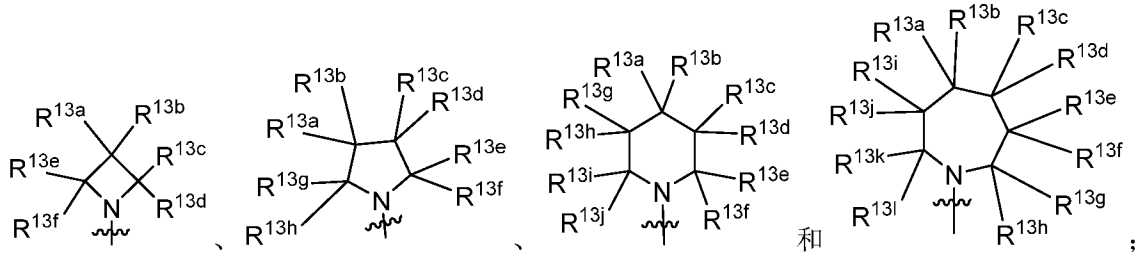
R⁴ 为 H、卤素、R^{4a} 或 R^{4b};

R⁵ 为 H、卤素、C₁₋₈ 烷基或 C₁₋₄ 卤代烷基;

R⁶ 为 H、卤素、C₁₋₈ 烷基、C₁₋₄ 卤代烷基、-OH、-O-R^{6a} 或 -O-R^{6b};

R⁷ 为 H、卤素、C₁₋₈ 烷基或 C₁₋₄ 卤代烷基;

R⁸ 选自由以下组成的组:



R^{13a} 、 R^{13b} 、 R^{13c} 、 R^{13d} 、 R^{13e} 、 R^{13f} 、 R^{13g} 、 R^{13h} 、 R^{13i} 、 R^{13j} 、 R^{13k} 和 R^{13l} 各自独立地为H、卤素、 R^{13m} 或 R^{13n} ；或 R^{13a} 和 R^{13b} 对、 R^{13c} 和 R^{13d} 对、 R^{13e} 和 R^{13f} 对、 R^{13g} 和 R^{13h} 对、 R^{13i} 和 R^{13j} 对或 R^{13k} 和 R^{13l} 对中的每一对可以独立地与它们各自连接的碳原子组成螺接到 R^8 环的饱和的或部分饱和的3元、4元、5元、6元单环；其中所述3元、4元、5元、6元单环含有0、1、2或3个N原子和0、1或2个选自O和S的原子，并且进一步地，其中所述3元、4元、5元、6元单环被选自以下的0、1、2或3个基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基、CN、 $-NR^aR^a$ 或氧代；

R^9 为H或 C_{1-6} 烷基；

R^{10} 为H、 R^{10a} 、 R^{10b} 或 R^{10c} ；

R^{11} 为H、 R^{11a} 或 R^{11b} ；

R^{12} 为 R^{12a} 或 R^{12b} ；

R^{15} 为H、卤素、 C_{1-8} 烷基、 C_{1-4} 卤代烷基、 $-O-C_{1-8}$ 烷基或 $-O-R^{15a}$ ，其中 R^{15a} 为含有0、1、2或3个N原子和0、1或2个选自O和S的原子饱和的或部分饱和的3元、4元、5元或6元单环；

R^{4a} 、 R^{6a} 、 R^{10a} 、 R^{11a} 、 R^{12a} 或 R^{13m} 为在每种情况下独立地选自：含有0、1、2或3个N原子和0、1或2个选自O和S的原子饱和的、部分饱和的或不饱和的3元、4元、5元、6元或7元单环或4元、5元、6元、7元、8元、9元、10元、11元或12元双环，其中所述单环和双环可各自独立任选被0、1、2或3个下列基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基、CN、 $-C(=O)R^b$ 、 $-C(=O)OR^a$ 、 $-C(=O)NR^aR^a$ 、 $-C(=NR^a)NR^aR^a$ 、 $-OC(=O)R^b$ 、 $-OC(=O)NR^aR^a$ 、 $-OC_{2-6}$ 烷基 NR^aR^a 、 $-OC_{2-6}$ 烷基 OR^a 、 $-SR^a$ 、 $-S(=O)R^b$ 、 $-S(=O)_2R^b$ 、 $-S(=O)_2NR^aR^a$ 、 $-NR^aR^a$ 、 $-N(R^a)C(=O)R^b$ 、 $-N(R^a)C(=O)OR^b$ 、 $-N(R^a)C(=O)NR^aR^a$ 、 $-N(R^a)C(=NR^a)NR^aR^a$ 、 $-N(R^a)S(=O)_2R^b$ 、 $-N(R^a)S(=O)_2NR^aR^a$ 、 $-NR^aC_{2-6}$ 烷基 NR^aR^a 、 $-NR^aC_{2-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 NR^aR^a 、 $-C_{1-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 $N(R^a)C(=O)R^b$ 、 $-C_{1-6}$ 烷基 $OC(=O)R^b$ 、 $-C_{1-6}$ 烷基 $C(=O)NR^aR^a$ 、 $-C_{1-6}$ 烷基 $C(=O)OR^a$ 、 R^{14} 和氧代；

R^{4b} 、 R^{6b} 、 R^{10b} 、 R^{11b} 、 R^{12b} 或 R^{13n} 为在每种情况下独立地选自： C_{1-6} 烷基，其中所述烷基可任选被0、1、2、3、4或5个下列基团取代：F、Cl、Br、 $-R^a$ 、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基和CN；

R^{10c} 为在每种情况下独立地选自： C_{1-6} 烷基，其中所述烷基可任选被0、1、2、3、4或5个下列基团取代：F、Cl、Br、 $-R^a$ 、 $-R^c$ 、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基和CN；

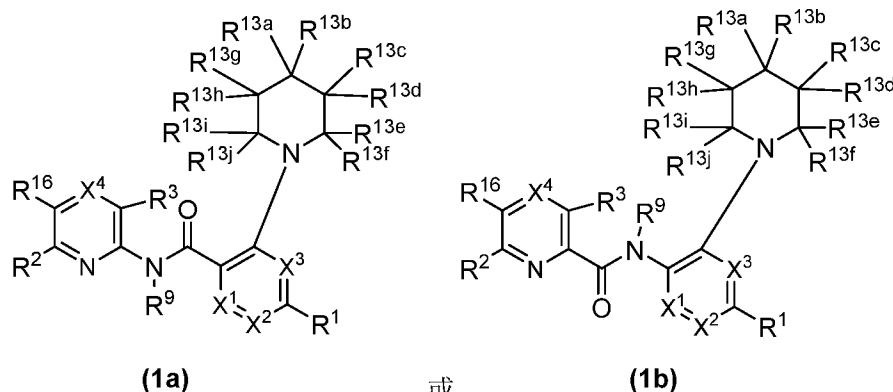
R^{14} 在每种情况下独立地选自由以下组成的组：含有0、1、2或3个N原子和0或1个选自O和S的原子饱和的、部分饱和的或不饱和的3元、4元、5元、6元或7元单环或4元、5元、6元、7元、8元、9元、10元、11元或12元双环，其中所述单环和双环各自独立可任选被0、1、2或3个下列基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基、CN、 $-C(=O)R^b$ 、 $-C(=O)OR^a$ 、 $-C(=O)NR^aR^a$ 、 $-C(=NR^a)NR^aR^a$ 、 $-OC(=O)R^b$ 、 $-OC(=O)NR^aR^a$ 、 $-OC_{2-6}$ 烷基 NR^aR^a 、 $-OC_{2-6}$ 烷基 OR^a 、 $-SR^a$ 、 $-S(=O)R^b$ 、 $-S(=O)_2R^b$ 、 $-S(=O)_2NR^aR^a$ 、 $-NR^aR^a$ 、 $-N(R^a)C(=O)R^b$ 、 $-N(R^a)C(=O)OR^b$ 、 $-N(R^a)C(=O)NR^aR^a$ 、 $-N(R^a)C(=NR^a)NR^aR^a$ 、 $-N(R^a)S(=O)_2R^b$ 、 $-N(R^a)S(=O)_2NR^aR^a$ 、 $-NR^aC_{2-6}$ 烷基 NR^aR^a 、 $-NR^aC_{2-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 NR^aR^a 、 $-C_{1-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 $N(R^a)C(=O)R^b$ 、 $-C_{1-6}$ 烷基 $OC(=O)R^b$ 、 $-C_{1-6}$ 烷基 $C(=O)NR^aR^a$ 、 $-C_{1-6}$ 烷基 $C(=O)OR^a$ 和氧代；

R^a 在每种情况下独立地为H或 R^b ；

R^b 在每种情况下独立地为 C_{1-6} 烷基、苯基或苄基，其中所述烷基可任选被0、1、2或3个下列基团取代：卤素、 $-OH$ 、 $-OC_{1-4}$ 烷基、 $-NH_2$ 、 $-NHC_{1-4}$ 烷基、 $-OC(=O)C_{1-4}$ 烷基或 $-N(C_{1-4}$ 烷基) C_{1-4} 烷基；并且其中所述苯基和苄基可各自独立任选被0、1、2或3个下列基团取代：卤素、 C_{1-4} 烷基、 C_{1-3} 卤代烷基、 $-OH$ 、 $-OC_{1-4}$ 烷基、 $-NH_2$ 、 $-NHC_{1-4}$ 烷基、 $-OC(=O)C_{1-4}$ 烷基或 $-N(C_{1-4}$ 烷基) C_{1-4} 烷基；并且

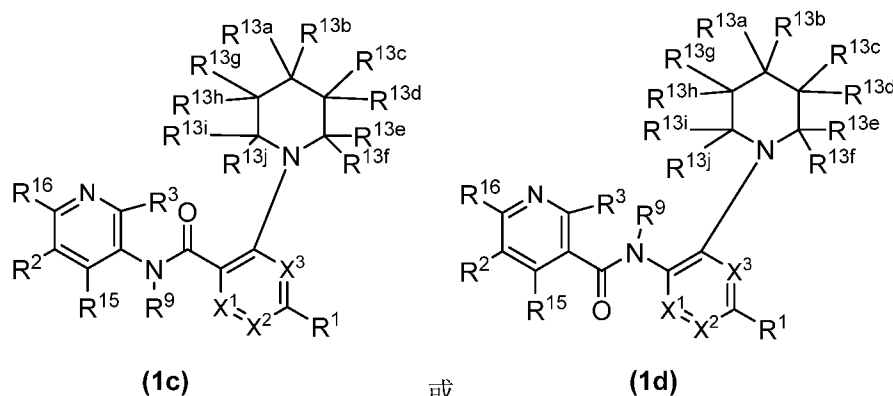
R^e 在每种情况下独立地为 $-OC(=O)C_{1-5}$ 烷基, 其中所述烷基可任选被 1、2 或 3 个下列基团取代: $-OH$ 或 $-NH_2$ 。

在另一优选例中, 其中所述通式(1)中, 其中所述通式(1)具有以下结构:



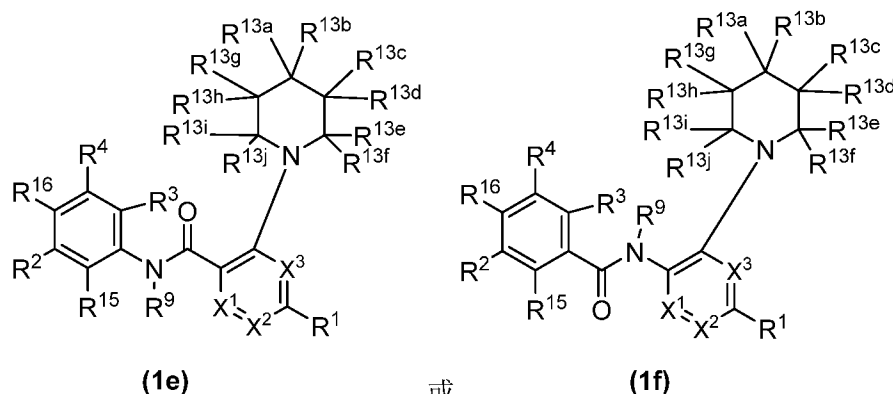
其中 R^{16} 为 $-C_{3-6}$ 环烷基、 $-OH$ 、 $-O-C_{1-4}$ 烷基、 $-O-C_{1-4}$ 卤代烷基、 $-O-C_{3-6}$ 环烷基、 $-O-C_{3-6}$ 卤代环烷基、 $-SH$ 、 $-S-C_{1-6}$ 烷基、 $-S-C_{1-4}$ 卤代烷基、 $-S-C_{3-6}$ 环烷基、 $-S-C_{3-6}$ 卤代环烷基、 $-NR^{20}R^{21}$ 或 $-NO_2$ 。

在另一优选例中, 其中所述通式(1)中, 其中所述通式(1)具有以下结构:



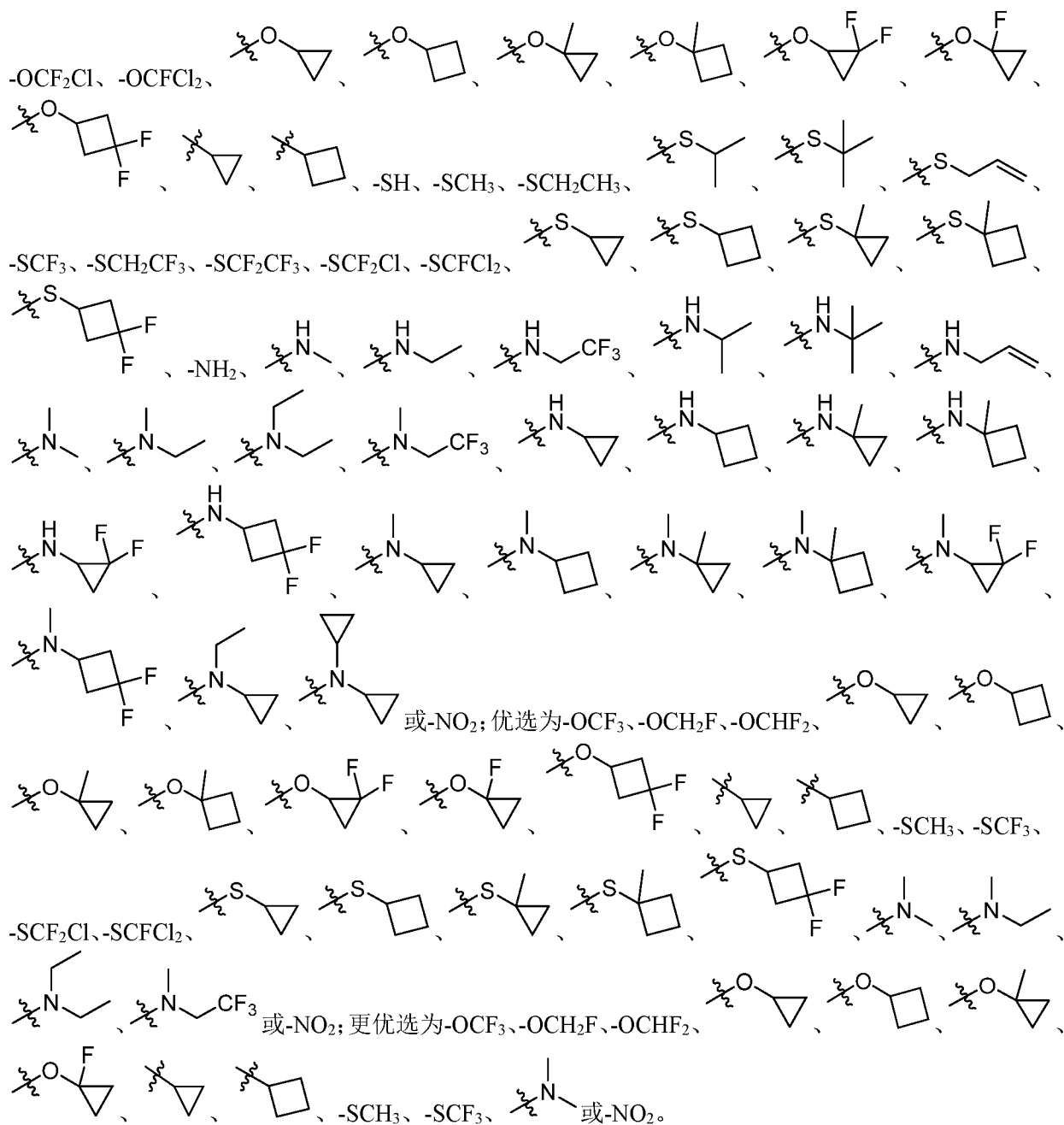
其中 R^{16} 为 $-C_{3-6}$ 环烷基、 $-OH$ 、 $-O-C_{1-4}$ 烷基、 $-O-C_{1-4}$ 卤代烷基、 $-O-C_{3-6}$ 环烷基、 $-O-C_{3-6}$ 卤代环烷基、 $-SH$ 、 $-S-C_{1-6}$ 烷基、 $-S-C_{1-4}$ 卤代烷基、 $-S-C_{3-6}$ 环烷基、 $-S-C_{3-6}$ 卤代环烷基、 $-NR^{20}R^{21}$ 或 $-NO_2$ 。

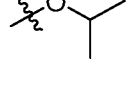
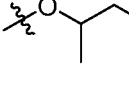
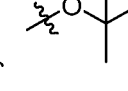
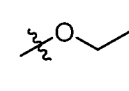
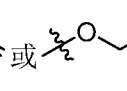
在另一优选例中, 其中所述通式(1)中, 其中所述通式(1)具有以下结构:



其中 R^{16} 为 $-C_{3-6}$ 环烷基、 $-OH$ 、 $-O-C_{1-4}$ 卤代烷基、 $-O-C_{3-6}$ 环烷基、 $-O-C_{3-6}$ 卤代环烷基、 $-SH$ 、 $-S-C_{1-6}$ 烷基、 $-S-C_{1-4}$ 卤代烷基、 $-S-C_{3-6}$ 环烷基、 $-S-C_{3-6}$ 卤代环烷基、 $-NR^{18}R^{19}$ 或 $-NO_2$ 。

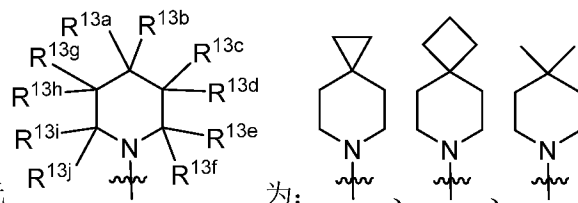
在另一优选例中, 其中所述通式(1)中, R^{16} 为 $-OH$ 、 $-OCF_3$ 、 $-OCH_2F$ 、 $-OCHF_2$ 、 $-OCH_2CF_3$ 、 $-OCF_2CF_3$ 、



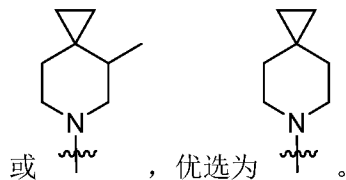
在另一优选例中，其中所述通式(1)中， R^{16} 为 $-\text{OCH}_3$ 、 $-\text{OCH}_2\text{CH}_3$ 、 $-\text{OCH}_2\text{CH}_2\text{CH}_3$ 、、
、、或；优选为 $-\text{OCH}_3$ 。

在另一优选例中，其中所述通式(1)中， R^9 为 H、甲基或乙基，优选为 H。

在另一优选例中，其中所述通式(1)中，其中 R^{13c} 、 R^{13d} 、 R^{13e} 、 R^{13f} 、 R^{13g} 、 R^{13h} 、 R^{13i} 、 R^{13j} 、 R^{13k} 和 R^{13l} 各自独立为 H、卤素、 C_{1-6} 烷基或 C_{1-4} 卤代烷基；并且 R^{13a} 和 R^{13b} 对中的 R^{13a} 和 R^{13b} 与它们各自连接的碳原子可以组合形成螺接到 R^8 环的饱和 3 元、4 元或 5 元单环；其中所述环含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子；优选， R^{13c} 、 R^{13d} 、 R^{13e} 、 R^{13f} 、 R^{13g} 、 R^{13h} 、 R^{13i} 、 R^{13j} 、 R^{13k} 和 R^{13l} 各自独立为 H、甲基或乙基；并且 R^{13a} 和 R^{13b} 对中的 R^{13a} 和 R^{13b} 与它们各自连接的碳原子可以组合形成螺接到 R^8 环的环丙基、环丁基或环戊基环。



在另一优选例中,其中所述通式(1)中,结构单元



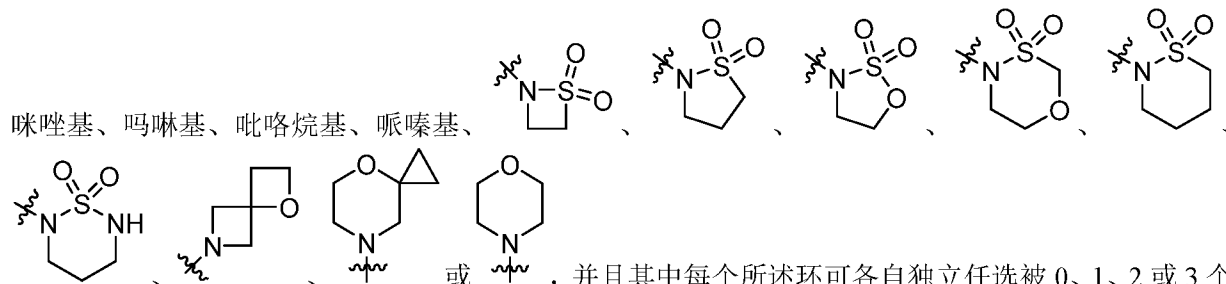
在另一优选例中,其中所述通式(1)中,其中 Z 为化学键、-NH-、-NH₂SO₂-、-SO₂NH-、-S(=O)(=NH)-、-S-、-S(=O)-、-SO₂-、-(C=O)-、-(C=O)NH-或-NH(C=O)-。

在另一优选例中,其中所述通式(1)中,其中 R¹⁰ 选自(a) H; 或(b) C₁₋₆ 烷基,所述烷基可任选被 0、1、2 或 3 个下列基团取代: F、Cl、Br、-OH 或 -OCH₃; 或(c)当所述基团-Z-R¹⁰ 为-N=S(=O)-(R¹⁰)₂, 其中所述两个 R¹⁰ 可以与它们各自连接的硫原子组合以形成含有 0、1、2 或 3 个 N 原子和 0 或 1 个选自 O 和 S 的原子的饱和的、部分饱和的或不饱和的 3 元、4 元、5 元、6 元或 7 元单环,其被选自以下的 0、1、2 或 3 个基团取代: F、Cl、Br、C₁₋₆ 烷基、C₁₋₄ 卤代烷基、-C₁₋₆ 烷基 OH、-OH、-OCH₃、-NH₂ 或氧代; 或(d) C₁₋₆ 烷基,所述 C₁₋₆ 烷基可任选被 1、2 或 3 个下列基团取代: -OC(=O)C₁₋₅ 烷基,其中所述 C₁₋₅ 烷基可任选被 1 或 2 个下列基团取代: -OH 或 -NH₂; 且所述 C₁₋₆ 烷基可任选被 0、1、2 或 3 个下列基团取代: F、Cl、Br、-OH 或 -OCH₃。

在另一优选例中,其中所述通式(1)中,其中 R¹ 为-CN 或基团-Z-R¹⁰, 其中 Z 为化学键、-NH-、-NH₂SO₂-、-SO₂NH-、-S(=O)(=NH)-、-S-、-S(=O)-、-SO₂-、-(C=O)-、-(C=O)NH-或-NH(C=O)-; 并且 R¹⁰ 选自:

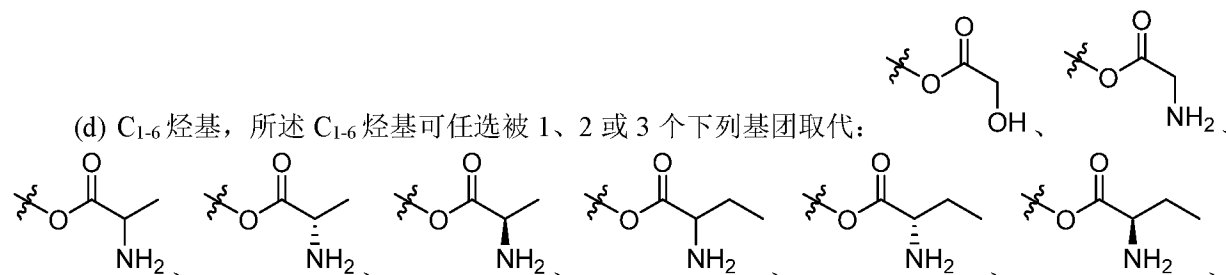
(a)H;

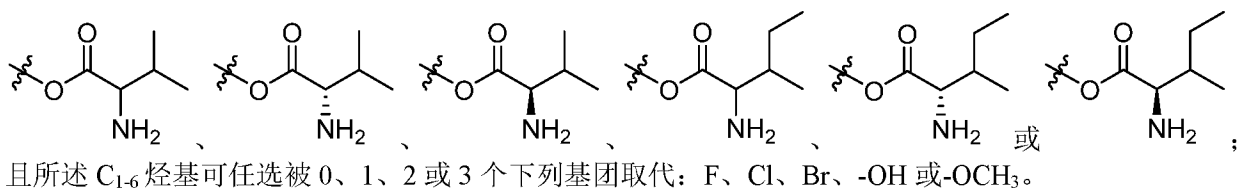
(b)环丙基、环丁基、环戊基、环己基、环氧乙烷基、氧杂环丁烷基、四氢呋喃基、氮杂环丁烷基、



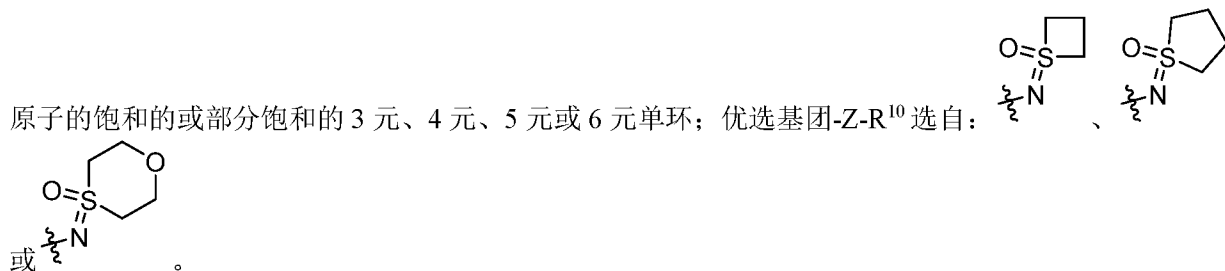
并且其中每个所述环可各自独立任选被 0、1、2 或 3 个下列基团取代: OH、F、甲基、-CH₂OH、-C(=O)OCH₃、-C(=O)OC(CH₃)₃、NH₂、CN 和氧代; 优选为氧杂环丁烷基、环丙基;

(c)被 0、1、2 或 3 个 OH、F、-C(=O)OCH₃、-NH₂、-NH(CH₃)或-N(CH₃)₂ 取代的 C₁₋₆ 烷基; 优选为被 0、1、2 或 3 个 OH 基团取代的 C₁₋₆ 烷基; 更优选为被 1 个 OH 基团取代的 C₁₋₆ 烷基; 或

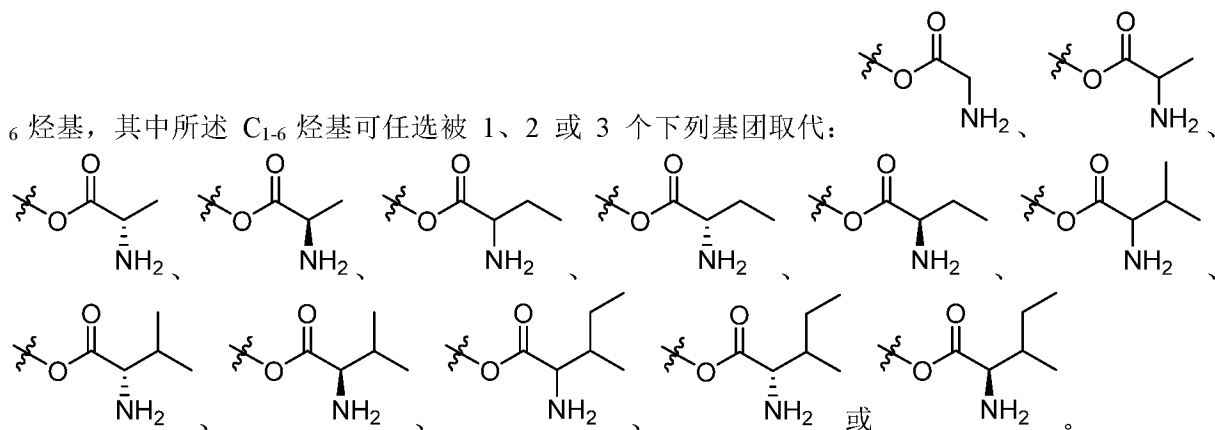




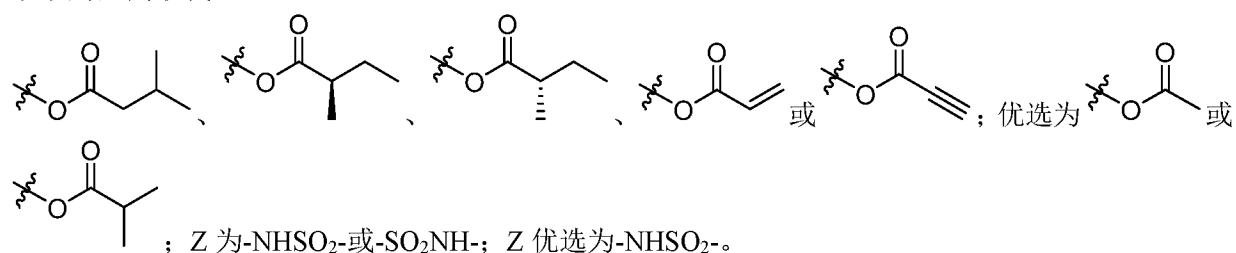
在另一优选例中，其中所述通式(1)中，其中所述基团-Z-R¹⁰ 为-N=S(=O)-(R¹⁰)₂，其中两个 R¹⁰ 对可以与它们各自连接的硫原子组合以形成含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的



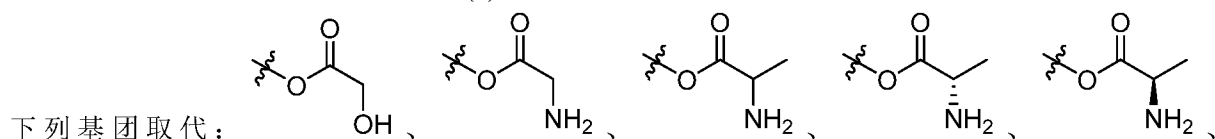
在另一优选例中，其中所述通式(1)中，其中 R¹ 为基团-Z-R¹⁰，其中 Z 为-NHSO₂-或-SO₂NH-；并且 R¹⁰ 为氧杂环丁烷基、环丙基，或 R¹⁰ 为被 0、1、2 或 3 个 OH 基团取代的 C₁₋₆ 烃基；或 R¹⁰ 为 C₁₋

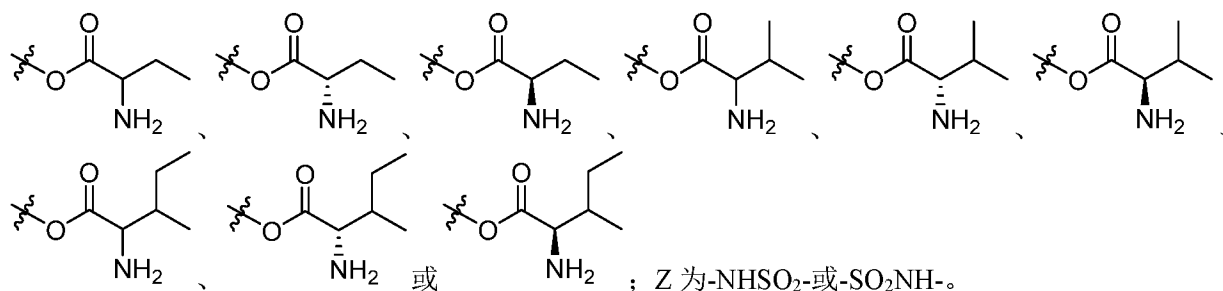


在另一优选例中，其中所述通式(1)中，其中 R¹⁰ 选自 C₁₋₆ 烃基，所述烃基可任选被 0、1、2 或 3 个下列基团取代：



在另一优选例中，其中所述通式(1)中，其中 R¹⁰ 选自 C₁₋₆ 烃基，所述烃基可任选被 1、2 或 3 个

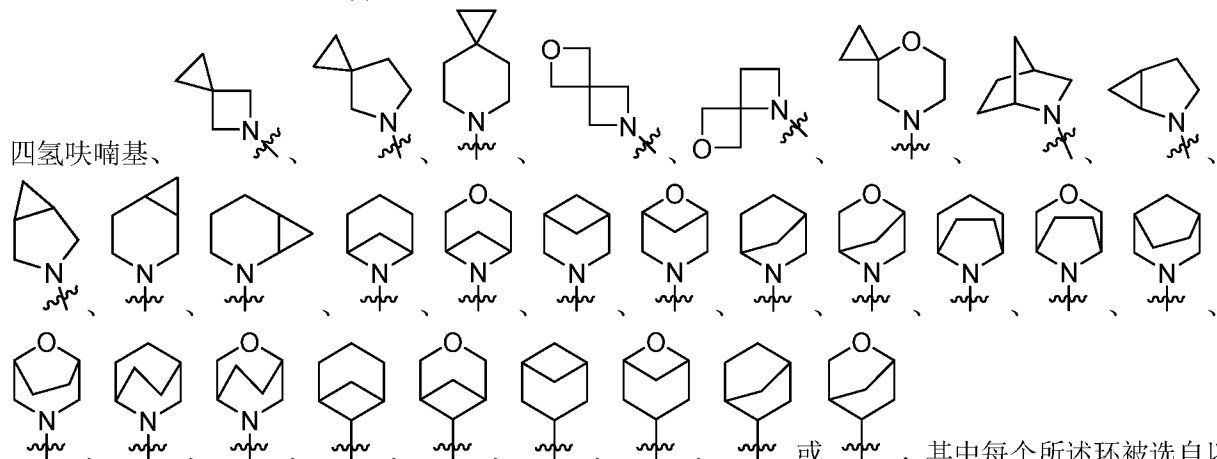




在另一优选例中，其中所述通式(1)中，其中 R² 为卤素或基团-Y-R¹²，其中 Y 为化学键、-NH-、-NH-(CH₂)₀₋₄-或-O-(CH₂)₀₋₄-；并且 R¹² 为含有 0、1、2 或 3 个 N 原子和 0 或 1 个选自 O 和 S 的原子的饱和的、部分饱和的或不饱和的 3 元、4 元、5 元、6 元或 7 元单环或 4 元、5 元、6 元、7 元、8 元、9 元、10 元、11 元或 12 元双环，其中所述单环和双环可各自独立任选被 0、1、2 或 3 个下列基团取代：F、Cl、Br、C₁₋₆ 烷基、C₁₋₄ 卤代烷基、-OH、-OC₁₋₄ 卤代烷基、CN、R¹⁴ 和氧代；或 R¹² 为 C₁₋₆ 烷基，所述烷基可任选被 0、1、2、3、4 或 5 个下列基团取代：F、Cl、Br、-OH、-OC₁₋₄ 卤代烷基或 CN。

在另一优选例中，其中所述通式(1)中，其中 R² 为饱和 5 元或 6 元单环，其中每个所述环含有 0、1 或 2 个 N 原子和 0 或 1 个 O 原子，并且其中每个所述环被选自以下的 0、1、2 或 3 个基团取代：F、Cl、Br、C₁₋₆ 烷基、C₁₋₄ 卤代烷基、-OH、-OC₁₋₄ 卤代烷基、CN、R¹⁴ 和氧代。

在另一优选例中，其中所述通式(1)中，其中 R² 为(a)卤素；(b)基团-Y-R¹²，其中 Y 为化学键；并且 R¹² 为吗啉基、哌啶基、氮杂环丁烷基、吡咯烷基、环丙基、环丁基、环戊基、环己基、哌嗪基、

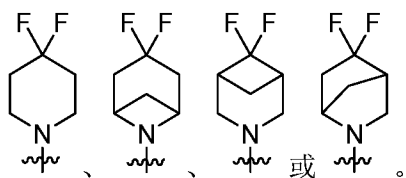


其中 Y 为-NH-、-O-、-O-(CH₂)-、-O-(CH₂)-(CH₂)-或-O-(CH₂)-(CH₂)-(CH₂)-，并且其中 R¹² 为 、或；或 R¹² 为 C₁₋₆ 烷基，所述烷基可任选被 0、1、2、3、4 或 5 个下列基团取代：F、Cl、Br、甲基、CF₃、-OH 或 CN。

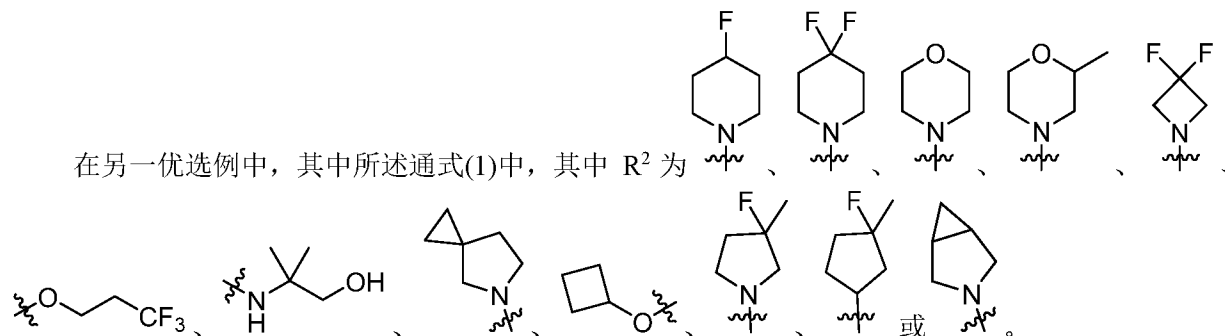
在另一优选例中，其中所述通式(1)中，其中 R² 为吗啉基或哌啶基，所述吗啉基和哌啶基可任选被 0、1、2 或 3 个下列基团取代：F、Cl、Br、甲基、CF₃、-OH、-OCHF₂ 和 CN。

在另一优选例中，其中所述通式(1)中，其中 R² 为被 1、2 或 3 个氟基团取代的哌啶基。

在另一优选例中，其中所述通式(1)中，其中 R² 为：



在另一优选例中, 其中所述通式(1)中, 其中 R^2 为被 1、2 或 3 个甲基基团取代的吗啉基。



在另一优选例中, 其中所述通式(1)中, 其中 R^{10} 选自环丙基、环丁基、环戊基、氧杂环丁烷基、氮杂环丁烷基、四氢呋喃基或 1,3,4-氧杂噻嗪烷基。

在另一优选例中, 其中所述通式(1)中, 其中 R^3 为 H。

在另一优选例中, 其中所述通式(1)中, 其中 R^4 选自(a)H; (b)被 0、1、2 或 3 个 OH 基团取代的 C_{1-6} 烷基; 或(c)环丙基; 或(d)F; R^4 优选为 H、F 或甲基; R^4 更优选为 H。

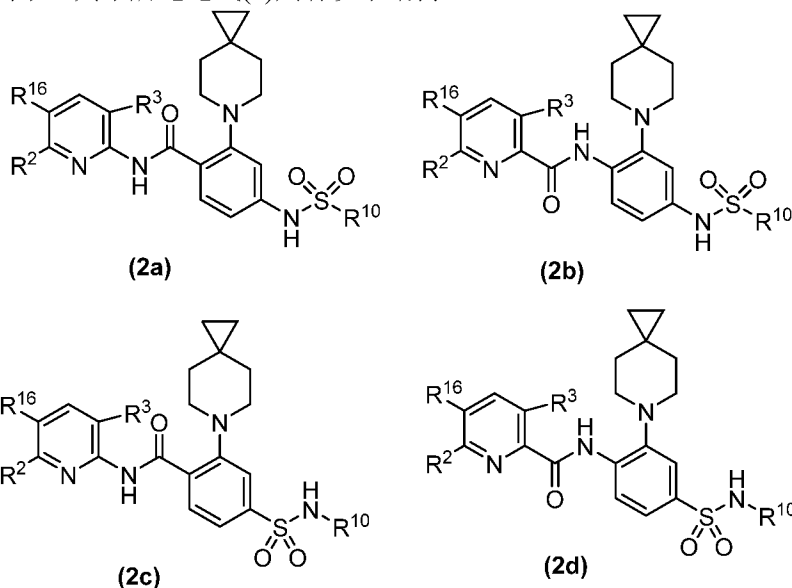
在另一优选例中, 其中所述通式(1)中, 其中 R^5 为 H 或 F, 优选为 H。

在另一优选例中, 其中所述通式(1)中, 其中 R^6 为 H 或 F, 优选为 H。

在另一优选例中, 其中所述通式(1)中, 其中 R^7 为 H。

在另一优选例中, 其中所述通式(1)中, 其中 R^{15} 为 H 或 F, 优选为 H。

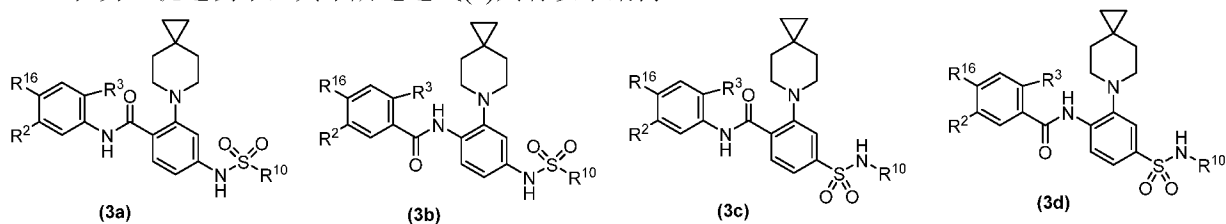
在另一优选例中, 其中所述通式(1)具有以下结构:



R^{16} 为 $-C_{3-6}$ 环烷基、 $-OH$ 、 $-O-C_{1-4}$ 烷基、 $-O-C_{1-4}$ 卤代烷基、 $-O-C_{3-6}$ 环烷基、 $-O-C_{3-6}$ 卤代环烷基、

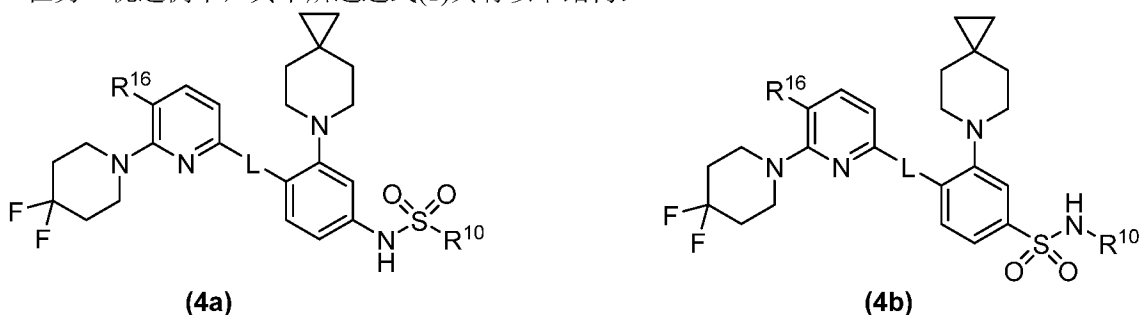
-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR²⁰R²¹ 或-NO₂, R²、R³、R¹⁰、R²⁰ 和 R²¹ 的定义如前所述, 并在具体实施例中举例说明。

在另一优选例中, 其中所述通式(1)具有以下结构:



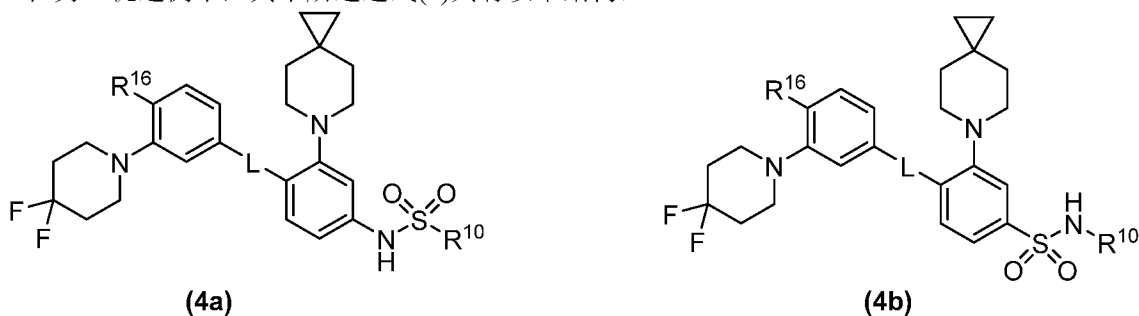
R¹⁶ 为-C₃₋₆ 环烷基、-OH、-O-C₁₋₄ 卤代烷基、-O-C₃₋₆ 环烷基、-O-C₃₋₆ 卤代环烷基、-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR¹⁸R¹⁹ 或-NO₂, R²、R³、R¹⁰、R¹⁸ 和 R¹⁹ 的定义如前所述, 并在具体实施例中举例说明。

在另一优选例中, 其中所述通式(1)具有以下结构:



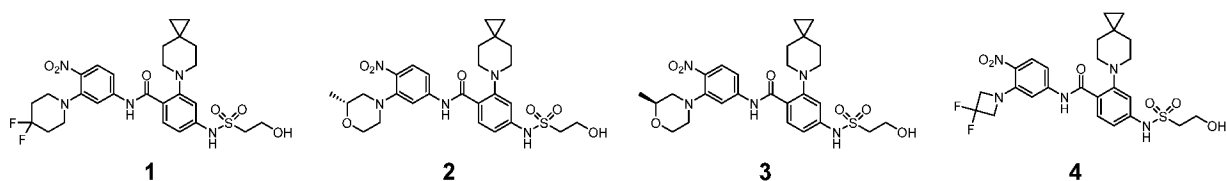
R¹⁶ 为-C₃₋₆ 环烷基、-OH、-O-C₁₋₄ 烷基、-O-C₁₋₄ 卤代烷基、-O-C₃₋₆ 环烷基、-O-C₃₋₆ 卤代环烷基、-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR²⁰R²¹ 或-NO₂, L、R¹⁰、R²⁰ 和 R²¹ 的定义如前所述, 并在具体实施例中举例说明。

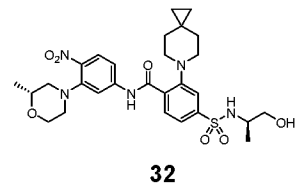
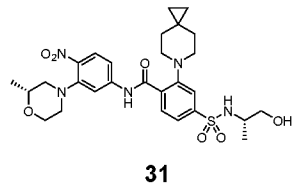
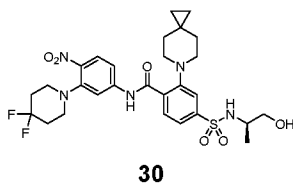
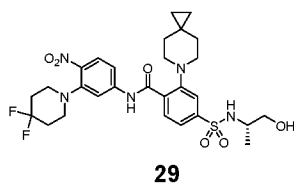
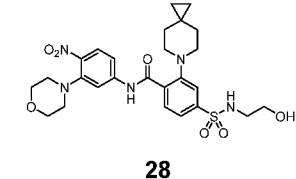
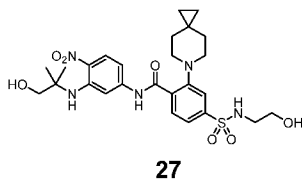
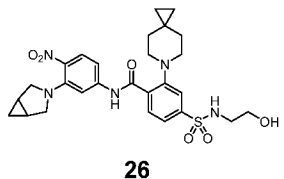
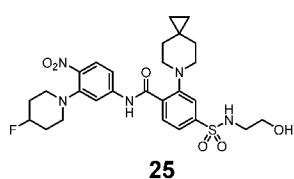
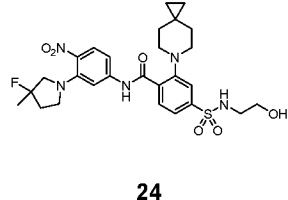
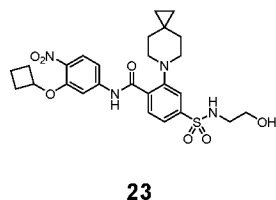
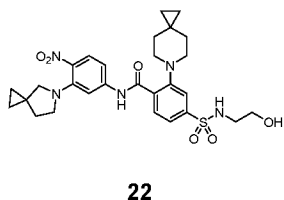
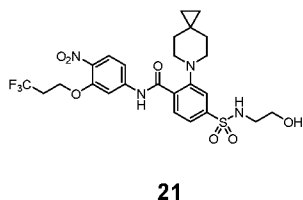
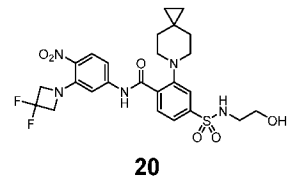
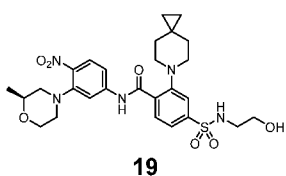
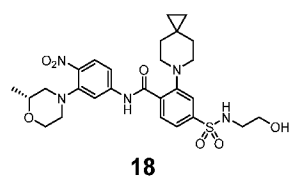
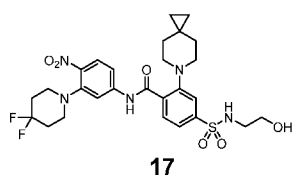
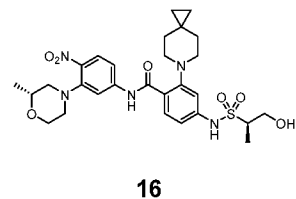
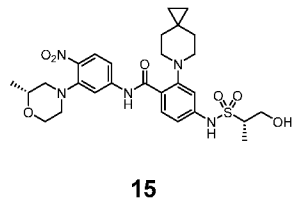
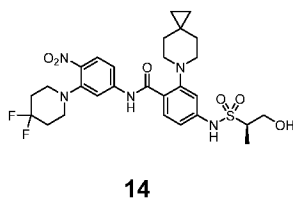
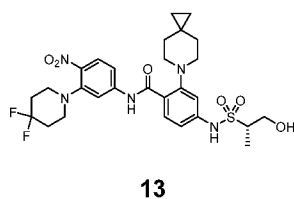
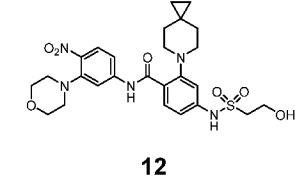
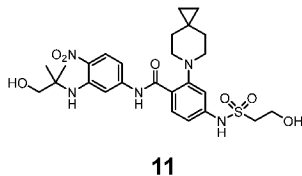
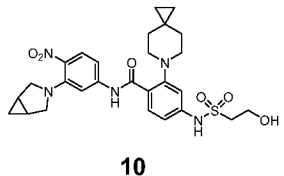
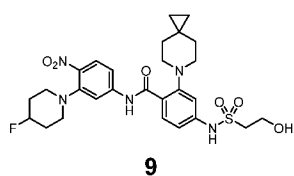
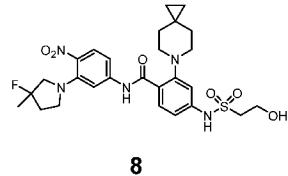
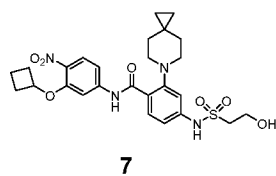
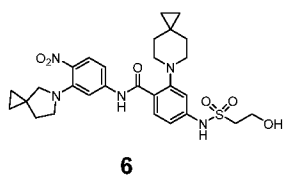
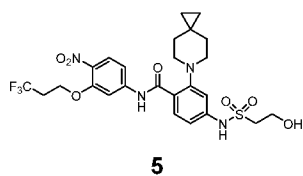
在另一优选例中, 其中所述通式(1)具有以下结构:

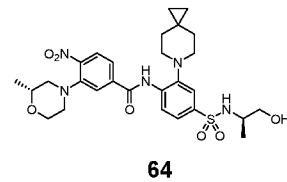
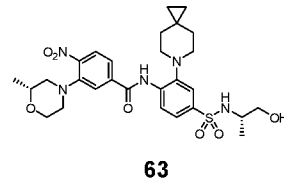
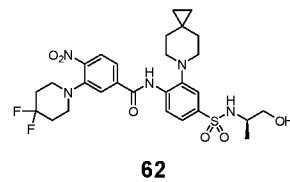
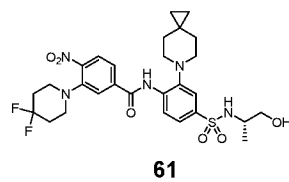
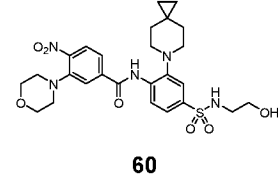
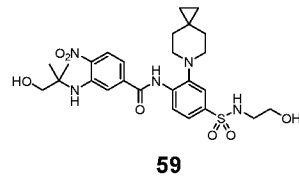
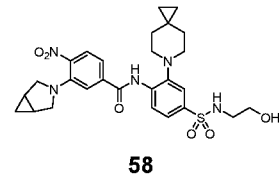
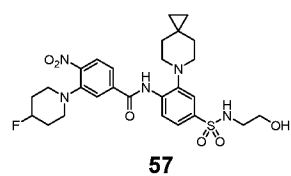
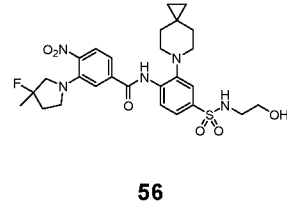
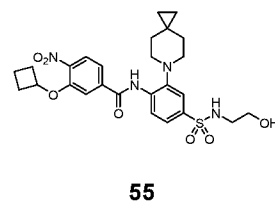
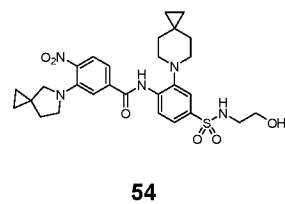
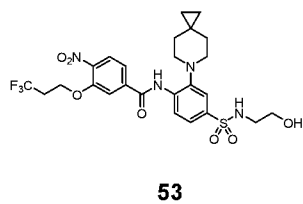
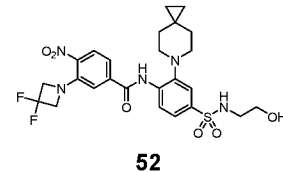
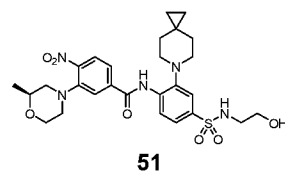
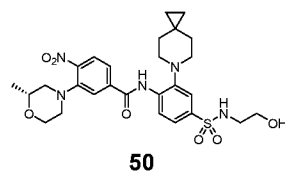
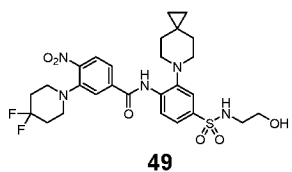
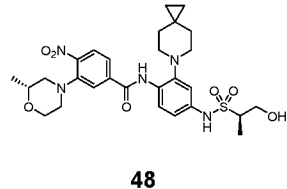
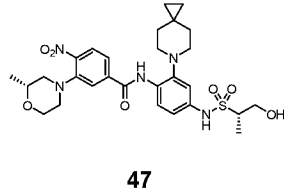
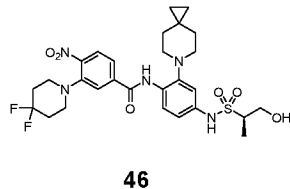
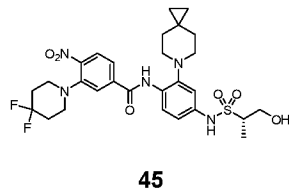
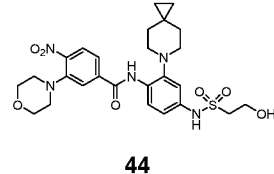
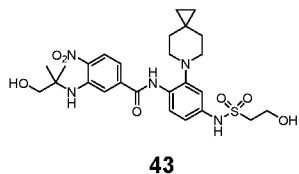
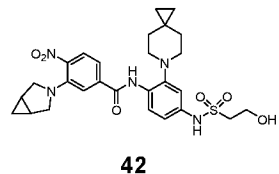
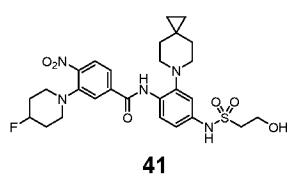
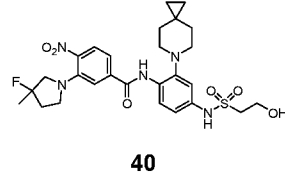
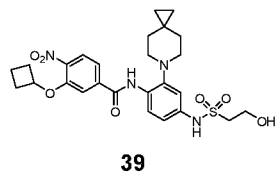
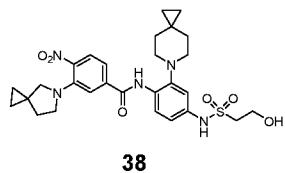
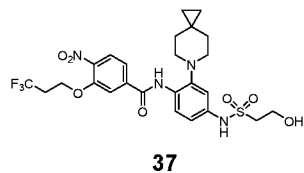
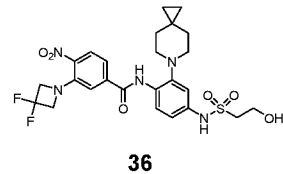
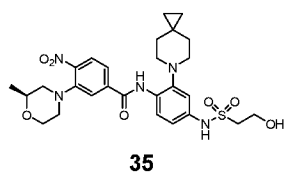
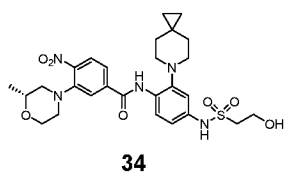
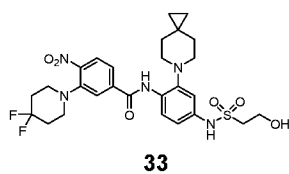


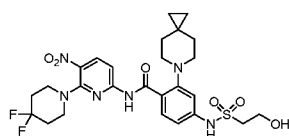
R¹⁶ 为-C₃₋₆ 环烷基、-OH、-O-C₁₋₄ 卤代烷基、-O-C₃₋₆ 环烷基、-O-C₃₋₆ 卤代环烷基、-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR¹⁸R¹⁹ 或-NO₂, L、R¹⁰、R¹⁸ 和 R¹⁹ 的定义如前所述, 并在具体实施例中举例说明。

在本发明的各种不同实施方式中, 通式(1)化合物具有以下结构之一:

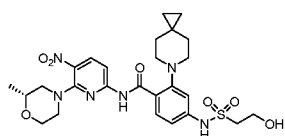




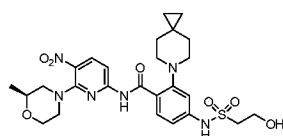




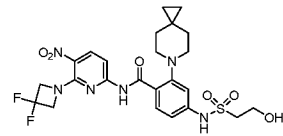
65



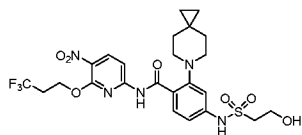
66



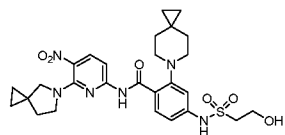
67



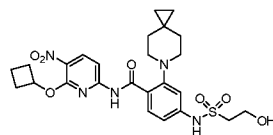
68



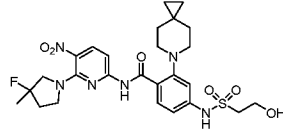
69



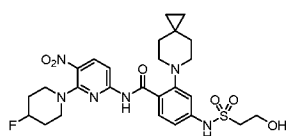
70



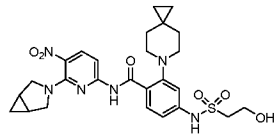
71



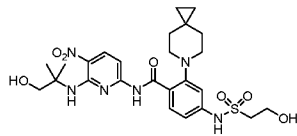
72



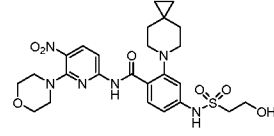
73



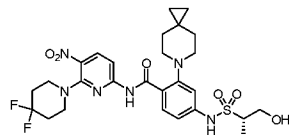
74



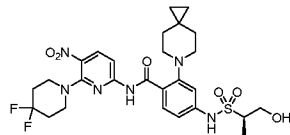
75



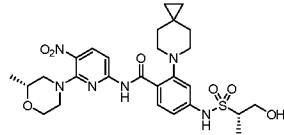
76



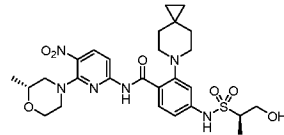
77



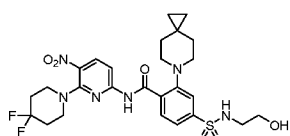
78



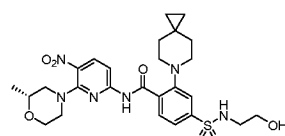
79



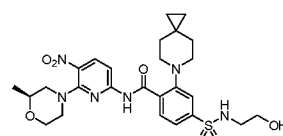
80



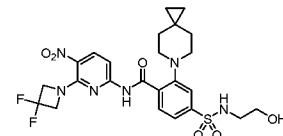
81



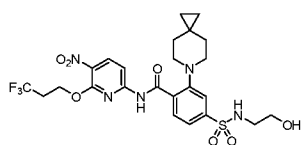
82



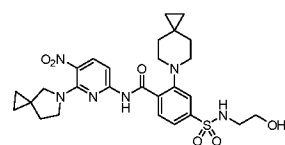
83



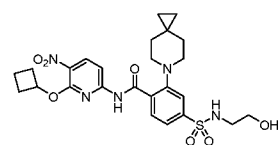
84



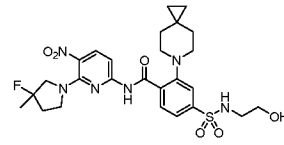
85



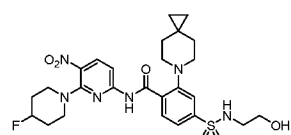
86



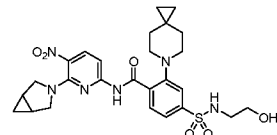
87



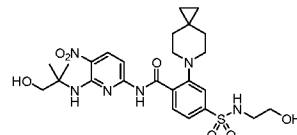
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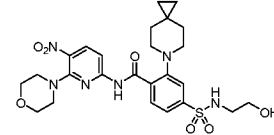
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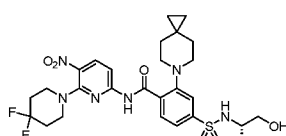
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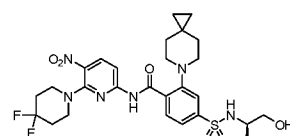
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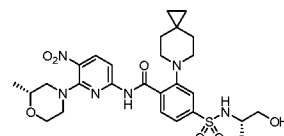
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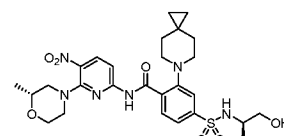
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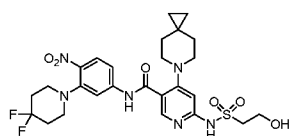
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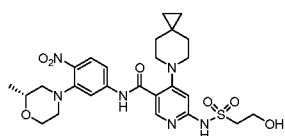
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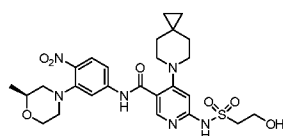
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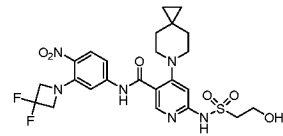
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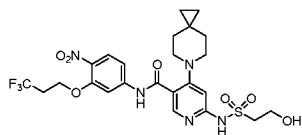
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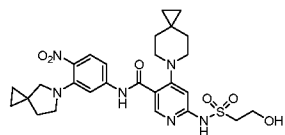
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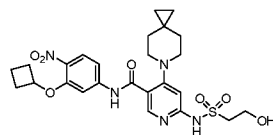
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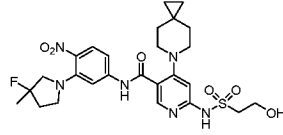
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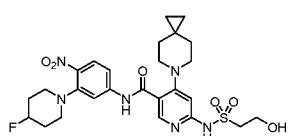
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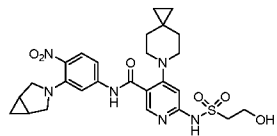
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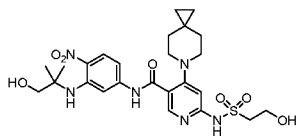
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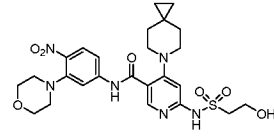
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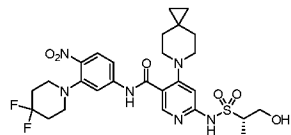
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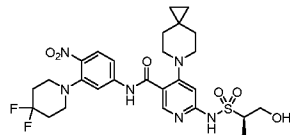
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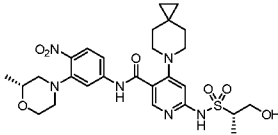
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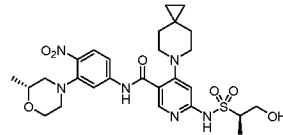
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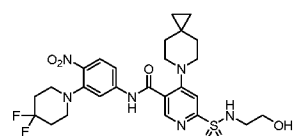
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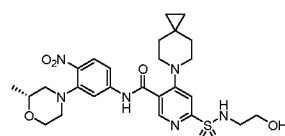
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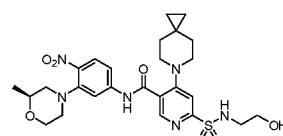
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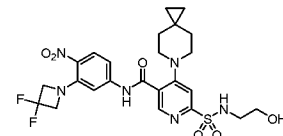
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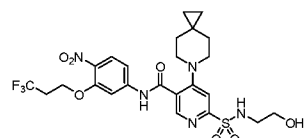
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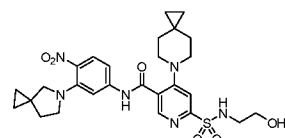
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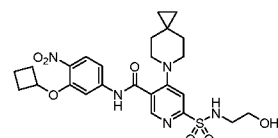
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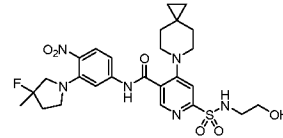
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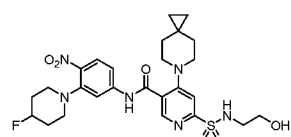
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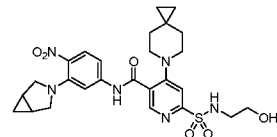
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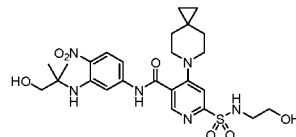
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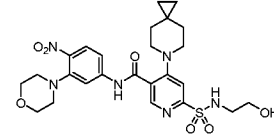
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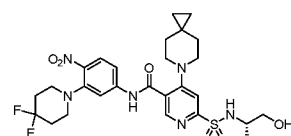
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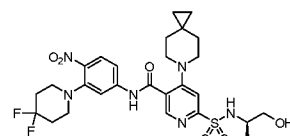
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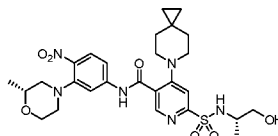
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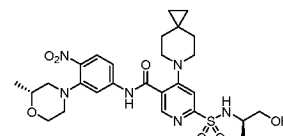
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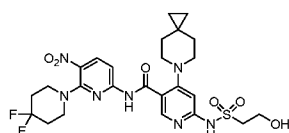
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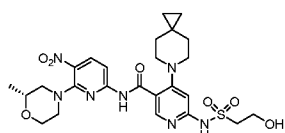
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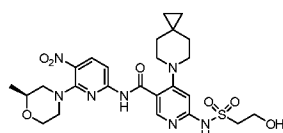
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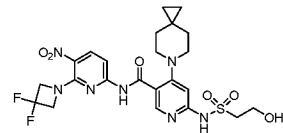
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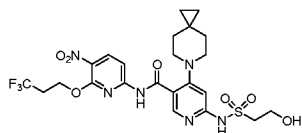
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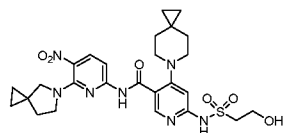
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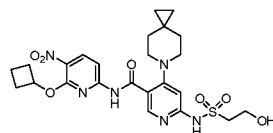
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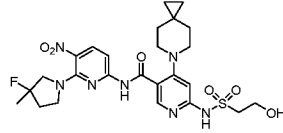
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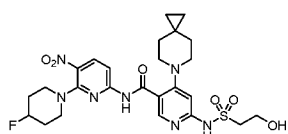
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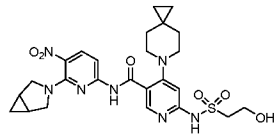
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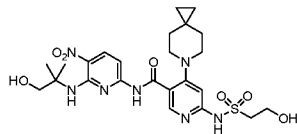
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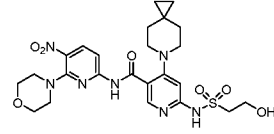
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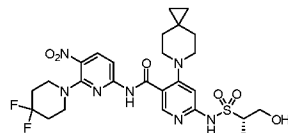
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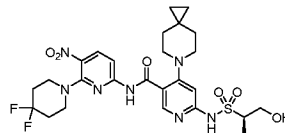
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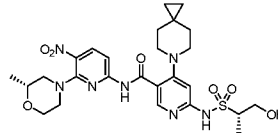
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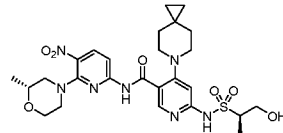
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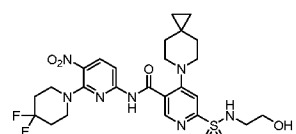
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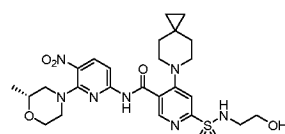
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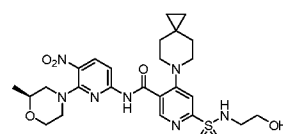
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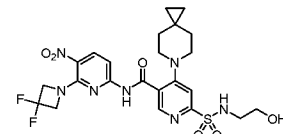
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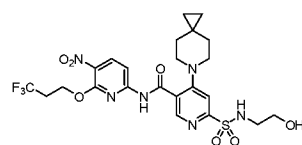
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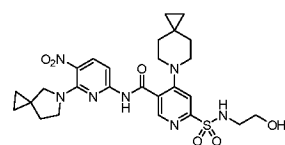
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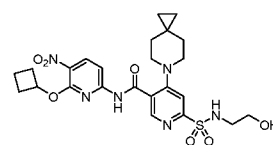
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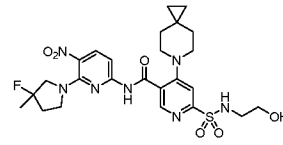
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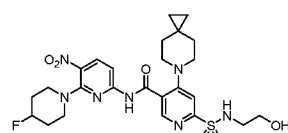
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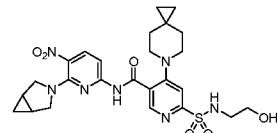
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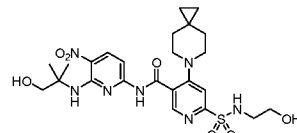
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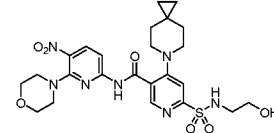
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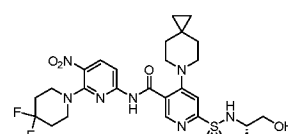
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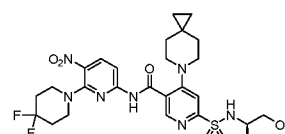
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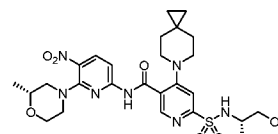
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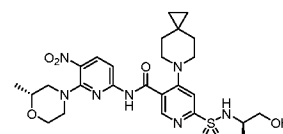
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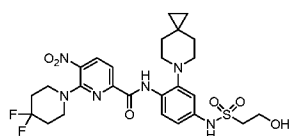
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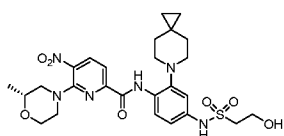
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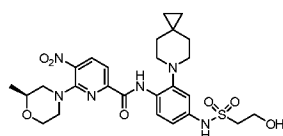
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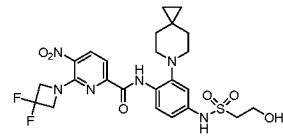
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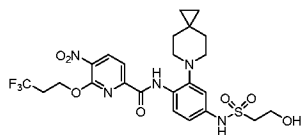
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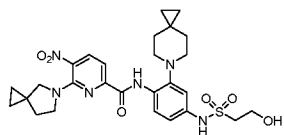
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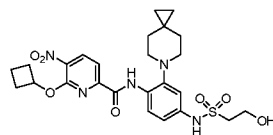
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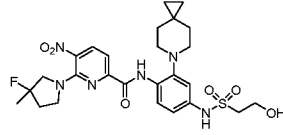
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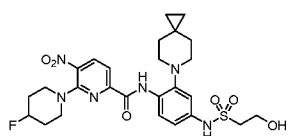
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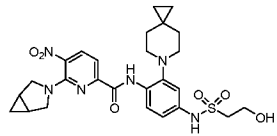
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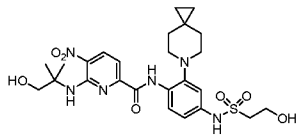
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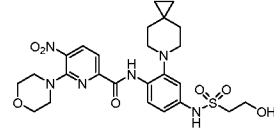
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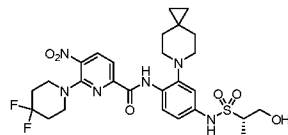
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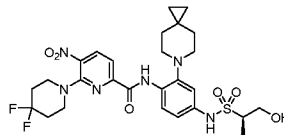
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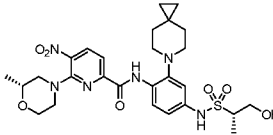
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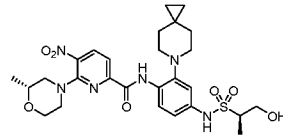
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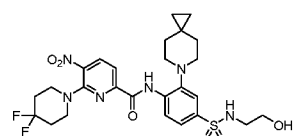
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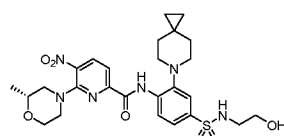
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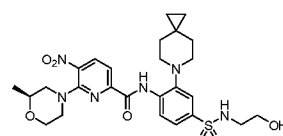
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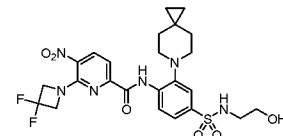
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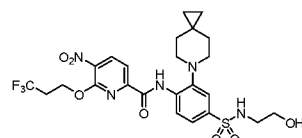
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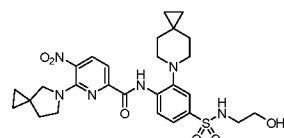
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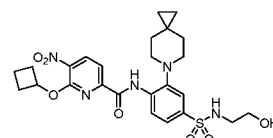
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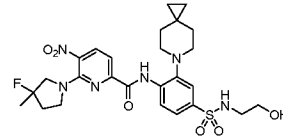
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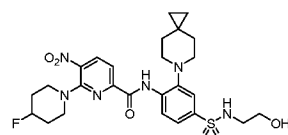
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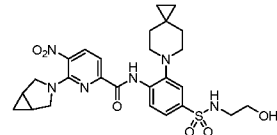
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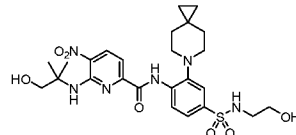
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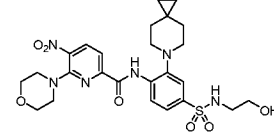
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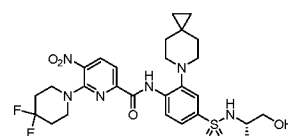
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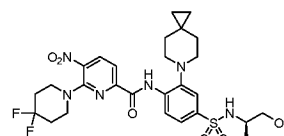
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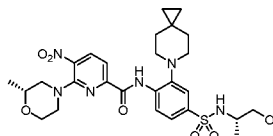
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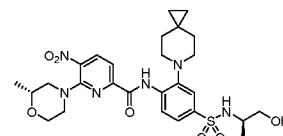
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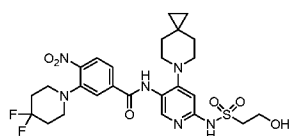
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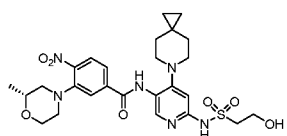
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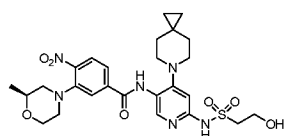
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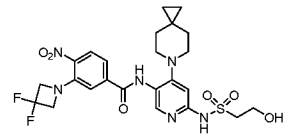
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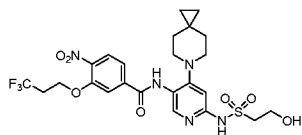
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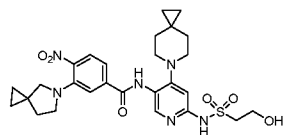
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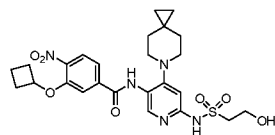
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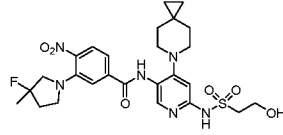
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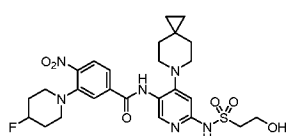
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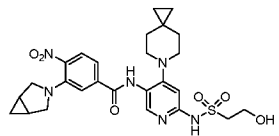
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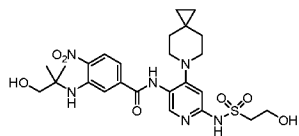
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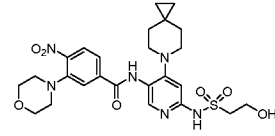
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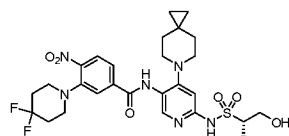
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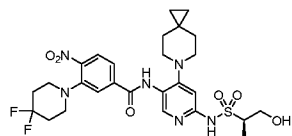
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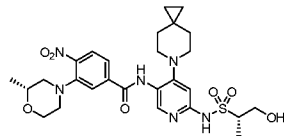
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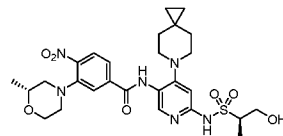
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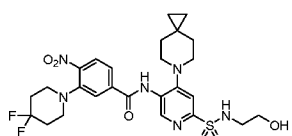
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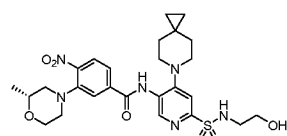
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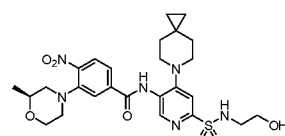
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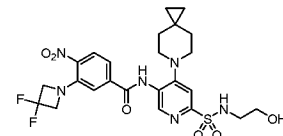
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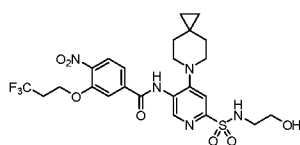
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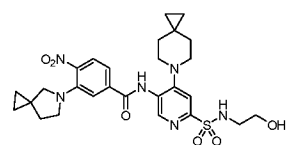
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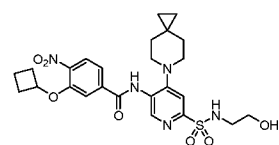
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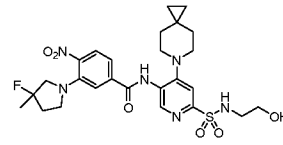
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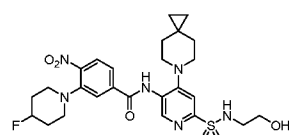
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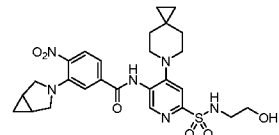
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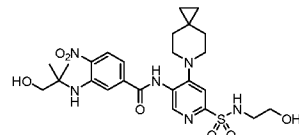
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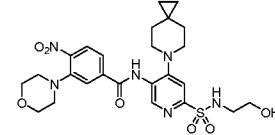
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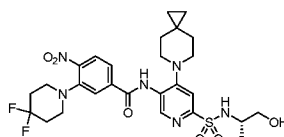
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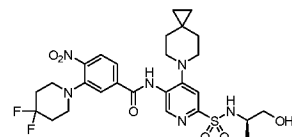
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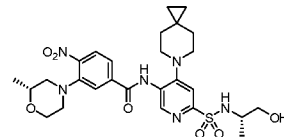
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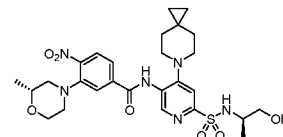
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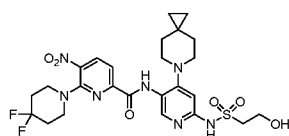
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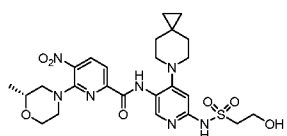
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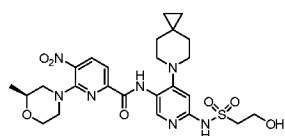
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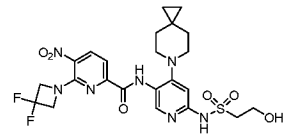
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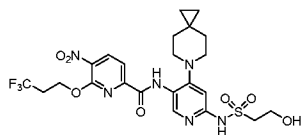
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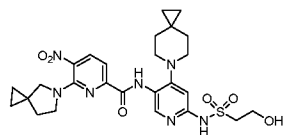
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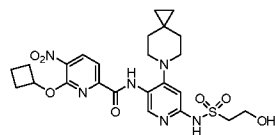
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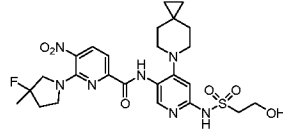
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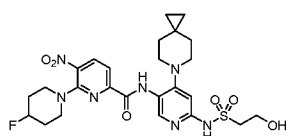
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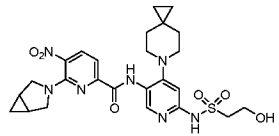
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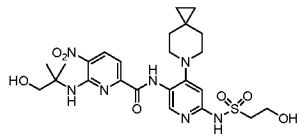
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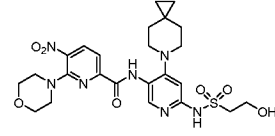
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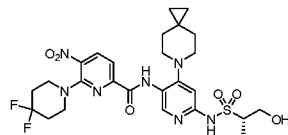
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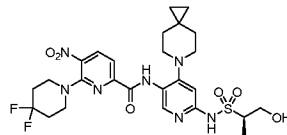
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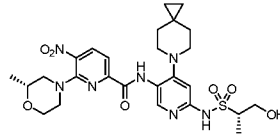
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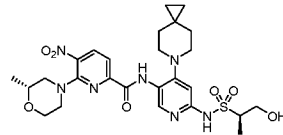
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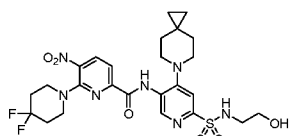
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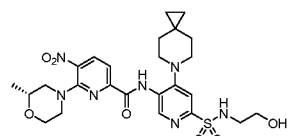
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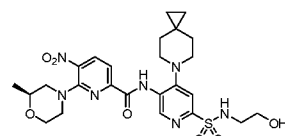
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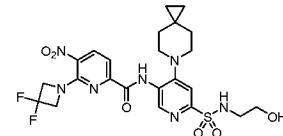
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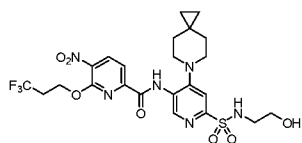
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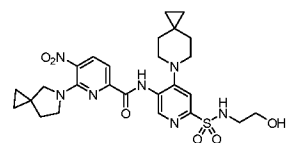
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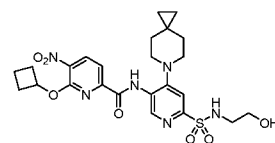
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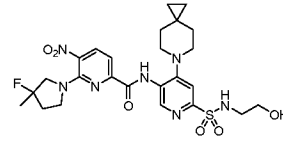
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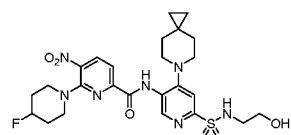
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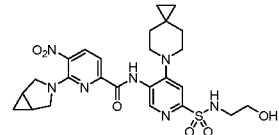
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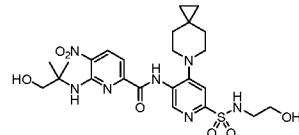
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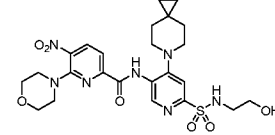
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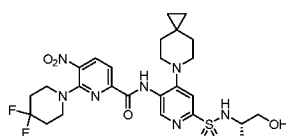
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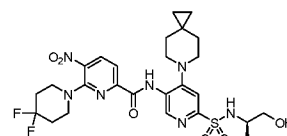
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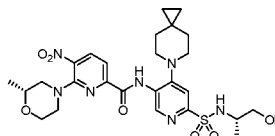
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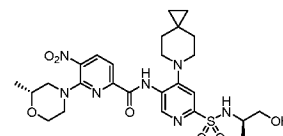
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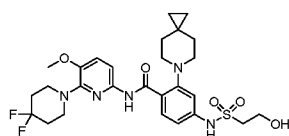
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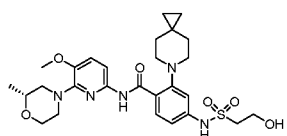
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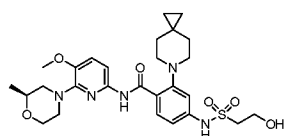
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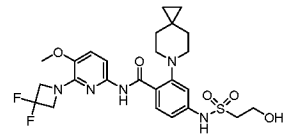
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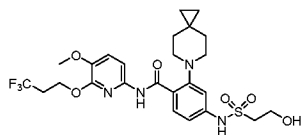
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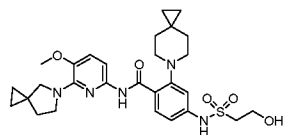
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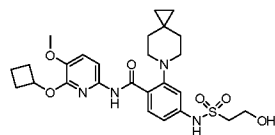
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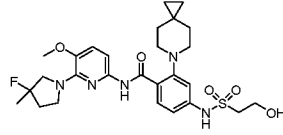
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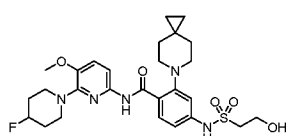
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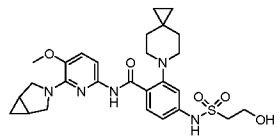
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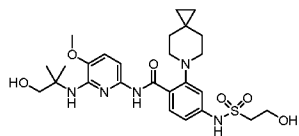
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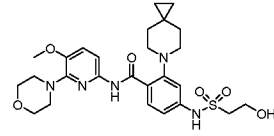
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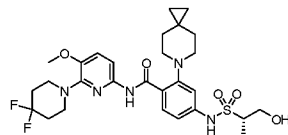
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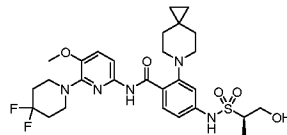
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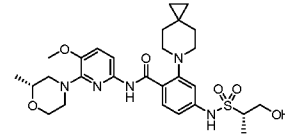
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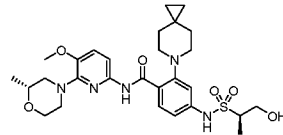
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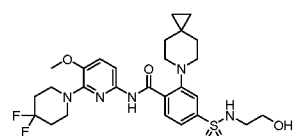
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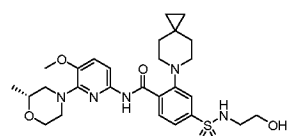
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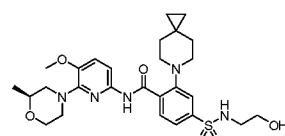
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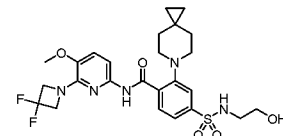
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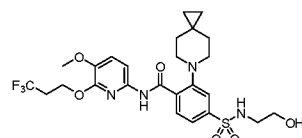
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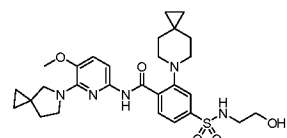
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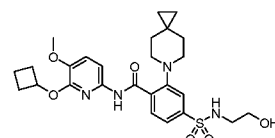
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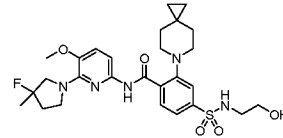
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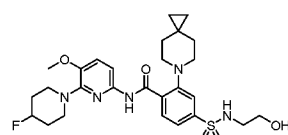
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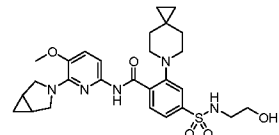
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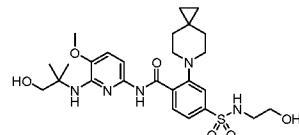
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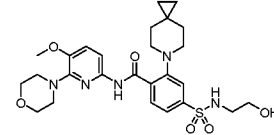
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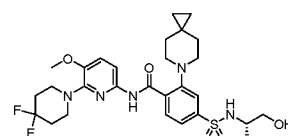
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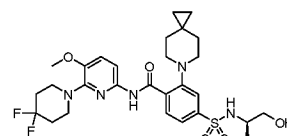
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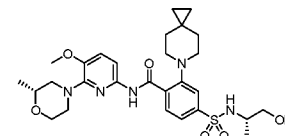
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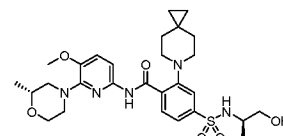
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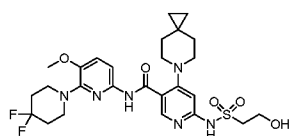
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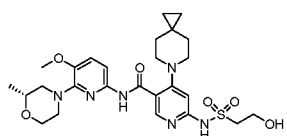
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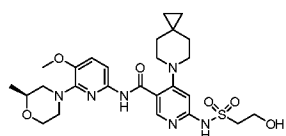
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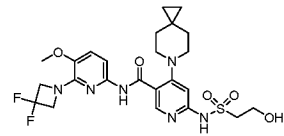
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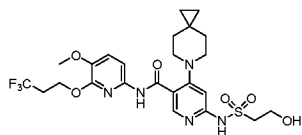
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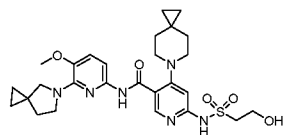
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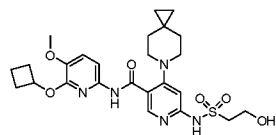
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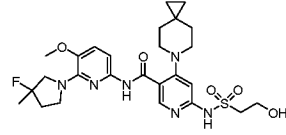
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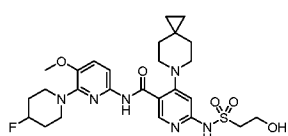
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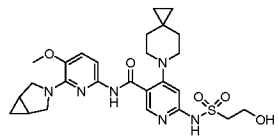
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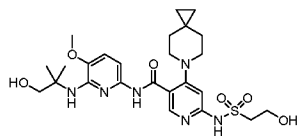
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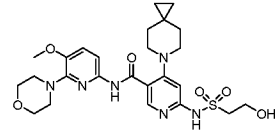
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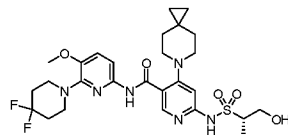
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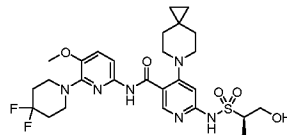
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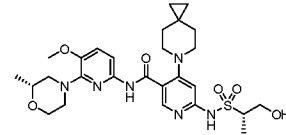
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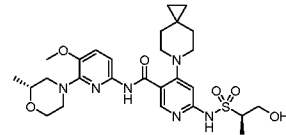
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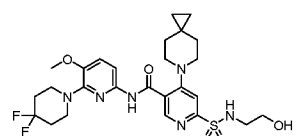
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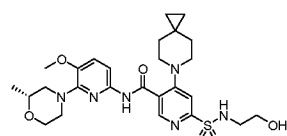
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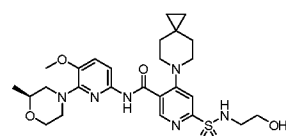
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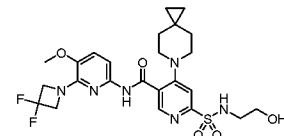
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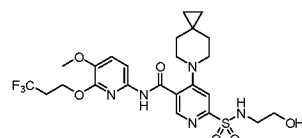
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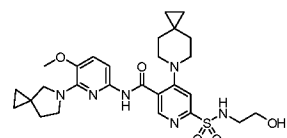
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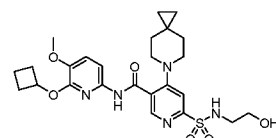
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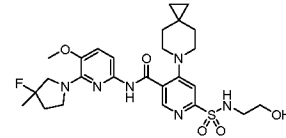
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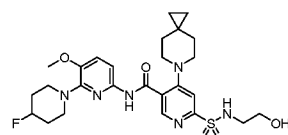
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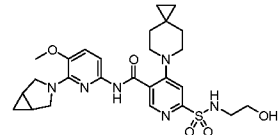
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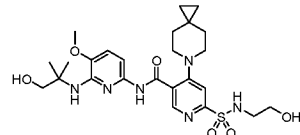
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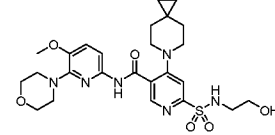
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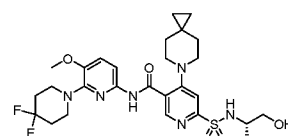
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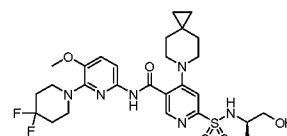
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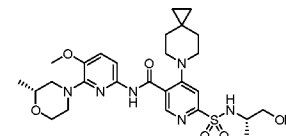
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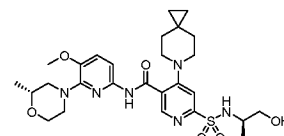
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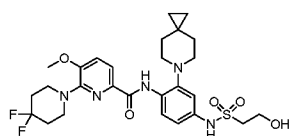
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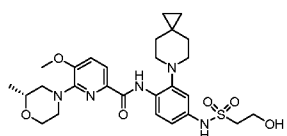
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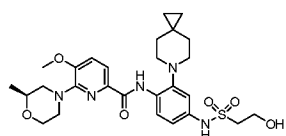
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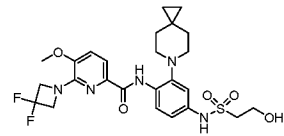
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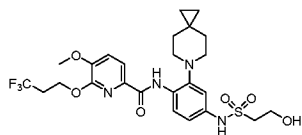
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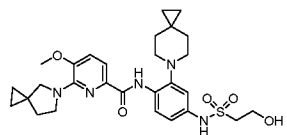
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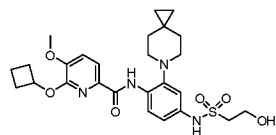
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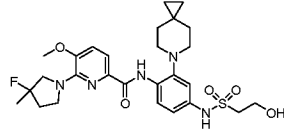
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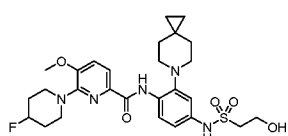
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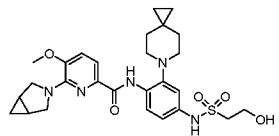
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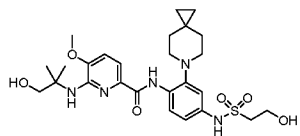
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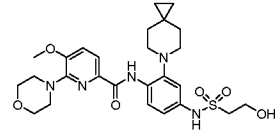
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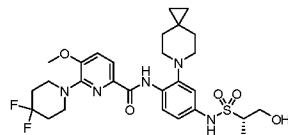
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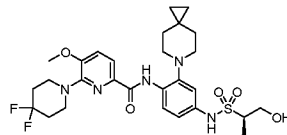
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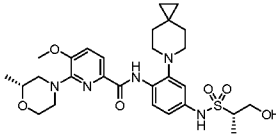
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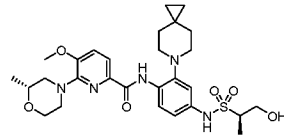
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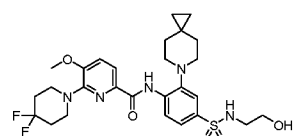
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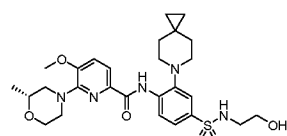
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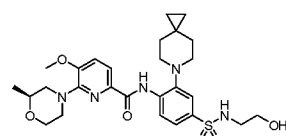
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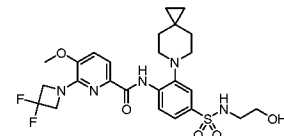
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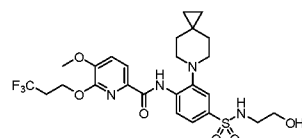
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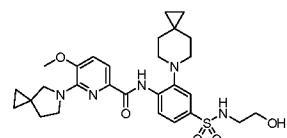
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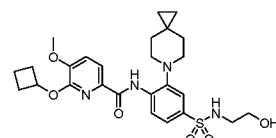
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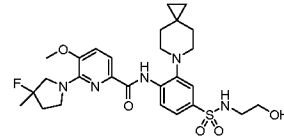
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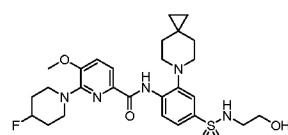
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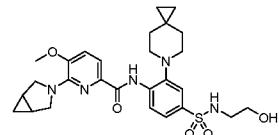
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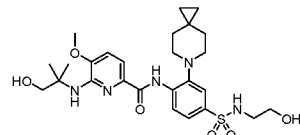
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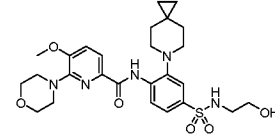
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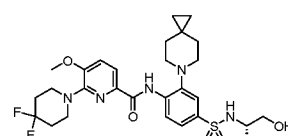
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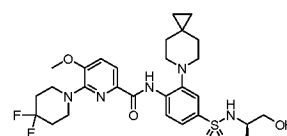
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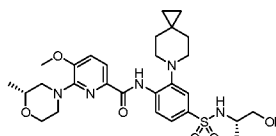
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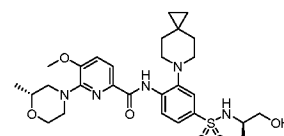
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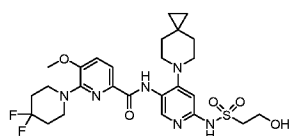
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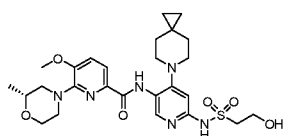
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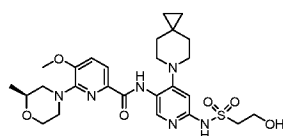
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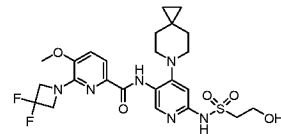
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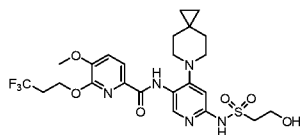
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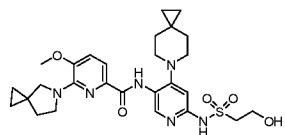
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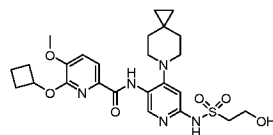
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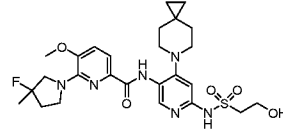
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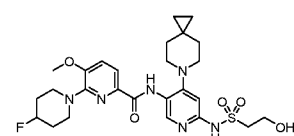
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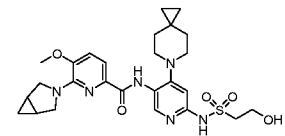
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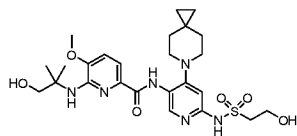
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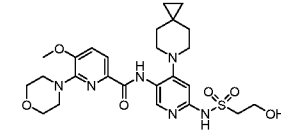
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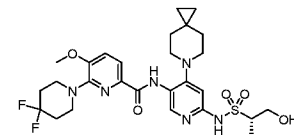
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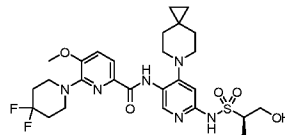
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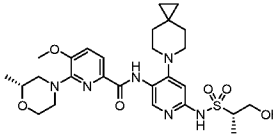
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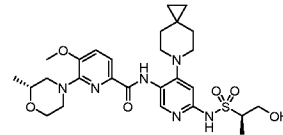
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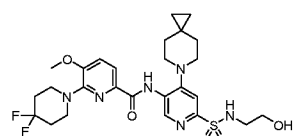
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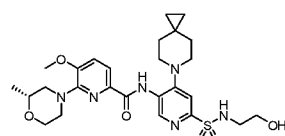
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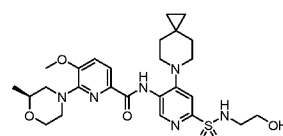
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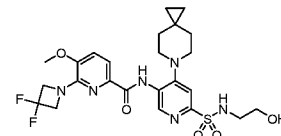
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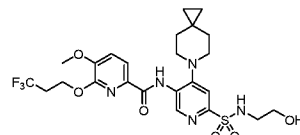
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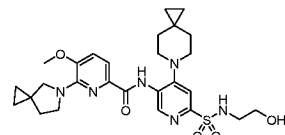
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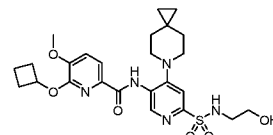
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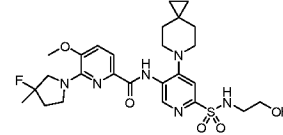
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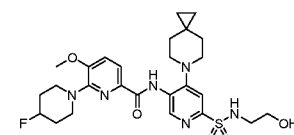
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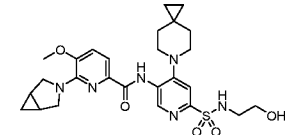
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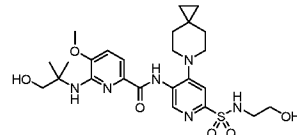
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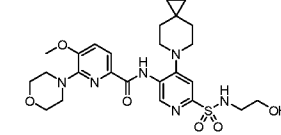
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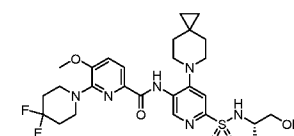
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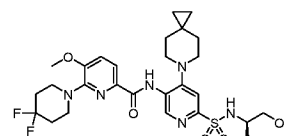
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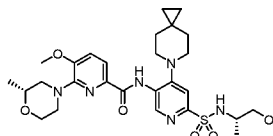
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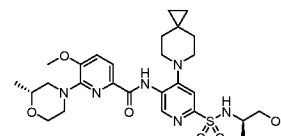
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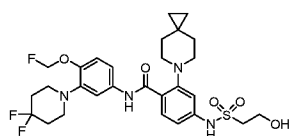
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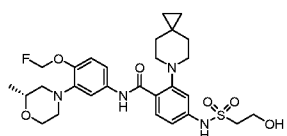
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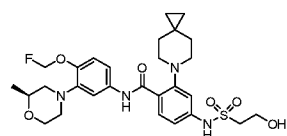
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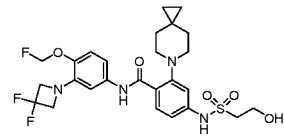
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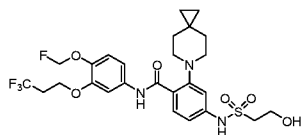
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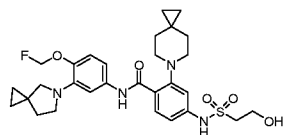
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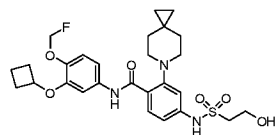
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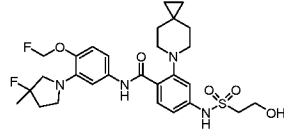
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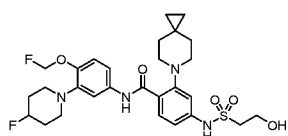
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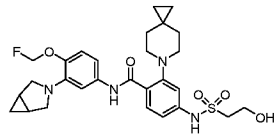
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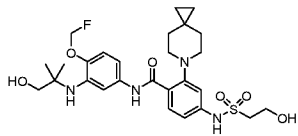
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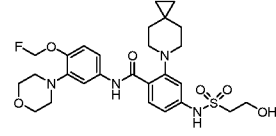
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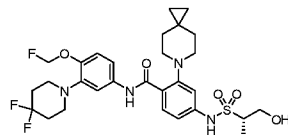
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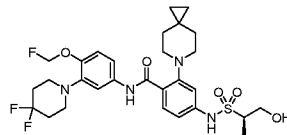
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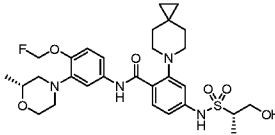
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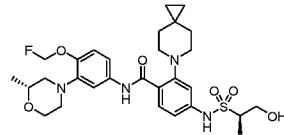
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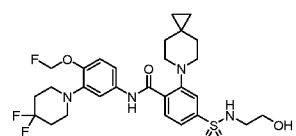
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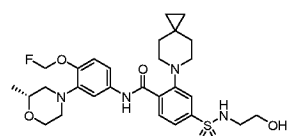
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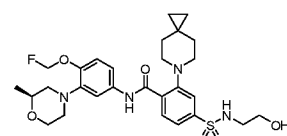
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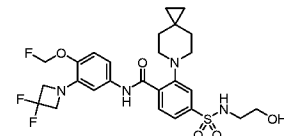
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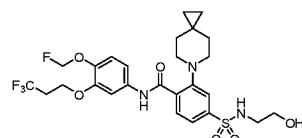
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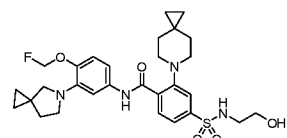
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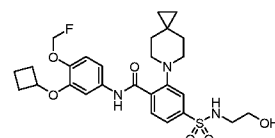
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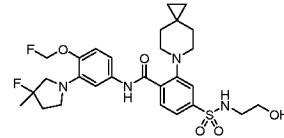
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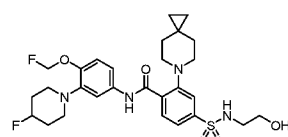
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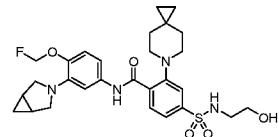
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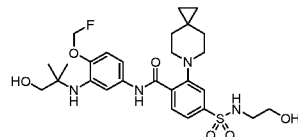
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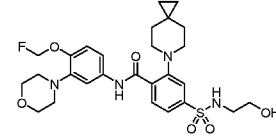
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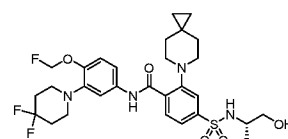
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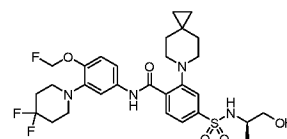
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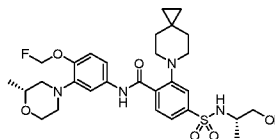
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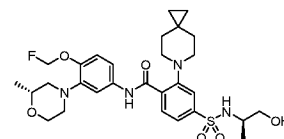
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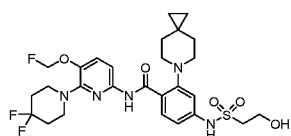
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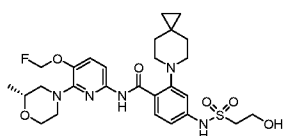
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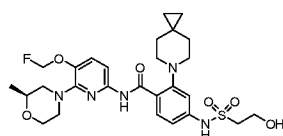
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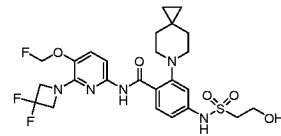
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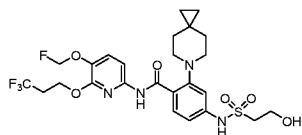
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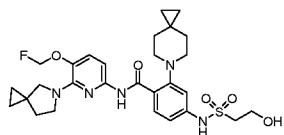
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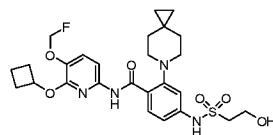
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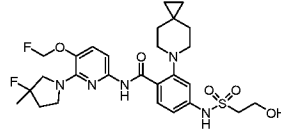
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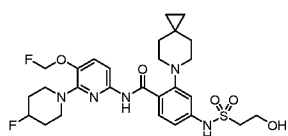
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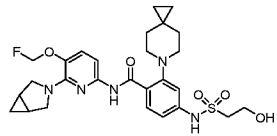
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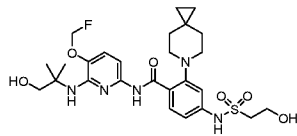
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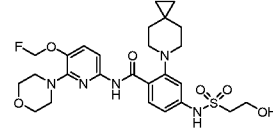
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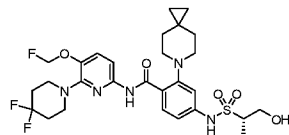
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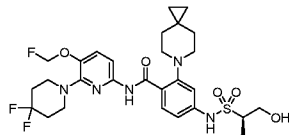
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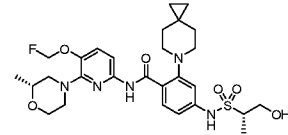
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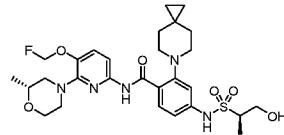
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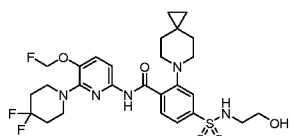
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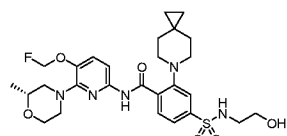
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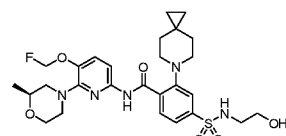
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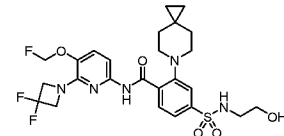
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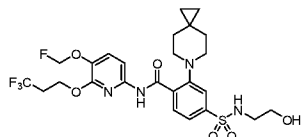
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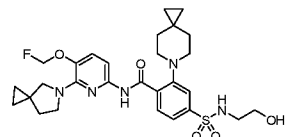
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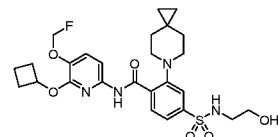
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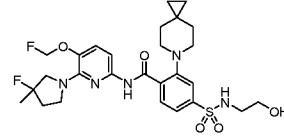
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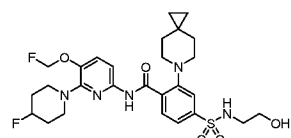
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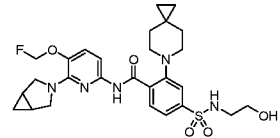
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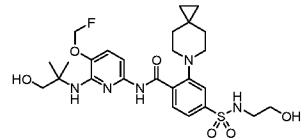
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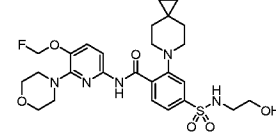
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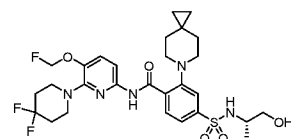
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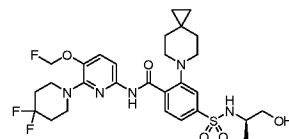
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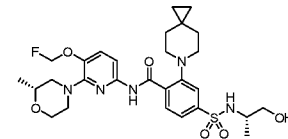
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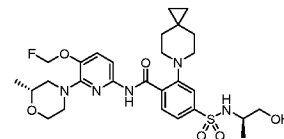
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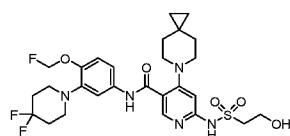
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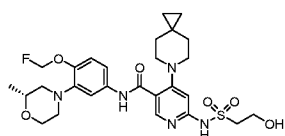
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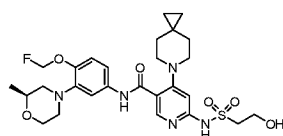
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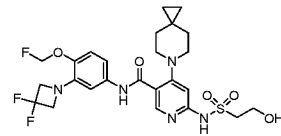
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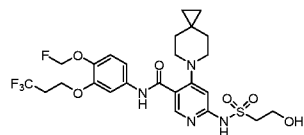
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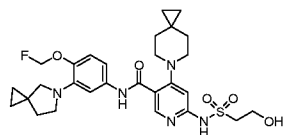
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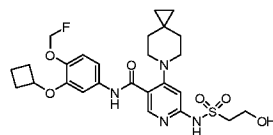
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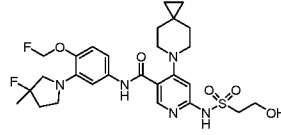
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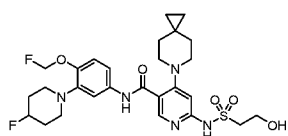
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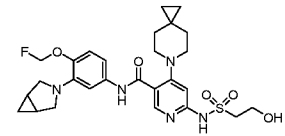
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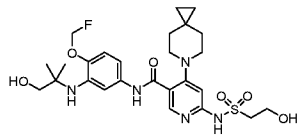
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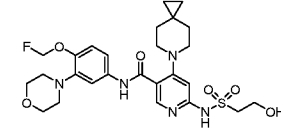
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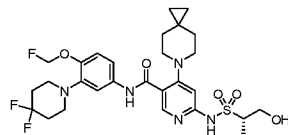
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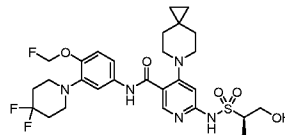
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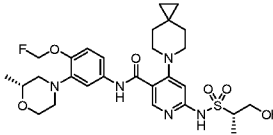
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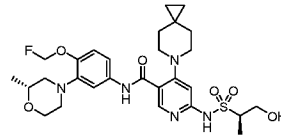
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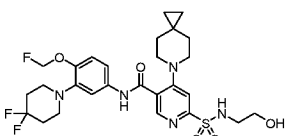
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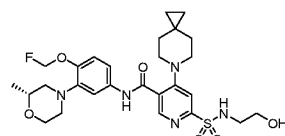
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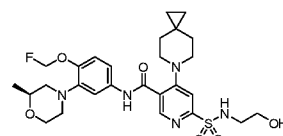
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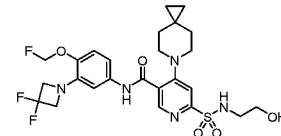
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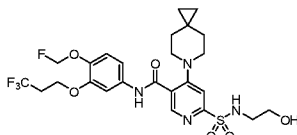
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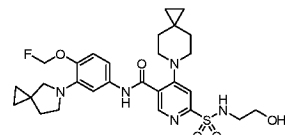
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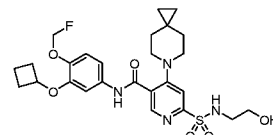
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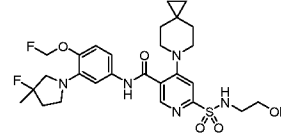
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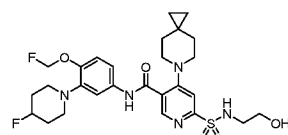
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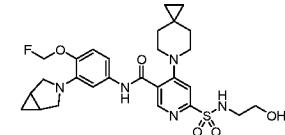
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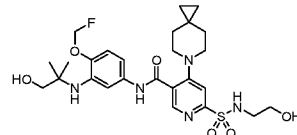
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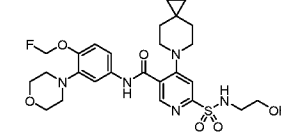
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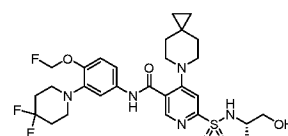
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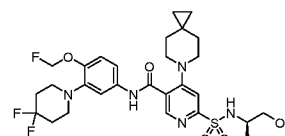
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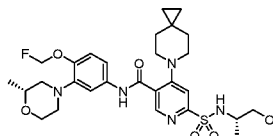
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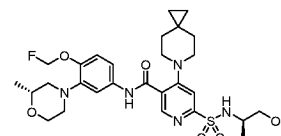
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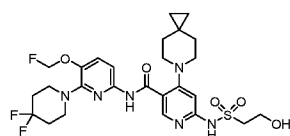
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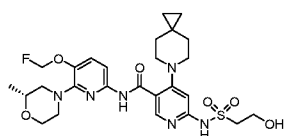
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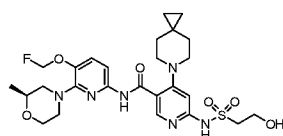
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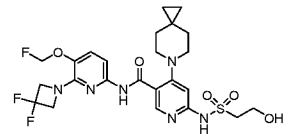
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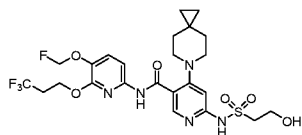
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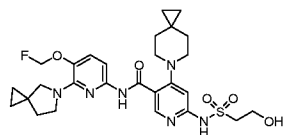
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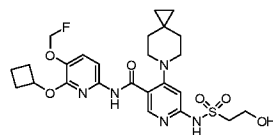
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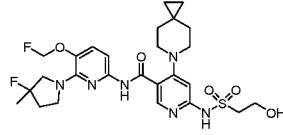
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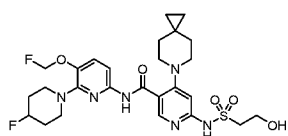
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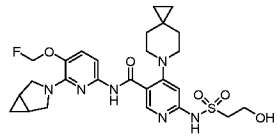
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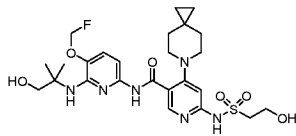
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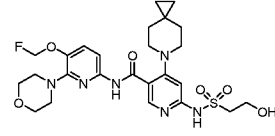
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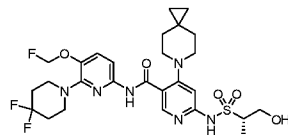
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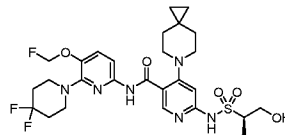
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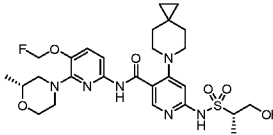
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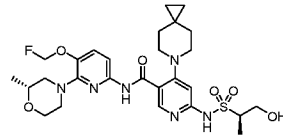
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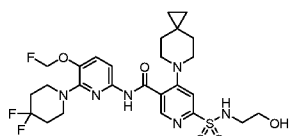
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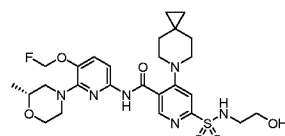
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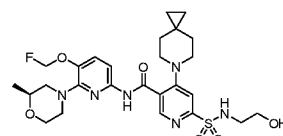
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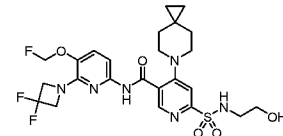
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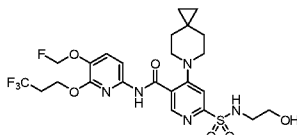
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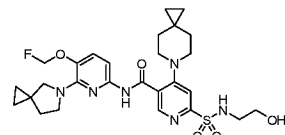
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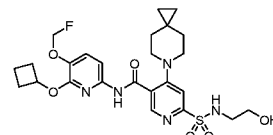
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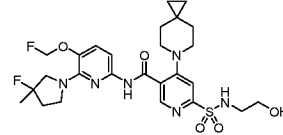
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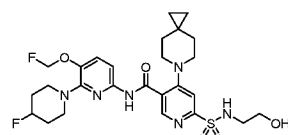
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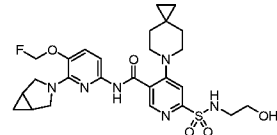
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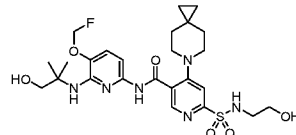
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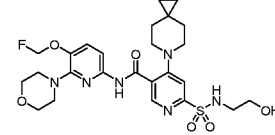
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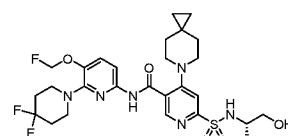
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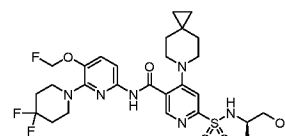
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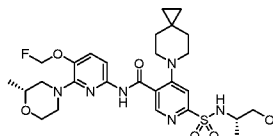
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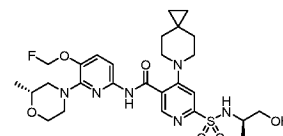
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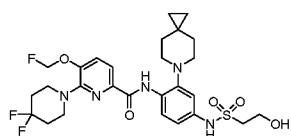
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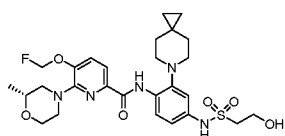
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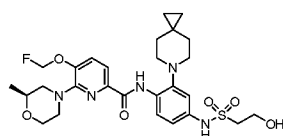
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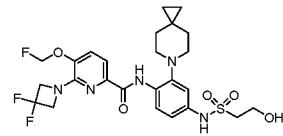
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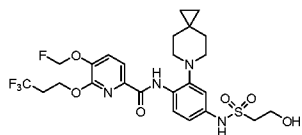
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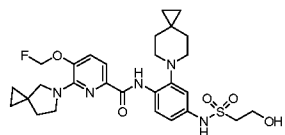
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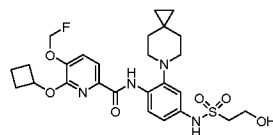
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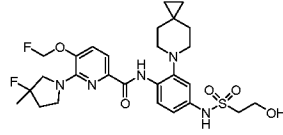
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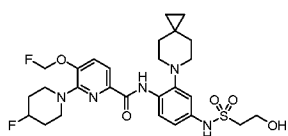
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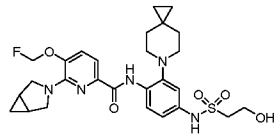
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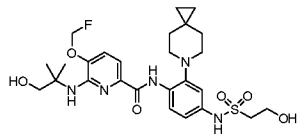
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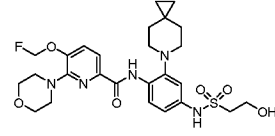
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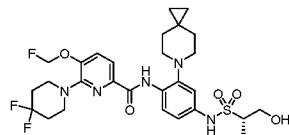
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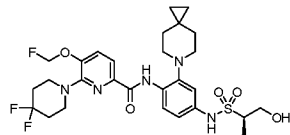
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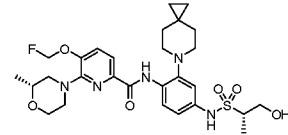
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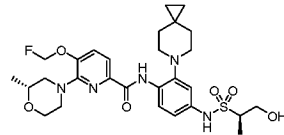
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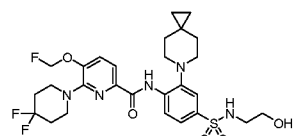
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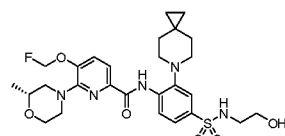
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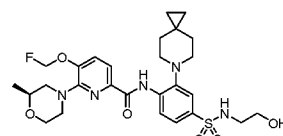
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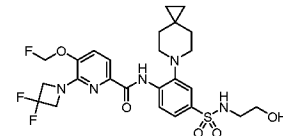
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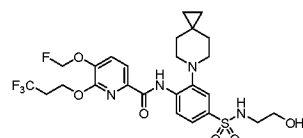
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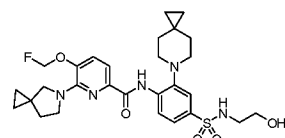
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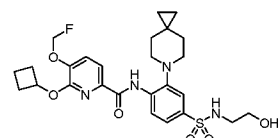
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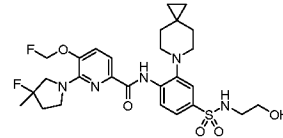
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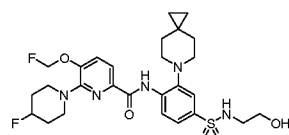
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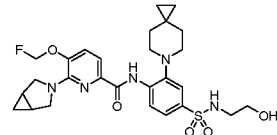
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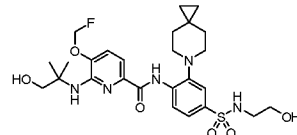
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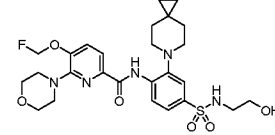
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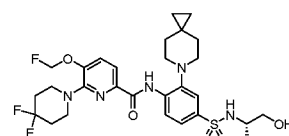
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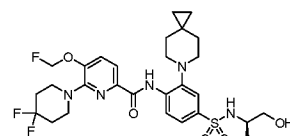
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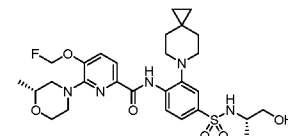
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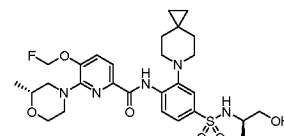
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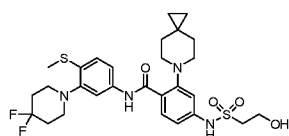
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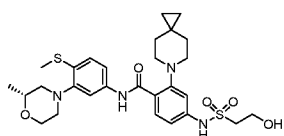
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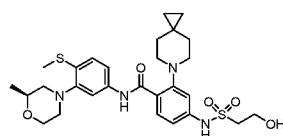
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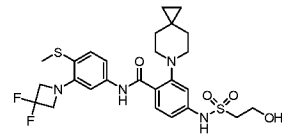
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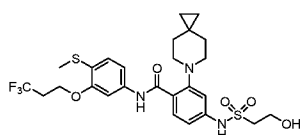
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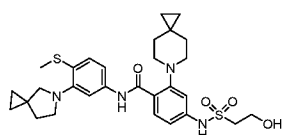
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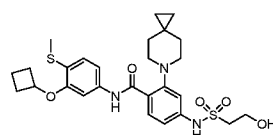
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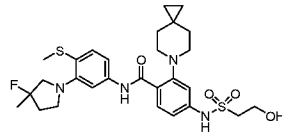
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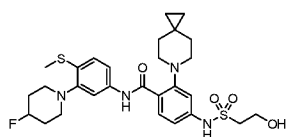
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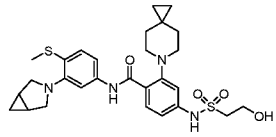
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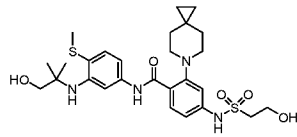
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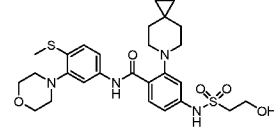
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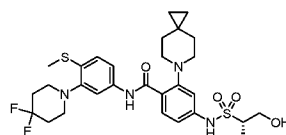
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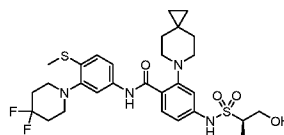
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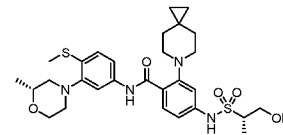
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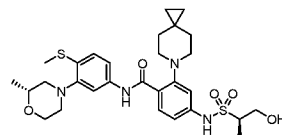
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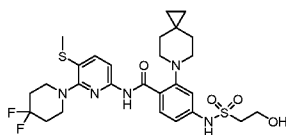
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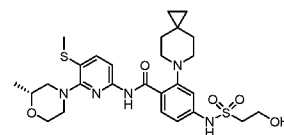
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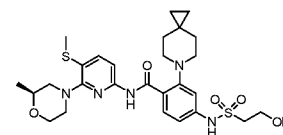
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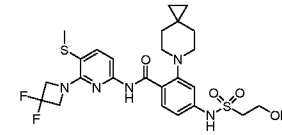
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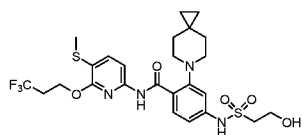
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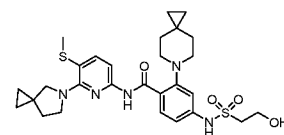
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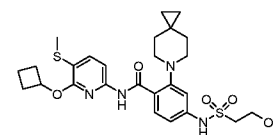
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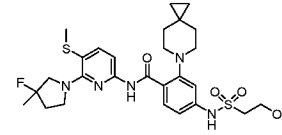
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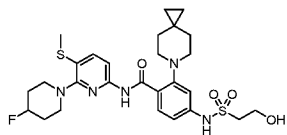
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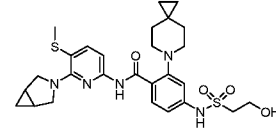
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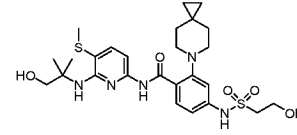
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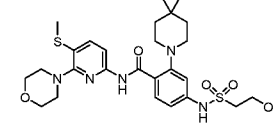
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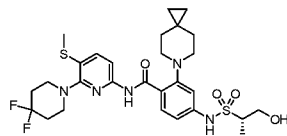
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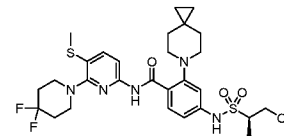
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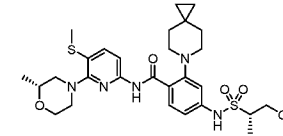
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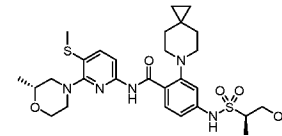
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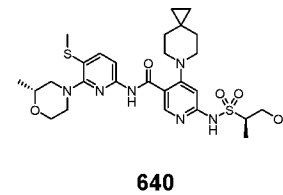
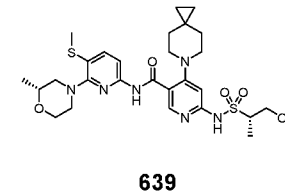
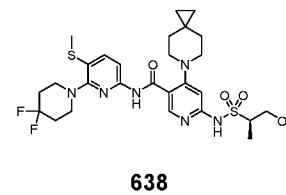
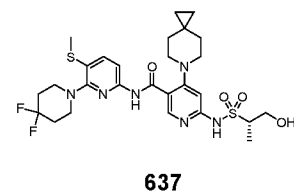
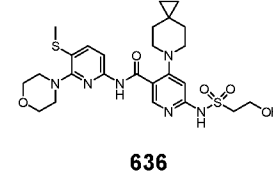
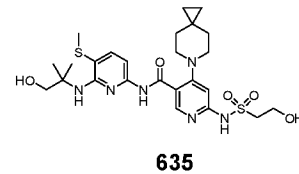
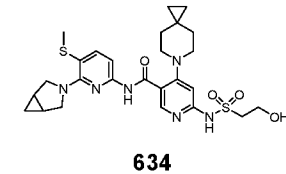
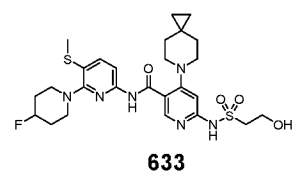
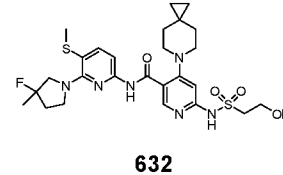
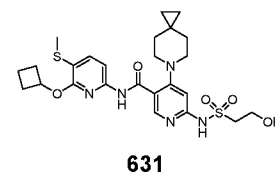
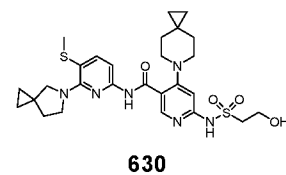
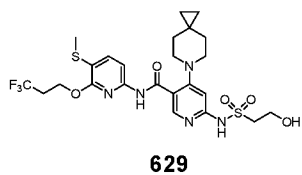
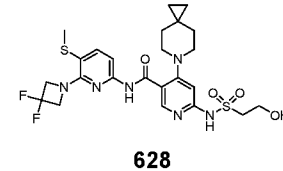
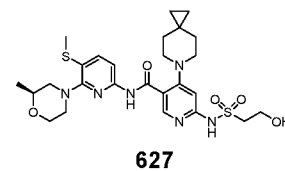
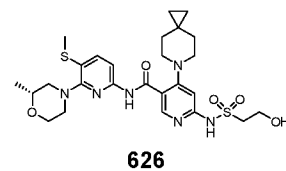
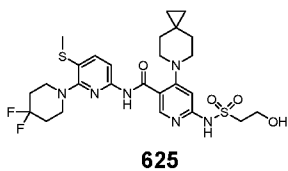
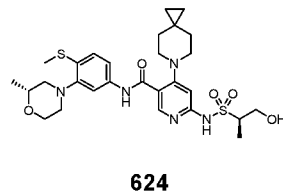
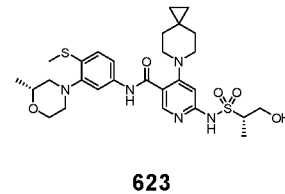
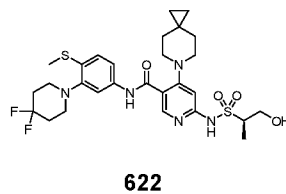
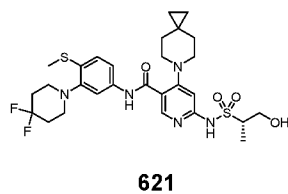
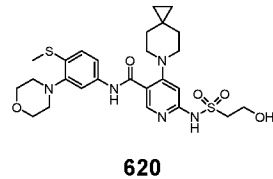
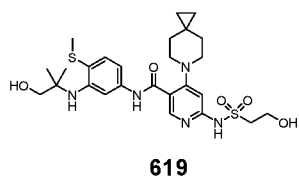
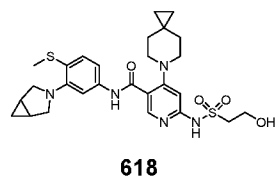
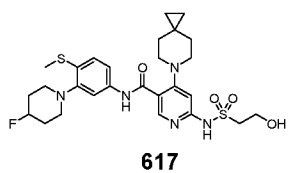
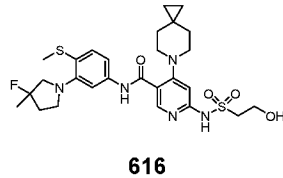
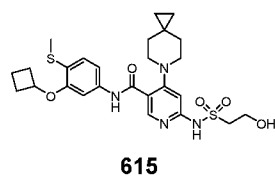
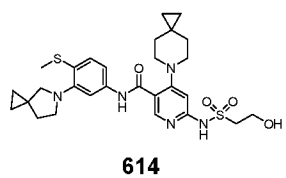
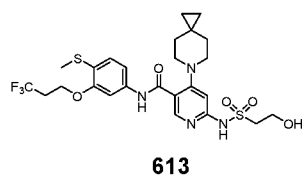
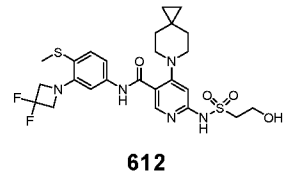
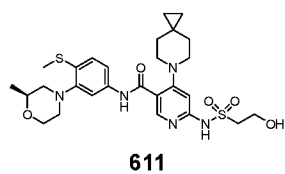
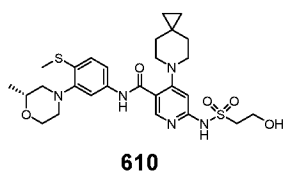
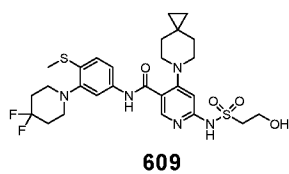
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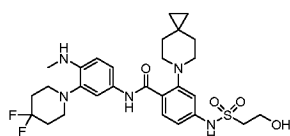


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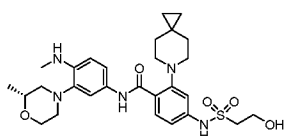


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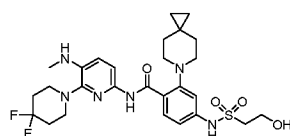




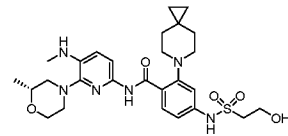
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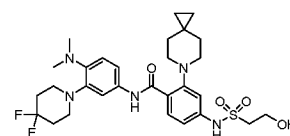
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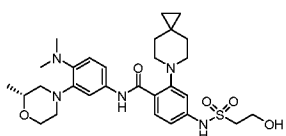
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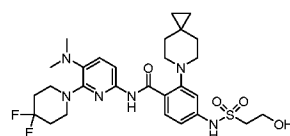
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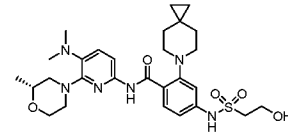
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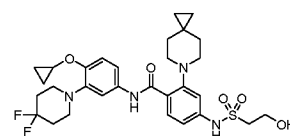
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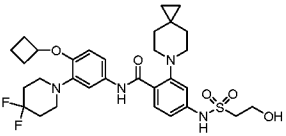
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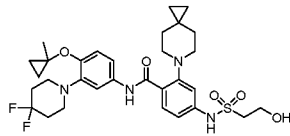
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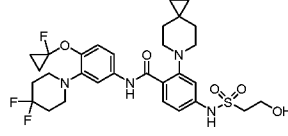
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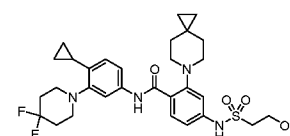
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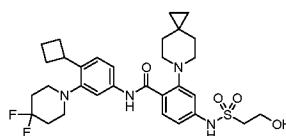
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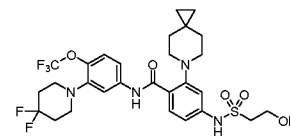
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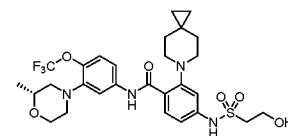
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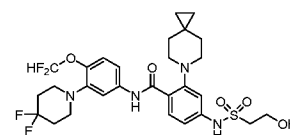
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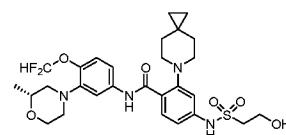
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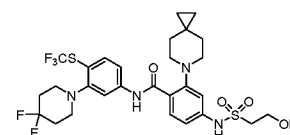
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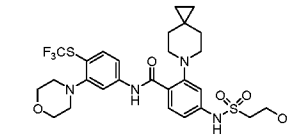
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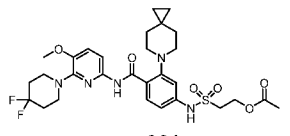
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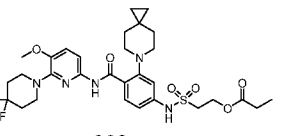
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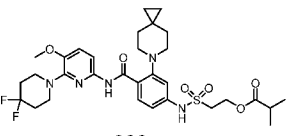
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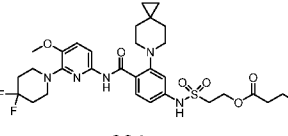
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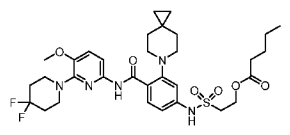
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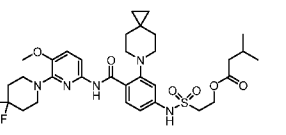
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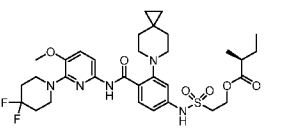
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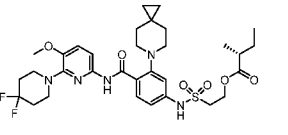
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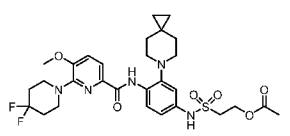
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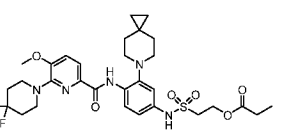
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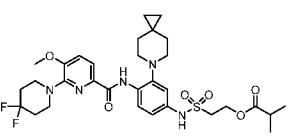
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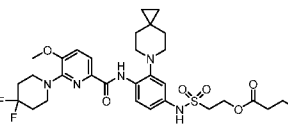
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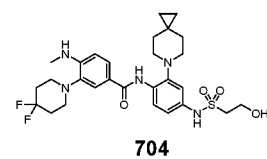
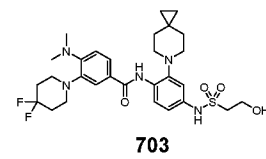
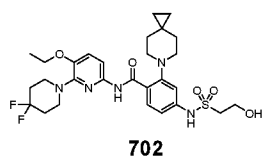
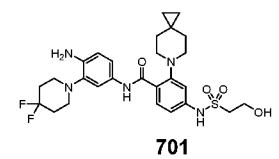
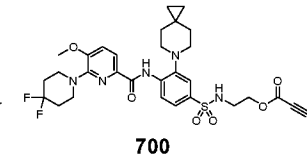
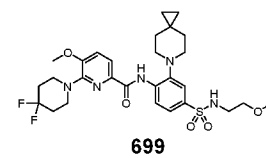
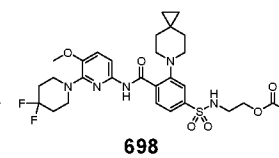
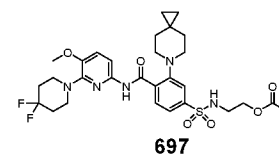
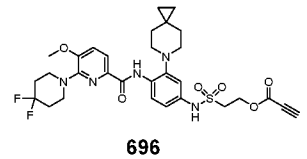
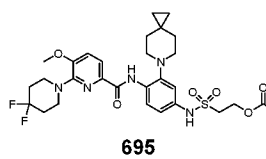
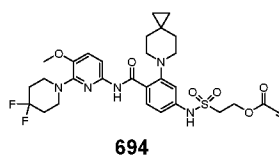
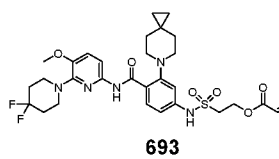
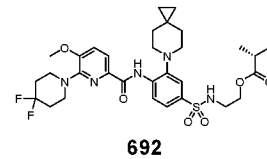
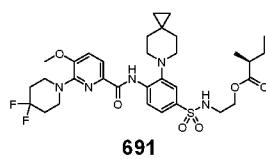
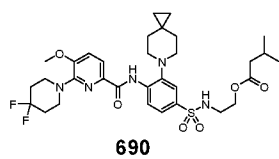
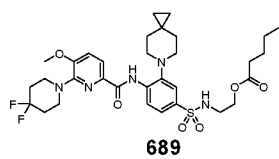
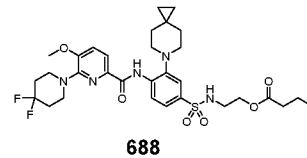
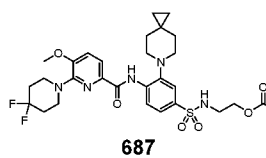
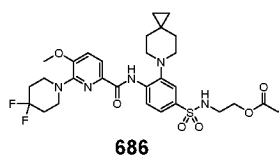
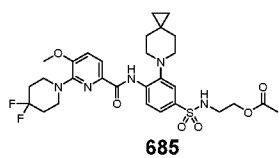
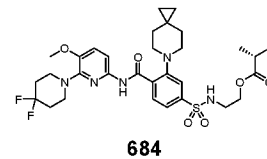
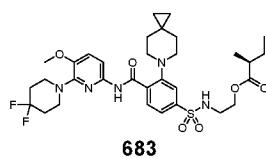
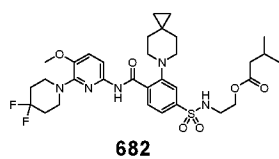
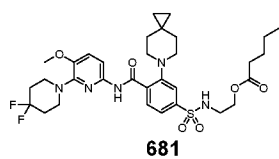
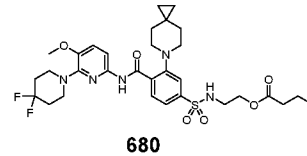
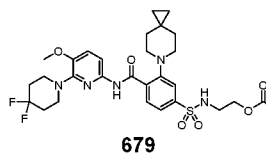
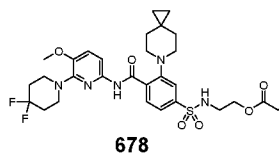
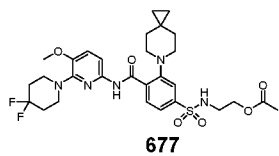
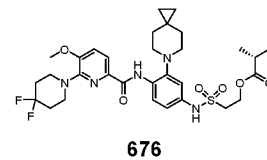
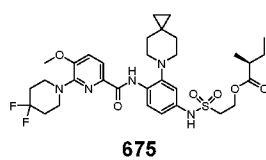
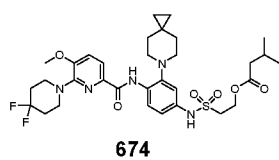
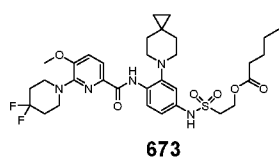
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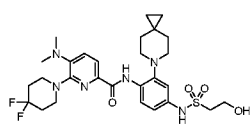


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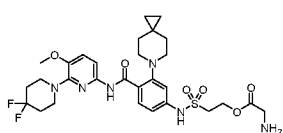


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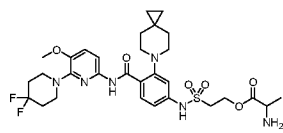




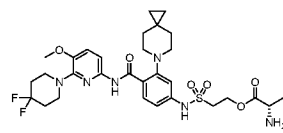
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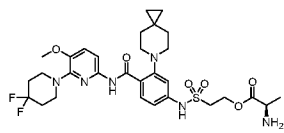
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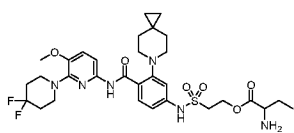
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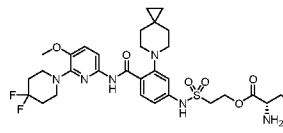
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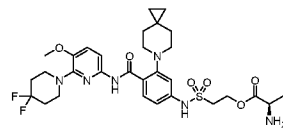
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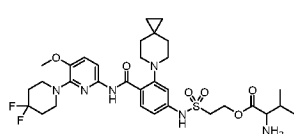
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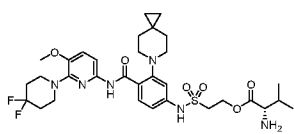
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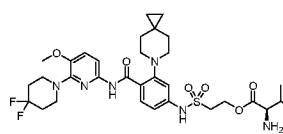
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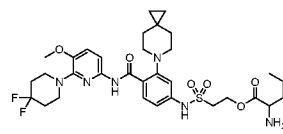
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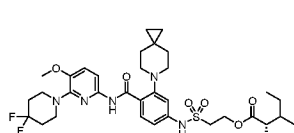
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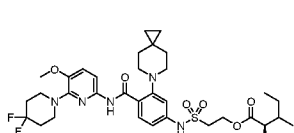
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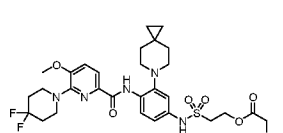
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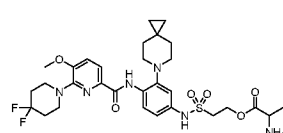
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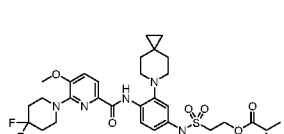
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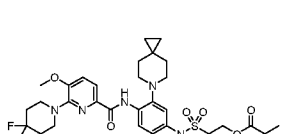
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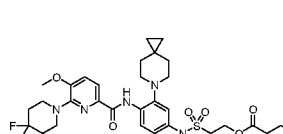
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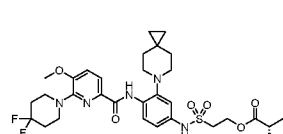
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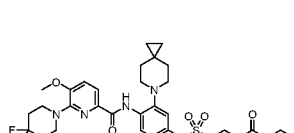
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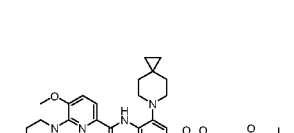
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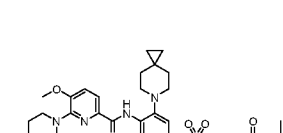
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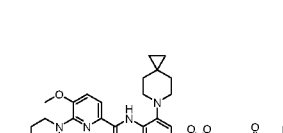
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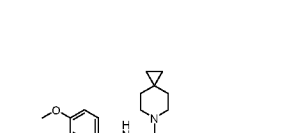
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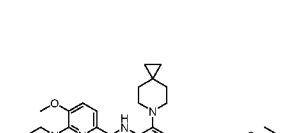
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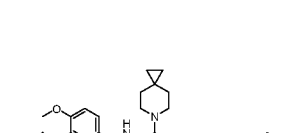
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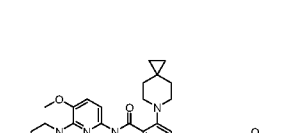
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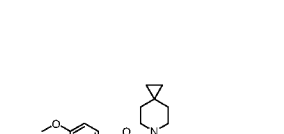
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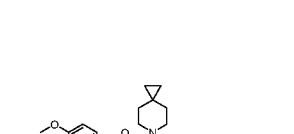
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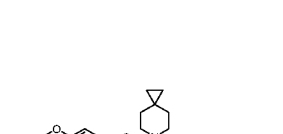
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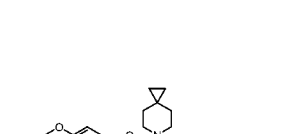
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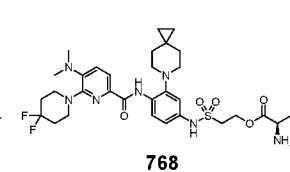
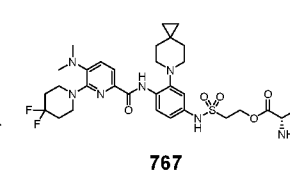
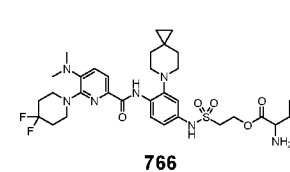
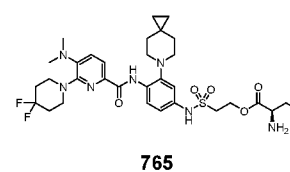
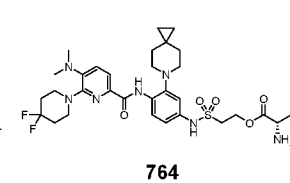
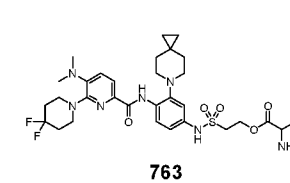
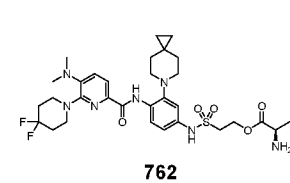
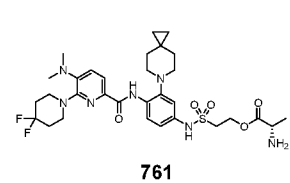
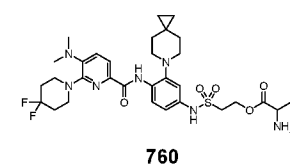
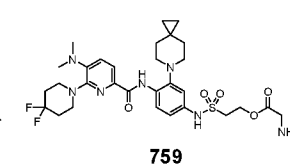
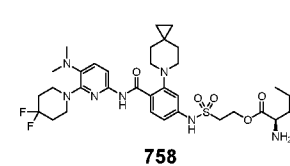
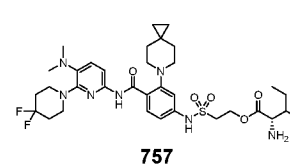
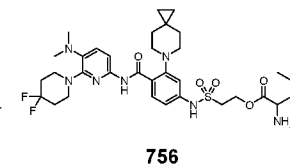
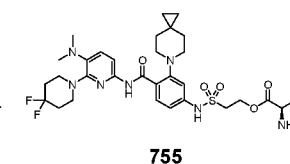
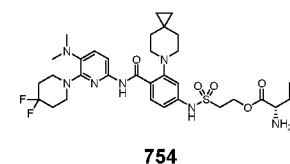
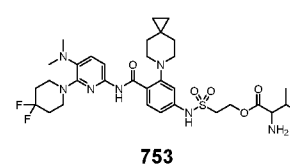
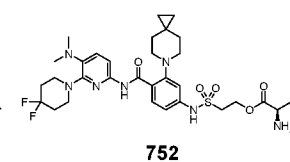
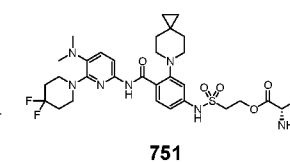
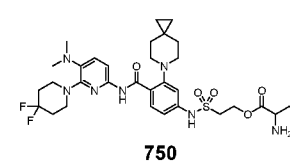
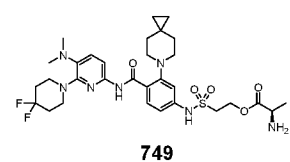
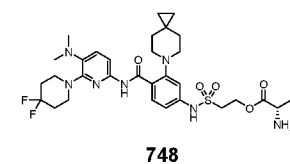
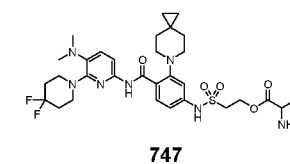
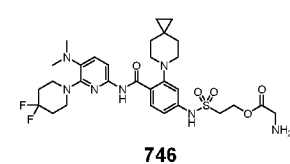
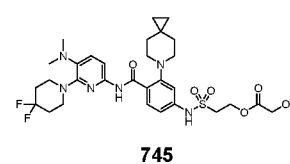
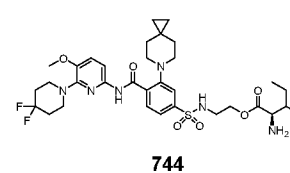
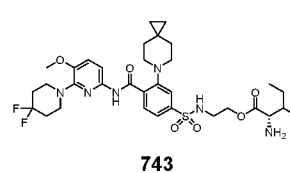
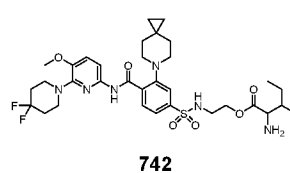
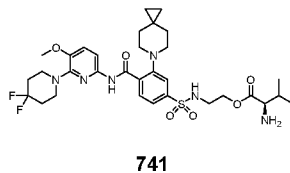
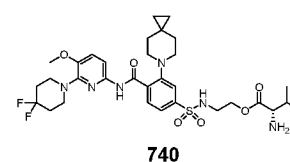
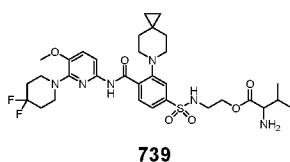
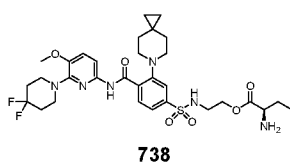
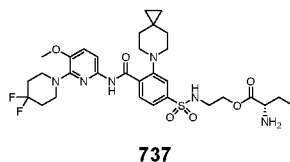
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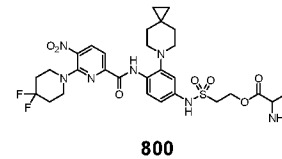
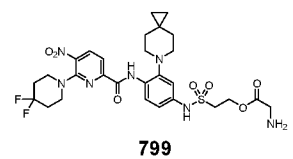
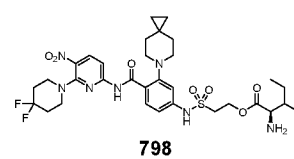
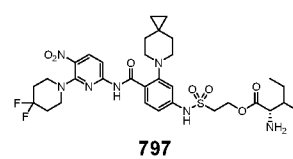
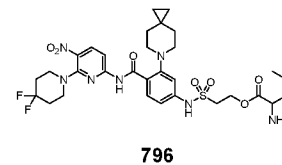
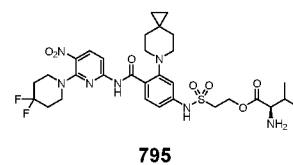
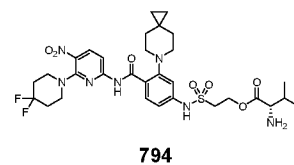
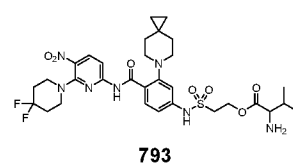
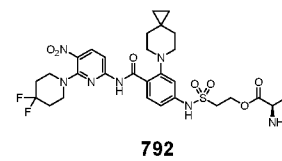
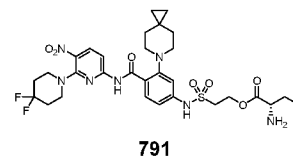
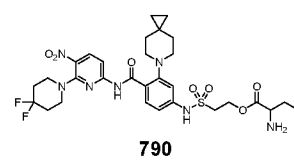
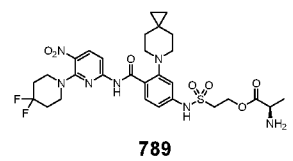
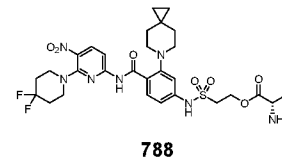
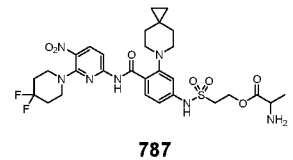
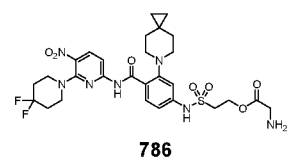
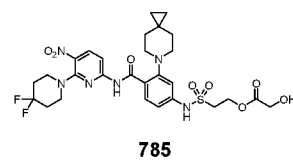
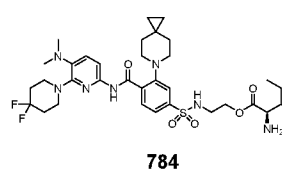
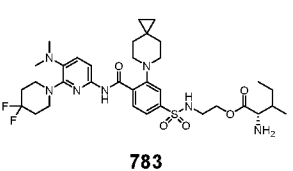
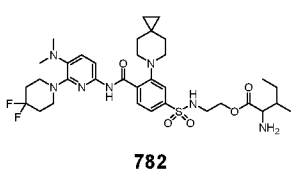
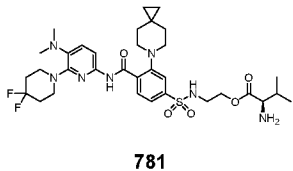
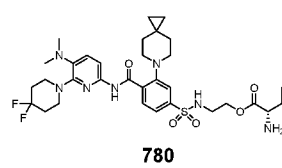
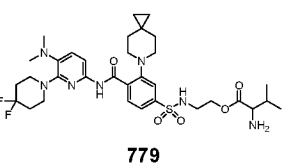
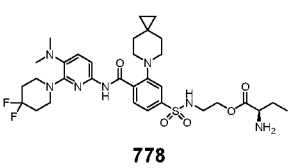
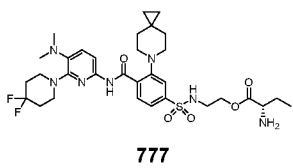
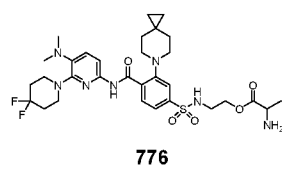
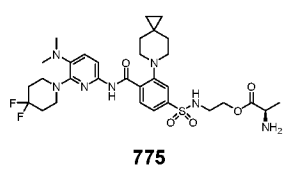
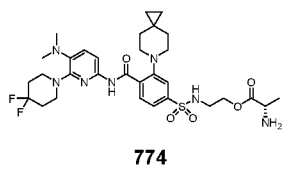
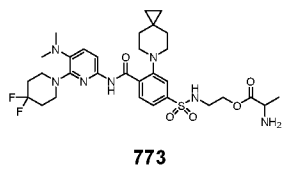
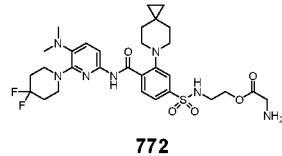
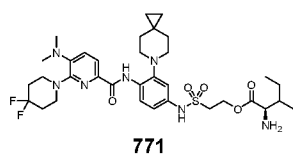
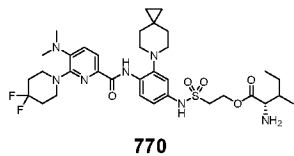
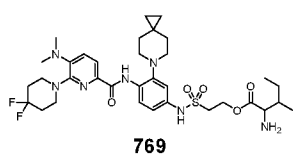


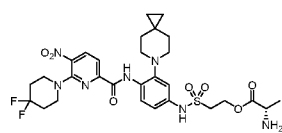
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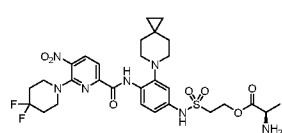
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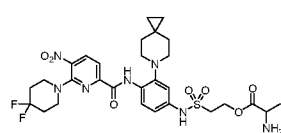




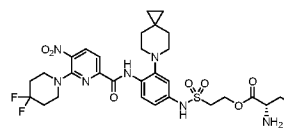
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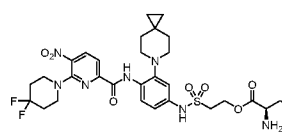
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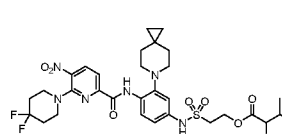
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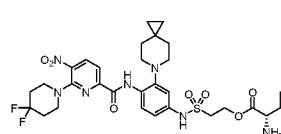
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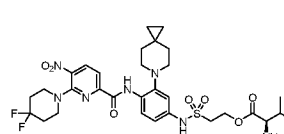
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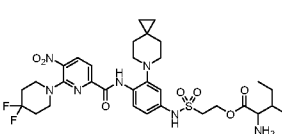
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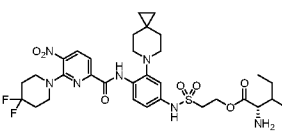
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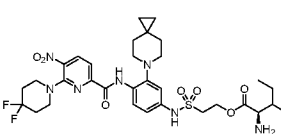
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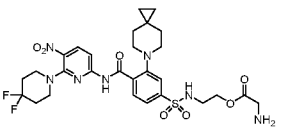
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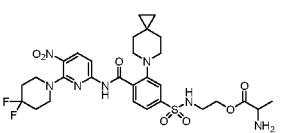
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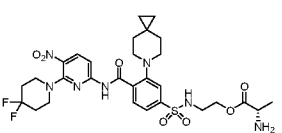
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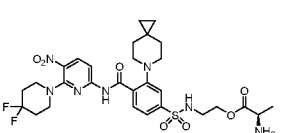
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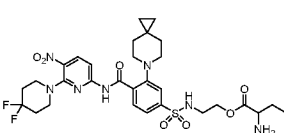
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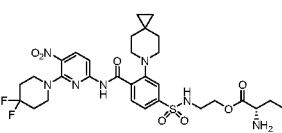
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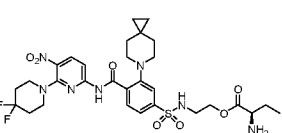
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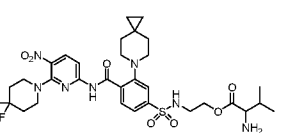
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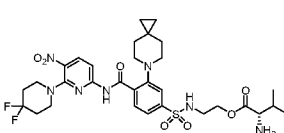
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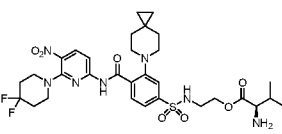
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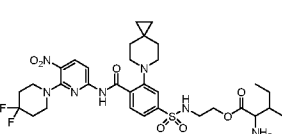
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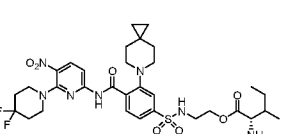
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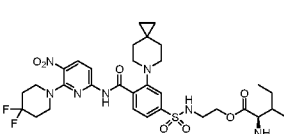
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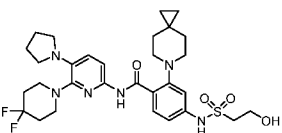
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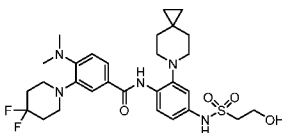
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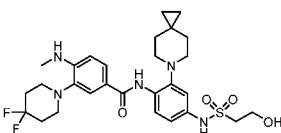
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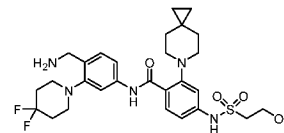
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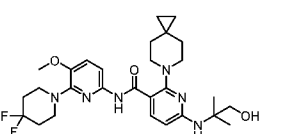
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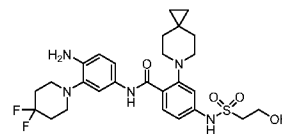
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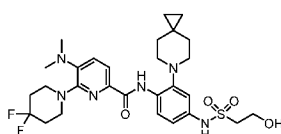
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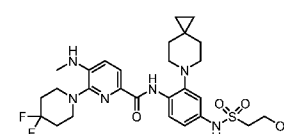
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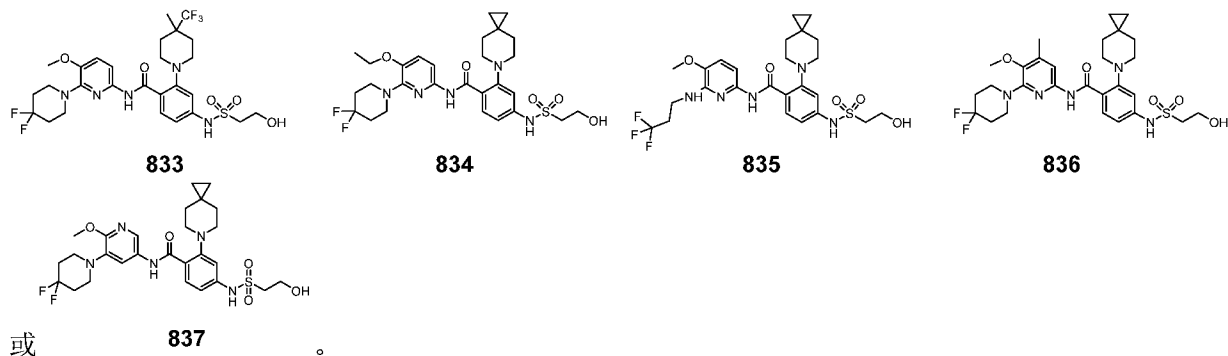
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本发明的另一个目的是提供了一种药物组合物，其含有药学上可接受的载体、稀释剂和/或赋形剂，以及本发明通式(1)化合物、或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物作为活性成分。

本发明的再一个目的提供了本发明的通式(1)所示的化合物、或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物或上述药物组合物用于制备治疗、调节或预防与 KIF18A 蛋白相关疾病的药物中的用途。其中，所述的疾病优选癌症，所述癌症为血液癌和实体瘤。

本发明的再一个目的还提供治疗、调节或预防与 KIF18A 蛋白介导的相关疾病的方法，包括对受试者给与治疗有效量的本发明的通式(1)所示的化合物、或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物或上述药物组合物。

通过合成和仔细研究了多类涉及具有 KIF18A 蛋白抑制作用的新化合物，发明人发现在通式(1)化合物中，化合物意外地具有很强的 KIF18A 蛋白抑制活性。

应理解，本发明的前述一般性描述和以下详细描述都是示例性和说明性的，旨在提供对所要求保护的本发明的进一步说明。

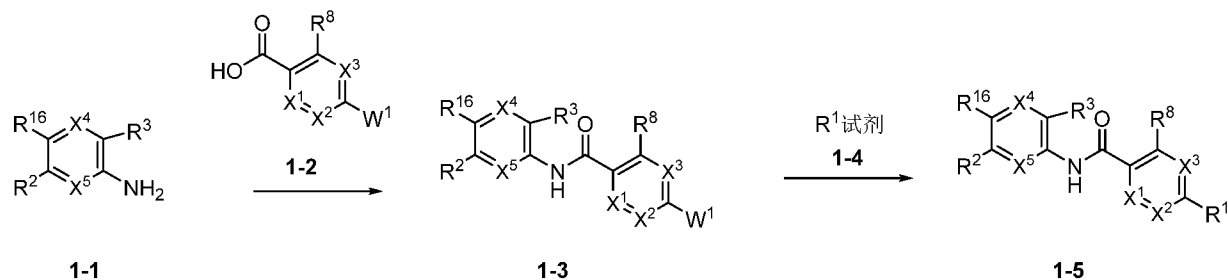
化合物的合成

下面具体地描述本发明化合物的制备方法，但这些具体方法不对本发明构成任何限制。

以上说明的化合物可使用标准的合成技术或公知的技术与文中结合的方法来合成。此外，在此提到的溶剂，温度和其他反应条件可以改变。用于化合物的合成的起始物料可以由合成或从商业来源上获得，如，但不限于 Aldrich Chemical Co. (Milwaukee, Wis.)或 Sigma Chemical Co. (St. Louis, Mo.)。本文所述的化合物和其他具有不同取代基的有关化合物可使用公知的技术和原料来合成，包括发现于 March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey 和 Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A 和 B (Plenum 2000, 2001), Green 和 Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999)中的方法。化合物制备的一般方法可通过使用适当的试剂和在此提供的分子式中引入不同基团的条件来改变。

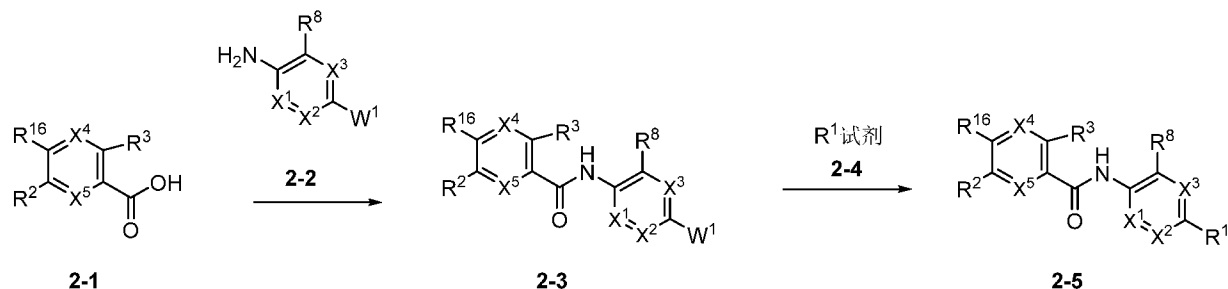
一方面，本文所述的化合物根据工艺中公知的方法。然而方法的条件，例如反应物、溶剂、碱、所用化合物的量、反应温度、反应所需时间等不限于下面的解释。本发明化合物还可以任选将在本说明书中描述的或本领域已知的各种合成方法组合起来而方便的制得，这样的组合可由本发明所属领域的技术人员容易的进行。一方面，本发明还提供了一种所述的化合物的制备方法，其中通式(1)化合物可采用下列一般反应流程 1、2、3 或 4 制备：

一般反应流程 1



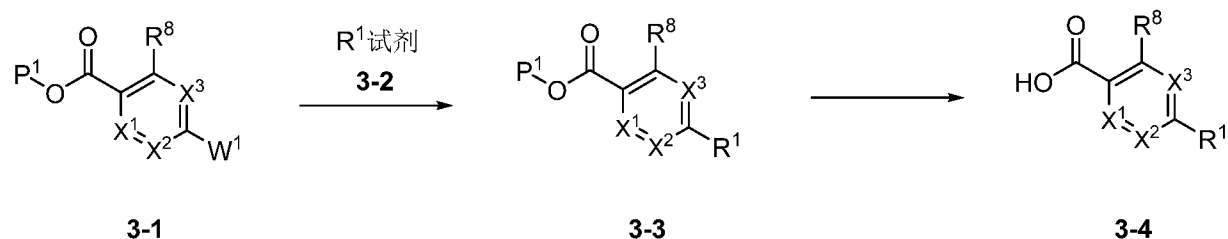
通式(1)化合物的实施方式可根据一般反应流程 1 制备, 其中 R¹、R²、R³、R⁸、R¹⁶、X¹、X²、X³、X⁴ 和 X⁵ 如上文中所定义; W¹ 表示氟、氯、溴或碘; H 表示氢; N 表示氮; R¹ 试剂例如(1)1-甲基环丙烷-1-磺酰胺、(2)3-甲基氧杂环丁烷-3-胺、(3)叔丁基 3-巯基氮杂环丁烷-1-甲酸酯、(4)2-氨磺酰基丙酸乙酯、(5)2-羟基丙烷-1-磺酰胺、(6)2-羟基乙烷-1-磺酰胺、(7)碘乙酸乙酯、(8)2-巯基丙烷-1-醇、(9)2-巯基-2-甲基丙烷-1-醇、(10)2-氨基乙-1-醇或(11)环丙烷硫醇。如一般反应流程 1 所示, 化合物 1-1 和化合物 1-2 发生酰胺化反应生成化合物 1-3, 化合物 1-3 与 R¹ 试剂 1-4 反应生成化合物 1-5。

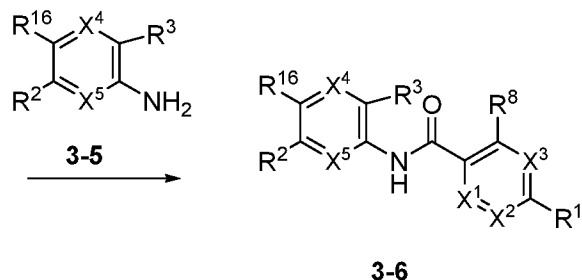
一般反应流程 2



通式(1)化合物的实施方式可根据一般反应流程 2 制备, 其中 R¹、R²、R³、R⁸、R¹⁶、X¹、X²、X³、X⁴ 和 X⁵ 如上文中所定义; W¹ 表示氟、氯、溴或碘, H 表示氢; N 表示氮; R¹ 试剂例如(1)1-甲基环丙烷-1-磺酰胺、(2)3-甲基氧杂环丁烷-3-胺、(3)叔丁基 3-巯基氮杂环丁烷-1-甲酸酯、(4)2-氨磺酰基丙酸乙酯、(5)2-羟基丙烷-1-磺酰胺、(6)2-羟基乙烷-1-磺酰胺、(7)碘乙酸乙酯、(8)2-巯基丙烷-1-醇、(9)2-巯基-2-甲基丙烷-1-醇、(10)2-氨基乙-1-醇或(11)环丙烷硫醇。如一般反应流程 2 所示, 化合物 2-1 和化合物 2-2 发生酰胺化反应生成化合物 2-3, 化合物 2-3 与 R¹ 试剂 2-4 反应生成化合物 2-5。

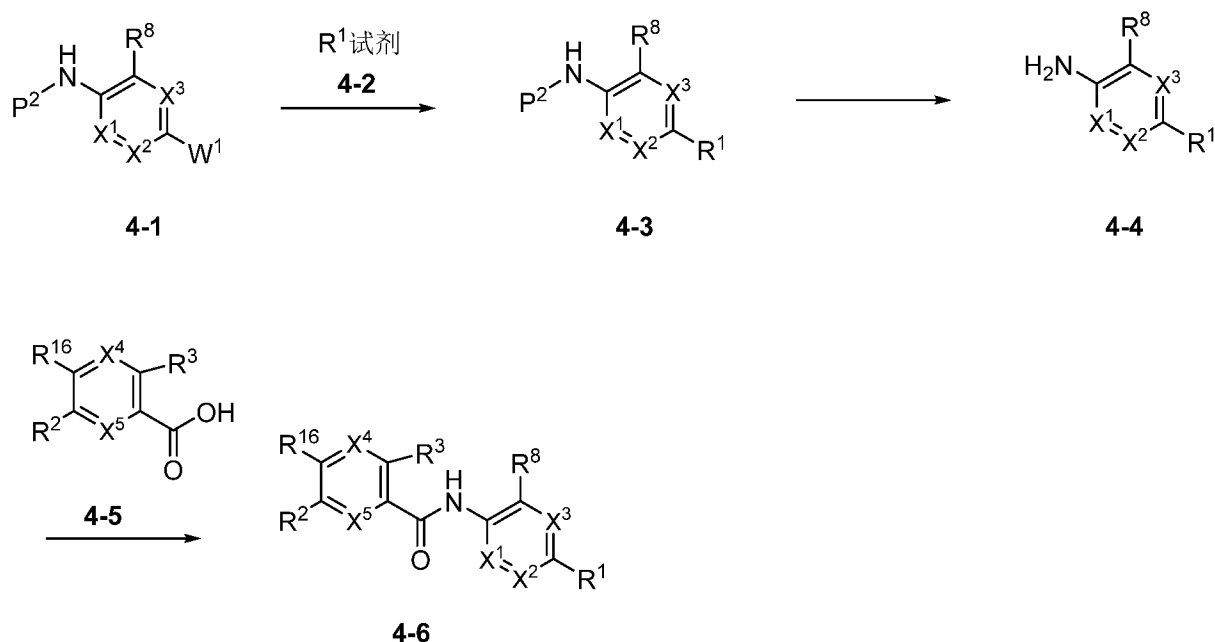
一般反应流程 3





通式(1)化合物的实施方式可根据一般反应流程 3 制备, 其中 R^1 、 R^2 、 R^3 、 R^8 、 R^{16} 、 X^1 、 X^2 、 X^3 、 X^4 和 X^5 如上文中所定义; W^1 表示氟、氯、溴或碘; H 表示氢; N 表示氮; P^1 为酯基的保护基; R^1 试剂例如(1)1-甲基环丙烷-1-磺酰胺、(2)3-甲基氧杂环丁烷-3-胺、(3)叔丁基 3-巯基氮杂环丁烷-1-甲酸酯、(4)2-氨磺酰基丙酸乙酯、(5)2-羟基丙烷-1-磺酰胺、(6)2-羟基乙烷-1-磺酰胺、(7)碘乙酸乙酯、(8)2-巯基丙烷-1-醇、(9)2-巯基-2-甲基丙烷-1-醇、(10)2-氨基乙-1-醇或(11)环丙烷硫醇。如一般反应流程 3 所示, 化合物 3-1 与 R^1 试剂 3-2 反应生成化合物 3-3, 化合物 3-3 脱去酯基保护基 P^1 得到化合物 3-4, 化合物 3-4 和化合物 3-5 发生酰胺化反应生成化合物 3-6。

一般反应流程 4



通式(1)化合物的实施方式可根据一般反应流程 4 制备, 其中 R^1 、 R^2 、 R^3 、 R^8 、 X^1 、 X^2 、 X^3 、 X^4 和 X^5 如上文中所定义; W^1 表示氟、氯、溴或碘; H 表示氢; N 表示氮; P^2 为胺基的保护基; R^1 试剂例如(1)1-甲基环丙烷-1-磺酰胺、(2)3-甲基氧杂环丁烷-3-胺、(3)叔丁基 3-巯基氮杂环丁烷-1-甲酸酯、(4)2-氨磺酰基丙酸乙酯、(5)2-羟基丙烷-1-磺酰胺、(6)2-羟基乙烷-1-磺酰胺、(7)碘乙酸乙酯、(8)2-巯基丙烷-1-醇、(9)2-巯基-2-甲基丙烷-1-醇、(10)2-氨基乙-1-醇或(11)环丙烷硫醇。如一般反应流程 4 所示, 化合物 4-1 与 R^1 试剂 4-2 反应生成化合物 4-3, 化合物 4-3 脱去胺基保护基 P^2 得到化合物 4-4, 化合物 4-4 和化合物 4-5 发生酰胺化反应生成化合物 4-6。

化合物的进一步形式

“药学上可接受”这里指一种物质，如载体或稀释液，不会使化合物的生物活性或性质消失，且相对无毒，如，给予个体某物质，不会引起不想要的生物影响或以有害的方式与任何其含有的组分相互作用。

术语“药学上可接受的盐”指一种化合物的存在形式，该形式不会引起对给药有机体的重要的刺激，且不会使化合物的生物活性和性质消失。在某些具体方面，药学上可接受的盐是通过通式化合物与酸或碱反应获得，其中所述的酸或碱包括，但不限于发现于 Stahl 和 Wermuth, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* 1st Ed., (Wiley, 2002)中的酸和碱。

应理解药学上可接受的盐的参考包括溶剂添加形式或结晶形式，尤其是溶剂化物或多晶型。溶剂化物含有化学计量或非化学计量的溶剂，且是在与药学上可接受溶剂如水，乙醇等，结晶化过程中选择性形成的。当溶剂是水时形成水合物，或当溶剂是乙醇时形成醇化物。通式(1)化合物的溶剂化物按照本文所述的方法，很方便的制得或形成。举例说明，通式(1)化合物的水合物从水/有机溶剂的混合溶剂中重结晶而方便的制得，使用的有机溶剂包括但不限于，四氢呋喃、丙酮、乙醇或甲醇。此外，在此提到的化合物能够以非溶剂化和溶剂化形式存在。总之，对于在此提供的化合物和方法为目的，溶剂化形式被认为相当于非溶剂化形式。

在其他具体实施例中，通式(1)化合物被制备成不同的形式，包括但不限于，无定形，粉碎形和毫微-粒度形式。此外，通式(1)化合物包括结晶型，也可以作为多晶型。多晶型包括化合物的相同元素组成的不同晶格排列。多晶型通常有不同的 X-射线衍射光谱、红外光谱、熔点、密度、硬度、晶型、光和电的性质、稳定性和溶解性。不同的因素如重结晶溶剂，结晶速率和贮存温度可能引起单一晶型为主导。

在另一个方面，通式(1)化合物可能存在手性中心和/或轴手性，并因此以消旋体、外消旋混合物、单一对映体、非对映异构体化合物和单一非对映体的形式、和顺反异构体的形式出现。每个手性中心或轴手性将独立地产生两个旋光异构体，并且所有可能的旋光异构体和非对映体混合物以及纯或部分纯的化合物包括在本发明的范围之内。本发明意味着包括这些化合物的所有这种异构形式。

本发明的化合物可以在一个或多个构成该化合物的原子上包含非天然比例的原子同位素。例如，可用放射性同位素标记化合物，比如氚(³H)、碘-125(¹²⁵I)和 C-14(¹⁴C)。又例如，可用重氢取代氢原子形成氘代化合物，氘与碳构成的键比普通氢和碳构成的键更坚固，相比于未氘代药物，通常氘代药物具有降低毒副作用、增加药物稳定性、增强疗效、延长药物体内半衰期等优势。本发明的化合物的所有同位素组成的变换，无论放射性与否，都包含在本发明的范围之内。

术语

如果无另外说明，用于本发明申请，包括说明书和权利要求书中的术语，定义如下。必须注意，在说明书和所附的权利要求书中，如果文中无另外清楚指示，单数形式“一个”包括复数意义。如果无另外说明，使用质谱、核磁、HPLC、蛋白化学、生物化学、重组 DNA 技术和药理学的常规方法。在本申请中，如果无另外说明，使用“或”或“和”指“和/或”。

除非另有规定，“C_{α-β} 烃基”意指在支链或线性关系中包含最小 α 个和最大 β 个碳原子的烃基，其中 α 和 β 表示整数。在该部分中描述的烃基还可以含有一个或两个双键或三键。C₀ 烃基的指定表示直

连键。C₁₋₆ 烃基的实例包括但不限于以下： 或 .

除非另有规定,“C_{αβ} 卤代烃基”意指如上所述的烃基,其中,任意数量(至少一个)的附接到烃基链的氢原子被 F、Cl、Br 或 I 替代。

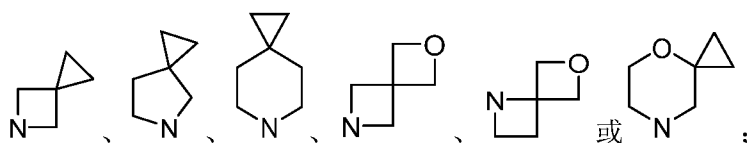
除非另有规定,“氧代”和“硫代”分别表示=O(如羰基)和=S(如硫代羰基)。

除非另有规定,“卤代”或“卤素”意指选自 F、Cl、Br 和 I 的卤素原子。

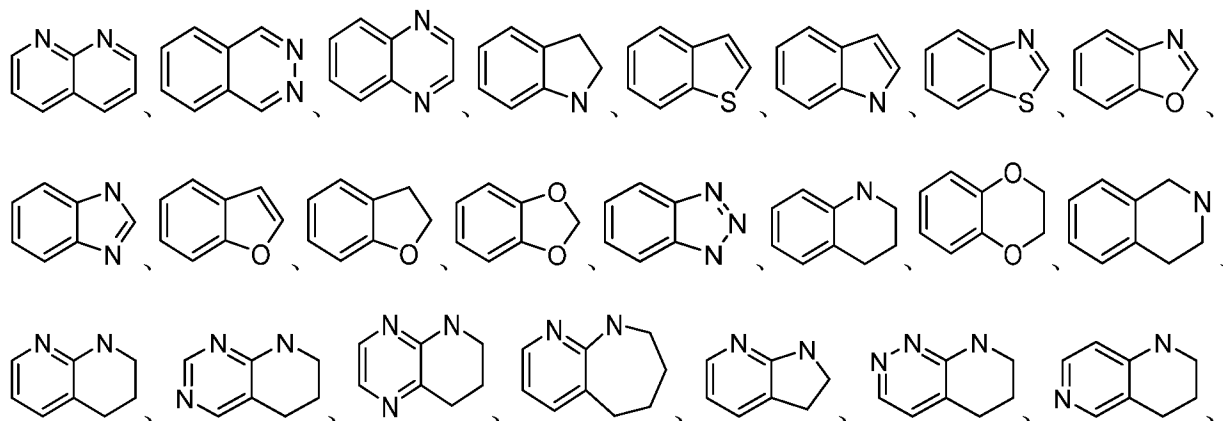
除非另有规定,“烷氧基”指通过醚氧原子键合到分子其余部分的烷基。代表性的烷氧基为具有 1-6 个碳原子的烷氧基,如甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基、异丁氧基、仲丁氧基和叔丁氧基。如本文所用,“烷氧基”包括未取代和取代的烷氧基,尤其是被一个或多个卤素所取代的烷氧基。优选的烷氧基选自 OCH_3 、 OCF_3 、 CHF_2O 、 $\text{CF}_3\text{CH}_2\text{O}$ 、 ^iPrO 、 ^nPrO 、 ^iBuO 、 ^nBuO 或 ^tBuO 。

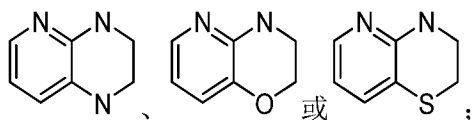
除非另有规定，“环烷基”是指单环非芳香族烃环系统。环烷基的成环碳原子可以任选地被氧化以形成氧代或硫离子基。环烷基还包括亚环烷基。在一些实施方案中，环烷基含有 0、1 或 2 个双键。在一些实施方案中，环烷基含有 1 或 2 个双键（部分不饱和环烷基）。环烷基的实例包括但不限于环丙基、环丁基、环戊基、环己基、环庚基、环戊烯基、环己烯基、环己二烯基、环庚三烯基等。

除非另有规定,“双环”意指具有两个连接环的基团。双环可以为碳环(所有环原子为碳原子)或杂环(除了碳原子之外,环原子包括例如 1、2 或 3 个杂原子,例如 N、O 或 S)。这两个环都可以是脂肪族的(例如萘烷和降冰片烷),或可以是芳香族(例如萘),或脂肪族和芳香族的组合(例如四氢化萘)。双环包括(a)螺环化合物,其中两个环只共享一个单原子(螺原子,其通常为季碳)。螺环化合物的实例包括但不限于:

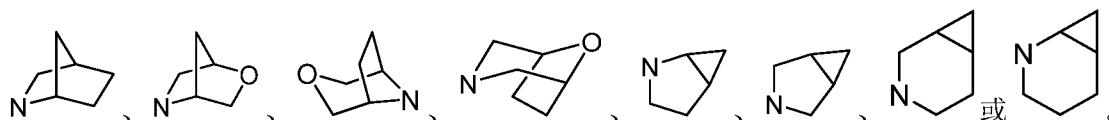


(b)稠合的双环化合物，其中两个环共享两个相邻原子。即环共享一个共价键，即桥头原子直接连接(例如 α -崖柏烯和萘烷)。稠合的双环的实例包括但不限于：



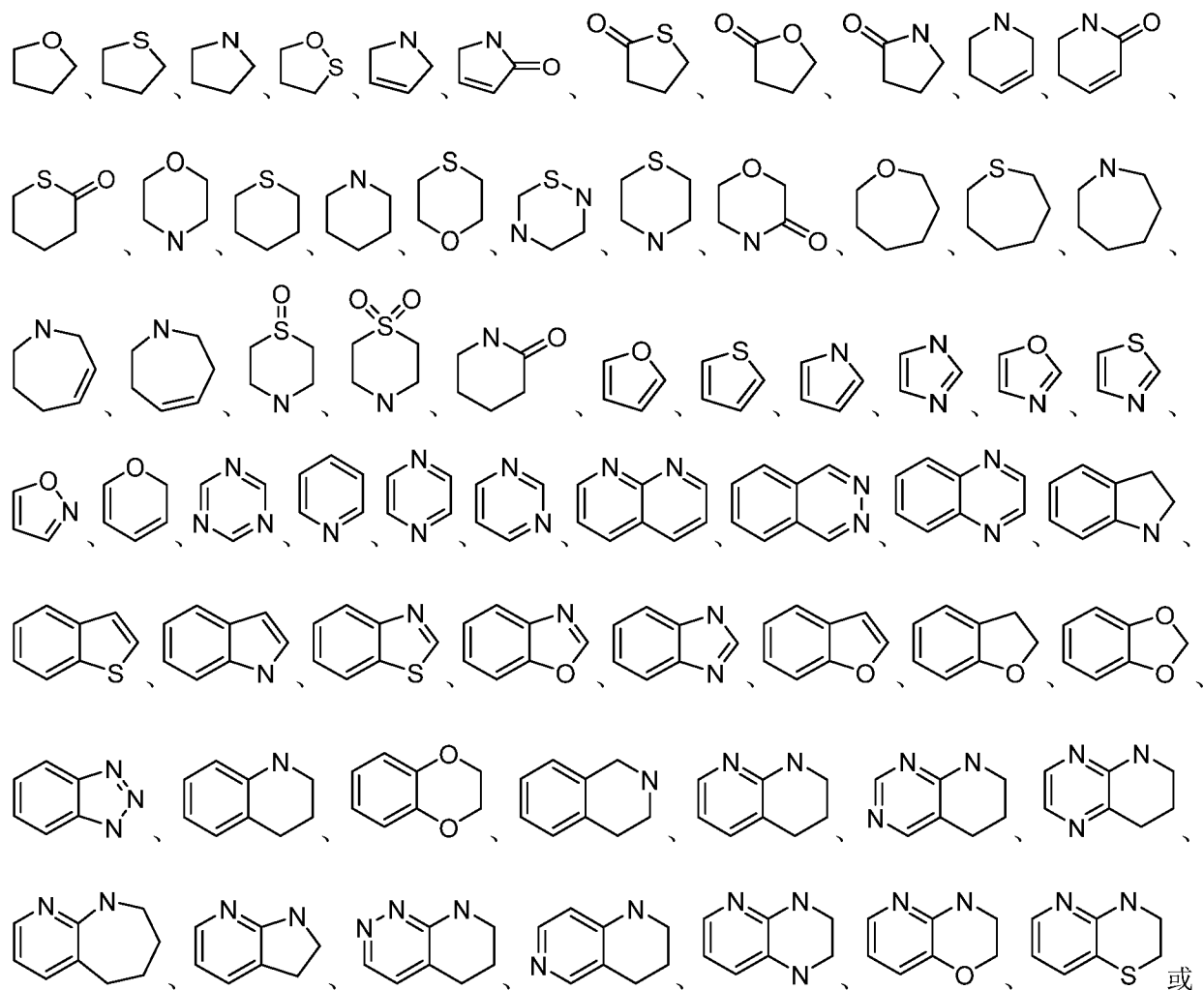


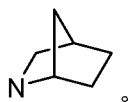
和(c)桥联的双环化合物, 其中两个环共享三个或更多个原子, 并通过包含至少一个原子的桥将两个桥头原子隔开。例如, 降冰片烷, 也称为双环[2.2.1]庚烷, 可以被认为是一对环戊烷环, 每个环共享它们的五个碳原子中的三个。桥联的双环的实例包括但不限于:



除非另有规定, “碳环”或“碳环的”意指本身或与其他术语组合包含的环, 表示“C_{α-β} 烃基”的环状形式。碳环的实例包括环丙基、环丁基、环戊基、环己基、环庚基、环戊烯基、环己烯基、环己二烯基、环庚三烯基、降茛基、降蒎基、降薅基、双环[1.1.1]戊烷基、双环[2.1.1]己烷基等。

除非另有规定, “杂环”或“杂环的”意指包含至少一个碳原子和至少一个选自 N、O 和 S 的其他原子的环。可在权利要求书中出现的杂环的实例包括但不限于以下:





“任选”或“任选地”指的是随后描述的事件或状况可能但不是必需出现，并且该描述包括其中所述事件或状况发生的情况以及所述事件或状况不发生的情况。

“饱和的、部分饱和的或不饱和的”包括被氢饱和的取代基、完全被氢不饱和的取代基和部分被氢饱和的取代基。

当其中一个变量选自化学键时，表示其连接的两个基团直接相连，比如 X-L-Y 中 L 代表化学键时表示该结构实际上是 X-Y。

当一个基团的数量为 0 时，比如 -N(C₀ 烷基)-C₀₋₄ 烷基-，表示该连接基团为 -NH-C₀₋₄ 烷基-。

当一个连接基团的数量为 0 时，比如 -(CH₂)₀-，表示该连接基团为化学键。

除非另有说明，用楔形实线键(／)和楔形虚线键(⋯)表示一个立体中心的绝对构型，用直形实线键(—)和直形虚线键(⋯)表示立体中心的相对构型，用波浪线(~~~~)表示楔形实线键(／)或楔形虚线键(⋯)，或用波浪线(~~~~)表示直形实线键(—)或直形虚线键(⋯)。

除非另有说明，用 === 表示单键或双键。

特定药学及医学术语

术语“可接受的”，如本文所用，指一个处方组分或活性成分对一般治疗目标的健康没有过分的有害影响。

术语“治疗”、“治疗过程”或“疗法”如本文所用，包括缓和、抑制或改善疾病的症状或状况；抑制并发症的产生；改善或预防潜在代谢综合症；抑制疾病或症状的产生，如控制疾病或情况的发展；减轻疾病或症状；使疾病或症状减退；减轻由疾病或症状引起的并发症，或预防或治疗由疾病或症状引起的征兆。如本文所用，某一化合物或药物组合物，给药后，可以使某一疾病、症状或情况得到改善，尤指其严重度得到改善，延迟发病，减缓病情进展，或减少病情持续时间。无论固定给药或临时给药、持续给药或间歇给药，可以归因于或与给药有关的情况。

“活性成分”指通式(1)所示化合物，以及通式(1)化合物的药学上可接受的无机或有机盐。本发明的化合物可以含有一个或多个不对称中心(手性中心或轴手性)，并因此以消旋体、外消旋混合物、单一对映体、非对映异构体化合物和单一非对映体的形式出现。可以存在的不对称中心，取决于分子上各种取代基的性质。每个这种不对称中心将独立地产生两个旋光异构体，并且所有可能的旋光异构体和非对映体混合物以及纯或部分纯的化合物包括在本发明的范围之内。本发明意味着包括这些化合物的所有这种异构形式。

“化合物(compound)”、“组合物(composition)”、“药剂(agent)”或“医药品(medicine or medicament)”等词在此可交替使用，且都是指当施用于个体(人类或动物)时，能够透过局部和/或全身性作用而诱发所亟求的药学和/或生理反应的一种化合物或组合物。

“施用(administered、administering 或 administration)”一词在此是指直接施用所述的化合物或组合物，或施用活性化合物的前驱药(prodrug)、衍生物(derivative)、或类似物(analog)等。

虽然用以界定本发明较广范围的数值范围与参数皆是约略的数值，此处已尽可能精确地呈现具体实施例中的相关数值。然而，任何数值本质上不可避免地含有因个别测试方法所致的标准偏差。在此处，“约”通常是指实际数值在一特定数值或范围的正负 10%、5%、1%或 0.5%之内。或者是，“约”一词代表实际数值落在平均值的可接受标准误差之内，视本领域技术人员的考虑而定。除了实验例之外，或除非另有明确的说明，当可理解此处所用的所有范围、数量、数值与百分比（例如用以描述材料用量、时间长短、温度、操作条件、数量比例及其它相似者）均经过“约”的修饰。因此，除非另有相反的说明，本说明书与附随权利要求书所揭示的数值参数皆为约略的数值，且可视需求而更动。至少应将这些数值参数理解为所指出的有效位数与采用一般进位法所得到的数值。

除非本说明书另有定义，此处所用的科学与技术词汇的含义与本领域技术人员所理解的惯用的意义相同。此外，在不和上下文冲突的情形下，本说明书所用的单数名词涵盖该名词的复数型；而所用的复数名词时亦涵盖该名词的单数型。

治疗用途

本发明提供了使用本发明通式(1)化合物或药物组合物通常可用于抑制 KIF18A 蛋白，因此可用于治疗与 KIF18A 蛋白活性相关的一种或多种病症。因此，在某些实施方式中，本发明提供了用于治疗 KIF18A 蛋白介导的病症的方法，所述方法包括向有需要的患者施用本发明化合物、或其药学上可接受的组合物的步骤。

在一些实施例中，提供了用于癌症治疗的方法，该方法包括给予有需要的个体有效量的任何前述的包括结构通式(1)化合物的药物组合物。在一些实施例中，癌症由 KIF18A 蛋白介导。在其它实施例中，该癌症是血液癌和实体瘤，包括但不限于，血液恶性肿瘤（白血病、淋巴瘤、骨髓瘤包括多发性骨髓瘤、骨髓异常增生综合症和骨髓增生性综合症）和实体瘤（癌例如前列腺、乳腺、肺、结肠、胰腺、肾、卵巢以及软组织癌和骨肉瘤，以及间质瘤）等。

给药途径

本发明的化合物及其药学上可接受的盐可制成各种制剂，其中包含安全、有效量范围内的本发明化合物或其药学上可接受的盐及药理上可以接受的赋形剂或载体。其中“安全、有效量”指的是：化合物的量足以明显改善病情，而不至于产生严重的副作用。化合物的安全、有效量根据治疗对象的年龄、病情、疗程等具体情况来确定。

“药学上可以接受的赋形剂或载体”指的是：一种或多种相容性固体或液体填料或凝胶物质，它们适合于人使用，而且必须有足够的纯度和足够低的毒性。“相容性”在此指的是组合物中各组份能与本发明的化合物以及它们之间相互掺和，而不明显降低化合物的药效。药理上可以接受的赋形剂或载体部分例子有纤维素及其衍生物(如羧甲基纤维素钠、乙基纤维素钠、纤维素乙酸酯等)、明胶、滑石、固体润滑剂(如硬脂酸、硬脂酸镁)、硫酸钙、植物油(如豆油、芝麻油、花生油、橄榄油等)、多元醇(如丙二醇、甘油、甘露醇、山梨醇等)、乳化剂(如吐温®)、润湿剂(如十二烷基硫酸钠)、着色剂、调味剂、稳定剂、抗氧化剂、防腐剂、无热原水等。

施用本发明化合物时，可以口服、直肠、肠胃外(静脉内、肌肉内或皮下)、局部给药。

用于口服给药的固体剂型包括胶囊剂、片剂、丸剂、散剂和颗粒剂。在这些固体剂型中，活性化

合物与至少一种常规惰性赋形剂(或载体)混合,如柠檬酸钠或磷酸二钙,或与下述成分混合:(a)填料或增容剂,例如,淀粉、乳糖、蔗糖、葡萄糖、甘露醇和硅酸;(b)粘合剂,例如,羟甲基纤维素、藻酸盐、明胶、聚乙烯基吡咯烷酮、蔗糖和阿拉伯胶;(c)保湿剂,例如,甘油;(d)崩解剂,例如,琼脂、碳酸钙、马铃薯淀粉或木薯淀粉、藻酸、某些复合硅酸盐、和碳酸钠;(e)缓溶剂,例如石蜡;(f)吸收加速剂,例如,季胺化合物;(g)润湿剂,例如鲸蜡醇和单硬脂酸甘油酯;(h)吸附剂,例如,高岭土;和(i)润滑剂,例如,滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、十二烷基硫酸钠,或其混合物。胶囊剂、片剂和丸剂中,剂型也可包含缓冲剂。

固体剂型如片剂、糖丸、胶囊剂、丸剂和颗粒剂可采用包衣和壳材制备,如肠衣和其它本领域公知的材料。它们可包含不透明剂,并且,这种组合物中活性化合物或化合物的释放可以延迟的方式在消化道内的某一部分中释放。可采用的包埋组分的实例是聚合物物质和蜡类物质。必要时,活性化合物也可与上述赋形剂中的一种或多种形成微胶囊形式。

用于口服给药的液体剂型包括药学上可接受的乳液、溶液、悬浮液、糖浆或酏剂。除了活性化合物外,液体剂型可包含本领域中常规采用的惰性稀释剂,如水或其它溶剂,增溶剂和乳化剂,例如,乙醇、异丙醇、碳酸乙酯、乙酸乙酯、丙二醇、1,3-丁二醇、二甲基甲酰胺以及油,特别是棉籽油、花生油、玉米胚油、橄榄油、蓖麻油和芝麻油或这些物质的混合物等。

除了这些惰性稀释剂外,组合物也可包含助剂,如润湿剂、乳化剂和悬浮剂、甜味剂、矫味剂和香料。

除了活性化合物外,悬浮液可包含悬浮剂,例如,乙氧基化异十八烷醇、聚氧乙烯山梨醇和脱水山梨醇酯、微晶纤维素、甲醇铝和琼脂或这些物质的混合物等。

用于肠胃外注射的组合物可包含生理上可接受的无菌含水或无水溶液、分散液、悬浮液或乳液,和用于重新溶解成无菌的可注射溶液或分散液的无菌粉末。适宜的含水和非水载体、稀释剂、溶剂或赋形剂包括水、乙醇、多元醇及其适宜的混合物。

用于局部给药的本发明化合物的剂型包括软膏剂、散剂、贴剂、喷射剂和吸入剂。活性成分在无菌条件下与生理上可接受的载体及任何防腐剂、缓冲剂,或必要时可能需要的推进剂一起混合。

本发明化合物可以单独给药,或者与其他药学上可接受的化合物联合给药。使用药物组合物时,是将安全有效量的本发明化合物适用于需要治疗的哺乳动物(如人),其中施用时剂量为药学上认为的有效给药剂量,对于 60kg 体重的人而言,日给药剂量通常为 1~2000 mg,优选 50~1000 mg。当然,具体剂量还应考虑给药途径、病人健康状况等因素,这些都是熟练医师技能范围内的。

本发明提到的上述特征,或实施例提到的特征可以任意组合。本案说明书所揭示的所有特征可与任何组合物形式并用,说明书中所揭示的各个特征,可以任何可提供相同、均等或相似目的的替代性特征取代。因此除有特别说明,所揭示的特征仅为均等或相似特征的一般性例子。

具体实施方式

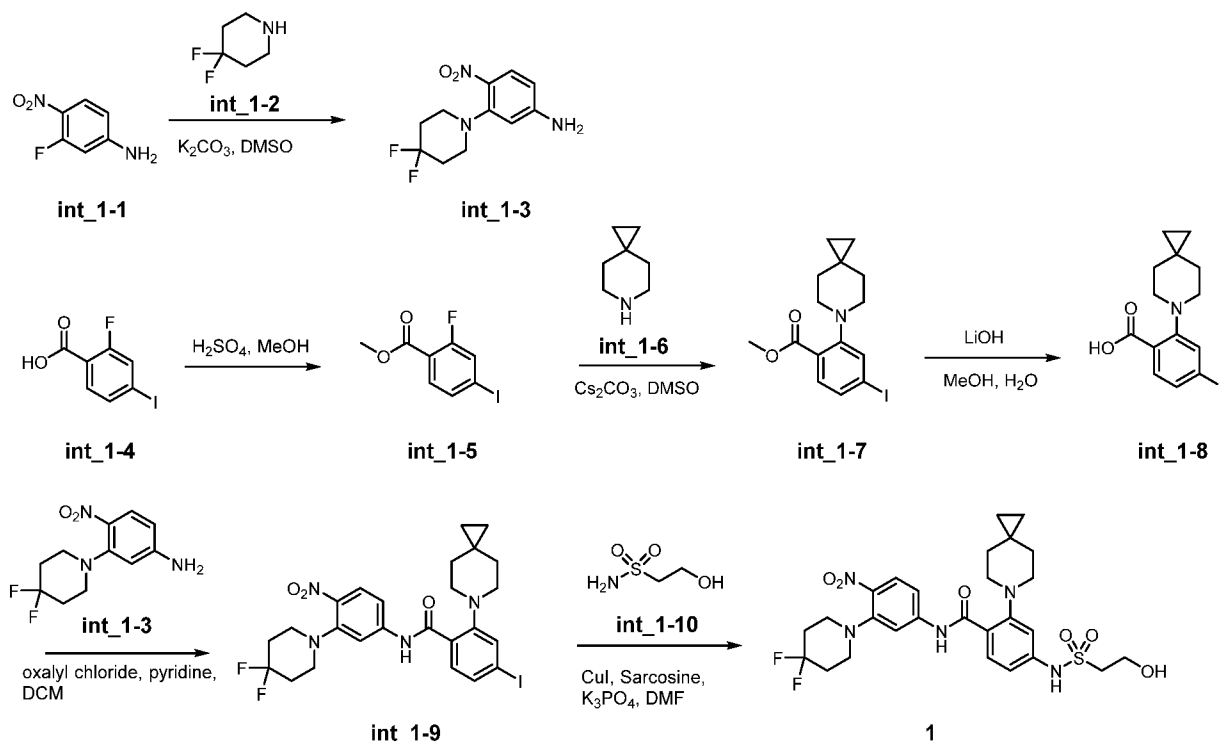
在下面的说明中将会详细阐述上述化合物、方法、药物组合物的各个具体方面、特性和优势,使本发明的内容变得十分明了。在此应理解,下述的详细说明及实例描述了具体的实施例,仅用于参考。在阅读了本发明的说明内容后,本领域的技术人员可对本发明作各种改动或修改,这些等价形势同样

落于本申请所限定的范围。

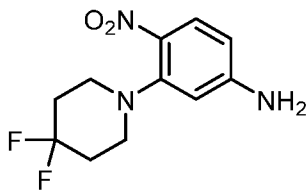
所有实施例中，¹H-NMR 用 Varian Mercury 400 核磁共振仪记录，化学位移以 δ (ppm) 表示；分离用硅胶未说明均为 200-300 目，洗脱液的配比均为体积比。

本发明采用下述缩略词：(Boc)₂O 代表二碳酸二叔丁酯；BOPCl 代表双(2-氧代-3-恶唑烷基)次磷酸氯；CDCl₃ 代表氘代氯仿；Cs₂CO₃ 代表碳酸铯；CuI 代表碘化亚铜；EtOAc 代表乙酸乙酯；Hexane 代表正己烷；HPLC 代表高效液相色谱；MeCN 代表乙腈；DCE 代表 1,2-二氯乙烷；DCM 代表二氯甲烷；DIPEA 代表二异丙基乙基胺；1,4-Dioxane 代表 1,4-二氧六环；DMF 代表 N,N-二甲基甲酰胺；DMAP 代表 4-(二甲氨基)吡啶；DMSO 代表二甲亚砜；hr 代表小时；HATU 代表 N-[(二甲基氨基)-1H-1,2,3-三唑-[4,5-b]吡啶-1-亚甲基]-N-甲基甲铵六氟磷酸酯-N-氧化物；IPA 代表异丙醇；min 代表分钟；K₂CO₃ 代表碳酸钾；KOAc 代表醋酸钾；K₃PO₄ 代表磷酸钾；LiBH₄ 代表硼氢化锂；min 代表分钟；MeOH 代表甲醇；MS 代表质谱；NMR 代表核磁共振；Pd/C 代表钯碳；Pd(PPh₃)₄ 代表四三苯基膦钯；Pd₂(dba)₃ 代表三(二亚苄基丙酮)二钯(0)；PE 代表石油醚；RuPhos-Pd-G₃ 代表(2-二环己基膦基-2'6'-二异丙氧基-11'-联苯)[2-(2'-氨基-11'-联苯基)]钯(II)甲磺酸盐；Sarcosine 代表肌氨酸；TFA 代表三氟乙酸；TMSCl 代表三甲基氯化硅；T₃P 代表 1-丙基磷酸酐；XantPhos 代表 4,5-双二苯基膦-9,9-二甲基氧杂蒽；X-Phos 代表 2-二环己基膦-2',4',6'-三异丙基联苯；TLC 代表薄层色谱；XPhos 代表 2-二环己基膦-2',4',6'-三异丙基联苯；XantPhos 代表 4,5-双二苯基膦-9,9-二甲基氧杂蒽。

实施例 1 化合物 1 的合成



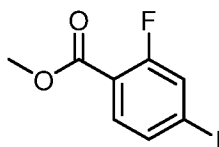
步骤 1: 化合物 int_1-3 的合成

**int_1-3**

将 **int_1-1** (800 mg, 5.124 mmol) 溶于 DMSO (10 mL) 中, 加入碳酸钾 (1.41 g, 10.249 mmol), **int_1-2** (1.24 g, 10.249 mmol), 升温至 80 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (1.2 g, 收率: 91.6%)。

ESI-MS m/z : 258 $[M+H]^+$ 。

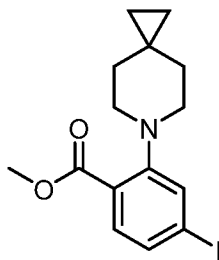
步骤 2: 化合物 **int_1-5** 的合成

**int_1-5**

将 **int_1-4** (15 g, 56.3 mmol) 溶于甲醇 (150 mL) 中, 加入浓硫酸 (2.5 mL), 升温至 80 °C 反应 4 小时, LC-MS 监测显示反应结束。反应液减压浓缩得到粗产物, 粗产物溶于乙酸乙酯, 有机相用饱和的碳酸氢钠溶液洗涤后, 再用饱和食盐水洗涤, 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到白色固体 (14 g, 收率: 89%), 可直接用于下一步反应。

ESI-MS m/z : 281 $[M+H]^+$ 。

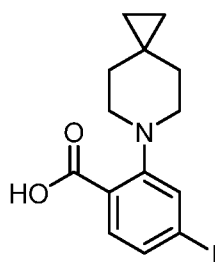
步骤 3: 化合物 **int_1-7** 的合成

**int_1-7**

将 **int_1-5** (14 g, 49.9 mmol) 溶于 DMSO (100 mL) 中, 加入碳酸铯 (23.4 g, 71.7 mmol)、**int_1-6** (6.98 g, 62.8 mmol), 升温至 90 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (500 mL) 稀释, 水相用乙酸乙酯萃取 (100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物, 粗产物经柱层析 (SiO₂, EtOAc : Hexane = 1:1) 得到目标产物 (16.3 g, 收率: 88%)。

ESI-MS m/z : 372 $[M+H]^+$ 。

步骤4: 化合物 int_1-8 的合成

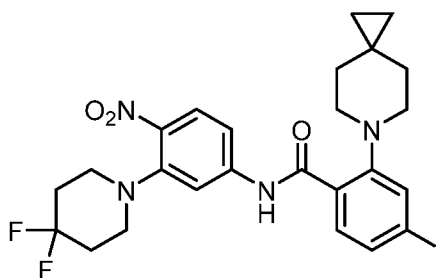


int_1-8

将 int_1-7 (16.3 g, 43.9 mmol)溶于甲醇(100 ml)和水(10 ml)的混合溶剂中, 室温下加入氢氧化锂 (2.1 g, 87.8 mmol), 室温搅拌反应 6 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物 (17 g, 粗产物)。粗产物可直接用于下一步反应。

ESI-MS m/z: 358 [M+H]⁺。

步骤5: 化合物 int_1-9 的合成

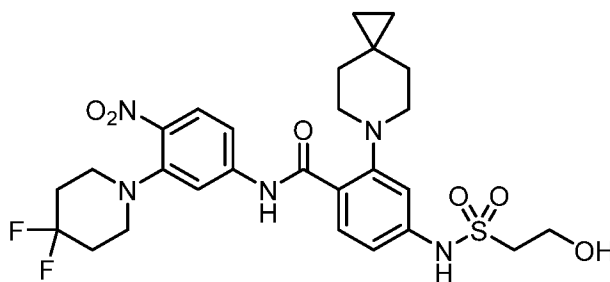


int_1-9

将 int_1-8 (1.1 g, 3.08 mmol)溶于 DCM (10 mL), 加入草酰氯 (888.4 mg, 7 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到固体。将固体溶于 DCM (10 mL), 加入 int_1-3 (792 mg, 3.08 mmol)和吡啶 (730 mg, 9.24 mmol), 反应液 40°C 搅拌 10 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, PE:EtOAc = 100:1)纯化得固体(1.4 g, 收率: 76.1%)。

ESI-MS m/z: 597 [M+H]⁺。

步骤6: 化合物 1 的合成



1

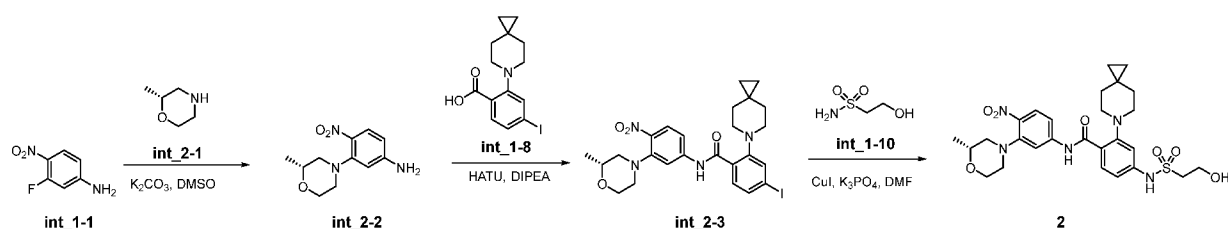
将 int_1-10 (291 mg, 2.374 mmol)、肌氨酸 (209.1 mg, 2.348 mmol)、碘化亚铜 (227 mg, 1.174 mmol)

和磷酸钾 (1.5 g, 7.041 mmol), 溶解在 DMF (20 mL) 中, 氩气置换三次, 加入 **int_1-9** (1.4 g, 2.347 mmol), 氩气保护下, 反应液加热到 90°C 反应 3 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析(SiO₂, EtOAc : Hexane = 1:1)纯化得固体(1 g, 收率: 71.8%)。

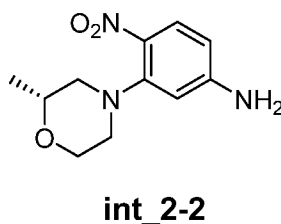
¹H NMR (400 MHz, DMSO-d₆) δ 11.92 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.49 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.32 (d, *J* = 6.5 Hz, 2H), 3.14 (t, *J* = 5.5 Hz, 4H), 2.95 (t, *J* = 5.2 Hz, 4H), 2.11 (tq, *J* = 14.6, 8.9, 7.2 Hz, 4H), 1.50 (s, 4H), 0.33 (s, 4H)。

ESI-MS *m/z*: 594 [M+H]⁺。

实施例 2 化合物 2 的合成



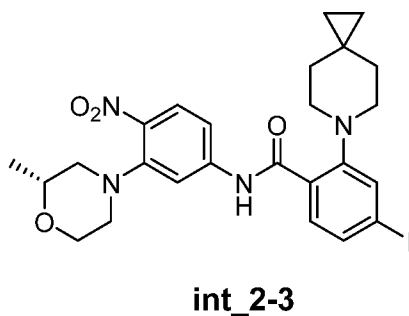
步骤 1: 化合物 **int_2-2** 的合成



将 **int_1-1** (200 mg, 1.281 mmol) 溶于 DMSO (5 mL) 中, 加入碳酸钾 (354 mg, 2.562 mmol)、**int_2-1** (259 mg, 2.562 mmol), 升温至 80 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (300 mg, 收率: 99%)。

ESI-MS *m/z*: 238 [M+H]⁺。

步骤 2: 化合物 **int_2-3** 的合成

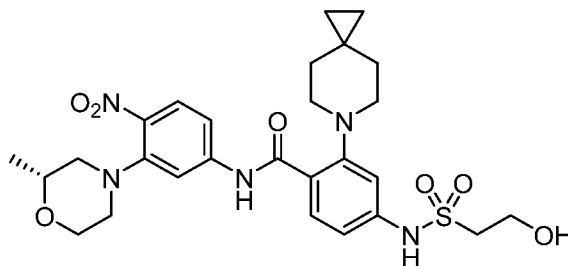


将 **int_1-8** (151 mg, 0.422 mmol) 溶于 DMF (4 mL), 加入 HATU (240 mg, 0.632 mmol)、DIPEA (163 mg, 1.264 mmol) 和 **int_2-2** (100 mg, 0.422 mmol), 反应液 80 °C 搅拌 10 小时。LC-MS 监测显示反应结

束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体(60 mg, 收率: 24.6%)。

ESI-MS m/z : 577 $[M+H]^+$ 。

步骤 3: 化合物 2 的合成



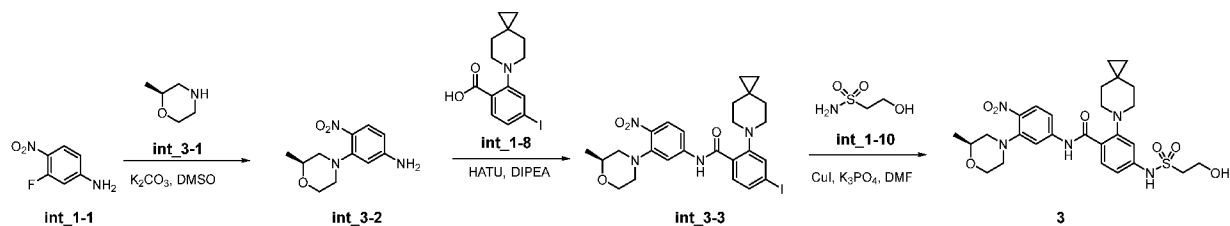
2

将 **int_1-10** (20 mg, 0.15 mmol)、(1S,2S)-N,N-二甲基环己烷 (7 mg, 0.05 mmol)、碘化亚铜 (10 mg, 0.05 mmol)和磷酸钾 (63 mg, 0.3 mmol), 溶解在 DMF (5 mL)中, 氩气置换三次, 加入 **int_2-3** (60 mg, 0.1 mmol), 氩气保护下, 反应液加热到 90 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(20 mg, 收率: 34.9%)。

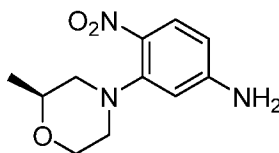
^1H NMR (400 MHz, Chloroform- d) δ 12.95 (s, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.83 (d, J = 2.3 Hz, 1H), 7.35 (s, 1H), 7.22 – 7.16 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 4.15 (s, 2H), 3.97 – 3.82 (m, 3H), 3.35 (d, J = 5.4 Hz, 2H), 3.16 (t, J = 10.5 Hz, 2H), 3.07 (q, J = 7.6, 6.5 Hz, 4H), 3.04 – 2.96 (m, 1H), 2.70 (t, J = 10.9 Hz, 2H), 1.66 (s, 4H), 1.21 (d, J = 6.2 Hz, 3H), 0.45 (s, 4H)。

ESI-MS m/z : 574 $[M+H]^+$ 。

实施例 3 化合物 3 的合成



步骤 1: 化合物 **int_3-2** 的合成

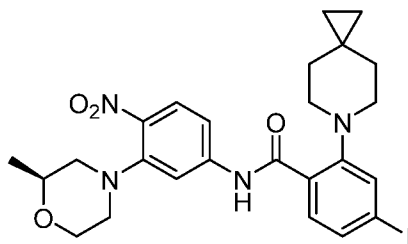


int_3-2

将 **int_1-1** (200 mg, 1.281 mmol)溶于 DMSO(10 mL)中, 加入碳酸钾 (354 mg, 2.562 mmol)、**int_3-1** (259 mg, 2.562 mmol), 升温至 80 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释, 水相用乙酸乙酯萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析得到目标产物 (280 mg, 收率: 92%)。

ESI-MS m/z : 238 $[M+H]^+$ 。

步骤 2: 化合物 int_3-3 的合成

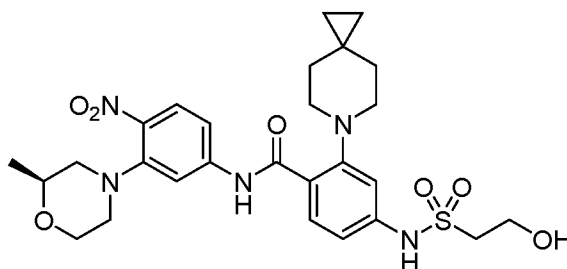


int_3-3

将 **int_1-8** (151 mg, 0.422 mmol) 溶于 DMF (4 mL), 加入 HATU (240 mg, 0.632 mmol)、DIPEA (163 mg, 1.264 mmol) 和 **int_3-2** (100 mg, 0.422 mmol), 反应液 80°C 搅拌 10 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (119 mg, 收率: 48.9%)。

ESI-MS m/z : 577 $[M+H]^+$ 。

步骤 3: 化合物 3 的合成



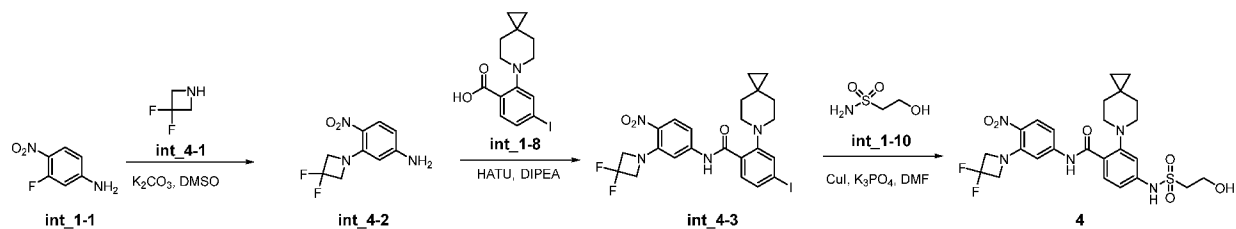
3

将 **int_1-10** (39 mg, 0.310 mmol)、(1S,2S)-N,N-二甲基环己烷 (15 mg, 0.103 mmol)、碘化亚铜 (20 mg, 0.103 mmol) 和磷酸钾 (132 mg, 0.620 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_3-3** (119 mg, 0.207 mmol), 氩气保护下, 反应液加热到 90°C 反应 3 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (50 mg, 收率: 42.3%)。

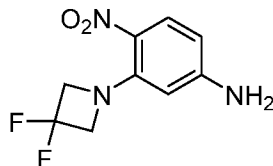
^1H NMR (400 MHz, DMSO- d_6) δ 12.00 (s, 1H), 7.99 (d, $J = 9.0$ Hz, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.65 (d, $J = 2.2$ Hz, 1H), 7.47 (dd, $J = 9.0, 2.1$ Hz, 1H), 7.14 (d, $J = 2.1$ Hz, 1H), 7.01 (dd, $J = 8.5, 2.0$ Hz, 1H), 3.85 (dd, $J = 11.4, 2.6$ Hz, 1H), 3.79 – 3.60 (m, 4H), 3.07 (dd, $J = 29.4, 12.0$ Hz, 2H), 2.95 (t, $J = 5.3$ Hz, 4H), 2.90 – 2.78 (m, 1H), 2.59 (dd, $J = 11.9, 9.8$ Hz, 1H), 1.52 (d, $J = 4.7$ Hz, 4H), 1.10 (d, $J = 6.2$ Hz, 3H), 0.33 (s, 4H)。

ESI-MS m/z : 574 $[M+H]^+$ 。

实施例 4 化合物 4 的合成



步骤 1: 化合物 int_4-2 的合成

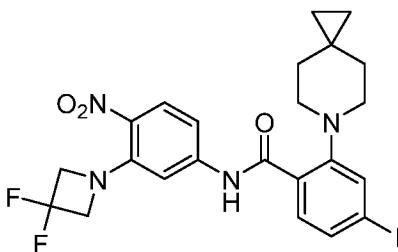


int_4-2

将 **int_1-1** (200 mg, 1.281 mmol) 溶于 DMSO (5 mL) 中, 加入碳酸钾 (710 mg, 5.124 mmol)、**int_4-1** (盐酸盐, 310 mg, 2.562 mmol), 升温至 80 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (300 mg, 收率: 100%)。

ESI-MS m/z : 230 $[M+H]^+$ 。

步骤 2: 化合物 int_4-3 的合成

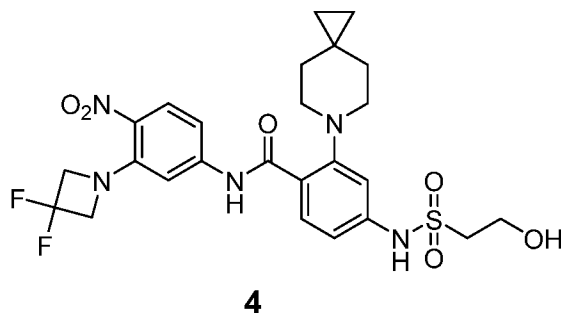


int_4-3

将 **int_1-8** (156 mg, 0.436 mmol) 溶于 DMF (3 mL), 加入 HATU (342 mg, 0.872 mmol)、DIPEA (165 mg, 1.308 mmol) 和 **int_4-2** (100 mg, 0.436 mmol), 反应液 80 °C 搅拌 10 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (130 mg, 收率: 52.6%)。

ESI-MS m/z : 569 $[M+H]^+$ 。

步骤 3: 化合物 4 的合成

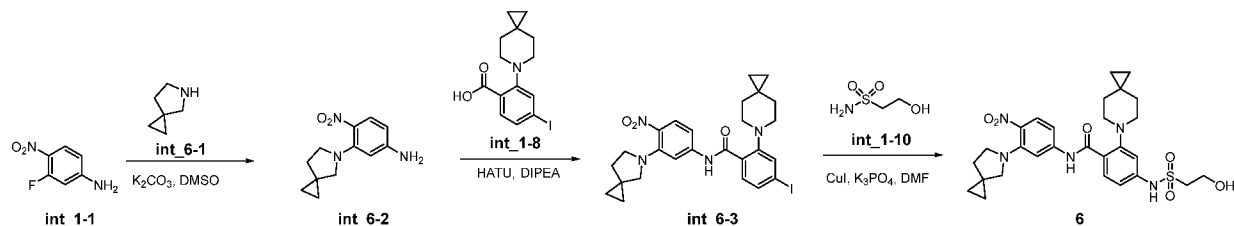


将 **int_1-10** (16 mg, 0.123 mmol)、(1S,2S)-N,N-二甲基环己烷 (9 mg, 0.062 mmol)、碘化亚铜 (12 mg, 0.062 mmol) 和磷酸钾 (80 mg, 0.369 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_4-3** (70 mg, 0.123 mmol), 氩气保护下, 反应液加热到 90 °C 反应 3 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (54 mg, 收率: 77.1%)。

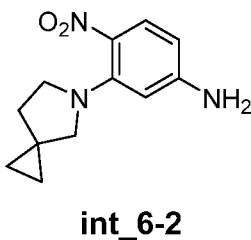
¹H NMR (400 MHz, Chloroform-d) δ 12.85 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.69 (s, 1H), 7.34 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.96 (s, 1H), 6.84 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 11.9 Hz, 4H), 4.16 (s, 2H), 3.34 (t, J = 5.3 Hz, 2H), 3.08 (t, J = 5.3 Hz, 4H), 1.63 (s, 4H), 0.45 (s, 4H)。

ESI-MS m/z : 566 [M+H]⁺。

实施例 5 化合物 6 的合成



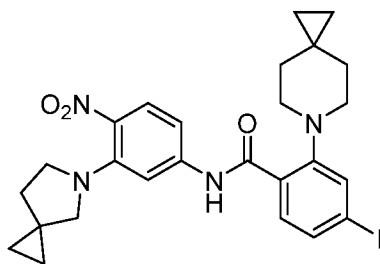
步骤 1: 化合物 **int_6-2** 的合成



将 **int_1-1** (200 mg, 1.281 mmol) 溶于 DMSO (5 mL) 中, 加入碳酸钾 (710 mg, 5.124 mmol)、**int_6-1** (盐酸盐, 171 mg, 1.281 mmol), 升温至 80 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析得到目标产物 (290 mg, 收率: 97.0%)。

ESI-MS m/z : 234 [M+H]⁺。

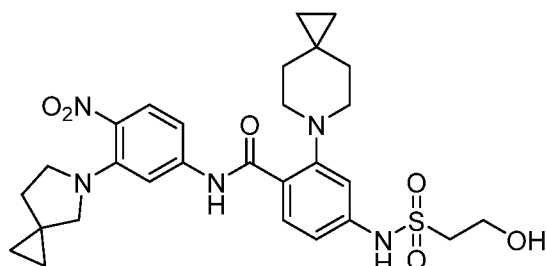
步骤 2: 化合物 **int_6-3** 的合成

**int_6-3**

将 **int_1-8** (100 mg, 0.28 mmol) 溶于 DMF (3 mL), 加入 HATU (342 mg, 0.872 mmol)、DIPEA (165 mg, 1.308 mmol) 和 **int_6-2** (65 mg, 0.28 mmol), 反应液 80°C 搅拌 16 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (70 mg, 收率: 43.8%)。

ESI-MS m/z : 573 $[M+H]^+$ 。

步骤 3: 化合物 6 的合成

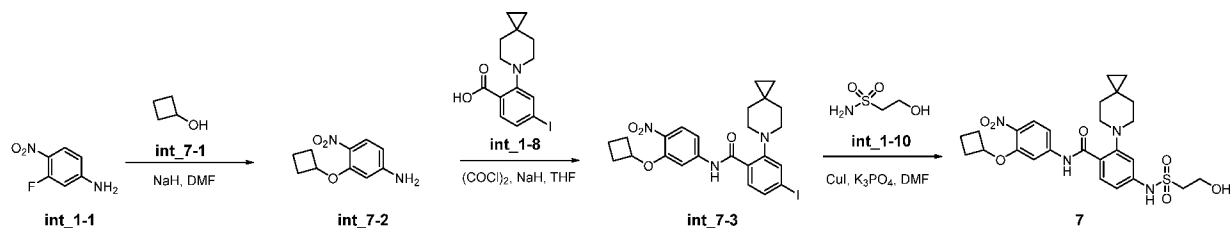
**6**

将 **int_1-10** (16 mg, 0.123 mmol)、(1S,2S)-N,N-二甲基环己烷 (9 mg, 0.062 mmol)、碘化亚铜 (12 mg, 0.062 mmol) 和磷酸钾 (80 mg, 0.369 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_6-3** (70 mg, 0.122 mmol), 氩气保护下, 反应液加热到 90 °C 反应 3 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (45 mg, 收率: 64.7%)。

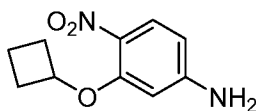
^1H NMR (400 MHz, Chloroform- d) δ 12.71 (s, 1H), 8.20 (d, $J = 8.3$ Hz, 1H), 7.90 – 7.76 (m, 2H), 7.33 (s, 1H), 7.06 (d, $J = 8.3$ Hz, 2H), 6.85 – 6.71 (m, 1H), 4.14 (t, $J = 5.0$ Hz, 2H), 3.46 (t, $J = 6.6$ Hz, 2H), 3.34 (t, $J = 5.1$ Hz, 2H), 3.16 (s, 2H), 3.07 (d, $J = 5.5$ Hz, 4H), 1.90 (t, $J = 6.7$ Hz, 2H), 1.65 (s, 4H), 0.62 (d, $J = 5.3$ Hz, 4H), 0.43 (s, 4H)。

ESI-MS m/z : 570 $[M+H]^+$ 。

实施例 6 化合物 7 的合成



步骤 1: 化合物 int_7-2 的合成

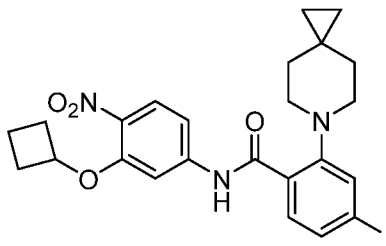


int_7-2

将 int_7-1 (372 mg, 5.17 mmol) 溶于 DMF (30 mL) 中, 氮气保护下 0°C 下加入 NaH (820 mg, 20.5 mmol, 60% 纯度), 反应液于氮气保护下 0°C 反应 1 小时, 加入 int_1-1 (400 mg, 2.564 mmol), 升温至 80 °C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (170 mg, 收率: 32%)。

ESI-MS m/z: 209 [M+H]⁺。

步骤 2: 化合物 int_7-3 的合成

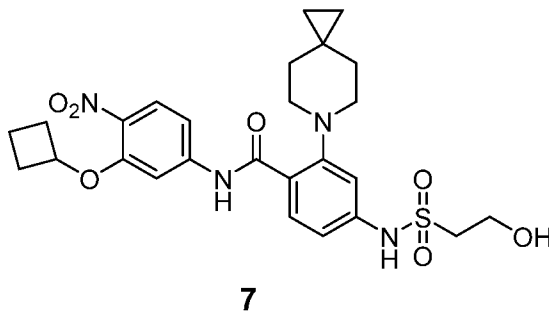


int_7-3

将 int_1-8 (129 mg, 0.361 mmol) 溶于 DCM (2 mL), 加入草酰氯 (1 mL), 反应液于室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 int_7-2 (50 mg, 0.24 mmol) 溶于四氢呋喃 (5 mL) 中, 在冰浴下慢慢加入钠氢 (100 mg), 反应液在室温反应 1 小时, 向反应液中加入制备得到的酰氯产物, 反应液在 40°C 反应 5 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用二氯甲烷萃取 (50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化得到目标产物 (77 mg, 收率: 59%)。

ESI-MS m/z: 548 [M+H]⁺。

步骤 3: 化合物 7 的合成



7

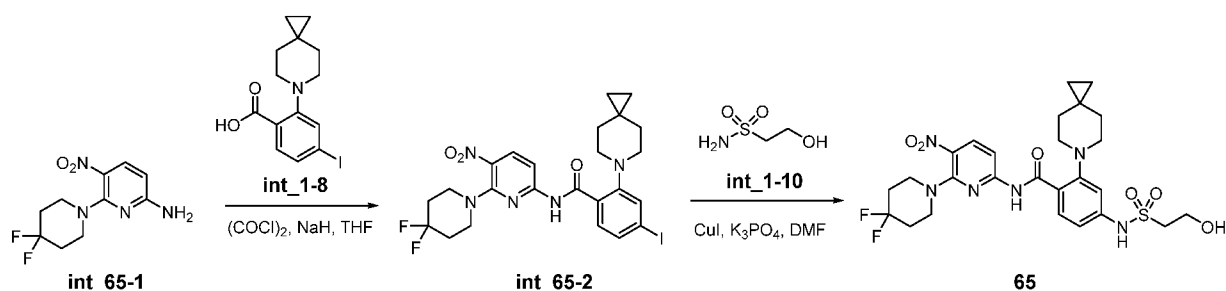
将 int_1-10 (36 mg, 0.29 mmol)、(1S,2S)-N,N-二甲基环己烷 (10 mg, 0.021 mmol)、碘化亚铜 (14

mg, 0.07 mmol)和磷酸钾 (90 mg, 0.42 mmol), 溶解在 DMF (7 mL)中, 氩气置换三次, 加入 **int_7-3** (77 mg, 0.14 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(44 mg, 收率: 57%)。

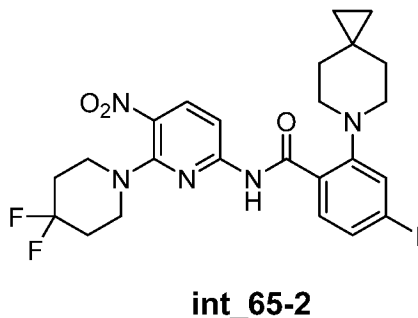
¹H NMR (400 MHz, DMSO-d₆) δ 11.80 (s, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.47 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.79 (t, *J* = 7.2 Hz, 1H), 3.74 (t, *J* = 6.6 Hz, 2H), 2.95 (t, *J* = 5.2 Hz, 4H), 2.22 – 2.04 (m, 2H), 1.91 – 1.61 (m, 2H), 1.49 (t, *J* = 5.0 Hz, 4H), 0.32 (s, 4H)。

ESI-MS *m/z*: 545 [M+H]⁺。

实施例 7 化合物 65 的合成



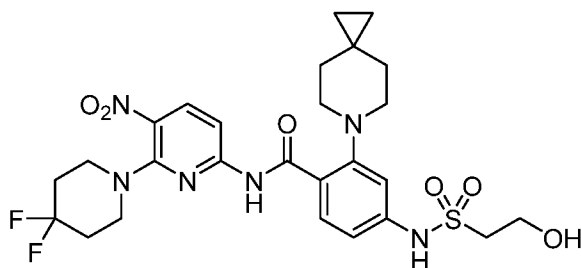
步骤 1: 化合物 **int_65-2** 的合成



将 **int_1-8** (100 mg, 0.279 mmol)溶于 DCM (8 mL), 加入草酰氯 (1 mL), 反应液于室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 **int_65-1** (72 mg, 0.279 mmol)溶于四氢呋喃(5 mL)中, 在冰浴下慢慢加入钠氢 (60 mg), 反应液在室温反应 1 小时, 向反应液中加入制备得到的酰氯产物, 反应液在 40°C反应 12 小时, LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释, 水相用二氯甲烷萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化得到目标产物 (130 mg, 收率: 78%)。

ESI-MS *m/z*: 598 [M+H]⁺。

步骤 2: 化合物 65 的合成



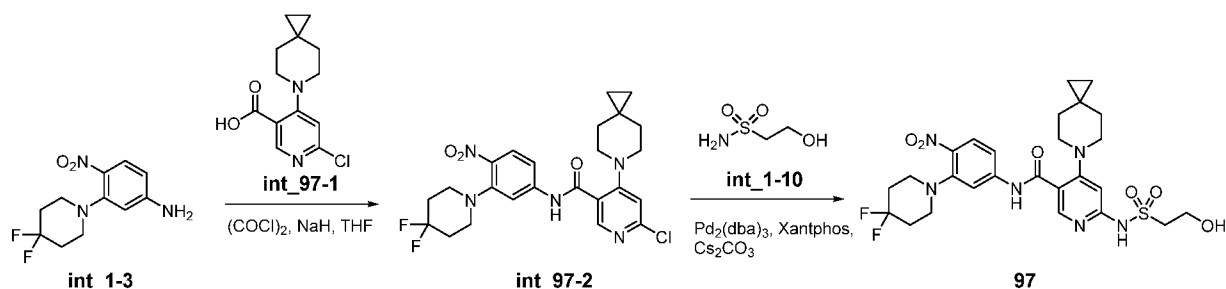
65

将 **int_1-10** (40 mg, 0.325 mmol)、(1*S*,2*S*)-*N,N*-二甲基环己烷 (15 mg, 0.108 mmol)、碘化亚铜 (20 mg, 0.108 mmol) 和磷酸钾 (138 mg, 0.651 mmol), 溶解在 DMF (10 mL) 中, 氩气置换三次, 加入 **int_65-2** (130 mg, 0.217 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (10 mg, 收率: 7.7%)。

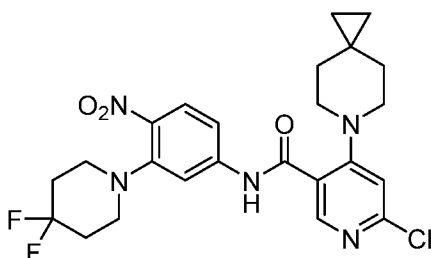
¹H NMR (400 MHz, DMSO-*d*₆) δ 13.70 (s, 1H), 8.44 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.75 (t, *J* = 6.5 Hz, 2H), 3.50 (t, *J* = 5.7 Hz, 4H), 3.33 (s, 2H), 2.99 (t, *J* = 5.2 Hz, 4H), 2.12 (d, *J* = 8.1 Hz, 4H), 1.86 – 1.48 (m, 4H), 0.40 (s, 4H)。

ESI-MS *m/z*: 595 [M+H]⁺。

实施例 8 化合物 97 的合成



步骤 1: 化合物 **int_97-2** 的合成

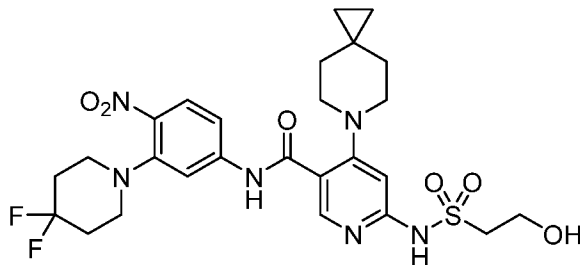
**int_97-2**

将 **int_97-1** (100 mg, 0.375 mmol) 溶于 DCM (8 mL), 加入草酰氯 (1 mL), 反应液于室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 **int_1-3** (96 mg, 0.375 mmol) 溶于四氢呋喃 (5 mL) 中, 在冰浴下慢慢加入钠氢 (60 mg), 反应液在室温反应 1 小时, 向反应液中加入制备得到的酰氯产物, 反应液在 40°C 反应 12 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用二氯甲烷萃取 (50 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化

得到目标产物 (128 mg, 收率: 68.1%)。

ESI-MS m/z : 506 $[M+H]^+$ 。

步骤 2: 化合物 97 的合成



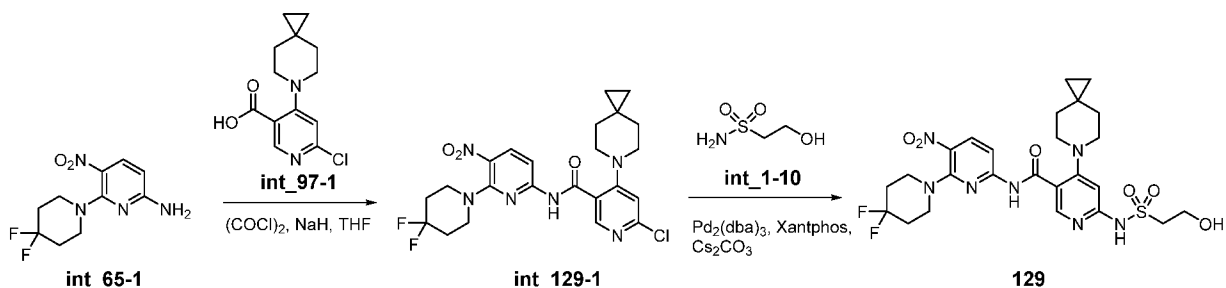
97

将 **int_1-10** (52 mg, 0.414 mmol)、碳酸铯 (135 mg, 0.414 mmol)、 $Pd_2(dba)_3$ (12 mg, 0.0138 mmol)、XantPhos (19 mg, 0.033 mmol) 和 **int_97-2** (128 mg, 0.253 mmol) 溶解在二氧六环 (10 mL) 中, 氩气置换三次, 氩气保护下, 反应液加热到 90 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (10 mg, 收率: 6.7%)。

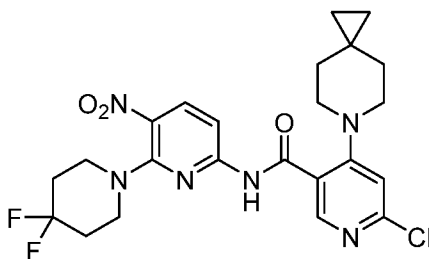
^1H NMR (400 MHz, DMSO- d_6) δ 10.69 (s, 1H), 7.99 (d, $J = 9.2$ Hz, 2H), 7.72 (s, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 6.53 (d, $J = 7.8$ Hz, 1H), 3.74 (t, $J = 6.9$ Hz, 2H), 3.11 (dd, $J = 13.5, 6.6$ Hz, 8H), 2.09 (d, $J = 15.1$ Hz, 4H), 1.37 (m, 4H), 0.28 (s, 4H)。

ESI-MS m/z : 595 $[M+H]^+$ 。

实施例 9 化合物 129 的合成



步骤 1: 化合物 int_129-1 的合成



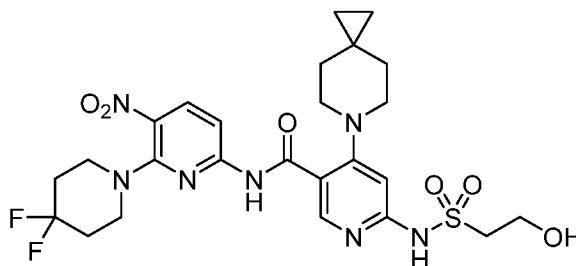
int_129-1

将 **int_97-1** (100 mg, 0.375 mmol) 溶于 DCM (8 mL), 加入草酰氯 (1 mL), 反应液于室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 **int_65-1** (96 mg, 0.375 mmol) 溶于四氢呋喃 (5 mL) 中, 在

冰浴下慢慢加入钠氢 (60 mg)，反应液在室温反应 1 小时，向反应液中加入制备得到的酰氯产物，反应液在 40°C 反应 12 小时，LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释，水相用二氯甲烷萃取(50 mL*3)，有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化得到目标产物 (140 mg, 收率: 74.4%)。

ESI-MS m/z : 507 $[M+H]^+$ 。

步骤 2: 化合物 129 的合成



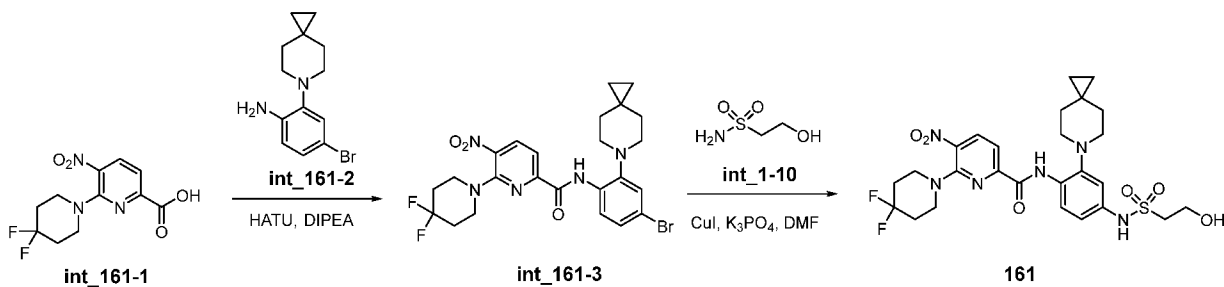
129

将 **int_1-10** (52 mg, 0.414 mmol)、碳酸铯 (135 mg, 0.414 mmol)、 $Pd_2(dba)_3$ (12 mg, 0.0138 mmol)、XantPhos (19 mg, 0.033 mmol) 和 **int_129-1** (140 mg, 0.276 mmol) 溶解在二氧六环 (10 mL) 中，氩气置换三次，氩气保护下，反应液加热到 90 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温，将反应液旋干，柱层析纯化得固体 (20 mg, 收率: 12.2%)。

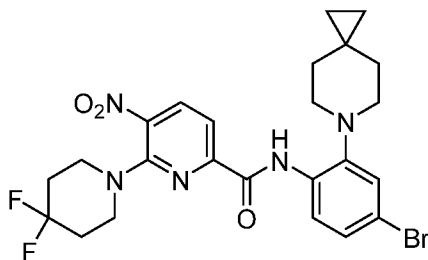
^1H NMR (400 MHz, DMSO- d_6) δ 12.69 (s, 1H), 8.57 (s, 1H), 8.39 (d, $J = 9.0$ Hz, 1H), 7.82 (d, $J = 8.9$ Hz, 1H), 6.33 (s, 1H), 4.80 (s, 1H), 3.65 (t, $J = 7.0$ Hz, 2H), 3.48 (t, $J = 5.7$ Hz, 4H), 3.17–3.12 (m, 2H), 2.93 (t, $J = 5.2$ Hz, 4H), 2.08 (d, $J = 14.6$ Hz, 4H), 1.65 (s, 4H), 0.35 (s, 4H)。

ESI-MS m/z : 596 $[M+H]^+$ 。

实施例 10 化合物 161 的合成



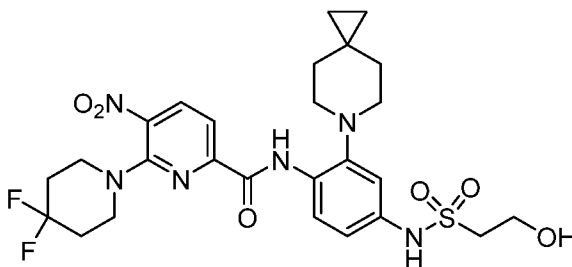
步骤 1: 化合物 **int_161-3** 的合成

**int_161-3**

将 **int_161-1** (100 mg, 0.348 mmol) 溶于 DMF (4 mL), 加入 HATU (264 mg, 0.696 mmol)、DIPEA (163 mg, 1.264 mmol) 和 **int_161-2** (98 mg, 0.348 mmol), 反应液 60°C 搅拌 4 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (150 mg, 收率: 78%)。

ESI-MS m/z : 550 $[M+H]^+$ 。

步骤 2: 化合物 161 的合成

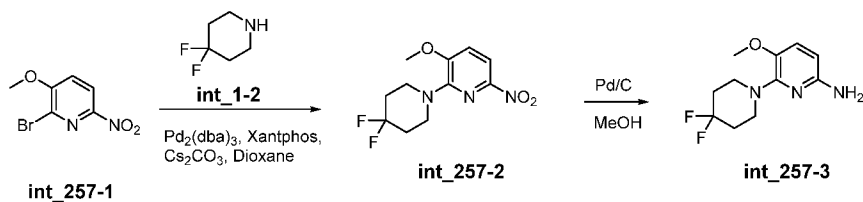
**161**

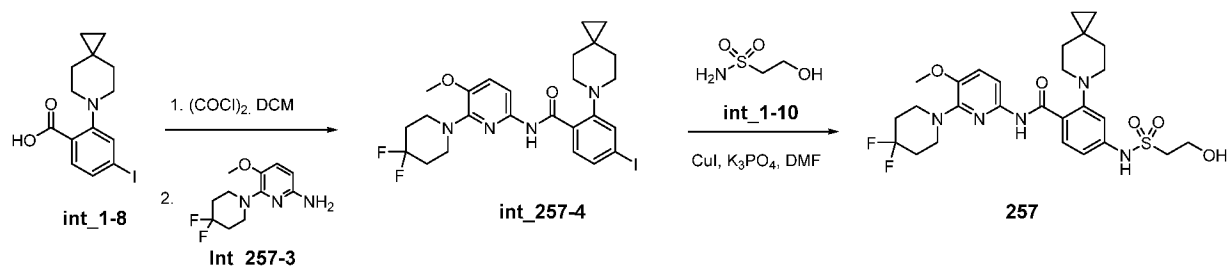
将 **int_1-10** (24 mg, 0.191 mmol)、肌氨酸 (6 mg, 0.064 mmol)、碘化亚铜 (12 mg, 0.062 mmol) 和磷酸钾 (80 mg, 0.369 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_161-3** (70 mg, 0.127 mmol), 氩气保护下, 反应液微波加热到 130°C 反应 3 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (22 mg, 收率: 19%)。

^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 1H), 8.54 (d, $J = 8.2$ Hz, 1H), 8.32 (d, $J = 8.8$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.02 (dd, $J = 8.8, 2.4$ Hz, 1H), 3.74 (t, $J = 6.7$ Hz, 2H), 3.64 (t, $J = 5.8$ Hz, 4H), 3.21 (t, $J = 6.7$ Hz, 2H), 2.83 (t, $J = 5.3$ Hz, 4H), 2.25 – 2.13 (m, 4H), 1.53 (s, 4H), 0.37 (s, 4H)。

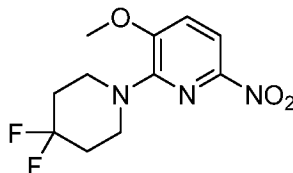
ESI-MS m/z : 595 $[M+H]^+$ 。

实施例 11 化合物 257 的合成





步骤 1: 化合物 int_257-2 的合成

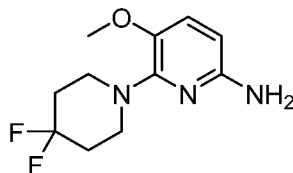


int_257-2

将 **int_257-1** (25 g, 107 mmol) 溶于二氧六环(400 mL)中, 加入 **int_1-2** (20 g, 161 mmol)、Pd₂(dba)₃ (5 g, 5.4 mmol)、Xantphos (3 g, 5.4 mmol) 和 Cs₂CO₃ (104 g, 321 mmol), 氮气保护下升温至 100 °C 反应 16 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 向滤液中加入水(500 mL)稀释, 水相用乙酸乙酯萃取(500 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析(SiO₂, 正己烷/乙酸乙酯 = 5:1)得到目标产物 (5.5 g, 收率: 19%)。

ESI-MS m/z: 274 [M+H]⁺。

步骤 2: 化合物 int_257-3 的合成

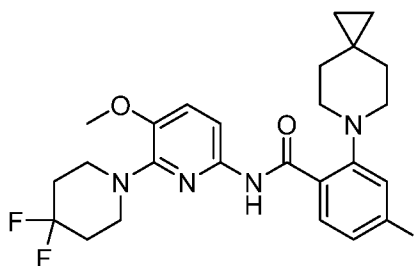


int_257-3

将 **int_257-2** (5.5 g, 20 mmol) 溶于甲醇 (100 mL), 加入 Pd/C (2.00 g, 10% purity), 反应体系用氢气置换 3 次, 反应液在 60 °C 于氢气氛围下反应 16 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (4.2 g, 收率: 86%)。粗产物可直接用于下一步反应。

ESI-MS m/z: 244 [M+H]⁺。

步骤 3: 化合物 int_257-4 的合成

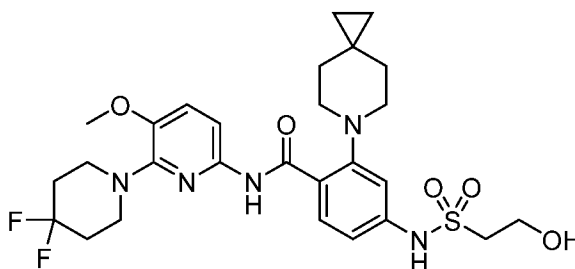
**int_257-4**

将 **int_1-8** (1.2 g, 3.36 mmol) 溶于 DCM (50 mL), 加入草酰氯 (888.4 mg, 7 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_257-3** (0.7 g, 3.4 mmol) 溶于四氢呋喃 (40 mL), 氮气保护下, 加入 NaH (720 mg, 18 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 5 : 1) 纯化得固体(1.2 g, 收率: 71%)。

ESI-MS m/z : 583 [M+H]⁺。

步骤 4: 化合物 **257** 的合成

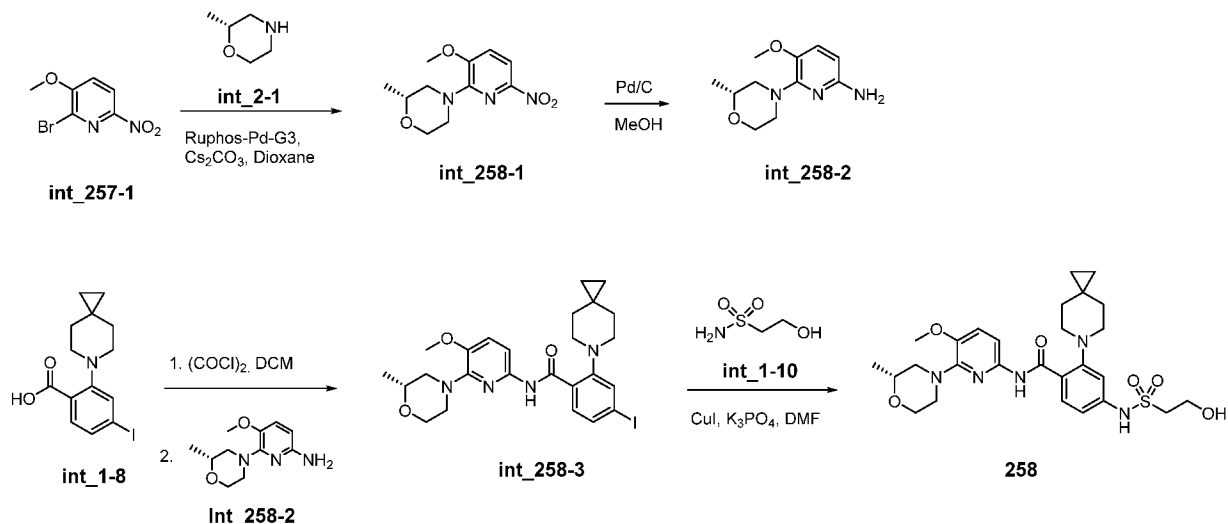
**257**

将 **int_257-4** (1 g, 1.7 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (122 mg, 0.85 mmol)、碘化亚铜 (164 mg, 0.85 mmol) 和磷酸钾 (1.1 g, 5.1 mmol), 溶解在 DMF (20 mL) 中, 氩气置换三次, 加入 **int_1-10** (0.43 g, 3.4 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析(SiO₂, 正己烷/乙酸乙酯 = 1:1) 纯化得固体(0.77 g, 收率: 77%)。

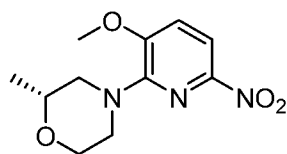
¹H NMR (400 MHz, DMSO-d₆) δ 12.81 (s, 1H), 10.16 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.6, 2.1 Hz, 1H), 4.93 (s, 1H), 3.81 (s, 3H), 3.76 (t, J = 6.5 Hz, 2H), 3.52 (t, J = 5.6 Hz, 4H), 3.35 (t, J = 6.5 Hz, 2H), 2.97 (t, J = 5.4 Hz, 4H), 2.09 (td, J = 14.1, 6.7 Hz, 4H), 1.72 (s, 4H), 0.38 (s, 4H)。

ESI-MS m/z : 580 [M+H]⁺。

实施例 12 化合物 **258** 的合成



步骤 1: 化合物 int_258-1 的合成

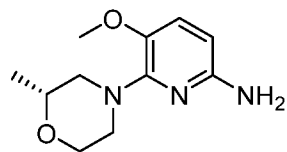


int_258-1

将 int_257-1 (1 g, 4.29 mmol) 溶于二氧六环(30 mL)中, 加入 int_2-1 (480 mg, 4.72 mmol)、Ruphos-Pd-G3 (360 mg, 0.429 mmol) 和 Cs₂CO₃ (2.8 g, 8.58 mmol), 氮气保护下升温至 100℃ 反应 12 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 向滤液中加入水(100 mL)稀释, 水相用乙酸乙酯萃取(100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析(SiO₂, 正己烷/乙酸乙酯 = 5:1)得到目标产物 (780 mg, 收率: 71.8%)。

ESI-MS m/z: 254 [M+H]⁺。

步骤 2: 化合物 int_258-2 的合成

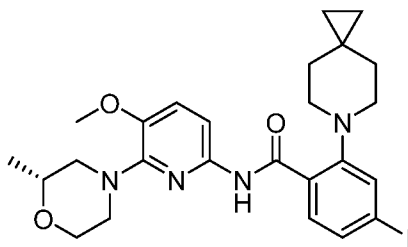


int_258-2

将 int_258-1 (780 mg, 3.08 mmol) 溶于甲醇 (20 mL), 加入 Pd/C (200 mg, 10% purity), 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 12 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (550 mg, 收率: 80%)。粗产物可直接用于下一步反应。

ESI-MS m/z: 224 [M+H]⁺。

步骤 3: 化合物 int_258-3 的合成

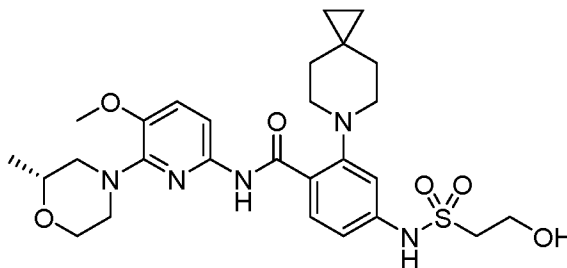
**int_258-3**

将 **int_1-8** (190 mg, 0.532 mmol) 溶于 DCM (10 mL), 加入草酰氯 (888.4 mg, 7 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_258-2** (120 mg, 0.532 mmol) 溶于四氢呋喃 (10 mL), 氮气保护下, 加入 NaH (72 mg, 1.8 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 2 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 5 : 1) 纯化得固体(250 mg, 收率: 82.7%)。

ESI-MS m/z : 563 $[M+H]^+$ 。

步骤 4: 化合物 258 的合成

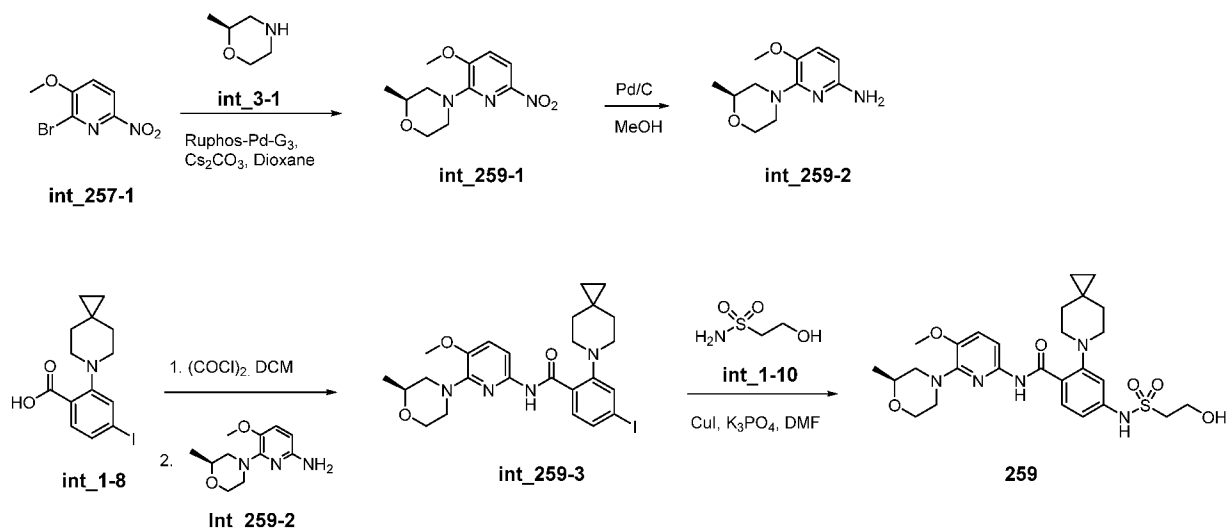
**258**

将 **int_258-3** (250 mg, 0.444 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (32 mg, 0.222 mmol)、碘化亚铜 (42 mg, 0.222 mmol) 和磷酸钾 (282 mg, 1.332 mmol), 溶解在 DMF (20 mL) 中, 氩气置换三次, 加入 **int_1-10** (111 mg, 0.888 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(150 mg, 收率: 60.4%)。

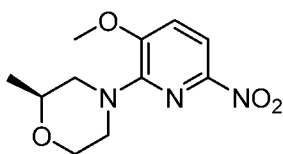
¹H NMR (400 MHz, DMSO-d₆) δ 12.77 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.09 (dd, J = 8.6, 2.1 Hz, 1H), 3.86 – 3.72 (m, 6H), 3.65 (td, J = 11.7, 3.0 Hz, 2H), 2.95 (d, J = 5.4 Hz, 4H), 2.76 (td, J = 12.3, 3.3 Hz, 1H), 2.51 (d, J = 12.9 Hz, 2H), 1.71 (s, 4H), 1.12 (d, J = 6.2 Hz, 3H), 0.36 (s, 4H)。

ESI-MS m/z : 560 $[M+H]^+$ 。

实施例 13 化合物 259 的合成



步骤 1: 化合物 int_259-1 的合成

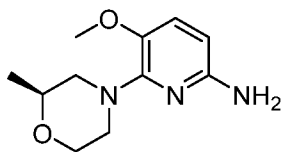


int_259-1

将 **int_257-1** (1 g, 4.29 mmol) 溶于二氧六环(30 mL)中, 加入 **int_3-1** (480 mg, 4.72 mmol)、Ruphos-Pd-G3 (360 mg, 0.429 mmol) 和 Cs_2CO_3 (2.7 g, 8.38 mmol), 氮气保护下升温至 100°C 反应 12 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 向滤液中加入水(100 mL)稀释, 水相用乙酸乙酯萃取(100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析(SiO_2 , 正己烷/乙酸乙酯 = 5:1)得到目标产物 (750 mg, 收率: 69.4%)。

ESI-MS m/z : 254 $[\text{M}+\text{H}]^+$ 。

步骤 2: 化合物 int_259-2 的合成

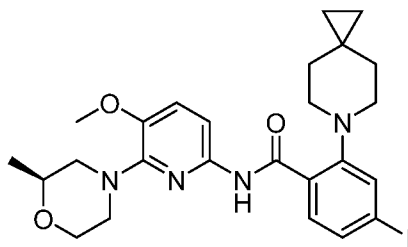


int_259-2

将 **int_259-1** (750 mg, 2.964 mmol) 溶于甲醇 (20 mL), 加入 Pd/C (200 mg, 10% purity), 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 12 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (560 mg, 收率: 84.7%)。粗产物可直接用于下一步反应。

ESI-MS m/z : 224 $[\text{M}+\text{H}]^+$ 。

步骤 3: 化合物 int_259-3 的合成

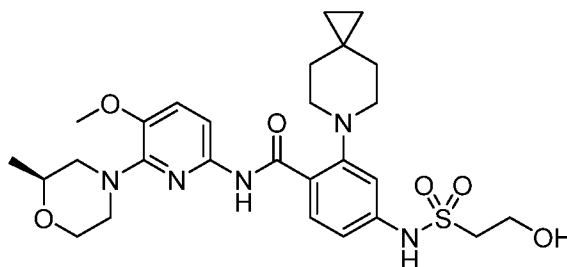
**int_259-3**

将 **int_1-8** (335 mg, 0.938 mmol) 溶于 DCM (10 mL), 加入草酰氯 (888.4 mg, 7 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_259-2** (200 mg, 0.893 mmol) 溶于四氢呋喃 (10 mL), 氮气保护下, 加入 NaH (170 mg, 4.465 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 2 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO_2 , 正己烷/乙酸乙酯 = 5 : 1) 纯化得固体 (340 mg, 收率: 67.7%)。

ESI-MS m/z : 563 $[\text{M}+\text{H}]^+$ 。

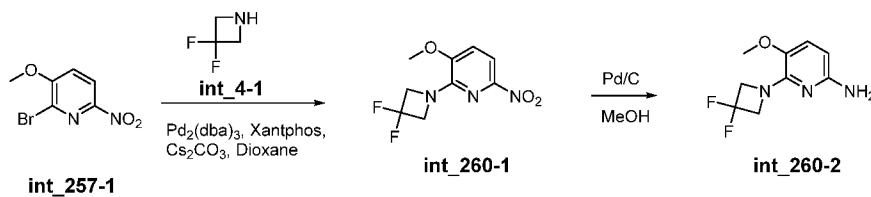
步骤 4: 化合物 259 的合成

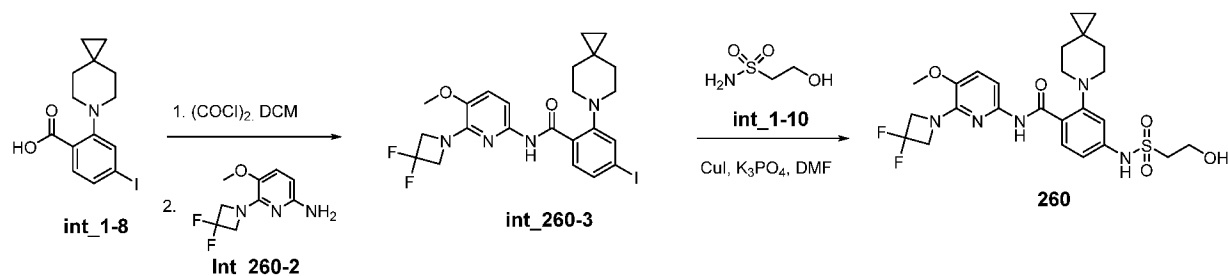
**259**

将 **int_259-3** (340 mg, 0.604 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (44 mg, 0.302 mmol)、碘化亚铜 (58 mg, 0.302 mmol) 和磷酸钾 (384 mg, 1.810 mmol), 溶解在 DMF (15 mL) 中, 氩气置换三次, 加入 **int_1-10** (151 mg, 1.210 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (150 mg, 收率: 44.4%)。

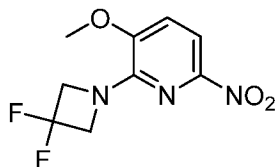
ESI-MS m/z : 560 $[\text{M}+\text{H}]^+$ 。

实施例 14 化合物 260 的合成





步骤 1: 化合物 int_260-1 的合成

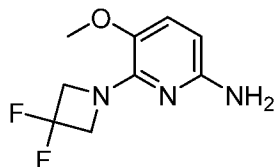


int_260-1

将 int_257-1 (200 mg, 0.858 mmol) 溶于二氧六环 (15 mL) 中, 加入 int_4-1 (盐酸盐, 167 mg, 1.287 mmol)、Pd₂(dba)₃ (78 mg, 0.086 mmol)、Xantphos (49 mg, 0.086 mmol) 和 Cs₂CO₃ (839 mg, 2.575 mmol), 氮气保护下升温至 100°C 反应 12 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 向滤液中加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (80 mg, 收率: 36.7%)。

ESI-MS m/z: 246 [M+H]⁺。

步骤 2: 化合物 int_260-2 的合成

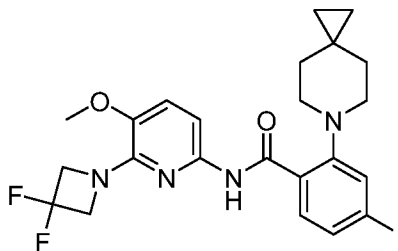


int_260-2

将 int_260-1 (80 mg, 0.858 mmol) 溶于甲醇 (10 mL), 加入 Pd/C (20 mg, 10% purity), 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 12 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (60 mg, 收率: 89.5%)。粗产物可直接用于下一步反应。

ESI-MS m/z: 216 [M+H]⁺。

步骤 3: 化合物 int_260-3 的合成

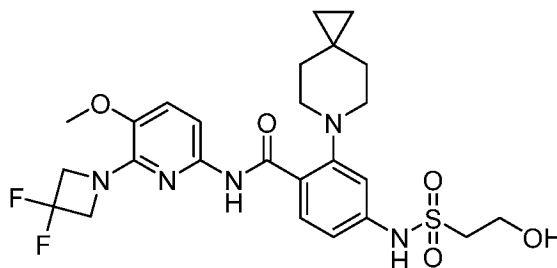
**int_260-3**

将 **int_1-8** (95 mg, 0.266 mmol) 溶于 DCM (10 mL), 加入草酰氯 (380.7 mg, 3 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_260-2** (60 mg, 0.279 mmol) 溶于四氢呋喃 (5 mL), 氮气保护下, 加入 NaH (100 mg, 4.166 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 2 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 5 : 1)纯化得固体(80 mg, 收率: 51.9%)。

ESI-MS m/z : 555 $[M+H]^+$ 。

步骤 4: 化合物 260 的合成

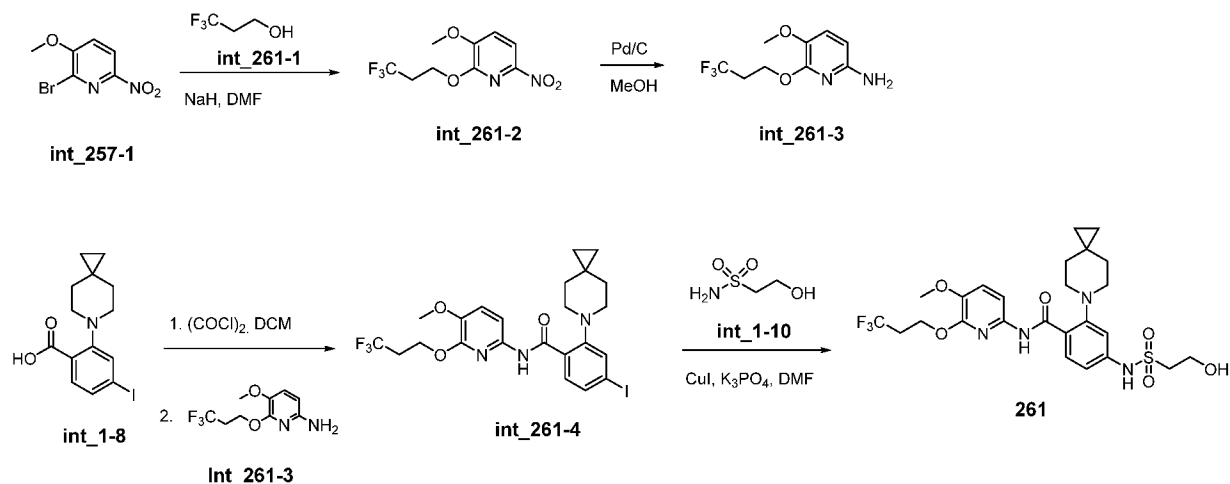
**260**

将 **int_260-3** (80 mg, 0.144 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (11 mg, 0.072 mmol)、碘化亚铜 (14 mg, 0.072 mmol) 和磷酸钾 (92 mg, 0.433 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_1-10** (36 mg, 0.289 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(40 mg, 收率: 50.6%)。

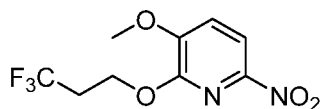
¹H NMR (400 MHz, DMSO-d₆) δ 13.03 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 2.1 Hz, 1H), 7.09 (dd, J = 8.6, 2.1 Hz, 1H), 4.40 (t, J = 12.6 Hz, 4H), 3.74 (d, J = 3.4 Hz, 5H), 3.33 (m, 2H), 2.94 (t, J = 5.5 Hz, 4H), 1.94 – 1.58 (m, 4H), 0.37 (s, 4H)。

ESI-MS m/z : 552 $[M+H]^+$ 。

实施例 15 化合物 261 的合成



步骤 1: 化合物 int_261-2 的合成

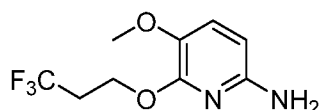


int_261-2

将 **int_261-1** (300 mg, 2.618 mmol) 溶于 DMF (30 mL) 中, 氮气保护下 0°C 下加入 NaH (208 mg, 5.2 mmol, 60% 纯度), 反应液于氮气保护下 0°C 反应 1 小时, 加入 **int_257-1** (610 mg, 2.618 mmol), 升温至 80°C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析得到目标产物 (500 mg, 收率: 71.8%)。

ESI-MS m/z : 267 $[M+H]^+$ 。

步骤 2: 化合物 int_261-3 的合成

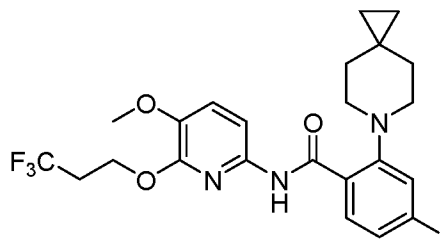


int_261-3

将 **int_261-2** (500 mg, 1.880 mmol) 溶于甲醇 (20 mL), 加入 Pd/C (50 mg, 10% purity), 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 12 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (410 mg, 收率: 92.3%)。粗产物可直接用于下一步反应。

ESI-MS m/z : 237 $[M+H]^+$ 。

步骤 3: 化合物 int_261-4 的合成

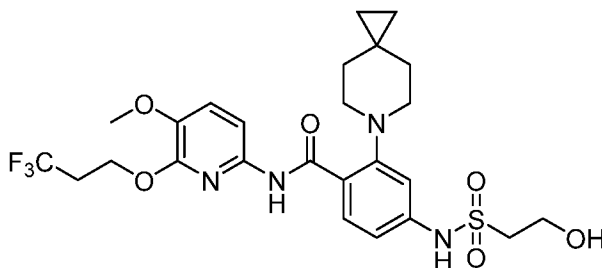
**int_261-4**

将 **int_1-8** (682 mg, 1.910 mmol) 溶于 DCM (10 mL), 加入草酰氯 (482 mg, 3 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_261-3** (450 mg, 1.910 mmol) 溶于四氢呋喃 (10 mL), 氮气保护下, 加入 NaH (366 mg, 9.550 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 2 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 5 : 1) 纯化得固体(500 mg, 收率: 45.9%)。

ESI-MS *m/z*: 576 [M+H]⁺。

步骤 4: 化合物 261 的合成

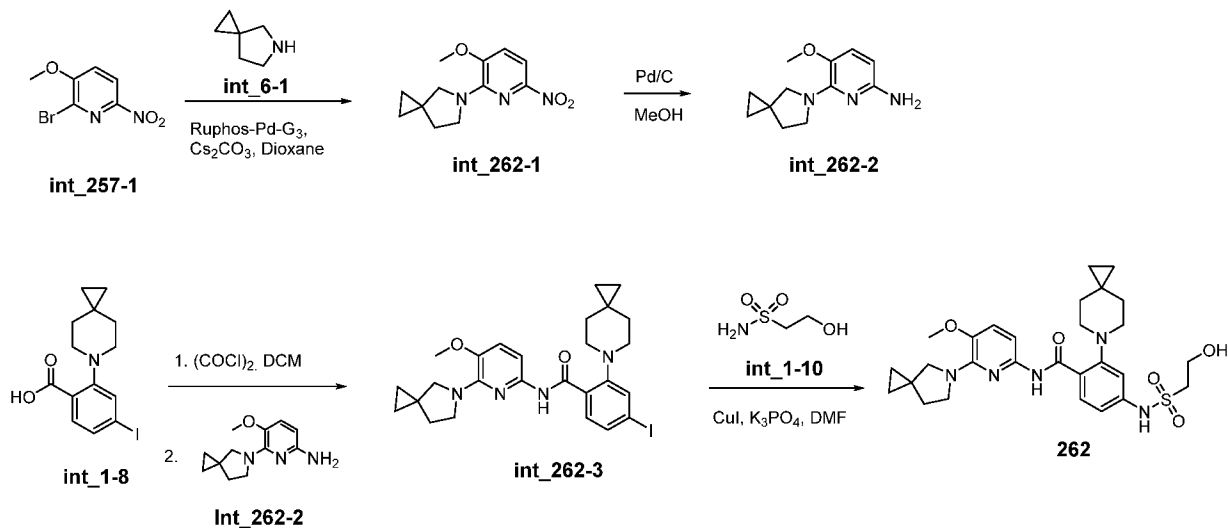
**261**

将 **int_261-4** (100 mg, 0.174 mmol), (1*S*,2*S*)-*N,N'*-二甲基-1,2-环己二胺 (13 mg, 0.087 mmol), 碘化亚铜 (17 mg, 0.087 mmol) 和磷酸钾 (111 mg, 0.523 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_1-10** (44 mg, 0.348 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(25 mg, 收率: 25.3%)。

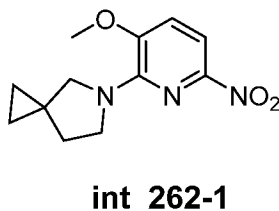
¹H NMR (400 MHz, Methanol-d₄) δ 8.11 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.27 (m, 2H), 7.14 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.58 (t, *J* = 6.3 Hz, 2H), 3.94 (t, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 3.36 (t, *J* = 6.2 Hz, 2H), 3.07 (t, *J* = 5.3 Hz, 4H), 2.75 (qt, *J* = 10.9, 6.3 Hz, 2H), 1.79 (s, 4H), 0.42 (s, 4H)。

ESI-MS *m/z*: 573 [M+H]⁺。

实施例 16 化合物 262 的合成



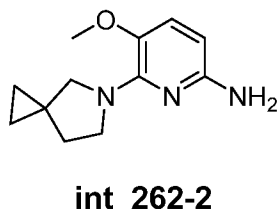
步骤 1: 化合物 int 262-1 的合成



将 **int_257-1** (348 mg, 1.5 mmol)溶于二氧六环(15 mL)中, 加入 **int_6-1** (盐酸盐, 200 mg, 1.5 mmol)、Ruphos-Pd-G3 (125 mg, 0.15 mmol)和 Cs₂CO₃ (977 mg, 3 mmol), 氮气保护下升温至 100 °C 反应 12 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 向滤液中加入水(50 mL)稀释, 水相用乙酸乙酯萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析得到目标产物 (320 mg, 收率: 68.6%)。

ESI-MS m/z : 250 $[M+H]^+$

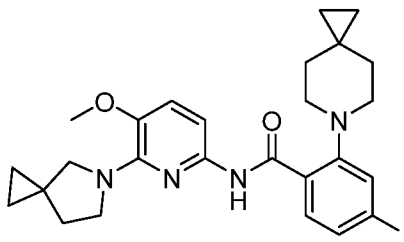
步骤 2: 化合物 int 262-2 的合成



将 **int_262-1** (320 mg, 1.28 mmol)溶于甲醇 (20 mL), 加入 Pd/C (30 mg, 10% purity), 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 12 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (165 mg, 收率: 57.8%)。粗产物可直接用于下一步反应。

ESI-MS m/z : 220 $[M+H]^+$

步骤 3: 化合物 int 262-3 的合成

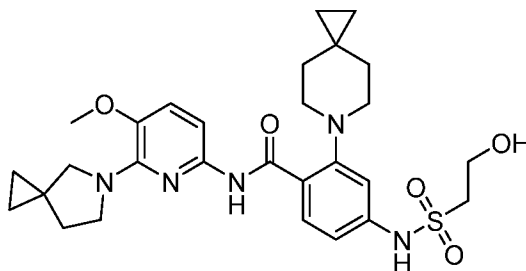
**int_262-3**

将 **int_1-8** (270 mg, 0.752 mmol) 溶于 DCM (10 mL), 加入草酰氯 (380.7 mg, 3 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_262-2** (165 mg, 0.752 mmol) 溶于四氢呋喃 (5 mL), 氮气保护下, 加入 NaH (150 mg, 3.76 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 2 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 5 : 1) 纯化得固体(170 mg, 收率: 40.4%)。

ESI-MS m/z : 559 $[M+H]^+$ 。

步骤 4: 化合物 262 的合成

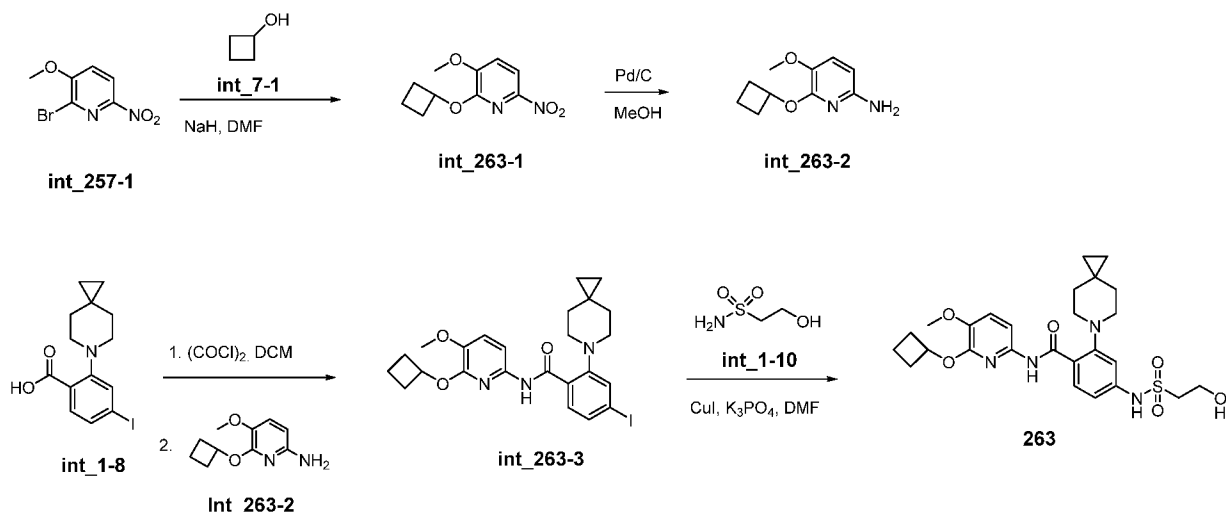
**262**

将 **int_262-3** (170 mg, 0.304 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (22 mg, 0.152 mmol)、碘化亚铜 (29 mg, 0.152 mmol) 和磷酸钾 (193 mg, 912 mmol), 溶解在 DMF (10 mL) 中, 氩气置换三次, 加入 **int_1-10** (76 mg, 0.608 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(120 mg, 收率: 71%)。

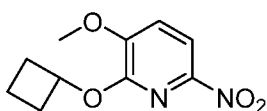
¹H NMR (400 MHz, DMSO-d₆) δ 12.75 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.6, 2.1 Hz, 1H), 3.74 (dt, J = 7.0, 3.6 Hz, 4H), 3.70 (s, 3H), 3.47 (s, 2H), 2.93 (d, J = 5.2 Hz, 4H), 1.79 (s, 6H), 0.57 (s, 4H), 0.33 (s, 4H)。

ESI-MS m/z : 556 $[M+H]^+$ 。

实施例 17 化合物 263 的合成



步骤 1: 化合物 int_263-1 的合成

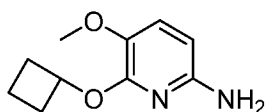


int_263-1

将 int_7-1 (460 mg, 1.974 mmol) 溶于 DMF (20 mL) 中, 氮气保护下 0°C 下加入 NaH (510 mg, 3.948 mmol, 60% 纯度), 反应液于氮气保护下 0°C 反应 1 小时, 加入 int_257-1 (1.5 g, 1.974 mmol), 升温至 80°C 反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (300 mg, 收率: 67.9%)。

ESI-MS m/z: 225 [M+H]⁺。

步骤 2: 化合物 int_263-2 的合成

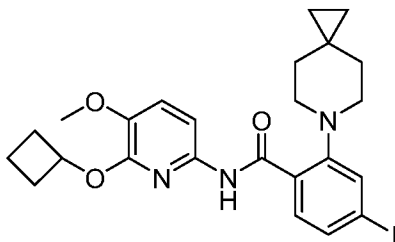


int_263-2

将 int_263-1 (300 mg, 1.339 mmol) 溶于甲醇 (30 mL), 加入 Pd/C (30 mg, 10% purity), 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 12 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (255 mg, 收率: 98%)。粗产物可直接用于下一步反应。

ESI-MS m/z: 195 [M+H]⁺。

步骤 3: 化合物 int_263-3 的合成

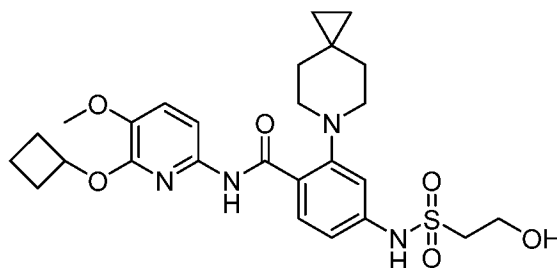
**int_263-3**

将 **int_1-8** (552 mg, 1.546 mmol) 溶于 DCM (10 mL), 加入草酰氯 (482 mg, 3 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_263-2** (300 mg, 1.546 mmol) 溶于四氢呋喃 (10 mL), 氮气保护下, 加入 NaH (180 mg, 4.5 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 2 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (510 mg, 收率: 63.8%)。

ESI-MS m/z : 534 $[M+H]^+$ 。

步骤 4: 化合物 263 的合成

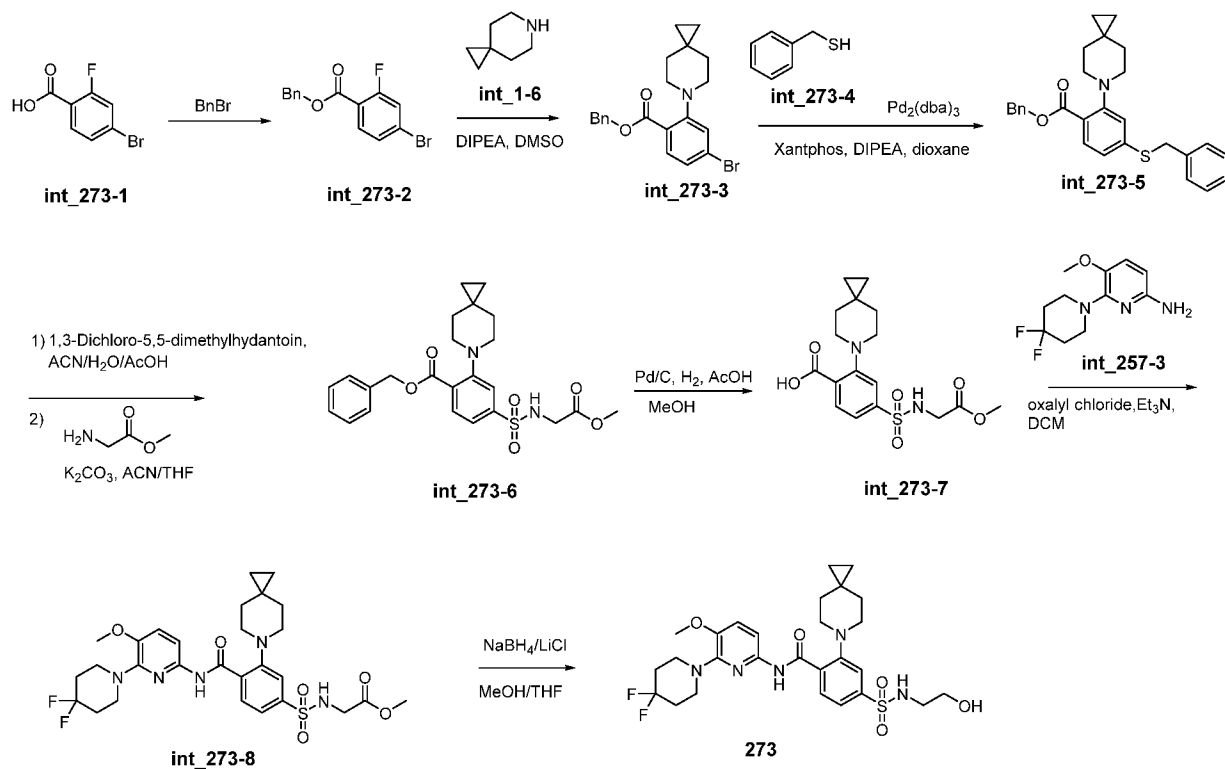
**263**

将 **int_263-3** (150 mg, 0.281 mmol), (1S,2S)-N,N'-二甲基-1,2-环己二胺 (21 mg, 0.141 mmol), 碘化亚铜 (27 mg, 0.141 mmol) 和磷酸钾 (180 mg, 0.843 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_1-10** (70 mg, 0.562 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (55 mg, 收率: 36.9%)。

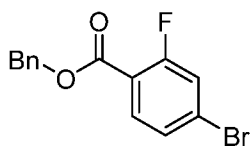
^1H NMR (400 MHz, DMSO- d_6) δ 12.63 (s, 1H), 8.04 (d, $J = 8.6$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.34 (d, $J = 8.6$ Hz, 1H), 7.24 (d, $J = 2.1$ Hz, 1H), 7.09 (dd, $J = 8.6, 2.1$ Hz, 1H), 5.31 – 5.19 (m, 1H), 3.74 (d, $J = 4.5$ Hz, 5H), 2.96 (t, $J = 5.3$ Hz, 4H), 2.48 – 2.39 (m, 2H), 2.08 (dtd, $J = 12.5, 10.0, 8.0$ Hz, 2H), 1.80 – 1.53 (m, 6H), 0.41 (s, 4H)。

ESI-MS m/z : 531 $[M+H]^+$ 。

实施例 18 化合物 273 的合成



步骤 1: 化合物 int_273-2 的合成

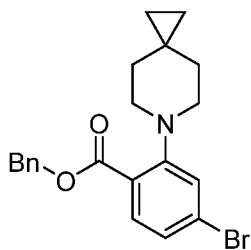


int_273-2

将 **int_273-1** (5 g, 22.8 mmol) 溶于 DMF (50 mL) 中, 加入碳酸钠 (4.9 g, 46.2 mmol), 苄溴 (5.9 g, 34.5 mmol), 室温反应 24 小时, LC-MS 监测显示反应结束。向反应液加入水 (200 mL) 稀释, 水相用乙酸乙酯萃取 (200 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析 (SiO_2 , 正己烷/乙酸乙酯 = 30:1) 得到目标产物 (6.9 g, 收率: 99%)。

ESI-MS m/z : 309 $[\text{M}+\text{H}]^+$ 。

步骤 2: 化合物 int_273-3 的合成



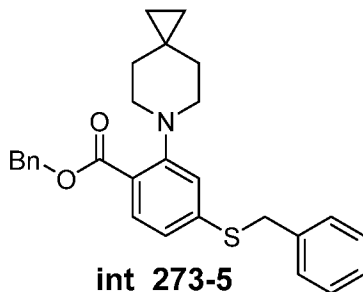
int_273-3

将 **int_273-2** (5 g, 16.2 mmol) 溶于 DMSO (20 mL) 中, 加入 DIPEA (6.3 g, 48.8 mmol) 和 **int_1-6** (盐酸盐, 4.8 g, 32.5 mmol), 升温至 100°C 反应 16 小时, LC-MS 监测显示反应结束。向反应液加入水

(100 mL)稀释, 水相用乙酸乙酯萃取(100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 粗产物经柱层析(SiO_2 , 正己烷/乙酸乙酯 = 30:1)得到目标产物 (6.1 g, 收率: 92%)。

ESI-MS m/z : 400 $[\text{M}+\text{H}]^+$ 。

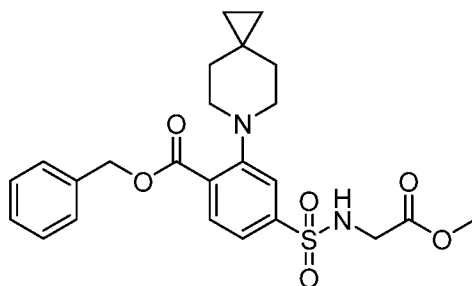
步骤 3: 化合物 int_273-5 的合成



将 **int_273-3** (6.1 g, 15.3 mmol)溶于二氧六环(40 mL)中, 加入苄硫醇 (5.7 g, 45.9 mmol)、 $\text{Pd}_2(\text{dba})_3$ (2 g, 2.2 mmol)、Xantphos (2 g, 3.6 mmol)和 DIPEA (7.9 g, 61.2 mmol), 氮气保护下升温至 100 °C 反应 16 小时, LC-MS 监测显示反应结束。向反应液加入水(100 mL)稀释, 水相用乙酸乙酯萃取(100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物, 粗产物经柱层析(SiO_2 , 正己烷/乙酸乙酯 = 10:1)得到目标产物 (6.7 g, 收率: 97%)。

ESI-MS m/z : 444 $[\text{M}+\text{H}]^+$ 。

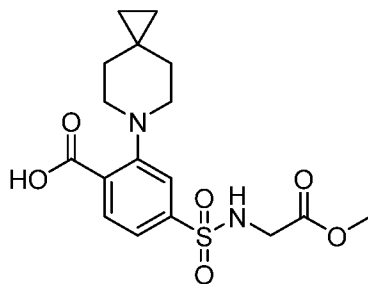
步骤 4: 化合物 int_273-6 的合成



将 **int_273-5** (16.3 g, 43.9 mmol)溶于乙腈/水/乙酸(40 mL/1 mL/0.5 mL)的混合溶剂中, 冰浴下加入二氯海因 (3.4 g, 17.3 mmol), 氮气保护下 0 °C 搅拌反应 0.5 小时。LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释, 水相用乙酸乙酯萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。将粗产物溶于乙腈和四氢呋喃(30 mL/10 mL)的混合溶液中, 加入甘氨酸甲酯盐酸盐 (5.4 g, 43 mmol)和加入碳酸钾 (12 g, 87 mmol), 室温下搅拌 1 小时。LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释, 水相用乙酸乙酯萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析(SiO_2 , 正己烷/乙酸乙酯 = 3:1)得到目标产物 (3.2 g, 收率: 80%)。

ESI-MS m/z : 473 $[\text{M}+\text{H}]^+$ 。

步骤 5: 化合物 int_273-7 的合成

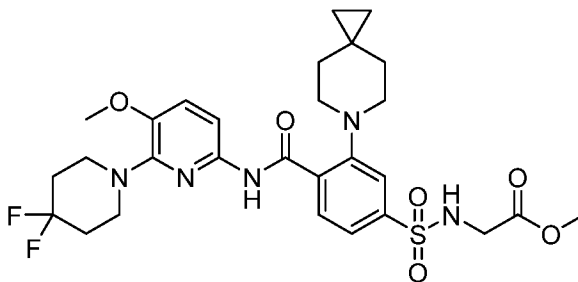


int_273-7

将 int_273-6 (3.2 g, 6.8 mmol) 溶于甲醇 (30 mL), 加入 Pd/C (1.00 g, 10% purity) 和 5 滴乙酸, 反应体系用氢气置换 3 次, 反应液在 50 °C 于氢气氛围下反应 16 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (2.5 g, 收率: 96%)。粗产物可直接用于下一步反应。

ESI-MS m/z: 383 [M+H]⁺。

步骤 6: 化合物 int_273-8 的合成



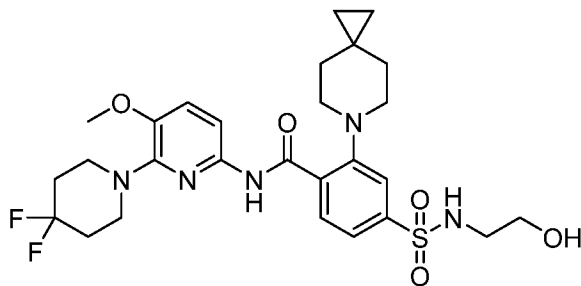
int_273-8

将 int_273-7 (0.5 g, 1.3 mmol) 溶于 DCM (15 mL), 加入草酰氯 (888 mg, 7 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将酰氯溶于四氢呋喃 (20 mL) 中, 在冰浴下慢慢加入 int_257-3 (318 mg, 1.3 mmol) 和三乙胺 (1.3 g, 13 mmol), 室温反应 1 小时, LC-MS 监测显示反应结束。向反应液加入水 (50 mL) 稀释, 水相用乙酸乙酯萃取 (50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (250 mg, 收率: 31%)。

¹H NMR (400 MHz, DMSO-d₆) δ 12.77 (s, 1H), 8.36 (s, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.66 (dd, J = 8.2, 1.7 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 2H), 3.52 (d, J = 6.3 Hz, 4H), 3.49 (s, 3H), 3.39 (d, J = 6.7 Hz, 2H), 3.03 (t, J = 5.4 Hz, 4H), 2.06 (t, J = 5.1 Hz, 2H), 1.70 (s, 4H), 0.36 (s, 4H)。

ESI-MS m/z: 608 [M+H]⁺。

步骤 7: 化合物 273 的合成

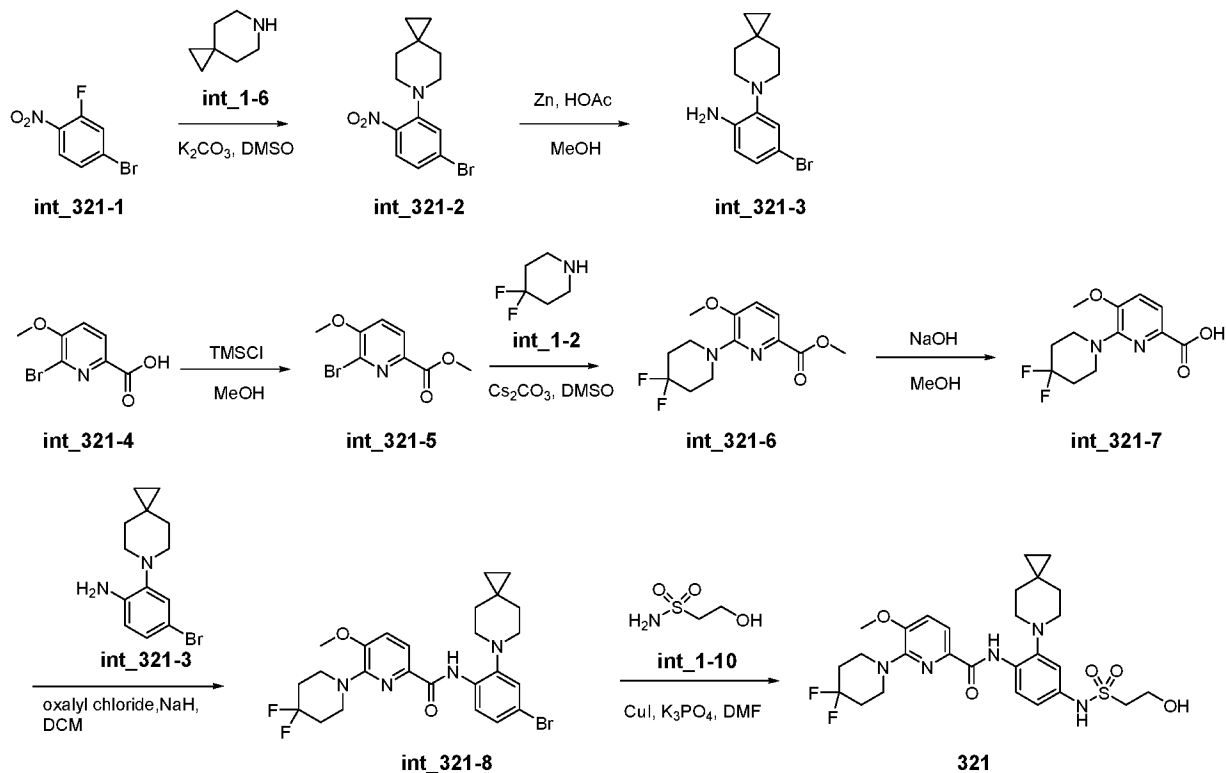
**273**

将 **int_273-8** (230 mg, 0.38 mmol) 溶解在甲醇和四氢呋喃 (5 mL/5 mL) 的混合溶剂中, 冰浴下慢慢加入硼氢化钠 (43 mg, 1.1 mmol) 和氯化锂 (48 mg, 1.1 mmol), 反应液在室温反应 3 小时。LC-MS 监测显示反应结束。向反应液加入水 (20 mL) 稀释, 水相用乙酸乙酯萃取 (20 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (210 mg, 收率: 95%)。

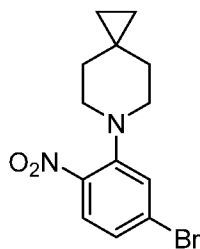
^1H NMR (400 MHz, DMSO- d_6) δ 12.75 (s, 1H), 8.23 (d, $J = 8.2$ Hz, 1H), 7.79 (dd, $J = 5.1, 3.4$ Hz, 2H), 7.67 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 4.73 (s, 1H), 3.80 (s, 3H), 3.51 (t, $J = 5.7$ Hz, 4H), 3.42 – 3.36 (m, 2H), 3.03 (t, $J = 5.3$ Hz, 4H), 2.81 (t, $J = 6.2$ Hz, 2H), 2.05 (q, $J = 11.2, 8.5$ Hz, 4H), 1.70 (m, 4H), 0.36 (s, 4H)。

ESI-MS m/z : 580 $[\text{M}+\text{H}]^+$ 。

实施例 19 化合物 321 的合成



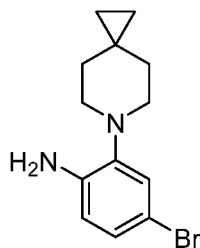
步骤 1: 化合物 int_321-2 的合成

**int_321-2**

将 **int_321-1** (1 g, 4.55 mmol) 溶于 DMF (20 mL) 中, 加入 **int_1-6** (670 mg, 4.55 mmol), 碳酸钾 (1.8 g, 13.64 mmol), 氩气保护下, 100°C 反应 3 小时, LC-MS 监测显示反应结束。减压浓缩反应液, 加入 100 mL 水, 水相用乙酸乙酯萃取 (200 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 (1.5 g, 收率: 100%)。

ESI-MS m/z : 311 $[M+H]^+$ 。

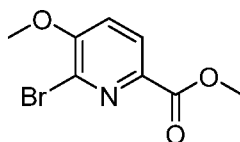
步骤 2: 化合物 **int_321-3** 的合成

**int_321-3**

将 **int_321-2** (1.5 g, 4.82 mmol) 溶于甲醇 (50 mL) 中, 加入 20 mL 乙酸, 冰浴下搅拌 10 分重后, 分批少量加入锌粉 (1.5 g, 24.10 mmol)。反应液升至室温反应 1 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物。向粗产物中加入 100 mL 水, 水相用二氯甲烷萃取 (200 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物 (1 g, 收率: 77%)。

ESI-MS m/z : 281 $[M+H]^+$ 。

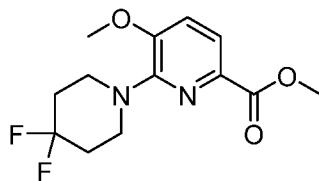
步骤 3: 化合物 **int_321-5** 的合成

**int_321-5**

将 **int_321-4** (5 g, 21.55 mmol) 混悬于甲醇 (100 mL) 中, 加入三甲基氯化硅 (7 g, 64.65 mmol)。反应液于室温反应 4 小时, 反应液逐渐澄清。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物 (5.2 g, 收率: 98%)。

ESI-MS m/z : 246 $[M+H]^+$ 。

步骤 4: 化合物 int_321-6 的合成

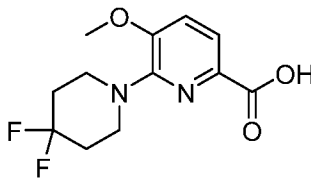


int_321-6

将 int_321-5 (5 g, 16.2 mmol) 溶于 1, 4-二氧六环 (100 mL) 中, 加入碳酸铯 (20 g, 63.4 mmol)、 $\text{Pd}_2(\text{dba})_3$ (1.9 g, 2.11 mmol) 和 Xantphos (1.2 g, 2.11 mmol)。氩气保护下, 升温至 100°C 反应 18 小时。LC-MS 监测显示反应结束。向反应液加入水 (300 mL) 稀释, 水相用二氯甲烷萃取 (300 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化 (SiO_2 , 正己烷/乙酸乙酯 = 10:1) 得到目标产物 (4.3 g, 收率: 71%)。

ESI-MS m/z : 287 $[\text{M}+\text{H}]^+$ 。

步骤 5: 化合物 int_321-7 的合成

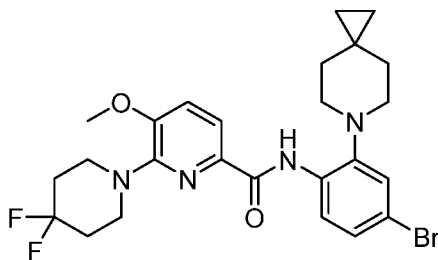


int_321-7

将 int_273-6 (4.3 g, 15.02 mmol) 溶于甲醇 (50 mL) 中, 室温搅拌下加入 NaOH (2M, 20 mL), 反应液在室温下反应 4 小时, LC-MS 监测显示反应结束。反应液过滤得到滤液, 将滤液减压浓缩得到固体, 向固体中加入水 (100 mL), 水相用二氯甲烷萃取 (50 mL*2), 水相减压蒸馏得到粗产物, 粗产物经柱层析纯化得到目标产物 (2 g, 收率: 58%)。

ESI-MS m/z : 273 $[\text{M}+\text{H}]^+$ 。

步骤 6: 化合物 int_321-8 的合成



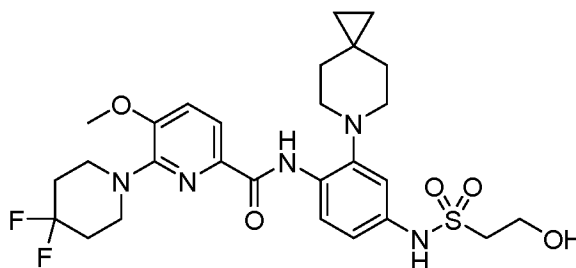
int_321-8

将 int_321-7 (2 g, 7.37 mmol) 溶于 DCM (100 mL), 加入草酰氯 (1.4 g, 11 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 int_321-3 (2.1 g, 7.37 mmol) 溶于四氢呋喃 (50 mL)

中, 在冰浴下慢慢加入钠氢 (2.9 g, 73.7 mmol, 60%纯度), 反应液在室温反应 1 小时, 向反应液中加入制备得到的酰氯产物, 反应液在 40°C 反应 5 小时, LC-MS 监测显示反应结束。向反应液加入水(100 mL)稀释, 水相用二氯甲烷萃取(100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化(SiO₂, 正己烷/乙酸乙酯 = 5:1)得到目标产物 (3.7 g, 收率: 95%)。

ESI-MS m/z : 535 $[M+H]^+$ 。

步骤 7: 化合物 321 的合成



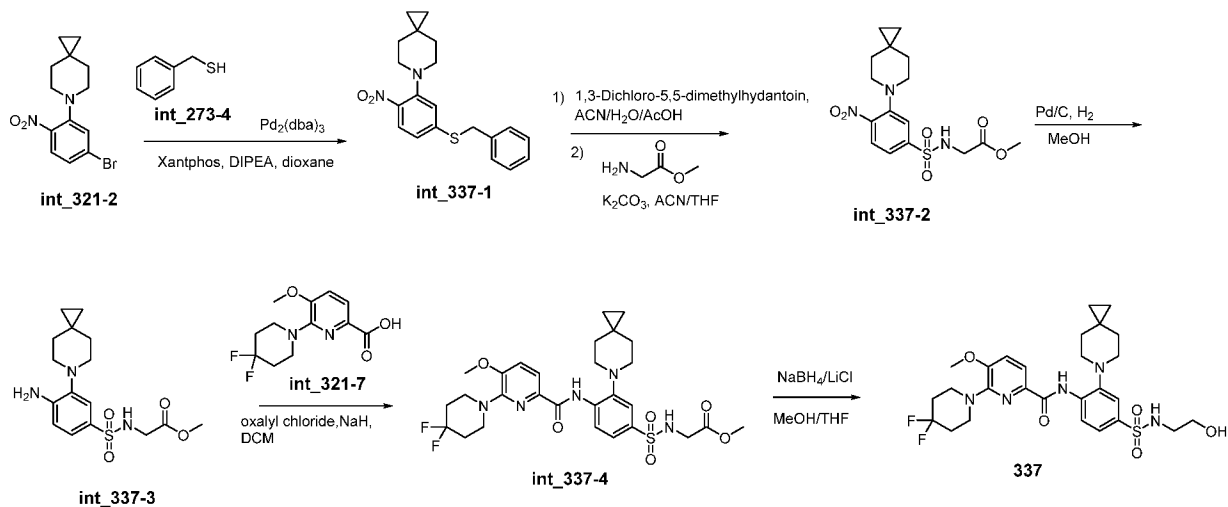
321

将 **int_321-8** (500 mg, 0.94 mmol)、N,N-二甲基甘氨酸 (66 mg, 0.47 mmol)、碘化亚铜 (89 mg, 0.47 mmol) 和磷酸钾 (596 mg, 2.8 mmol), 溶解在 DMF (20 mL) 中, 氩气置换三次, 加入 **int_1-10** (266 mg, 1.87 mmol), 氩气保护下, 微波反应液加热到 130°C 反应 3.5 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(260 mg, 收率: 48%)。

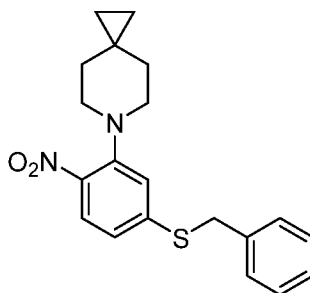
¹H NMR (400 MHz, DMSO-d₆) δ 10.37 (s, 1H), 8.39 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 8.7, 2.4 Hz, 1H), 3.90 (s, 3H), 3.71 (t, J = 6.7 Hz, 2H), 3.56 (t, J = 5.5 Hz, 4H), 3.18 (t, J = 6.7 Hz, 2H), 2.78 (t, J = 5.3 Hz, 4H), 2.13 (tt, J = 13.7, 5.6 Hz, 4H), 1.52 (s, 4H), 0.33 (s, 4H)。

ESI-MS m/z : 580 $[M+H]^+$ 。

实施例 20 化合物 337 的合成



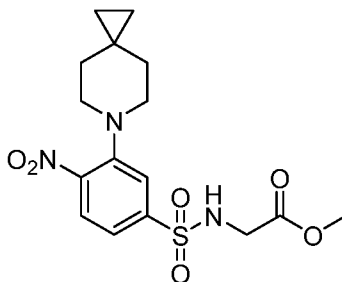
步骤 1: 化合物 int_337-1 的合成

**int_337-1**

将 **int_321-2** (2 g, 6.43 mmol) 溶于二氧六环(30 mL)中, 加入苄硫醇 (2.4 g, 19.28 mmol)、 $\text{Pd}_2(\text{dba})_3$ (300 mg, 0.33 mmol)、Xantphos (300 mg, 0.54 mmol) 和 DIPEA (3.3 g, 25.72 mmol), 氮气保护下升温至 100 °C 反应 16 小时, LC-MS 监测显示反应结束。向反应液加入水(100 mL)稀释, 水相用乙酸乙酯萃取(100 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物, 粗产物经柱层析得到目标产物 (1.7 g, 收率: 74.9%)。

ESI-MS m/z : 355 $[\text{M}+\text{H}]^+$ 。

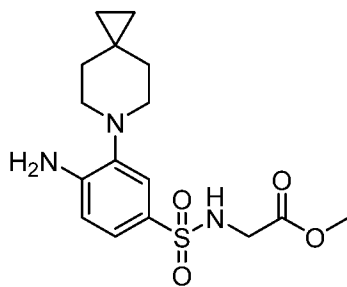
步骤 2: 化合物 **int_337-2** 的合成

**int_337-2**

将 **int_337-1** (360 mg, 1.02 mmol) 溶于乙腈/水/乙酸(30 mL/1 mL/1 mL)的混合溶剂中, 冰浴下加入二氯海因 (402 mg, 2.04 mmol), 氮气保护下 0 °C 搅拌反应 0.5 小时。LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释, 水相用乙酸乙酯萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。将粗产物溶于乙腈和四氢呋喃(30 mL/10 mL)的混合溶液中, 加入甘氨酸甲酯盐酸盐 (1 g, 7.96 mmol) 和加入碳酸钾 (3.3 g, 24 mmol), 室温下搅拌 1 小时。LC-MS 监测显示反应结束。向反应液加入水(50 mL)稀释, 水相用乙酸乙酯萃取(50 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (100 mg, 收率: 25.6%)。

ESI-MS m/z : 384 $[\text{M}+\text{H}]^+$ 。

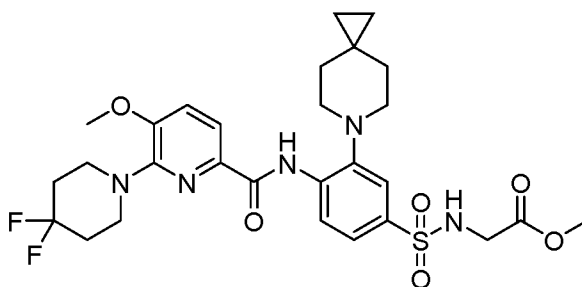
步骤 3: 化合物 **int_337-3** 的合成

**int_337-3**

将 **int_337-2** (100 mg, 0.261 mmol) 溶于甲醇 (10 mL), 加入 Pd/C (30 mg, 10% purity) 和 5 滴乙酸, 反应体系用氢气置换 3 次, 反应液在室温于氢气氛围下反应 16 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物 (90 mg, 收率: 97.8%)。粗产物可直接用于下一步反应。

ESI-MS m/z : 354 $[M+H]^+$ 。

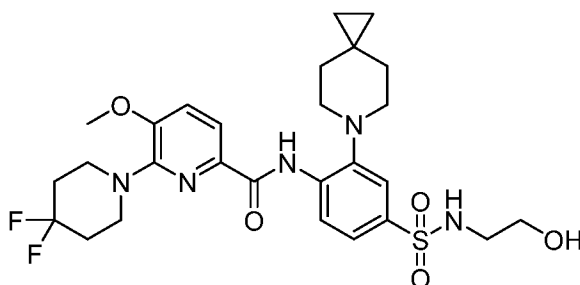
步骤 4: 化合物 **int_337-4** 的合成

**int_337-4**

将 **int_321-7** (220mg, 0.809mmol) 溶于 DCM (10 mL), 加入草酰氯 (1 g, 8 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 **int_337-3** (140 mg, 0.396 mmol) 溶于四氢呋喃 (10 mL) 中, 在冰浴下慢慢加入钠氢 (56 mg, 1.4 mmol, 60% 纯度), 反应液在室温反应 1 小时, 向反应液中加入制备得到的酰氯产物, 反应液在 40°C 反应 5 小时, LC-MS 监测显示反应结束。向反应液加入水 (30 mL) 稀释, 水相用二氯甲烷萃取 (30 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化得到目标产物 (100 mg, 收率: 41.7%)。

ESI-MS m/z : 608 $[M+H]^+$ 。

步骤 5: 化合物 **337** 的合成

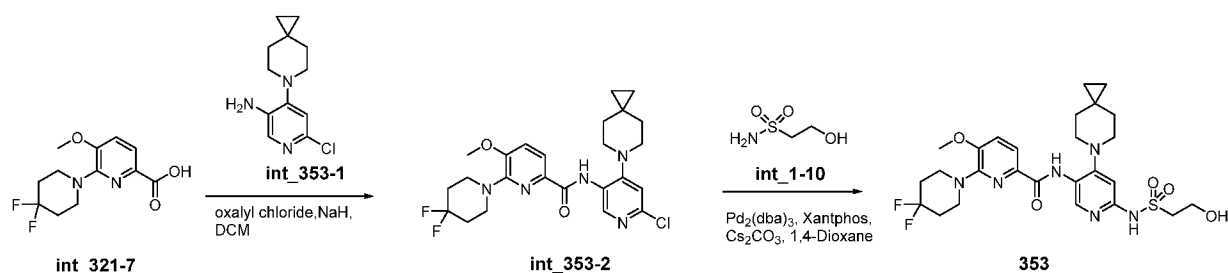
**337**

将 **int_337-4** (100 mg, 0.165 mmol) 溶解在甲醇和四氢呋喃 (5 mL/5 mL) 的混合溶剂中, 冰浴下慢慢加入硼氢化钠 (38 mg, 1 mmol) 和氯化锂 (42 mg, 1 mmol), 反应液在室温反应 3 小时。LC-MS 监测显示反应结束。向反应液加入水 (20 mL) 稀释, 水相用乙酸乙酯萃取 (20 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (82 mg, 收率: 85.8%)。

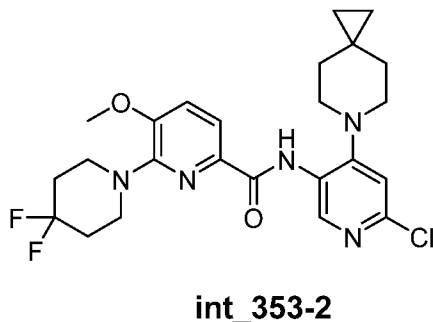
^1H NMR (400 MHz, DMSO- d_6) δ 10.66 (s, 1H), 8.58 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 4.69 (d, J = 6.5 Hz, 1H), 3.91 (s, 3H), 3.58 (d, J = 6.5 Hz, 4H), 2.81 (dt, J = 37.8, 5.6 Hz, 6H), 2.15 (d, J = 7.6 Hz, 4H), 1.55 (s, 4H), 0.35 (s, 4H)。

ESI-MS m/z : 580 $[\text{M}+\text{H}]^+$ 。

实施例 21 化合物 353 的合成



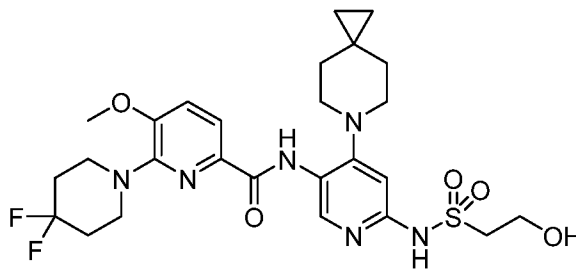
步骤 1: 化合物 **int_353-2** 的合成



将 **int_321-7** (50 mg, 0.184 mmol) 溶于 DCM (5 mL), 加入草酰氯 (12 mg, 1 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 **int_353-1** (44 mg, 0.185 mmol) 溶于四氢呋喃 (5 mL) 中, 在冰浴下慢慢加入钠氢 (50 mg, 1.25 mmol, 60% 纯度), 反应液在室温反应 1 小时, 向反应液中加入制备得到的酰氯产物, 反应液在室温反应 5 小时, LC-MS 监测显示反应结束。向反应液加入水 (10 mL) 稀释, 水相用二氯甲烷萃取 (10 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化得到目标产物 (50 mg, 收率: 55%)。

ESI-MS m/z : 492 $[\text{M}+\text{H}]^+$ 。

步骤 2: 化合物 353 的合成

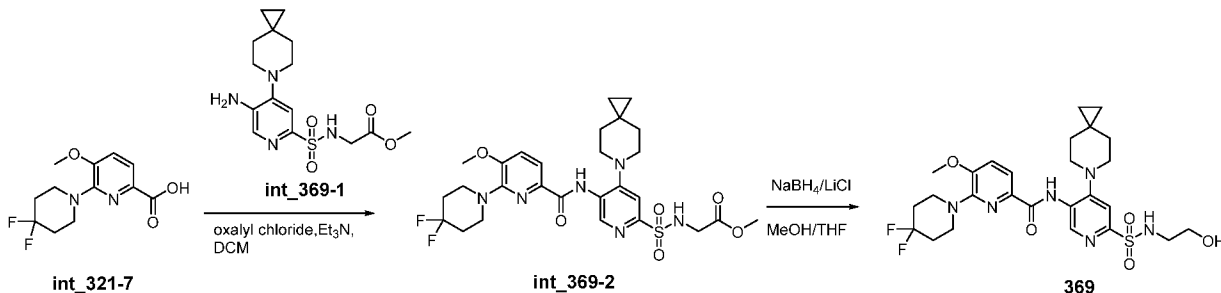
**353**

将 **int_353-2** (190 mg, 0.39 mmol)、碳酸铯(129.8 mg, 1.16 mmol)、 $\text{Pd}_2(\text{dba})_3$ (95 mg, 0.218 mmol)和 Xantphos (95 mg, 0.346 mmol), 溶解在 1,4-二氧六环 (10 mL)中, 氩气置换三次, 加入 **int_1-10** (97.2 mg, 0.78 mmol), 氩气保护下, 反应液加热到 110 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(56 mg, 收率: 27%)。

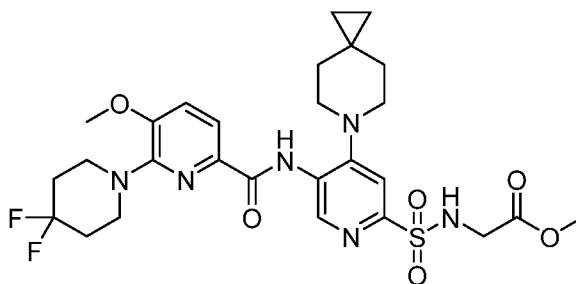
^1H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.66 (s, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 6.35 (s, 1H), 3.89 (s, 3H), 3.64 (t, $J = 6.6$ Hz, 2H), 3.54 (d, $J = 3.1$ Hz, 4H), 3.09 (t, $J = 6.6$ Hz, 2H), 2.78 (d, $J = 5.5$ Hz, 4H), 2.19 – 2.03 (m, 4H), 1.47 (s, 4H), 0.30 (s, 4H)。

ESI-MS m/z : 581 $[\text{M}+\text{H}]^+$ 。

实施例 22 化合物 369 的合成



步骤 1: 化合物 **int_369-2** 的合成

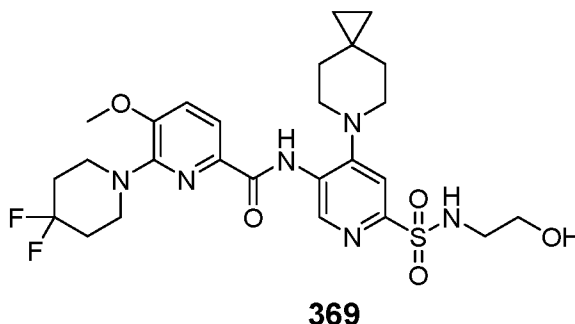
**int_369-2**

将 **int_321-7** (27 mg, 0.1 mmol)溶于 DCM (5 mL), 加入草酰氯 (12 mg, 1 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。将 **int_369-1** (37 mg, 0.1 mmol)溶于四氢呋喃(5 mL)中, 在冰浴下慢慢加入三乙胺 (202 mg, 2 mmol)和制备得到的酰氯产物, 反应液在 40 °C 反应 12 小时, LC-MS 监测显示反应结束。向反应液加入水(10 mL)稀释, 水相用二氯甲烷萃取(10 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析纯化得到目标产物 (2 mg, 收率: 3.3%)。

^1H NMR (400 MHz, DMSO- d_6) δ 10.16 (s, 1H), 9.38 (s, 1H), 8.29 (t, $J = 6.1$ Hz, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.63 (s, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 3.92 (s, 3H), 3.85 (d, $J = 5.8$ Hz, 2H), 3.56 (d, $J = 11.2$ Hz, 6H), 3.31 (s, 2H), 2.99 (t, $J = 5.2$ Hz, 3H), 2.21 – 1.95 (m, 4H), 1.53 (t, $J = 5.3$ Hz, 4H), 0.34 (s, 4H)。

ESI-MS m/z : 609 $[\text{M}+\text{H}]^+$ 。

步骤 2: 化合物 369 的合成

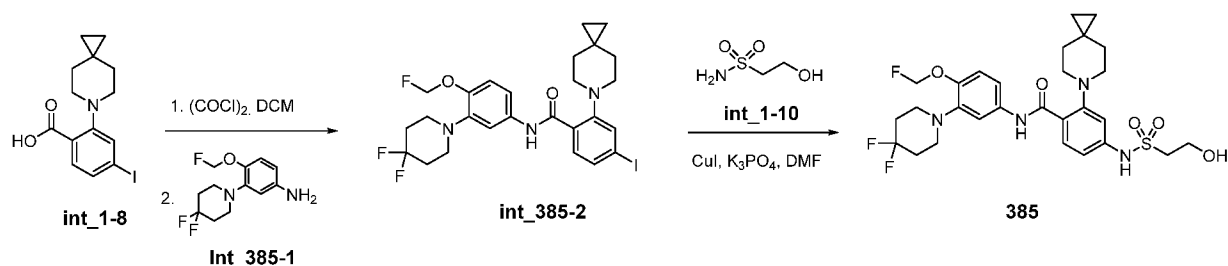


将 **int_369-2** (70 mg, 0.115 mmol) 溶解在甲醇和四氢呋喃 (5 mL/5 mL) 的混合溶剂中, 冰浴下慢慢加入硼氢化钠 (38 mg, 1 mmol) 和氯化锂 (42 mg, 1 mmol), 反应液在室温反应 3 小时。LC-MS 监测显示反应结束。向反应液加入水 (20 mL) 稀释, 水相用乙酸乙酯萃取 (20 mL*3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物。粗产物经柱层析得到目标产物 (9 mg, 收率: 12.9%)。

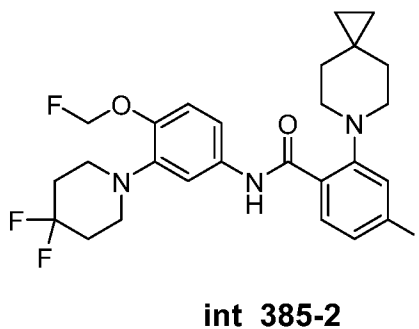
^1H NMR (400 MHz, DMSO- d_6) δ 10.15 (s, 1H), 9.40 (s, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.67 (d, $J = 9.2$ Hz, 2H), 7.50 (d, $J = 8.3$ Hz, 1H), 4.63 (t, $J = 5.6$ Hz, 1H), 3.92 (s, 3H), 3.57 (t, $J = 5.6$ Hz, 4H), 3.44 – 3.34 (m, 2H), 2.97 (dt, $J = 26.4, 6.1$ Hz, 6H), 2.27 – 2.04 (m, 4H), 1.53 (t, $J = 5.2$ Hz, 4H), 0.34 (s, 4H)。

ESI-MS m/z : 581 $[\text{M}+\text{H}]^+$ 。

实施例 23 化合物 385 的合成



步骤 1: 化合物 int_385-2 的合成

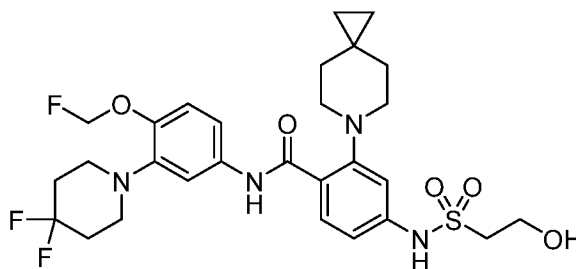


将 **int_1-8** (150 mg, 0.42 mmol) 溶于 DCM (50 mL), 加入草酰氯 (507 mg, 4 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_385-1** (70 mg, 0.28 mmol) 溶于四氢呋喃 (40 mL), 氮气保护下, 加入 NaH (67 mg, 1.68 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 8 : 1)纯化得固体(140 mg, 收率: 87%)。

ESI-MS m/z : 600 $[M+H]^+$ 。

步骤 2: 化合物 385 的合成



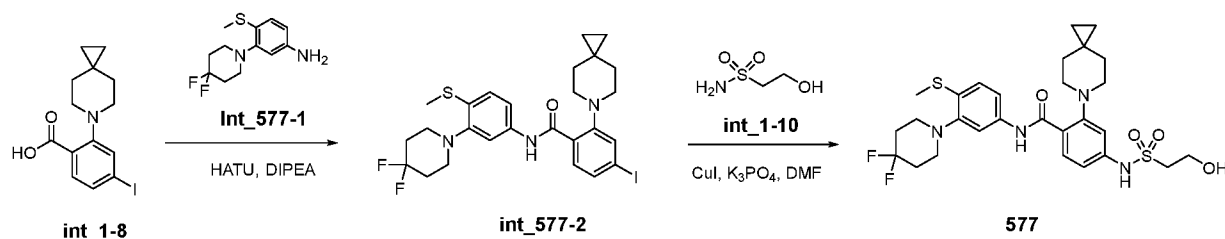
385

将 **int_385-2** (140 mg, 0.23 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (16 mg, 0.115 mmol)、碘化亚铜 (22 mg, 0.115 mmol) 和磷酸钾 (146 mg, 0.69 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 **int_1-10** (58 mg, 0.46 mmol), 氩气保护下, 反应液加热到 90 °C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(77 mg, 收率: 56.2%)。

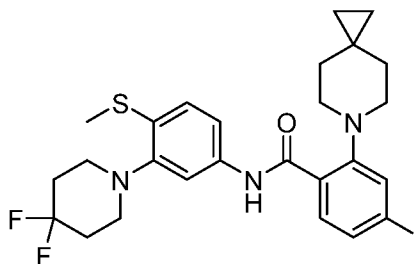
¹H NMR (400 MHz, Chloroform-d) δ 12.45 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.33 (s, 1H), 7.20 – 7.16 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.02 (t, J = 9.3 Hz, 1H), 5.80 (s, 1H), 5.66 (s, 1H), 4.13 (d, J = 5.7 Hz, 2H), 3.37 – 3.29 (m, 2H), 3.23 (t, J = 5.6 Hz, 4H), 3.07 (s, 4H), 2.14 (tt, J = 13.1, 5.4 Hz, 4H), 1.62 (s, 4H), 0.43 (s, 4H)。

ESI-MS m/z : 597 $[M+H]^+$ 。

实施例 24 化合物 577 的合成



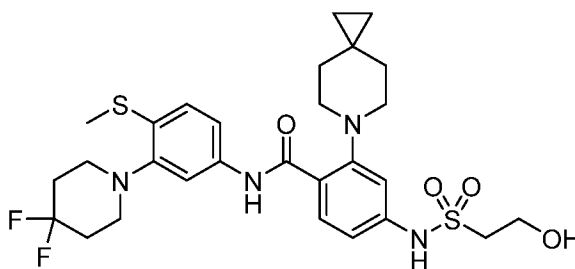
步骤 1: 化合物 **int_577-2** 的合成

**int_577-2**

将 **int_1-8** (138 mg, 0.387 mmol) 溶于 DCM (50 mL), 加入 **int_577-1** (100 mg, 0.387 mmol)、HATU (294 mg, 0.774 mmol) 和 DIPEA (193.8 mg, 1.5 mmol) 溶于 DMF (10 mL), 氮气保护下, 反应液升至 60°C 搅拌 2 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (130 mg, 收率: 56%)。

ESI-MS m/z : 598 $[M+H]^+$ 。

步骤 2: 化合物 577 的合成

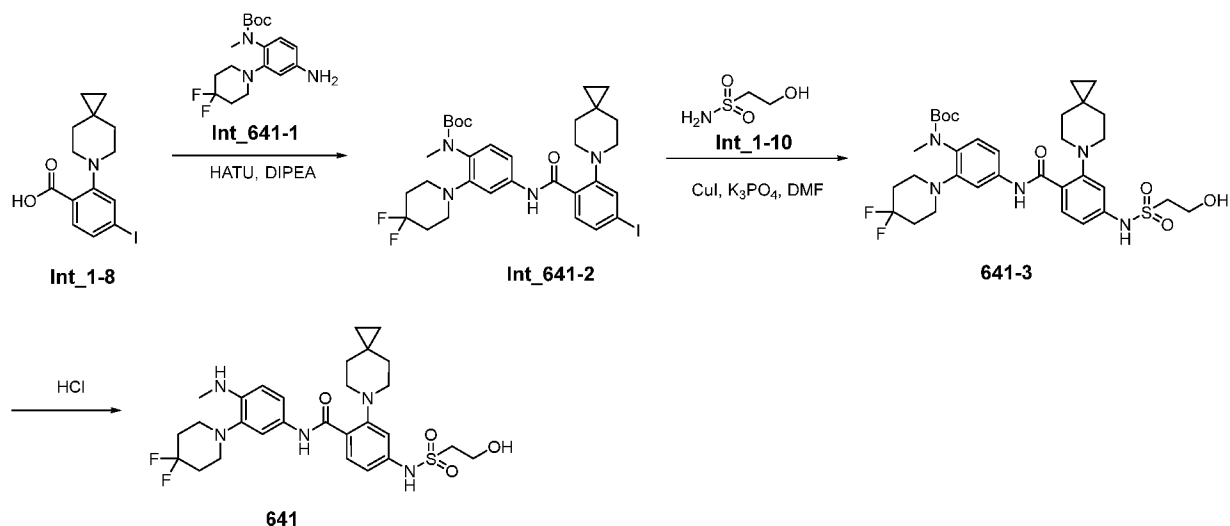
**577**

将 **int_577-2** (130 mg, 0.217 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (9 mg, 0.065 mmol)、碘化亚铜 (12 mg, 0.065 mmol) 和磷酸钾 (138 mg, 0.653 mmol), 溶解在 DMF (10 mL) 中, 氩气置换三次, 加入 **int_1-10** (54 mg, 0.435 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (80 mg, 收率: 62%)。

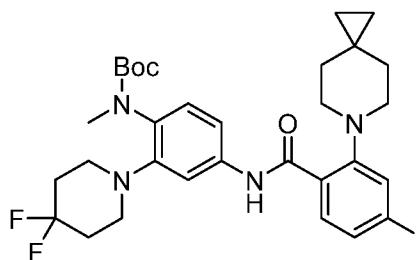
^1H NMR (400 MHz, DMSO- d_6) δ 11.76 (s, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.63 (d, $J = 2.2$ Hz, 1H), 7.48 (dd, $J = 8.5, 2.1$ Hz, 1H), 7.17 (d, $J = 8.6$ Hz, 1H), 7.12 (d, $J = 2.1$ Hz, 1H), 6.99 (dd, $J = 8.5, 2.0$ Hz, 1H), 3.74 (t, $J = 6.5$ Hz, 2H), 3.27 (d, $J = 6.6$ Hz, 2H), 3.01 (t, $J = 5.6$ Hz, 4H), 2.94 (t, $J = 5.3$ Hz, 4H), 2.39 (s, 3H), 2.10 (dt, $J = 14.3, 7.9$ Hz, 4H), 1.53 (s, 4H), 0.34 (s, 4H)。

ESI-MS m/z : 595 $[M+H]^+$ 。

实施例 25 化合物 641 的合成



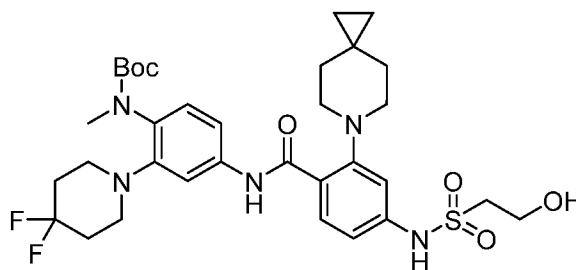
步骤 1: 化合物 int_641-2 的合成



将 **int_1-8** (100 mg, 0.29 mmol) 溶于 DCM (50 mL), 加入 **int_641-1** (100 mg, 0.29 mmol)、HATU (220 mg, 0.585 mmol) 和 DIPEA (193.8 mg, 1.5 mmol) 溶于 DMF (8 mL), 氮气保护下, 反应液室温搅拌 12 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (110 mg, 收率: 55.2%)。

ESI-MS m/z : 681 $[M+H]^+$ 。

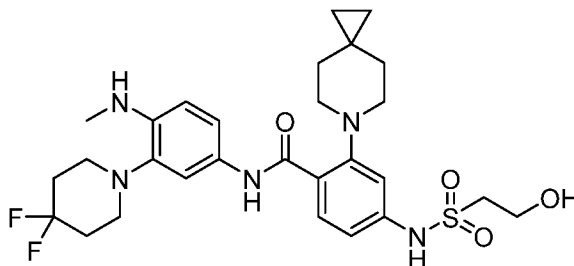
步骤 2: 化合物 641-3 的合成



将 **int_641-2** (160 mg, 0.235 mmol)、(1S,2S)-(+)-N,N'-二甲基-1,2-环己二胺 (17 mg, 0.117 mmol)、碘化亚铜 (22 mg, 0.117 mmol) 和磷酸钾 (150 mg, 0.705 mmol), 溶解在 DMF (10 mL) 中, 氩气置换三次, 加入 **int_1-10** (60 mg, 0.47 mmol), 氩气保护下, 反应液加热到 90 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (110 mg, 收率: 69.1%)。

ESI-MS m/z : 678 $[M+H]^+$ 。

步骤 3: 化合物 641 的合成



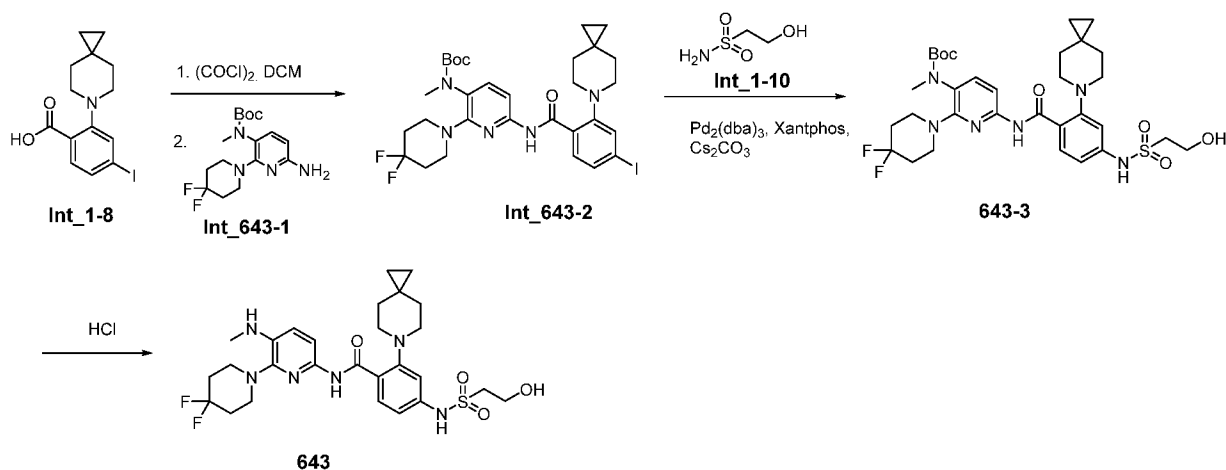
641

将 **int_641-3** (110 mg, 0.162 mmol) 溶解在甲醇/盐酸 (4 N, 15 mL) 中, 反应液于室温反应 12 小时。LC-MS 监测显示反应结束。将反应液旋干, 柱层析纯化得固体 (60 mg, 收率: 64.5%)。

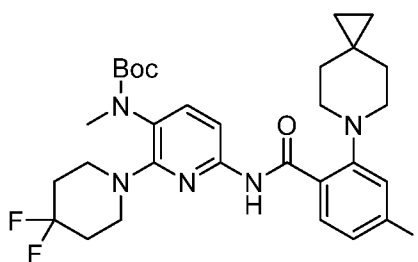
^1H NMR (400 MHz, Chloroform- d) δ 12.26 (s, 1H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 2.3$ Hz, 1H), 7.34 (s, 1H), 7.25 (d, $J = 3.0$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 6.63 (d, $J = 8.6$ Hz, 1H), 4.09 (t, $J = 5.1$ Hz, 2H), 3.30 (t, $J = 5.1$ Hz, 2H), 3.07–2.98 (m, 8H), 2.87 (s, 3H), 2.12 (ddt, $J = 16.7, 11.5, 5.6$ Hz, 4H), 1.62 (s, 4H), 0.40 (s, 4H)。

ESI-MS m/z : 578 $[M+H]^+$ 。

实施例 26 化合物 643 的合成



步骤 1: 化合物 int_643-2 的合成



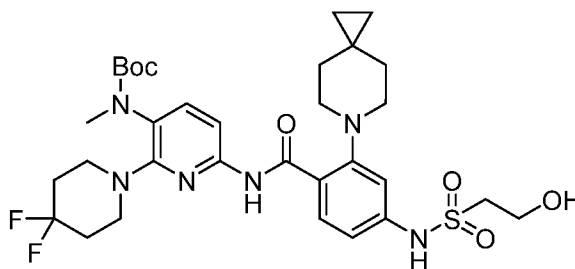
Int_643-2

将 **int_1-8** (1.17 g, 3.3 mmol) 溶于 DCM (50 mL), 加入草酰氯 (1.9 g, 15 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_643-1** (800 mg, 3.3 mmol) 溶于四氢呋喃 (50 mL), 氮气保护下, 加入三乙胺 (666 mg, 6.6 mmol), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液室温下搅拌 6 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO_2 , 正己烷/乙酸乙酯 = 7 : 1) 纯化得固体(1.1 g, 收率: 57.8%)。

ESI-MS m/z : 682 $[\text{M}+\text{H}]^+$ 。

步骤 2: 化合物 643-3 的合成

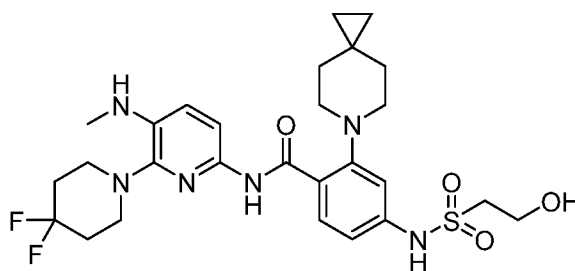


643-3

将 **int_643-2** (1.1 g, 1.89 mmol)、碳酸铯 (921 mg, 2.83 mmol)、 $\text{Pd}_2(\text{dba})_3$ (35 mg, 0.037 mmol) 和 X-Phos (27 mg, 0.056 mmol) 溶解在 1,4-二氧六环 (40 mL) 中, 加入 **int_1-10** (473 mg, 3.78 mmol), 氩气保护下, 反应液加热到 90 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(550 mg, 收率: 50.45%)。

ESI-MS m/z : 679 $[\text{M}+\text{H}]^+$ 。

步骤 3: 化合物 643 的合成



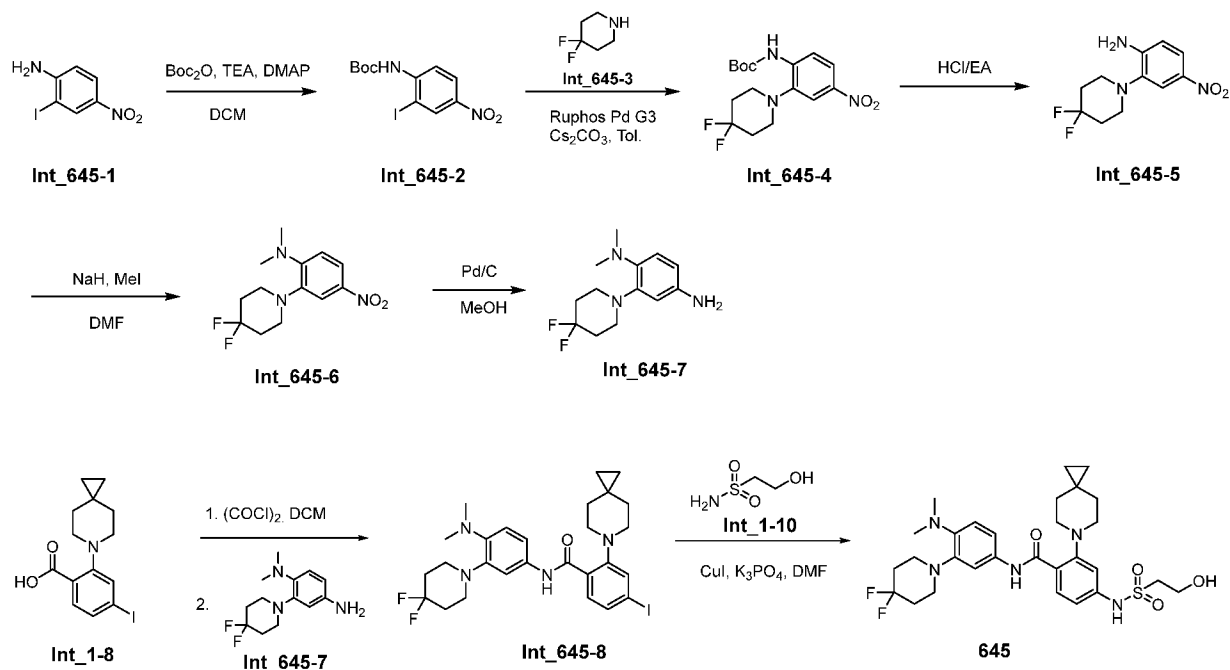
643

将 **int_643-3** (100 mg, 0.147 mmol) 溶解在甲醇/盐酸 (4 N, 15 mL) 中, 反应液于室温反应 12 小时。LC-MS 监测显示反应结束。将反应液旋干, 柱层析纯化得固体(57 mg, 收率: 67%)。

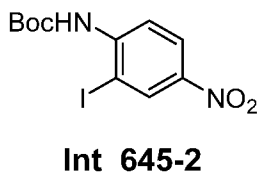
^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 8.02 (d, $J = 8.6$ Hz, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.21 (d, $J = 2.1$ Hz, 1H), 7.08 (dd, $J = 8.6, 2.1$ Hz, 1H), 6.91 (d, $J = 8.6$ Hz, 1H), 4.98 (q, $J = 5.2$ Hz, 1H), 3.73 (t, $J = 6.5$ Hz, 2H), 3.12 (t, $J = 5.7$ Hz, 4H), 2.94 (d, $J = 5.2$ Hz, 4H), 2.71 (d, $J = 5.1$ Hz, 3H), 2.16 (tt, $J = 11.8, 5.2$ Hz, 4H), 1.73 (s, 4H), 0.35 (s, 4H)。

ESI-MS m/z : 579 $[\text{M}+\text{H}]^+$ 。

实施例 27 化合物 645 的合成



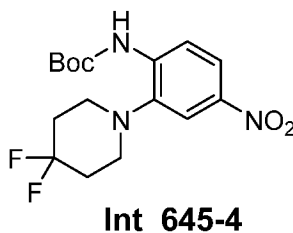
步骤 1: 化合物 int_645-2 的合成



将 int_645-1 (10.0 g, 37.8 mmol) 溶于 DCM (20 mL) 中, 加入 Boc_2O (8.27 g, 37.8 mmol, 8.70 mL), TEA (4.98 g, 49.2 mmol, 6.85 mL) and DMAP (231 mg, 1.89 mmol), 反应液于 25 °C 反应 16 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 将滤液减压浓缩得到粗产物。粗产物经柱层析 (SiO_2 , 正己烷/乙酸乙酯=5:1) 得到目标产物 (10 g, 收率: 68.6%)。

^1H NMR (400MHz, DMSO-d_6) δ = 8.62 (s, 1H), 8.58 (d, J = 2.8 Hz, 1H), 8.22 (dd, J = 2.8, 9.0 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 1.54 - 1.46 (m, 9H)。

步骤 2: 化合物 int_645-4 的合成

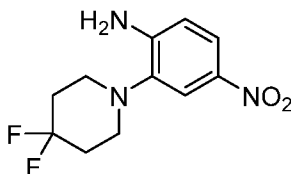


将 int_645-2 (10.00 g, 27.4 mmol), int_645-3 (6.65 g, 54.9 mmol), RuPhos Pd G3 (2.30 g, 2.75 mmol), Cs_2CO_3 (26.8 g, 82.4 mmol) 溶于甲苯 (50 mL) 中, 氮气置换三次, 升温至 100 °C 于氮气氛围下反应 2 小

时, LC-MS 监测显示反应结束。反应液过滤, 滤液减压浓缩得到粗产物, 粗产物加入水(300 mL)并用乙酸乙酯萃取(100 mL * 3), 有机相用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物, 粗产物经柱层析(SiO_2 , 正己烷/乙酸乙酯=3:1)得到目标产物(6 g, 收率: 44.6%)。

^1H NMR (400MHz, DMSO-d_6) δ = 8.49 (s, 1H), 8.14 - 8.07 (m, 1H), 8.06 - 8.00 (m, 1H), 7.98 (d, J = 2.5 Hz, 1H), 2.97 (br t, J = 5.4 Hz, 4H), 2.31 - 2.13 (m, 4H), 1.53 - 1.50 (m, 9H)。

步骤 3: 化合物 int_645-5 的合成

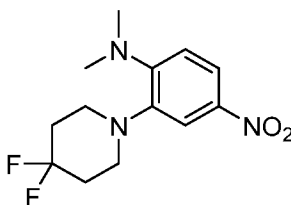


Int_645-5

将 int_645-4 (3.60 g, 10.1 mmol)溶于 DCM(20 mL)中, HCl/EtOAc 溶液 (4 M, 2.52 mL), 反应液在 25 °C 反应 16 小时, LC-MS 监测显示反应结束。反应液过滤得到滤液, 滤液减压浓缩得到粗产物 (2.4 g, 收率: 81.1%), 粗产物直接用于下一步反应。

^1H NMR (400MHz, DMSO-d_6) δ = 7.82 (dd, J = 2.6, 8.9 Hz, 1H), 7.74 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 2.92 (br s, 4H), 2.28 - 2.11 (m, 4H)。

步骤 4: 化合物 int_645-6 的合成

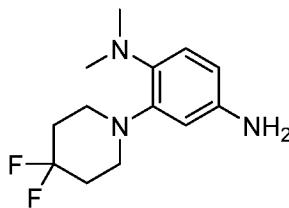


Int_645-6

将 int_645-5 (2.40 g, 8.17 mmol)溶于 DMF(20 mL)中, 于 0 °C 氮气保护下, 向反应液中加入 NaH (1.63 g, 40.86 mmol, 60% purity, 5.00 eq)以及 MeI (5.80 g, 40.9 mmol, 2.54 mL, 5.00 eq)。加毕, 将反应液升至室温并继续反应 16 小时, LC-MS 监测显示反应结束。向反应液中加入 30 mL 冰水, 继续搅拌 0.5 小时, 然后加入水(300 mL)并用乙酸乙酯萃取(100 mL * 3), 合并有机相并用无水硫酸钠干燥。有机相过滤、减压蒸馏得到粗产物, 粗产物经柱层析(SiO_2 , 正己烷/乙酸乙酯=3:1)得到目标产物(2 g, 收率: 83.7%)。

^1H NMR (400MHz, DMSO-d_6) δ = 7.86 (dd, J = 2.7, 9.0 Hz, 1H), 7.70 (d, J = 2.6 Hz, 1H), 6.98 (d, J = 9.1 Hz, 1H), 3.10 (br d, J = 7.2 Hz, 4H), 2.99 (s, 6H), 2.26 - 2.09 (m, 4H)。

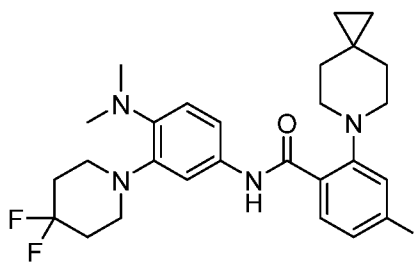
步骤 5: 化合物 int_645-7 的合成

**Int_645-7**

将 **int_645-6** (2.00 g, 7.01 mmol) 溶于甲醇 (20 mL), 加入 Pd/C (1.00 g, 7.01 mmol, 10% purity), 反应体系用氢气置换 3 次, 反应液在 25 °C 于氢气氛围下反应 16 小时。LC-MS 监测显示反应结束。将反应液过滤, 滤液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 二氯甲烷/甲醇 = 10 : 1) 纯化得固体 (0.85 g, 收率: 46.6%)。

¹H NMR (400MHz, DMSO-d₆) δ = 6.65 (d, *J* = 8.3 Hz, 1H), 6.23 (d, *J* = 2.3 Hz, 1H), 6.18 (dd, *J* = 2.4, 8.3 Hz, 1H), 4.60 (s, 2H), 3.12 (br s, 4H), 2.63 (s, 6H), 2.19 - 1.99 (m, 4H)。

步骤 6: 化合物 **int_645-8** 的合成

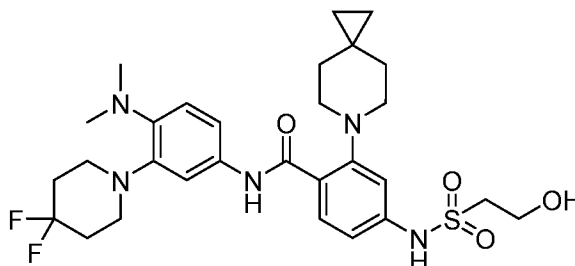
**Int_645-8**

将 **int_1-8** (1.2 g, 3.36 mmol) 溶于 DCM (50 mL), 加入草酰氯 (888.4 mg, 7 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_645-7** (760 mg, 3 mmol) 溶于四氢呋喃 (40 mL), 氮气保护下, 加入 NaH (720 mg, 18 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40 °C 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 15 : 1) 纯化得固体 (1.75 g, 收率: 98.3%)。

ESI-MS *m/z*: 595 [M+H]⁺。

步骤 7: 化合物 **645** 的合成

**645**

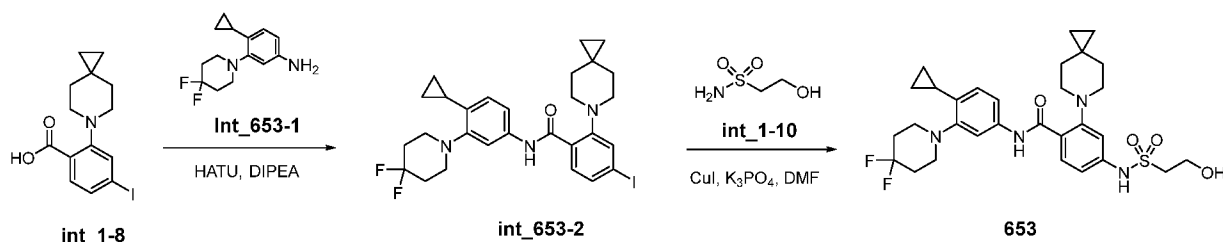
将 **int_645-8** (1.75 g, 2.95 mmol)、(1*S*,2*S*)-(+)-*N,N'*-二甲基-1,2-环己二胺 (210 mg, 1.475 mmol)、

碘化亚铜 (281 mg, 1.475 mmol)和磷酸钾 (1.879 g, 8.85 mmol), 溶解在 DMF (50 mL)中, 氩气置换三次, 加入 **int_1-10** (553 mg, 4.42 mmol), 氩气保护下, 反应液加热到 90 °C 反应 3 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析(SiO₂, 二氯甲烷/甲醇 = 100:1)纯化得固体(580 mg, 收率: 33.2%)。

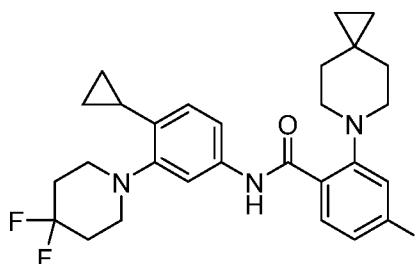
¹H NMR (400 MHz, Chloroform-d) δ 12.36 (s, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.33 (s, 1H), 7.13 (s, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.12 (s, 2H), 3.30 (dt, J = 12.2, 5.1 Hz, 6H), 3.06 (t, J = 5.4 Hz, 4H), 2.82 (s, 6H), 2.12 (d, J = 15.2 Hz, 4H), 1.65 (s, 4H), 0.41 (s, 4H)。

ESI-MS m/z : 592 [M+H]⁺。

实施例 28 化合物 653 的合成



步骤 1: 化合物 **int_653-2** 的合成

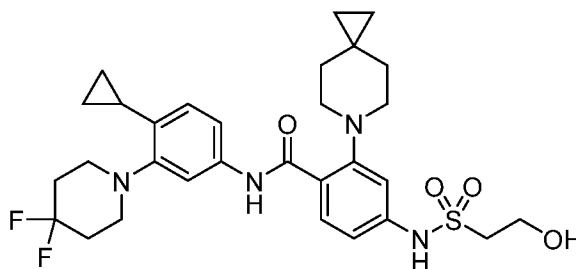


int_653-2

将 **int_1-8** (140 mg, 0.396 mmol)溶于 DCM (50 mL), 加入 **int_653-1** (100 mg, 0.396 mmol)、HATU (300 mg, 0.792 mmol)和 DIPEA (206.8 mg, 1.6 mmol)溶于 DMF (8 mL), 氮气保护下, 反应液室温搅拌 12 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (90 mg, 收率: 38.4%)。

ESI-MS m/z : 592 [M+H]⁺。

步骤 2: 化合物 **653** 的合成



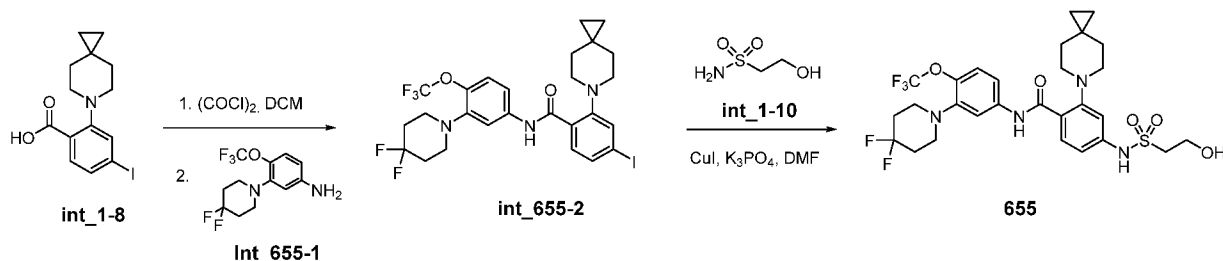
653

将 **int_653-2** (90 mg, 0.152 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (11 mg, 0.076 mmol)、碘化亚铜 (14 mg, 0.076 mmol) 和磷酸钾 (96 mg, 0.456 mmol), 溶解在 DMF (8 mL) 中, 氩气置换三次, 加入 **int_1-10** (38 mg, 0.304 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (25 mg, 收率: 55%)。

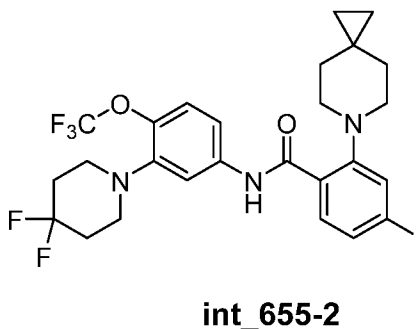
¹H NMR (400 MHz, Chloroform-d) δ 12.40 (s, 1H), 8.19 (d, $J = 8.3$ Hz, 1H), 7.67 (s, 1H), 7.32 (s, 1H), 7.24 (s, 1H), 7.02 (d, $J = 9.7$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 4.13 (s, 2H), 3.32 (d, $J = 5.7$ Hz, 2H), 3.19 (d, $J = 5.8$ Hz, 4H), 3.06 (d, $J = 5.9$ Hz, 4H), 2.70 (s, 1H), 2.16 (dd, $J = 18.3, 10.7$ Hz, 4H), 1.62 (s, 4H), 1.01 – 0.95 (m, 2H), 0.71 (dd, $J = 5.6, 1.8$ Hz, 2H), 0.41 (s, 4H)。

ESI-MS m/z : 589 $[M+H]^+$ 。

实施例 29 化合物 655 的合成



步骤 1: 化合物 **int_655-2** 的合成

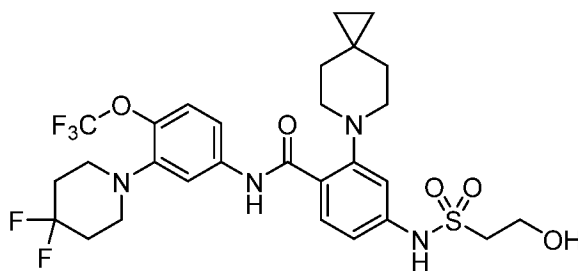


将 **int_1-8** (216.8 mg, 0.607 mmol) 溶于 DCM (50 mL), 加入草酰氯 (761.4 mg, 6 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_655-1** (150 mg, 0.507 mmol) 溶于四氢呋喃 (5 mL), 氮气保护下, 加入 NaH (300 mg, 7.5 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (320 mg, 收率: 99%)。

ESI-MS m/z : 636 $[M+H]^+$ 。

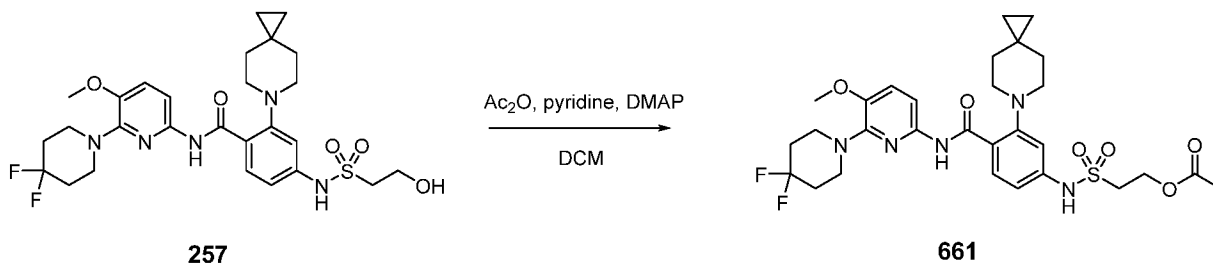
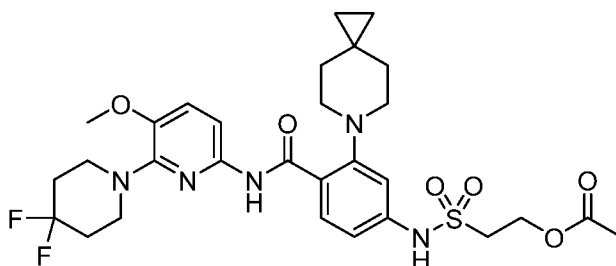
步骤 2: 化合物 655 的合成

**655**

将 **int_655-2** (350 mg, 0.55 mmol)、(1*S*,2*S*)-*N,N'*-二甲基-1,2-环己二胺 (39 mg, 0.27 mmol)、碘化亚铜 (53 mg, 0.28 mmol) 和磷酸钾 (351 mg, 1.66 mmol), 溶解在 DMF (7 mL) 中, 氩气置换三次, 加入 **int_1-10** (138 mg, 1.1 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (250 mg, 收率: 72%)。

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.78 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 2.5 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.30 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.29 (m, 2H), 3.13 (t, *J* = 5.6 Hz, 4H), 2.95 (t, *J* = 5.3 Hz, 4H), 2.09 (p, *J* = 8.1 Hz, 4H), 1.52 (s, 4H), 0.33 (s, 4H)。

ESI-MS *m/z*: 633 [M+H]⁺。

实施例 30 化合物 661 的合成**步骤 1: 化合物 661 的合成****661**

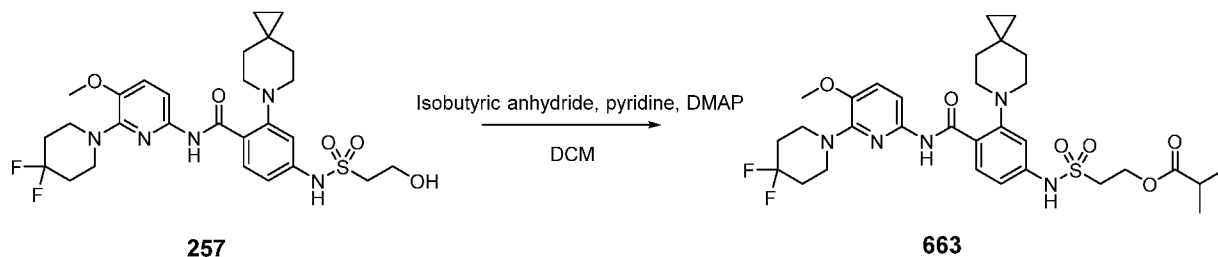
将 **257** (1 g, 1.7 mmol) 溶于二氯甲烷 (20 mL) 中, 加入乙酸酐 (176 mg, 1.7 mmol), 吡啶 (273 mg, 3.5 mmol) 和 DMAP (11 mg, 0.09 mmol), 室温下反应 16 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物, 粗产物经柱层析得到目标产物 (0.7 g, 收率: 70%)。

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.81 (s, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.06 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 3.78 (s,

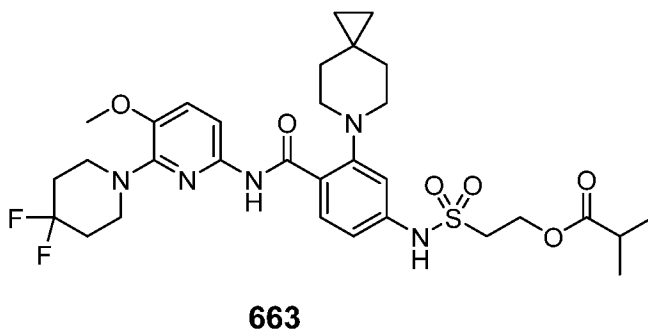
3H), 3.56 (t, $J = 5.7$ Hz, 2H), 3.49 (t, $J = 5.5$ Hz, 4H), 2.94 (t, $J = 5.2$ Hz, 4H), 2.05 (dt, $J = 16.4, 6.8$ Hz, 4H), 1.87 (s, 3H), 1.71 (m, 4H), 0.35 (s, 4H)。

ESI-MS m/z : 622 $[M+H]^+$ 。

实施例 31 化合物 663 的合成



步骤 1: 化合物 663 的合成

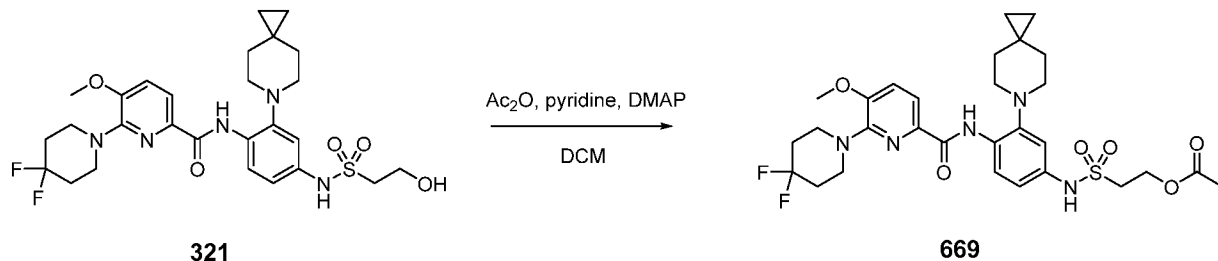


将 **257** (1 g, 1.7 mmol) 溶于二氯甲烷 (20 mL) 中, 加入异丁酸酐 (273 mg, 1.72 mmol), 吡啶 (273 mg, 3.5 mmol) 和 DMAP (11 mg, 0.09 mmol), 室温下反应 16 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物, 粗产物经柱层析得到目标产物 (1.05 g, 收率: 93.7%)。

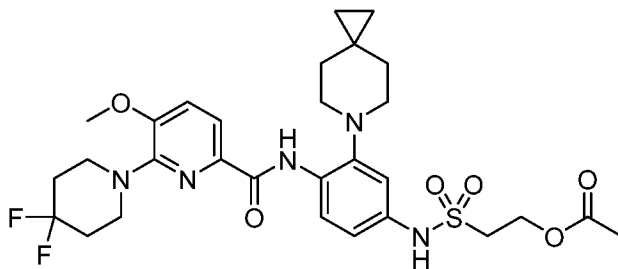
^1H NMR (400 MHz, DMSO- d_6) δ 12.79 (s, 1H), 10.43 (s, 1H), 8.04 (d, $J = 8.6$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.34 (d, $J = 8.6$ Hz, 1H), 7.19 (d, $J = 2.2$ Hz, 1H), 7.08 (dd, $J = 8.7, 2.1$ Hz, 1H), 4.31 (t, $J = 5.5$ Hz, 2H), 3.79 (s, 3H), 3.59 (t, $J = 5.6$ Hz, 2H), 3.50 (t, $J = 5.7$ Hz, 4H), 2.94 (t, $J = 5.3$ Hz, 4H), 2.38 (p, $J = 7.0$ Hz, 1H), 2.07 (q, $J = 9.6, 6.0$ Hz, 4H), 1.73 (m, 4H), 0.98 (d, $J = 7.0$ Hz, 6H), 0.35 (s, 4H)。

ESI-MS m/z : 650 $[M+H]^+$ 。

实施例 32 化合物 669 的合成



步骤 1: 化合物 669 的合成



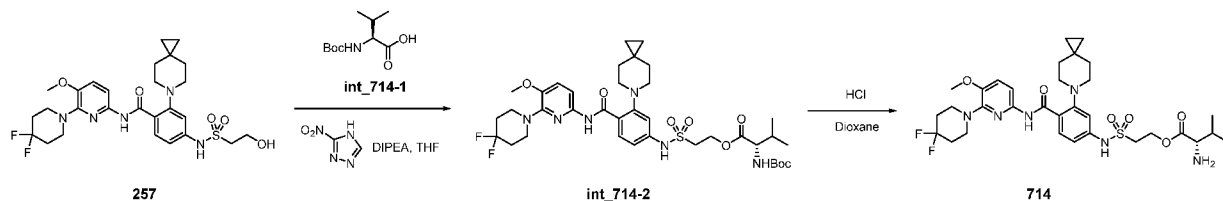
669

将 **321** (455 mg, 0.784 mmol)溶于二氯甲烷(14 mL)中, 加入乙酸酐 (80 mg, 0.784 mmol), 吡啶 (125 mg, 1.58 mmol)和 DMAP (5.2 mg, 0.04 mmol), 室温下反应 16 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物, 粗产物经柱层析得到目标产物 (233 mg, 收率: 48%)。

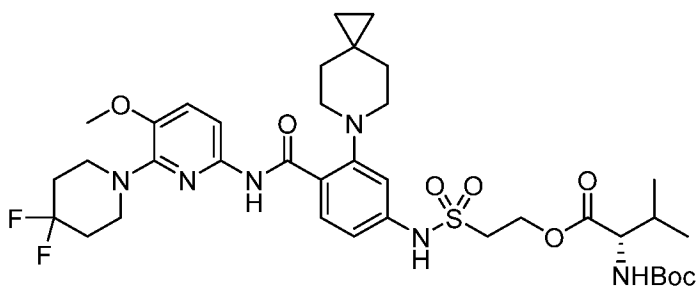
^1H NMR (400 MHz, DMSO- d_6) δ 10.37 (s, 1H), 9.73 (s, 1H), 8.31 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 6.97 (dd, $J = 8.8, 2.4$ Hz, 1H), 4.27 (t, $J = 6.0$ Hz, 2H), 3.90 (s, 3H), 3.56 (s, 4H), 3.41 (t, $J = 6.0$ Hz, 2H), 2.79 (d, $J = 5.3$ Hz, 4H), 2.12 (d, $J = 15.3$ Hz, 4H), 1.95 (s, 3H), 1.53 (s, 4H), 0.33 (s, 4H)。

ESI-MS m/z : 622 $[\text{M}+\text{H}]^+$ 。

实施例 33 化合物 **714** 的合成



步骤 1: 化合物 int_714-2 的合成



int_714-2

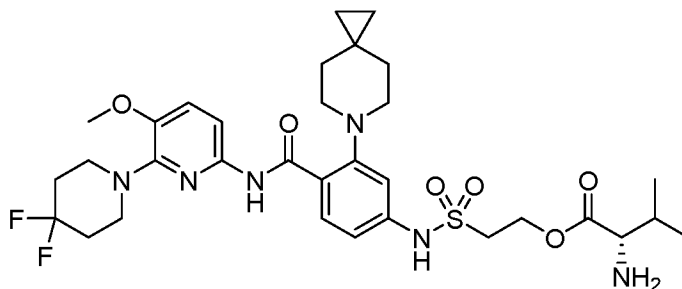
将 **257** (1 g, 1.73 mmol)溶于四氢呋喃(20 mL)中, 加入 **int_714-1** (1.87 g, 8.63 mmol), BOPCl (1.10 g, 4.31 mmol), 3-硝基-4H-1,2,4-三唑 (491.94 mg, 4.31 mmol), DIPEA (1.11 g, 8.63 mmol, 1.50 mL), 室温下反应 16 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物, 粗产物经柱层析纯化(SiO_2 , 乙酸乙酯/甲醇= 1:1)得到目标产物 (1.16 g, 收率: 86.3%)。

^1H NMR (400 MHz, DMSO- d_6) δ 12.79 (s, 1H), 8.03 (d, $J = 8.6$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.34 (d, $J = 8.7$ Hz, 1H), 7.20 (s, 1H), 7.08 (t, $J = 8.6$ Hz, 2H), 4.35 (s, 2H), 3.79 (m, 4H), 3.54 (s, 2H), 3.49 (d, $J =$

5.9 Hz, 4H), 2.95 (s, 4H), 2.20 – 1.94 (m, 4H), 1.89-1.82 (m, 5H), 1.33 (s, 9H), 0.74 (dd, $J = 6.8, 4.7$ Hz, 5H), 0.35 (s, 4H)。

ESI-MS m/z : 779 $[M+H]^+$ 。

步骤 2: 化合物 714 的合成



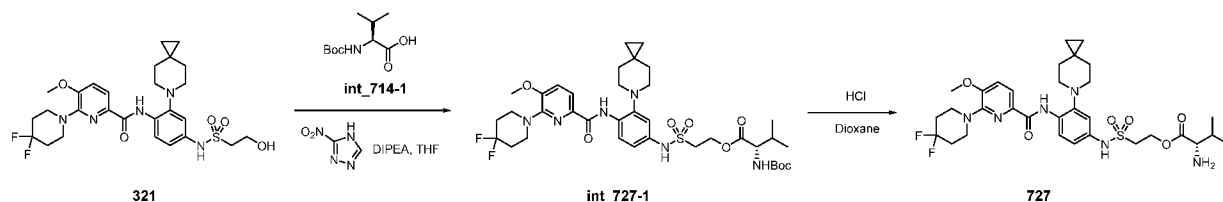
714

将 **int_714-2** (1.16 g, 1.49 mmol) 溶于 HCl/二氧六环溶液中(4 M, 11.6 mL)中, 室温下反应 1 小时, LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物, 向粗产物中加入饱和 NaHCO_3 溶液 (15 mL) 将 pH 值调为 7~8, 水相用二氯甲烷萃(20 mLX2), 合并有机相并用无水硫酸钠干燥。有机相过滤、减压蒸馏得到目标产物 (300 mg, 收率: 29.6%)。

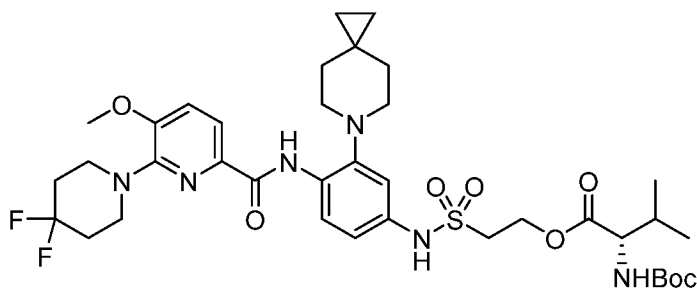
^1H NMR: (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), δ 8.05 (d, $J = 8.6$ Hz, 1H), 7.82 (d, $J = 8.5$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 7.21 (d, $J = 2.2$ Hz, 1H), 7.09 (dd, $J = 8.6, 2.1$ Hz, 1H), 4.37 (t, $J = 5.7$ Hz, 2H), 3.81 (s, 3H), 3.64 - 3.55 (m, 2H), 3.54 - 3.41 (m, 4H), 3.05 (d, $J = 5.3$ Hz, 1H), 2.97 (br s, 4H), 2.15 - 2.02 (m, 4H), 1.93 - 1.52 (m, 5H), δ 0.81 (d, $J = 6.8$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H), 0.37 (s, 4H)。

ESI-MS m/z : 679 $[M+H]^+$ 。

实施例 34 化合物 727 的合成



步骤 1: 化合物 **int_727-1** 的合成

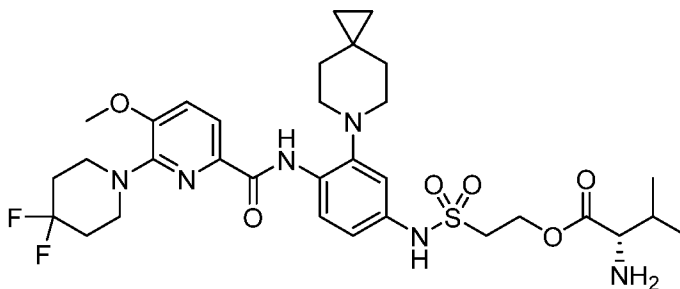


int_727-1

将 **321** (1.3 g, 2.25 mmol) 溶于四氢呋喃(100 mL)中, 加入 **int_714-1** (2.4 g, 11.22 mmol), BOPCl (1.4 g, 5.61 mmol), 3-硝基-4H-1, 2, 4-三唑 (640 mg, 5.61 mmol), DIPEA (646.25 mg, 5 mmol), 室温下反应 4 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物, 粗产物经柱层析纯化(SiO₂, 正己烷/乙酸乙酯=5:1 到 1:1)得到目标产物 (1.1 g, 收率: 62.9%)。

ESI-MS m/z : 779 $[M+H]^+$ 。

步骤 2: 化合物 **727** 的合成



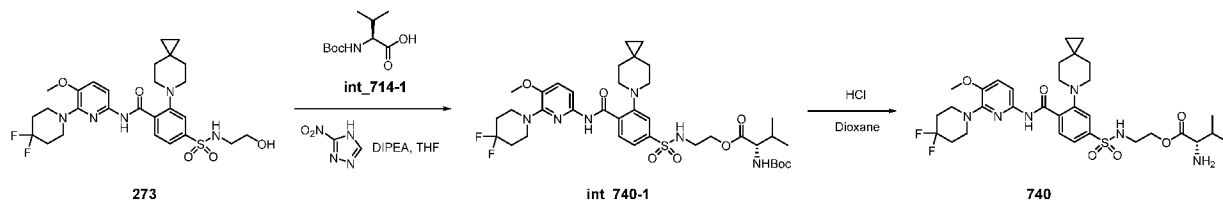
727

将 **int_727-1** (550 mg, 0.71 mmol) 溶于 HCl/二氧六环溶液(4 M, 11 mL)中, 室温下反应 1 小时, LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物, 向粗产物中加入饱和 NaHCO₃ 溶液 (6 mL) 将 pH 值调为 7~8, 水相用二氯甲烷萃(6 mLX3), 合并有机相并用无水硫酸钠干燥。有机相过滤、减压蒸馏得到产物, 将产物进一步通过 prep-HPLC 纯化(column: Phenomenex C18 250*50 mm*10 μ m; mobile phase: [water (ammonia hydroxide v/v)-ACN]; B%: 43%-73%, 8 min.)得到目标产物 (291 mg, 收率: 58.8%)。

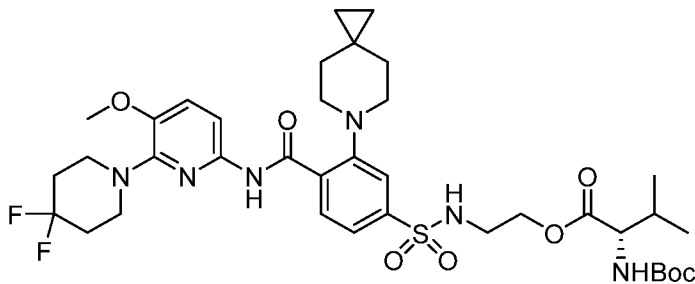
¹H NMR: (400 MHz, DMSO-d₆) δ 10.44 - 10.34 (m, 1H), 8.34 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 7.06 - 6.96 (m, 1H), 4.35 (t, J = 6.0 Hz, 2H), 3.93 (s, 3H), 3.65 - 3.54 (m, 4H), 3.07 (br d, J = 5.3 Hz, 1H), 2.82 (br t, J = 4.9 Hz, 4H), 2.22 - 2.10 (m, 4H), 1.85 - 1.71 (m, 1H), 1.67 - 1.42 (m, 4H), 0.88 - 0.73 (m, 6H), 0.35 (s, 4H)。

ESI-MS m/z : 679 $[M+H]^+$ 。

实施例 35 化合物 **740** 的合成



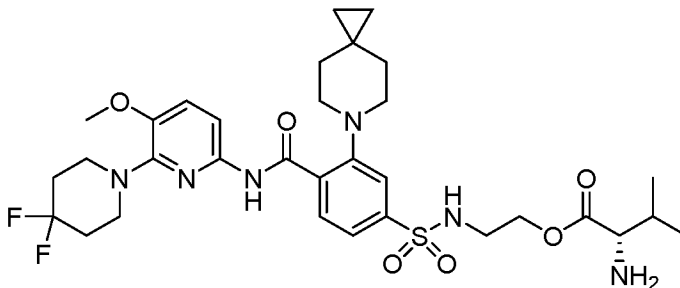
步骤 1: 化合物 **int_740-1** 的合成

**int_740-1**

将 **273** (1.3 g, 2.25 mmol) 溶于四氢呋喃(100 mL)中, 加入 **int_714-1** (2.4 g, 11.22 mmol), BOPCl (1.4 g, 5.61 mmol), 3-硝基-4H-1, 2, 4-三唑 (640 mg, 5.61 mmol), DIPEA (646.25 mg, 5 mmol), 室温下反应 4 小时, LC-MS 监测显示反应结束。将反应液过滤得到滤液, 滤液减压浓缩得到粗产物, 粗产物经柱层析纯化得到目标产物 (1 g, 收率: 65.8%)。

ESI-MS m/z : 779 $[M+H]^+$ 。

步骤 2: 化合物 **740** 的合成

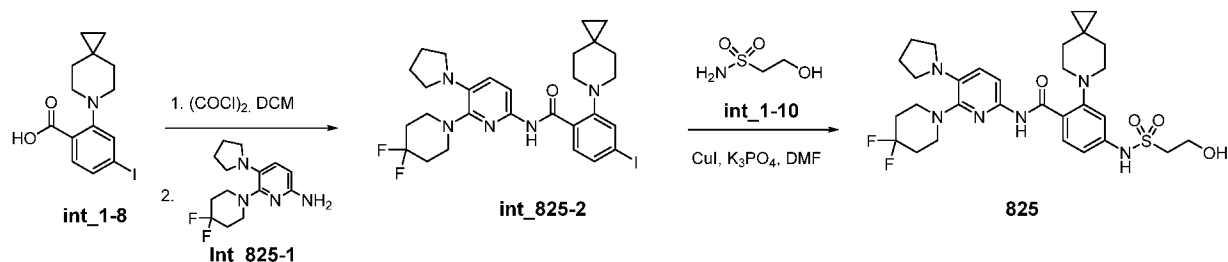
**740**

将 **int_740-1** (800 mg, 1.03 mmol) 溶于 HCl/二氧六环溶液中(4 M, 11 mL)中, 室温下反应 1 小时, LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物, 向粗产物中加入饱和 NaHCO_3 溶液 (8 mL) 将 pH 值调为 7~8, 水相用二氯甲烷萃(8 mLX3), 合并有机相并用无水硫酸钠干燥。有机相过滤、减压蒸馏得到目标产物 (310 mg, 收率: 44.3%)。

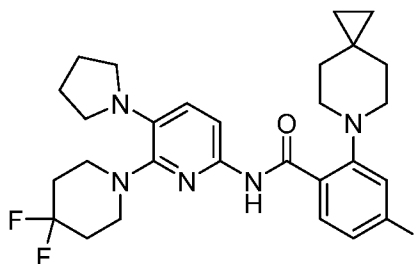
^1H NMR: (400 MHz, Chloroform- d) δ 12.53 (s, 1H), 8.36 – 8.34 (m, 1H), 7.85 – 7.80 (m, 1H), 7.73 (s, 1H), 7.66 – 7.64 (m, 1H), 7.11 – 7.04 (m, 1H), 4.21 - 4.10 (m, 2H), 4.13 (s, 3H), 3.52 - 3.35 (m, 4H), 3.25 - 3.20 (m, 1H), 3.20 - 3.10 (m, 2H), 3.05 (m, 4H), 2.12 - 2.10 (m, 4H), 1.90 - 1.71 (m, 1H), 1.75 - 1.42 (m, 4H), 0.75 - 0.85 (m, 6H), 0.34 (s, 4H)。

ESI-MS m/z : 679 $[M+H]^+$ 。

实施例 36 化合物 **825** 的合成



步骤 1: 化合物 int_825-2 的合成



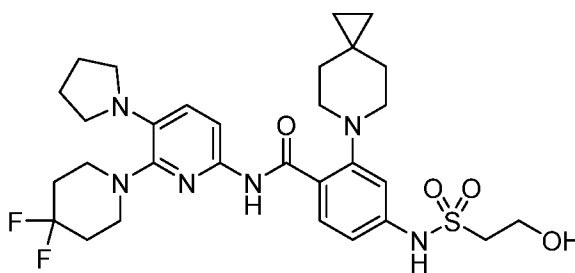
int_825-2

将 int_1-8 (95 mg, 0.266 mmol) 溶于 DCM (50 mL), 加入草酰氯 (380 mg, 3 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 int_825-1 (75 mg, 0.266 mmol) 溶于四氢呋喃 (6 mL), 氮气保护下, 加入 NaH (100 mg, 2.5 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 10 : 1) 纯化得固体(59 mg, 收率: 35.7%)。

ESI-MS m/z: 622 [M+H]⁺

步骤 2: 化合物 825 的合成



825

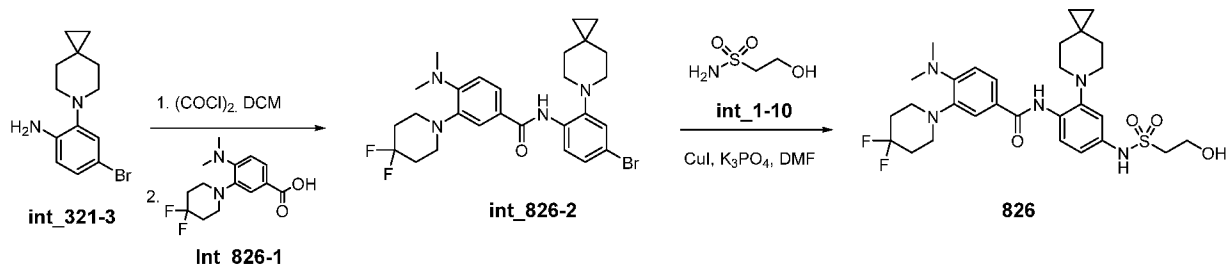
将 int_825-2 (59 mg, 0.095 mmol)、(1S,2S)-N,N'-二甲基-1,2-环己二胺 (7 mg, 0.047 mmol)、碘化亚铜 (10 mg, 0.047 mmol) 和磷酸钾 (60 mg, 0.285 mmol), 溶解在 DMF (5 mL) 中, 氩气置换三次, 加入 int_1-10 (24 mg, 0.189 mmol), 氩气保护下, 反应液加热到 90°C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(7 mg, 收率: 12.1%)。

¹H NMR (400 MHz, DMSO-d₆) δ 12.84 (s, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.14 (m, 2H), 7.07 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.73 (t, *J* = 6.5 Hz, 2H), 3.38 (t, *J* = 5.6 Hz, 4H), 3.31 (t, *J* = 6.5 Hz, 2H), 3.06 (d, *J* = 5.9 Hz, 4H), 2.95 (d, *J* = 5.4 Hz, 4H), 2.10 (tt, *J* = 13.1, 5.5 Hz, 4H), 1.93 – 1.50 (m,

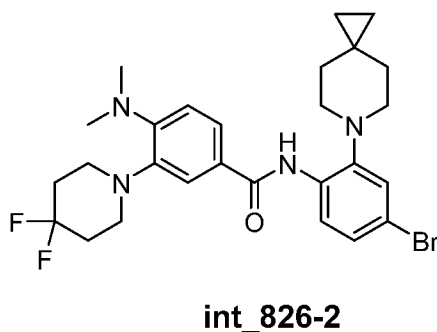
8H), 0.36 (s, 4H)。

ESI-MS m/z : 619 $[M+H]^+$ 。

实施例 37 化合物 826 的合成



步骤 1: 化合物 int_826-2 的合成

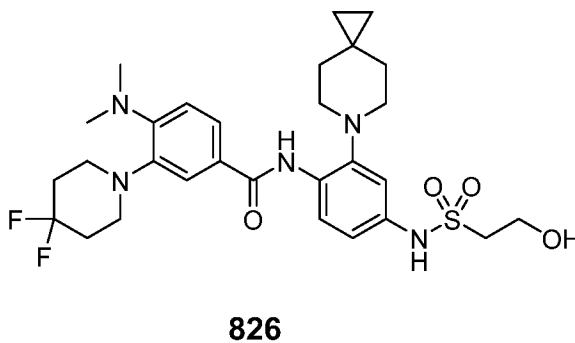


将 **int_321-3** (187.6 mg, 0.605 mmol) 溶于 DCM (10 mL), 加入草酰氯 (760 mg, 6 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_826-1** (170 mg, 0.605 mmol) 溶于四氢呋喃 (10 mL), 氮气保护下, 加入 NaH (170 mg, 4.25 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 $40^\circ C$ 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO_2 , 正己烷/乙酸乙酯 = 10 : 1)纯化得固体(190 mg, 收率: 58.1%)。

ESI-MS m/z : 547 $[M+H]^+$ 。

步骤 2: 化合物 826 的合成



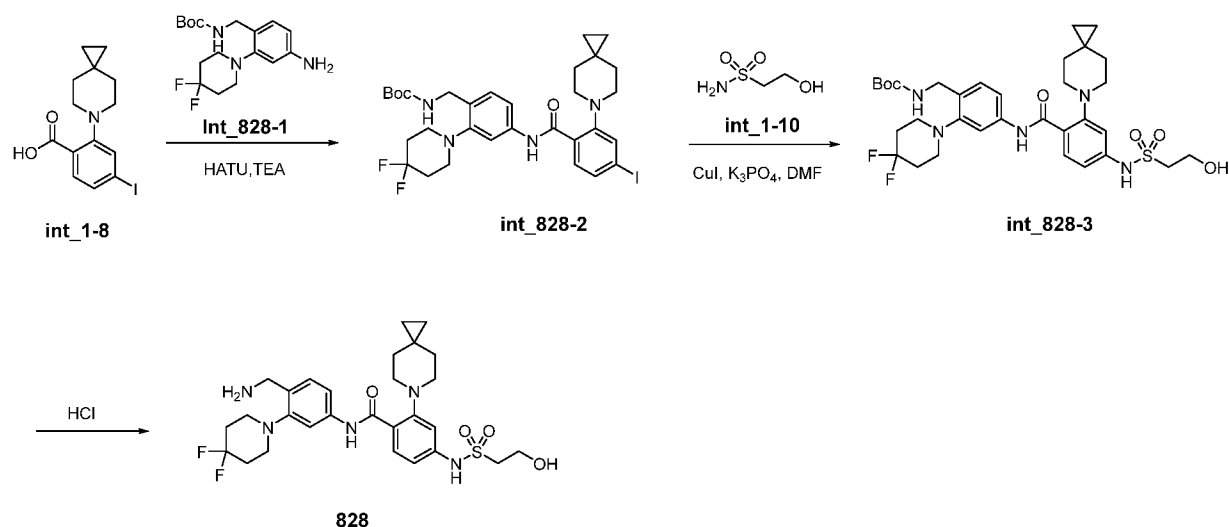
将 **int_826-2** (190 mg, 0.345 mmol)、N,N-二甲基甘氨酸 (25 mg, 0.173 mmol)、碘化亚铜 (33 mg, 0.173 mmol) 和磷酸钾 (219 mg, 1.035 mmol), 溶解在 DMF (4 mL) 中, 氩气置换三次, 加入 **int_1-10** (65 mg, 0.518 mmol), 氩气保护下, 反应液加热到 $130^\circ C$ 反应 3 小时。LC-MS 监测显示反应结束。将反

应液冷却至室温，将反应液旋干，柱层析纯化得固体(51 mg, 收率: 25%)。

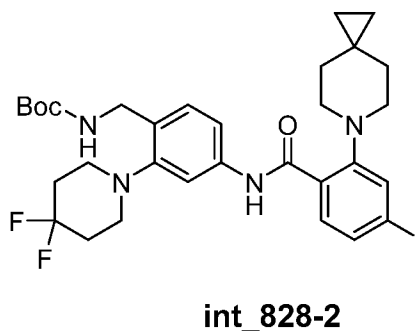
^1H NMR (400 MHz, DMSO- d_6) δ 9.36 (s, 1H), 8.06 (d, $J = 8.7$ Hz, 1H), 7.55 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.48 (d, $J = 2.2$ Hz, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.95 (dd, $J = 8.7, 2.4$ Hz, 1H), 3.72 (t, $J = 6.8$ Hz, 2H), 3.18 (q, $J = 7.0$ Hz, 6H), 2.88 (s, 6H), 2.82 (t, $J = 5.3$ Hz, 4H), 2.21 – 2.10 (m, 4H), 1.51 (s, 4H), 0.34 (s, 4H)。

ESI-MS m/z : 592 $[\text{M}+\text{H}]^+$ 。

实施例 38 化合物 828 的合成



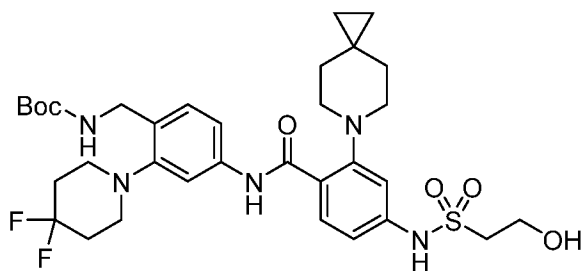
步骤 1: 化合物 **int_828-2** 的合成



将 **int_1-8** (356 mg, 1 mmol) 溶于 DCM (50 mL)，加入 **int_828-1** (340 mg, 1 mmol)、HATU (760 mg, 2 mmol) 和 TEA (304 mg, 3 mmol) 溶于 DMF (8 mL)，氮气保护下，反应液室温搅拌 12 小时。LC-MS 监测显示反应结束。将反应液减压浓缩得到粗产物。粗产物经过柱层析纯化得固体 (500 mg, 收率: 83.6%)。

ESI-MS m/z : 681 $[\text{M}+\text{H}]^+$ 。

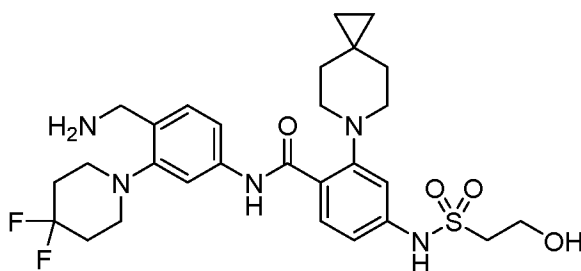
步骤 2: 化合物 828-3 的合成

**int_828-3**

将 **int_828-2** (200 mg, 0.29 mmol)、(1S,2S)-(+)-N,N'-二甲基-1,2-环己二胺 (20 mg, 0.145 mmol)、碘化亚铜 (30 mg, 0.145 mmol) 和磷酸钾 (180 mg, 0.87 mmol), 溶解在 DMF (8 mL) 中, 氩气置换三次, 加入 **int_1-10** (60 mg, 0.47 mmol), 氩气保护下, 反应液加热到 90 °C 反应 12 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体 (140 mg, 收率: 70.3%)。

ESI-MS m/z : 678 $[M+H]^+$ 。

步骤 3: 化合物 828 的合成

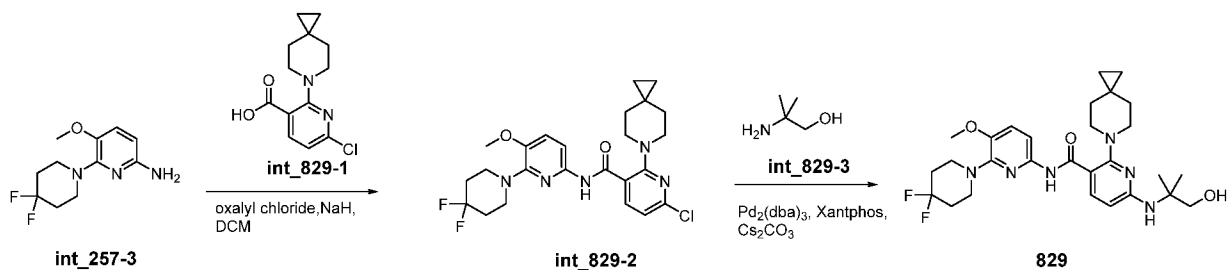
**828**

将 **int_828-3** (80 mg, 0.118 mmol) 溶解在甲醇/盐酸 (4 N, 10 mL) 中, 反应液于室温反应 12 小时。LC-MS 监测显示反应结束。将反应液旋干, 柱层析纯化得固体 (50 mg, 收率: 73.5%)。

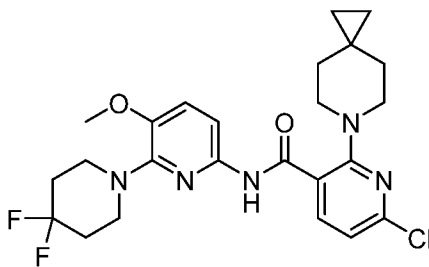
^1H NMR (400 MHz, DMSO- d_6) δ 12.10 (s, 1H), 7.76 (d, $J = 8.6$ Hz, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.48 (dd, $J = 8.3, 2.0$ Hz, 1H), 7.41 (s, 1H), 7.00 (d, $J = 2.1$ Hz, 1H), 6.86 (dd, $J = 8.6, 2.0$ Hz, 1H), 3.84 (s, 2H), 3.71 (t, $J = 6.6$ Hz, 2H), 3.18 – 3.10 (m, 2H), 2.94 (dt, $J = 11.8, 5.5$ Hz, 8H), 2.19 – 2.07 (m, 4H), 1.54 (s, 4H), 0.34 (s, 4H)。

ESI-MS m/z : 578 $[M+H]^+$ 。

实施例 39 化合物 829 的合成



步骤 1: 化合物 int_829-2 的合成

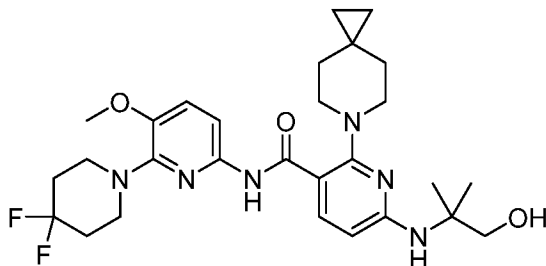
**int_829-2**

将 **int_257-3** (100 mg, 0.374 mmol) 溶于 DCM (10 mL), 加入草酰氯 (380 mg, 3 mmol), 反应液室温搅拌 2 小时后, 减压浓缩除去溶剂得到酰氯产物。

将 **int_829-1** (100 mg, 0.411 mmol) 溶于四氢呋喃 (10 mL), 氮气保护下, 加入 NaH (80 mg, 2 mmol, 纯度 60%), 室温搅拌 0.5 小时后, 于室温下加入前述制备得到的酰氯, 反应液升至 40°C 搅拌 10 小时。LC-MS 监测显示反应结束。冰浴下加入甲醇淬灭反应, 将反应液减压浓缩得到粗产物。粗产物经过柱层析(SiO₂, 正己烷/乙酸乙酯 = 6 : 1)纯化得固体(90 mg, 收率: 44.5%)。

ESI-MS *m/z*: 492 [M+H]⁺。

步骤 2: 化合物 829 的合成

**829**

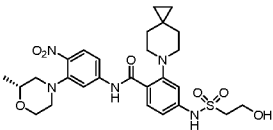
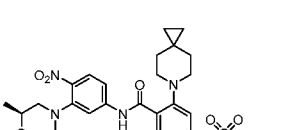
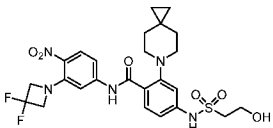
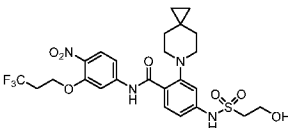
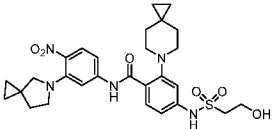
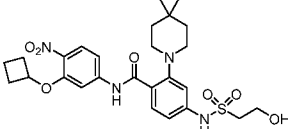
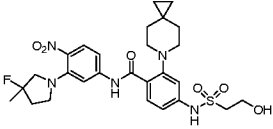
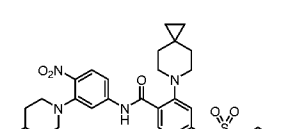
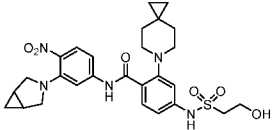
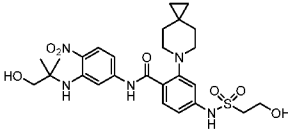
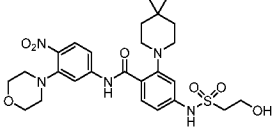
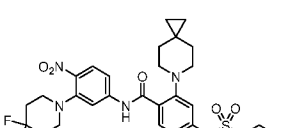
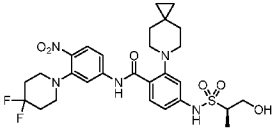
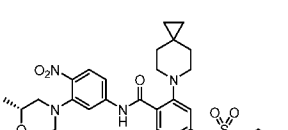
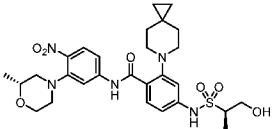
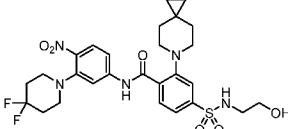
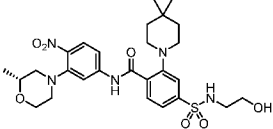
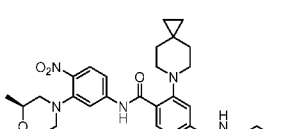
将 **int_829-2** (90 mg, 0.183 mmol)、**int_829-3** (33 mg, 0.366 mmol)、碳酸铯 (90 mg, 0.274 mmol)、Pd₂(dba)₃ (17 mg, 0.0183 mmol) 和 XantPhos (10 mg, 0.0183 mmol), 溶解在 1,4-二氧六环 (8 mL) 中, 氩气置换三次, 氩气保护下, 反应液加热到 95 °C 反应 16 小时。LC-MS 监测显示反应结束。将反应液冷却至室温, 将反应液旋干, 柱层析纯化得固体(50 mg, 收率: 50.5%)。

¹H NMR (400 MHz, DMSO-d₆) δ 11.82 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.18 (s, 2H), 3.78 (s, 3H), 3.51 (d, *J* = 5.8 Hz, 4H), 3.12 (t, *J* = 5.4 Hz, 4H), 2.05 (tt, *J* = 13.7, 5.4 Hz, 4H), 1.64 (d, *J* = 5.7 Hz, 4H), 1.22 (s, 6H), 0.33 (s, 4H)。

ESI-MS *m/z*: 545 [M+H]⁺。

使用上述合成方法, 采用不同原料, 可以得到表 1 中目标化合物 **5**, **8-64**, **66-96**, **98-128**, **130-160**, **162-256**, **264-272**, **274-320**, **322-336**, **338-352**, **354-368**, **370-384**, **386-576**, **578-640**, **642**, **644**, **646-652**, **654**, **656-660**, **662**, **664-668**, **670-713**, **715-726**, **728-739**, **741-824**, **827**, **830-837**。

表 1

化合物	化合物结构	MS (M+H) ⁺	化合物	化合物结构	MS (M+H) ⁺
2		574	3		574
4		566	5		587
6		570	7		545
8		576	9		576
10		556	11		562
12		560	13		608
14		608	15		588
16		588	17		594
18		574	19		574

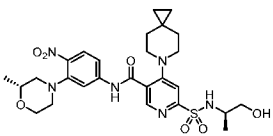
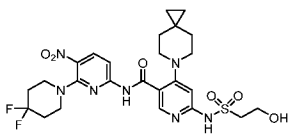
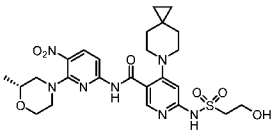
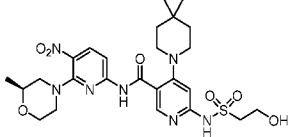
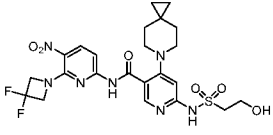
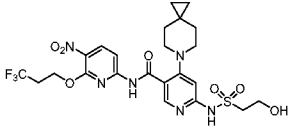
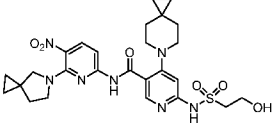
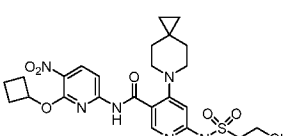
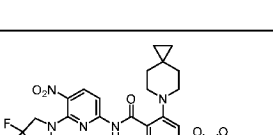
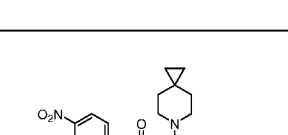
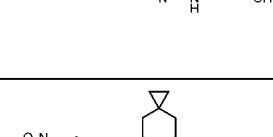
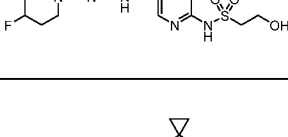
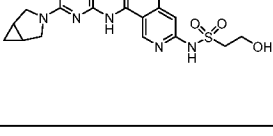
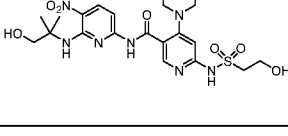
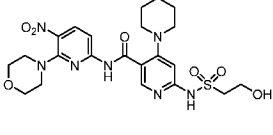
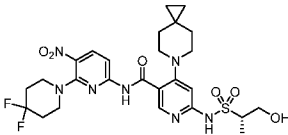
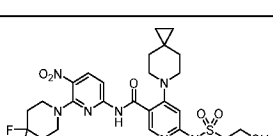
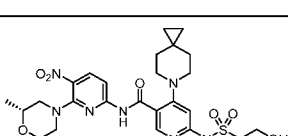
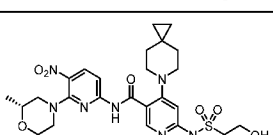
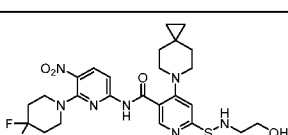
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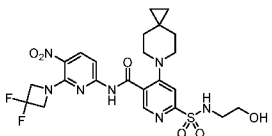
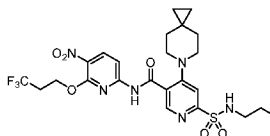
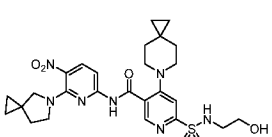
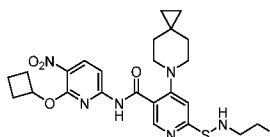
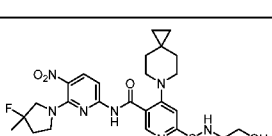
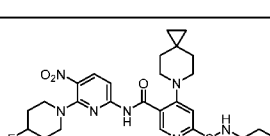
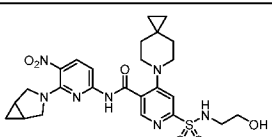
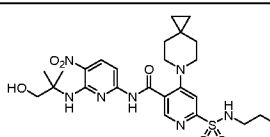
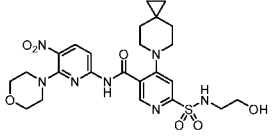
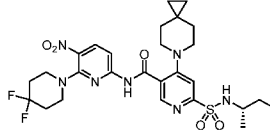
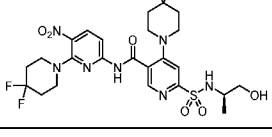
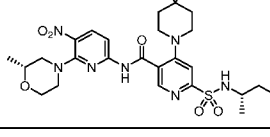
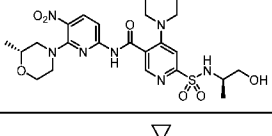
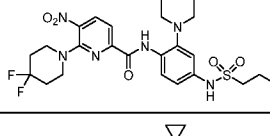
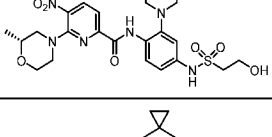
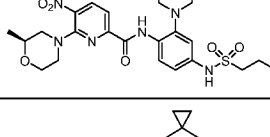
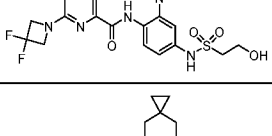
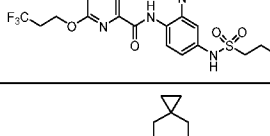
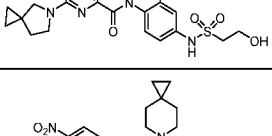
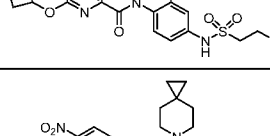
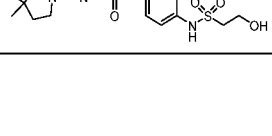
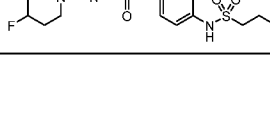
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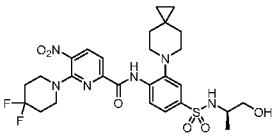
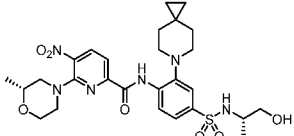
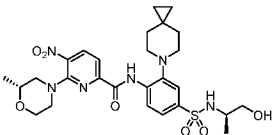
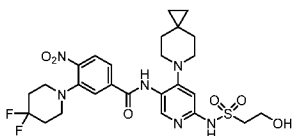
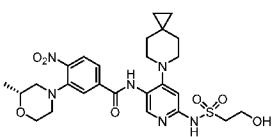
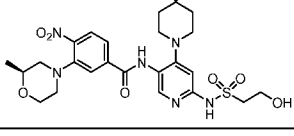
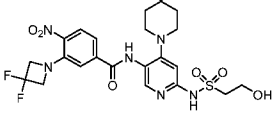
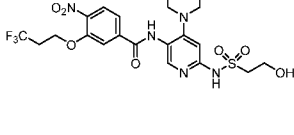
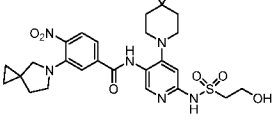
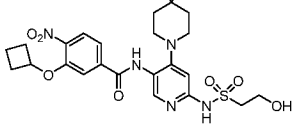
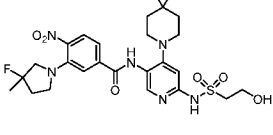
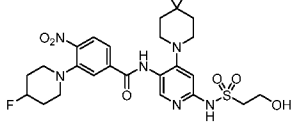
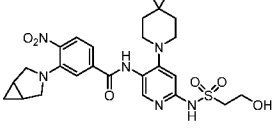
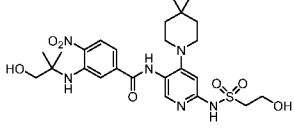
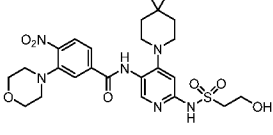
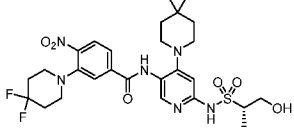
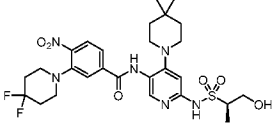
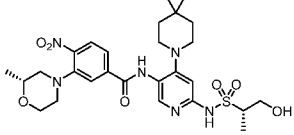
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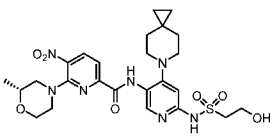
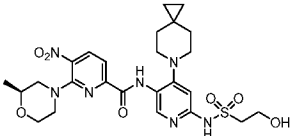
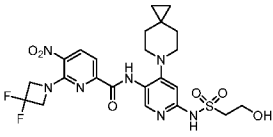
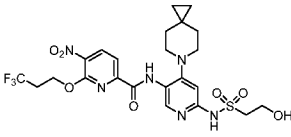
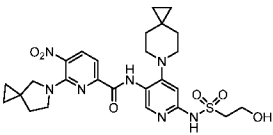
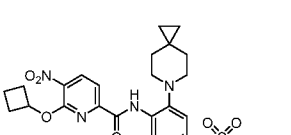
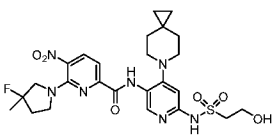
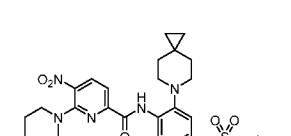
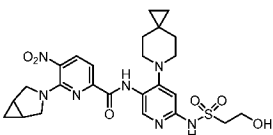
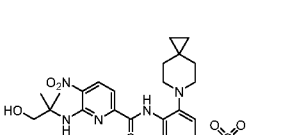
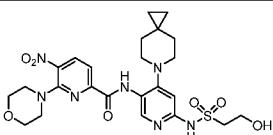
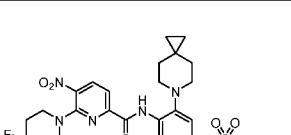
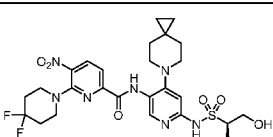
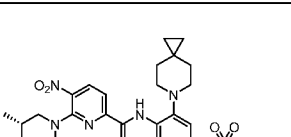
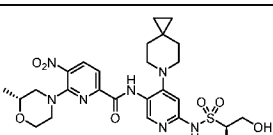
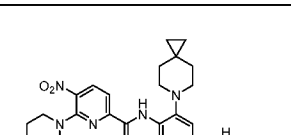
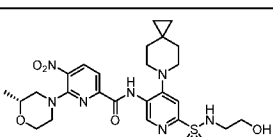
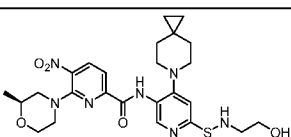
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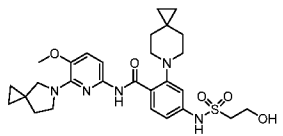
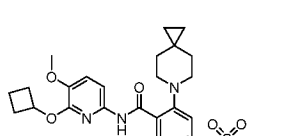
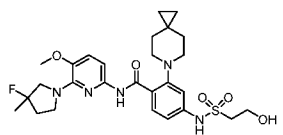
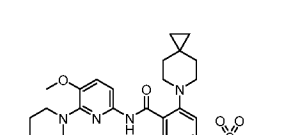
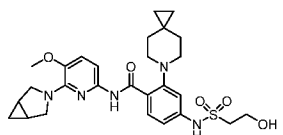
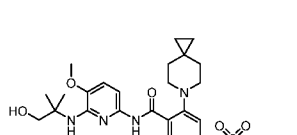
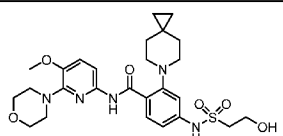
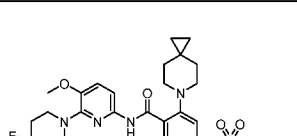
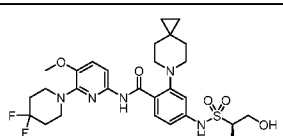
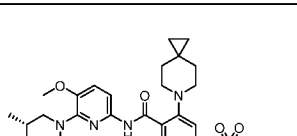
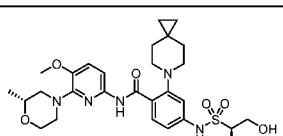
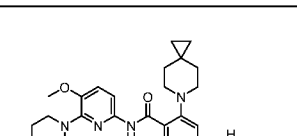
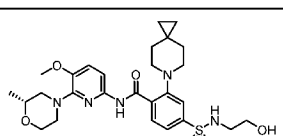
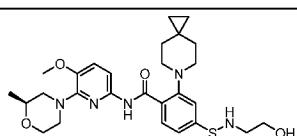
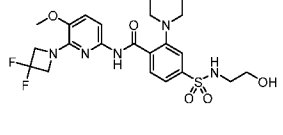
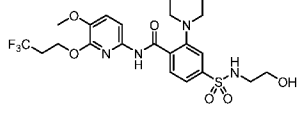
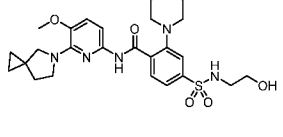
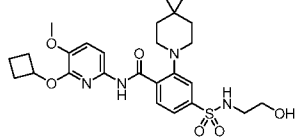
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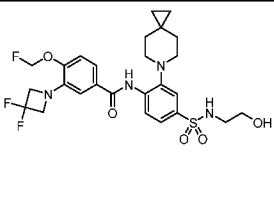
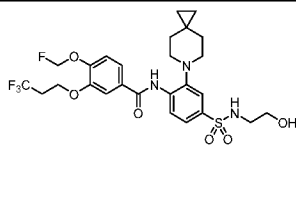
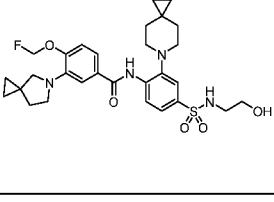
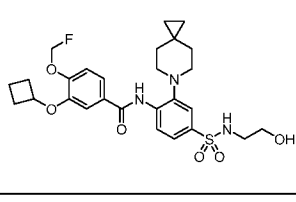
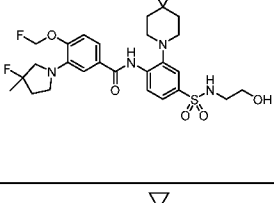
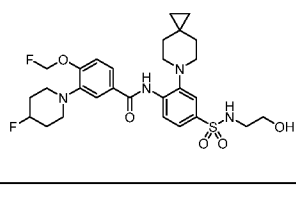
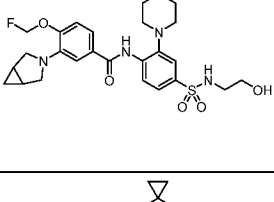
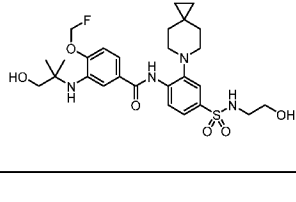
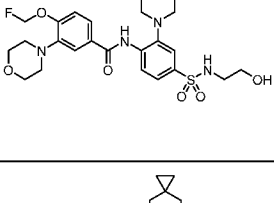
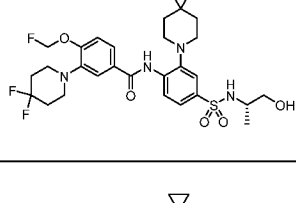
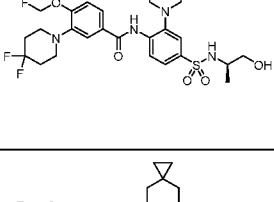
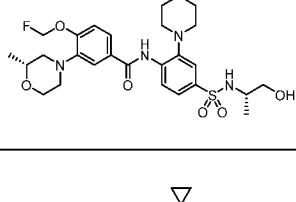
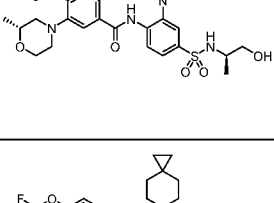
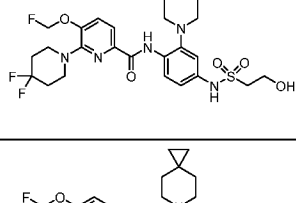
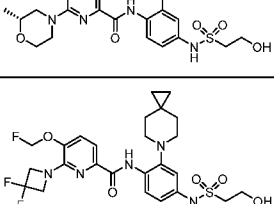
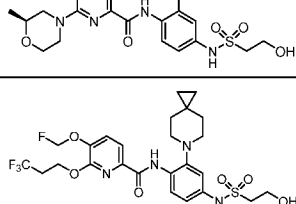
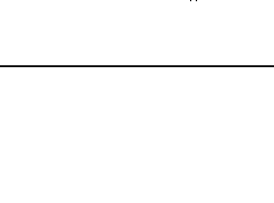
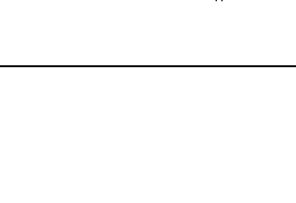
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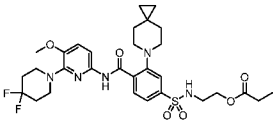
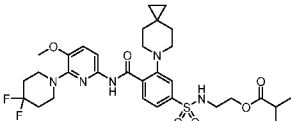
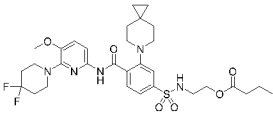
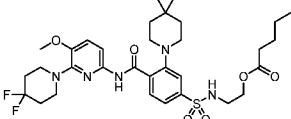
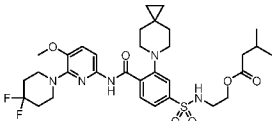
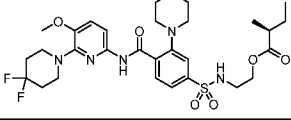
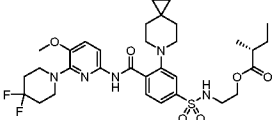
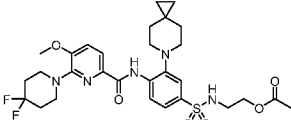
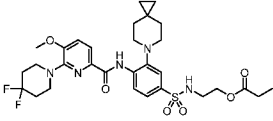
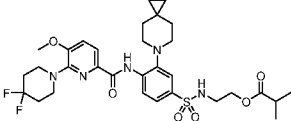
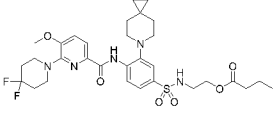
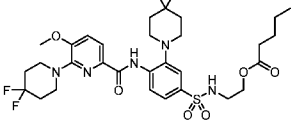
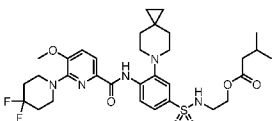
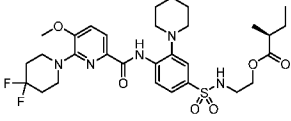
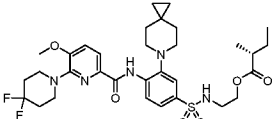
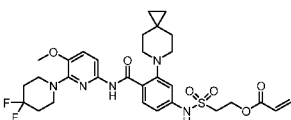
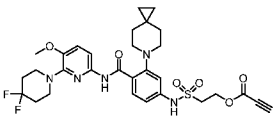
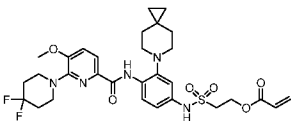
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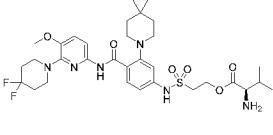
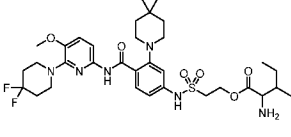
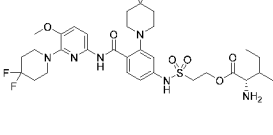
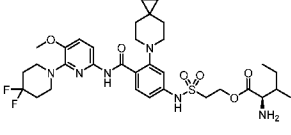
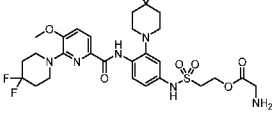
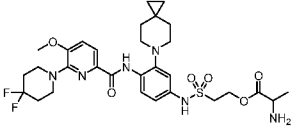
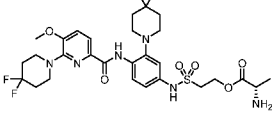
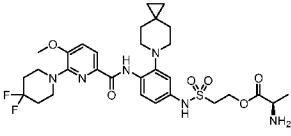
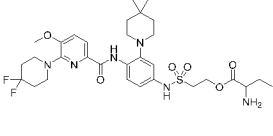
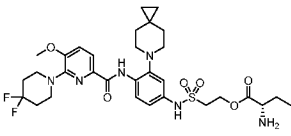
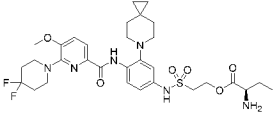
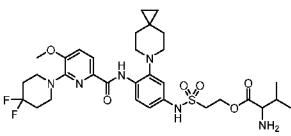
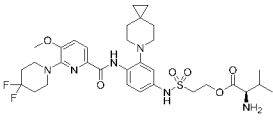
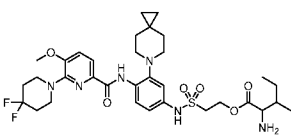
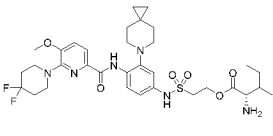
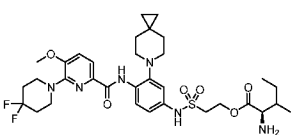
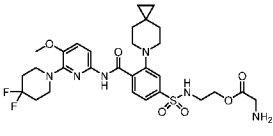
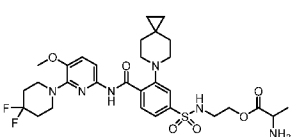
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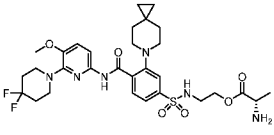
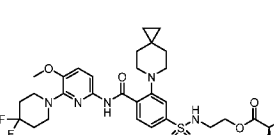
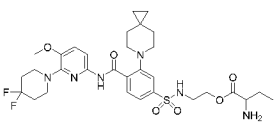
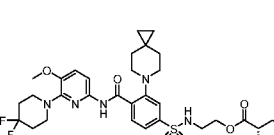
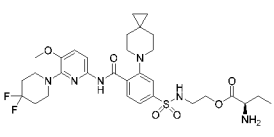
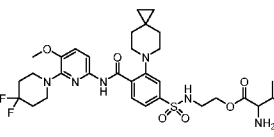
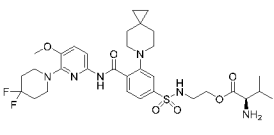
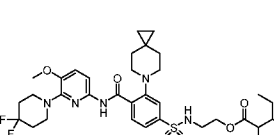
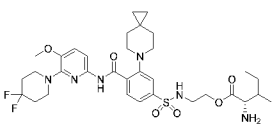
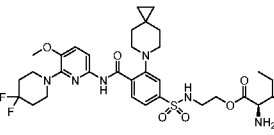
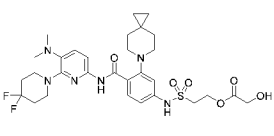
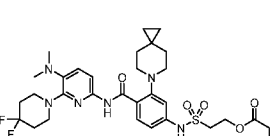
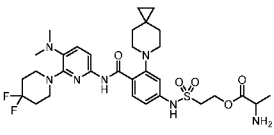
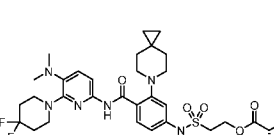
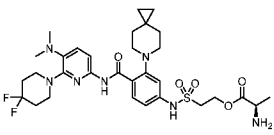
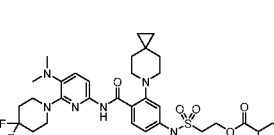
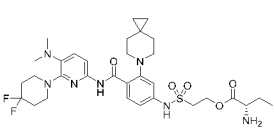
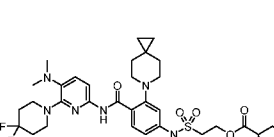
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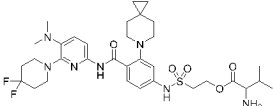
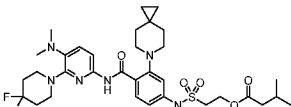
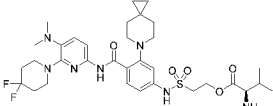
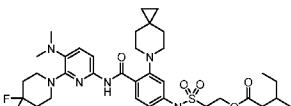
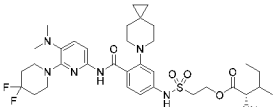
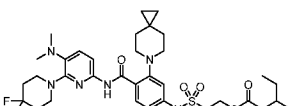
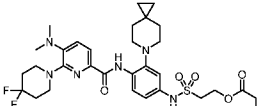
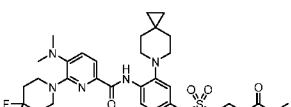
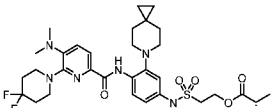
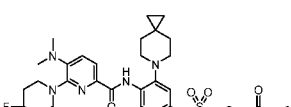
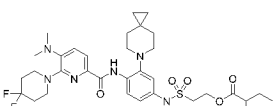
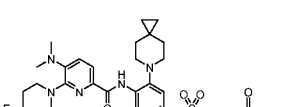
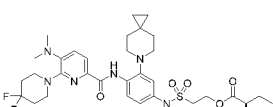
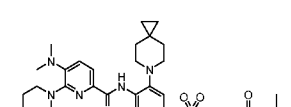
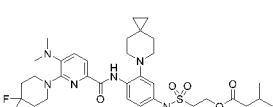
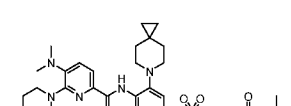
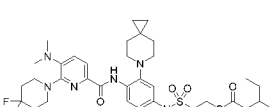
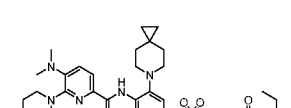
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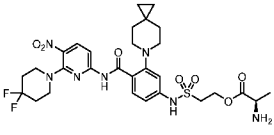
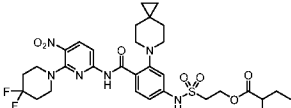
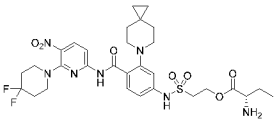
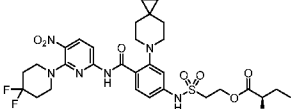
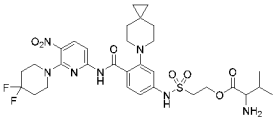
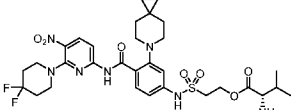
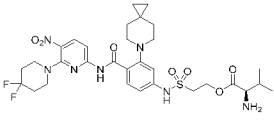
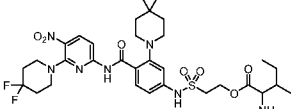
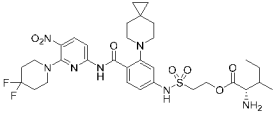
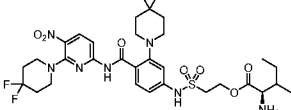
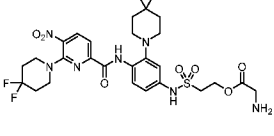
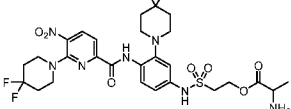
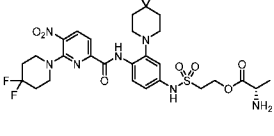
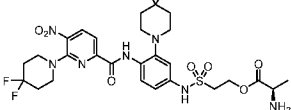
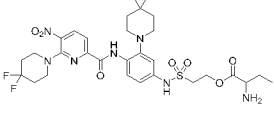
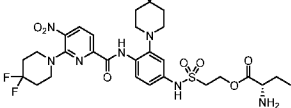
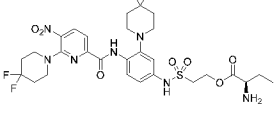
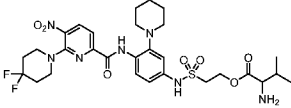
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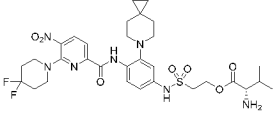
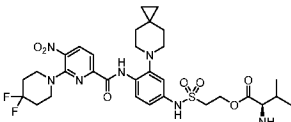
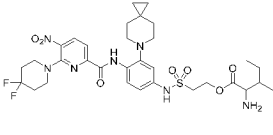
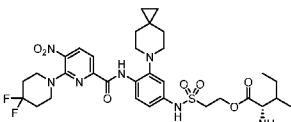
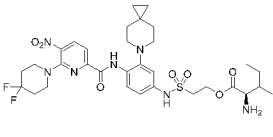
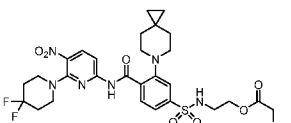
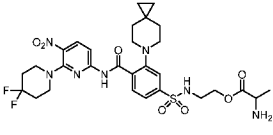
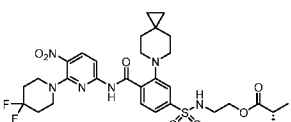
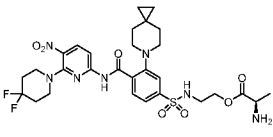
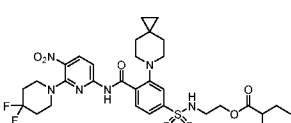
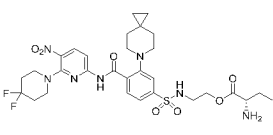
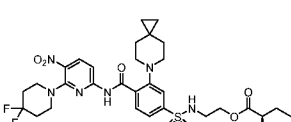
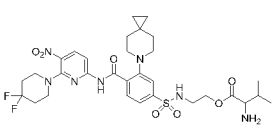
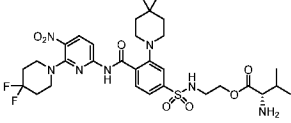
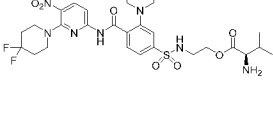
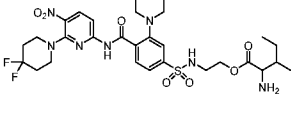
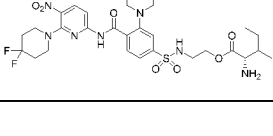
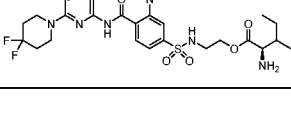
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730		693	731		693
732		637	733		651

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738		665	739		679
741		679	742		693
743		693	744		693
745		651	746		650
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749		664	750		678
751		678	752		678

753		692	754		692
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757		706	758		706
759		650	760		664
761		664	762		664
763		678	764		678
765		678	766		692
767		692	768		692
769		706	770		706

771		706	772		650
773		664	774		664
775		664	776		678
777		678	778		678
779		692	780		692
781		692	782		706
783		706	784		706
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805		680	806		694

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809		708	810		708
811		708	812		652
813		666	814		666
815		666	816		680
817		680	818		680
819		694	820		694
821		694	822		708
823		708	824		708

825		619	826		592
827		578	828		578
829		545	830		564
831		593	832		579
833		636	834		594
835		572	836		594
837		580			

表 2 表 1 中部分化合物的核磁数据

化合物	核磁
827	^1H NMR (400 MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.53 (s, 1H), 7.10 (s, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 5.86 (d, J = 5.8 Hz, 1H), 3.72 (t, J = 6.8 Hz, 2H), 3.18 (t, J = 6.6 Hz, 2H), 2.92 (s, 4H), 2.81 (d, J = 5.3 Hz, 7H), 2.18 (s, 4H), 1.53 (s, 4H), 0.34 (s, 4H).
830	^1H NMR (400 MHz, Chloroform- d) δ 12.21 (s, 1H), 8.22 – 8.04 (m, 1H), 7.69 (s, 1H), 7.44 – 7.29 (m, 1H), 7.21 – 6.95 (m, 2H), 6.75 (d, J = 8.3 Hz, 1H), 4.11 (s, 2H), 3.31 (s, 2H), 3.06 (s, 8H), 2.14 (t, J = 14.6 Hz, 4H), 1.61 (s, 4H), 0.43 (s, 4H).

831	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.35 (s, 1H), 9.57 (s, 1H), 8.33 (d, <i>J</i> = 8.8 Hz, 1H), 7.73 (d, <i>J</i> = 8.1 Hz, 1H), 7.35 (d, <i>J</i> = 8.2 Hz, 1H), 7.15 (d, <i>J</i> = 2.4 Hz, 1H), 6.98 (dd, <i>J</i> = 8.8, 2.4 Hz, 1H), 4.91 (s, 1H), 3.71 (t, <i>J</i> = 6.8 Hz, 2H), 3.53 (t, <i>J</i> = 5.6 Hz, 4H), 3.19 (t, <i>J</i> = 6.7 Hz, 2H), 2.85 (s, 6H), 2.78 (d, <i>J</i> = 5.5 Hz, 4H), 2.26 – 2.12 (m, 4H), 1.53 (s, 4H), 0.34 (s, 4H).
832	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.33 (s, 1H), 8.33 (d, <i>J</i> = 8.8 Hz, 1H), 7.79 (d, <i>J</i> = 8.2 Hz, 1H), 7.12 (d, <i>J</i> = 2.4 Hz, 1H), 6.96 (d, <i>J</i> = 8.9 Hz, 2H), 5.94 (d, <i>J</i> = 5.4 Hz, 1H), 3.71 (t, <i>J</i> = 6.7 Hz, 2H), 3.18 (dd, <i>J</i> = 12.3, 6.2 Hz, 6H), 2.80 (d, <i>J</i> = 5.4 Hz, 7H), 2.23 (s, 4H), 1.57 (s, 4H), 0.33 (s, 4H).
833	¹ H NMR (400 MHz, Chloroform-d) δ 11.25 (s, 1H), 8.16 (d, <i>J</i> = 8.5 Hz, 1H), 7.92 (d, <i>J</i> = 8.6 Hz, 1H), 7.52 (s, 1H), 7.14 (d, <i>J</i> = 8.6 Hz, 1H), 7.01 (d, <i>J</i> = 10.2 Hz, 1H), 6.68 (s, 1H), 4.15 (s, 2H), 3.87 (s, 3H), 3.49 (d, <i>J</i> = 5.6 Hz, 4H), 3.33 – 3.30 (m, 2H), 3.21 (d, <i>J</i> = 12.3 Hz, 2H), 2.99 (t, <i>J</i> = 11.9 Hz, 2H), 1.69 (d, <i>J</i> = 14.0 Hz, 4H), 1.43 – 1.38 (m, 4H), 1.27 (s, 3H).
834	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.89 (s, 1H), 7.95 (d, <i>J</i> = 8.7 Hz, 1H), 7.77 (d, <i>J</i> = 8.5 Hz, 1H), 7.31 (d, <i>J</i> = 8.5 Hz, 1H), 7.10 (d, <i>J</i> = 2.2 Hz, 1H), 6.95 (dd, <i>J</i> = 8.8, 2.1 Hz, 1H), 4.02 (q, <i>J</i> = 6.9 Hz, 2H), 3.72 (t, <i>J</i> = 6.5 Hz, 2H), 3.53 (t, <i>J</i> = 5.7 Hz, 4H), 3.18 (d, <i>J</i> = 6.5 Hz, 2H), 2.93 (s, 4H), 2.10 – 2.02 (m, 4H), 1.70 (s, 4H), 1.33 (t, <i>J</i> = 6.9 Hz, 3H), 0.36 (s, 4H).
835	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.35 (s, 1H), 7.96 (d, <i>J</i> = 8.6 Hz, 1H), 7.46 (d, <i>J</i> = 8.3 Hz, 1H), 7.15 (d, <i>J</i> = 2.1 Hz, 1H), 7.05 (d, <i>J</i> = 8.4 Hz, 1H), 7.01 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 6.25 (t, <i>J</i> = 5.8 Hz, 1H), 3.76 (s, 3H), 3.72 (t, <i>J</i> = 6.5 Hz, 2H), 3.62 – 3.56 (m, 2H), 2.94 (t, <i>J</i> = 5.2 Hz, 4H), 2.58 (qt, <i>J</i> = 11.7, 7.2 Hz, 2H), 1.88 – 1.37 (s, 4H), 0.33 (s, 4H).
836	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.04 (d, <i>J</i> = 8.6 Hz, 1H), 7.71 (s, 1H), 7.23 (d, <i>J</i> = 2.2 Hz, 1H), 7.09 (dd, <i>J</i> = 8.7, 2.1 Hz, 1H), 3.74 (t, <i>J</i> = 6.5 Hz, 2H), 3.65 (s, 3H), 3.54 (t, <i>J</i> = 5.5 Hz, 4H), 2.94 (t, <i>J</i> = 5.2 Hz, 4H), 2.20 (s, 3H), 2.08 (dq, <i>J</i> = 13.4, 6.6, 5.3 Hz, 4H), 1.71 (s, 4H), 0.36 (s, 4H).
837	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.13 (s, 1H), 8.49 (s, 1H), 7.91 (d, <i>J</i> = 8.5 Hz, 1H), 7.17 (d, <i>J</i> = 2.1 Hz, 1H), 7.03 (dd, <i>J</i> = 8.5, 2.0 Hz, 1H), 6.48 (s, 1H), 3.80 (s, 3H), 3.74 (t, <i>J</i> = 6.5 Hz, 2H), 3.34 (d, <i>J</i> = 6.6 Hz, 2H), 3.12 (d, <i>J</i> = 5.8 Hz, 4H), 2.95 (t, <i>J</i> = 5.1 Hz, 4H), 1.98 (d, <i>J</i> = 12.5 Hz, 4H), 1.43 (s, 4H), 0.31 (s, 4H).

生物实施例 1 本发明化合物体外抑制 KIF18A 酶活试验

KIF18A 酶测定：使用微管刺激的 ATP 酶活实验测量用化合物处理后的 KIF18A 酶活性。该测定测量由 ATP 酶反应生成的 ADP。在 22 个浓度点范围内，将化合物在 DMSO 中连续稀释 2 倍。使用杆状病毒系统表达重组人 KIF18A(1-467His-标记的)蛋白。使用 ADP-Glo 激酶/ATP 酶测定试剂盒对反

应中的 KIF18A 蛋白、微管(Microtubules)和 ATP 的浓度进行优化以进行标准化的同质酶测定。制备反应缓冲液[(15 mM Tris, pH 7.5), 10 mM MgCl₂, 0.01%PluronicF-68, 1 μM 紫杉醇和 30 μg/mL 猪微管]。向制备的反应缓冲液中添加化合物和 KIF18A 蛋白(30 nM)并在室温下孵育 15min, 接下来向反应混合物中添加 ATP(K_m, 75 μM), 在室温下再孵育 15min。将 5 μl 的 ADP-Glo 试剂和 2.5 μL 的反应混合物混合并在室温下孵育 40 min。添加 10 μL ADP-Glo 检测试剂, 并在室温下孵育 40 min。使用酶标仪读取发光, 与 DMSO 组相比, 进而计算化合物抑制百分比和 IC₅₀。结果见下表 3。

表 3 本发明化合物对 KIF18A 的抑制活性(IC₅₀, nM)

化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀
1	+++	2	+++	3	+++	4	+++	5	+++
6	+++	7	+++	8	+++	9	+++	10	+++
11	+++	12	+++	13	+++	14	+++	15	+++
16	+++	17	+++	18	+++	19	+++	20	+++
21	+++	22	+++	23	+++	24	+++	25	+++
26	+++	27	+++	28	+++	29	+++	30	+++
31	+++	32	+++	33	+++	34	+++	35	++
36	+++	37	+++	38	+++	39	+++	40	+++
41	+++	42	+++	43	+++	44	+++	45	++
46	++	47	++	48	++	49	++	50	++
51	++	52	++	53	++	54	++	55	++
56	++	57	++	58	++	59	++	60	++
61	++	62	++	63	++	64	++	65	+++
66	+++	67	+++	68	+++	69	+++	70	+++
71	+++	72	+++	73	+++	74	+++	75	+++
76	+++	77	+++	78	+++	79	+++	80	+++
81	+++	82	+++	83	+++	84	+++	85	+++
86	+++	87	+++	88	+++	89	+++	90	+++
91	+++	92	+++	93	+++	94	+++	95	+++
96	+++	97	+++	98	+++	99	+++	100	+++
101	+++	102	+++	103	+++	104	+++	105	+++
106	+++	107	+++	108	+++	109	+++	110	+++

111	+++	112	+++	113	+++	114	+++	115	+++
116	+++	117	+++	118	+++	119	+++	120	+++
121	+++	122	+++	123	+++	124	+++	125	+++
126	+++	127	+++	128	+++	129	+++	130	+++
131	+++	132	+++	133	+++	134	+++	135	+++
136	+++	137	+++	138	+++	139	+++	140	+++
141	+++	142	+++	143	+++	144	+++	145	+++
146	+++	147	+++	148	+++	149	+++	150	+++
151	+++	152	+++	153	+++	154	+++	155	+++
156	+++	157	+++	158	+++	159	+++	160	+++
161	+++	162	+++	163	+++	164	+++	165	+++
166	+++	167	+++	168	+++	169	+++	170	+++
171	+++	172	+++	173	+++	174	+++	175	+++
176	+++	177	++	178	++	179	++	180	++
181	++	182	++	183	++	184	++	185	++
186	++	187	++	188	++	189	++	190	++
191	++	192	++	193	+++	194	+++	195	+++
196	+++	197	+++	198	+++	199	+++	200	+++
201	+++	202	+++	203	+++	204	+++	205	+++
206	+++	207	+++	208	+++	209	++	210	++
211	++	212	++	213	++	214	++	215	++
216	++	217	++	218	++	219	++	220	++
221	++	222	++	223	++	224	++	225	+++
226	+++	227	+++	228	+++	229	+++	230	+++
231	+++	232	+++	233	+++	234	+++	235	+++
236	+++	237	+++	238	+++	239	+++	240	+++
241	++	242	++	243	++	244	++	245	++
246	++	247	++	248	++	249	++	250	++
251	++	252	++	253	++	254	++	255	++

256	++	257	+++	258	+++	259	+++	260	+++
261	+++	262	+++	263	+++	264	+++	265	+++
266	+++	267	+++	268	+++	269	+++	270	+++
271	+++	272	+++	273	+++	274	+++	275	+++
276	+++	277	+++	278	+++	279	+++	280	+++
281	+++	282	+++	283	+++	284	+++	285	+++
286	+++	287	+++	288	+++	289	+++	290	+++
291	+++	292	+++	293	+++	294	+++	295	+++
296	+++	297	+++	298	+++	299	+++	300	+++
301	+++	302	+++	303	+++	304	+++	305	+++
306	+++	307	+++	308	+++	309	+++	310	+++
311	+++	312	+++	313	+++	314	+++	315	+++
316	+++	317	+++	318	+++	319	+++	320	+++
321	+++	322	+++	323	+++	324	+++	325	+++
326	+++	327	+++	328	+++	329	+++	330	+++
331	+++	332	+++	333	+++	334	+++	335	+++
336	+++	337	+++	338	+++	339	+++	340	+++
341	+++	342	+++	343	+++	344	+++	345	+++
346	+++	347	+++	348	+++	349	+++	350	+++
351	+++	352	+++	353	+++	354	+++	355	+++
356	+++	357	+++	358	+++	359	+++	360	+++
361	+++	362	+++	363	+++	364	+++	365	+++
366	+++	367	+++	368	+++	369	+++	370	+++
371	+++	372	+++	373	+++	374	+++	375	+++
376	+++	377	+++	378	+++	379	+++	380	+++
381	+++	382	+++	383	+++	384	+++	385	+++
386	+++	387	+++	388	+++	389	+++	390	+++
391	+++	392	+++	393	+++	394	+++	395	+++
396	+++	397	+++	398	+++	399	+++	400	+++

401	+++	402	+++	403	+++	404	+++	405	+++
406	+++	407	+++	408	+++	409	+++	410	+++
411	+++	412	+++	413	+++	414	+++	415	+++
416	+++	417	+++	418	+++	419	+++	420	+++
421	+++	422	+++	423	+++	424	+++	425	+++
426	+++	427	+++	428	+++	429	+++	430	+++
431	+++	432	+++	433	+++	434	+++	435	+++
436	+++	437	+++	438	+++	439	+++	440	+++
441	+++	442	+++	443	+++	444	+++	445	+++
446	+++	447	+++	448	+++	449	+++	450	+++
451	+++	452	+++	453	+++	454	+++	455	+++
456	+++	457	+++	458	+++	459	+++	460	+++
461	+++	462	+++	463	+++	464	+++	465	+++
466	+++	467	+++	468	+++	469	+++	470	+++
471	+++	472	+++	473	+++	474	+++	475	+++
476	+++	477	+++	478	+++	479	+++	480	+++
481	+++	482	+++	483	+++	484	+++	485	+++
486	+++	487	+++	488	+++	489	+++	490	+++
491	+++	492	+++	493	+++	494	+++	495	+++
496	+++	497	+++	498	+++	499	+++	500	+++
501	+++	502	+++	503	+++	504	+++	505	+++
506	+++	507	+++	508	+++	509	+++	510	+++
511	+++	512	+++	513	+++	514	+++	515	+++
516	+++	517	+++	518	+++	519	+++	520	+++
521	+++	522	+++	523	+++	524	+++	525	+++
526	+++	527	+++	528	+++	529	++	530	++
531	++	532	++	533	++	534	++	535	++
536	++	537	++	538	++	539	++	540	++
541	++	542	++	543	++	544	++	545	+++

546	+++	547	+++	548	+++	549	+++	550	+++
551	+++	552	+++	553	+++	554	+++	555	+++
556	+++	557	+++	558	+++	559	+++	560	+++
561	++	562	++	563	++	564	++	565	++
566	++	567	++	568	++	569	++	570	++
571	++	572	++	573	++	574	++	575	++
576	++	577	+++	578	+++	579	+++	580	+++
581	+++	582	+++	583	+++	584	+++	585	+++
586	+++	587	+++	588	+++	589	+++	590	+++
591	+++	592	+++	593	+++	594	+++	595	+++
596	+++	597	+++	598	+++	599	+++	600	+++
601	+++	602	+++	603	+++	604	+++	605	+++
606	+++	607	+++	608	+++	609	+++	610	+++
611	+++	612	+++	613	+++	614	+++	615	+++
616	+++	617	+++	618	+++	619	+++	620	+++
621	+++	622	+++	623	+++	624	+++	625	+++
626	+++	627	+++	628	+++	629	+++	630	+++
631	+++	632	+++	633	+++	634	+++	635	+++
636	+++	637	+++	638	+++	639	+++	640	+++

+++表示 IC₅₀ 小于或等于 100 nM

++表示 IC₅₀ 为 100 nM 至 500 nM

+表示 IC₅₀ 大于 500 nM

从表 3 数据可知, 本发明化合物对 KIF18A 的酶活性有较好的抑制活性。

生物实施例 2 本发明化合物对 HT-29 细胞的体外抗增殖活性

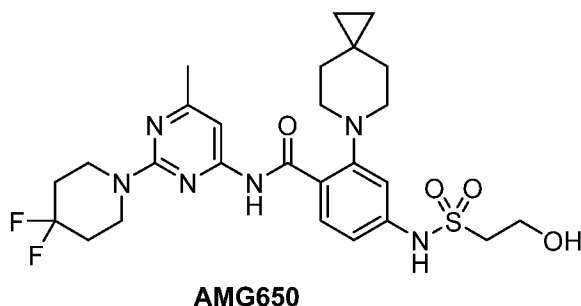
3000/孔 HT-29 细胞铺于 384 孔板, 过夜贴壁后, 加入 DMSO 或者最高浓度为 5 μ M, 1:5 梯度稀释的化合物。加药后 72 小时, 通过测定细胞内 ATP 含量, 评价细胞存活。与 DMSO 组相比计算化合物抑制细胞存活的百分比, 计算 IC₅₀ 值, 结果见下表 4。

表 4 本发明化合物对 HT-29 细胞的抗增殖活性(IC₅₀, nM)

化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀
1	75.31	3	1600.00	4	191.20	6	825.90

7	339.10	65	55.34	97	>2000	129	134.50
161	66.11	257	11.10	258	190.00	259	281.90
260	55.21	261	75.72	262	242.40	263	85.65
289	27.71	305	40.36	321	59.30	337	48.78
353	74.56	385	145.60	593	97.88	641	75.82
643	34.17	645	71.30	647	334.20	655	1171.00
661	25.76	663	34.99	669	25.78	701	76.69
702	71.18	703	183.80	704	64.19	705	146.00
833	52.94	835	70.70	836	253.20	AMG650	109

参比化合物AMG650为WO2020132648A1中的化合物4。



从表4数据可见本发明部分化合物对HT-29细胞较AMG650有更强的抗增殖活性。

生物实施例 3 本发明化合物对 HCT116 细胞的体外抗增殖活性

3000/孔 HCT116 细胞铺于 384 孔板, 过夜贴壁后, 加入 DMSO 或者最高浓度为 5 μM , 1:5 梯度稀释的化合物。加药后 72 小时, 通过测定细胞内 ATP 含量, 评价细胞存活。与 DMSO 组相比计算化合物抑制细胞存活的百分比, 计算 IC_{50} 值。结果见下表 5。

表5 本发明化合物对 HCT116 细胞的抗增殖活性(IC₅₀, nM)

化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀	化合物	IC ₅₀
1	>10000	3	>10000	4	>10000	6	>10000
7	>10000	65	>10000	97	>10000	129	>10000
161	>10000	257	>10000	258	>10000	259	>10000
260	>10000	261	>10000	262	>10000	263	>10000
289	>10000	305	>10000	321	>10000	337	>10000
353	>10000	385	>10000	593	>10000	641	>10000
643	>10000	645	>10000	647	>10000	655	>10000
661	>10000	663	>10000	669	>10000	701	>10000
702	>10000	703	>10000	704	>10000	705	>10000

833	>10000	835	>10000	836	>10000	AMG650	>10000
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从表5数据可见本发明化合物以及AMG650对HCT116细胞都不具有抗增殖活性。

生物实施例 4 体内药效研究 – 小鼠 HT29 皮下移植瘤模型

BALB/c 裸小鼠左侧背部皮下接种 5×10^6 个 HT29 细胞，待肿瘤生长至 100-150 mm³，随机分组后，分别灌胃给药，组 1：溶媒对照组；组 2：化合物 661 (80 mg/kg)；组 3：化合物 669 (80 mg/kg)；组 4：化合物 677 (80 mg/kg)；组 5：化合物 714 (80 mg/kg)；组 6：化合物 727 (80 mg/kg)；组 7：化合物 740 (80 mg/kg)；组 8：AMG650 (80 mg/kg)，每天一次。每周两次以及给药终点测量肿瘤体积。按照肿瘤生长率抑制率 (TGI) = $1 - (\text{给药组第 28 天肿瘤体积} - \text{给药组第一天肿瘤体积}) / (\text{溶媒对照组第 28 天肿瘤体积} - \text{给药组第一天肿瘤体积})$ ，计算化合物肿瘤生长抑制率。结果见表 6。

表 6 小鼠 HT29 皮下移植瘤生长抑制率

组	化合物	剂量	给药第 1 天肿瘤 体积 (mm ³)	给药第 28 天肿瘤 体积 (mm ³)	TGI
1	对照	不适用	121	1606	不适用
2	661	80 mg/kg	121	704	61%
3	669	80 mg/kg	121	1158	30%
4	677	80 mg/kg	121	797	55%
5	714	80 mg/kg	121	424	80%
6	727	80 mg/kg	121	519	73%
7	740	80 mg/kg	121	605	67%
8	AMG650	80 mg/kg	121	649	64%

由表 6 可见，本发明中的化合物在 80 mg/kg 剂量下，在携带 HT29 小鼠皮下移植瘤模型中能够抑制肿瘤生长。并且化合物 714、化合物 727 以及化合物 740 对于 HT29 小鼠皮下移植瘤的抑制效果强于 AMG650。

生物实施例 5 HT29 细胞组蛋白 H3 Ser10 位点的磷酸化测定(免疫荧光法)

HT29 细胞种植于 96 孔板(Fisher 160376)中，每孔细胞量为 8000 个，次日加入经梯度稀释的化合物，加入化合物 6 小时后，用 1X PBS 清洗一次，4%PFA 固定 15 分钟，1X PBS 洗三遍，0.02%Triton-X100 通透 10 分钟。之后利用封闭缓冲液封闭 15~30 分钟，加入 1:3000 浓度一抗(Phospho-Histone H3 (Ser10) (D7N8E) XP® Rabbit mAb #53348)后，将孔板放置于 4℃ 过夜。次日加入 1X PBS 洗三遍后，加入 1:1000 浓度二抗(Fluorescein(FITC)-conjugated Affinipure Goat Anti-Rabbit IgG(H+L))，避光孵育 1~2 小时后，1X PBS 洗三遍；之后 DAPI 染色细胞核，完成后，利用 MD ImageXpress Pico 个人型高内涵成像分析系统拍照。对 HT29 细胞 H3 Ser10 位点的磷酸化比例(FITC/DAPI)进行定量。评价化合物对于 HT29 细胞有丝分裂期的影响，计算化合物 EC₅₀。结果见下表 7。

表 7 本发明化合物对 HT29 细胞 H3 Ser10 位点的磷酸化诱导(EC₅₀, nM)

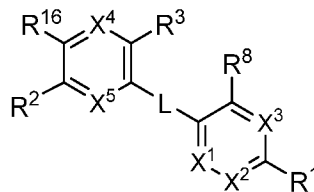
化合物	EC ₅₀ (nM)	化合物	EC ₅₀ (nM)	化合物	EC ₅₀ (nM)
65	45.5	161	26.4	257	8.4
273	8.5	321	15.8	353	42.2
641	21.7	645	69.6	661	23.7
663	28.3	714	39.2	AMG650	52.3

由表 7 可见，本发明中的化合物对 HT-29 细胞 H3 Ser10 位点的磷酸化有较强的诱导活性，且相比 AMG650，本发明中的化合物对 H3 Ser10 位点的磷酸化诱导活性较 AMG650 更强。

虽然以上描述了本发明的具体实施方式，但是本领域的技术人员应当理解，这些仅是举例说明，在不背离本发明的原理和实质的前提下，可以对这些实施方式做出多种变更或修改。因此，本发明的保护范围由所附权利要求书限定。

权利要求

1. 一种如通式(1)所示的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物：



(1)

通式(1)中：

X¹ 为 -CR⁵= 或 N；

X² 为 -CR⁶= 或 N；

X³ 为 -CR⁷= 或 N；

X⁴ 为 -CR⁴= 或 N；

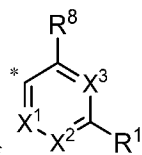
X⁵ 为 -CR¹⁵= 或 N；

当 X⁵ 为 -CR¹⁵= 且 X⁴ 为 -CR⁴= 时，R¹⁶ 为 -C₃₋₈ 环烷基、-OR¹⁷、-SR¹⁸、-NR¹⁸R¹⁹ 或 -NO₂；

当 X⁵ 为 -CR¹⁵= 且 X⁴ 为 N 时，R¹⁶ 为 -O-C₁₋₈ 烃基、-C₃₋₈ 环烷基、-OR¹⁷、-SR¹⁸、-NR²⁰R²¹ 或 -NO₂；

当 X⁵ 为 N 时，R¹⁶ 为 -O-C₁₋₈ 烃基、-C₃₋₈ 环烷基、-OR¹⁷、-SR¹⁸、-NR²⁰R²¹ 或 -NO₂；

L 为 -(C=O)-NR⁹-* 或 -NR⁹-(C=O)-*；和 X¹、X²、X³、X⁴ 和 X⁵ 中，不超过 4 个为 N；



*代表连接的是

R¹⁷ 为 H、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基，其中所述 -C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基可任选被 0、1、2 或 3 个下列基团取代：H、卤素或 -C₁₋₄ 烃基。

R¹⁸ 和 R¹⁹ 各自独立地为 H、-C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基，其中所述 -C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基可任选被 0、1、2 或 3 个下列基团取代：H、卤素或 -C₁₋₄ 烃基。

R²⁰ 和 R²¹ 各自独立地为 H、-C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基，其中所述 -C₁₋₈ 烃基、-C₁₋₈ 卤代烃基、-C₃₋₈ 环烷基或 -C₃₋₈ 卤代环烷基可任选被 0、1、2 或 3 个下列基团取代：H、卤素或 -C₁₋₄ 烃基；或 R²⁰ 和 R²¹ 可以与它们各自连接的氮原子组合以形成含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子的饱和的或部分饱和的 3 元、4 元、5 元或 6 元单环或 4 元、5 元、6 元、7 元、8 元、9 元、10 元、11 元或 12 元双环；

R¹ 为 -CN 或 -Z-R¹⁰，其中 Z 为化学键、-C₀₋₄ 烃基-、-NR¹¹-、-NR¹¹SO₂-、-SO₂NR¹¹-、-NR¹¹-S(=O)(=NH)-、-S(=O)(=NH)-、-S-、-S(=O)-、-SO₂-、-C₀₋₄ 烃基-O-、-(C=O)-、-(C=O)NR¹¹-、-C(=N-OH)-或 -NR¹¹(C=O)-；或所述基团 -Z-R¹⁰ 为 -N=S(=O)-(R¹⁰)₂，其中所述两个 R¹⁰ 可以与它们各自连接的硫原子组合以形成含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子的饱和的或部分饱和的 3 元、4 元、5 元或 6 元单环；

R² 为卤素或基团 -Y-R¹²，其中 Y 为化学键、-C₀₋₄ 烃基-、-N(C₀₋₁ 烃基)-C₀₋₄ 烃基-、-C(=O)NR^aR^a (C₁₋₄ 烃基)-、-O-C₀₋₄ 烃基-、-S-、-S(=O)-、-SO₂-、-SO₂NR¹²-或 -S(=O)(=NH)-；

R³ 为 H、卤素、C₁₋₈ 烃基或 C₁₋₄ 卤代烃基；

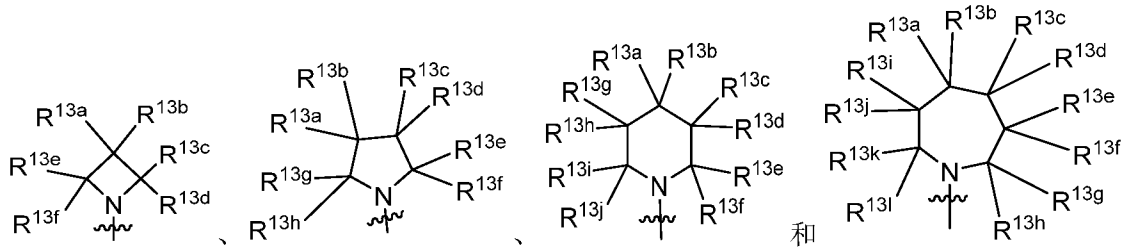
R⁴ 为 H、卤素、R^{4a} 或 R^{4b}；

R⁵ 为 H、卤素、C₁₋₈ 烷基或 C₁₋₄ 卤代烷基；

R⁶ 为 H、卤素、C₁₋₈ 烷基、C₁₋₄ 卤代烷基、-OH、-O-R^{6a} 或 -O-R^{6b}；

R⁷ 为 H、卤素、C₁₋₈ 烃基或 C₁₋₄ 卤代烃基；

R⁸ 选自由以下组成的组：



R^{13a} 、 R^{13b} 、 R^{13c} 、 R^{13d} 、 R^{13e} 、 R^{13f} 、 R^{13g} 、 R^{13h} 、 R^{13i} 、 R^{13j} 、 R^{13k} 和 R^{13l} 各自独立地为H、卤素、 R^{13m} 或 R^{13n} ；或 R^{13a} 和 R^{13b} 对、 R^{13c} 和 R^{13d} 对、 R^{13e} 和 R^{13f} 对、 R^{13g} 和 R^{13h} 对、 R^{13i} 和 R^{13j} 对或 R^{13k} 和 R^{13l} 对中的每一对可以独立地与它们各自连接的碳原子组成螺接到 R^8 环的饱和的或部分饱和的3元、4元、5元、6元单环；其中所述3元、4元、5元、6元单环含有0、1、2或3个N原子和0、1或2个选自O和S的原子，并且进一步地，其中所述3元、4元、5元、6元单环被选自以下的0、1、2或3个基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基、CN、 $-NR^aR^a$ 或氧代；

R^9 为H或 C_{1-6} 烷基；

R^{10} 为H、 R^{10a} 、 R^{10b} 或 R^{10c} ；

R^{11} 为H、 R^{11a} 或 R^{11b} ；

R^{12} 为 R^{12a} 或 R^{12b} ；

R^{15} 为H、卤素、 C_{1-8} 烷基、 C_{1-4} 卤代烷基、 $-O-C_{1-8}$ 烷基或 $-O-R^{15a}$ ，其中 R^{15a} 为含有0、1、2或3个N原子和0、1或2个选自O和S的原子的饱和的或部分饱和的3元、4元、5元或6元单环；

R^{4a} 、 R^{6a} 、 R^{10a} 、 R^{11a} 、 R^{12a} 或 R^{13m} 为在每种情况下独立地选自：含有0、1、2或3个N原子和0、1或2个选自O和S的原子的饱和的、部分饱和的或不饱和的3元、4元、5元、6元或7元单环或4元、5元、6元、7元、8元、9元、10元、11元或12元双环，其中所述单环和双环可各自独立任选被0、1、2或3个下列基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基、CN、 $-C(=O)R^b$ 、 $-C(=O)OR^a$ 、 $-C(=O)NR^aR^a$ 、 $-C(=NR^a)NR^aR^a$ 、 $-OC(=O)R^b$ 、 $-OC(=O)NR^aR^a$ 、 $-OC_{2-6}$ 烷基 NR^aR^a 、 $-OC_{2-6}$ 烷基 OR^a 、 $-SR^a$ 、 $-S(=O)R^b$ 、 $-S(=O)_2R^b$ 、 $-S(=O)_2NR^aR^a$ 、 $-NR^aR^a$ 、 $-N(R^a)C(=O)R^b$ 、 $-N(R^a)C(=O)OR^b$ 、 $-N(R^a)C(=O)NR^aR^a$ 、 $-N(R^a)C(=NR^a)NR^aR^a$ 、 $-N(R^a)S(=O)_2R^b$ 、 $-N(R^a)S(=O)_2NR^aR^a$ 、 $-NR^aC_{2-6}$ 烷基 NR^aR^a 、 $-NR^aC_{2-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 NR^aR^a 、 $-C_{1-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 $N(R^a)C(=O)R^b$ 、 $-C_{1-6}$ 烷基 $OC(=O)R^b$ 、 $-C_{1-6}$ 烷基 $C(=O)NR^aR^a$ 、 $-C_{1-6}$ 烷基 $C(=O)OR^a$ 、 R^{14} 和氧代；

R^{4b} 、 R^{6b} 、 R^{10b} 、 R^{11b} 、 R^{12b} 或 R^{13n} 为在每种情况下独立地选自： C_{1-6} 烷基，其中所述烷基可任选被0、1、2、3、4或5个下列基团取代：F、Cl、Br、 $-R^a$ 、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基和CN；

R^{10c} 为在每种情况下独立地选自： C_{1-6} 烷基，其中所述烷基可任选被0、1、2、3、4或5个下列基团取代：F、Cl、Br、 $-R^a$ 、 $-R^c$ 、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基和CN；

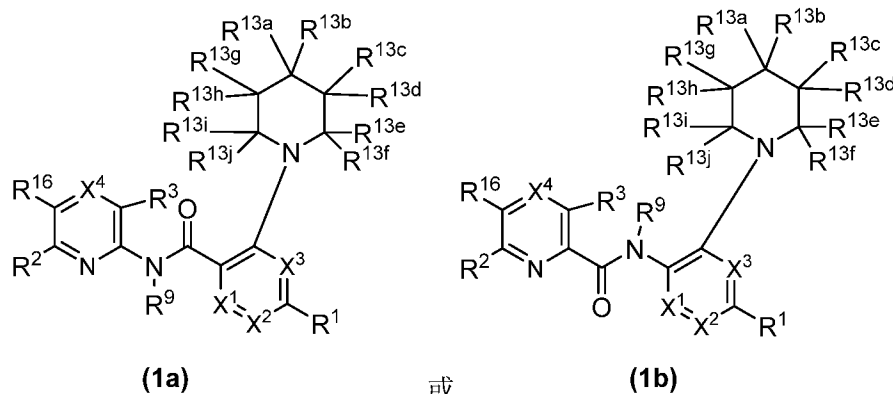
R^{14} 在每种情况下独立地选自由以下组成的组：含有0、1、2或3个N原子和0或1个选自O和S的原子的饱和的、部分饱和的或不饱和的3元、4元、5元、6元或7元单环或4元、5元、6元、7元、8元、9元、10元、11元或12元双环，其中所述单环和双环各自独立可任选被0、1、2或3个下列基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、 $-OR^a$ 、 $-OC_{1-4}$ 卤代烷基、CN、 $-C(=O)R^b$ 、 $-C(=O)OR^a$ 、 $-C(=O)NR^aR^a$ 、 $-C(=NR^a)NR^aR^a$ 、 $-OC(=O)R^b$ 、 $-OC(=O)NR^aR^a$ 、 $-OC_{2-6}$ 烷基 NR^aR^a 、 $-OC_{2-6}$ 烷基 OR^a 、 $-SR^a$ 、 $-S(=O)R^b$ 、 $-S(=O)_2R^b$ 、 $-S(=O)_2NR^aR^a$ 、 $-NR^aR^a$ 、 $-N(R^a)C(=O)R^b$ 、 $-N(R^a)C(=O)OR^b$ 、 $-N(R^a)C(=O)NR^aR^a$ 、 $-N(R^a)C(=NR^a)NR^aR^a$ 、 $-N(R^a)S(=O)_2R^b$ 、 $-N(R^a)S(=O)_2NR^aR^a$ 、 $-NR^aC_{2-6}$ 烷基 NR^aR^a 、 $-NR^aC_{2-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 NR^aR^a 、 $-C_{1-6}$ 烷基 OR^a 、 $-C_{1-6}$ 烷基 $N(R^a)C(=O)R^b$ 、 $-C_{1-6}$ 烷基 $OC(=O)R^b$ 、 $-C_{1-6}$ 烷基 $C(=O)NR^aR^a$ 、 $-C_{1-6}$ 烷基 $C(=O)OR^a$ 和氧代；

R^a 在每种情况下独立地为H或 R^b ；

R^b 在每种情况下独立地为 C_{1-6} 烷基、苯基或苄基，其中所述烷基可任选被0、1、2或3个下列基团取代：卤素、 $-OH$ 、 $-OC_{1-4}$ 烷基、 $-NH_2$ 、 $-NHC_{1-4}$ 烷基、 $-OC(=O)C_{1-4}$ 烷基或 $-N(C_{1-4}$ 烷基) C_{1-4} 烷基；并且其中所述苯基和苄基可各自独立任选被0、1、2或3个下列基团取代：卤素、 C_{1-4} 烷基、 C_{1-3} 卤代烷基、 $-OH$ 、 $-OC_{1-4}$ 烷基、 $-NH_2$ 、 $-NHC_{1-4}$ 烷基、 $-OC(=O)C_{1-4}$ 烷基或 $-N(C_{1-4}$ 烷基) C_{1-4} 烷基；并且

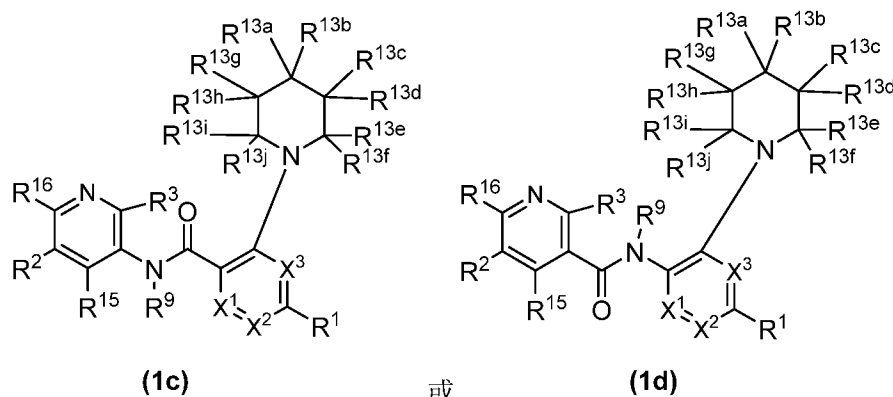
R⁹ 在每种情况下独立地为 -OC(=O)C₁₋₅ 烷基, 其中所述烷基可任选被 1、2 或 3 个下列基团取代: -OH 或 -NH₂。

2. 如权利要求 1 所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)具有以下结构:



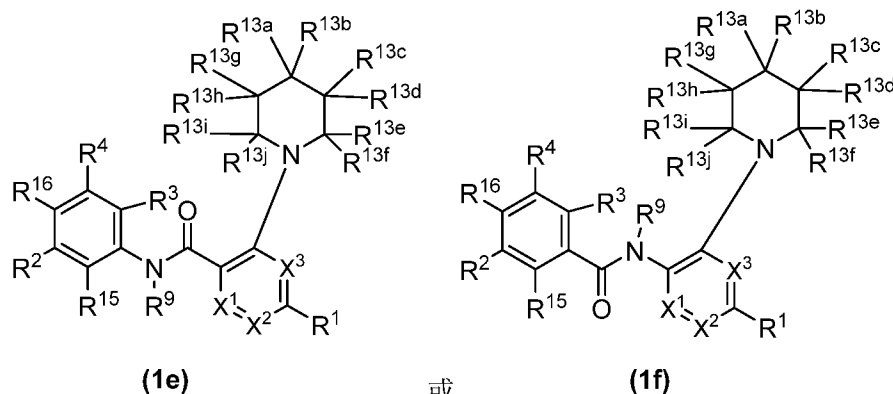
其中 R¹⁶ 为 -C₃₋₆ 环烷基、-OH、-O-C₁₋₄ 烷基、-O-C₁₋₄ 卤代烷基、-O-C₃₋₆ 环烷基、-O-C₃₋₆ 卤代环烷基、-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR²⁰R²¹ 或 -NO₂。

3. 如权利要求 1 所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)具有以下结构:



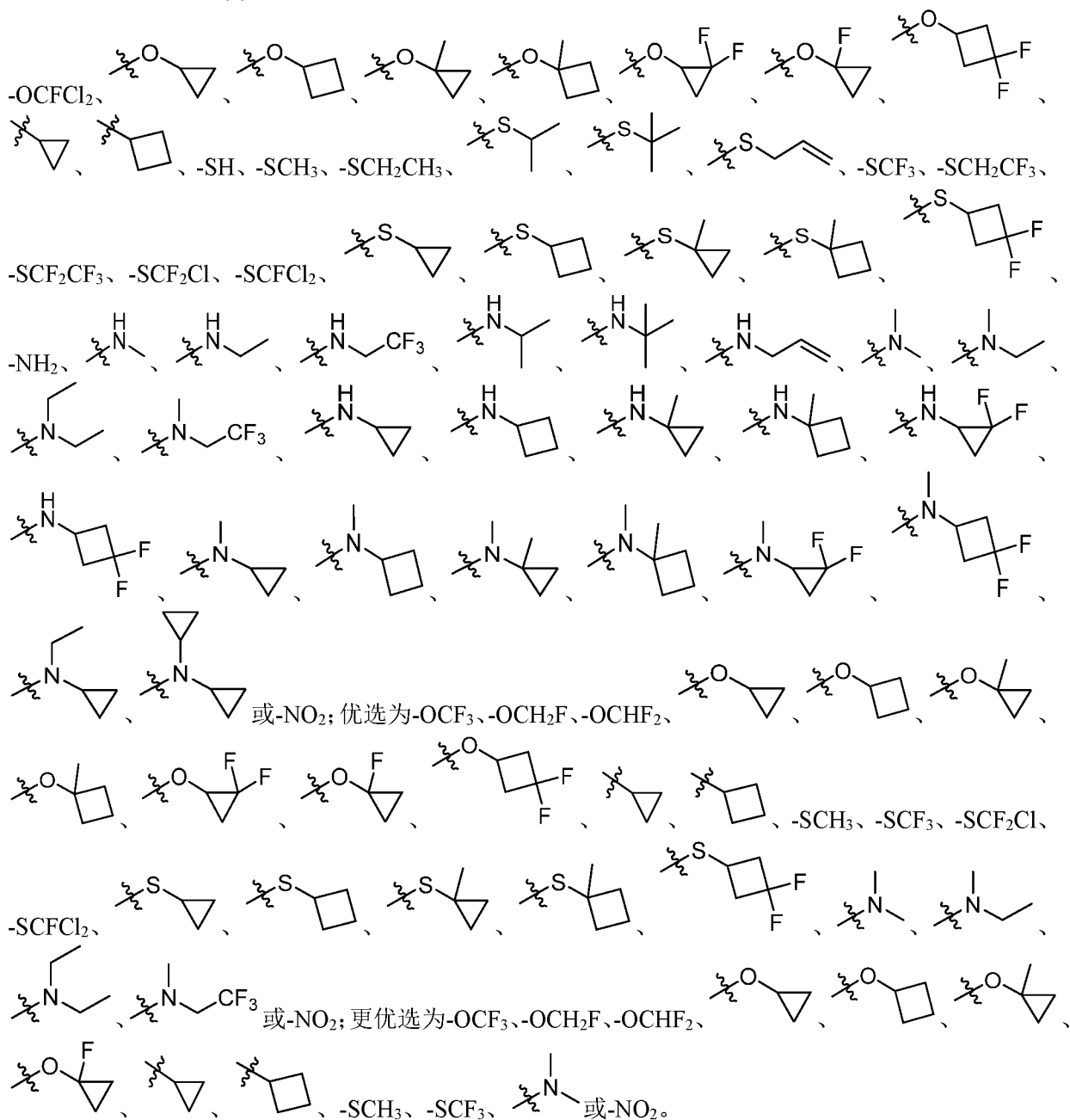
其中 R¹⁶ 为 -C₃₋₆ 环烷基、-OH、-O-C₁₋₄ 烷基、-O-C₁₋₄ 卤代烷基、-O-C₃₋₆ 环烷基、-O-C₃₋₆ 卤代环烷基、-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR²⁰R²¹ 或 -NO₂。

4. 如权利要求 1 所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)具有以下结构:



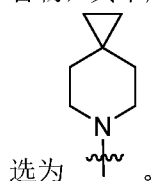
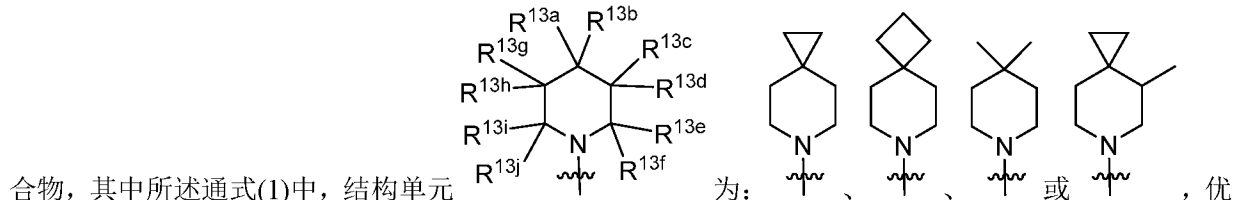
其中 R¹⁶ 为 -C₃₋₆ 环烷基、-OH、-O-C₁₋₄ 卤代烷基、-O-C₃₋₆ 环烷基、-O-C₃₋₆ 卤代环烷基、-SH、-S-C₁₋₆ 烷基、-S-C₁₋₄ 卤代烷基、-S-C₃₋₆ 环烷基、-S-C₃₋₆ 卤代环烷基、-NR¹⁸R¹⁹ 或 -NO₂。

5. 如权利要求 1-4 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, R^{16} 为 -OH、-OCF₃、-OCH₂F、-OCHF₂、-OCH₂CF₃、-OCF₂CF₃、-OCF₂Cl、



螺接到 R^8 环的饱和 3 元、4 元或 5 元单环；其中所述环含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子；优选， R^{13c} 、 R^{13d} 、 R^{13e} 、 R^{13f} 、 R^{13g} 、 R^{13h} 、 R^{13i} 、 R^{13j} 、 R^{13k} 和 R^{13l} 各自独立为 H、甲基或乙基；并且 R^{13a} 和 R^{13b} 对中的 R^{13a} 和 R^{13b} 与它们各自连接的碳原子可以组合形成螺接到 R^8 环的环丙基、环丁基或环戊基环。

9. 如权利要求 1-8 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂



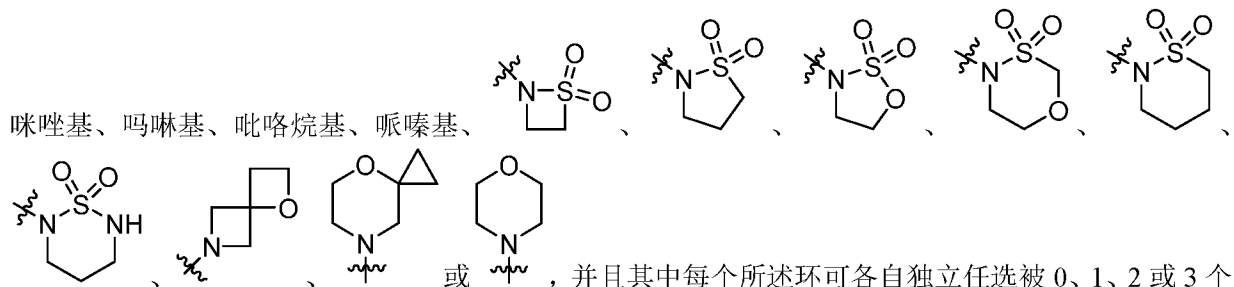
10. 如权利要求 1-9 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物，其中所述通式(1)中，其中 Z 为化学键、-NH-、-NH₂SO₂-、-SO₂NH-、-S(=O)(=NH)-、-S-、-S(=O)-、-SO₂-、-(C=O)-、-(C=O)NH-或-NH(C=O)-。

11. 如权利要求 1-10 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物，其中所述通式(1)中，其中 R^{10} 选自(a)H；或(b) C_{1-6} 烷基，所述烷基可任选被 0、1、2 或 3 个下列基团取代：F、Cl、Br、-OH 或 -OCH₃；或(c)当所述基团-Z- R^{10} 为-N=S(=O)-(R¹⁰)₂，其中所述两个 R^{10} 可以与它们各自连接的硫原子组合以形成含有 0、1、2 或 3 个 N 原子和 0 或 1 个选自 O 和 S 的原子的饱和的、部分饱和的或不饱和的 3 元、4 元、5 元、6 元或 7 元单环，其被选自以下的 0、1、2 或 3 个基团取代：F、Cl、Br、 C_{1-6} 烷基、 C_{1-4} 卤代烷基、- C_{1-6} 烷基 OH、-OH、-OCH₃、-NH₂ 或氧代；或(d) C_{1-6} 烷基，所述 C_{1-6} 烷基可任选被 1、2 或 3 个下列基团取代：-OC(=O) C_{1-5} 烷基，其中所述 C_{1-5} 烷基可任选被 1 或 2 个下列基团取代：-OH 或 -NH₂；且所述 C_{1-6} 烷基可任选被 0、1、2 或 3 个下列基团取代：F、Cl、Br、-OH 或 -OCH₃。

12. 如权利要求 1-11 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物，其中所述通式(1)中，其中 R^1 为-CN 或基团-Z- R^{10} ，其中 Z 为化学键、-NH-、-NH₂SO₂-、-SO₂NH-、-S(=O)(=NH)-、-S-、-S(=O)-、-SO₂-、-(C=O)-、-(C=O)NH-或-NH(C=O)-；并且 R^{10} 选自：

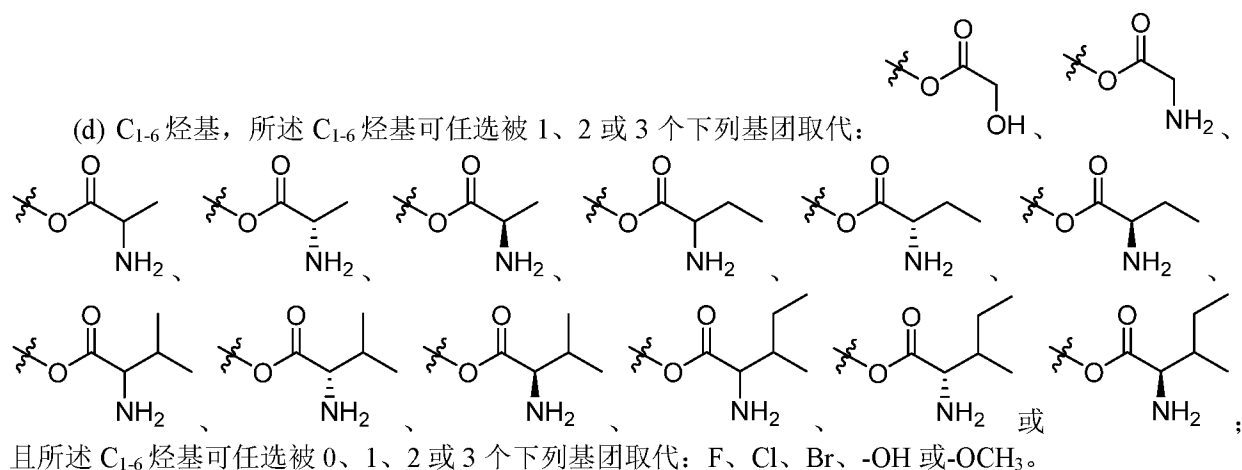
(a)H；

(b)环丙基、环丁基、环戊基、环己基、环氧乙烷基、氧杂环丁烷基、四氢呋喃基、氮杂环丁烷基、

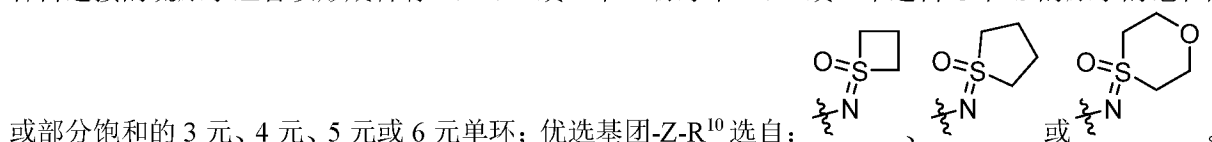


下列基团取代：OH、F、甲基、-CH₂OH、-C(=O)OCH₃、-C(=O)OC(CH₃)₃、NH₂、CN 和氧代；优选为氧杂环丁烷基、环丙基；

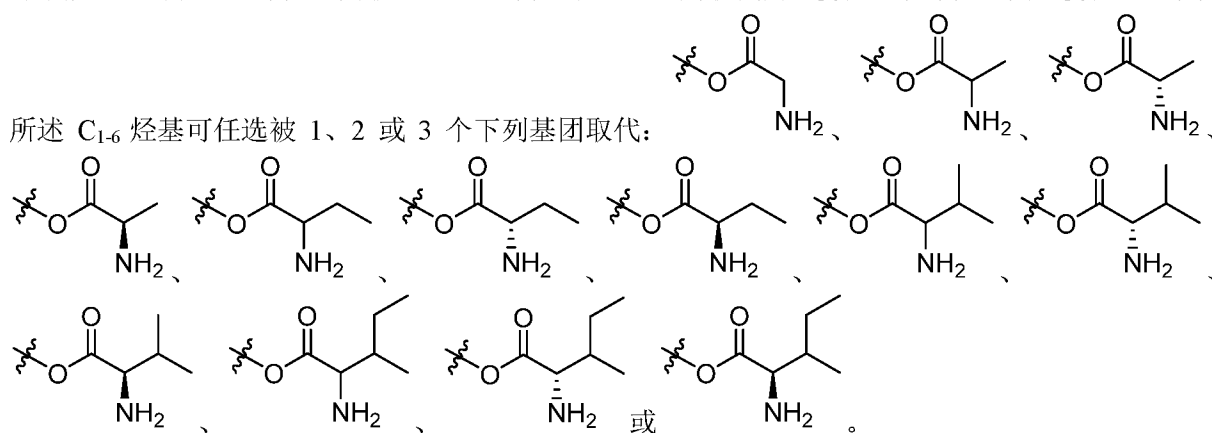
(c)被 0、1、2 或 3 个 OH、F、-C(=O)OCH₃、-NH₂、-NH(CH₃)或-N(CH₃)₂ 取代的 C_{1-6} 烷基；优选为被 0、1、2 或 3 个 OH 基团取代的 C_{1-6} 烷基；更优选为被 1 个 OH 基团取代的 C_{1-6} 烷基；或



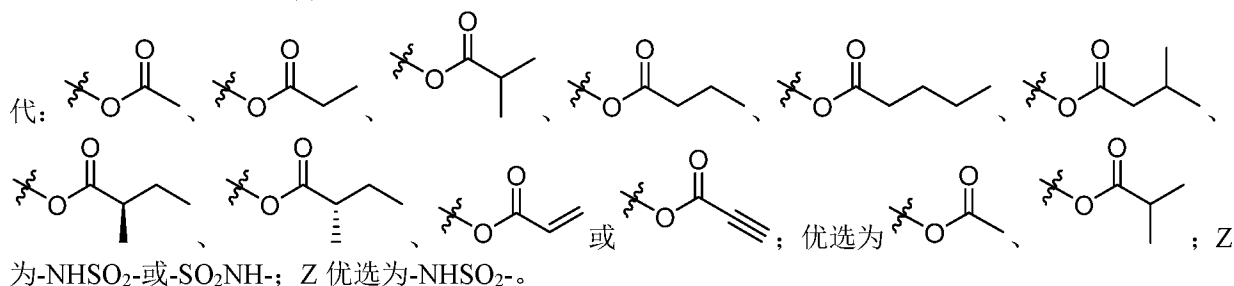
13. 如权利要求 1-12 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中所述基团-Z-R¹⁰ 为-N=S(=O)-(R¹⁰)₂, 其中两个 R¹⁰ 对可以与它们各自连接的硫原子组合以形成含有 0、1、2 或 3 个 N 原子和 0、1 或 2 个选自 O 和 S 的原子的饱和的



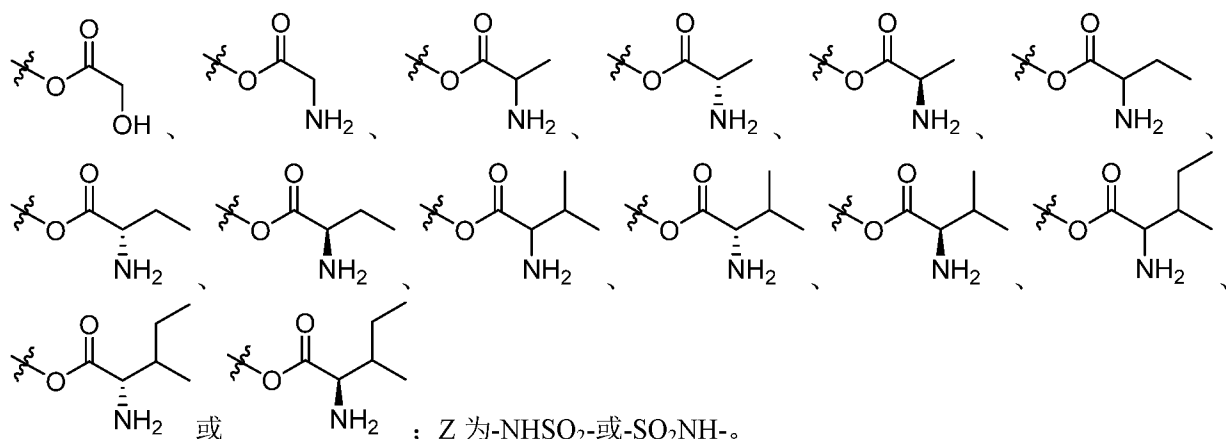
14. 如权利要求 1-12 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R¹ 为基团-Z-R¹⁰, 其中 Z 为-NHSO₂-或-SO₂NH-; 并且 R¹⁰ 为氧杂环丁烷基、环丙基, 或 R¹⁰ 为被 0、1、2 或 3 个 OH 基团取代的 C₁₋₆ 烷基; 或 R¹⁰ 为 C₁₋₆ 烷基, 其中



15. 如权利要求 1-10 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R¹⁰ 选自 C₁₋₆ 烷基, 所述烷基可任选被 0、1、2 或 3 个下列基团取



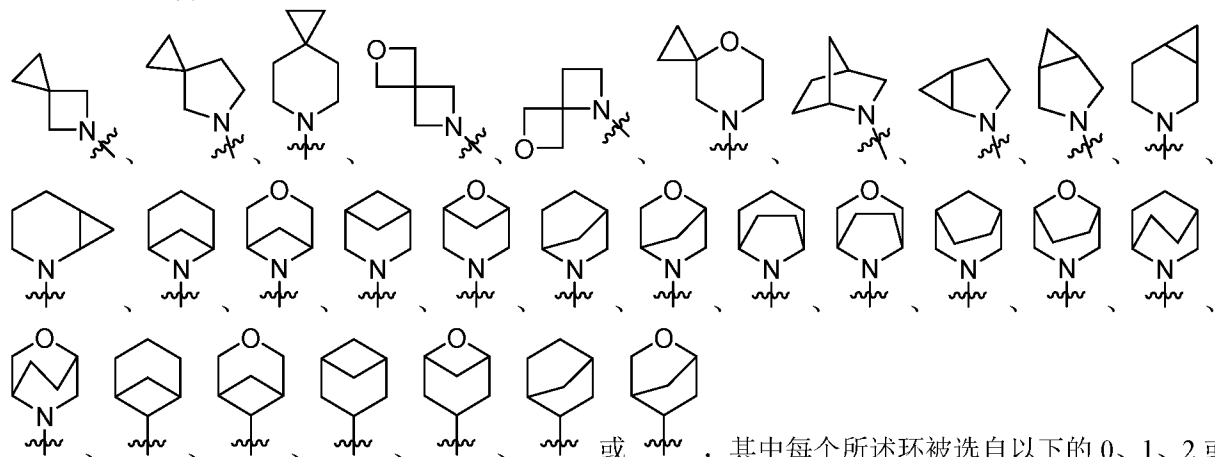
16. 如权利要求 1-10 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R¹⁰ 选自 C₁₋₆ 烷基, 所述烷基可任选被 1、2 或 3 个下列基团取代:



17. 如权利要求 1-16 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R² 为卤素或基团-Y-R¹², 其中 Y 为化学键、-NH-、-NH-(CH₂)₀₋₄-或 -O-(CH₂)₀₋₄-; 并且 R¹² 为含有 0、1、2 或 3 个 N 原子和 0 或 1 个选自 O 和 S 的原子的饱和的、部分饱和的或不饱和的 3 元、4 元、5 元、6 元或 7 元单环或 4 元、5 元、6 元、7 元、8 元、9 元、10 元、11 元或 12 元双环, 其中所述单环和双环可各自独立任选被 0、1、2 或 3 个下列基团取代: F、Cl、Br、C₁₋₆ 烷基、C₁₋₄ 卤代烷基、-OH、-OC₁₋₄ 卤代烷基、CN、R¹⁴ 和氧代; 或 R¹² 为 C₁₋₆ 烷基, 所述烷基可任选被 0、1、2、3、4 或 5 个下列基团取代: F、Cl、Br、-OH、-OC₁₋₄ 卤代烷基或 CN。

18. 如权利要求 1-17 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R² 为饱和 5 元或 6 元单环, 其中每个所述环含有 0、1 或 2 个 N 原子和 0 或 1 个 O 原子, 并且其中每个所述环被选自以下的 0、1、2 或 3 个基团取代: F、Cl、Br、C₁₋₆ 烷基、C₁₋₄ 卤代烷基、-OH、-OC₁₋₄ 卤代烷基、CN、R¹⁴ 和氧代。

19. 如权利要求 1-18 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R² 为(a)卤素; (b)基团-Y-R¹², 其中 Y 为化学键; 并且 R¹² 为吗啉基、哌啶基、氮杂环丁烷基、吡咯烷基、环丙基、环丁基、环戊基、环己基、哌嗪基、四氢呋喃基、

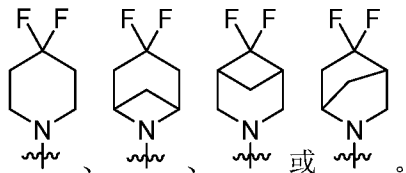


-O-、-O-(CH₂)-、-O-(CH₂)-(CH₂)-或-O-(CH₂)-(CH₂)-(CH₂)-, 并且其中 R¹² 为 ; 或 R¹² 为 C₁₋₆ 烷基, 所述烷基可任选被 0、1、2、3、4 或 5 个下列基团取代: F、Cl、Br、甲基、CF₃、-OH 或 CN。

20. 如权利要求 1-19 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(1)中, 其中 R² 为吗啉基或哌啶基, 所述吗啉基和哌啶基可任选被 0、1、2 或 3 个下列基团取代: F、Cl、Br、甲基、CF₃、-OH、-OCHF₂ 和 CN。

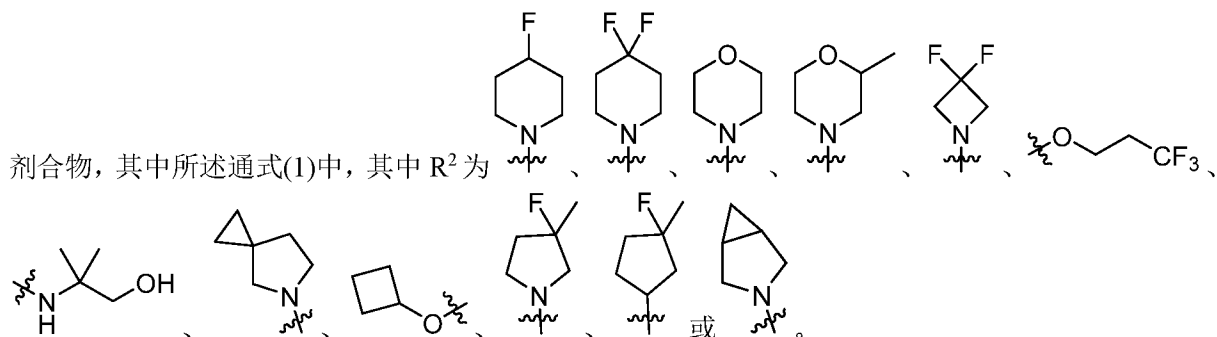
21. 如权利要求 1-20 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^2 为被 1、2 或 3 个氟基团取代的哌啶基。

22. 如权利要求 1-19 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^2 为:



23. 如权利要求 1-20 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^2 为被 1、2 或 3 个甲基基团取代的吗啶基。

24. 如权利要求 1-19 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^2 为



25. 如权利要求 1-11 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^{10} 选自环丙基、环丁基、环戊基、氧杂环丁烷基、氮杂环丁烷基、四氢呋喃基或 1,3,4-氧杂噻嗪烷基。

26. 如权利要求 1-25 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^3 为 H。

27. 如权利要求 1-26 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^4 选自(a)H; (b)被 0、1、2 或 3 个 OH 基团取代的 C_{1-6} 烷基; 或 (c)环丙基; 或(d)F; R^4 优选为 H、F 或甲基; R^4 更优选为 H。

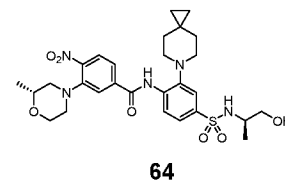
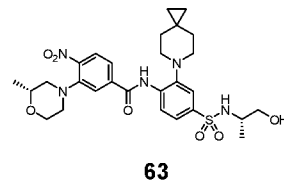
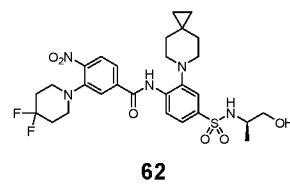
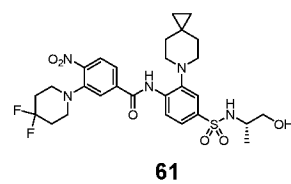
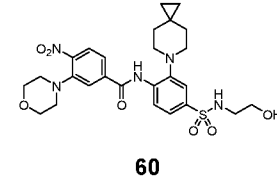
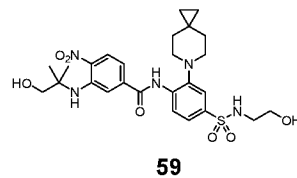
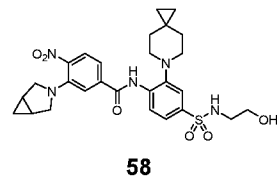
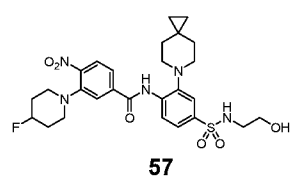
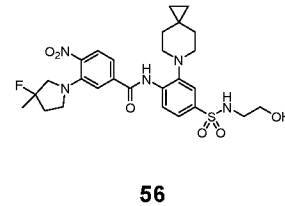
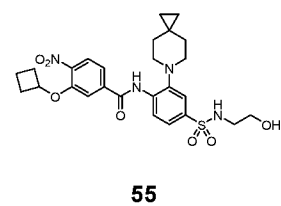
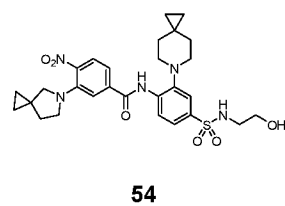
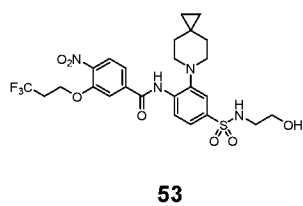
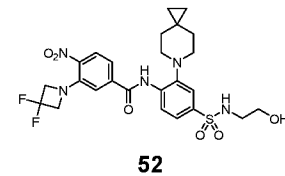
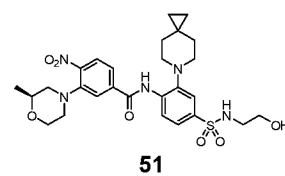
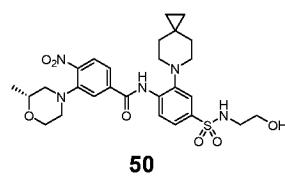
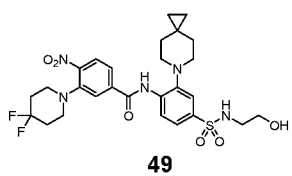
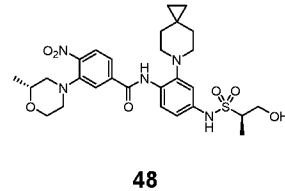
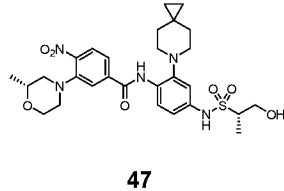
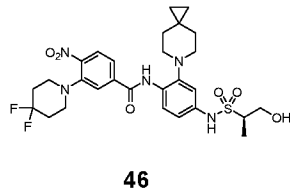
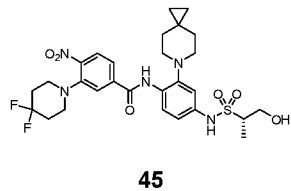
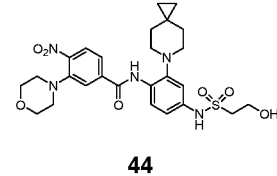
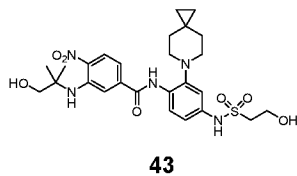
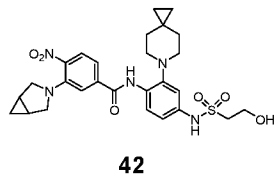
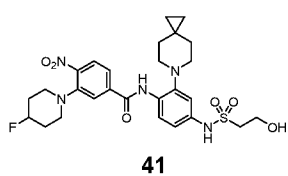
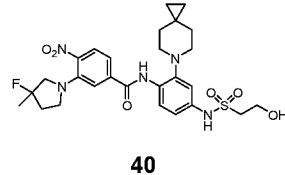
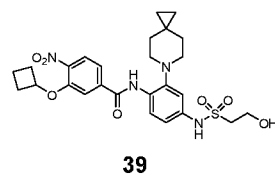
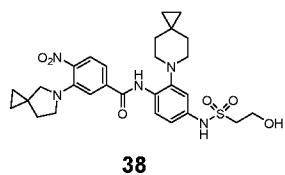
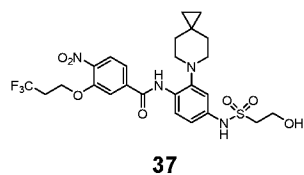
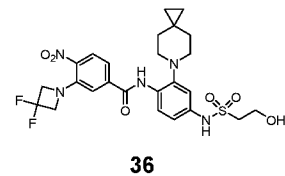
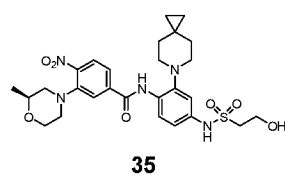
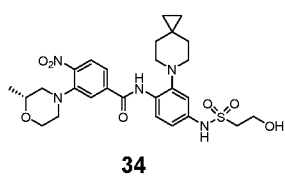
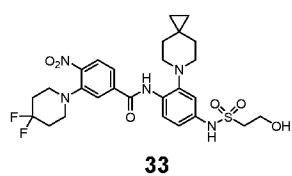
28. 如权利要求 1-27 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^5 为 H 或 F, 优选为 H。

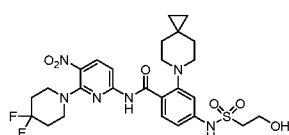
29. 如权利要求 1-28 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^6 为 H 或 F, 优选为 H。

30. 如权利要求 1-29 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^7 为 H。

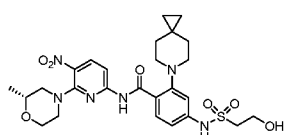
31. 如权利要求 1-30 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述通式(I)中, 其中 R^{15} 为 H 或 F, 优选为 H。

32. 如权利要求 1-31 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物, 其中所述化合物具有以下结构之一:

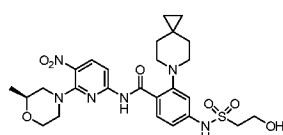




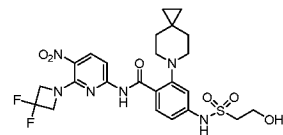
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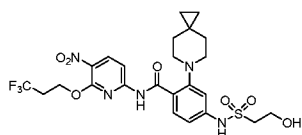
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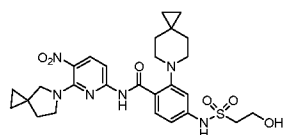
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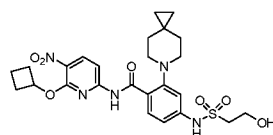
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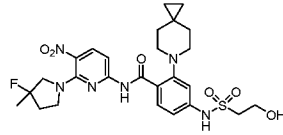
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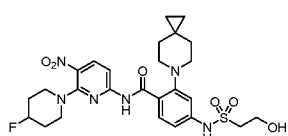
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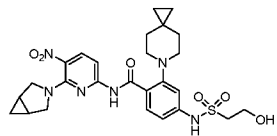
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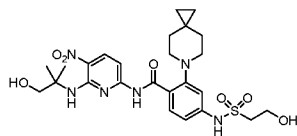
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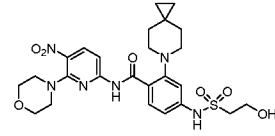
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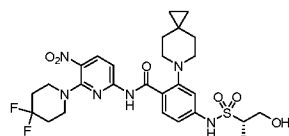
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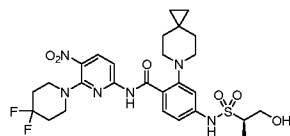
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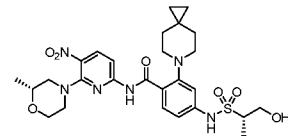
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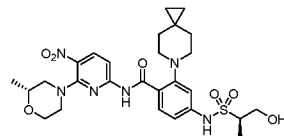
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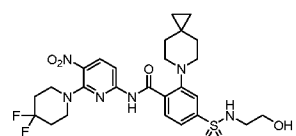
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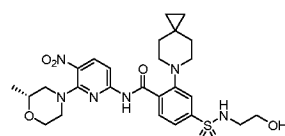
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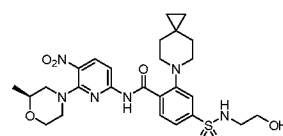
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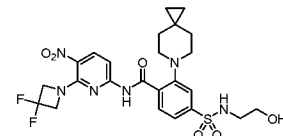
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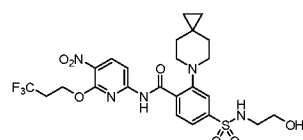
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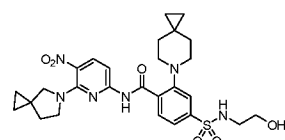
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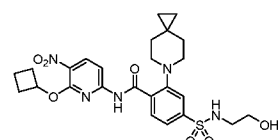
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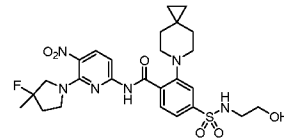
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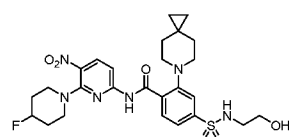
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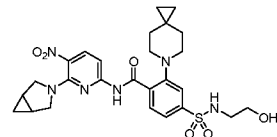
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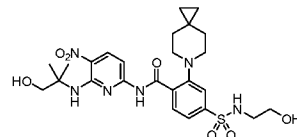
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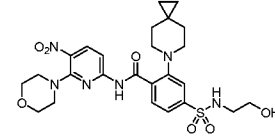
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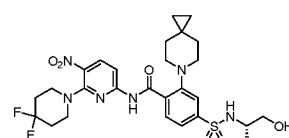
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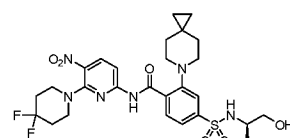
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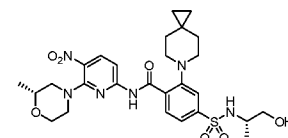
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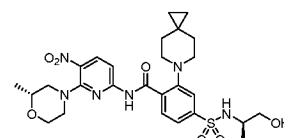
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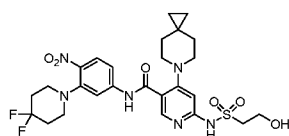
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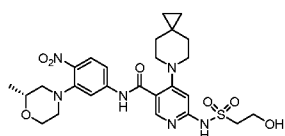
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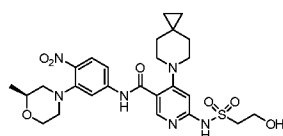
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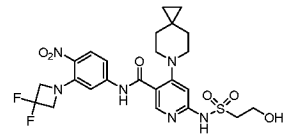
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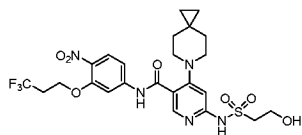
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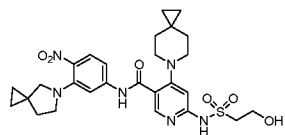
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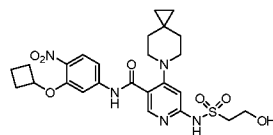
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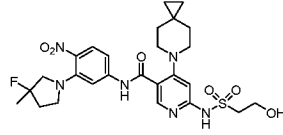
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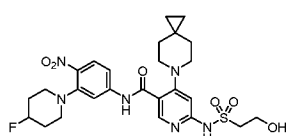
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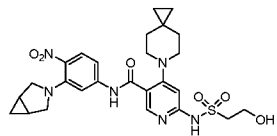
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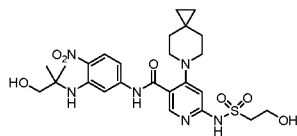
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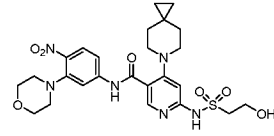
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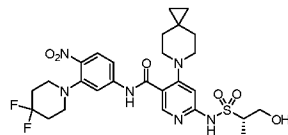
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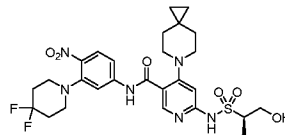
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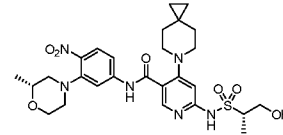
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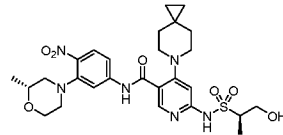
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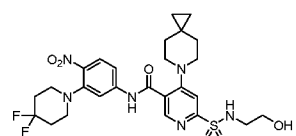
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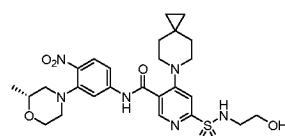
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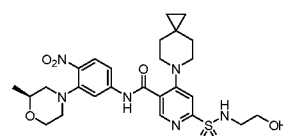
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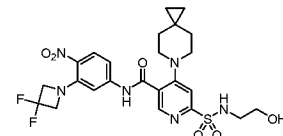
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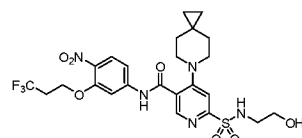
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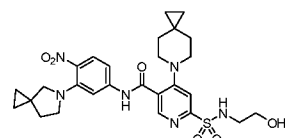
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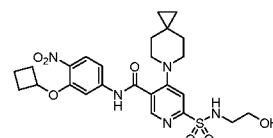
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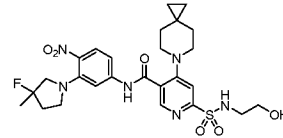
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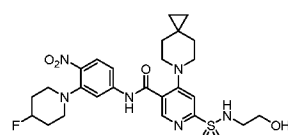
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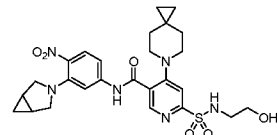
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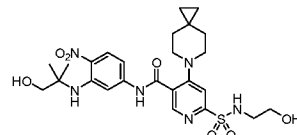
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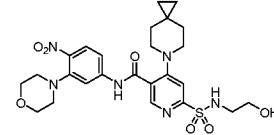
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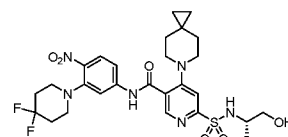
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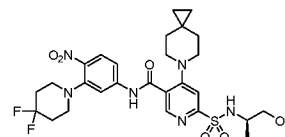
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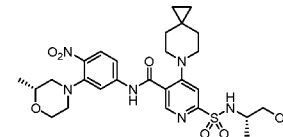
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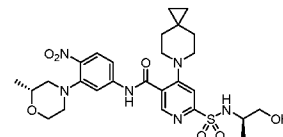
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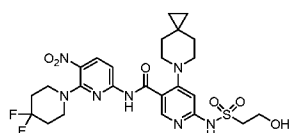
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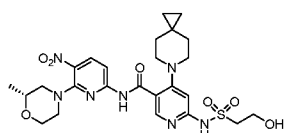
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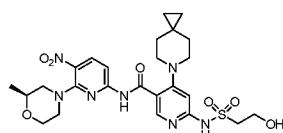
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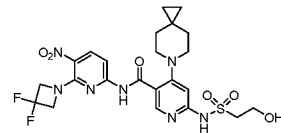
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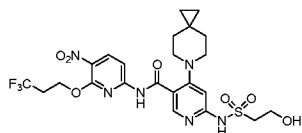
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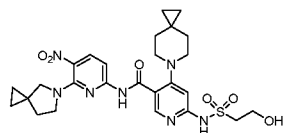
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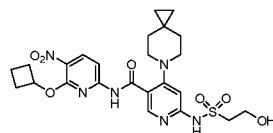
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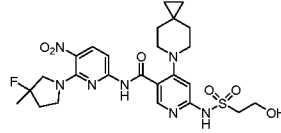
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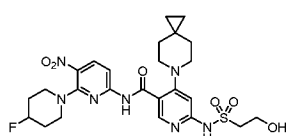
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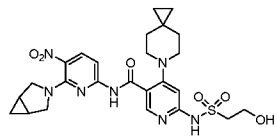
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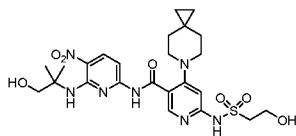
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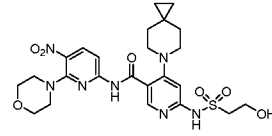
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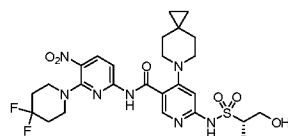
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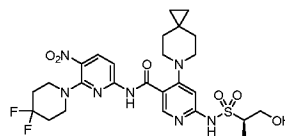
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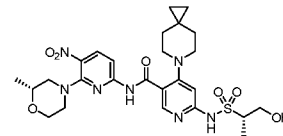
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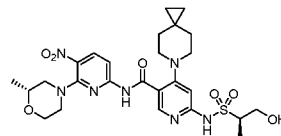
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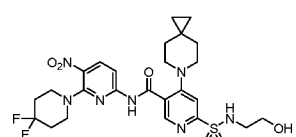
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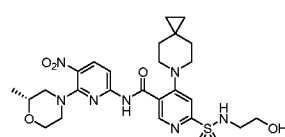
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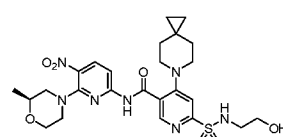
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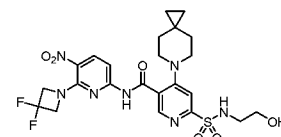
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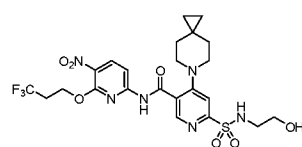
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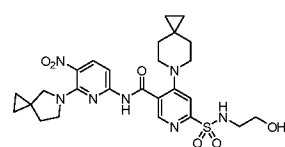
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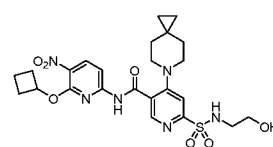
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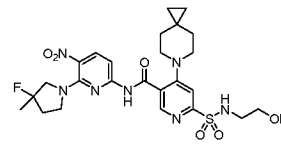
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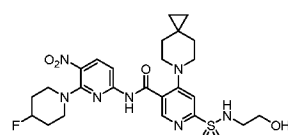
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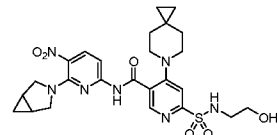
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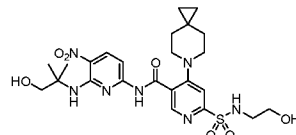
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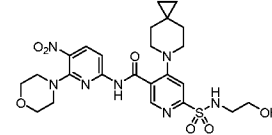
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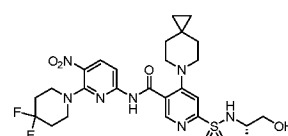
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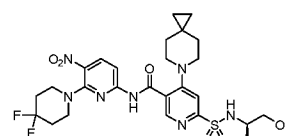
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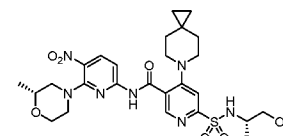
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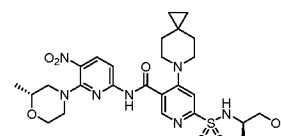
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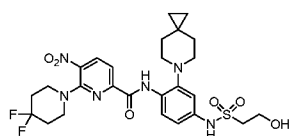
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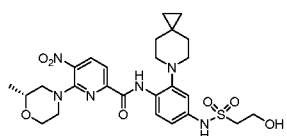
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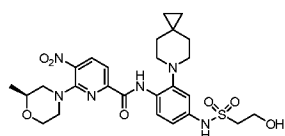
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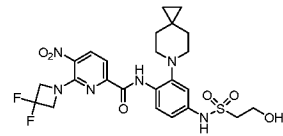
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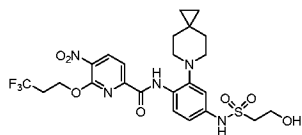
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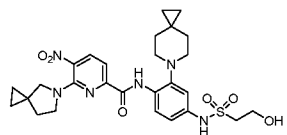
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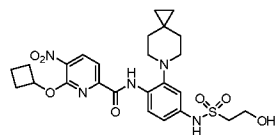
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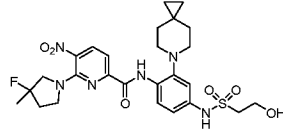
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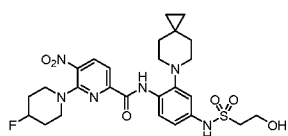
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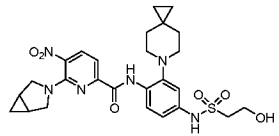
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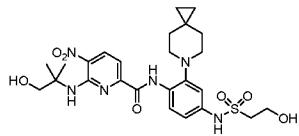
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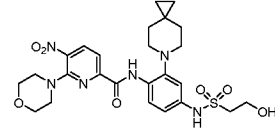
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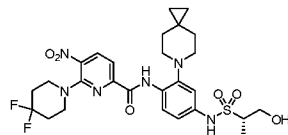
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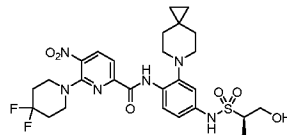
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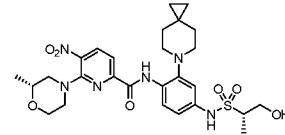
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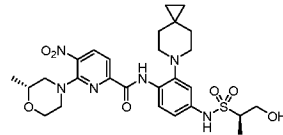
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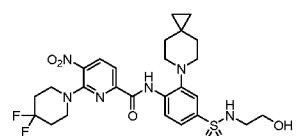
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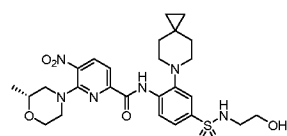
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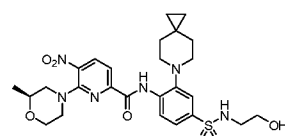
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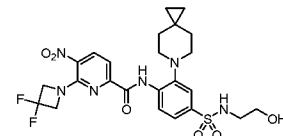
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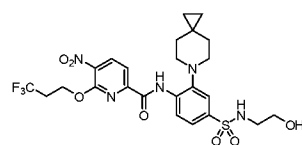
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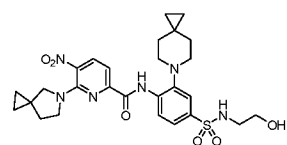
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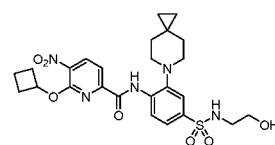
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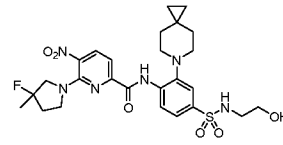
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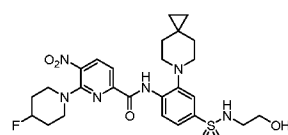
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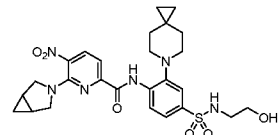
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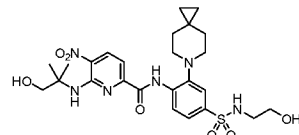
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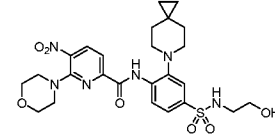
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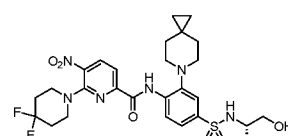
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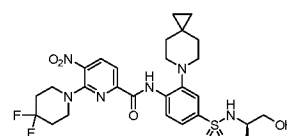
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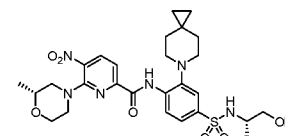
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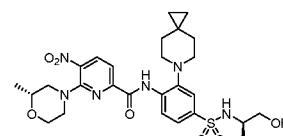
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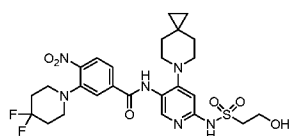
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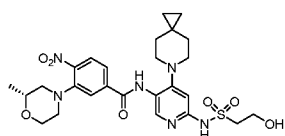
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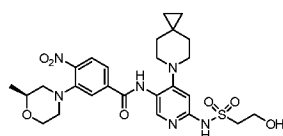
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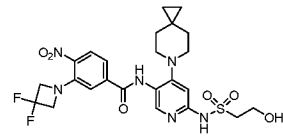
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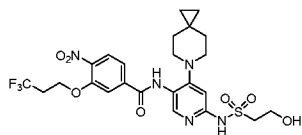
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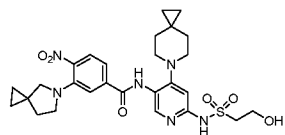
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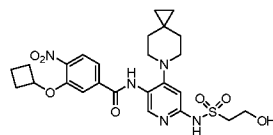
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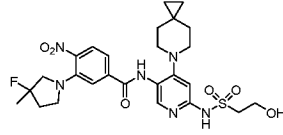
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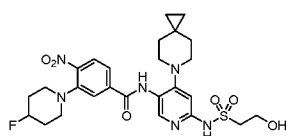
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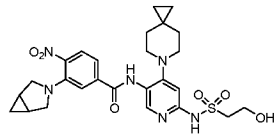
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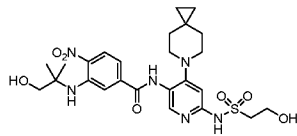
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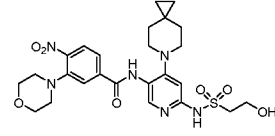
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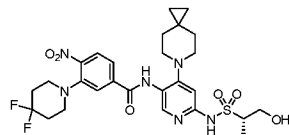
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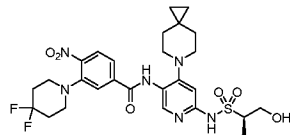
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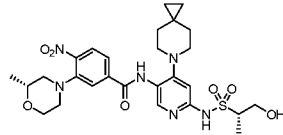
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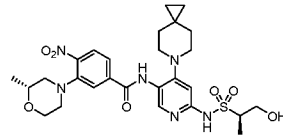
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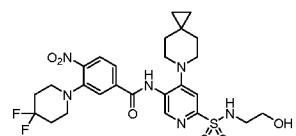
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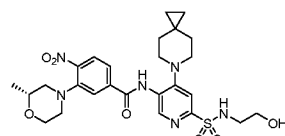
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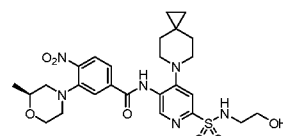
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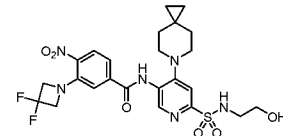
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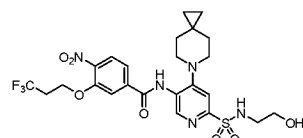
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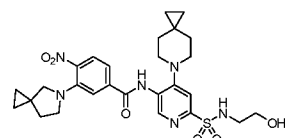
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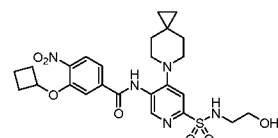
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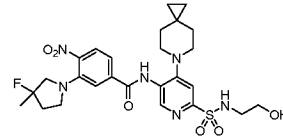
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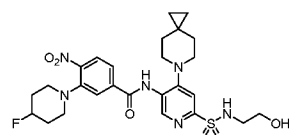
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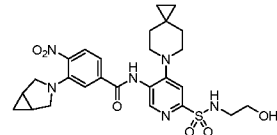
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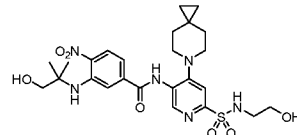
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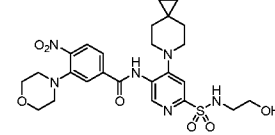
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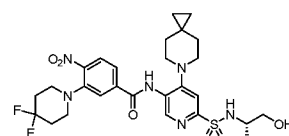
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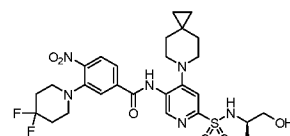
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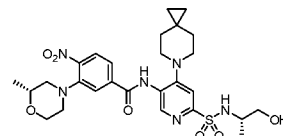
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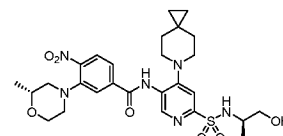
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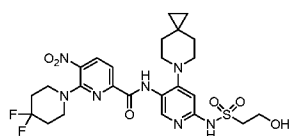
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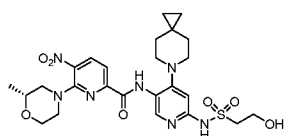
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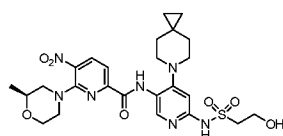
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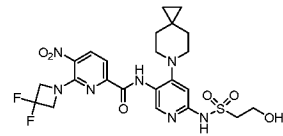
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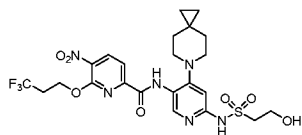
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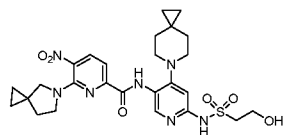
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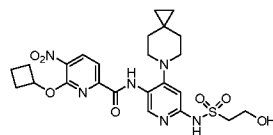
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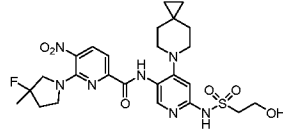
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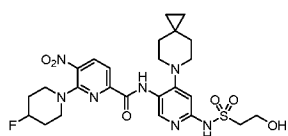
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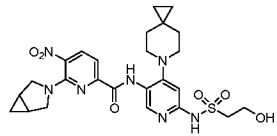
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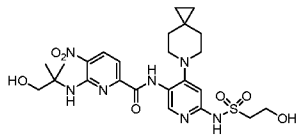
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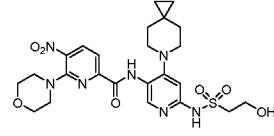
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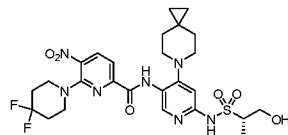
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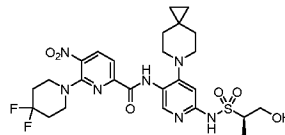
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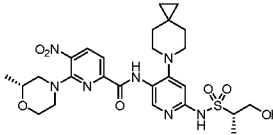
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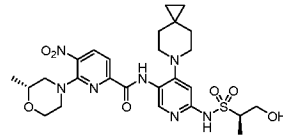
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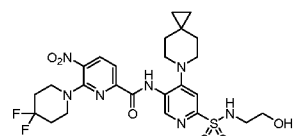
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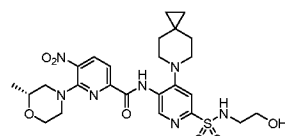
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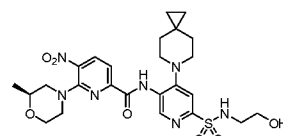
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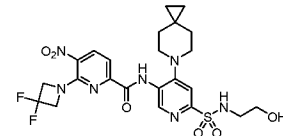
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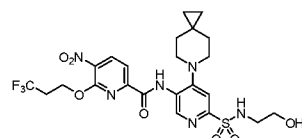
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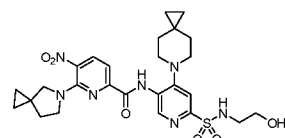
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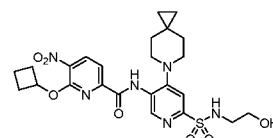
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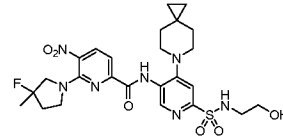
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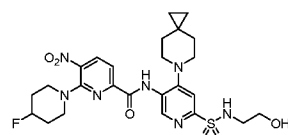
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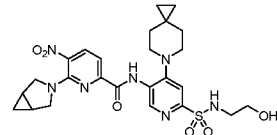
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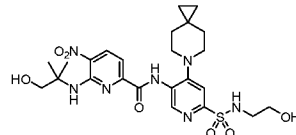
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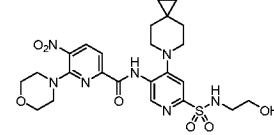
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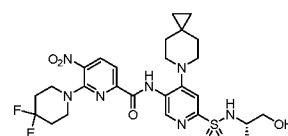
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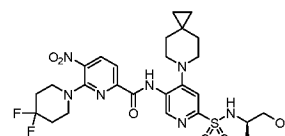
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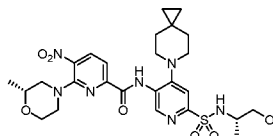
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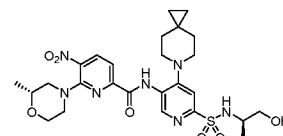
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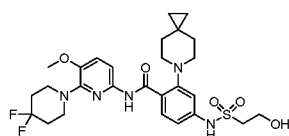
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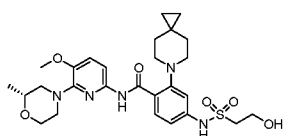
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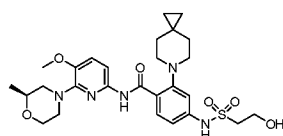
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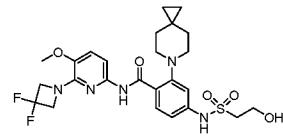
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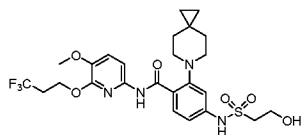
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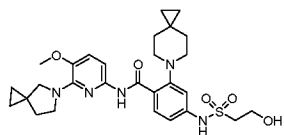
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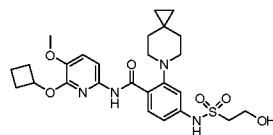
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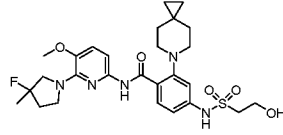
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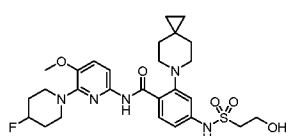
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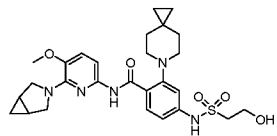
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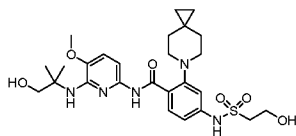
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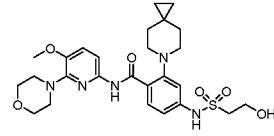
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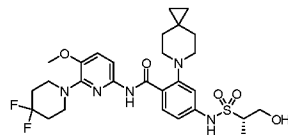
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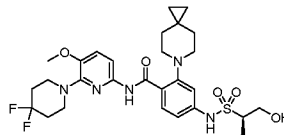
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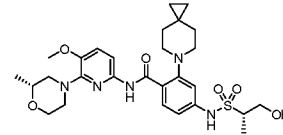
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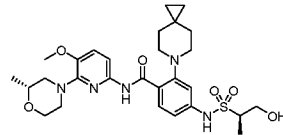
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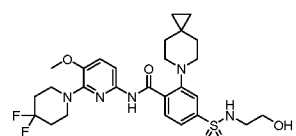
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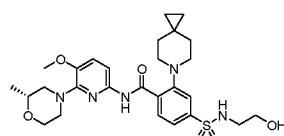
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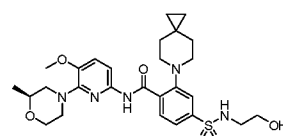
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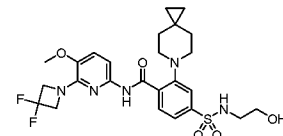
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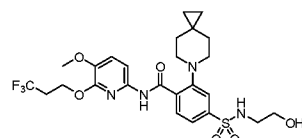
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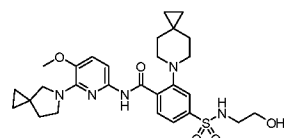
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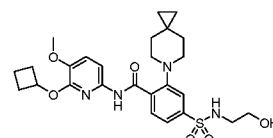
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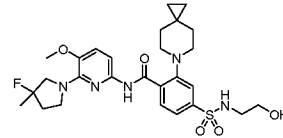
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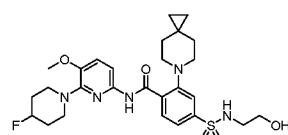
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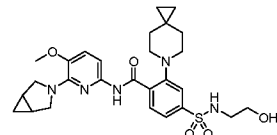
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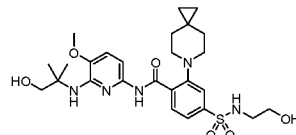
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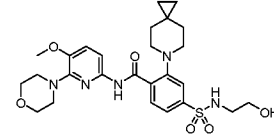
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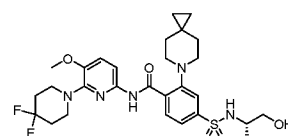
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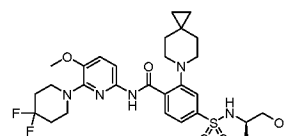
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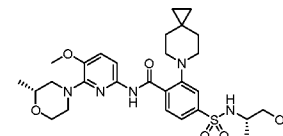
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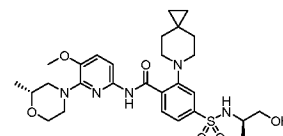
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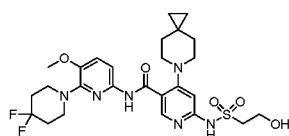
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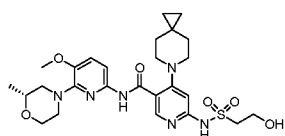
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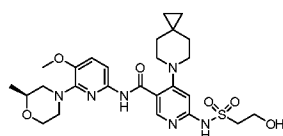
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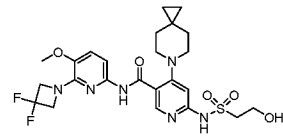
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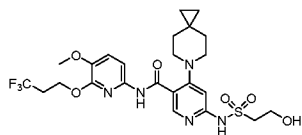
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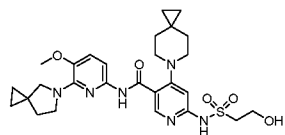
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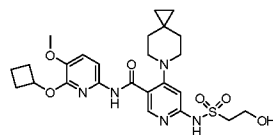
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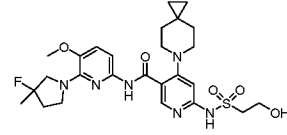
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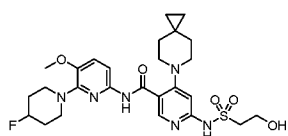
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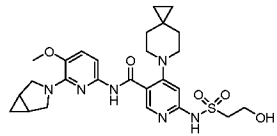
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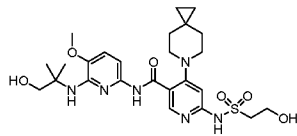
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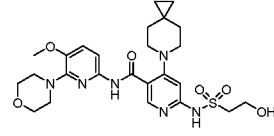
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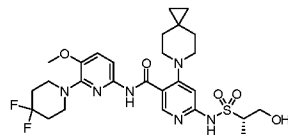
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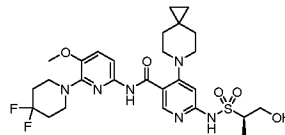
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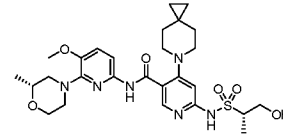
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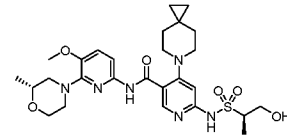
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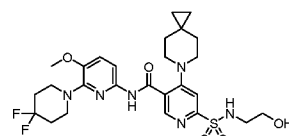
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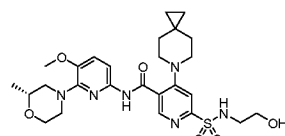
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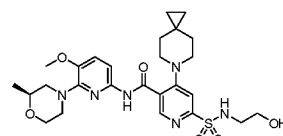
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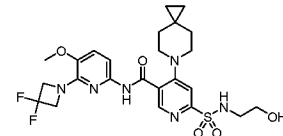
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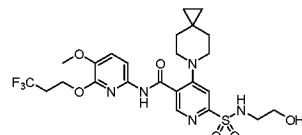
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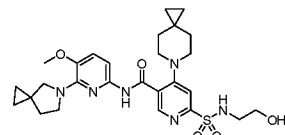
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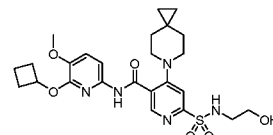
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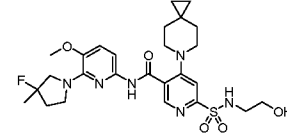
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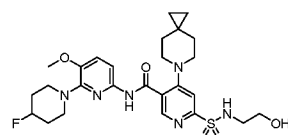
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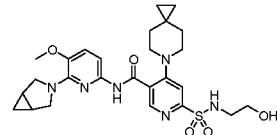
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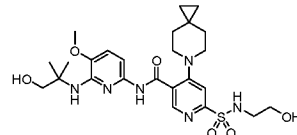
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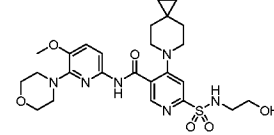
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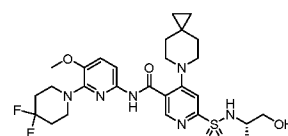
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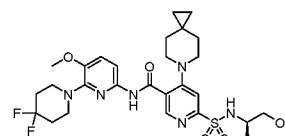
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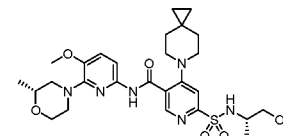
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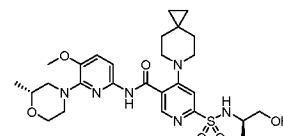
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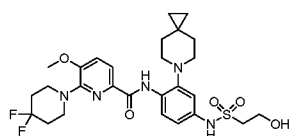
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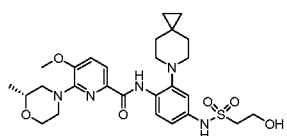
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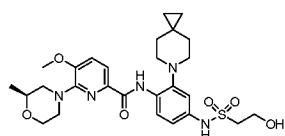
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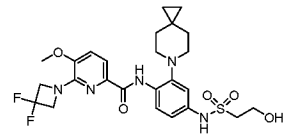
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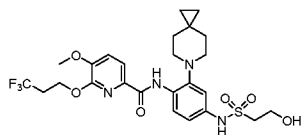
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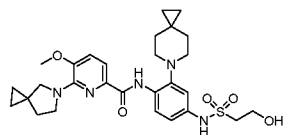
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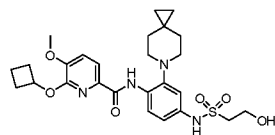
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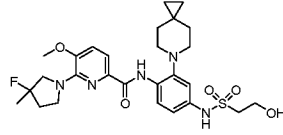
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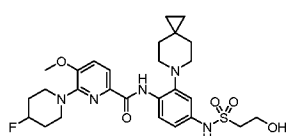
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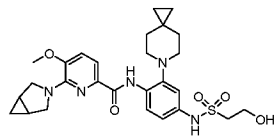
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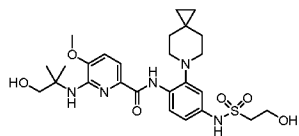
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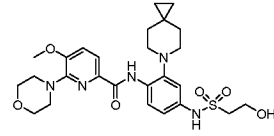
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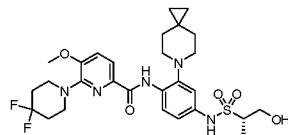
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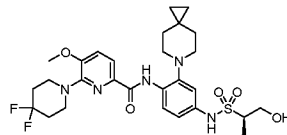
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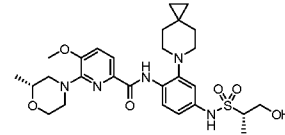
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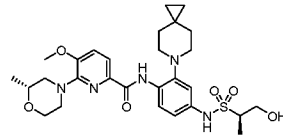
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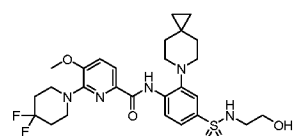
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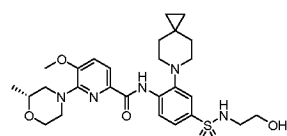
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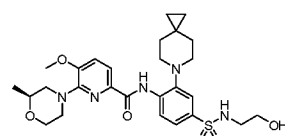
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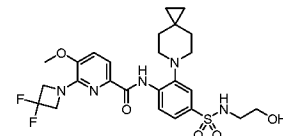
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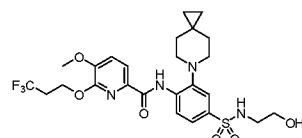
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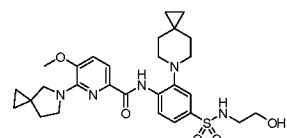
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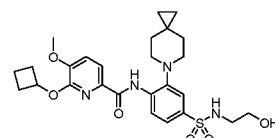
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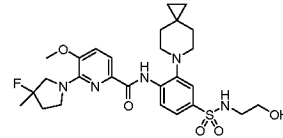
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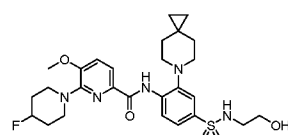
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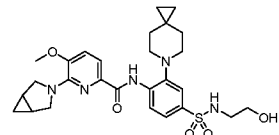
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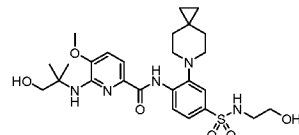
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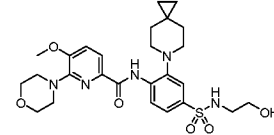
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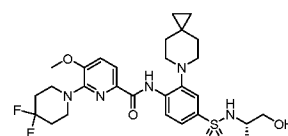
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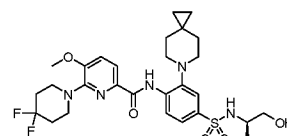
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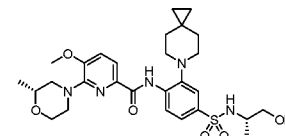
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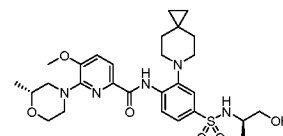
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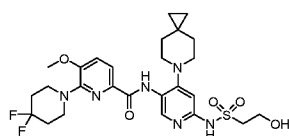
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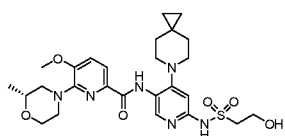
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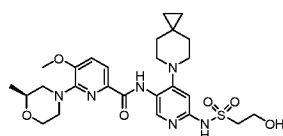
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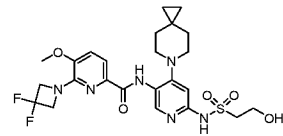
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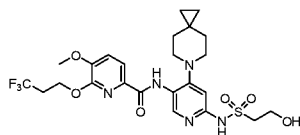
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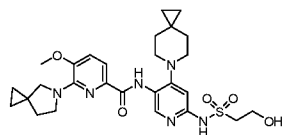
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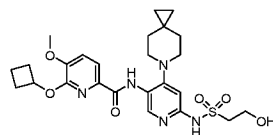
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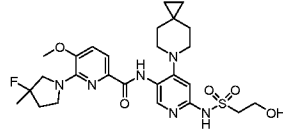
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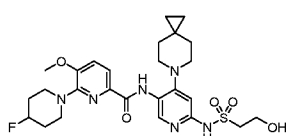
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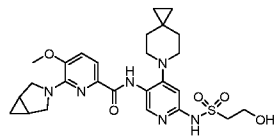
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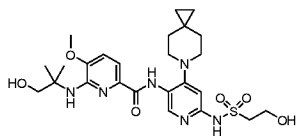
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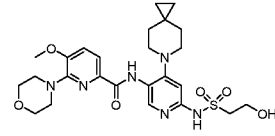
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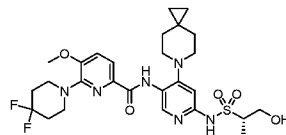
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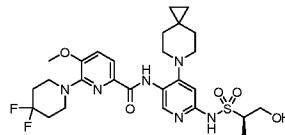
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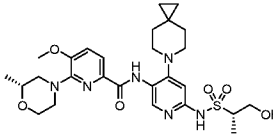
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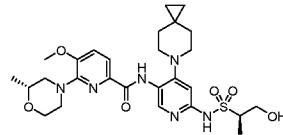
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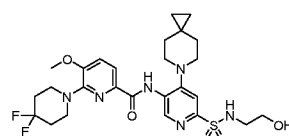
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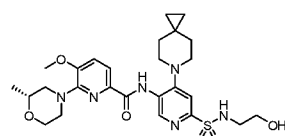
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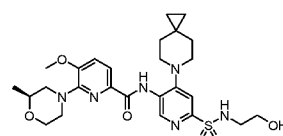
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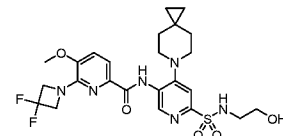
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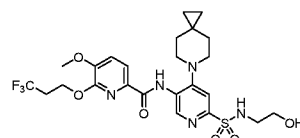
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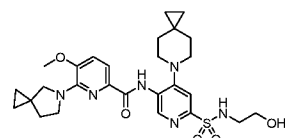
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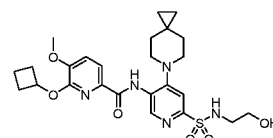
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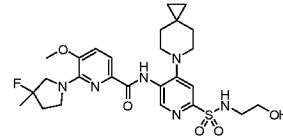
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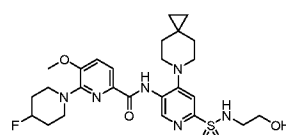
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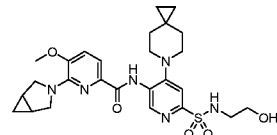
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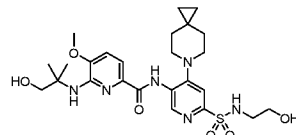
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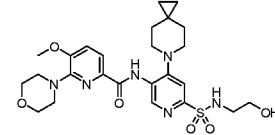
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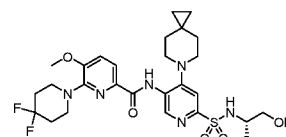
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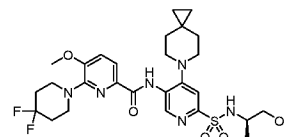
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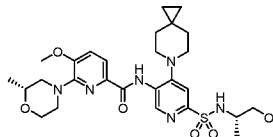
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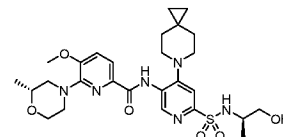
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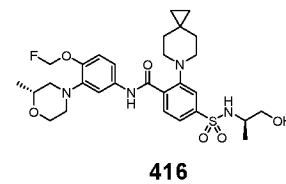
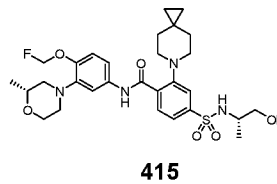
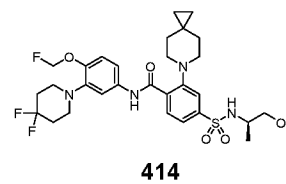
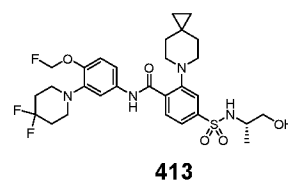
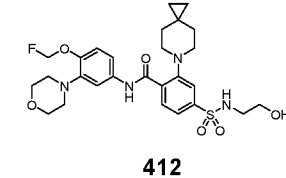
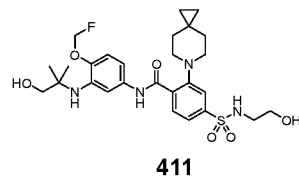
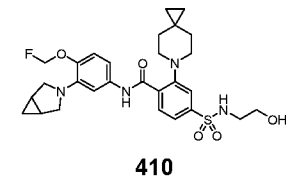
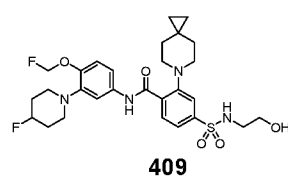
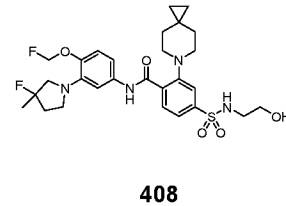
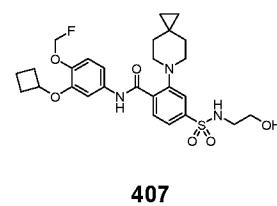
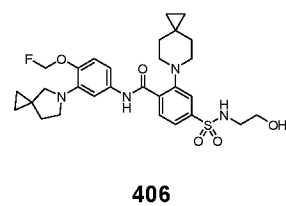
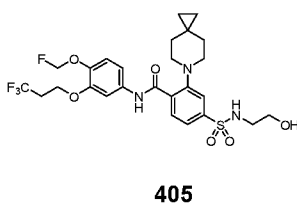
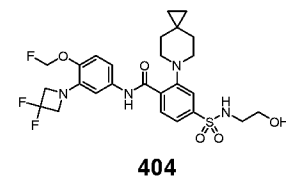
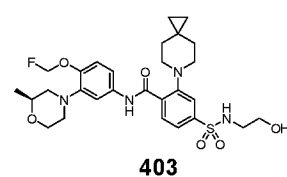
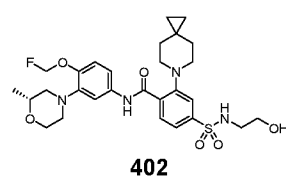
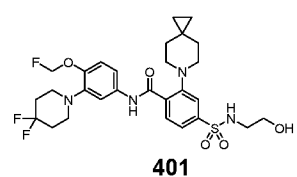
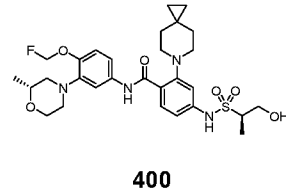
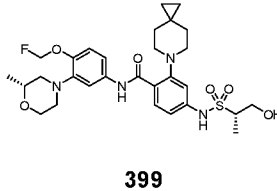
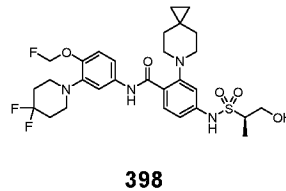
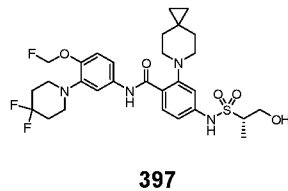
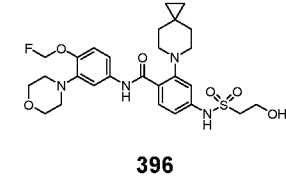
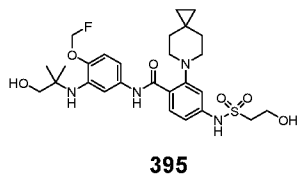
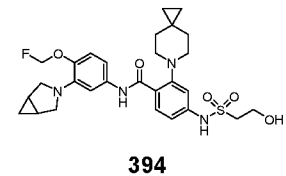
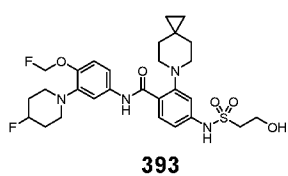
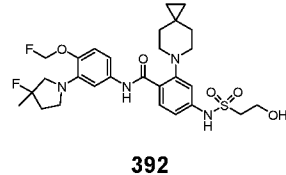
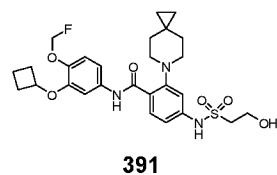
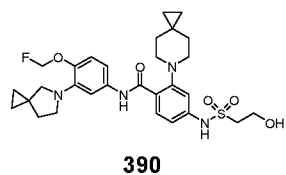
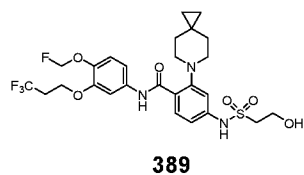
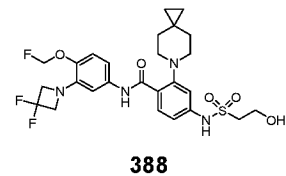
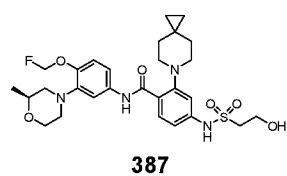
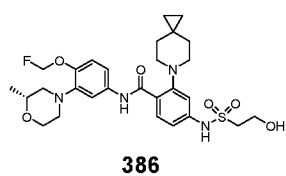
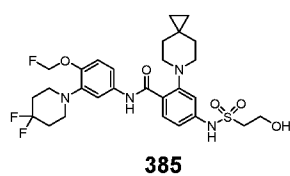
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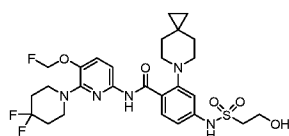


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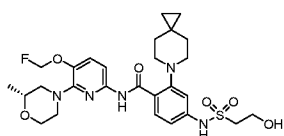


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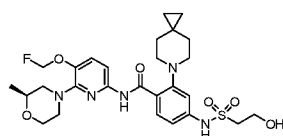




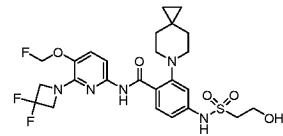
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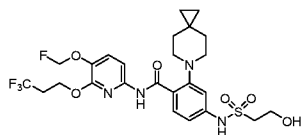
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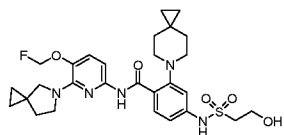
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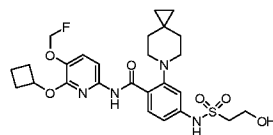
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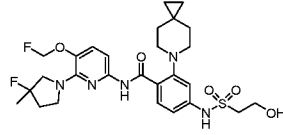
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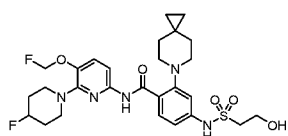
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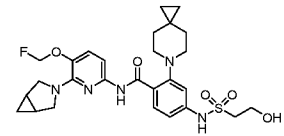
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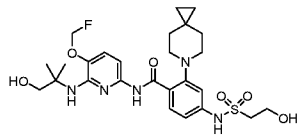
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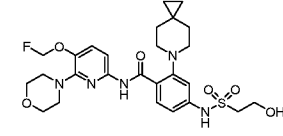
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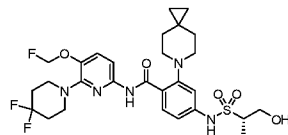
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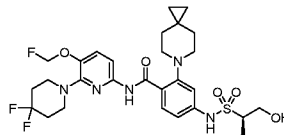
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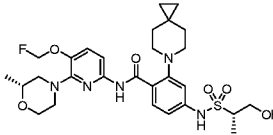
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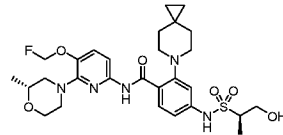
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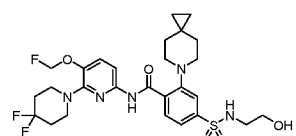
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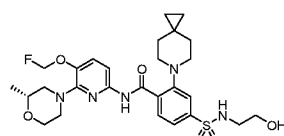
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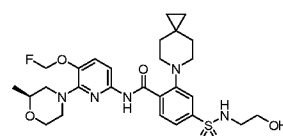
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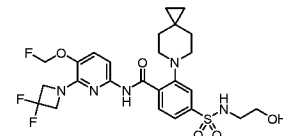
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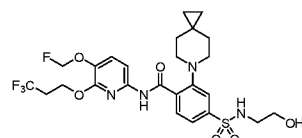
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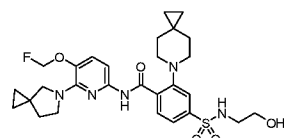
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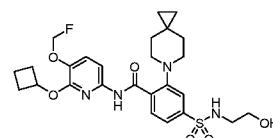
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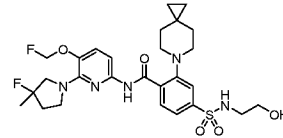
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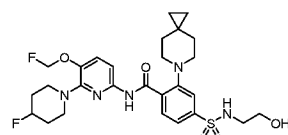
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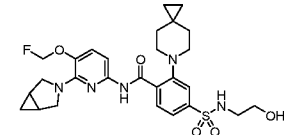
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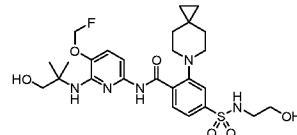
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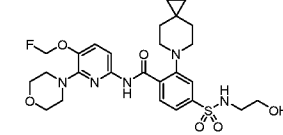
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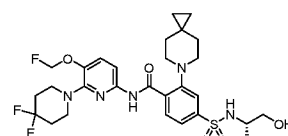
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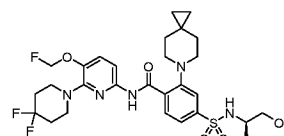
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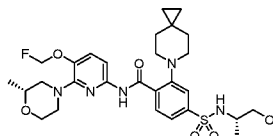
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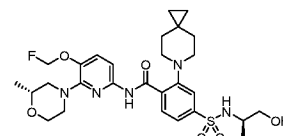
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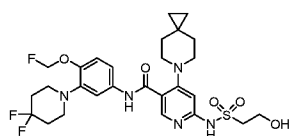
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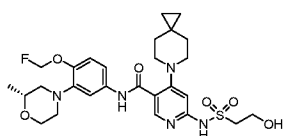
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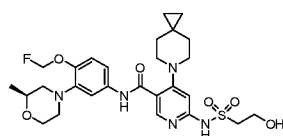
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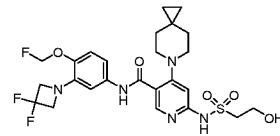
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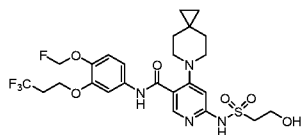
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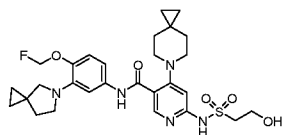
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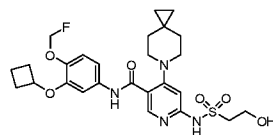
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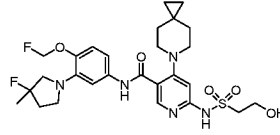
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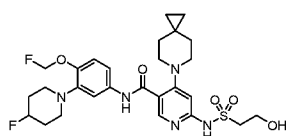
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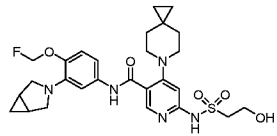
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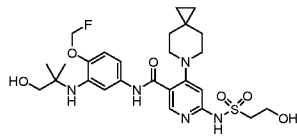
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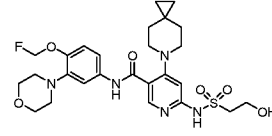
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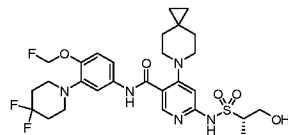
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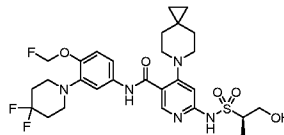
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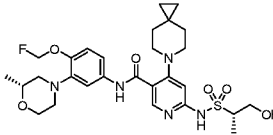
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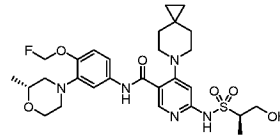
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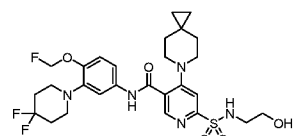
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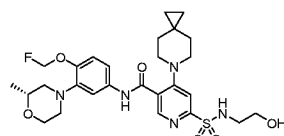
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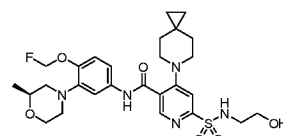
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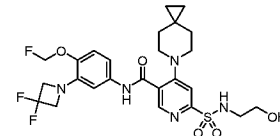
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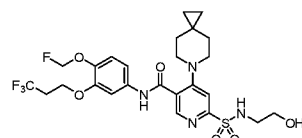
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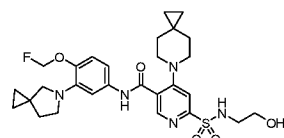
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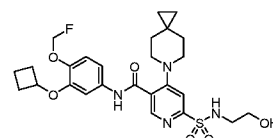
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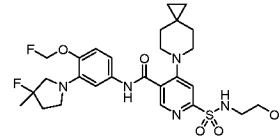
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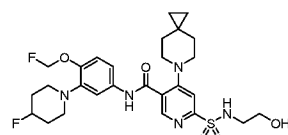
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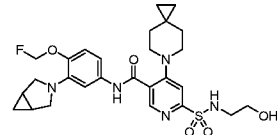
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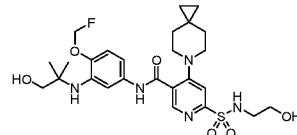
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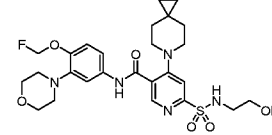
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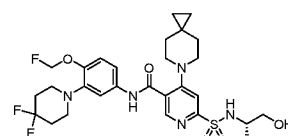
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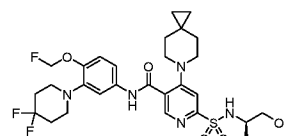
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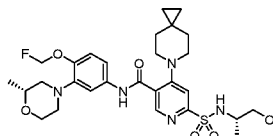
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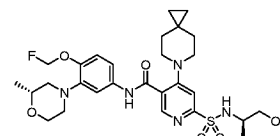
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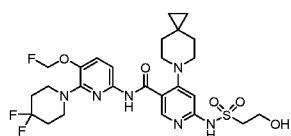
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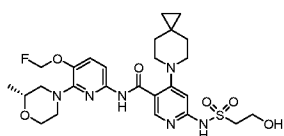
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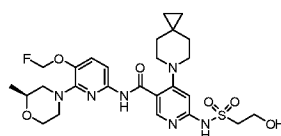
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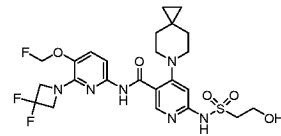
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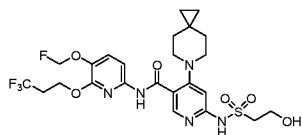
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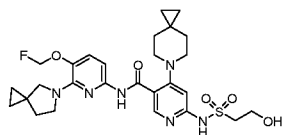
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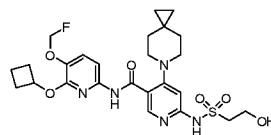
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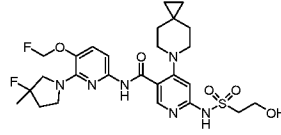
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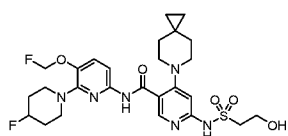
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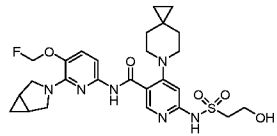
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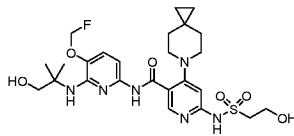
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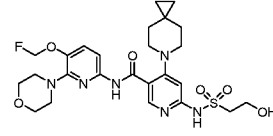
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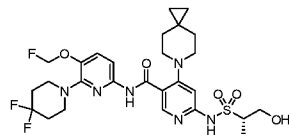
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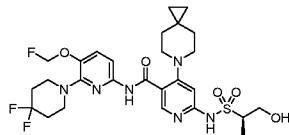
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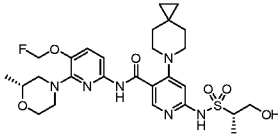
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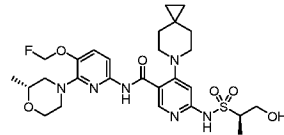
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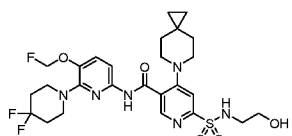
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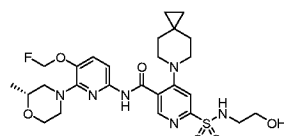
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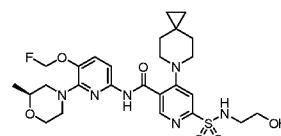
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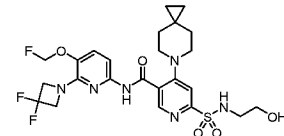
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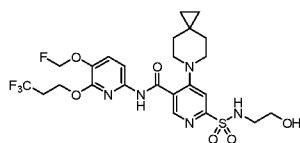
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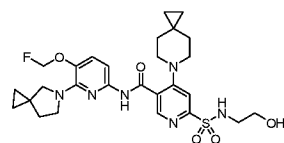
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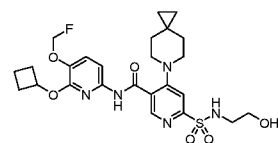
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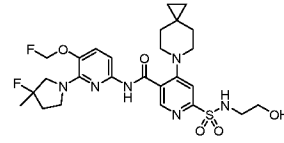
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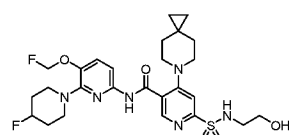
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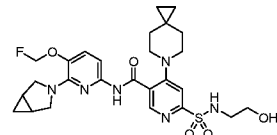
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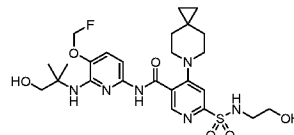
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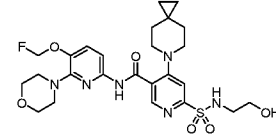
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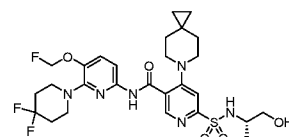
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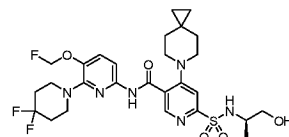
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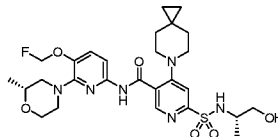
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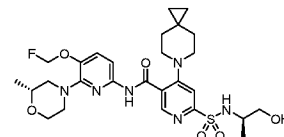
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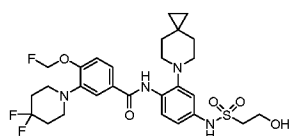
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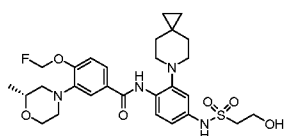
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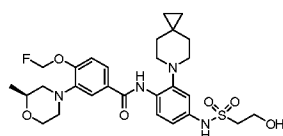
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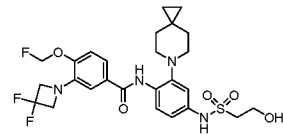
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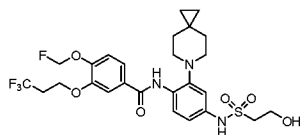
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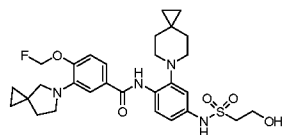
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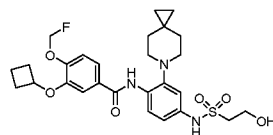
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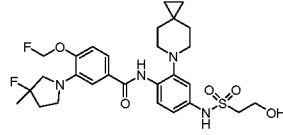
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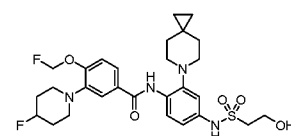
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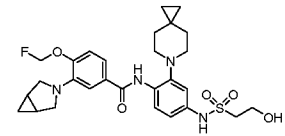
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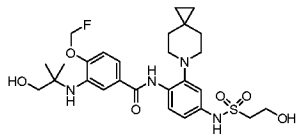
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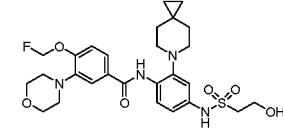
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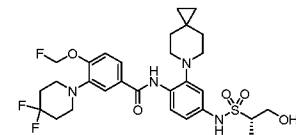
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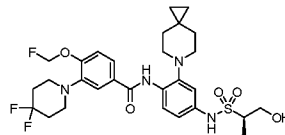
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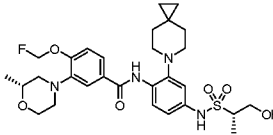
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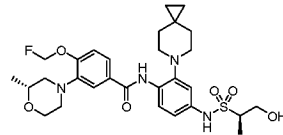
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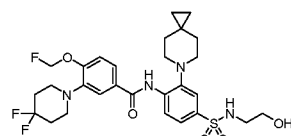
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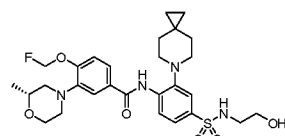
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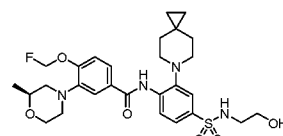
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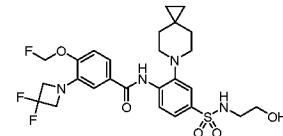
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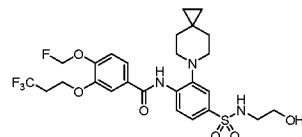
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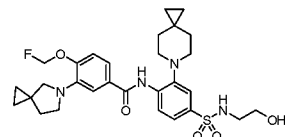
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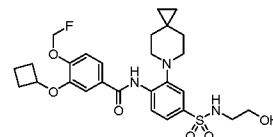
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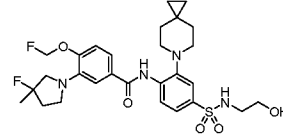
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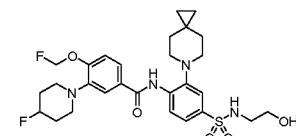
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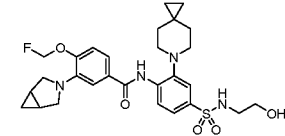
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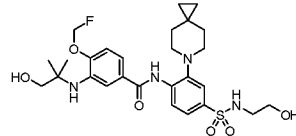
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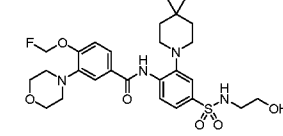
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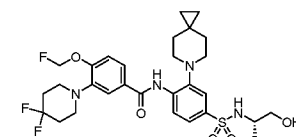
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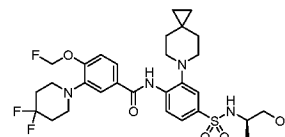
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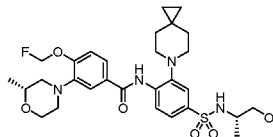
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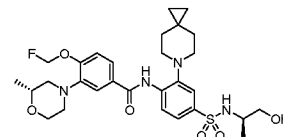
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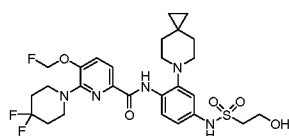
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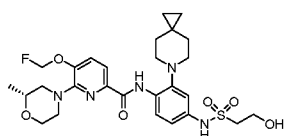
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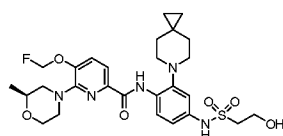
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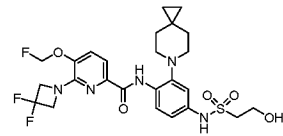
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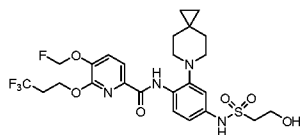
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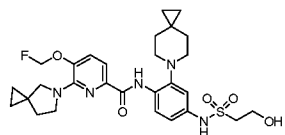
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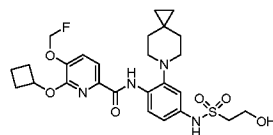
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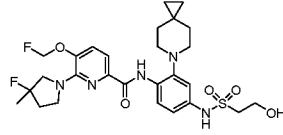
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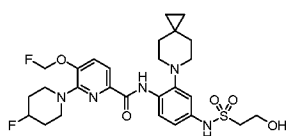
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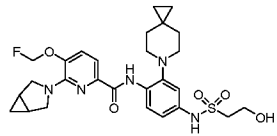
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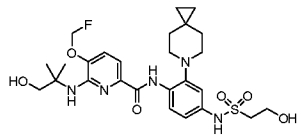
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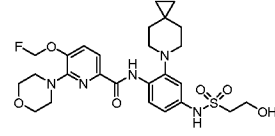
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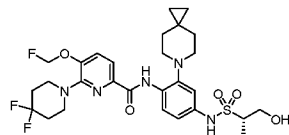
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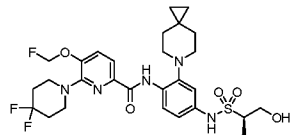
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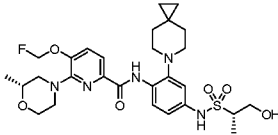
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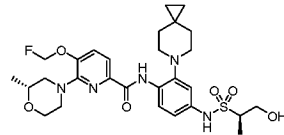
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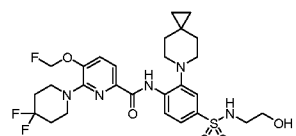
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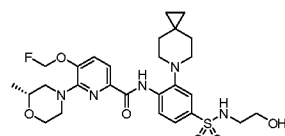
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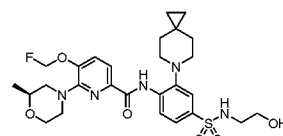
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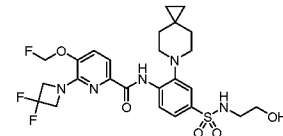
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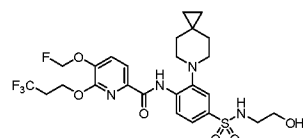
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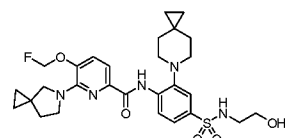
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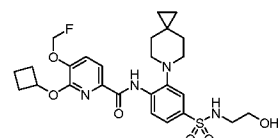
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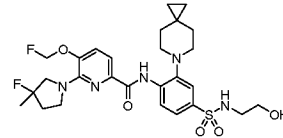
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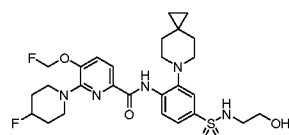
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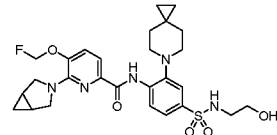
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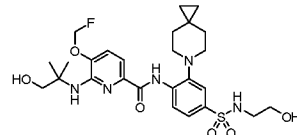
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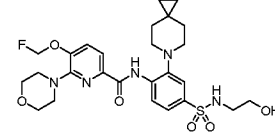
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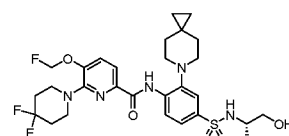
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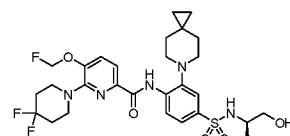
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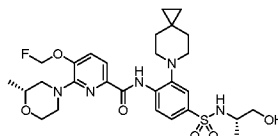
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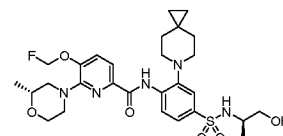
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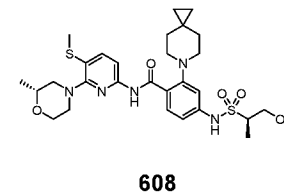
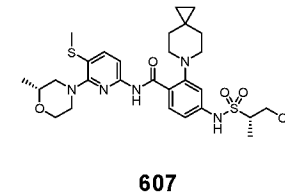
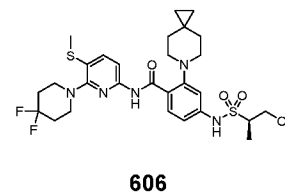
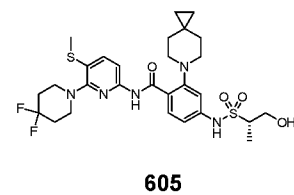
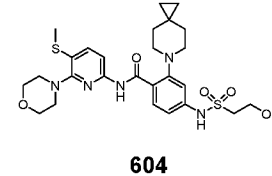
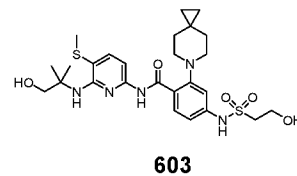
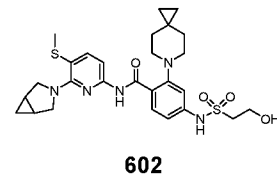
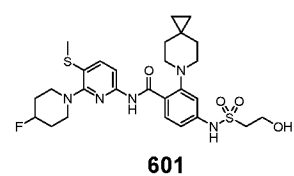
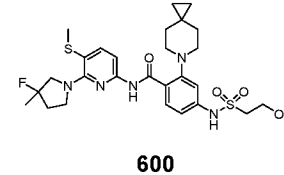
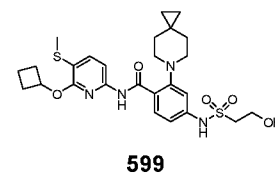
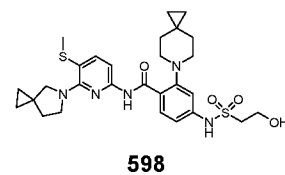
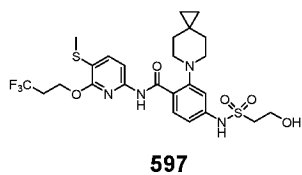
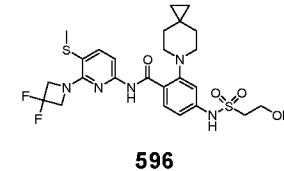
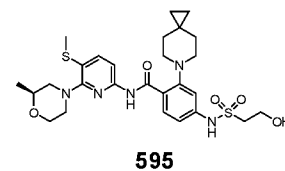
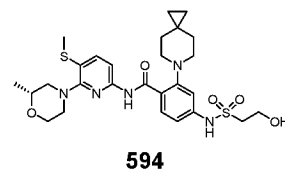
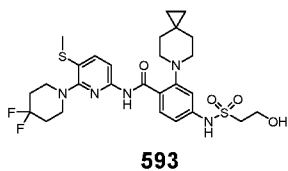
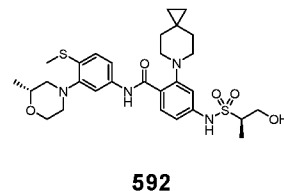
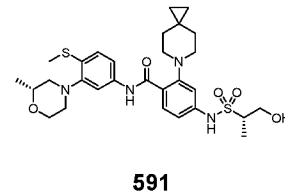
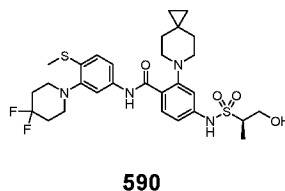
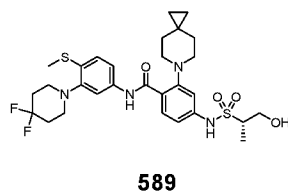
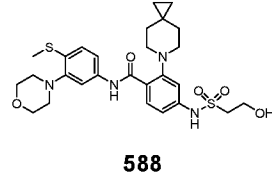
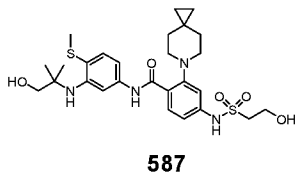
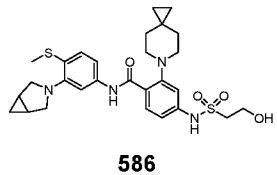
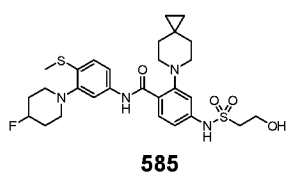
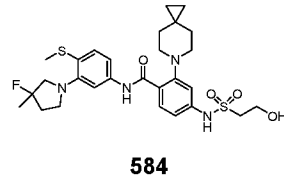
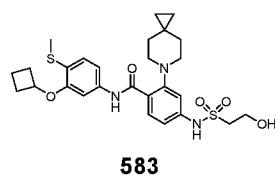
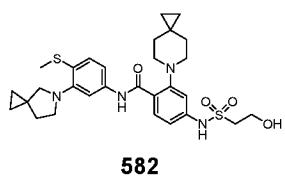
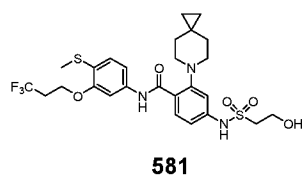
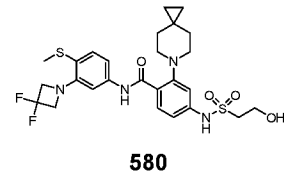
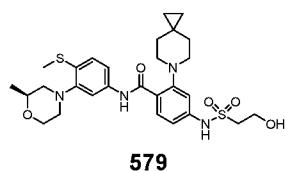
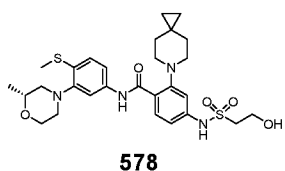
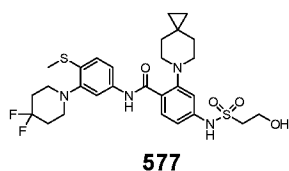
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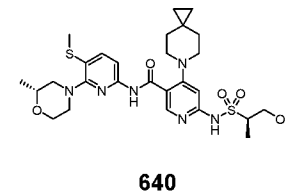
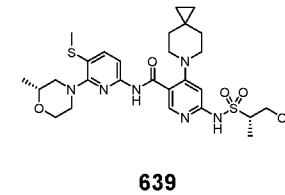
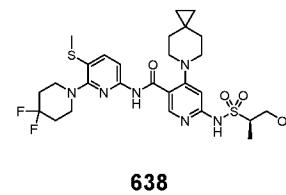
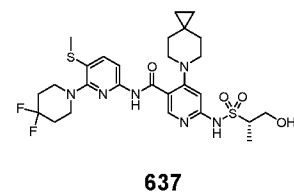
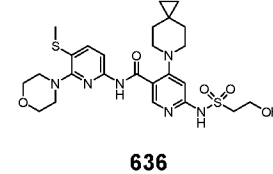
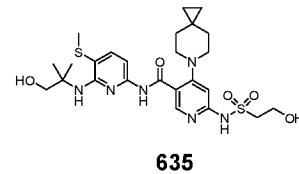
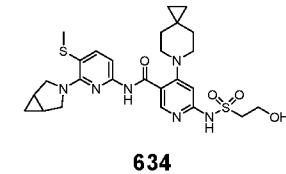
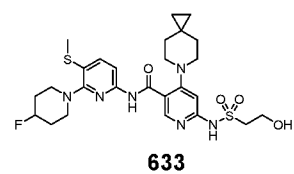
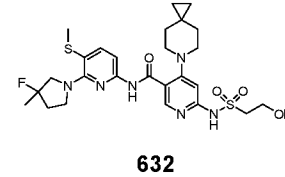
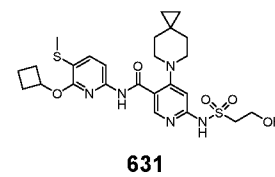
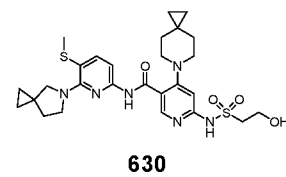
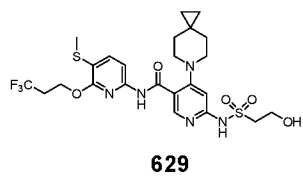
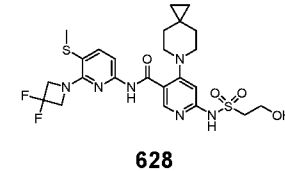
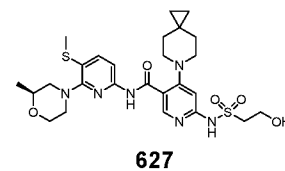
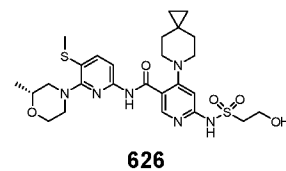
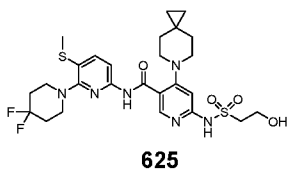
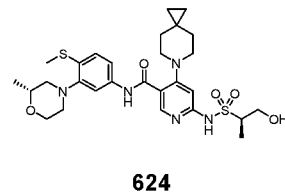
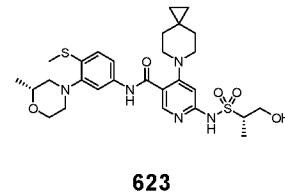
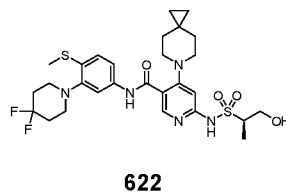
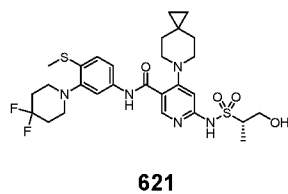
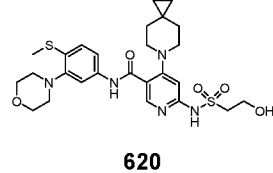
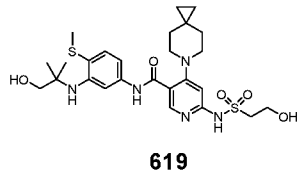
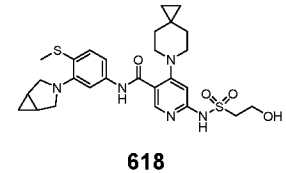
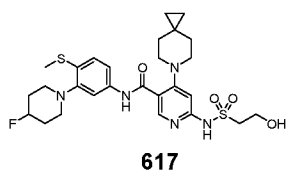
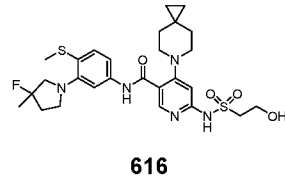
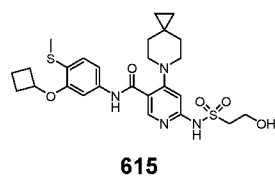
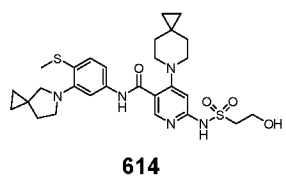
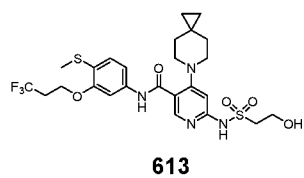
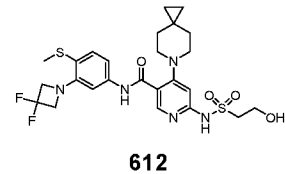
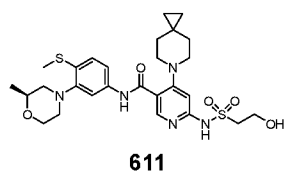
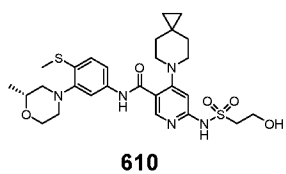
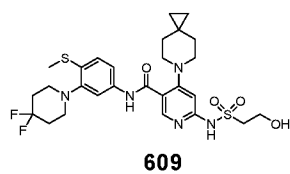


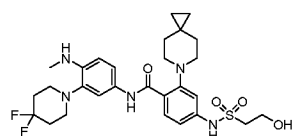
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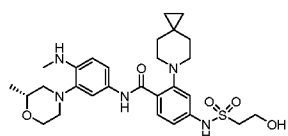
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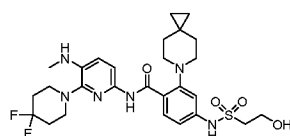




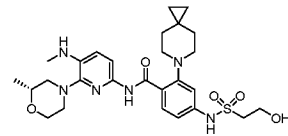
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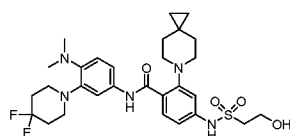
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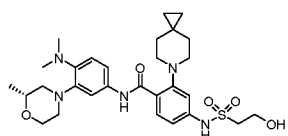
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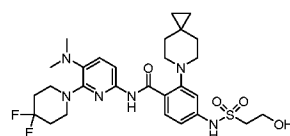
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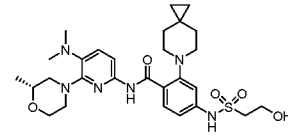
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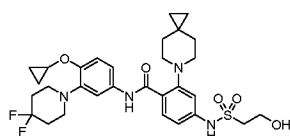
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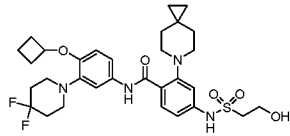
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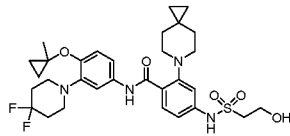
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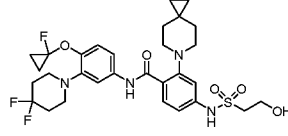
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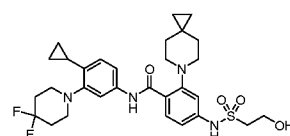
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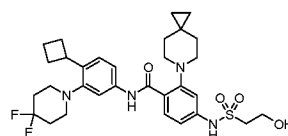
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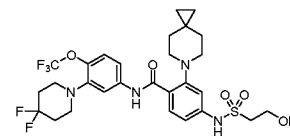
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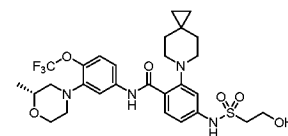
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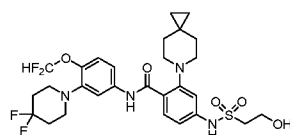
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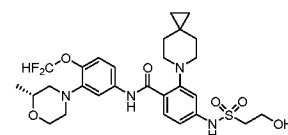
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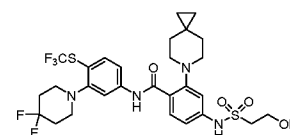
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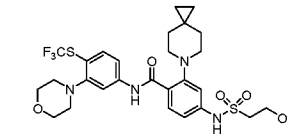
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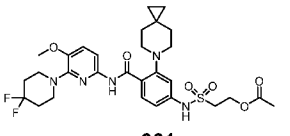
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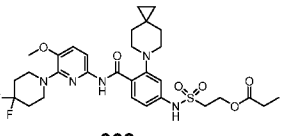
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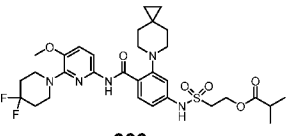
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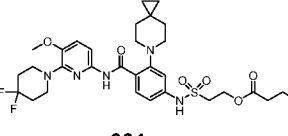
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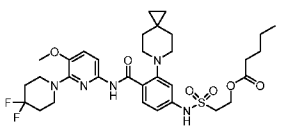
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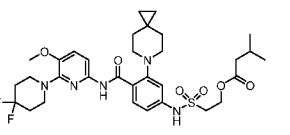
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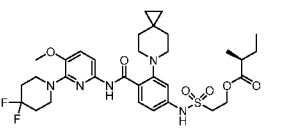
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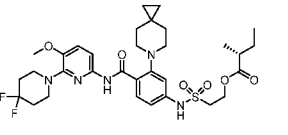
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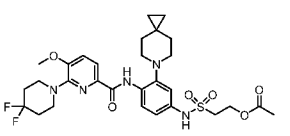
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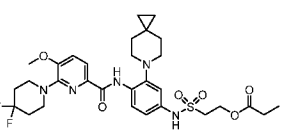
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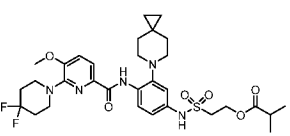
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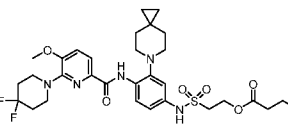
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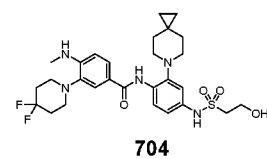
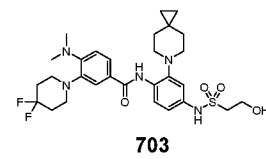
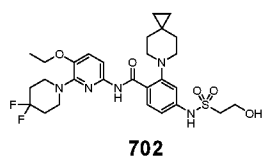
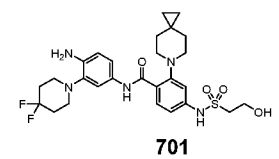
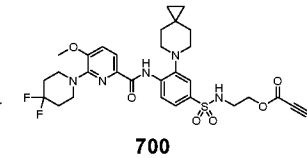
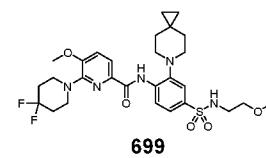
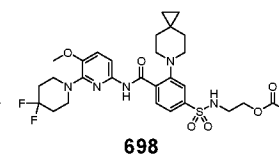
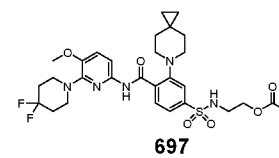
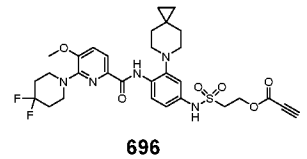
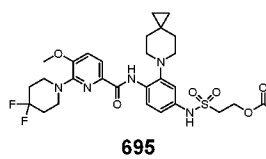
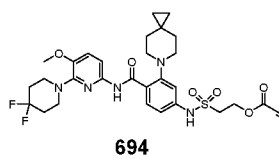
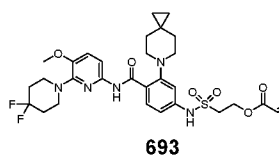
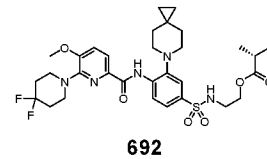
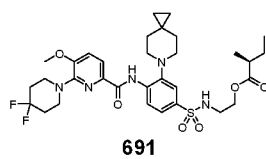
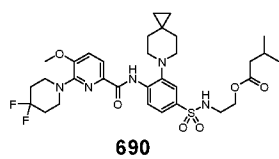
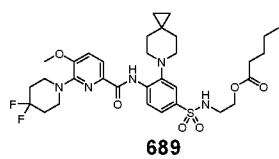
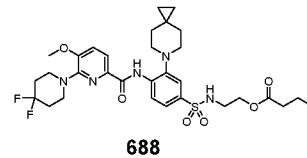
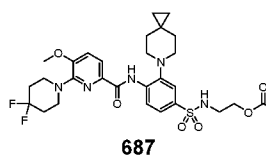
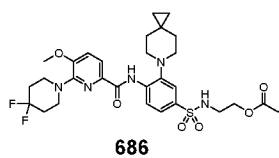
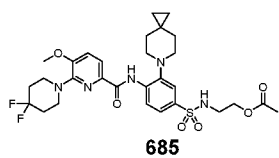
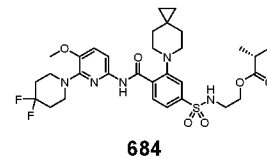
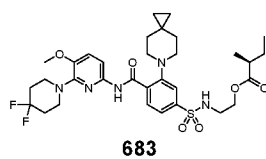
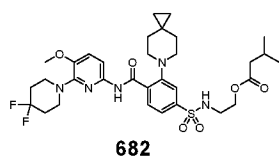
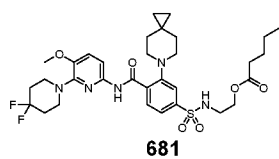
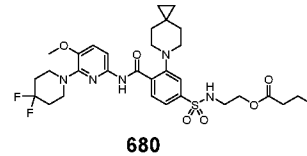
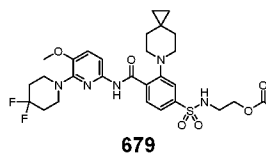
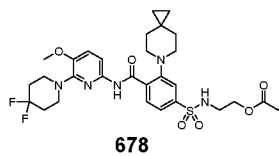
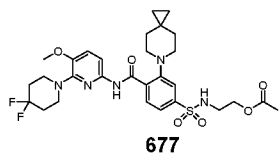
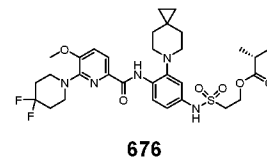
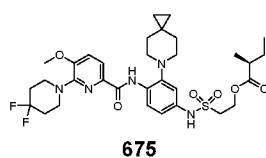
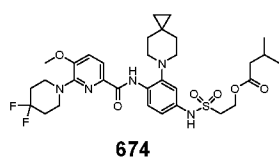
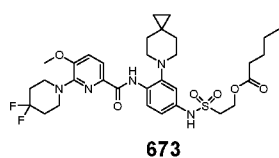
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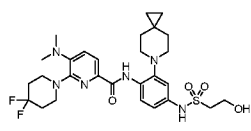


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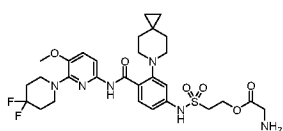


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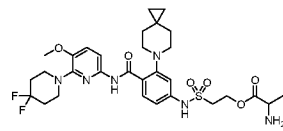




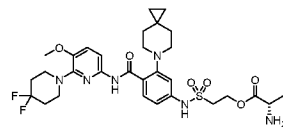
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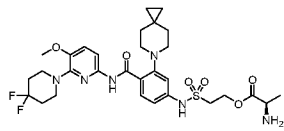
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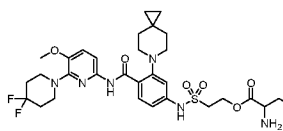
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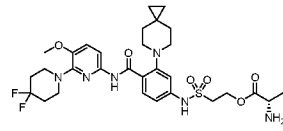
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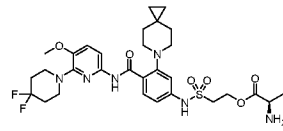
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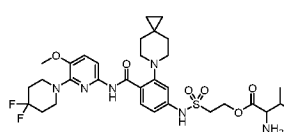
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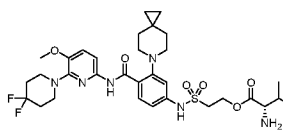
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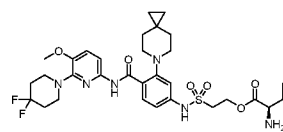
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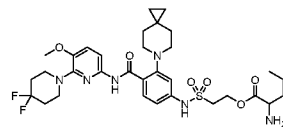
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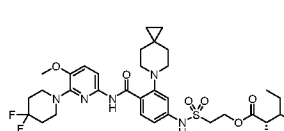
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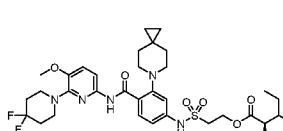
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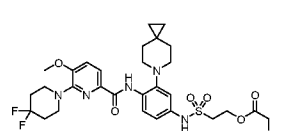
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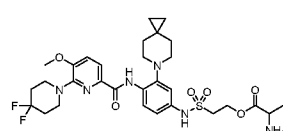
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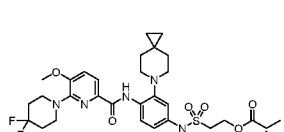
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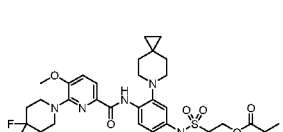
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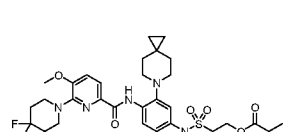
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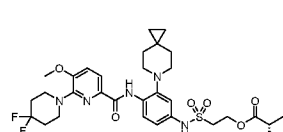
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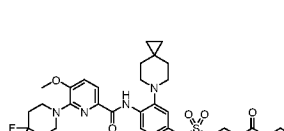
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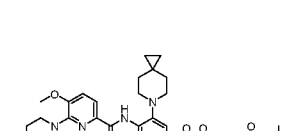
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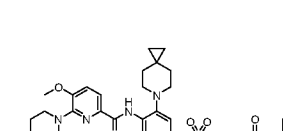
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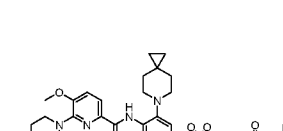
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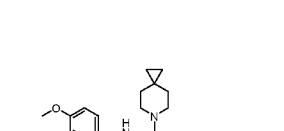
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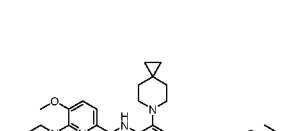
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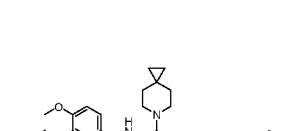
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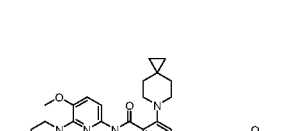
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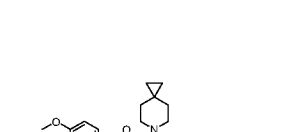
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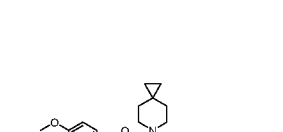
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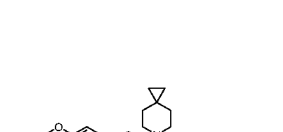
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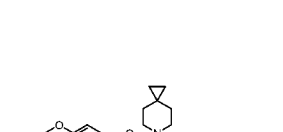
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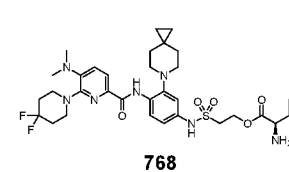
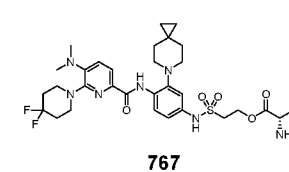
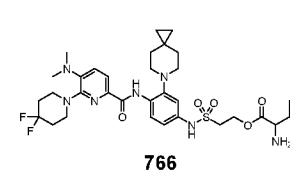
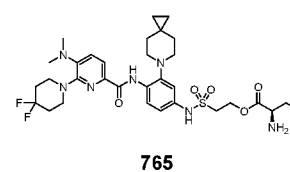
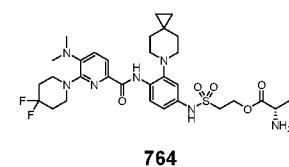
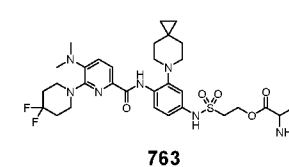
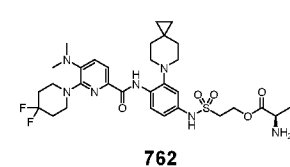
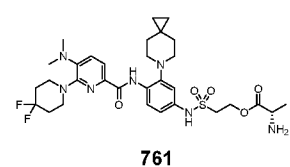
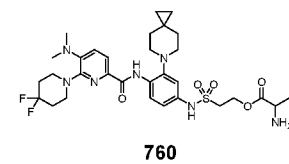
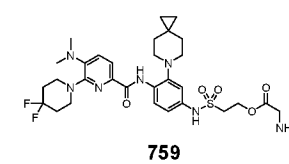
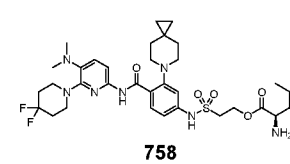
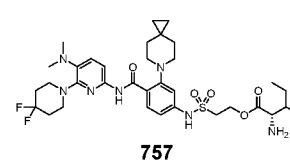
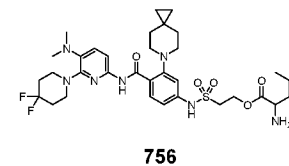
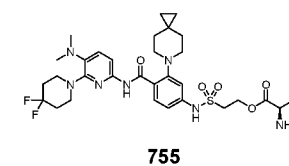
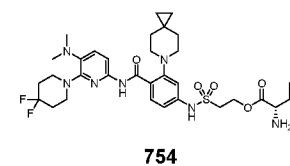
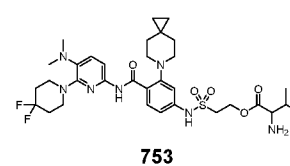
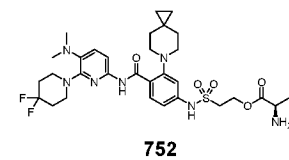
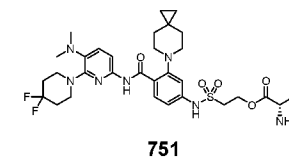
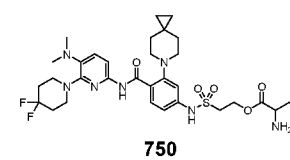
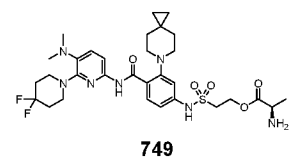
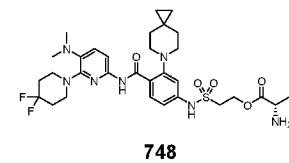
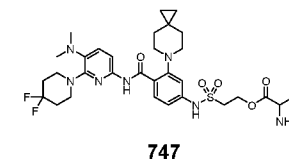
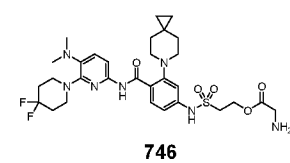
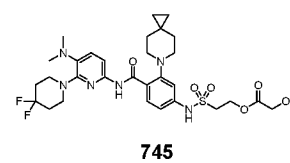
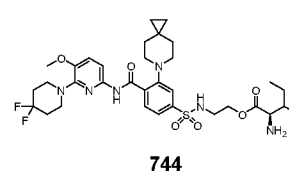
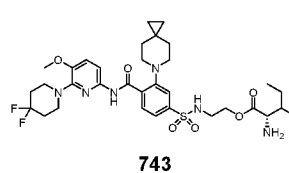
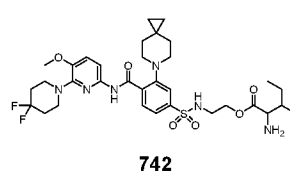
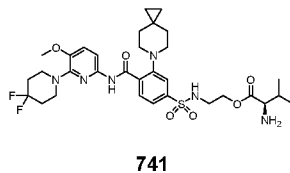
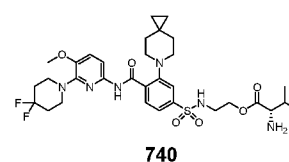
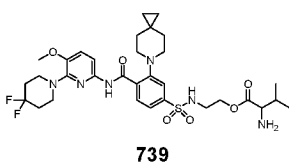
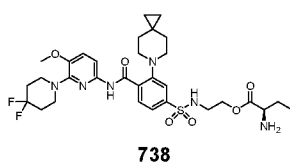
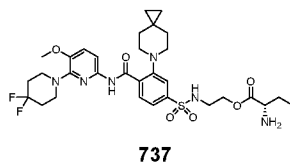
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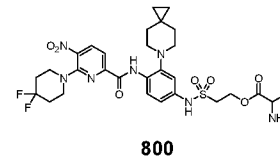
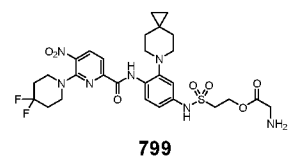
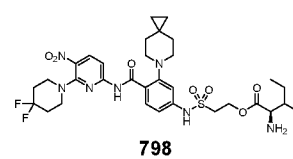
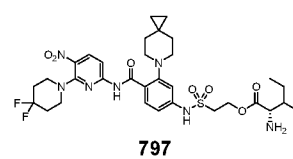
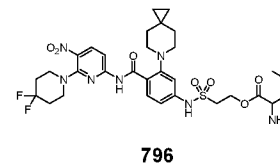
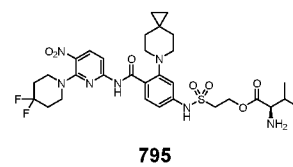
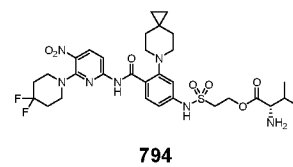
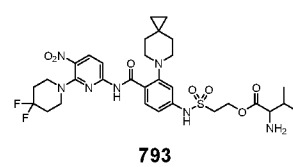
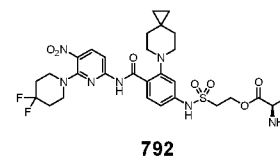
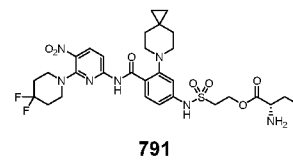
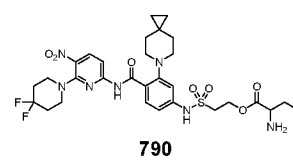
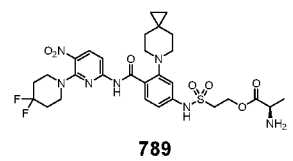
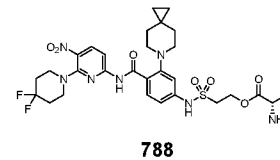
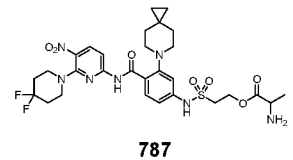
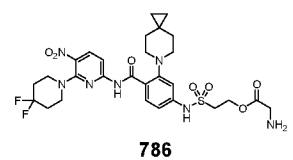
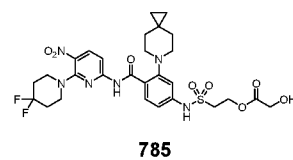
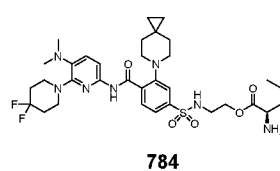
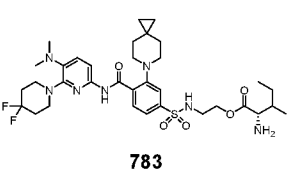
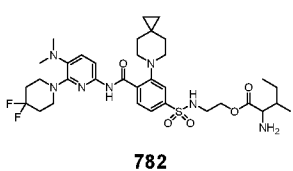
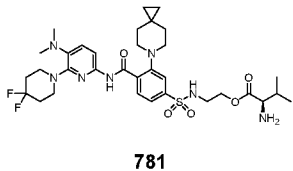
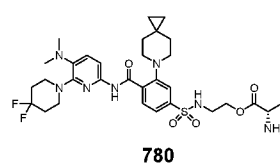
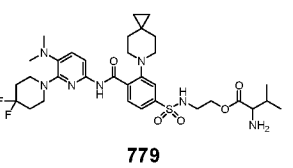
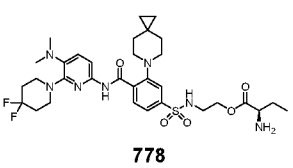
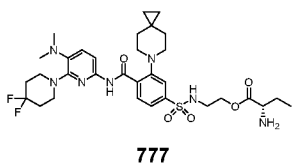
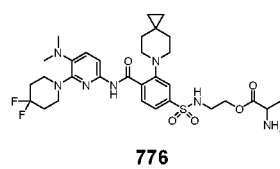
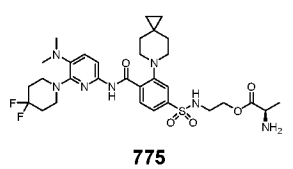
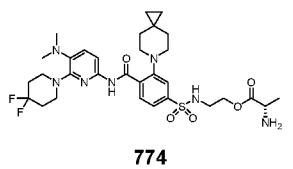
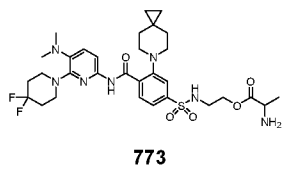
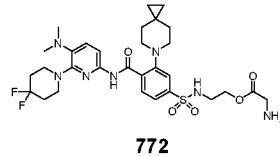
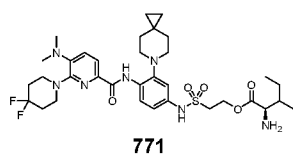
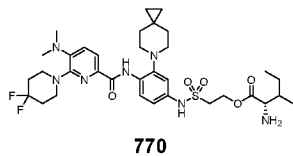
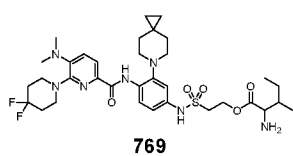


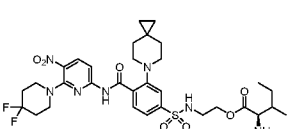
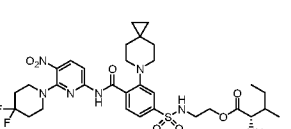
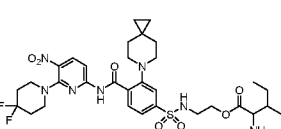
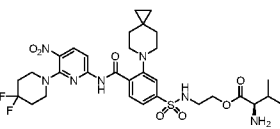
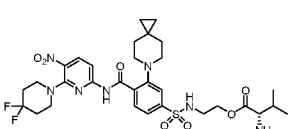
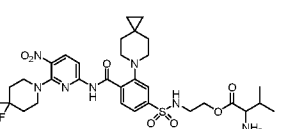
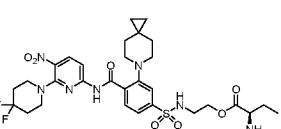
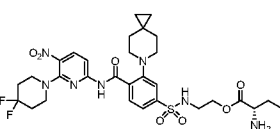
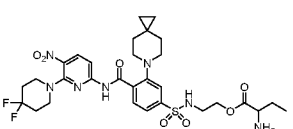
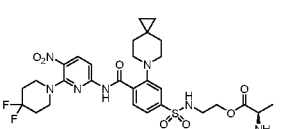
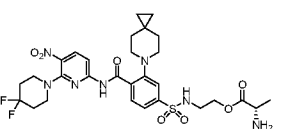
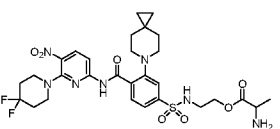
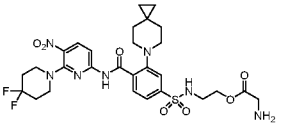
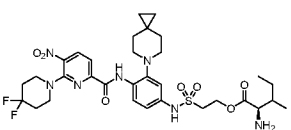
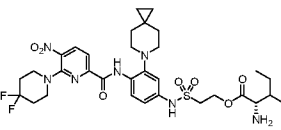
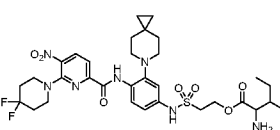
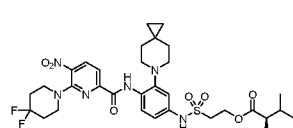
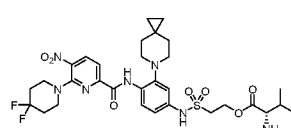
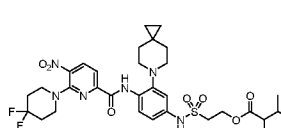
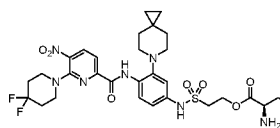
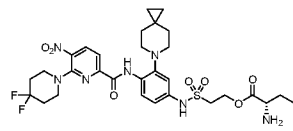
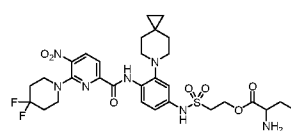
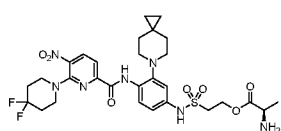
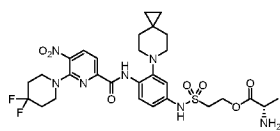
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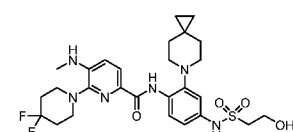
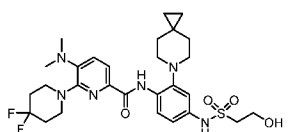
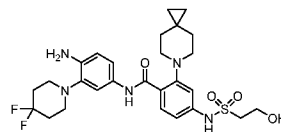
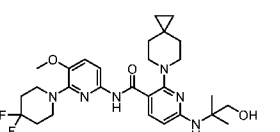
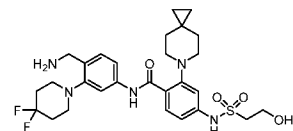
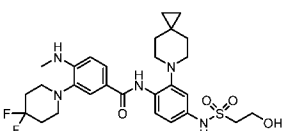
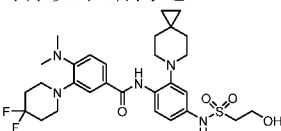
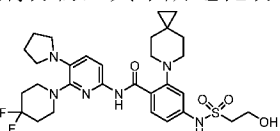
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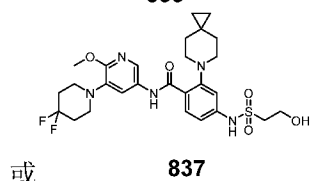
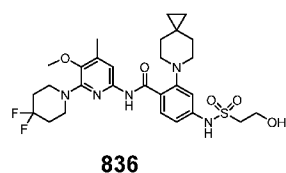
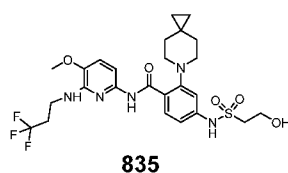
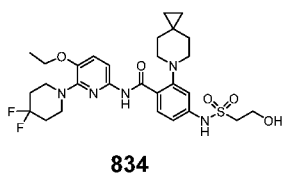
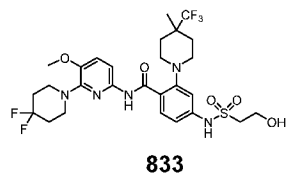






33. 如权利要求 1-31 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物，其中所述化合物具有以下结构之一：





或

。

34. 一种药物组合物，其特征在于，其含有药学上可接受的赋形剂或载体，以及如权利要求 1-33 中任一项所述的化合物、或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物作为活性成分。

35. 一种如权利要求 1-33 中任一项所述的化合物或其各异构体、各晶型、药学上可接受的盐、水合物或溶剂合物或如权利要求 34 所述的药物组合物在制备治疗由 KIF18A 蛋白介导的相关疾病药物中的用途。

36. 如权利要求 35 所述的用途，其中所述的疾病是癌症，所述癌症是血液癌和实体瘤。

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/132954

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/12(2006.01)i; C07D 401/14(2006.01)i; C07D 405/14(2006.01)i; C07D 413/14(2006.01)i; A61K 31/444(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, CNTXT, DWPI, WPABS, CAPLUS(STN), REGISTRY(STN), CNKI: structural formula search, 氮杂螺, 磺酰胺, 哌啶, 癌症, 肿瘤, ATP酶, KIF18A, azaspiro, sulfonamido, piperidin, tumor

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020132651 A1 (AMGEN INC.) 25 June 2020 (2020-06-25) description, paragraphs [0007]-[0009] and [0037], and tables 10 and A	1-36
X	WO 2021026098 A1 (AMGEN INC.) 11 February 2021 (2021-02-11) description, paragraphs [0009]-[0039] and [0139], and table A	1-36
X	WO 2021026100 A1 (AMGEN INC.) 11 February 2021 (2021-02-11) description, paragraphs [0009]-[0041], and tables 10 and A	1-36
X	WO 2020132653 A1 (AMGEN INC.) 25 June 2020 (2020-06-25) description, paragraphs [0009] and [0417]	1-36
X	WO 2021026099 A1 (AMGEN INC.) 11 February 2021 (2021-02-11) description, paragraphs [0009]-[0033] and [0331]	1-36
A	WO 2020132648 A1 (AMGEN INC.) 25 June 2020 (2020-06-25) description, paragraphs [0009] and [0039]	1-36
A	WO 2021211549 A1 (AMGEN INC.) 21 October 2021 (2021-10-21) entire document	1-36
A	WO 2020132649 A1 (AMGEN INC.) 25 June 2020 (2020-06-25) entire document	1-36



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

12 December 2022

Date of mailing of the international search report

22 December 2022

Name and mailing address of the ISA/CN

China National Intellectual Property Administration (ISA/
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Facsimile No. (86-10)62019451

Authorized officer

Telephone No.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2022/132954

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				US	2022073504	A1	10 March 2022
				AU	2019403488	A1	24 June 2021
				EP	3897855	A1	27 October 2021
				JP	2022514268	A	10 February 2022
				CA	3123042	A1	25 June 2020
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				CN	114302880	A	08 April 2022
				US	2022289724	A1	15 September 2022
				EP	4007752	A1	08 June 2022
				JP	2022542967	A	07 October 2022
				AU	2020326627	A1	17 March 2022
WO	2021026100	A1	11 February 2021	EP	4007638	A1	08 June 2022
				CN	114391012	A	22 April 2022
				US	2022372018	A1	24 November 2022
				JP	2022542392	A	03 October 2022
				CA	3147276	A1	11 February 2021
				AU	2020325115	A1	17 March 2022
WO	2020132653	A1	25 June 2020	AU	2019401495	A1	24 June 2021
				EP	3898592	A1	27 October 2021
				JP	2022513971	A	09 February 2022
				MA	54547	A	30 March 2022
				CA	3123044	A1	25 June 2020
				US	2022002311	A1	06 January 2022
WO	2021026099	A1	11 February 2021	JP	2022542319	A	30 September 2022
				AU	2020324406	A1	17 March 2022
				CA	3147272	A1	11 February 2021
				CN	114401953	A	26 April 2022
				EP	4007753	A1	08 June 2022
WO	2020132648	A1	25 June 2020	UY	38526	A	30 June 2020
				CA	3123871	A1	25 June 2020
				CN	113226473	A	06 August 2021
				PE	20211475	A1	05 August 2021
				US	2022106293	A1	07 April 2022
				US	2020239441	A1	30 July 2020
				CL	2021001634	A1	10 December 2021
				JP	2022513972	A	09 February 2022
				TW	202034924	A	01 October 2020
				CR	20210387	A	19 August 2021
				BR	112021011989	A2	08 September 2021
				IL	283639	A	29 July 2021
				AU	2019403486	A1	24 June 2021
				KR	20210106474	A	30 August 2021
				CO	2021008224	A2	30 July 2021
				EP	3897852	A1	27 October 2021
				EA	202191730	A1	24 August 2021
				AR	117490	A1	11 August 2021
				MA	54543	A	30 March 2022
				SG	11202106520V	A	29 July 2021

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2022/132954

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2021211549	A1	21 October 2021	CA	3177740	A1	21 October 2021
				AU	2021257801	A1	27 October 2022
				TW	202203919	A	01 February 2022
WO	2020132649	A1	25 June 2020	EP	3898616	A1	27 October 2021
				MA	54546	A	30 March 2022
				AU	2019404576	A1	24 June 2021
				US	2022056015	A1	24 February 2022
				CA	3123227	A1	25 June 2020
				JP	2022513967	A	09 February 2022

国际检索报告

国际申请号

PCT/CN2022/132954

A. 主题的分类

C07D 401/12(2006.01)i; C07D 401/14(2006.01)i; C07D 405/14(2006.01)i; C07D 413/14(2006.01)i; A61K 31/444(2006.01)i; A61P 35/00(2006.01)i

按照国际专利分类(IPC)或者同时按照国家分类和IPC两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

C07D; A61K; A61P

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称, 和使用的检索词(如使用))

CNABS, CNTXT, DWPI, WPABS, CAPLUS(STN), REGISTRY(STN), CNKI: 结构式检索, 氮杂螺, 磺酰胺, 哌啶, 癌症, 肿瘤, ATP酶, KIF18A, azaspiro, sulfonamido, piperidin, tumor

C. 相关文件

类 型*	引用文件, 必要时, 指明相关段落	相关的权利要求
X	WO 2020132651 A1 (AMGEN INC.) 2020年6月25日 (2020 - 06 - 25) 说明书第[0007]-[0009]、[0037]段, 表10、表A	1-36
X	WO 2021026098 A1 (AMGEN INC.) 2021年2月11日 (2021 - 02 - 11) 说明书第[0009]-[0039]、[0139]段, 表A	1-36
X	WO 2021026100 A1 (AMGEN INC.) 2021年2月11日 (2021 - 02 - 11) 说明书第[0009]-[0041]段, 表10, 表A	1-36
X	WO 2020132653 A1 (AMGEN INC.) 2020年6月25日 (2020 - 06 - 25) 说明书第[0009]、[0417]段	1-36
X	WO 2021026099 A1 (AMGEN INC.) 2021年2月11日 (2021 - 02 - 11) 说明书第[0009]-[0033]、[0331]段	1-36
A	WO 2020132648 A1 (AMGEN INC.) 2020年6月25日 (2020 - 06 - 25) 说明书第[0009]、[0039]段	1-36
A	WO 2021211549 A1 (AMGEN INC.) 2021年10月21日 (2021 - 10 - 21) 全文	1-36
A	WO 2020132649 A1 (AMGEN INC.) 2020年6月25日 (2020 - 06 - 25) 全文	1-36

☐ 其余文件在C栏的续页中列出。

☒ 见同族专利附件。

* 引用文件的具体类型:

“A” 认为不特别相关的表示了现有技术一般状态的文件

“E” 在国际申请日的当天或之后公布的在先申请或专利

“L” 可能对优先权要求构成怀疑的文件, 或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件(如具体说明的)

“O” 涉及口头公开、使用、展览或其他方式公开的文件

“P” 公布日先于国际申请日但迟于所要求的优先权日的文件

“T” 在申请日或优先权日之后公布, 与申请不相抵触, 但为了理解发明之理论或原理的在后文件

“X” 特别相关的文件, 单独考虑该文件, 认定要求保护的发明不是新颖的或不具有创造性

“Y” 特别相关的文件, 当该文件与另一篇或者多篇该类文件结合并且这种结合对于本领域技术人员为显而易见时, 要求保护的发明不具有创造性

“&” 同族专利的文件

国际检索实际完成的日期

2022年12月12日

国际检索报告邮寄日期

2022年12月22日

ISA/CN的名称和邮寄地址

中国国家知识产权局(ISA/CN)

中国北京市海淀区蓟门桥西土城路6号 100088

传真号 (86-10)62019451

受权官员

甘雨

电话号码 (86-10)53962246

国际检索报告
关于同族专利的信息

国际申请号

PCT/CN2022/132954

检索报告引用的专利文件			公布日 (年/月/日)	同族专利			公布日 (年/月/日)
WO	2020132651	A1	2020年6月25日	MA	54550	A	2022年3月30日
				US	2022073504	A1	2022年3月10日
				AU	2019403488	A1	2021年6月24日
				EP	3897855	A1	2021年10月27日
				JP	2022514268	A	2022年2月10日
				CA	3123042	A1	2020年6月25日
WO	2021026098	A1	2021年2月11日	CA	3146693	A1	2021年2月11日
				CN	114302880	A	2022年4月8日
				US	2022289724	A1	2022年9月15日
				EP	4007752	A1	2022年6月8日
				JP	2022542967	A	2022年10月7日
				AU	2020326627	A1	2022年3月17日
WO	2021026100	A1	2021年2月11日	EP	4007638	A1	2022年6月8日
				CN	114391012	A	2022年4月22日
				US	2022372018	A1	2022年11月24日
				JP	2022542392	A	2022年10月3日
				CA	3147276	A1	2021年2月11日
				AU	2020325115	A1	2022年3月17日
WO	2020132653	A1	2020年6月25日	AU	2019401495	A1	2021年6月24日
				EP	3898592	A1	2021年10月27日
				JP	2022513971	A	2022年2月9日
				MA	54547	A	2022年3月30日
				CA	3123044	A1	2020年6月25日
				US	2022002311	A1	2022年1月6日
WO	2021026099	A1	2021年2月11日	JP	2022542319	A	2022年9月30日
				AU	2020324406	A1	2022年3月17日
				CA	3147272	A1	2021年2月11日
				CN	114401953	A	2022年4月26日
				EP	4007753	A1	2022年6月8日
WO	2020132648	A1	2020年6月25日	UY	38526	A	2020年6月30日
				CA	3123871	A1	2020年6月25日
				CN	113226473	A	2021年8月6日
				PE	20211475	A1	2021年8月5日
				US	2022106293	A1	2022年4月7日
				US	2020239441	A1	2020年7月30日
				CL	2021001634	A1	2021年12月10日
				JP	2022513972	A	2022年2月9日
				TW	202034924	A	2020年10月1日
				CR	20210387	A	2021年8月19日
				BR	112021011989	A2	2021年9月8日
				IL	283639	A	2021年7月29日
				AU	2019403486	A1	2021年6月24日
				KR	20210106474	A	2021年8月30日
				CO	2021008224	A2	2021年7月30日
				EP	3897852	A1	2021年10月27日
				EA	202191730	A1	2021年8月24日
				AR	117490	A1	2021年8月11日
				MA	54543	A	2022年3月30日
				SG	11202106520V	A	2021年7月29日

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检索报告引用的专利文件			公布日 (年/月/日)	同族专利			公布日 (年/月/日)
WO	2021211549	A1	2021年10月21日	CA	3177740	A1	2021年10月21日
				AU	2021257801	A1	2022年10月27日
				TW	202203919	A	2022年2月1日
WO	2020132649	A1	2020年6月25日	EP	3898616	A1	2021年10月27日
				MA	54546	A	2022年3月30日
				AU	2019404576	A1	2021年6月24日
				US	2022056015	A1	2022年2月24日
				CA	3123227	A1	2020年6月25日
				JP	2022513967	A	2022年2月9日