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(81) 指定国(除另有指明，要求每一种可提供的国家保护): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW。

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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:
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WO 2023/025159 A1

(54) **Title:** IRAK4 DEGRADATION AGENT, AND PREPARATION METHOD THEREFOR AND USE THEREOF

(54) 发明名称: IRAK4降解剂及其制备方法和应用

(57) **Abstract:** An IRAK4 degradation agent as represented by structural formula PTM-L-ULM (I), and a preparation method therefor and the use thereof. The provided compound can effectively inhibit and/or degrade IRAK4 kinase protein in a cell and inhibit an immune cell from producing IL-6.

(57) 摘要: 一种如结构式PTM-L-ULM (I)所示的IRAK4 降解剂及其制备方法和应用。提供的化合物能够有效地抑制和/或降解细胞中的IRAK4 激酶蛋白和抑制免疫细胞产生IL-6。

IRAK4 降解剂及其制备方法和应用

本申请要求申请日为 2021 年 8 月 23 日的中国专利申请 202110966608X 的优先权、2022 年 5 月 19 日的中国专利申请 2022105581585 的优先权和 2022 年 8 月 17 日的中国专利申请 2022109894485 的优先权。本申请引用上述中国专利申请的全文。

技术领域

本发明属于药物领域，具体的本发明涉及靶向 IRAK4 蛋白降解的化合物、药物组合物及其制备方法和其在制备治疗和/或预防由 IRAK4 介导的相关疾病或病症的药物中的应用，如癌症、免疫性疾病和炎性疾病。

背景技术

白介素-1 受体激酶 4(IRAK4)是一种丝氨酸/苏氨酸特异性蛋白激酶，具有生物学上重要的激酶活性，在激活免疫系统中起重要作用。研究表明，IRAK4 是白细胞介素(IL)-1β 家族受体(包括 IL-1R、IL-18R、IL-33R、IL-36R)和 Toll 样受体(TLR)信号传导通路下游的关键因子，IRAK4 缺失的小鼠和 IRAK4 缺失的患者均对 TLR(TLR3 除外)和 IL-1β 家族的刺激不起反应。

根据有无 MyD88 的参与，TLR/IL-1β 介导的信号通路可分为 MyD88 依赖型信号通路和 MyD88 非依赖性通路，其中 IL-1R 和 TLR2、TLR4、TLR7/8、TLR9 所介导的信号转导通路都依赖 MyD88 作为调节因子激活下游的炎症信号通路。TLR/IL-1β 与配体结合后，募集 MyD88 分子，MyD88 通过其 N 末端死亡结构域进一步募集 IRAK4 到 TLR/IL-1β 复合物中，并与 IRAK1 或 IRAK2 相互作用且将其激活，从而向下游传递信号至 E3 泛素连接酶 TNF 受体相关因子(TRAF6)，活化丝氨酸/苏氨酸激酶 TAK1，进而激活 NF－κB 及 MAPK 信号通路，引起多种炎症细胞因子和抗凋亡分子的释放。IRAK4 依赖性的 TLR/IL-1β 信号通路已经被证明与多种疾病相关：如多发性硬化、动脉粥样硬化、心肌梗死、心肌炎伏格特-小柳-原田综合征(Vogt-Koyanagi-Harada syndrome)、系统性红斑狼疮(SLE)、肥胖、1 型糖尿病、类风湿性关节炎、脊椎关节炎(特别是牛皮癣性脊椎关节炎和别克捷列夫氏病(Bekhterev's disease))、红斑狼疮、银屑病、白癜风、巨细胞动脉炎、慢性炎性肠道疾病和病毒性疾病，例如 HIV(人免疫缺陷病毒)、肝炎病毒；皮肤病如银屑病、特应性皮炎、金德勒综合征(Kindler's syndrome)、大疱性类天疱疮、变应性接触性皮炎、斑秃、反常性痤疮(acneinversa)和寻常痤疮；其他炎症性疾病如过敏症、贝切特氏病、痛风、成人斯蒂尔氏病(adult-onset Still's disease)、心包炎和慢性炎性肠道疾病例如溃疡性结肠炎和克罗恩氏病(Crohn's disease)、移植排斥反应和移植物抗宿主反应；妇科疾病例如子宫内膜异位症(adenomyosis)、痛经、交媾困难和子宫内膜组织异位症(endometriosis)，特别是与子宫内膜异位症相关的疼痛和其他与子宫内膜异位症相关的症状例如痛经、交媾困难、排尿困难和大便困难；眼部疾病如视网膜缺血、角膜炎、过敏性结膜炎、干燥性角结膜炎、黄斑变性和眼色素层炎；纤维化疾病如肝纤维化、心肌炎、原发性胆汁性肝硬化、囊性纤维化；慢性肝脏疾

病，例如脂肪肝肝炎，特别是非酒精性脂肪性肝病(NAFLD)和/或非酒精性脂肪性肝炎(NASH)、酒精性脂肪性肝炎(ASH)；心血管疾病和神经障碍，例如心肌再灌注损伤、心肌梗死、高血压,以及阿尔茨海默氏病、中风、颅脑创伤、肌萎缩性侧索硬化(ALS)和帕金森氏症；瘙痒和疼痛(包括急性、慢性、炎性和神经性疼痛)如痛觉过敏、异常性疼痛、经前痛、与子宫内膜异位症相关的疼痛、手术后疼痛、间质性膀胱炎、CRPS(复杂性局部疼痛综合征)、三叉神经痛、前列腺炎、脊髓损伤引起的疼痛、炎症引发的疼痛、下腰痛、癌痛、化疗相关的疼痛、HIV 治疗诱发的神经病、烧伤引起的疼痛和慢性疼痛；肿瘤疾病如某些淋巴瘤：ABC-DLBCL(活化 B 细胞弥漫性大细胞 B 细胞淋巴瘤)、套细胞淋巴瘤和沃尔丹斯特伦疾病(disease)，以及慢性淋巴细胞性白血病、黑色素瘤、胰腺肿瘤和肝细胞癌、ras-依赖性肿瘤、乳腺癌、卵巢癌、结肠直肠癌、头颈部癌、肺癌、前列腺癌。

IRAK4 介导的信号传导途径的调节主要与其激酶功能有关，但是，也有一些报道表明在某些细胞类型中，IRAK4 对下游过程的信号调节与 IRAK4 的非激酶功能有关。 Cushing 等人就表示，尽管在 IL-1β 刺激的人皮肤成纤维细胞中 IRAK4 磷酸化水平降低，但 IRAK4 的药理抑制作用并不会导致 IL-6 和 TNF-α 的抑制。支持这些结果的是，IRAK4 缺乏的成纤维细胞与野生型细胞相比，IRAK4 的支架功能对于 IL1 信号传导很重要，但是它的激酶作用却是多余的。同时，Chiang 和他的同事也表示，IRAK4 激酶活性在人类 B 细胞和 T 细胞、树突状细胞和单核细胞中不是必要的，且 siRNA 基因切除也显示 IRAK4 在这些细胞中具有支架功能作用。现已报道了多种针对 IRAK4 的强效的选择性抑制剂，如 CA-4948、BAY-1834845、BMS-986126 以及 PF-06650833 等，这些抑制剂都能选择性的抑制 IRAK4 的激酶活性，主要用于自身免疫性疾病，炎性疾病和肿瘤性疾病的预防和治疗。然而，一方面由于 IRAK4 具有支架蛋白和活性激酶的作用，且另一方面传统的小分子抑制剂易产生耐药性，因此，仅抑制 IRAK4 激酶活性可能不足以产生治疗效果。

蛋白降解靶向嵌合体(Proteolysis Targeting Chimeria， PROTAC)是一种不同于传统小分子抑制剂的技术，传统小分子抑制剂通常需要作用于靶蛋白的活性位点才能抑制其活性，而 PROTAC 为一种异质双功能分子，其一端为可识别靶蛋白的小分子抑制剂，通过连接链，另一端为可识别 E3 泛素连接酶的 E3 泛素连接酶配体，这种双功能分子在体内识别靶蛋白和 E3 泛素连接酶，将靶蛋白和 E3 泛素连接酶拉近，形成三元复合物，将靶蛋白泛素化后，在体内通过泛素－蛋白酶体途径将靶蛋白降解。相较于传统小分子抑制剂，一方面 PROTAC 只需要将靶蛋白与 E3 泛素连接酶拉近，使底物降解，这种作用模式使得这种技术可以应用于一些不可成药靶点；另一方面，由于靶蛋白在被降解后，PROTAC 分子还可释放出来继续参与下一蛋白的降解过程，因此这种具有催化效果的降解作用，使得较少的 PROTAC 药物剂量就可以实现高效的降解；再一方面，传统的小分子抑制剂易产生耐药性常常是因为发生了点突变，使得小分子抑制剂失去了对靶点的抑制作用，而 PROTAC 可以直接将靶蛋白降解，在一定程度上能过避免点突变产生的耐药性。因此，相较于传统小分子抑制剂，运用 PROTAC 技术进行新药小分子研发具有很高的优势和可行性，有望成为下一代极具前途的新型药物。PROTAC 技术也已被应用于多种靶点药物的改造，如雄性激素受体、雌性激素蛋白受体、BTK 等等。

US2019/0151295、US2019/0192688、WO2019/160915 和 WO2020/113233 中公开了几类靶向 IRAK4 的降解剂，更多的靶向 IRAK4 的降解剂丞待开发。

发明内容

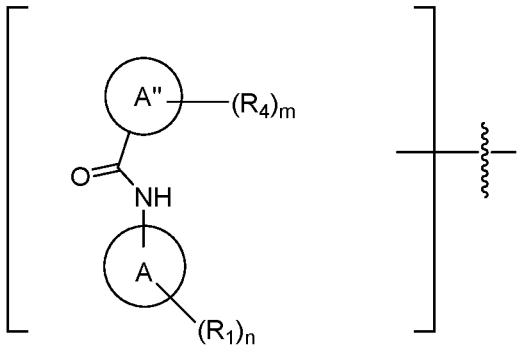
本发明提供了式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐；

PTM-L-ULM

I

其中：

所述 PTM 具有下式结构



PTM-1

其中所述 PTM-1 中：

m 是 0、1、2、3 或者 4；

n 是 0、1、2、3 或者 4；

环 A"为 6-10 元芳基或含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

环 A 为 6-10 元芳基或含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

各个 R_1 独立地选自：C_1-C_4 烷基、-O(C_1-C_4 烷基)、-N(C_1-C_4 烷基)$_{1-2}$、C_3-C_8 环烷基、-O(C_3-C_8 环烷基)、-NH(C_3-C_8 环烷基)、3-8 元杂环烷基、-O(3-8 元杂环烷基)、-NH(3-8 元杂环烷基)、6-10 元芳基、-O(6-10 元芳基)、-NH(6-10 元芳基)、5-6 元杂芳基、-O(5-6 元杂芳基)、-NH(5-6 元杂芳基)、CN、卤素、-OH、-NH_2、-NHC(O)(C_1-C_4 烷基)、-NHS(O)(C_1-C_4 烷基)、-NHS(O)$_2$(C_1-C_4 烷基)、-COOH、-C(O)NH_2、-S(O)$_2$H、-S(O)$_2NH_2$、-C(O)(C_1-C_4 烷基)、-C(O)NH(C_1-C_4 烷基)、-C(O)N(C_1-C_4 烷基)$_2$、-C(O)O(C_1-C_4 烷基)、-S(O) (C_1-C_4 烷基)、-S(O)$_2$(C_1-C_4 烷基)、-S(O)$_2$NH(C_1-C_4 烷基)、-S(O)$_2$N(C_1-C_4 烷

基)$_2$或者-S(O)NH(C_1-C_4烷基)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4烷基、-O(C_1-C_4烷基)、甲基哌啶、-S(O)$_2$H、-S(O)$_2$(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_{1-2}$和C(O)O(C_1-C_4烷基)的基团取代；

或者所述R_1与其所连接的原子一起形成环烷基、杂环烷基、芳基或杂芳基；

各个R_4独立地为氢、C_1-C_4烷基、-O(C_1-C_4烷基)、C_3-C_8环烷基、3-8元杂环烷基、6-10元芳基、5-6元杂芳基、CN、卤素、-OH、-NHC(O)(C_1-C_4烷基)、-NHS(O)(C_1-C_4烷基)、-NHS(O)$_2$(C_1-C_4烷基)、-COOH、-C(O)NH$_2$、-S(O)$_2$H、-S(O)$_2$NH$_2$、-C(O)(C_1-C_4烷基)、-C(O)NH(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_2$、-C(O)O(C_1-C_4烷基)、-S(O)(C_1-C_4烷基)、-S(O)$_2$(C_1-C_4烷基)、-S(O)$_2$NH(C_1-C_4烷基)、-S(O)$_2$N(C_1-C_4烷基)$_2$、-S(O)NH(C_1-C_4烷基)或者X(R_2)(R_3)，所述烷基、环烷基、杂环烷基、芳基和杂芳基任选被选自卤素、氰基、-OH、C_1-C_4烷基、-O(C_1-C_4烷基)、甲基哌啶、-S(O)$_2$H、-S(O)$_2$(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_{1-2}$、和-C(O)O(C_1-C_4烷基)的基团取代；

X为O、S、CH_2或者N；

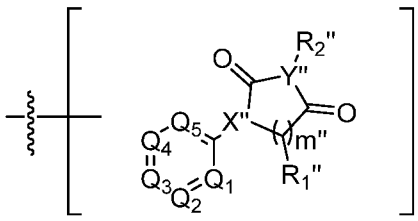
R_2、R_3独立地选自：氢、C_1-C_6烷基、C_3-C_8环烷基、3-8元杂环烷基、6-10元芳基或者5-6元杂芳基，所述烷基、环烷基、杂环烷基、芳基、杂芳基各自独立地任选地被一个或多个选自卤素、OH、氧代基、N(R_b)$_2$、氧代基吡咯烷基和吗啉基取代，或R_2和R_3与它们所连接的原子一起形成C_3-C_8环烷基或者3-8元杂环烷基，所述环烷基和杂环烷基任选地被一个或多个选自R_a的取代基取代；

R_a独立地选自氧代基、C_1-C_4烷基、C_3-C_6环烷基、CF_3、CHF_2、OH、卤素或NH_2，所述烷基任选被C_3-C_6环烷基或CF_3取代；且

R_b独立地选自H或C_1-C_4烷基；

L为连接链，其通过共价键连接PTM和ULM；

所述ULM具有下式结构



ULM-1

其中所述ULM-1中的：

X"为C或N；

Y"为C、N、O或者S；

Q_1、Q_2、Q_3、Q_4和Q_5各自独立地为CR_3"或N；

R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8元杂环烷基、

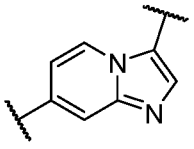
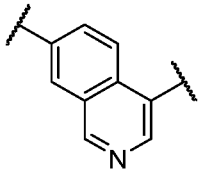
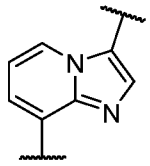
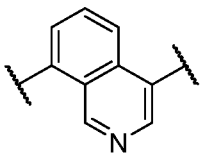
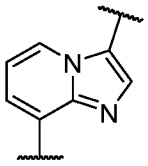
6-10 元芳基、5-10 元杂芳基、-O(C_1-C_6 烷基)、-O-(C_3-C_8 环烷基)、-O-(3-8 元杂环烷基)、N(C_1-C_6 烷基)$_{1-2}$、NH(C_3-C_8 环烷基)、NH(3-8 元杂环烷基)、-O-(6-10 芳基)或-O-(5-10 元杂芳基)；所述烷基、环烷基、杂环烷基、芳基和杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；或者 R_3"与其所连接的原子一起形成环烷基、杂环烷基、杂芳基或者芳基；

m"为 1、2 或 3；

R_1"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基或-O(C_1-C_6 烷基)，所述烷基、环烷基、杂环烷基、芳基和杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰 基和氨基的基团取代；

R_2"为氢、氘、C_1-C_6烷基或者 C_3-C_6环烷基，所述 C_1-C_6烷基和 C_3-C_6环烷基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基和-OC(O)(C_1-C_6烷基)的基团取代。

优选的，本发明某些实施方式中，R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-O(C_1-C_6烷基)、-O-(C_3-C_8环烷基)、-O-(3-8 元杂环烷基)、N(C_1-C_6烷基)$_{1-2}$、NH(C_3-C_8环烷基)、NH(3-8 元杂环烷基)、-O-(6-10 芳基)或-O-(5-10 元杂芳基)；所述烷基、环烷基、杂环烷基、芳基和杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；或者 R_3"与其所连接的原子一起形成环烷基或杂环烷基。

优选的，本发明某些实施方式中，R_3"与其所连接的原子一起形成杂芳基不为  、  、  、  或  。

优选的，本发明某些实施方式中，

其中所述 PTM-1 中：

m 是 0 或者 1；

n 是 0、1 或者 2；

环 A"为 6-10 元芳基或含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

环 A 为 6-10 元芳基或者 5-6 元杂芳基；

R_1 独立地选自：C_1-C_4 烷基、-O(C_1-C_4 烷基)、-N(C_1-C_4 烷基)$_{1-2}$、C_3-C_8 环烷基、-O(C_3-C_8 环烷基)、-NH(C_3-C_8环烷基)、3-8 元杂环烷基、-O(3-8 元杂环烷基)、-NH(3-8 元杂环烷基)、6-10 元芳基、-O(6-

10 元芳基)、-NH(6-10 元芳基)、5-6 元杂芳基、-O(5-6 元杂芳基)、-NH(5-6 元杂芳基)、CN、卤素、-OH、$-NH_2$、-NHC(O)(C_1-C_4烷基)、-NHS(O)(C_1-C_4烷基)、$-NHS(O)_2$(C_1-C_4烷基)、-COOH、$-C(O)NH_2$、$-S(O)_2H$、$-S(O)_2NH_2$、-C(O)(C_1-C_4 烷基)、-C(O)NH(C_1-C_4 烷基)、$-C(O)N(C_1$-C_4 烷基$)_2$、-C(O)O(C_1-C_4 烷基)、-S(O) (C_1-C_4 烷基)、$-S(O)_2$(C_1-C_4 烷基)、$-S(O)_2NH(C_1$-C_4 烷基)、$-S(O)_2N(C_1$-C_4 烷基$)_2$、-S(O)NH(C_1-C_4 烷基)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4 烷基、-O(C_1-C_4 烷基)、甲基哌啶、$-S(O)_2H$、$-S(O)_2$(C_1-C_4 烷基)、$-C(O)N(C_1$-C_4 烷基$)_{1\text{-}2}$、或者-C(O)O(C_1-C_4烷基)的基团取代；

或者所述 R_1 与其所连接的原子一起形成环烷基、杂环烷基、芳基、杂芳基；

R_4 为氢、C_1-C_4 烷基、-O(C_1-C_4 烷基)、C_3-C_8 环烷基、3-8 元杂环烷基、6-10 元芳基、5-6 元杂芳基、CN、卤素、-OH、-NHC(O)(C_1-C_4 烷基)、-NHS(O)(C_1-C_4 烷基)、$-NHS(O)_2$(C_1-C_4 烷基)、-COOH、$-C(O)NH_2$、$-S(O)_2H$、$-S(O)_2NH_2$、-C(O)(C_1-C_4 烷基)、-C(O)NH(C_1-C_4 烷基)、$-C(O)N(C_1$-C_4 烷基$)_2$、-C(O)O(C_1-C_4烷基)、-S(O) (C_1-C_4烷基)、$-S(O)_2$(C_1-C_4烷基)、$-S(O)_2NH(C_1$-C_4烷基)、$-S(O)_2N(C_1$-C_4烷基$)_2$、-S(O)NH(C_1-C_4 烷基)或$-X(R_2)(R_3)$，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4 烷基、-O(C_1-C_4 烷基)、甲基哌啶、$-S(O)_2H$、$-S(O)_2$(C_1-C_4 烷基)、$-C(O)N(C_1$-C_4烷基$)_{1\text{-}2}$、或者-C(O)O(C_1-C_4烷基)的基团取代；或者

X 为 O、S、CH_2 或者 N；

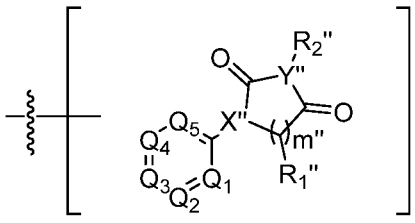
R_2、R_3 独立地选自：氢、C_1-C_6 烷基、C_3-C_8 环烷基、3-8 元杂环烷基、6-10 芳基或者 5-6 元杂芳基，所述烷基、环烷基、杂环烷基、芳基、杂芳基各自独立地任选地被一个或多个选自卤素、OH、氧代基、$N(R_b)_2$、氧代基吡咯烷基或吗啉基取代，或 R_2 和 R_3 与它们所连接的原子一起形成 C_3-C_8 环烷基或者 3-8 元杂环烷基，所述环烷基或者杂环烷基任选地被一个或多个选自 R_a 的取代基取代；

R_a 独立地选自氧代基、C_1-C_4 烷基、C_3-C_6 环烷基、CF_3、CHF_2、OH、卤素或 NH_2，所述烷基任选被 C_3-C_6环烷基或 CF_3 取代；且

R_b 独立地选自 H 或 C_1-C_4烷基；

L 为连接链，其通过共价键连接 PTM 和 ULM；

所述 ULM 具有下式结构



ULM-1

其中所述 ULM-1 中的：

X"为 C 或 N；

Y"为 C、N、O 或者 S；

Q_1、Q_2、Q_3、Q_4、Q_5各自独立地为 CR_3"或 N；

R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-O(C_1-C_6烷基)、-O-(C_3-C_8环烷基)、-O-(3-8 元杂环烷基)、N(C_1-C_6烷基)$_{1-2}$、NH(C_3-C_8环烷基)、NH(3-8 元杂环烷基)、-O-(6-10 芳基)、-O-(5-10 元杂芳基)；所述烷基、环烷基、杂环烷基、芳基、杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；或者 R_3"与其所连接的原子一起形成环烷基、杂环烷基、杂芳基或者芳基；

m"为 1、2 或 3；

R_1"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-O(C1-C6 烷基)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；

R_2"为氢、氘、C_1-C_6烷基或者 C_3-C_6环烷基，所述 C_1-C_6烷基和 C_3-C_6环烷基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基或-OC(O)(C_1-C_6烷基)的基团取代。

优选的，本发明某些实施方式中，

其中所述 PTM-1 中：

m 是 0、1、2、3 或者 4；

n 是 0、1、2、3 或者 4；

环 A"为 6-10 元芳基或含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

环 A 为 6-10 元芳基或含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

R_1 独立地选自：C_1-C_4烷基、-O(C_1-C_4烷基)、-N(C_1-C_4烷基)$_{1-2}$、C_3-C_8环烷基、-O(C_3-C_8环烷基)、-NH(C_3-C_8环烷基)、3-8 元杂环烷基、-O(3-8 元杂环烷基)、-NH(3-8 元杂环烷基)、6-10 元芳基、-O(6-10 元芳基)、-NH(6-10 元芳基)、5-6 元杂芳基、-O(5-6 元杂芳基)、-NH(5-6 元杂芳基)、CN、卤素、-OH、$-NH_2$、-NHC(O)(C_1-C_4烷基)、-NHS(O)(C_1-C_4烷基)、-NHS(O)$_2$(C_1-C_4烷基)、-COOH、$-C(O)NH_2$、$-S(O)_2H$、$-S(O)_2NH_2$、-C(O)(C_1-C_4烷基)、-C(O)NH(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_2$、-C(O)O(C_1-C_4烷基)、-S(O) (C_1-C_4烷基)、-S(O)$_2$(C_1-C_4烷基)、-S(O)$_2$NH(C_1-C_4烷基)、-S(O)$_2$N(C_1-C_4烷基)$_2$、-S(O)NH(C_1-C_4烷基)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4烷基、-O(C_1-C_4烷基)、甲基哌啶、$-S(O)_2H$、-S(O)$_2$(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_{1-2}$、或者-C(O)O(C_1-C_4烷基)的基团取代；

或者所述 R_1 与其所连接的原子一起形成环烷基、杂环烷基、芳基、杂芳基；

R_4为氢、C_1-C_4烷基、-O(C_1-C_4烷基)、C_3-C_8环烷基、3-8元杂环烷基、6-10元芳基、5-6元杂芳基、CN、卤素、-OH、-NHC(O)(C_1-C_4烷基)、-NHS(O)(C_1-C_4烷基)、-NHS(O)$_2$(C_1-C_4烷基)、-COOH、-C(O)NH_2、-S(O)$_2$H、-S(O)$_2NH_2$、-C(O)(C_1-C_4烷基)、-C(O)NH(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_2$、-C(O)O(C_1-C_4烷基)、-S(O) (C_1-C_4烷基)、-S(O)$_2$(C_1-C_4烷基)、-S(O)$_2$NH(C_1-C_4烷基)、-S(O)$_2$N(C_1-C_4烷基)$_2$、-S(O)NH(C_1-C_4烷基)或-X(R_2)(R_3)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4烷基、-O(C_1-C_4烷基)、甲基哌啶、-S(O)$_2$H、-S(O)$_2$(C_1-C_4烷基)、-C(O)N(C_1-C_4烷基)$_{1\text{-}2}$、或者-C(O)O(C_1-C_4烷基)的基团取代；

X为O、S、CH_2或者N；

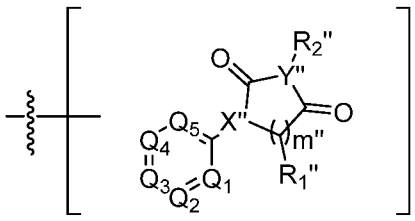
R_2、R_3独立地选自：氢、C_1-C_6烷基、C_3-C_8环烷基、3-8元杂环烷基、6-10元芳基或者5-6元杂芳基，所述烷基、环烷基、杂环烷基、芳基、杂芳基各自独立地任选地被一个或多个选自卤素、OH、氧代基、N(R_b)$_2$、氧代基吡咯烷基或吗啉基取代，或R_2和R_3与它们所连接的原子一起形成C_3-C_8环烷基或者3-8元杂环烷基，所述环烷基或者杂环烷基任选地被一个或多个选自R_a的取代基取代；

R_a独立地选自氧代基、C_1-C_4烷基、C_3-C_6环烷基、CF_3、CHF_2、OH、卤素或NH_2，所述烷基任选被C_3-C_6环烷基或CF_3取代；且

R_b独立地选自H或C_1-C_4烷基；

L为连接链，其通过共价键连接PTM和ULM；

所述ULM具有下式结构



ULM-1

其中所述ULM-1中的：

X"为C或N；

Y"为C、N、O或者S；

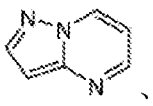
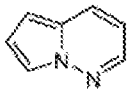
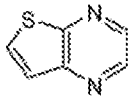
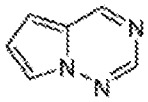
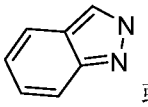
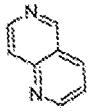
Q_1、Q_2、Q_3、Q_4、Q_5各自独立地为CR_3"或N；

R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8元杂环烷基、6-10元芳基、5-10元杂芳基、-O(C_1-C_6烷基)、-O-(C_3-C_8环烷基)、-O-(3-8元杂环烷基)、N(C_1-C_6烷基)$_{1\text{-}2}$、NH(C_3-C_8环烷基)、NH(3-8元杂环烷基)、-O-(6-10芳基)、-O-(5-10元杂芳基)；所述烷基、环烷基、杂环烷基、芳基、杂芳基任选的被1-3个独立地选自羟基、卤素、氰基、氨基的基团取代；或者R_3"与其所连接的原子一起形成环烷基、杂环烷基、杂芳基或者芳基；

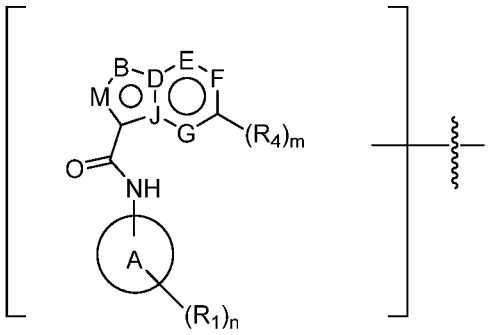
m"为 1、2 或 3；

R_1"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-O(C_1-C_6 烷基)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；

R_2"为氢、氘、C_1-C_6烷基或者 C_3-C_6环烷基，所述 C_1-C_6烷基和 C_3-C_6环烷基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基或-OC(O)(C_1-C_6烷基)的基团取代。

优选的，本发明某些实施方式中，所述 PTM-1 中，环 A"为含有 1 个、2 个、或者 3 个选自 N、O 或 S 杂原子的 9-10 元双环杂芳基；优选环 A"为  、 、 、 、  、  、  、  或  。

优选的，本发明某些实施方式中，所述 PTM 为



PTM-2

其中所述 PTM-2 中：

B 为 CH、N、O 或者 S；

M 为 CH、N、O 或者 S；

D 为 CH 或者 N；

E 为 CH 或者 N；

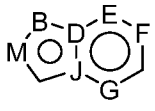
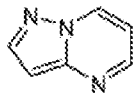
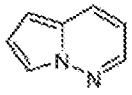
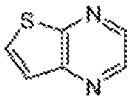
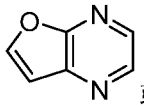
F 为 CH 或者 N；

G 为 CH 或者 N；

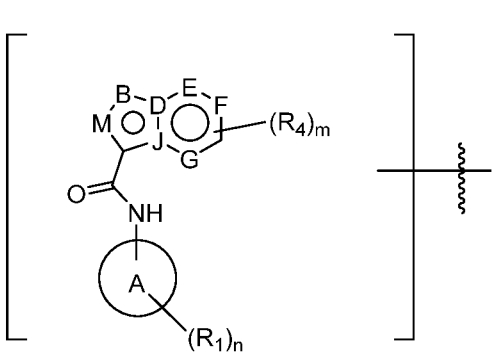
J 为 CH 或者 N；

当 B 或 M 为 S 或者 O 时，D 是 CH，E 是 N，F 为 CH，G 是 N 且 J 是 CH；且 B 和 M 不能同时为 S 和/或者 O；

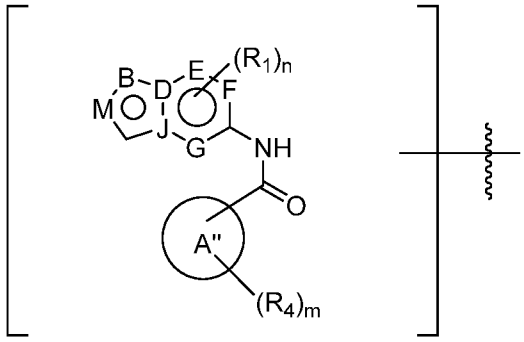
所述环 A、R_1、n、R_4、m 如 PTM-1 中所定义的描述。

优选的，本发明某些实施方式中，所述 PTM-2 中的  为  、  、  、  或 。

优选的，本发明某些实施方式中，所述 PTM 为



PTM-2'



PTM-2"

其中所述 PTM-2′，PTM-2″中：

B 为 CH、N、O 或者 S；

M 为 CH、N、O 或者 S；

D 为 CH 或者 N；

E 为 CH 或者 N；

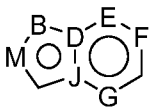
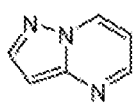
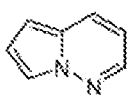
F 为 CH 或者 N；

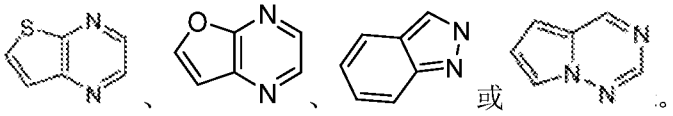
G 为 CH 或者 N；

J 为 CH 或者 N；

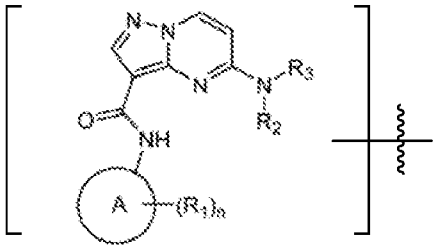
当 B 或 M 为 S 或者 O 时，D 是 CH，E 是 N，F 为 CH，G 是 N 且 J 是 CH；且 B 和 M 不能同时为 S 和/或者 O；

所述环 A、环 A"、R_1、n、R_4、m 如 PTM-1 中所定义的描述。

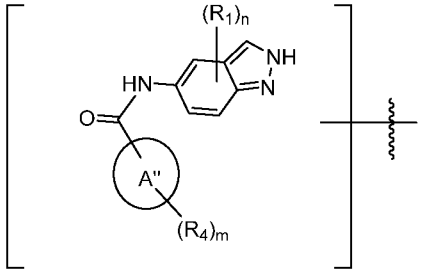
优选的，本发明某些实施方式中，所述 PTM-2′中的  为  、  、



优选的，本发明某些实施方式中，所述 PTM 为：



PTM-3



PTM-3'

其中所述环 A、环 A"、R_1、R_2、R_3、R_4、m 和 n 如 PTM-1 中所定义和描述。

优选的，本发明某些实施方式中，所述 PTM-1、PTM-2、PTM-2′和 PTM-3 中：

环 A 是苯基或含有 1 个、2 个或者 3 个选自 N、O 杂原子的 5-6 元杂芳基；优选环 A 为苯基、吡啶基、吡咯基、吡唑基、咪唑基、嘧啶基、三唑基、四唑基、噻吩基、噻唑基、呋喃基、噁唑基、异噁唑基或异噻唑基；进一步优选环 A 为吡唑基或噻吩基。

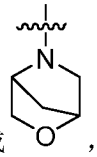
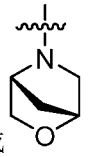
优选的，本发明某些实施方式中，所述 PTM-1、PTM-2、PTM-2′和 PTM-3 中 n 为 1 或 2；优选 n 为 2。

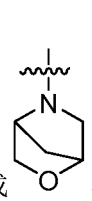
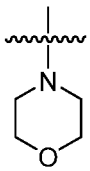
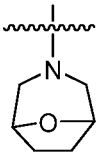
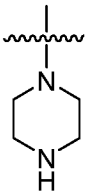
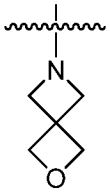
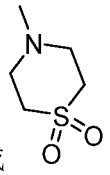
优选的，本发明某些实施方式中，所述 PTM-1、PTM-2、PTM-2′和 PTM-3 中 R_1 独立地选自：C_1-C_4烷基、C_3-C_6环烷基、3-6 元杂环烷基、CN或卤素，所述烷基、环烷基和杂环烷基任选被卤素、OH、CH_3 或 OCH_3 取代；优选的 R_1 独立地选自：C_1-C_4 烷基、C_3-C_6 环烷基、含有 1 个或者 2 个选自 N 杂原子的 3-6 元杂环烷基、CN 或卤素，所述烷基、环烷基和杂环烷基任选被卤素、OH、CH_3 或 OCH_3 取代；进一步优选的所述 R_1 为 CHF_2、CF_3、环己基、哌啶基、甲基、氰基或者哌嗪基。

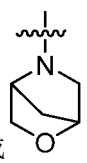
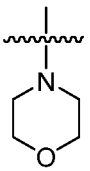
优选的，本发明某些实施方式中，所述 PTM-1、PTM-2、和 PTM-3 中 R_1 独立地选自：C_1-C_4 烷基、C_3-C_6 环烷基、3-6 元杂环烷基、CN 或卤素，所述烷基、环烷基和杂环烷基任选被卤素、OH、CH_3 或 OCH_3 取代；优选的 R_1 独立地选自：C_1-C_4 烷基、C_3-C_6 环烷基、含有 1 个或者 2 个选自 N 杂原子的 3-6 元杂环烷基、CN 或卤素，所述烷基、环烷基和杂环烷基任选被卤素、OH、CH_3 或 OCH_3 取代；进一步优选的所述 R_1 为 CHF_2、CF_3、环己基、哌啶基或者哌嗪基。

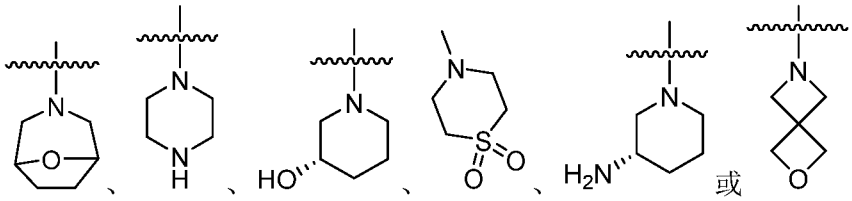
本发明某些实施方式中，R_1 独立地选自：C_1-C_4 烷基、C_3-C_6 环烷基、含有 1 个或者 2 个选自 N 杂原子的 3-6 元杂环烷基、CN 或卤素，所述烷基、环烷基和杂环烷基任选被卤素、OH、C_1-C_4 烷基或 C_1-C_4 烷氧基取代。

优选的，本发明某些实施方式中，所述 PTM-1、PTM-2 和 PTM-3 中 R_2、R_3 各自独立地选自：氢、C_1-C_6 烷基、C_3-C_8 环烷基或 3-8 元杂环烷基，各自任选地被一个或多个卤素、OH、$N(R_b)_2$ 或吗

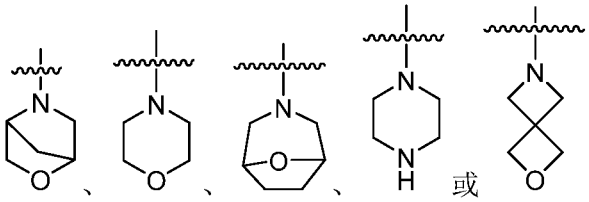
啉基取代，或 R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；R_a 独立地选自 C_1-C_4 烷基、C_3-C_6 环烷基、CF_3、CHF_2、OH、卤素或 NH_2，所述烷基任选被 C_1-C_4 烷基、C_3-C_6 环烷基或 CF_3 取代；且 R_b 独立地选自 H 或 C_1-C_4 烷基；更优选的，R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元除连接 N 原子外另外含有 1 个选自 N 或者 O 杂氧原子的杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代;所述 R_a 独立地选自 C_1-C_4 烷基、CF_3、CHF_2、OH、卤素或 NH_2；进一步优选的所述 R_2 和 R_3 与它们所连接的氮原子一起形成  ，更进一步优选的所述 R_2 和 R_3 与它们所连接的氮原子一起形成  。

优选的，本发明某些实施方式中，R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元除连接 N 原子外另外含有 1 个选自 N、S 或者 O 杂氧原子的杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代;所述 R_a 独立地选自 C_1-C_4 烷基、被 1 个、2 个或 3 个卤素取代的 C_1-C_4 烷基（优选为被 1 个、2 个或 3 个氟取代的 C_1-C_4 烷基，更优选为被 1 个、2 个或 3 个氟取代的甲基）、OH、卤素或 NH_2；优选的所述 R_2 和 R_3 与它们所连接的氮原子一起形成  、  、  、  、  、  或 。

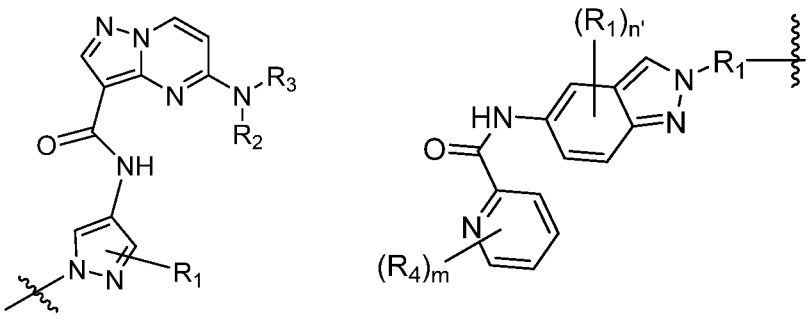
优选的，本发明某些实施方式中，所述 PTM-1、PTM-2′和 PTM-3 中 R_2、R_3 各自独立地选自：氢、C_1-C_6 烷基、C_3-C_8 环烷基或 3-8 元杂环烷基，各自任选地被一个或多个卤素、OH、$N(R_b)_2$ 或吗啉基取代，或 R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；R_a 独立地选自 C_1-C_4 烷基、C_3-C_6 环烷基、CF_3、CHF_2、OH、卤素或 NH_2，所述烷基任选被 C_3-C_6 环烷基或 CF_3 取代；且 R_b 独立地选自 H 或 C_1-C_4 烷基；优选的，R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元除连接 N 原子外另外含有 1 个选个 N 或者 O 杂氧原子的杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；所述 R_a 独立地选自 C_1-C_4 烷基、CF_3、CHF_2、OH、卤素或 NH_2；优选的所述 R_2 和 R_3 与它们所连接的氮原子一起形成  、  、



优选的，本发明某些实施方式中，所述 PTM-1、PTM-2′和 PTM-3 中 R_2 和 R_3 各自独立地选自：氢、C_1-C_6 烷基、C_3-C_8 环烷基和 3-8 元杂环烷基，各自任选地被一个或多个卤素、OH、$N(R_b)_2$ 和吗啉基取代，或 R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；R_a 独立地选自 C_1-C_4 烷基、C_3-C_6 环烷基、CF_3、CHF_2、OH、卤素或 NH_2，所述烷基任选被 C_1-C_4 烷基、C_3-C_6 环烷基和 CF_3 取代；且 R_b 独立地选自 H 和 C_1-C_4 烷基；优选的，R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元除连接 N 原子外另外含有 1 个选个 N 或者 O 杂氧原子的杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；所述 R_a 独立地选自 C_1-C_4 烷基、CF_3、CHF_2、OH、卤素和 NH_2；优选的所述 R_2 和 R_3 与它们所连接的氮原子一起形成



优选的，本发明某些实施方式中，所述 PTM 具有下式结构：



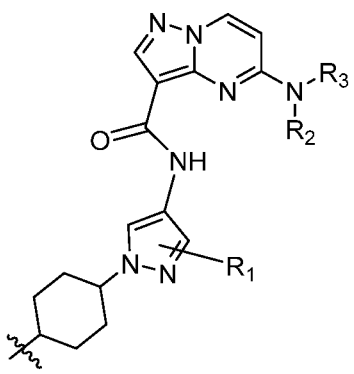
PTM-3a PTM-3a'

其中，

n′是 0、1、2 或者 3；

所述 R_1、R_2、R_3、R_4、m 和 n 如 PTM-1、PTM-2、PTM-2′和 PTM-3 中所描述和定义。

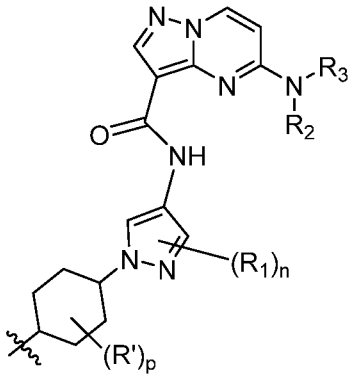
优选的，本发明某些实施方式中，所述 PTM 具有下式结构：



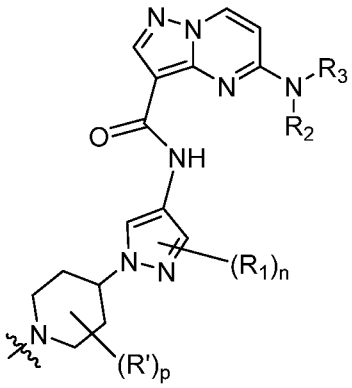
PTM-3b

其中所述 R_1、R_2、R_3、R_4、m 和 n 如 PTM-1、PTM-2、PTM-2′和 PTM-3 中所描述和定义。

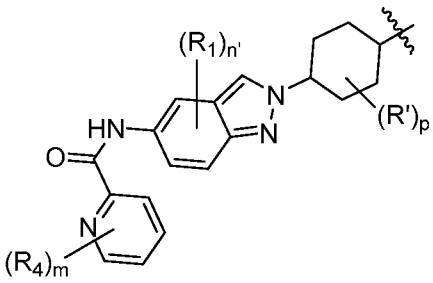
优选的，本发明某些实施方式中，所述 PTM 具有下式结构：



PTM-3b'



PTM-3c'



PTM-3d'

其中，

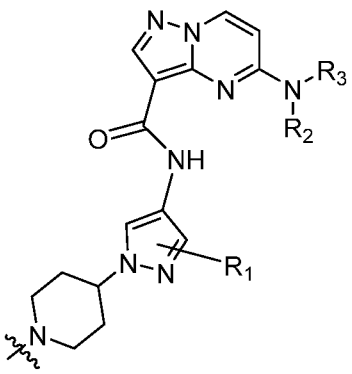
n′是 0、1、2 或者 3；

R 各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6 烷基或-O(C_1-C_6 烷基)，所述烷基任选的被 1-3 个独立地选自羟基、卤素、氰基和氨基的基团取代；

p 为 0、1、2、3、4、5、6、7、8 或 9；

所述 R_1、R_2、R_3、R_4、m 和 n 如 PTM-1、PTM-2′和 PTM-3 中所描述和定义。

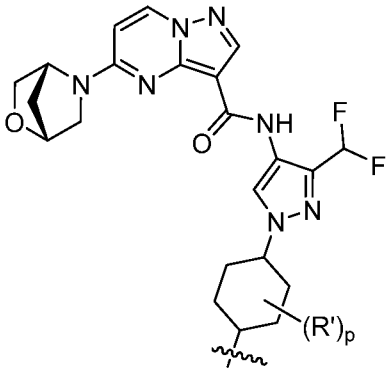
优选的，本发明某些实施方式中，所述 PTM 具有下式结构：



PTM-3c

其中所述 R_1、R_2 和 R_3 如 PTM-1、PTM-2′和 PTM-3 中所描述和定义。

优选的，本发明某些实施方式中，所述 PTM 具有下式结构：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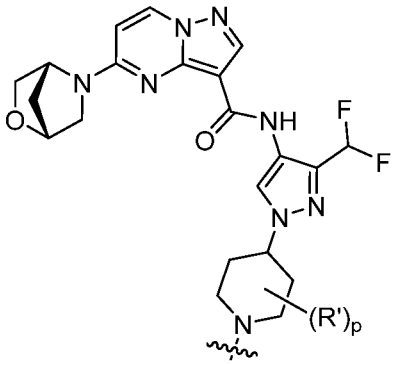
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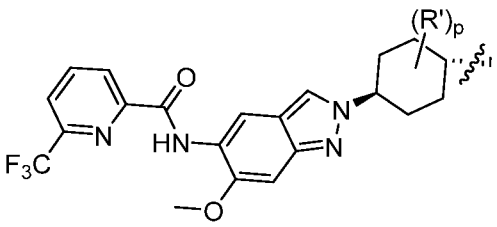
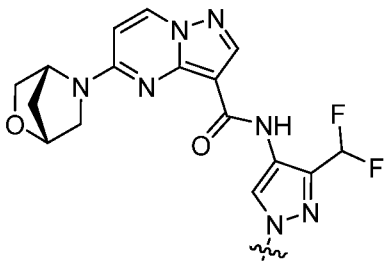
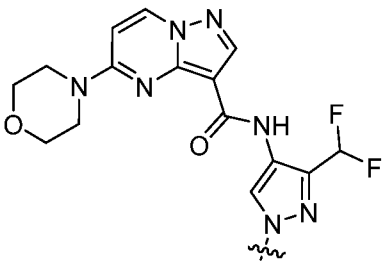
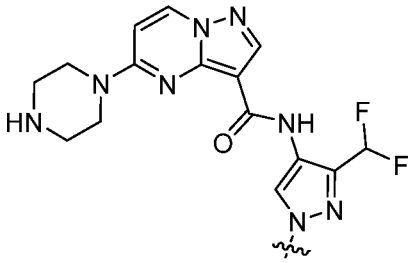
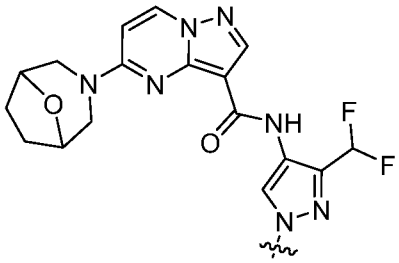

。

其中所述 R′和 p 如 PTM-3b′、PTM-3c′、PTM-3d′中所定义和描述。

优选的，本发明某些实施方式中，所述 PTM 具有下式结构：


、

、


、

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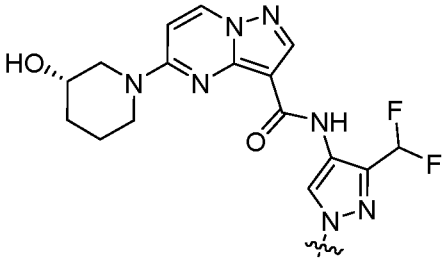
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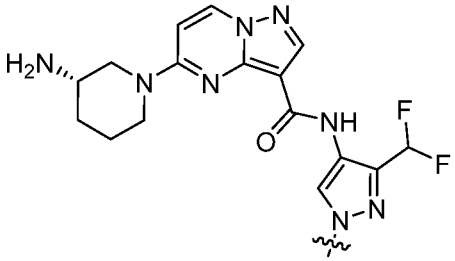
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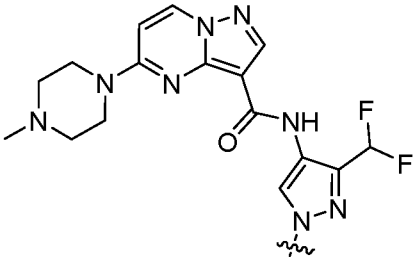
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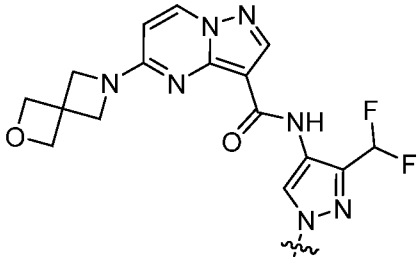
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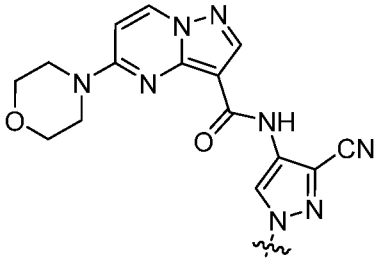
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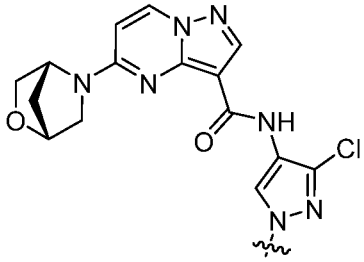
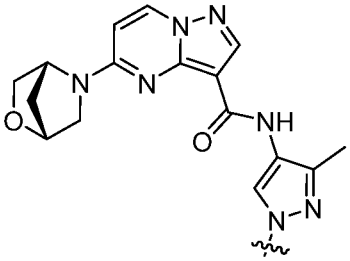
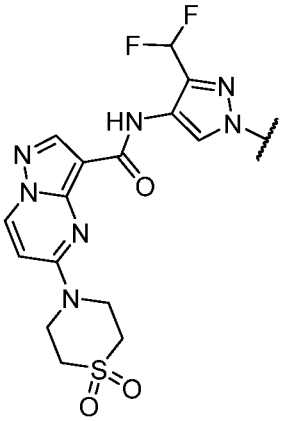

、

或

。

本发明某些实施方式中，所述 ULM-1 中的 Q_1、Q_2、Q_3、Q_4、Q_5 中的 1 个或者 2 个为 N，其余各自独立地为 CR_3"。

本发明某些实施方式中，所述 ULM-1 中的 Q_1、Q_2、Q_3、Q_4、Q_5 各自独立地为 CR_3"。

本发明某些实施方式中，所述 ULM-1 中的 X"为 N。

本发明某些实施方式中，所述 ULM-1 中的 X"为 C。

本发明某些实施方式中，所述 ULM-1 中的 Y"为 N。

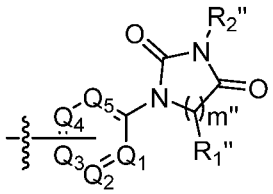
本发明某些实施方式中，所述 ULM-1 中的 R_1"各自独立地为氢、氘、-F、-Cl、或 C_1-C_6 烷基，所述烷基任选被 1-3 个卤素取代；优选 R_1"为氢。

本发明某些实施方式中，所述 ULM-1 中的 R_2"为氢或 C_1-C_6 烷基，所述烷基任选被 1-3 个卤素取代；优选 R_2"为氢。

本发明某些实施方式中，所述 ULM-1 中的 R_3"各自独立地为氢、氘、卤素、-O(C_1-C_6 烷基)、或 C_1-C_6 烷基，所述烷基任选被 1-3 个卤素取代；优选 R_3"各自独立地为氢、氘、F、Cl、甲基、甲氧基、乙氧基、三氟甲氧基、2-羟基丙-2 基或三氟甲基。

本发明某些实施方式中，R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6 烷基或-O(C_1-C_6 烷基)；所述烷基任选的被 1-3 个独立地选自羟基和卤素基团取代。

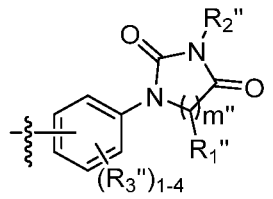
本发明某些实施方式中，所述 ULM 具有下式结构



ULM-1a

其中所述 Q_1、Q_2、Q_3、Q_4、Q_5、R_1"、R_2"和 m"如上述 ULM-1 中所定义。

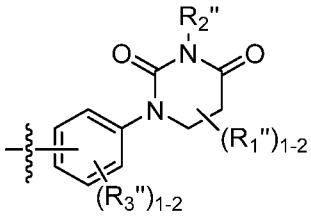
本发明某些实施方式中，所述 ULM 具有下式结构



ULM-1b

其中所述 R_1"、R_2"、R_3"和 m"如上述 ULM-1 中所定义。

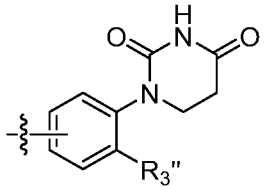
本发明某些实施方式中，所述 ULM 具有下式结构



ULM-1c

其中所述 R_1"、R_2"和 R_3"如上述 ULM-1 中所定义。

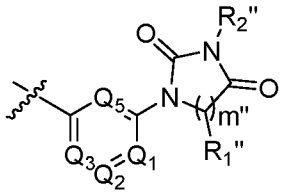
本发明某些实施方式中，所述 ULM 具有下式结构



ULM-1d

其中所述 R_3"如上述 ULM-1 中所定义。

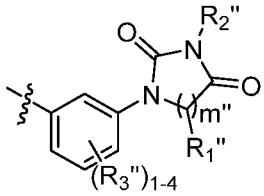
本发明某些实施方式中，所述 ULM 具有下式结构



ULM-1e

其中所述 Q_1、Q_2、Q_3、Q_5、R_1"、R_2"、m"如上述 ULM-1 中所定义。

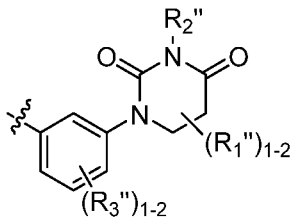
本发明某些实施方式中，所述 ULM 具有下式结构



ULM-1f

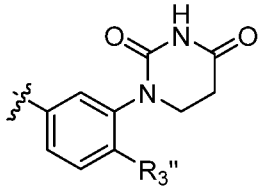
其中所述 R_1"、R_2"、R_3"、m"如上述 ULM-1 中所定义。

本发明某些实施方式中，所述 ULM 具有下式结构



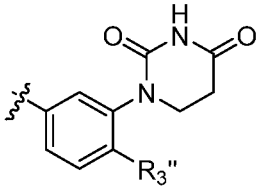
ULM-1g

其中所述 R_1"、R_2"、R_3"如上述 ULM-1 中所定义。

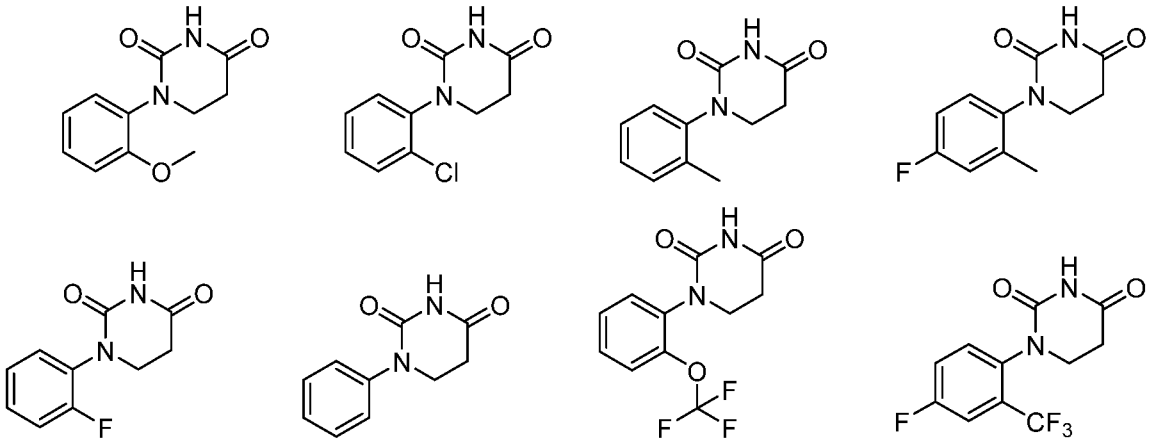


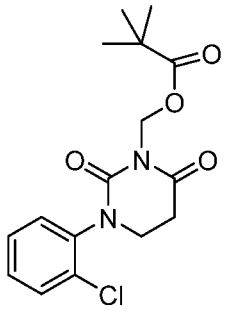
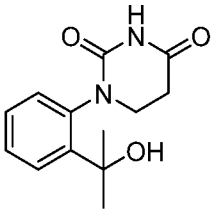
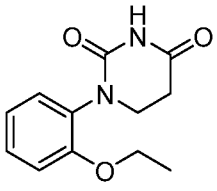
ULM-1h

其中所述 R_3"如上述 ULM-1 中所定义。

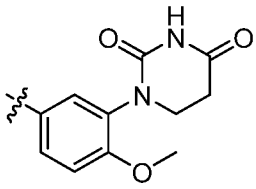
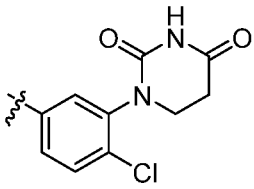
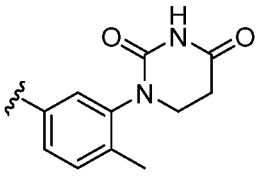
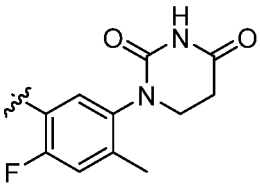
本发明某些实施方式中，所述ULM具有下式结构  ；R_3"为卤素、C_1-C_6烷基或-O(C_1-C_6烷基)。

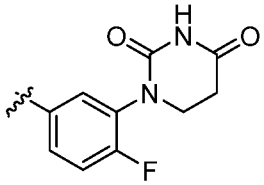
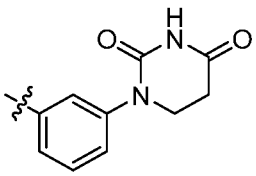
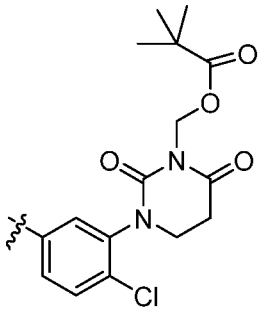
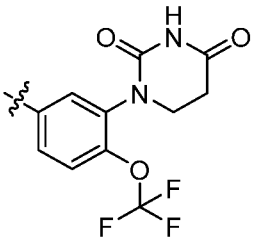
本发明某些实施方式中，所述 ULM 选自

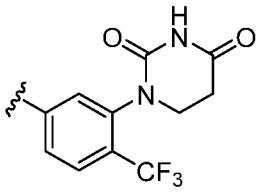
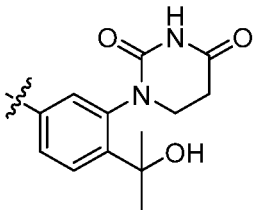
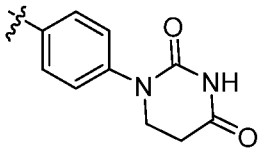
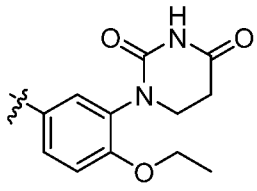


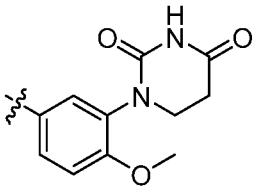
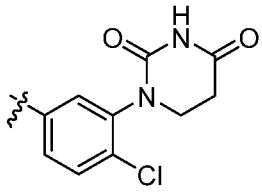
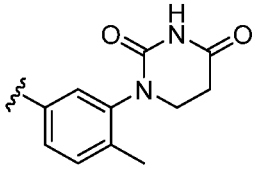
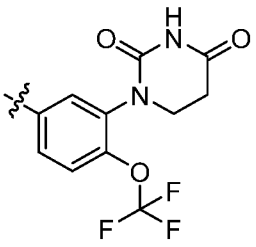


或  。

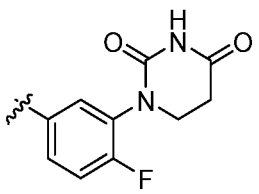
本发明某些实施方式中，所述 ULM 选自

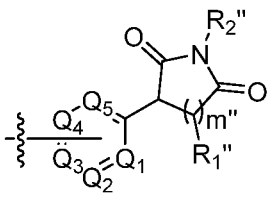








或  ，优选为

 、  、  、  或

 。

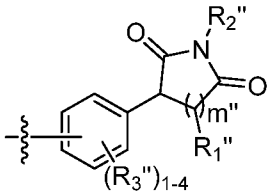
本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1aa

其中所述 Q_1、Q_2、Q_3、Q_4、Q_5、R_1"、R_2"、m"如上述 ULM-1 中所定义。

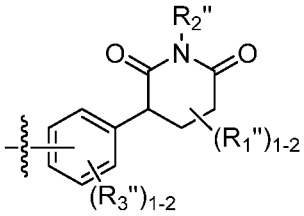
本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1bb

其中所述 R_1"、R_2"、R_3"、m"如上述 ULM-1 中所定义。

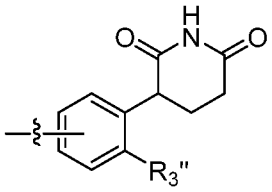
本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1cc

其中所述 R_1"、R_2"、R_3"如上述 ULM-1 中所定义。

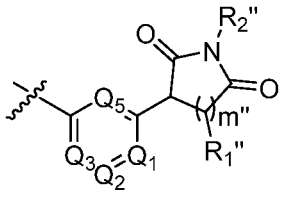
本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1dd

其中所述 R_3"如上述 ULM-1 中所定义。

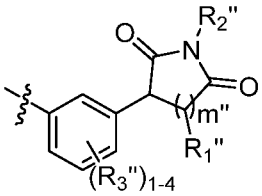
本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1ee

其中所述 Q_1、Q_2、Q_3、Q_5、R_1"、R_2"、m"如上述 ULM-1 中所定义。

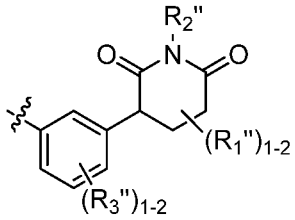
本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1ff

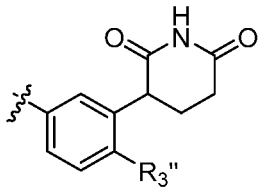
其中所述 R_1"、R_2"、R_3"、m"如上述 ULM-1 中所定义。

本发明某些实施方式中, 所述 ULM 具有下式结构



ULM-1gg

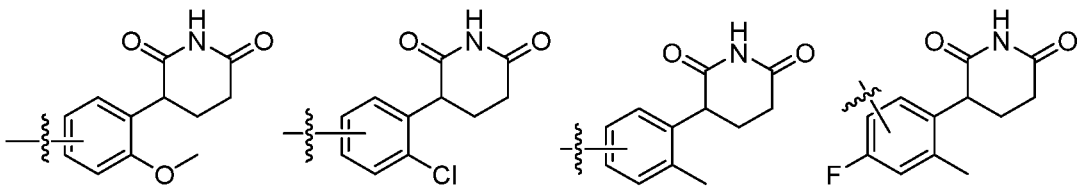
其中所述 R_1"、R_2"、R_3"如上述 ULM-1 中所定义。

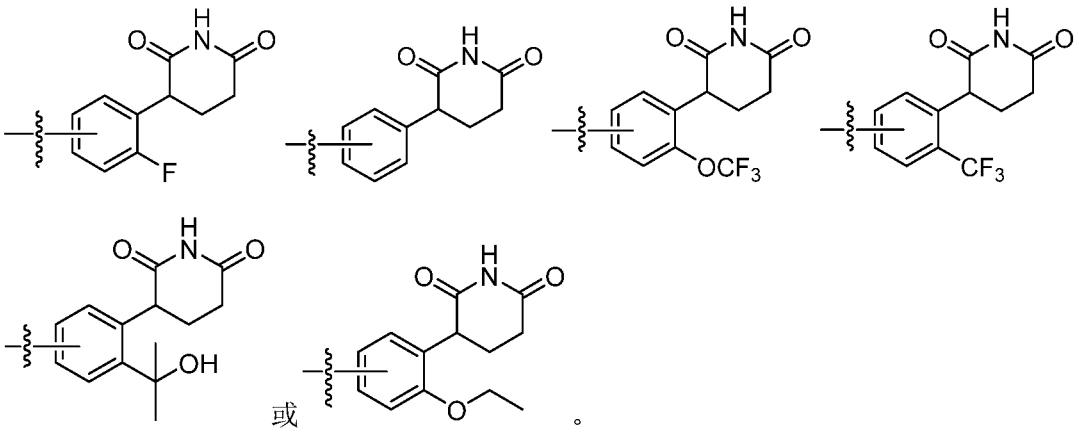


ULM-1hh

其中所述 R_3"如上述 ULM-1 中所定义。

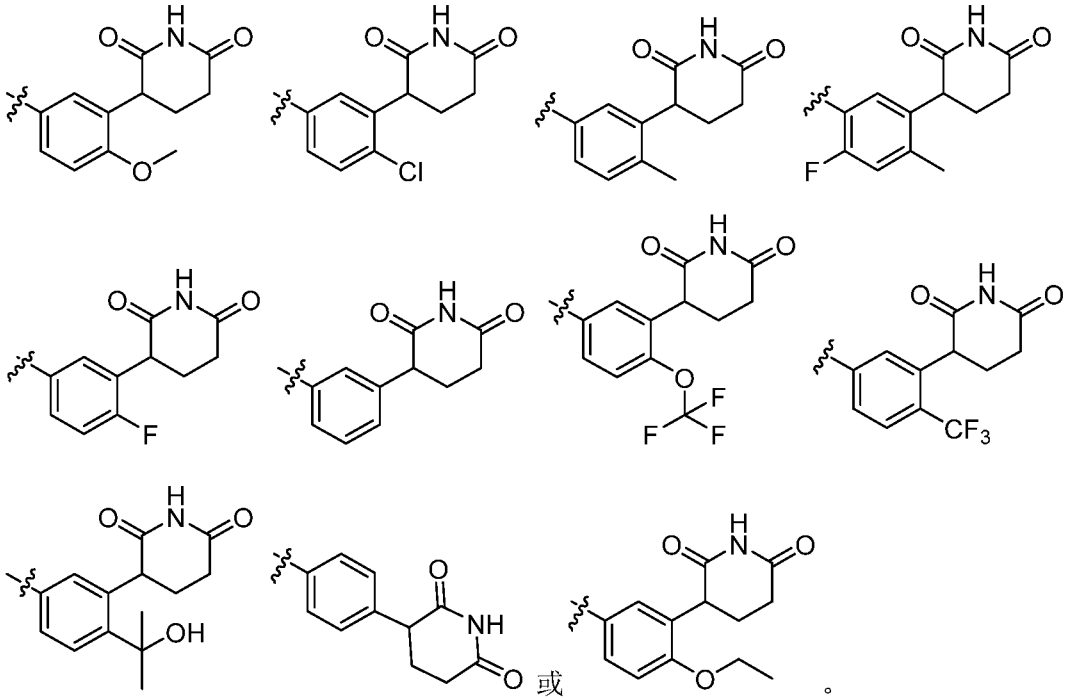
本发明某些实施方式中，所述 ULM 选自





或 。

本发明某些实施方式中，所述 ULM 选自



或 。

本发明某些实施方式中，L 为键。

本发明某些实施方式中，L 为-$(CH_2)_j$-，所述-$(CH_2)_j$-中的 1 个或多个亚甲基任选地被选自-$NR^{3'}$-、-O-、-S-、-S(O)-、-S(O)$NR^{3'}$-、-$NR^{3'}$S(O)-、-$S(O)_2$-、-$S(O)_2NR^{3'}$-、-$NR^{3'}S(O)_2$-、-$NR^{4'}S(O)_2NR^{3'}$-、-$CR^{1'}R^{2'}$-、-C(O)-、-C(O)O-、-OC(O)-、-$NR^{3'}$C(O)O-、-OC(O)$NR^{3'}$-、-C(O)$NR^{3'}$-、-$NR^{3'}$C(O)-、-$NR^{4'}$C(O)$NR^{3'}$-、-P(O)-、-P(O)O-、-OP(O)-、-OP(O)O-、亚乙烯基、亚乙炔基、C_3-C_{12} 亚环烷基、含有 1 个或多个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基、6-10 元亚芳基或 5-10 元亚杂芳基的基团替代，所述亚乙烯基、亚环烷基、亚杂环烷基、亚芳基和亚杂芳基各自独立地任选地被 1 个或多个选自卤素、-$OR^{3'}$、-$NR^{3'}R^{4'}$、氧代、硝基、氰基、C1-C6 烷基、-S(C1-C6 烷基)、C3-C10 环烷基、3-10 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-C(O)$R^{1'}$、-C(O)$OR^{3'}$、-OC(O)$R^{1'}$、-C(O)$NR^{3'}$、-$NR^{3'}$C(O)$R^{1'}$、-S(O)$R^{1'}$、-S(O)$NR^{3'}$、-$S(O)_2R^{1'}$、-$S(O)_2NR^{3'}$、-$NR^{3'}S(O)_2R^{1'}$、-$NR^{4'}S(O)_2NR^{3'}$、-

$OC(O)NR^{3'}$和 $NR^{4'}C(O)NR^{3'}$的取代基取代，所述烷基、环烷基、杂环烷基、芳基和杂芳基各自独立地任选地被 1 个或多个选自卤素、-OH、$-NR^{3'}R^{4'}$、氧代、硝基、氰基、C_1-C_6烷基、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基和 5-10 元杂芳基的取代基取代；$R^{1'}$和 $R^{2'}$各自独立为卤素、-OH、$-NR^{3'}R^{4'}$、C_1-C_6烷基、氯代 C_1-C_6烷基、羟基 C_1-C_6烷基、$-O(C_1$-C_6烷基)、$-NH(C_1$-C_6烷基)、$-NH(C_1$-C_6烷基)$_2$、C_3-C_{10}环烷基、$-O(C_3$-C_{10}环烷基)、$-NH(C_3$-C_{10}环烷基)、3-10 元杂环烷基、-O(3-10 元杂环烷基)、-NH(3-10 元杂环烷基)、6-10 元芳基、-O(6-10 元芳基)、-NH(6-10 元芳基)、5-10 元杂芳基、-O(5-10 元杂芳基)或-NH(5-10 元杂芳基)，$R^{3'}$和 $R^{4'}$各自独立地为氢、氘、C_1-C_6烷基、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基或 5-10 元杂芳基；j 为 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24 或 25。

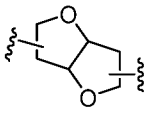
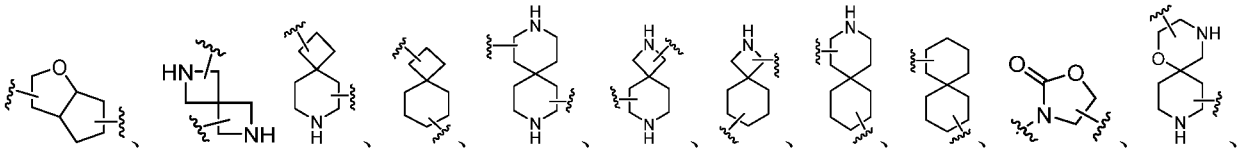
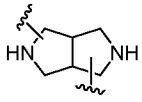
本发明某些实施方式中，L 为$-(CH_2)_j-$，所述$-(CH_2)_j-$中的 1 个或多个亚甲基任选地被选自$-NR^{3'}-$、-O-、-S-、-S(O)-、$-S(O)NR^{3'}-$、$-NR^{3'}S(O)-$、$-S(O)_2-$、$-S(O)_2NR^{3'}-$、$-NR^{3'}S(O)_2-$、$-NR^{4'}S(O)_2NR^{3'}-$、$-CR^{1'}R^{2'}-$、-C(O)-、-C(O)O-、-OC(O)-、$-NR^{3'}C(O)O-$、$-OC(O)NR^{3'}-$、$-C(O)NR^{3'}-$、$-NR^{3'}C(O)-$、$-NR^{4'}C(O)NR^{3'}-$、-P(O)-、-P(O)O-、-OP(O)-、-OP(O)O-、亚乙烯基、亚乙炔基、C_3-C_{12}亚环烷基、含有 1 个或多个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基、6-10 元亚芳基或 5-10 元亚杂芳基的基团替代，所述亚乙烯基、亚环烷基、亚杂环烷基、亚芳基和亚杂芳基各自独立地任选地被 1 个或多个选自卤素、$-OR^{3'}$、$-NR^{3'}R^{4'}$、氧代、硝基、氰基、C1-C6 烷基、-S(C1-C6 烷基)、C3-C10 环烷基、3-10 元杂环烷基、6-10 元芳基、5-10 元杂芳基、$-C(O)R^{1'}$、$-C(O)OR^{3'}$、$-OC(O)R^{1'}$、$-C(O)NR^{3'}$、$-NR^{3'}C(O)R^{1'}$、$-S(O)R^{1'}$、$-S(O)NR^{3'}$、$-S(O)_2R^{1'}$、$-S(O)_2NR^{3'}$、$-NR^{3'}S(O)_2R^{1'}$、$-NR^{4'}S(O)_2NR^{3'}$、$-OC(O)NR^{3'}$和 $NR^{4'}C(O)NR^{3'}$的取代基取代，所述烷基、环烷基、杂环烷基、芳基和杂芳基各自独立地任选地被 1 个或多个选自卤素、-OH、$-NR^{3'}R^{4'}$、氧代、硝基、氰基、C_1-C_6烷基、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基和 5-10 元杂芳基的取代基取代；$R^{1'}$和 $R^{2'}$各自独立为卤素、-OH、$-NR^{3'}R^{4'}$、C_1-C_6烷基、氯代 C_1-C_6烷基、羟基 C_1-C_6烷基、$-O(C_1$-C_6烷基)、$-NH(C_1$-C_6烷基)、$-NH(C_1$-C_6烷基)$_2$、C_3-C_{10}环烷基、$-O(C_3$-C_{10}环烷基)、$-NH(C_3$-C_{10}环烷基)、3-10 元杂环烷基、-O(3-10 元杂环烷基)、-NH(3-10 元杂环烷基)、6-10 元芳基、-O(6-10 元芳基)、-NH(6-10 元芳基)、5-10 元杂芳基、-O(5-10 元杂芳基)或-NH(5-10 元杂芳基)，$R^{3'}$和 $R^{4'}$各自独立地为氢、氘、C_1-C_6烷基、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基或 5-10 元杂芳基；j 为 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24 或 25。

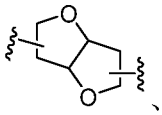
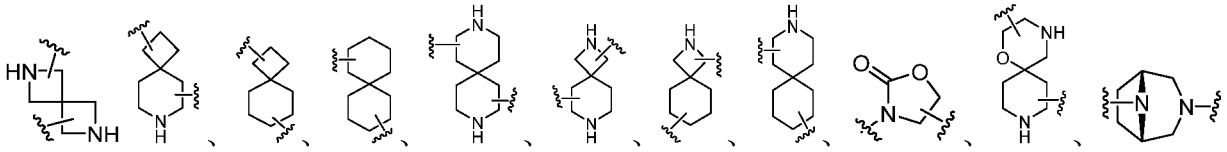
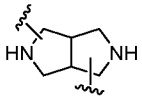
优选的，本发明某些实施方式中，L 为$-(CH_2)_j-$，所述$-(CH_2)_j-$中的 1 个或多个亚甲基任选地被选自$-NR^{3'}-$、-O-、$-CR^{1'}R^{2'}-$、-C(O)-、-S(O)-、$-S(O)_2-$、-C(O)O-、-OC(O)-、$-C(O)NR^{3'}-$、$-NR^{3'}C(O)-$、$-S(O)_2NR^{3'}-$、$-NR^{3'}S(O)_2-$、亚乙烯基、亚乙炔基、苯基、8-10 元双环亚芳基、3-7 元饱和/或部分不饱和的亚环烷基、4-11 元的饱和/或部分不饱和的亚螺环烷基、4-11 元的饱和/或部分不饱和的亚稠环烷基、8-10 元双环饱和/或部分不饱和的亚环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-7 元饱和/或部分不饱和的亚杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和/或部分不饱

和的亚螺杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和/或部分不饱和的亚稠杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 8-10 元双环饱和/或部分不饱和的亚杂环烷基、具有 1-4 个独立地选自氮、氧或硫杂原子的 5-6 元亚杂芳基、或具有 1-5 个选自氮、氧或硫杂原子的 8-10 元双环杂芳基的基团替代，所述亚乙烯基、亚乙炔基、亚环烷基、亚杂环烷基、苯基、亚螺杂环烷基、亚稠杂环烷基、亚螺环烷基、亚稠环烷基和亚杂芳基各自独立地任选地被 1 个或多个选自卤素、氧代、$-NR^{3'}R^{4'}$、$-OR^{3'}$、硝基、-CN、C_1-C_6 烷基、C_3-C_{10} 环烷基和 3-10 元杂环烷基的取代基取代，所述烷基、环烷基和杂环烷基任选被 1 个或多个选自卤素、-OH、$-NH_2$、-CN、C_1-C_4 烷基和 C_3-C_6 环烷基的取代基取代，$R^{1'}$和 $R^{2'}$各自独立为卤素、-OH、$-NH_2$、C_1-C_4 烷基、C_1-C_4 氯代烷基、C_1-C_4 羟基烷基、$-O(C_1$-C_4 烷基)、$-NH(C_1$-C_4 烷基)、$-NH(C_1$-C_4 烷基)、C_3-C_6 环烷基、$-O(C_3$-C_6 环烷基)、$-NH(C_3$-C_6环烷基)、3-6 元杂环烷基、-O(3-6 元杂环烷基)或$-NH(C_3$-C_6环烷基)；$R^{3'}$和 $R^{4'}$各自独立地为氢、氘、C_1-C_4烷基、C_3-C_6环烷基或 3-6 元杂环烷基，j 为 2、3、4、5、6、7、8、9、10、11 或 12。

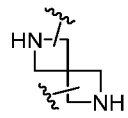
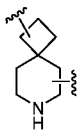
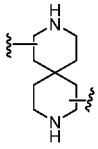
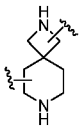
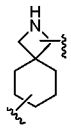
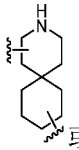
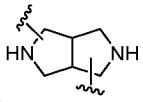
优选的，本发明某些实施方式中，L 为$-(CH_2)_j-$，所述$-(CH_2)_j-$中的 1 个或多个亚甲基任选地被选自$-NR^{3'}-$、-O-、$-CR^{1'}R^{2'}-$、-C(O)-、-S(O)-、$-S(O)_2-$、-C(O)O-、-OC(O)-、$-C(O)NR^{3'}-$、$-NR^{3'}C(O)-$、$-S(O)_2NR^{3'}-$、$-NR^{3'}S(O)_2-$、亚乙烯基、亚乙炔基、苯基、8-10 元双环亚芳基、3-7 元饱和/或部分不饱和的单环亚环烷基、4-11 元的饱和/或部分不饱和的亚螺环烷基、4-11 元的饱和/或部分不饱和的亚稠环烷基、8-10 元双环饱和/或部分不饱和的亚环烷基、具有 1-2 个独立地选自氮或氧杂原子的 4-7 元饱和/或部分不饱和的亚杂环烷基、具有 1-2 个独立地选自氮或氧杂原子的 4-11 元饱和/或部分不饱和的亚螺杂环烷基、具有 1-2 个独立地选自氮或氧杂原子的 4-11 元饱和/或部分不饱和的亚稠杂环烷基、具有 1-2 个独立地选氮或氧杂原子的 8-10 元双环饱和/或部分不饱和的亚杂环烷基、具有 1-4 个独立地选自氮或氧杂原子的 5-6 元亚杂芳基、或具有 1-5 个选自氮或氧杂原子的 8-10 元双环杂芳基的基团替代，所述亚乙烯基、亚乙炔基、亚环烷基、亚杂环烷基、苯基、亚螺杂环烷基、亚稠杂环烷基、亚稠环烷基、亚螺环烷基和亚杂芳基各自独立地任选地被 1 个或多个选自卤素、氧代、$-NR^{3'}R^{4'}$、$-OR^{3'}$、硝基、-CN、C_1-C_6 烷基、C_3-C_6 环烷基和 3-6 元杂环烷基的取代基取代，所述烷基、环烷基、杂环烷基任选被 1 个或多个选自卤素、-OH、$-NH_2$、-CN、C_1-C_4烷基和 C_3-C_6环烷基的取代基取代，$R^{1'}$和 $R^{2'}$各自独立为卤素、-OH、$-NH_2$、C_1-C_4 烷基、C_1-C_4 氯代烷基、C_1-C_4 羟基烷基、$-O(C_1$-C_4 烷基)、$-NH(C_1$-C_4 烷基)、$-NH(C_1$-C_4 烷基)、C_3-C_6 环烷基、$-O(C_3$-C_6 环烷基)、$-NH(C_3$-C_6 环烷基)、3-6 元杂环烷基、-O(3-6 元杂环烷基)或$-NH(C_3$-C_6 环烷基)；$R^{3'}$和 $R^{4'}$各自独立地为氢、氘、C_1-C_4 烷基、C_3-C_6环烷基或 3-6 元杂环烷基，j 为 2、3、4、5、6、7、8、9 或 10。

优选的，本发明某些实施方式中，L 为$-(CH_2)_j-$，所述$-(CH_2)_j-$中的 1 个、2 个、3 个或者 4 个亚甲基任选地被选自-NH-、$-NCH_3-$、$-NCH_2CH_3-$、-O-、$-C(CH_3)_2-$、-CHF-、$-CHCF_3-$、-C(O)-、-C(O)O-、-OC(O)-、-C(O)NH-、$-C(O)NCH_3-$、-NHC(O)-、$-NCH_3C(O)-$、亚乙烯基、亚乙炔基、亚环丙基、亚环丁基、亚环戊基、亚环己基、亚氧杂环丙基、亚氧杂环丁基、亚氧杂环戊基、亚氧杂环己基、亚

氮杂环丙基、亚氮杂环丁基、亚氮杂环戊基、亚哌啶基、亚哌嗪基、亚吗啉基、亚高吗啉基、亚苯基、亚吡咯基、亚噻吩基、亚呋喃基、亚咪唑基、亚吡唑基、亚三唑基、亚四唑基、亚噁唑基、亚异噁唑基、亚噻唑基、亚异噻唑基、亚吡啶基、亚嘧啶基、亚哒嗪基、亚吡嗪基、  、  和  的基团替代，且所述替代基团任选地被 1 个或多个选自卤素、氧代、-$NR^{3'}R^{4'}$、-$OR^{3'}$、C_1-C_4 烷基的取代基取代，所述烷基任选被 1 个或多个选自卤素、-OH 和-NH_2 的取代基取代，$R^{3'}$和 $R^{4'}$各自独立地为氢、氘或 C_1-C_4 烷基，j 为 2、3、4、5、6、7 或 8。

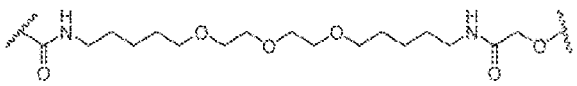
优选的，本发明某些实施方式中，L 为-$(CH_2)_j$-，所述-$(CH_2)_j$-中的 1 个、2 个或者 3 个亚甲基任选地被选自-NH-、-NCH_3-、-NCH_2CH_3-、-O-、-$C(CH_3)_2$-、-CHF-、-$CHCF_3$-、-C(O)-、-C(O)O-、-OC(O)-、-C(O)NH-、-$C(O)NCH_3$-、-NHC(O)-、-$NCH_3C(O)$-、亚环丙基、亚环丁基、亚环戊基、亚环己基、亚氧杂环丙基、亚氧杂环丁基、亚氧杂环戊基、亚氧杂环己基、亚氮杂环丙基、亚氮杂环丁基、亚氮杂环戊基、亚哌啶基、亚哌嗪基、亚吗啉基、亚高吗啉基、  、  和  的基团替代，且所述替代基团任选地被 1 个或多个选自 F、Cl、氧代、-$NR^{3'}R^{4'}$、-$OR^{3'}$和 C_1-C_4烷基的取代基取代，所述烷基任选被1个或多个选自卤素、-OH和-NH_2的取代基取代，$R^{3'}$、$R^{4'}$各自独立地为氢、氘、甲基、乙基和丙基，j 为 2、3、4、5、6、7、或 8。

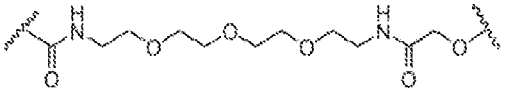
优选的，本发明某些实施方式中，L 为-$(CH_2)_j$ -，所述-$(CH_2)_j$-中的 1 个、2 个或者 3 个亚甲基任选地被选自-O-、-NH-、-NCH_3-、-NCH_2CH_3-、-C(O)-、-C(O)NH-、-NHC(O)-、-$NCH_3C(O)$-、-

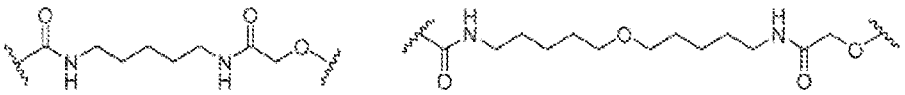
C(O)NCH$_3$-、  、  、  、  、  、  或  的基团替代，j 为 2、3、4、5、6、7 或 8。

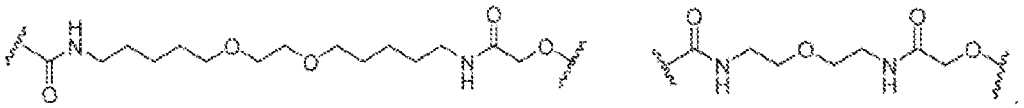
优选的，本发明某些实施方式中，L 选自-(CH$_2$)$_{j-1}$-C(O)-，所述-(CH$_2$)$_{j-1}$-C(O)-中的亚甲基如上述 L 中所定义，任选被 1 个或多个基团所替代，所述 j 如上述 L 中所定义。

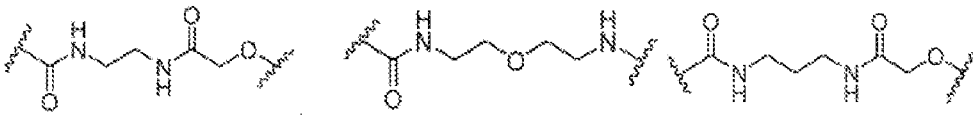
优选的，本发明某些实施方式中，L 选自

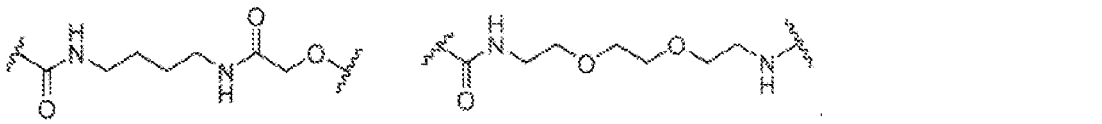


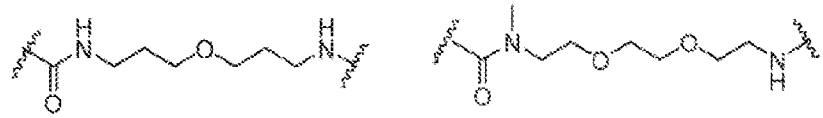


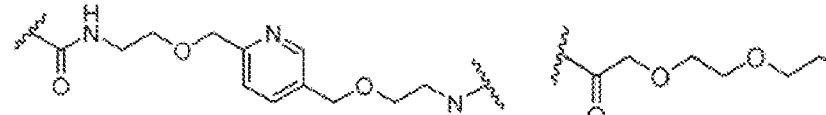


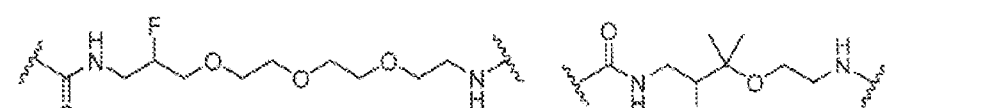


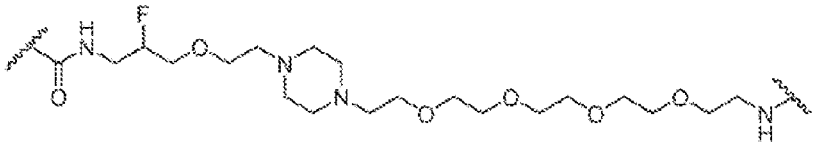


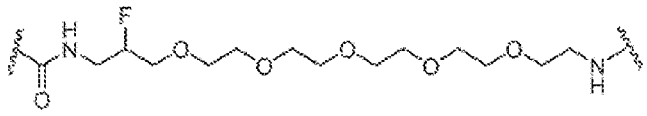


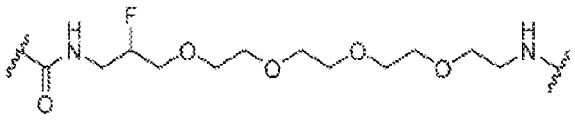


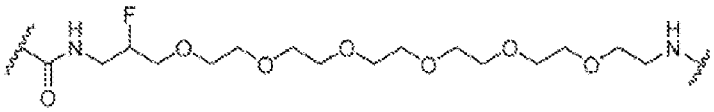


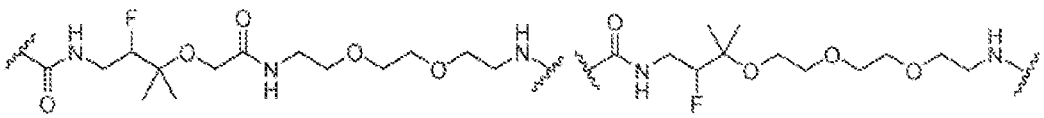


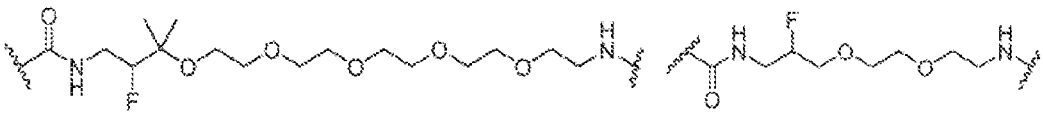


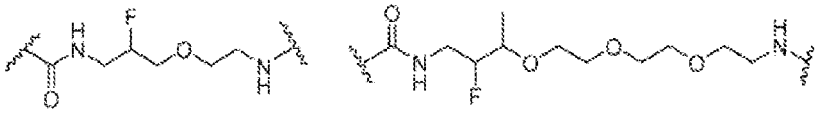


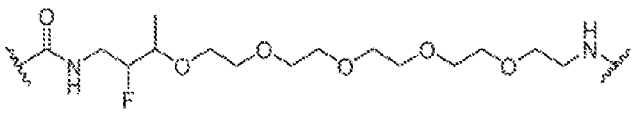


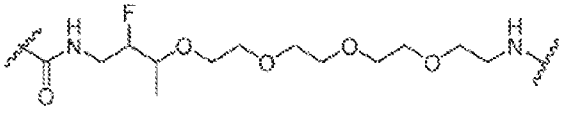


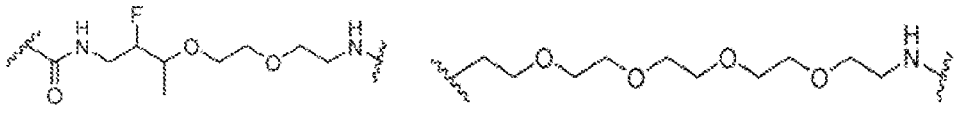


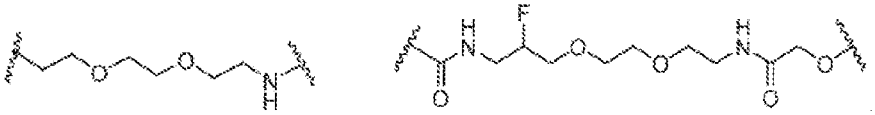


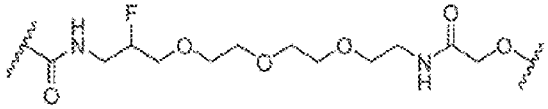


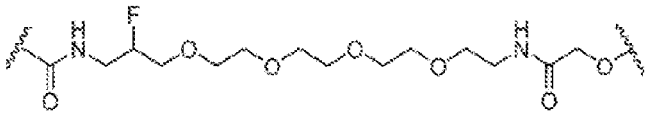


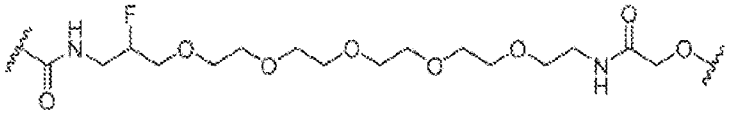


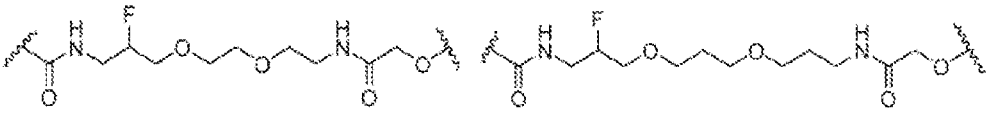


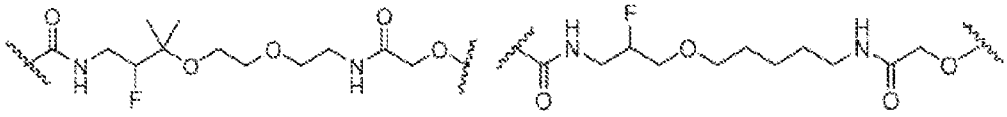


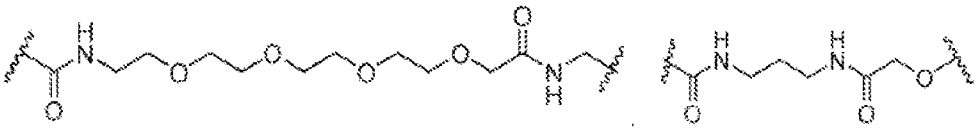


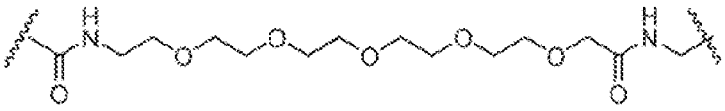


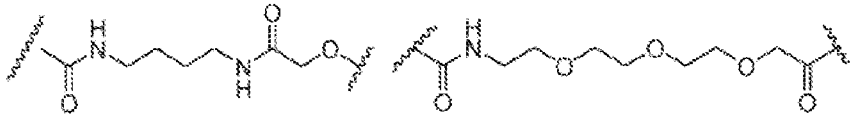


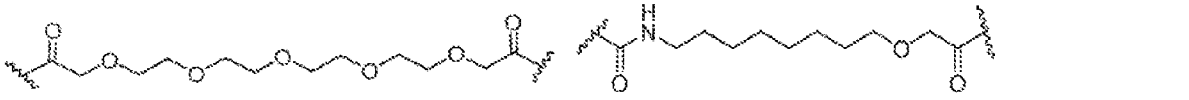


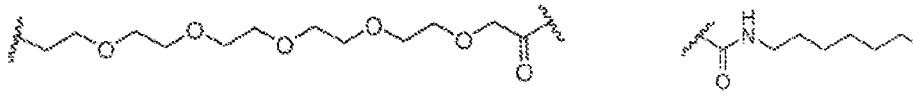


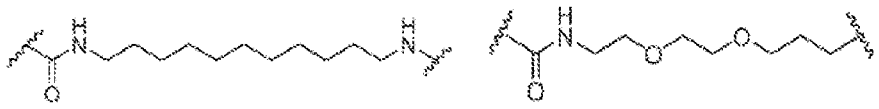


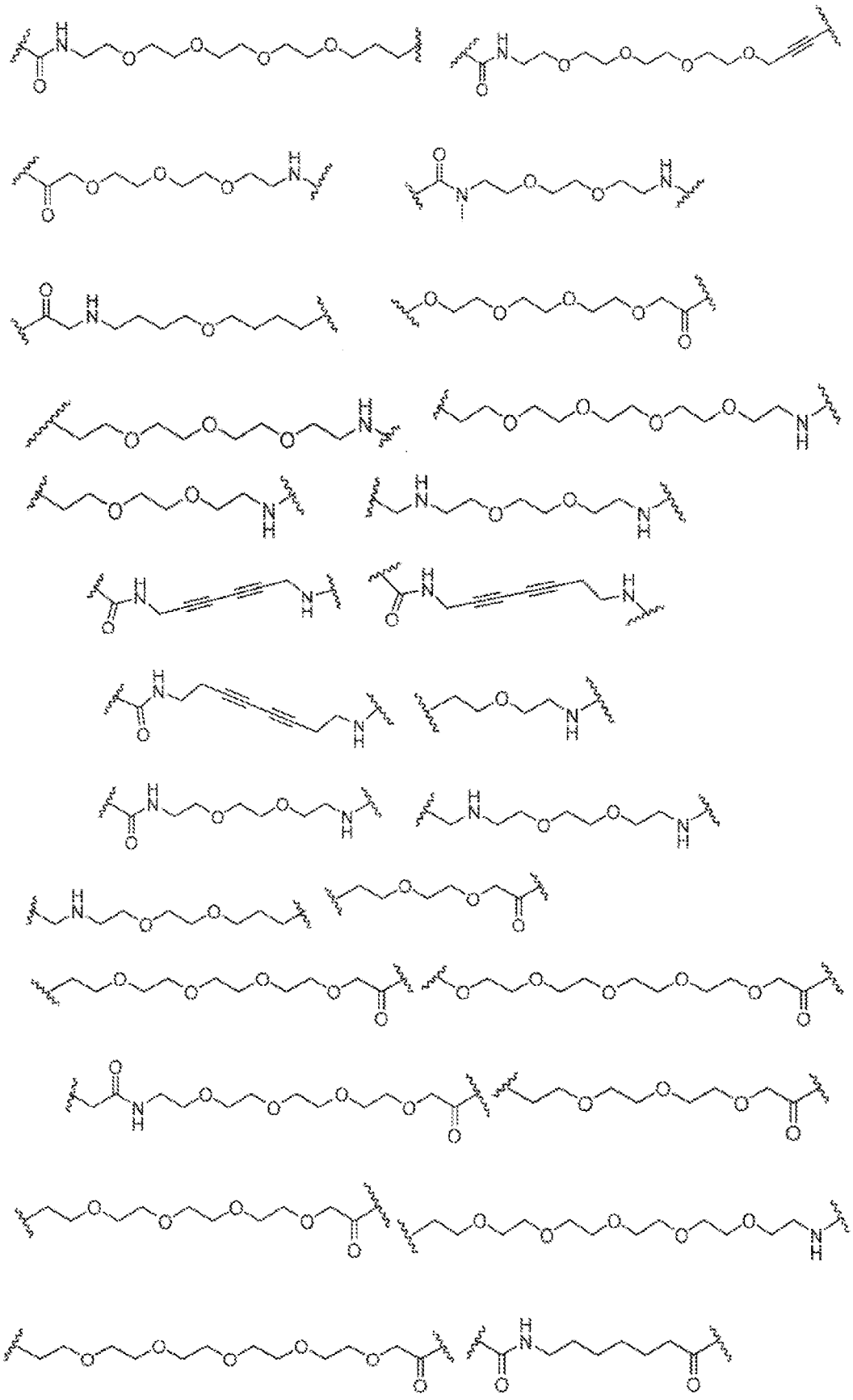


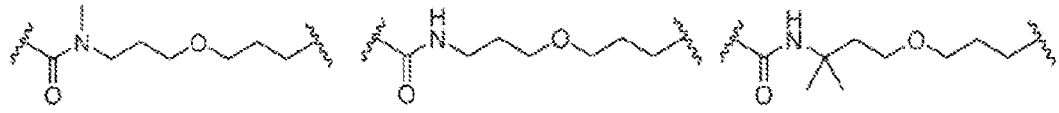


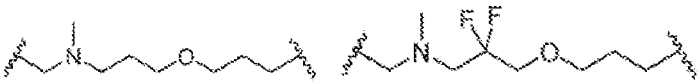


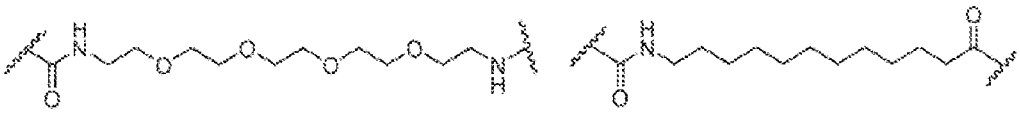


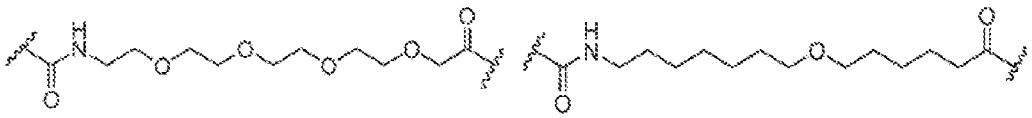


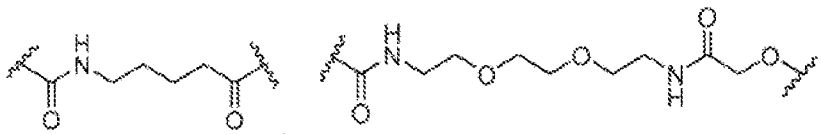


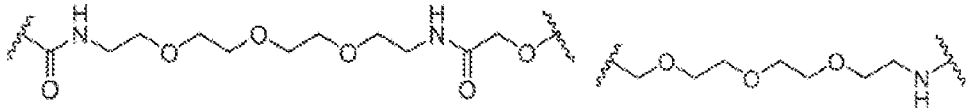


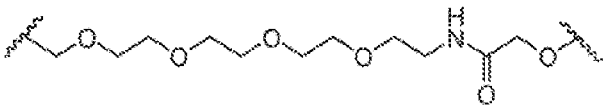


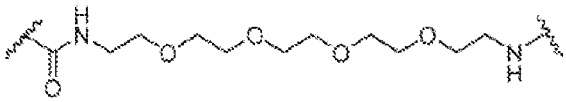


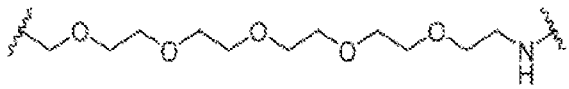


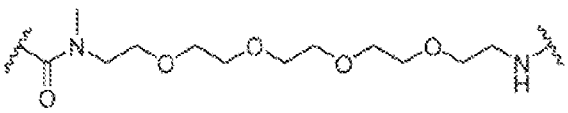


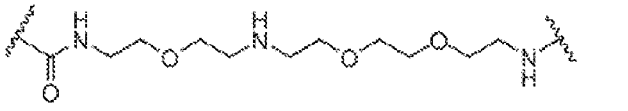


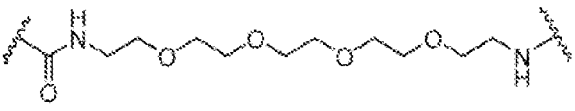


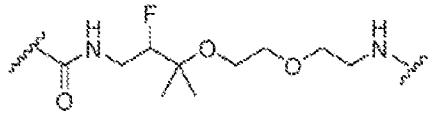


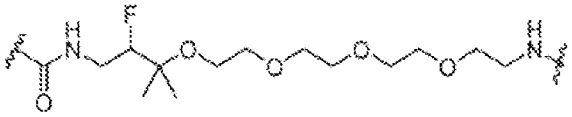


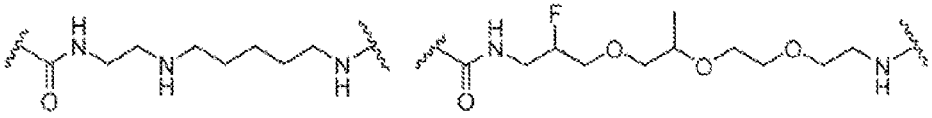


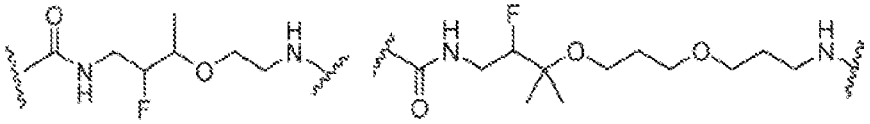


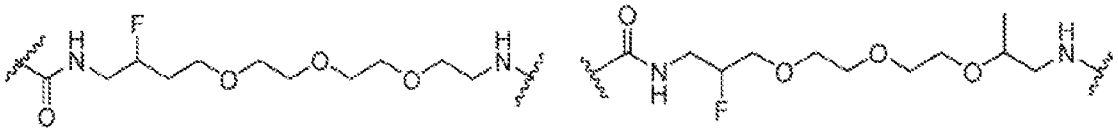


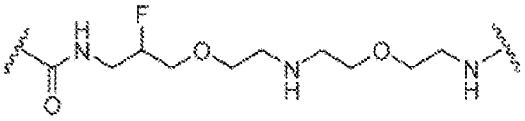


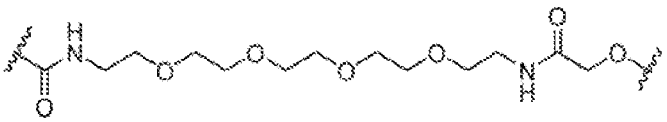


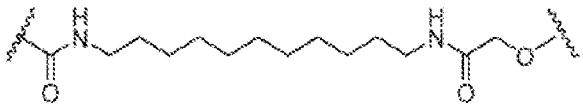


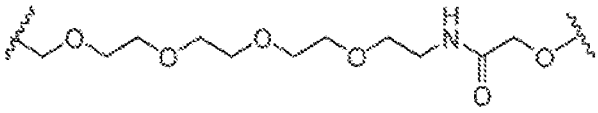


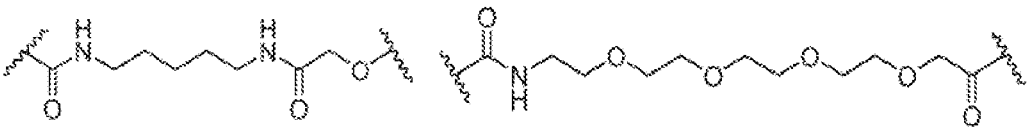


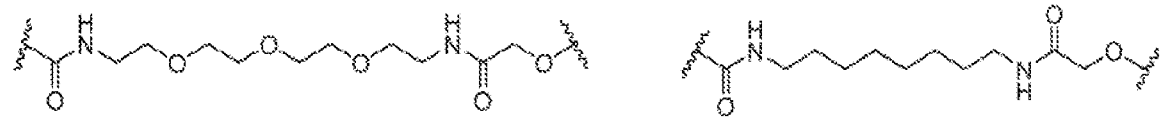


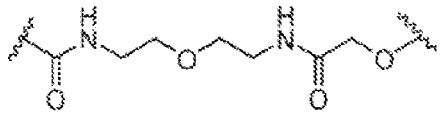


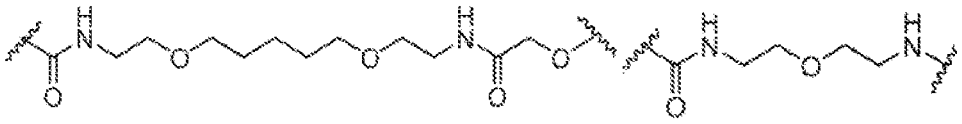


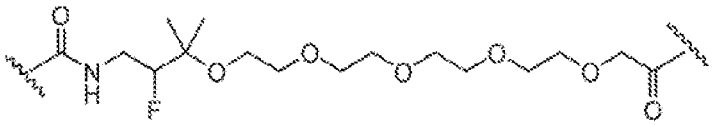


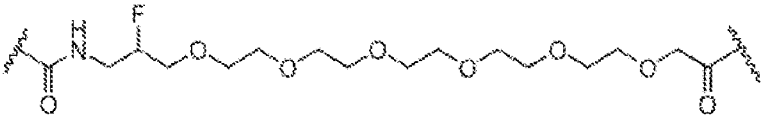


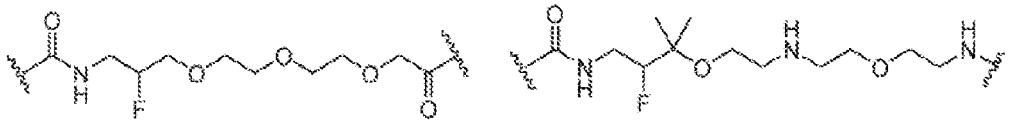


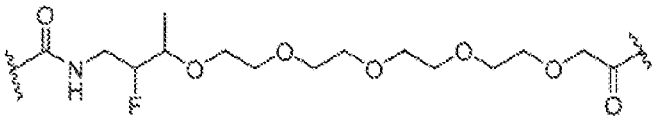


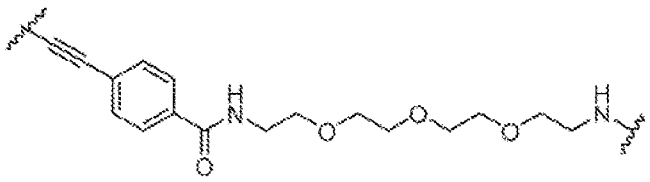


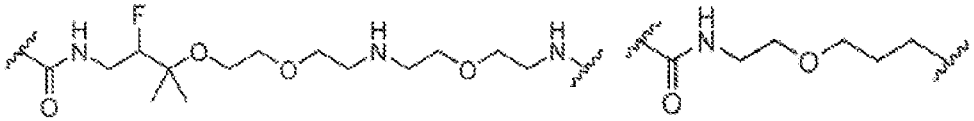


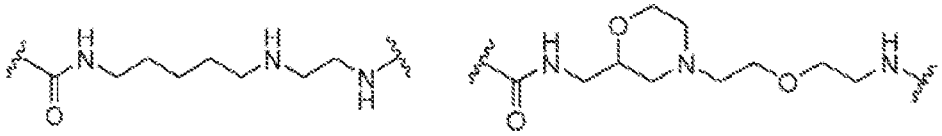


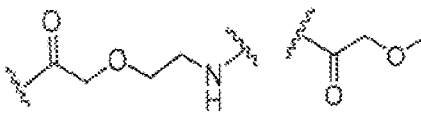


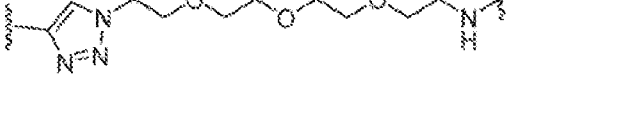


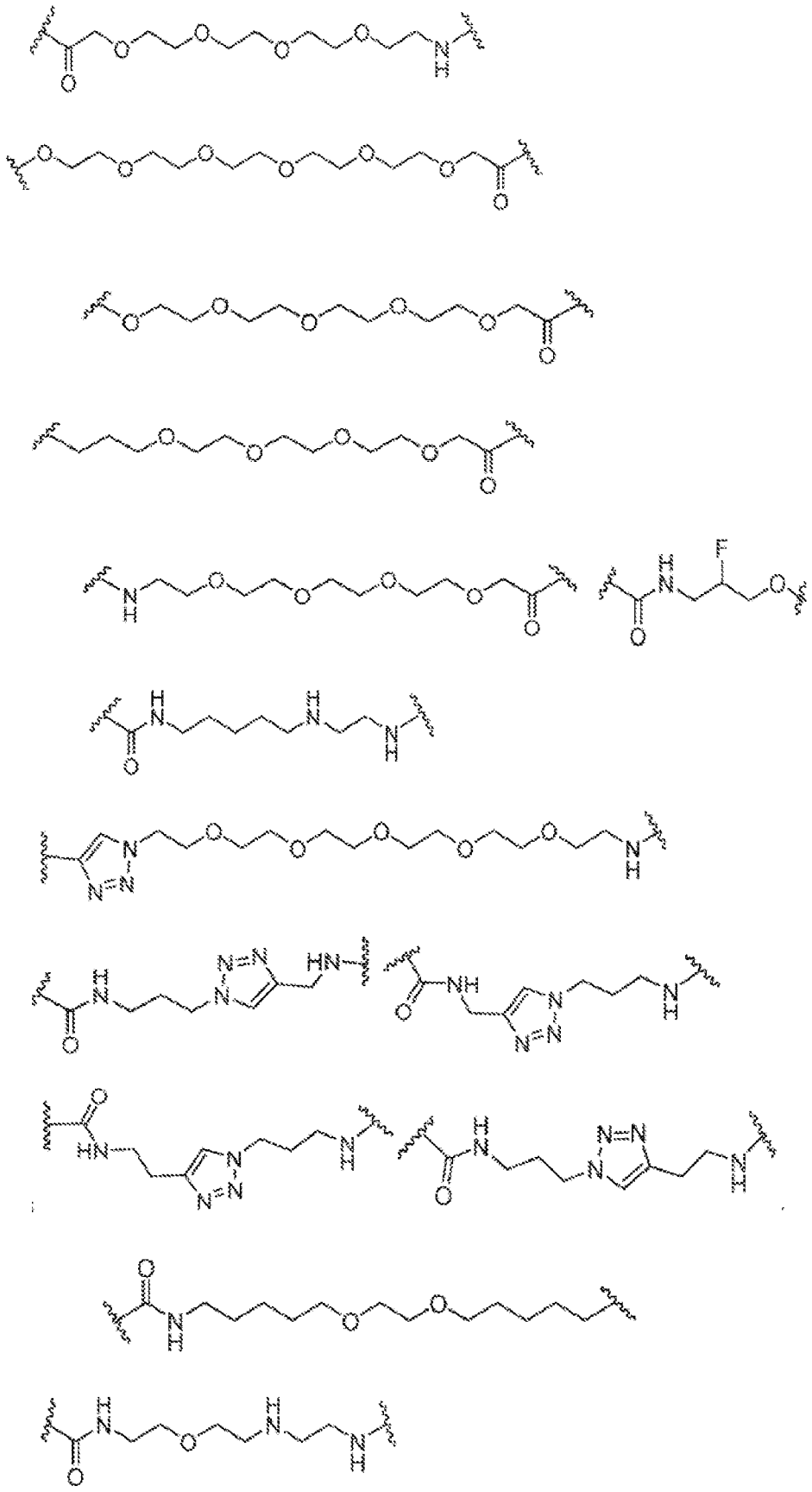


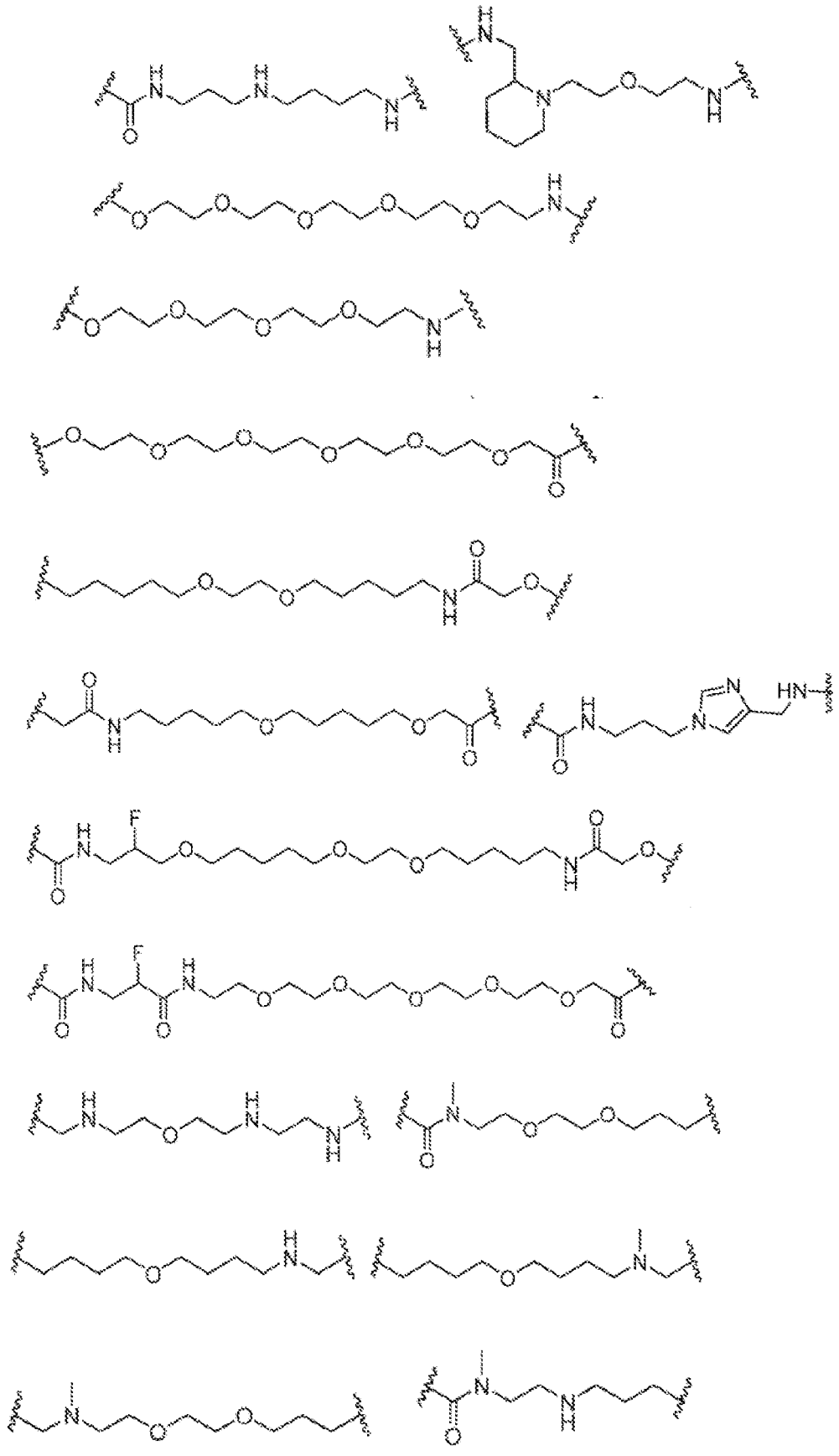


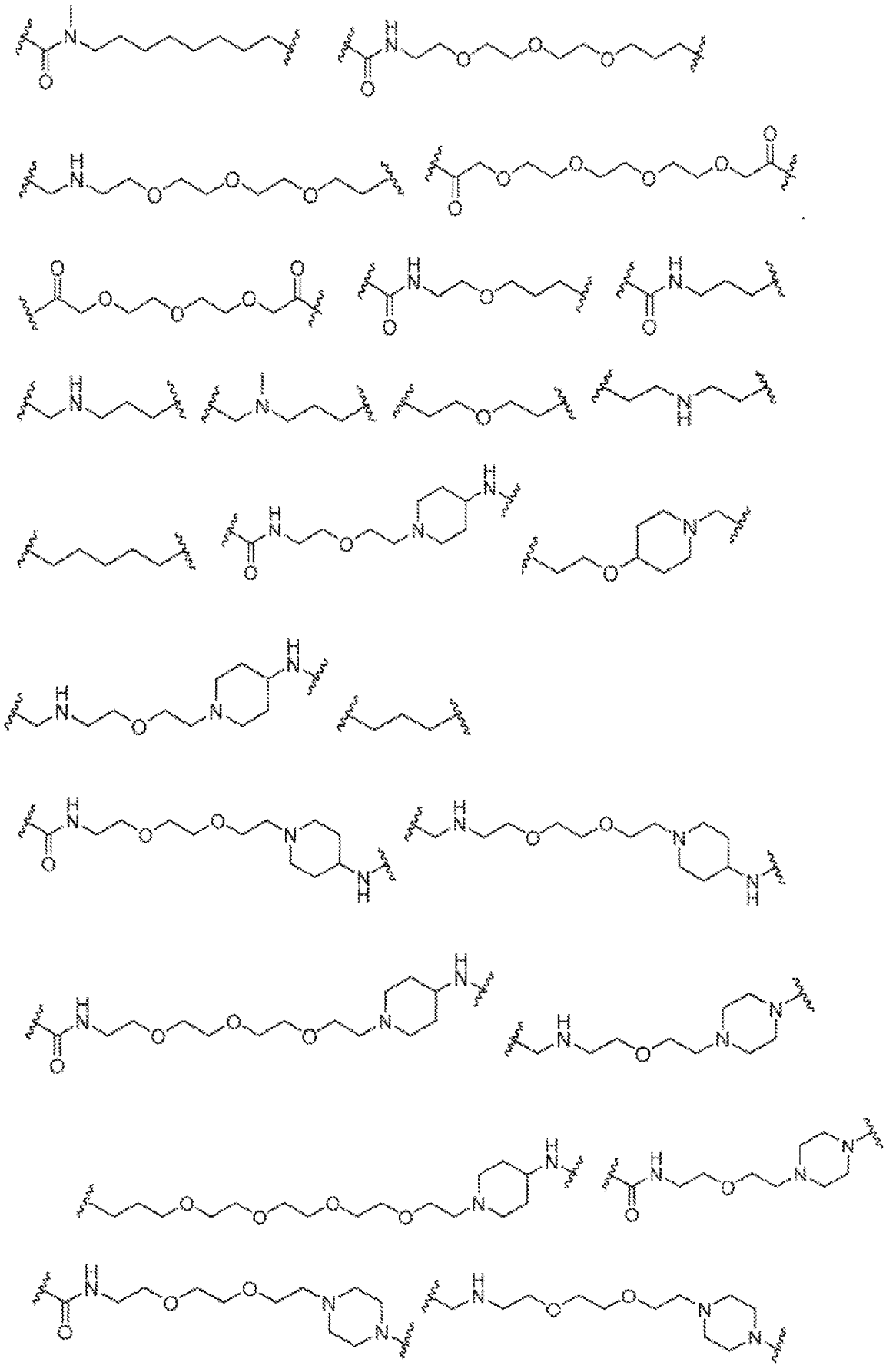


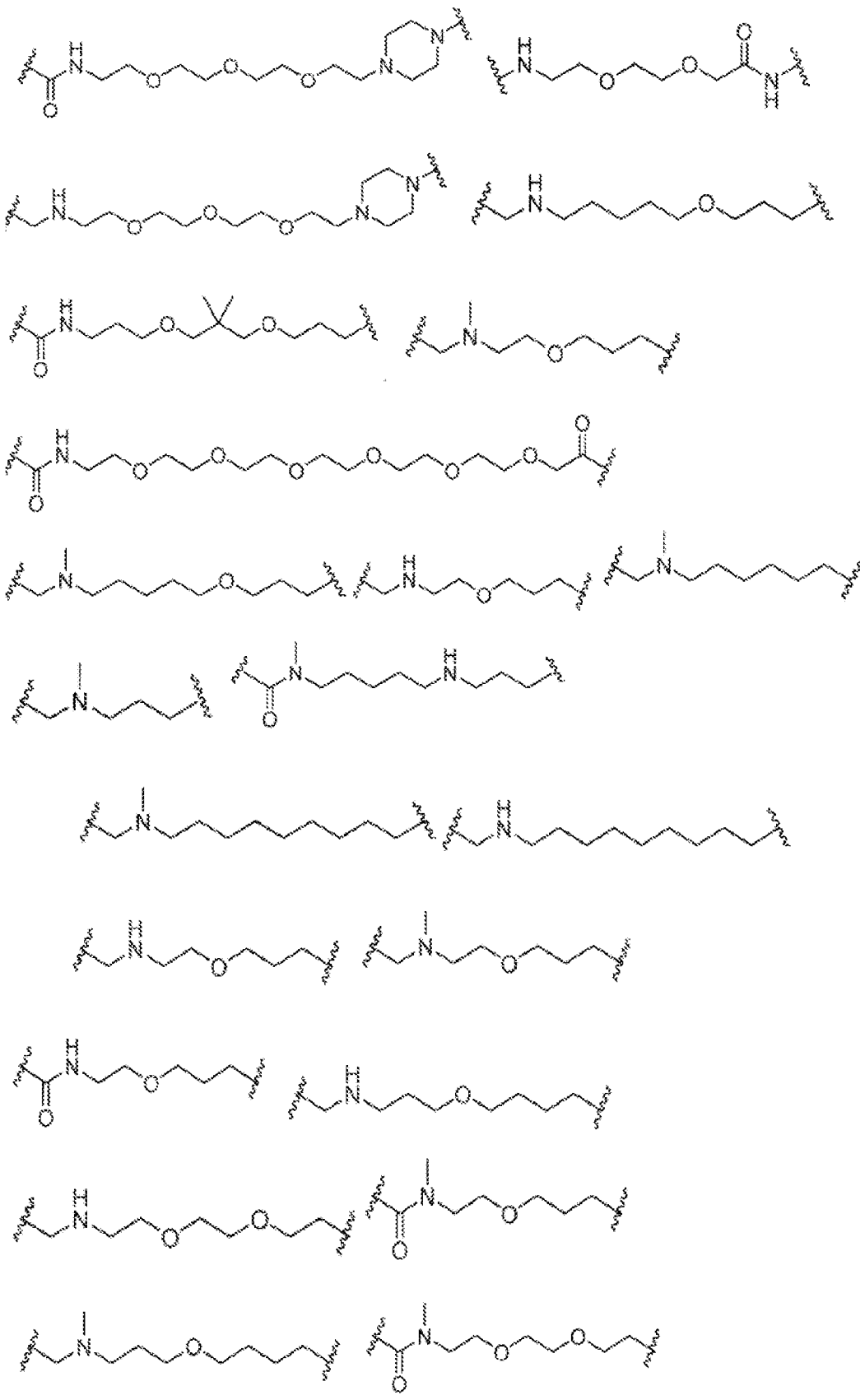


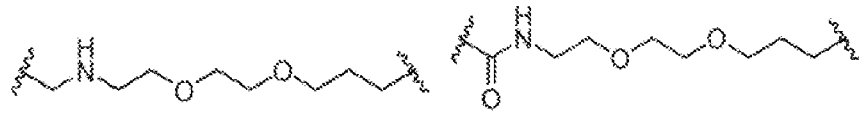


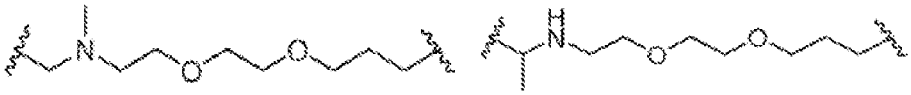


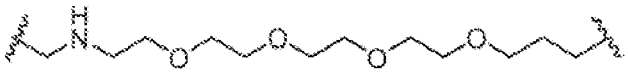


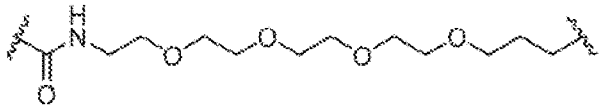


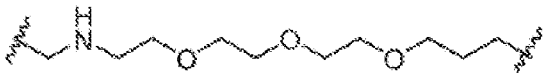


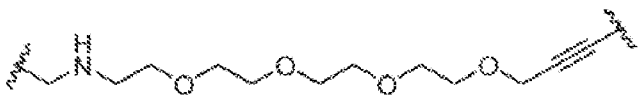


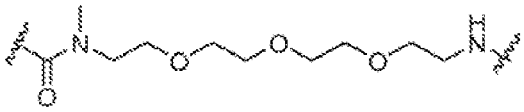


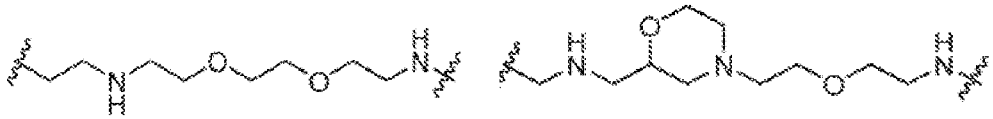


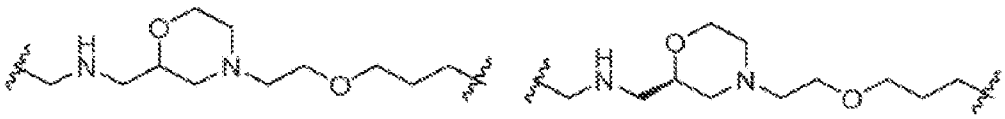


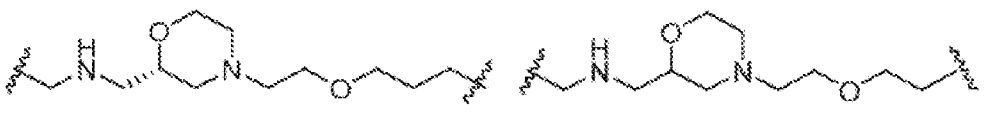


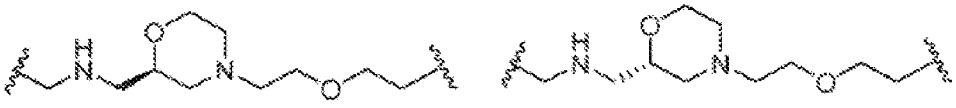


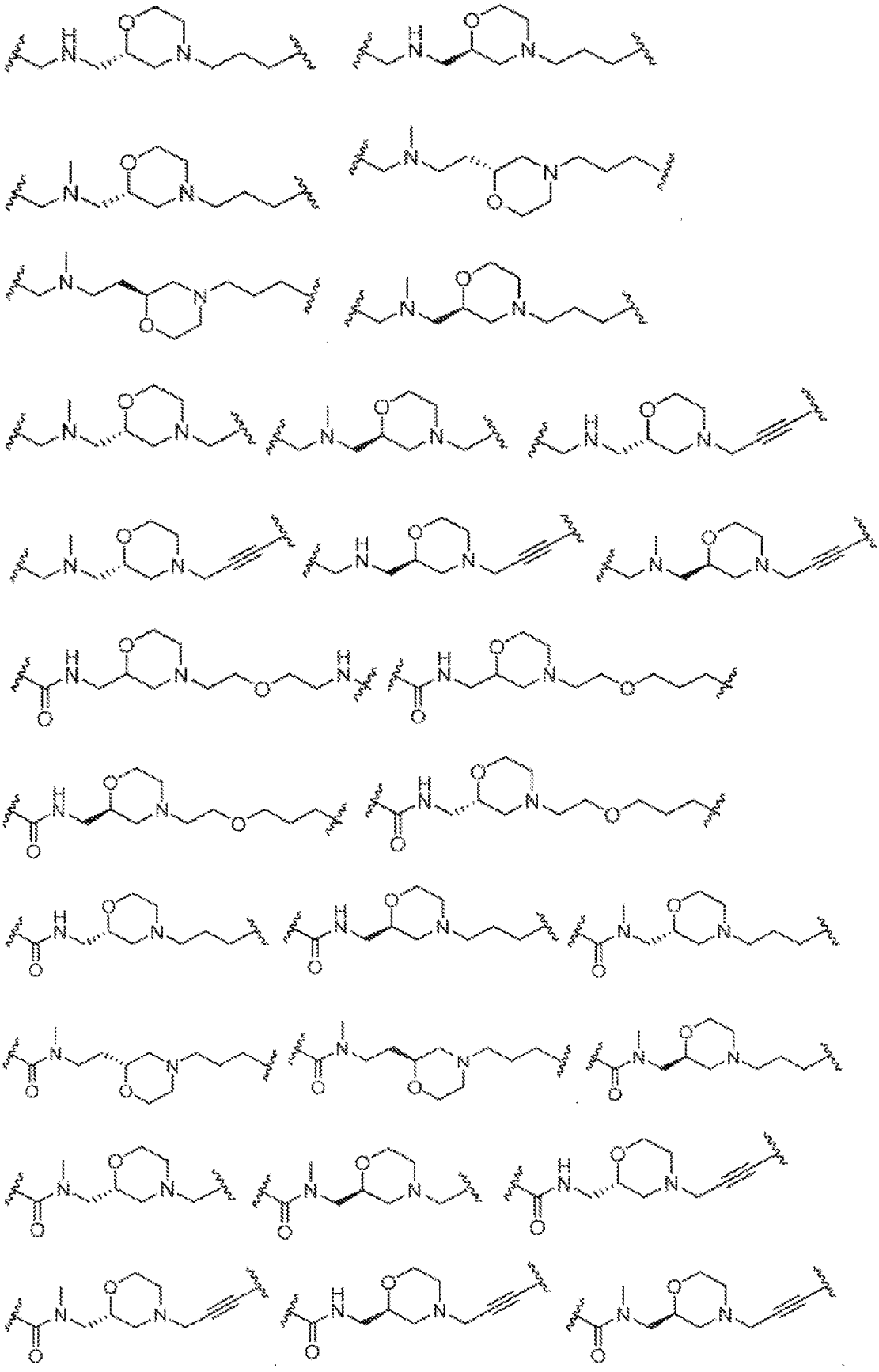


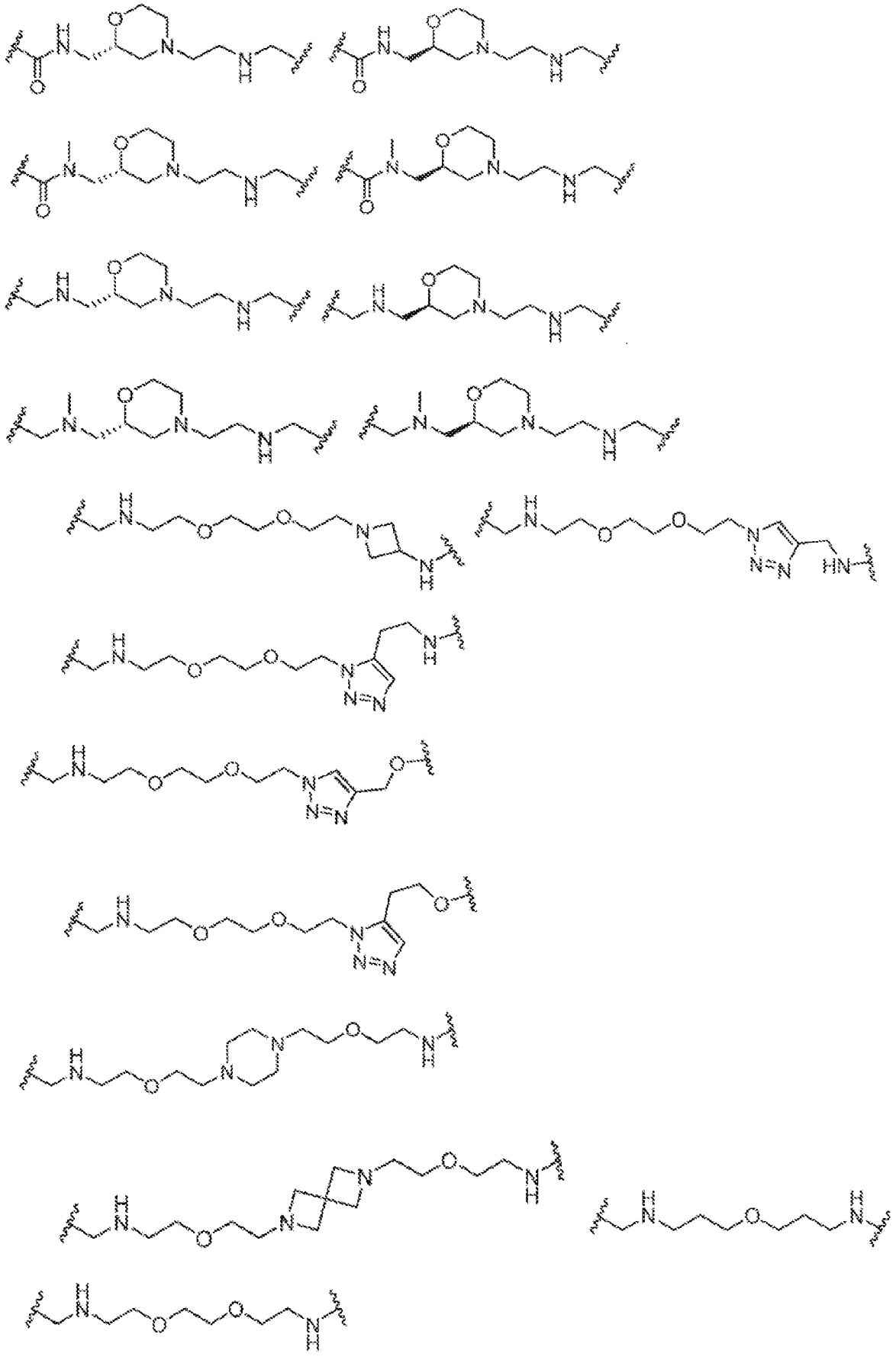


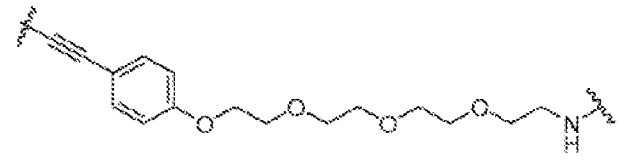


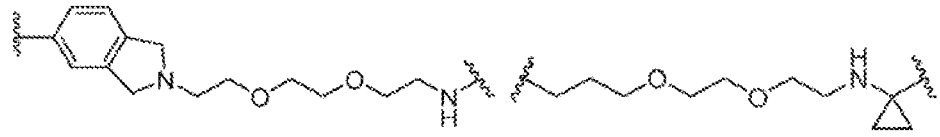


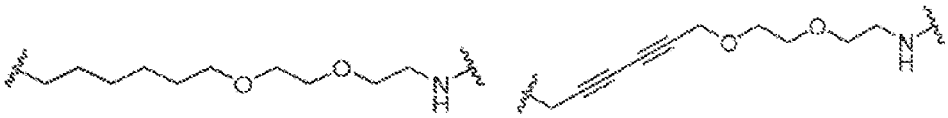


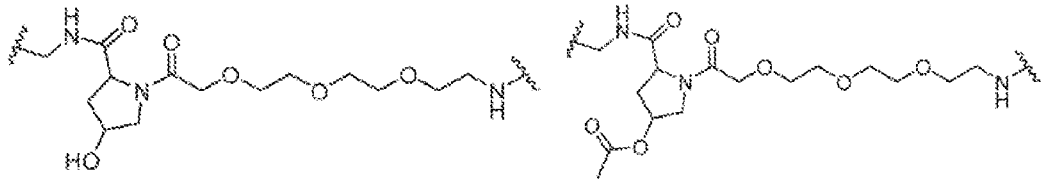


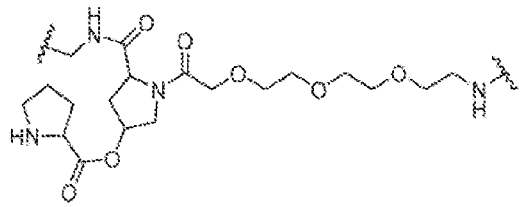


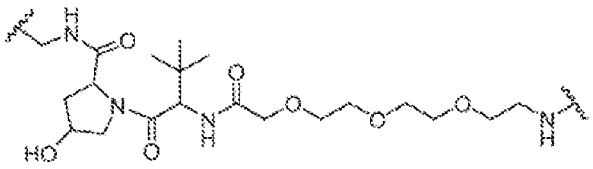


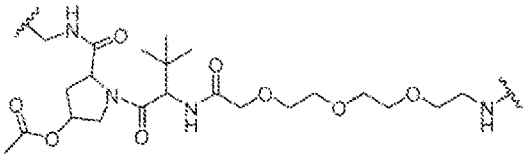


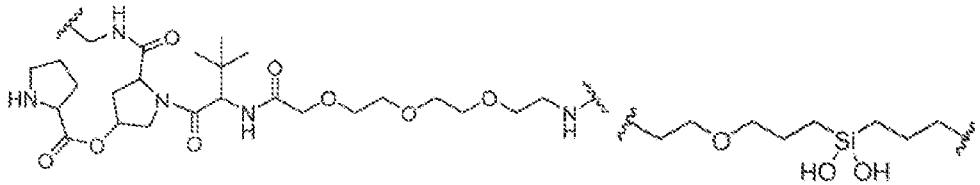


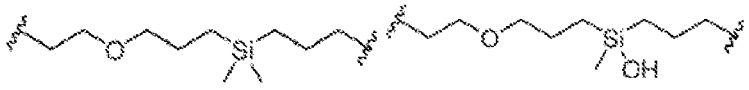


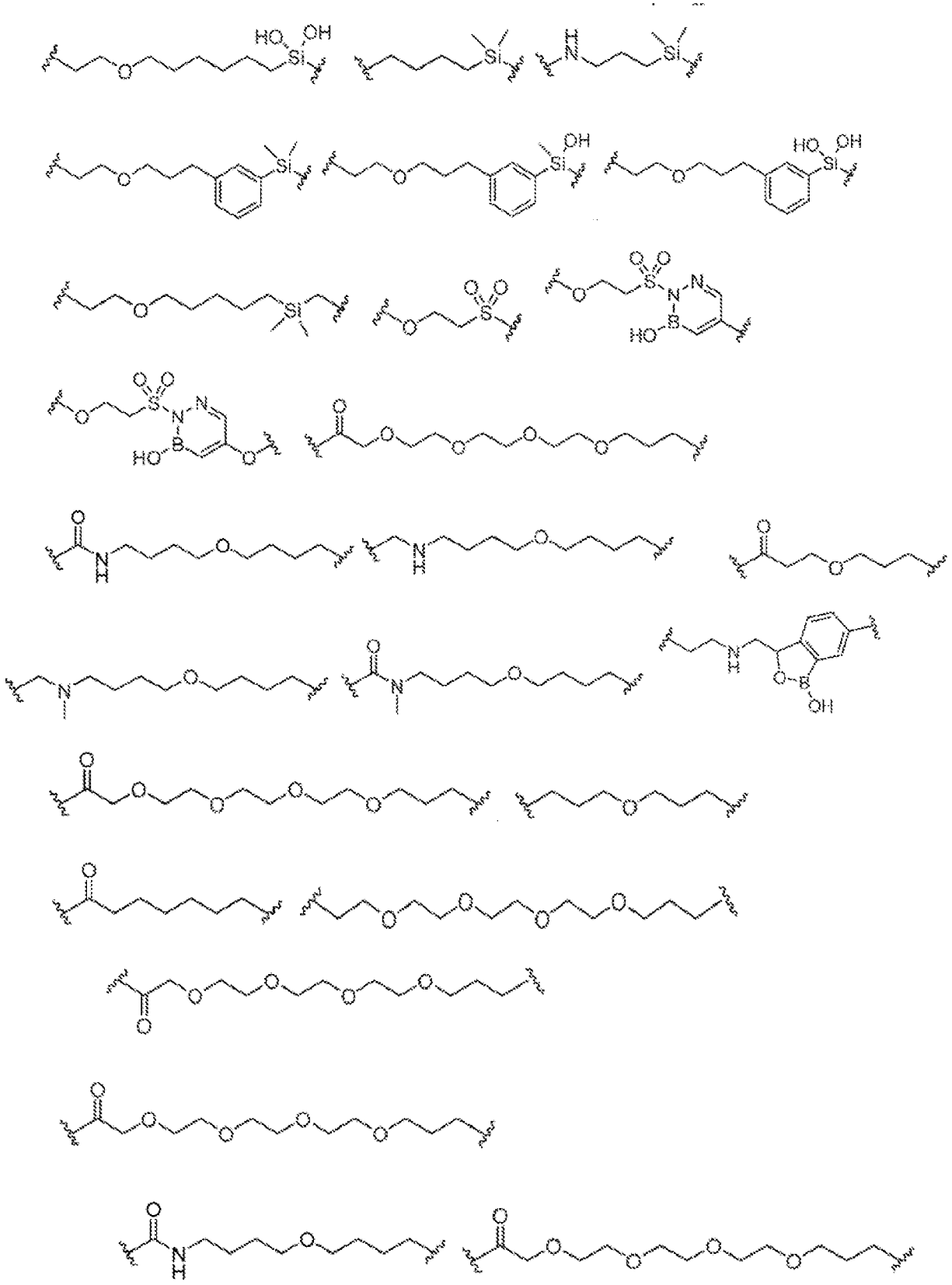


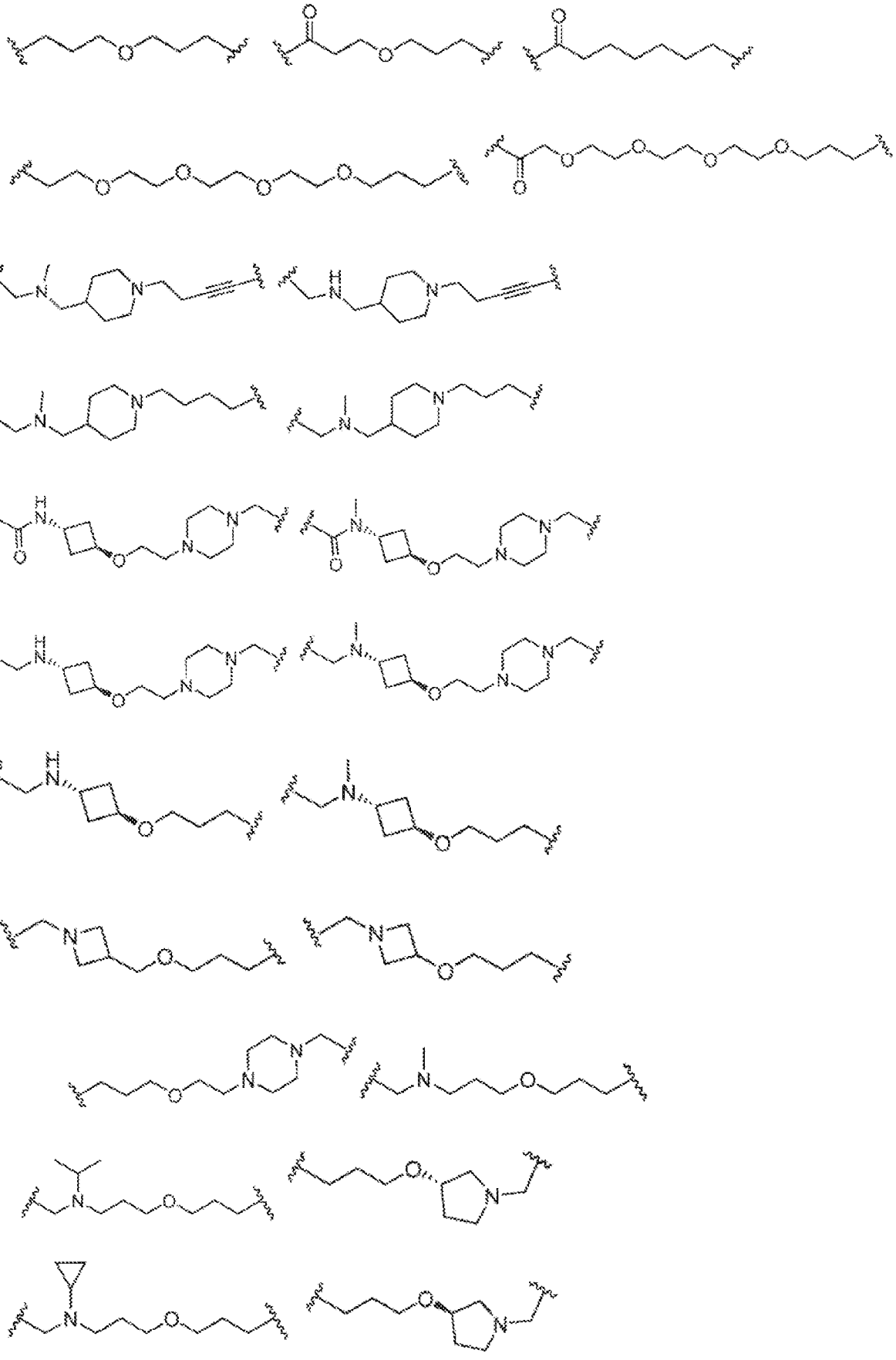


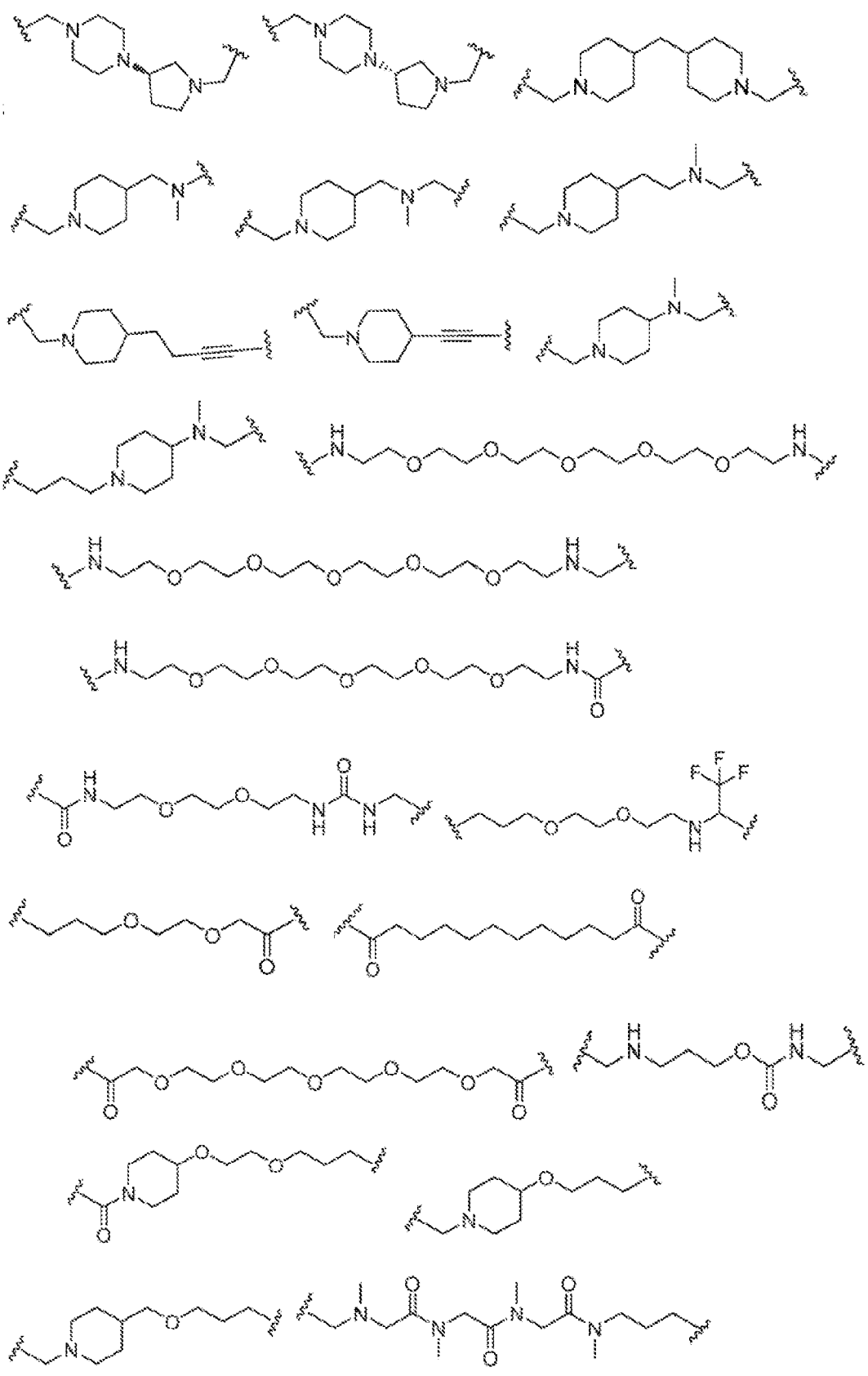


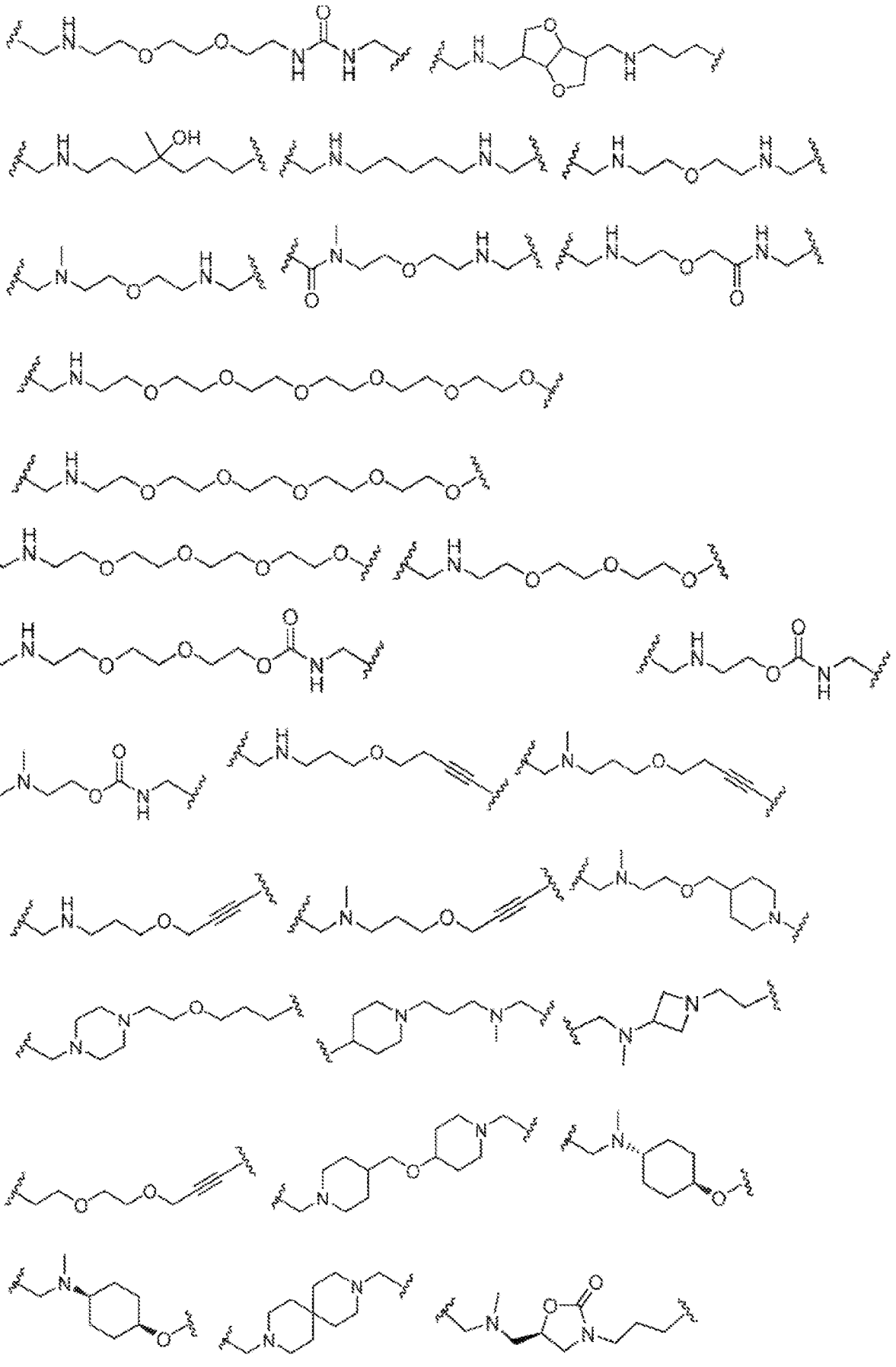


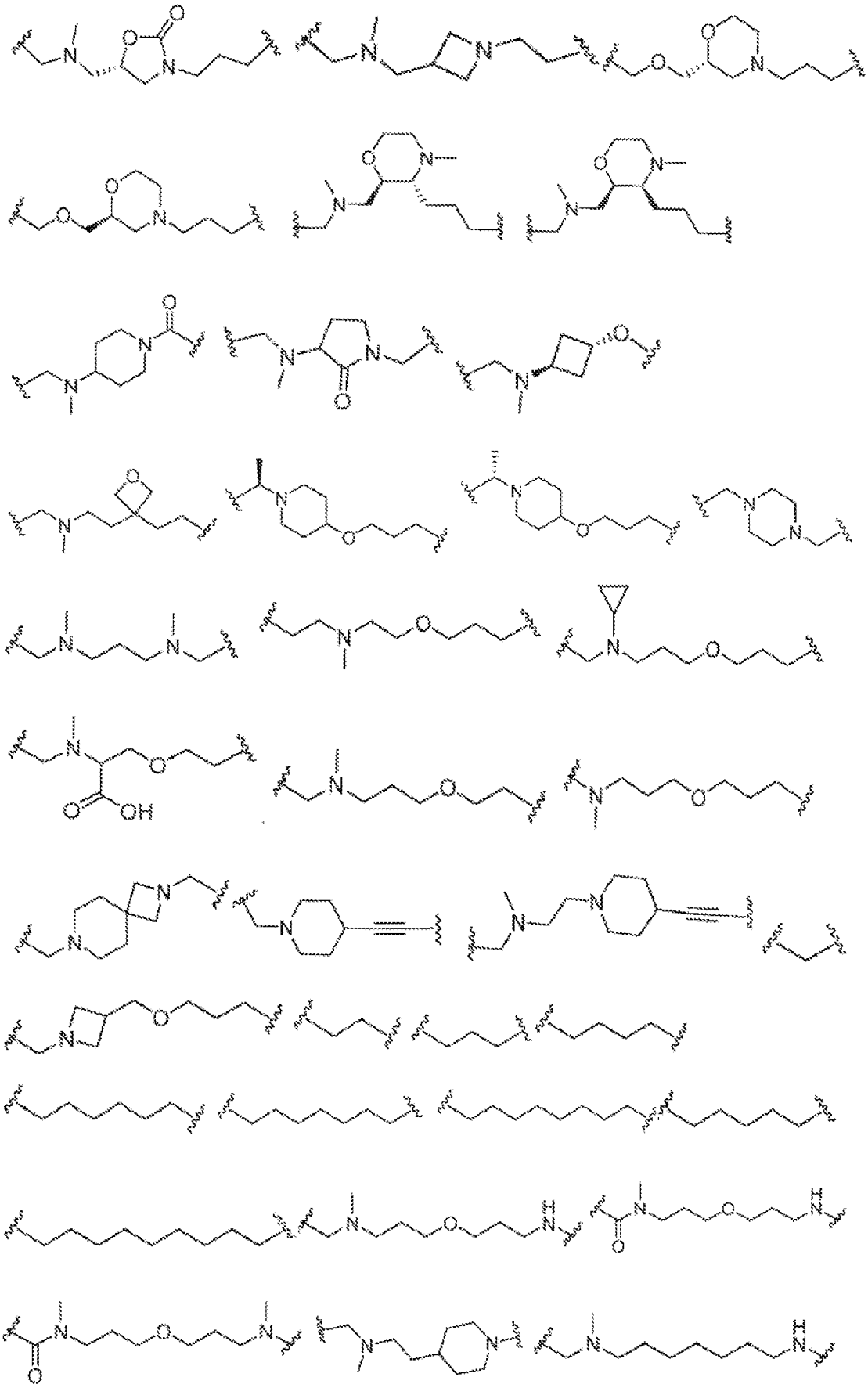


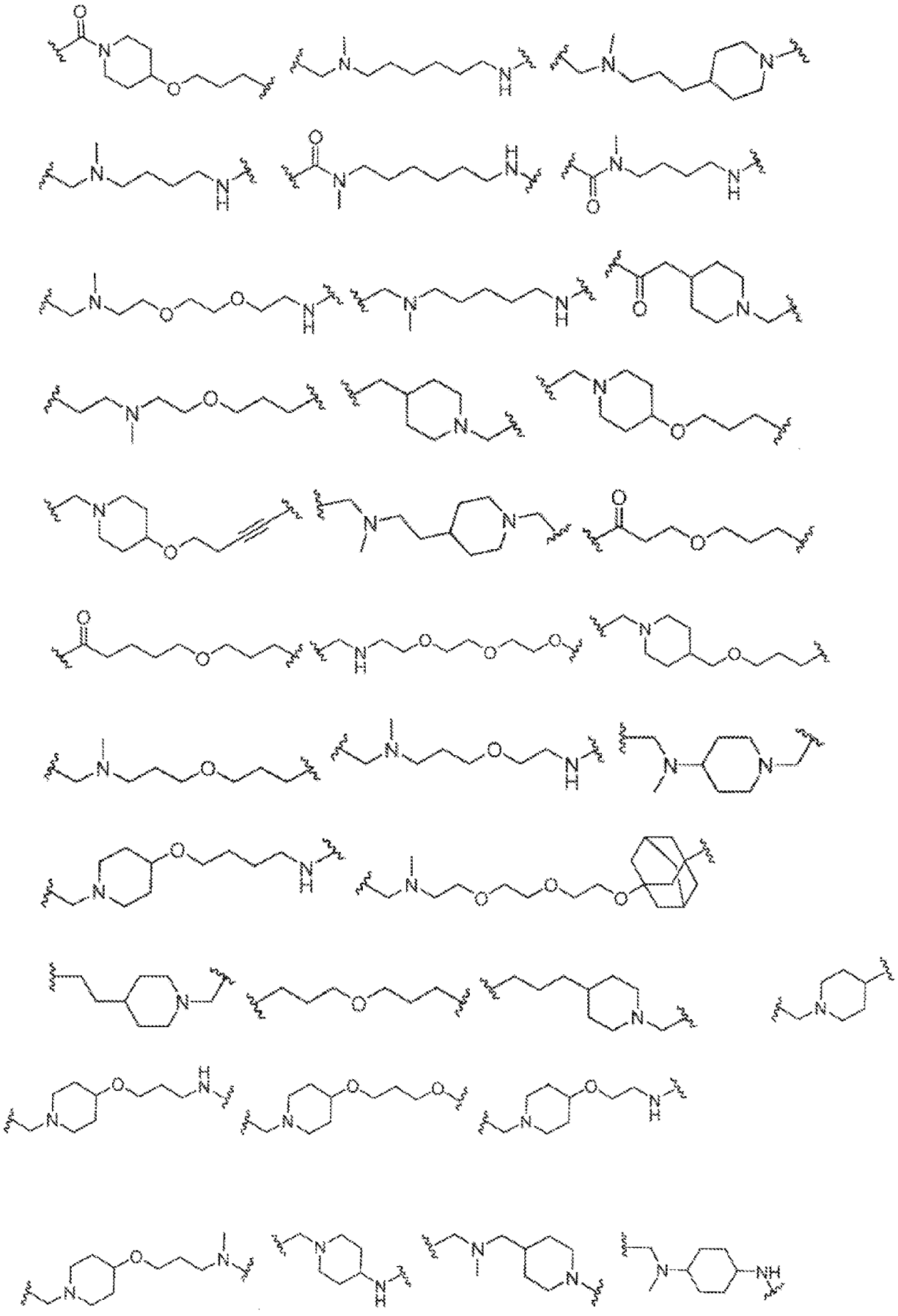


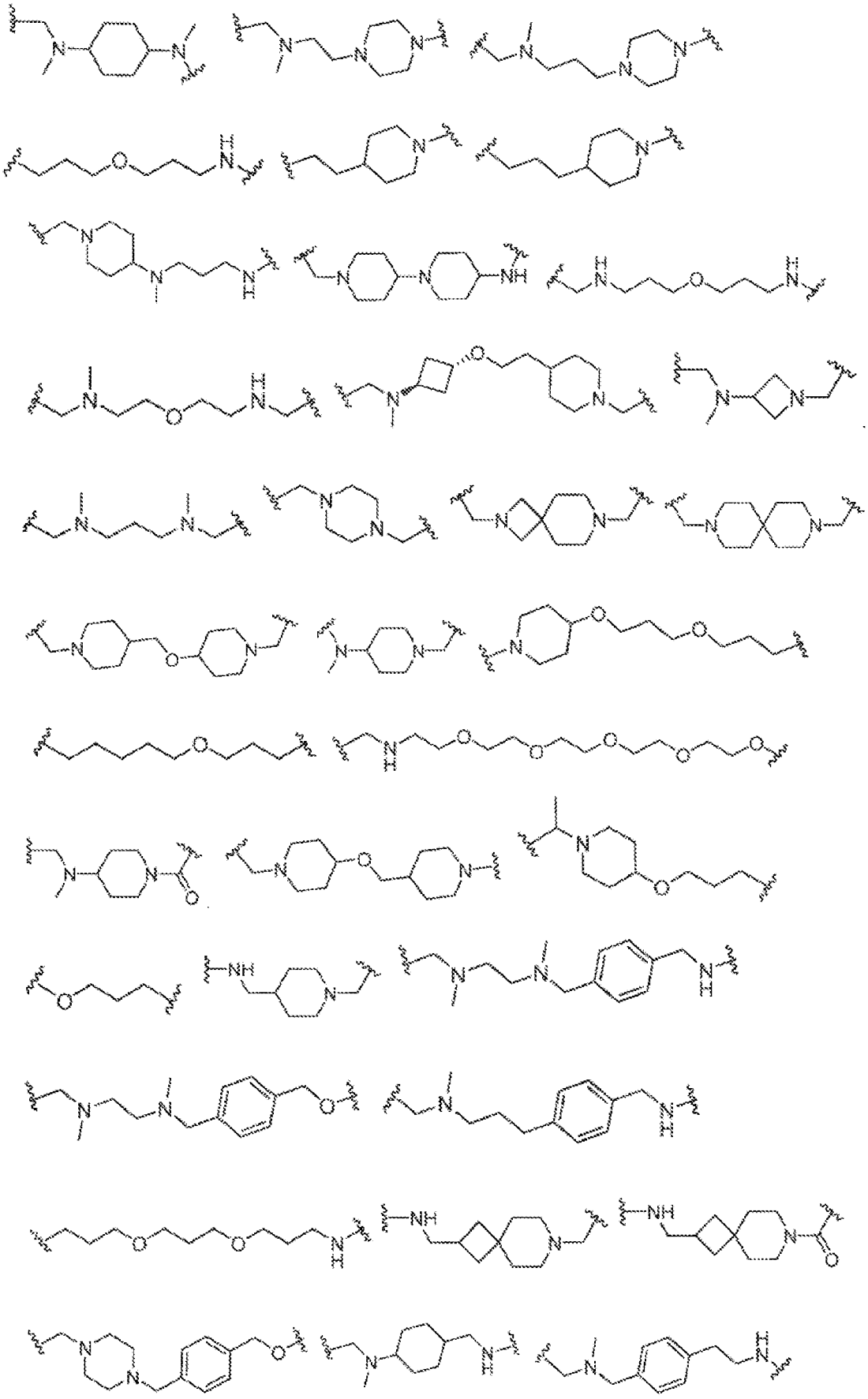


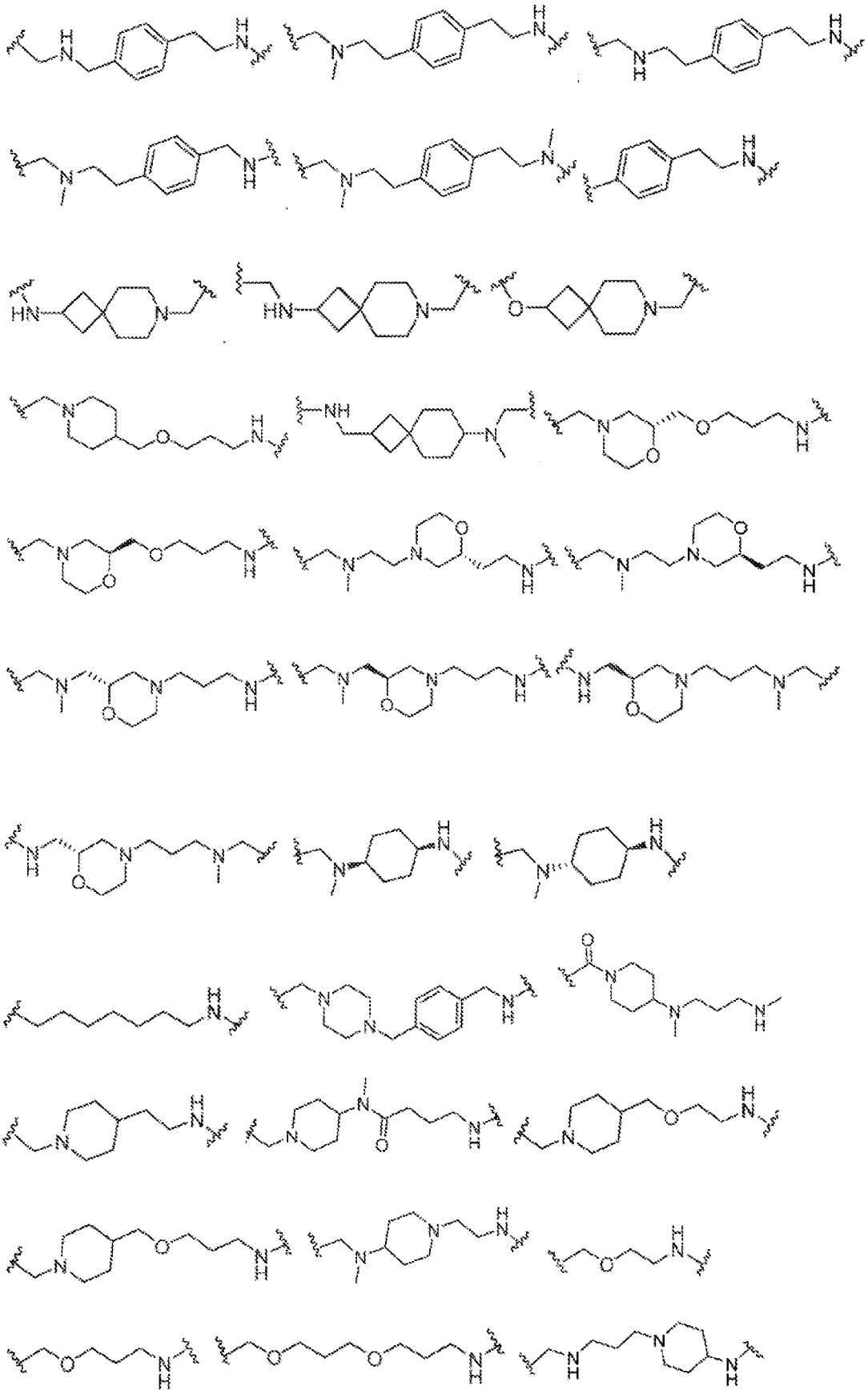


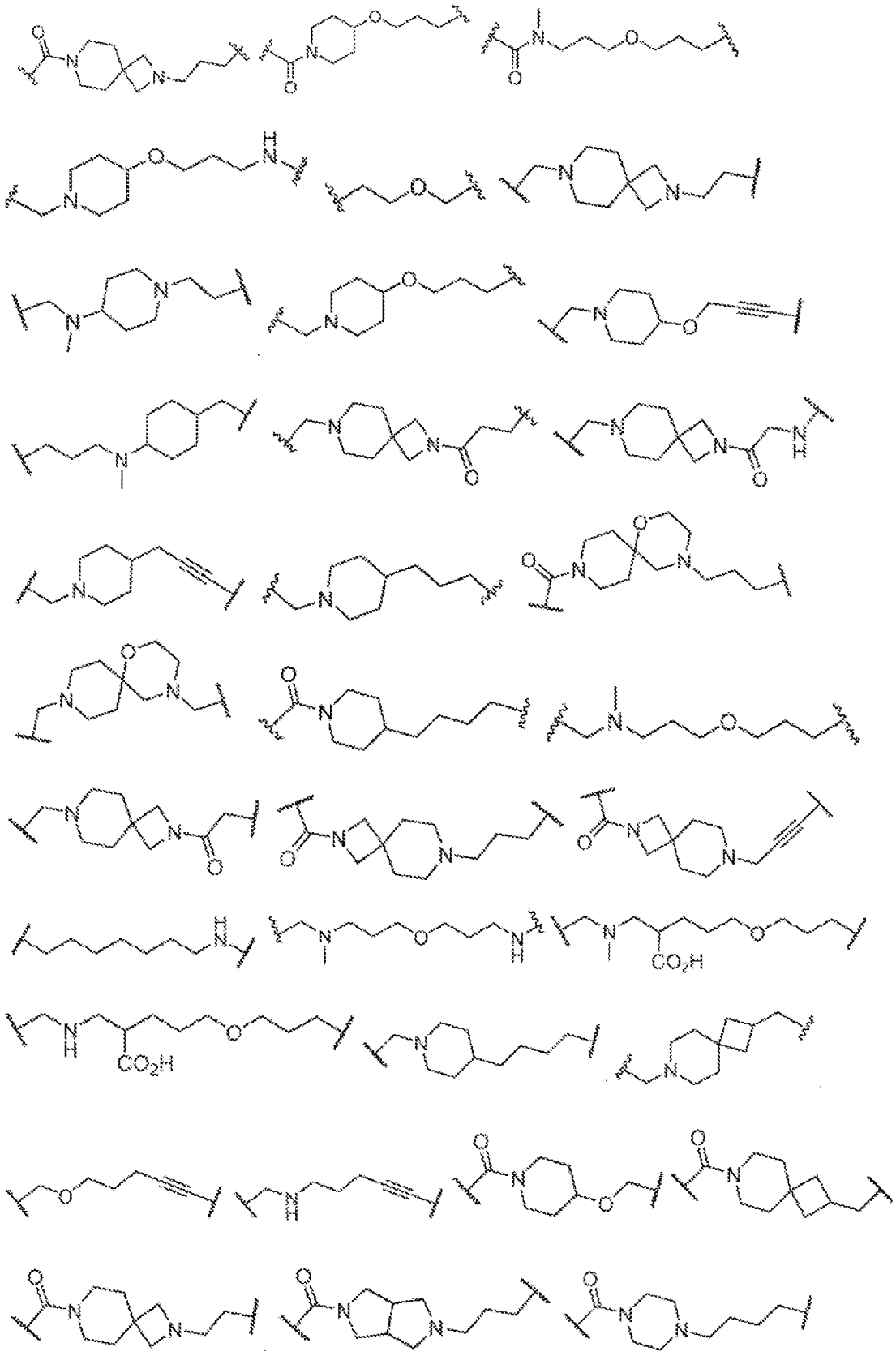


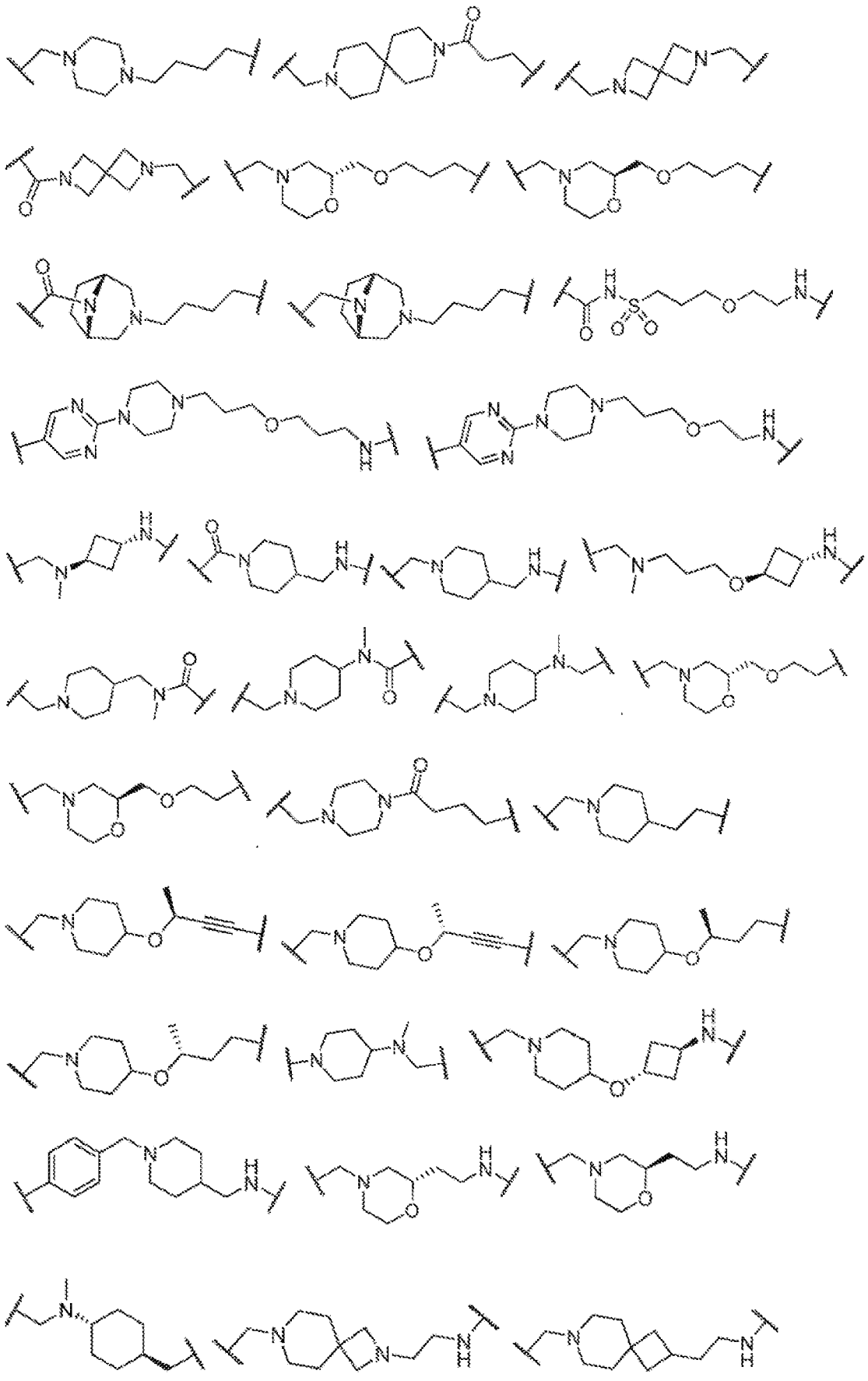


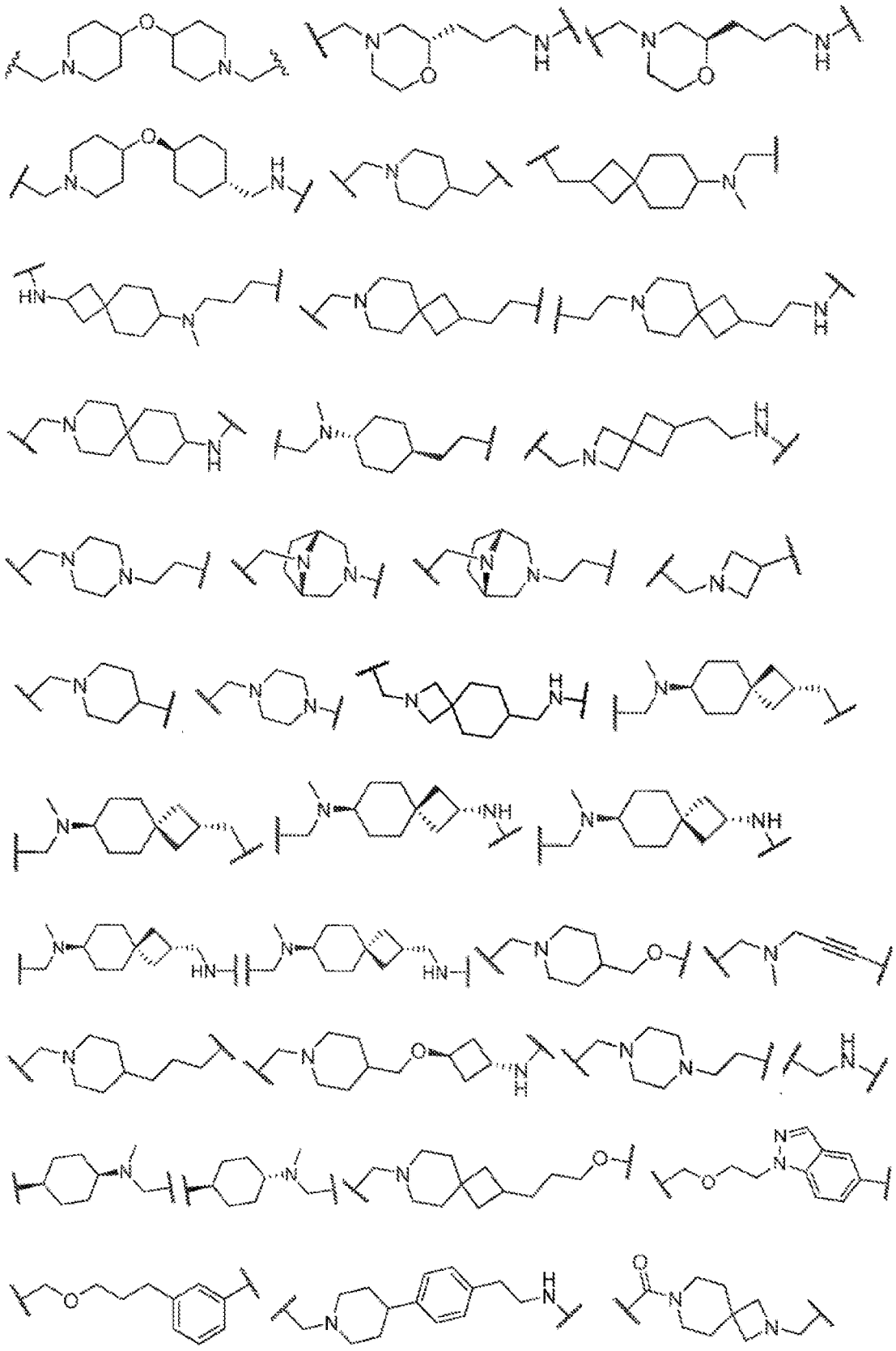


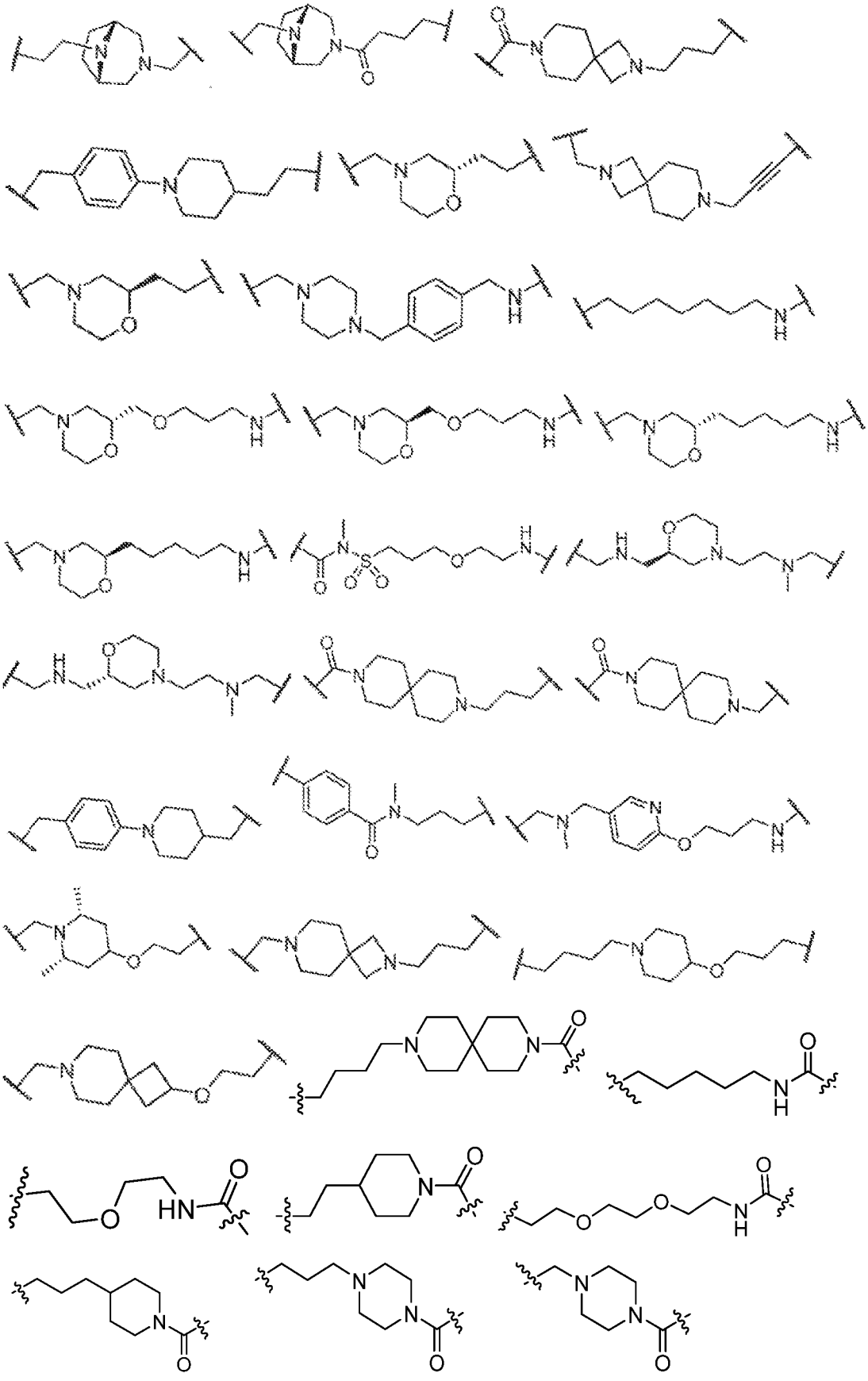


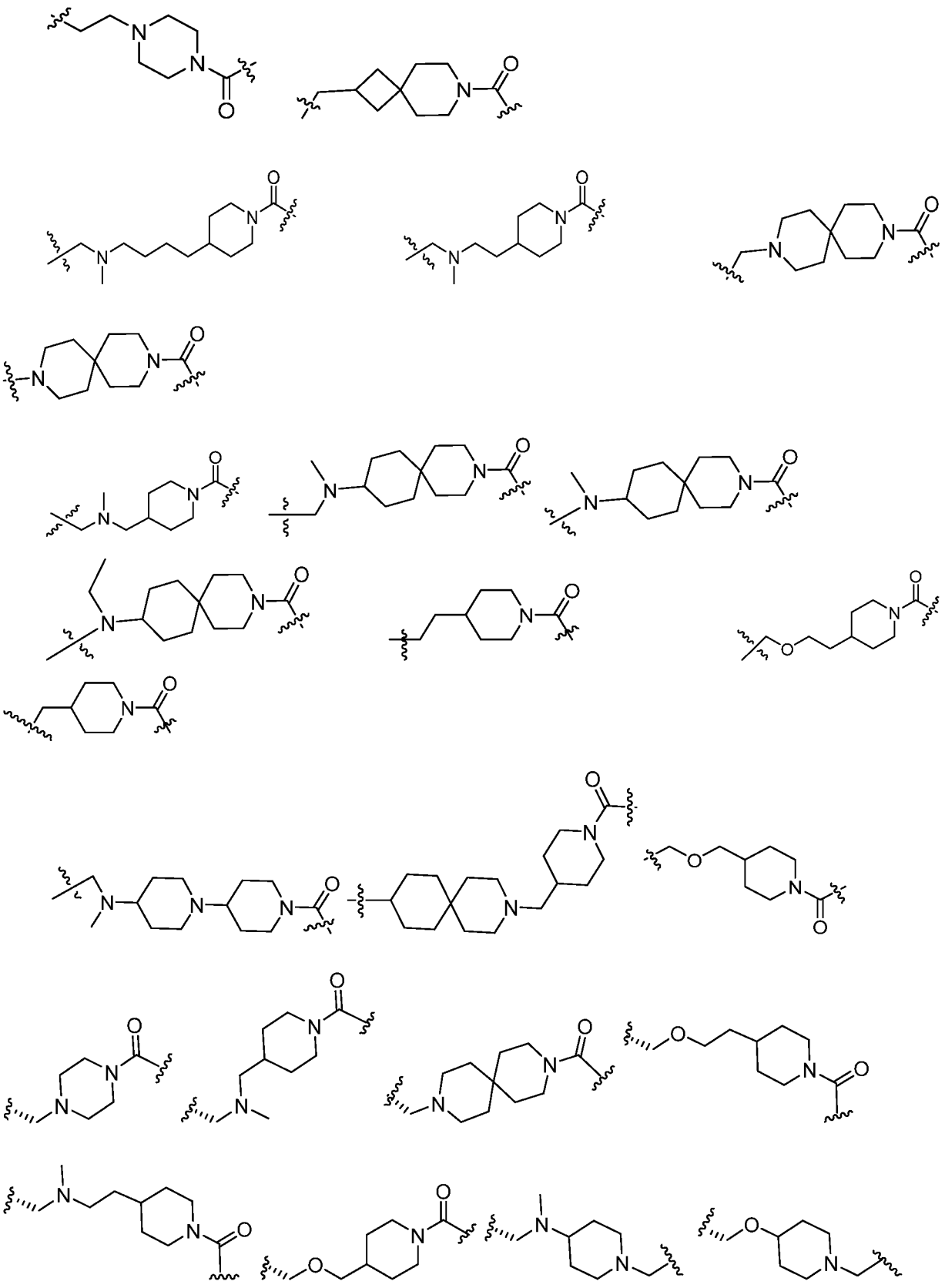


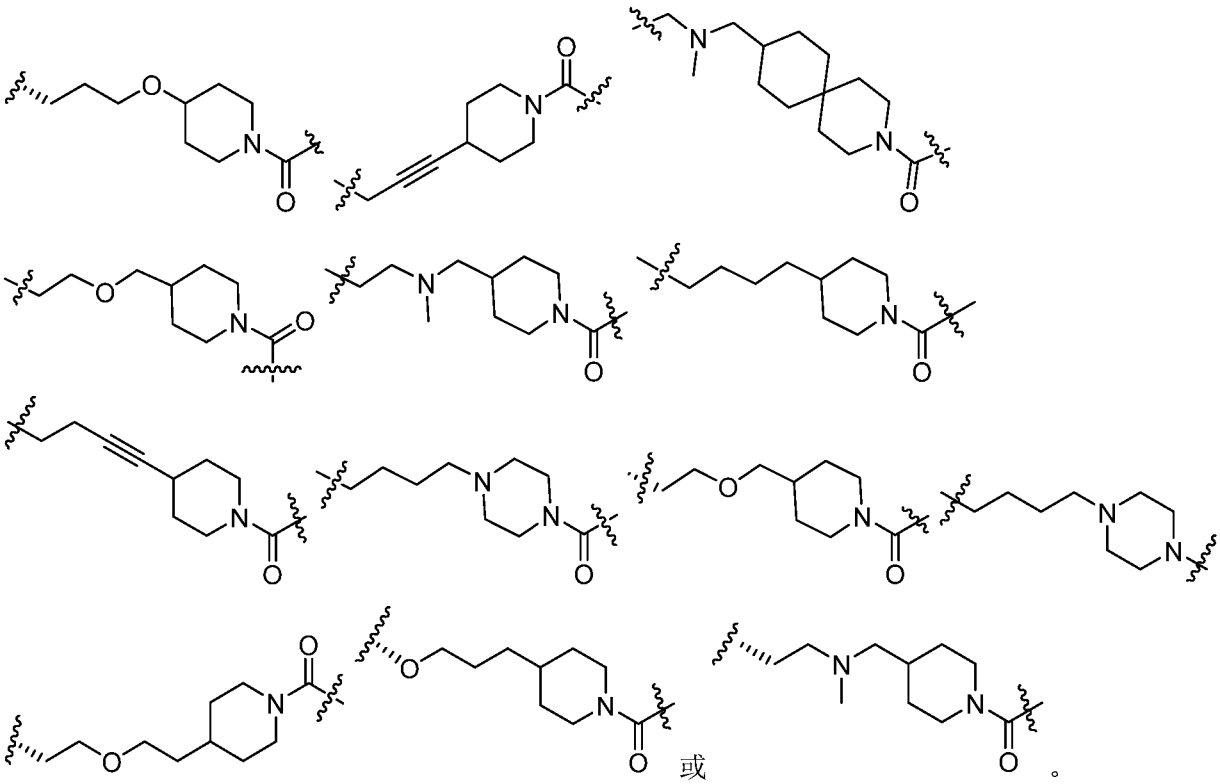






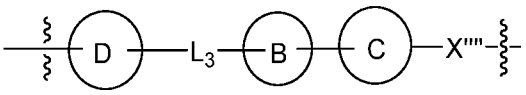






或。

优选的，本发明某些实施方式中，所述 L 为 LA，



LA

其中所述 LA 中：

环 D 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

环 B 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

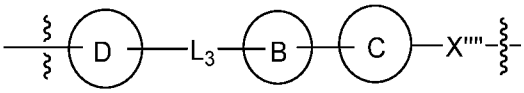
环 C 为不存在、C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

X""为键、-NH-、-NCH_3-、-O-、-$C(CH_3)_2$-、-S-、-C=C-、-C≡C-、-CHF-、-$CHCF_3$-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(O)O-、-OC(O)-、-C(O)NH-、-$C(O)NCH_3$-、-NHC(O)-或-$NCH_3C(O)$-；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基任选地被选自氘、-O-、-NH-、-N(C_1-C_6 烷基)-、-

N(C_1-C_6 卤代烷基)-、-N(C_1-C_6 羟基烷基)-或-N(C_3-C_8 环烷基)-替代，k 为 0、1、2、3、4、5、 6、7、8、9 或 10。

优选的，本发明某些实施方式中，所述 L 为 LA，



LA

其中所述 LA 中：

环 D 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

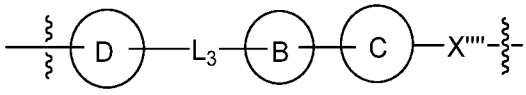
环 B 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

环 C 为不存在、C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

X""为键、-NH-、-NCH_3-、-O-、-$C(CH_3)_2$-、-S-、-C=C-、-C≡C-、-CHF-、-$CHCF_3$-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(O)O-、-OC(O)-、-C(O)NH-、-$C(O)NCH_3$-、-NHC(O)-或-$NCH_3C(O)$-；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基任选地被选自-O-、-NH-、-N(C_1-C_6 烷基)-、-N(C_1-C_6 卤代烷基)-、-N(C_1-C_6 羟基烷基)-或-N(C_3-C_8 环烷基)-替代，k 为 0、1、2、3、4、5、 6、7、8、9 或 10。

优选的，本发明某些实施方式中，所述 L 为 LA，



LA

其中所述 LA 中：

环 D 不存在、6-10 元芳基、5-10 元杂芳基或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

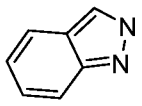
环 B 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷

基、C_1-C_6羟基烷基或-O-(C_1-C_6烷基)的取代基取代；

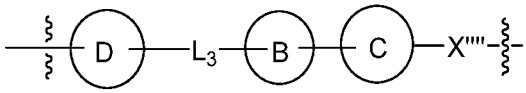
环 C 为不存在、C_3-C_{12}亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6羟基烷基或-O-(C_1-C_6烷基)的取代基取代；

X""为 键 、-NH-、-NCH_3-、-O-、-$C(CH_3)_2$-、-S-、-C=C-、-C≡C-、-CHF-、-$CHCF_3$-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(O)O-、-OC(O)-、-C(O)NH-、-$C(O)NCH_3$-、-NHC(O)-、-$(CH_2)_t$-或-$NCH_3C(O)$-；所述-$(CH_2)_t$-中的一个或多个亚甲基任选地被选自-O-、-NH-、-C≡C-、-N(C_1-C_6 烷基)-、-C(O)-替代，t 为 0、1、2、3、4、5、6 或 7。

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基任选地被选自-O-、-NH-、-N(C_1-C_6烷基)-、-N(C_1-C_6卤代烷基)-、-N(C_1-C_6羟基烷基)-、-C≡C-、-C(O)-或-N(C_3-C_8环烷基)-替代，k 为 0、1、2、3、4、5、6、7、8、9 或 10。优选的，本发明某些实施方式中，当环 A"为含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元双环杂芳基，环 D 为 6-10 元芳基、5-10 元杂芳基、C_3-C_{12}亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6烷基、C_1-C_6卤代烷基、C_1-C_6羟基烷基和-O-(C_1-C_6烷基)的取代基取代。

优选的，本发明某些实施方式中，当环 A"为  时，所述环 D 为 C_3-C_{12}亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基独立地被 1 个、2 个或 3 个羟基或被 1 个、2 个或 3 个-O-(C_1-C_6烷基)取代。

本发明某些实施方式中，所述 L 为 LA，



LA

其中所述 LA 为方案 1、方案 2、方案 3 或方案 4

方案 1、

环 D 为 C_3-C_{12}亚环烷基或含有 1-2 个 N 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、-O-(C_1-C_6烷基)或羟基；

环 B 为 C_3-C_{12}亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6烷基、C_1-C_6卤代烷基、C_1-C_6羟基烷基或-O-(C_1-C_6烷基)的取代基取代；

环 C 为不存在；

X""为-C(O)-；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基任选被选自-O-、-NH-、-N(C_1-C_6烷基)-、-N(C_1-C_6

卤代烷基)-、-C(O)-、-N(C_1-C_6羟基烷基)-或-N(C_3-C_8环烷基)-替代，k为0、1、2、3、4、5、6、7、8、9或10；

方案2、

环D为C_3-C_{12}亚环烷基或含有1-2个N杂原子的3-12元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、甲氧基或羟基；

环B为含有1个或者2个氮杂原子的7-11元的亚螺杂环烷基或者亚稠杂环烷基；

环C为不存在；

X""为-C(O)-；

L_3为-$(CH_2)_k$-，k为1、2、3、4、5、6、7、8、9或10；

方案3、

环D为C_3-C_{12}亚环烷基或含有1-2个N杂原子的3-12元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、羟基或甲氧基；

环B为含有1-2个选自N、O或S杂原子的3-12元亚杂环烷基；

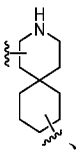
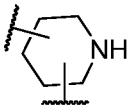
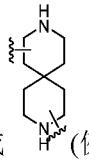
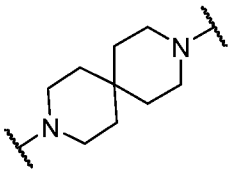
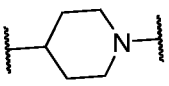
环C为不存在；

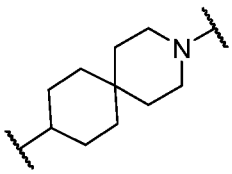
X""为-C(O)-；

L_3为-$(CH_2)_k$-，k为1、2、3或4。

方案4、

环D为亚环己基或含有1-2个N杂原子的6元亚杂环烷基，所述亚环己基和6元亚杂环烷基任选被选自卤素、羟基或甲氧基；

环B为  、  或  (例如  、 

)；

环C为不存在；

X""为-C(O)-；

L_3为-$(CH_2)_k$-，所述L_3中的一个或两个亚甲基被选自-O-、-NH-、-N(C_1-C_6烷基)-、-N(C_1-C_6卤代烷基)-、-C(O)-、-N(C_1-C_6羟基烷基)-或-N(C_3-C_8环烷基)-替代，k为1、2、3或4。

优选的，本发明某些实施方式中，所述LA中，环D不存在。

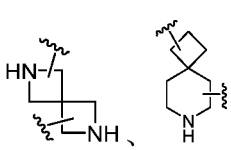
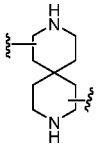
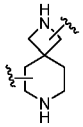
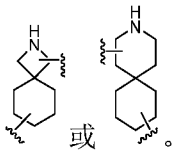
优选的，本发明某些实施方式中，所述 LA 中，环 D 为含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基、含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 D 为 6-10 元芳基、含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基、含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 D 为含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基、含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 D 为含有 1 个或者 1 个氮杂原子的 7-11 元的亚螺杂环烷基。

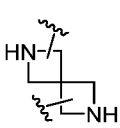
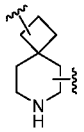
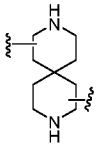
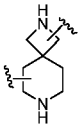
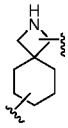
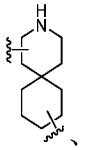
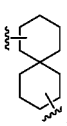
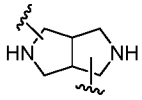
优选的，本发明某些实施方式中，所述 LA 中，环 D 为含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 D 为  、、  、  、  或。

优选的，本发明某些实施方式中，所述 LA 中，环 B 不存在。

优选的，本发明某些实施方式中，所述 LA 中，环 B 为含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基、含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 B 为含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基。

优选的，本发明某些实施方式中，所述LA中，环B为亚哌啶基、亚哌嗪基、  、  、  、  、  、  、  或  。

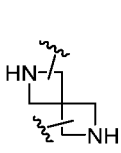
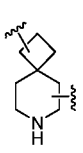
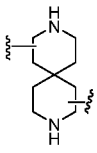
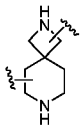
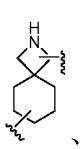
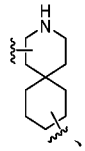
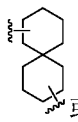
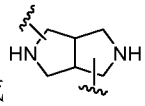
优选的，本发明某些实施方式中，环 C 为 4-11 元的饱和或部分不饱和的亚螺环烷基、4-11 元的饱和或部分不饱和的亚稠环烷基、8-10 元双环饱和或部分不饱和的亚环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-7 元饱和或部分不饱和的亚杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原

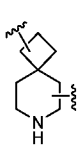
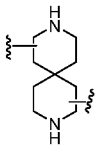
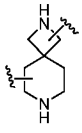
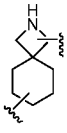
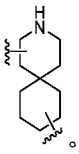
子的 4-11 元饱和或部分不饱和的亚螺杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和/或部分不饱和的亚稠杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 8-10 元双环饱和/或部分不饱和的亚杂环烷基，所述环烷基和杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6烷基、C_1-C_6卤代烷基、C_1-C_6羟基烷基和-O-(C_1-C_6烷基)的取代基取代。

优选的，本发明某些实施方式中，所述 LA 中，环 C 为 3-7 元饱和或部分不饱和的亚环烷基、4-11 元的饱和或部分不饱和的亚螺环烷基、4-11 元的饱和或部分不饱和的亚稠环烷基、8-10 元双环饱和或部分不饱和的亚环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-7 元饱和或部分不饱和的亚杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和或部分不饱和的亚螺杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和/或部分不饱和的亚稠杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 8-10 元双环饱和/或部分不饱和的亚杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 C 为含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基、含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 C 为含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基。

优选的，本发明某些实施方式中，所述 LA 中，环 C 为  、  、  、  、  、  、  或  。

优选的，本发明某些实施方式中，所述 LA 中，环 C 为  、  、  、  或  。

优选的，本发明某些实施方式中，所述 LA 中，X""为键、-CH_2-或-C(O)-。

优选的，本发明某些实施方式中，所述 LA 中，X""为键或-C(O)-。

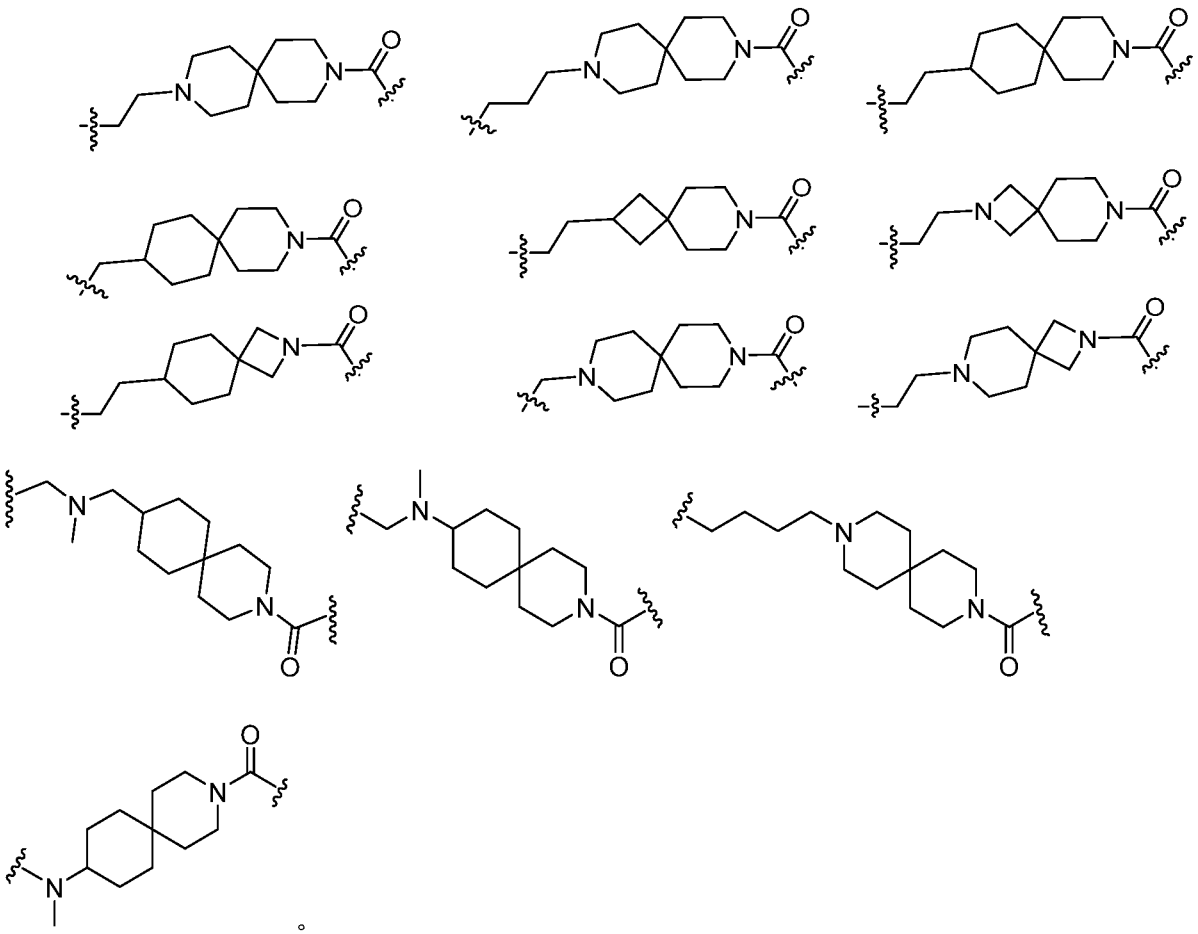
优选的，本发明某些实施方式中，所述 LA 中，X""为-C(O)-。

优选的，本发明某些实施方式中，所述 LA 中，L_3为-$(CH_2)_k$-，所述 L_3 中一个亚甲基任选地被选自-O-、-NH-、-NCH_3-或-NCH_2CH_3-的基团替代；k 为 1、2、3 或者 4。

优选的，本发明某些实施方式中，所述 LA 中，L_3为-$(CH_2)_k$-，所述 L_3 中一个或两个亚甲基任选地被选自氘-C(O)-、-O-、-NH-、-NCH_3-或-NCH_2CH_3-的基团替代；k 为 1、2、3 或者 4。

优选的，本发明某些实施方式中，所述 LA 中环 D 和环 B 不存在，环 C 为含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基；X""为-C(O)-；L_3 为-$(CH_2)_k$-；k 为 1、2、3、4 或者 5。

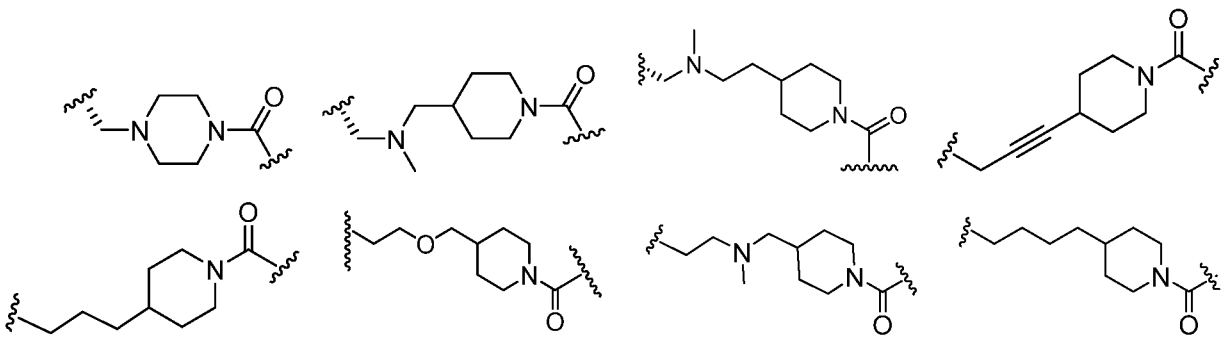
优选的，本发明某些实施方式中，式 L 选自

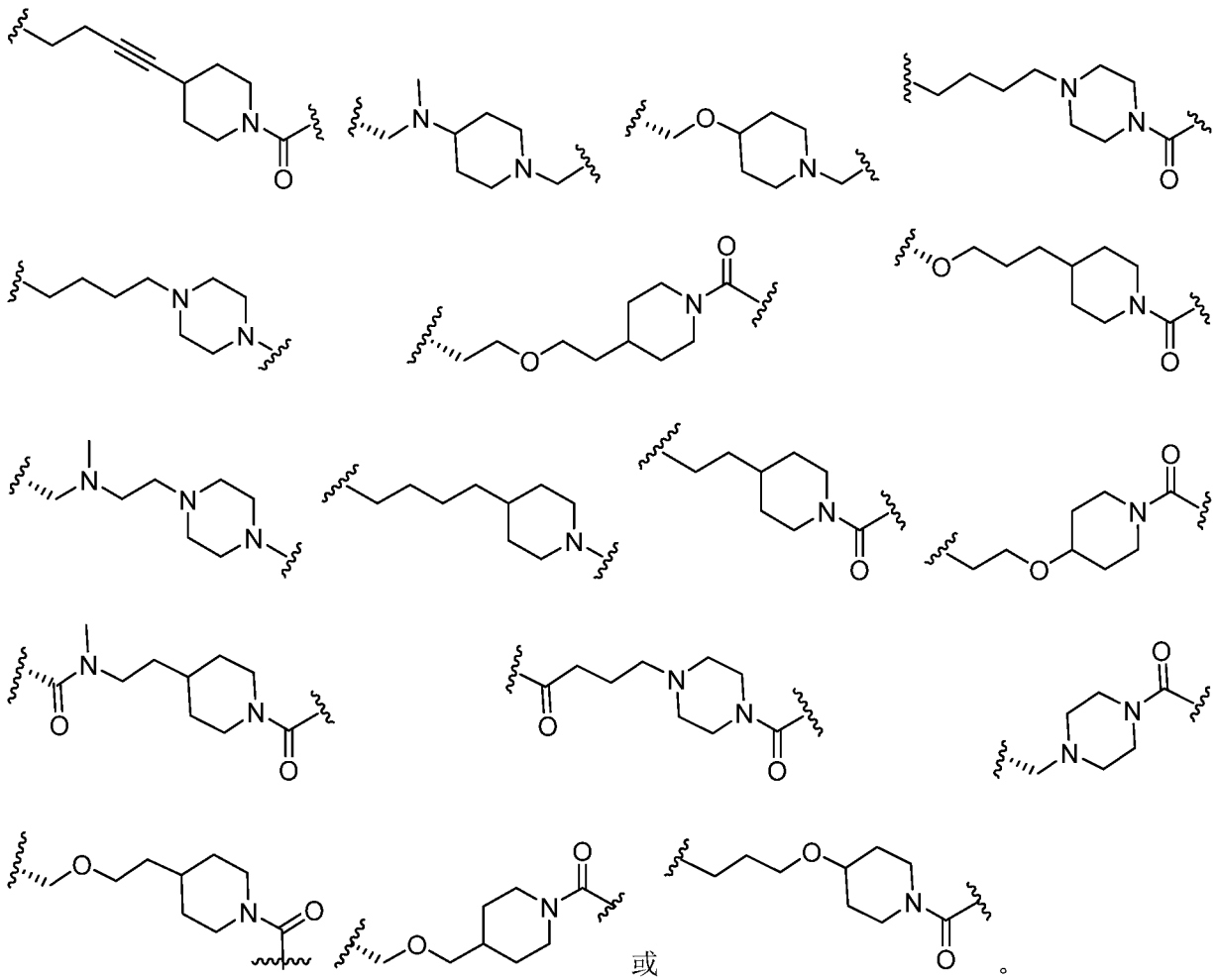


。

优选的，本发明某些实施方式中，所述 LA 中环 D 和环 B 不存在，环 C 为含有 1 个或者 2 个氮杂原子的 4-7 元的杂环烷基；X""为-C(O)-、键或-CH_2-；L_3 为-$(CH_2)_k$-；k 为 1、2、3、4 或者 5。

优选的，本发明某些实施方式中，式 L 选自

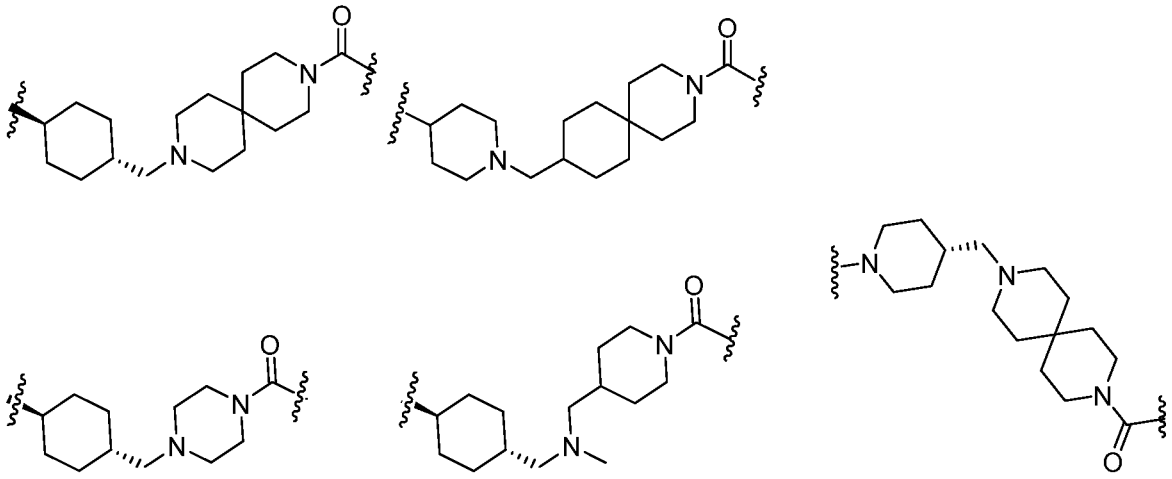


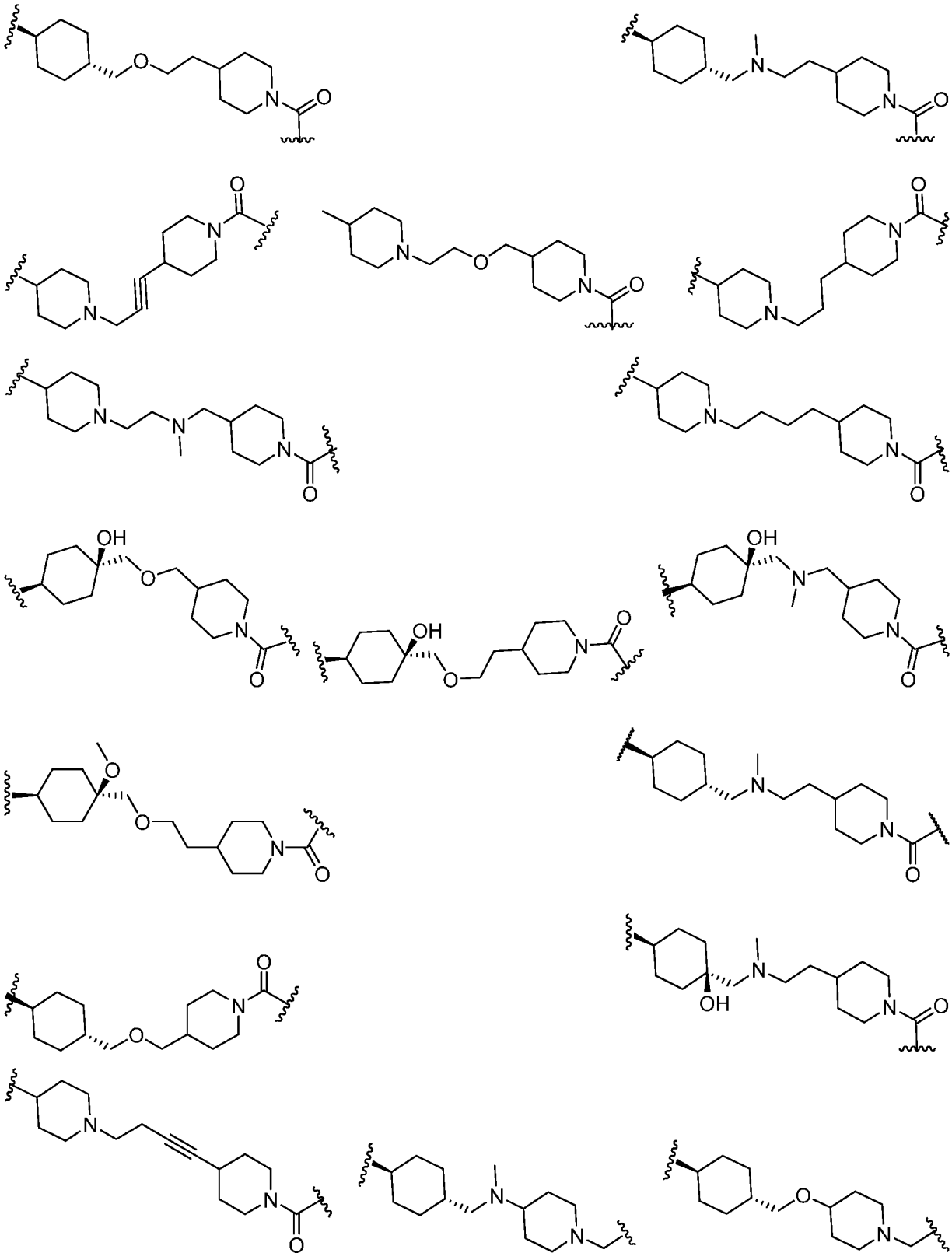


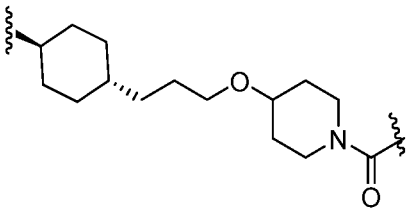
或 。

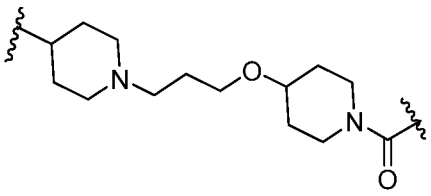
优选的，本发明某些实施方式中，所述 LA 中环 D 为 C_4-C_7 元环烷基或 4-7 元杂环烷基；环 B、环 C 为不存在或为含有 1 个或者 2 个氮杂原子的 5-11 元的亚杂环烷基；X""为-C(O)-或-$(CH_2)_t$-，t 为 0、1、2、3、4 或 5；L_3 为-$(CH_2)_k$-，k 为 1、2、3、4 或者 5。

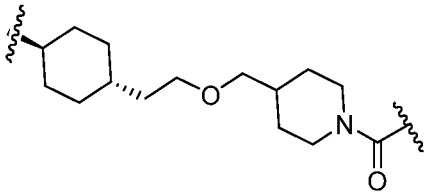
优选的，本发明某些实施方式中，式 L 选自

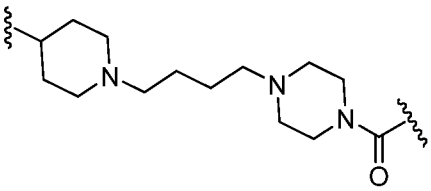


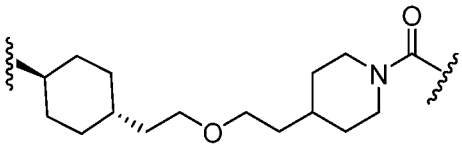


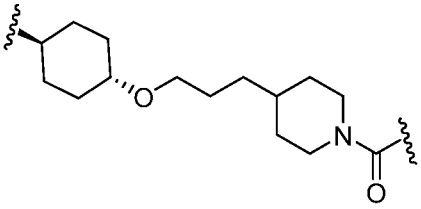


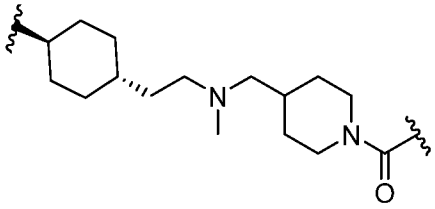


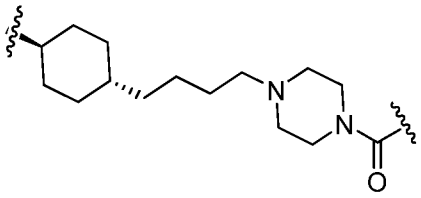


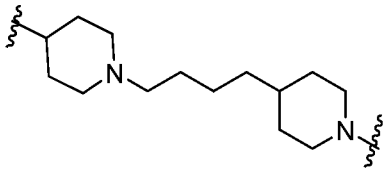


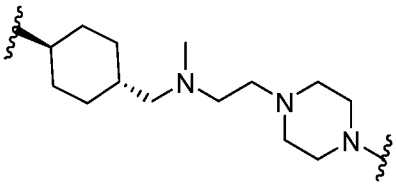


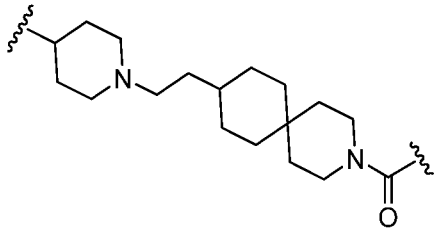


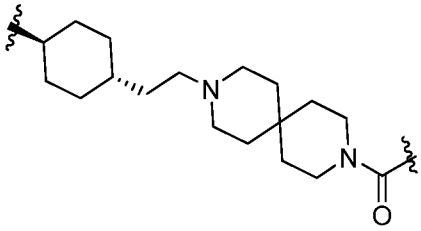


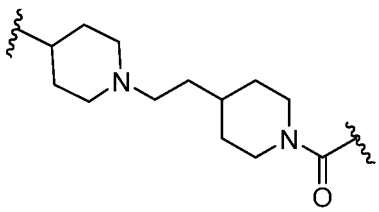


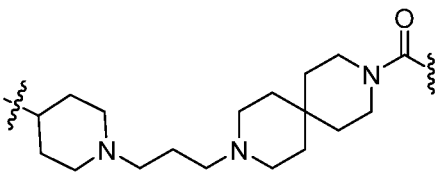


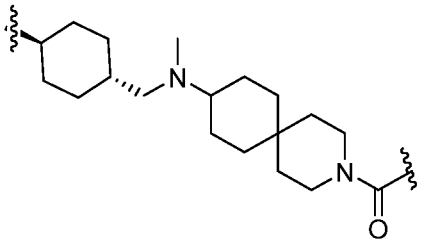


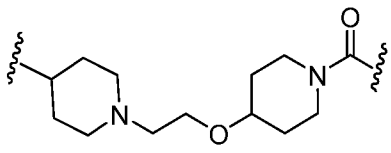


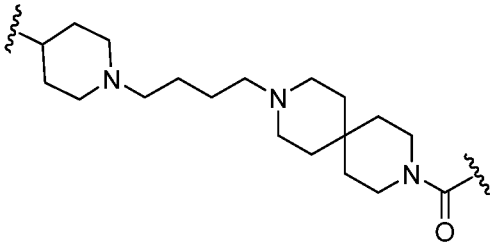


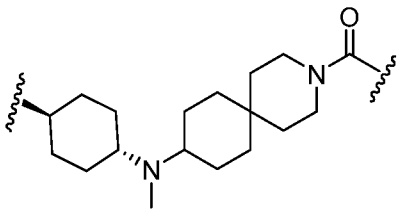


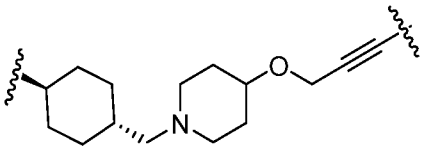


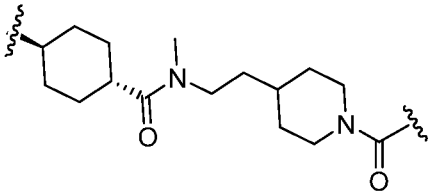


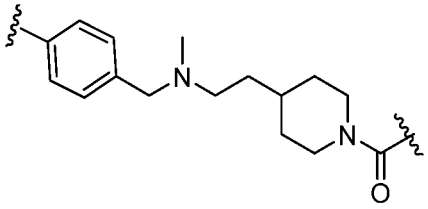


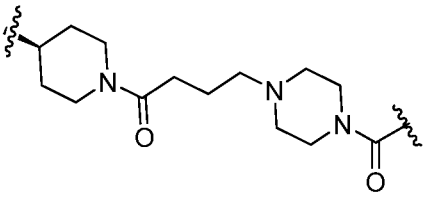


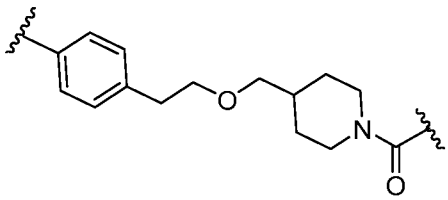


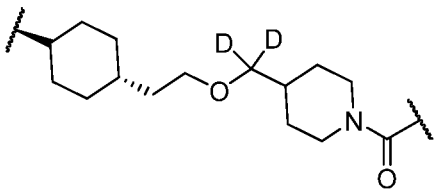


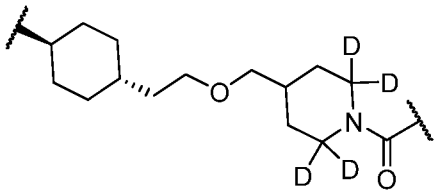


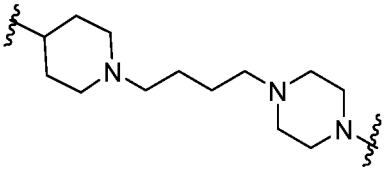


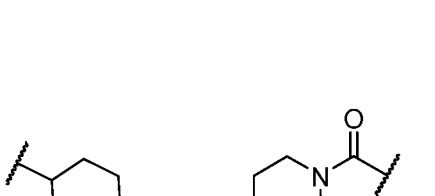


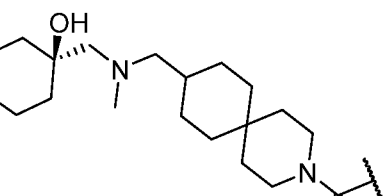


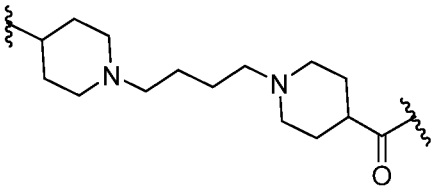
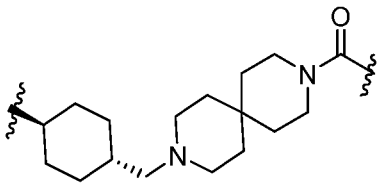








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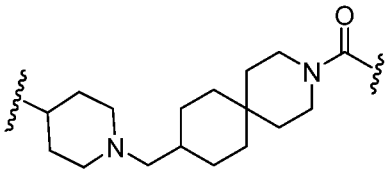
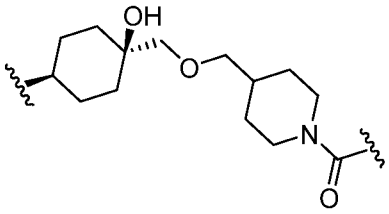
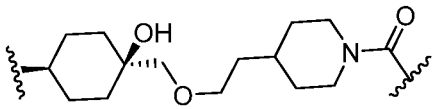
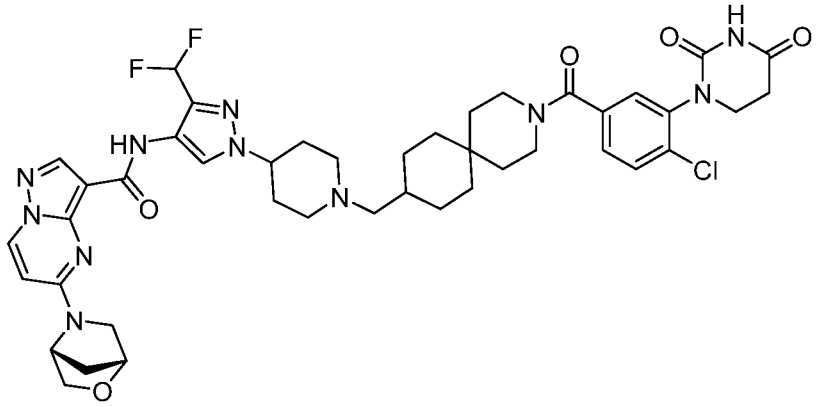
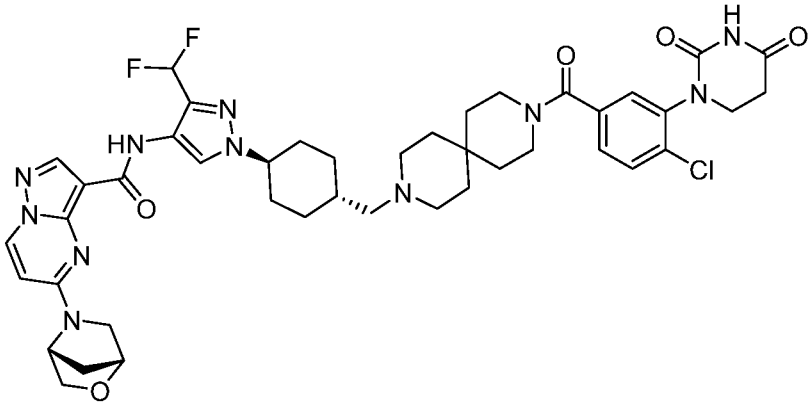
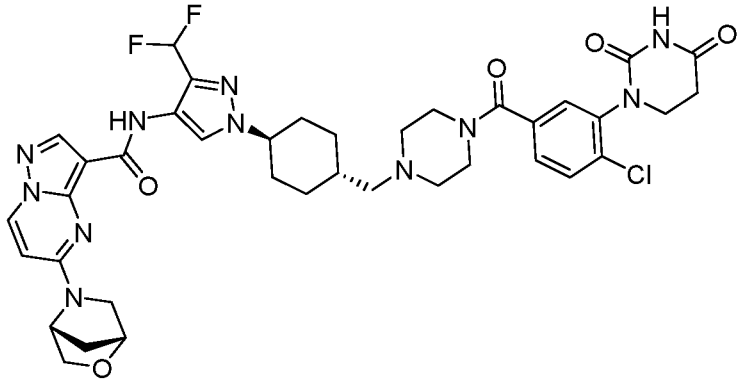
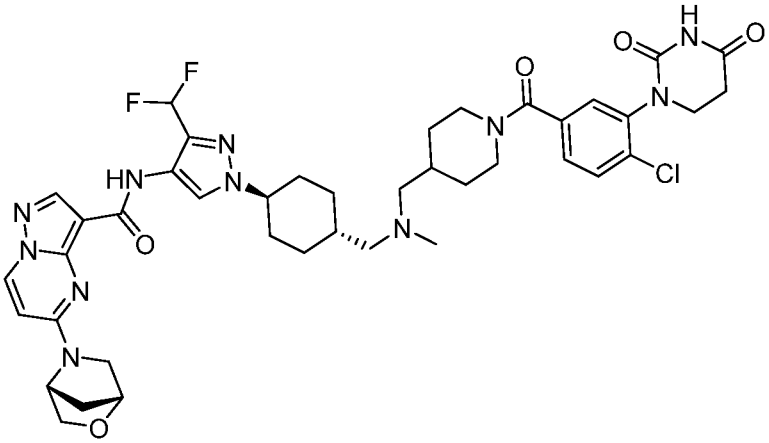
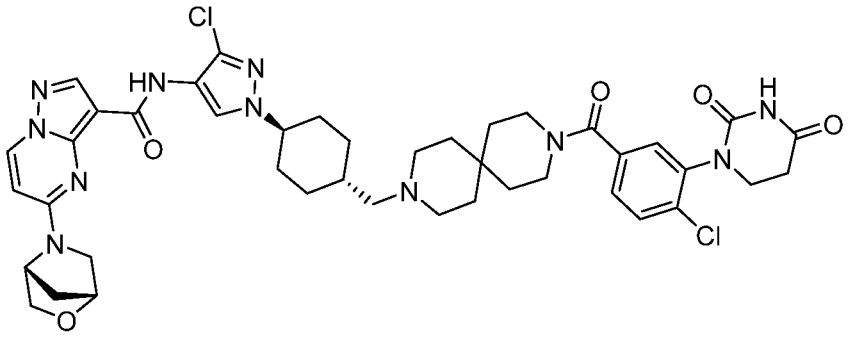




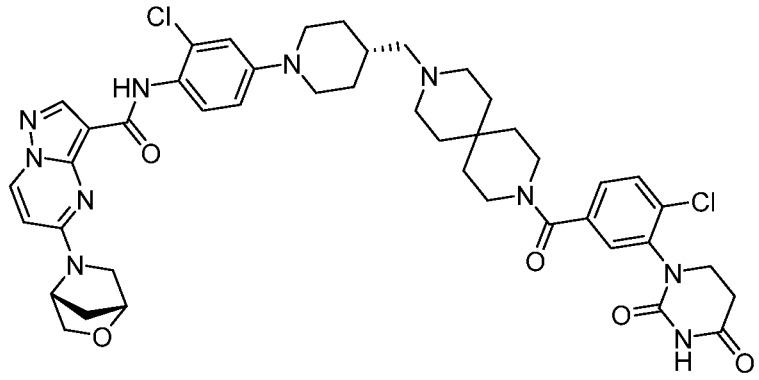


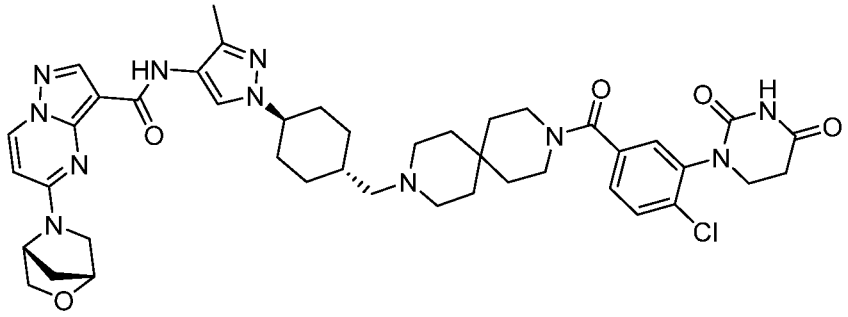


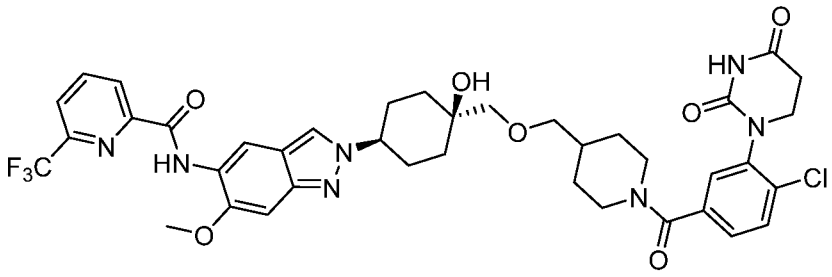


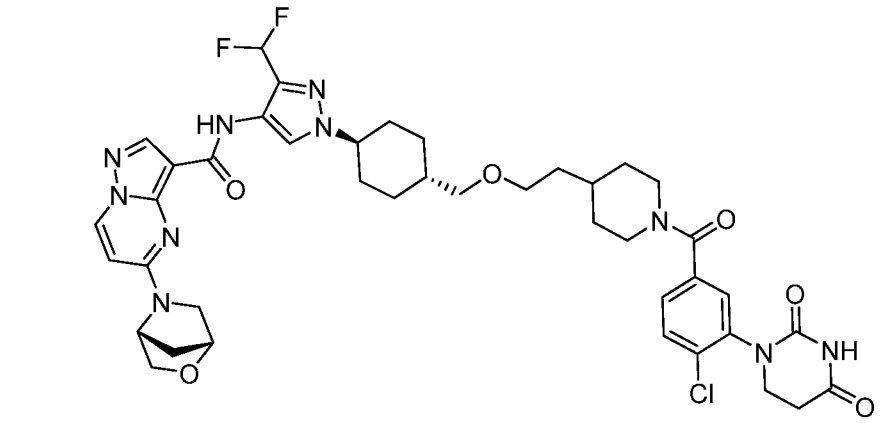


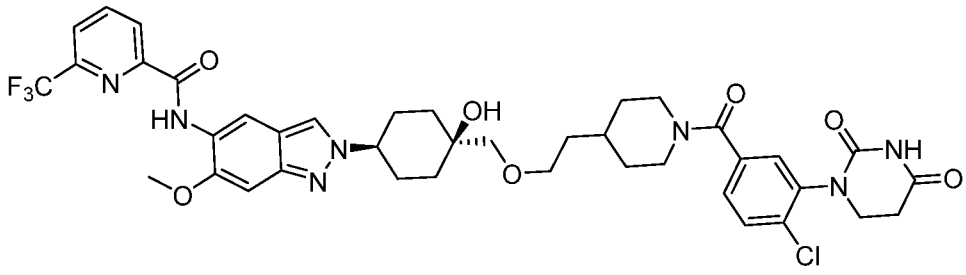


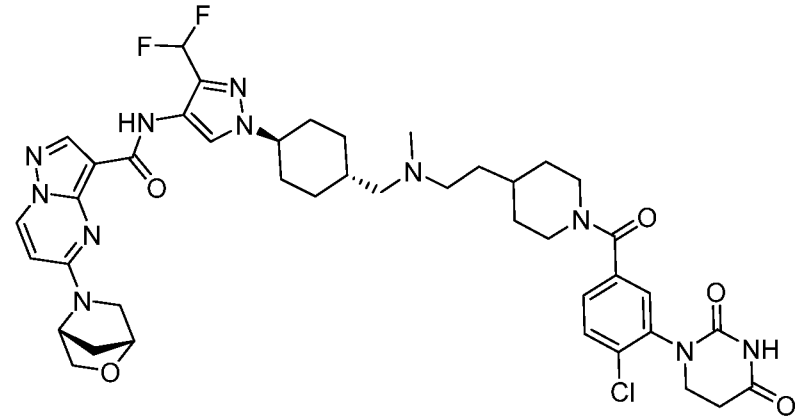


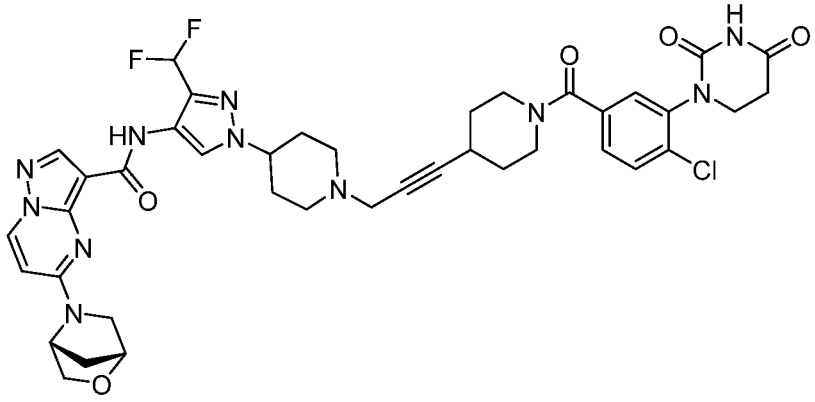


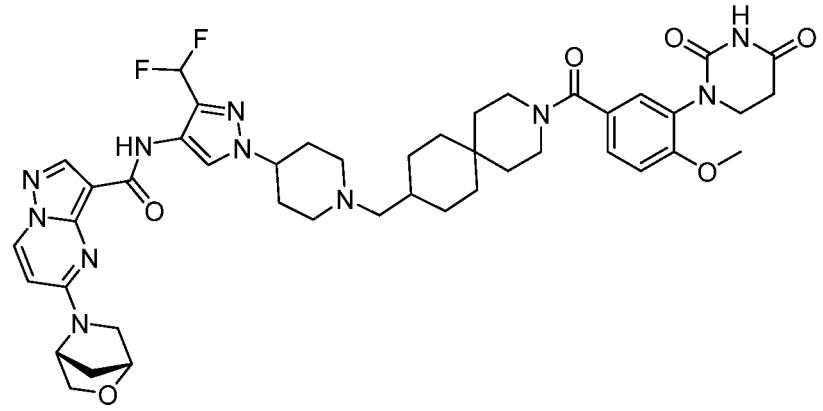


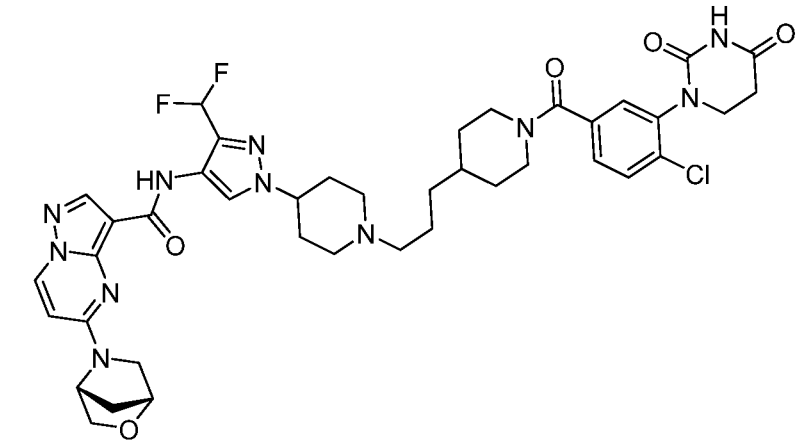


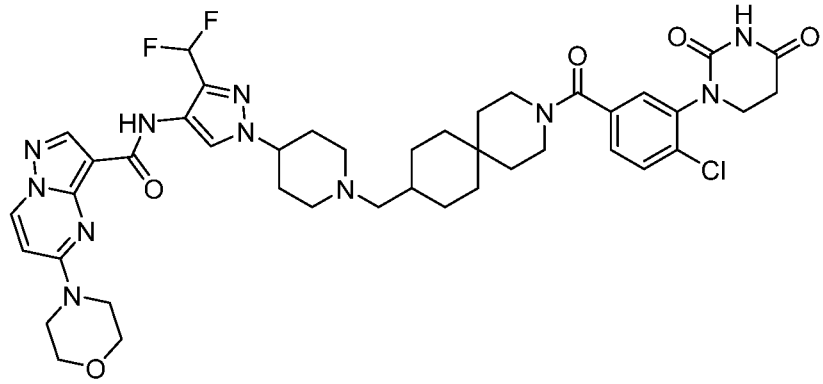


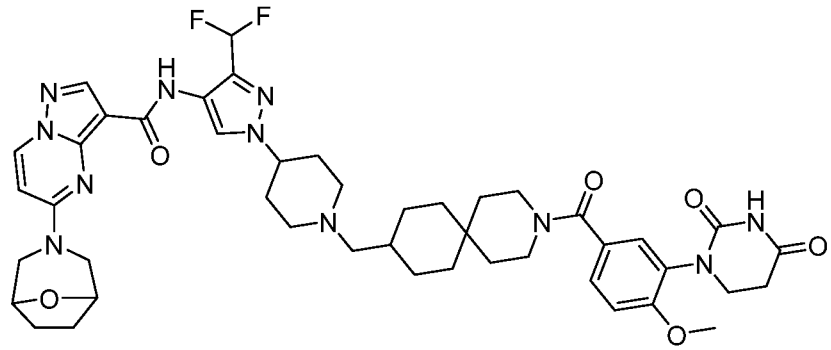


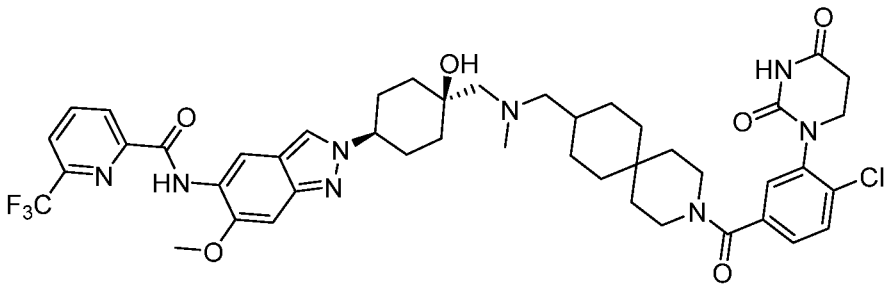


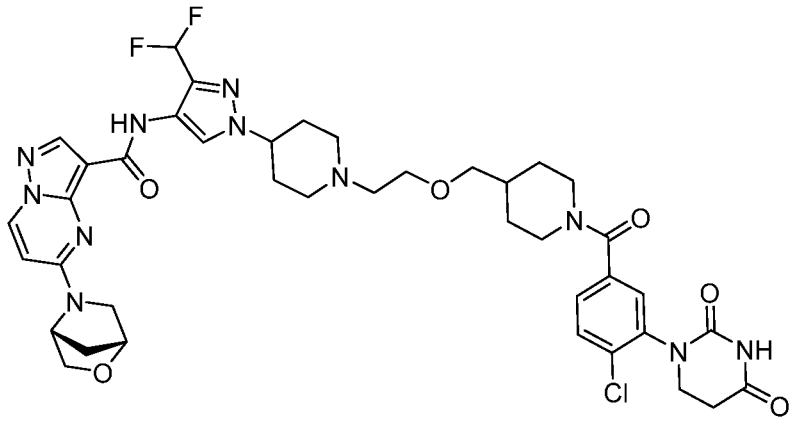


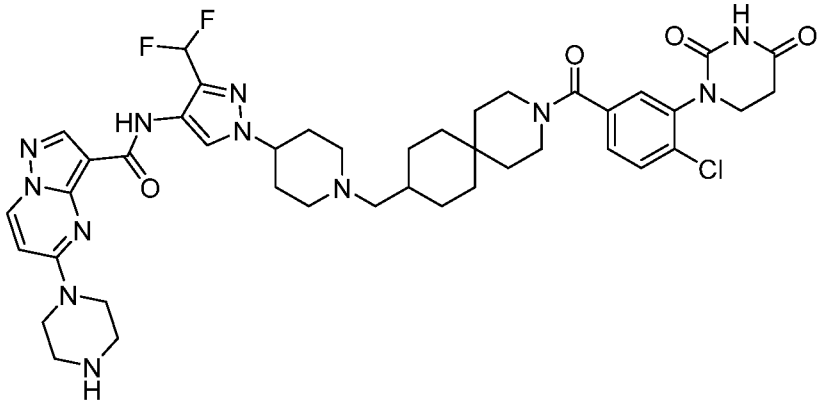


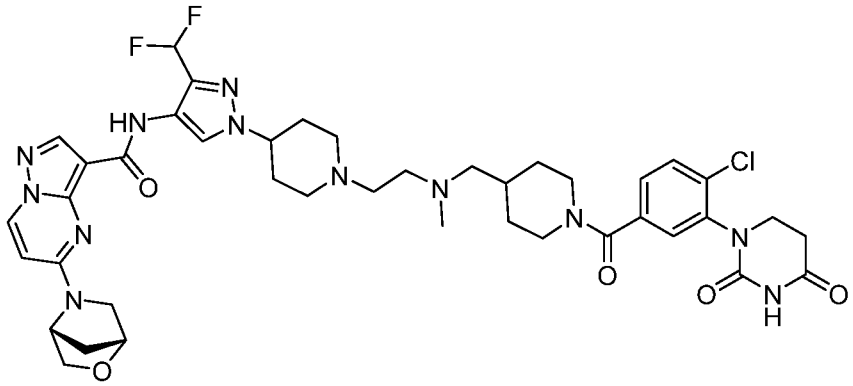


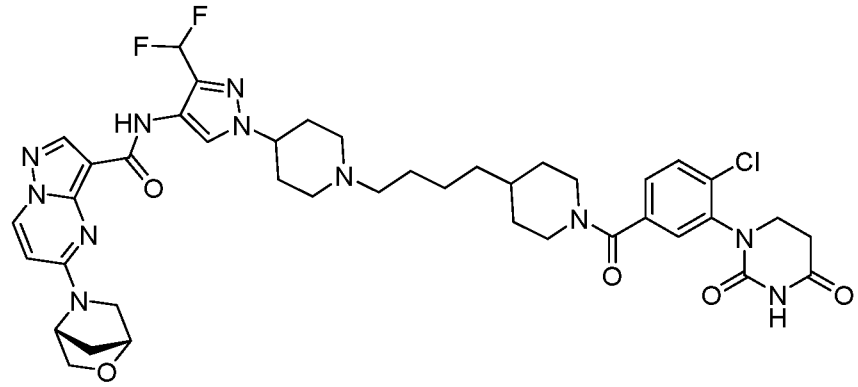


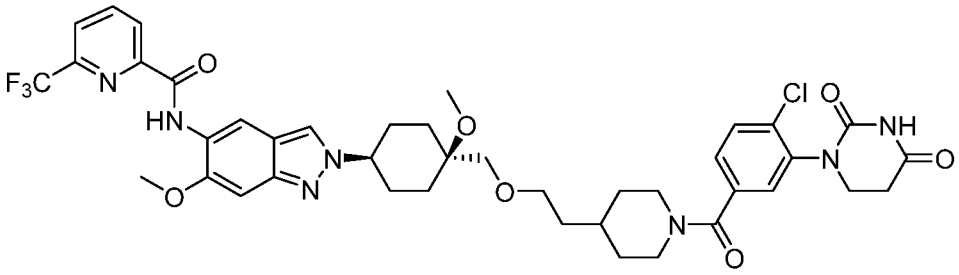


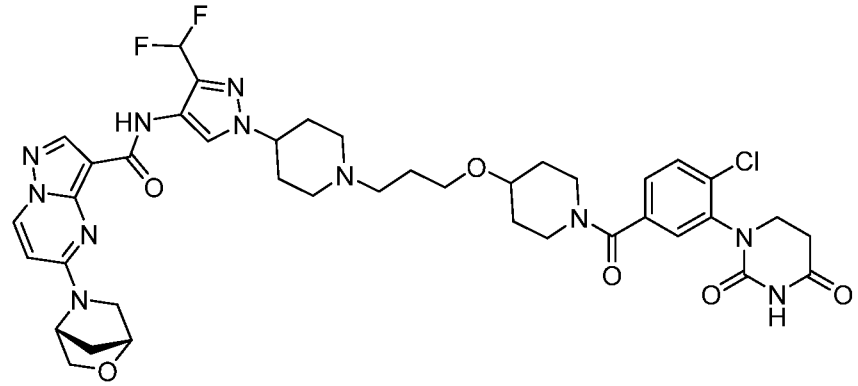


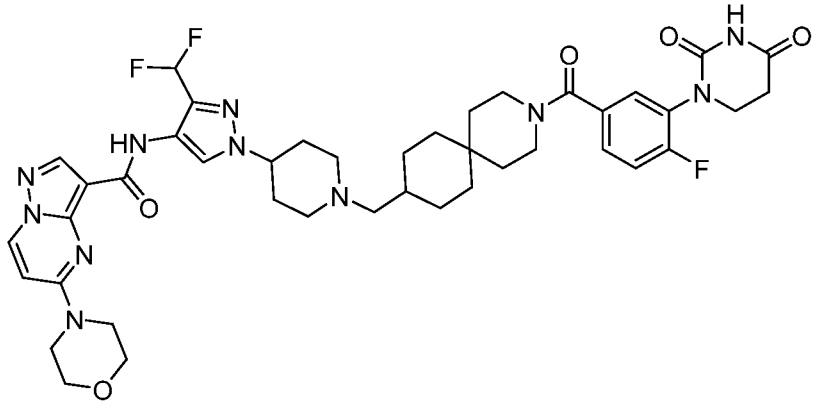


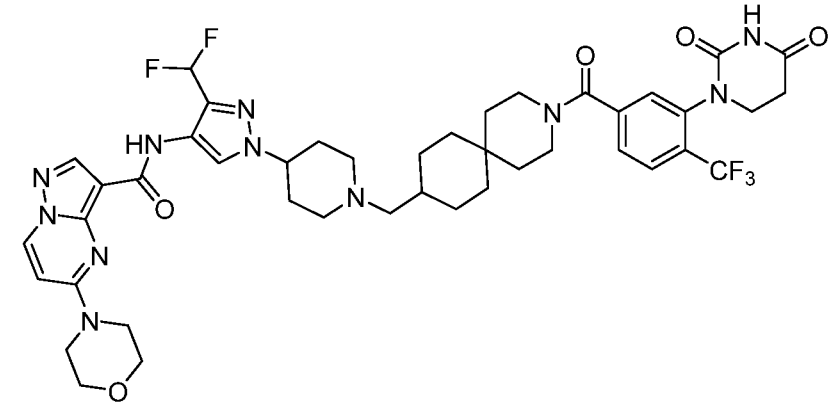


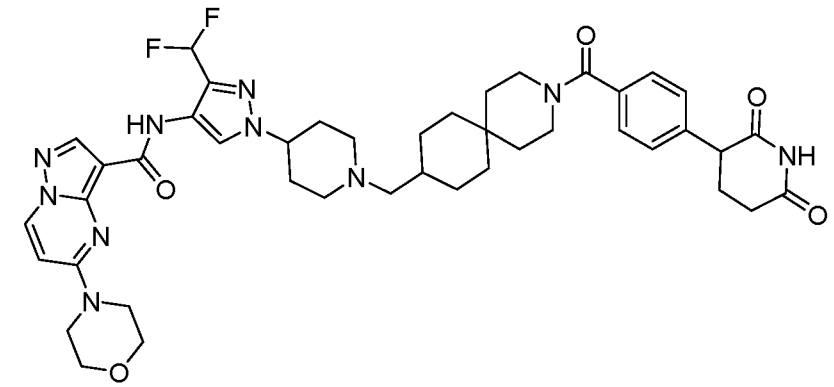


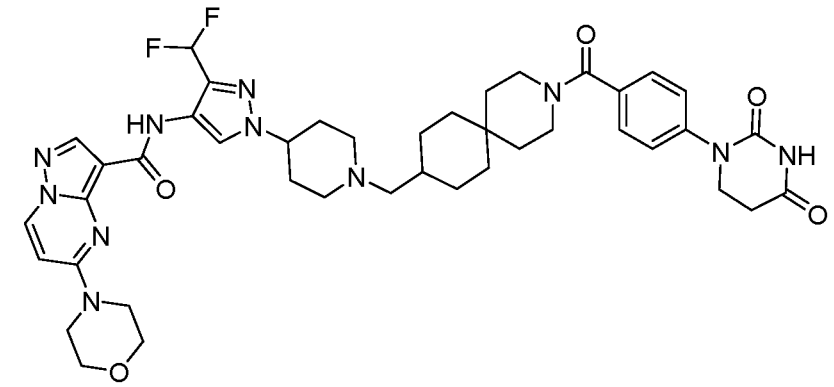


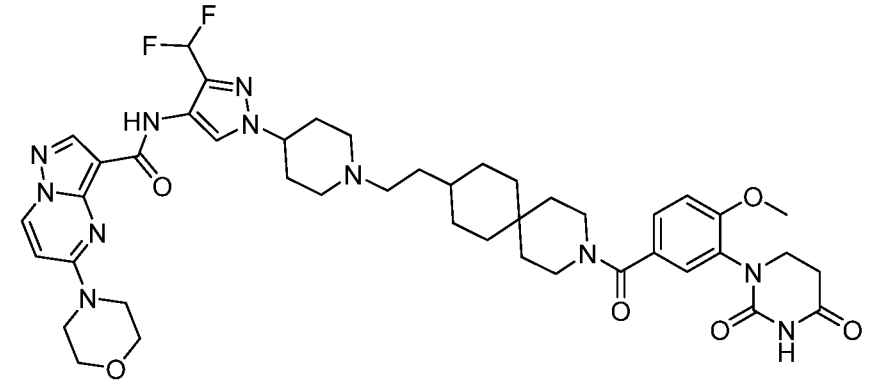


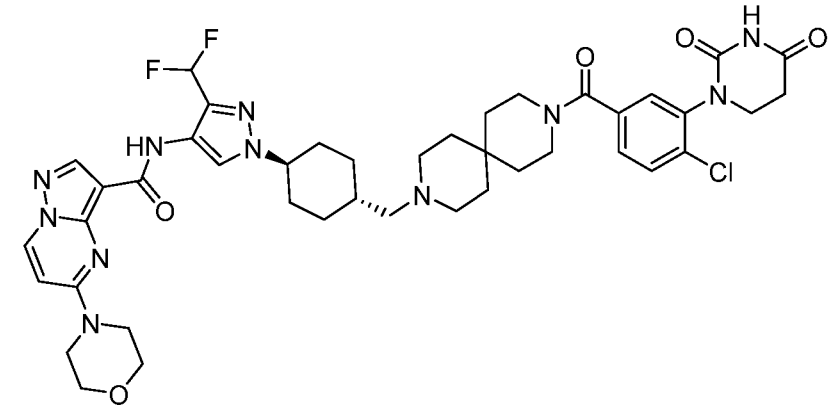


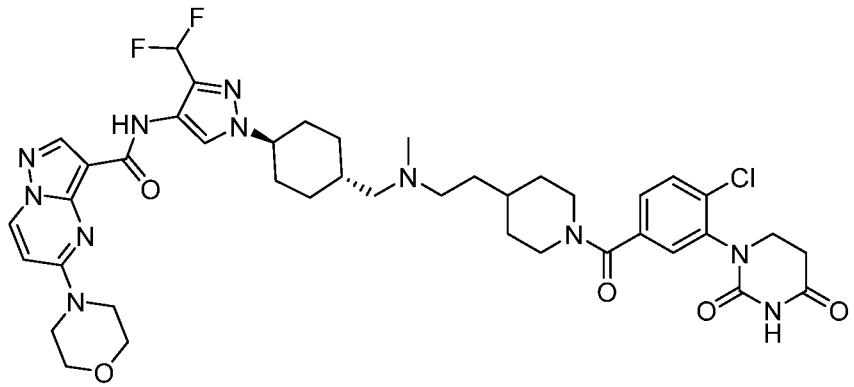


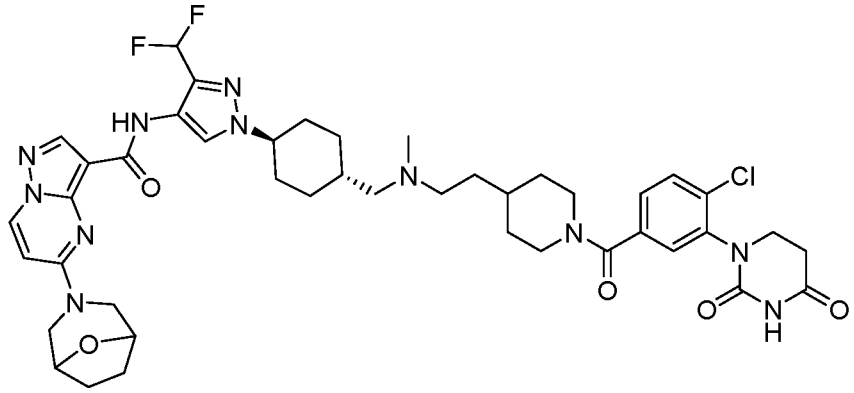


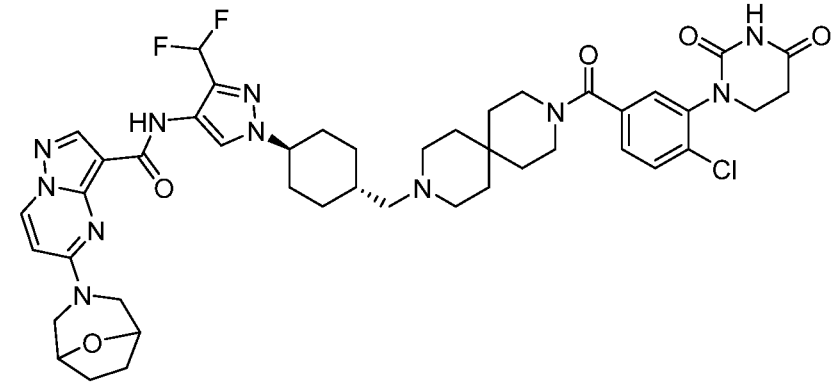


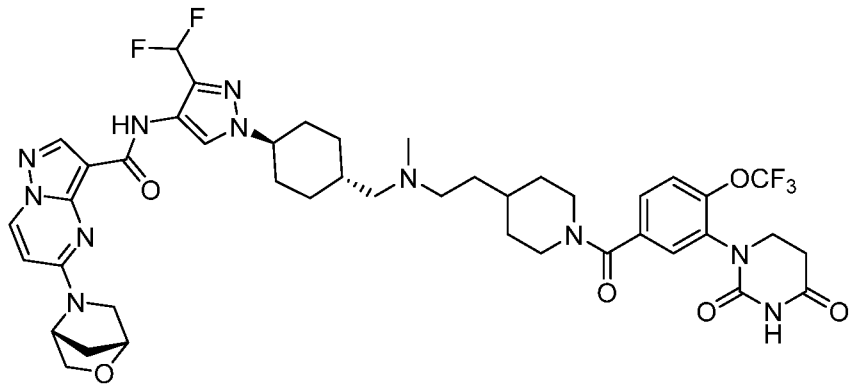


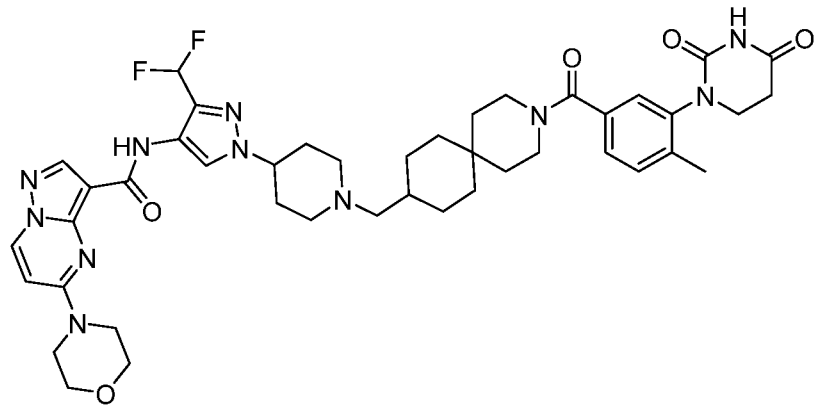


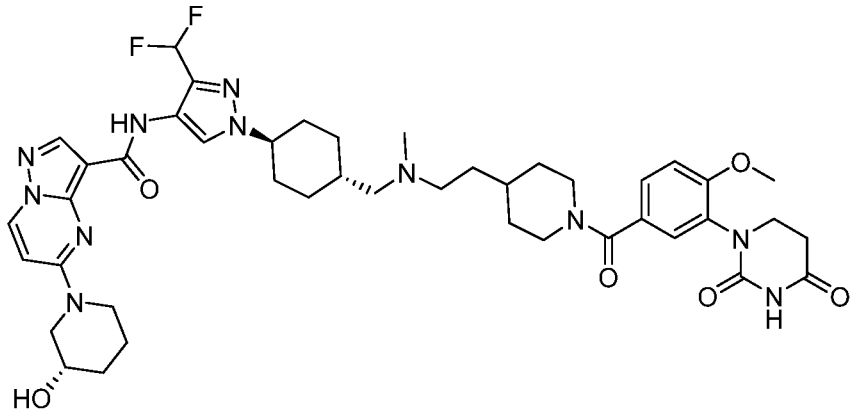


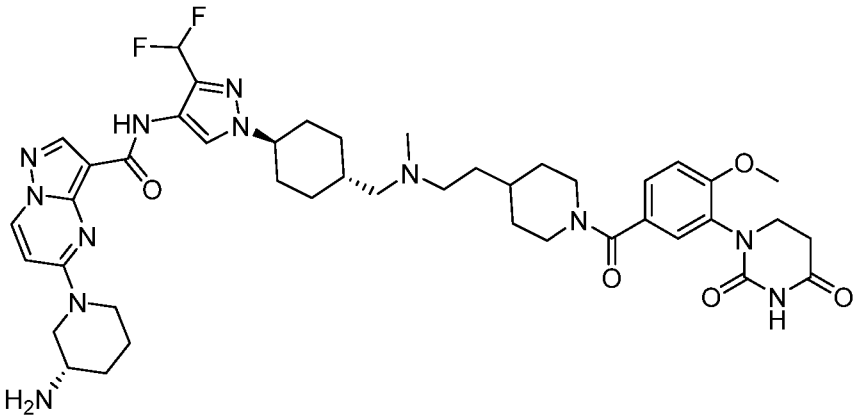


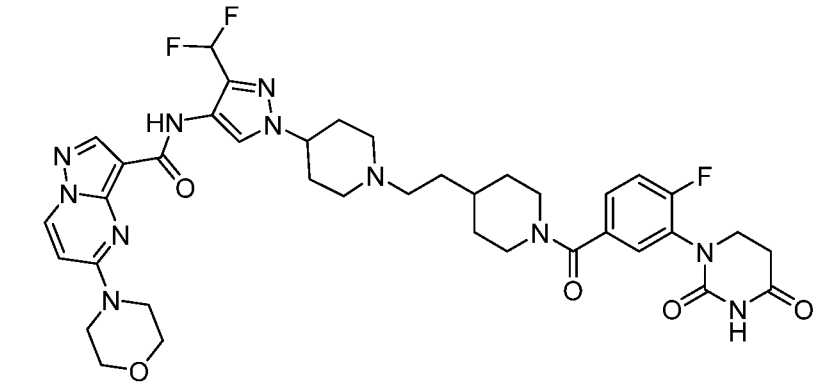


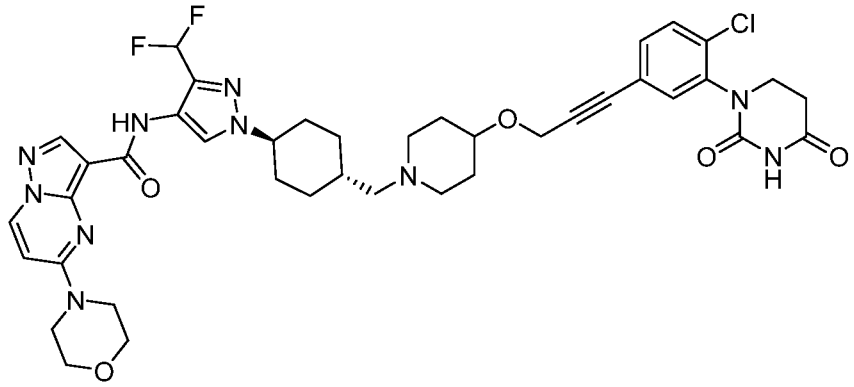


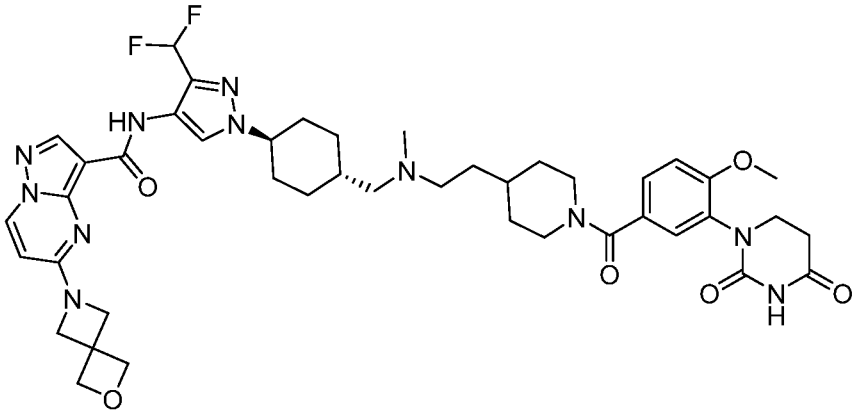


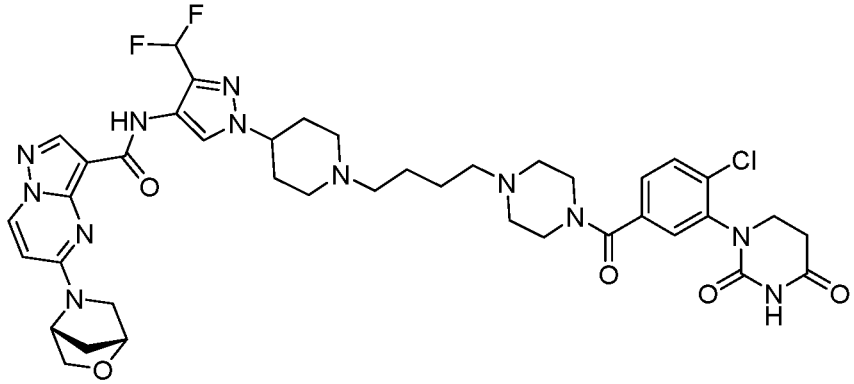


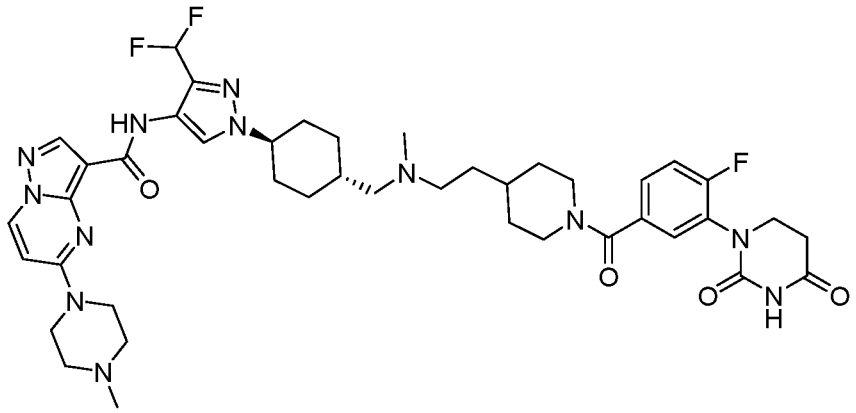


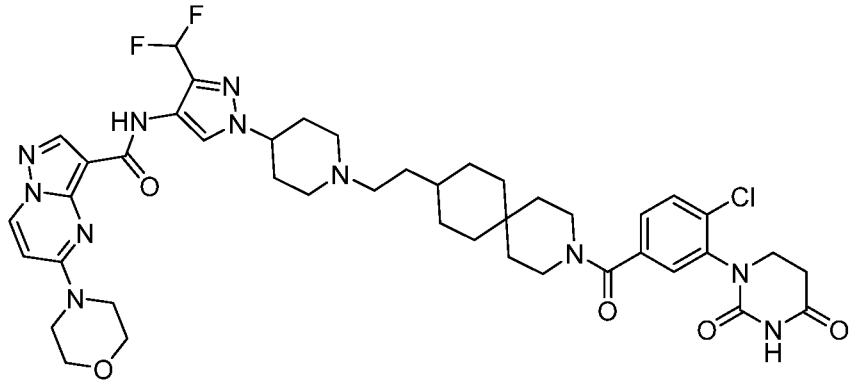


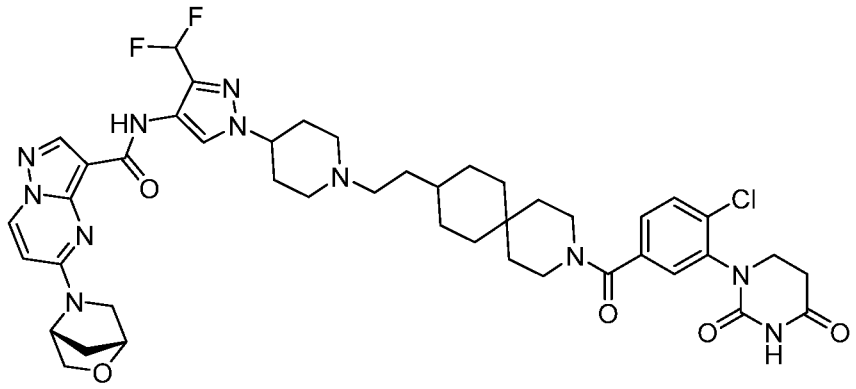


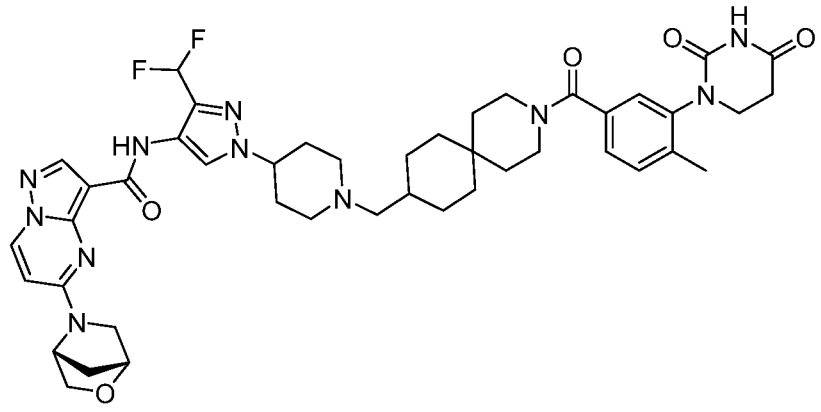


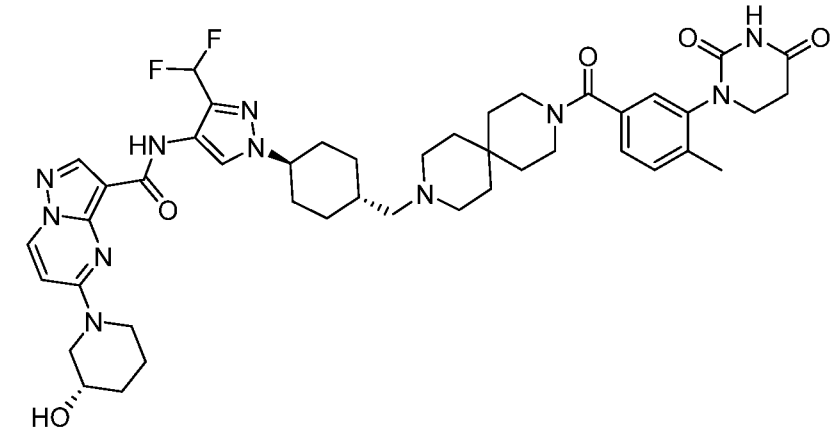


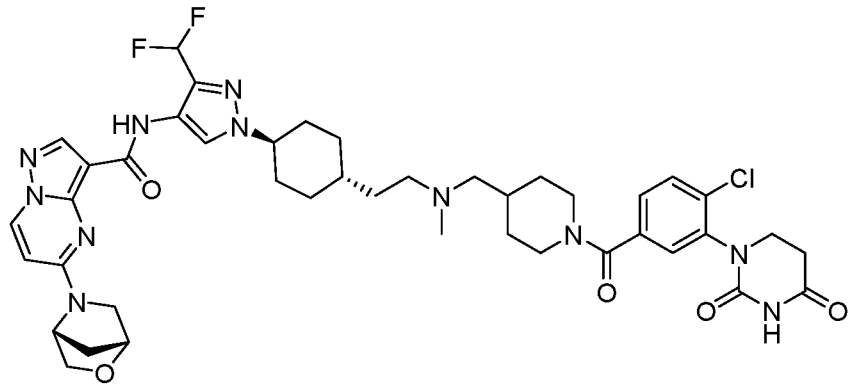


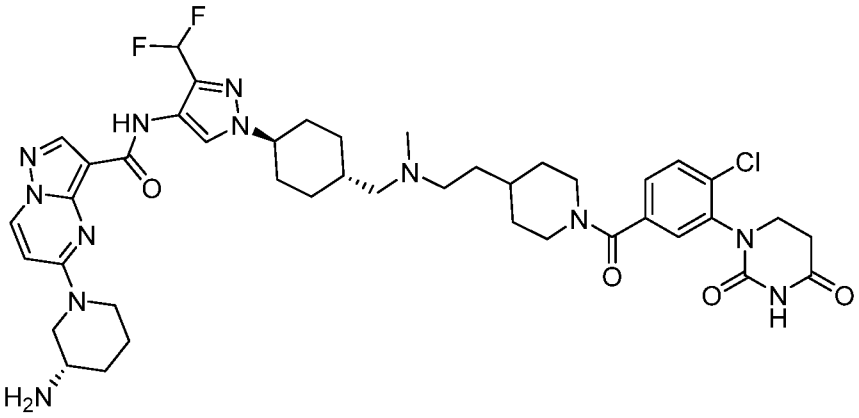


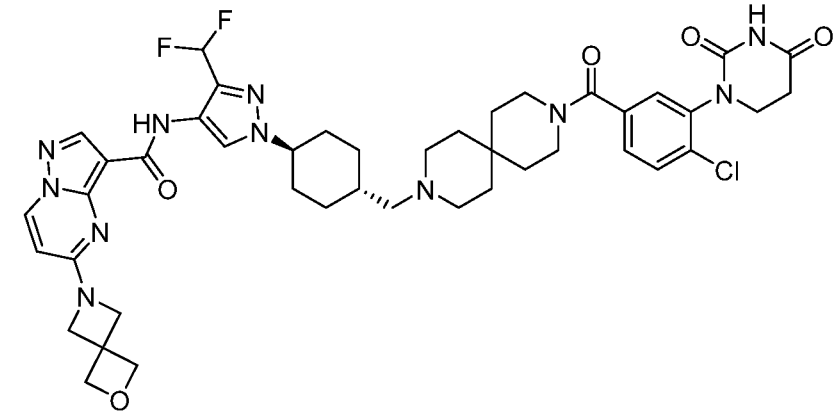


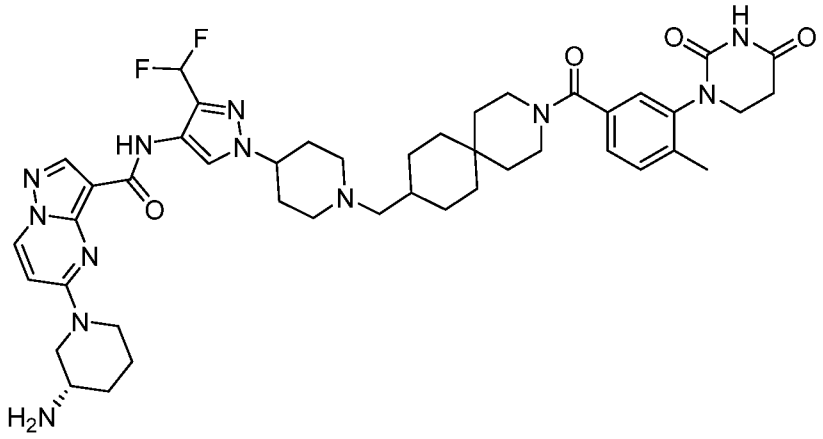


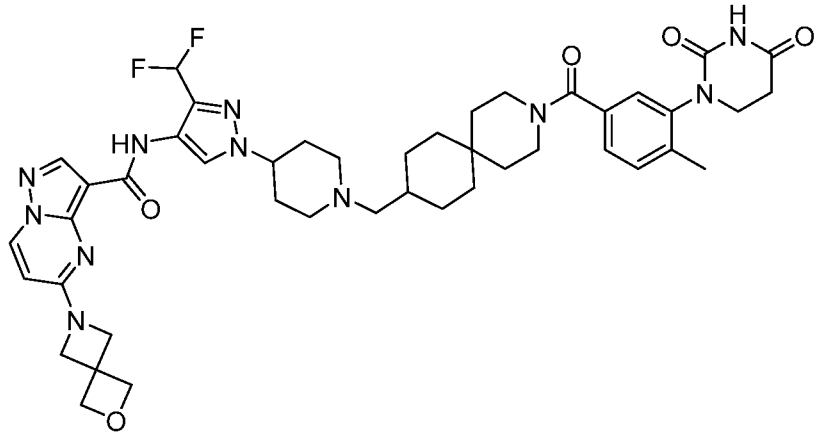


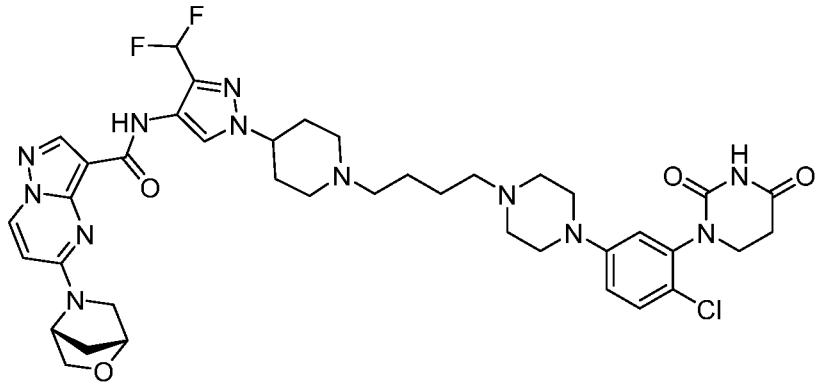


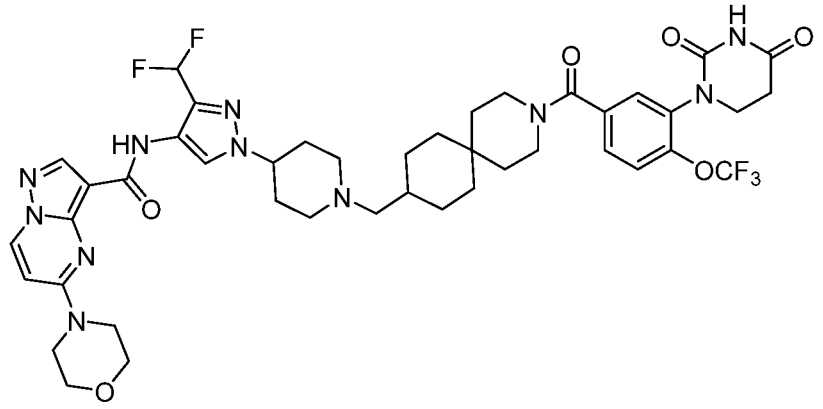


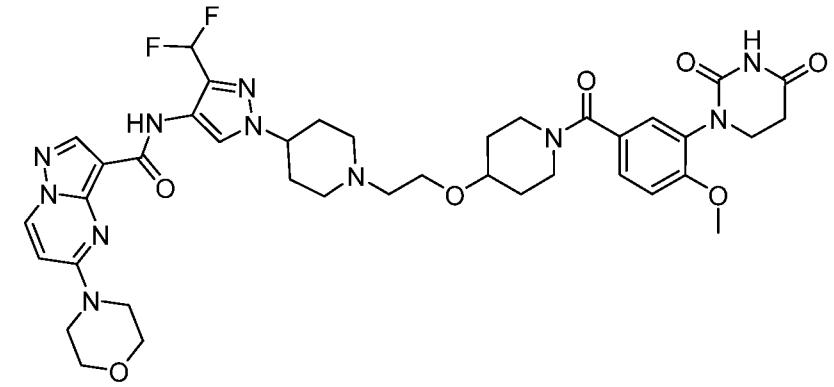


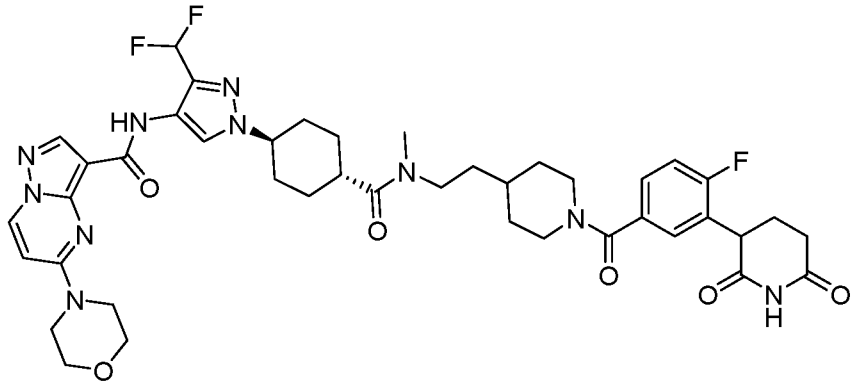


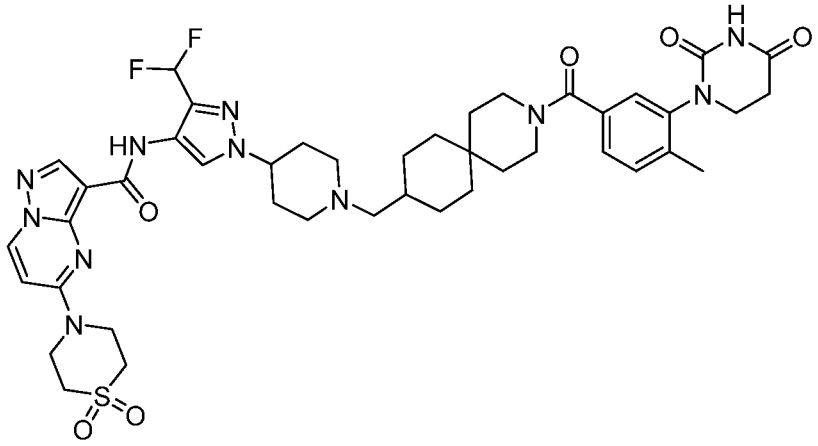


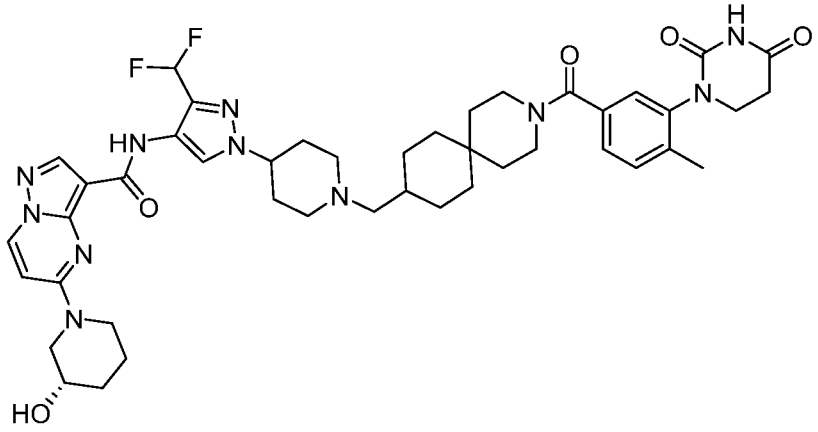


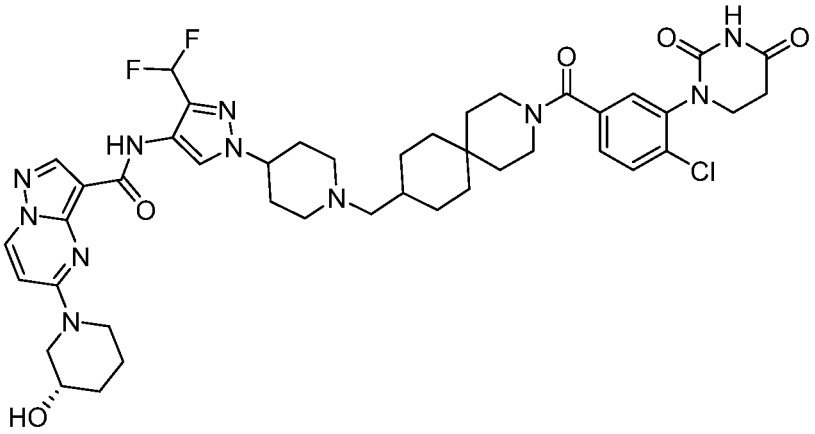


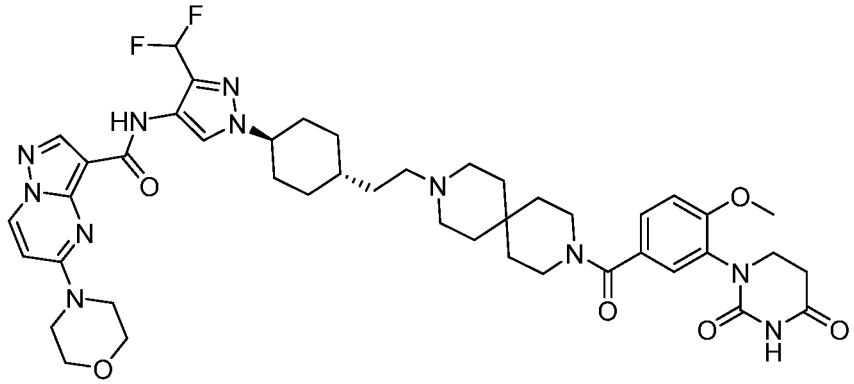


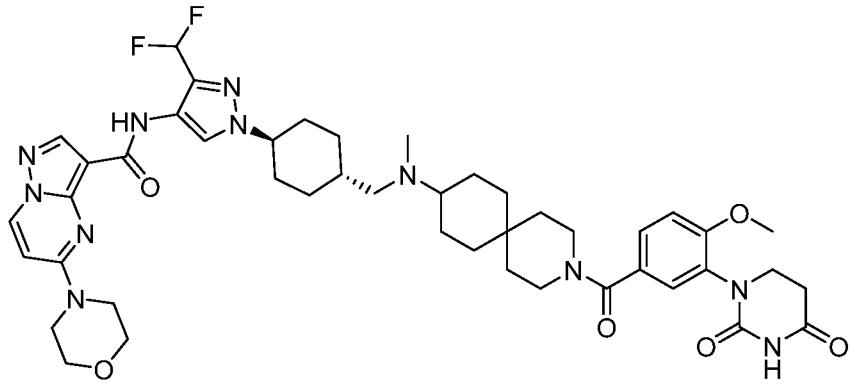


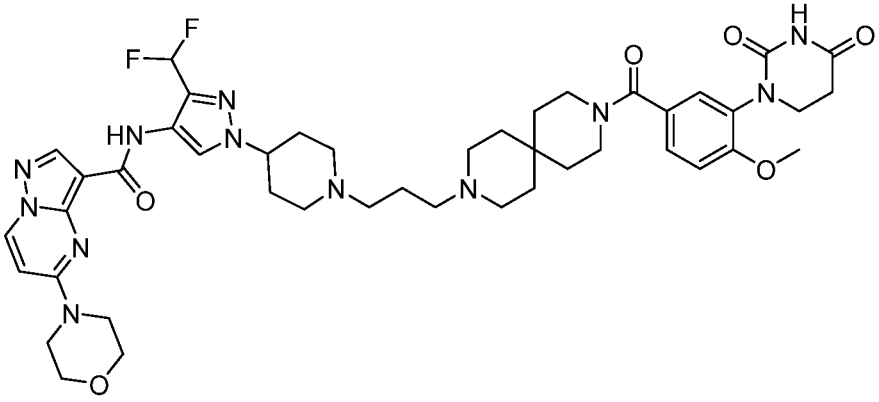


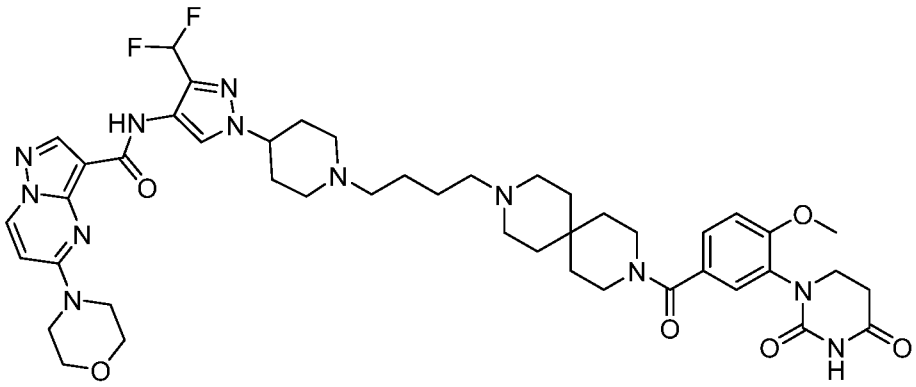


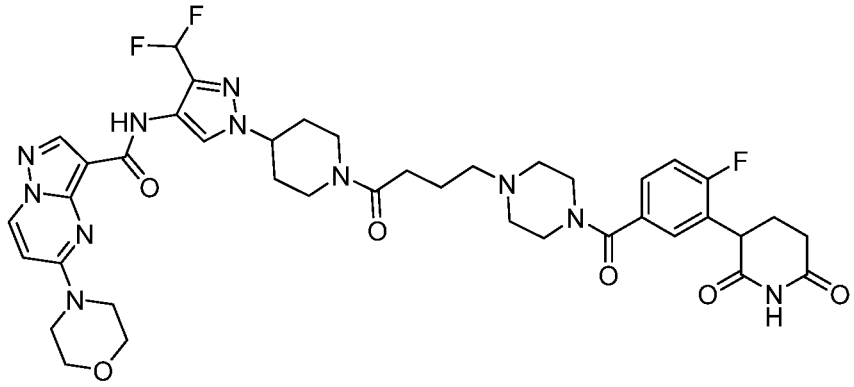


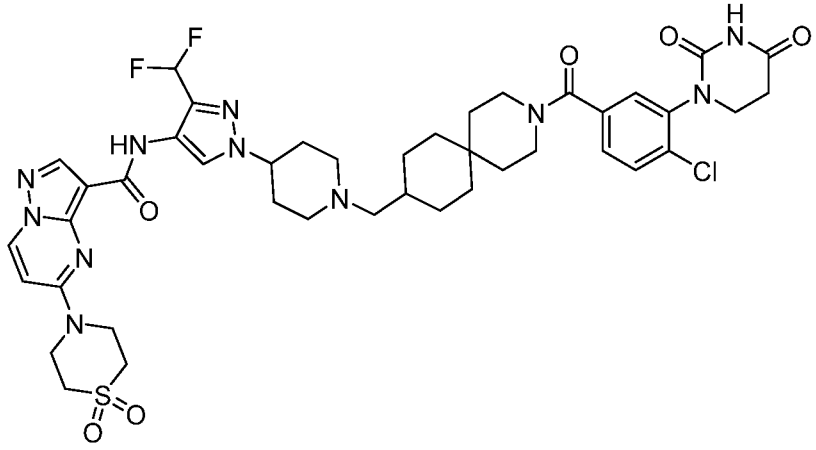


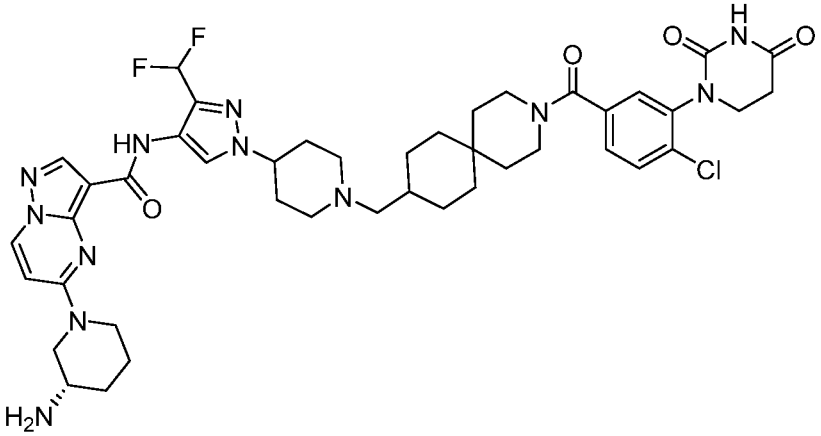


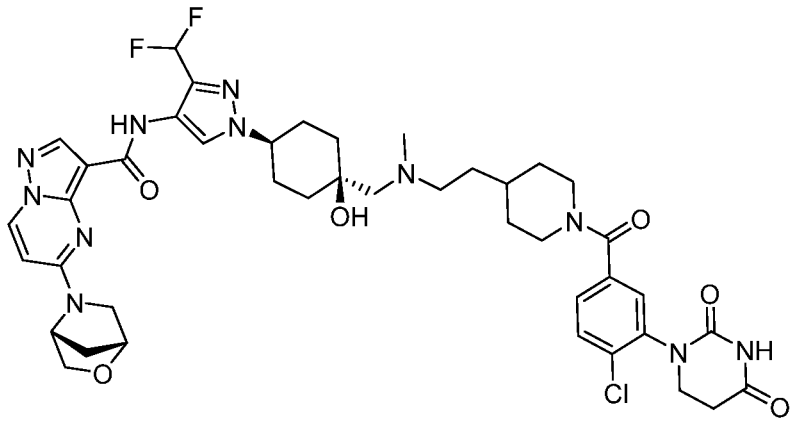




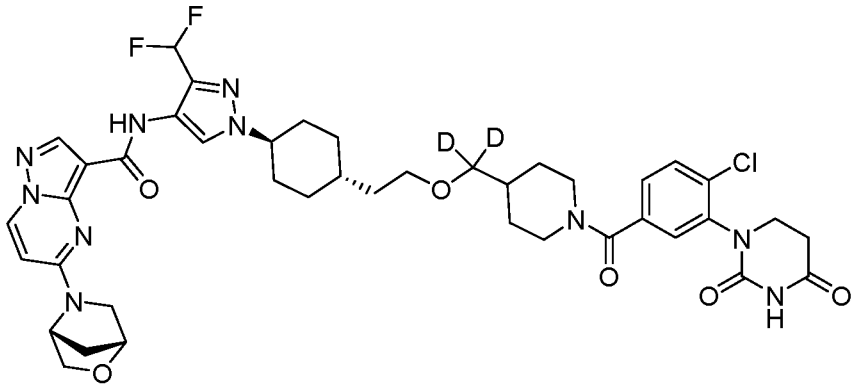




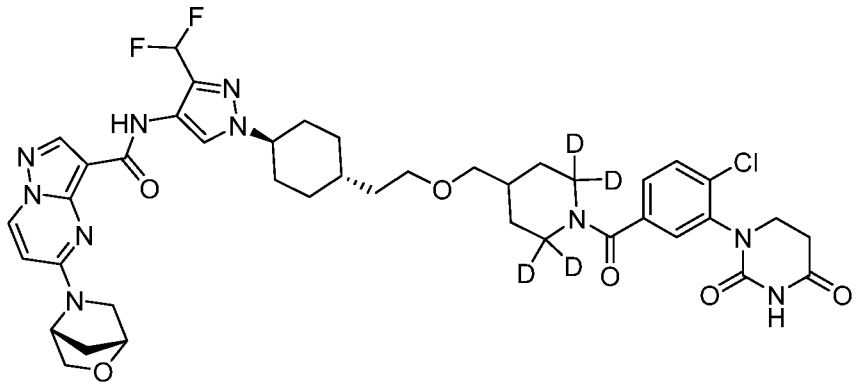




优选的，本发明某些实施方式中，式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐为

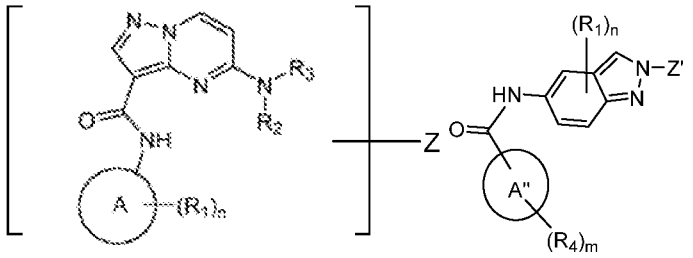


或

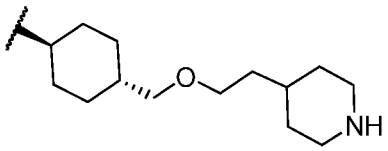
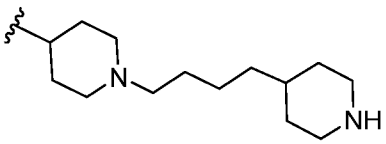
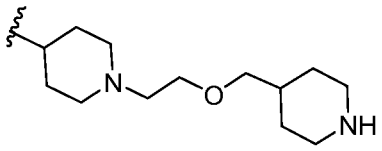
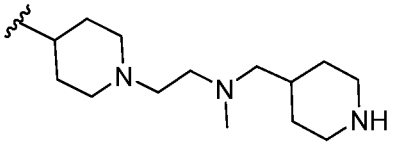
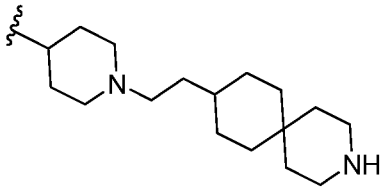
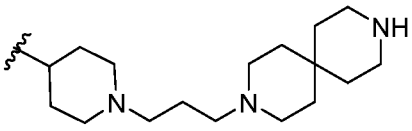
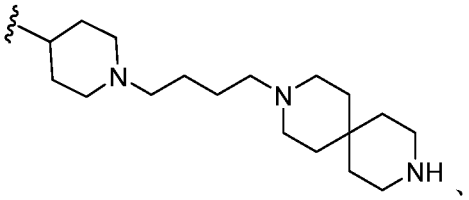
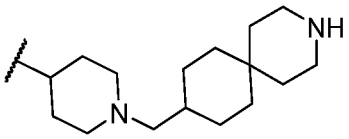
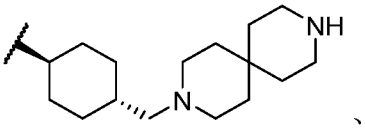
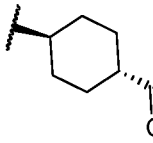
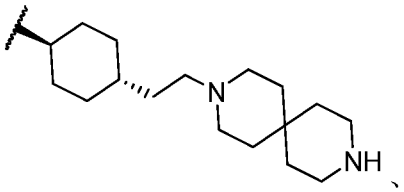
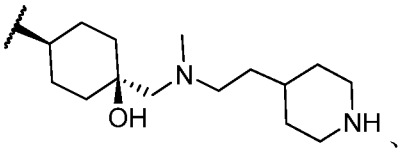
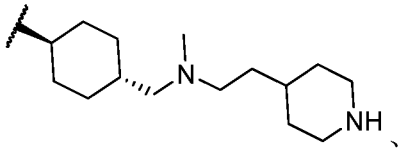
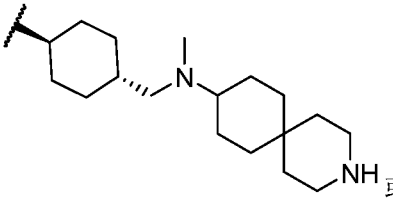
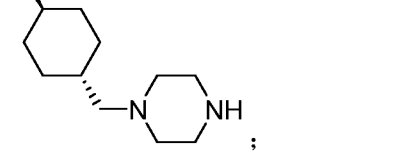


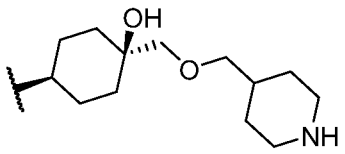
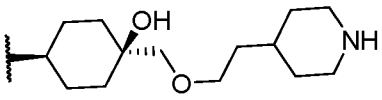
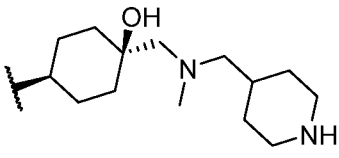
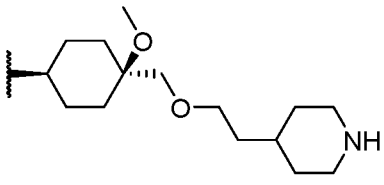
。

本发明还公开了一种式VII或VIII化合物，其立体异构体、对映异构体、非对映异构体、氘代化物或其盐：

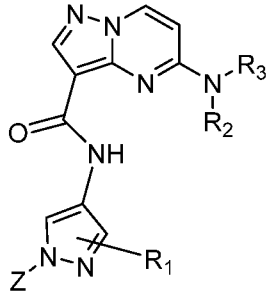


VII VIII

Z 为  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、、或；

Z’为  、  、  或  ；

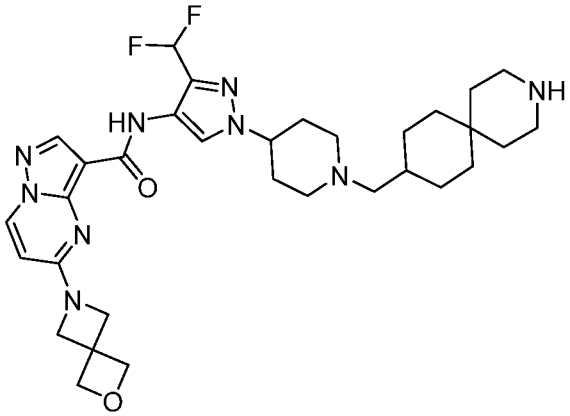
其中，m、n、A、A’、R_1、R_2、R_3和R_4如前所述。

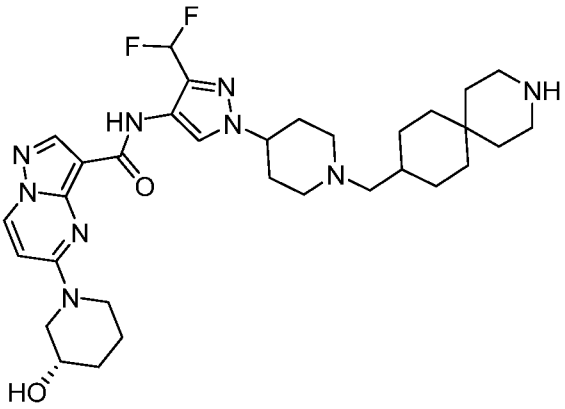


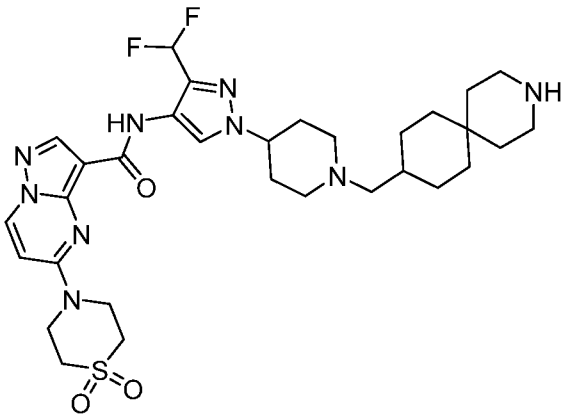
VII-1

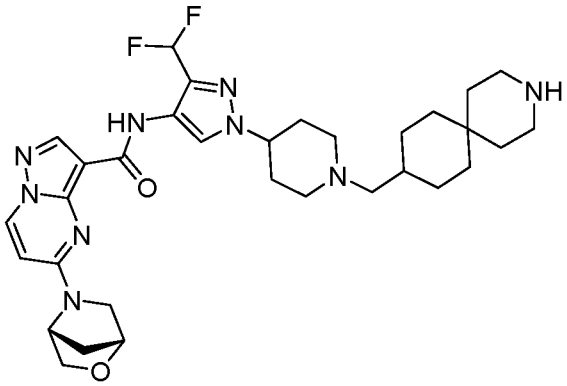
本发明某些实施方式中，所述式VII化合物为式VII-1所示化合物 。

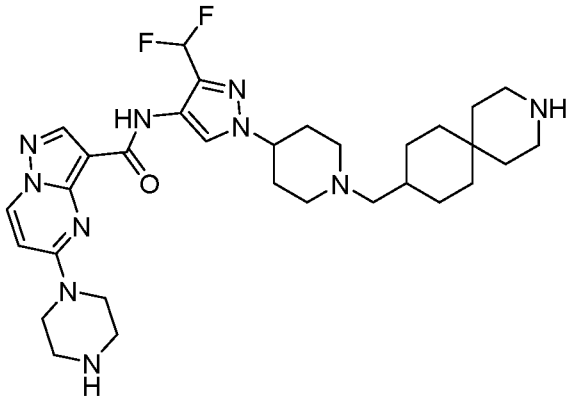
本发明某些实施方式中，

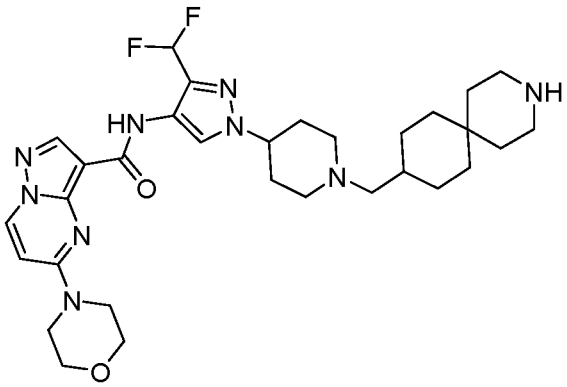
所述式VII化合物为如下任一化合物：  、

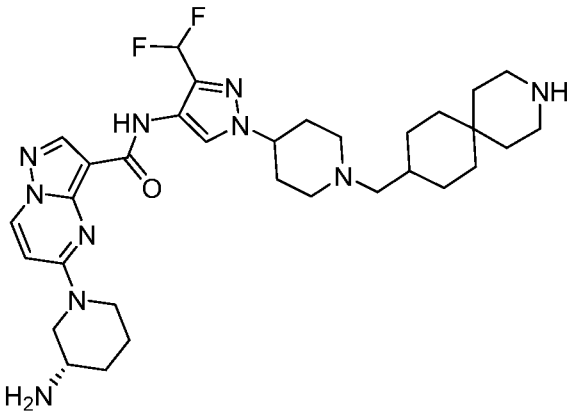


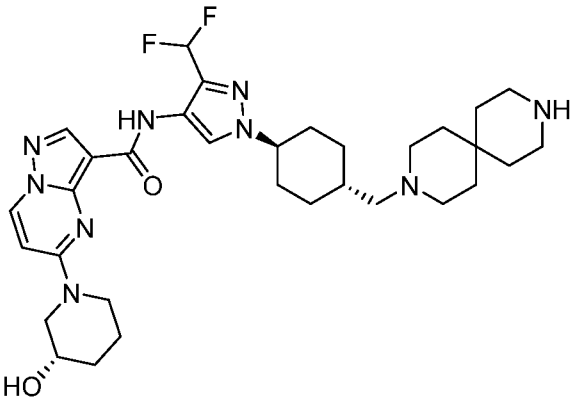


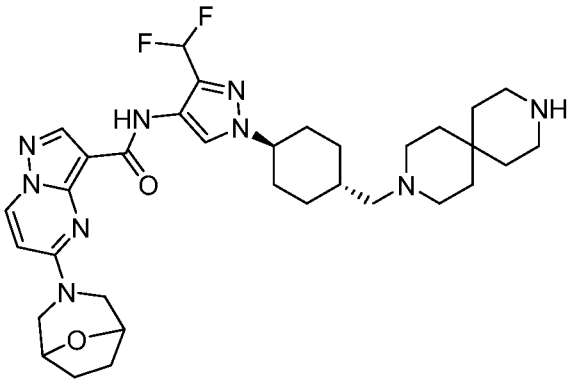


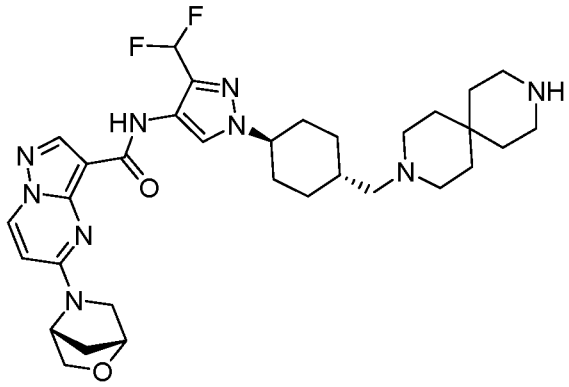


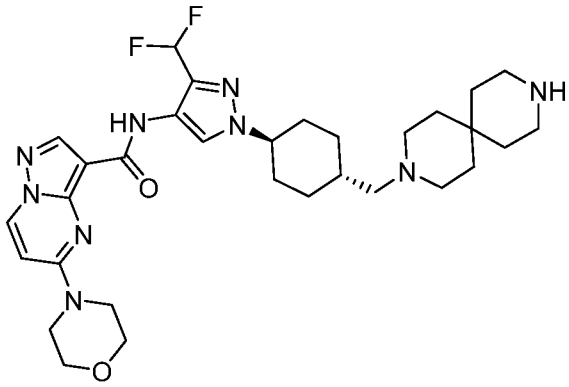


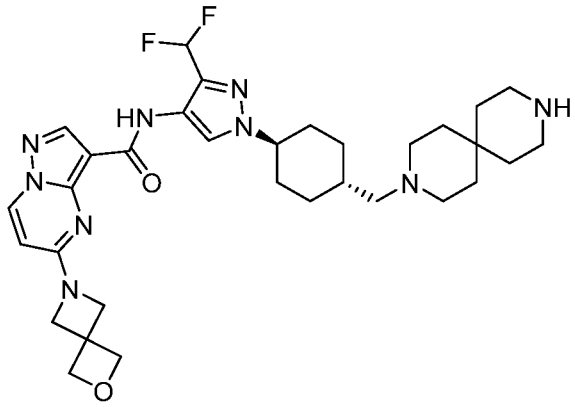


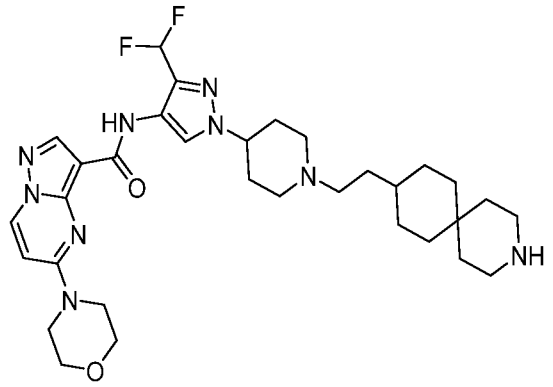


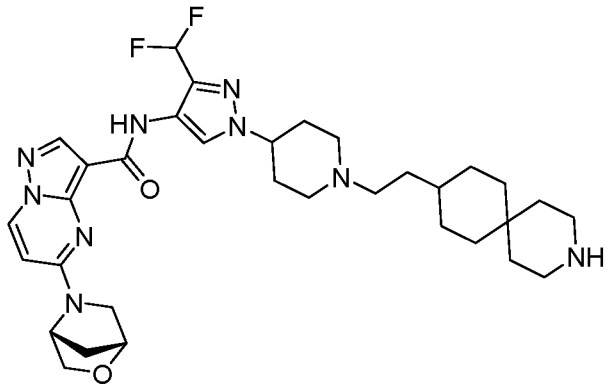


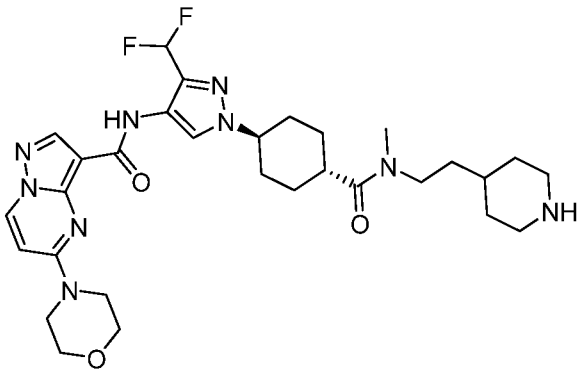


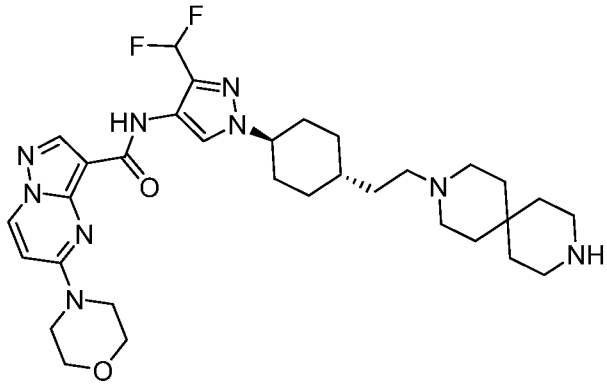


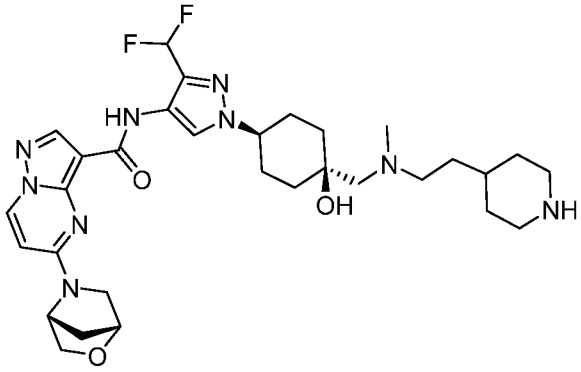


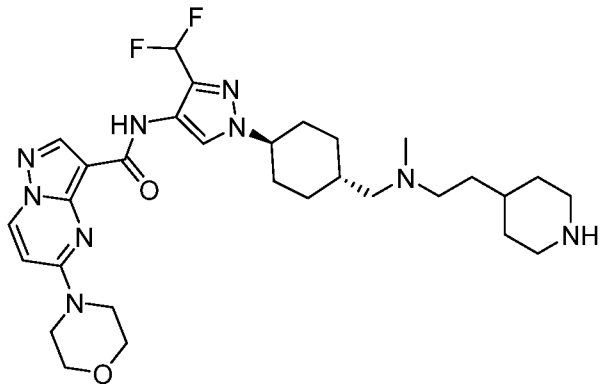


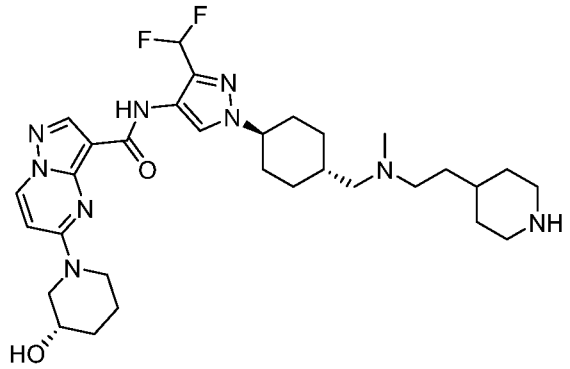


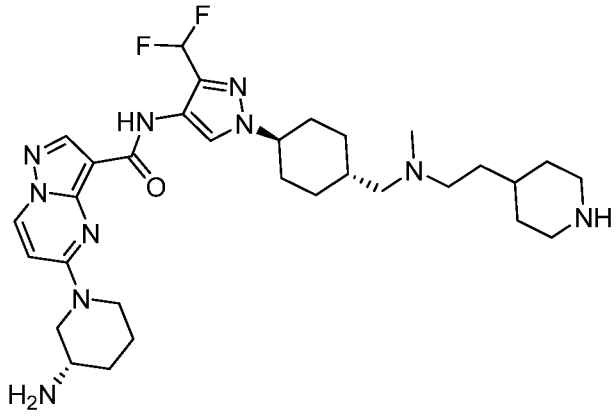


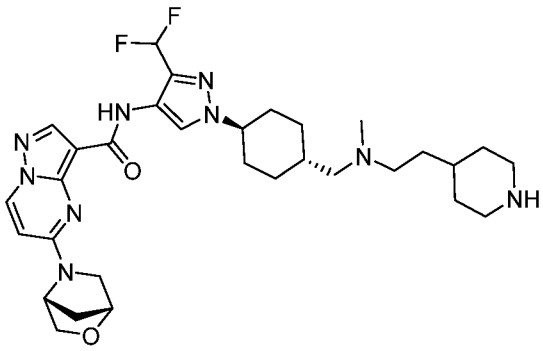


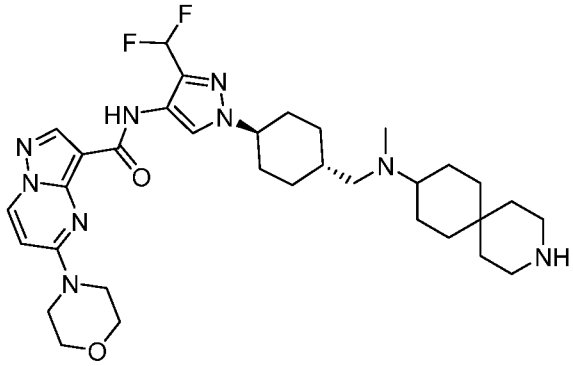


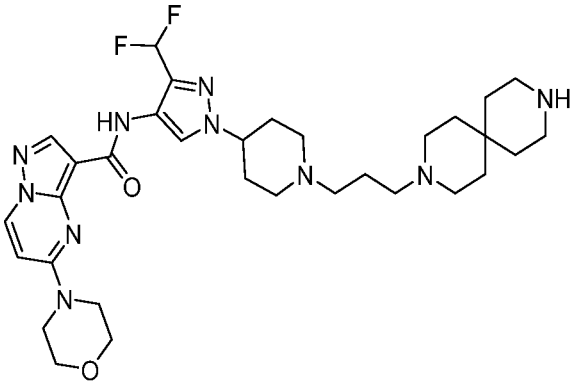


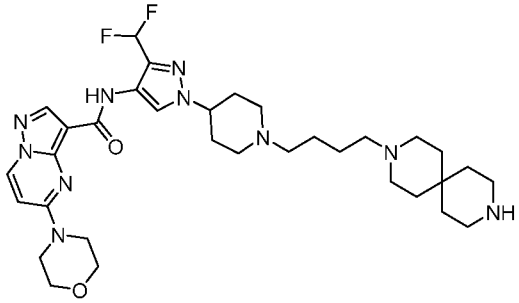


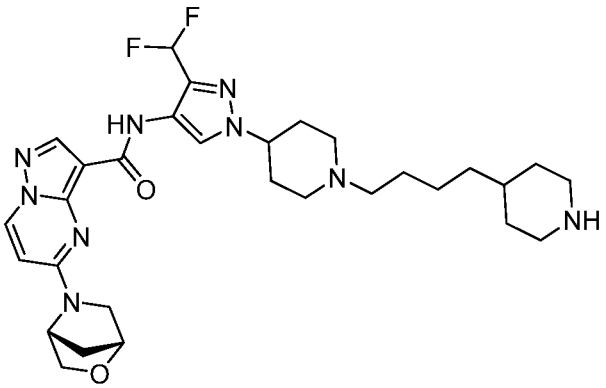


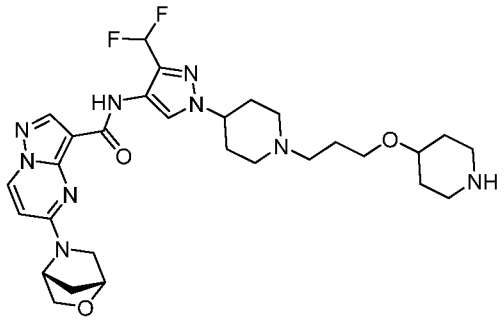








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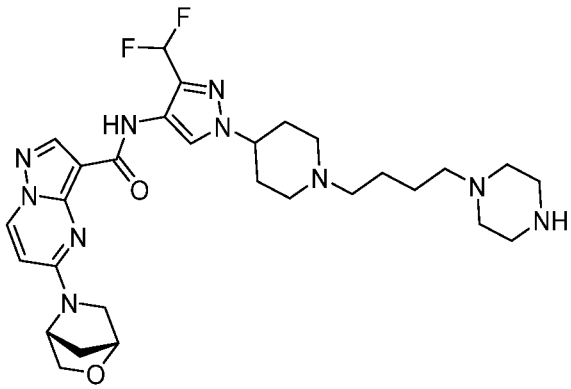
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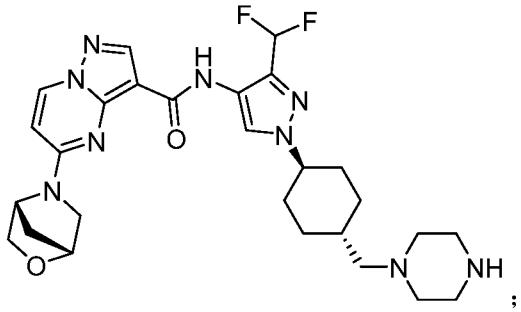
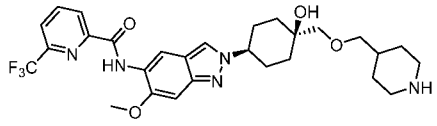

；

和/或，所述式VIII化合物为如下任一化合物：

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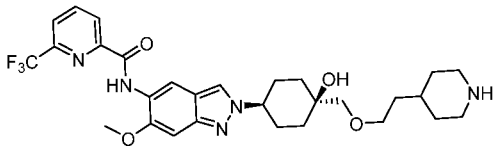
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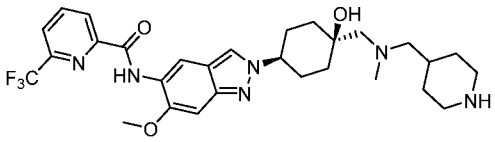
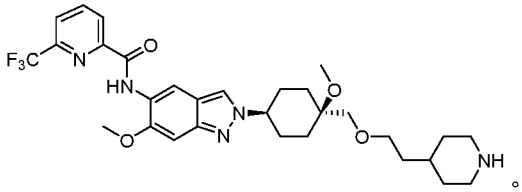
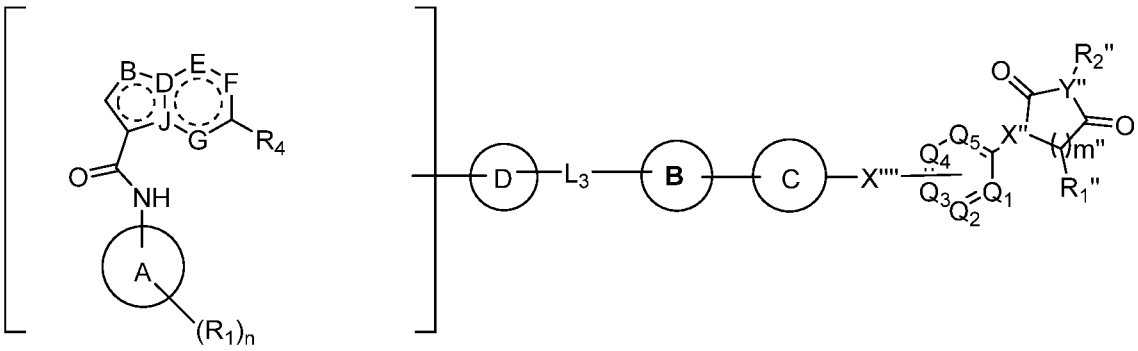

或

。

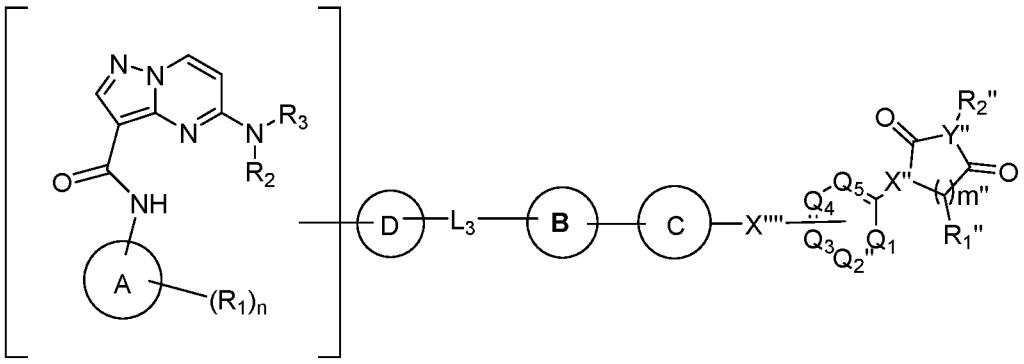
优选的，本发明某些实施方式中，式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐为式II化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐，



II

其中所述 R_1、n、R_4、B、D、E、F、G、J 和环 A 如 PTM-2'中所定义和描述；所述 Q_1、Q_2、Q_3、Q_4、Q_5、X"、Y"、m"、R_1"、R_2"如本文 ULM-1 中所定义和描述；所述 L_3、环 D、环 B、环 C 和 X""如本文 LA 中所定义和描述。

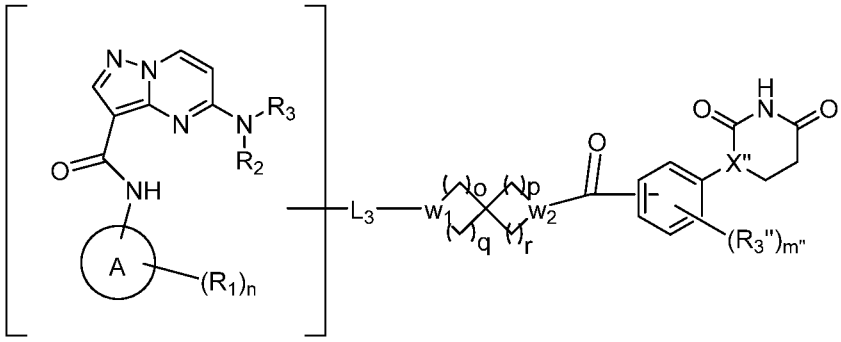
优选的，本发明某些实施方式中，式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐为式III化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐，



III

其中所述 R_1、n、R_2、R_3、环 A 如 PTM-3 中所定义和描述；所述 Q_1、Q_2、Q_3、Q_4、Q_5、X"、Y"、m"、R_1"、R_2"如本文 ULM-1 中所定义和描述；所述 L_3、环 D、环 B、环 C 和 X""如本文 LA 中所定义和描述。

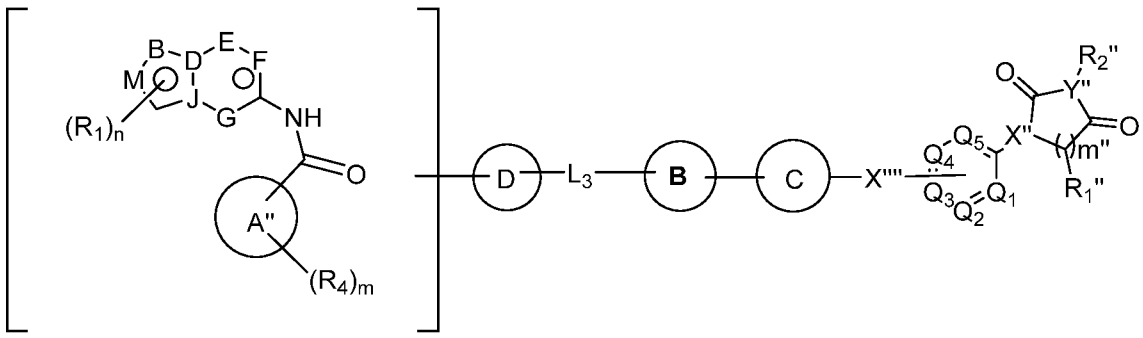
优选的，本发明某些实施方式中，式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐为式IV化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐，



IV

其中所述 R_1、n、R_2、R_3、环 A 如 PTM-3 中所定义和描述；所述 X"、m"、R_3"如本文 ULM-1 中所定义和描述；所述 L_3 如本文 LA 中所定义和描述；o、p、q、r 各自独立地为 1 或者 2；w_1、w_2 各自独立地为 CH 或者 N，且至少有一个为 N。

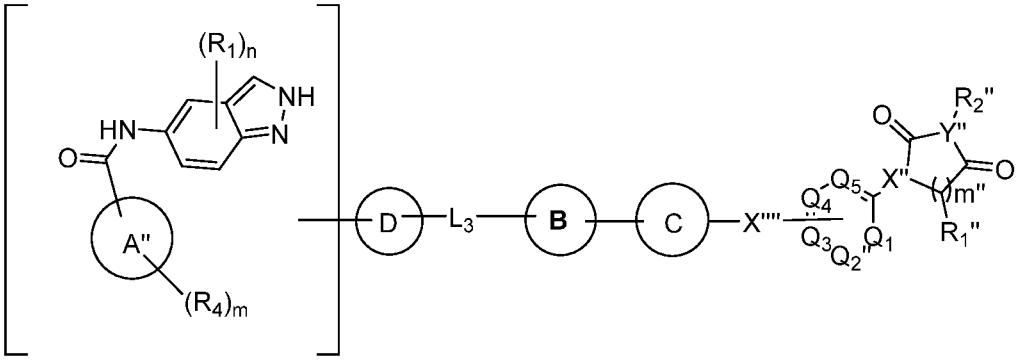
优选的，本发明某些实施方式中，式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐为式V化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐，



V

其中所述 R_1、n、R_4、B、D、E、F、G、J 和环 A″如 PTM-2′中所定义和描述；所述 Q_1、Q_2、Q_3、Q_4、Q_5、X"、Y"、m"、R_1"、R_2"如本文 ULM-1 中所定义和描述；所述 L_3、环 D、环 B、环 C 和 X"" 如本文 LA 中所定义和描述。

优选的，本发明某些实施方式中，式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐为式VI化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、代谢物、水合物、溶剂化物、前药和/或其药学上可接受的盐，



VI

其中所述 R_1、n、R_2、R_3、环 A″如 PTM-3 中所定义和描述；所述 Q_1、Q_2、Q_3、Q_4、Q_5、X"、Y"、m"、R_1"、R_2"如本文 ULM-1 中所定义和描述；所述 L_3、环 D、环 B、环 C 和 X""如本文 LA 中所定义和描述。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐的制备方法。

本发明提供了药物组合物，包括治疗有效量的式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，以及药学上可接受的载体、稀释剂或赋形剂。

本发明提供了药物组合物，包括治疗有效量的式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，以及药学上可接受的载体。

本发明提供了一种降解 IRAK4 蛋白的方法，包括使式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物与 IRAK4 蛋白接触。

本发明提供了一种物质 A 在制备 IRAK4 蛋白降解剂中的应用，所述物质 A 包括如前所述式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其前述药物组合物。

本发明所述式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物用作治疗或预防 IRAK4 介导的疾病或病症的药物使用。

本发明所述式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物用作治疗或预防 TLR(除 TLR3R 以外)或 IL-1β 受体家族(包括 IL-1R、IL-18R、IL-33R、IL-36R)介导的疾病或病症的药物使用。

本发明所述式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物用作治疗或预防 IRAK4 介导的疾病或病症的药物使用，所述 IRAK4 介导的疾病或病症为 MyD88 所驱动的疾病或病症。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防 IRAK4 介导的疾病或病症的药物中的应用。

本发明中，所述 IRAK4 介导的疾病或病症为 MyD88 所驱动的疾病或病症。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防 TLR(除 TLR3R 以外)或 IL-1β 受体家族(包括 IL-1R、IL-18R、IL-33R、IL-36R)介导的疾病或病症的药物中的应用。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防 IRAK4 调控的疾病或病症的药物中的应用，所述 IRAK4 介导的疾病或病症为 MyD88 所驱动的疾病或病症。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防癌症、神经退化性病症、病毒性疾病、自身免疫性疾病、炎性疾病、遗传性病症、激素相关疾病、代谢病症、与器官移植相关疾病、免疫缺陷病症、破坏性骨病、增生性病症、感染性疾病、与细胞死亡相关的病况、凝血酶诱发的血小板凝集、肝病、涉及 T 细胞活化的病理性免疫病况、心血管病症或 CNS 病症疾病的药物中的应用。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防癌症或增生性疾病中药物的应用，所述癌症或增生性疾病为脑癌、肾癌、肝癌、肾上腺癌、膀胱癌、乳癌、胃癌、卵巢癌、结肠癌、直肠癌、前列腺癌、胰腺癌、肺癌、阴道癌、宫颈癌、睾丸癌、泌尿生殖道癌、食道癌、喉癌、皮肤癌、骨癌、甲状腺癌、肉瘤、神经胶母细胞瘤、神经母细胞瘤、多发性骨髓瘤、胃肠癌、颈部或头部肿瘤、表皮过度增生、牛皮藓、前列腺增生、腺瘤、腺癌、角化棘皮瘤、表皮样癌、大细胞癌、非小细胞肺癌、淋巴瘤、霍奇金氏和非霍奇金氏、乳腺癌、滤泡癌、未分化性瘤、乳头装瘤、精原细胞瘤、黑素瘤、ABC DLBCL、霍奇金氏淋巴瘤、原发性皮肤 T 细胞淋巴瘤、慢性淋巴细胞性白血病、冒烟型惰性多发性骨髓瘤、白血病、弥漫性大 B 细胞淋巴瘤 DLBCL、慢性淋巴细胞性白血病 CLL、慢性淋巴细胞性淋巴瘤、原发性渗出性淋巴瘤、伯基特淋巴瘤(Burkitt's Lymphoma)／白血病、急性淋巴细胞性白血病、B 细胞前淋巴细胞

白血病、淋巴浆细胞淋巴瘤、瓦尔登斯特伦氏巨球蛋白血症(Waldenstroms′s macroglobulinemia WM)脾边缘区淋巴瘤、多发性骨髓瘤、或浆细胞瘤或血管内大 B 细胞淋巴瘤。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防神经退化性疾病的药物中的应用，所述神经退化性疾病为阿尔茨海默症、帕金森氏病、肌肉萎缩性侧索硬化、亨廷顿氏病(Huntington′s disease)、大脑缺血或有创伤性损伤、谷氨酸神经毒性、低氧症、癫痫症、糖尿病治疗、代谢综合症、肥胖、器官移植或移植物抗宿主疾病造成的神经退化性疾病。

本发明提供了式I、式II、式III、式IV、式V、式VI化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物在制备治疗或预防炎性疾病药物中的应用，所述炎性疾病为眼病，如眼过敏、结膜炎、干眼症或春季结膜炎、影响鼻部的疾病，包括过敏性鼻炎；自身免疫性血液病症，如溶血性贫血、再生不全性贫血、纯红细胞贫血和特发性血小板减少、全身性红斑性狼疮症、类风湿性关节炎、多软骨炎、硬皮病、皮肌炎、慢性活性肝炎、重症肌无力、史蒂芬－约翰逊综合症、特发性口炎性腹泻、字体免疫性发炎性肠病、肠易综合症、乳糜泻、齿根骨膜炎、肺透明膜病、肾病、肾小球疾病、酒精性肝病、多发性硬化症、内分泌性眼病、格雷弗氏病(Grave′s disease)、肉瘤病、干眼症、春季结膜角膜炎、间质性肺纤维化、牛皮藓性关节炎、全身性幼年型特发性关节炎、肾炎、血管炎、间质性膀胱炎、憩室炎、肾小球肾炎、慢性肉芽肿性疾病、子宫内膜异位、钩端螺旋体病肾病、青光眼、视网膜疾病、老化、头痛、疼痛、复杂区域疼痛综合症、心肥大、肌肉萎缩、分解代谢症、肥胖、胎儿生长缓慢、高胆固醇血症、心脏病、慢性心脏衰竭、间皮瘤、无汗性外胚层发育不良、白塞氏病、色素失禁症、佩吉特氏病(Paget′s disease)、胰脏炎、遗传性周期性发热综合症、哮喘、急性肺损伤、急性呼吸窘迫综合症、嗜伊红血球增多、过敏反应、全身性过敏反应、鼻窦炎、眼过敏、二氧化硅诱发的疾病、COPD、肺病、囊肿性纤维化、肝纤维化、肾纤维化、酒精性脂肪肝、非酒精性脂肪肝、心脏纤维化、银屑病、克罗恩病、炎症性肠病、酸诱发的肺损伤、肺动脉高压、多发性神经病、白内障、与全身性硬化症结合的肌肉炎症、包涵体肌炎、重症肌无力、甲状腺炎、阿狄森氏病(Addison′s disease)、扁平苔藓、1 型糖尿病、2 型糖尿病、阑尾炎、异位性皮炎、哮喘、过敏、细支气管炎、支气管炎、滑囊炎、子宫颈炎、胆管炎、胆囊炎、慢性移植排斥反应、结肠炎、结膜炎、膀胱炎、泪腺炎、皮炎、皮肌炎、脑炎、心内膜炎、子宫内膜炎、肠炎、小肠结肠炎、上踝炎、附睾炎、筋膜炎、纤维组织炎、胃炎、胃肠炎、亨诺－许兰紫斑病(Henoch-Schonlein purpura)、肝炎、化脓性汗腺炎、免疫球蛋白 A 肾病、间质性肺病、喉炎、乳腺炎、脑膜炎、脊髓炎、心肌炎、肌炎、肾炎、卵巢炎、睾丸炎、骨炎、耳炎、胰脏炎、腮腺炎、心包炎、腹膜炎、咽炎、胸膜炎、静脉炎、局部肺炎、肺炎、多发性肌炎、直肠炎、前列腺炎、肾盂肾炎、鼻炎、输卵管炎、窦炎、口腔炎、关节膜炎、肌腱炎、扁桃腺炎、溃疡性结肠炎、葡萄膜炎、阴道炎、血管炎、外阴炎、斑秃、多形

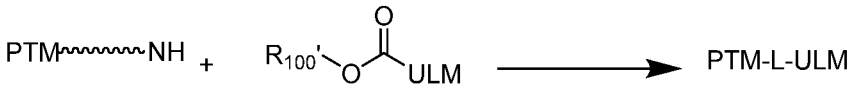
性红斑、疱疹样皮炎、硬化病、白斑病、超敏性血管炎、荨麻疹、大疱性类天疱疮、寻常天疱疮、落叶型天疱疮、副肿瘤性天疱疮、获得性大疱性表皮松懈、急性和慢性痛风、慢性痛风性关节炎、牛皮藓、牛皮藓性关节炎、类风湿性关节炎、幼年型类风湿性关节炎、隐热蛋白相关周其综合症或骨关节炎。

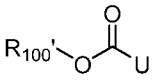
本发明提供一种治疗或预防由 IRAK4 介导的疾病或病症的方法，包括向有需要的患者施用治疗有效量的式I、式II、式III或式IV化合物、和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物。

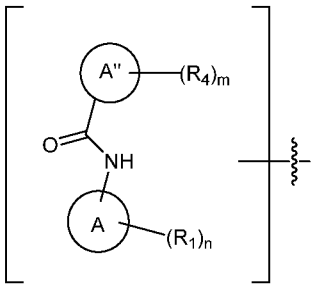
本发明提供一种治疗或预防由 IRAK4 介导的疾病或病症的方法，包括向有需要的患者施用治疗有效量的式I、式II、式III或式IV化合物、和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物，所述 IRAK4 介导的疾病或病症为 MyD88 所驱动的疾病或病症。

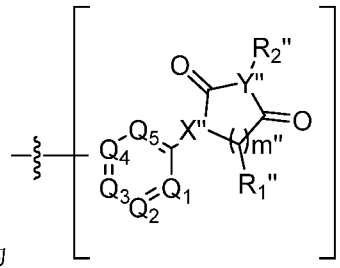
本发明提供一种治疗或预防由 TLR(除 TLR3R 以外)或 IL-1 受体家族(包括 IL-1R、IL-18R、IL-33R、IL-36R)介导的疾病或病症的方法，包括向有需要的患者施用治疗有效量的式I、式II、式III或式IV化合物、和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐，或其药物组合物。

本发明提供了式I化合物、和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐的制备方法，



其中所述 为连接链 L 的部分；所述 NH 可为伯胺或仲胺；所述 NH 基团通过与 

中的酯基在碱性条件下发生取代反应而制备式I化合物，所述 R_{100}'为五氟苯基或者对硝基苯基；所述 PTM 为 

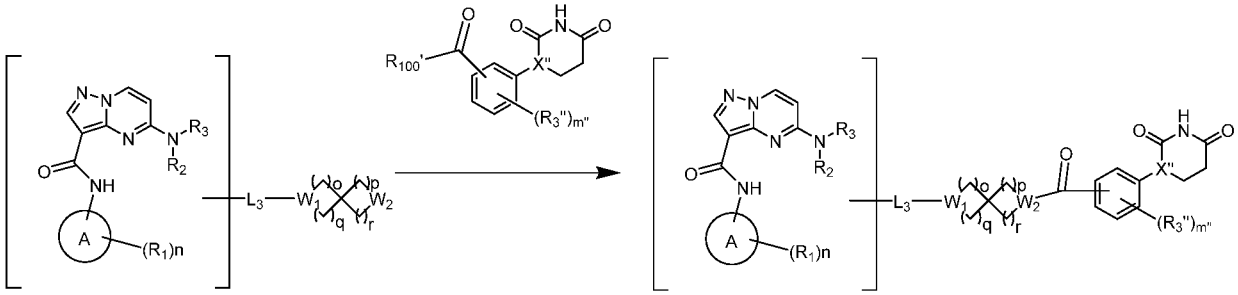
，其中所述环 A、环 A"、n、R_1、R_4、m 如 PTM-1 中所定义和描述；所述 ULM 为 

；所述 Q_1、Q_2、Q_3、Q_4、Q_5、X"、Y"、

m"、R_1"、R_2"如本文 ULM-1 中所定义；所述取代反应中的碱包括但不限于三乙胺、N,N-二异丙基乙胺、碳酸钾、碳酸钠、碳酸氢钠。

本发明提供了式II化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐的制备方法，

本发明提供了式IV化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐的制备方法，



IVa IVb IV

其中所述环 A、n、R_1、R_2、R_3如 PTM-3 中所定义和描述；L_3如 LA 中所定义和描述；W_2为 NH；W_1为 CH、或者 N；o、p、q、r 各自独立地为 1 或者 2；X"为 CH 或者 N； R3"、m"如 ULM-1 中多定义和描述；所述 R_{100}'为五氟苯基或者对硝基苯基；所述式IVa 与式IVb 发生取代反应得到式IV化合物；所述取代反应中的碱包括但不限于三乙胺、N,N-二异丙基乙胺、碳酸钾、碳酸钠、碳酸氢钠。

详细说明：除非有相反陈述、下列用在说明书和权利要求书中的术语具有下述含义。

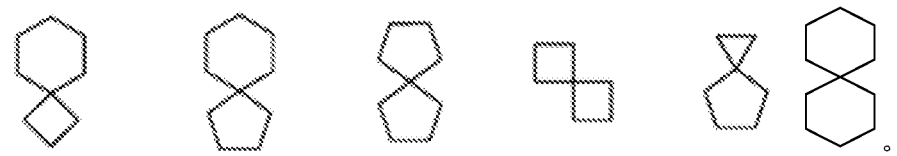
“烷基”是指饱和的脂肪族烃基团，包括直链或支链烷基；C_1-C_8 烷基是指含有 1-8 个碳原子的烷基，例如甲基、乙基、正丙基、异丙基、正丁基、异丁基、 叔丁基、仲丁基、正戊基、1、1-二甲基丙基、1、2-二甲基丙基、2、2-二甲基丙基、1-乙基丙基、 2-甲基丁基、3-甲基丁基、正己基、1-乙基-2-甲基丙基、1、1、2-三甲基丙基、1、1-二甲基丁 基、1、2-二甲基丁基、2、2-二甲基丁基、1、3-二甲基丁基、2-乙基丁基、2-甲基戊基、3-甲基 戊基、4-甲基戊基、2、3-二甲基丁基、正庚基、2-甲基己基、3-甲基己基、4-甲基己基、5-甲基己基、2、3-二甲基戊基、2、4-二甲基戊基、2、2-二甲基戊基、3、3-二甲基戊基、2-乙基戊基、 3-乙基戊基、正辛基、2、3-二甲基己基、2、4-二甲基己基、2、5-二甲基己基、2、2-二甲基己 基、3、3-二甲基己基、4、4-二甲基己基、2-乙基己基、3-乙基己基、4-乙基己基、2-甲基-2-乙 基戊基、2-甲基-3-乙基戊基或其各种支链异构体；优选 C_1-C_6 烷基；进一步优选 C_1-C_4 烷基。所述烷基可以是取代的或未取代的。

“环烷基”指饱和或部分不饱和的单环或多环环状烃取代基；“C_3-C_{12} 环烷基”指包括 3 至 12 个碳原子的环烷基；“C_3-C_8 元环烷基”指包括 3 至 8 个碳原子的环烷基；“C_5-C_{10} 元环烷基”指包括 5 至 10 个碳原子的环烷基；

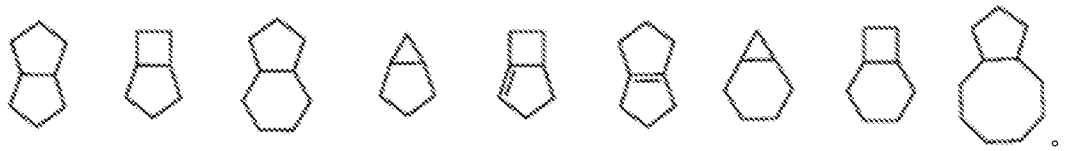
单环环烷基的非限制性实施例包含环丙基、环丁基、环戊基、环戊烯基、环己基、环己烯基、环己二烯基、环庚基、环庚三烯基、环辛基等，优选环丙基、环丁基、环戊基、环己基；优选 C_3-C_8

元环烷基；进一步优选 C_3-C_6环烷基。

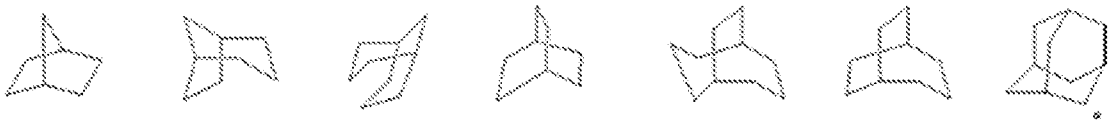
多环环烷基包括螺环、稠环和桥环的环烷基。“螺环烷基”指单环之间共用一个碳原子(称螺原子)的多环基团，他们可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统。根据环与环之间共用螺原子的数目将螺环烷基分为单螺环烷基、双螺环烷基基或多螺环烷基，优选双螺环烷基。螺环烷基的非限制性实施例包含：



“稠环烷基”指系统中的每个环与体系中的其他环共享毗邻的一对碳原子的全碳多环基团，其中一个或多个环可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统。根据组成环的数目可以分为双环、三环、四环或多环稠环烷基，优选双环稠环烷基。稠环烷基的非限制性实施例包含：



“桥环烷基”指任意两个环共用两个不直接连接的碳原子的全碳多环基团，他们可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统，根据组成环的数目可以分为双环、三环、四环或多环桥环烷基。桥环烷基的非限制性实施例包含：

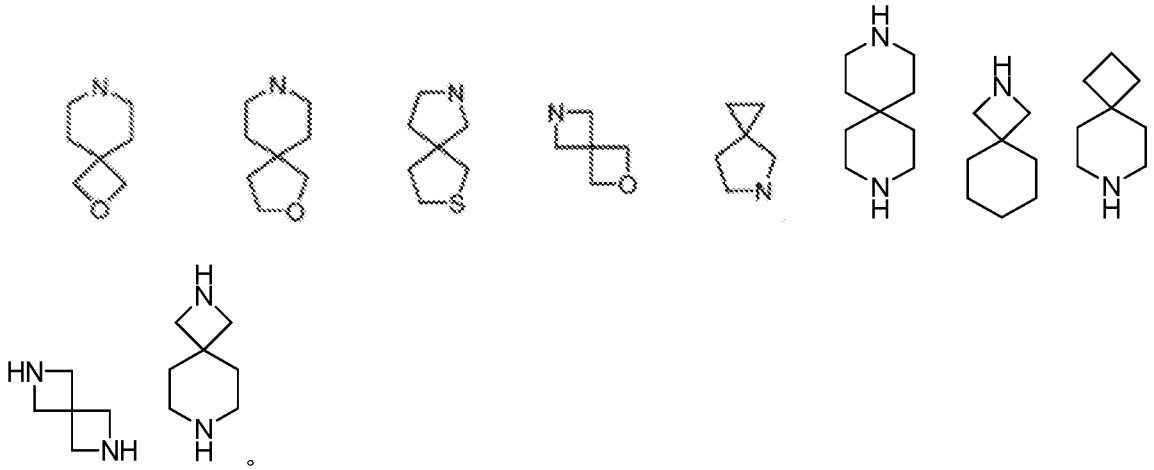


所述环烷基环可以稠合于芳基、杂芳基或杂环烷基环上，其中与母体结构连接在一起的环为环烷基，非限制性实施例包括茚满基、四氢萘基、苯并环庚烷基等。所述环烷基可以是任选取代的或未取代的。

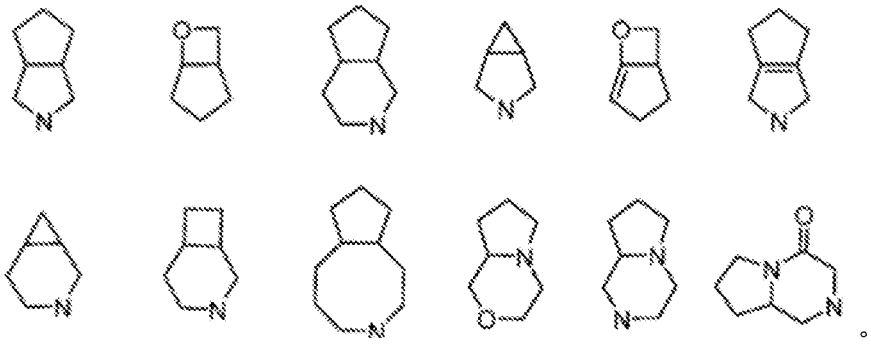
“杂环烷基”指饱和的或部分不饱和的单环或多环环状烃取代基，其中一个或多个环原子选自氮、氧或 $S(O)_r$(其中 r 是整数 0、1 或 2)，但不包含-O-O-、-O-S-或-S-S-的环部分，其余环原子为碳。“3-12 元杂环烷基”指包含 3 至 12 个环原子的环基，“5-10 元杂环烷基”指包含 5 至 10 个环原子的环基，“3-8 元杂环烷基”指包含 3 至 8 个环原子的环基，优选含有 1-3 个选自 N、O 或 S 杂原子的“3-12 元杂环烷基”，进一步优选含有 1 个或 2 个 N 原子的 3-12 元杂环烷基。

单环杂环烷基的非限制性实施例包含吡咯烷基、哌啶基、哌嗪基、吗啉基、硫代吗啉基、高哌嗪基等，优选哌啶基和哌嗪基。

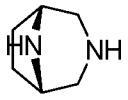
多环杂环烷基包括螺环、稠环和桥环的杂环烷基。“螺杂环烷基”指单环之间共用一个原子(称螺原子)的多环杂环烷基团，其中一个或多个环原子选自氮、氧或 S(O)r(其中 r 是整数 0、 1、2)，其余环原子为碳。他们可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统。根据环与环之间共用螺原子的数目将螺环烷基分为单螺杂环烷基、双螺杂环烷基或多螺杂环烷基，优选含有 1-3 个选自 N、O 或 S 杂原子的饱和的“3-12 元双螺杂环烷基”；进一步优选含有 1 个或 2 个 N 原子的饱和的“3-12 元双螺杂环烷基”。螺杂环烷基的非限制性实施例包含：



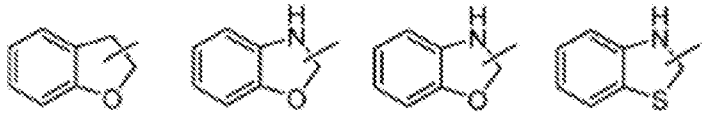
“稠杂环烷基”指系统中的每个环与体系中的其他环共享毗邻的一对原子的多环杂环烷基团，一个或多个环可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统，其中一个或多个环原子选自氮、氧或 S(O)r(其中 r 是整数 0、1、2)，其余环原子为碳。根据组成环的数目可以分为双环、三环、四环或多环稠杂环烷基，优选含有 1-3 个选自 N、O 或 S 杂原子的 “3-12 元双环稠杂环烷基”；进一步优选含有 1 个或 2 个 N 原子的饱和的“3-12 元双环稠杂环烷基”。稠杂环烷基的非限制性实施例包含：



“桥杂环烷基”指任意两个环共用两个不直接连接的原子的多环杂环烷基团，他们可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统，其中一个或多个环原子选自氮、氧或 $S(O)_r$(其中 r 是整数 0、1、2)，其余环原子为碳。根据组成环的数目可以分为双环、三环、四环或多环桥环烷基，桥杂环烷基的非限制性实施例包含：

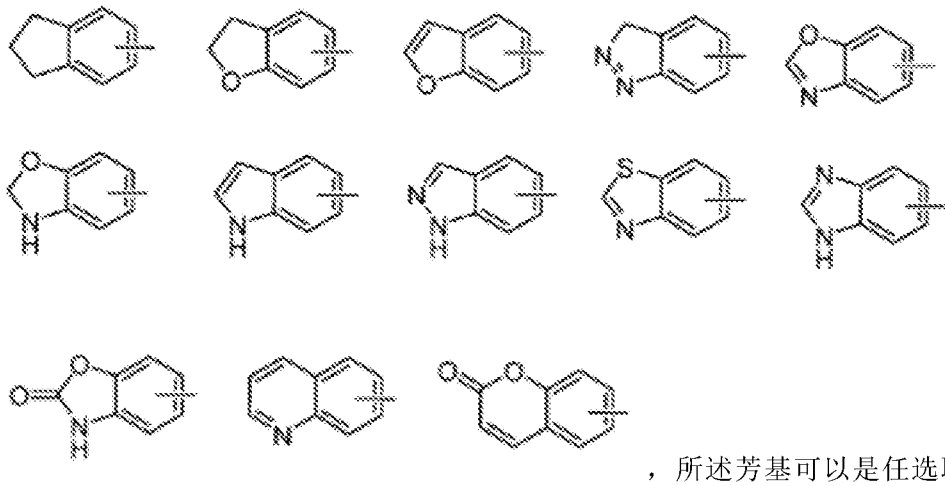


所述杂环烷基环可以稠合于芳基、杂芳基或环烷基环上，其中与母体结构连接在一起的环为杂环烷基，非限制性实施例包含：



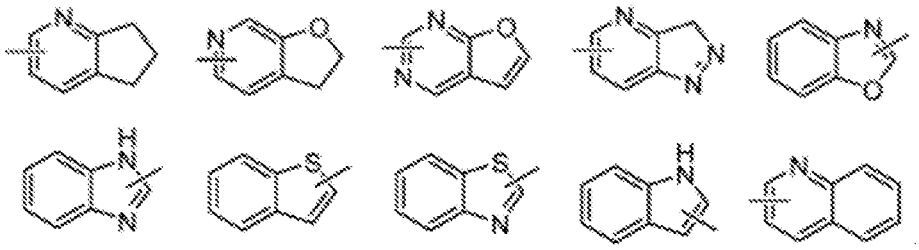
，所述杂环烷基可以是任选取代的或未取代的。

“芳基”指全碳单环或稠合多环(也就是共享毗邻碳原子对的环)且具有共轭的 π 电子体系的多环基团， “6-10 元芳基”指含有 6-10 个碳的全碳芳基，例如苯基和萘基；优选苯基。所述芳基环可以稠合于杂芳基、杂环烷基或环烷基环上，其中与母体结构连接在一起的环为芳基环，非限制性实施例包含：



，所述芳基可以是任选取代的或未取代的。

“杂芳基”指包含 1 至 4 个杂原子的杂芳族体系，所述杂原子包括氮、氧或 $S(O)_r$(其中 r 是整数 0、1、2)，5-6 元杂芳基指含有 5-6 个环原子的杂芳族体系，5-10 元杂芳基指含有 5-10 个环原子的杂芳族体系，优选 5-6 元杂芳基；进一步优选含有 1 个或 2 个 N 原子的 5-6 元杂芳基；非限制实施例包括呋喃基、噻吩基、吡啶基、吡咯基、N-烷基吡咯基、嘧啶基、吡嗪基、吡唑、咪唑基、三唑基、四唑基等；优选吡啶基。所述杂芳基环可以稠合于芳基、杂环烷基或环烷基环上，其中与母体结构连接在一起的环为杂芳基环，非限制性实施例包含：

 ，所述杂芳基可以是任选取代的或未取代的。

“烯基”指由至少两个碳原子和至少一个碳-碳双键组成的如上述所定义的烷基，“C_{2-8}烯基”指含有2-8个碳的直链或支链烯基，包括但不限于乙烯基、1-丙烯基、2-丙烯基、1-、2-或3丁烯基等，优选“C_{2-6}烯基”，进一步优选“C_{2-4}烯基”。所述烯基可以是取代的或未取代的。

“炔基”指至少两个碳原子和至少一个碳-碳三键组成的如上所定义的烷基，“C_{2-8}炔基”指含有 2-8个碳的直链或支链炔基，包括但不限于乙炔基、1-丙炔基、2-丙炔基、1-、2-或 3-丁炔基，优选“C_{2-6}炔基”，进一步优选“C_{2-4}炔基”。所述炔基可以是取代的或未取代的。

“亚基”指二价基团，如亚烷基指二价烷基，亚烯基指二价烯基，亚炔基指二价炔基，亚环烷基指二价环烷基，亚杂环烷基指二价杂环烷基，亚芳基指二价芳基，亚杂芳基指二价杂芳基，所述烷基、烯基、炔基、环烷基、杂环烷基、芳基、杂芳基如上所定义，所述亚基可以是任选取代的或未取代的。

“烷氧基”指-O-(烷基)，其中所述烷基如上所定义。“C_1-C_8烷氧基”指含 1-8 个碳的烷基氧基，非限制性实施例包括甲氧基、乙氧基、丙氧基、丁氧基等。所述烷氧基可以是任选取代的或未取代的。

“环烷氧基”指-O-(未取代的环烷基)，其中所述环烷基如上所定义。C_3-C_8环烷氧基指含 3-8 个碳的环烷基氧基，非限制性实施例包括环丙氧基、环丁氧基、环戊氧基、环己氧基等。所述环烷氧基可以是任选取代的或未取代的。

“卤代烷基”指被一个或多个氟、氯、溴或碘原子取代的烷基，其中所述烷基如上所定义，非限制性实施例包括二氟甲基、二氯甲基、二溴甲基、三氟甲基、三氯甲基、三溴甲基等。

“卤代烷氧基”指烷基上的氢被一个或多个氟、氯、溴或碘原子取代的基团，其中所述烷氧基如上所定义。例如二氟甲氧基、二氯甲氧基、二溴甲氧基、三氟甲氧基、三氯甲氧基、三溴甲氧基等。

“羟基烷基”指任选被一个或多个-OH 取代的烷基，其中所述烷基如上所定义，非限制性实施例包括羟甲基、羟乙基、羟基丙基、羟基异丙基。

“氨基烷基”指任选被一个或多个-NH_2取代的烷基，其中所述烷基如上所定义，非限制性实施例包括氨基甲基、氨基乙基、氨基丙基、氨基异丙基。

“氨”和“胺”是本领域公认的，并且指取代或未取代的氨。

“氧代”指=O 基团。

“卤素”指氟、氯、溴或碘。

“氰基”指-CN。

“羟基”指-OH。

“Raney-Ni”指雷尼镍(氢活性催化还原剂)。

“HATU”指 2-(7-氮杂苯并三氮唑)-N,N,N',N'-四甲基脲六氟磷酸酯。

“DIEA”指二异丙基乙胺。

“MeOH”指甲醇。

“$NaBH_3CN$”指氰基硼氢化钠。

“$LiAlH_4$”指铝锂氢。

“THF”指四氢呋喃。

“DMF”指二甲基甲酰胺。

“Py-BOP”指六氟磷酸苯并三唑-1-基-氧基三吡咯烷基磷。

“HATU”指 2-(7-偶氮苯并三氮唑)-N,N,N',N'-四甲基脲六氟磷酸酯。

“TFA”指三乙胺。

“EA”指乙酸乙酯。

“CbzCl”指氯甲酸苄酯。

“Cs_2CO_3”指碳酸铯。

“$NaHCO_3$”指碳酸氢钠。

“IBX”指 2-碘酰基苯甲酸。

“STAB”指三乙酰氧基硼氢化钠。

“DMSO”指二甲基亚砜。

“K_2CO_3”指碳酸钾。

“DCM”指二氯甲烷。

“KI”指碘化钾。

“NH_4Cl”指氯化铵。

“Na_2SO_4”指硫酸钠。

“$LiBH_4$”指硼氢化锂。

“NMP”指 N-甲基吡咯烷酮。

“*i*-PrOH”指异丙醇。

“EtOH”指乙醇。

“Pd $(OH)_2$/C”指氢氧化钯/碳。

“DCE”指 1,2-二氯乙烷。

“PE”指石油醚。

“sat.”指饱和溶液。

“PCC”指氯铬酸吡啶盐。

“CuI”指碘化亚铜。

“TsCl”指 4-甲苯磺酰氯。

“HNO_3”指硝酸。

“$NaBH(OAc)_3$”指醋酸硼氢化钠。

“Dess-Martin”指(1,1,1-三乙酰氧基)-1,1-二氢-1,2-苯碘酰-3(1H)-酮。

“DMP”指邻苯二甲酸二甲酯。

“TEA”指三乙胺。

“DAST”指二乙氨基三氟化硫。

“NBS”指 N-溴代丁二酰亚胺。

“$(Ph)_2NH$”指二苯基氨。

“$Pd_2(dba)_3$”指三(二亚苄基丙酮)二钯。

“Xantphos”指 4,5-双二苯基膦-9,9-二甲基氧杂蒽。

“NaOt-Bu”指叔丁醇钠。

“DPBS”指杜氏磷酸缓冲液。

“PBS”指磷酸缓冲盐溶液。

“SDS-PAGE”指十二烷基硫酸钠-聚丙烯酰胺凝胶电泳。

“PVDF”指聚偏二氟乙烯。

“多个”独立地指 1、2、3、4、5、6、7、8、9 或 10 个。

“任选”意味着随后所描述地事件或环境可以但不必发生，该说明包括该事件或环境发生或不发生地场合。例如，“任选被烷基取代的杂环烷基团”意味着烷基可以但不必须存在，该说明包括杂环烷基团被烷基取代的情形和杂环烷基团不被烷基取代的情形。

“取代的”指基团中的一个或多个氢原子、优选为最多 5 个、进一步优选为 1～3 个氢原子彼此独立地被相应数目的取代基取代。不言而喻、取代基仅处在它们的可能的化学位置、本领域技术人员能够在不付出过多努力的情况下确定(通过实验或理论)可能或不可能的取 代。例如、具有游离氢的氨基或羟基与具有不饱和(如烯属)键的碳原子结合时可能是不稳定的。

“药物组合物”表示含有一种或多种本文所述化合物或其生理学上/可药用的盐或 前体药物与其他化学组分的混合物、以及其他组分例如生理学/可药用的载体和赋形剂。药物组合物的目的是促进对生物体的给药、利于活性成分的吸收进而发挥生物活性。

本发明还提供式式I、式II、式III、式IV化合物药学上可接受的盐。术语“药学上可接受的盐”是指相对无毒的本发明化合物的酸加成盐或碱加成盐。所述酸加成盐为本发明式(I)化合物与合适的无机酸或者有机酸形成的盐，这些盐可在化合物最后的分离和提纯过程中制备，或者可用纯化的式(I)

化合物以其游离碱形式与适宜的有机酸或无机酸进行反应来制备。代表性酸加成盐包括氢溴酸盐、盐酸盐、硫酸盐、硫酸氢盐、亚硫酸盐、乙酸盐、草酸盐、戊酸盐、油酸盐、棕榈酸盐、硬脂酸盐、月硅酸盐、硼酸盐、苯甲酸盐、乳酸盐、磷酸盐、磷酸氢盐、碳酸盐、碳酸氢盐、甲苯甲酸盐、柠檬酸盐、马来酸盐、富马酸盐、琥珀酸盐、酒石酸盐、苯甲酸盐、甲磺酸盐、对甲苯磺酸盐、葡萄糖酸盐、乳糖酸盐和月桂基磺酸盐等。所述碱加成盐为式(I)化合物与合适的无机碱或者有机碱形成的盐，包括例如与碱金属、碱土金属、季铵阳离子形成的盐，例如钠盐、锂盐、钾盐、钙盐、镁盐、四甲基季铵盐、四乙基季铵盐等；胺盐包括与氨(NH_3)、伯胺、仲胺或叔胺形成的盐，如甲胺盐、二甲胺盐、三甲胺盐、三乙胺盐、乙胺盐等。

本发明的化合物或其药学上可接受的盐可给药于哺乳动物包括人，可口服、直肠、肠胃外(静脉内、肌肉内或皮下)、局部给药(粉剂、软膏剂或滴剂)、或瘤内给药。

本发明化合物的给药剂量可以大约为 0.05-300mg/kg 体重/天，优选 10-300mg/kg 体重/天，优选 10-150mg/kg 体重/天。

本发明化合物或其药学上可接受的盐可以配制为用于口服给药的固体剂型，包括但不限于胶囊剂、片剂、丸剂、散剂和颗粒剂等。在这些固体剂型中，本发明式(I)化合物作为活性成分与至少一种常规惰性赋形剂(或载体)混合，例如与柠檬酸钠或磷酸二钙，或与下述成分混合：(1)填料或增容剂，如淀粉、乳糖、蔗糖、葡萄糖、甘露醇和硅酸等；(2)粘合剂，如羟甲基纤维素、藻酸盐、明胶、聚乙烯基吡咯烷酮、蔗糖和阿拉伯胶等；(3)保湿剂，如甘油等；(4)崩解剂，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等；(5)缓溶剂，如石蜡等；(6)吸收加速剂，如季铵化合物等；(7)润湿剂如鲸蜡醇和单硬脂酸甘油酯等；(8)吸附剂，如高岭土等；和(9)润滑剂，如滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、十二烷基硫酸钠等，或其混合物。胶囊剂、片剂和丸剂中也可包含缓冲剂。

所述固体剂型如片剂、糖丸、胶囊剂、丸剂和颗粒剂可采用包衣和壳材料例如肠溶衣和其他本领域公知的材料进行包衣或微囊化。它们可包含不透明剂，并且这种组合物中活性成分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质和蜡类物质。必要时、活性成分也可与上述赋形剂中的一种或多种形成微胶囊形式。

本发明化合物或其药学上可接受的盐可以配制为用于口服给药的液体剂型，包括但不限于药学上可接受的乳液、溶液、悬浮液、糖浆和酊剂等。除了作为活性成分的式(I)化合物或其药学上可接受的盐外，液体剂型可包含本领域中常规采用的惰性稀释剂如水和其他溶剂、增溶剂和乳化剂，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类，特别是棉籽油、花生油、玉米胚油、橄榄油、蓖麻油和芝麻油等或这些物质的混合物等。除了这些惰性稀释剂外，本发明液体剂型也可包含常规助剂，如润湿剂、乳化剂和悬浮剂、甜味剂、矫味剂和香料等。

所述悬浮剂包括如乙氧基化异十八烷醇、聚氧乙烯山梨醇和脱水山梨醇只、微晶纤维素、甲醇铝和琼脂等或这些物质的混合物。

本发明化合物或其药学上可接受的盐可以配制为用于肠胃外注射的剂型包括但不限于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，以及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。

本发明化合物或其药学上可接受的盐也可以配制为用于局部给药的剂型包括如软膏剂、散剂、栓剂、滴剂、喷射剂和吸入剂等。作为活性成分的本发明式(I)化合物或其药学上可接受的盐在无菌条件下和生理上可接受的载体及任选的防腐剂、缓冲剂，或必要时可能需要的推进剂一起混合。

本发明还提供药物组合物，它含有本发明式(I)化合物或其药学上可接受的盐作为活性成分，以及药学上可接受载体、赋形剂或稀释剂。在制备药物组合物时，通常是将本发明式(I)化合物或其药学上可接受的盐与药学上可接受载体、赋形剂或稀释剂混合。

可以按常规制备方法将所述本发明组合物配制为常规药物制剂。例如片剂、丸剂、胶囊剂、散剂、颗粒剂、乳液剂、混浮剂、分散液、溶液剂、糖浆剂、酏剂、软膏剂、滴剂、栓剂、吸入剂、喷射剂等。

本发明所述的化合物或其药学上可接受的盐可以单独给药，或者(如果需要)与其他药学上可接受的治疗剂联合给药，如与其他抗肿瘤药物、抗炎症药物或自身免疫性药物组合。待组合的各成分可同时或顺序的给予，以单一制剂形式或以不同制剂的形式给予。所述组合不仅可包括本发明化合物和一种其他活性剂的组合，也可包括本发明化合物和两种或更多种其他活性剂的组合。

本发明通过 IRAK4 激酶活性测试实验证明本发明所述化合物能够有效的与 IRAK4 靶蛋白结合或产生抑制效果；通过 Western-Blot 证明本发明所述化合物能够有效的特异性的降解 THP-1 细胞中的 IRAK4 蛋白；通过 LPS 诱导正常人全血 PBMC 分泌的细胞因子浓度测定实验证明本发明化合物能有效的抑制免疫细胞 IL-6 的产生；通过 Western-Blot 证明本发明所述化合物对人 PBMC 细胞中 IRAK4 长链(IRAK4-L)和 IRAK4 短链(IRAK4-S)均具有显著的降解效果。本发明所述式I、式II、式III、式IV化合物，和/其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药和/或其药学上可接受的盐可有效的降解 IRAK4 蛋白，从而达到预防或治疗与 IRAK4 相关的疾病或病症的效果。

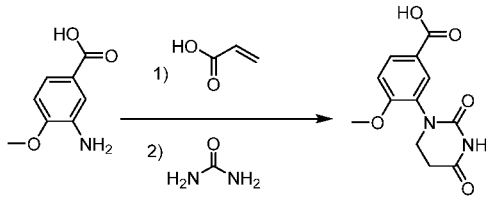
具体实施方式

下面将结合实施例对本发明做进一步详细、完整地说明，但决非限制本发明，本发明也并非仅局限于实施例的内容。本发明实施例中的起始原料是已知的并且可以在市场上买到、或者可以采用或按照本领域已知的方法来合成。在无特殊说明的情况下，本发明实施例中未注明具体条件的实验方法，通常按照常规条件，或按照原料或商品制造厂商所建议的条件。

I 化合物制备实施例

中间体 1：3-(2,4-二氧代基四氢嘧啶-1(*2H*)-基)-4-甲氧基苯甲酸

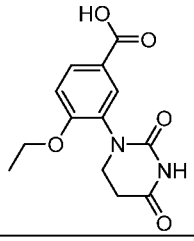
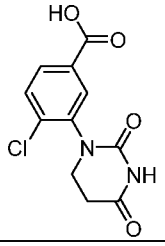
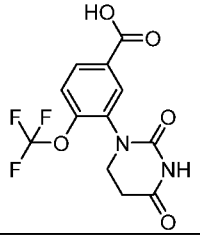
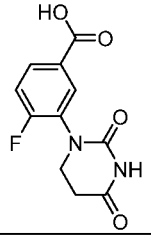
步骤 1：3-(2,4-二氧代基四氢嘧啶-1(*2H*)-基)-4-甲氧基苯甲酸的制备

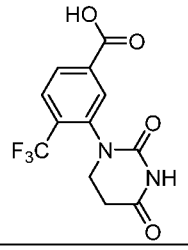
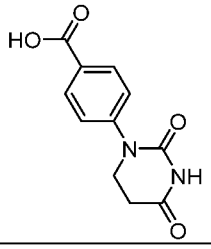
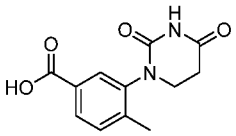


将 3-氨基-4-甲氧基苯甲酸 (5.0 g, 2.93 mmol)悬浮于丙烯酸 (8.05 mL, 117 mmol)中，并在 100 ℃下搅拌反应 3 h，然后将反应液搅拌冷却至室温。加入乙酸 (33 ml)，将搅拌的悬浮液在 100 ℃加热 10 分钟，加入尿素 (11.00 g, 183 mmol)，反应液在 120 ℃搅拌过夜。将反应液加入到冰水和浓盐酸 (37%)的混合液中，搅拌，将得到的悬浮液在 5 ℃的冰箱中保存过夜，然后过滤，固体用水洗涤并干燥，得到固体。将固体在盐酸溶液 (0.05M)中研磨，过滤，甲基叔丁基醚洗涤，40 ℃下减压干燥，得到目标产物 3-(2,4-二氧代基四氢嘧啶-1(*2H*)-基)-4-甲氧基苯甲酸。

1H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 10.34 (s, 1H), 7.92 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 3.94 - 3.82 (m, 3H), 3.60 (t, *J* = 6.7 Hz, 2H), 2.69 (s, 2H).

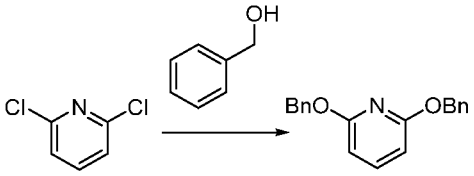
以下中间体参照中间体1的方法制备：

中间体	结构	名称	LC-MS
中间体2		3-(2,4-二氧代基四氢嘧啶-1(*2H*)-基)-4-乙氧基苯甲酸	(ESI,*m/z*):[M+H]$^+$=279.1
中间体3		4-氯-3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸	(ESI,*m/z*):[M+H]$^+$=269.0
中间体4		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酸	(ESI,*m/z*):[M+H]$^+$=319.1
中间体5		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-氟苯甲酸	(ESI,*m/z*):[M+H]$^+$=253.0

中间体6		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-(三氟甲基)苯甲酸	(ESI,*m/z*):[M+H]$^+$=303.0
中间体7		4-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸	(ESI,*m/z*):[M+H]$^+$=235.1
中间体35		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸	(ESI,*m/z*):[M+H]$^+$=249.1

中间体 8：3-(2,6-二氧代基哌啶-3-基)-4-氟苯甲酸

步骤 1：2,6-双(苄氧基)吡啶的制备

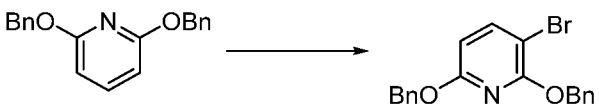


在 0 ℃下，向氢化钠 (60%矿物油混合物, 54.0 g, 1.35 mol)的 *N*,*N*-二甲基甲酰胺 (600 mL)溶液中加入苄醇 (109.6 g, 1.01 mol)。搅拌 30 分钟后，随后加入 2,6-二氯吡啶 (50.0 g, 0.338 mol)。将该反应混合物加热至 80 ℃并搅拌反应过夜，冷却至室温后，将反应混合物用冰水 (1000 mL)淬灭。过滤固体并干燥，得到目标产物 2,6-双(苄氧基)吡啶。

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.68 (t, J = 8.4 Hz, 1H), 7.48-7.36 (m, 10H), 6.45 (d, J = 8.4 Hz, 2H), 5.38 (s, 4H).

LC-MS: (ESI, *m/z*): [M+H]$^+$=292.2.

步骤 2：2,6-双(苄氧基)-3-溴吡啶的制备



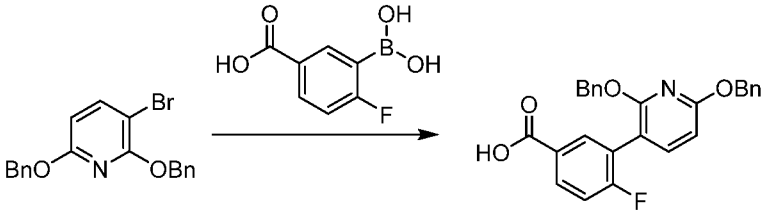
向 2,6-双(苄氧基)吡啶 (75.9 g, 0.26 mol)在乙腈 (600 mL)中的溶液中添加 *N*-溴代琥珀酰亚胺 (41.7g, 0.23mol)。将该反应混合物在 80 ℃下搅拌反应 2 小时。反应完成后，将反应混合物减压浓缩。浓缩物用乙酸乙酯 (500 mL)稀释，并用水和饱和食盐水洗涤。收集有机层并经无水硫酸钠干燥，过滤并

浓缩。浓缩物经硅胶柱纯化，得到目标产物 2,6-双(苄氧基)-3-溴吡啶。

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.88 (d, J = 8.4 Hz, 1H), 7.45-7.37 (m, 10H), 6.44 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H), 5.33 (s, 2H).

LC-MS: (ESI, m/z): $[M+H]^+$=372.1.

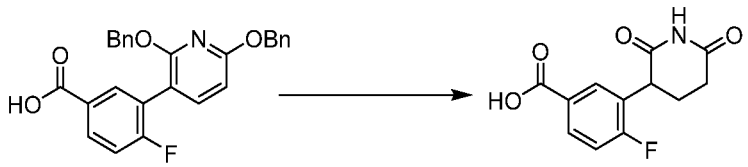
步骤 3：3-(2,6-双(苄氧基)吡啶-3-基)-4-氟苯甲酸的制备



向 2,6-双(苄氧基)-3-溴吡啶 (3.1 g, 8.37 mmol)和 3-硼酸基-4-氟苯甲酸 (1.85 g, 10.05 mmol)的二氧六环 (31 mL)和水 (7.5 mL)的混合物中加入 $PdCl_2$(dppf)-氯仿复合物 (612 mg, 0.84 mmol)和碳酸钠 (1.77 g, 16.74 mmol)。在氮气保护下将反应混合物加热至 90 ℃并保持反应 16 小时。反应完成后，加入 15% 盐酸溶液 (20 mL)，并用乙酸乙酯 (100 mL×3)萃取，用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥后减压浓缩，并将浓缩物经硅胶柱纯化，得到目标产物 3-(2,6-双(苄氧基)吡啶-3-基)-4-氟苯甲酸。

LC-MS: (ESI, m/z): $[M+H]^+$= 430.2

步骤 4: 3-(2,6-二氧代基哌啶-3-基)-4-氟苯甲酸的制备

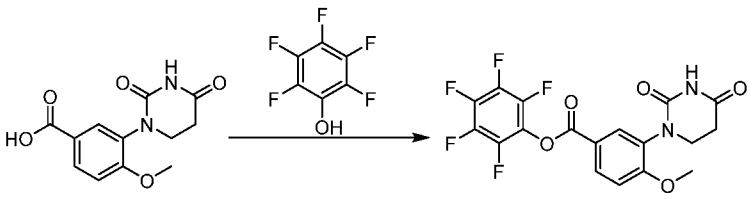


向 3-(2,6-双(苄氧基)吡啶-3-基)-4-氟苯甲酸 (1.50 g, 3.49 mmol)在甲醇 (10 mL)中的溶液中加入钯/碳 (10%, 120 mg)。室温下，反应混合物在氢气氛围下搅拌反应 48 小时。反应完成后，反应混合物经硅藻土过滤，并将滤液减压浓缩。浓缩物经柱纯化，得到目标产物 3-(2，6-二氧代基哌啶-3-基)-4-氟苯甲酸。

LC-MS: (ESI, m/z): $[M+H]^+$= 252.1

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 10.92 (s, 1H), 7.91 –7.95 (m, 2H), 7.30-7.34 (m, 1H), 4.15-4.19 (m, 1H), 2.70-2.79 (m, 1H), 2.53-2.57 (m, 1H), 2.23-2.27 (m, 1H), 2.01-2.07 (m, 1H).

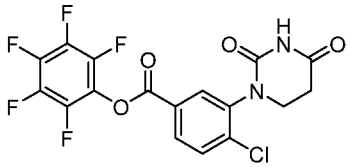
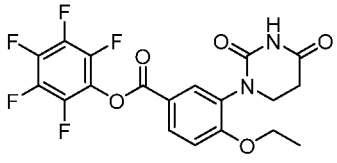
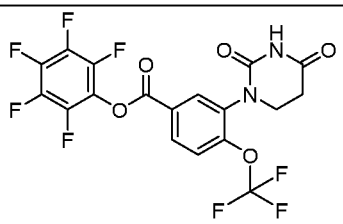
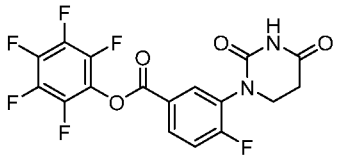
中间体 9：3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯基酯

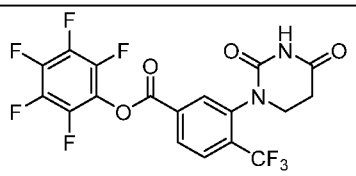
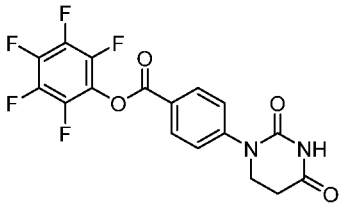
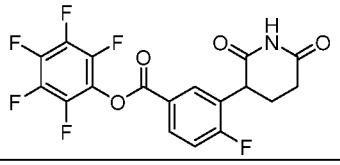
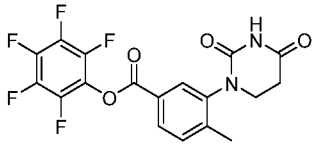


3-(2,4-二氧代基四氢嘧啶-1(*2H*)-基)-4-甲氧基苯甲酸 (2.0 g, 7.58 mmol)，2,3,4,5,6-五氟苯酚 (1.67 g, 9.09 mmol)和 *N*,*N*'-二环己基碳酰亚胺 (1.87 g, 9.09 mmol)在 *N*,*N*-二甲基甲酰胺 (20 mL)溶液中的混合物在室温下搅拌反应 3 h。将反应液倒入水 (200 mL)中并搅拌 0.5 h，溶液用乙酸乙酯 (200 mL×3)萃取。收集有机相，并用水 (500 mL×2)和饱和食盐水 (300 mL)洗涤，用无水硫酸钠干燥，过滤并浓缩。浓缩物经硅胶柱纯化，得到目标产物 3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯基酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=431.1

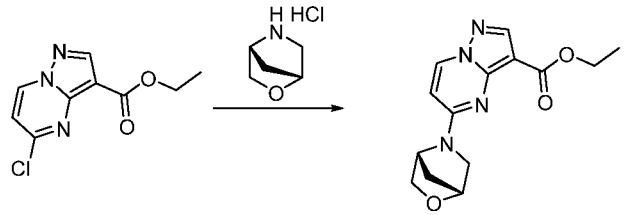
以下中间体参照中间体9的方法制备：

中间体	结构	名称	LC-MS
中间体10		4-氯-3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯基酯	(ESI,*m/z*):$[M+H]^+$=435.0
中间体11		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-乙氧基苯甲酸五氟苯基酯	(ESI,*m/z*):$[M+H]^+$=445.1
中间体12		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酸五氟苯基酯	(ESI,*m/z*):$[M+H]^+$=485.0
中间体13		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-氟苯甲酸五氟苯基酯	(ESI,*m/z*):$[M+H]^+$=419.0

中间体14		3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-(三氟甲基)苯甲酸五氟苯基酯	(ESI,*m/z*):[M+H]$^+$=469.0
中间体15		4-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯基酯	(ESI,*m/z*):[M+H]$^+$=401.0
中间体16		3-(2,6-二氧代基哌啶-3-基)-4-氟苯甲酸五氟苯基酯	(ESI,*m/z*):[M+H]$^+$=418.0
中间体36		3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸五氟苯酯	(ESI,*m/z*):[M+H]$^+$=415.0

中间体17：5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑[1,5-a]嘧啶-3-甲酸

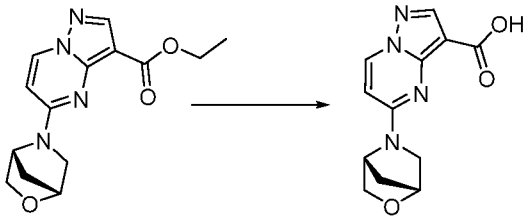
步骤1：5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酸乙酯的制备



5-氯吡唑并[1,5-a]嘧啶-3-甲酸乙酯 (5.0 g, 22.1 mmol)和 (1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷盐酸盐 (3.0 g, 22.1 mmol)用乙腈 (60 mL)溶解，加入 *N*,*N*-二异丙基乙胺 (11.4 g, 88.5 mmol)，60 ℃搅拌 2 小时，减压旋出溶剂后加水 (100 mL)，用乙酸乙酯 (100 mL x 3)提取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩得到目标粗产物 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酸乙酯。

LC-MS: (ESI, *m/z*): [M+H] $^+$=289.0.

步骤2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑[1,5-a]嘧啶-3-甲酸的制备



将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酸乙酯 (5.5 g, 19.0 mmol)加入到乙醇 (50 mL)和四氢呋喃 (25 mL)中，加入氢氧化锂饱和水溶液 (912 mg 氢氧化锂加 0.75mL 水配置而成的水溶液)，反应混合物室温下搅拌过夜，减压浓缩，浓缩物直接反相纯化 (0.05%甲酸, 15%乙腈)得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑[1,5-a]嘧啶-3-甲酸。

LC-MS: (ESI, *m/z*): $[M+H]^+$=261.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.76 (dd, *J* = 7.6, 3.8 Hz, 1H), 8.22 (d, *J* = 3.8 Hz, 1H), 6.90-6.30 (m, 1H), 5.30-5.00 (m, 1H), 4.85-4.74 (m, 1H), 3.93-3.70 (m, 2H), 3.65-3.50 (m, 2H), 1.90 – 2.05 (m, 2H).

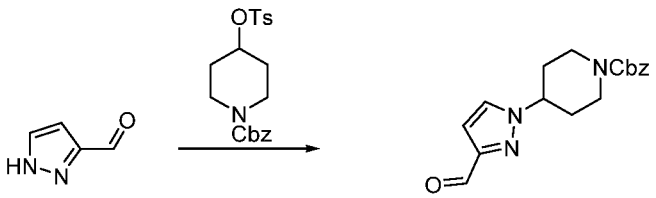
中间体 18： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)-N-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(甲苯磺酰氧基)哌啶-1-甲酸苄酯的制备

将 4-羟基哌啶-1-甲酸苄酯 (8.0 g, 34 mmol)，对甲苯磺酰氯 (7.8 g, 40.1 mmol)，三乙胺 (10.3 g, 102 mmol)和 4-二甲氨基吡啶 (0.41 g, 3.4 mmol)在二氯甲烷 (100 mL)溶液中的混合物于室温下搅拌反应过夜。反应混合物用水 (100 mL)稀释并用二氯甲烷 (100 mL × 3)萃取。收集有机层并用饱和食盐水 (200 mL)洗涤，用无水硫酸钠干燥，过滤浓缩。浓缩物经柱纯化，得到目标产物 4-(甲苯磺酰氧基)哌啶-1-甲酸苄酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=412.1.

步骤 2： 4-(3-甲醛基-1H-吡咯-1-基)哌啶-1-甲酸苄基酯的制备

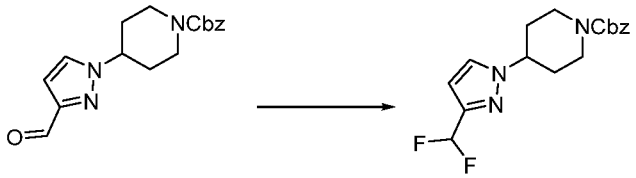


将 1*H*-吡唑-3-甲醛 (2.5 g, 26 mmol)，4-(甲苯磺酰氧基)哌啶-1-甲酸苄酯 (12.5 g, 32.1 mmol)，碳酸

铯(25.4g, 78 mmol)和碘化钾 (5.33 g, 32.1 mmol)在*N*,*N*-二甲基甲酰胺 (50 mL)溶液中的混合物中在 50 ℃下搅拌反应过夜。反应混合物用水 (250 mL)稀释并用乙酸乙酯 (250 mL × 3)萃取。收集有机层并用饱和食盐水 (500 mL)洗涤，用无水硫酸钠干燥，过滤并浓缩。浓缩物经柱纯化，得到目标产物 4-(3-甲醛基-1H-吡咯-1-基)哌啶-1-甲酸苄基酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=336.3.

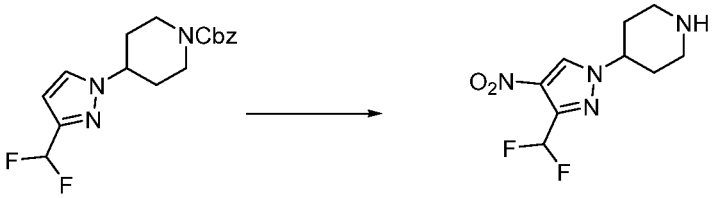
步骤 3： 4-(3-(二氟甲基)-1H-吡唑-1-基)哌啶-1-甲酸苄酯的制备



在 0 ℃下，向 4-(3-甲醛基-1H-吡咯-1-基)哌啶-1-甲酸苄酯 (1.5 g, 4.8mmol)在二氯甲烷 (50 mL)溶液中的混合物加入二乙胺基三氟化硫 (4.62 g, 28.7 mmol)。反应混合物在室温下搅拌反应过夜。反应混合物减压浓缩，浓缩物经柱纯化，得到目标产物 4-(3-(二氟甲基)-1H-吡唑-1-基)哌啶-1-甲酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=336.1.

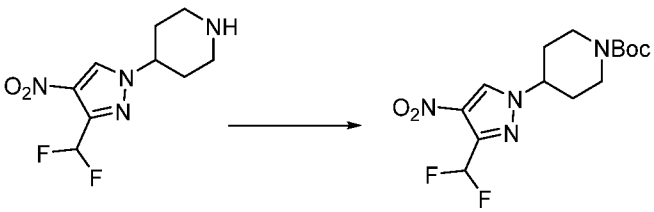
步骤 4： 4-(3-(二氟甲基)-4-硝基-1H-吡唑-1-基)哌啶的制备



在 0 ℃下，向 4-(3-(二氟甲基)-1H-吡唑-1-基)哌啶-1-甲酸苄酯 (1.0 g, 3.0 mmol)在硫酸 (5 mL)中的混合物中加入硝酸 (1 mL)。反应混合物在室温下搅拌反应过夜。将反应混合物倒入冰水 (30 mL)中并用甲醇/二氯甲烷(10%, 50 mL × 3)萃取。收集有机层，有机层饱和食用盐水 (100 mL)洗涤，用无水硫酸钠干燥，过滤并减压浓缩，得到目标产物 4-(3-(二氟甲基)-4-硝基-1H-吡唑-1-基)哌啶。所得粗品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=247.1.

步骤 5： 4-(3-(二氟甲基)-4-硝基-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯的制备

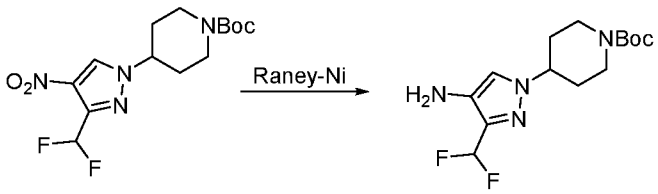


将 4-(3-(二氟甲基)-4-硝基-1H-吡唑-1-基)哌啶 (650 mg, 2.6 mmol)，二碳酸二叔丁酯 (680 mg, 3.1 mmol)，三乙胺(788 mg, 7.8mmol)和 4-二甲氨基吡啶 (32 mg, 0.26 mmol)在二氯甲烷 (10 mL)溶液中的

混合物于室温下搅拌反应过夜。反应混合物用水 (20 mL)稀释并用二氯甲烷 (20 mL × 3)萃取。收集有机层并用饱和食盐水 (50 mL)洗涤，用无水硫酸钠干燥，过滤并浓缩。浓缩物经色谱层析中纯化，得到目标产物 4-(3-(二氟甲基)-4-硝基-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M-57+2H]^+$=291.1.

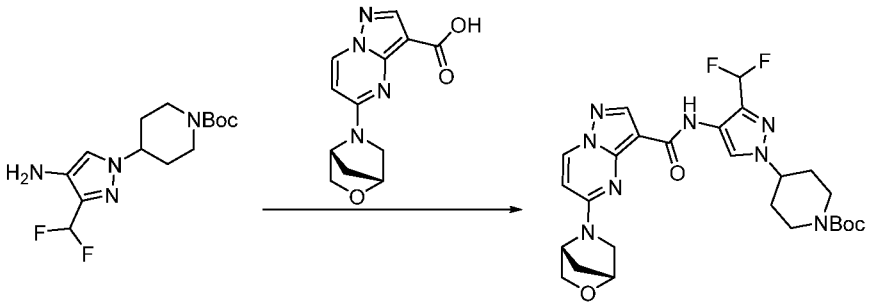
步骤 6： 4-(4-氨基-3-(二氟甲基)-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯的制备



向 4-(3-(二氟甲基)-4-硝基-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯 (710 mg, 2.052 mmol)在乙醇 (20 mL)的溶液中加入 Raney- Ni (70 mg)和水合肼 (85%, 1.0 mL)。反应混合物在室温下搅拌反应 2 小时，过滤，滤液减压浓缩，得到目标产物 4-(4-氨基-3-(二氟甲基)-1H-吡唑-1-基)哌啶-1-甲酸叔丁酯。所得粗品无需进一步纯化即可用于下一步。

LC-MS: (ESI, *m/z*): $[M-57+2H]^+$=261.3.

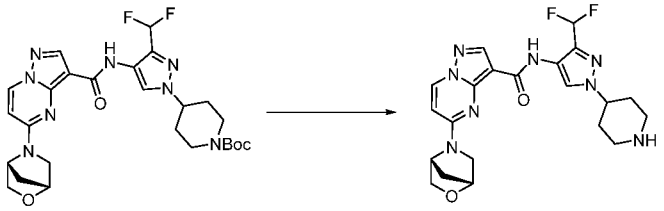
步骤 7： 4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-甲酸叔丁酯的制备



向 4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-甲酸叔丁酯 (560 mg, 1.77 mmol)在 *N*,*N*-二甲基甲酰胺 (5 mL)溶液中的混合物中加入 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (461 mg, 1.77 mmol)，HATU (874 mg, 2.3 mmol)和 *N*,*N*-二异丙基乙胺 (685 mg, 5.1 mmol)。反应混合物在室温下搅拌反应 2 小时。用水 (100 mL)淬灭反应混合物。所得溶液用乙酸乙酯 (50 mL × 3)萃取。收集有机层并用饱和食盐水 (150 mL)洗涤，用无水硫酸钠干燥，过滤并浓缩。浓缩物经色谱层析柱纯化。得到目标产物 4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-甲酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=559.2.

步骤 8： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

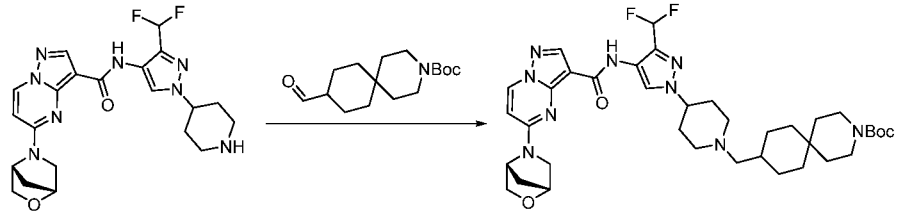


将 4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-甲酸叔丁酯 (540 mg, 0.97 mmol)在三氟乙酸/二氯甲烷 (8 mL, 1:3)中的溶液在室温下搅拌反应 1 小时。减压浓缩得到粗品 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。粗产物直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=459.2.

中间体 19： *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

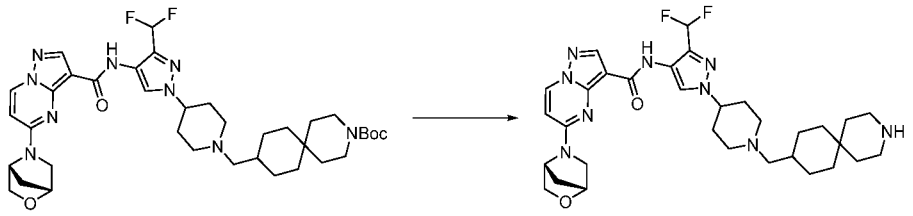
步骤 1： 9-((4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-甲酸叔丁酯的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (200 mg, 粗品, 0.334 mmol)的甲醇 (10 mL)溶液加入 *N*,*N*-二异丙基乙胺 (0.5 mL)，9-甲酰基-3-氮杂螺[5.5]十一烷-3-甲酸叔丁酯 (94 mg, 0.334 mmol)，混合物搅拌 30 分钟后，加入氰基硼氢化钠 (106 mg, 1.67 mmol)，反应混合物室温搅拌反应 3 小时。所得混合物用水 (30 mL)稀释并用乙酸乙酯 (30 mL × 3)萃取。收集有机层并用饱和食盐水 (50 mL)洗涤，用无水硫酸钠干燥，过滤并浓缩。浓缩物经色谱层析柱纯化，得到目标产物 9-((4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-甲酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=724.4.

步骤 2： *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

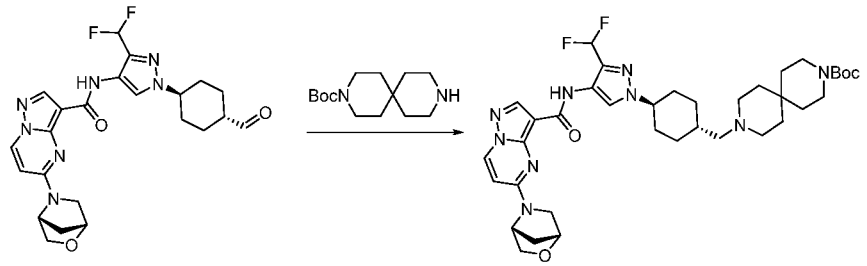


将 9-((4-(4-(5-(((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-甲酸叔丁酯 (130 mg, 0.18 mmol)在三氟乙酸/二氯甲烷 (6 mL, 1:2)中的混合物在室温下搅拌反应 1 小时。减压浓缩得到粗品 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。粗产物直接用于下一步。

LC-MS：(ESI, *m/z*): $[M+H]^+$=624.4.

中间体 20： *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

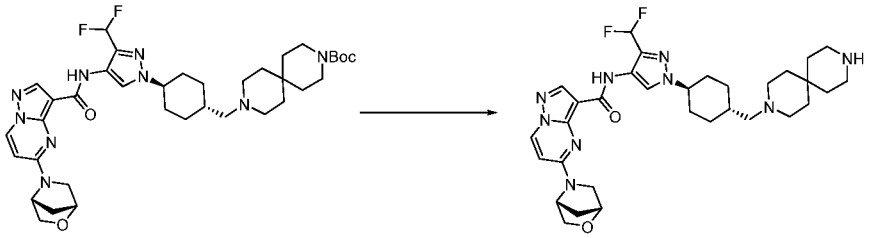
步骤 1： 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-甲酸叔丁基酯的制备



将在四氢呋喃 (15 mL)溶液中的 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, 0.31 mmol)，3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (86 mg, 0.34 mmol)和三乙酰氧基硼氢化钠 (326 mg, 1.55 mmol)的反应混合物在室温下搅拌反应过夜。用水 (50 mL)淬灭反应混合物。所得溶液用二氯甲烷 (20 mL × 3)萃取。收集有机层并用饱和食盐水 (60 mL)洗涤，用无水硫酸钠干燥，过滤并浓缩。浓缩物经柱层析纯化，得到 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-甲酸叔丁基酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=724.3.

步骤 2： *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

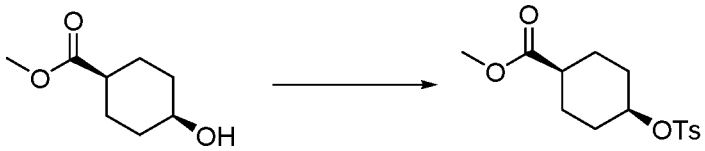


向搅拌的 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺基)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-甲酸叔丁基酯 (200 mg, 0.27 mmol)二氯甲烷 (5 mL)溶液中加入三氟乙酸 (2 mL)。反应混合物在室温下搅拌反应 2 小时。浓缩反应混合物，得到粗产物 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。粗产物直接用于下一步。

LC-MS: (ESI, *m/z*): $[M+H]^+$=624.3.

中间体 21. ((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇

步骤 1： (1*S*,4*S*)-4-(对甲苯磺酰氧基)环己烷-1-羧酸甲酯的制备

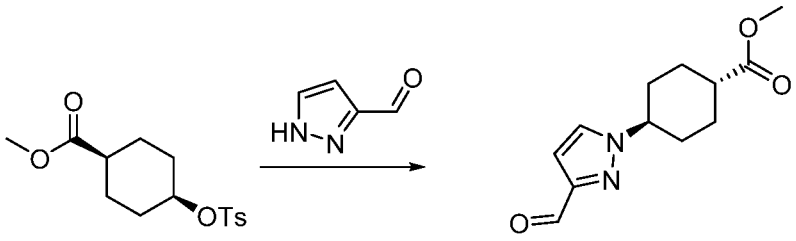


化合物 (1*S*,4*S*)-4-羟基环己烷-1-羧酸甲酯 (5.0 g,31.6 mmol)溶解于 DCM (50 mL)中，加入 DMAP (1.9 g, 15.8 mmol)，TEA (16.0 g, 158 mmol)和 TsCl (9.1 g, 47.5 mmol)，室温搅拌过夜，反应液中加水 (100 mL)，用 DCM (100 mL x 3)萃取，有机相用饱和食盐水 (200 mL)洗涤，经无水硫酸钠干燥，过滤，粗品使用柱层析 (EA/PE=1:1)纯化得到 (1*S*,4*S*)-4-(对甲苯磺酰氧基)环己烷-1-羧酸甲酯。

LC-MS: (ES, *m/z*): $[M+NH_4^+]^+$=330.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.76 (m, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 4.66 (s, 1H), 3.59 (s, 3H), 2.42 (s, 3H), 1.67 – 1.53 (m, 8H).

步骤2： (1*R*,4*R*)-4-(3-醛基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备

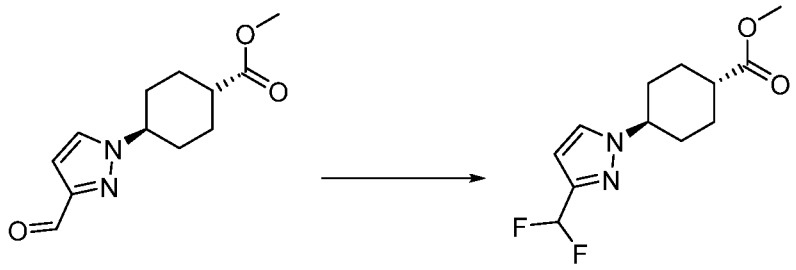


将 1*H*-吡唑-3-甲醛 (2.4 g,25.0 mmol)溶解于 DMF (50 mL))中，加入 (1*S*,4*S*)-4-(对甲苯磺酰氧基)环己烷-1-羧酸甲酯 (9.4 g, 30.0 mmol)，Cs_2CO_3 (24.5 g,75 mmol)和 KI (5.0 g,30.0 mmol)，50 ℃搅拌过夜，加水 (500 mL)，搅拌 5 min 后用 EA (500 mL x 3)萃取，有机相用饱和食盐水 (500 mL)洗涤，经无水硫酸钠干燥，过滤，粗品使用柱层析 (EA:PE=7:13)纯化得到 (1*R*,4*R*)-4-(3-醛基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ES, *m/z*): $[M+H]^+$=237.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.97 (d, *J* = 2.4Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.39 – 4.29 (m, 1H), 3.62 (s, 3H), 2.47 – 2.38 (m, 1H), 2.14 – 2.01(m, 4H), 1.91 – 1.77 (m, 2H), 1.62 – 1.48 (m, 2H).

步骤 3： (1*R*,4*R*)-4-(3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备

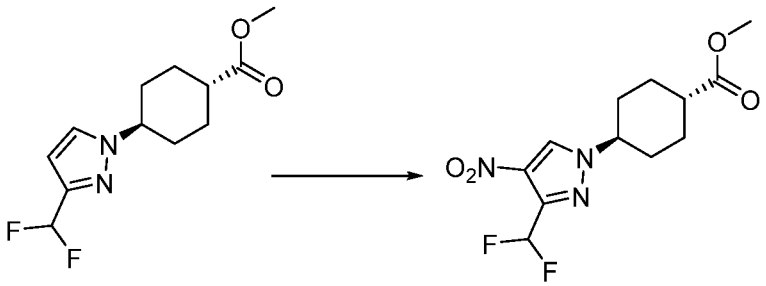


将 (1*R*,4*R*)-4-(3-醛基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (1.0 g,4.2 mmol)溶解于无水 DCM (20 mL)中，0 ℃下加入 DAST (4.1 g, 25.4 mmol)，缓慢升至室温搅拌过夜。冰浴下滴加饱和碳酸氢钠水溶液淬灭反应，分液，水相用二氯甲烷萃取 2 次，减压浓缩，粗品使用柱层析 (EA:PE=1:4)纯化得到 (1*R*,4*R*)-4-(3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ES, *m/z*): $[M+H]^+$=259.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.08-6.85 (m, 1H), 6.49 (s, 1H), 4.28-4.17 (m, 1H), 3.62 (s, 3H), 2.47-2.36 (m, 1H), 2.15-1.95 (m, 4H), 1.86 – 1.73 (m, 2H), 1.61 – 1.48 (m, 2H).

步骤 4： (1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备

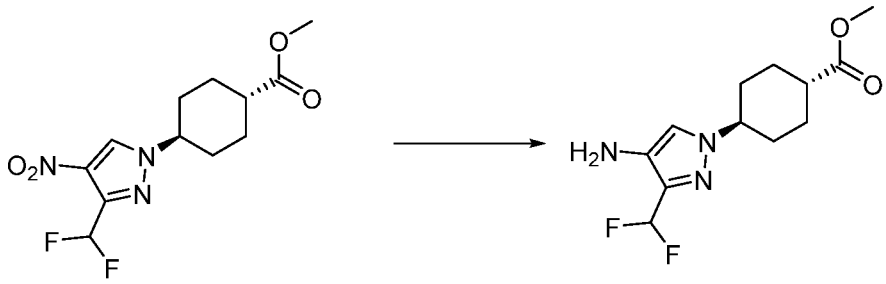


将 (1*R*,4*R*)-4-(3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (1.0 g, 3.9 mmol)用浓 H_2SO_4 (5 mL)溶解，0 ℃下滴加浓 HNO_3 (1 mL)，缓慢升至室温搅拌过夜。将反应液缓慢倒入冰水混合物 (20 mL)中，过滤，滤饼用水洗 3 次，然后真空干燥得到 (1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己烷

-1-羧酸甲酯，所得产品直接用于下一步反应。

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 7.39-7.20 (m, 1H), 4.42-4.30 (m, 1H), 3.62 (s, 3H), 2.46 – 2.37 (m, 1H), 2.16 – 2.00 (m, 4H), 1.93-1.72 (m, 2H), 1.59-1.40 (m, 2H).

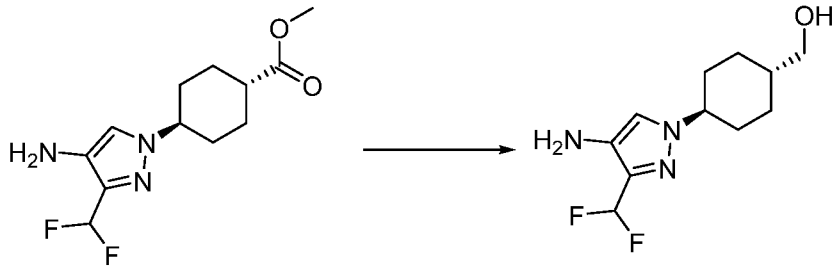
步骤 5： (1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备



将 (1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (880 mg, 2.9 mmol)溶解于 THF (10 mL)中，加入 Pd/C (440 mg, 50%)，用 H_2 置换 3 次，并在 H_2 氛围中室温下搅拌 4 h。反应液经硅藻土过滤，滤液减压浓缩得到 (1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。所得粗品直接用于下一步反应。

LC-MS: (ES, *m/z*): $[M+H]^+$=274.1.

步骤 6： ((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇的制备



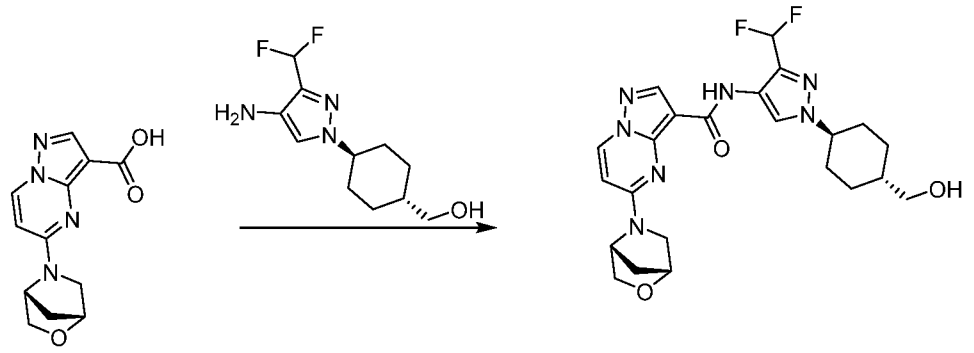
将 (1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (750 mg,2.7 mmol)溶解于无水 THF (5 mL)中，0 ℃下加入 BH_3/THF (27.5 mL, 1M/THF, 27.5 mmol)，缓慢升至室温搅拌过夜。冰浴下向反应液中滴加 MeOH 至无明显气泡产生，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 ((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇。

LC-MS: (ES, *m/z*): $[M+H]^+$=246.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, *J* = 14.3 Hz, 1H), 7.06 – 6.68 (m, 1H), 4.46 (t, *J* = 5.3 Hz, 1H), 4.03 (s, 2H), 3.94 (td, *J* = 8.2, 4.0 Hz, 1H), 3.27 – 3.22 (m, 2H), 1.97 (d, *J* = 9.5 Hz, 2H), 1.83 (d, *J* = 11.4 Hz, 2H), 1.69-1.57 (m, 2H), 1.39 (d, *J* = 2.9 Hz, 1H), 1.12 – 0.97 (m, 2H).

中间体 22. 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

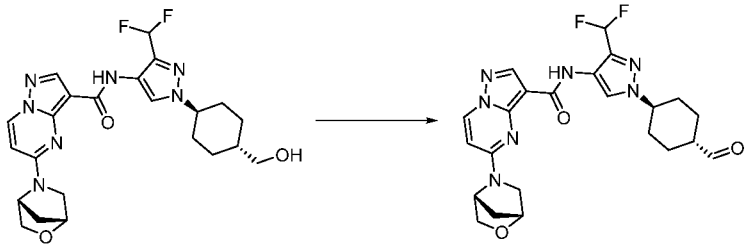


将 ((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (360 mg, 1.5 mmol)溶解于 DMF (10 mL)中，加入 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (380 mg, 1.5 mmol)，DIEA (566 mg, 4.4 mmol)和 HATU (726 g, 1.9 mmol)，室温搅拌过夜，加水 (50 mL)，搅拌 5min 后用 EA (50 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ES, *m/z*): $[M+H]^+$=488.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (d, *J* = 5.4 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.2 Hz, 1H), 8.23 (d, *J* = 5.4 Hz, 1H), 7.30-6.94 (m, 1H), 6.90-6.34 (m, 1H), 5.33-5.03 (m, 1H), 4.77 (d, *J* = 16.7 Hz, 1H), 4.52-4.30 (m, 1H), 4.22 – 4.05 (m, 1H), 3.89 – 3.69 (m, 2H), 3.67 – 3.42 (m, 2H), 3.17-2.97 (m, 2H), 2.12 – 1.80 (m, 6H), 1.80 – 1.61 (m, 2H), 1.48-1.36 (m, 1H), 1.19-1.01 (m, 2H).

步骤 2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



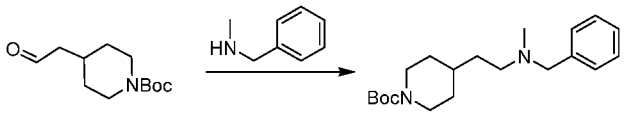
向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (400 mg, 0.82 mmol)的 ACN (20 mL)溶液中加入 IBX (460 mg, 1.64 mmol)，然后反应液再 85 ℃搅拌 1 h。反应额有减压浓缩后，加水 (50 mL)，用乙酸乙酯 (50 mL × 3)萃取，有机相用饱和氯化钠溶液 (100 mL)洗涤，无水硫酸钠干燥后浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ES, *m/z*): $[M+H]^+$=486.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 9.51 (d, J = 5.7 Hz, 1H), 8.78 (d, J = 7.7 Hz, 1H), 8.44 – 8.35 (m, 1H), 8.26 (d, J = 5.2 Hz, 1H), 7.27-6.98 (m, 1H), 6.93-6.40 (m 1H), 5.30-5.05 (m, 1H), 4.77 (d, J = 16.6 Hz, 1H), 4.26-4.15 (m, 1H), 3.84 – 3.72 (m, 2H), 3.67 – 3.59 (m, 2H), 3.45 (d, J = 9.9 Hz, 1H), 2.45-2.35 (m, 1H), 2.18-1.74 (m, 8H), 1.45-1.28 (m, 2H).

中间体23：5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(2-(苯基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



N_2保护下，向 4-(2-氧代乙基)哌啶-1-羧酸叔丁酯 (1 g, 4.41 mmol)的DCE (3 mL)溶液中加N-甲基-1-苯基甲胺 (1.067 g, 8.82 mmol)和AcOH (0.79 g, 13.23 mmol)，混合液在室温搅拌30min后，再加入STAB (2.8 g, 13.23 mmol)，然后反应液在室温搅拌2 h。反应液中加水 (20 mL)稀释，用EA (30 mL × 2)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (MeOH:DCM=0~1:20)纯化得到 4-(2-(苯基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

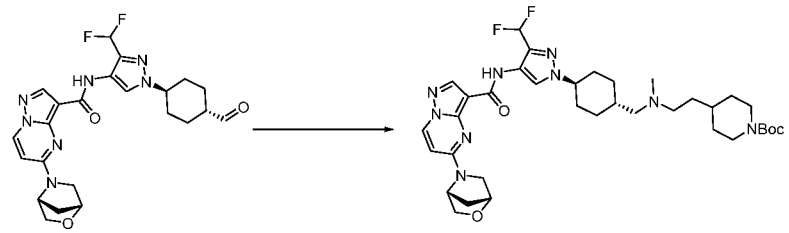
LC-MS: (ESI, m/z): $[M+H]^+$ = 333.2.

步骤 2： 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯的制备

向 4-(2-(苯基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (1 g, 3.01 mmol)的THF (3 mL)溶液中加$Pd(OH)_2$/C (250 mg)，然后反应液在H_2氛围中室温下搅拌2 h。反应液经硅藻土过滤，滤液减压浓缩得到 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 243.2.

步骤 3： 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备

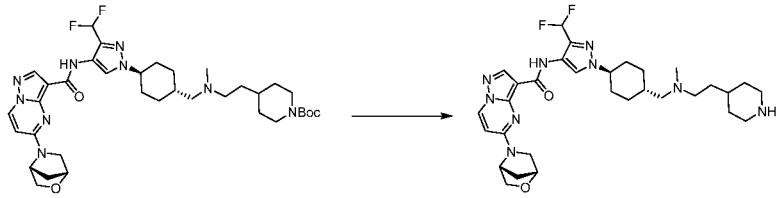


向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (300 mg, 0.618 mmol)的THF (3 mL)溶液中加4-(2-(甲基氨基)乙基)

哌啶-1-羧酸叔丁酯 (329 mg, 0.928 mmol)和STAB (419 mg, 1.862 mmol)，然后反应在N2氛围中室温下搅拌2 h。反应加水 (20 mL)淬灭，用DCM (20 mL × 2)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (MeOH:DCM=0~1:9)纯化得到 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$= 712.4.

步骤4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

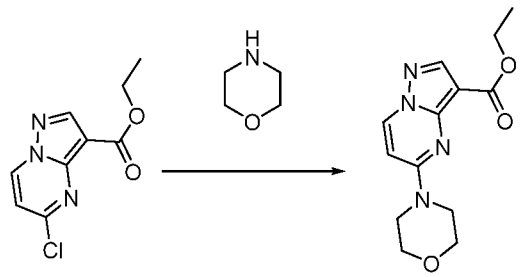


向 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (200 mg, 0.281 mmol)的DCM (3 mL)溶液中加TFA (1 mL)，然后反应液在N2氛围中室温下搅拌2 h。反应液直接减压浓缩得到5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$= 612.4.

中间体 24：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

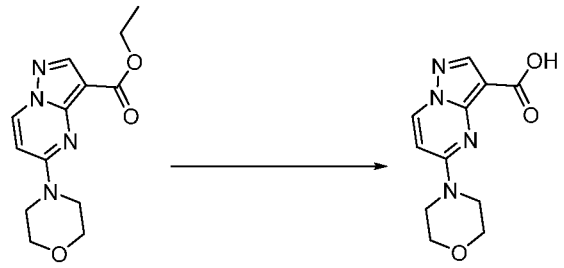
步骤 1： 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



将5-氯吡唑并[1,5-a]嘧啶-3-羧酸叔丁酯 (6 g, 27 mmol)，吗啡啉 (2.3 g, 27 mmol)和*N*,*N*-二异丙基乙胺 (10.4 g, 81 mmol)溶于乙腈 (60 mL)中并升温至60 ℃搅拌过夜，反应液直接减压浓缩，粗品使用柱层析 (乙酸乙酯)纯化得到 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

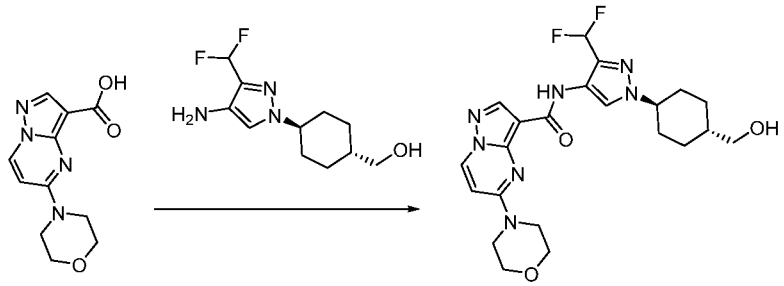
LC-MS: (ESI, m/z): $[M+H]^+$=277.3.

步骤2：5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸的制备



将 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (4.3 g, 16 mmol)溶于混合溶液 (甲醇/水=5:1, 40 mL)中，氢氧化锂 (2.6 g, 64 mmol)加入并升温至 60 ℃搅拌 2 小时，反应液用稀盐酸 (2 mol/L)调节 pH 值=2，过滤，固体真空干燥得到 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸。

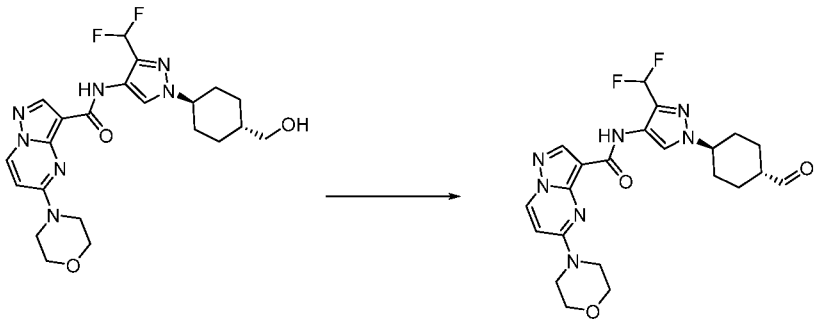
步骤 3：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸 (248 mg, 1.0 mmol)，((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (245 mg, 1.0 mmol) 和 HATU (494 mg, 1.3 mmol) 溶于DMF (5 mL)中，加入DIEA (387 mg, 3.0 mmol)，反应液室温搅拌16 h。反应结束后反应液用水 (50 mL)稀释，搅拌，过滤，滤饼用水 (5 mL x 3)洗涤，真空干燥得到*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$ = 476.1.

步骤4：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

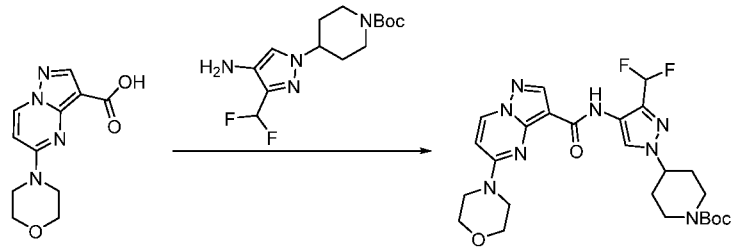


将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 0.17 mmol) 溶于DCM (4 mL)中，然后加入Dess-Martin (144 mg, 0.34 mmol)试剂，反应液室温搅拌过夜。过滤，固体用DCM洗涤 (10 mL x 3)，有机相减压浓缩，粗品经正向柱层析纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+ = 474.1$.

中间体25： *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

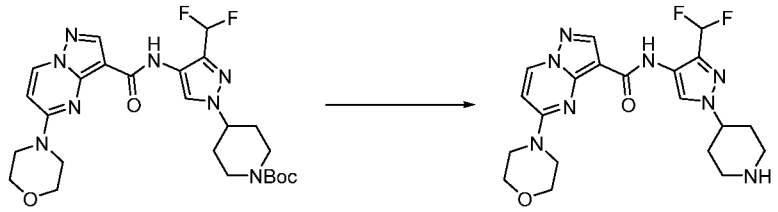
步骤 1： 4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯的制备



25 ℃时向 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸 (470 mg, 1.9 mmol)和DIEA (1 mL, 4.7 mmol)的DMF (20 ml)溶液中加入HATU (900 mg, 2.4 mmol)，混合物在25 ℃搅拌2 h后再加入4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (0.5 g, 1.5 mmol)，反应液再在25 ℃搅拌过夜。反应液中加水 (30 mL)，然后用EA (50 mL × 3)萃取，合并有机相，并用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经flash柱 (EA)纯化得到 4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+ = 547.4$.

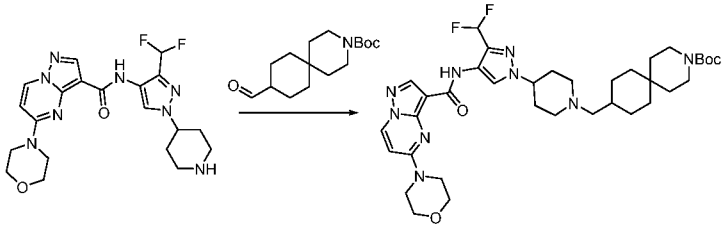
步骤 2： *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



25 ℃时向 4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (0.2 g, 0.366 mmol)的DCM (3 mL)溶液中加TFA (1 mL)。反应液在25 ℃搅拌1 h。反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+ = 447.2$.

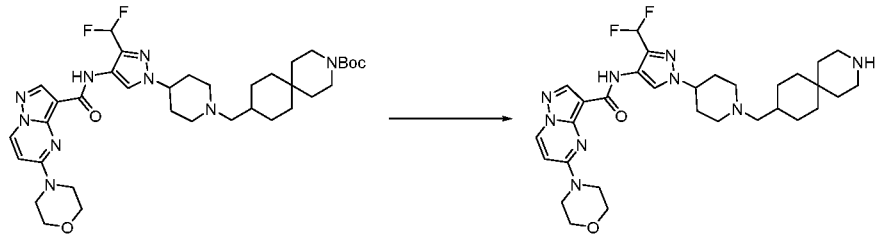
步骤 3： 9-((4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



25 ℃时向 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (200 mg, 0.45 mmol)和DIEA (0.5 ml, 1.35 mmol)的MeOH (5 mL)溶液中加入9-醛基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (150 mg, 0.45 mmol)和$NaBH_3CN$ (100 mg, 2.25 mmol)。反应液在25 ℃搅拌16 h。过滤，减压浓缩，所得粗品经flash柱 (MeOH:DCM=3:97)纯化得到 9-((4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 712.4.

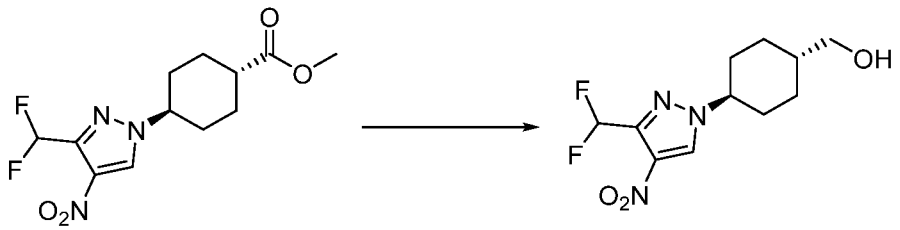
步骤 4： *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



25 ℃时向 9-((4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (0.14 g, 0.2 mmol)的DCM (3 mL)溶液中加TFA (1 mL)。反应液在25 ℃搅拌1 h。反应液直接减压浓缩得到 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。所得产品直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$ = 612.5.

中间体26：((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)甲醇



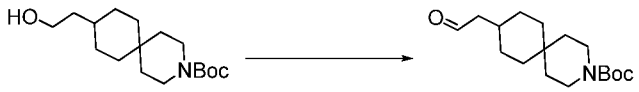
将(1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (4.0 g, 13.2 mmol)的 THF (50 mL)溶液冷却到-20 ℃，滴加 $LiAlH_4$ (1M THF 溶液, 16 mL)，反应液室温搅拌 0.5 小时后，缓慢加入 15%的氢氧化钠溶液 (8 mL)，加水 (50 mL)，用 MeOH/DCM 混合溶液 (V/V=1:9, 50 mL x 3)萃取，无水硫酸钠干燥，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 ((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-

1*H*-吡唑-1-基)环己基)甲醇。

LC-MS: (ESI, m/z): $[M-56]^+$=276.0.

中间体 27：*N*-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

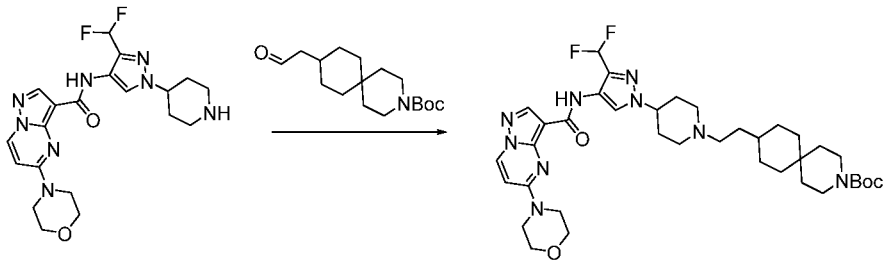
步骤 1： 9-(2-氧代乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将9-(2-羟基乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (250 mg, 0.842 mmol) 和 PCC (543.8 mg, 2.523 mmol) 加入到 DCM (5 mL) 中，室温搅拌 2 h, 然后过滤, 加入水 (20 mL)，用乙酸乙酯 (25 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，得到粗品 9-(2-氧代乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M-56]^+$= 240.1.

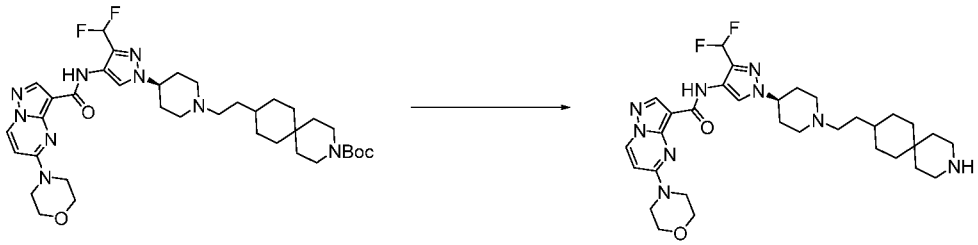
步骤 2： 9-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (140 mg, 0.314 mmol)和 9-(2-氧代乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (185 mg, 0.628 mmol) 加入到THF 中, 然后加入三乙酰氧基硼氢化钠 (133 mg, 0.628 mmol)，室温搅拌2 h, 加入水 (20 mL)，用乙酸乙酯 (25 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (MeOH:DCM = 1:19)纯化得到 9-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=726.4.

步骤 3：*N*-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

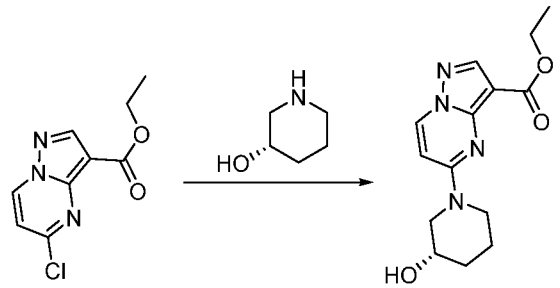


将 9-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (121 mg, 0.167 mmol) 加入到 TFA (0.5 mL)和 DCM (2.5 mL)中，室温搅拌 2 h，反应液减压浓缩，得到粗品 *N*-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=626.4.

中间体28：*N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

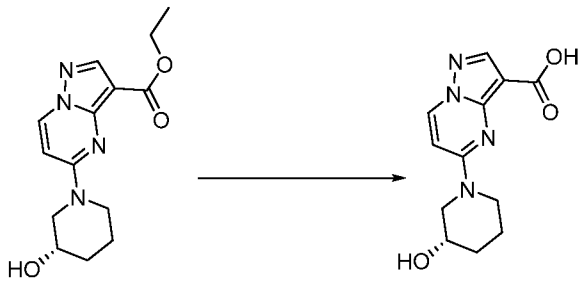
步骤1： (*S*)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



将5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (1.0 g, 4.4 mmol)，(*S*)-哌啶-3-醇 (445 mg, 4.4 mmol)和*N*,*N*-二异丙基乙胺 (1.7 g, 13.3 mmol)用乙腈 (10 mL)溶解，反应液升温至60 ℃搅拌过夜。反应液直接减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=87:13)纯化得到 (*S*)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$=291.1.

步骤2：(*S*)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备

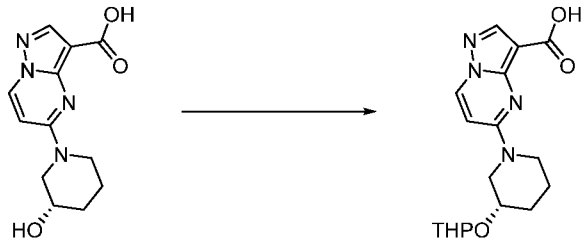


将 (*S*)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (1.1 g, 3.9 mmol)用混合溶液 (甲醇/水=5:1,

10 mL)溶解，加入氢氧化锂 (643 mg, 16 mmol)并升温至 60 ℃搅拌 2 小时。 反应液用稀盐酸 (2 mol/L)调节 pH 值=2, 过滤，滤饼真空干燥得到 (*S*)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, m/z): $[M+H]^+$=263.1.

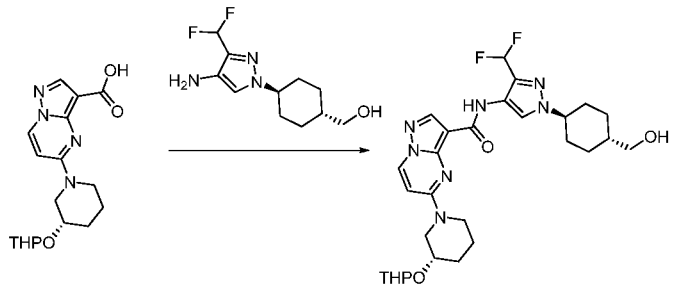
步骤 3： 5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备



(*S*)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸 (300 mg, 1.14 mmol)用四氢呋喃 (15 mL)溶解，加入3,4-二氢-2*H*-吡喃 (962 mg, 11.4 mmol)和四丁基三溴化铵 (111 mg, 0.23 mmol)，升温至60 ℃，搅拌过夜。反应液减压浓缩，粗品使用柱层析 (乙酸乙酯)纯化得到 5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, m/z): $[M+H]^+$=347.2.

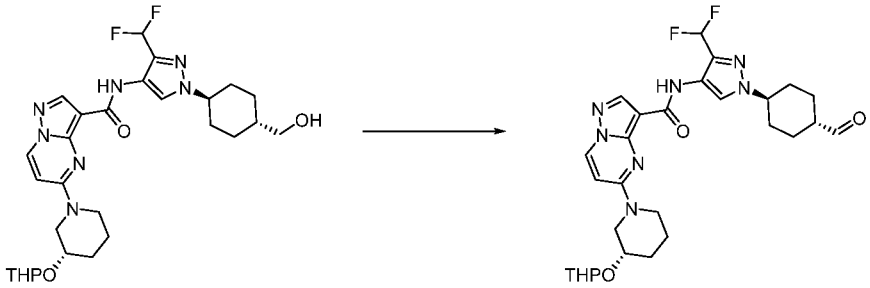
步骤4： *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸 (180 mg, 0.52 mmol)和((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (137 mg, 0.52 mmol)用 DMF (10 mL)溶解，搅拌下加入*N*,*N*-二异丙基乙胺 (201 mg, 1.56 mmol)和 py-BOP (348 mg, 0.67 mmol)，60 ℃下搅拌过夜。反应液冷却至室温，加水 (100 mL)，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=574.3.

步骤 5： *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

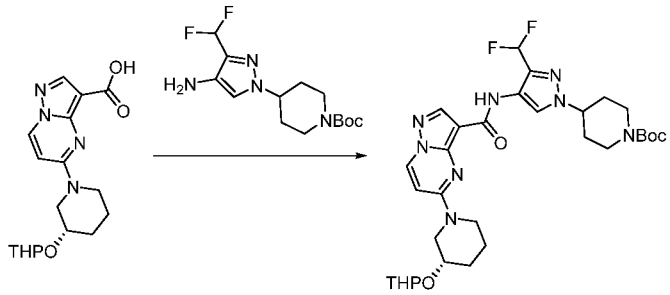


N-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (200 mg, 0.35 mmol)用乙腈 (20 mL)溶解，加入IBX (196 mg, 0.70 mmol)，80 ℃下搅拌 2小时。反应液减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9）纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=572.3.

中间体29：(*S*)-*N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

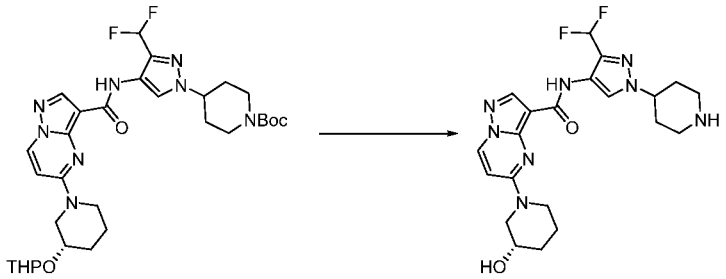
步骤 1： 4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯的制备



5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸（210 mg, 0.61 mmol）和 4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (191 mg, 0.61 mmol)用 DMF (10 mL)溶解，搅拌下加入 *N*,*N*-二异丙基乙胺 (236 mg, 1.83 mmol)和 Py-BOP (475 mg, 0.91 mmol)，加热至 60 ℃搅拌过夜。反应液中加水 (100 mL)，乙酸乙酯 (30 mL x 3)萃取，有机相经饱和食盐水 (60 mL)洗涤，无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=645.3.

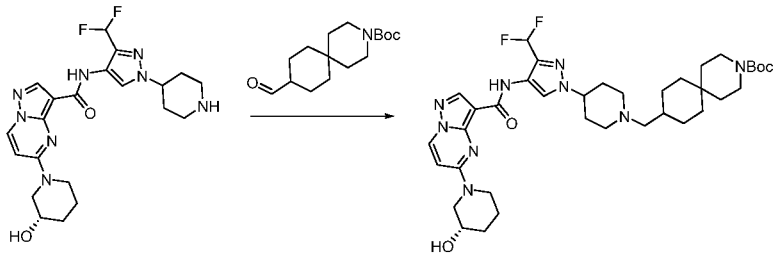
步骤 2： (*S*)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (180 mg, 0.28 mmol)用二氯甲烷 (3 mL)溶解，三氟乙酸 (1 mL)加入并室温搅拌 1小时。反应液直接减压浓缩得到 (*S*)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=461.2.

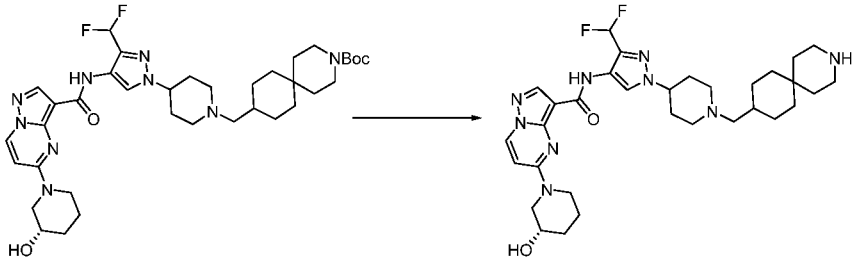
步骤3： (*S*)-9-((4-(3-(二氟甲基)-4-(5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将 (*S*)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (180 mg, 粗品, 0.28 mmol)和 9-甲酰基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (87 mg, 0.31 mmol)用四氢呋喃 (10 mL)溶解，搅拌下加入三乙酰氧基硼氢化钠 (180 mg, 0.84 mmol)，室温搅拌过夜。反应液中加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 (*S*)-9-((4-(3-(二氟甲基)-4-(5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=726.3.

步骤 4：(*S*)-*N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

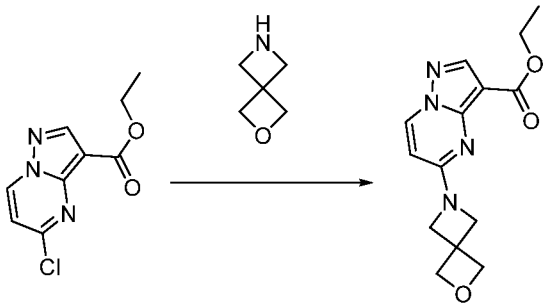


(*S*)-9-((4-(3-(二氟甲基)-4-(5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (160 mg, 0.22 mmol)用二氯甲烷 (3 mL)溶解，加入三氟乙酸 (1 mL)，室温搅拌 2小时。反应液直接减压浓缩得到 (*S*)-*N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=626.4.

中间体30： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

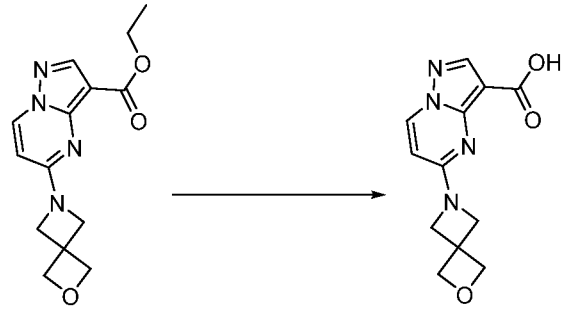
步骤1： 5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



将5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (1.0 g，4.4 mmol)，2-氧-6-氮杂螺[3.3]庚烷 (439 mg, 4.4 mmol)和*N*,*N*-二异丙基乙胺 (1.7 g, 13.3 mmol)用乙腈 (10 mL)溶解，反应液升温至60 ℃搅拌过夜。反应液直接减压浓缩，粗品使用柱层析 (乙酸乙酯)纯化得到 5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$=289.2.

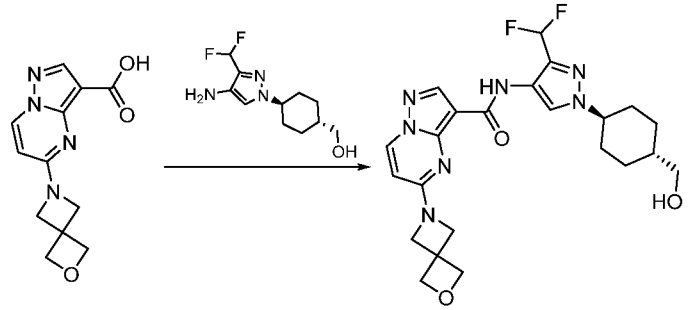
步骤2：5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备



将 5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (1.1 g, 3.8 mmol）用 10 mL 混合溶液（甲醇/水=5:1）溶解，氢氧化锂（639 mg, 15 mmol）加入并升温至 60 ℃搅拌 2 小时, 反应液用 2 mol/L 稀盐酸调节 pH 值=2, 过滤，固体真空干燥得到 5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, m/z): $[M+H]^+$=261.1.

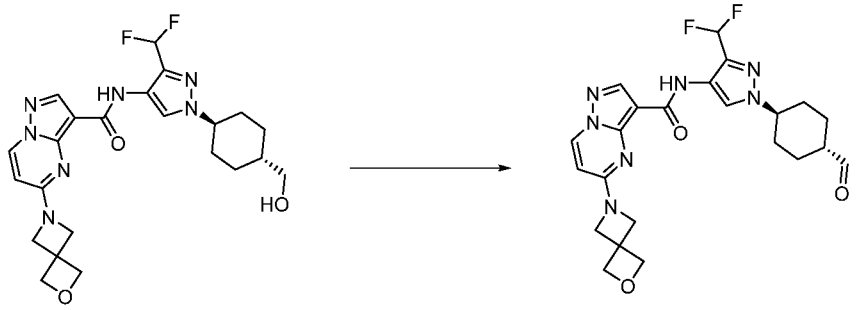
步骤 3：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸（ 110 mg, 0.41 mmol）和((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (100 mg, 0.41 mmol) 用 DMF (3 mL)溶解，加入 HATU (202 mg, 0.53 mmol)和 DIEA (212 mg, 1.6 mmol)，反应液升温至 90 ℃搅拌过夜，用水 (80 mL)稀释，乙酸乙酯 (100 mL x 2)萃取，用饱和食盐水洗，无水硫酸钠干燥，减压浓缩，粗品使用柱层析（ PE: EA=1：9)纯化得到化合物 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=488.2.

步骤 4：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

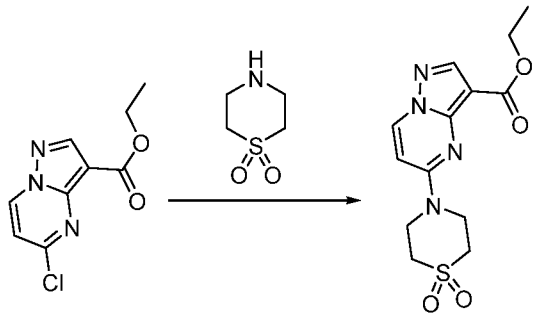


将化合物 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (120 mg, 0.246 mmol)用 DCM (3 mL)溶解，然后加入 PCC (107 mg, 0.493 mmol)，反应液室温搅拌 2 小时。反应液用水 (20 mL)稀释，二氯甲烷 (25 mL x 4)萃取，有机相用无水硫酸钠干燥，减压浓缩，粗品使用柱层析 (DCM：MEOH=1:10)纯化得到化合物 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=486.3.

中间体 31： *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺

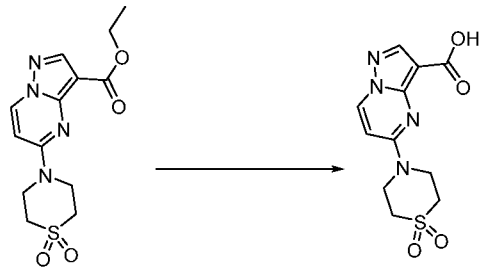
步骤 1：5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



将5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (1.0 g, 4.4 mmol)，硫代吗啡啉1,1-二氧化物 (906 mg, 5.3 mmol)和*N*,*N*-二异丙基乙胺 (2.3 g, 18 mmol)溶于乙腈 (10 mL)中并升温至60 ℃搅拌过夜，反应液直接减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=9:1)纯化得到 5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$=325.0.

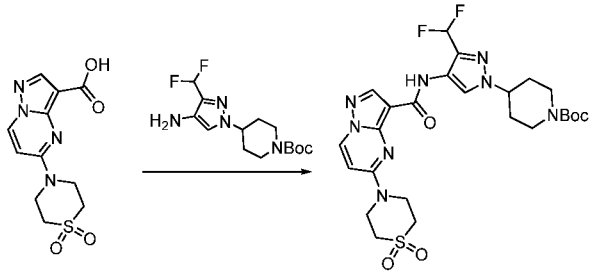
步骤2：5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-羧酸的制备



将 5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (900 mg, 2.8 mmol)溶于混合溶液(甲醇/水=5:1, 10 mL)中，加入氢氧化锂 (470 mg, 11.2 mmol)并升温至 60 ℃搅拌 2 小时，反应液用稀盐酸 (2 mol/L)调节 pH 值=3, 过滤，滤饼真空干燥得到 5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, m/z): $[M+H]^+$=297.0.

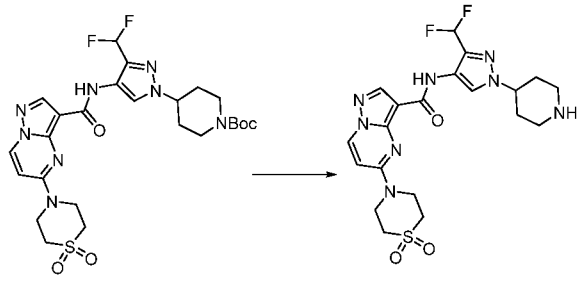
步骤 3： 4-(3-(二氟甲基)-4-(5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯的制备



将 5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-羧酸 (150 mg, 0.51 mmol)和 4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-甲酸叔丁酯 (161 mg, 0.51 mmol)用 DMF (5 mL)溶解，搅拌下加入 DIEA (271 mg, 2.1 mmol)和 HATU (251 mg, 0.66 mmol)，反应液室温搅拌 12 小时。反应液终加水 (60 mL)稀释，用乙酸乙酯 (60 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=7:3)纯化得到 4-(3-(二氟甲基)-4-(5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+Na]^+$=617.1.

步骤 4：*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将4-(3-(二氟甲基)-4-(5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (80 mg, 0.13 mmol)用二氯甲烷 (2 mL)溶解，加入三氟乙酸 (0.4 mL)并室温搅拌2小时。反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=495.2.

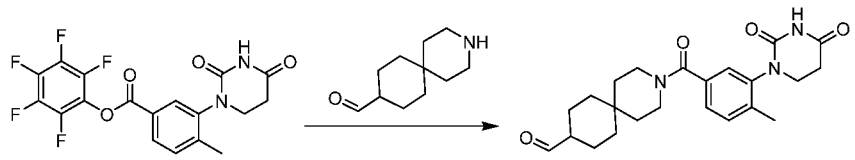
中间体32： 3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛

步骤1：3-氮杂螺[5.5]十一烷-9-甲醛的制备

将 9-甲酰基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (200 mg, 0.71 mmol)溶于 DCM (2 mL)中， 加入 TFA (0.4 mL)，反应液室温搅拌 1 小时。直接减压浓缩得到 3-氮杂螺[5.5]十一烷-9-甲醛。

LC-MS: (ESI, m/z): $[M+H]^+$=182.2.

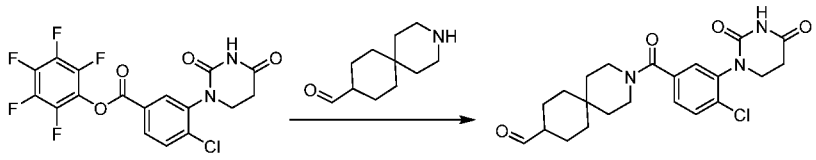
步骤2：3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛的制备



将 3-氮杂螺[5.5]十一烷-9-甲醛 (345 mg, 0.71 mmol)和 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸五氟苯酯 (295 mg, 0.71 mmol)溶于 DMSO (5 mL)中，室温搅拌 1 小时。反应液终加入水 (50 mL)，EA 萃取 (30 mL x 3)，合并有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经正相柱层析纯化得到 3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛。

LC-MS: (ESI, m/z): $[M+H]^+$=412.2.

中间体33： 3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛

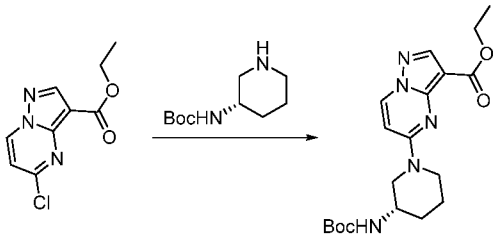


制备方法参照中间体32。

LC-MS: (ESI, m/z): $[M+H]^+$=432.1.

中间体34：(*S*)-(1-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯

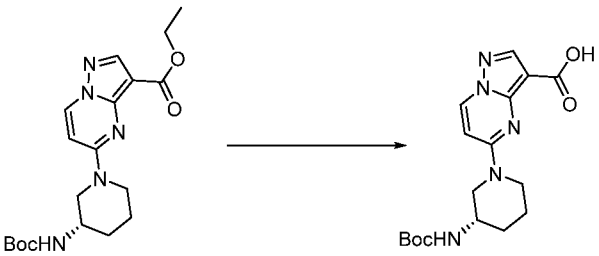
步骤 1: (*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



将5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (2.0 g, 8.9 mmol)，(*S*)-哌啶-3-基羧酸叔丁酯 (1.8 g, 8.9 mmol)和*N*,*N*-二异丙基乙胺 (3.5 g, 27 mmol)用乙腈 (20 mL)溶解，反应液加热至60 ℃搅拌过夜，直接减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=9:1)纯化得到 (*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$=390.0.

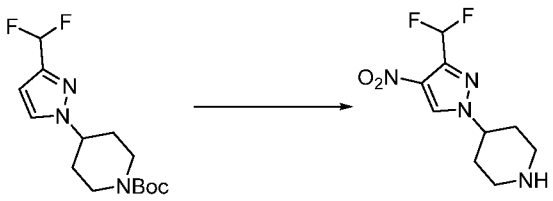
步骤 2：(*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备



将 (*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (3.2 g, 8.2 mmol)用混合溶液 (甲醇/水=5:1, 30 mL)溶解，加入氢氧化锂 (787 mg, 32.8 mmol)并升温至 60 ℃搅拌 2 小时, 反应液用稀盐酸 (2 mol/L)调节至 pH 值=2, 过滤，滤饼真空干燥得到 (*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, m/z): $[M+H]^+$=362.5.

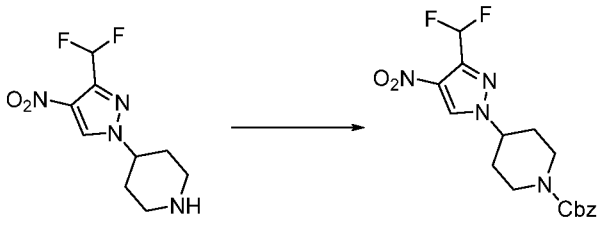
步骤 3： 4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)哌啶的制备



4-(3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (1 g, 3 mmol)用浓硫酸 (10 mL)溶解并冷却到零度，缓慢滴加浓硝酸 (1 mL)，反应液室温搅拌过夜。反应液缓慢倒入冰水 (300 mL)中，水相用碳酸钠调节pH值=8，用甲醇/二氯甲烷混和溶液 (10/1, 60 mL x 3)萃取，无水硫酸钠干燥，过滤，减压浓缩得到 4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)哌啶。

LC-MS: (ESI, m/z): $[M+H]^+$=247.0.

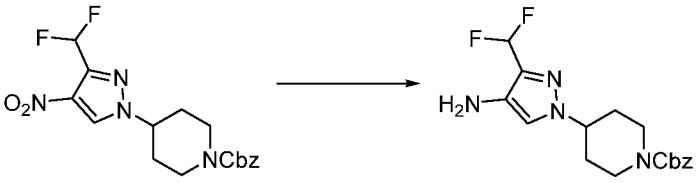
步骤4： 4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯的制备



4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)哌啶 (460 mg, 1.9 mmol)用二氯甲烷 (6 mL)溶解， 加入 DIEA (735 mg, 5.7 mmol)和 CbzCl (391 mg, 2.3 mmol)并室温搅拌 2 小时。反应液中加水 (80 mL)，用二氯甲烷 (100 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=1:1)纯化得到 4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=381.2.

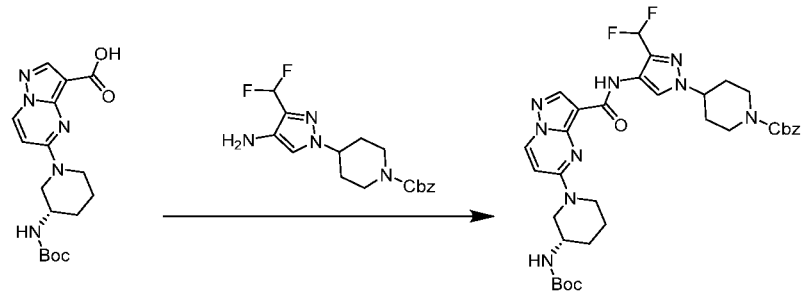
步骤5：4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯的制备



4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯 (500 mg, 1.3 mmol)，铁粉 (294 mg, 5.2 mmol)和NH_4Cl (418 mg, 7.9 mmol)加入到水 (10 mL)中，反应液加热到在90 ℃搅拌2小时，过滤，加水 (80 mL)稀释，用乙酸乙酯 (100 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，得到 4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$= 351.2.

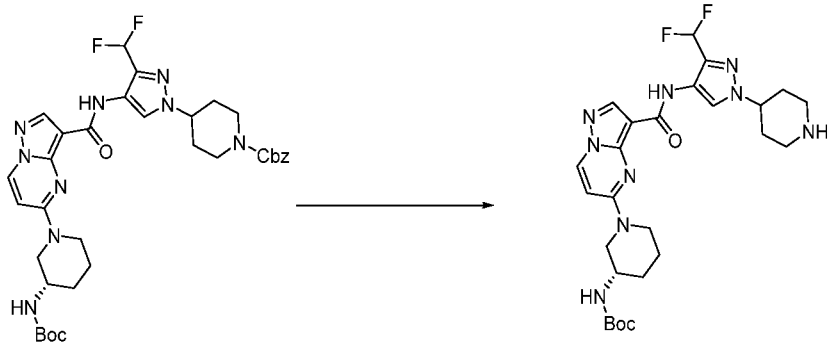
步骤 6： (*S*)-4-(4-(5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯的制备



将 (*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸 (56 mg, 0.15 mmol)， 4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯 (54 mg, 0.15 mmol)和 Py-BOP (240 mg, 0.45 mmol)溶于 DMF (5 mL)中，然后加入 DIEA (60 mg, 0.45 mmol)，室温搅拌 16 小时。反应液中加入水 (50 mL)，乙酸乙酯 (30 mL x 3) 萃取，合并有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经正相柱层析纯化得到 (*S*)-4-(4-(5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=694.4.

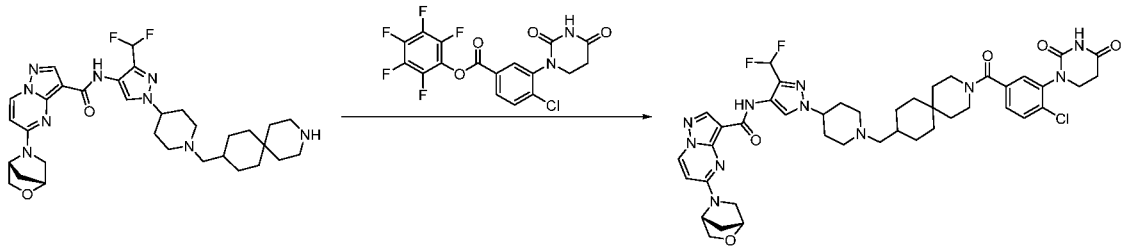
步骤 7：(*S*)-(1-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯的制备



将 (*S*)-4-(4-(5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸苄酯 (90 mg, 0.13 mmol)溶于THF (3 mL)中，加入Pd/C (10%, 50 mg)，置换H_2三次，在氢气保护下室温搅拌1小时。反应液经硅藻土过滤，滤饼用THF洗涤 (10 mL x 3)，滤液减压浓缩得到粗品 (*S*)-(1-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$= 560.3.

实施例 1： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

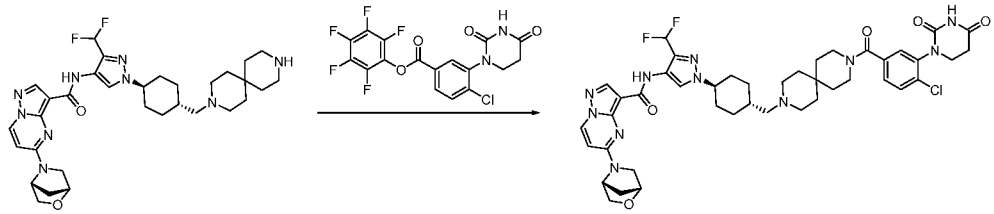


将 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, 粗品, 0.18 mmol)，4-氯-3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯基酯 (78 mg, 0.18 mmol)和 *N*,*N*-二异丙基乙胺 (116 mg, 0.9 mmol)在二甲亚砜 (5 mL)中的溶液在室温下搅拌过夜。将所得混合物倒入水 (50 mL)中并搅拌 10 分钟。过滤，滤饼通过制备型 HPLC 纯化，得到目标产物 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=874.5.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.9 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.0 Hz, 1H), 8.26 (d, *J* = 5.7 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.27-6.96 (m, 1H), 6.90 – 6.41 (m, 1H), 5.30-5.05 (m, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 4.26-4.14 (m, 1H), 3.86 – 3.70 (m, 3H), 3.66 – 3.41 (m, 5H), 3.30-3.25 (m, 2H), 2.96-2.84 (m, 2H), 2.79 – 2.70 (m, 2H), 2.22-2.08 (m, 2H), 2.06 – 1.83 (m, 8H), 1.75-1.65 (m, 2H), 1.63 – 1.24 (m, 7H), 1.19 – 0.91 (m, 4H).

实施例 2：5-((1*R*,4*R*)-2-氧杂-5-氮杂双环 [2.2.1]庚烷-5-基)-N-(1-((1r,4*R*)-4-((9-(4-氯 -3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1H-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺



制备方法参照实施例 1。

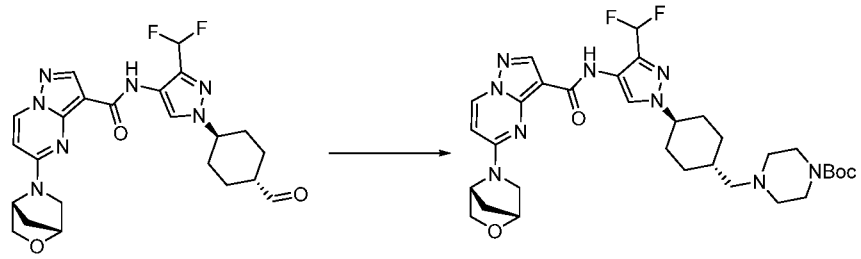
LC-MS: (ESI, *m/z*): $[M+H]^+$=874.4

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 6.3 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.38 (d, *J* = 4.4 Hz, 1H), 8.25 (d, *J* = 5.7 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26-6.95 (m, 1H), 6.91-6.41 (m, 1H), 5.32-5.03 (m, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 4.17 (t, *J* = 12.9 Hz, 1H), 3.84 – 3.71 (m, 3H), 3.67-3.57 (m, 4H), 3.45 (d, *J* = 9.8 Hz, 1H), 3.30-3.25 (m, 2H), 2.79 – 2.71 (m, 2H), 2.38-2.24 (m, 4H), 2.13 – 1.77 (m, 8H), , 1.79-1.66 (m, 2H), 1.60-1.35 (m, 9H), 1.12-0.92 (m,

2H).

实施例 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌嗪-1-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

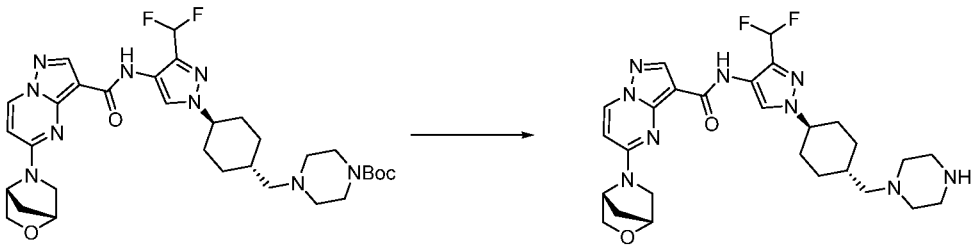
步骤 1： 4-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)哌嗪-1-羧酸叔丁酯的制备



5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (130 mg, 0.268 mmol)和哌嗪-1-羧酸叔丁酯 (60 mg, 0.322 mmol)用四氢呋喃(10 mL)溶解，室温搅拌，三乙酰氧基硼氢化钠 (284 mg, 1.34 mmol)加入并室温搅拌 2 小时，加水(30 mL)，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析(甲醇:二氯甲烷=1:9)纯化得到 4-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)哌嗪-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=656.3.

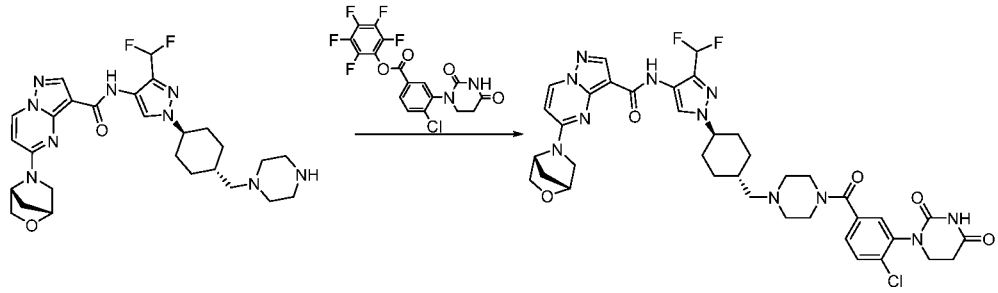
步骤 2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(哌嗪-1-基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



4-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)哌嗪-1-羧酸叔丁酯 (120 mg, 0.183mmol)用二氯甲烷(5 mL)溶解，加入三氟乙酸(1 mL)并室温搅拌2小时。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(哌嗪-1-基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=556.3

步骤 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌嗪-1-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



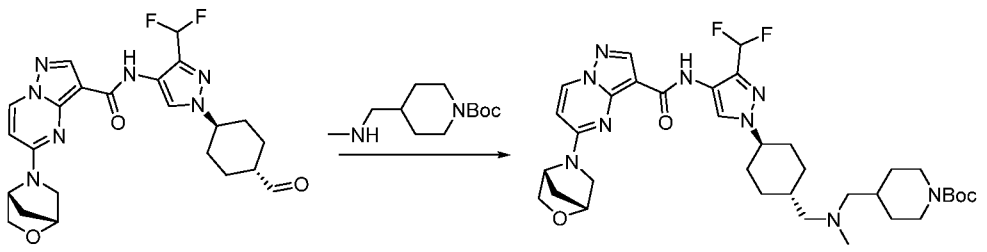
5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(哌嗪-1-基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (120 mg, 0.185 mmol, 三氟乙酸盐)和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (96 mg, 0.22 mmol)用二甲亚砜 (10 mL)溶解，室温搅拌，DIEA (0.5 mL)加入并室温搅拌2小时，加水 (50 mL)，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，减压浓缩，粗品经过 pre-HPLC纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌嗪-1-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=806.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.49 (d, *J* = 6.0 Hz, 1H), 8.78 (d, *J* = 7.8 Hz, 1H), 8.38 (d, *J* = 4.3 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.27-6.94 (m, 1H), 6.89-6.38 (m, 1H), 5.32-5.02 (m, 1H), 4.77 (d, *J* = 17.6 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.86 – 3.71 (m, 3H), 3.68 – 3.57 (m, 4H), 3.45 (d, *J* = 10.3 Hz, 2H), 2.80-2.70 (m, 2H), 2.45 – 2.25 (m, 4H), 2.16 (d, *J* = 7.0 Hz, 2H), 2.11 – 1.83 (m, 7H), 1.1-1.67 (m, 2H), 1.68 – 1.50 (m, 1H), 1.16 – 0.98 (m, 2H).

实施例 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

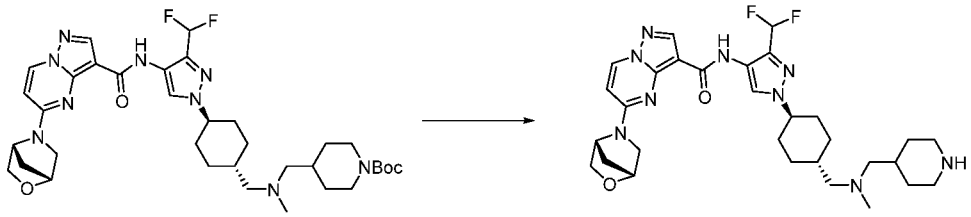
步骤 1： 4-(((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯的制备



5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (130 mg, 0.268 mmol)和 4-((甲基氨基)甲基)哌啶-1-羧酸叔丁酯 (73 mg, 0.320 mmol)用四氢呋喃 (10 mL)溶解，室温搅拌，加入三乙酰氧基硼氢化钠 (284 mg, 1.34 mmol)并室温搅拌 2 小时，加水 (30 mL)，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 4-(((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=698.4.

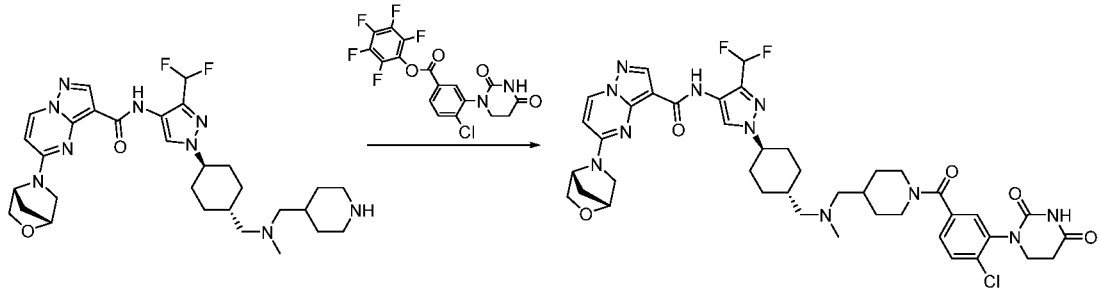
步骤 2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(哌啶-4-基甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



4-(((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯 (150 mg, 0.215mmol)用二氯甲烷 (5 mL)溶解，加入三氟乙酸 (1 mL)并室温搅拌2小时，直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(哌啶-4-基甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=598.3.

步骤 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(哌啶-4-基甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, 0.251 mmol,三氟乙酸盐)和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (134 mg, 0.309 mmol)用二甲亚砜 (10 mL)溶解，

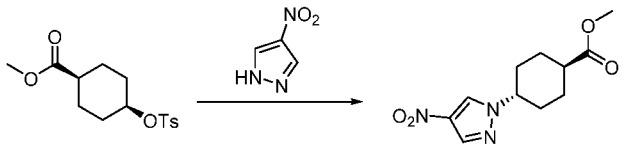
室温搅拌，DIEA (0.5 mL)加入并室温搅拌2小时，加水 (50 mL)，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，减压浓缩，粗品经过 pre-HPLC纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=848.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.38 (d, *J* = 4.4 Hz, 1H), 8.25 (d, *J* = 5.5 Hz, 1H), 8.17 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.27-7.94 (m, 1H), 6.90-6.42 (m, 1H), 5.33-5.00 (m, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 4.52-4.33 (m, 1H), 4.17 (t, *J* = 10.6 Hz, 1H), 3.86-3.70 (m, 3H), 3.68-3.53 (m, 3H), 3.45 (d, *J* = 10.1 Hz, 1H), 3.14-2.96 (m, 1H), 2.90 – 2.68 (m, 3H), 2.25 – 1.46 (m, 19H), 1.18 – 0.88 (m, 4H).

实施例 5： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： (1*R*,4*R*)-4-(4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备

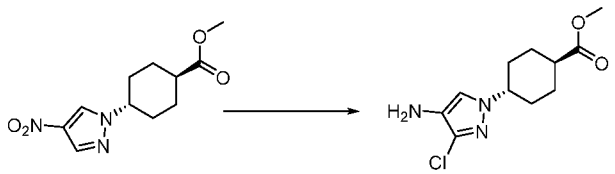


4-硝基-1*H*-吡唑 (1.8 g, 15.9 mmol)和(1*S*,4*S*)-4-(对甲苯磺酰基)环己烷-1-羧酸甲酯 (5.2 g,16.7 mmol)用 DMF(50 mL)溶解，Cs_2CO_3 (15.6 g, 47.7 mmol)和 KI (2.78 g, 16.7 mmol)加入，50 ℃搅拌过夜，加水 (200 mL)并搅拌 10 min，用乙酸乙酯 (100 mLx3)萃取，饱和食盐水(150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA:PE=7:11)纯化得到 (1*R*,4*R*)-4-(4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=254.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.26 (s, 1H), 4.33-4.25 (m, 1H), 3.63 (s, 3H), 2.42 – 2.35 (m, 1H), 2.15 – 2.00 (m, 4H), 1.89 – 1.76 (m, 2H), 1.59 – 1.45 (m, 2H).

步骤 2： (1*R*,4*R*)-4-(4-氨基-3-氯-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备

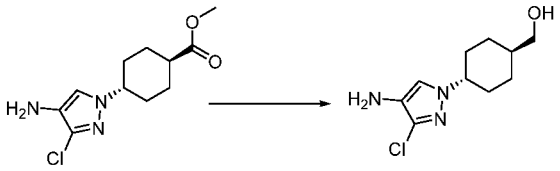


(1*R*,4*R*)-4-(4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (1.4 g, 5.5 mmol)溶解在乙醇 (45 mL)中，加入 HCl (4.6 mL, 55.3 mmol)和 Pd (5%, 氧化铝负载, 140 mg)，N_2 保护下滴加三乙基硅烷 (3.85 g, 33.2 mmol)，

室温搅拌过夜。用 $NaHCO_3$ 饱和溶液调节 pH 至 8，乙酸乙酯 (150 mL × 3)萃取，饱和食盐水 (200 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:19)纯化得到 (1*R*,4*R*)-4-(4-氨基-3-氯-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=258.1 和$[M+14]^+$=272.1.

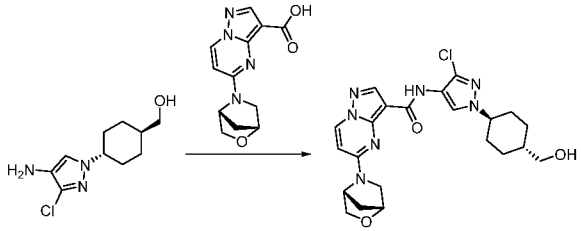
步骤 3： ((1*R*,4*R*)-4-(4-氨基-3-氯-1*H*-吡唑-1-基)环己基)甲醇的制备



(1*R*,4*R*)-4-(4-氨基-3-氯-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (1.0 g, 3.9 mmol)用 THF (20 mL)溶解，BH_3/THF (1M, 39 mL, 39 mmol)加入，室温下反应过夜。加入 MeOH (10 mL)淬灭后，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:19)纯化得到 ((1*R*,4*R*)-4-(4-氨基-3-氯-1*H*-吡唑-1-基)环己基)甲醇。

LC-MS: (ESI, *m/z*): $[M+H]^+$=230.2.

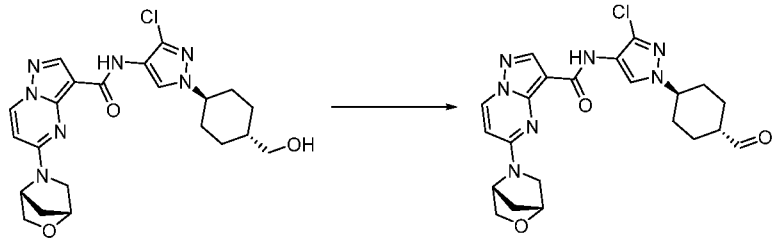
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-(羟基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (260 mg, 1.0 mmol)的 DMF (10 mL)溶液中加入 ((1*R*,4*R*)-4-(4-氨基-3-氯-1*H*-吡唑-1-基)环己基)甲醇 (300 mg, 1.3 mmol)，HATU (570 mg, 1.5 mmol)和 DIEA (387 mg, 3.0 mmol)，室温搅拌过夜。加水 (100 mL)并搅拌 10 min，用乙酸乙酯 (100 mL x 3)萃取，饱和食盐水 (150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-(羟基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=472.0.

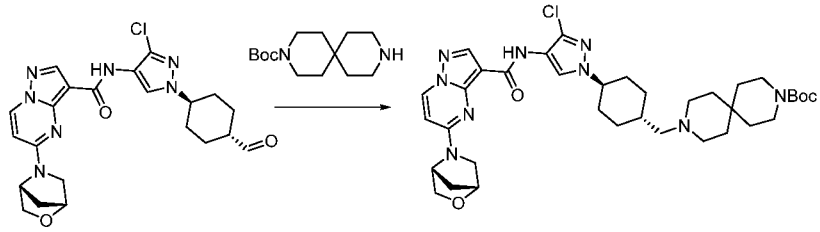
步骤 5： 5-((1*R*,4*R*)-2-氧代-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-(羟基甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (250 mg, 0.53 mmol)的 ACN (20 mL)溶液中加入 IBX (297 mg, 1.06 mmol)，85 ℃搅拌 1.5 h，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 5-((1*R*,4*R*)-2-氧代-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=470.2.

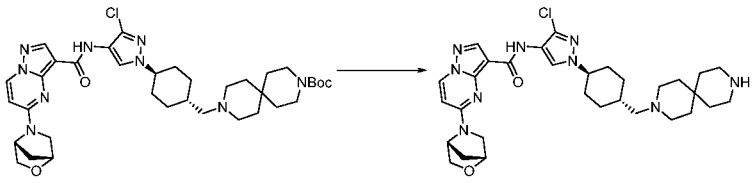
步骤 6： 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-氯-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



向 5-((1*R*,4*R*)-2-氧代-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (210 mg, 0.45 mmol)和 3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (114 mg, 0.45 mmol)的 THF (10 mL)溶液中加入 STAB (285 mg, 1.34 mmol)，室温搅拌过夜，减压浓缩，加水 (30 mL)，用乙酸乙酯 (30 mLx3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-氯-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=708.2.

步骤 7： *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-氯-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

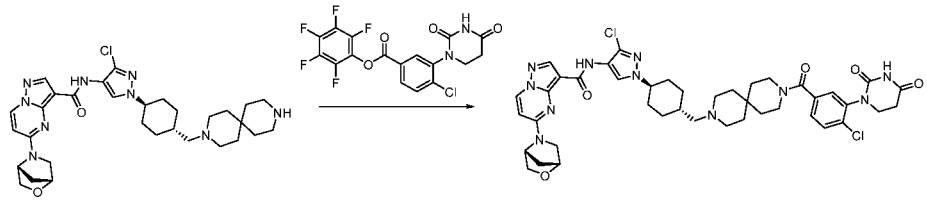


向 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-

氯-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (190 mg, 0.27 mmol)的 DCM (5 mL)溶液中加入 TFA (1 mL)，室温搅拌 2 小时，减压浓缩得到*N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-氯-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=608.3.

步骤 8： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



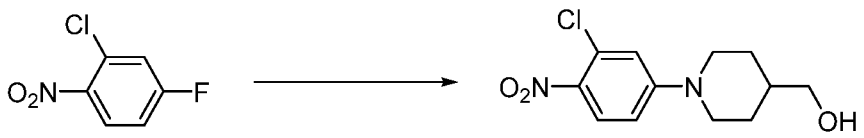
将 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-氯-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (190 mg, 0.31 mmol)和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (136 mg, 0.31 mmol)用DMSO (5 mL)溶解，然后加入DIEA (202 mg, 1.6 mmol)，反应液在室温搅拌2小时。加入水 (50 mL)到反应液中，搅拌10分钟，过滤，固体通过反相制备纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-氯-1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=858.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.44 (d, *J* = 8.7 Hz, 1H), 8.80 (d, *J* = 7.7 Hz, 1H), 8.24 (d, *J* = 3.5 Hz, 1H), 8.06 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 6.95-6.39 (m, 1H), 5.30-5.00 (m, 1H), 4.79 (s, 1H), 4.25 – 4.15 (m, 1H), 3.92 – 3.38 (m, 9H), 2.80 – 2.68 (m, 2H), 2.40 – 2.20 (m, 4H), 2.11 (d, *J* = 6.5 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.94 – 1.76 (m, 6H), 1.70 – 1.30 (m, 9H), 1.10 – 0.95 (m, 2H).

实施例 6： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： (1-(3-氯-4-硝基苯基)哌啶-4-基)甲醇的制备

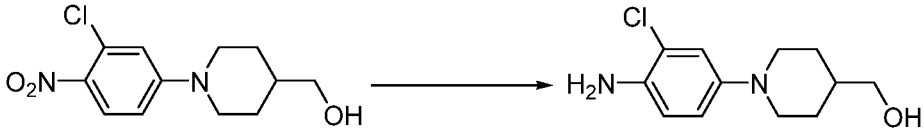


将 K_2CO_3 (1.57 g, 11.4 mmol)和 2-(哌啶-4-基)乙烷-1-醇 (0.78 g, 6.8 mmol)加入 2-氯-4-氟-1-硝基苯

(1.0 g,5.7 mmol)的 DMF (20 mL)中，100 ℃搅拌 1 h，加水 (200 mL)并搅拌 10 min，用乙酸乙酯 (100 mLx3)萃取，饱和食盐水 (150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA:PE=1:1)纯化得到 (1-(3-氯-4-硝基苯基)哌啶-4-基)甲醇。

LC-MS: (ESI, *m/z*): $[M+H]^+$=271.0.

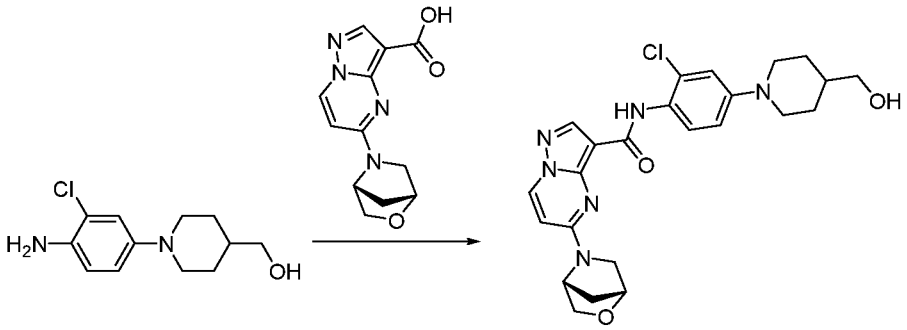
步骤 2： (1-(4-氨基-3-氯苯基)哌啶-4-基)甲醇的制备



将 (1-(3-氯-4-硝基苯基)哌啶-4-基)甲醇 (1.3 g, 4.8 mmol)溶解在乙醇(30 mL)中，加入 Raney-Ni (1 mL)和 N_2H_4-H_2O (1 mL)，室温搅拌 1 h，过滤，浓缩干燥得到 (1-(4-氨基-3-氯苯基)哌啶-4-基)甲醇。

LC-MS: (ESI, *m/z*): $[M+H]^+$=241.1.

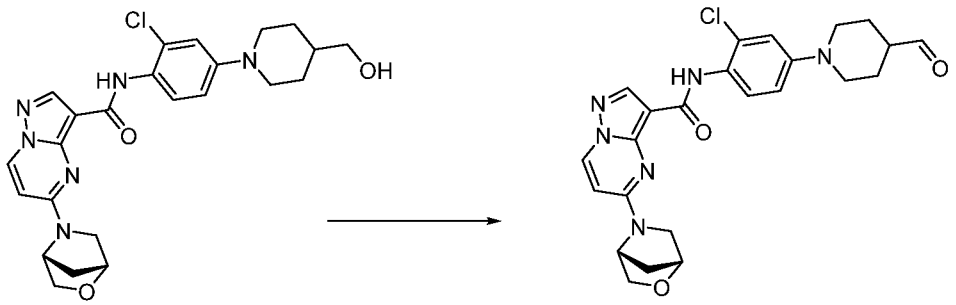
步骤 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-(羟基甲基)哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 (1-(4-氨基-3-氯苯基)哌啶-4-基)甲醇 (1.0 g, 4.2 mmol)的 DMF(20 mL)溶液中加入 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (0.6 g, 2.3 mmol)，HATU (1.33 g, 3.5 mmol)和 DIEA (0.89 g, 6.9 mmol)，室温搅拌过夜，加水 (200 mL)并搅拌 10 min，用乙酸乙酯 (100 mL x 3)萃取，饱和食盐水 (150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-(羟基甲基)哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=483.1.

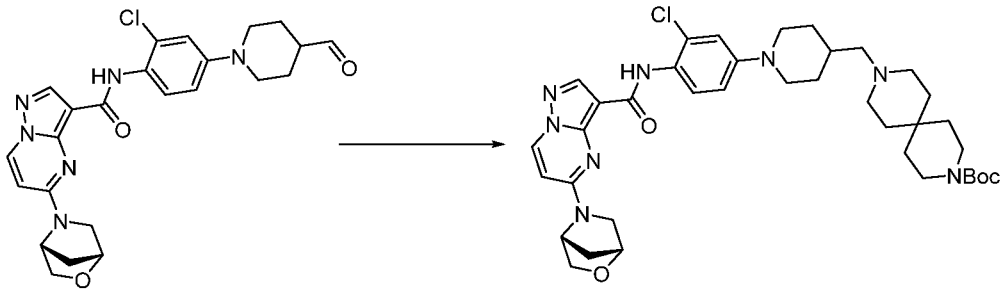
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-醛基哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-(羟基甲基)哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (500 mg, 1.0 mmol)的 CAN (20 mL)溶液中加入 IBX (560 mg, 2.0 mmol)，100 ℃搅拌 1.5 h，反应液直接减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-醛基哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=481.1.

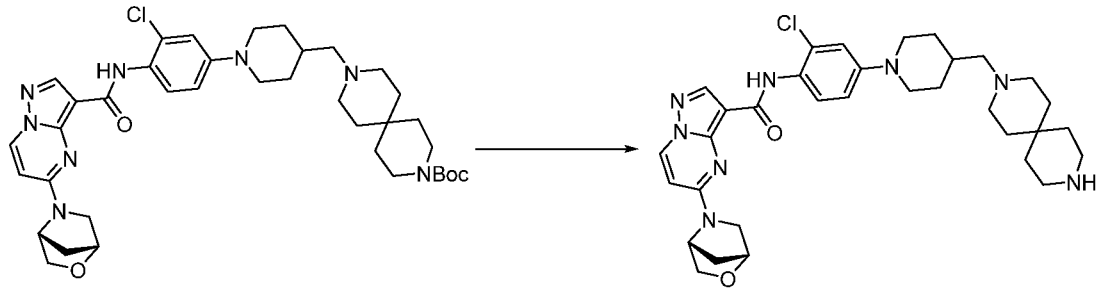
步骤 5： 9-((1-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-氯苯基)哌啶-4-基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-醛基哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (400 mg, 0.83 mmol)和 3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (232 mg, 0.91 mmol)的 THF (10 mL)溶液中加入 STAB (528 mg, 2.49 mmol)室温搅拌过夜，减压浓缩，加水 (20 mL)，用乙酸乙酯 (20 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:9)纯化得到 9-((1-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-氯苯基)哌啶-4-基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=719.3.

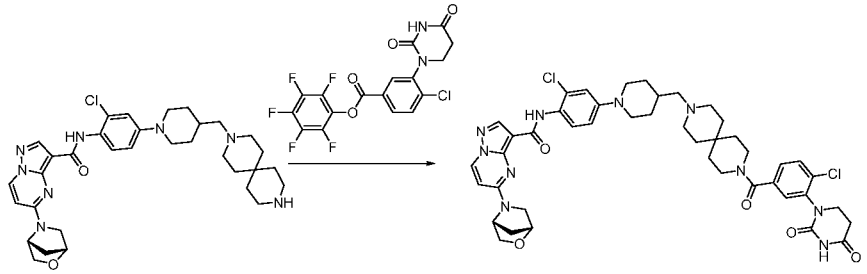
步骤 6： *N*-(4-(4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)哌啶-1-基)-2-氯苯基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]十一烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



9-((1-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-氯苯基)哌啶-4-基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (150 mg, 0.21 mmol)的 DCM (5 mL)溶液中加入 TFA (1 mL)，室温搅拌 2 小时，减压浓缩得到 *N*-(4-(4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)哌啶-1-基)-2-氯苯基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]十一烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=619.2.

步骤 7： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



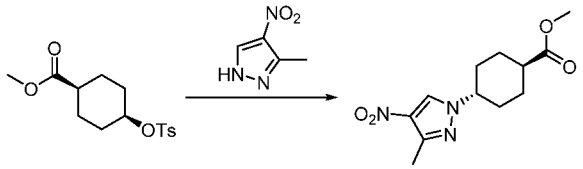
将 *N*-(4-(4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)哌啶-1-基)-2-氯苯基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]十一烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, 0.24 mmol) 和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (105 mg, 0.24 mmol)用DMSO (5 mL)溶解，DIEA (155 mg, 1.2 mmol)加入，然后反应液室温搅拌2小时，水 (50 mL)加入到反应液中，搅拌2分钟，过滤，固体通过反相制备纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(2-氯-4-(4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)哌啶-1-基)苯基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=869.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.60 (d, *J* = 11.9 Hz, 1H), 8.80 (d, *J* = 7.7 Hz, 1H), 8.26 (d, *J* = 3.3 Hz, 1H), 8.08 (dd, *J* = 15.0, 9.1 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.99-6.92 (m, 1H), 6.90-6.44 (m, 1H), 5.34-5.04 (m, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 3.84 – 3.70 (m, 3H), 3.68-3.43 (m, 7H), 3.30 – 3.20 (m, 2H), 2.78 – 2.70 (m, 2H), 2.64 (t, *J* = 11.6 Hz, 2H), 2.39 – 2.21 (m, 4H), 2.14 (d, *J* = 6.9 Hz, 2H), 2.07 – 1.92 (m, 2H), 1.82 – 1.30 (m, 11H), 1.23 – 1.08 (m, 2H).

实施例 7： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： (1*R*,4*R*)-4-(3-甲基-4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备

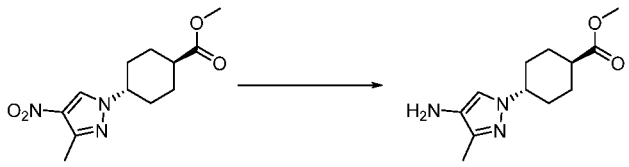


将 (1*S*,4*S*)-4-(对甲苯磺酰基)环己烷-1-羧酸甲酯 (2.0 g, 15.7 mmol), 3-甲基-4-硝基-1*H*-吡唑 (5.9 g, 18.8 mmol)，Cs_2CO_3 (15.4 g, 47.1 mmol)和KI (3.1 g, 18.8 mmol)的DMF (30.0 mL)溶液在120 ℃搅拌2 h。反应液中加水 (200 mL)，然后用EA (200 mL x 2)萃取。合并有机相，经无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析纯化 (EA:PE=0~1:5)得到 (1*R*,4*R*)-4-(3-甲基-4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 268.0.

^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 4.24-4.14 (m, 1H), 3.61 (s, 3H), 2.42 (s, 3H), 2.44-2.34 (m, 1H), 2.14-1.96 (m, 4H), 1.87 – 1.71 (m, 2H), 1.62 – 1.41 (m, 2H).

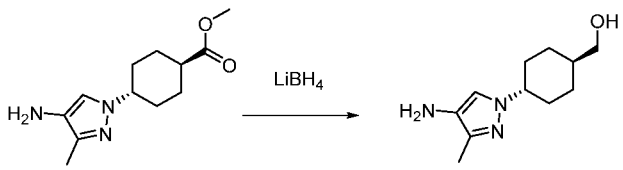
步骤 2： (1*R*,4*R*)-4-(4-氨基-3-甲基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备



将 (1*R*,4*R*)-4-(3-甲基-4-硝基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (2.0 g, 7.4 mmol)，Fe (2.5 g, 37.0 mmol)和NH_4Cl (4.8 g, 74.0 mmol)的MeOH (50.0 mL)溶液在80 ℃搅拌3 h。反应液经硅藻土过滤，滤液减压浓缩。所得粗品经Prep-HPLC (乙腈/0.05% NH_4OH水溶液, 5%~95%)纯化得到 (1*R*,4*R*)-4-(4-氨基-3-甲基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 238.3.

步骤 3： ((1*R*,4*R*)-4-(4-氨基-3-甲基-1*H*-吡唑-1-基)环己基)甲醇的制备

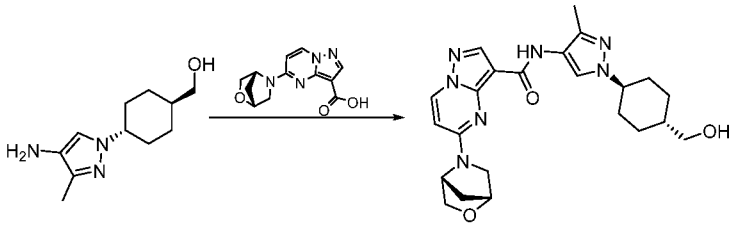


将 (1*R*,4*R*)-4-(4-氨基-3-甲基-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (300.0 mg, 1.3 mmol)和$LiBH_4$ (111.0

mg, 4.0 mmol)的THF/MeOH (10.0 mL/2.0 mL)溶液在60 ℃搅拌1 h。反应加水 (20.0 mL)淬灭，然后用DCM (50 mL x 2)萃取。有机相经无水Na_2SO_4干燥，过滤，减压浓缩。 所得粗品经柱层析纯化(MeOH:DCM=0~1:9)得到 ((1*R*,4*R*)-4-(4-氨基-3-甲基-1*H*-吡唑-1-基)环己基)甲醇。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 210.1.

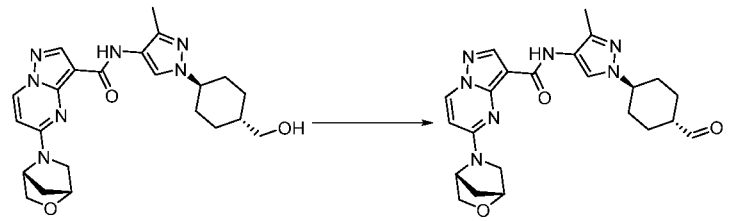
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(羟基甲基)环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (260.0 mg, 1.0 mmol)，HATU (418.0 mg, 1.1 mmol)和DIEA (387.0 mg, 3.0 mmol)的DMF (500.0 mL)溶液中加 ((1*R*,4*R*)-4-(4-氨基-3-甲基-1*H*-吡唑-1-基)环己基)甲醇 (230.0 mg, 1.1 mmol)。反应液在室温搅拌1.0 h。反应液中加入冷水 (250.0 mL)。所得悬浊液过滤，滤饼经水洗并真空干燥得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(羟基甲基)环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。所得粗品无需纯化，直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 452.1.

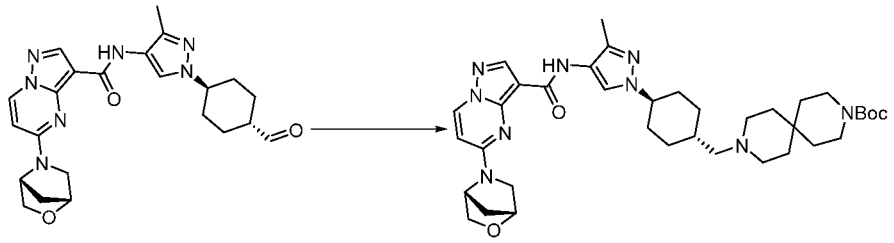
步骤 5： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-醛基环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(羟基甲基)环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (320.0 mg, 0.7 mmol)和IBX (392 mg, 1.4 mmol)在ACN (10 mL)中的混合物在60 ℃搅拌1 h。反应液经硅藻土过滤，滤液减压浓缩。所得粗品经柱层析纯化(MeOH:DCM=0~1:9)得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-醛基环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 450.1.

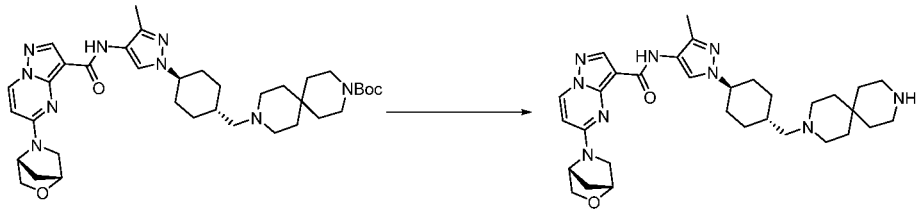
步骤 6： 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-甲基-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-醛基环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (250.0 mg, 0.6 mmol)和3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (203.0 mg, 0.8 mmol)的THF (10 mL)溶液中加STAB (381.6 mg, 1.8 mmol)。然后反应液在25 ℃搅拌1.0 h。反应液经硅藻土过滤，滤液减压浓缩。所得粗品经柱层析纯化 (MeOH:DCM=0~1:9)得到 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-甲基-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 688.3$.

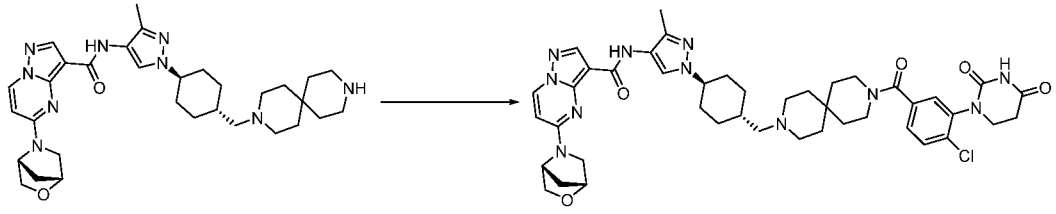
步骤 7： *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-甲基-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-甲基-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (300.0 mg, 0.4 mmol)的TFA/DCM (1.0 mL/3.0 mL)溶液在室温搅拌 1.0 h。反应液直接真空减压浓缩得到*N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-甲基-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。所得粗品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 588.6$.

步骤 8： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



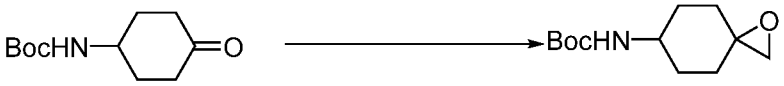
向 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-甲基-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (200.0 mg, 0.3 mmol)的 DMSO (5.0 mL)溶液中加 DIEA (54.20 mg, 0.42 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (143.2 mg, 0.33 mmol)，反应混合物在室温搅拌 2 h。反应液中加水 (15.0 mL)，然后用 DCM (30.0 mL x 2)萃取。合并有机相，用食盐水洗，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 Prep-HPLC (乙腈/0.05% NH_4HCO_3 水溶液, 5%~95%)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-甲基-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺.

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 838.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.21 (d, *J* = 7.6 Hz, 1H), 8.80 (d, *J* = 7.8 Hz, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.92-6.43 (m, 1H), 5.25-5.05 (m, 1H), 4.78 (s, 1H), 4.05-3.88 (m, 1H), 3.88 – 3.57 (m, 7H), 3.45 (d, *J* = 10.1 Hz, 1H), 3.30 – 3.26 (m, 2H), 2.78 – 2.68 (m, 2H), 2.41-1.93 (m, 12H), 1.86 (d, *J* = 11.5 Hz, 2H), 1.77-1.62 (m, 2H), 1.60-1.31 (m, 10H), 1.11-0.95 (m, 2H).

实施例 8：*N*-(2-((1*S*,4*S*)-4-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲氧基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺

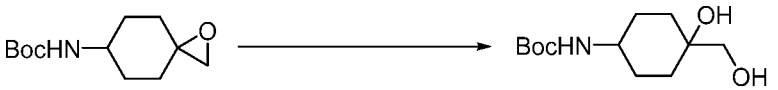
步骤 1：(1-氧杂螺[2.5]辛烷-6-基)氨基甲酸叔丁酯的制备



0 ℃时，搅拌下向 $Me_3OS^+I^-$ (6.2 g, 28.2 mmol)的 DMSO (50 mL)溶液中加入 NaH (1.17 g, 29.3 mmol)，反应混合物在室温搅拌 1 h，然后滴加 (4-氧代环己基)氨基甲酸叔丁酯 (5.0 g, 23.5 mmol)的 DMSO (20 mL)溶液，滴加完毕，反应液在室温继续搅拌 1 h。反应液中加水 (700 mL)，用 EtOAc (100 mL × 3)萃取。有机相用饱和食盐水 (300 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。粗产物经柱层析 (EA:PE=0~1:1)纯化得到 (1-氧杂螺[2.5]辛烷-6-基)氨基甲酸叔丁酯。

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, *J* = 7.2 Hz, 1H), 3.37 (m, 1H), 2.57 (s, 2H), 1.83 (td, *J* = 13.3, 4.1 Hz, 2H), 1.77 – 1.64 (m, 2H), 1.48 – 1.40 (m, 2H), 1.38 (s, 9H), 1.20 (d, *J* = 13.1 Hz, 2H).

步骤 2：(4-羟基-4-(羟基甲基)环己基)氨基甲酸叔丁酯的制备

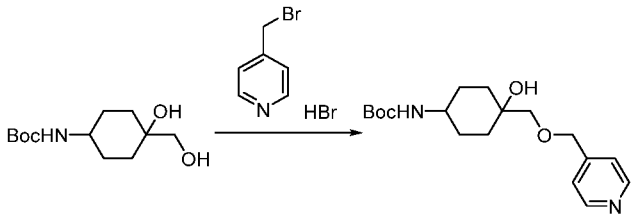


搅拌下向 (1-氧杂螺[2.5]辛烷-6-基)氨基甲酸叔丁酯 (4.7 g, 20.7 mmol 的 NMP (50 mL)溶液中加入 2N NaOH (47 mL)，然后反应液在 100℃搅拌 2 h。反应液中加水 (500 mL)，用 EA (100 mL × 3)萃取。有机相用饱和食盐水 (300 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。粗品经 flash 柱

(MeOH:DCM=0~1:9)纯化得到 (4-羟基-4-(羟基甲基)环己基)氨基甲酸叔丁酯。

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (d, J = 7.9 Hz, 1H), 4.46 (t, J = 5.8 Hz, 1H), 3.81 (s, 1H), 3.11 (t, J = 6.8 Hz, 3H), 1.56 – 1.45 (m, 4H), 1.44 – 1.34 (m, 13H).

步骤 3： (4-羟基-4-((吡啶-4-基甲氧基)甲基)环己基)氨基甲酸叔丁酯的制备

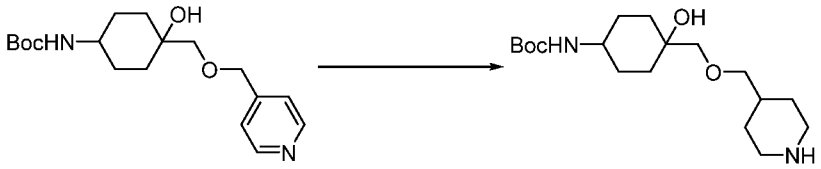


0 ℃时向 (4-羟基-4-(羟基甲基)环己基)氨基甲酸叔丁酯 (600 mg, 2.4 mmol)的 THF (20 mL)溶液中加 NaH (292 mg, 7.3 mmol)，反应混合物保持在 0 ℃搅拌 20 min，然后在室温再继续搅拌 30 min 后加入 4-(溴甲基)吡啶溴化氢盐 (617 mg, 2.4 mmol)。反应液在室温搅拌过夜。反应液中加水 (30 mL)，用 EA (20 mL × 3)萃取，有机相用饱和食盐水 (60 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗产物经 flash 柱 (EA :PE=0~4:1)纯化得到 (4-羟基-4-((吡啶-4-基甲氧基)甲基)环己基)氨基甲酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=337.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 5.8 Hz, 2H), 7.34 (d, J = 5.6 Hz, 2H), 6.69 (d, J = 7.6 Hz, 1H), 4.55 (s, 2H), 4.19 (s, 1H), 3.23 (s, 2H), 3.18 – 3.07 (m, 1H), 1.60-1.48 (m, 6H), 1.42-1.35 (m, J = 9.2 Hz, 11H).

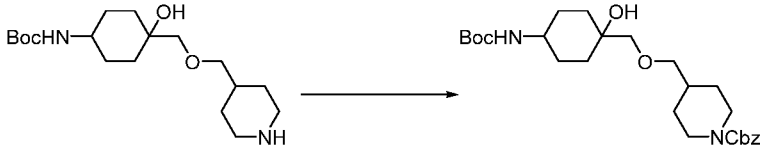
步骤 4： (4-羟基-4-((哌啶-4-基甲氧基)甲基)环己基)氨基甲酸叔丁酯的制备



将 (4-羟基-4-((吡啶-4-基甲氧基)甲基)环己基)氨基甲酸叔丁酯 (700 mg, 2.07 mmol)和 Pd/C (400 mg)的 i-PrOH/H_2O (18 mL/21 mL)混合液在 H_2 氛围中 75℃ 下搅拌过夜。反应液经硅藻土过滤，滤液减压浓缩得到 (4-羟基-4-((哌啶-4-基甲氧基)甲基)环己基)氨基甲酸叔丁酯。所得粗品直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=343.2.

步骤 5： 4-(((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸苄酯的制备

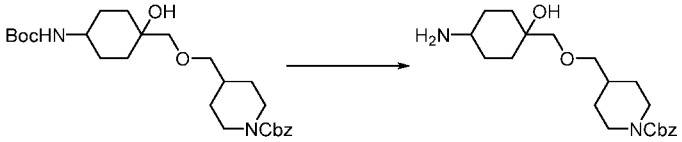


将 (4-羟基-4-((哌啶-4-基甲氧基)甲基)环己基)氨基甲酸叔丁酯 (630 mg, 1.83 mmol)，CbzCl (376

mg, 2.20 mmol)的 ACN (10 mL)溶液和饱和 $NaHCO_3$ 水溶液 (10 mL)室温搅拌过夜。反应液先减压浓缩，再用 DCM (50 mL × 3)萃取。有机相用饱和食盐水 (150 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。粗品经 flash 柱 (EA:PE=0~7:3)纯化得到 4-(((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=499.3.

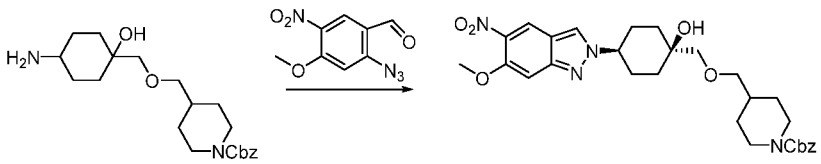
步骤 6： 4-(((4-氨基-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸苄酯的制备



-10~0 ℃下，边搅拌边向 4-(((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸苄酯 (300 mg, 0.63 mmol)的 DCM (12 mL)溶液中加入 TFA (3 mL)，然后反应液在室温搅拌 2 h。反应混合液用 DIEA 调节 pH 至 9.0，然后直接减压浓缩得到 4-(((4-氨基-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸苄酯。所得粗产品无需纯化，直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=377.2.

步骤 7： 4-((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)甲基)哌啶-1-羧酸苄酯的制备

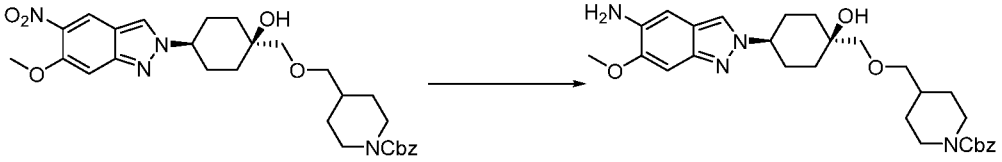


搅拌下向 4-(((4-氨基-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸苄酯 (237 mg, 0.63 mmol)的甲苯 (10 mL)溶液中加 2-叠氮-4-甲氧基-5-硝基苯甲醛 (170 mg, 0.76 mmol)。反应液在 100 ℃ 搅拌 3 h。反应液直接减压浓缩。粗产物先经 flash 柱 （EA:PE=0~4:1）纯化，再经 Prep-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%~95%)纯化得到 4-((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)甲基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=553.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.37 (s, 1H), 7.40 – 7.29 (m, 5H), 7.26 (s, 1H), 5.07 (s, 2H), 4.45 (t, *J* = 12.0 Hz, 1H), 4.36 (s, 1H), 4.06 – 3.99 (m, 2H), 3.90 (s, 3H), 3.29 (d, *J* = 6.2 Hz, 2H), 3.20 (s, 2H), 2.85-2.75 (m, 2H), 2.35 – 2.20 (m, 2H), 1.89 (d, *J* = 11.8 Hz, 2H), 1.76-1.61 (m, 7H), 1.15-1.02 (m, 2H).

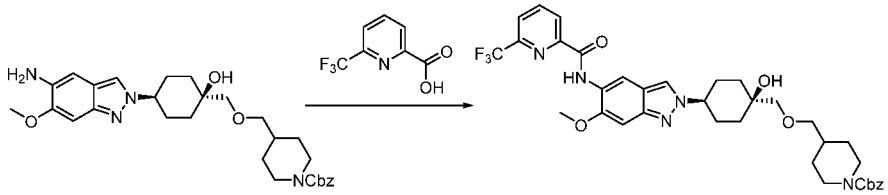
步骤 8： 4-((((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸叔丁酯的制备



向 4-((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)甲基)哌啶-1-羧酸苄酯(200 mg, 0.36 mmol)的 EtOH (20 mL)溶液中加 Raney-Ni (0.3 mL)和 N_2H_4 H_2O (0.3 mL)。反应液在室温搅拌 2 h。反应液经硅藻土过滤，滤液直接减压浓缩得到 4-((((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸叔丁酯。所得粗产物直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=523.2.

步骤 9： 4-((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)甲基)哌啶-1-羧酸苄酯的制备

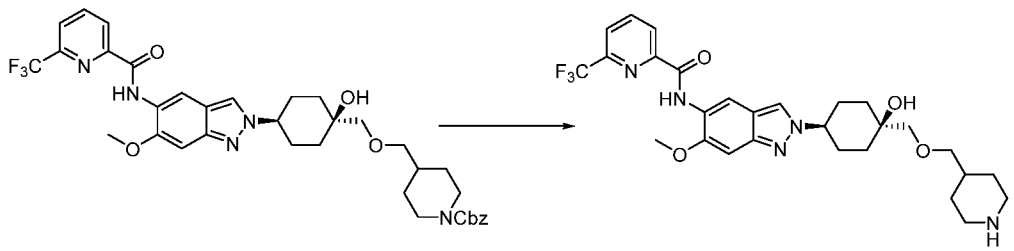


搅拌下向 4-((((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基)甲氧基)甲基)哌啶-1-羧酸叔丁酯 (190 mg, 0.36 mmol)的 DMF (5 mL)溶液中加 6-(三氟甲基)吡啶甲酸 (90 mg, 0.47 mmol)，HATU (178 mg, 0.47 mmol)和 DIEA (140 mg, 1.08 mmol)。然后反应液在室温搅拌 2 h。反应液中加水 (30 mL)，用 EA (20 mL × 3)。有机相用饱和食盐水 (60 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash 柱 (EA:PE=0~4:1)纯化得到 4-((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)甲基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=696.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.69 (s, 1H), 8.47 (d, *J* = 7.7 Hz, 1H), 8.41 (t, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.29 (m, 5H), 7.16 (s, 1H), 5.08 (s, 2H), 4.40 – 4.29 (m, 2H), 4.15-3.95 (m 5H), 3.29 (d, *J* = 6.2 Hz, 2H), 3.21 (s, 2H), 2.91-2.70 (m, 2H), 2.35-2.15 (m, 2H), 1.90 (d, *J* = 9.5 Hz, 2H), 1.85-1.60 (m, 7H), 1.12-.1.02 (m, 2H).

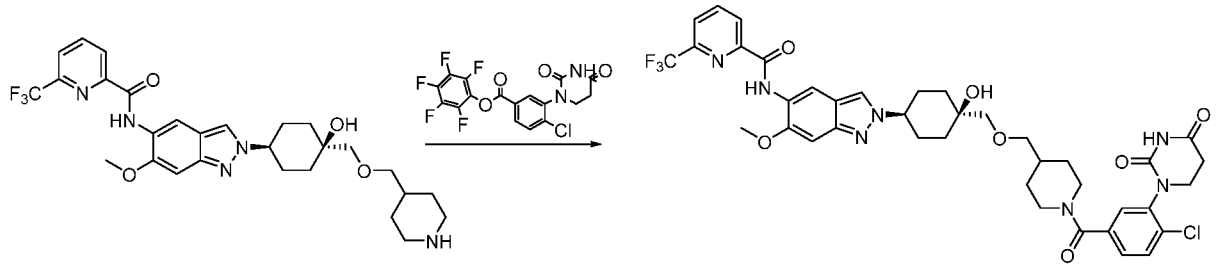
步骤 10： *N*-(2-((1*S*,4*S*)-4-羟基-4-((哌啶-4-基甲氧基)甲基)环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



向 4-((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲哚-2-基)环己基)甲氧基)甲基)哌啶-1-羧酸苄酯 (170 mg, 0.24 mmol)的 EA (20 mL)溶液中加入 Pd $(OH)_2$/C (80 mg)。然后反应液在 H_2 氛围中 70 ℃下搅拌过夜。反应液经硅藻土过滤，滤液直接减压浓缩得到 *N*-(2-((1*S*,4*S*)-4-羟基-4-((哌啶-4-基甲氧基)甲基)环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=562.3.

步骤 11： *N*-(2-((1*S*,4*S*)-4-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲氧基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



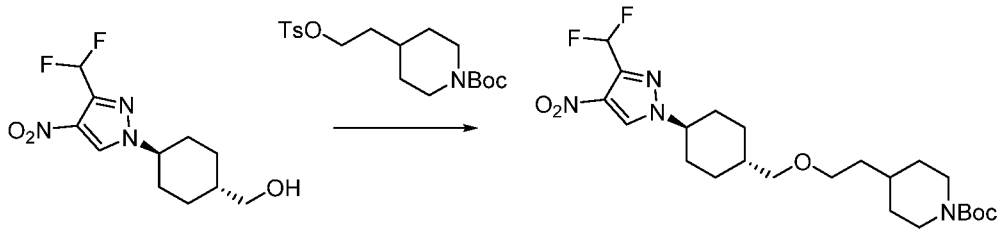
将 *N*-(2-((1*S*,4*S*)-4-羟基-4-((哌啶-4-基甲氧基)甲基)环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺 (130 mg, 0.23 mmol)，4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (121 mg, 0.28 mmol)和 DIEA (89 mg, 0.69 mmol)在 DMSO (6 mL)中的混合液在室温搅拌过夜。反应液加水 (50 mL)稀释，用 DCM (20 mL × 3)。有机相用饱和食盐水 (60 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 Prep-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%~95%)纯化得到 *N*-(2-((1*S*,4*S*)-4-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲氧基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=812.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* = 7.5 Hz, 2H), 8.69 (s, 1H), 8.46 (d, *J* = 7.7 Hz, 1H), 8.40 (t, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.40 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.16 (s, 1H), 4.58 – 4.29 (m, 3H), 3.99 (s, 3H), 3.84 – 3.55 (m, 3H), 3.33 – 3.28 (m, 2H), 3.22 (s, 2H), 3.13-3.03 (m, 1H), 2.88 – 2.70 (m, 3H), 2.35-2.20 (m, 2H), 1.94 – 1.59 (m, 9H), 1.21-1.15 (m, 2H).

实施例 9： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙氧基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

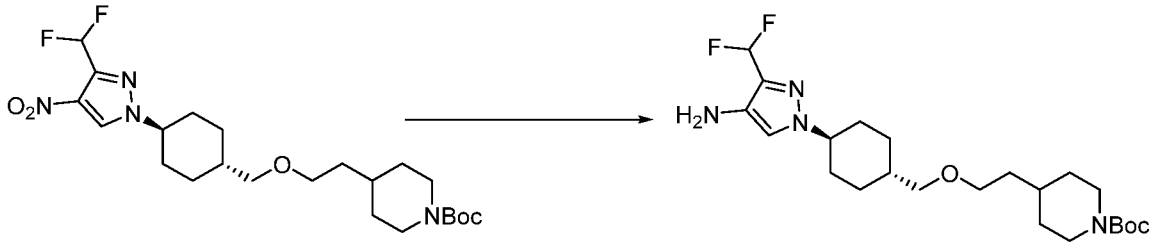
步骤 1： 4-(2-(((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯的制备



0 ℃向 ((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)甲醇 (1.0 g, 3.64 mmol)的无水 THF (30 mL)溶液中加 NaH (60%, 580 mg, 14.5 mmol)，然后在室温搅拌 1 h 后，加入 4-(2-(对甲苯磺酰基)乙基)哌啶-1-羧酸叔丁酯 (2.79 g, 7.28 mmol)和 KI (1.21 g, 7.28 mmol)，反应液在 70℃搅拌过夜。向反应液中缓慢加水 (50 mL)，用 EtOAc (100 mL ×3)萃取，合并的有机相用饱和食盐水 (50 mL)洗涤，减压浓缩。所得粗品经 flash 柱 (EA:PE=0~7:13)纯化得到 4-(2-(((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=509.2.

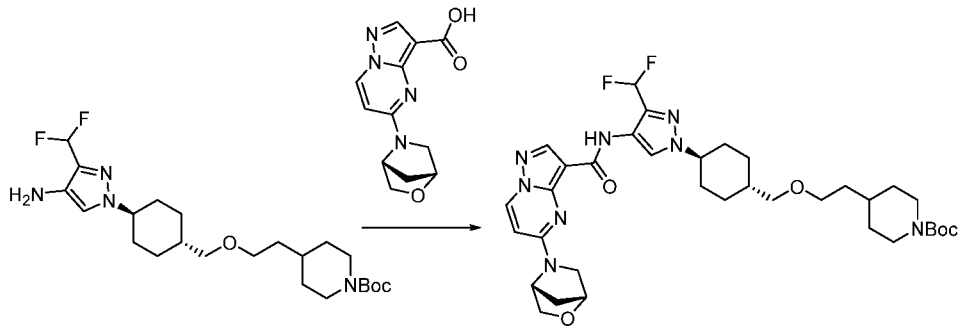
步骤 2： 4-(2-(((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯的制备



向 4-(2-(((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯 (185 mg, 0.38 mmol)的乙醇 (10 mL)溶液中加 Raney-Ni (0.4 mL)和水合肼 (85%, 0.4 mL)，然后反应液在室温搅拌 1 h。过滤，滤液直接减压浓缩得到 4-(2-(((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=457.2.

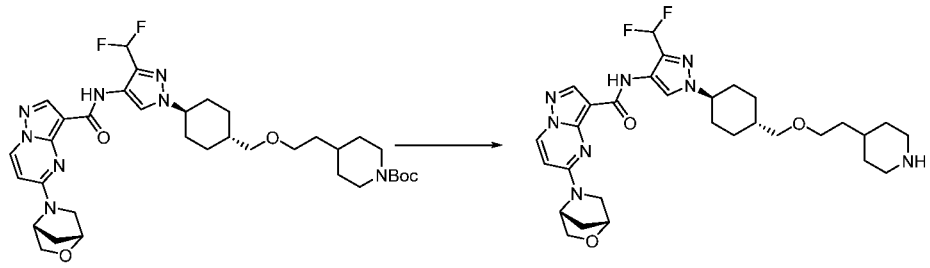
步骤 3： 4-(2-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基 l)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯的制备



向 4-(2-(((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯(150 mg, 0.33 mmol)的 DMF (5 mL)溶液中加入 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (86 mg, 0.33 mmol)，HATU(188 mg,0.50 mmol)和 DIEA(128 mg, 0.99 mmol)。反应液在室温搅拌 2 h。反应液中加水 (50 mL)稀释，然后用 EA (50 mL ×3)萃取。有机相用饱和食盐水(150 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经反相 (CH_3CN/H_2O (0.5% FA), 5%~95%,)纯化得到 4-(2-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基 l)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=721.2.

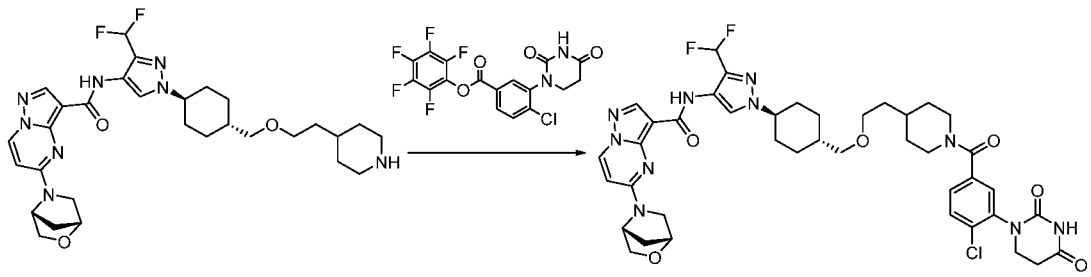
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(2-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基 l)环己基)甲氧基)乙基)哌啶-1-羧酸叔丁酯 (80 mg, 0.11 mmol)在 TFA/DCM (3 mL, 1/5)中的反应液在室温搅拌 1 h。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。所得产物直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=599.3

步骤 5： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙氧基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 0.13 mmol)， 3-(2,4-二氧代四氢

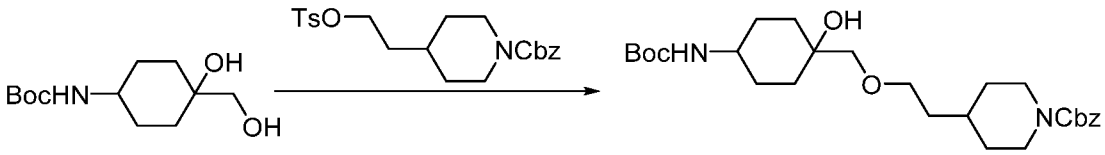
嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (58 mg, 0.13 mmol)和 DIEA (86 mg, 0.66 mmol)的 DMSO (5 mL)溶液在室温搅拌过夜。反应液倒入水中 (50 mL)并搅拌 10 min。过滤，滤饼经 flash 柱（MeOH:DCM=0~1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙氧基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=849.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.3 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.29 – 6.93 (m, 1H), 6.90-6.40 (m, 1H), 5.30-5.03 (m, 1H), 4.77 (d, *J* = 17.2 Hz, 1H), 4.50-4.35 (m, 1H), 4.24-4.11 (m, 1H), 3.86 – 3.70 (m, 3H), 3.66 – 3.52 (m, 3H), 3.50-3.40 (m, 3H), 3.22 (d, *J* = 6.4 Hz, 2H), 3.12-2.95 (m, 1H), 2.83-2.70 (m, 3H), 2.08 – 1.91 (m, 4H), 1.88 – 1.54 (m, 8H), 1.55 – 1.44 (m, 2H), 1.19-1.04 (m, 4H).

实施例 10： *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙氧基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺

步骤 1： 4-(2-((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备

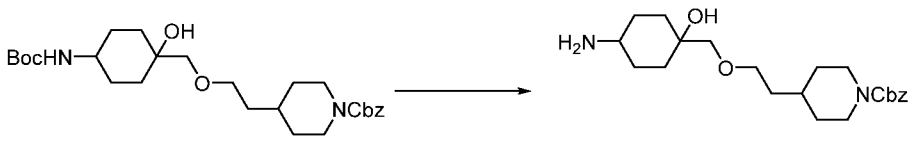


0 ℃向 (4-羟基-4-(羟基甲基)环己基)氨基甲酸叔丁酯 (770 mg, 3.13 mmol)的 THF (20 mL)溶液中加 NaH (376 mg, 9.4 mmol)，并在 0 ℃搅拌 2 h，然后加入 4-(2-(对甲苯磺酰基)乙基)哌啶-1-羧酸苄酯 (2.62 g, 6.26 mmol)和 KI (1.04 g, 6.26 mmol)。反应液在 70 ℃搅拌过夜。反应液加水 (50 mL)稀释，用 EA (30 mL × 3)萃取。有机相用饱和食盐水 (100 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash 柱 (EA:PE=0~3:2)得到 4-(2-((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=513.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 – 7.29 (m, 5H), 6.67 (d, *J* = 7.5 Hz, 1H), 5.06 (s, 2H), 4.05-3.90 (m, 3H), 3.42 (t, *J* = 6.4 Hz, 2H), 3.10 (s, 3H), 2.88-2.68 (m, 2H), 1.65 (d, *J* = 12.6 Hz, 2H), 1.55-1.32 (m, 20H), 1.13-0.92 (m, 2H).

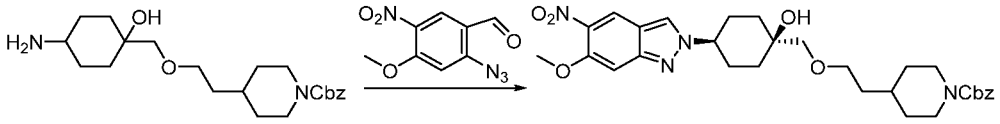
步骤 2： 4-(2-((4-氨基-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备



-10~0 ℃时，搅拌下向 4-(2-((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯(270 mg, 0.55 mmol)的 DCM (3 mL)溶液中加 TFA (1.2 mL)，然后反应液在室温搅拌 2 h。反应液中加 DIEA 调节 pH 至 9.0，减压浓缩得到 4-(2-((4-氨基-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=391.2.

步骤 3：4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备



搅拌下向 4-(2-((4-氨基-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (400 mg, 0.55 mmol) 的甲苯(15 mL)溶液中加 2-叠氮-4-甲氧基-5-硝基苯甲醛 (150 mg, 0.66 mmol)。反应液在 100 ℃搅拌 3 h。反应液减压浓缩，所得粗品经 flash 柱 (EA:PE=0~9:1)纯化得到 4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=567.3.

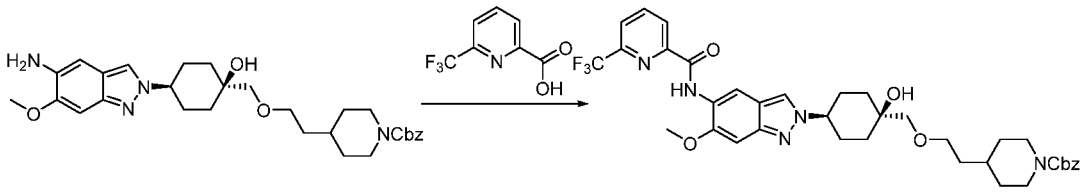
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.38 (s, 1H), 7.41 – 7.29 (m, 5H), 7.27 (s, 1H), 5.07 (s, 2H), 4.50-4.40 (m, 1H), 4.34 (s, 1H), 4.05-3.95 (m, 2H), 3.91 (s, 3H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.21 (s, 2H), 2.90-2.70 (m, 2H), 2.35 – 2.19 (m, 2H), 1.90 (d, *J* = 9.7 Hz, 2H), 1.75-1.50 (m, 7H), 1.50-1.40 (m, 2H), 1.11 – 0.98 (m, 2H).

步骤 4：4-(2-(((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备

向 4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯(250 mg, 0.44 mmol)的 EtOH (20 mL)溶液中加 Raney-Ni (0.5 mL)和 $N_2H_4.H_2O$ (0.5 mL)。反应液在室温搅拌 2 h。反应液经硅藻土过滤，滤液减压浓缩得到 4-(2-(((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。所得产物直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=537.3

步骤 5：4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备

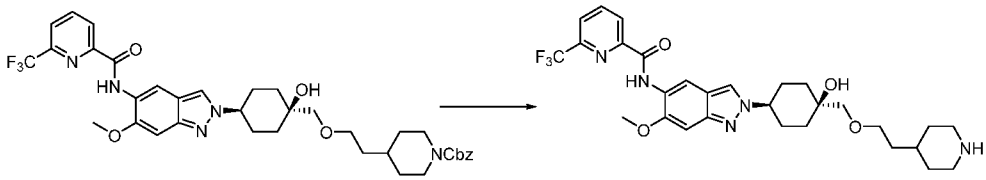


边搅拌边向 4-(2-(((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (236 mg, 0.44 mmol)的 DMF (5 mL)溶液中加 6-(三氟甲基)吡啶甲酸 (101 mg, 0.53 mmol)，HATU (217 mg, 0.57 mmol)和 DIEA (170 mg, 1.32 mmol)。然后反应液在室温搅拌 2 h。反应液中加水 (50 mL)稀释，用 EA (20 mL × 3)萃取。有机相用饱和食盐水 (60 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash 柱 (EA:PE=0~4:1)纯化得到 4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=710.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.69 (s, 1H), 8.46 (d, *J* = 7.7 Hz, 1H), 8.40 (t, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.16 (s, 1H), 5.06 (s, 2H), 4.40-4.20 (m, 2H), 4.10-3.90 (m, 5H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.21 (s, 2H), 2.90-2.70 (m, 2H), 2.32 – 2.18 (m, 2H), 1.90 (d, *J* = 10.4 Hz, 2H), 1.72-1.53 (m, 7H), 1.52-1.40 (m, 2H), 1.15-1.00 (m, 2H).

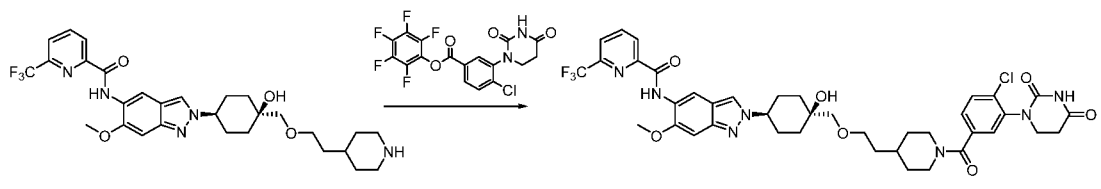
步骤 6： *N*-(2-((1*S*,4*S*)-4-羟基-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



向 4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (200 mg, 0.28 mmol)的 EA (20 mL)溶液中加 Pd $(OH)_2$/C (100 mg)。然后反应液在 H_2 氛围中 70 ℃下搅拌过夜。反应液经硅藻土过滤，滤液浓缩得到 *N*-(2-((1*S*,4*S*)-4-羟基-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺，所得产品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=576.2.

步骤 7： *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙氧基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



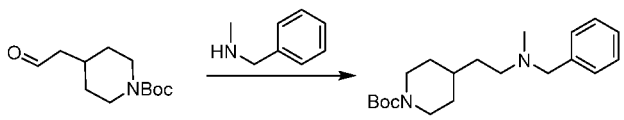
将 *N*-(2-((1*S*,4*S*)-4-羟基-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺 (130 mg, 0.22 mmol)，4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (118 mg, 0.27 mmol)和 DIEA (87 mg, 0.68 mmol 的 DMSO (3 mL)溶液在室温搅拌过夜。反应液加水 (30 mL)稀释，用 DCM (10 mL × 3)萃取。有机相用饱和食盐水 (30 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash 柱 (MeOH:DCM=0~1:9)纯化得到 *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙氧基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=826.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* = 5.7 Hz, 2H), 8.69 (s, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 8.41 (t, *J* = 7.8 Hz, 1H), 8.33 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.16 (s, 1H), 4.50-4.26 (m, 3H), 3.98 (s, 3H), 3.83 – 3.53 (m, 3H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.21 (s, 2H), 3.13-2.97 (m, 1H), 2.86 – 2.71 (m, 3H), 2.32 – 2.18 (m, 2H), 1.90 (d, *J* = 9.8 Hz, 2H), 1.85-1.45 (m, 9H), 1.15-1.05 (m, 2H).

实施例 11： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(2-(苯基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



N_2保护下，向 4-(2-氧代乙基)哌啶-1-羧酸叔丁酯 (1 g, 4.41 mmol)的DCE (3 mL)溶液中加*N*-甲基-1-苯基甲胺 (1.067 g, 8.82 mmol)和AcOH (0.79 g, 13.23 mmol)，混合液在室温搅拌30min后，再加入STAB (2.8 g, 13.23 mmol)，然后反应液在室温搅拌2 h。反应液中加水 (20 mL)稀释，用EA (30 mL×2)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (MeOH:DCM=0~1:20)纯化得到 4-(2-(苯基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 333.2.

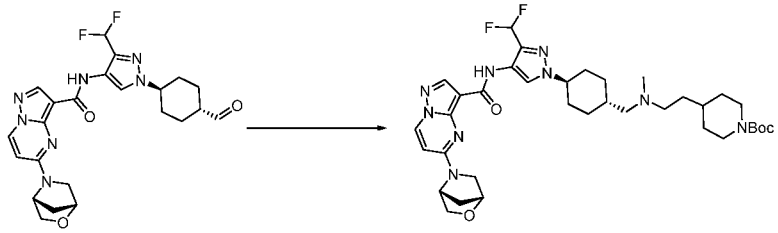
步骤 2： 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯的制备

向 4-(2-(苯基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (1 g, 3.01 mmol)的THF (3 mL)溶液中加$Pd(OH)_2/C$ (250 mg)，然后反应液在H_2氛围中室温下搅拌2 h。反应液经硅藻土过滤，滤液减压浓缩得

到 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 243.2.

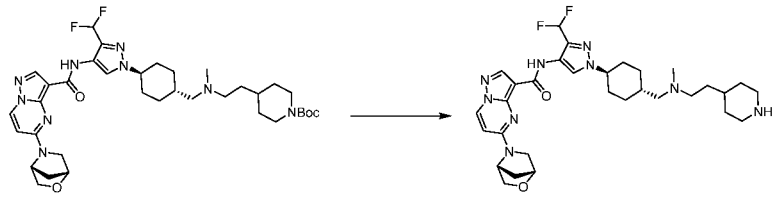
步骤 3： 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (300 mg, 0.618 mmol)的THF (3 mL)溶液中加4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (329 mg, 0.928 mmol)和STAB (419 mg, 1.862 mmol)，然后反应在N2氛围中室温下搅拌2 h。反应加水 (20 mL)淬灭，用DCM (20 mL × 2)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (MeOH:DCM=0~1:9)纯化得到 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 712.4.

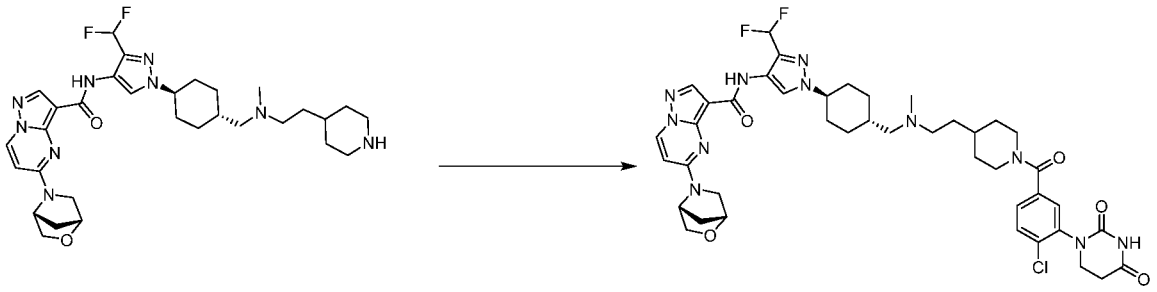
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (200 mg, 0.281 mmol)的DCM (3 mL)溶液中加TFA (1 mL)，然后反应液在N2氛围中室温下搅拌2 h。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 612.4.

步骤 5： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



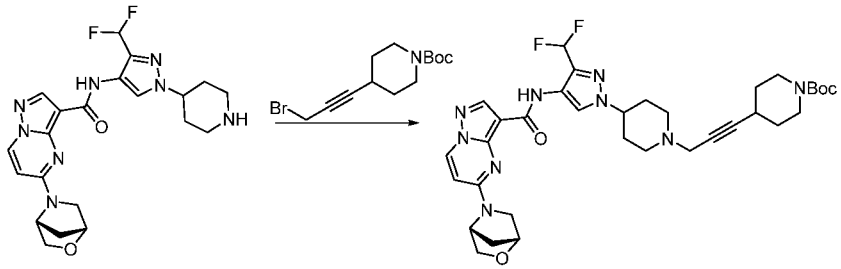
向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (175 mg, 0.521 mmol)的 DMSO (3 mL)溶液中加 DIEA (109 mg, 1.564 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (134 mg, 1.043 mmol)，然后反应液在室温搅拌 3 h。反应液中加水 (15 mL)，用 DCM (30 mL × 2)萃取，无水 Na_2SO_4 干燥，有机相减压浓缩，所得粗品经 Prep-HPLC (乙腈/0.05% NH_4HCO_3 水溶液, 5%~95%)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 862.1$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 6.0 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.38 (d, *J* = 4.4 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.26-6.95 (m, 1H), 6.90-6.42 (m, 1H), 5.31-5.05 (m, 1H), 4.77 (d, *J* = 17.3 Hz, 1H), 4.52-4.34 (m, 1H), 4.24-4.12 (m, 1H), 3.86-3.70 (m, 3H), 3.65 – 3.53 (m, 3H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.11-2.94 (m, 1H), 2.77 – 2.65 (m, 3H), 2.29 (t, *J* = 7.0 Hz, 2H), 2.15 – 2.07 (m, 5H), 2.05 – 1.82 (m, 6H), 1.80 – 1.68 (m, 3H), 1.66-1.46 (m, 3H), 1.41-1.32 (m, 2H), 1.18 – 0.95 (m, 4H).

实施例 12： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丙-2-炔基-1-基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(3-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丙-1-炔基-1-基)哌啶-1-羧酸叔丁酯的制备

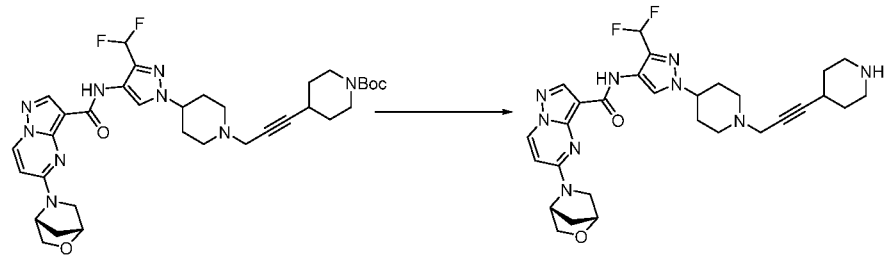


将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡

唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, TFA 盐, 0.33 mmol)，4-(3-溴丙-1-炔基-1-基)哌啶-1-羧酸叔丁酯 (99 mg, 0.33 mmol)和 K_2CO_3 (227 mg, 1.65 mmol)在 THF (20 mL)中的混合液在 70 ℃搅拌过夜。反应液加水 (20 mL)稀释，用 DCM (20 mL × 3)萃取，无水 Na_2SO_4 干燥，减压浓缩，所得粗品经 flash 柱(EA:PE=0~1)纯化得到 4-(3-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丙-1-炔基-1-基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=680.3.

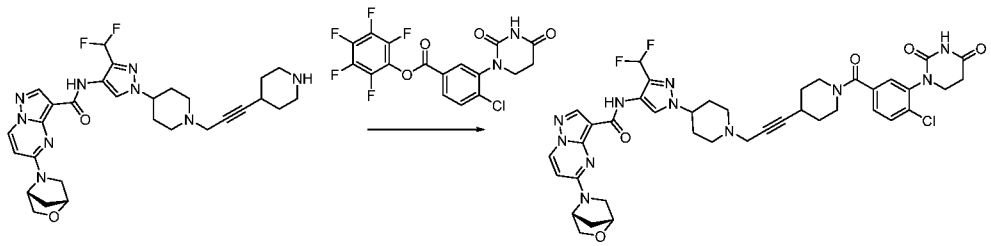
步骤 2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(3-(哌啶-4-基)丙-2-炔基-1-基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(3-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丙-1-炔基-1-基)哌啶-1-羧酸叔丁酯 (70 mg, 0.10 mmol) 的 TFA/DCM (3 mL, 1/5)混合液在室温搅拌 1 h。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(3-(哌啶-4-基)丙-2-炔基-1-基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。所得产品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=580.2.

步骤 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丙-2-炔基-1-基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



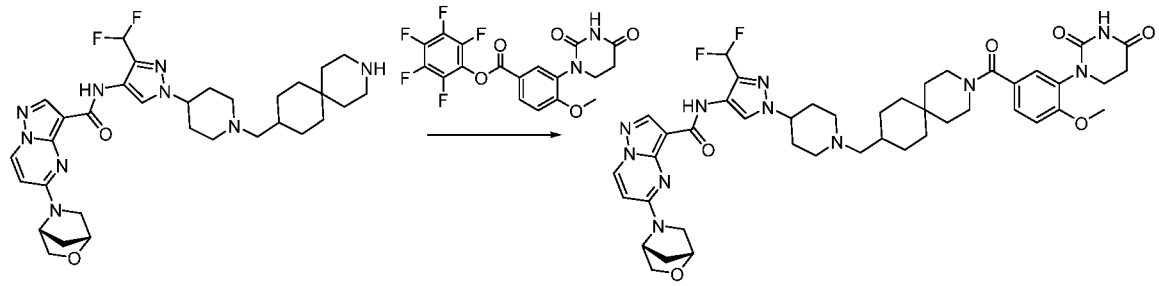
将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(3-(哌啶-4-基)丙-2-炔基-1-基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (70 mg, crude, 0.12 mmol)，4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (52 mg, 0.12 mmol)和 DIEA (774 mg, 0.60 mmol)在 DMSO (5 mL)中的混合液在室温搅拌过夜。反应液倒入水 (50 mL)中并搅拌 10 min。过滤，滤饼经 flash 柱(MeOH:DCM=0~1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-(1-(4-氯-3-

(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丙-2-炔基-1-基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=830.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.51 (d, *J* = 5.8 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.42 (s, 1H), 8.26 (d, *J* = 5.6 Hz, 1H),7.64 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.28-6.97 (m, 1H), 6.90-6.43 (m, 1H), 5.30-5.02 (m, 1H), 4.77 (d, *J* = 18.9 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.18 – 3.90 (m, 1H), 3.88-3.70 (m, 3H), 3.68 – 3.56 (m, 3H), 3.54 – 3.36 (m, 3H), 3.30 – 3.21 (m, 2H), 3.00 – 2.64 (m, 5H), 2.40 -2.20 (m, 2H), 2.12 – 1.73 (m, 8H), 1.62 – 1.42 (m, 2H).

实施例 13： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺



将 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (160 mg, 0.26 mmol)，3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (110 mg, 0.26 mmol)和 DIEA (168 mg, 1.3 mmol)在 DMSO (5 mL)中的混合物在室温搅拌过夜。反应液倒入水中 (50 mL)并搅拌 10 min。过滤，滤饼经 Prep-HPLC 纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=870.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.0 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.27 – 6.95 (m, 2H), 6.91-6.40 (m, 1H), 5.31-5.00 (m, 1H), 4.77 (d, *J* = 17.5 Hz, 1H), 4.27-4.15 (m, 1H), 3.86 – 3.71 (m, 5H), 3.65 – 3.39 (m, 8H), 2.89 (d, *J* = 10.4 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.15 (d, *J* = 6.1 Hz, 2H), 2.08 – 1.87 (m, 8H), 1.76-1.65 (m, 2H), 1.63-1.38 (m, 5H), 1.36-1.21 (m, 2H), 1.19-0.95 (m, 4H).

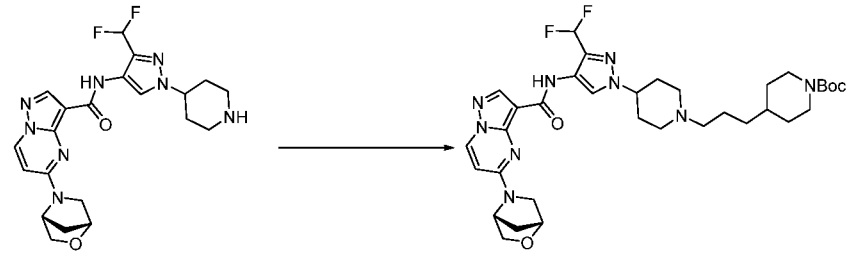
实施例 14： 5-((1*R*,4*R*)-2 氧杂--5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(3-氧代丙基)哌啶-1-羧酸叔丁酯的制备

将 IBX (2.88 g, 10.285 mmol)加入到 4-(3-羟基丙基)哌啶-1-羧酸叔丁酯 (1.0 g, 4.115 mmol)的 ACN (30 mL)溶液中，80 ℃搅拌 2 h，反应完成后，用乙酸乙酯 (50 mL × 3)萃取，饱和食盐水 (150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (PE:EA=1:1)纯化得到 4-(3-氧代丙基)哌啶-1-羧酸叔丁酯。

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (t, J = 1.5 Hz, 1H), 3.96-3.86 (m, 2H), 2.70-2.60 (m, 2H), 2.46 (td, J = 7.5, 1.4 Hz, 2H), 1.66-1.56 (m, 3H), 1.56-1.36 (m, 4H), 1.39 (s, 9H).

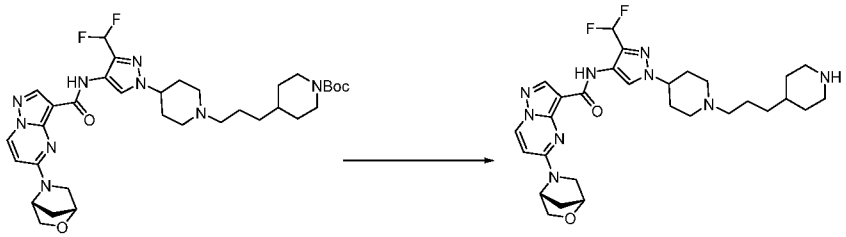
步骤 2： 4-(3-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丙基)哌啶-1-羧酸叔丁酯的制备



4-(3-氧代丙基)哌啶-1-羧酸叔丁酯 (95 mg, 0.394 mmol)和 STAB (208 mg, 0.981 mmol)加入到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, 0.327 mmol)的 THF (30 mL)溶液中，室温搅拌 2 h，用乙酸乙酯 (40 mL × 3)萃取，饱和食盐水 (150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (PE:EA=3:7)纯化得到 4-(3-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): [M+H]$^+$=684.2.

步骤 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(3-(哌啶-4-基)丙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

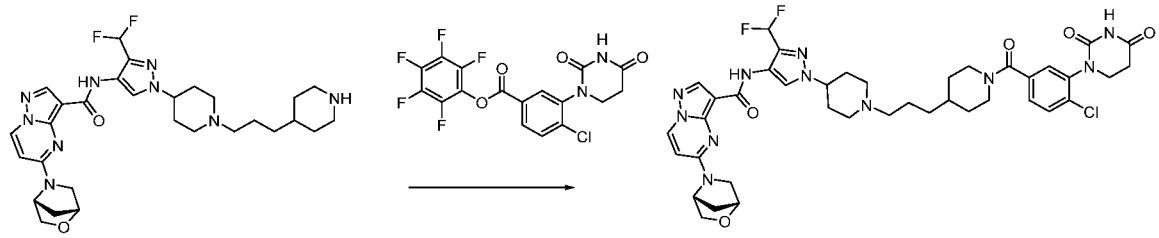


将 TFA (5 ml)加入到 4-(3-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丙基)哌啶-1-羧酸叔丁酯 (200 mg, 0.293 mmol)的 DCM (20 mL)溶液中，常温下搅拌 2 h，加饱和 $NaHCO_3$ 溶液调成碱性，用乙酸乙酯 (60 mL × 3)萃取，饱和

食盐水 (150 mL)洗涤有机相，减压浓缩，得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(3-(哌啶-4-基)丙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=584.2.

步骤 4： 5-((1*R*,4*R*)-2 氧杂--5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



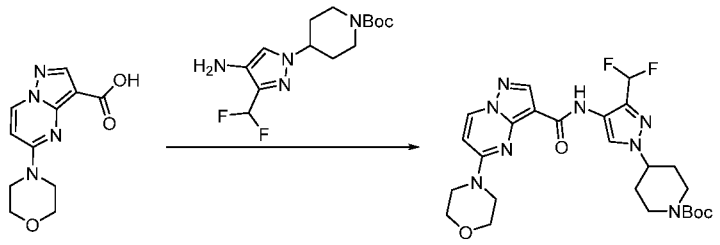
将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(3-(哌啶-4-基)丙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150 mg, 0.257 mmol)和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (134 mg, 0.308 mmol)用DMSO (5 mL)溶解，DIEA (100 mg, 0.775 mmol)加入，然后室温搅拌2小时，水 (50 mL)加入到反应液中，搅拌2分钟，过滤，滤饼通过反相制备纯化得到 5-((1*R*,4*R*)-2氧杂--5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=834.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.40 (d, *J* = 3.7 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.27 – 6.96 (m, 1H), 6.90-6.40 (m, 1H), 5.30-5.05 (m, 1H), 4.77 (d, *J* = 17.5 Hz, 1H), 4.52-4.33 (m, 1H), 4.26-4.14 (m, 1H), 3.85 – 3.72 (m, 3H), 3.66 – 3.57 (m, 3H), 3.45 (d, *J* = 10.2 Hz, 1H), 3.11-2.89 (m, 3H), 2.79 – 2.66 (m, 3H), 2.30 (t, *J* = 6.9 Hz, 2H), 2.09-1.84 (m, 9H), 1.82-1.69 (m, 1H), 1.68-1.58 (m, 1H), 1.56-1.40 (m, 3H), 1.30-1.20 (m, 2H), 1.16-1.02 (m, 2H).

实施例 15： *N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

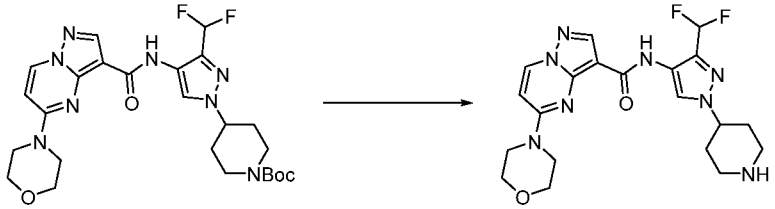
步骤 1： 4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯的制备



25 ℃时向 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸 (470 mg, 1.9 mmol)和DIEA (1 mL, 4.7 mmol)的DMF (20 ml)溶液中加入HATU (900 mg, 2.4 mmol)，混合物在25 ℃搅拌2 h后再加入4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (0.5 g, 1.5 mmol)，反应液再在25 ℃搅拌过夜。反应液中加水 (30 mL)，然后用EA (50 mL × 3)萃取，合并有机相，并用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经flash柱 (EA)纯化得到 4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 547.4$.

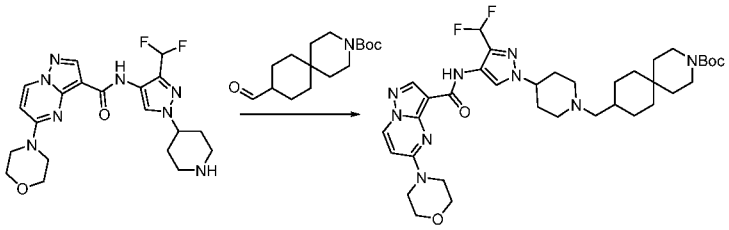
步骤 2： *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



25 ℃时向 4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (0.2 g, 0.366 mmol)的DCM (3 mL)溶液中加TFA (1 mL)。反应液在25 ℃搅拌1 h。反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 447.2$.

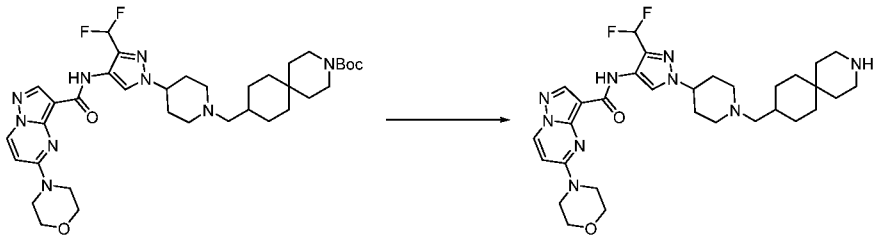
步骤 3： 9-((4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



25 ℃时向 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (200 mg, 0.45 mmol)和DIEA (0.5 ml, 1.35 mmol)的MeOH (5 mL)溶液中加入9-醛基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (150 mg, 0.45 mmol)和$NaBH_3CN$ (100 mg, 2.25 mmol)。反应液在25 ℃搅拌16 h。过滤，减压浓缩，所得粗品经flash柱 (MeOH:DCM=3:97)纯化得到 9-((4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 712.4$.

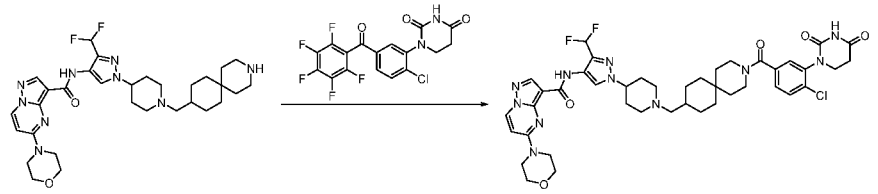
步骤 4： *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



25 ℃时向 9-((4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (0.14 g, 0.2 mmol)的DCM (3 mL)溶液中加TFA (1 mL)。反应液在25 ℃搅拌1 h。反应液直接减压浓缩得到 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。所得产品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 612.5$.

步骤 5： *N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



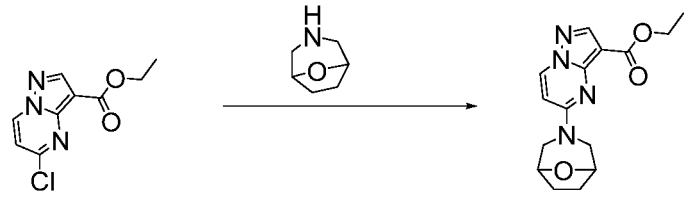
25 ℃时向 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (110 mg, 0.18 mmol)和1-(2-氯-5-五氟苯甲酰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (90 mg, 0.19 mmol)的DMSO (2 mL)溶液中加DIEA (0.1 mL, 0.54 mmol)。反应液在25 ℃搅拌16 h。反应液倒入水中 (10 mL)，过滤，滤饼经Prep-HPLC纯化得到 .

LC-MS: (ESI, *m/z*): $[M+H]^+ = 862.4$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.25-6.95 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.26-4.14 (m, 1H), 3.87 – 3.68 (m, 9H), 3.66 – 3.50 (m, 3H), 3.31 – 3.20 (m, 2H), 2.95-2.83 (m, 2H), 2.80 – 2.68 (m, 2H), 2.21-2.08 (m, 2H), 2.07 – 1.87 (m, 6H), 1.70 (d, *J* = 8.7 Hz, 2H), 1.63 – 1.41 (m, 5H), 1.38 – 1.25 (m, 2H), 1.16 – 1.02 (m, 4H).

实施例16： 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

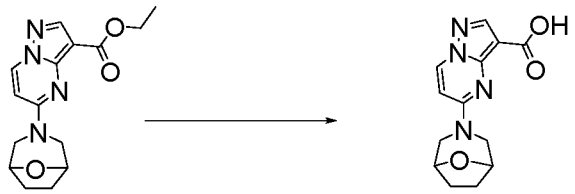
步骤 1： 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



向 5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (2.0 g, 8.9 mmol)的ACN (20 mL)溶液中加8-氧杂-3-氮杂双环[3.2.1]辛烷 (1.3 g, 8.9 mmol)和DIEA (3.4 g, 26 mmol)，然后反应液加热到60 ℃反应2 h。反应加水 (200 mL)淬灭，用EA (200 mL × 2)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗产物经层析柱 (PE:EA=1~5:1)纯化得到 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 303.2.

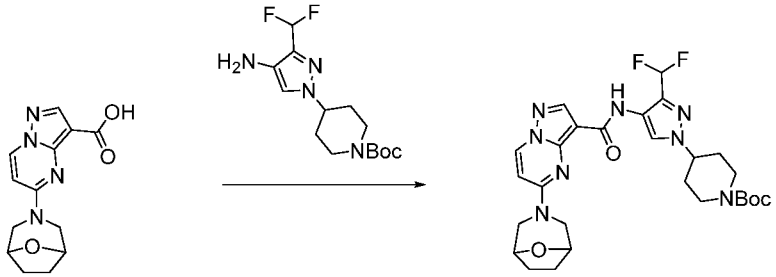
步骤 2： 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备



向 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (2.6 g, 8.6 mmol) 的H_2O/MeOH (3 ml/26 mL) 混合液中加LiOH (1.4 g, 34 mmol)，然后反应液加热到60 ℃反应12 h。反应液经硅藻土过滤，滤液减压浓缩。所得粗产物经Prep-HPLC (乙腈/0.05% NH_4OH 水溶液, 5%~95%)纯化得到 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 275.3.

步骤 3： 4-(4-(5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯的制备



向 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸 (274 mg,1 mmol)的DMF (5 mL)溶液中加4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (316 mg, 1 mmol)，HATU (456 mg, 1.2 mmol)和DIEA (387 mg, 3 mmol)，然后反应液在25 ℃反应12 h。反应液倒入水中，然后用EA (50 mL × 2)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗产物经层析柱 (MeOH:DCM=0~1:9)纯化得到 4-(4-(5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯。

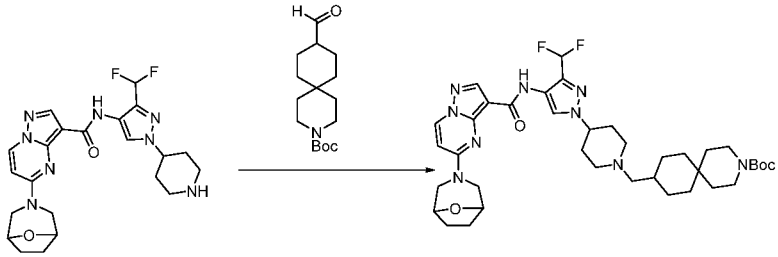
LC-MS: (ESI, *m/z*): $[M+H]^+$ = 573.4.

步骤4： 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

将 4-(4-(5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (240 mg, 0.42 mmol)的HCl/1.4-二氧六环 (5 mL)溶液在室温搅拌1 h。反应液直接减压浓缩得到 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 473.4.

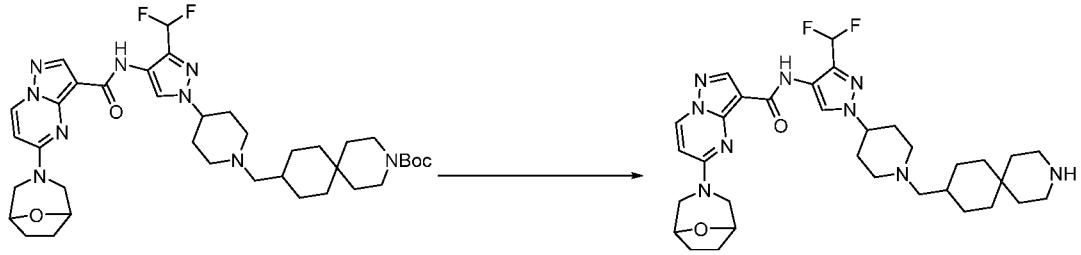
步骤 5： 9-((4-(4-(5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



向 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (130 mg, 0.27 mmol)的THF (10 mL)溶液中加9-醛基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (77 mg, 0.27 mmol和STAB (175 mg, 0.8 mmol)。然后反应液在25 ℃搅拌12 h。反应液经硅藻土过滤，滤液减压浓缩。所得粗产物经柱层析 (MeOH:DCM=0~1:9)纯化得到 9-((4-(4-(5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 738.3.

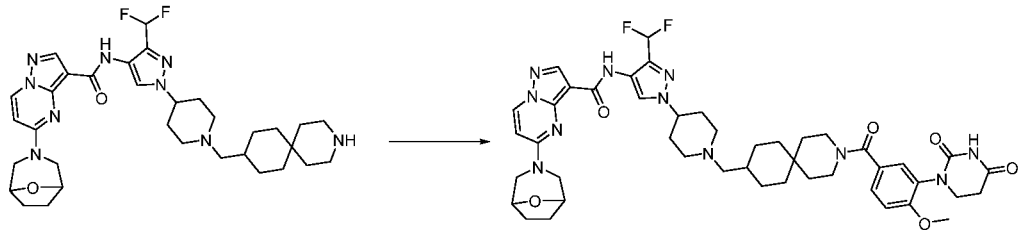
步骤 6： *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 9-((4-(4-(5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (100 mg, 0.14 mmol) 的HCl/1.4-二氧六环 (4 mL)溶液在25 ℃搅拌1 h。然后反应液直接减压浓缩得到 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 638.3$.

步骤 7： 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



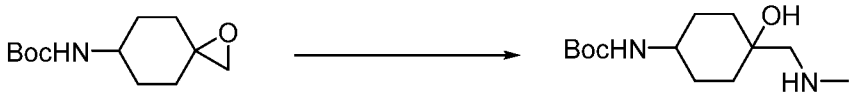
向 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (150.0 mg, 0.24 mmol)的 DMSO (2 mL)溶液中加 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (123 mg, 0.28 mmol)和 DIEA (93 mg, 0.72 mmol)，然后反应液在室温搅拌 12 h。 反应液倒入水 (20 mL)中，用 EA (30 mL × 2)萃取，有机相用无水 Na_2SO_4 干燥，减压浓缩。所得粗品经 Prep-HPLC (乙腈/0.05% NH_4HCO_3 水溶液, 5% ~95%)纯化得到 5-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 884.5$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.41 (s, 1H), 8.81 (d, *J* = 7.8 Hz, 1H), 8.39 (s, 1H), 8.28 (d, *J* = 1.3 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.27 – 6.95 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 4.50-4.37 (m, 2H), 4.30-4.00 (m, 2H), 3.84 (s, 3H), 3.68-3.34 (m, 6H), 3.28-3.11 (m, 2H), 2.98-2.78 (m, 2H), 2.73-2.60 (m, 2H), 2.22 – 1.63 (m, 14H), 1.61 – 1.17 (m, 8H), 1.18-0.93 (m, 4H).

实施例 17： *N*-(2-((1*S*,4*S*)-4-((((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)(甲基)氨基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲哚-5-基)-6-(三氟甲基)吡啶甲酰胺

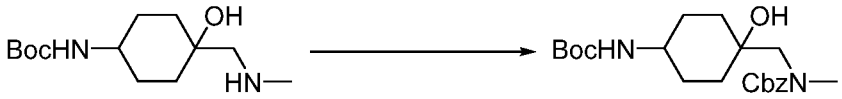
步骤 1： (4-羟基-4-(甲基氨基)甲基)环己基)氨基甲酸叔丁酯的制备



向 (1-氧杂螺[2.5]辛烷-6-基)氨基甲酸叔丁酯 (4.2g, 18.42 mmol)的 EtOH/H_2O (90 mL/15 mL)混合液中加甲胺 (40 mL, 25%~30%水溶液)。然后反应液在 25 ℃搅拌过夜。反应液直接减压浓缩，所得粗品经 flash (MeOH:DCM=0~1:1)纯化得到 (4-羟基-4-(甲基氨基)甲基)环己基)氨基甲酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=259.2.

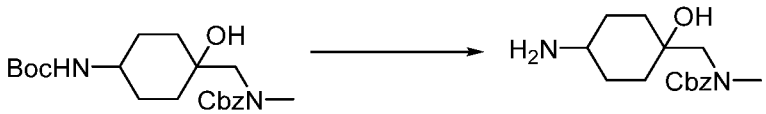
步骤 2： ((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲基)(甲基)氨基甲酸苄酯的制备



将 (4-羟基-4-(甲基氨基)甲基)环己基)氨基甲酸叔丁酯 (1.2 g, 4.61 mmol)和氯甲酸苄酯 (941 mg, 5.53 mmol)的 ACN/sat.$NaHCO_3$ (20 mL/20 mL)的混合液在室温搅拌过夜。反应液用水 (50 mL)稀释，然后用 EA (50 mL × 3)萃取。有机相用饱和食盐水 (150 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash (EA:PE=0~7:3)纯化得到 ((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲基)(甲基)氨基甲酸苄酯。

LC-MS: (ESI, *m/z*): $[M+Na]^+$=415.2.

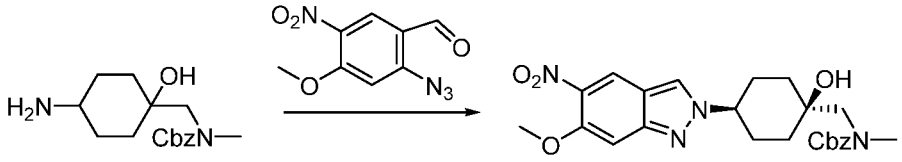
步骤 3： ((4-氨基-1-羟基环己基)甲基)(甲基)氨基甲酸苄酯的制备



0 ℃时，边搅拌边向 ((4-((叔丁氧羰基)氨基)-1-羟基环己基)甲基)(甲基)氨基甲酸苄酯 (1.5 g, 3.81 mmol)的 DCM (15 mL)溶液中加 TFA (5 mL)，然后反应液在 0 ℃搅拌 2 h。反应液用 DIEA 调节 pH 至 9.0，然后直接减压浓缩得到 ((4-氨基-1-羟基环己基)甲基)(甲基)氨基甲酸苄酯，所得粗品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=293.1.

步骤 4： (((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲哚-2-基)环己基)甲基)(甲基)氨基甲酸苄酯的制备

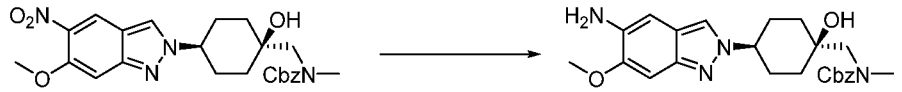


搅拌下向 ((4-氨基-1-羟基环己基)甲基)(甲基)氨基甲酸苄酯 (1.5 g, 3.8 mmol)的甲苯 (40 mL)溶液中加 2-叠氮-4-甲氧基-5-硝基苯甲醛 (1.2 g, 5.7 mmol)。反应液在 100 ℃搅拌 3 h。反应液直接减压浓缩。所得粗品经 flash 柱 (EA:PE=0~1)纯化得到 (((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基甲酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=469.2

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.38 (s, 1H), 7.45 – 7.23 (m, 6H), 5.09 (s, 2H), 4.66-4.36 (m, 2H), 3.91 (s, 3H), 3.28 (s, 2H), 3.10-2.95 (m, 3H), 2.30-2.20 (m, 2H), 1.95-1.60 (m, 2H), 1.78-1.63 (m, 2H), 1.59 – 1.41 (m, 2H).

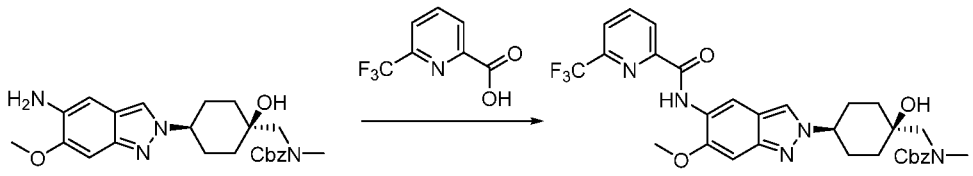
步骤 5： (((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基甲基)(甲基)氨基甲酸苄酯的制备



向 (((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基甲酸苄酯 (1.1 g, 2.34 mmol)的 EtOH (20 mL)溶液中加 $N_2H_4·H_2O$ (1.2 mL)和 Raney-Ni (0.5 mL)。反应液在室温搅拌 2 h。反应液经硅藻土过滤，滤液减压浓缩得到 (((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基甲基)(甲基)氨基甲酸苄酯，所得粗品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=439.2

步骤 6： (((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰)-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基甲酸苄酯的制备

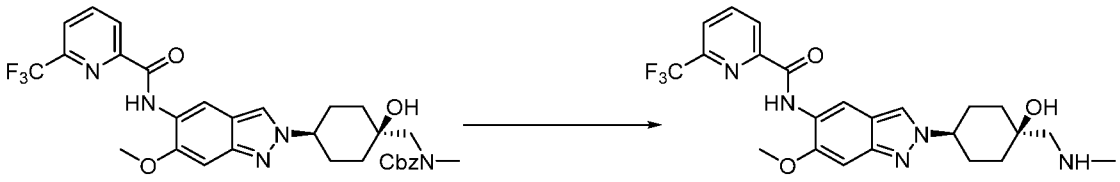


搅拌下向 (((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-羟基环己基甲基)(甲基)氨基甲酸苄酯 (940 mg, 2.14 mmol)的 DMF (10 mL)溶液中加 6-(三氟甲基)吡啶甲酸 (538 mg, 2.78 mmol)，HATU (1.06 g, 2.78 mmol)和 DIEA (828 mg, 6.42 mmol)。然后反应液在室温搅拌过夜。反应液加水 (100 mL)稀释，用 EA (30 mL × 3)萃取。有机相用饱和食盐水 (100 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash 柱 (EA:PE=0~9:1)纯化得到 (((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰)-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基甲酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=612.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.69 (s, 1H), 8.46 (d, *J* = 7.5 Hz, 1H), 8.40 (t, *J* = 7.8 Hz, 1H), 8.31 (s, 1H), 8.21 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.42 – 7.28 (m, 5H), 7.16 (s, 1H), 5.09 (s, 2H), 4.60-4.31 (m, 2H), 3.98 (s, 3H), 3.28 (s, 2H), 3.10-2.95 (m, 3H), 2.30-2.15 (m, 2H), 1.95-1.60 (m, 2H), 1.67 (t, *J* = 14.9 Hz, 2H), 1.57 – 1.40 (m, 2H).

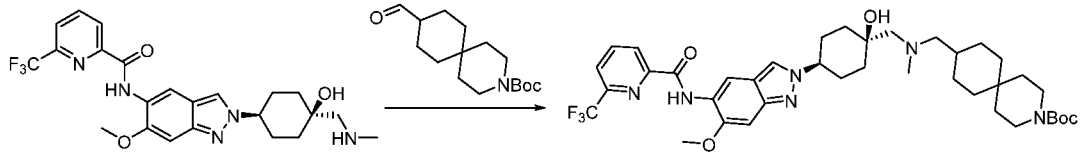
步骤 7：*N*-(2-((1*S*,4*S*)-4-羟基-4-((甲基氨基)甲基)环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



向 (((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰)-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基甲酸苄酯 (500 mg, 0.81 mmol)的 EA (20 mL)溶液中加 Pd $(OH)_2$/C (200 mg)。然后反应液在 H_2 氛围下 70 ℃下搅拌过夜。反应液经硅藻土过滤，滤液减压浓缩得到 *N*-(2-((1*S*,4*S*)-4-羟基-4-((甲基氨基)甲基)环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺，所得粗品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=478.1.

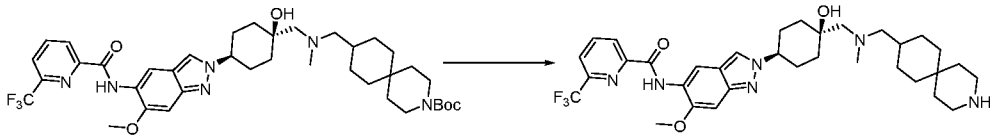
步骤 8： 9-(((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将 *N*-(2-((1*S*,4*S*)-4-羟基-4-((甲基氨基)甲基)环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺 (200 mg, 0.41 mmol)，9-醛基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (141 mg, 0.50 mmol)和 STAB (434 mg, 2.05 mmol)在 THF (10 mL)中的混合液在室温搅拌过夜。反应液加水 (30 mL)稀释，然后用 DCM (10 mL × 3)萃取。有机相用饱和食盐水 (30 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 flash 柱 (MeOH:DCM=0~1:9)纯化得到 9-(((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=743.3.

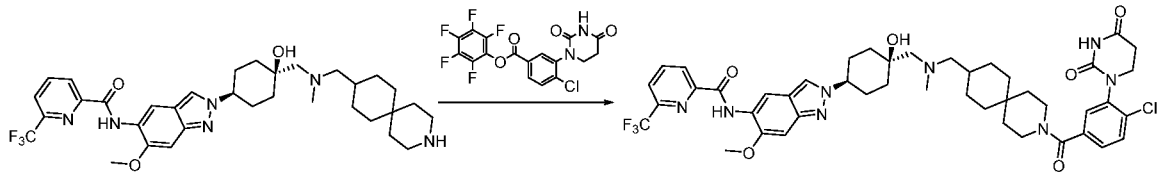
步骤 9： *N*-(2-((1*S*,4*S*)-4-((((3-氮杂螺[5.5]十一烷-9-基)甲基)(甲基)氨基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



0 ℃向 9-(((((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲基)(甲基)氨基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (200 mg, 0.27 mmol)的 DCM (5 mL) 溶液中加 TFA (2 mL)。然后反应液在室温搅拌 2 h。反应液用 DIE 调节 pH 至 9.0。有机相用水 (100 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩得到 *N*-(2-((1*S*,4*S*)-4-((((3-氮杂螺[5.5]十一烷-9-基)甲基)(甲基)氨基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺，所得粗品直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$=643.3.

步骤 10： *N*-(2-((1*S*,4*S*)-4-((((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)(甲基)氨基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



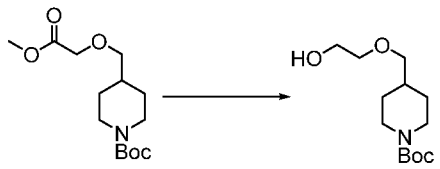
将 *N*-(2-((1*S*,4*S*)-4-((((3-氮杂螺[5.5]十一烷-9-基)甲基)(甲基)氨基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺 (130 mg, 0.20 mmol)，4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (105 mg, 0.24 mmol)和 DIEA (77 mg, 0.60 mmol)在 DMSO (5 mL)中的混合液在室温搅拌过夜。反应液加水 (50 mL)稀释，然后用 DCM (20 mL × 3)萃取，有机相用饱和食盐水 (60 mL)洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 Prep-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%~95%)纯化得到 *N*-(2-((1*S*,4*S*)-4-((((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)(甲基)氨基)甲基)-4-羟基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$=893.1.

^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 2H), 8.69 (s, 1H), 8.47 (d, *J* = 7.8 Hz, 1H), 8.41 (t, *J* = 7.8 Hz, 1H), 8.32 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.7 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.15 (s, 1H), 4.37-4.27 (m, 1H), 4.10-3.90 (m, 4H), 3.82 – 3.49 (m, 4H), 3.35-3.25 (m, 1H), 2.80-2.70 (m, 2H), 2.36-2.15 (m, 9H), 1.95-1.85 (m, 2H), 1.78 – 1.22 (m, 14H), 1.18-0.98 (m, 4H).

实施例 18： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲氧基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

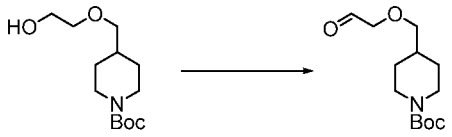
步骤 1： 4-((2-羟基乙氧基)甲基)哌啶-1-羧酸叔丁酯的制备



0 ℃时N_2保护下向 4-((2-甲氧基-2-氧代乙氧基)甲基)哌啶-1-羧酸甲酯 (1.1 g, 3.83 mmol)的无水THF (30 mL)溶液中滴加$LiAlH_4$ (1.0 mol/L, 5.8 mL)，然后反应液在室温搅拌3 h。边搅拌边向反应液中缓慢滴加15% NaOH 溶液，过滤，滤液用EA (30 mL × 2)，有机相用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (MeOH:DCM=0~3:97)纯化得到 4-((2-羟基乙氧基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 260.1.

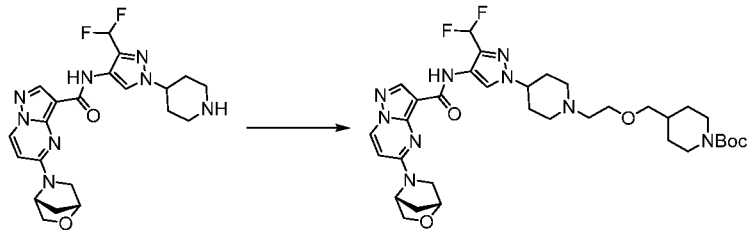
步骤 2： 4-((2-氧代乙氧基)甲基)哌啶-1-羧酸叔丁酯的制备



将 4-((2-羟基乙氧基)甲基)哌啶-1-羧酸叔丁酯 (700 mg, 2.7 mmol)和IBX (1.5 g, 5.4 mmol)在乙腈 (15 mL)中的混合液在80 ℃搅拌2 h。过滤，加水 (30 mL)稀释，用EA (30 mL × 2)萃取，有机相用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (EA:PE=0~2:3)纯化得到 4-((2-氧代乙氧基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M-t-Bu]^+$ = 202.1.

步骤 3： 4-((2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙氧基)甲基)哌啶-1-羧酸叔丁酯的制备

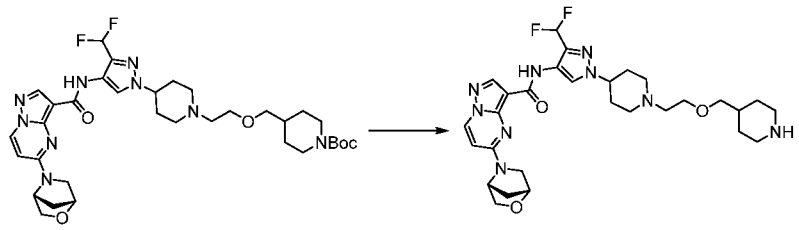


向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (220.0 mg, 0.48 mmol)和4-((2-氧代乙氧基)甲基)哌啶-1-羧酸叔丁酯 (185.2 mg, 0.72 mmol)的THF (5 mL)溶液中加STAB (277.8 mg, 1.44 mmol)。然后反应液在室温搅拌4 h。加水 (20 mL)淬灭反应，然后用DCM (20 mL × 2)萃取，有机相用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经柱层析 (MeOH:DCM=0~1:9)纯化得到 4-((2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙氧基)甲基)

哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 700.2$.

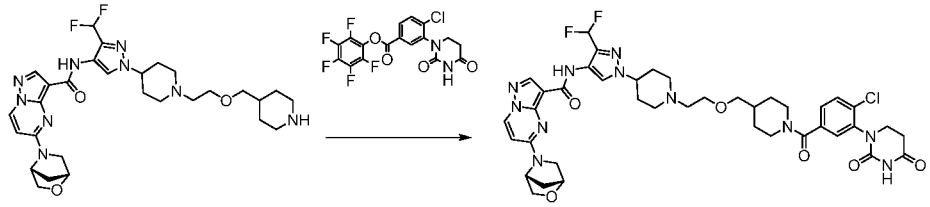
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基甲氧基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 4-((2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙氧基)甲基)哌啶-1-羧酸叔丁酯 (150.0 mg, 0.214 mmol)的DCM (3.0 mL)溶液中加TFA (1.0 mL)，反应液在室温搅拌2 h。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基甲氧基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 600.4$.

步骤 5： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲氧基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



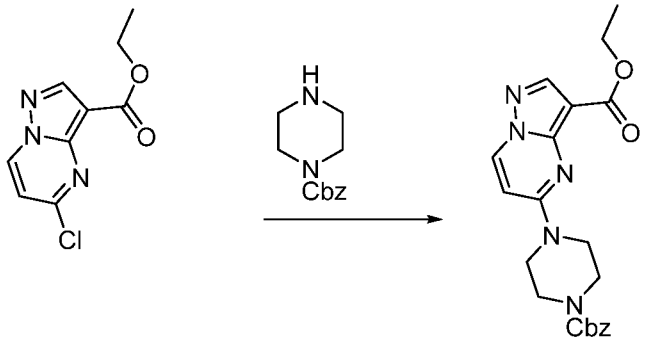
向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基甲氧基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (120.0 mg, 0.2 mmol)的 DMSO (5.0 mL)溶液中加 DIEA (77.5 mg, 0.6 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (95.6 mg, 0.22 mmol)，然后反应液在室温搅拌 2 h。反应加水 (15 mL)淬灭，然后用 DCM (30 mL × 2)萃取，有机相用饱和食盐水洗涤，无水 Na_2SO_4 干燥，过滤，减压浓缩。所得粗品经 Prep-HPLC (乙腈/0.05% NH_4HCO_3 水溶液, 5%~95%)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲氧基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 850.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.6 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 3.8 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.25-6.95 (m, 1H), 6.91-6.40 (m, 1H), 5.30-5.05 (m, 1H), 4.77 (d, J = 17.6 Hz, 1H), 4.55-4.35 (m, 1H), 4.28-4.10 (m, 1H), 3.83-3.75 (m, 3H), 3.66-3.57 (m, 3H), 3.53-3.42 (m, 3H), 3.30-3.26 (m, 2H), 3.06-2.96 (m, 3H), 2.77-2.66 (m, 3H), 2.34-2.20 (m, 3H), 2.06-1.85 (m, 10H), 1.14-1.08(m , 2H).

实施例 19： *N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备

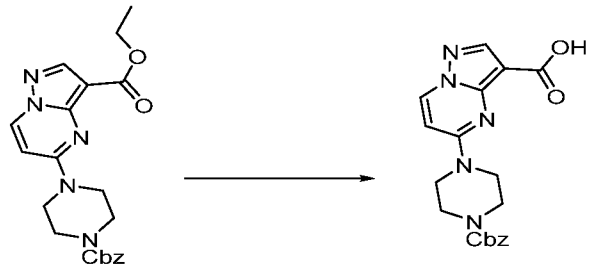


将 5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (3.0 g, 13.3 mmol)和 benzyl 哌嗪-1-羧酸苄酯 (2.9 g, 13.3mmol)溶于 ACN (30 mL)溶液中，再加 DIEA (5.2 g, 40 mmol)，将反应液加热到 60 ℃搅拌 2 小时，减压浓缩，粗品用乙酸乙酯 (100 mL)溶解，饱和食盐水洗，减压浓缩，粗品用柱层析 (PE:EA=2:1)纯化得到 5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$=410.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 7.9 Hz, 1H), 8.22 (s, 1H), 7.41 – 7.33 (m, 5H), 6.86 (d, J = 7.9 Hz, 1H), 5.13 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.88-3.74 (m, 4H), 3.62-3.49 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H).

步骤 2： 5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备

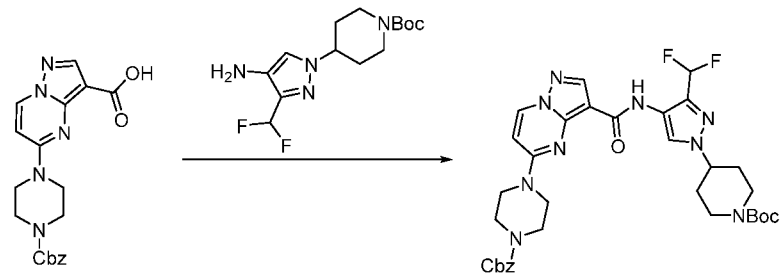


将 5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (2.6 g, 6.3 mmol)溶于甲醇 (26 mL)中，加入氢氧化锂 (1.0 g, 25.2 mmol)，反应液 60 ℃搅拌 2 小时，反应结束后向反应液加稀盐酸 (2

mol/L)使反应液 pH 至 2，然后过滤，所得滤饼用水洗并真空干燥得到 5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸。

LC-MS: (ESI, *m/z*): $[M+H]^+$=382.2.

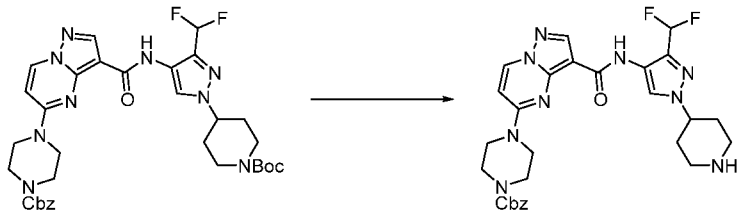
步骤 3： 4-(3-((1-(1-(叔丁氧羰基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯的制备



25 ℃时向 5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸 (270 mg, 0.4 mmol和DIEA (0.5 ml, 1.0 mmol)的DMF (5 ml)溶液中加HATU (380 mg, 0.50 mmol)，然后在室温搅拌2 h后再加4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (0.21 g, 0.3 mmol)，反应液在25 ℃搅拌过夜。反应加水(30 mL)淬灭，用EA (50 mL × 3)萃取，有机相用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩，所得粗品经层析柱 (MeOH:DCM=0~3:97)纯化得到 4-(3-((1-(1-(叔丁氧羰基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 680.4.

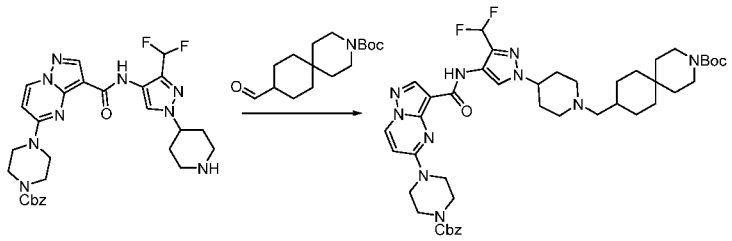
步骤 4： 4-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯的制备



向 4-(3-((1-(1-(叔丁氧羰基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯 (0.29 g, 0.42 mmol)的 DCM (5 mL)溶液中加 TFA (1 mL)，然后反应液在室温搅拌 2 h。反应液直接减压浓缩得到 4-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯.

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 580.5.

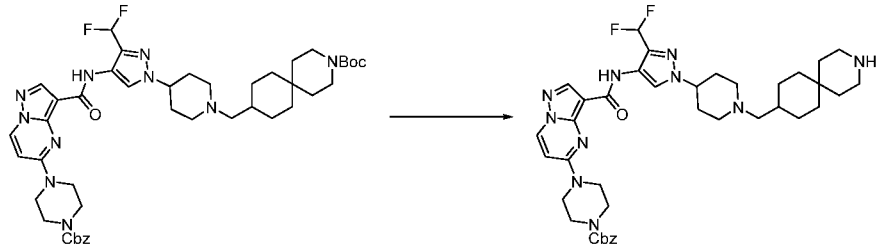
步骤 5： 9-((4-(4-(5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



向 4-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯 (230 mg, 0.4 mmol)和DIEA (0.35 mL, 2.0 mmol)的MeOH (10 mL)溶液中9-醛基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (144 mg, 0.45 mmol)和$NaBH_3CN$ (138 mg, 1.2 mmol)。反应液在25 ℃搅拌过夜。反应加水 (30 mL)淬灭，然后用EA (50 mL × 3)萃取，有机相用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩，所得粗品经flash柱 (MeOH:DCM=0~3:97)纯化得到 9-((4-(4-(5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 845.5.

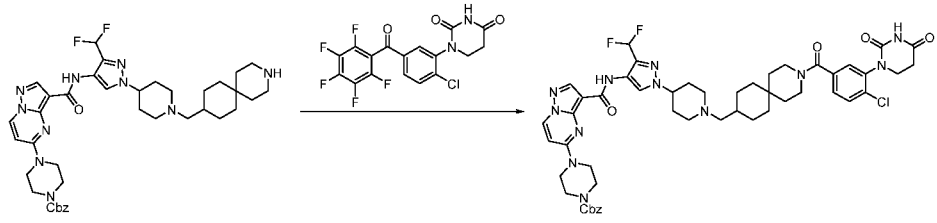
步骤 6： 4-(3-((1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯的制备



向 9-((4-(4-(5-(4-((苄氧基)羰基)哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (0.29 g, 0.34 mmol)的DCM (3 mL)溶液中加TFA (1 mL)，然后在25 ℃搅拌1 h。反应液直接减压浓缩得到 4-(3-((1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 745.4.

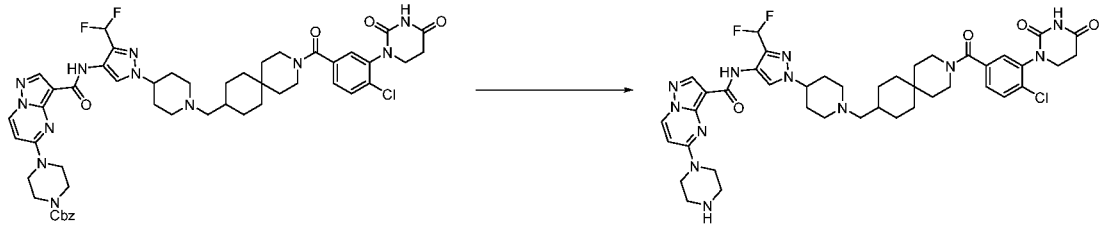
步骤 7： 4-(3-((1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯的制备



向 4-(3-((1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯 (240 mg, 0.32 mmol)和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (144 mg, 0.33 mmol)的DMSO (5 mL)溶液中加DIEA (0.1 mL, 0.6 mmol)。然后反应液在25 ℃搅拌16 h。反应液中加水 (30 mL)，用EA (50 mL × 3)萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，过滤，减压浓缩。所得粗品经flash柱 (MeOH:DCM=0~3:97)纯化得到 4-(3-((1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 995.0$.

步骤 8： *N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



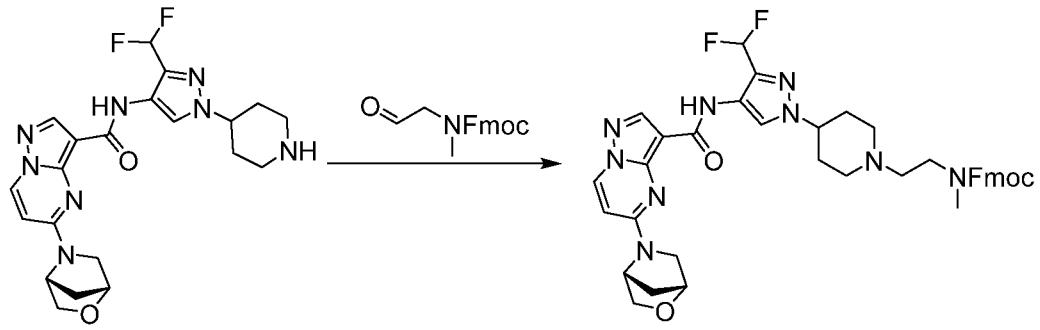
0 ℃时向 4-(3-((1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌嗪-1-羧酸苄酯 (290 mg, 0.29 mmol)的 DCM (15 mL)溶液中加碘代三甲硅烷 (0.85 mL, 0.6 mmol)，然后反应液在 25 ℃搅拌 16 h。反应液倒入水中，用 DCM (20 mL × 3)萃取，无水 Na_2SO_4 干燥，过滤，减压浓缩，所得粗品经 Prep-HPLC 纯化得到 *N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 861.1$.

^{1}H NMR (400 MHz, MeOD) δ 8.62 (d, J = 7.9 Hz, 1H), 8.43 (brs, 2.67H, FA), 8.35 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.08 – 6.77 (m, 2H), 4.57-4.43 (m, 1H), 4.15-4.03 (m, 4H), 3.79 (t, J = 6.4 Hz, 2H), 3.75-3.65 (m, 2H), 3.63-3.48 (m, 2H), 3.47-3.37 (m, 2H), 3.37-3.30 (m, 2H), 3.05-2.95 (m, 2H), 2.95-2.77 (m, 4H), 2.43-2.27 (m, 4H), 1.92-1.75 (m, 3H), 1.74-1.65 (m, 3H), 1.65-1.45 (m, 2H), 1.39-1.12 (m, 5H).

实施例 20： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲基)(甲基)氨基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

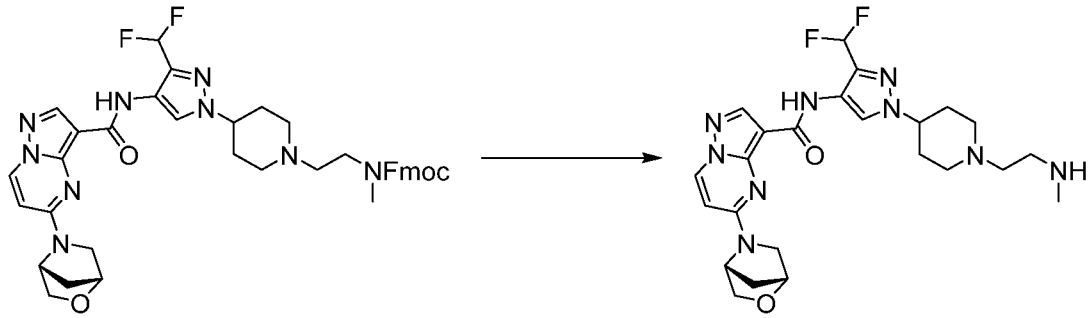
步骤 1： (2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)(甲基)氨基甲酸(9*H*-芴-9-基)甲基酯的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (120 mg, 0.26 mmol)的THF (10 mL)溶液中加甲基(2-氧代乙基)羧酸(9*H*-芴-9-基)甲基 (91 mg, 0.31 mmol)和STAB (165 mg, 0.78 mmol)。反应液在室温搅拌16 h。反应加水 (50 mL)淬灭，用DCM (20 mL × 3)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经flash柱(MeOH:DCM=0~1:9)纯化得到 (2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)(甲基)氨基甲酸(9*H*-芴-9-基)甲基酯。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 738.5$.

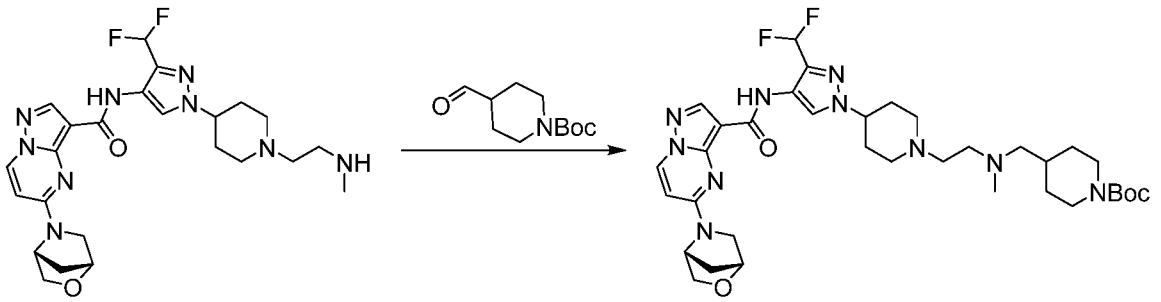
步骤 2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(甲基氨基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 (2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)(甲基)氨基甲酸(9*H*-芴-9-基)甲基酯 (120 mg, 0.16 mmol)的DCM (5 mL)溶液中加吡啶 (0.1 mL)。反应液在室温搅拌16 h。反应液直接减压浓缩。所得粗品经flash柱(MeOH:DCM=0~1:9)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(甲基氨基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 516.6$.

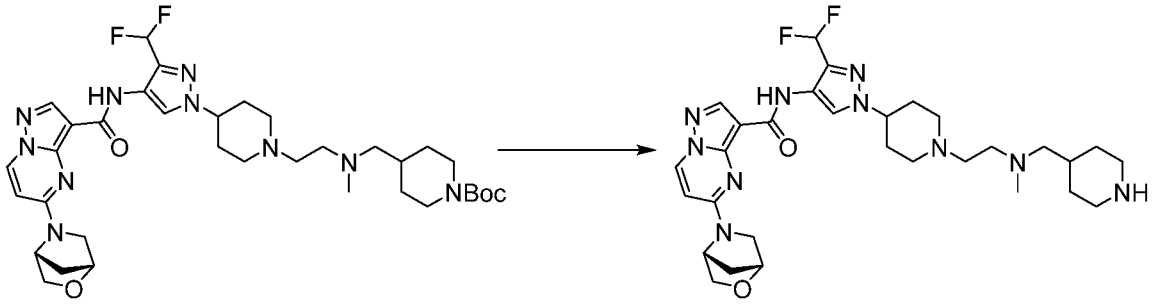
步骤 3： 4-(((2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯的制备



向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(甲基氨基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (90 mg, 0.17 mmol)的THF (10 mL溶液中加4-醛基哌啶-1-羧酸叔丁酯 (54 mg, 0.26 mmol)和STAB (108 mg, 0.51 mmol)。反应液在室温搅拌16 h。反应加水 (50 mL)淬灭，用DCM (20 mL × 3)萃取。有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗品经flash柱 （MeOH:DCM=0~1:4）纯化得到4-(((2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 713.4.

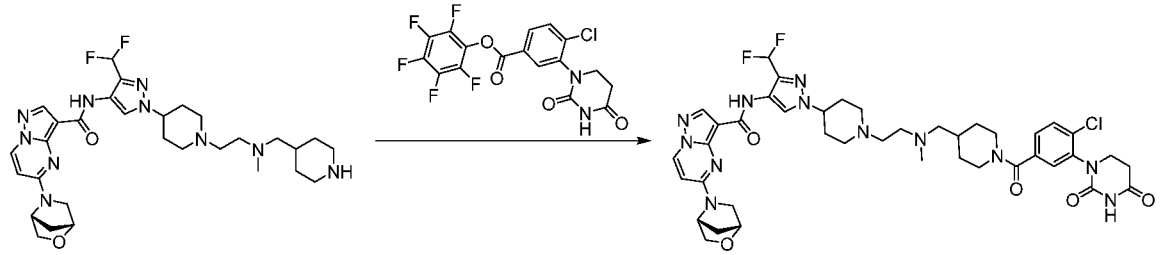
步骤 4： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(甲基(哌啶-4-基甲基)氨基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 4-(((2-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯 (100 mg, 0.14 mmol)的DCM (5 mL)溶液中加TFA (1 mL)。反应液在室温搅拌2 h。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(甲基(哌啶-4-基甲基)氨基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，所得产物直接用于下一步反应。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 613.3.

步骤 5： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲基)(甲基)氨基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



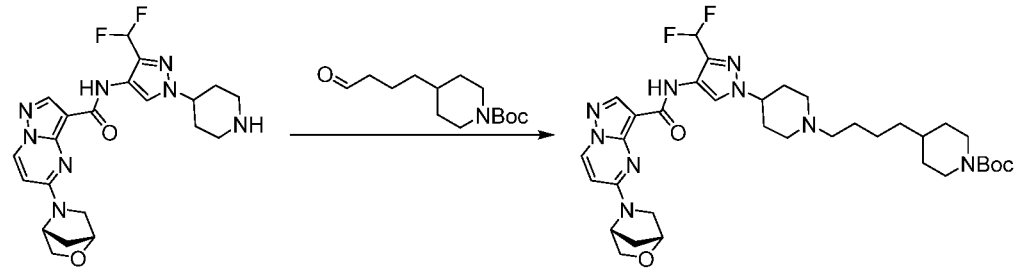
向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(2-(甲基(哌啶-4-基甲基)氨基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 0.13 mmol)和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (67 mg, 0.156 mmol)的DMSO (2 mL)溶液中加DIEA (52 mg, 0.4 mmol)。然后反应液在室温搅拌2 h。反应液倒入水中，过滤，滤饼经Prep-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5%~95%)纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)甲基)(甲基)氨基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+ = 863.3$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 3.6 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.25-6.95 (m, 1H), 6.92-6.43 (m, 1H), 5.40-5.06 (m, 1H), 4.77 (d, *J* = 17.3 Hz, 1H), 4.60-4.40 (m, 1H), 4.30-4.10 (m, 1H), 3.92-3.75 (m 3H), 3.68 – 3.56 (m, 3H), 3.55-3.45 (m, 1H), 3.10-2.90 (m, 3H), 2.84 – 2.68 (m, 3H), 2.48-2.40 (m, 4H), 2.24-1.55 (m, 16H),

实施例 21： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(4-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丁基)哌啶-1-羧酸叔丁酯的制备

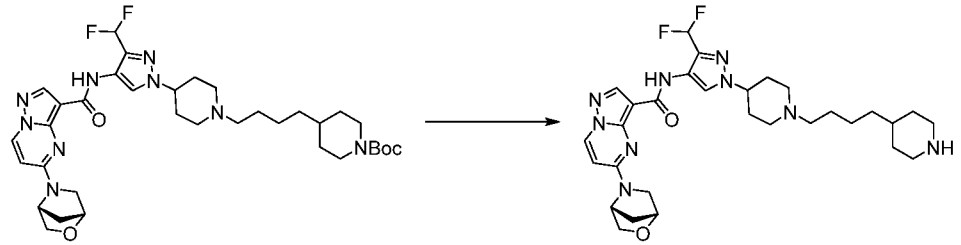


向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (110 mg, 0.24 mmol)的THF (5 mL)溶液中加4-(4-氧代丁基)哌啶-1-羧酸叔丁

酯 (100 mg, 0.36 mmol)和STAB (170 mg, 0.71 mmol)。反应液在25 ℃搅拌2 h。 反应加水 (30 mL)淬灭，用DCM (30 mL × 3)萃取，有机相用无水Na_2SO_4干燥，过滤，减压浓缩。所得粗产物经flash柱(MeOH:DCM=0~3:97)纯化得到4-(4-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丁基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 698.0.

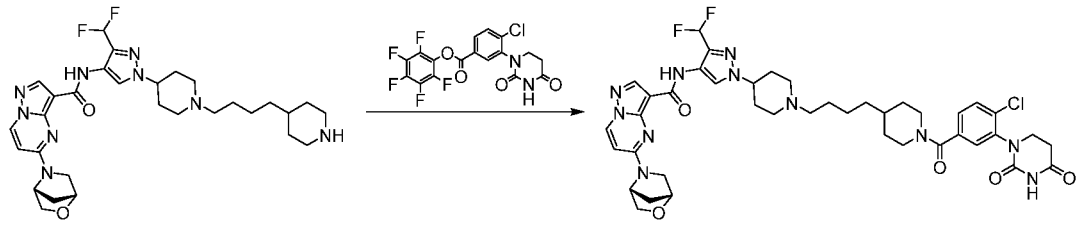
步骤 2： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(4-(哌啶-4-基)丁基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 4-(4-(4-(4-(5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)丁基)哌啶-1-羧酸叔丁酯 (0.2 g, 0.26 mmol)的DCM (5 mL)溶液中加TFA (1 mL)。反应液在25 ℃搅拌2 h。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(4-(哌啶-4-基)丁基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 598.1.

步骤 3： 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



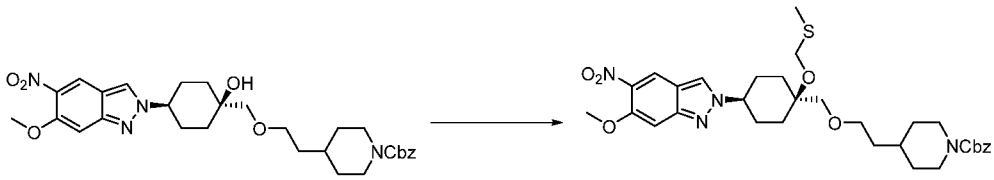
向 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-(4-(哌啶-4-基)丁基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (160 mg, 0.26 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (130 mg, 0.26 mmol)的 DMSO (4 mL)溶液中加 DIEA (0.14 mL, 0.78 mmol)。反应液在 25 ℃搅拌 2 h。反应加水 (10 mL)淬灭，用 DCM (20 mL × 3)萃取，用无水 Na_2SO_4 干燥，过滤，减压浓缩，所得粗品经 Prep-HPLC 纯化得到 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, *m/z*): $[M+H]^+$ = 848.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.50 (d, J = 5.3 Hz, 1H), 8.78 (d, J = 7.7 Hz, 1H), 8.40 (s, 1H), 8.25 (d, J = 5.0 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.20-7.00 (m, 1H), 6.98-6.45 (m, 1H), 5.40-5.05 (m, 1H), 4.77 (d, J = 17.3 Hz, 1H), 4.54-4.34 (m, 1H), 4.28-4.12 (m, 1H), 3.83 – 3.72 (m, 3H), 3.67 – 3.57 (m, 3H), 3.45 (d, J = 9.6 Hz, 1H), 3.02-2.85 (m, 3H), 2.80-2.70 (m, 2H), 2.36-2.26 (m, 2H), 2.08 – 1.88 (m, 8H), 1.76 – 1.47 (m, 4H), 1.47-1.22 (m, 6H), 1.18-1.02 (m, 2H).

实施例 22： *N*-(2-(((1*S*,4*S*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙氧基)甲基)-4-甲氧基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶酰胺

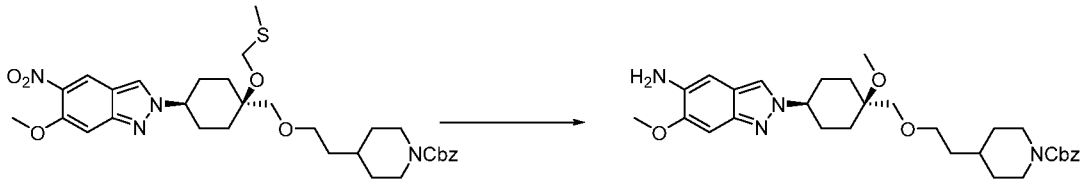
步骤 1：4-(2-(((1*S*,4*S*)-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)-1-((甲硫基)甲氧基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备



将化合物 4-(2-(((1*S*,4*S*)-1-羟基-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (700 mg, 1.24 mmol)和 Ac_2O (151 mg, 1.48 mmol)溶于无水 DMSO (20 mL)中，氮气保护下室温搅拌 16 h。反应液中加入水 (50 mL)，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (150 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩。粗品使用柱层析 (乙酸乙酯:石油醚=1:9)纯化，得到 4-(2-(((1*S*,4*S*)-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)-1-((甲硫基)甲氧基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=627.2.

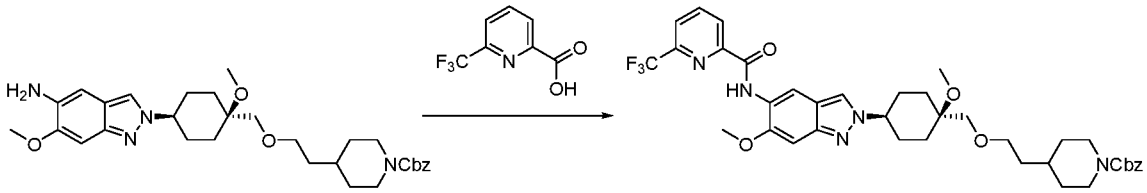
步骤 2：4-(2-(((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-甲氧基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备



将化合物 4-(2-(((1*S*,4*S*)-4-(6-甲氧基-5-硝基-2*H*-吲唑-2-基)-1-((甲硫基)甲氧基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (600 mg, 0.96 mmol)和预处理后的 Raney-Ni (200 mg) (预处理方法：先用水洗 3 次，再用丙酮洗 3 次，最后用乙醇洗 3 次)溶于无水乙醇 (50 mL)中，氢气气氛下，室温搅拌 3 h，过滤，滤液直接减压浓缩，粗品使用反相硅胶柱 (ACN:H_2O=1:1，流速 40 mL/min)纯化，得到 4-(2-(((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-甲氧基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=551.3.

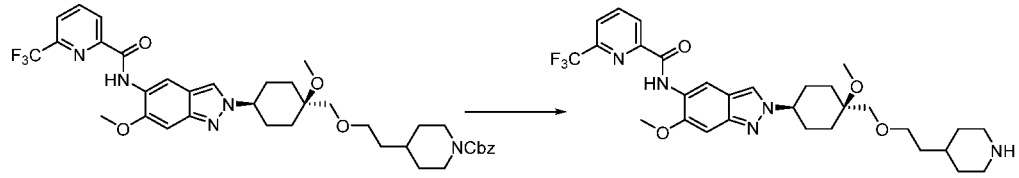
步骤 3：4-(2-(((1*S*,4*S*)-1-甲氧基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯的制备



将化合物 6-(三氟甲基)吡啶甲酸 (60 mg, 0.3 mmol), HATU (114 mg, 0.3 mmol) 和 DIEA (100 mg, 0.78 mmol) 溶于 DMF (10 mL)中，室温搅拌 20 min 后，加入 4-(2-(((1*S*,4*S*)-4-(5-氨基-6-甲氧基-2*H*-吲唑-2-基)-1-甲氧基环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (150 mg, 0.26 mmol)，室温反应 1 h。反应液中加入水 (100 mL)，用乙酸乙酯 (30 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩。粗品使用柱层析 (乙酸乙酯:石油醚=1:1)纯化，得到 4-(2-(((1*S*,4*S*)-1-甲氧基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=724.4.

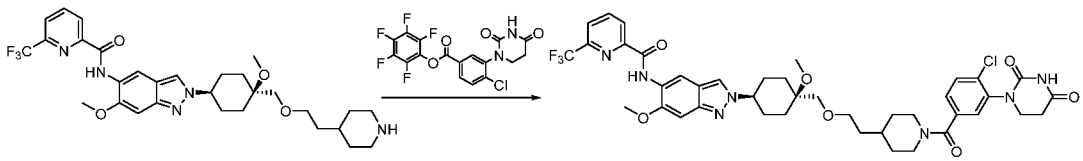
步骤 4：*N*-(6-甲氧基-2-((1*S*,4*S*)-4-甲氧基-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



4-(2-(((1*S*,4*S*)-1-甲氧基-4-(6-甲氧基-5-(6-(三氟甲基)吡啶甲酰胺)-2*H*-吲唑-2-基)环己基)甲氧基)乙基)哌啶-1-羧酸苄酯 (70 mg, 0.097mmol)溶解于三氟乙酸 (3 mL)中，升温至90 ℃搅拌1小时，反应液直接减压浓缩得到*N*-(6-甲氧基-2-((1*S*,4*S*)-4-甲氧基-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=590.4.

步骤 5：*N*-(2-((1*S*,4*S*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙氧基)甲基)-4-甲氧基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺的制备



N-(6-甲氧基-2-((1*S*,4*S*)-4-甲氧基-4-((2-(哌啶-4-基)乙氧基)甲基)环己基)-2*H*-吲唑-5-基)-6-(三氟甲

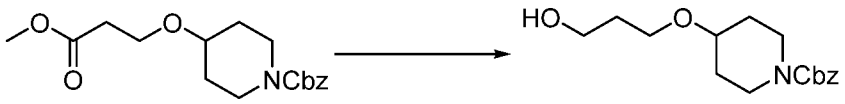
基)吡啶甲酰胺 (70 mg, 0.097 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入4-氯-3-(2,4-二氧代四氢嘧啶-1(2H)-基)苯甲酸五氟苯酯 (48 mg, 0.11 mmol)和 *N,N*-二异丙基乙胺 (37 mg, 0.29 mmol)。室温下搅拌2小时后，加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，饱和食盐水 (3 x 60 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩得到粗品，粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%~ 95%)纯化得到 *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙氧基)甲基)-4-甲氧基环己基)-6-甲氧基-2*H*-吲唑-5-基)-6-(三氟甲基)吡啶甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=840.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* = 4.5 Hz, 2H), 8.68 (s, 1H), 8.49 – 8.37 (m, 2H), 8.32 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.18 (s, 1H), 4.52-4.30 (m, 2H), 3.98 (s, 3H), 3.80 – 3.52 (m, 3H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.34 (s, 2H), 3.19 (s, 3H), 3.15-2.95 (m, 1H), 2.85 – 2.70 (m, 3H), 2.19-1.97 (m, 2H), -1.96-1.85 (m, 4H), 1.85-1.55 (m, 3H), 1.55-1.45 (m, 4H), 1.25-1.05 (m, 2H).

实施例 23：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)氧)丙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

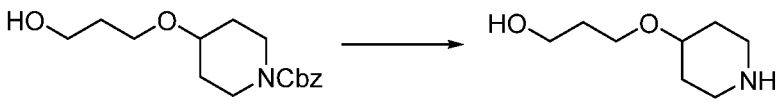
步骤 1： 4-(3-羟基丙氧基)哌啶-1-羧酸苄酯的制备



4-(3-甲氧基-3-氧丙基)哌啶-1-羧酸苄酯 (500 mg, 1.49 mmol)溶解于无水THF (10 mL)中，0 ℃下加入BH_3/THF溶液 (15 mL, 14.9 mmol)，室温搅拌16小时。向反应液加入甲醇淬灭，减压浓缩得到粗品。粗品使用柱层析 (乙酸乙酯:石油醚=9:1)纯化得到 4-(3-羟基丙氧基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=294.2.

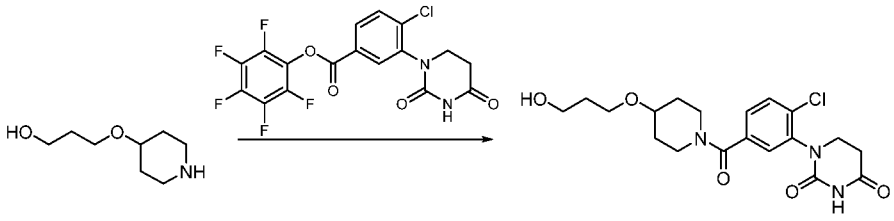
步骤 2： 3-(哌啶-4-基氧)丙烷-1-醇的制备



4-(3-羟基丙氧基)哌啶-1-羧酸苄酯 (200 mg, 0.68 mmol)溶解于乙酸乙酯 (10 mL)中，加入$Pd(OH)_2$/C (80 mg)，在氢气氛围下升温至70 ℃，搅拌过夜。反应液冷却至室温，过滤，滤液减压浓缩得到 3-(哌啶-4-基氧)丙烷-1-醇，粗品无需纯化直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=160.2.

步骤 3：1-(2-氯-5-(4-(3-羟基丙氧基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



3-(哌啶-4-基氧)丙烷-1-醇 (100 mg, 0.62 mmol)溶解于DMSO (10 mL)中，加入4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (300 mg, 0.69 mmol)和DIEA (240 mg, 1.86 mmol)，室温下搅拌2小时。向反应液加入水 (100 mL)，用二氯甲烷 (30 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩得到粗品。粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 1-(2-氯-5-(4-(3-羟基丙氧基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

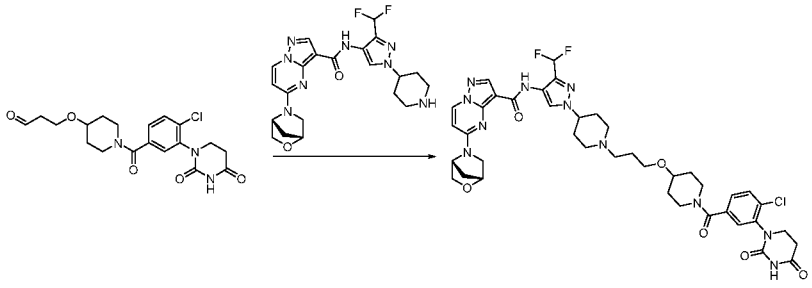
LC-MS: (ESI, m/z): $[M+H]^+$=410.1.

步骤 4：3-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)氧)丙醛的制备

1-(2-氯-5-(4-(3-羟基丙氧基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (60 mg, 0.147 mmol)溶解于DCM (5 mL)中，加入PCC (63 mg, 0.294 mmol)，室温下搅拌16小时。反应液减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 3-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)氧)丙醛。

LC-MS: (ESI, m/z): $[M+H]^+$=408.1.

步骤 5：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)氧)丙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



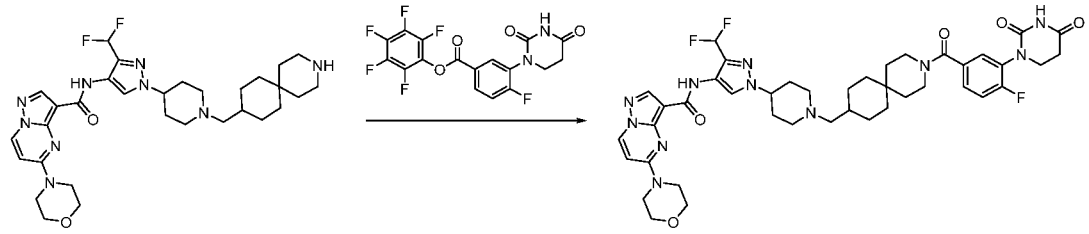
3-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)氧)丙醛 (55 mg, 0.135 mmol)溶于THF (5 mL)中，加 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (粗产品:70 mg, 0.135 mmol)和 STAB (86 mg, 0.405 mmol)，室温下搅拌 2 小时。向反应液加入水 (100 mL)，用乙酸乙酯 (30 mL x 3)萃取，有机相用饱和氯化钠水溶

液 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩得到粗品。粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%~95%)纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(3-((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)氧)丙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=850.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 3.2 Hz, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 7.67 – 7.55 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.30-6.92 (m, 1H), 6.88-6.45 (m, 1H), 5.28-5.08 (m, 1H), 4.77 (d, *J* = 17.7 Hz, 1H), 4.30-4.10 (m, 1H), 4.02 – 3.68 (m, 4H), 3.62-3.47 (m, 7H), 3.30-3.10 (m, 2H), 3.00-2.85 (m, 2H), 2.78 – 2.69 (m, 2H), 2.45-2.31 (m, 2H), 2.10-1.55 (m, 12H), 1.52-1.37 (m, 2H).

实施例 24：*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

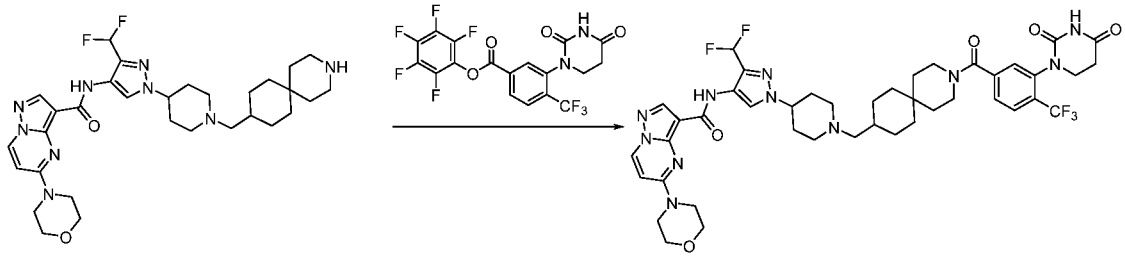


N-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.14 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酸五氟苯酯 (58 mg, 0.14 mmol)和 *N*,*N*-二异丙基乙胺 (54 mg, 0.42 mmol)。室温下搅拌2小时后，加水 (50 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%～95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=846.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 2H), 7.23-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.84 – 3.69 (m, 10H), 3.65-3.49 (m, 2H), 3.31 – 3.24 (m, 2H), 2.89 (d, *J* = 10.3 Hz, 2H), 2.73 (t, *J* = 6.6 Hz, 2H), 2.20-2.04 (m, 2H), 2.04-1.80 (m, 6H), 1.70-1.43 (m, 7H), 1.43-1.20 (m, 2H), 1.20-0.96 (m, 4H).

实施例 25： *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

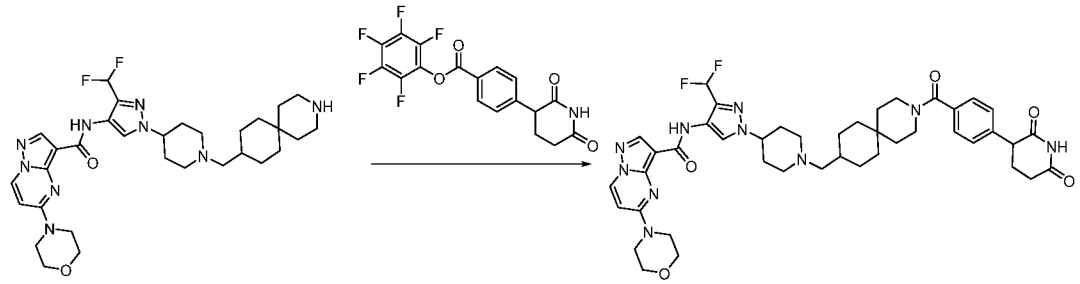


N-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.14 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-(三氟甲基)苯甲酸五氟苯酯 (65 mg, 0.14 mmol)和 *N*,*N*-二异丙基乙胺 (54 mg, 0.42 mmol)。室温下搅拌 2 小时后，加水 (50 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%～95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=896.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.23-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.28-4.12 (m, 1H), 3.94-3.80 (m, 1H), 3.80-3.70 (m, 8H), 3.65-3.55 (m, 2H), 3.51 – 3.41 (m, 1H), 3.30-3.20 (m, 2H), 2.94-2.80 (m, 2H), 2.75-2.60 (m, 2H), 2.24-2.06 (m, 2H), 2.06-1.90 (m, 6H), 1.80-1.60 (m, 2H), 1.60-1.30 (m, 6H), 1.30-1.20 (m, 1H), 1.17-0.92 (m, 4H).

实施例 26： *N*-(3-(二氟甲基)-1-(1-((3-(4-(2,6-氧代哌啶-3-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺



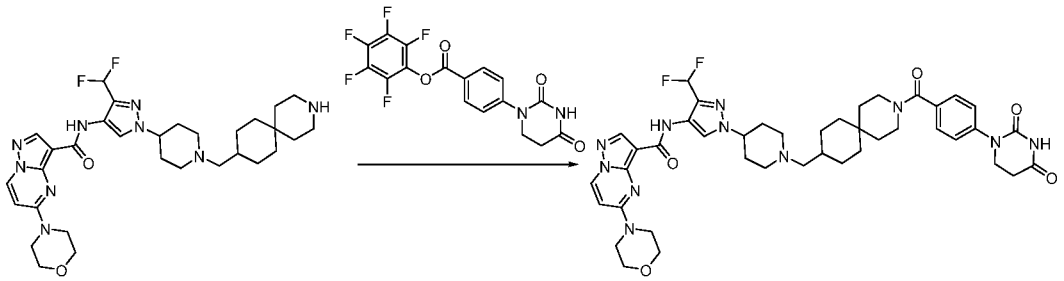
N-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.14 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 4-(2,6-二氧代哌啶-3-基)苯甲酸五氟苯酯 (56 mg, 0.14 mmol)和 *N*,*N*-二异丙基乙胺 (54 mg, 0.42 mmol)。室温下搅拌 2 小时后，加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，饱和食盐水 (60 mL x 3)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩得到粗品，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%～95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-((3-(4-(2,6-氧代哌啶-3-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-

吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=827.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 9.40 (s, 1H), 8.83 (d, J = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.40-7.25 (m, 4H), 7.23-6.95 (m, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.35-4.06 (m, 1H), 3.97-3.88 (m, 1H), 3.84 – 3.73 (m, 8H), 3.64-3.50 (m, 2H), 3.31-3.22 (m, 2H), 2.92-2.80 (m, 2H), 2.75-2.62 (m, 1H), 2.56-2.51 (m, 1H), 2.30-1.90 (m, 10H), 1.76-1.25 (m, 9H), 1.20-0.93 (m, 4H).

实施例 27： *N*-(3-(二氟甲基)-1-(1-((3-(4-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

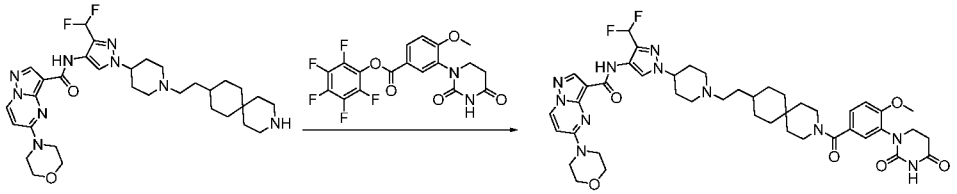


N-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.14 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 4-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (56 mg, 0.14 mmol)和 *N*,*N*-二异丙基乙胺 (54 mg, 0.42 mmol)。室温下搅拌 2 小时后，加水 (50 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5% ~ 95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-((3-(4-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=828.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.40 (s, 1H), 8.83 (d, J = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.39 (s, 4H), 7.23-6.97 (m, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.26 – 4.15 (m, 1H), 3.92-3.70 (m, 10H), 3.68-3.50 (m, 2H), 3.31 – 3.22 (m, 2H), 2.89 (d, J = 10.1 Hz, 2H), 2.72 (t, J = 6.6 Hz, 2H), 2.24-2.09 (m, 2H), 2.07 – 1.84 (m, 6H), 1.75-1.29 (m, 9H), 1.18-0.92 (m, 4H).

实施例 28： *N*-(3-(二氟甲基)-1-(1-(2-(3-(3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺



将 *N*-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡

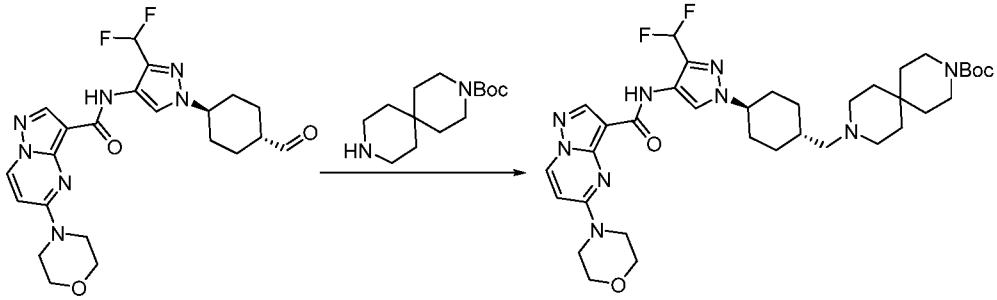
唑并[1,5-a]嘧啶-3-甲酰胺 (103 mg, 0.165 mmol) 和 3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (85 mg, 0.198 mmol) 加入到 DMSO (3 mL) 中，然后加入 DIEA (63.8 mg, 0.495 mmol)， 室温搅拌 16 h, 然后加入水 (20 mL)，用乙酸乙酯 (25 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，粗品经 Prep-HPLC 制备纯化 (乙腈/0.5%甲酸水溶液, 5%~95%)得到产物 *N*-(3-(二氟甲基)-1-(1-(2-(3-(3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的甲酸盐。

LC-MS: (ESI, m/z): $[M+H]^+ = 872.5$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.40 (s, 1H), 8.83 (d, J = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 8.27 (s, 0.62H, HCOOH), 7.42 – 7.28 (m, 2H), 7.26 – 6.94 (m, 2H), 6.91 (d, J = 7.9 Hz, 1H), 4.30-4.10 (m, 1H), 3.84 (s, 3H), 3.79-3.61(m, 8H), 3.62 – 3.54 (m, 6H), 2.97-2.91 (m, 2H), 2.71-2.65 (m, 2H), 2.37-2.17 (m, 2H), 2.05 – 1.85 (m, 6H), 1.75-1.62 (m, 2H), 1.55 – 1.17 (m, 9H), 1.17-0.93 (m, 4H).

实施例 29： *N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

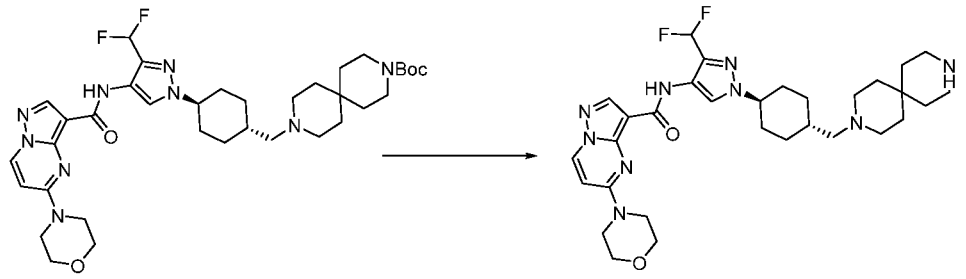
步骤1： 9-(((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (50 mg, 0.10 mmol) 和 3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (24 mg, 0.10 mmol) 溶于 THF (3 mL) 中，在搅拌下向反应液中加入三乙酰氧基硼氢化钠 (67 mg, 0.32 mmol)，反应液室温搅拌 2 h。向反应液中加入水 (50 mL)，乙酸乙酯萃取 (30 mL x 3)，合并有机相，无水硫酸钠干燥，减压浓缩，粗品经正向柱层析纯化得到 9-(((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+ = 712.3$.

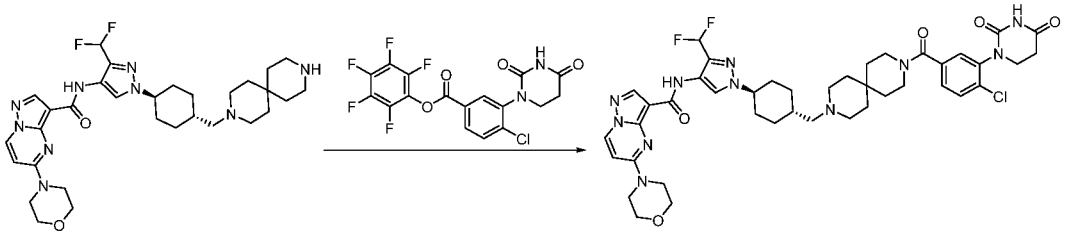
步骤2：*N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 9-(((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (95 mg, 0.13 mmol) 溶于 DCM (3 mL)，加入 TFA (1 mL)，反应液室温搅拌 1 h。反应液直接减压浓缩得到 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (粗品)，直接用于下步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=612.3.

步骤3： *N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



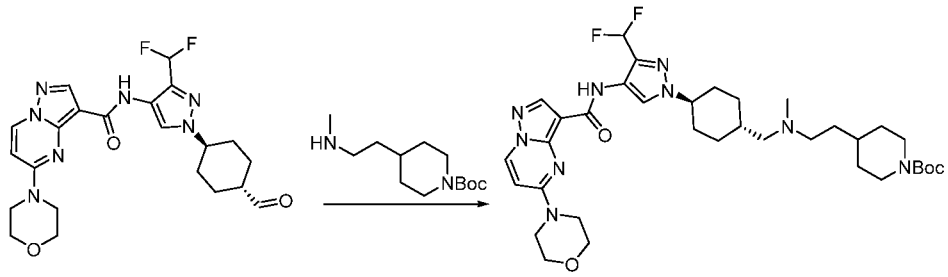
将 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (130 mg, 0.13 mmol) 和4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (57 mg, 0.13 mmol) 溶于DMSO (5 mL)中，在搅拌下向反应液中加入DIEA (84 mg, 0.65 mmol)后，使反应液在室温下搅拌反应1 h。反应结束后将反应液倒入水 (50 mL)中，用EA萃取 (30 mL x 3)，合并有机相并用饱和食盐水 (80 mL)洗涤，经无水硫酸钠干燥，过滤，滤液减压浓缩后经prep-HPLC分离纯化得到 *N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$ = 862.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.39 (s, 1H), 8.82 (d, J = 6.3 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.25-6.95 (m, 1H), 6.90 (d, J = 7.6 Hz, 1H), 4.27-4.07 (m, 1H), 3.90-3.50 (m, 12H), 3.40-3.30 (m, 2H), 2.79-2.70 (m, 2H), 2.43-2.23 (m, 4H), 2.20-1.95 (m, 4H), 1.93-1.83 (m, 2H), 1.82-1.30 (m, 11H), 1.09-0.94 (m, 2H).

实施例 30： *N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

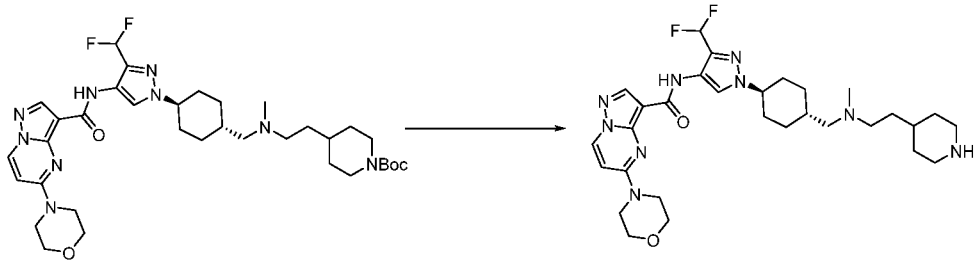
步骤 1： 4-(2-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (110 mg, 0.23 mmol)用 THF (10 mL)溶解，加入 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (56 mg, 0.23 mmol)和 STAB (146 mg, 0.69 mmol)，室温反应 2 h，加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品用柱层析 (MeOH:DCM=1:11)纯化得到 4-(2-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=700.4.

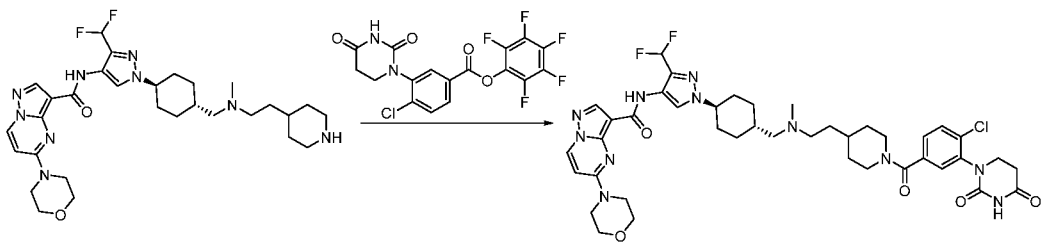
步骤 2：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(2-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (95 mg，0.14 mmol)溶于 DCM (3 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应额有直接减压浓缩得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=600.3.

步骤 3：*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的准备



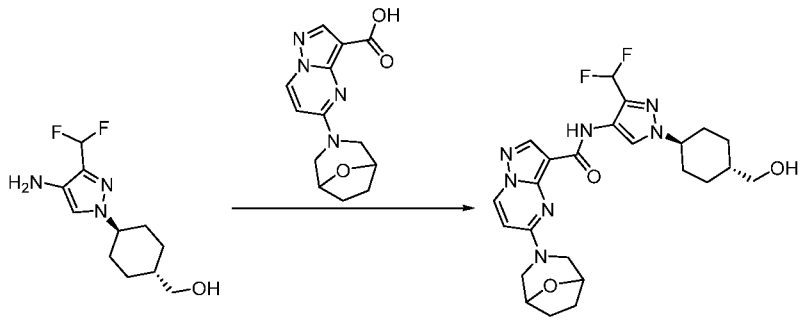
将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (95 mg, 0.14 mmol)溶于 DMSO (5 mL)，加入 DIEA (77 mg, 0.60 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (61 mg, 0.14 mmol)，室温反应 2 h。加水 (50 mL)并搅拌 5 分钟，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备得到 *N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰基)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=850.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.39 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.24-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.49 – 4.38 (m, 1H), 4.23-4.13 (m, 1H), 3.83 – 3.76 (m, 4H), 3.75 – 3.70 (m, 4H), 3.66 – 3.52 (m, 2H), 3.10 – 2.95 (m, 1H), 2.84-2.67 (m, 3H), 2.29 (t, *J* = 7.0 Hz, 2H), 2.14 – 2.01 (m, 7H), 1.93-1.84 (m, 2H), 1.82 – 1.46 (m, 7H), 1.41 – 1.32 (m, 2H), 1.17 – 0.95 (m, 4H).

实施例 31： 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1：5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

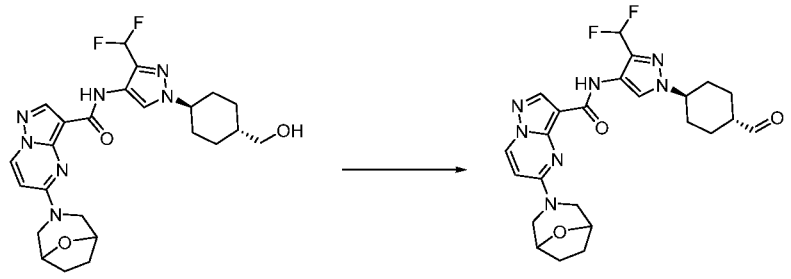


将((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (410 mg, 1.67 mmol)溶于 DMF (10 mL)，加入 5-(8-氧-3-氮杂螺双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-羧酸 (459 mg, 1.67 mmol)，HATU (825 mg, 2.17 mmol)和 DIEA (646 mg, 5.01 mmol)，室温反应 2 h。加水 (50 mL)并搅拌 5 分钟，

用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析纯化得到 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=502.3.

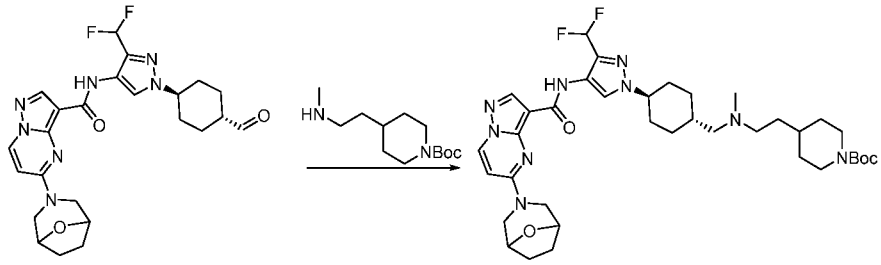
步骤 2：5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲醛环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (290 mg，0.58 mmol)，溶于 ACN (10 mL)，加入 IBX (324 mg, 1.16 mmol)，85 °C 反应 1.5 h，减压浓缩除去 ACN，加水 (30 mL)，用乙酸乙酯 (30 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析纯化得到 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲醛环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=500.3.

步骤 3： 4-(2-((((1*R*,4*R*)-4-(4-(5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备

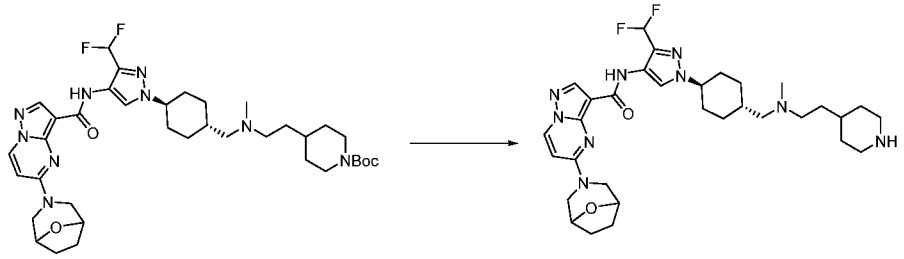


将 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲醛环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.20 mmol)用 THF (10 mL)溶解，加入 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (48 mg, 0.20 mmol)和 STAB (127 mg, 0.6 mmol)，室温反应 2 h，加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:11)纯化得到 4-(2-((((1*R*,4*R*)-4-(4-(5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔

丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=726.4.

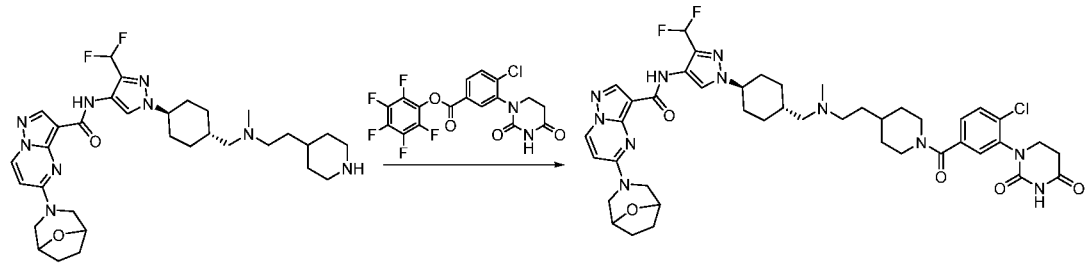
步骤 4：5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(2-((((1*R*,4*R*)-4-(4-(5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (110 mg, 0.15 mmol)溶于 DCM (3 mL)中，加入 TFA (1 mL)，室温反应 1 h，减压浓缩，得到 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=626.3.

步骤 5：5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



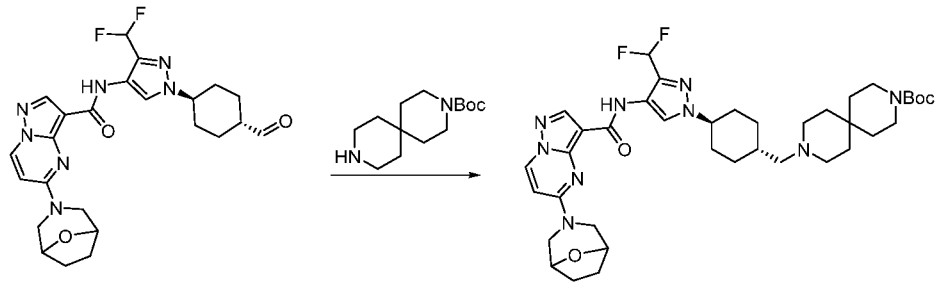
将 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (110 mg, 0.15 mmol)溶于 DMSO (5 mL)，加入 DIEA (97 mg, 0.75 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (65 mg, 0.15 mmol)，室温反应 2 h。加水 (50 mL)并搅拌 5 分钟，用乙酸乙酯 (50 mL x 3)提取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备得到 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=876.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.41 (s, 1H), 8.82 (d, J = 7.9 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 1.9 Hz, 1H), 7.38 (dd, J = 8.2, 2.0 Hz, 1H), 7.30-6.95 (m, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.48 – 4.42 (m, 2H), 4.26 – 4.09 (m, 2H), 3.79 – 3.50 (m, 4H), 3.27 – 3.17 (m, 2H), 3.10 -2.90 (m, 1H), 2.85-2.70 (m, 3H), 2.29 (t, J = 6.8 Hz, 2H), 2.15 – 2.07 (m, 5H), 2.07-2.01 (m, 2H), 1.95 -1.83 (m, 4H), 1.82 – 1.47 (m, 9H), 1.41 – 1.31 (m, 2H), 1.17 – 0.96 (m, 4H).

实施例 32： 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

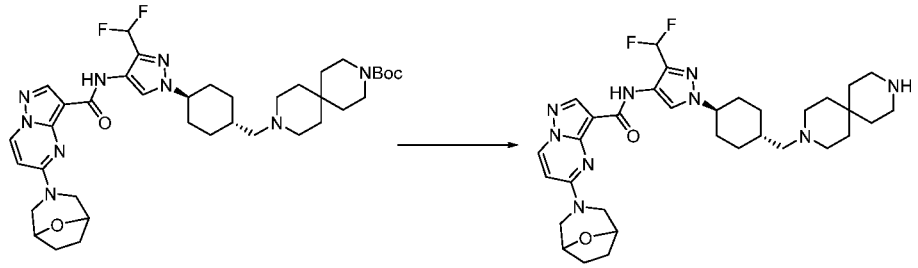
步骤 1： 9-(((1*R*,4*R*)-4-(4-(5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲醛环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.20 mmol)用 THF (10 mL)溶解，加入 3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (48 mg, 0.20 mmol)和 STAB (127 mg, 0.6 mmol)，室温反应 2 h，加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=1:11)纯化得到 9-(((1*R*,4*R*)-4-(4-(5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=738.5.

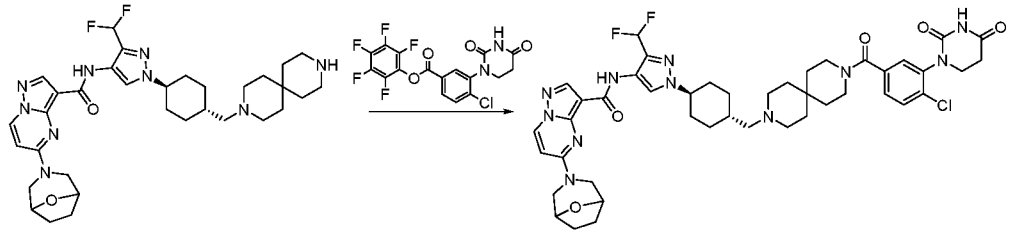
步骤 2：*N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 9-(((1*R*,4*R*)-4-(4-(5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-3-(二氟甲

基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (105 mg, 0.14 mmol)溶于 DCM (3 mL)中，加入 TFA (1 mL)，室温反应 1 h。减压浓缩，得到 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，直接用于下一步。

步骤 3：5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

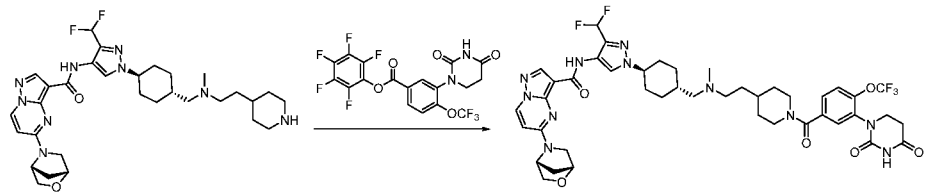


将 *N*-(1-((1*R*,4*R*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (110 mg, 0.14 mmol)溶于 DMSO (5 mL)，加入 DIEA (90 mg, 0.70 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (61 mg, 0.14 mmol)，室温反应 2 h。加水 (50 mL)并搅拌 5 分钟，用乙酸乙酯(50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备得到 5-(8-氧-3-氮杂双环[3.2.1]辛烷-3-基)-*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=888.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.41 (s, 1H), 8.81 (d, *J* = 7.9 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.24-6.97 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.47-4.41 (m, 2H), 4.31-3.93 (m, 3H), 3.81 – 3.72 (m, 1H), 3.67 – 3.51 (m, 3H), 3.25-3.15 (m, 2H), 2.77-2.72 (m, 2H), 2.35-2.25 (m, 4H), 2.15-2.07 (m, 2H), 2.16-2.98 (m, 2H), 1.96-1.29 (m, 19H), 1.10-0.92 (m, 2H).

实施例 33： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

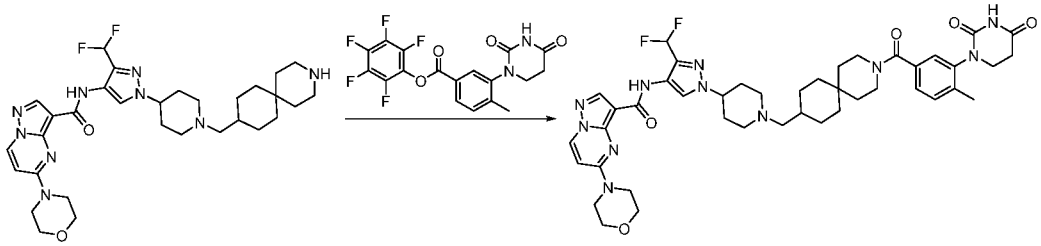


5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (90 mg, 0.12 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酸五氟苯酯 (68 mg, 0.14 mmol)和 *N*,*N*-二异丙基乙胺 (46 mg, 0.36 mmol)。室温下搅拌2小时后，加水 (50 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%～95%)纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=912.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.50 (d, *J* = 6.1 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.2 Hz, 1H), 8.25 (t, *J* = 4.6 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.28 – 6.95 (m, 1H), 6.88-6.44 (m, 1H), 5.28-5.08 (m, 1H), 4.77 (d, *J* = 18.1 Hz, 1H), 4.52-4.40 (m, 1H), 4.24-4.15 (m, 1H), 3.86 – 3.42 (m, 7H), 3.10-2.95 (m, 1H), 2.80-2.60 (m, 3H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.14-1.48 (m, 17H), 1.43-1.30 (m, 2H), 1.20 – 0.93 (m, 4H).

实施例 34： *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺



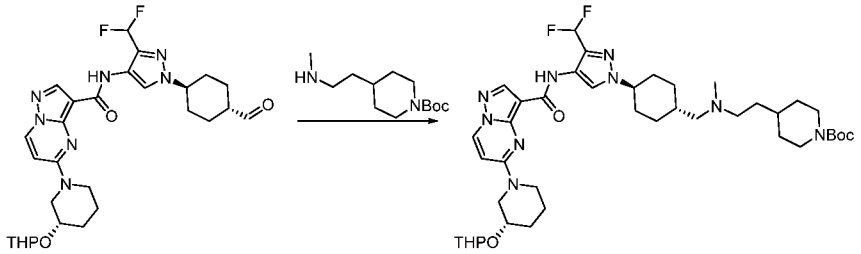
N-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.12 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸五氟苯酯（58 mg, 0.14 mmol）和 *N*,*N*-二异丙基乙胺（46 mg, 0.36 mmol）。室温下搅拌 2 小时后，加水（50 mL），过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%～95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=842.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.37 – 7.29 (m, 2H), 7.28-6.96 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.25-4.15 (m, 1H), 3.83-3.63 (m, 9H), 3.61-3.47 (m, 3H), 3.32 – 3.24 (m, 2H), 2.95-2.65 (m, 4H), 2.25-1.85 (m, 11H), 1.70 (d, J = 9.3 Hz, 2H), 1.58-1.15 (m, 7H), 1.12-0.91 (m, 4H).

实施例 35： *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

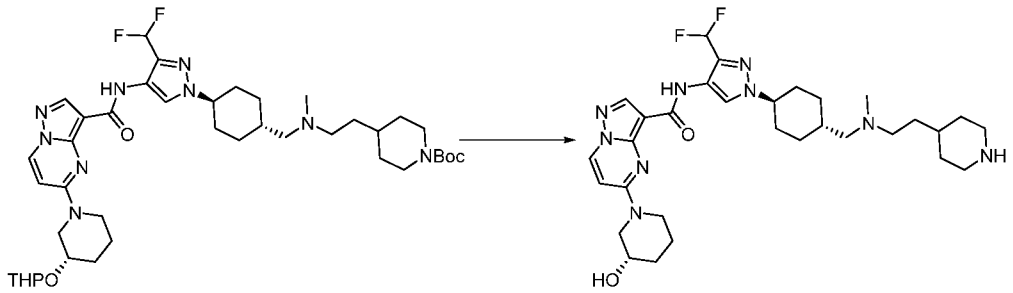
步骤1： 4-(2-((((1*S*,4*R*)-4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



N-(3-(二氟甲基)-1-((1*R*,4*S*)-4-甲酰环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (120 mg, 0.21 mmol)和 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (51 mg, 0.21 mmol)用四氢呋喃 (10 mL)溶解，搅拌下加入三乙酰氧基硼氢化钠 (222 mg, 1.05 mmol)。室温搅拌过夜，加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，饱和食盐水 (60 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 4-(2-((((1*S*,4*R*)-4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=798.5.

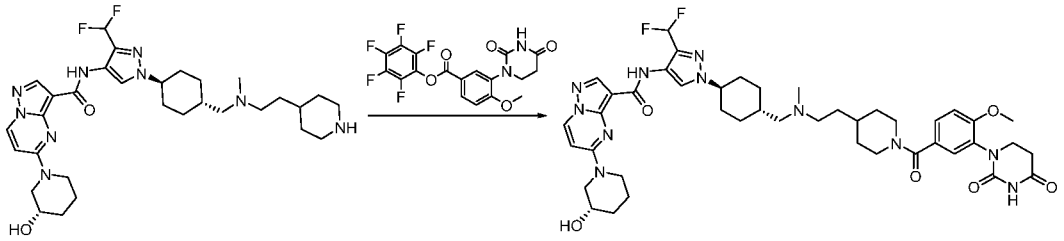
步骤 2： *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



4-(2-((((1*S*,4*R*)-4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (80 mg, 0.10 mmol)用二氯甲烷 (3 mL)溶解，三氟乙酸 (1 mL)加入并室温搅拌 2小时，反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=614.3.

步骤3：*N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



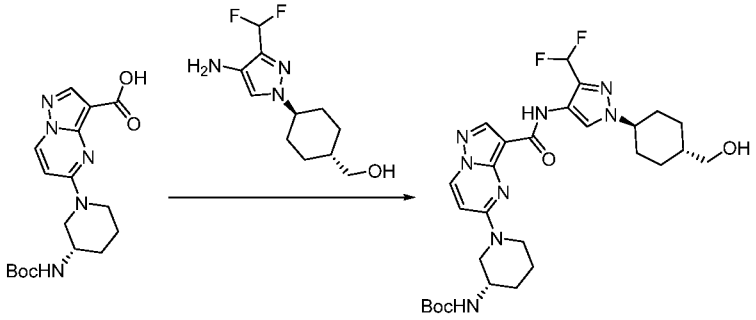
N-(3-(二氟甲基)-1-((1*R*,4*S*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 0.10 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (47 mg, 0.11 mmol)和 *N*,*N*-二异丙基乙胺 (38 mg, 0.30 mmol)。室温下搅拌过夜，加水 (50 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5% ~ 95%)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=860.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.37 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 8.24 (d, *J* = 5.1 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.24 – 6.94 (m, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.89 (d, *J* = 4.1 Hz, 1H), 4.50-4.15 (m, 2H), 4.03-3.80 (m, 5H), 3.72-3.53 (m, 4H), 3.51-3.40 (m, 1H), 3.10-2.65 (m, 4H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.15 -1.95 (m, 7H), 1.92-1.25 (m, 15H), 1.17 – 0.95 (m, 4H).

实施例 36： 5-((*S*)-3-氨基哌啶-1-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)氨基甲酰)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯的制备

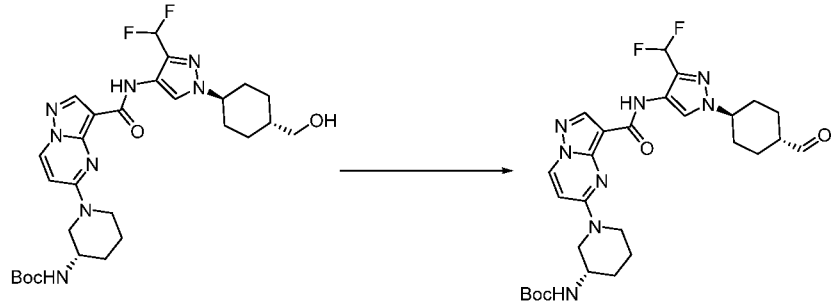


将 (*S*)-5-(3-((叔丁氧羰基)氨基)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酸 (150 mg, 0.42 mmol)溶于 DMF

(10 mL)，加入((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (112 mg, 0.46 mmol)，DIEA (163 mg, 1.26 mmol)和 py-BOP (284 mg, 0.55 mmol)，室温反应 2 h。加水 (50 mL)并搅拌 5 分钟，用乙酸乙酯 (50 mL x 3)提取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA:PE=0~1)纯化得到 ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)氨基甲酰)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=589.3.

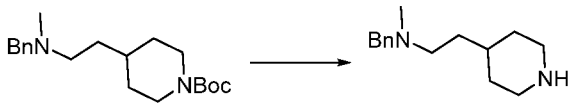
步骤 2：((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)氨基甲酰)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯的制备



将 ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)氨基甲酰)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯 (190 mg, 0.32 mmol)，溶于 ACN (10 mL)，加入 IBX (181 mg, 0.65 mmol)，85 °C 反应 1.5 h。向反应液中加水 (30 mL)，用乙酸乙酯 (30 mL x 3)萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA:PE=0~1)纯化得到 ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)氨基甲酰)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=586.6.

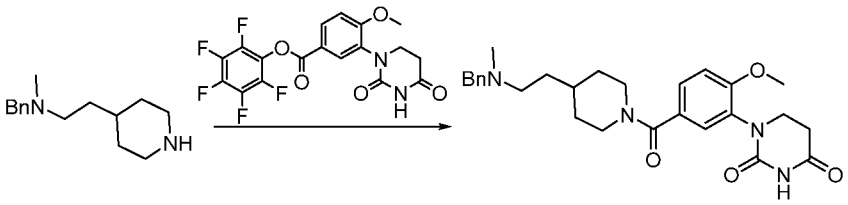
步骤 3：*N*-苄基-*N*-甲基-2-(哌啶-4-基)乙烷-1-胺的制备



将 4-(2-(苄基(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (345 mg, 1.04 mmol)溶于 DCM (5 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应液直接减压浓缩得到 *N*-苄基-*N*-甲基-2-(哌啶-4-基)乙烷-1-胺，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=233.2.

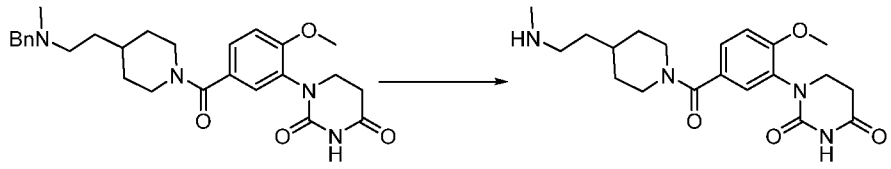
步骤 5：1-(5-(4-(2-(苄基(甲基)氨基)乙基)哌啶-1-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将 *N*-苄基-*N*-甲基-2-(哌啶-4-基)乙烷-1-胺 (250 mg, 1.04 mmol)溶于 DMSO (10 mL)，加入 DIEA (671 mg, 5.2 mmol)和 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (451 mg, 1.04 mmol)，室温反应 2 h。反应液中加水 (100 mL)并搅拌 5 分钟，用乙酸乙酯 (100 mL x 3)萃取，饱和食盐水 (150 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1:9)纯化得到 1-(5-(4-(2-(苄基(甲基)氨基)乙基)哌啶-1-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=479.2.

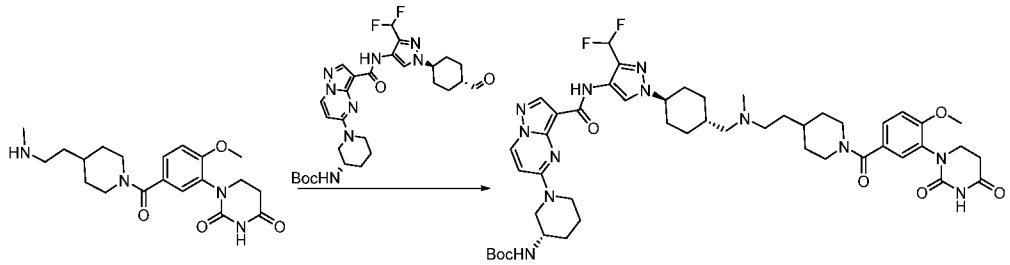
步骤 6：1-(2-甲氧基-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将 1-(5-(4-(2-(苄基(甲基)氨基)乙基)哌啶-1-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (240 mg，0.5 mmol)溶于 MeOH (10 mL)中，加入 Pd/C (72 mg, 30%)，室温反应 2 h。过滤后减压浓缩，得到1-(2-甲氧基-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮，直接用于下一步。

LC-MS: (ESI, m/z): $[M+Na]^+$=411.1.

步骤 7： ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯的制备

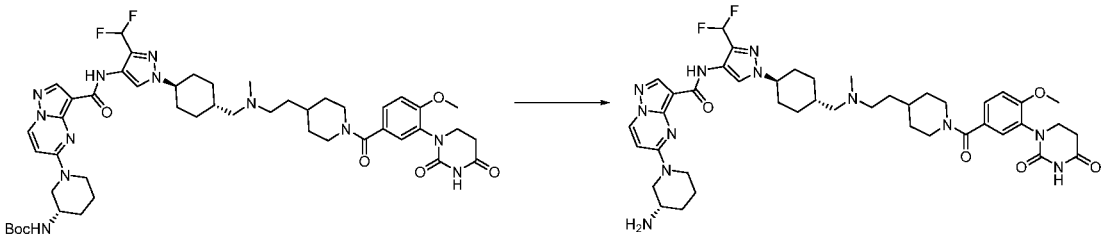


将 1-(2-甲氧基-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (95 mg, 0.24 mmol)用 THF (10 mL)溶解，加入((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)氨基甲酰)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯 (120 mg, 0.20 mmol)和 STAB (127 mg, 0.60 mmol)，室温反应 2 h。反应液中加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1；9)纯化得到

((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=959.4.

步骤 8：5-((*S*)-3-氨基哌啶-1-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



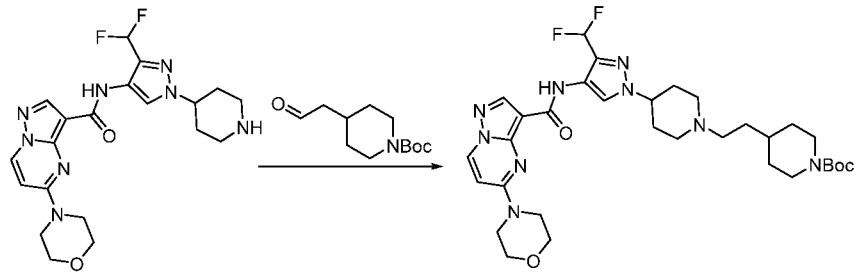
将 ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)羰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯 (100 mg, 0.10 mmol)溶于 DCM (5 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应液直接减压浓缩，粗品使用反相制备纯化得到 5-((*S*)-3-氨基哌啶-1-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=859.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.36 (s, 1H), 8.74 (d, J = 8.0 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.36 (dd, J = 8.4, 2.1 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.27 – 6.97 (m, 2H), 6.88 (d, J = 8.1 Hz, 1H), 4.52-4.15 (m, 4H), 3.84 (s, 3H), 3.59 (t, J = 6.6 Hz, 2H), 3.24 – 2.93 (m, 3H), 2.80-2.60 (m, 4H), 2.40-2.25 (m, 2H), 2.16 – 1.99 (m, 8H), 1.95-1.80 (m, 3H), 1.80 – 1.29 (m, 13H), 1.17 – 0.96 (m, 4H).

实施例 37： *N*-(3-(二氟甲基)-1-(1-(2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)哌啶-4-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

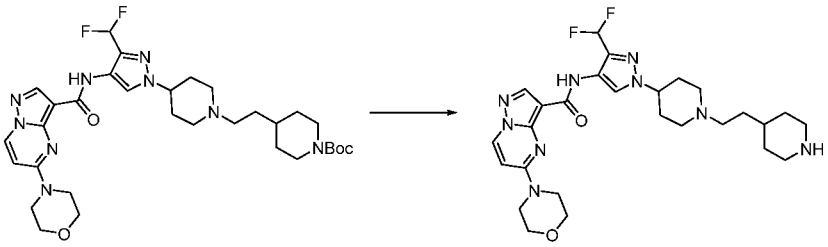
步骤1： 4-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)哌啶-1-羧酸叔丁酯的制备



将 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (125 mg, 0.280 mmol) 加入到 4-(2-氧代乙基)哌啶-1-羧酸叔丁酯 (95.466 mg, 0.421 mmol) 的 THF (3 mL) 溶液中，加入 STAB (178.5 mg, 0.842 mmol)， 室温搅拌 2 h。反应液用水 (20 mL)稀释，乙酸乙酯 (25 mL x 4) 萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE =3:7)得到 4-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 658.5.

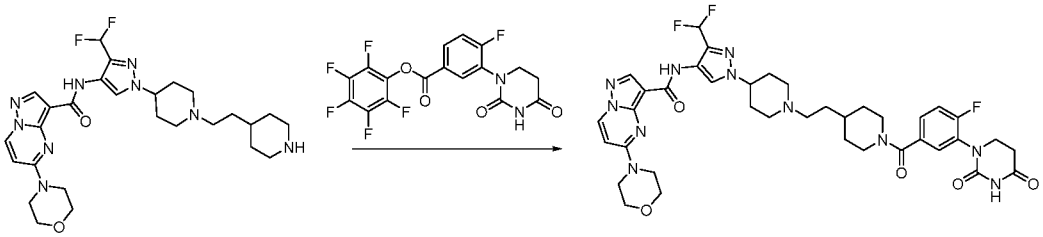
步骤2：*N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡零吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将4-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)哌啶-1-羧酸叔丁酯 (160 mg, 0.347 mmol) 加入到 TFA (1 mL) 和 DCM (3 mL) 中,室温搅拌2 h。反应液直接减压浓缩得到粗产品 *N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡零吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=558.4.

步骤3：*N*-(3-(二氟甲基)-1-(1-(2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)哌啶-4-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



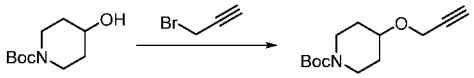
将 *N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡零吡唑并[1,5-a]嘧啶-3-甲酰胺(121 mg, 0.217 mmol) 加入到 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酸五氟苯酯 (90.8 mg, 0.217 mmol) 的 DMSO (5 mL)溶液中，加入DIEA (84.1 mg, 0.652 mmol)，室温搅拌16 h。反应液用水 (40 mL)稀释，乙酸乙酯 (40 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，粗品使用反相制备 (乙腈– 0.05% NH_4HCO_3水溶液, 5%~ 95%) 得到产物 *N*-(3-(二氟甲基)-1-(1-(2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)哌啶-4-基)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+ = 792.3$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.40 (s, 1H), 8.82 (s, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.59-7.27 (m, 3H), 7.24-6.83 (m, 2H), 4.51-4.15 (m, 2H), 3.83-3.55 (m, 11H), 3.12-2.85 (m, 3H), 2.81-2.64 (m, 3H), 2.38-2.30 (m, 2H), 2.08-1.55 (m, 9H), 1.46-1.31 (m, 2H), 1.20-0.99 (m, 2H).

实施例 38： *N*-(1-((1*R*,4*R*)-4-((4-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)丙-2-炔-1-基)氧)哌啶-1-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

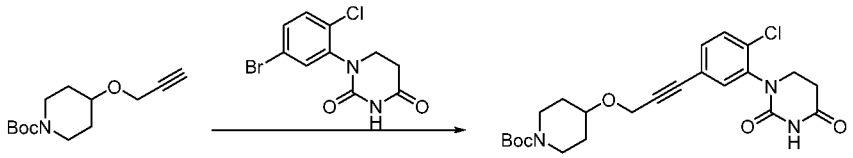
步骤 1： 4-(丙基-2-炔-1-基氧)哌啶-1-羧酸叔丁酯的制备



在 0 ℃ 下, 将 NaH (2.98 g, 124.2 mmol) 缓慢加入到 4-羟基哌啶-1-羧酸叔丁酯 (5 g, 24.84 mmol) 的无水THF (60 mL) 中并搅拌 30 min， 然后加入3-溴丙基-1-炔 (5.91 g, 49.68 mmol), 反应液缓慢升至室温并搅拌5 h, 然后过滤, 加入水 (100 mL)，用乙酸乙酯 (60 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE = 1:9)得到 4-(丙基-2-炔-1-基氧)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M-56]^+ = 184.1$.

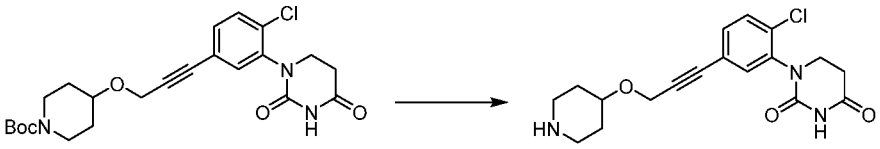
步骤2： 4-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)丙-2-炔-1-基)氧)哌啶-1-羧酸叔丁酯的制备



将4-(丙基-2-炔-1-基氧)哌啶-1-羧酸叔丁酯 (232 mg, 0.971 mmol)加入到 1-(5-溴-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (350 mg, 1.164 mmol)的无水DMF (10 mL)中，加入 CuI (47.5 mg, 0.146 mmol)，$CsCO_3$ (948 mg, 2.913 mmol)和$Pd(PPh_3)_2Cl_2$ (102.1 mg, 0.146 mmol)，反应液在N_2保护下 80 ℃搅拌4 h。反应液中加入水 (40 mL)，用乙酸乙酯 (40 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE = 2:3)得到 4-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)丙-2-炔-1-基)氧)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+ = 462.2$.

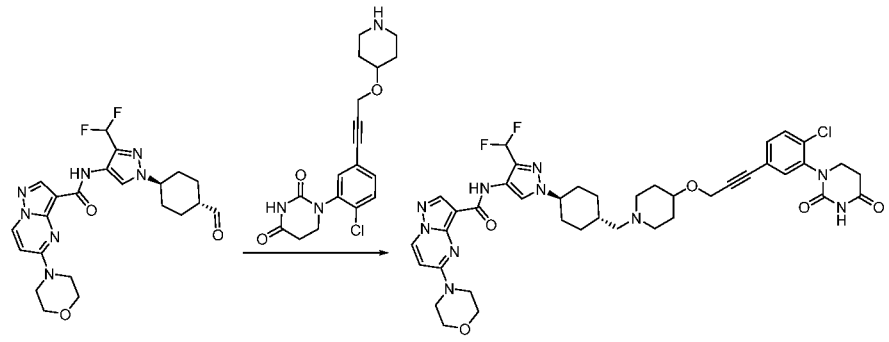
步骤3：1-(2-氯-5-(3-(哌啶-4-基氧)丙-1-炔-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将 4-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)丙-2-炔-1-基)氧)哌啶-1-羧酸叔丁酯 (160 mg, 0.347 mmol)加入到TFA (1 mL) 和DCM (3 mL)中，室温搅拌2 h。反应液直接减压浓缩得到粗产品 1-(2-氯-5-(3-(哌啶-4-基氧)丙-1-炔-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$ = 362.1.

步骤4：*N*-(1-((1*R*,4*R*)-4-((4-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)丙-2-炔-1-基)氧)哌啶-1-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



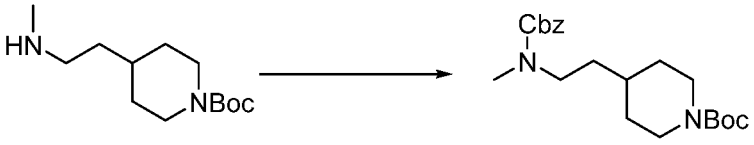
将 1-(2-氯-5-(3-(哌啶-4-基氧)丙-1-炔-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (137.4 mg, 0.381 mmol)和 DIEA (73.6 mg, 0.570 mmol)加入到 THF (5 mL)中并室温搅拌 10 min，然后加入 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (90 mg, 0.190 mmol) 并搅拌 10 min，然后加入 STAB (120.9 mg, 0.914 mmol)，反应液室温搅拌 2 h。反应液中加水 (20 mL)加入，乙酸乙酯 (25 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，粗品使用反相制备 (乙腈– 0.05% FA 水溶液, 5%～95%) 得到 *N*-(1-((1*R*,4*R*)-4-((4-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)丙-2-炔-1-基)氧)哌啶-1-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$ =819.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 7.67-7.54 (m, 2H), 7.48-7.41 (m, 1H), 7.27-6.94 (m, 1H), 6.92-6.86 (m, 1H), 4.43 (s, 2H), 4.23-4.13 (m, 1H), 3.86 – 3.65 (m, 10H), 3.64 – 3.54 (m, 2H), 2.77 – 2.65 (m, 4H), 2.10 – 1.66 (m, 11H), 1.63-1.40 (m, 3H), 1.13 – 0.93 (m, 2H).

实施例 39：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

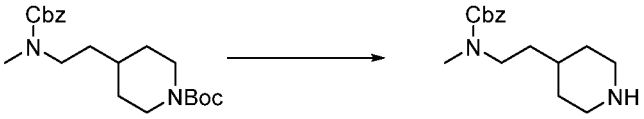
步骤 1：4-(2-(((苄氧基)羰基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



将 4-(2-(甲胺基)乙基)哌啶-1-羧酸叔丁酯 (200 mg, 0.82 mmol)溶于二氯甲烷 (4 mL)中，加入三乙胺 (249, 2.46 mmol)和 CbzCl (139 mg, 0.82 mmol)，反应液室温搅拌 1 个小时。反应液加水 (50 mL)稀释，二氯甲烷 (80 mL x 3)萃取，用无水硫酸钠干燥，减压浓缩，粗品经柱层析 (PE:EA=3:7)纯化得到化合物 4-(2-(((苄氧基)羰基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H-100]^+$=277.2.

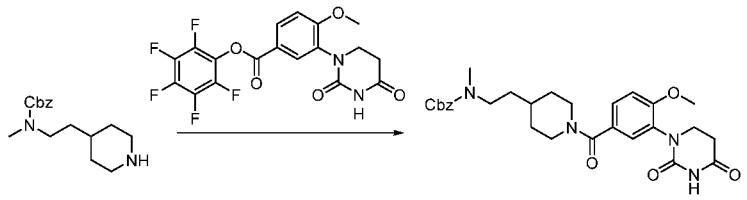
步骤 2： 苄基甲基(2-(哌啶-4-基)乙基)氨基甲酸酯的制备



将化合物 4-(2-(((苄氧基)羰基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (200 mg, 0.53 mmol)溶于氯化氢/1-4,二氧六环 (4 mL)溶液中，反应液室温下搅拌 1 小时。反应液直接减压浓缩得到苄基甲基(2-(哌啶-4-基)乙基)氨基甲酸酯。

LC-MS: (ESI, m/z): $[M+H]^+$=277.2.

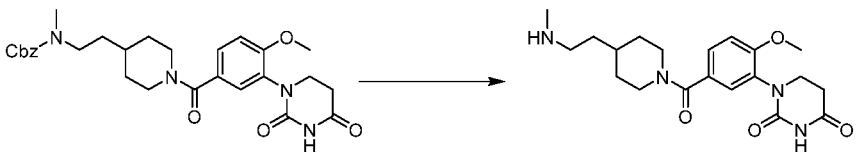
步骤 3：苄基(2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基甲酸酯的制备



将化合物苄基甲基(2-(哌啶-4-基)乙基)氨基甲酸酯 (200 mg, 0.72 mmol)和 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (309 mg, 0.72 mmol)加入到 DMSO (4 mL)溶液 中，然后加入 DIEA (278 mg, 2.1 mmol)，反应液室温搅拌 3 小时。反应液用水 (50 mL)稀释，乙酸乙酯 (70 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，粗品使用柱层析(PE:EA=1:3)纯化得到化合物苄基(2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基甲酸酯。

LC-MS: (ESI, m/z): $[M+H]^+$=523.2.

步骤 4：1-(2-甲氧基-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备

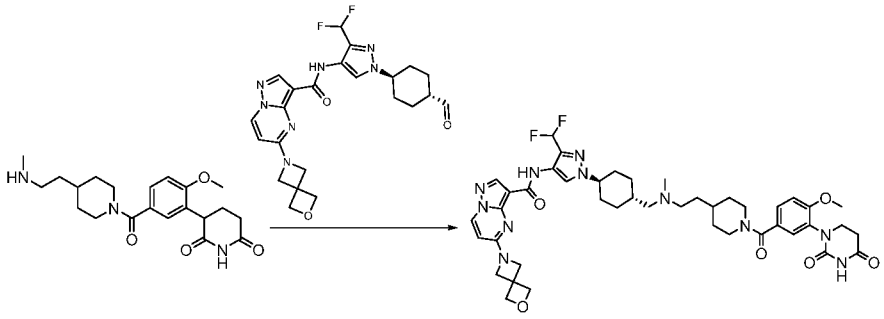


将化合物苄基(2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨

基甲酸酯 (120 mg 0.23 mmol)溶于甲醇 (3 mL)溶液 中，加入钯碳 (10%，24 mg)，反应液室温搅拌 1 小时。反应液经硅藻过抽滤，滤液减压浓缩得到化合物 1-(2-甲氧基-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=389.2.

步骤 5：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



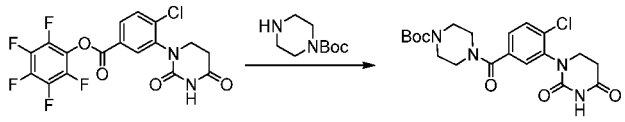
将化合物 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 0.165 mmol)和 1-(2-甲氧基-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (64 mg, 0.165 mmol)溶于 DCE (3 mL)中，STAB (70 mg, 0.330 mmol)加入，反应液室温搅拌 2 小时。反应液用水 (20 mL)稀释，乙酸乙酯 (25 mL x 4)萃取，用饱和食盐水洗，无水硫酸钠干燥，减压浓缩，粗品使用反相制备得到化合物 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=858.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.69 (s, 1H), 8.76 (d, *J* = 7.6 Hz, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.35 (s, 1H), 7.42-7.00 (m, 3H), 6.38 (d, *J* = 7.6 Hz, 1H), 4.78-4.70 (m, 4H), 4.48-4.35 (m, 4H), 4.25-4.10 (m, 1H), 3.84 (s, 3H), 3.59 (t, *J* = 5.0 Hz, 2H), 3.30-3.10 (m, 3H), 2.75-2.63 (m, 2H), 2.36-2.25 (m, 2H), 2.20-1.99 (m, 7H), 1.93-1.83 (m, 2H), 1.77-1.50 (m, 7H), 1.44-1.30 (m, 2H), 1.20-0.96 (m, 4H).

实施例 40： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-基)正丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

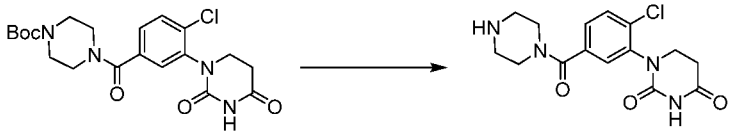
步骤 1： 4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-羧酸叔丁酯的制备



将 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (450 mg, 1.037 mmol)和哌嗪-1-羧酸叔丁酯 (386.28 mg, 2.074 mmol)加入到 DMSO (5 mL)中，后加入DIEA (401.31 mg, 3.111 mmol), 室温搅拌 2 h。反应液中加入水 (20 mL)，用乙酸乙酯 (25 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正向柱层析 (MeOH:DCM = 1:19)纯化得到 4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+Na]^+$=459.1

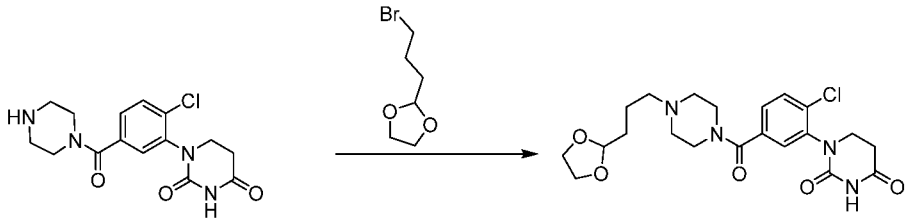
步骤 2：1-(2-氯-5-(哌嗪-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-羧酸叔丁酯 (402 mg, 0.922 mmol) 加入到 TFA (0.5 Ml)和 DCM (2.5 mL) 中，室温搅拌 2 h。反应液直接减压浓缩得到粗品 1-(2-氯-5-(哌嗪-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$= 337.0.

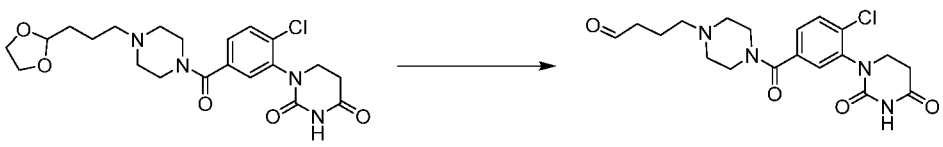
步骤 3：1-(5-(4-(3-(1,3-二氧杂环戊烷-2-基)丙基)哌嗪-1-羰基)-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将 1-(2-氯-5-(哌嗪-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (295 mg, 0.878 mmol)和2-(3-溴丙基)-1,3-二氧杂环戊烷 (256.9 mg, 1.316 mmol) 加入到 DMF (5 mL)中，然后加入$CsCO_3$ (858.2 mg, 2.634 mmol)，反应液 100 ℃ 搅拌 16 h。反应液中加入水 (40 mL)，用乙酸乙酯 (30 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正向柱层析 (MeOH:DCM = 1:11）纯化得到 1-(5-(4-(3-(1,3-二氧杂环戊烷-2-基)丙基)哌嗪-1-羰基)-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$= 451.1.

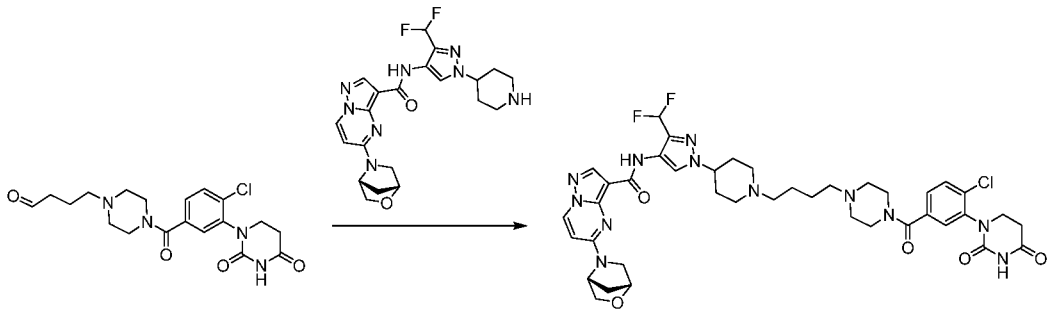
步骤 4：4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-基)正丁醛的制备



将 1-(5-(4-(3-(1,3-二氧杂环戊烷-2-基)丙基)哌嗪-1-羰基)-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (100 mg, 0.22 mmol)溶于 DCM (0.5 mL)中，加入 TFA (0.5 mL)，室温反应 48 h。反应液中加入 DCE (10 mL)，DIEA (1 mL)，室温下减压浓缩得到 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-基)正丁醛，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=407.1。

步骤 5： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-基)正丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



向 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-基)正丁醛 (粗品)的 DCE 溶液中加入 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (40 mg, 0.087 mmol)，室温搅拌 0.5 h，加入 STAB (55 mg, 0.26 mmol)，室温反应 2 h，加水 (30 mL)稀释，用乙酸乙酯 (30 mL x 3)提取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌嗪-1-基)正丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

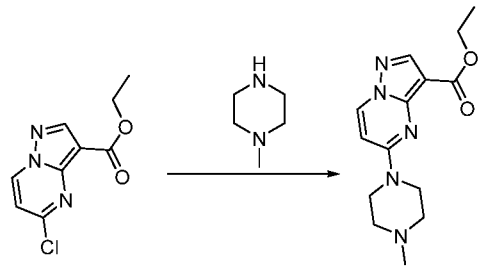
LC-MS: (ESI, m/z): $[M+H]^+$=849.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 3.9 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.40 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.26-6.95 (m, 1H), 6.87-6.44 (m, 1H), 5.28-5.07 (m, 1H), 4.77 (d, *J* = 16.2 Hz, 1H), 4.25 – 4.12 (m, 1H), 3.84-3.70 (m, 3H), 3.67 – 3.55 (m, 4H), 3.45 (d, *J* = 10.2 Hz, 1H), 2.93 (d, *J* = 10.9 Hz, 2H), 2.82-2.70 (m, 2H), 2.45 – 2.25 (m, 9H), 2.12 – 1.78 (m, 9H), 1.51 – 1.38 (m, 4H).

实施例 41： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)

哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

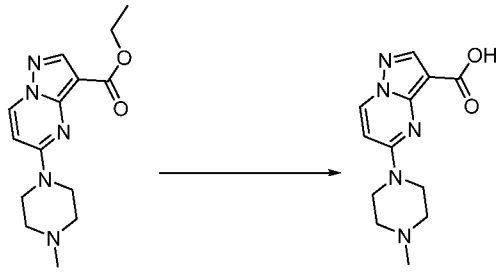
步骤 1：5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯的制备



将5-氯吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (1 g, 4.4 mmol)，1-甲基哌嗪 (445 mg, 4.4 mmol)和*N*,*N*-二异丙基乙胺 (1.7 g, 13.3 mmol)溶于乙腈 (10 mL)并升温至60 ℃搅拌过夜。反应液直接减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯。

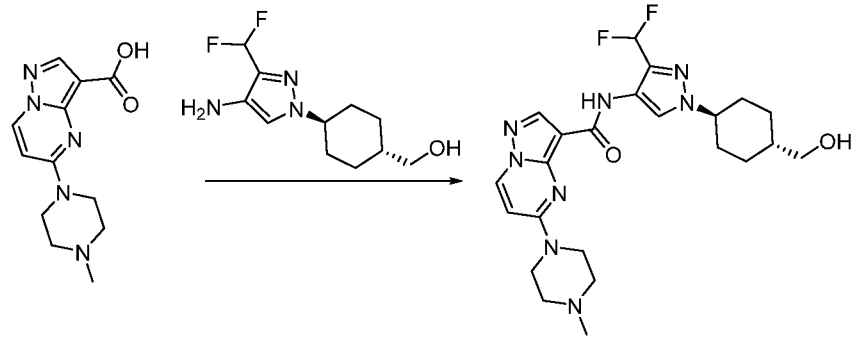
LC-MS: (ESI, m/z): $[M+H]^+$=290.3.

步骤2：5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸的制备



将 5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸乙酯 (900 mg, 3.1 mmol)溶于混合溶液(甲醇/水=5:1, 10 mL)中，加入氢氧化锂 (520 mg, 12.4 mmol)并升温至 60 ℃搅拌 2 小时，反应液用盐酸 (2 mol/L)调节 pH 值=3, 过滤，滤饼真空干燥得到 5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸。

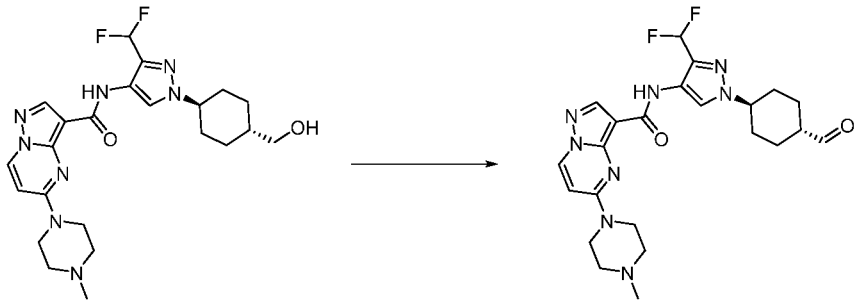
步骤 3：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酸 (265 mg, 1.02 mmol)溶于 DMF (10 mL)，加入((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)甲醇 (250 mg, 1.02 mmol)，DIEA (395 mg, 3.06 mmol)和 pyBOP (690 mg, 1.33 mmol)，50 ℃反应过夜。反应液中加水 (50 mL)并搅拌 5 分钟，用乙酸乙酯 (50 mL x 3)萃取，饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1:9)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=489.2.

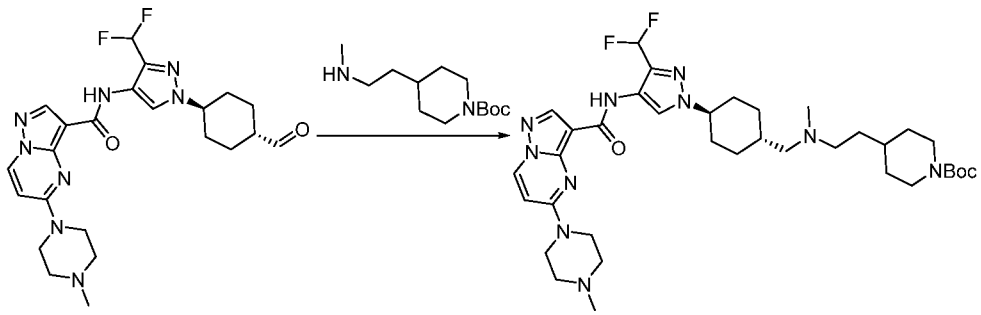
步骤 4： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(羟甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (350 mg, 0.72 mmol)，溶于 ACN (10 mL)，加入 IBX (402 mg, 1.43 mmol)，85 ℃反应 1.5 h。反应液减压浓缩除去 ACN，然后加水 (30 mL)，用乙酸乙酯 (30 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1:9)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=487.3.

步骤 5： 4-(2-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备

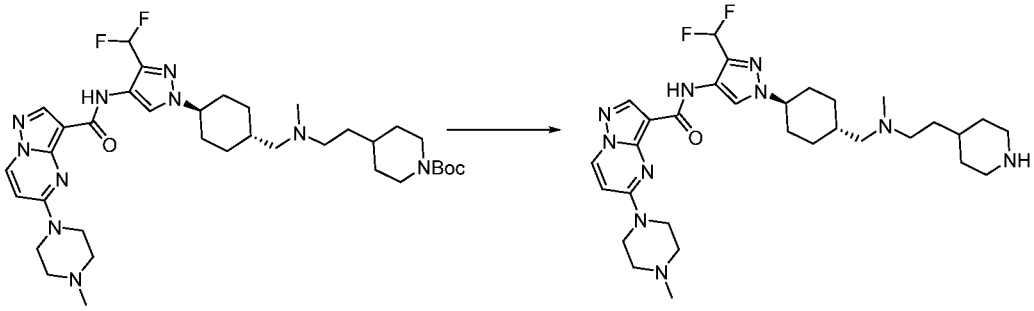


将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-甲酰基环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (180 mg, 0.37 mmol)和 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (107 mg, 0.44 mmol)用

四氢呋喃 (10 mL)溶解，加入 STAB (235 mg, 1.11 mmol)，室温反应 2 h。反应液中加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1:9)纯化得到 4-(2-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=713.4.

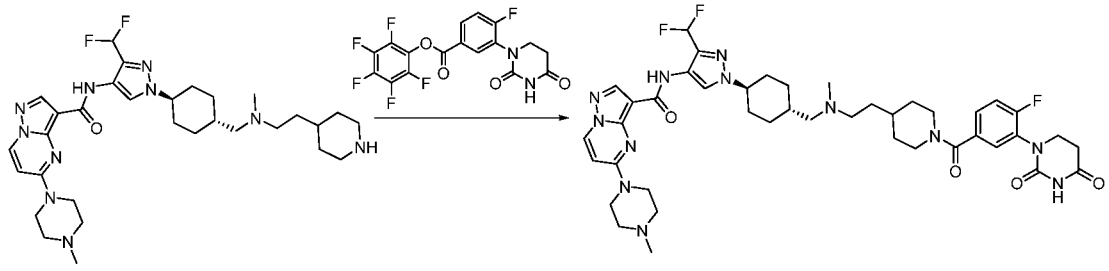
步骤 6： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(2-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (220 mg, 0.31 mmol)溶于 DCM (5 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。所得产物直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=613.3.

步骤 7： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



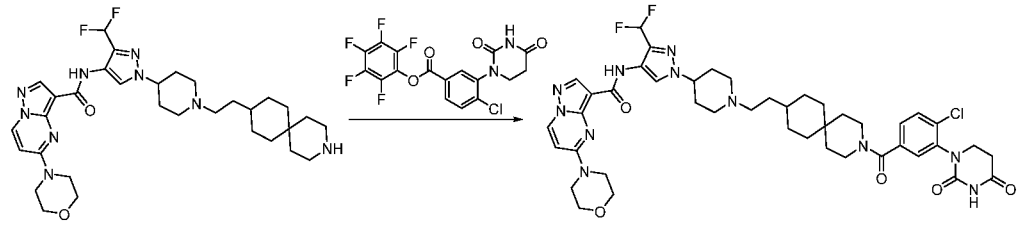
将 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (220 mg, 0.31 mmol)溶于 DMSO (10 mL)，加入 DIEA (200 mg, 1.55 mmol)和 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酸五氟苯酯 (130 mg, 0.31 mmol)，室温反

应 2 h。反应液中加水 (100 mL)并搅拌 5 分钟，用乙酸乙酯 (100 mL x 3)萃取，有机相用饱和食盐水 (150 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-氟苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-(4-甲基哌嗪-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=847.8.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.41 (s, 1H), 8.79 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.27 (s, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.26-6.97 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.50 – 4.37 (m, 1H), 4.22 – 4.10 (m, 1H), 3.85-3.75 (m, 6H), 3.70 – 3.50 (m, 2H), 3.10 – 2.95 (m, 1H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.45 – 2.38 (m, 4H), 2.32-2.25 (m, 2H), 2.24 (s, 3H), 2.11 – 1.97 (m, 7H), 1.93-1.85 (m, 2H), 1.81-1.45 (m, 6H), 1.41 – 1.31 (m, 2H), 1.18 – 0.95 (m, 4H).

实施例 42： *N*-(1-(1-(2-(3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺



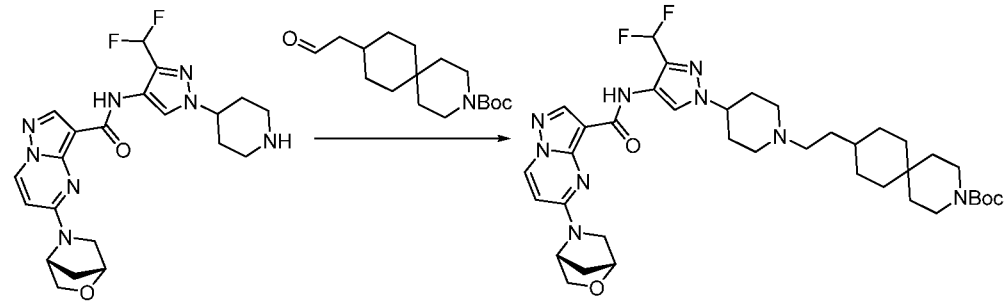
N-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (23 mg, 0.03 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (14 mg, 0.03 mmol)和 *N*,*N*-二异丙基乙胺 (38 mg, 0.30 mmol)，室温下搅拌 2 小时。反应液中加水 (20 mL)，过滤，滤饼经 p-TLC (甲醇:二氯甲烷=1:9)纯化得到 *N*-(1-(1-(2-(3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=876.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.26-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.31-4.11 (m, 1H), 3.86-3.66 (m, 9H), 3.61-3.50 (m, 3H), 3.29 – 3.24 (m, 1H), 2.99-2.90 (m, 2H), 2.80 – 2.71 (m, 2H), 2.43-2.30 (m, 2H), 2.15-1.84 (m, 6H), 1.73-1.60 (m, 2H), 1.55-1.23 (m, 10H), 1.16-1.01 (m, 4H).

实施例 43： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-(3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

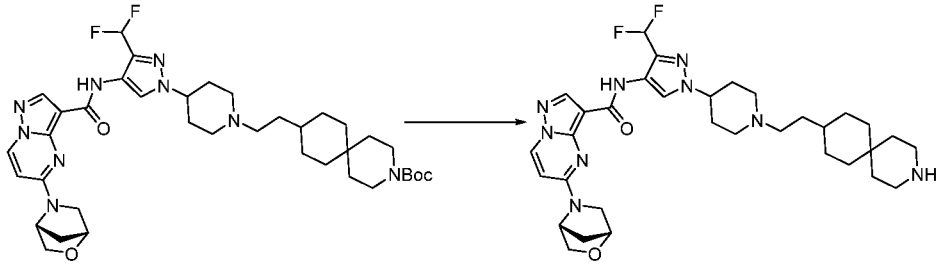
步骤 1：9-(2-(4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (50 mg, 0.11 mmol)和 9-(2-氧代乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (40 mg, 0.13 mmol)用四氢呋喃 (10 mL)溶解，加入三乙酰氧基硼氢化钠 (70 mg, 0.33 mmol)，室温搅拌 2 小时。反应液中加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，有机相饱和食盐水 (60 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品经 p-TLC (甲醇:二氯甲烷=1:9)纯化得到 9-(2-(4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=738.4.

步骤 2： *N*-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

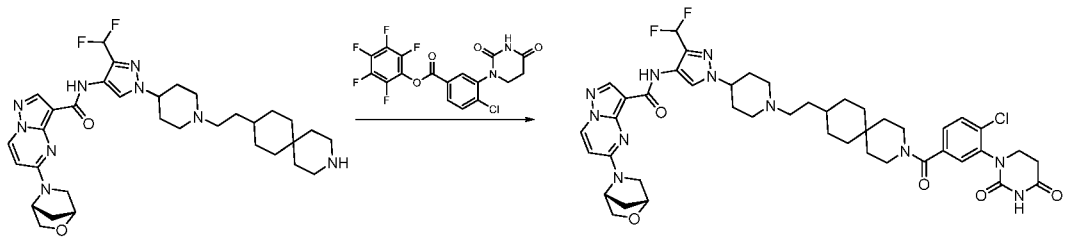


9-(2-(4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)乙基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (40 mg, 0.05 mmol)用二氯甲烷 (3 mL)溶解，三氟乙酸 (1 mL)加入并室温搅拌 2小时。反应液直接减压浓缩得到 *N*-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。所得产品无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=638.3.

步骤 3： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-(3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]

嘧啶-3-甲酰胺的制备



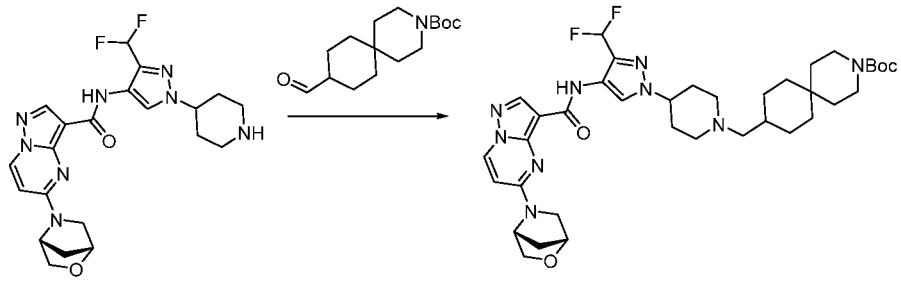
N-(1-(1-(2-(3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (40 mg, 0.05 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (24 mg, 0.05 mmol)和 *N*,*N*-二异丙基乙胺 (64 mg, 0.50 mmol)，室温下搅拌过夜。反应液中加水 (30 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5% ~ 95%)纯化得到5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(2-(3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)乙基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=888.3.

^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 3.9 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26-6.97 (m, 1H), 6.88-6.47 (m, 1H), 5.28-5,07 (m, 1H), 4.77 (d, *J* = 17.8 Hz, 1H), 4.30-4.10 (m, 1H), 3.85 – 3.72 (m, 3H), 3.67 – 3.41 (m, 5H), 3.30 – 3.24 (m, 2H), 2.97-2.88 (m, 2H), 2.80-2.70 (m, 2H), 2.35-2.27 (m, 2H), 2.03-1.80 (m, 8H), 1.72-1.65 (m, 2H), 1.55-1.26 (m, 9H), 1.24-0.97 (m, 4H).

实施例 44： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1：9-((4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备

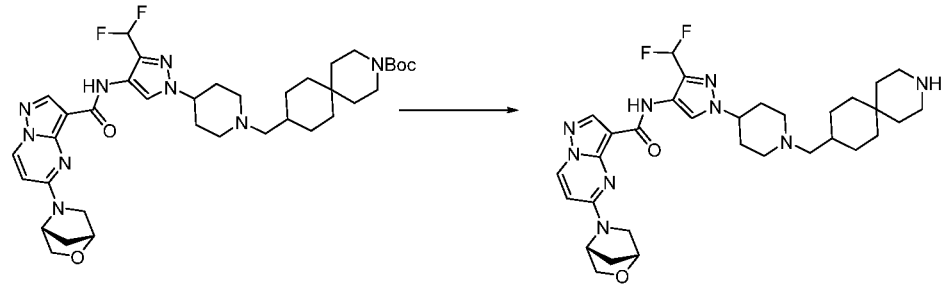


将 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 粗品)用 THF (10 mL)溶解，加入 9-甲酰基-3-氮杂螺[5.5]十一烷-3-

羧酸叔丁酯 (50 mg, 0.18 mmol)和 STAB (115 mg, 0.54 mmol)，室温反应 2 h。反应液中加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1:9)纯化得到 9-((4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=724.3.

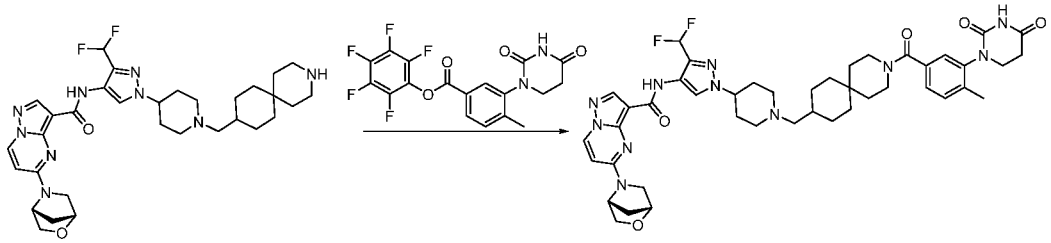
步骤 2：*N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 9-((4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-基)甲基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (100 mg, 0.14 mmol)溶于 DCM (4 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应液直接减压浓缩得到 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=624.4.

步骤 3： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.14 mmol)溶于 DMSO (10 mL)，加入 DIEA (90 mg, 0.70 mmol)和 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸五氟苯酯 (58 mg, 0.14 mmol)，室温反应 2 h。反应液中加水 (100 mL)并搅拌 5 分钟，用乙酸乙酯 (100 mL x 3)萃取，有机相用饱和食盐水 (150 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备纯化得到 5-

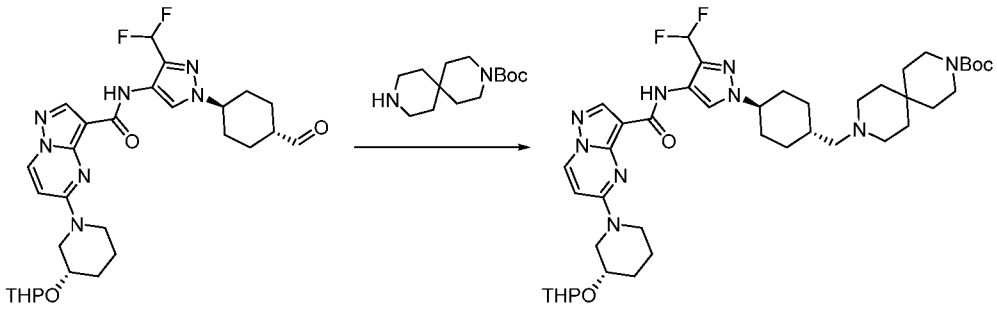
((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=854.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 3.6 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.26 – 6.96 (m, 2H), 6.88-6.44 (m, 1H), 5.28-5.07 (m, 1H), 4.77 (d, *J* = 17.6 Hz, 1H), 4.31-4.11 (m, 1H), 3.88 – 3.71 (m, 3H), 3.63-3.45 (m, 5H), 2.95 – 2.85 (m, 2H), 2.81 – 2.65 (m, 2H), 2.25 -2.10 (m, 5H), 2.07 – 1.87 (m, 8H),

实施例 45：*N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-((9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

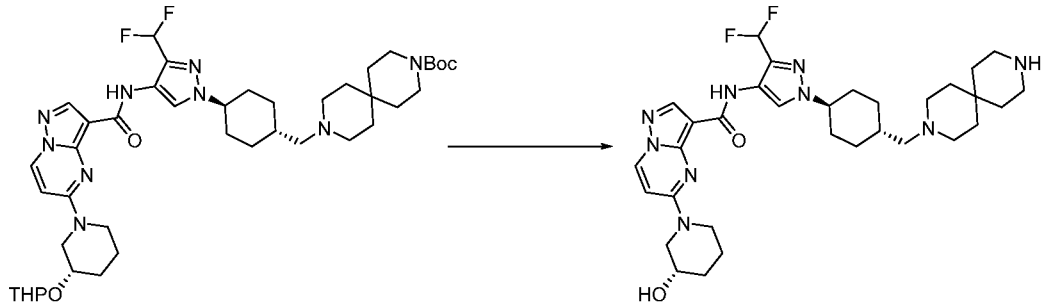
步骤 1：9-(((1*S*,4*R*)-4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



N-(3-(二氟甲基)-1-((1*R*,4*S*)-4-甲醛环己基)-1*H*-吡唑-4-基)-5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺(90 mg, 0.15 mmol)和 3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (40 mg, 0.15 mmol)用四氢呋喃 (10 mL)溶解，加入三乙酰氧基硼氢化钠 (95 mg, 0.45 mmol)，室温搅拌 2 小时，加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，有机相用饱和食盐水 (60 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 9-(((1*S*,4*R*)-4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=810.4.

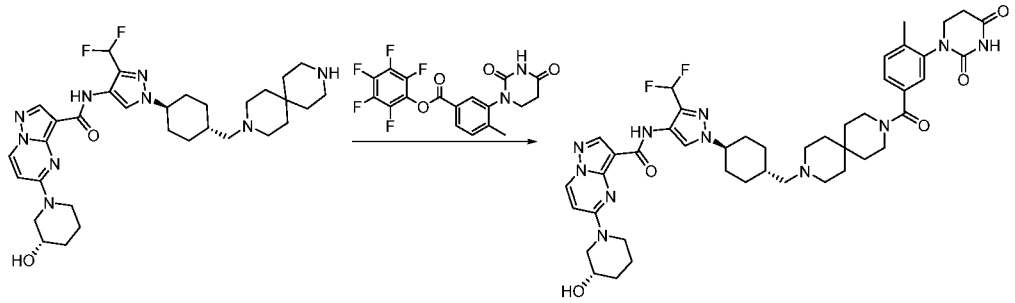
步骤 2： *N*-(1-((1*R*,4*S*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



9-(((1*S*,4*R*)-4-(3-(二氟甲基)-4-(5-((3*S*)-3-((四氢-2*H*-吡喃-2-基)氧)哌啶-1-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (100 mg, 0.12 mmol)用二氯甲烷 (3 mL)溶解，三氟乙酸 (1 mL)加入并室温搅拌1小时。反应液直接减压浓缩得到 *N*-(1-((1*R*,4*S*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=626.3.

步骤3： *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-((9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



N-(1-((1*R*,4*S*)-4-((3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.12 mmol)用二甲亚砜 (3 mL)溶解，加入3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸五氟苯酯 (55 mg, 0.13 mmol)和 *N*,*N*-二异丙基乙胺 (155 mg, 1.2 mmol)，室温搅拌过夜。反应液中加水 (30 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5%～95%)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*S*)-4-((9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-1*H*-吡唑-4-基)-5-((*S*)-3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

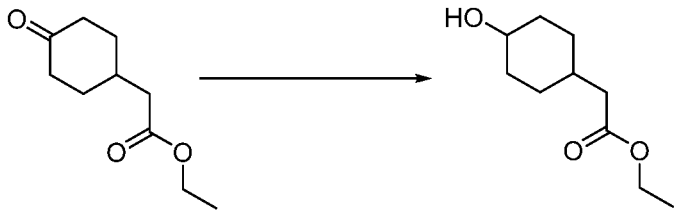
LC-MS: (ESI, m/z): $[M+H]^+$=856.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 9.38 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.36 (s, 1H), 8.24 (s, 1H), 7.36 – 7.29 (m, 2H), 7.27 – 6.94 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.93-4.88 (m, 1H), 4.20-4.10 (m, 1H), 4.01 – 3.74 (m, 3H), 3.70-3.44 (m, 6H), 3.33 – 3.25 (m, 2H), 2.84-2.64 (m, 2H), 2.40-2.21 (m, 4H), 2.21

(s, 3H), 2.15-1.96 (m, 4H), 1.87-1.70 (m, 6H), 1.65-1.26 (m, 11H), 1.10-0.95 (m, 2H).

实施例 46： 5-((1*R*,4*R*)-2-氧-5-氮[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(2-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)甲基)(甲基)氨基)乙基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

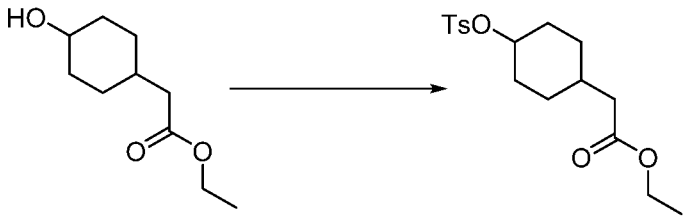
步骤 1： 2-(4-羟基环己基)乙酸乙酯的制备



在 0 ℃ 下, 将 $NaBH_4$ (3.28 g, 86.96 mmol) 缓慢加入到2-(4-氧代环己基)乙酸乙酯 (8 g, 43.48 mmol) 的无水甲醇 (100 mL)溶液中并搅拌2 h，然后加入10% 的NH_4Cl 水溶液淬灭反应, 用水 (100 mL)稀释，乙酸乙酯 (150 mL x 4)萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，减压浓缩，得到粗产品 2-(4-羟基环己基)乙酸乙酯。

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.60-3.47 (m, 1H), 2.25 – 2.14 (m, 2H), 2.05-1.93 (m, 2H), 1.81 – 1.69 (m, 3H), 1.35 – 1.20 (m, 5H), 1.11 – 0.97 (m, 2H).

步骤 2：2-(4-(对甲苯磺酰氧基)环己基)乙酸乙酯的制备

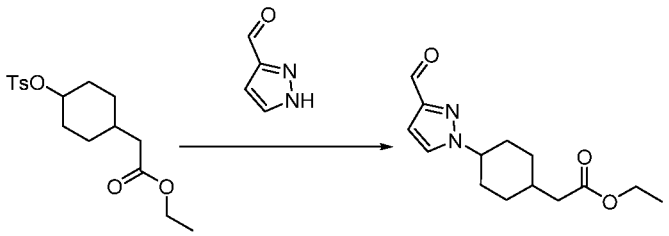


将TsCl (11.55 g, 60.48 mmol)加入到 2-(4-羟基环己基)乙酸乙酯 (7.5 g, 40.32 mmol) 的 DCM (120 mL)溶液中，DMAP (1.49 g, 12.10 mmol)和TEA (12.3 g, 120.96 mmol)加入， N_2 保护下室温搅拌16 h，用水 (100 mL)稀释，乙酸乙酯 (80 mL x 4)萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE = 3:7)得到 2-(4-(对甲苯磺酰氧基)环己基)乙酸乙酯。

LC-MS: (ESI, m/z): $[M+18]^+$ = 358.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 4.41 – 4.30 (m, 1H), 4.04-4.01 (m, 2H), 2.42 (s, 3H), 2.16 (dd, *J* = 23.3, 6.9 Hz, 2H), 1.81 – 1.73 (m, 2H), 1.70 – 1.55 (m, 3H), 1.48 – 1.36 (m, 2H), 1.17-1.13 (m, 3H), 1.09 – 0.94 (m, 2H).

步骤 3：2-(4-(3-甲酰基-1*H*-吡唑-1-基)环己基) 乙酸乙酯的制备

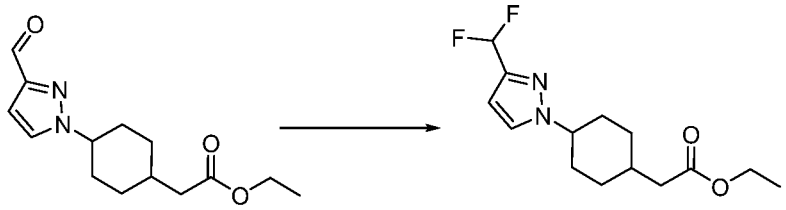


将 2-(4-(对甲苯磺酰氧基)环己基)乙酸乙酯 (9.1 g, 26.76 mmol)加入到1*H*-吡唑-3-甲醛(2.98 g, 26.76 mmol)的 DMF (120 mL)溶液中，然后加入$CsCO_3$ (14.4 g, 36.49 mmol)和KI (5.85 g, 29.19 mmol)，N_2 保护下50 ℃搅拌16 h。用水 (100 mL)稀释，乙酸乙酯 (80 mL x 4）萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE = 1:4)得到 2-(4-(3-甲酰基-1*H*-吡唑-1-基)环己基) 乙酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 265.3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.54 (s, 1H), 6.81 (s, 1H), 4.35-4.28 (m, 1H), 4.18-4.08 (m, 2H), 2.64-2.34 (m, 2H), 2.28-2.15 (m, 4H), 2.06-1.81 (m, 3H), 1.79-1.65 (m, 2H), 1.30-1.21 (m, 3H).

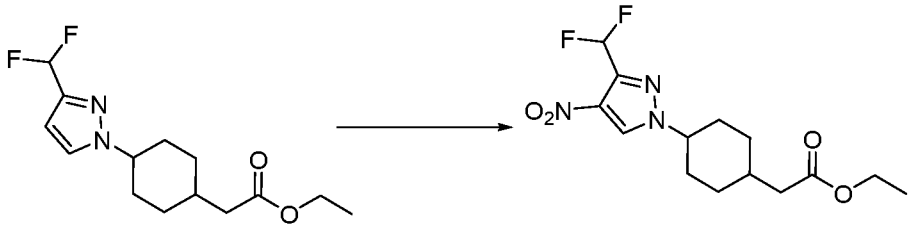
步骤 4：2-(4-(3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙酸乙酯的制备



将 2-(4-(3-甲酰基-1*H*-吡唑-1-基)环己基) 乙酸乙酯 (7.2 g, 27.27 mmol)溶解于无水二氯甲烷 (100 mL)中， 在0 ℃下缓慢加入DAST (17.58 g, 109.08 mmol)，N_2 保护下室温搅拌16 h。反应液中缓慢加入甲醇 (50 mL)，用水 (100 mL)稀释，用乙酸乙酯 (80 mL x 4)萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE = 3:17)得到 2-(4-(3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 287.0.

步骤 5： 2-(4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)乙酸乙酯的制备

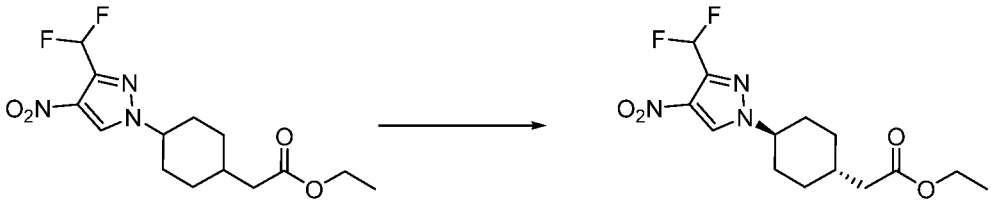


将 2-(4-(3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙酸乙酯 (2.7 g, 9.44 mmol)加入到 HNO_3 (2.9 g, 47.2

mmol) 的 乙酸溶液 (30 mL)中，加入乙酸酐 (1.9 g, 18.9 mmol)，N_2 保护下50 ℃ 搅拌16 h。反应液中加入水 (100 mL)，用乙酸乙酯 (80 mL x 4)萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (EA:PE = 1:9)纯化得到 2-(4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)乙酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 332.2.

步骤 6：2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)乙酸乙酯的制备

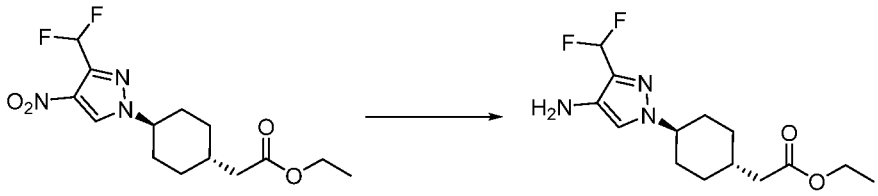


将 2-(4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)乙酸乙酯 (1.45 g, 4.38 mmol)经SFC制备纯化 (乙腈– 0.1% FA水溶液, 5%~95%)得到产物 2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)乙酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$ = 332.2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.24-6.98 (m, 1H), 4.32-4.28 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.35 (d, *J* = 7.5 Hz, 2H), 2.28-2.13 (m, 3H), 2.02-1.98 (m, 2H), 1.76-1.74 (m, 2H), 1.57- 1.49 (m, 2H), 1.26 (t, *J* = 5.2 Hz, 3H).

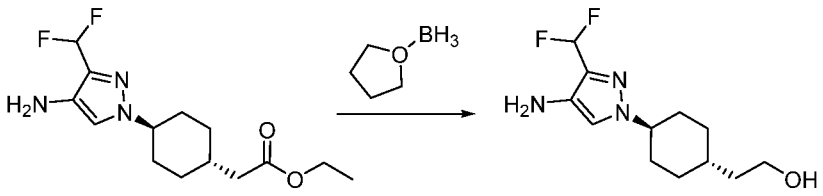
步骤 7：2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙酸乙酯的制备



将 2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-硝基-1*H*-吡唑-1-基)环己基)乙酸乙酯 (850 mg, 2.56 mmol)加入到无水乙醇 (4 mL)溶液中， Raney-Ni固水混合物 (1 mL)和水合肼 (0.8 mL)加入, 常温搅拌2 h。反应液过滤，滤饼用乙醇洗涤，滤液直接减压浓缩得到 2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙酸乙酯。

LC-MS: (ESI, m/z): $[M+H]^+$ =302.5.

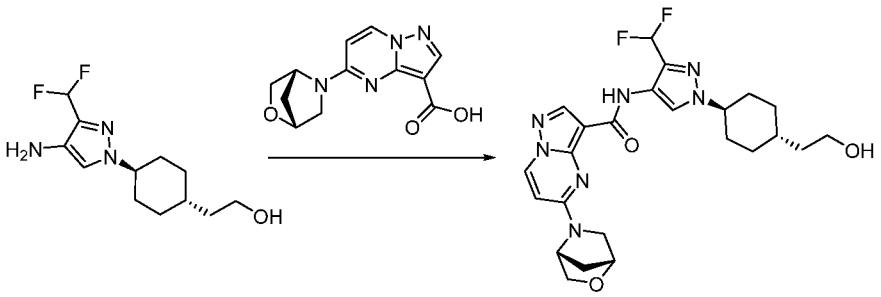
步骤 8：2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基-1-醇的制备



将 2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙酸乙酯 (100 mg, 0.33 mmol)溶解于无水四氢呋喃 (5 mL)中，氮气氛围下，向溶液中缓慢加入硼烷四氢呋喃溶液 (4.98 mL, 4.98 mmol)，反应液升温至50 ℃并搅拌3小时。反应液冷却至室温，缓慢滴加甲醇至无气泡产生，所得溶液减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基-1-醇。

LC-MS: (ESI, m/z): $[M+H]^+$=260.2.

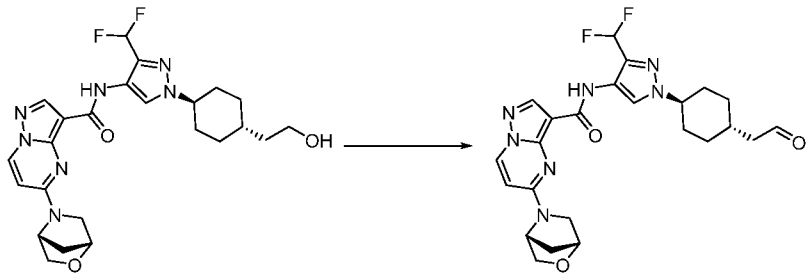
步骤 9：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-羟基乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基-1-醇 (80 mg, 0.30 mmol)和 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧酸 (156 mg, 0.60 mmol)用 DMF (5 mL)溶解，搅拌下加入 *N*,*N*-二异丙基乙胺 (116 mg, 0.90 mmol)和 Py-BOP (203 mg, 0.39 mmol)，60 ℃下搅拌过夜。反应液冷却至室温，加水 (50 mL)，用乙酸乙酯 (30 mL x 3）萃取，饱和食盐水 (50 mL)洗涤有机相，经无水硫酸钠干燥，过滤，减压浓缩，粗品经 p-TLC (甲醇:二氯甲烷=1:9)纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-羟基乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=502.2.

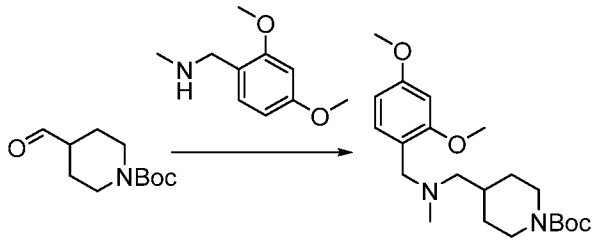
步骤 10：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-氧代乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-羟基乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.20 mmol)用乙腈 (10 mL)溶解，加入IBX (112 mg, 0.40 mmol)，80 ℃下搅拌 2小时。反应液减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-氧代乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=500.2.

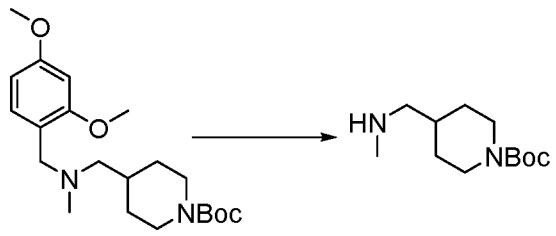
步骤 11：4-(((2,4-二甲氧基苯基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯的制备



4-甲酰基哌啶-1-羧酸叔丁酯 (200 mg, 1.0 mmol)和1-(2,4-二甲氧基苯基)-*N*-甲基甲胺(190 mg, 1.1 mmol)用四氢呋喃 (10 mL)溶解，然后加入三乙酰氧基硼氢化钠 (636 mg, 3.0 mmol)，室温下搅拌2小时。反应液中加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=4:1)纯化得到 4-(((2,4-二甲氧基苯基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=379.2.

步骤 12：4-((甲氨基)甲基)哌啶-1-羧酸叔丁酯的制备

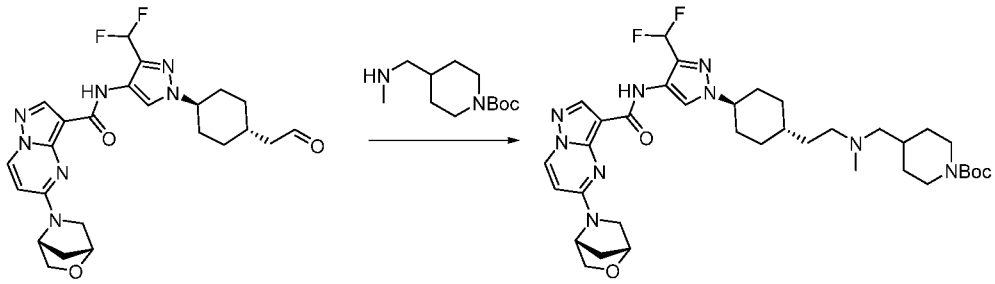


将4-(((2,4-二甲氧基苯基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯 (100 mg, 0.26 mmol)用乙酸乙酯 (10

mL)溶解，加入10%钯炭 (32 mg, 0.03 mmol)，所得混合物在氢气氛围下升温至70 ℃并搅拌过夜。反应液冷却至室温后，用硅藻土过滤，滤液直接减压浓缩得到 4-((甲氨基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=229.2.

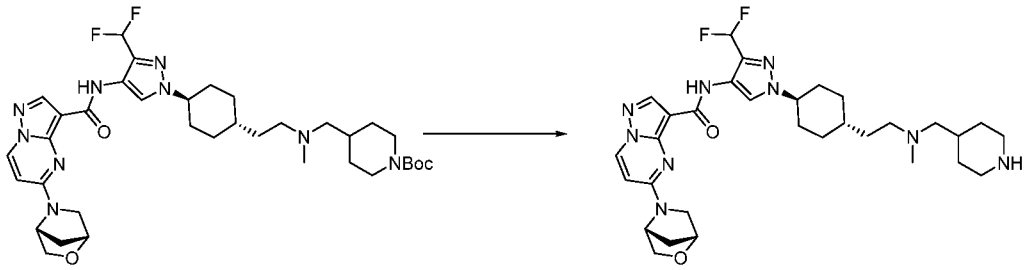
步骤 13： 4-(((2-((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)比作并[1,5-a]嘧啶-3-羧氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯的制备



将 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-氧代乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (60 mg, 0.12 mmol)和 4-((甲氨基)甲基)哌啶-1-羧酸叔丁酯 (60 mg, 0.26 mmol)用四氢呋喃 (10 mL)溶解，然后加入三乙酰氧基硼氢化钠 (127 mg, 0.6 mmol)，室温下搅拌 2 小时。反应液中加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:9)纯化得到 4-(((2-((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)比作并[1,5-a]嘧啶-3-羧氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=712.4.

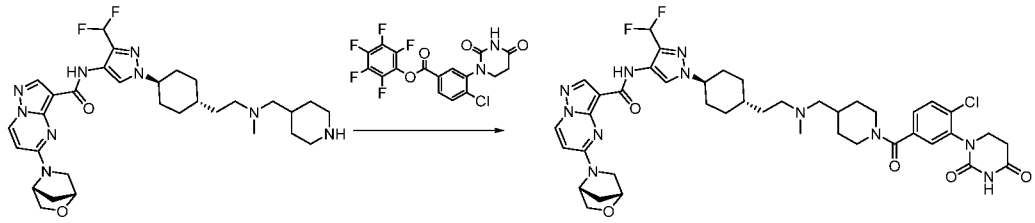
步骤14：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-(甲基(哌啶-4-基甲基)氨基)乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(((2-((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)比作并[1,5-a]嘧啶-3-羧氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基)(甲基)氨基)甲基)哌啶-1-羧酸叔丁酯 (70 mg, 0.10 mmol)用二氯甲烷 (3 mL)溶解，然后加入三氟乙酸 (1 mL)并室温搅拌 1 小时。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-(甲基(哌啶-4-基甲基)氨基)乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=612.3.

步骤 15：5-((1*R*,4*R*)-2-氧-5-氮[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(2-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)甲基)(甲基)氨基)乙基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



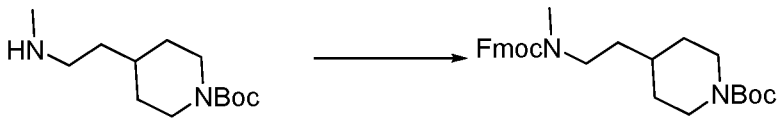
将 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-(甲基(哌啶-4-基甲基)氨基)乙基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (70 mg, 0.10 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (43 mg, 0.10 mmol)和 *N*,*N*-二异丙基乙胺 (130 mg, 1.0 mmol)，室温下搅拌 2 小时。反应液中加水 (50 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.10% FA 水溶液, 5%~ 95%)纯化得到 5-((1*R*,4*R*)-2-氧-5-氮[2.2.1]庚烷-5-基)-*N*-(1-((1*R*,4*R*)-4-(2-(((1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)甲基)(甲基)氨基)乙基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=862.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 6.3 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.42 (d, *J* = 4.0 Hz, 1H), 8.25 (d, *J* = 5.5 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 8.3, 1.9 Hz, 1H), 7.26-6.97 (m, 1H), 6.88-6.45 (m, 1H), 5.28-5.08 (m, 1H), 4.77 (d, *J* = 16.7 Hz, 1H), 4.50-4.38 (m, 1H), 4.30-4.22 (m, 1H), 3.84 – 3.71 (m, 3H), 3.66 – 3.58 (m, 3H), 3.48-3.43 (m, 1H), 3.10-3.02 (m, 1H), 2.84 – 2.69 (m, 3H), 2.35-2.25 (m, 2H), 2.18-2.08 (m, 5H), 2.08 – 1.91 (m, 4H), 1.85-1.70 (m, 4H), 1.70-1.55 (m, 4H), 1.49-1.40 (m, 4H), 1.20-1.04 (m, 2H).

实施例 47：5-((*S*)-3-氨基哌啶-1-基)-*N*-(1-((1*R*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(2-((((9*H*-芴-9-基)甲氧基)羰基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备

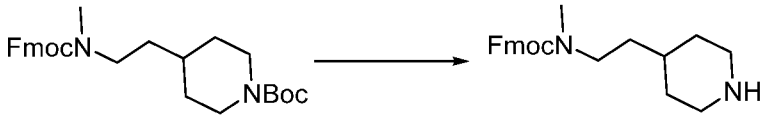


将 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (240 mg, 1.0 mmol)用 DCM (20 mL)溶解，加入 FmocCl

(311 mg, 1.2 mmol)和吡啶 (237 mg, 3.0 mmol)，室温反应过夜。反应液加水 (50 mL)稀释，用 DCM (30 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA:PE=0~4:1)纯化得到 4-(2-((((9*H*-芴-9-基)甲氧基)羰基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+Na]^+$=487.3.

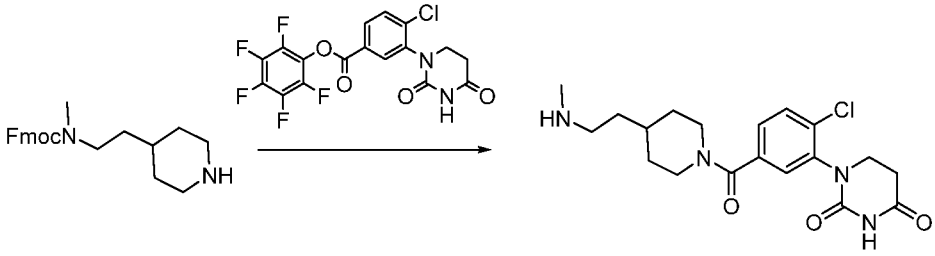
步骤 2：(9*H*-芴-9-基)甲基 甲基(2-(哌啶-4-基)乙基)氨基甲酸的制备



将 4-(2-((((9*H*-芴-9-基)甲氧基)羰基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (210 mg, 0.45 mmol)溶于 DCM (4 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应液直接减压浓缩得到 (9*H*-芴-9-基)甲基 甲基(2-(哌啶-4-基)乙基)氨基甲酸，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=365.2.

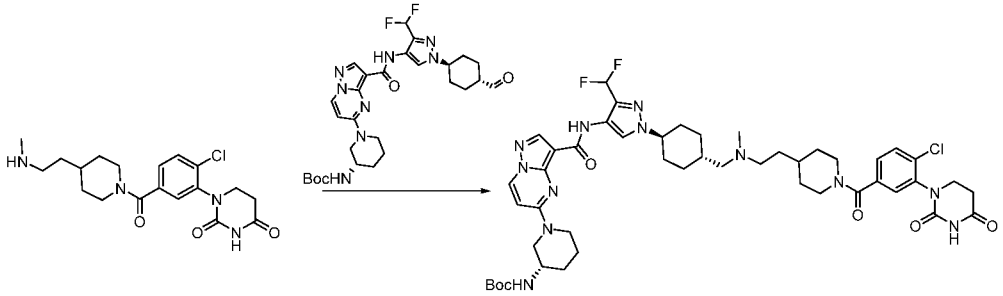
步骤 3：1-(2-氯-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将(9H-芴-9-基)甲基 甲基(2-(哌啶-4-基)乙基)氨基甲酸 （210 mg, 0.45 mmol）溶于 DMSO (5 mL)，加入 DIEA (264 mg, 2.05 mmol)和 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (178 mg, 0.41 mmol)，室温反应过夜。反应溶液使用反相色谱纯化 (45% ACN/ 0.1% NH_4HCO_3 水溶液)纯化得到 1-(2-氯-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=393.1.

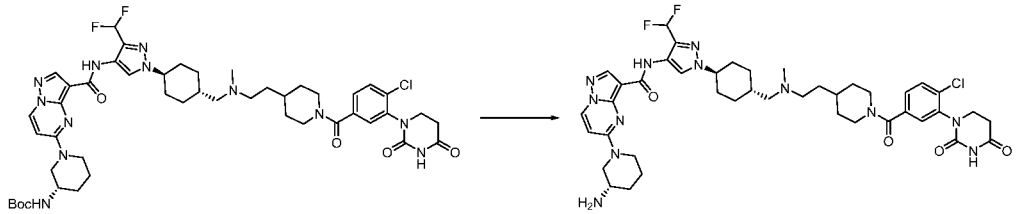
步骤 4： ((*S*)-1-(3-((1-((1*R*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯的制备



将 1-(2-氯-5-(4-(2-(甲基氨基)乙基)哌啶-1-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (50 mg, 0.13 mmol)用 THF (10 mL)溶解，加入 ((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-甲酰基环己基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯 (30 mg, 0.05 mmol)和 STAB (83 mg, 0.39 mmol)，反应 0.5 小时后，((*S*)-1-(3-((3-(二氟甲基)-1-((1*R*,4*S*)-4-甲酰基环己基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯 (60 mg, 0.10 mmol)1 小时内分两次加入，然后室温反应 2 小时。反应液中加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相经饱和食盐水 (100 mL)洗涤，无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (MeOH:DCM=0~1:9)纯化得到 ((*S*)-1-(3-((1-((1*R*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=963.3.

步骤 5：5-((*S*)-3-氨基哌啶-1-基)-*N*-(1-((1*R*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 ((*S*)-1-(3-((1-((1*R*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯 (100 mg, 0.10 mmol)溶于 DCM (5 mL)中，加入 TFA (1 mL)，室温反应 1 h。反应液直接减压浓缩，然后加入 $NaHCO_3$ 饱和溶液调节 pH 至 8~9，用 MeOH/DCM (10%, 20 mL x 3)萃取，有机相用无水硫酸钠干燥，过滤，浓缩，粗品使用反相制备纯化得到 5-((*S*)-3-氨基哌啶-1-基)-*N*-(1-((1*R*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

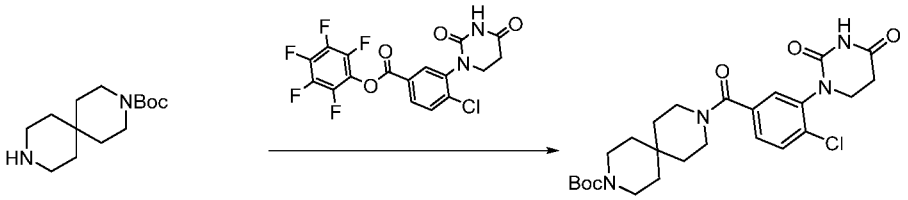
LC-MS: (ESI, m/z): $[M+H]^+$=863.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 – 9.87 (s, 1H), 9.36 (s, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.26-6.97 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.50-4.25 (m, 2H), 4.18 (t, *J* = 11.9 Hz, 2H), 3.80-3.70 (m, 1H), 3.70-3.51 (m, 2H), 3.26 – 3.18 (m, 1H), 3.08-2.97 (m, 2H), 2.85 – 2.64 (m, 5H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.14-2.07 (m, 5H), 2.07-1.97 (m, 2H), 1.95-1.83 (m, 3H), 1.80-1.30 (m, 12H), 1.18 – 0.95 (m, 4H).

实施例 48：*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]

嘧啶-3-甲酰胺

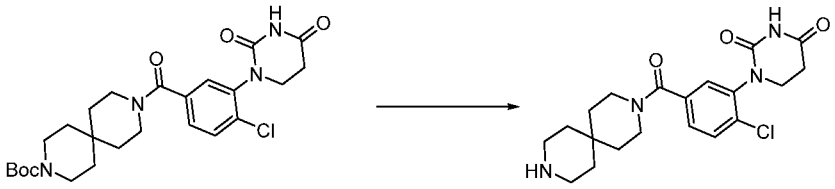
步骤 1：9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (100 mg, 0.39 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (205 mg, 0.47 mmol)和 *N*,*N*-二异丙基乙胺 (153 mg, 1.18 mmol)，室温搅拌过夜。反应液中加水 (50 mL)，用乙酸乙酯 (30 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品经柱层析 (乙酸乙酯)纯化得到9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M\text{-}Boc]^+$=405.1.

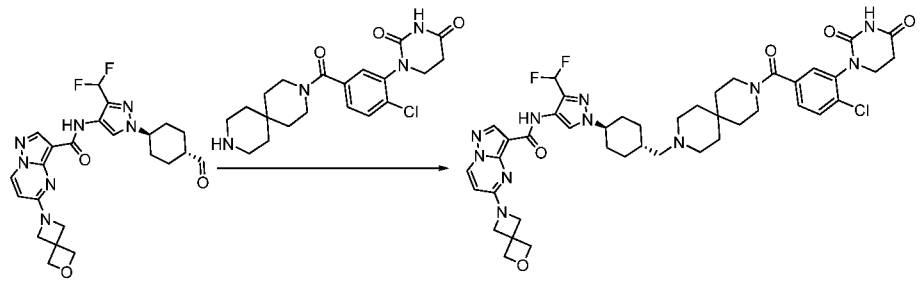
步骤 2：1-(2-氯-5-(3,9-二氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (170 mg, 0.34 mmol)用二氯甲烷 (2.5 mL)溶解，三氟乙酸 (0.5 mL)加入并室温搅拌2小时。反应液直接减压浓缩得到 1-(2-氯-5-(3,9-二氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=405.1.

步骤 3： *N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



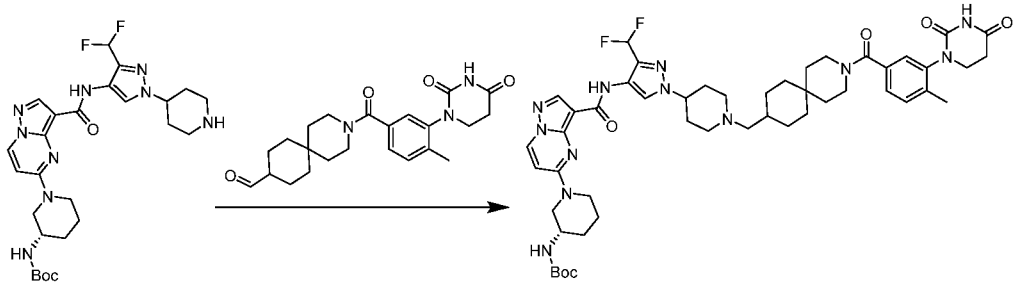
N-(3-(二氟甲基)-1-((1*R*,4*R*)-4-醛基环己基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (50 mg, 0.10 mmol)和1-(2-氯-5-(3,9-二氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (42 mg, 0.10 mmol)用二氯乙烷 (10 mL)溶解，加入三乙酰氧基硼氢化钠 (44 mg, 0.20 mmol)，升温至70 ℃搅拌过夜。反应液中加水 (50 mL)，用二氯甲烷 (20 mL x 3)萃取，经无水硫酸钠干燥，过滤，减压浓缩，粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5%~ 95%)纯化得到*N*-(1-((1*R*,4*R*)-4-((9-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)甲基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=874.2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.44 (s, 1H), 8.39 (d, *J* = 5.3 Hz, 2H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.58-7.48 (m, 2H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.38 – 7.34 (m, 1H), 6.97-6.65 (m, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 4.98-4.85 (m, 4H), 4.47-4.37 (m, 4H), 4.13-4.06 (m, 1H), 3.86-3.74 (m, 4H), 3.46-3.38 (m, 2H), 3.00-2.74 (m, 3H), 2.39-2.29 (m, 3H), 2.29-2.10 (m, 3H), 2.10-2.00 (m, 2H), 1.92-1.76 (m, 3H), 1.40-1.10 (m, 10H), 0.95-0.85 (m, 1H).

实施例 49：(*S*)-5-(3-氨基哌啶-1-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： (*S*)-(1-(3-((3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯的制备

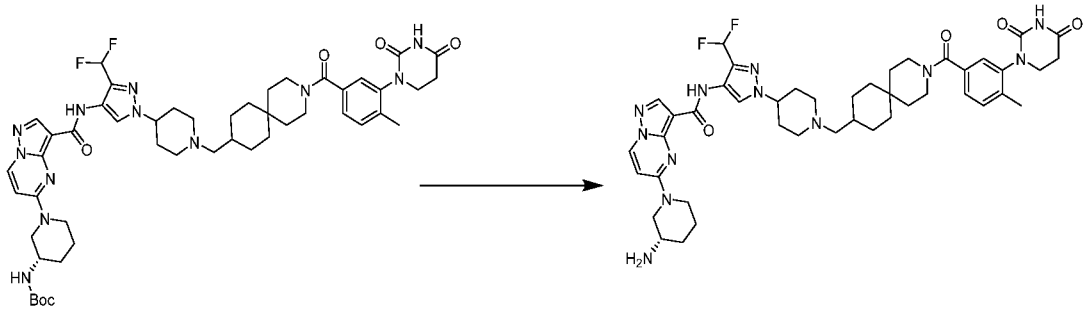


将 (*S*)-(1-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯 (45 mg, 0.08 mmol)和3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛 (33 mg, 0.08 mmol)溶于DMF (2 mL)中， $NaBH(OAc)_3$ (51 mg, 0.24 mmol)加入，室

温搅拌2小时。反应液中加入水 (50 mL)，用乙酸乙酯 (30 mL x 3)萃取，合并上层有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经正相柱层析纯化得到 (*S*)-(1-(3-((3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+ = 955.5$.

步骤 2：(*S*)-5-(3-氨基哌啶-1-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 (*S*)-(1-(3-((3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯 (30 mg, 0.03 mmol)溶于 DCM (0.5 mL)中， 然后加入 TFA (0.1 mL)，室温搅拌 1 小时。饱和 $NaHCO_3$ 水溶液加入到反应液中直至溶液 pH 值至弱碱性，用混合有机溶剂 (MeOH:DCM=1:10, 30 mL x 3)萃取，无水硫酸钠干燥，过滤，减压浓缩，粗品经 p-HPLC 纯化得到 (*S*)-5-(3-氨基哌啶-1-基)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

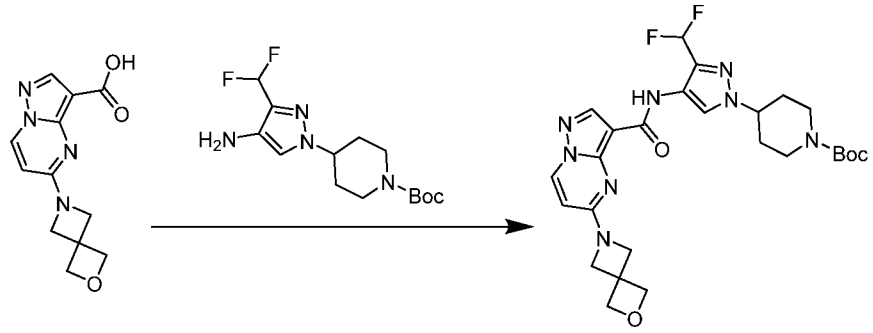
LC-MS: (ESI, m/z): $[M+H]^+ = 855.7$.

^{1}H NMR (400 MHz, MeOD) δ 8.49 (d, *J* = 8.0 Hz, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.04 – 6.74 (m, 2H), 4.60-4.50 (m, 1H), 4.50-4.25 (m, 2H), 4.25-4.15 (m, 1H), 3.97-3.79 (m, 1H), 3.80-3.63 (m, 3H), 3.50-3.38 (m, 3H), 3.15-3.08 (m, 1H), 3.06-3.01 (m, 2H), 2.94 – 2.79 (m, 3H), 2.31 (s, 3H), 2.27-2.21 (m, 2H), 2.21-2.04 (m, 7H), 1.93-1.83 (m, 1H), 1.83-1.76 (m, 2H), 1.70-1.44 (m, 8H), 1.22-1.02 (m, 4H).

实施例 50：*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1：4-(4-(5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡

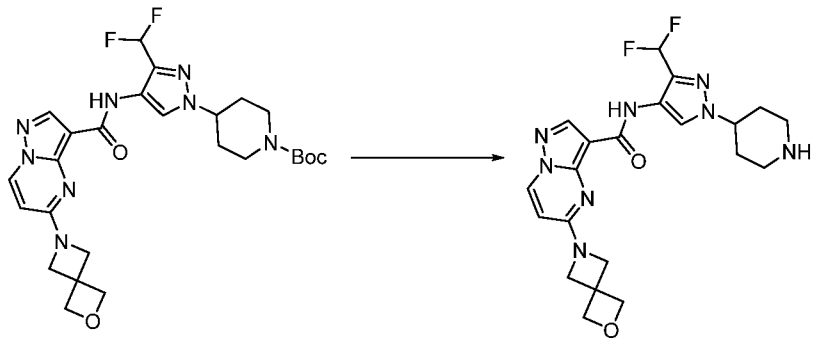
唑-1-基)哌啶-1-羧酸叔丁酯的制备



将5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酸 (130 mg, 0.5 mmol)，4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (158 mg, 0.5 mmol)和 Py-BOP (780 mg, 1.5 mmol)用DMF (6 mL)溶解，然后加入DIEA (780 mg, 1.5 mmol)，室温搅拌16小时。反应液中加入水 (50 mL)，乙酸乙酯 (30 mL x 3)萃取，合并上层有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经正相柱层析纯化得到 4-(4-(5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+ = 559.2$.

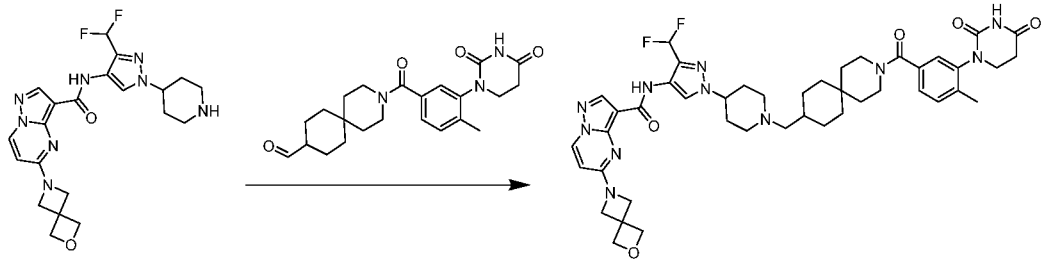
步骤 2： *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将4-(4-(5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-羧酰氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)哌啶-1-羧酸叔丁酯 (250 mg, 0.45 mmol)用DCM (4 mL)溶解，然后加入TFA (1 mL)，室温搅拌1小时。反应液直接减压浓缩得到粗品 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+ = 459.3$.

步骤 3：*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



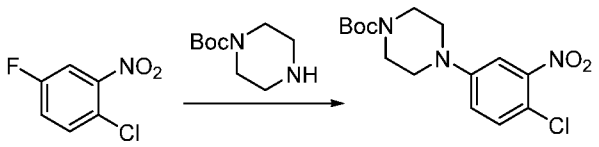
将*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (114 mg, 0.25 mmol)和3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛 (102 mg, 0.25 mmol)用THF (5mL)溶解，三乙酰氧基硼氢化钠 (160 mg, 0.75 mmol)加入，室温搅拌16小时。反应液中加入水 (50 mL)，乙酸乙酯 (30 mL x 3) 萃取，合并上层有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经 prep-HPLC纯化得到白色固体 *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-(2-氧-6-氮杂螺[3.3]庚烷-6-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=854.6.

^{1}H NMR (400 MHz, MeOD) δ 8.47 (d, *J* = 7.8 Hz, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.36-7.27 (m, 2H), 7.05-6.95 (m, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 4.62-4.50 (m, 2H), 4.50-4.39 (m, 4H), 4.26-4.11 (m, 1H), 3.95-3.82 (m, 1H), 3.77-3.60 (m, 3H), 3.49-3.40 (m, 2H), 3.05-2.97 (m, 2H), 2.89 – 2.79 (m, 2H), 2.37-2.20 (m, 5H), 2.20-2.09 (m, 6H), 1.83-1.75 (m, 2H), 1.71-1.41 (m, 7H), 1.37-1.27 (m, 2H), 1.24-1.08 (m, 4H).

实施例 51： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

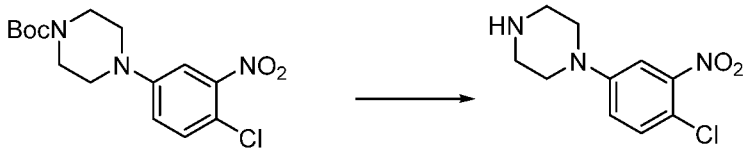
步骤 1： 4-(4-氯-3-硝基苯基)哌嗪-1-羧酸叔丁酯的制备



1-氯-4-氟-2-硝基苯 (10.0 g, 56.81 mmol)用 DMSO (100 mL)溶解，然后加入哌嗪-1-羧酸叔丁酯 (21 g, 85.27 mmol)和 DIEA (52 mL)，加热至 110 ℃反应 48 h。反应液中国加水 (1000 mL)并搅拌 10 min，乙酸乙酯 (600 mL x 3)萃取，有机相用饱和食盐水 (1000 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (PE:EA=5:1)纯化得到 4-(4-氯-3-硝基苯基)哌嗪-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M-t-Bu]^+$=286.0.

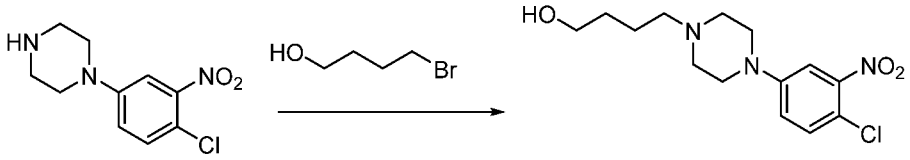
步骤 2：1-(4-氯-3-硝基苯基)哌嗪的制备



将 4-(4-氯-3-硝基苯基)哌嗪-1-羧酸叔丁酯 (3.73g, 10.9 mmol)用 DCM (30 mL)溶解，然后加入 TFA (10 mL)，室温搅拌 1 小时。反应液直接减压浓缩得到 1-(4-氯-3-硝基苯基)哌嗪。

LC-MS: (ESI, m/z): $[M+H]^+$=242.0.

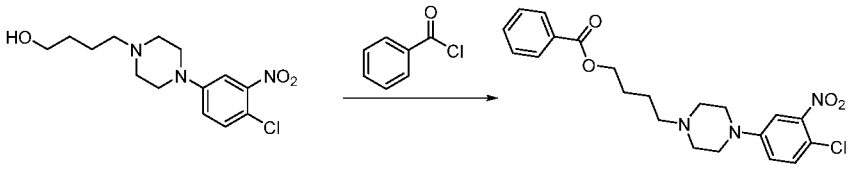
步骤 3：4-(4-(4-氯-3-硝基苯基)哌嗪-1-基)丁基-1-醇的制备



1-(4-氯-3-硝基苯基)哌嗪 (4.0 g, 10.9 mmol)用 DMF (25 mL)溶解，然后加入 4-溴丁基-1-醇 (1.75 g, 11.4 mmol)，碳酸钾 (4.51g, 32.7 mmol)和 KI (1.89 g, 11.4mmol)，反应液加热至 60 ℃搅拌过夜。反应液中加水 (200 mL)稀释并搅拌 10 min，乙酸乙酯 (100 mL x 3)萃取，有机相用饱和食盐水 (150 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (DCM:MeOH=1:19)纯化得到 4-(4-(4-氯-3-硝基苯基)哌嗪-1-基)丁基-1-醇。

LC-MS: (ESI, m/z): $[M+H]^+$=314.1.

步骤 4：4-(4-(4-氯-3-硝基苯基)哌嗪-1-基)丁基苯甲酸酯的制备



将 4-(4-(4-氯-3-硝基苯基)哌嗪-1-基)丁基-1-醇 (1.0 g, 3.19 mmol)用 THF (15 mL)溶解， 然后加入苯甲酰氯 (0.58 g, 4.15 mmol)和 TEA (0.97g, 9.57mmol)，反应液加热至 70 ℃搅拌过夜。反应液中加水 (50 mL)，乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (DCM:MeOH=1:13)纯化得到 4-(4-(4-氯-3-硝基苯基)哌嗪-1-基)丁基苯甲酸酯。

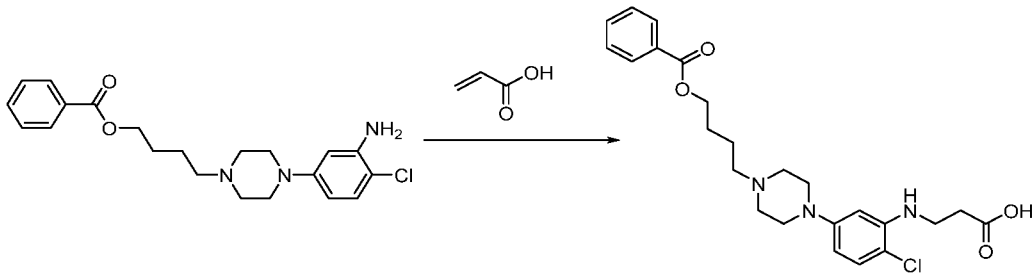
LC-MS: (ESI, m/z): $[M+H]^+$=418.1.

步骤 5：4-(4-(3-氨基-4-氯苯基)哌嗪-1-基)丁基苯甲酸酯的制备

将 4-(4-(4-氯-3-硝基苯基)哌嗪-1-基)丁基苯甲酸酯 (1.2 g, 2.87 mmol)用乙醇 (15mL)溶解，加入水合肼 (1.5 mL)和 Raney-Ni (固液混合物, 1.5 mL)，常温反应 1 h。过滤，滤液减压浓缩得到 4-(4-(3-氨基-4-氯苯基)哌嗪-1-基)丁基苯甲酸酯。

LC-MS: (ESI, m/z): $[M+H]^+$=388.1.

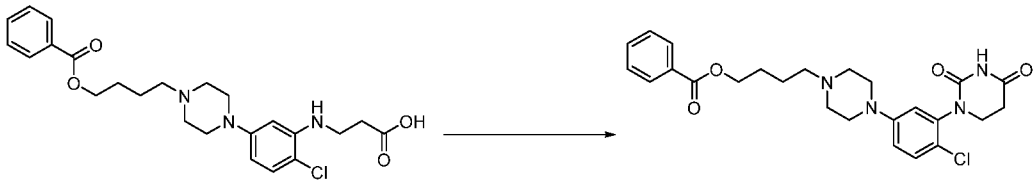
步骤 6：3-((5-(4-(4-(苯酰氧基)丁基)哌嗪-1-基)-2-氯苯基)氨基)丙酸的制备



将 4-(4-(3-氨基-4-氯苯基)哌嗪-1-基)丁基苯甲酸酯 (1.0 g, 2.6mmol)用乙酸/水混合液 (1/5, 12 mL)溶解，然后加入丙烯酸 (0.558 g, 7.75 mmol)，反应液加热至 110 ℃搅拌过夜。反应液中加水 (50 mL)，乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析（DCM/MeOH =12%）纯化得到3-((5-(4-(4-(苯酰氧基)丁基)哌嗪-1-基)-2-氯苯基)氨基)丙酸。

LC-MS: (ESI, m/z): $[M+H]^+$=460.1.

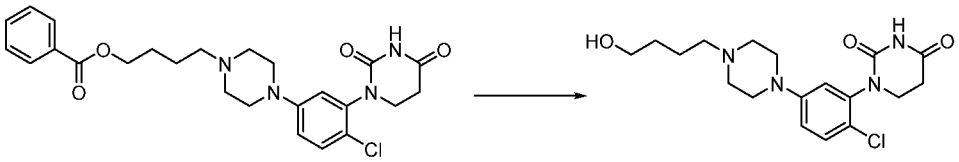
步骤 7：4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)丁基苯甲酸酯的制备



将 3-((5-(4-(4-(苯酰氧基)丁基)哌嗪-1-基)-2-氯苯基)氨基)丙酸 (1.12 g, 2.44mmol)用乙酸 (15 mL)溶解，然后加入尿素 (2.92 g, 48.8 mmol)，反应液加热至 110 ℃搅拌 48 小时。反应液中加水 (50 mL)，用 MeOH/DCM 混合有机溶剂 (10%, 50 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (DCM:MeOH=1:9)纯化得到 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)丁基苯甲酸酯。

LC-MS: (ESI, m/z): $[M+H]^+$=485.1.

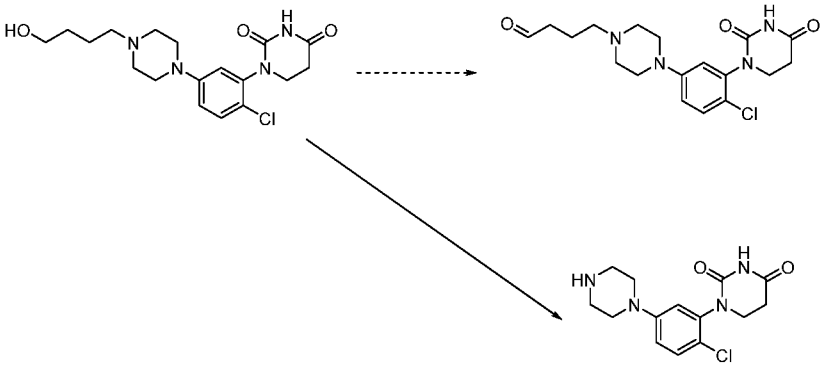
步骤 8：1-(2-氯-5-(4-(4-羟基丁基)哌嗪-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)丁基苯甲酸酯 (0.74 g, 1.5mmol)加入到浓盐酸 (15 mL)中，加热至70 ℃搅拌过夜。反应液直接减压浓缩，粗品使用反相 (ACN/H_2O=16%, 0.1% FA水溶液)纯化得到 1-(2-氯-5-(4-(4-羟基丁基)哌嗪-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=381.1.

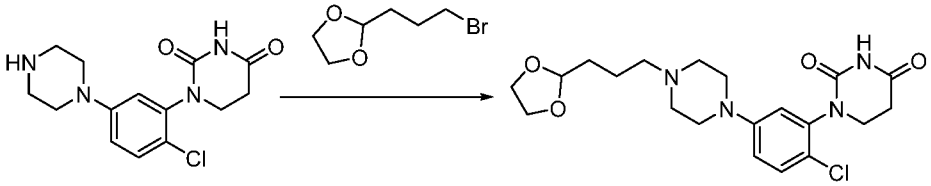
步骤 9： 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)正丁醛的制备



将 1-(2-氯-5-(4-(4-羟基丁基)哌嗪-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (280 mg, 0.74mmol)用 DCM (10 mL)溶解，然后加入 Dess-Martin (628 mg, 1.48 mmol)，反应液室温搅拌过夜。直接减压浓缩，粗品经反相 (ACN/H_2O=16%, 0.1% FA 水溶液)纯化，所得产物经分析并不是 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)正丁醛，实际得到 1-(2-氯-5-(哌嗪-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=309.2.

步骤 10：1-(5-(4-(3-(1,3-二氧戊烷-2-基)丙基)哌嗪-1-基)-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备

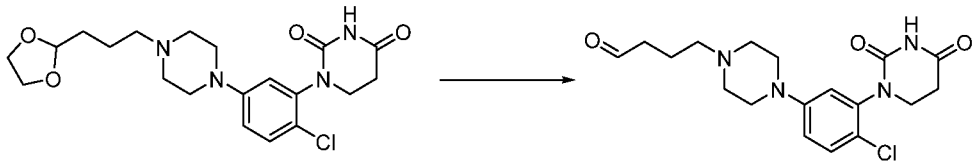


将 1-(2-氯-5-(哌嗪-1-基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (65 mg, 0.21 mmol)用 ACN (10 mL)溶解，然后加入 2-(3-溴丙基)-1,3-二氧戊烷 (41 mg, 0.21 mmol)，K_2CO_3 (87 mg, 0.63 mmol)和 KI (18 mg, 0.21 mmol)，反应液加热至 80 ℃搅拌过夜。减压浓缩除去 ACN，然后加水 (50 mL)，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层

析 (DCM:MeOH=1:9)纯化得到 1-(5-(4-(3-(1,3-二氧戊烷-2-基)丙基)哌嗪-1-基)-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=423.1.

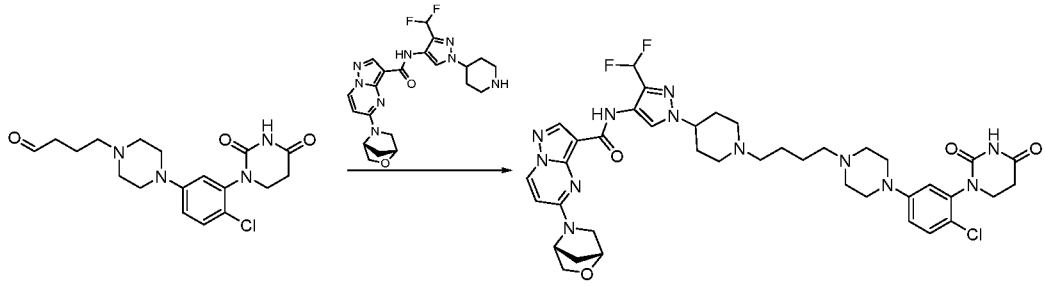
步骤 11：4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)正丁醛的制备



将1-(5-(4-(3-(1,3-二氧戊烷-2-基)丙基)哌嗪-1-基)-2-氯苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (20 mg, 0.047mmol)用DCM (1 mL)溶解，然后加入TFA (1 mL)，室温反应48 h后，加入DCE (10 mL)和DIEA (1mL)，室温下减压浓缩得到 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)正丁醛(粗品，二氯乙烷溶液)，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=379.1.

步骤 12：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



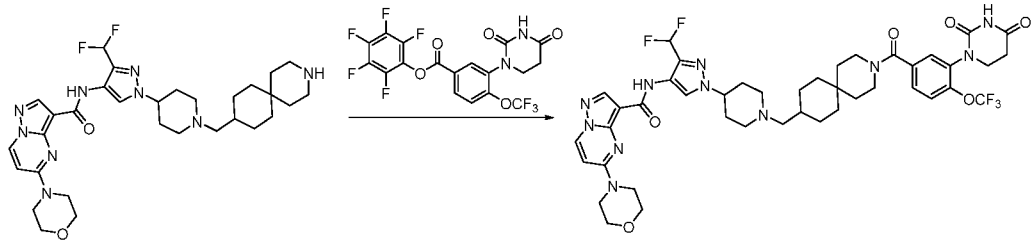
向 4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)正丁醛 (粗品)的 DCE 溶液中加入 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (20 mg, 0.044 mmol)，室温搅拌 0.5 h 后，加入 STAB (28 mg, 0.13 mmol)，室温反应 2 h。反应液中加水 (30 mL)稀释，用乙酸乙酯 (30 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-(1-(4-(4-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯基)哌嗪-1-基)丁基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=821.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.40 (d, *J* = 3.9 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.27-6.96 (m, 2H), 6.92 (dd, J = 9.0, 2.9 Hz, 1H), 6.88-6.44 (m, 1H), 5.28-5.07 (m, 1H), 4.77 (d, J = 17.3 Hz, 1H), 4.26-4.15 (m, 1H), 3.85-3.42 (m,

6H), 3.23-3.10 (m, 4H), 2.94 (d, J = 11.9 Hz, 2H), 2.80-2.62 (m, 2H), 2.49-2.46 (m, 4H), 2.40-2.25 (m, 4H), 2.05-1.80 (m, 8H), 1.53-1.41 (m, 4H).

实施例 52： *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺



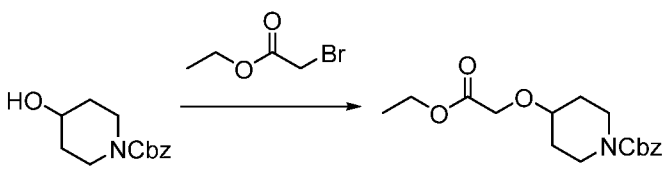
将 *N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.164 mmol)和 3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酸五氟苯基酯 (87 mg, 0.180 mmol)溶于 DMSO (5 mL)中，加入 DIEA (65 mg, 0.492 mmol)，反应液室温搅拌过夜。反应液中加水 (20 mL)稀释，乙酸乙酯 (25 mL x 4)萃取，有机相用饱和食盐水洗涤，无水硫酸钠干燥，减压浓缩，粗品使用反相制备得到化合物 *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-(三氟甲氧基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=912.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.24 – 6.87 (m, 2H), 4.24-4.17 (m, 1H), 3.83-3.50 (m, 13H), 3.30-3.26 (m, 1H), 2.93-2.85 (m, 2H), 2.75-2.65 (m, 2H), 2.18-2.10 (m, 2H), 2.05-1.88 (m, 6H), 1.70 (d, *J* = 9.0 Hz, 2H), 1.61-1.42 (m, 5H), 1.35-1.20 (m, 2H), 1.12-0.95 (m, 4H).

实施例 53：*N*-(3-(二氟甲基)-1-(1-(2-((1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)氧)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1： 4-(2-乙氧基-2-氧代乙氧基)哌啶-1-羧酸苄酯的制备

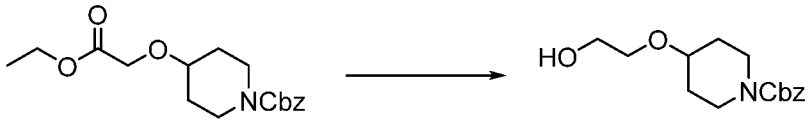


将4-羟基哌啶-1-羧酸苄酯 (3 g, 12.8 mmol)用无水四氢呋喃 (30 mL)溶解，在零度下加入钠氢 (1.1 g, 25.6 mmol)并搅拌60分钟，2-溴乙酸乙酯 (2.6 g, 15.4 mmol)加入，反应液室温搅拌过夜。反应液中加水 (100 mL)，用乙酸乙酯 (150 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使

用柱层析 (乙酸乙酯:石油醚=1:1)纯化得到 4-(2-乙氧基-2-氧代乙氧基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+Na]^+$=344.1.

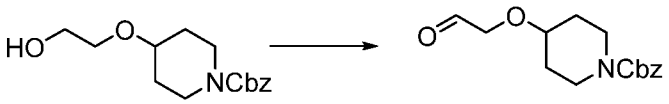
步骤 2： 4-(2-羟基乙氧基)哌啶-1-羧酸苄酯的制备



4-(2-乙氧基-2-氧代乙氧基)哌啶-1-羧酸苄酯 (1.1 g, 3.4 mmol)用无水四氢呋喃 (10 mL)溶解，在零度下加硼烷四氢呋喃溶液 (2.9 g, 34 mmol)，反应液室温搅拌过夜，在零度下缓慢加水 (100 mL)，用乙酸乙酯 (100 mL x 3)萃取，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=7:3)纯化得到 4-(2-羟基乙氧基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+Na]^+$=302.1.

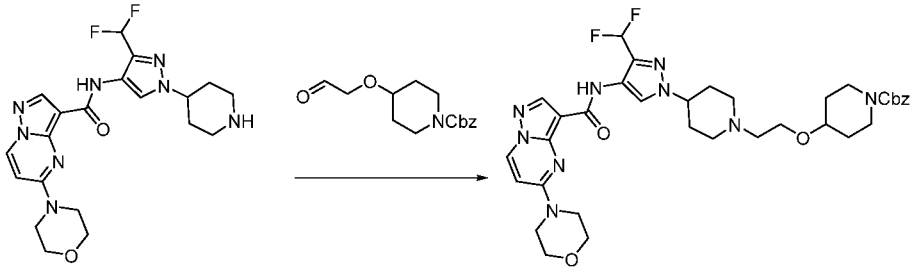
步骤 3： 4-(2-氧代乙氧基)哌啶-1-羧酸苄酯的制备



4-(2-羟基乙氧基)哌啶-1-羧酸苄酯 (400 mg, 1.4 mmol)用 DCM (4 mL)溶解，加入 PCC (602 mg, 2.8 mmol)，反应液室温搅拌 3 小时。过滤，直接减压浓缩得到 4-(2-氧代乙氧基)哌啶-1-羧酸苄酯，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=278.1.

步骤 4： 4-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙氧基)哌啶-1-羧酸苄酯的制备

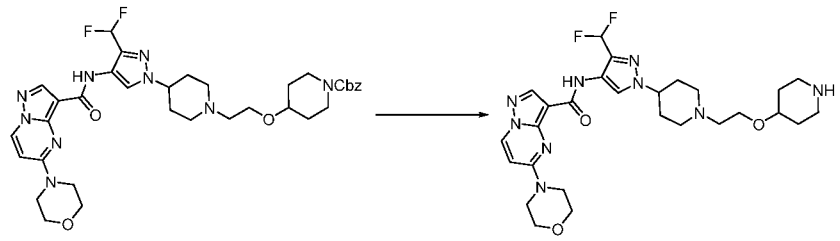


将 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺(120 mg, 0.27 mmol)和 4-(2-氧代乙氧基)哌啶-1-羧酸苄酯 (75 mg, 0.27 mmol)用四氢呋喃 (5 mL)溶解，搅拌下加入三乙酰氧基硼氢化钠 (172 mg, 0.81 mmol)，室温搅拌 3 小时。反应液中加水 (50 mL)，用乙

酸乙酯 (60 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯乙烷=1:7)纯化得到 4-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙氧基)哌啶-1-羧酸苄酯。

LC-MS: (ESI, m/z): $[M+H]^+$=708.3.

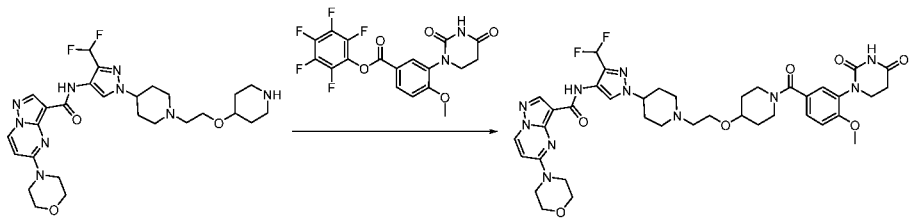
步骤 5：*N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基氧)乙基)拍档-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将4-(2-(4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)哌啶-1-基)乙氧基)哌啶-1-羧酸苄酯 (50 mg, 0.07 mmol)用四氢呋喃 (3 mL)溶解，然后加入钯碳 (10%, 10 mg)并室温搅拌 1小时。反应液经硅藻土过滤，滤液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基氧)乙基)拍档-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=574.4.

步骤 6：*N*-(3-(二氟甲基)-1-(1-(2-((1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)氧)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



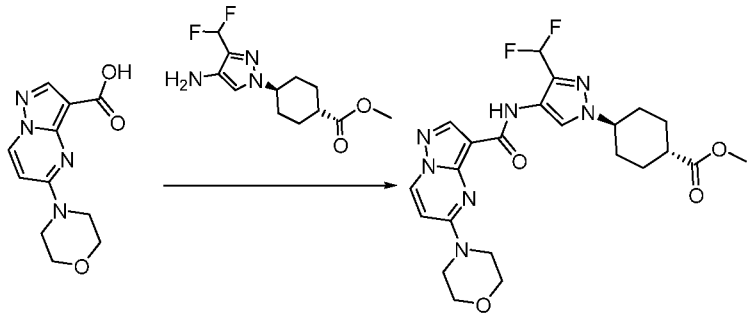
将*N*-(3-(二氟甲基)-1-(1-(2-(哌啶-4-基氧)乙基)拍档-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (26 mg, 0.045 mmol)和3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (20 mg, 0.045 mmol)用DMSO (2 mL)溶解，搅拌下加入*N*,*N*-二异丙基乙胺 (18 mg, 0.14 mmol)，室温搅拌3小时。反应液中加水 (20 mL)，用乙酸乙酯 (20 mL x 3)萃取，有机相经饱和食盐水 (30 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5% ~ 95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-(2-((1-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)哌啶-4-基)氧)乙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=820.6.

^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (d, J = 8.0 Hz, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.47-7.38 (m, 2H), 7.19 (d, J = 8.6 Hz, 1H), 7.00-6.72 (m, 2H), 3.92 (s, 3H), 3.89-3.77 (m, 8H), 3.70-3.67 (m, 3H), 3.15-3.10 (m, 1H), 2.80 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 5.5 Hz, 2H), 2.40-2.28 (m, 2H), 2.19 (t, J = 7.6 Hz, 1H), 2.14-2.08 (m, 2H), 2.04-1.90 (m, 3H), 1.64-1.55 (m, 2H), 1.34-1.26 (m, 8H).

实施例 54：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((2-(1-(3-(2,6-二氧代吡啶-3-基)-4-氟苯甲酰 l)哌啶-4-基)乙基)(甲基)氨甲酰基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

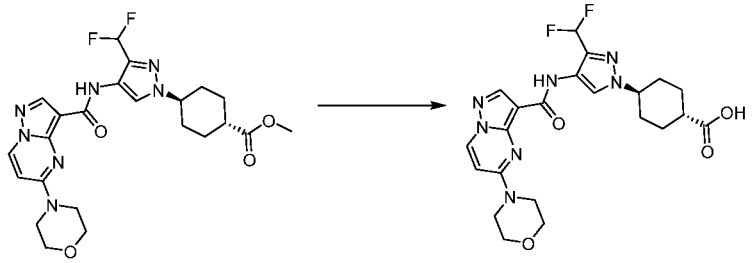
步骤 1： (1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯的制备



将 5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸 (200 mg, 0.73 mmol)溶于 DMF (4 mL)中， (1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (182 mg, 0.73 mmol)，HATU (139 mg, 0.95 mmol)和 DIEA (377 mg, 2.92 mmol)加入，反应液室温搅拌过夜。反应液加水 (50 mL)稀释，乙酸乙酯 (40 mL x 3)萃取，有机相用饱和食盐水洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA:PE=9:1)纯化得到 (1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯。

LC-MS: (ESI, m/z): $[M+H]^+$=504.1.

步骤 2：(1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己烷-1-羧酸的制备

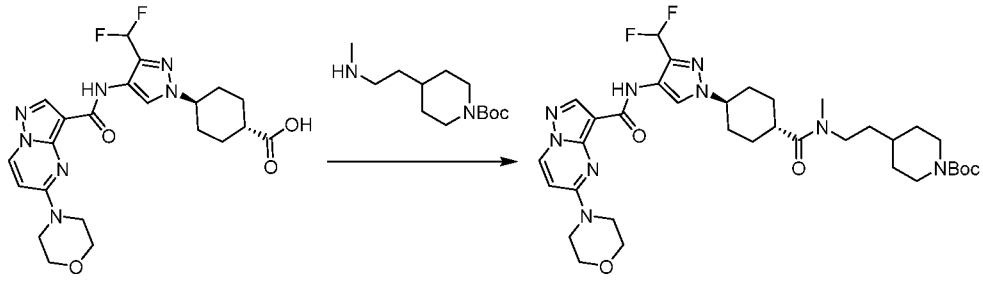


将 (1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己烷-1-羧酸甲酯 (230 mg, 0.46 mmol)用混合溶液甲醇/水 (5 mL, V/V =5/1)溶解，加入氢氧化锂 (44 mg, 1.84

mmol)，反应液加热至 60 ℃搅拌 2 小时。反应液用稀盐酸 (2 mol/L)调节至 pH=4，乙酸乙酯 (40 mL x 3)萃取，有机相用饱和食盐水洗涤，经无水硫酸钠干燥，过滤，减压浓缩得到 (1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己烷-1-羧酸，直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=490.6.

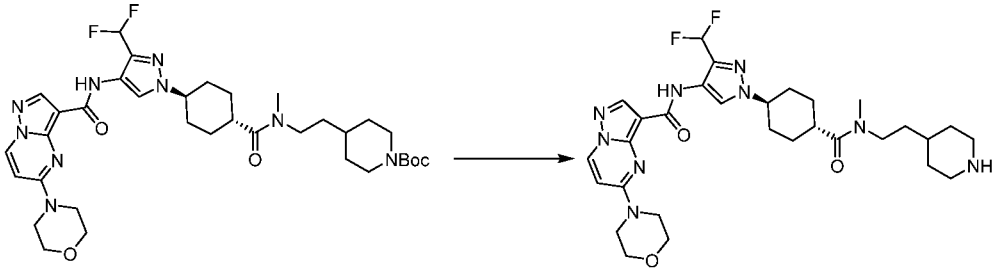
步骤 3： 4-(2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)-*N*-甲基环己烷-1-羧酰氨基)乙基)哌啶-1-羧酸叔丁酯的制备



将 (1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己烷-1-羧酸 (140 mg, 0.29 mmol)和 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (70 mg, 0.29 mmol)溶于 DMF (4 mL)中，加入 HATU (144 mg, 0.38 mmol)和 DIEA (155 mg, 1.2 mmol)，反应液室温搅拌过夜。反应液加水 (40 mL)稀释，用乙酸乙酯 (40 mL x 4)萃取，有机相经饱和食盐水洗，无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (EA)纯化得到 4-(2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)-*N*-甲基环己烷-1-羧酰氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=714.8.

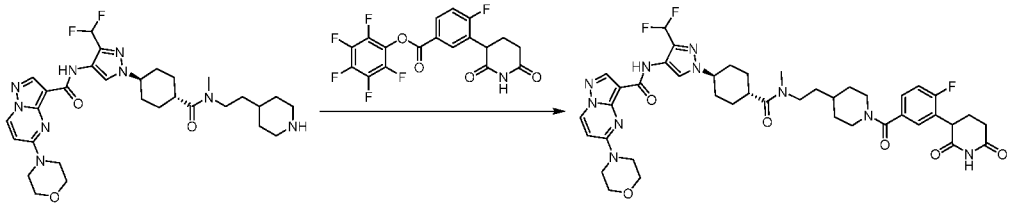
步骤 4：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(甲基(2-(哌啶-4-基)乙基)氨甲酰基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 4-(2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)-*N*-甲基环己烷-1-羧酰氨基)乙基)哌啶-1-羧酸叔丁酯 (130 mg, 0.18 mmol)溶于二氯甲烷 (3 mL)中，加入三氟乙酸 (0.3 mL)并室温搅拌 1 小时。反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(甲基(2-(哌啶-4-基)乙基)氨甲酰基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=614.2.

步骤 5： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((2-(1-(3-(2,6-二氧代吡啶-3-基)-4-氟苯甲酰 l)哌啶-4-基)乙基)(甲基)氨甲酰基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

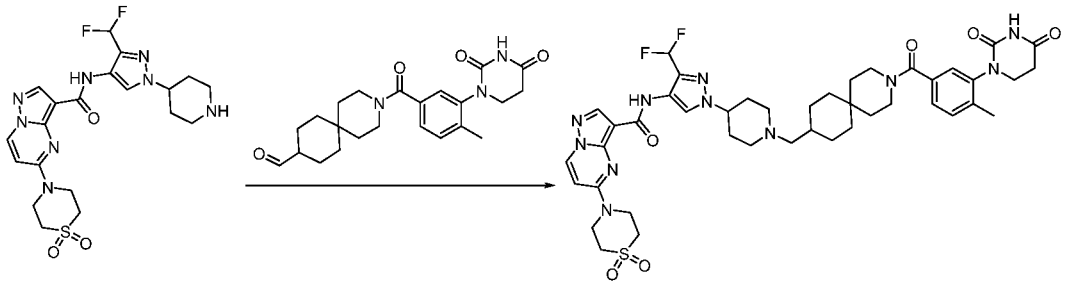


将*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(甲基(2-(哌啶-4-基)乙基)氨甲酰基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (130 mg, 0.18 mmol)和3-(2,6-二氧代基哌啶-3-基)-4-氟苯甲酸五氟苯基酯 (75.3 mg, 0.18 mmol)溶于DMSO (2 mL)中，加入DIEA (93 mg, 0.72 mmol)，反应液室温搅拌3小时。反应液中加水 (20 mL)稀释，乙酸乙酯 (20 mL x 3)萃取，有机相用饱和食盐水 (30 mL)洗涤，无水硫酸钠干燥，过滤，减压浓缩，粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5%~ 95%)纯化得到*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((2-(1-(3-(2,6-二氧代吡啶-3-基)-4-氟苯甲酰l)哌啶-4-基)乙基)(甲基)氨甲酰基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=847.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.29 (s, 1H), 7.40 – 7.33 (m, 2H), 7.31 – 7.23 (m, 1H), 7.23-6.96 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.52-4.20 (m, 2H), 4.12 (dd, *J* = 12.7, 4.9 Hz, 1H), 3.88-3.66 (m, 8H), 3.62-3.48 (m, 1H), 3.433.34 (m, 1H), 3.01 (s, 3H), 2.82 – 2.62 (m, 4H), 2.60-2.54 (m, 1H), 2.29-2.17 (m, 1H), 2.08-1.98 (m, 3H), 1.95 – 1.67 (m, 6H), 1.66 – 1.35 (m, 6H), 1.21 – 1.02 (m, 2H).

实施例 55： *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-)-5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



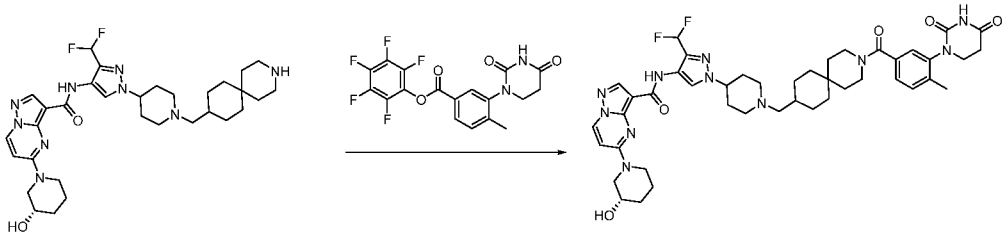
将*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (60 mg, 0.1 mmol)和3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-

甲醛 (41 mg, 0.1 mmol)用四氢呋喃 (2 mL)溶解，搅拌下加入三乙酰氧基硼氢化钠 (84 mg, 0.4 mmol)并室温搅拌3小时。反应液中加水 (50 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5%~ 95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-)-5-(1,1-二氧代硫代吗啡啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=890.1

^{1}H NMR (400 MHz, CD_3OD-d_4) δ 8.64 (d, J = 7.9 Hz, 1H), 8.37 (d, *J* = 5.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.36-7.29 (m, 2H), 7.06-6.77 (m, 2H), 4.60-4.52 (m, 2H), 4.42-4.34 (m, 4H), 4.25-4.14 (m, 1H), 3.92-3.82 (m, 1H), 3.77-3.62 (m, 3H), 3.49-3.40 (m, 2H), 3.30-3.22 (m, 4H), 3.06-3.00 (m, 2H), 2.92-2.82 (m, 2H), 2.31 (s, 3H), 2.28-2.22 (m, 2H), 2.20-2.06 (m, 6H), 1.82-1.72 (m, 2H), 1.70-1.63 (m, 2H), 1.55-1.39 (m, 2H), 1.33-1.25 (m, 2H), 1.24-1.12 (m, 3H).

实施例 56： (*S*)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺



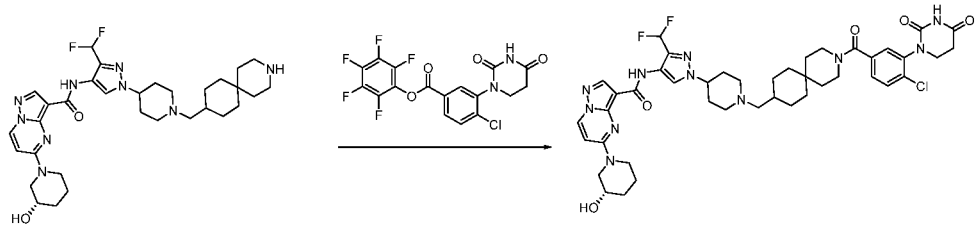
将 (*S*)-*N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 粗品, 0.11 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酸五氟苯酯 (46 mg, 0.11 mmol)和 *N*,*N*-二异丙基乙胺 (142 mg, 1.1 mmol)，室温搅拌过夜。反应液中加水 (50 mL)，过滤，滤饼经 Pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5%~ 95%)纯化得到 (*S*)-*N*-(3-(二氟甲基)-1-(1-((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=856.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.38 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.37-7.29 (m, 2H), 7.26-6.96 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J* = 2.0 Hz, 1H), 4.26-4.14 (m, 1H), 4.00-3.75 (m, 3H), 3.70-3.39 (m, 6H), 3.30-3.24 (m, 2H), 2.93-2.64 (m, 4H), 2.21 (s, 3H), 2.18-2.10 (m, 2H), 2.06-1.65 (m, 10H), 1.61-1.22 (m, 9H), 1.16-0.95 (m, 4H).

实施例 57： (*S*)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-

9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺



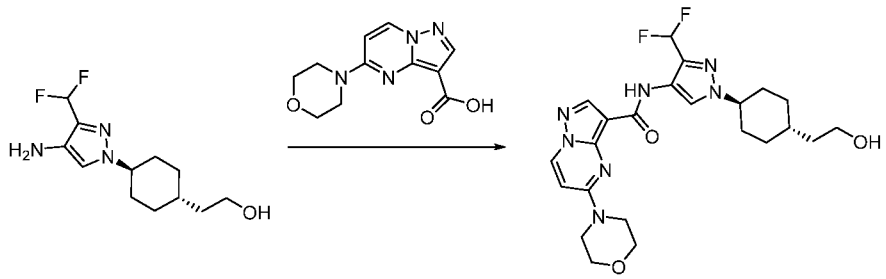
将 (*S*)-*N*-(1-(1-((3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 粗品, 0.11 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 perfluorophenyl 4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯酯 (48 mg, 0.11 mmol)和 *N*,*N*-二异丙基乙胺 (142 mg, 1.1 mmol)，室温下搅拌过夜。反应液中加水 (30 mL)，过滤，滤饼经 Pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5% ~ 95%)纯化得到 (*S*)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(3-羟基哌啶-1-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=876.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.38 (s, 1H), 8.72 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.26-6.97 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.25-4.15 (m, 1H), 3.97-3.40 (m, 9H), 3.30-3.18 (m, 2H), 2.93-2.85 (m, 2H), 2.78-2.72 (m, 2H), 2.20-2.10 (m, 2H), 2.05-1.65 (m, 10H), 1.60-1.31 (m, 9H), 1.20-0.94 (m, 4H).

实施例 58：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-羟基乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

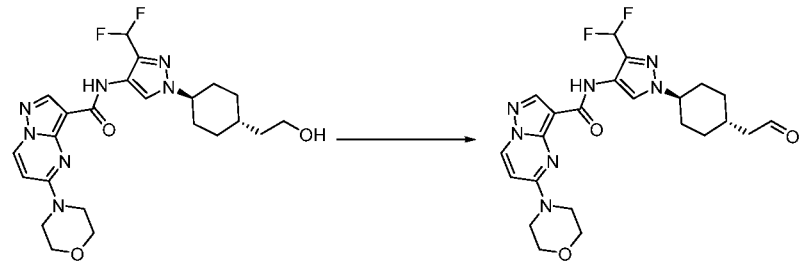


2-((1*R*,4*R*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)环己基)乙基-1-醇 (70 mg, 0.27 mmol)和5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酸 (74 mg, 0.30 mmol)用DMF (10 mL)溶解，搅拌下加入*N*,*N*-二异丙基乙胺 (104 mg, 0.81 mmol)和Py-BOP (210 mg, 0.40 mmol)，反应液加热至60 ℃搅拌过夜。反应液中加水 (100 mL)，乙酸乙酯 (30 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓

缩，粗品经 p-TLC (甲醇:二氯甲烷=1:9)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-羟基乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=490.2.

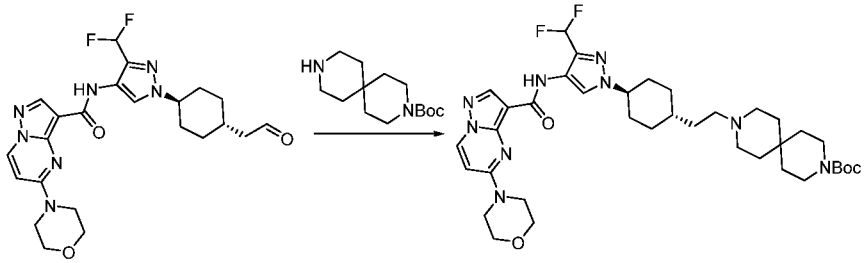
步骤 2：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-氧代乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-羟基乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (70 mg, 0.14 mmol)用二氯甲烷 (5 mL)溶解，加入Dess-Martin试剂 (118 mg, 0.28 mmol)，室温下搅拌 1小时。反应液中加水 (20 mL)，用二氯甲烷 (20 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品经p-TLC (甲醇:二氯甲烷=1:9)纯化得到*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-氧代乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=488.1.

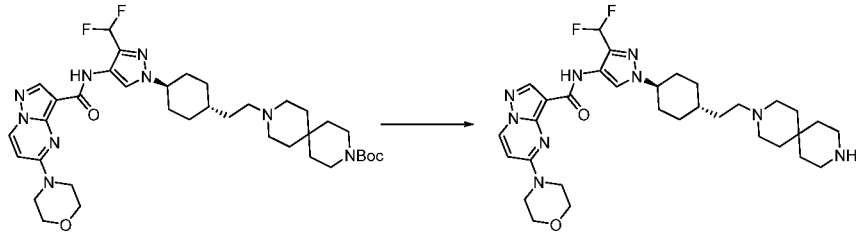
步骤 3： 9-(2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)乙基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-氧代乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (50 mg, 0.10 mmol)和3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (30 mg, 0.12 mmol)用四氢呋喃（10 mL）溶解，搅拌下加入三乙酰氧基硼氢化钠 (64 mg, 0.30 mmol)，室温搅拌2小时。反应液中加水 (20 mL)，用二氯甲烷 (20 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品经 p-TLC (甲醇:二氯甲烷=1:9)纯化得到9-(2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)乙基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=726.6.

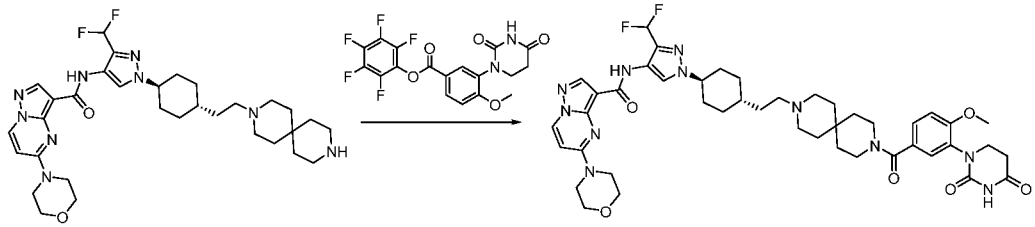
步骤 4：*N*-(1-((1*R*,4*R*)-4-(2-(3,9-二氮杂螺[5.5]十一烷-3-基)乙基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



9-(2-((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)乙基)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (60 mg, 0.08 mmol)用二氯甲烷 (3 mL)溶解，三氟乙酸 (1 mL)加入，室温搅拌 1 小时。反应液直接减压浓缩得到*N*-(1-((1*R*,4*R*)-4-(2-(3,9-二氮杂螺[5.5]十一烷-3-基)乙基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=626.4.

步骤 5：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



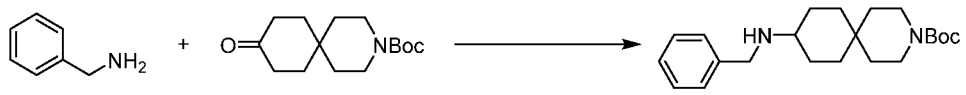
将 *N*-(1-((1*R*,4*R*)-4-(2-(3,9-二氮杂螺[5.5]十一烷-3-基)乙基)环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (60 mg, 粗品, 0.08 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入 3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯酯 (39 mg, 0.09 mmol)和 *N*,*N*-二异丙基乙胺 (103 mg, 0.8 mmol)，室温搅拌 2 小时。反应液中加水 (30 mL)，过滤，滤饼经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3 水溶液, 5% ~ 95%)纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(2-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)乙基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=872.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.40 (s, 1H), 8.82 (d, *J* = 7.9 Hz, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.25 – 6.95 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.30-4.20 (m, 1H), 3.84 (s, 3H), 3.82-3.70 (m, 8H), 3.62-3.30 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.36 – 2.22 (m, 6H), 2.10-1.98 (m, 2H), 1.87-1.73 (m, 2H), 1.70-1.30 (m, 15H).

实施例 59： *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

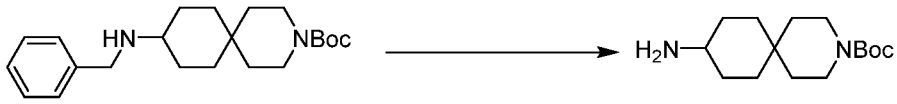
步骤 1： 9-(苄氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



苄胺 (0.267 g, 2.5 mmol)和9-氧代-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (0.66 g, 2.5 mmol)用THF (10 mL)溶解，然后加入$NaBH(OAc)_3$ (1.58 g, 7.48 mmol)，反应液室温搅拌2 h。反应液中加水 (20 mL)稀释，乙酸乙酯 (20 mL x 3)萃取，合并有机相，用饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:24)纯化得到 9-(苄氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=359.3.

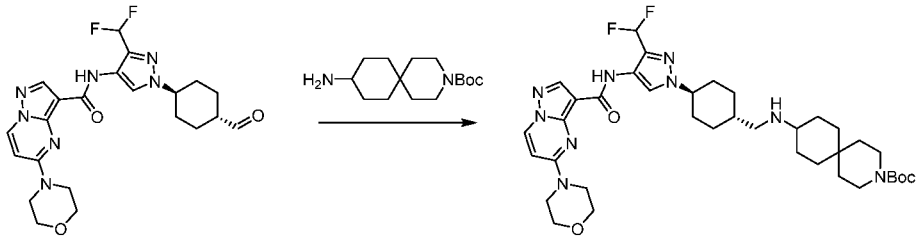
步骤 2：9-氨基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



将9-(苄氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (330 mg, 0.92 mmol)，Pd/C (100 mg)和 $Pd(OH)_2$ (100 mg)加入到甲醇 (10 mL)中，氢气置换3次，室温搅拌2小时。过滤，减压浓缩得到 9-氨基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$= 269.2.

步骤 3：9-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备

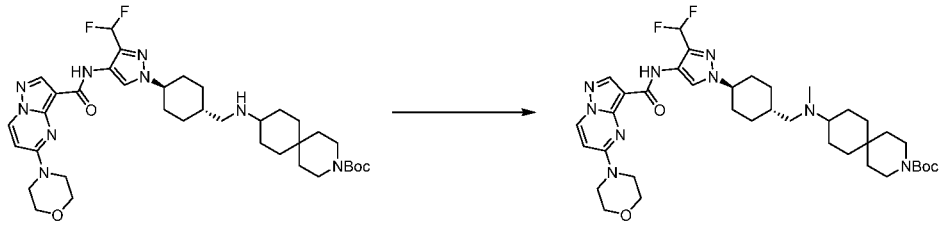


N-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(醛基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (100 mg, 0.21 mmol)和 9-氨基-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (70 mg, 0.23 mmol)用THF (4 mL)溶解，加入$NaBH(OAc)_3$ (135 mg, 0.63 mmol)并室温搅拌2小时。反应液用水 (20 mL)稀释，乙酸乙酯 (20 mL x 3)萃取，合并有机相，饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:24)纯化得到 9-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨

基)-1*H*-吡唑-1-基)环己基)甲基)氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=726.5.

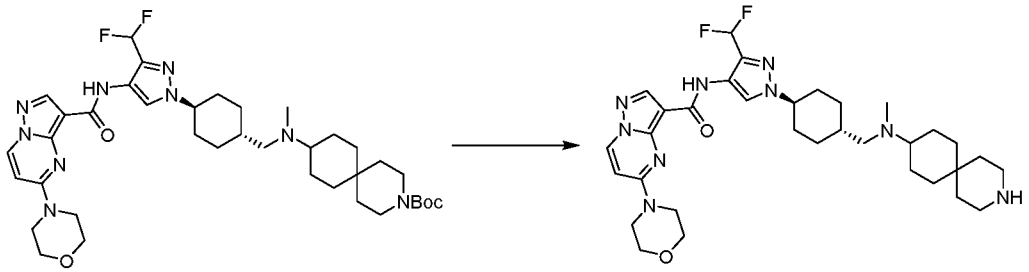
步骤 4： 9-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备



向9-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (100 mg, 0.13 mmol)和甲醛水溶液 (37%, 1 mL)的THF (10 mL)中加入$NaBH(OAc)_3$ (100 mg, 0.47 mmol)，加热到60 °C搅拌2 h。反应液用水 (20 mL)稀释，乙酸乙酯 (20 mL x 3)萃取，合并有机相，饱和食盐水洗涤，无水Na_2SO_4干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:19)纯化得到 9-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$= 740.4.

步骤 5：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(3-氮杂螺[5.5]十一烷-9-基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

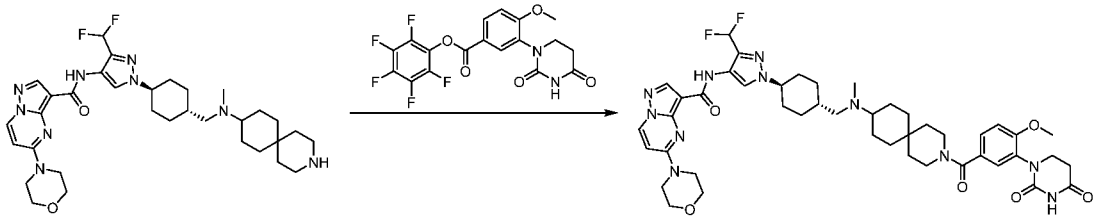


9-((((1*R*,4*R*)-4-(3-(二氟甲基)-4-(5-吗啡啉吡唑并[1,5-a]嘧啶-3-羧酰氨基)-1*H*-吡唑-1-基)环己基)甲基)(甲基)氨基)-3-氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (0.10 g, 0.13 mmol)用 DCM (5 mL)溶解，TFA (1 mL)加入并室温搅拌 2 小时，反应液直接减压浓缩得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(3-氮杂螺[5.5]十一烷-9-基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺，无须纯化直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$= 640.4.

步骤 6：*N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

的制备



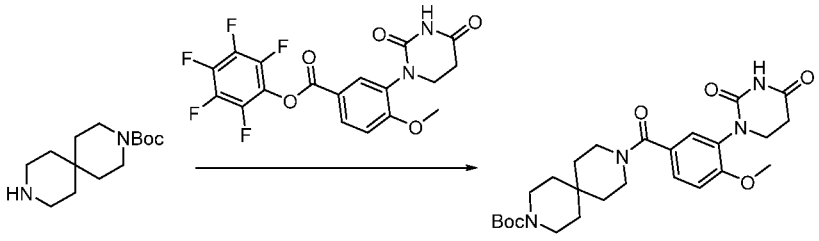
N-(3-(二氟甲基)-1-((1*R*,4*R*)-4-((甲基(3-氮杂螺[5.5]十一烷-9-基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (70 mg, 0.1 mmol)和3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯基酯 (51 mg, 0.12 mmol)用DMSO (1 mL)溶解，加入DIEA (130 mg, 1 mmol)并室温搅拌2 h。反应液用水 (10 mL)稀释，过滤，滤饼用Prep-HPLC纯化得到 *N*-(3-(二氟甲基)-1-((1*R*,4*R*)-4-(((3-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)(甲基)氨基)甲基)环己基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+ = 886.4$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.39 (s, 1H), 8.82 (d, J = 7.9 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.32 (s, 1H), 7.22-6.95 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 4.22-4.12 (m, 1H), 3.84 (s, 3H), 3.81-3.75 (m, 4H), 3.74-3.70 (m, 4H), 3.62- 3.55 (m, 5H), 2.68 (t, J = 6.4 Hz, 2H), 2.37-2.26 (m, 2H), 2.25-2.23 (m, 2H), 2.21 (s, 3H), 2.06-2.00 (m, 2H), 1.95-1.85 (m, 2H), 1.78-1.70 (m, 4H), 1.56-1.24 (m, 9H), 1.14-0.97 (m, 4H).

实施例 60：*N*-(3-(二氟甲基)-1-(1-(3-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

步骤 1：9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯的制备

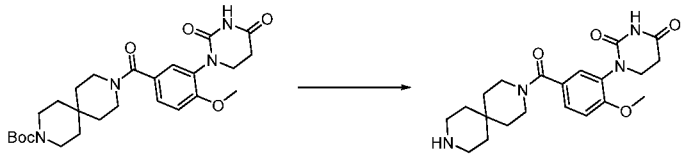


将3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯 (200 mg, 0.79 mmol)用二甲亚砜 (4 mL)溶解，搅拌下加入3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酸五氟苯基酯 (340 mg, 0.79 mmol)和 *N*,*N*-二异丙基乙胺 (413 mg, 3.24 mmol)，反应液室温搅拌3小时。反应液加水 (40 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=9:1)纯化得到 9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂

螺[5.5]十一烷-3-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=501.2.

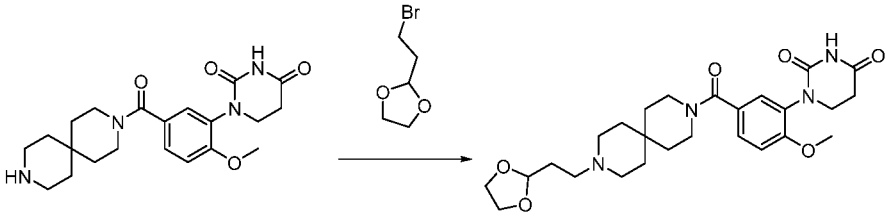
步骤2：1-(2-甲氧基-5-(3,9-氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-羧酸叔丁酯(230 mg, 0.46 mmol)用二氯甲烷 (3 mL)溶解，加入三氟乙酸 (0.3 mL)并室温搅拌 1小时。反应液直接减压浓缩得到 1-(2-甲氧基-5-(3,9-氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=401.1.

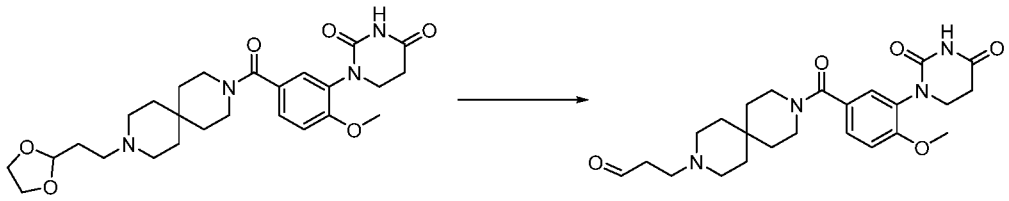
步骤3：1-(5-(9-(2-(1,3-二氧戊烷-2-基)乙基)-3,9-二氮杂螺[5.5]十一烷-3-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将 1-(2-甲氧基-5-(3,9-氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (180 mg, 0.45 mmol)和 2-(2-溴乙基)-1,3-二氧戊烷 (121 mg, 0.67 mmol)用 DMF (5 mL)溶解，搅拌下加入 K_2CO_3 (186 mg,1.3 mmol)，反应液加热至 80 ℃并搅拌 12 小时。反应液加水 (80 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (80 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析(甲醇:二氯甲烷=1:7)纯化得到 1-(5-(9-(2-(1,3-二氧戊烷-2-基)乙基)-3,9-二氮杂螺[5.5]十一烷-3-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=501.7.

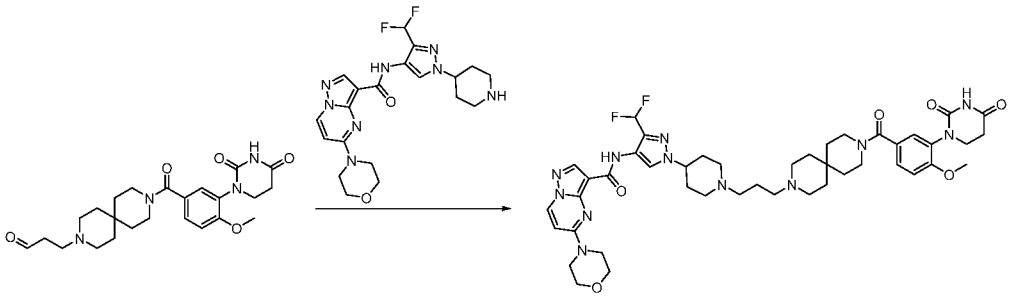
步骤 4：3-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丙醛的制备



1-(5-(9-(2-(1,3-二氧戊烷-2-基)乙基)-3,9-二氮杂螺[5.5]十一烷-3-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (200 mg, 0.5 mmol)用丙酮 (5 mL)溶解，加入盐酸 (2 mol/L, 10 mL)，室温下搅拌6小时。反应液用碳酸氢钠调节反应液pH=8，乙酸乙酯 (50 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，得到 3-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丙醛，无需纯化直接用于下一步反应。

LC-MS: (ESI, m/z): $[M+H]^+$=457.7.

步骤5：*N*-(3-(二氟甲基)-1-(1-(3-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



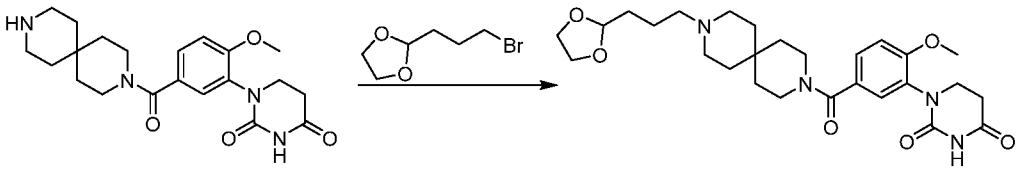
将3-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丙醛 (70 mg, 0.15 mmol)和*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (67 mg, 0.15 mmol)用二氯乙烷 (5 mL)溶解，搅拌下加入三乙酰氧基硼氢化钠 (126 mg, 0.6 mmol)，反应液室温搅拌3小时。反应液加水 (50 mL)稀释，用二氯甲烷 (60 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品经 pre-HPLC (CH_3CN/0.08% NH_4HCO_3水溶液, 5%~ 95%)纯化得到 *N*-(3-(二氟甲基)-1-(1-(3-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丙基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=887.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.26-6.97 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.25-4.15 (m, 1H), 3.84 (s, 3H), 3.82-3.70 (m, 8H), 3.62-3.33 (m, 6H), 2.95-2.89 (m, 2H), 2.72-2.62 (m, 2H), 2.36-2.23 (m, 8H), 2.05-1.80 (m, 6H), 1.60-1.24 (m, 10H).

实施例 61：*N*-(3-(二氟甲基)-1-(1-(4-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丁基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

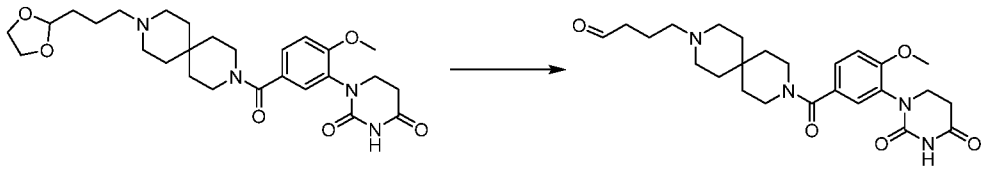
步骤1：1-(5-(9-(3-(1,3-二氧戊烷-2-基)丙基)-3,9-二氮杂螺[5.5]十一烷-3-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮的制备



将 1-(2-甲氧基-5-(3,9-氮杂螺[5.5]十一烷-3-羰基)苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (151 mg, 0.377 mmol),和 2-(3-溴丙基)-1,3-二氧戊烷 (110.5 mg, 0.566 mmol)加入到 乙腈 (5 mL)中，加入K_2CO_3 (518.3 mg, 1.132 mmol)，反应液加热至80 ℃搅拌16 h。反应液中加入水 (40 mL)稀释，用乙酸乙酯 (30 mL x 4)萃取，饱和食盐水洗，无水硫酸钠干燥，减压浓缩，通过正相柱层析 (MeOH:DCM = 1:7)纯化得到 1-(5-(9-(3-(1,3-二氧戊烷-2-基)丙基)-3,9-二氮杂螺[5.5]十一烷-3-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=515.3.

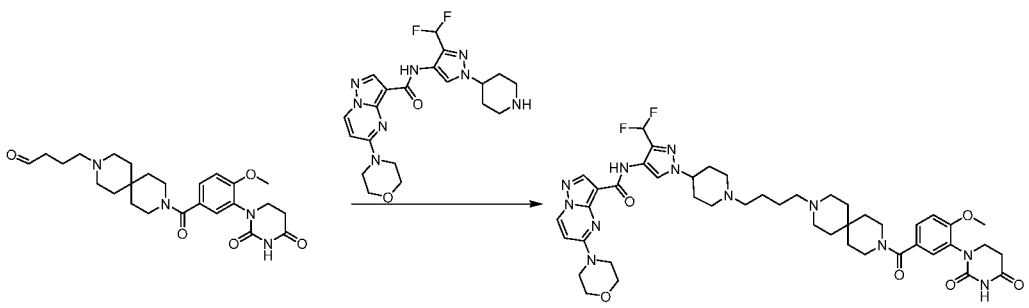
步骤2：4-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)正丁醛的制备



将 1-(5-(9-(3-(1,3-二氧戊烷-2-基)丙基)-3,9-二氮杂螺[5.5]十一烷-3-羰基)-2-甲氧基苯基)二氢嘧啶-2,4(1*H*,3*H*)-二酮 (80 mg, 0.16 mmol)溶于 DCM (2 mL)中，加入 TFA (0.5 mL)并室温搅拌过夜。反应液中加入 DCE (10 mL)和 DIEA (1 mL)，直接室温减压浓缩 10 min，得到 4-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)正丁醛，直接用于下一步。

LC-MS: (ESI, m/z): $[M+H]^+$=471.5.

步骤 3：*N*-(3-(二氟甲基)-1-(1-(4-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丁基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



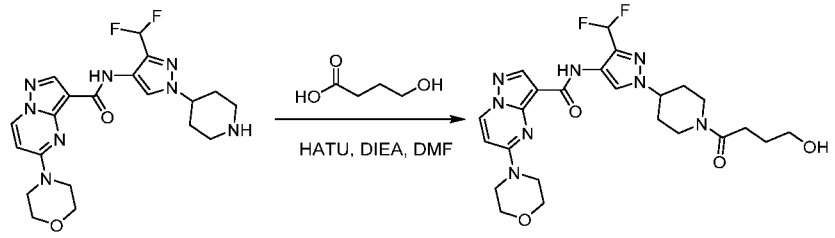
向 4-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)正丁醛(粗品，DCE 溶液)加入 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (70 mg, 0.15 mmol)，室温搅拌 0.5 小时，然后加入 STAB (97 mg, 0.46 mmol)并室温搅拌 2 h。反应液中加水 (30 mL)稀释，用乙酸乙酯 (30 mL x 3)萃取，有机相用饱和食盐水 (50 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用反相制备纯化得到*N*-(3-(二氟甲基)-1-(1-(4-(9-(3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)-4-甲氧基苯甲酰)-3,9-二氮杂螺[5.5]十一烷-3-基)丁基)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=901.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.41 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.28 (s, 1H), 8.15 (s, 1H), 7.38 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.33 (d, *J* = 1.9 Hz, 1H), 7.24 – 6.95 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.33-4.23 (m, 1H), 3.85 (s, 3H), 3.83-3.75 (m, 4H), 3.74-3.68 (m, 4H), 3.64-3.52 (m, 6H), 3.07-2.95 (m, 6H), 2.95-2.86 (m, 2H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.18 (t, *J* = 11.2 Hz, 2H), 2.05-1.93 (m, 4H), 1.73-1.57 (m, 6H), 1.56-1.42 (m, 6H).

实施例 62：*N*-(3-(二氟甲基)-1-(1-(4-(4-(3-(2,6-二氧代哌啶-3-基)-4-氟苯甲酰)哌嗪-1-基)丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺

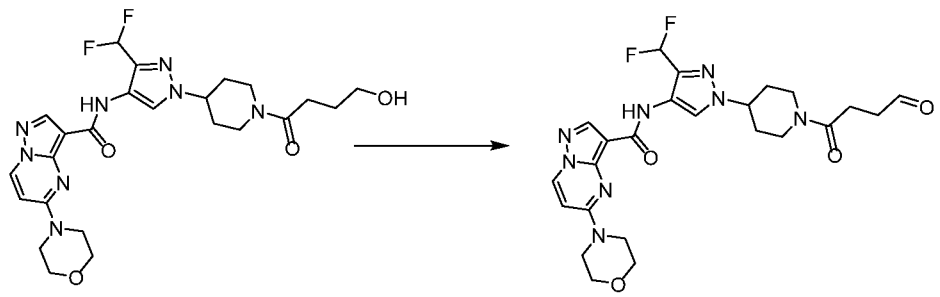
步骤 1：*N*-(3-(二氟甲基)-1-(1-(4-羟基丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 *N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (160 mg, 0.35 mmol)，4-羟基丁酸 (36 mg, 0.35 mmol)和 HATU (130 mg, 0.42 mmol)溶于 DMF (5 mL)中，然后加入 DIEA (135 mg, 1.35 mmol)，反应液加热至 90 ℃搅拌 16 小时。反应液中加入水 (50 mL)，乙酸乙酯萃取 (30 mL x 3)，合并有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经正相柱层析纯化得到 *N*-(3-(二氟甲基)-1-(1-(4-羟基丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=533.4.

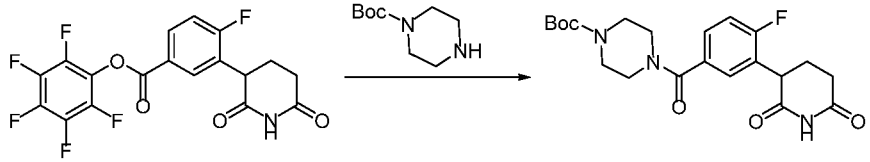
步骤2： *N*-(3-(二氟甲基)-1-(1-(4-氧代丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将*N*-(3-(二氟甲基)-1-(1-(4-羟基丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 ((26 mg, 0.05 mmol)溶于DCM (2 mL)中，加入DMP (42 mg, 0.10 mmol)并室温搅拌2小时。过滤，滤饼用THF洗涤 (10 mL x 3)，滤液减压浓缩得到 *N*-(3-(二氟甲基)-1-(1-(4-氧代丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$ = 531.5.

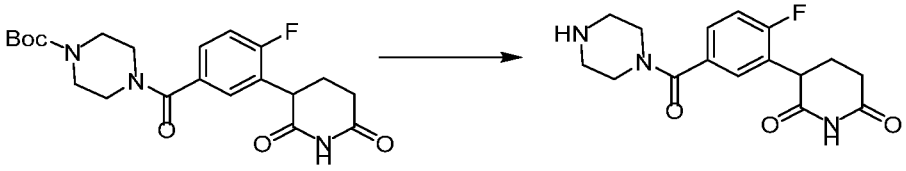
步骤3： 4-(3-(2,6-氧代哌啶-3-基)-4-氟苯甲酰)哌嗪-1-羧酸叔丁酯的制备



将3-(2,6-二氧代基哌啶-3-基)-4-氟苯甲酸五氟苯基酯(56 mg, 0.30 mmol)和 哌嗪-1-羧酸叔丁酯 (125 mg, 0.30 mmol)溶于DMSO (2 mL)中，加入DIEA (112 mg, 0.90 mmol)并室温搅拌2小时。反应液中加入水 (50 mL)，乙酸乙酯萃取 (30 mL x 3)，合并有机相并用饱和食盐水 (50 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经正相柱层析纯化得到 4-(3-(2,6-氧代哌啶-3-基)-4-氟苯甲酰)哌嗪-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M-Boc]^+$ = 320.2.

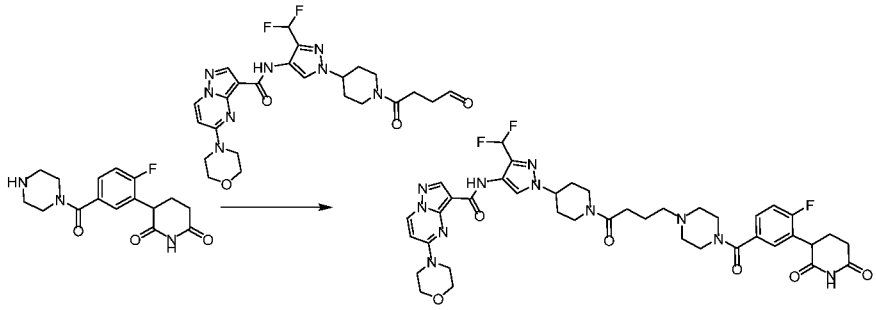
步骤4：3-(2-氟-5-(哌嗪-1-羰基)苯基)哌啶-2,6-二酮的制备



将4-(3-(2,6-氧代哌啶-3-基)-4-氟苯甲酰)哌嗪-1-羧酸叔丁酯 (80 mg, 0.19 mmol)溶于DCM (0.5 mL)中，加入TFA (0.1 mL)并室温搅拌1小时。反应液减压浓缩得到 3-(2-氟-5-(哌嗪-1-羰基)苯基)哌啶-2,6-二酮。

LC-MS: (ESI, m/z): $[M+H]^+$=320.2.

步骤5：*N*-(3-(二氟甲基)-1-(1-(4-(4-(3-(2,6-二氧代哌啶-3-基)-4-氟苯甲酰)哌嗪-1-基)丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺的制备

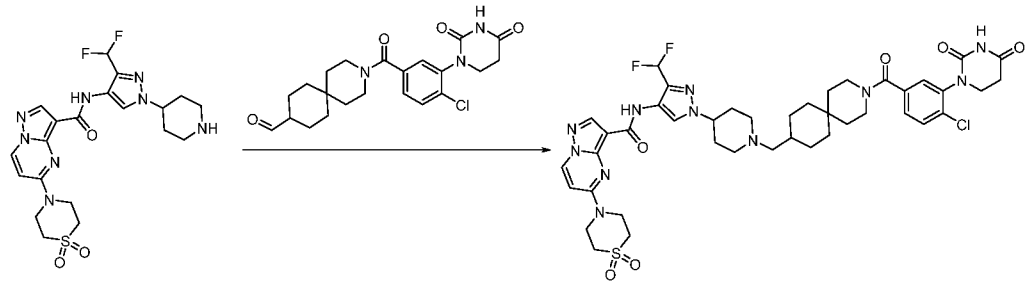


将*N*-(3-(二氟甲基)-1-(1-(4-氧代丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺 (55 mg, 0.10 mmol)和3-(2-氟-5-(哌嗪-1-羰基)苯基)哌啶-2,6-二酮 (32 mg, 0.10 mmol)溶于DCE (2 mL)中，加入$NaBH(OAc)_3$ (63 mg, 0.30 mmol)并室温搅拌2小时。反应液中加入水 (20 mL)，乙酸乙酯萃取 (20 mL x 3)，合并有机相并用饱和食盐水 (30 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经Prep-HPLC纯化得到 *N*-(3-(二氟甲基)-1-(1-(4-(4-(3-(2,6-二氧代哌啶-3-基)-4-氟苯甲酰)哌嗪-1-基)丁酰)哌啶-4-基)-1*H*-吡唑-4-基)-5-吗啡啉吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=834.1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.40 (s, 1H), 8.82 (d, J = 4.3 Hz, 1H), 8.42 (s, 1H), 8.29 (s, 1H), 7.37 (s, 2H), 7.29-6.87 (m, 3H), 4.55-4.49 (m, 2H), 4.14-4.07 (m, 1H), 4.02-3.95 (m, 1H), 3.89-3.65 (m, 10H), 3.20-3.13 (m, 2H), 2.88-2.53 (m, 4H), 2.46-2.16 (m, 9H), 2.10-1.95 (m, 3H), 1.90-1.83 (m, 1H), 1.83-1.56 (m, 3H).

实施例 63：*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺



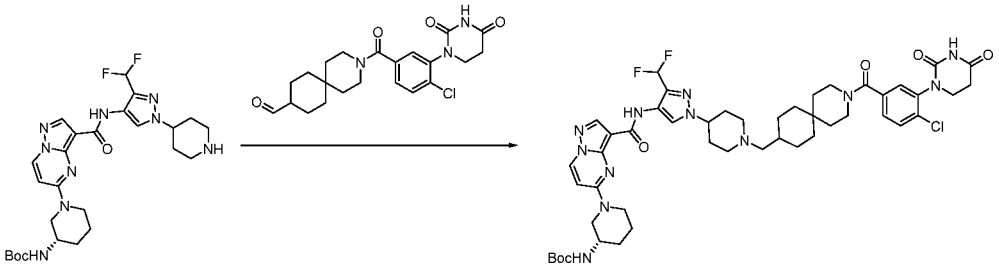
将*N*-(3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (80 mg, 0.16 mmol)和 3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛 (70 mg, 0.16 mmol)溶于THF (3 mL)中，加入三乙酰氧基硼氢化钠 (102 mg, 0.48 mmol) 并室温搅拌16小时。反应液中加入水 (50 mL)，EA (30 mL x 3) 萃取，有机相用饱和食盐水 (30 mL)洗，无水硫酸钠干燥，过滤，减压浓缩，粗品经 Prep-HPLC分离纯化得到 *N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)-5-(1,1-二氧代硫代吗啉基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=910.4.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.25 (s, 1H), 8.92 (d, J = 7.9 Hz, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.25 – 6.97 (m, 2H), 4.31-4.20 (m, 5H), 3.77-3.70 (m, 1H), 3.67-3.57 (m, 3H), 3.33-3.23 (m, 5H), 2.90 (d, J = 9.3 Hz, 2H), 2.75-2.67 (m, 3H), 2.18-2.11 (m, 2H), 2.07-1.87 (m, 6H), 1.73-1.65 (m, 2H), 1.62-1.23 (m, 7H), 1.15-0.92 (m, 4H).

实施例 64：(*S*)-5-(3-氨基哌啶-1-基)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

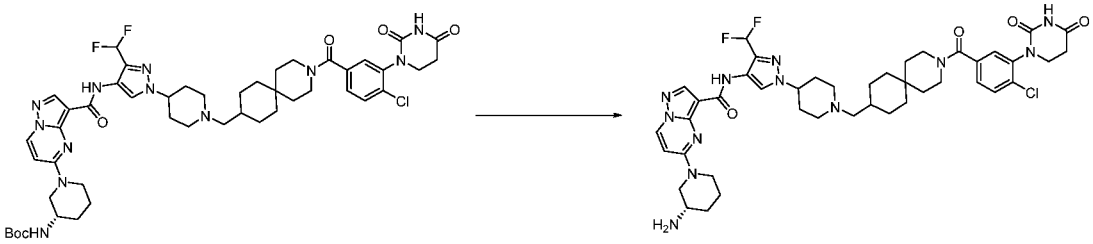
步骤 1：(*S*)-(1-(3-((1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯的制备



(*S*)-(1-(3-((3-(二氟甲基)-1-(哌啶-4-基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)氨基甲酸叔丁酯 (70 mg, 0.12 mmol)和3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-甲醛 (70 mg, 0.15 mmol)用THF (2 mL)溶解，加入$NaBH(OAc)_3$ (56 mg, 0.37 mmol)，反应液室温搅拌2 h。反应液用水 (20 mL)稀释，乙酸乙酯 (20 mL x 3)，合并有机相，用饱和食盐水洗涤，无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (甲醇:二氯甲烷=1:24)纯化得到 (*S*)-(1-(3-((1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=975.4.

步骤 2：(*S*)-5-(3-氨基哌啶-1-基)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



将 (*S*)-(1-(3-((1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲

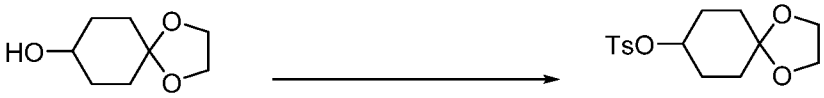
基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)氨甲酰基)吡唑并[1,5-a]嘧啶-5-基)哌啶-3-基)羧酸叔丁酯 (30 mg, 0.03 mmol)用DCM (5 mL)溶解，加入TFA (1 mL)，反应液室温搅拌1小时。反应液直接减压浓缩，粗品使用Prep-HPLC纯化得到 (*S*)-5-(3-氨基哌啶-1-基)-*N*-(1-(1-((3-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)-3-氮杂螺[5.5]十一烷-9-基)甲基)哌啶-4-基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=875.3.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 7.9 Hz, 1H), 8.37 (s, 1H), 8.34-8.30 (m, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.26-6.95 (m, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 4.23-4.13 (m, 2H), 3.82-3.74 (m, 1H), 3.70-3.40 (m, 7H), 3.30-3.10 (m, 3H), 2.97-2.92 (m, 2H), 2.77-2.73 (m, 2H), 2.25-1.75 (m, 11H), 1.75- 1.15 (m, 12H), 1.15-0.96 (m, 4H).

实施例 65： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*S*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)-4-羟基环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺

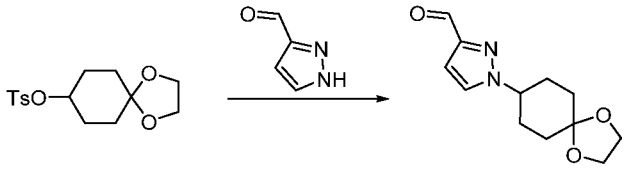
步骤 1：1,4-二氧杂螺[4.5]癸烷-8-基 4-甲基苯磺酸盐的制备



1,4-二氧杂螺[4.5]癸烷-8-醇 (25.7 g, 163 mmol)用二氯甲烷 (100 mL)溶解，搅拌下加入TsCl (46.6 g, 244 mmol)，TEA (49.3 g, 488 mmol)和DMAP (4.0 g, 33.0 mmol)。反应液室温搅拌过夜。减压浓缩，加水 (200 mL)，用乙酸乙酯 (100 mL x 3)萃取，有机相用饱和食盐水 (200 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=3:7)纯化得到 1,4-二氧杂螺[4.5]癸烷-8-基 4-甲基苯磺酸盐。

LC-MS: (ESI, m/z): $[M+Na]^+$=335.1.

步骤2：1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑-3-甲醛的制备

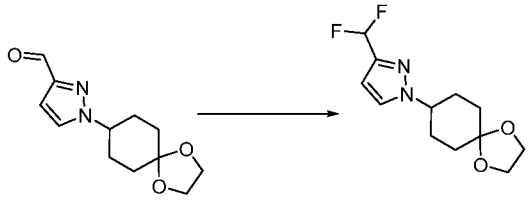


1,4-二氧杂螺[4.5]癸烷-8-基 4-甲基苯磺酸盐 (48.5 g, 156.25 mmol)和1*H*-吡唑-3-甲醛 (12.5 g, 130.21 mmol)用DMF (200 mL)溶解，搅拌下加入碳酸铯 (127.0 g, 390.63 mmol)和 KI (25.9 g, 156.25 mmol)，反应液加热至50 ℃搅拌过夜。反应液用水 (2000 mL)稀释，乙酸乙酯 (200 mL x 4)萃取，有机相用饱和食盐水 (300 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=1:4)纯化得到 1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑-3-甲醛。

LC-MS: (ESI, m/z): $[M+H]^+$=237.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.99 (d, J = 2.3 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 4.49 – 4.39 (m, 1H), 3.96 – 3.86 (m, 4H), 2.08 – 1.99 (m, 4H), 1.84 – 1.75 (m, 2H), 1.75 – 1.64 (m, 2H).

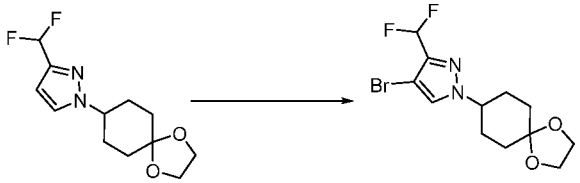
步骤 3：3-(二氟甲基)-1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑的制备



1-(1,4-氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑-3-甲醛 (13.3 g, 56.36 mmol)用无水二氯甲烷 (50 mL)溶解，在0 ℃下缓慢加入DAST (54.4 g, 338.14 mmol)，反应液室温搅拌过夜。反应液中缓慢加入甲醇淬灭反应，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=3:7)纯化得到 3-(二氟甲基)-1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑。

LC-MS: (ESI, m/z): [M+H]$^+$=259.1.

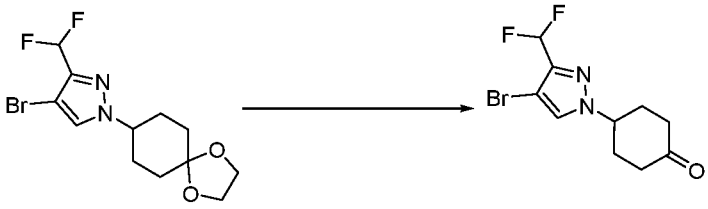
步骤4：4-溴-3-(二氟甲基)-1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑的制备



3-(二氟甲基)-1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑 (8.6 g, 33.33 mmol)用DMF (50 mL)溶解，搅拌下加入NBS (7.12 g, 40.00 mmol)，反应液加热到60 ℃搅拌2小时。反应液用水 (500 mL)稀释，乙酸乙酯 (100 mL x 4)萃取，有机相用饱和食盐水 (200 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=3:7)纯化得到 4-溴-3-(二氟甲基)-1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑。

LC-MS: (ESI, m/z): [M+H]$^+$=337.0.

步骤5：4-(4-溴-3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-酮的制备



4-溴-3-(二氟甲基)-1-(1,4-二氧杂螺[4.5]癸烷-8-基)-1*H*-吡唑 (10.4 g, 30.95 mmol)用丙酮 (40 mL)溶解，搅拌下加入HCl (2 mol/L, 60 mL)，反应液0 ℃下搅拌1 h。反应液用饱和碳酸氢钠溶液调至弱碱性，乙酸乙酯 (100 mL x 4)萃取，有机相用饱和食盐水 (200 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=1:4)纯化得到 4-(4-溴-3-(二氟甲基)-1*H*-吡唑-1-

基)环己烷-1-酮。

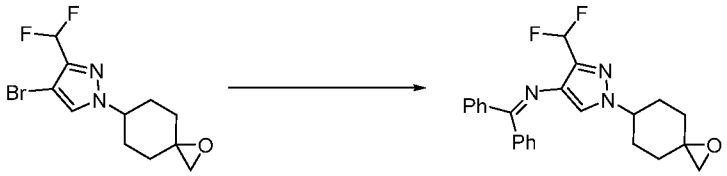
LC-MS: (ESI, m/z): $[M+H]^+$=293.0.

步骤6：4-溴-3-(二氟甲基)-1-(1-氧杂螺[2.5]辛烷-6-基)-1*H*-吡唑的制备

三甲基碘化亚砜 (1.36 g, 6.16 mmol)用二甲基亚砜 (20 mL)溶解，在0 ℃下加入NaH (246 mg, 10.27 mmol)，反应液室温搅拌1 h后，加入4-(4-溴-3-(二氟甲基)-1*H*-吡唑-1-基)环己烷-1-酮 (1.2 g, 5.14 mmol)，然后于室温搅拌过夜。反应液用水 (100 mL)稀释，乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (100 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (乙酸乙酯:石油醚=1:4)纯化得到 4-溴-3-(二氟甲基)-1-(1-氧杂螺[2.5]辛烷-6-基)-1*H*-吡唑。

LC-MS: (ESI, m/z): $[M+H]^+$=307.0.

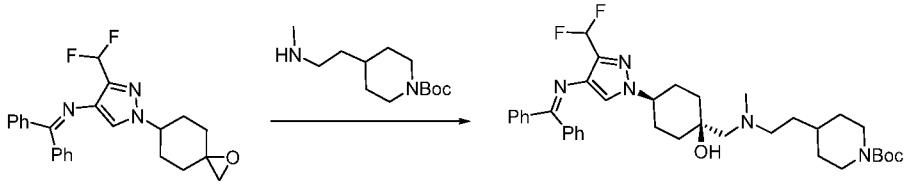
步骤7：*N*-(3-(二氟甲基)-1-(1-氧杂螺[2.5]辛烷-6-基)-1*H*-吡唑-4-基)-1,1-二苯甲胺的制备



将4-溴-3-(二氟甲基)-1-(1-氧杂螺[2.5]辛烷-6-基)-1*H*-吡唑 (800 mg, 3.104 mmol)和 $(Ph)_2NH$ (618 mg, 3.415 mmol)用1,4-dioxane二氧六环 (40 mL)溶解，搅拌下加入$Pd_2(dba)_3$ (568 mg, 0.62 mmol)，Xantphos (717 mg, 1.24 mmol)和 NaOt-Bu (894 mg, 9.31 mmol)，反应液在氮气保护下加热到90 ℃搅拌过夜。反应液直接减压浓缩，加水 (100 mL)稀释，用乙酸乙酯 (50 mL x 3)萃取，有机相用饱和食盐水 (300 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 （乙酸乙酯:石油醚=1:3)纯化得到 *N*-(3-(二氟甲基)-1-(1-氧杂螺[2.5]辛烷-6-基)-1*H*-吡唑-4-基)-1,1-二苯甲胺。

LC-MS: (ESI, m/z): $[M+H]^+$=408.1.

步骤8： 4-(2-((((1*S*,4*S*)-4-(3-(二氟甲基)-4-((二苯基亚甲基)氨基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备

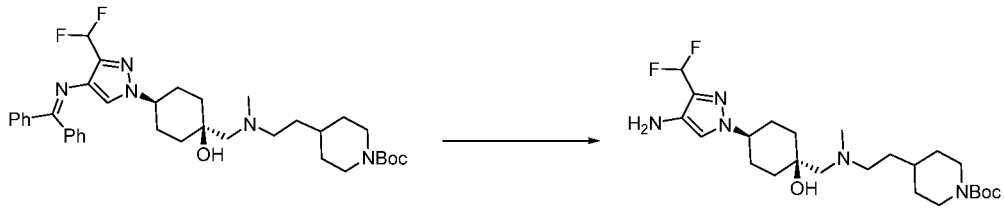


N-(3-(二氟甲基)-1-(1-氧杂螺[2.5]辛烷-6-基)-1*H*-吡唑-4-基)-1,1-二苯甲胺 (180 mg, 0.44 mmol)和 4-(2-(甲基氨基)乙基)哌啶-1-羧酸叔丁酯 (128 mg, 0.53 mmol)用乙醇 (4 mL)溶解，再加入水 (2 mL)，加

入K_2CO_3 (122 mg, 0.88 mmol)。反应液用微波110 ℃反应半个小时后，加水 (10 mL)，用甲醇/二氯甲烷溶液(V/V=1/9, 25 mL x 4)萃取，有机相用饱和食盐水 (30 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (二氯甲烷:甲醇=1:9)纯化得到 4-(2-((((1*S*,4*S*)-4-(3-(二氟甲基)-4-((二苯基亚甲基)氨基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=650.5.

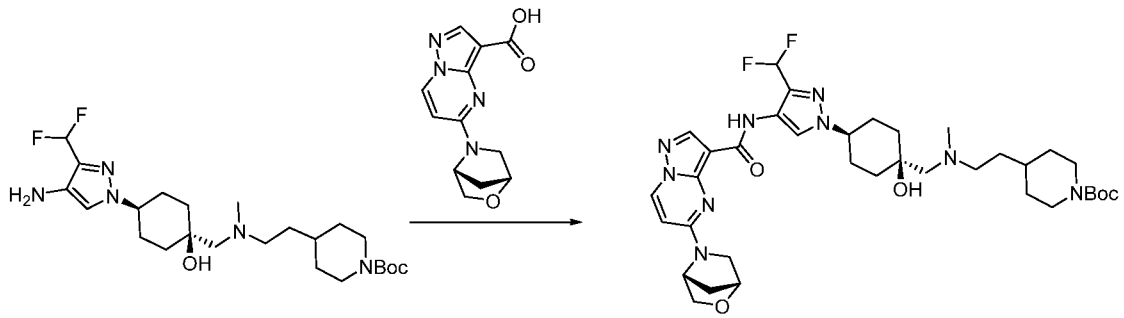
步骤9：4-(2-((((1*S*,4*S*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备



4-(2-((((1*S*,4*S*)-4-(3-(二氟甲基)-4-((二苯基亚甲基)氨基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (150 mg, 0.23 mmol)用四氢呋喃 (2 mL)溶解，加入HCl (2 mol/L, 1 mL)，反应液室温搅拌30分钟。反应液中加水 (10 mL)稀释，用乙酸乙酯 (25 mL x 2)萃取。水相用饱和碳酸氢钠溶液调至弱碱性，用甲醇/二氯甲烷混合溶液 (V/V=1/9， 25 mL x 3)萃取，有机相饱和食盐水 (30 mL)洗涤，经无水硫酸钠干燥，过滤，减压浓缩得到 4-(2-((((1*S*,4*S*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=486.2.

步骤10： 4-(2-((((1*S*,4*S*)-4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯的制备

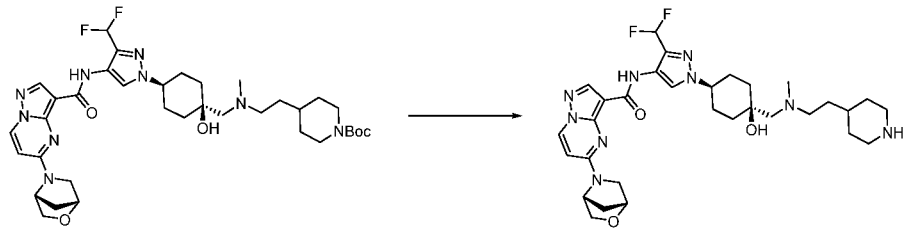


将 4-(2-((((1*S*,4*S*)-4-(4-氨基-3-(二氟甲基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (85 mg, 0.17 mmol)和 5-((1*R*,4*R*)-2-氧杂-5-氮杂双环[2.2.1]庚烷-5-基)吡唑[1,5-a]嘧啶-3-甲酸 (91 mg, 0.34 mmol)用 DMF (5 mL)溶解，搅拌下加入 *N*,*N*-二异丙基乙胺 (68 mg, 0.51 mmol)和 HATU (158 mg, 0.26 mmol)，反应液室温搅拌过夜。反应液用水 (50 mL)稀释，用甲醇/二氯甲烷混合溶液 (V/V=1/9, 25 mL x 3)萃取，有机相经无水硫酸钠干燥，过滤，减压浓缩，粗品使用柱层析 (二氯

甲烷:甲醇=1:9)纯化得到4-(2-((((1*S*,4*S*)-4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯。

LC-MS: (ESI, m/z): $[M+H]^+$=728.3.

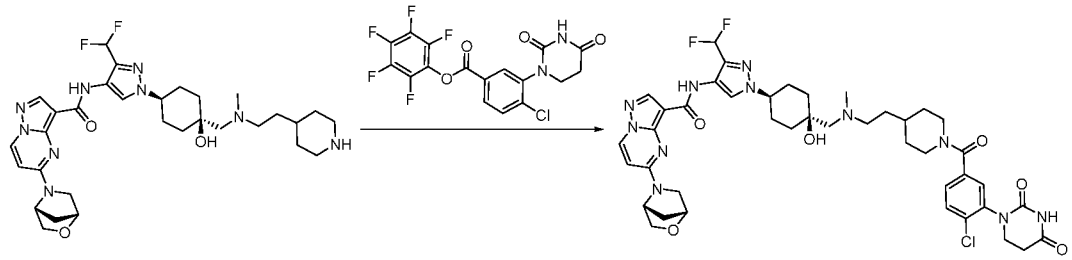
步骤 11：5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*S*,4*S*)-4-羟基-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



4-(2-((((1*S*,4*S*)-4-(4-(5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)吡唑并[1,5-a]嘧啶-3-羧氨基)-3-(二氟甲基)-1*H*-吡唑-1-基)-1-羟基环己基)甲基)(甲基)氨基)乙基)哌啶-1-羧酸叔丁酯 (120 mg, 0.16 mmol)用二氯甲烷 (2.5 mL)溶解，加入三氟乙酸 (0.5 mL)并室温搅拌 2小时。反应液直接减压浓缩得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*S*,4*S*)-4-羟基-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺，无需纯化直接用于下一步反应 。

LC-MS: (ESI, m/z): $[M+H]^+$=628.3.

步骤12： 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*S*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)-4-羟基环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺的制备



5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(3-(二氟甲基)-1-((1*S*,4*S*)-4-羟基-4-((甲基(2-(哌啶-4-基)乙基)氨基)甲基)环己基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺 (120 mg, 0.19 mmol)用二甲亚砜 (3 mL)溶解，搅拌下加入4-氯-3-(2,4-二氧代基四氢嘧啶-1(2*H*)-基)苯甲酸五氟苯基酯 (100 mg, 0.23 mmol)和 *N*,*N*-二异丙基乙胺 (148 mg, 1.14 mmol)，反应液室温搅拌2 h。反应液加水 (5 mL)稀释，过滤，固体用p-TLC (二氯甲烷:甲醇=10:1)纯化得到 5-((1*R*,4*R*)-2-氧-5-氮杂双环[2.2.1]庚烷-5-基)-*N*-(1-((1*S*,4*S*)-4-(((2-(1-(4-氯-3-(2,4-二氧代四氢嘧啶-1(2*H*)-基)苯甲酰)哌啶-4-基)乙基)(甲基)氨基)甲基)-4-羟基环己基)-3-(二氟甲基)-1*H*-吡唑-4-基)吡唑并[1,5-a]嘧啶-3-甲酰胺。

LC-MS: (ESI, m/z): $[M+H]^+$=878.2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.51 (s, 1H), 8.78 (d, J = 7.7 Hz, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.55 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.26-6.96 (m, 1H), 6.90-6.42 (m, 1H), 5.33-5.05 (m, 1H), 4.77 (d, J = 17.1 Hz, 1H), 4.50-4.39 (m, 1H), 4.20-3.97 (m, 2H), 3.87-3.70 (m, 3H), 3.64-3.40 (m, 4H), 3.12-2.92 (m, 1H), 2.82-2.67 (m, 3H), 2.46-2.38 (m, 2H), 2.32-2.21 (m, 5H), 2.12- 1.92 (m, 4H), 1.86-1.55 (m, 7H), 1.52-1.32 (m, 4H), 1.18-1.04 (m, 2H).

II生物活性测试实施例

测试实施例 1：IRAK4 激酶活性测试

用KinEASE-STK S1丝/苏氨酸激酶试剂盒(Cisbio)检测化合物对IRAK4激酶活性的抑制作用，具体方法为：化合物溶解于二甲亚砜中，再用试剂盒的缓冲液进行等梯度稀释，使受试化合物在反应体系中的终浓度范围为10000 nM～0.038 nM，再依次加入2.5 nM IRAK4激酶 (Carna)、1 μM生物素化的多肽底物 (Cisbio)和7 μM三磷酸腺苷 (Sigma-Aldrich)在37 ℃下孵育120 min。随后向反应体系中加入偶联有铕系元素化合物的抗磷酸化丝/苏氨酸抗体 (Cisbio)和偶联有修饰化的XL665链霉亲和素(Cisbio)以终止反应，在室温下孵育1h后，在酶标仪EnVision(PerkinElmer)上以HTRF模式测定各孔在激发波长为337nm，读取各孔在发射波长为620 nm和665 nm的荧光强度，使用公式Ratio＝(665 nm/620 nm)×10^4算出Ratio值。通过与对照组荧光强度比值进行对比，计算化合物在各浓度下的抑制率，进而通过GraphPad Prism 7以对数浓度-抑制率进行非线性曲线拟合，得出化合物的IC_{50}值。

表1：

实施例	IC_{50} (nM)
实施例 1	30.3
实施例 2	15.5
实施例 3	67.2
实施例 4	37.0
实施例 5	359.7
实施例 6	524.4
实施例 7	313.4
实施例 8	10.6
实施例 9	131
实施例 10	12.92
实施例 11	18.5
实施例 12	270.4

实施例 13	19.3
实施例 14	124.3
实施例 15	14.2
实施例 16	8.8
实施例 17	15.1
实施例 18	66.9
实施例 19	3.8
实施例 20	89.2
实施例 21	9.9
实施例 22	9.29
实施例 23	22.96
实施例 24	6.08
实施例 25	14.13
实施例 26	14.30
实施例 27	13.50
实施例 28	12.87
实施例 29	17.04
实施例 30	4.64
实施例 31	8.05
实施例 32	7.74
实施例 33	23.90
实施例 34	11.03
实施例 35	3.36
实施例 36	3.86
实施例 37	13.08
实施例 38	19.97
实施例 39	17.04
实施例 40	34.50

实施例 41	25.52
实施例 42	18.64
实施例 43	45.01
实施例 44	13.45
实施例 45	2.98
实施例 46	277.70
实施例 47	7.86
实施例 48	36.07
实施例 49	7.05
实施例 50	36.74
实施例 51	27.10
实施例 52	23.83
实施例 54	9.82
实施例 55	21.31
实施例 56	3.87
实施例 57	4.57
实施例 59	8.71
实施例 60	21.94
实施例 61	9.06
实施例 62	28.86
实施例 63	36.24
实施例 64	5.93
实施例 65	52.15

“-”表示未检测。

实验结果：本发明所述化合物能够有效的与靶蛋白相结合，且抑制 IRAK4 激酶活性。

测试实施例2：化合物对THP-1细胞中IRAK4的降解

24孔细胞培养板每孔接种0.95 mL THP-1细胞(中国科学院干细胞库)，细胞密度为5×10^5个/孔；细胞板置于5% 二氧化碳培养箱中37 ℃培养过夜，然后再加入50 μL化合物二甲亚砜溶液，化合物终浓度在0.03~3000 nM范围内，继续培养24小时后，收集细胞至1.5 mL的离心管中，1000 rpm、4 ℃离心

5分钟。细胞沉淀用1×DPBS清洗2次，重悬的细胞用200 μL裂解液(细胞裂解液为Western及IP细胞裂解液(碧云天)，补充1 mM苯甲基磺酰氟和蛋白酶抑制剂混合物(碧云天))裂解，冰上静置30分钟后14000 g、4 ℃离心10分钟，取上清液用蛋白免疫印迹法(Western Blot)检测IRAK4蛋白水平。

人IRAK4 AlphaLISA检测

上述细胞裂解液同时使用人IRAK4 AlphaLISA检测试剂盒(PerkinElmer，AL3117C)测定IRAK4降解作用，具体方法为取2 μL待测的细胞裂解上清液样品加入白色384孔板(PerkinElmer，6007299)，然后再加入4 μL的5×抗IRAK4受体微珠(PerkinElmer, 终浓度为10 μg/mL)，23 ℃孵育30分钟。接着再加入4 μL的5×生物素标记的抗IRAK4抗体(PerkinElmer, 终浓度为1 nM)，23 ℃孵育60分钟。最后在各孔中加入10 μL的2×链霉亲和素标记的供体微珠(终浓度为40 μg/mL)，23 ℃避光孵育30分钟。孵育结束后，在酶标仪EnVision(PerkinElmer，2105)上以AlphaScreen标准设置模式测定AlphaLISA信号值，据此计算IRAK4浓度。再用GraphPad Prism 7以对数浓度-抑制率进行非线性曲线拟合，得出化合物的DC_{50}和D_{max}值。

表2：

实施例	DC_{50}(nM)	D_{max}(%)
实施例 1	3.7	90.0
实施例 2	1.8	95.8
实施例 3	-	-
实施例 4	-	-
实施例 5	-	-
实施例 6	-	-
实施例 7	148.5	76.4
实施例 8	8.8	86.8
实施例 9	128.6	81.0
实施例 10	2.8	99.3
实施例 11	12.7	90.7
实施例 12	-	-
实施例 13	5.5	84.4
实施例 14	-	-
实施例 15	2.5	92.1
实施例 16	6.4	87.9

实施例 17	10.37	99.4
实施例 18	54.3	62.5
实施例 19	5.1	97.7
实施例 20	78.6	86.96
实施例 21	9.6	95.5
实施例 22	3.42	96.53
实施例 23	10.10	93.65
实施例 24	6.16	96.32
实施例 25	62.13	97.82
实施例 28	3.18	89.42
实施例 29	2.75	98.48
实施例 30	5.23	90.09
实施例 31	6.10	91.10
实施例 32	3.46	90.53
实施例 34	3.55	87.11
实施例 35	0.78	100
实施例 36	3.45	96.02
实施例 37	41.96	81.07
实施例 39	10.86	93.89
实施例 40	32.75	79.18
实施例 42	3.66	91.70
实施例 43	15.08	79.51
实施例 44	6.30	80.45
实施例 45	0.82	96.16
实施例 47	4.84	99.01
实施例 48	5.55	94.41
实施例 49	3.22	97.07
实施例 50	5.94	82.09

实施例 52	18.45	95.43
实施例 54	8.13	88.18
实施例 55	7.52	79.18
实施例 56	0.41	96.44
实施例 57	0.58	96.57
实施例 59	7.92	70.81
实施例 60	9.36	96.59
实施例 61	28.96	87.91
实施例 63	9.18	79.3
实施例 64	7.47	96.06
实施例 65	14.26	87.24

“-”表示未检测。

实验结果：本发明所述化合物能够有效的降解细胞中的IRAK4激酶蛋白，且具有优良的降解活性。

测试实施例3： LPS诱导正常人全血、PBMC分泌的细胞因子浓度测定

(1) LPS诱导正常人全血分泌的细胞因子浓度测定

在 96 孔透明细胞板(Labserv，310109008)每孔中铺 190 μL 肝素钠抗凝的新鲜的正常人全血 (年龄为 22-50 的健康人，现采集的血液)，然后在相应的孔中加入 10 μL 稀释后的化合物溶液，使化合物的终浓度在 10~20000 nM 范围内。二甲亚砜终浓度为 0.1%。加化合物处理的细胞板贴上封板膜，置于 5%二氧化碳培养箱中 37 ℃培养 20 小时后，加入 10 μL LPS (0111:B4) (Sigma，L4391)，终浓度为 100 ng/mL。细胞板贴上封板膜，再次置于 5%二氧化碳培养箱中 37 ℃培养 5 小时后，2000 rpm 离心 10 分钟，每孔取 30 μL 上清血浆转移到一块新的 96 孔透明细胞板，用于细胞因子浓度测试，冻存于-80 ℃待测。

白介素-6(IL-6)AlphaLISA 检测。

使用白介素-6(IL-6)AlphaLISA 检测试剂盒(PerkinElmer，AL223 C)测定 LPS 诱导的人全血(年龄为 22-50 的健康人，现采集的血液)的上清血浆样品中的 IL-6 浓度。

按照产品说明书配制不同浓度的 IL-6 标准液，浓度范围为 0~100000 pg/mL。取 2 μL 各浓度的 IL-6 标准液和待测的细胞上清液样品分别加入白色 384 孔板(PerkinElmer，6007299)，然后在各孔中加入 8 μL 的 5×抗 IL-6 受体微珠(PerminElmer, 终浓度为 10 μg/mL)和生物素标记的抗 IL-6 抗体 (PerminElmer, 终浓度为 1 nM)混合溶液，23 ℃孵育 60 分钟。最后在各孔中加入 10 μL 的 2×链霉亲和素标记的供体微珠(终浓度为 40 μg/mL)，再 23 ℃避光孵育 30 分钟。孵育结束后，在酶标仪

EnVision(PerkinElmer，2105)上以 AlphaScreen 标准设置模式测定 AlphaLISA 信号值。通过各浓度 IL-6 标准液的 AlphaLISA 信号值绘制标准曲线，再根据待测样品的 AlphaLISA 信号值在标准曲线上相应的浓度，从而确定各细胞裂解上清液的 IL-6 浓度。再与对照组 IL-6 浓度进行对比，计算化合物在各浓度下的抑制率，进而通过 GraphPad Prism 7 以对数浓度-抑制率进行非线性曲线拟合，计算化合物的 IC_{50} 值。

(2) LPS 诱导人 PBMC 分泌的细胞因子浓度测定

冻存的人 PBMC（妙顺，PB010C）复苏后重悬至 RPMI 1640 培养基 (Gibco，A1049101)，补充 10 %胎牛血清（Gibco，10099141），100 U/mL 青霉素和 100 μg/mL 链霉素(Gibco，15140122)。同一天在 96 孔透明细胞板（Labserv，310109008）每孔中铺 150 μL 的 PBMC，使细胞密度为 2×105 个/孔。然后在相应的铺有细胞的孔中加入 50 μL 稀释后的化合物溶液，使化合物的终浓度在 0.026~10000 nM 范围内。DMSO 终浓度为 0.25%。加药处理的细胞板置于 5% CO2 培养箱中 37℃培养 1 小时或者 20 小时后，加入 10 μL LPS (0111:B4) (Sigma，L4391），终浓度为 100 ng/mL。细胞板再次置于 5% CO2 培养箱中 37℃培养 5 小时后，2000 rpm 离心 10 分钟，每孔取 100 μL 细胞上清液转移到一块新的 96 孔透明细胞板，用于细胞因子浓度测试，冻存于-80℃待测。

白介素-6（IL-6）AlphaLISA 检测

使用白介素-6（IL-6）AlphaLISA检测试剂盒（PerkinElmer，AL223 C）测定LPS诱导人PBMC细胞上清液中的IL-6浓度。

按照产品说明书配制不同浓度的 IL-6 标准液，浓度范围为 0~100000 pg/mL。取 2 μL 各浓度的 IL-6 标准液和待测的细胞上清液样品分别加入白色 384 孔板（PerkinElmer，6007299），然后在各孔中加入 8 μL 的 5×抗 IL-6 受体微珠（终浓度为 10 μg/mL）和生物素标记的抗 IL-6 抗体（终浓度为 1 nM）混合溶液，23℃孵育 60 分钟。最后在各孔中加入 10 μL 的 2×链霉亲和素标记的供体微珠（终浓度为 40 μg/mL），再 23℃避光孵育 30 分钟。孵育结束后，在酶标仪 EnVision（PerkinElmer，2105）上以 AlphaScreen 标准设置模式测定 AlphaLISA 信号值。通过各浓度 IL-6 标准液的 AlphaLISA 信号值绘制标准曲线，再根据待测样品的 AlphaLISA 信号值在标准曲线上相应的浓度，从而确定各细胞裂解上清液的 IL-6 浓度。再与对照组 IL-6 浓度进行对比，计算化合物在各浓度下的抑制率，进而通过 GraphPad Prism 7 以对数浓度-抑制率进行非线性曲线拟合，计算化合物的 IC_{50} 值。

表 3：

实施例	人全血 IC_{50}(nM)	hPBMC IC_{50}(nM)
实施例 1	287	3.1
实施例 2	246	2.2

实验结果：本发明化合物对免疫细胞产生 IL-6 具有很好的抑制作用。

权利要求

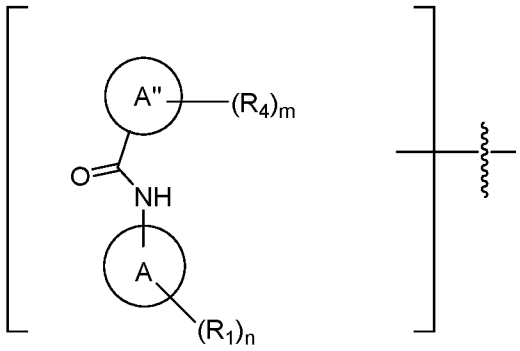
1. 式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐：

PTM-L-ULM

I

其中：

所述 PTM 具有下式结构



PTM-1

其中所述 PTM-1 中：

m 是 0、1、2、3 或者 4；

n 是 0、1、2、3 或者 4；

环 A"为 6-10 元芳基或含有 1 个、2 个或者和 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

环 A 为 6-10 元芳基或含有 1 个、2 个或者和 3 个选自 N、O 或 S 杂原子的 5-11 元单环或双环杂芳基；

各个 R_1 独立地选自：C_1-C_4 烷基、-O(C_1-C_4 烷基)、-N(C_1-C_4 烷基)$_{1-2}$、C_3-C_8 环烷基、-O(C_3-C_8 环烷基)、-NH(C_3-C_8 环烷基)、3-8 元杂环烷基、-O(3-8 元杂环烷基)、-NH(3-8 元杂环烷基)、6-10 元芳基、-O(6-10 元芳基)、-NH(6-10 元芳基)、5-6 元杂芳基、-O(5-6 元杂芳基)、-NH(5-6 元杂芳基)、CN、卤素、-OH、-NH_2、-NHC(O)(C_1-C_4 烷基)、-NHS(O)(C_1-C_4 烷基)、-NHS(O)$_2$(C_1-C_4 烷基)、-COOH、-C(O)NH_2、-S(O)$_2$H、-S(O)$_2NH_2$、-C(O)(C_1-C_4 烷基)、-C(O)NH(C_1-C_4 烷基)、-C(O)N(C_1-C_4 烷基)$_2$、-C(O)O(C_1-C_4 烷基)、-S(O) (C_1-C_4 烷基)、-S(O)$_2$(C_1-C_4 烷基)、-S(O)$_2$NH(C_1-C_4 烷基)、-S(O)$_2$N(C_1-C_4 烷基)$_2$ 或者-S(O)NH(C_1-C_4 烷基)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4 烷基、-O(C_1-C_4 烷基)、甲基哌啶、-S(O)$_2$H、-S(O)$_2$(C_1-C_4 烷基)、-C(O)N(C_1-C_4 烷基)$_{1-2}$ 和-C(O)O(C_1-C_4 烷基)的基团取代；

或者所述 R_1 与其所连接的原子一起形成环烷基、杂环烷基、芳基或杂芳基；

各个 R_4 独立地为氢、C_1-C_4 烷基、-O(C_1-C_4 烷基)、C_3-C_8 环烷基、3-8 元杂环烷基、6-10 元芳基、5-6 元杂芳基、CN、卤素、-OH、-NHC(O)(C_1-C_4 烷基)、-NHS(O)(C_1-C_4 烷基)、-NHS(O)$_2$(C_1-C_4 烷基)、-COOH、-C(O)NH_2、-S(O)$_2$H、-S(O)$_2NH_2$、-C(O)(C_1-C_4 烷基)、-C(O)NH(C_1-C_4 烷基)、-C(O)N(C_1-C_4 烷基)$_2$、-C(O)O(C_1-C_4 烷基)、-S(O) (C_1-C_4 烷基)、-S(O)$_2$(C_1-C_4 烷基)、-S(O)$_2$NH(C_1-C_4 烷基)、-S(O)$_2$N(C_1-C_4 烷基)$_2$、-S(O)NH(C_1-C_4 烷基)或者 X(R_2)(R_3)，所述烷基、环烷基、杂环烷基、芳基、杂芳基任选被选自卤素、氰基、-OH、C_1-C_4 烷基、-O(C_1-C_4 烷基)、甲基哌啶、-S(O)$_2$H、-S(O)$_2$(C_1-C_4 烷基)、-C(O)N(C_1-C_4 烷基)$_{1-2}$、和-C(O)O(C_1-C_4 烷基)的基团取代；X 为 O、S、CH_2 或者 N；

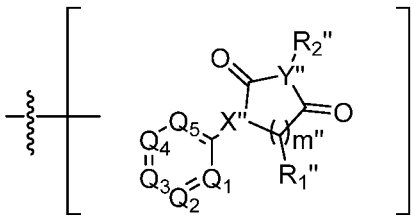
R_2、R_3 独立地选自：氢、C_1-C_6 烷基、C_3-C_8 环烷基、3-8 元杂环烷基、6-10 元芳基或者 5-6 元杂芳基，所述烷基、环烷基、杂环烷基、芳基、杂芳基各自独立地任选地被一个或多个选自卤素、OH、氧代基、N(R_b)$_2$、氧代基吡咯烷基和吗啉基取代，或 R_2 和 R_3 与它们所连接的原子一起形成 C_3-C_8 环烷基或者 3-8 元杂环烷基，所述环烷基或者杂环烷基任选地被一个或多个选自 R_a 的取代基取代;

R_a 独立地选自氧代基、C_1-C_4 烷基、C_3-C_6 环烷基、CF_3、CHF_2、OH、卤素或 NH_2，所述烷基任选被 C_3-C_6 环烷基或 CF_3 取代；且

R_b 独立地选自 H 或 C_1-C_4 烷基；

L 为连接链，其通过共价键连接 PTM 和 ULM；

所述 ULM 具有下式结构



ULM-1

其中所述 ULM-1 中的：

X"为 C 或 N；

Y"为 C、N、O 或者 S；

Q_1、Q_2、Q_3、Q_4 和 Q_5 各自独立地为 CR_3"或 N；

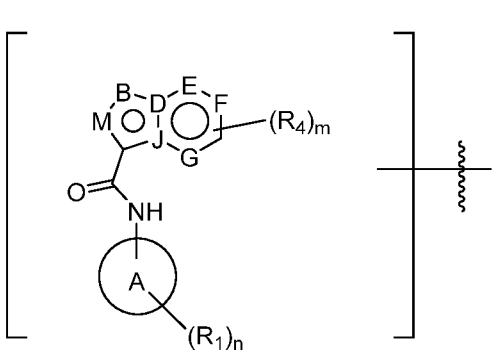
R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6 烷基、C_3-C_8 环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-O(C_1-C_6 烷基)、-O-(C_3-C_8 环烷基)、-O-(3-8 元杂环烷基)、N(C_1-C_6 烷基)$_{1-2}$、NH(C_3-C_8 环烷基)、NH(3-8 元杂环烷基)、-O-(6-10 芳基)或-O-(5-10 元杂芳基)；所述烷基、环烷基、杂环烷基、芳基和杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；或者 R_3"与其所连接的原子一起形成环烷基、杂环烷基、杂芳基或者芳基；

m"为 1、2 或 3；

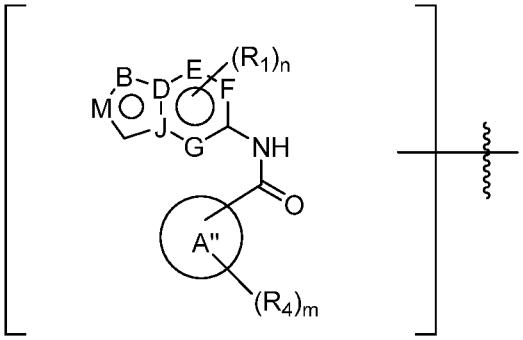
R_1"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6烷基、C_3-C_8环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基或-O(C_1-C_6 烷基)，所述烷基、环烷基、杂环烷基、芳基和杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基和氨基的基团取代；

R_2"为氢、氘、C_1-C_6烷基或者 C_3-C_6环烷基，所述 C_1-C_6烷基和 C_3-C_6环烷基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基和-OC(O)(C_1-C_6烷基)的基团取代。

2. 如权利要求 1 所述的式 I 化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 PTM 为



PTM-2'



PTM-2"

其中所述 PTM-2'，PTM-2"中：

B 为 CH、N、O 或者 S；

M 为 CH、N、O 或者 S；

D 为 CH 或者 N；

E 为 CH 或者 N；

F 为 CH 或者 N；

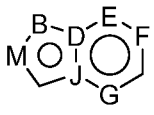
G 为 CH 或者 N；

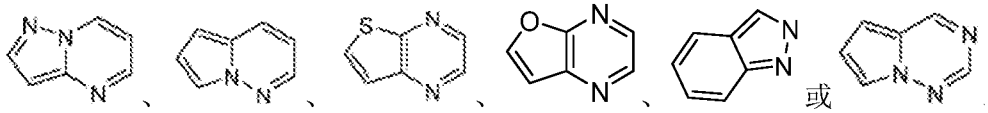
J 为 CH 或者 N；

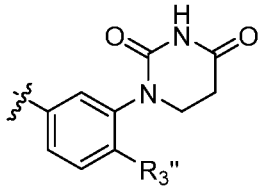
当 B 或者 M 为 S 或者 O 时，D 是 CH，E 是 N，F 为 CH, G 是 N 且 J 是 CH，且 B 和 M 不能同时为 S 和/或者 O；

所述环 A、环 A"、R_1、n、R_4和 m 如权利要求 1 中 PTM-1 中所定义和描述。

3. 如权利要求 2 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水

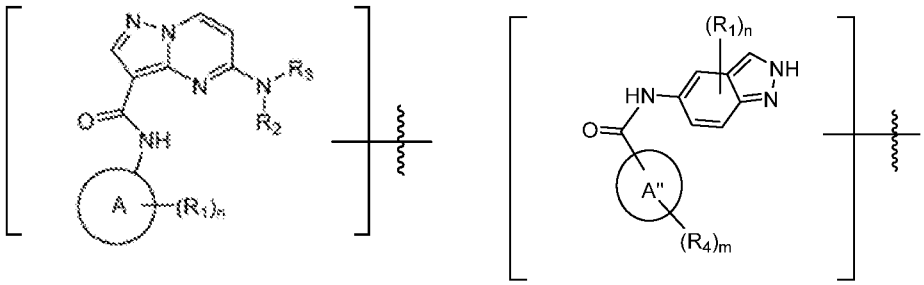
合物、溶剂化物、前药或其药学上可接受的盐，其特征在于所述 PTM-2'中的  为



和/或，所述 ULM 具有下式结构  ；R_3"为卤素、C_1-C_6 烷基或-O(C_1-C_6 烷基)；

和/或，所述药学上可接受的盐为甲酸盐。

4. 如权利要求 2 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 PTM 为



PTM-3 PTM-3'

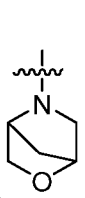
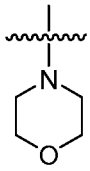
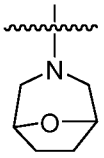
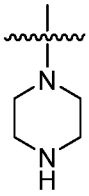
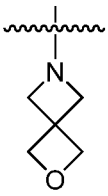
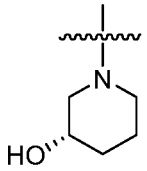
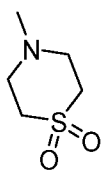
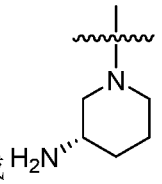
其中所述环 A、环 A"、R_1、R_2、R_3、R_4、m 和 n 如权利要求 1 中 PTM-1 中所定义和描述。

5. 如权利要求 1、2 或 4 任一项所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述环 A 是苯基或含有 1 个、2 个或者 3 个选自 N、O 杂原子的 5-6 元杂芳基；优选环 A 为苯基、吡啶基、吡咯基、吡唑基、咪唑基、嘧啶基、三唑基、四唑基、噻吩基、噻唑基、呋喃基、噁唑基、异噁唑基、异噻唑基；进一步优选环 A 为吡唑基或噻吩基；

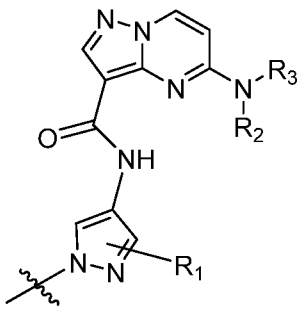
和/或，R_3"各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6 烷基、C_3-C_8 环烷基、3-8 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-O(C_1-C_6 烷基)、-O-(C_3-C_8 环烷基)、-O-(3-8 元杂环烷基)、N(C_1-C_6 烷基)$_{1-2}$、NH(C_3-C_8 环烷基)、NH(3-8 元杂环烷基)、-O-(6-10 芳基)或-O-(5-10 元杂芳基)；所述烷基、环烷基、杂环烷基、芳基和杂芳基任选的被 1-3 个独立地选自羟基、卤素、氰基、氨基的基团取代；或者 R_3"与其所连接的原子一起形成环烷基或杂环烷基；

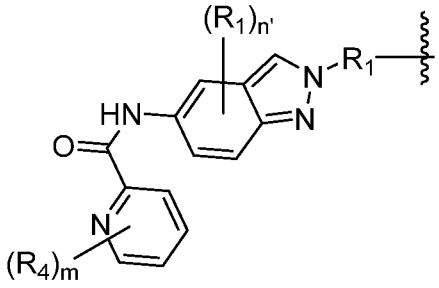
和/或，所述 R_1 独立地选自：C_1-C_4 烷基、C_3-C_6 环烷基、3-6 元杂环烷基、CN 或卤素，所述烷基、

环烷基和杂环烷基任选被卤素、OH、CH_3 或 OCH_3 取代；优选的 R_1 独立地选自：C_1-C_4 烷基、C_3-C_6 环烷基、含有 1 个或者 2 个选自 N 杂原子的 3-6 元杂环烷基、CN 或卤素，所述烷基、环烷基和杂环烷基任选被卤素、OH、CH_3 或 OCH_3 取代；进一步优选的所述 R_1 为 CHF_2、CF_3、环己基、哌啶基、甲基、氰基或者哌嗪基；

和/或，所述 R_2、R_3 各自独立地选自：氢、C_1-C_6 烷基、C_3-C_8 环烷基或 3-8 元杂环烷基，各自任选地被一个或多个卤素、OH、$N(R_b)_2$ 或吗啉基取代，或 R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；R_a 独立地选自 C_1-C_4 烷基、C_3-C_6 环烷基、CF_3、CHF_2、OH、卤素或 NH_2，所述烷基任选被 C_3-C_6 环烷基或 CF_3 取代；且 R_b 独立地选自 H 或 C_1-C_4 烷基；优选的，R_2 和 R_3 与它们所连接的氮原子一起形成 3-8 元除连接 N 原子外另外含有 1 个选个 N 或者 O 杂氧原子的杂环烷基，所述杂环烷基任选地被一个或多个选自 R_a 的取代基取代；所述 R_a 独立地选自 C_1-C_4 烷基、CF_3、CHF_2、OH、卤素或 NH_2；进一步优选的所述 R_2 和 R_3 与它们所连接的氮原子一起形成  、  、  、  、  、  、  或  。

6. 如权利要求 1、2 或 4 任一项所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 PTM 具有下式结构：


PTM-3a


PTM-3a'

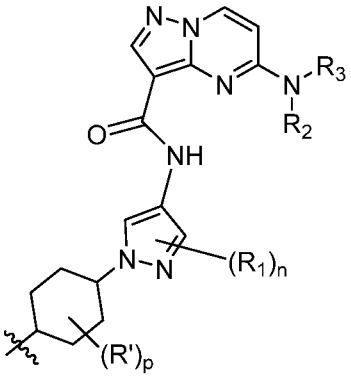
其中，

n′是 0、1、2 或者 3；

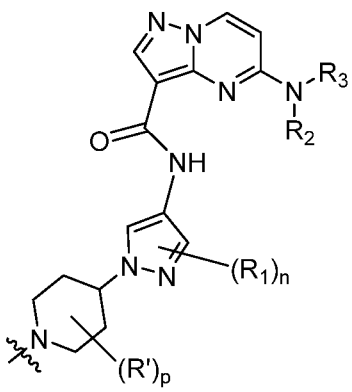
所述 R_1、R_2、R_3、R_4、m 和 n 如权利要求 1 中 PTM-1、PTM-2’和 PTM-3 中所定义和描述。

7. 如权利要求 1、2 或 4 任一项所述的式I化合物，其立体异构体、对映异构体、非对映异构体、

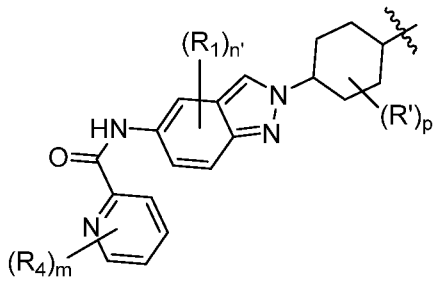
氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 PTM 具有下式结构：



PTM-3b'



PTM-3c'



PTM-3d'

其中，

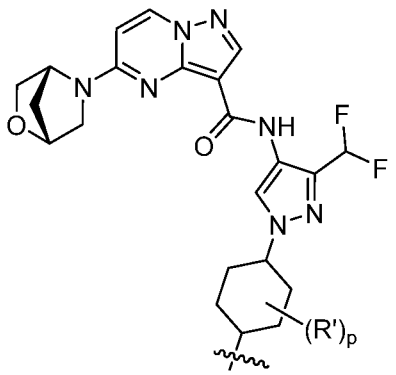
n′是 0、1、2 或者 3；

R′为各自独立地为氢、氘、羟基、氨基、氰基、卤素、C_1-C_6 烷基或-O(C_1-C_6 烷基)，所述烷基任选的被 1-3 个独立的选自羟基、卤素、氰基和氨基的基团取代；

p 为 0、1、2、3、4、5、6、7、8 或 9；

所述 R_1、R_2、R_3、R_4、m 和 n 如权利要求 1 中 PTM-1、PTM-2’和 PTM-3 中所定义和描述；

较佳地，所述 PTM 具有下式结构：



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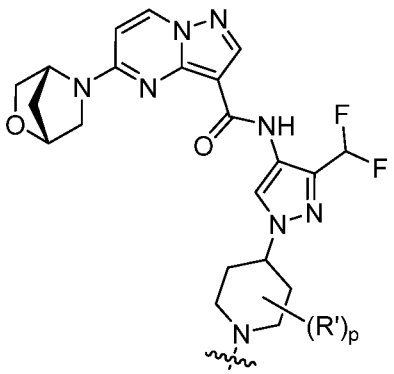

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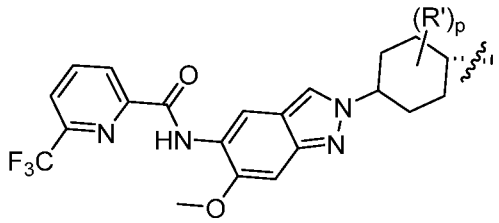
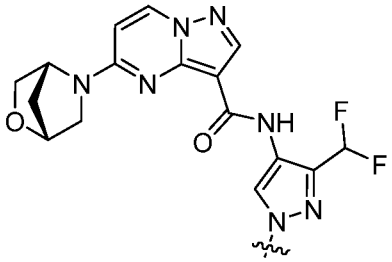
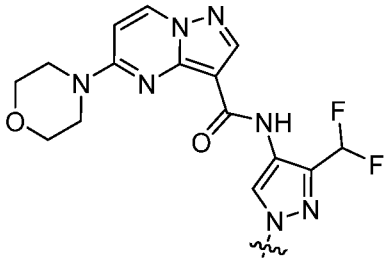
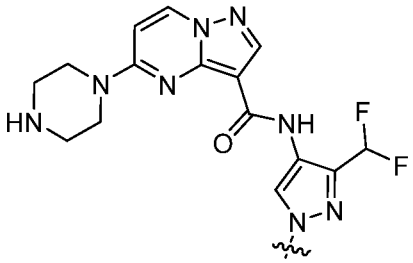
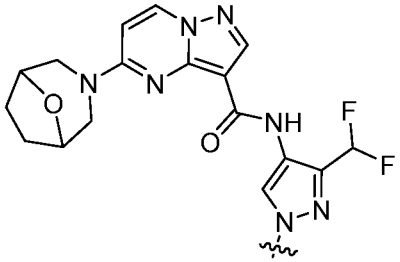
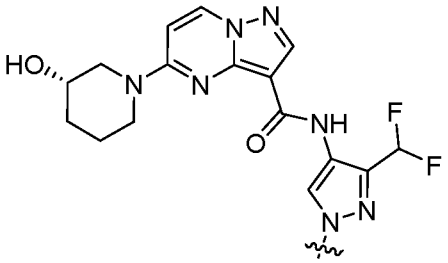
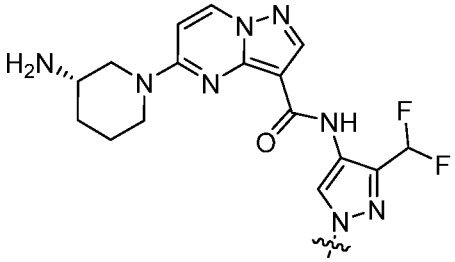
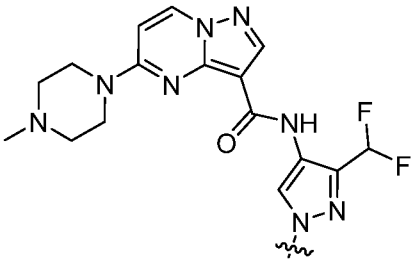
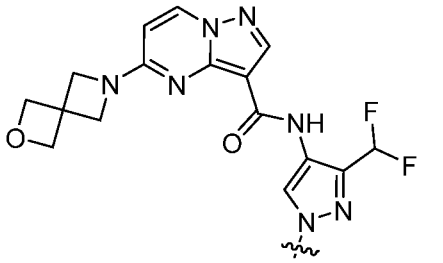
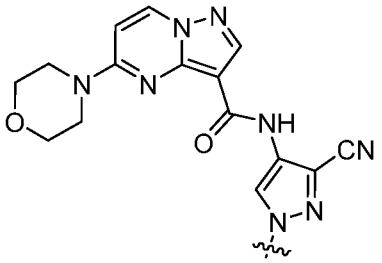


或，所述 PTM 具有下式结构：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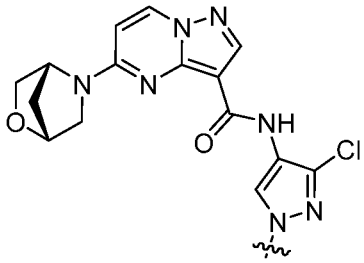
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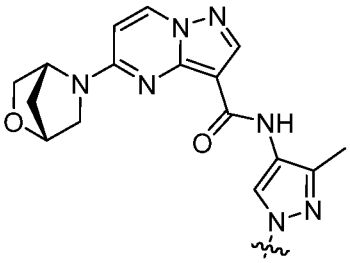
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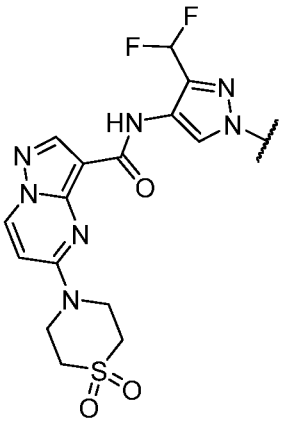
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8. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 ULM-1 中的 Q_1、Q_2、Q_3、Q_4、Q_5 中的 1 个或者 2 个为 N，其余各自独立地为 CR_3"。

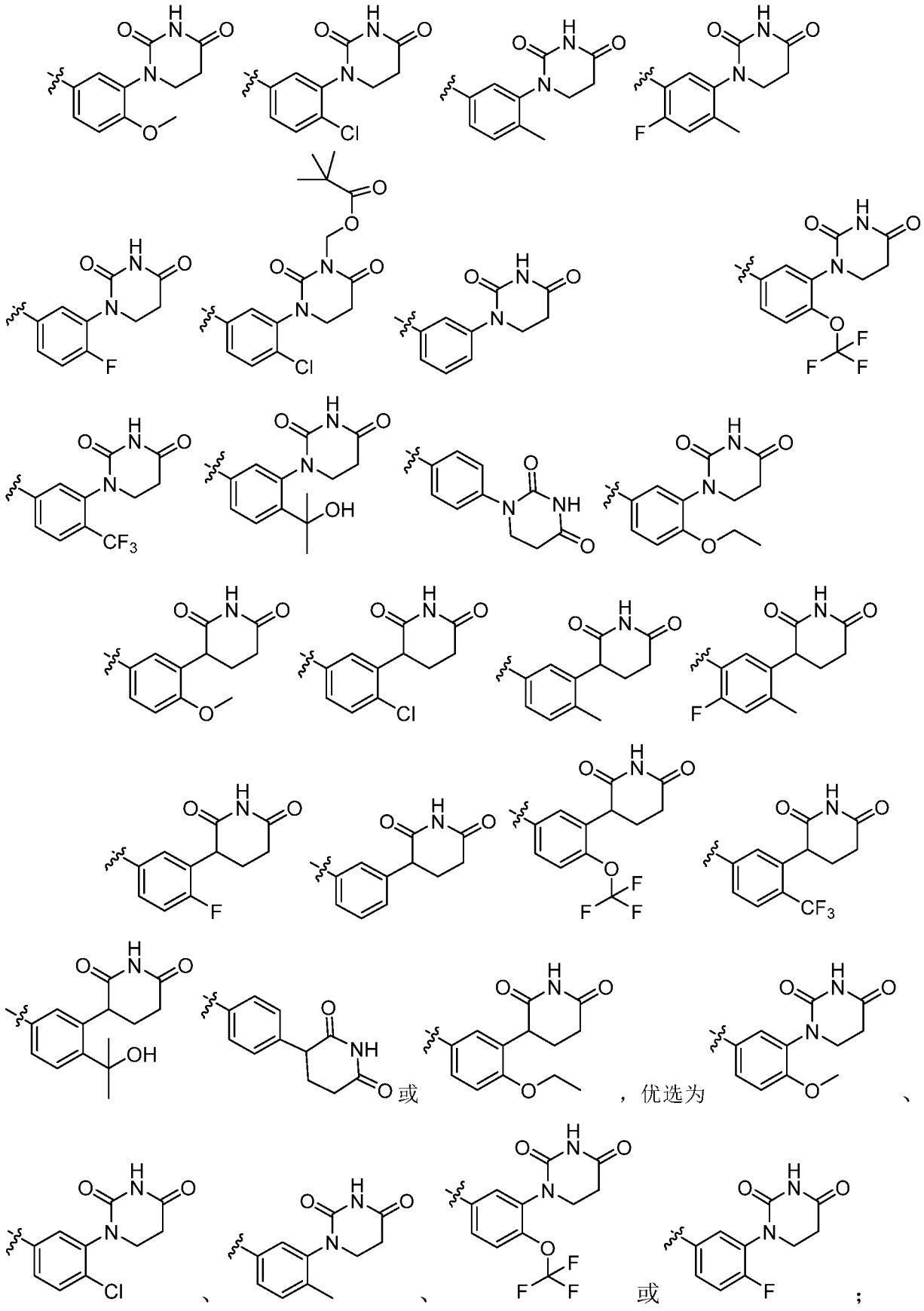
9. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所 ULM-1 中的 Q_1、Q_2、Q_3、Q_4、Q_5 各自独立地为 CR_3"；和/或，所述 ULM-1 中的 Y"为 N；

和/或，所述 ULM-1 中的 R_1"各自独立地为氢、氘、-F、-Cl、或 C_1-C_6 烷基，所述烷基任选被 1-3 个卤素取代；优选 R_1"为氢；

和/或，所述 ULM-1 中的 R_2"为氢或 C_1-C_6 烷基，所述烷基任选被 1-3 个卤素取代；优选 R_2"为氢。

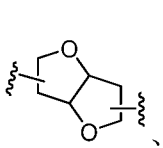
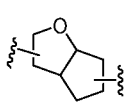
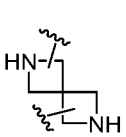
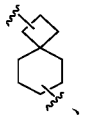
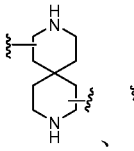
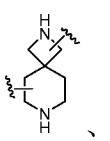
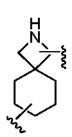
10. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 ULM-1 中的 R_3"各自独立地为氢、氘、卤素、-O(C_1-C_6 烷基)、或 C_1-C_6 烷基，所述烷基任选被 1-3 个卤素取代；优选 R_3"各自独立地为氢、氘、F、Cl、甲基、甲氧基、乙氧基、三氟甲氧基、2-羟基丙-2 基或三氟甲基。

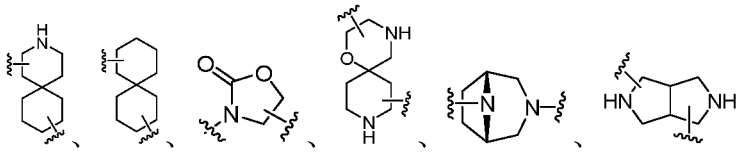
11. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 ULM 选自

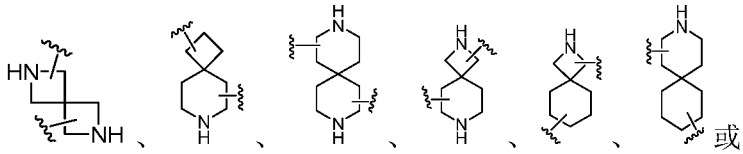
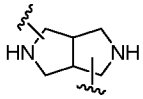


和/或，所述 L 为键。

12. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于所述 L 为-$(CH_2)_j$-，所述-$(CH_2)_j$-中的 1 个或多个亚甲基任选地被选自-$NR^{3'}$-、-O-、-S-、-S(O)-、-S(O)$NR^{3'}$-、-$NR^{3'}$S(O)-、-$S(O)_2$-、-$S(O)_2NR^{3'}$-、-$NR^{3'}S(O)_2$-、-$NR^{4'}S(O)_2NR^{3'}$-、-$CR^{1'}R^{2'}$-、-C(O)-、-C(O)O-、-OC(O)-、-$NR^{3'}$C(O)O-、-OC(O)$NR^{3'}$-、-C(O)$NR^{3'}$-、-$NR^{3'}$C(O)-、-$NR^{4'}$C(O)$NR^{3'}$-、-P(O)-、-P(O)O-、-OP(O)-、-OP(O)O-、亚乙烯基、亚乙炔基、C_3-C_{12}亚环烷基、含有 1 个或多个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基、6-10 元亚芳基或 5-10 元亚杂芳基的基团替代，所述亚乙烯基、亚环烷基、亚杂环烷基、亚芳基和亚杂芳基各自独立地任选地被 1 个或多个选自卤素、-$OR^{3'}$、-$NR^{3'}R^{4'}$、氧代、硝基、氰基、C_1-C_6烷基、-S(C_1-C_6烷基)、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基、5-10 元杂芳基、-C(O)$R^{1'}$、-C(O)$OR^{3'}$、-OC(O)$R^{1'}$、-C(O)$NR^{3'}$、-$NR^{3'}$C(O)$R^{1'}$、-S(O)$R^{1'}$、-S(O)$NR^{3'}$、-$S(O)_2R^{1'}$、-$S(O)_2NR^{3'}$、-$NR^{3'}S(O)_2R^{1'}$、-$NR^{4'}S(O)_2NR^{3'}$、-OC(O)$NR^{3'}$、-$NR^{4'}$C(O)$NR^{3'}$的取代基取代，所述烷基、环烷基、杂环烷基、芳基、杂芳基各自独立地任选地被 1 个或多个选自卤素、-OH、-$NR^{3'}R^{4'}$、氧代、硝基、氰基和C_1-C_6烷基、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基、5-10 元杂芳基的取代基取代；$R^{1'}$、$R^{2'}$各自独立为卤素、-OH、-$NR^{3'}R^{4'}$、C_1-C_6烷基、氯代 C_1-C_6烷基、羟基 C_1-C_6烷基、-O(C_1-C_6烷基)、-NH(C_1-C_6烷基)、-NH(C_1-C_6烷基)、C_3-C_{10}环烷基、-O(C_3-C_{10}环烷基)、-NH(C_3-C_{10}环烷基)、3-10 元杂环烷基、-O(3-10 元杂环烷基)、-NH(3-10 元杂环烷基)、6-10 元芳基、-O(6-10 元芳基)、-NH(6-10 元芳基)、5-10 元杂芳基、-O(5-10 元杂芳基)或-NH(5-10 元杂芳基)，$R^{3'}$和$R^{4'}$各自独立地为氢、氘、C_1-C_6烷基、C_3-C_{10}环烷基、3-10 元杂环烷基、6-10 元芳基或 5-10 元杂芳基；j 为 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24 或 25。

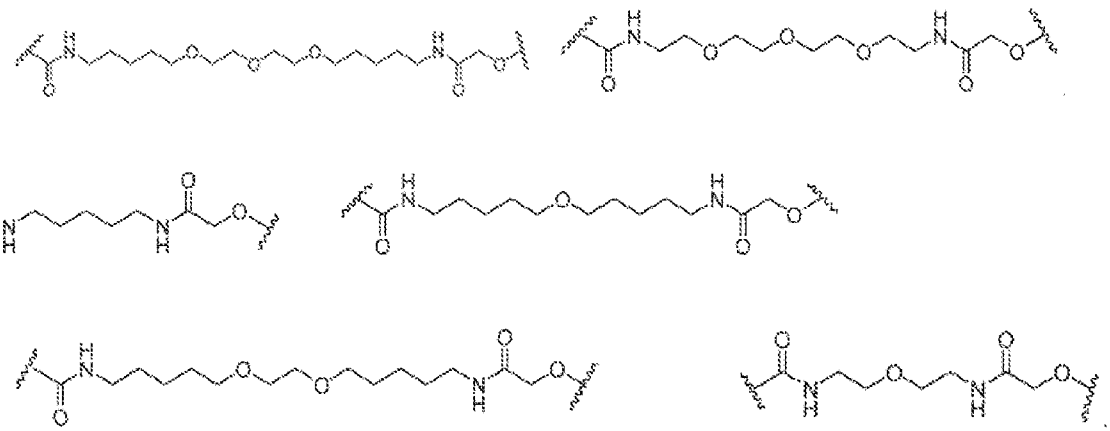
13. 如权利要求 12 所述的式I化合物，和/或其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药和/或其药学上可接受的盐，其特征在于所述 L 为-$(CH_2)_j$，所述-$(CH_2)_j$-中的 1 个、2 个、3 个或者 4 个亚甲基任选地被选自-NH-、-NCH_3-、-NCH_2CH_3-、-O-、-$C(CH_3)_2$-、-CHF-、-$CHCF_3$-、-C(O)-、-C(O)O-、-OC(O)-、-C(O)NH-、-C(O)NCH_3-、-NHC(O)-、-NCH_3C(O)-、亚乙烯基、亚乙炔基、亚环丙基、亚环丁基、亚环戊基、亚环己基、亚氧杂环丙基、亚氧杂环丁基、亚氧杂环戊基、亚氧杂环己基、亚氮杂环丙基、亚氮杂环丁基、亚氮杂环戊基、亚哌啶基、亚哌嗪基、亚吗啉基、亚高吗啉基、亚苯基、亚吡咯基、亚噻吩基、亚呋喃基、亚咪唑基、亚吡唑基、亚三唑基、亚四唑基、亚噁唑基、亚异噁唑基、亚噻唑基、亚异噻唑基、亚吡啶基、亚嘧啶基、亚哒嗪基、亚吡嗪基、  、  、  、  、  、  、  、

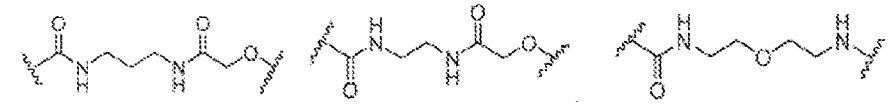

的基团替代，且所述替代基团任选地被1个或多个选自卤素、氧代、$-NR^{3'}R^{4'}$、$-OR^{3'}$、C_1-C_4烷基的取代基取代，所述烷基任选被1个或多个选自卤素、-OH、$-NH_2$的取代基取代，$R^{3'}$、$R^{4'}$各自独立地为氢、氘、C_1-C_4烷基，j为2、3、4、5、6、7或8。

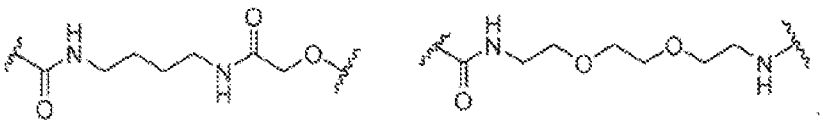
14. 如权利要求12所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药和/或其药学上可接受的盐，其特征在于所述 L 为$-(CH_2)_j$ -，所述$-(CH_2)_j$-中的1个、2个或者3个亚甲基任选地被选自-O-、-NH-、$-NCH_3$-、$-NCH_2CH_3$-、-C(O)-、-C(O)NH-、-NHC(O)-、$-NCH_3C(O)$-、$-C(O)NCH_3$-、 

的基团替代，j为2、3、4、5、6、7或8。

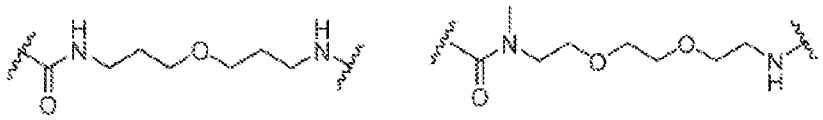
15. 如权利要求12所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药和/或其药学上可接受的盐，其特征在于所述 L 为$-(CH_2)_{j-1}$-C(O)-，所述-$(CH_2)_{j-1}$-C(O)-中的亚甲基如权利要求11中所定义，任选被1个或多个基团所替代，所述j如权利要求20中所定义。

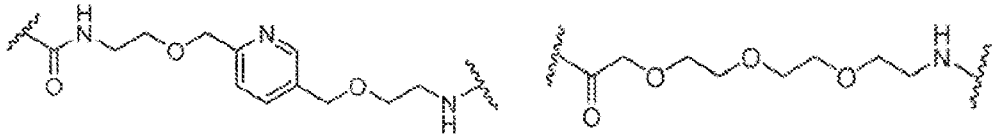
16. 如权利要求12所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药和/或其药学上可接受的盐，其特征在于所述L为

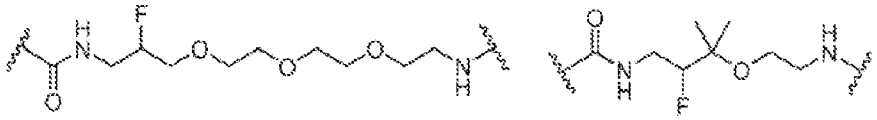


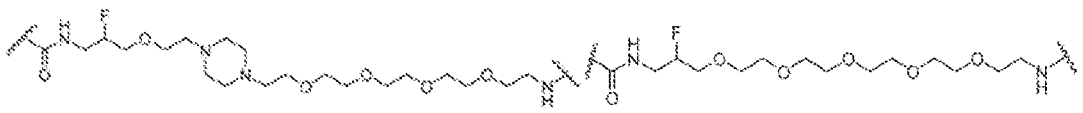


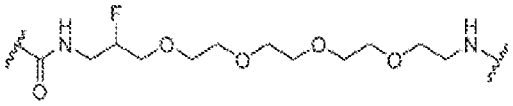


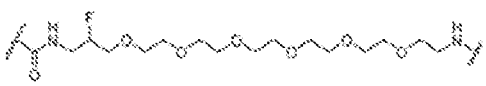


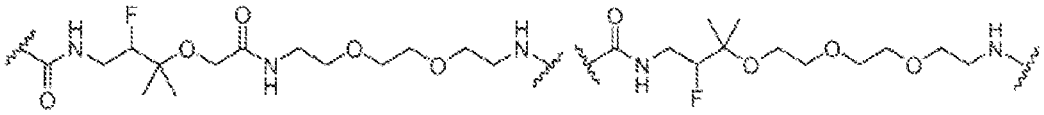


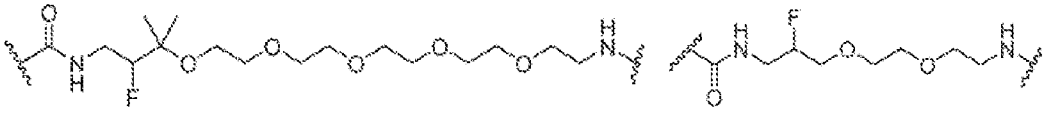


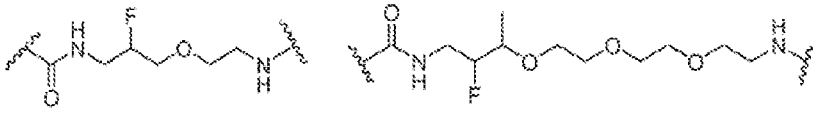


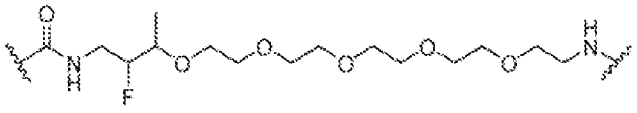


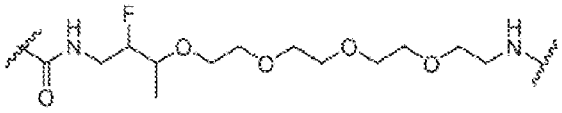


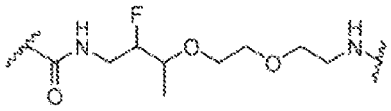


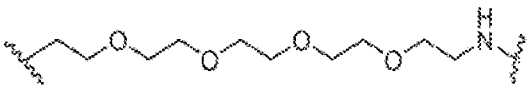


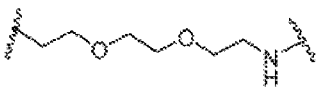


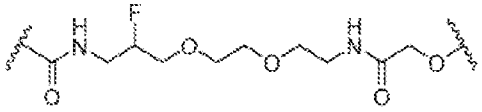


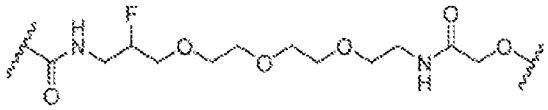


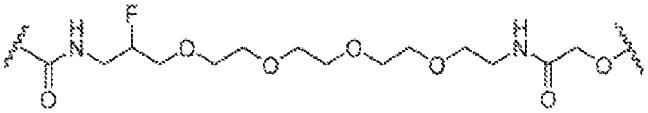


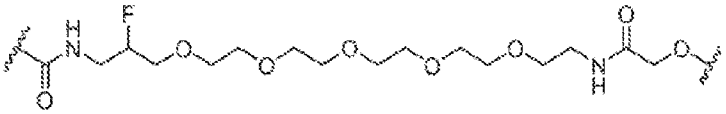


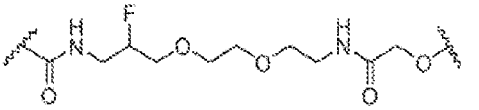


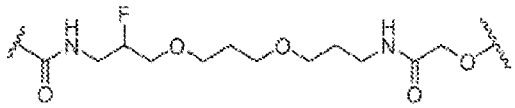


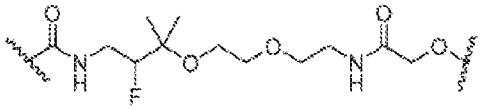


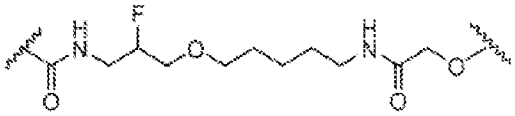


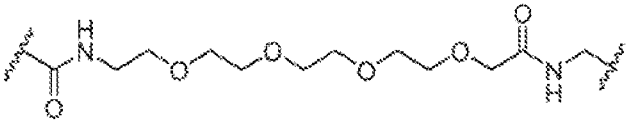


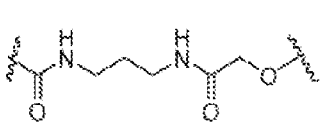


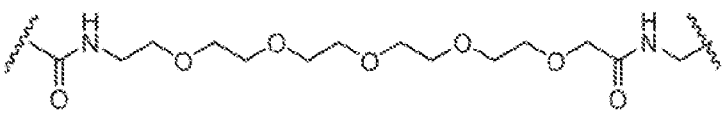


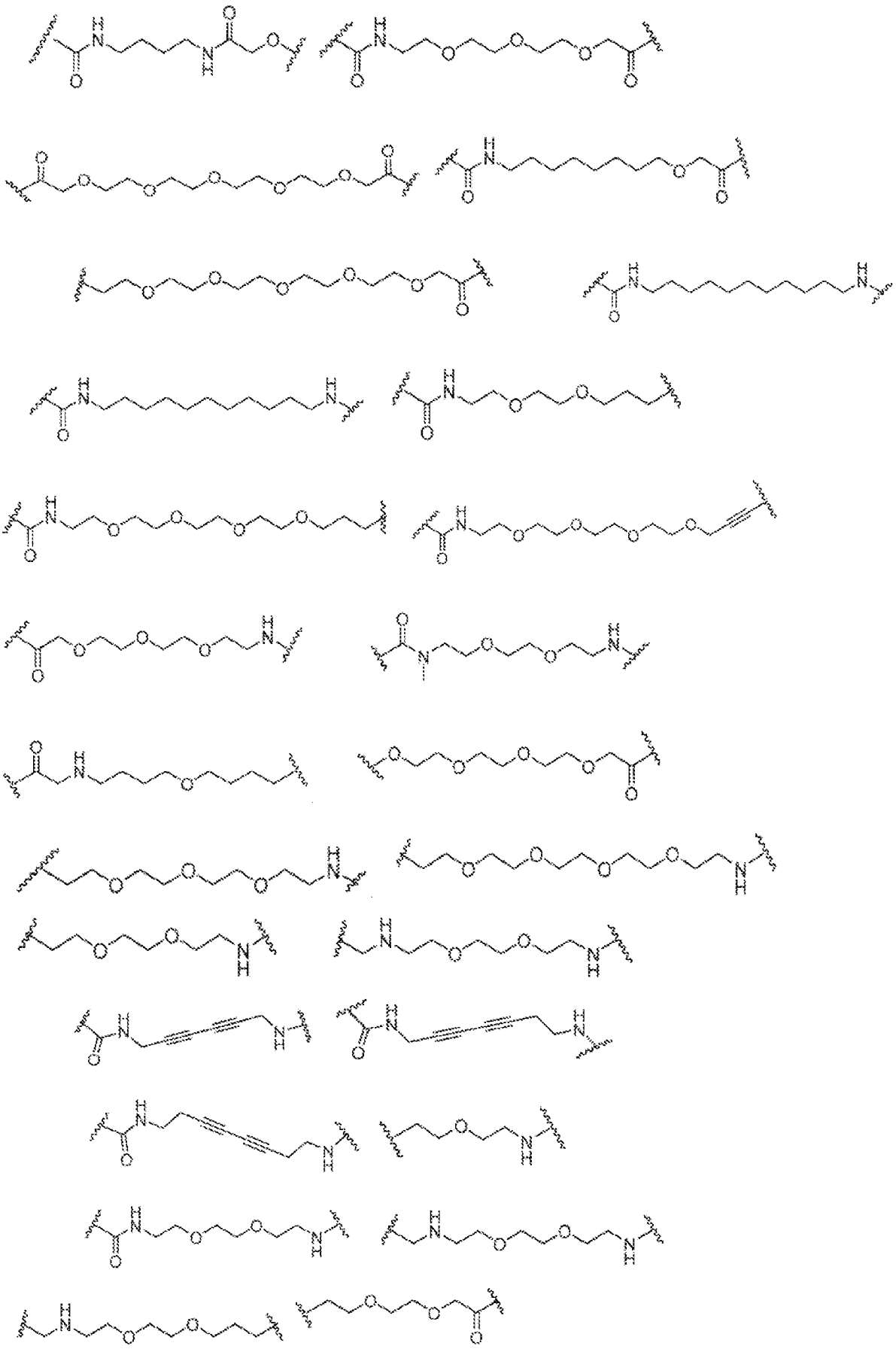


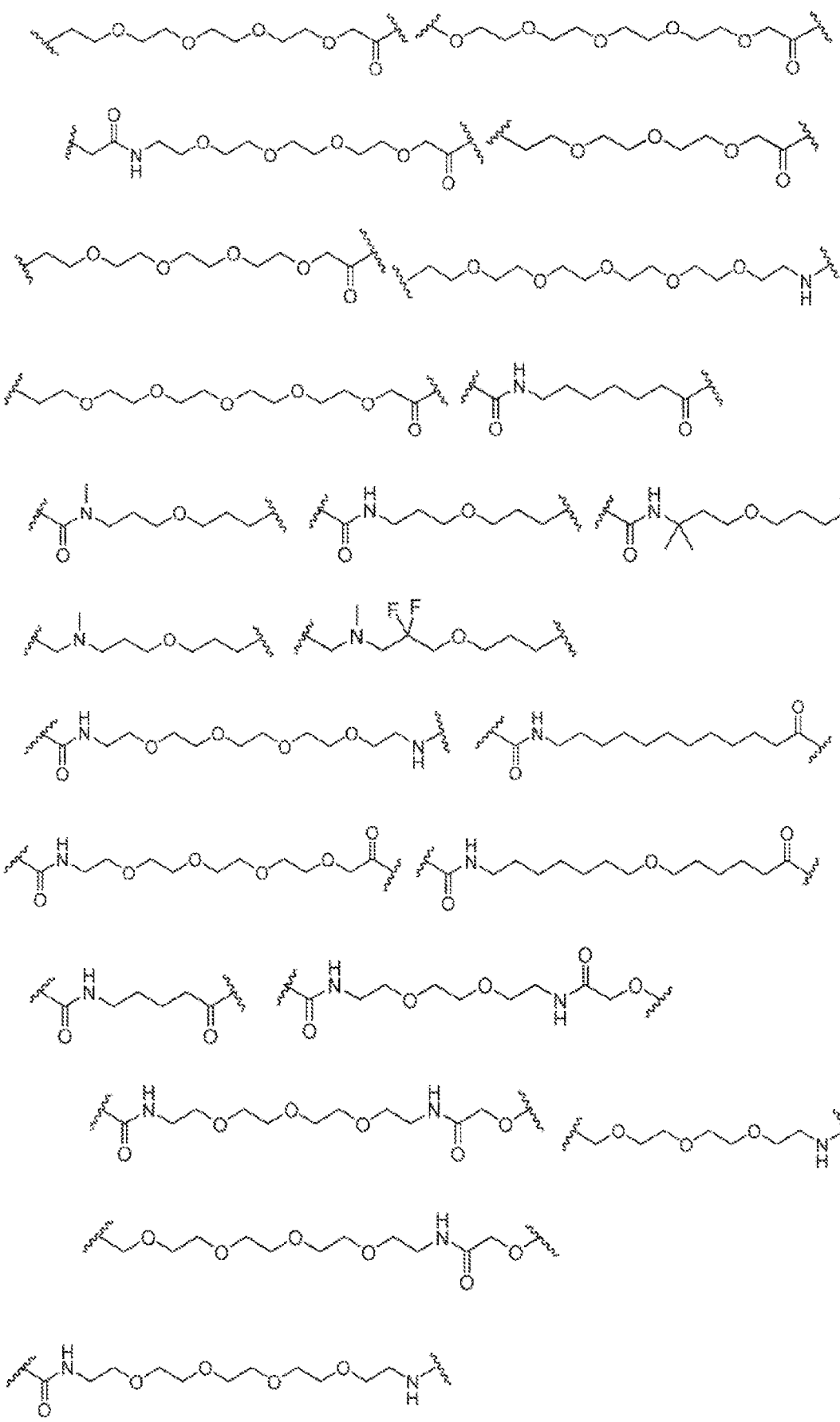


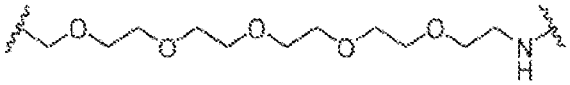


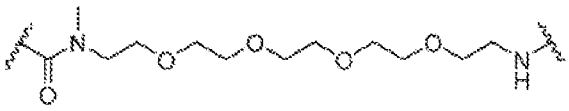


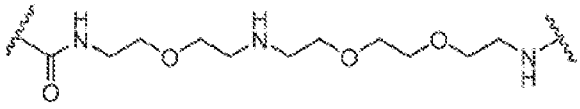


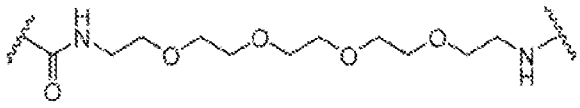


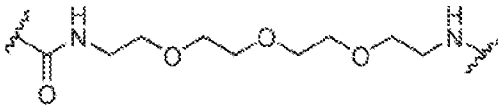


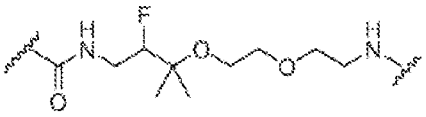


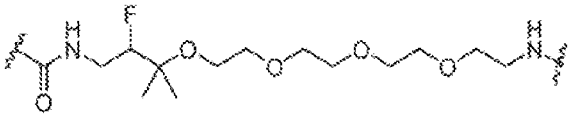


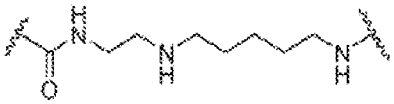


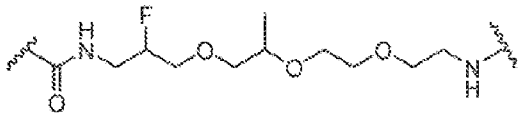


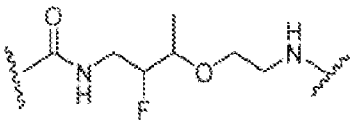


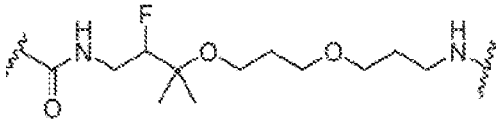


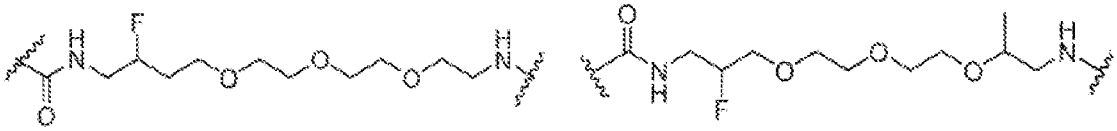


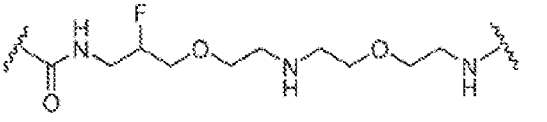


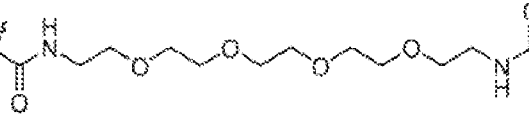


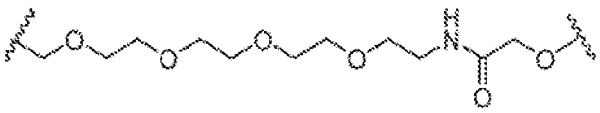


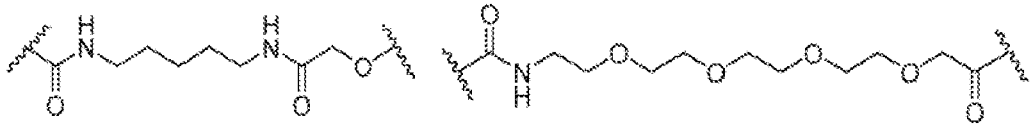


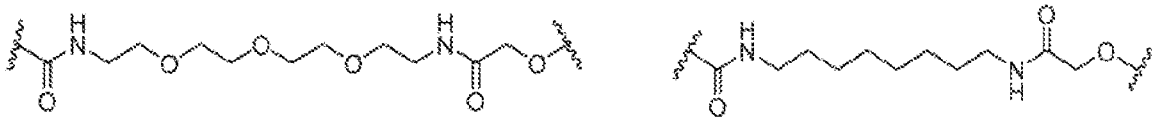


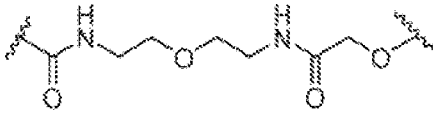


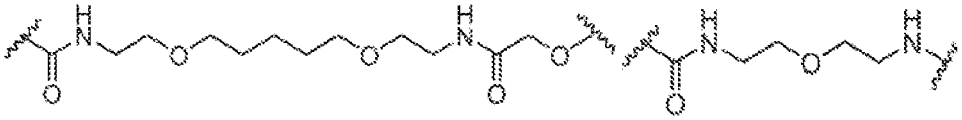


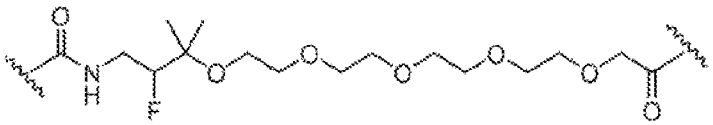


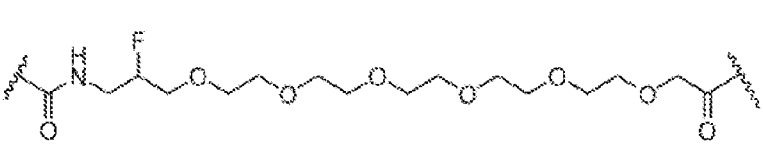


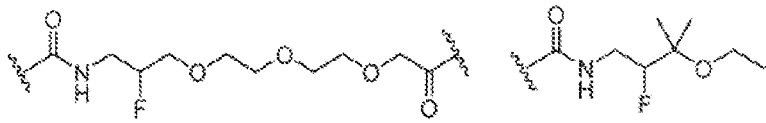


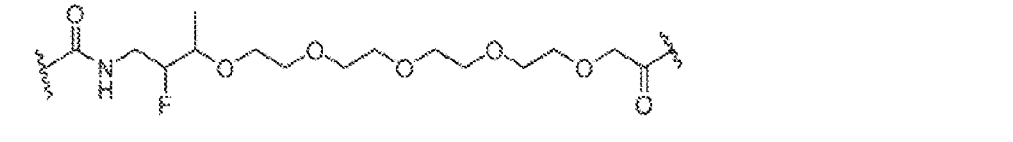


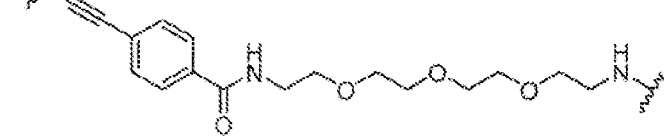


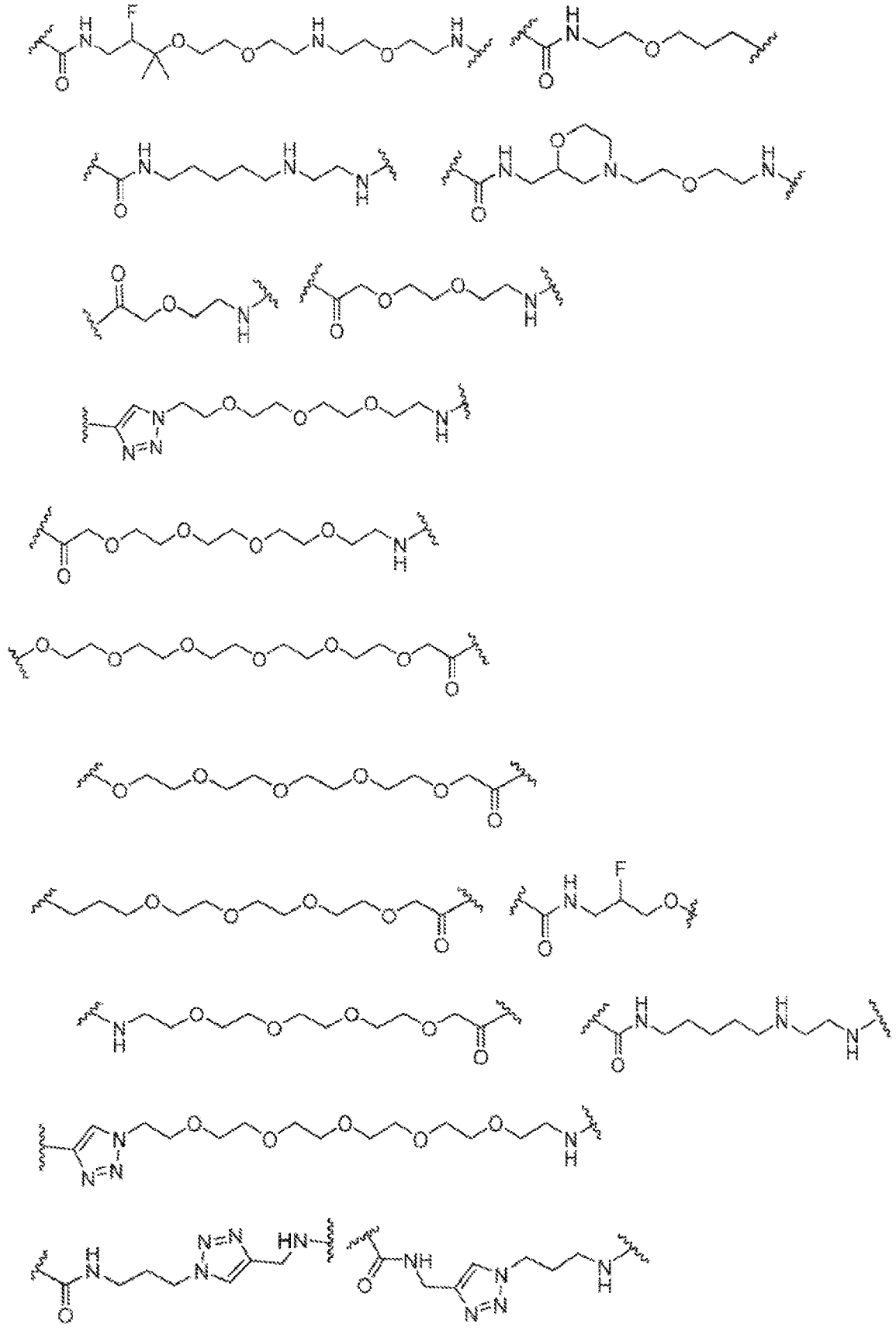


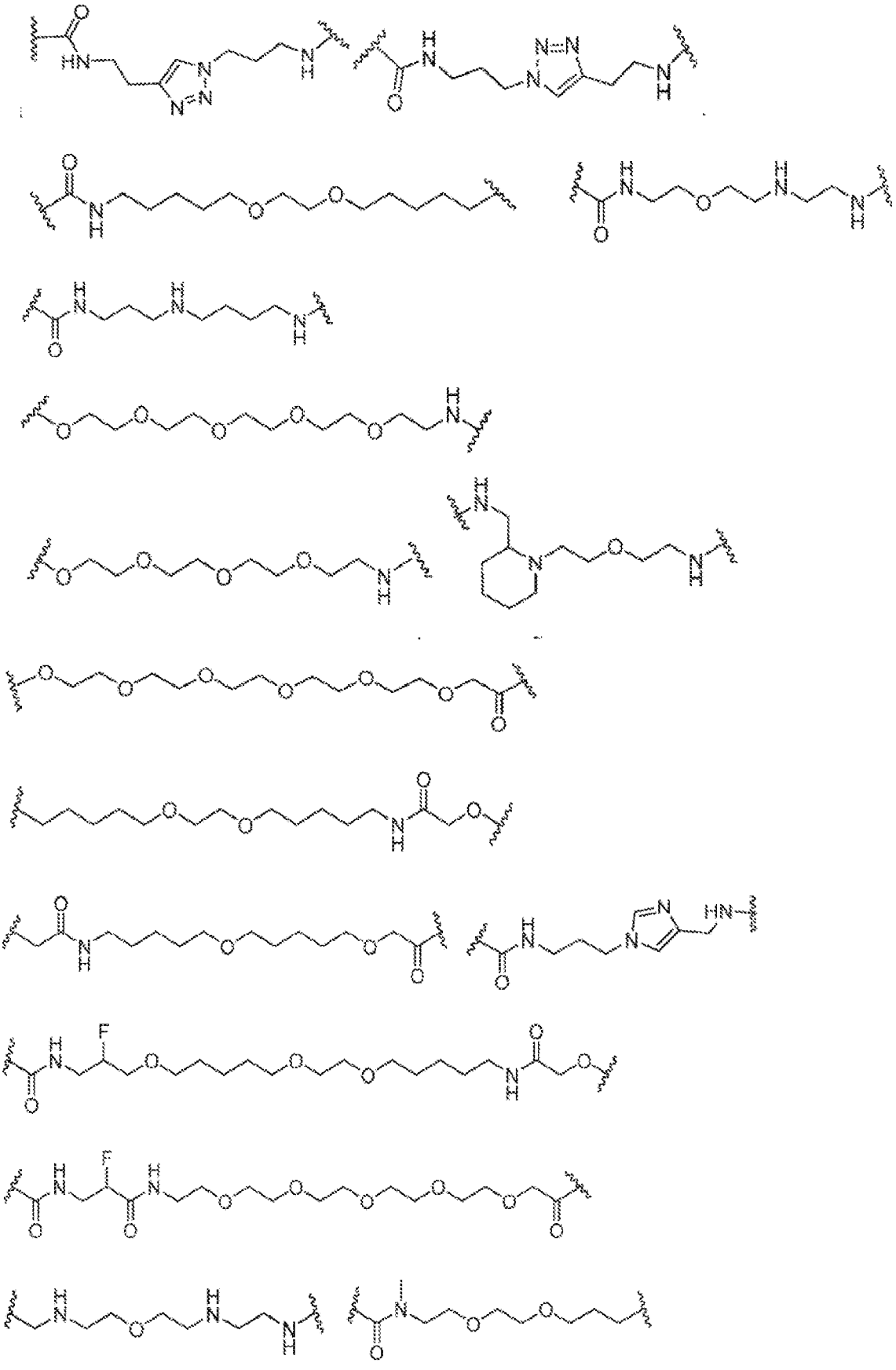


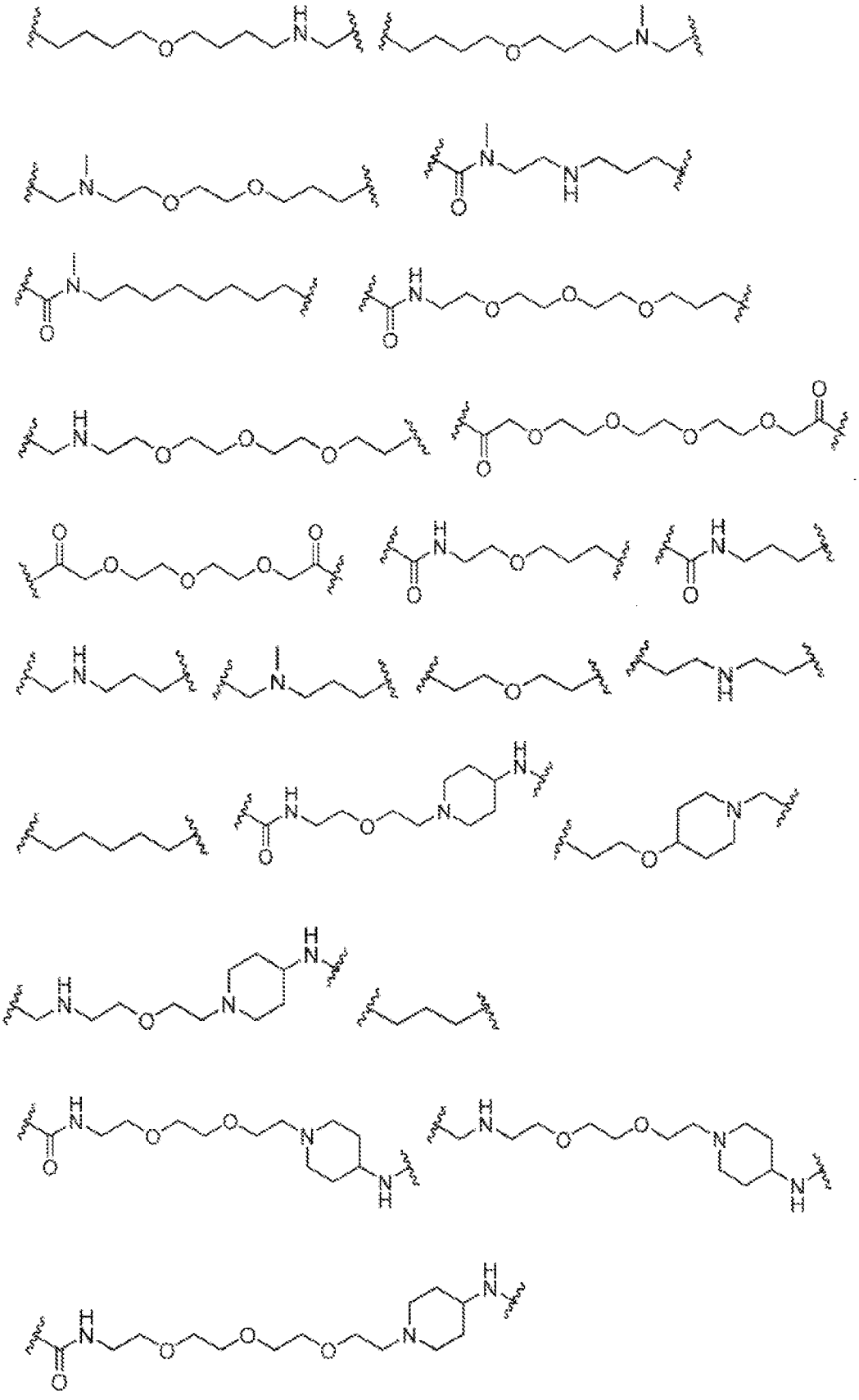


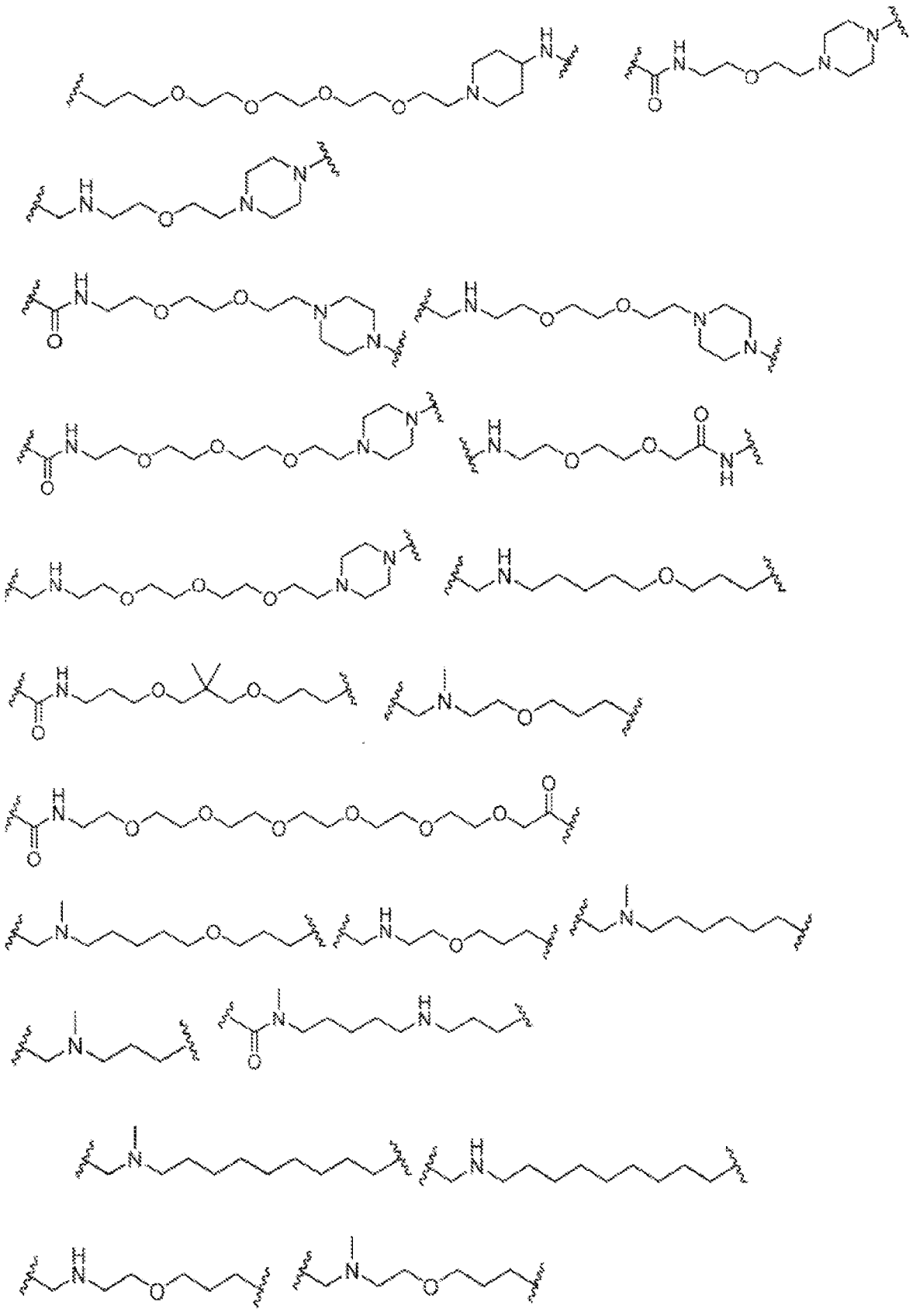


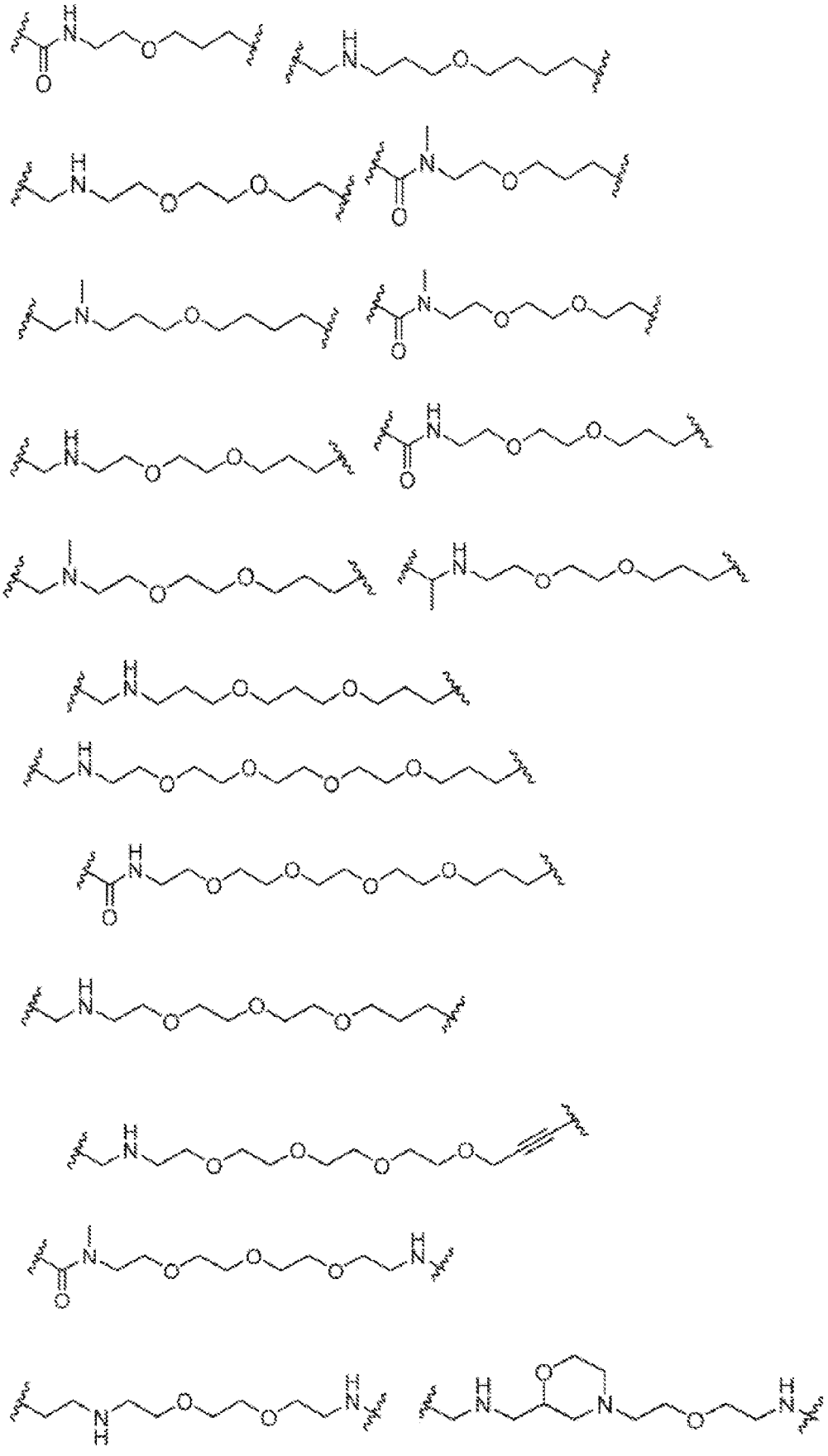


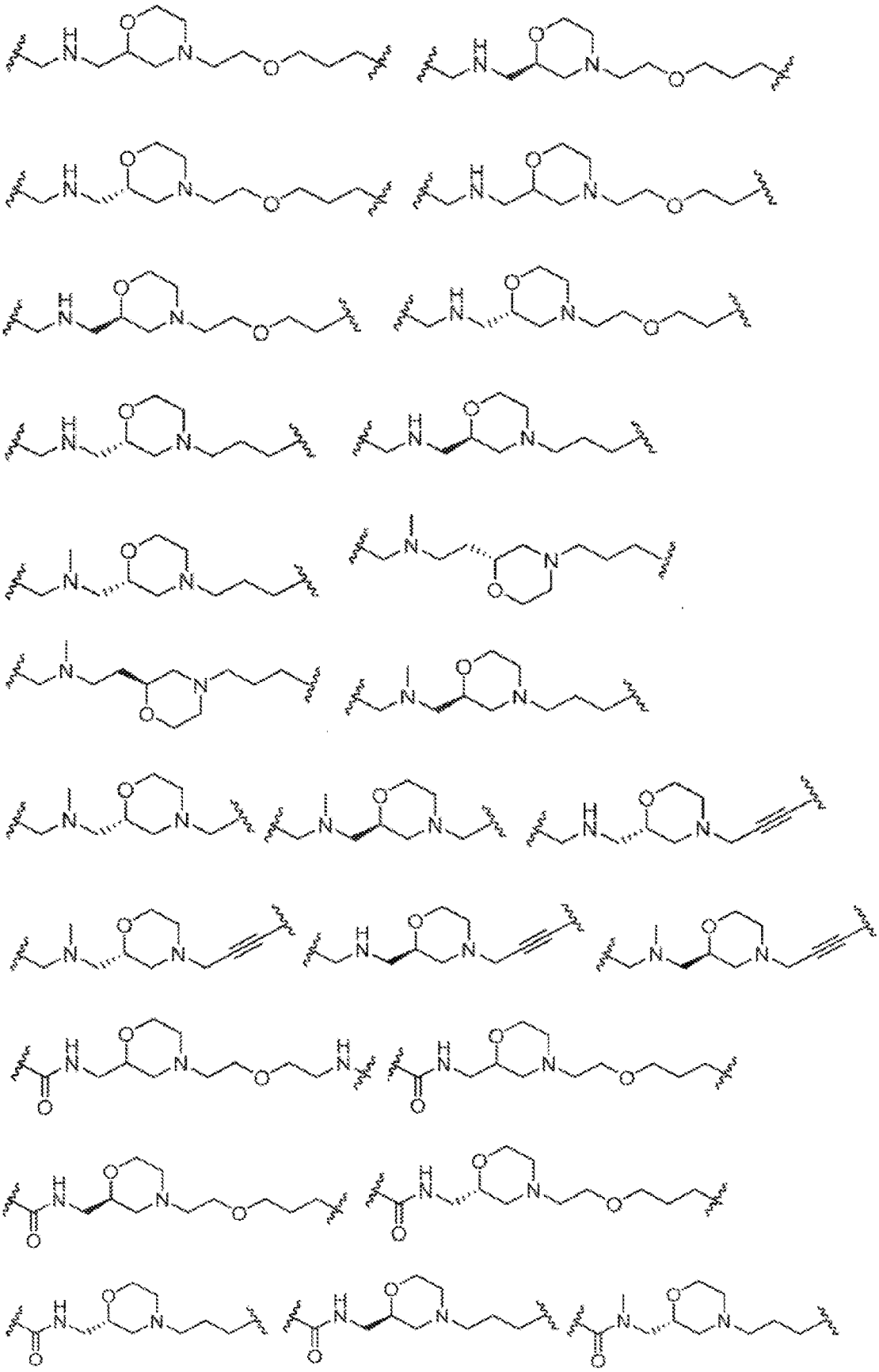


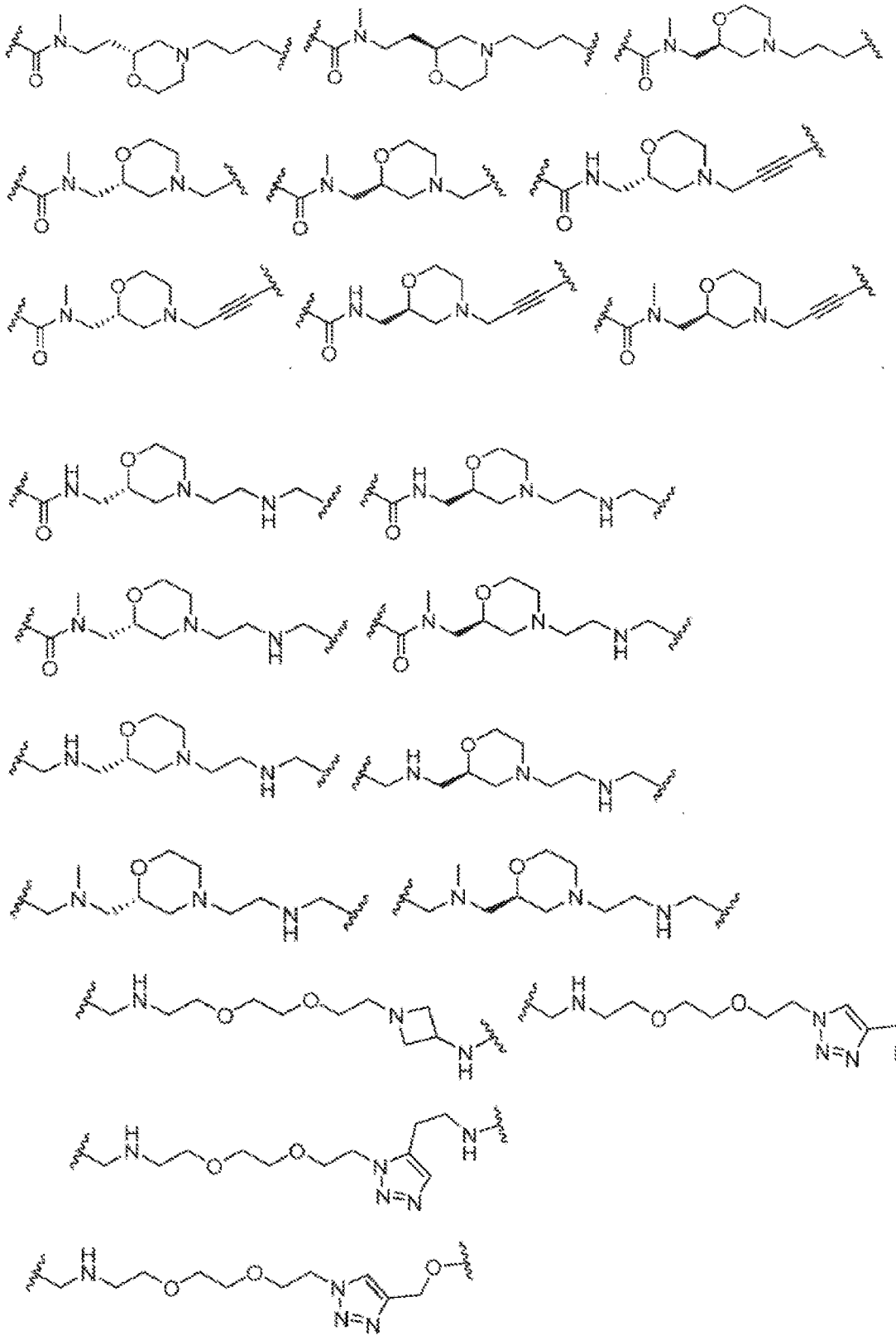


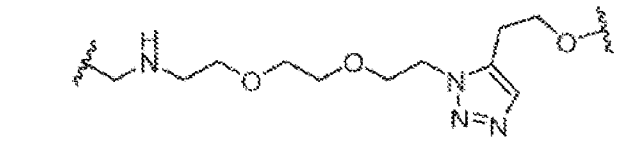


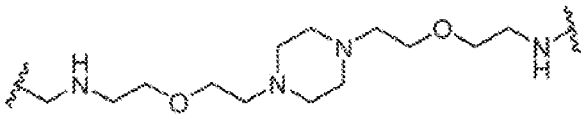


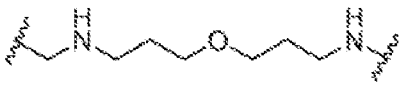


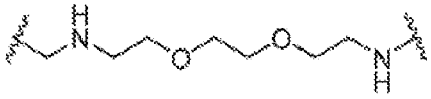


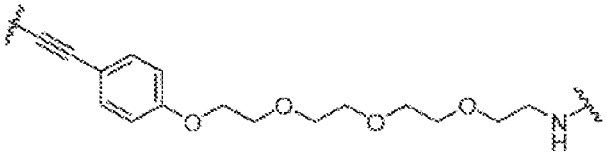


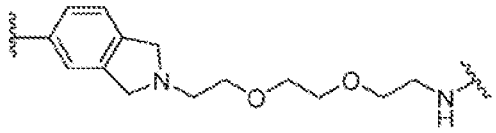


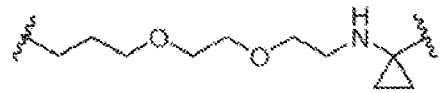


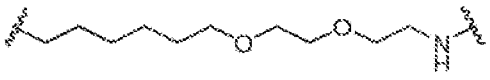


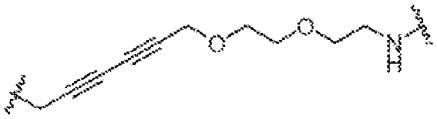


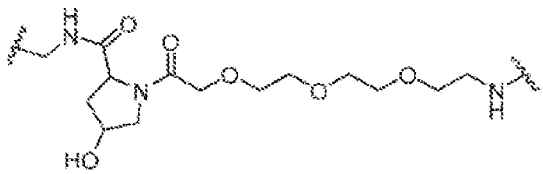


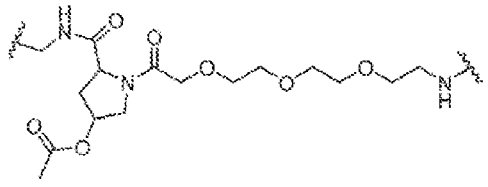


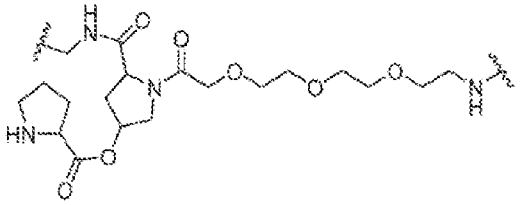


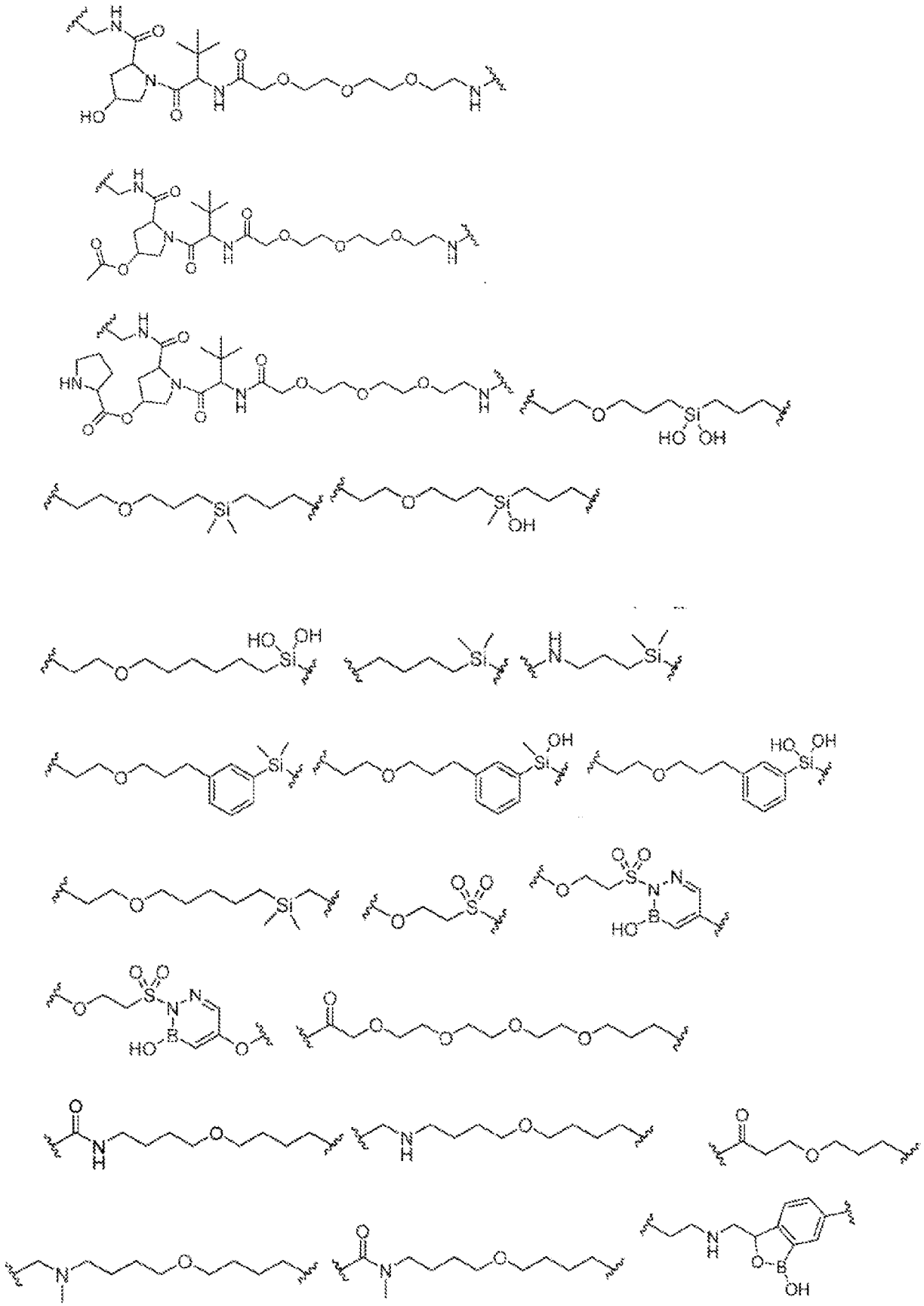


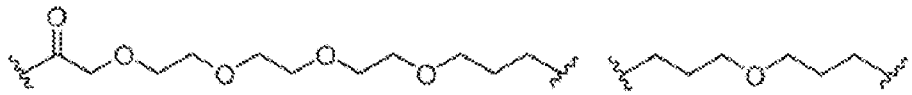


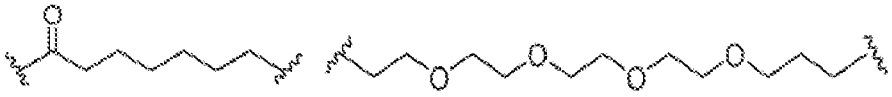


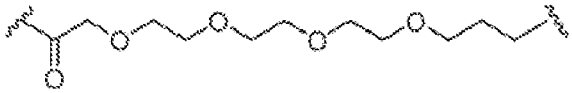


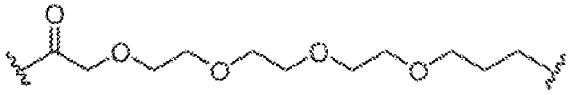


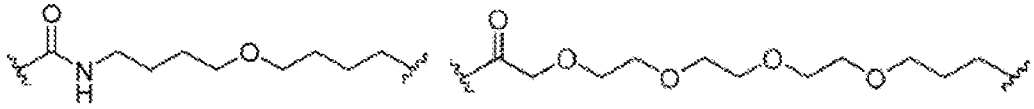


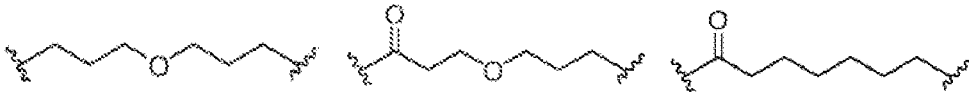


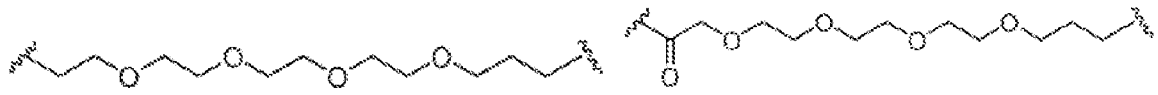


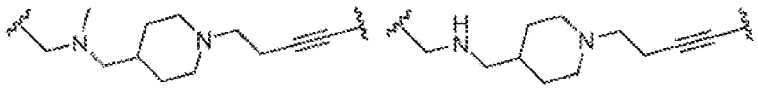


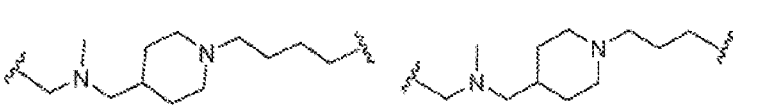


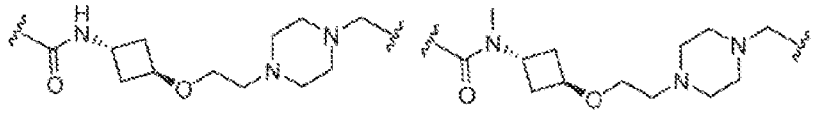


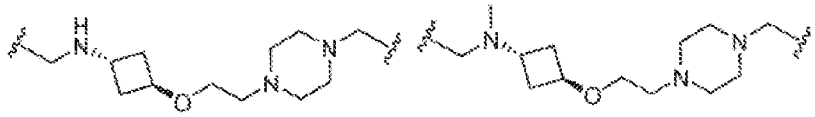


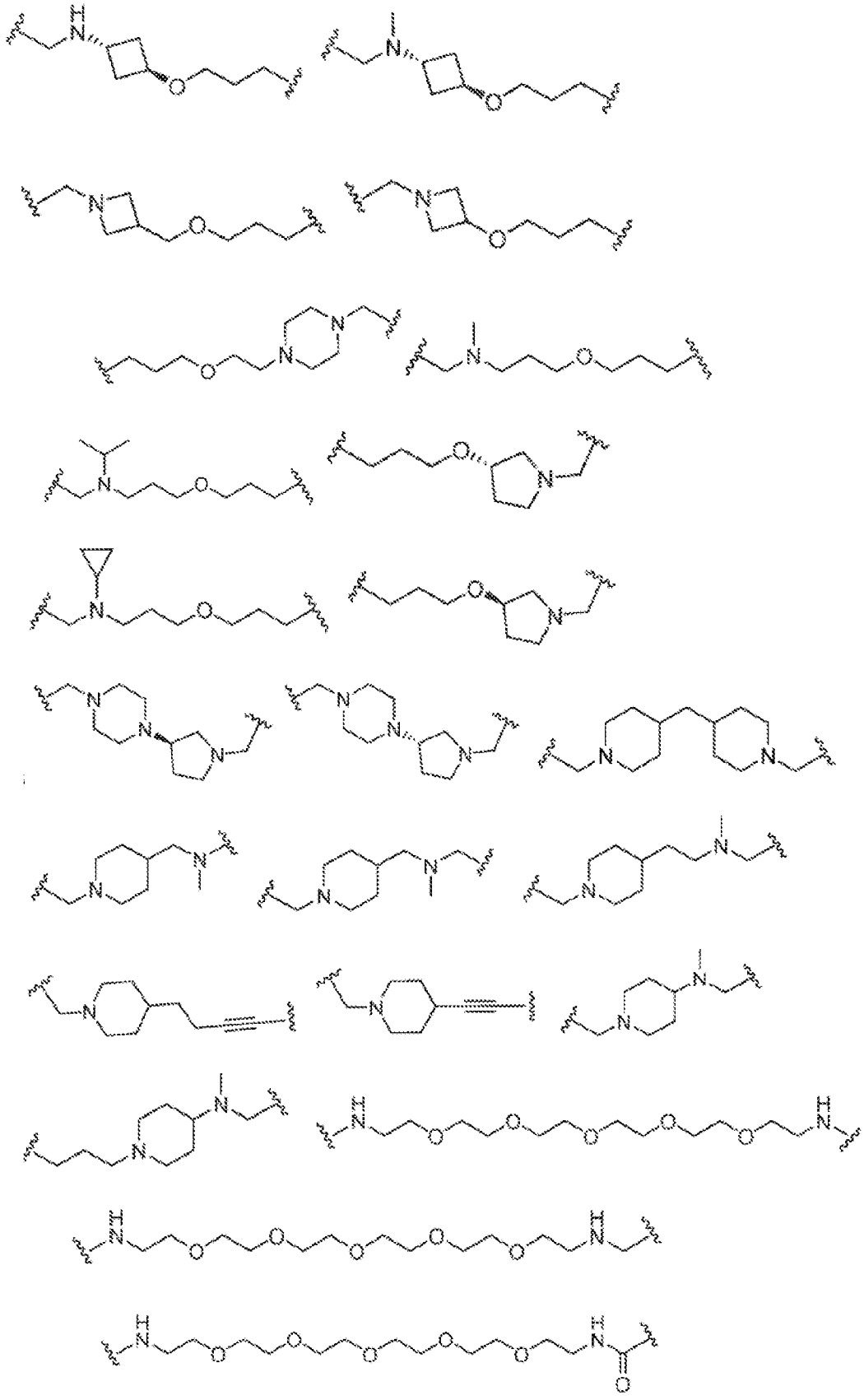


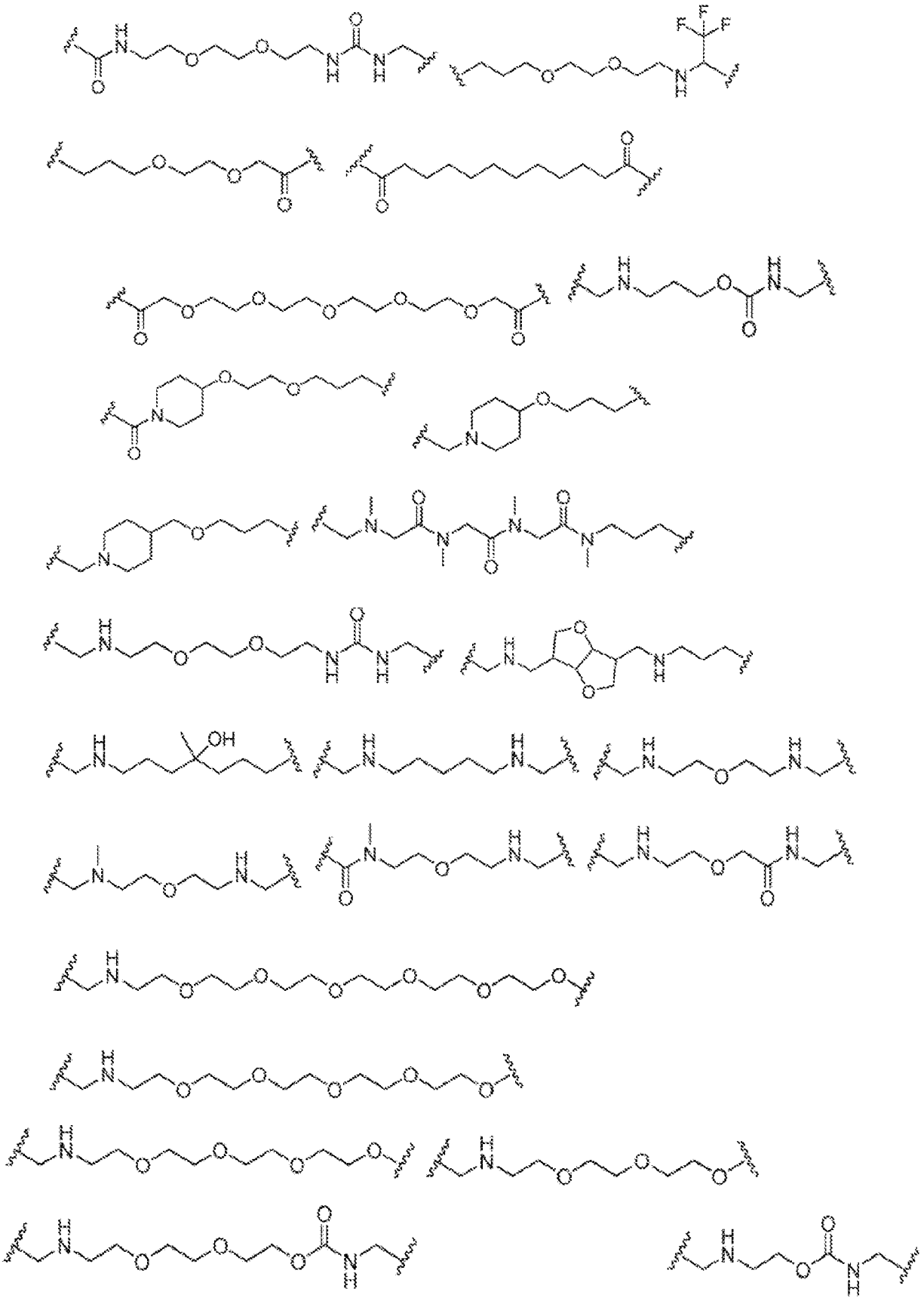


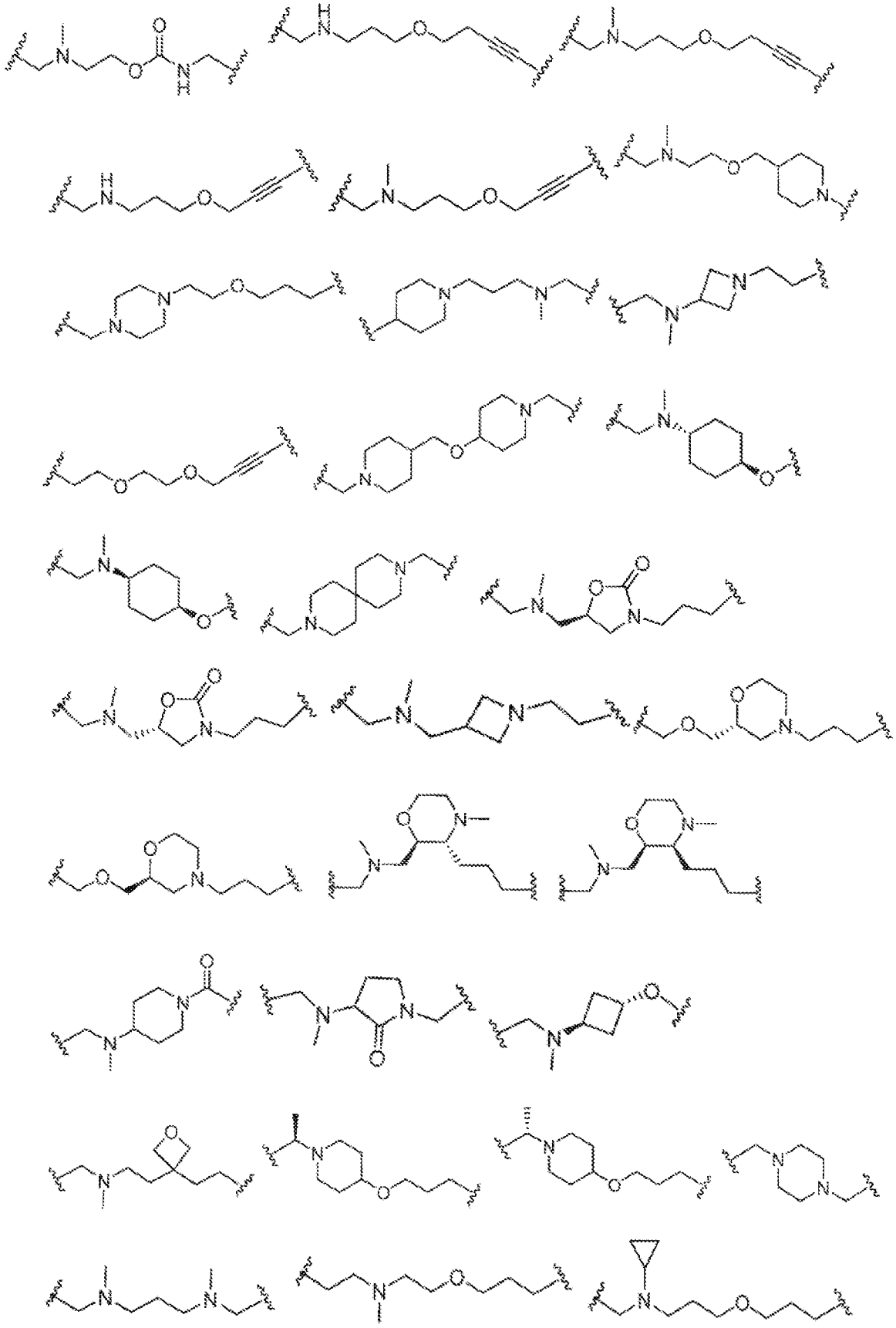


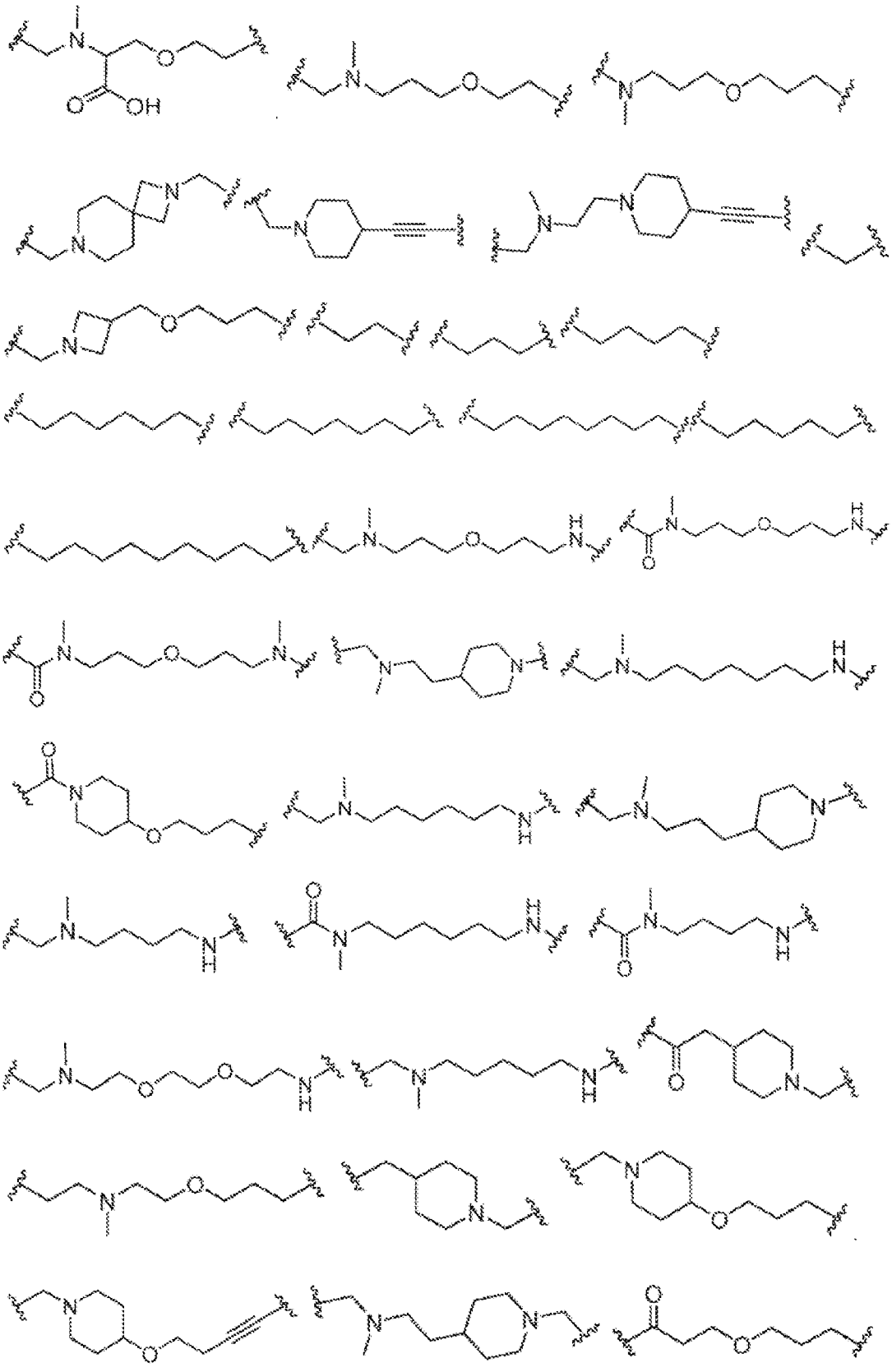


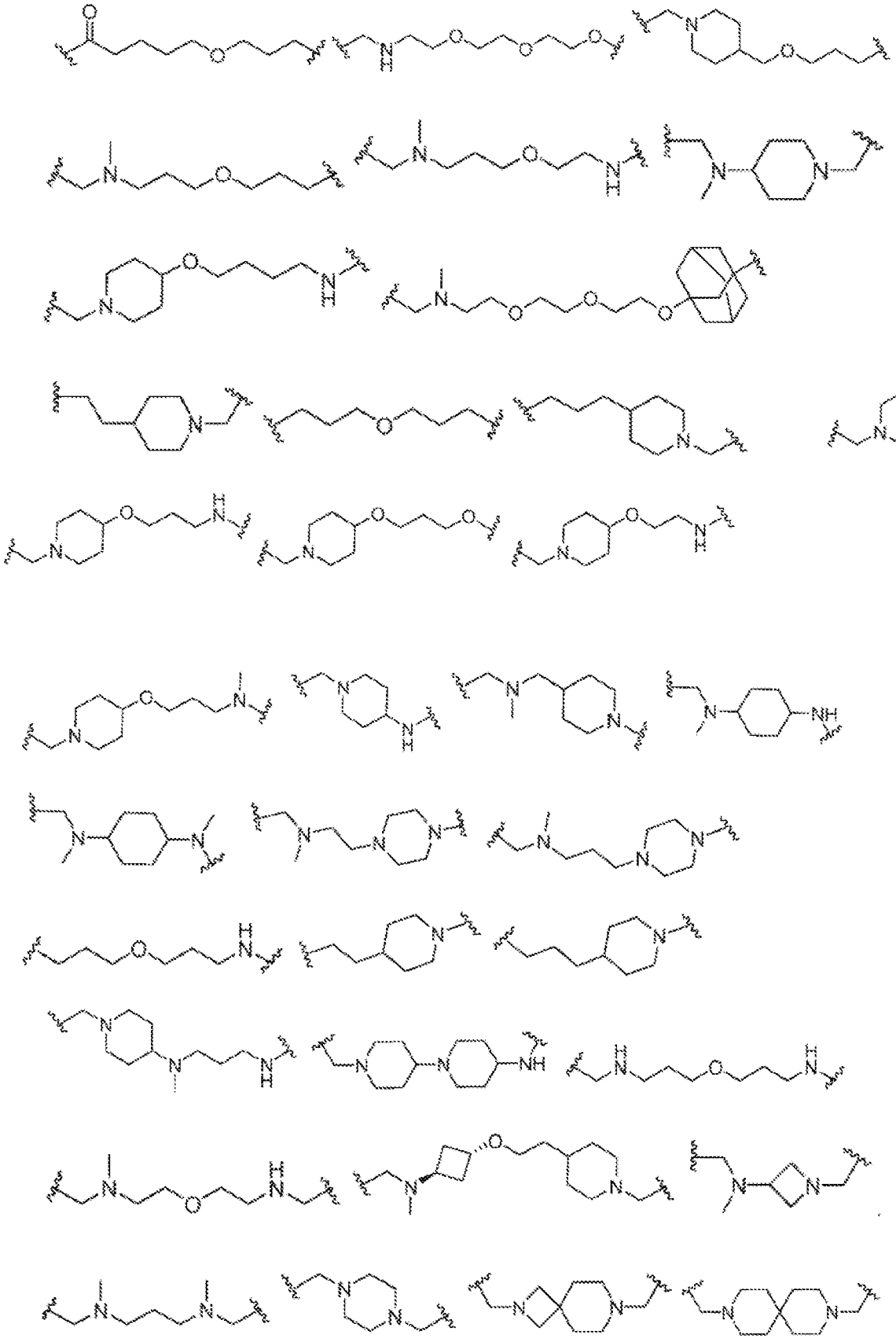


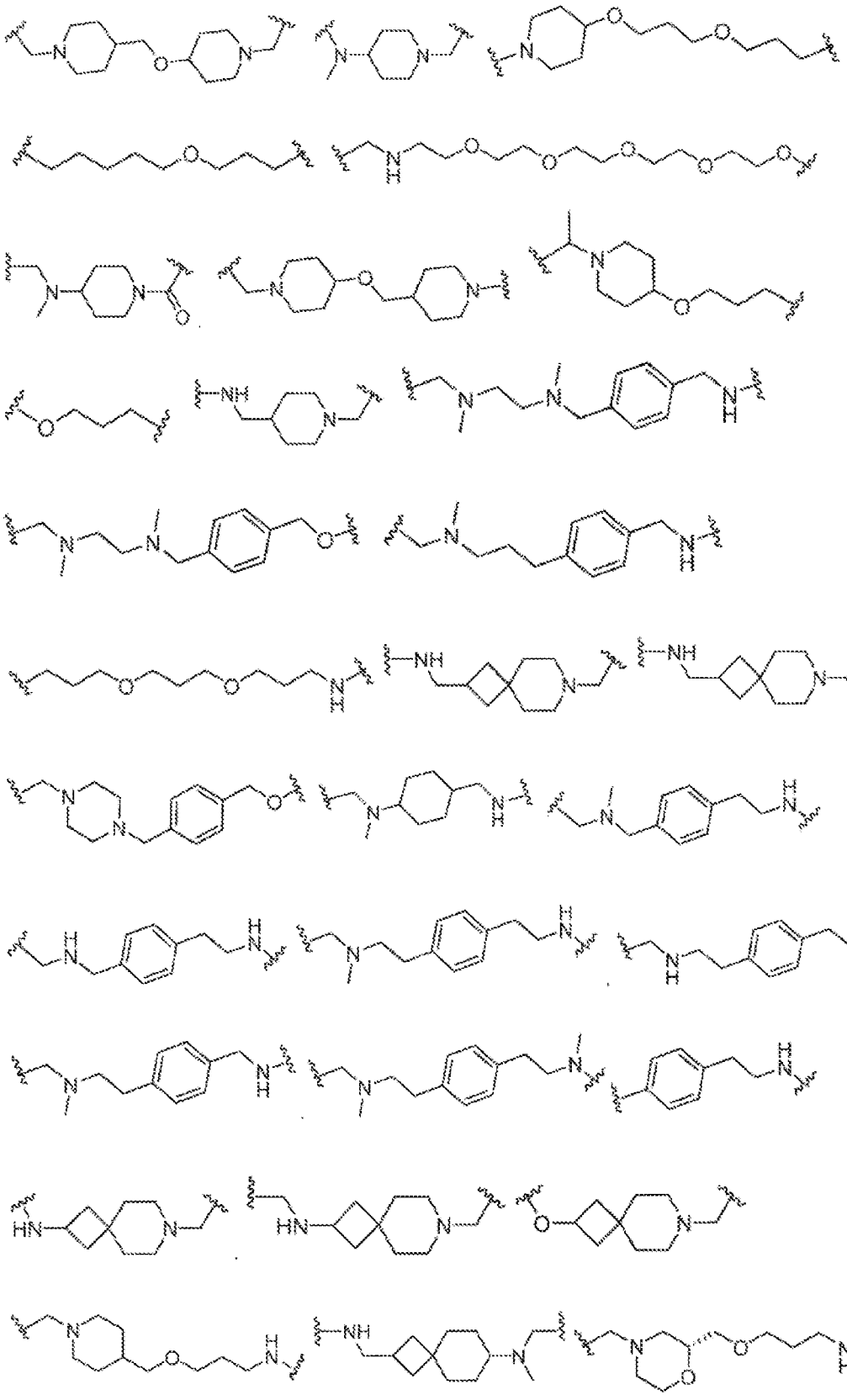


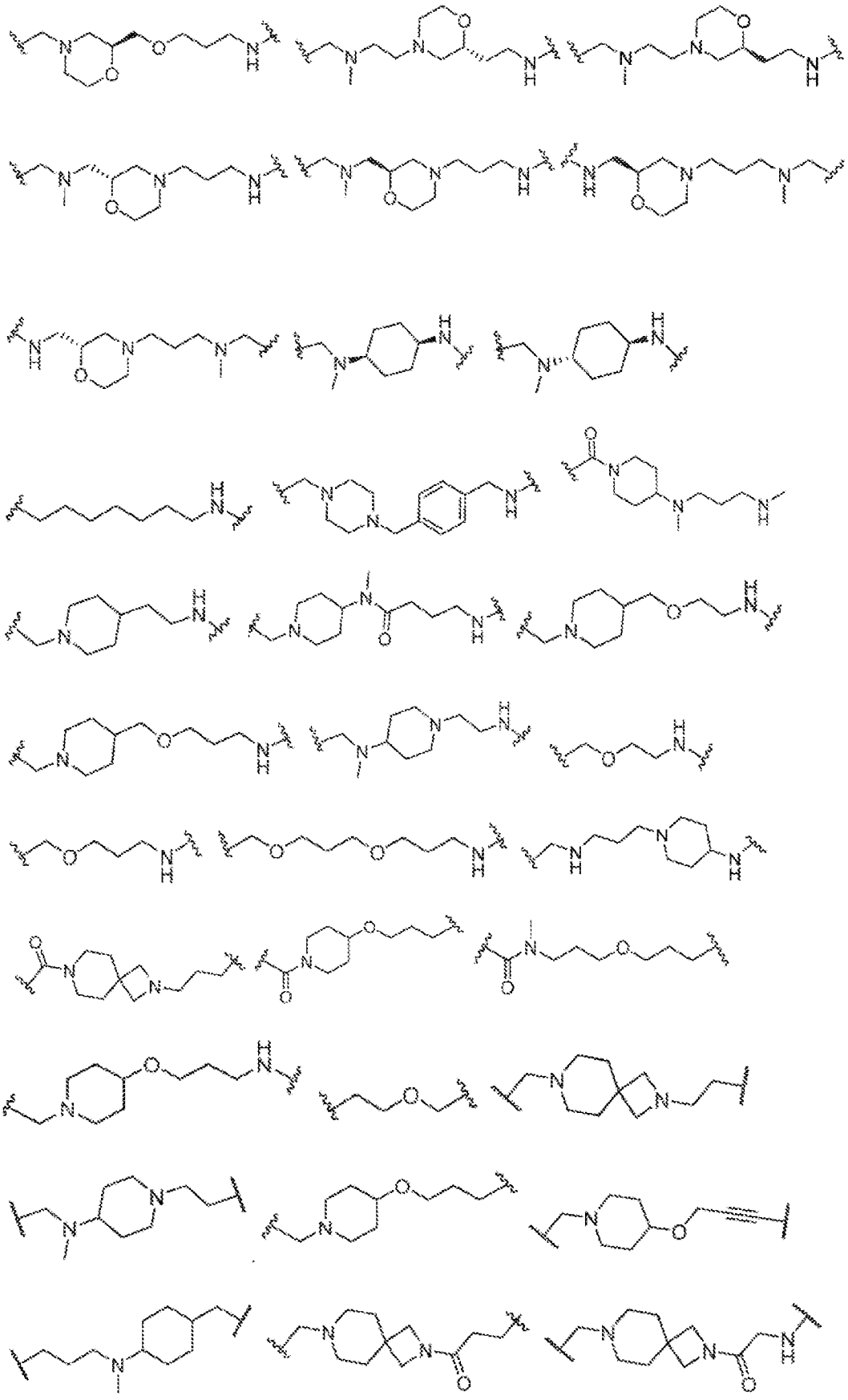


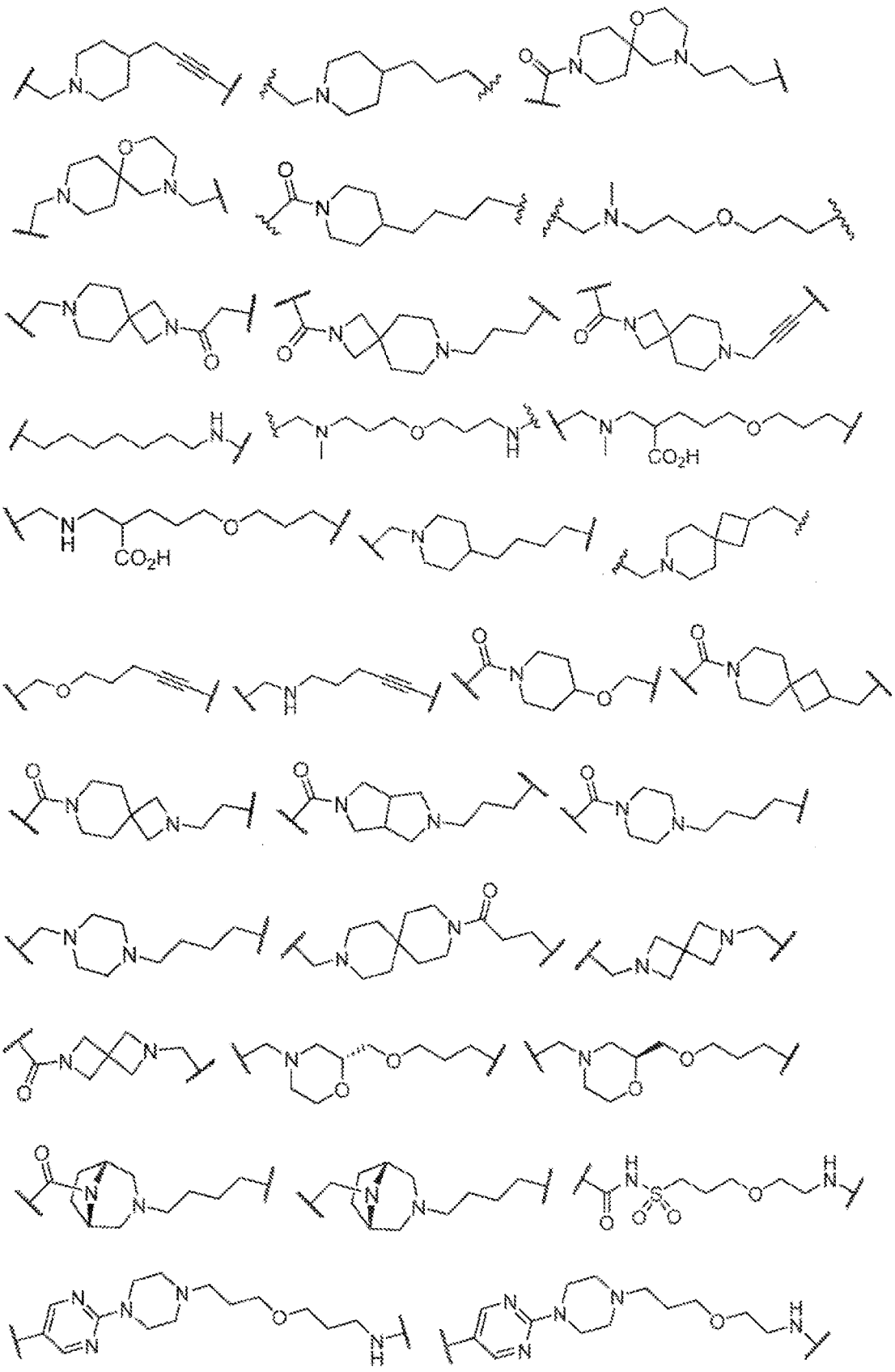


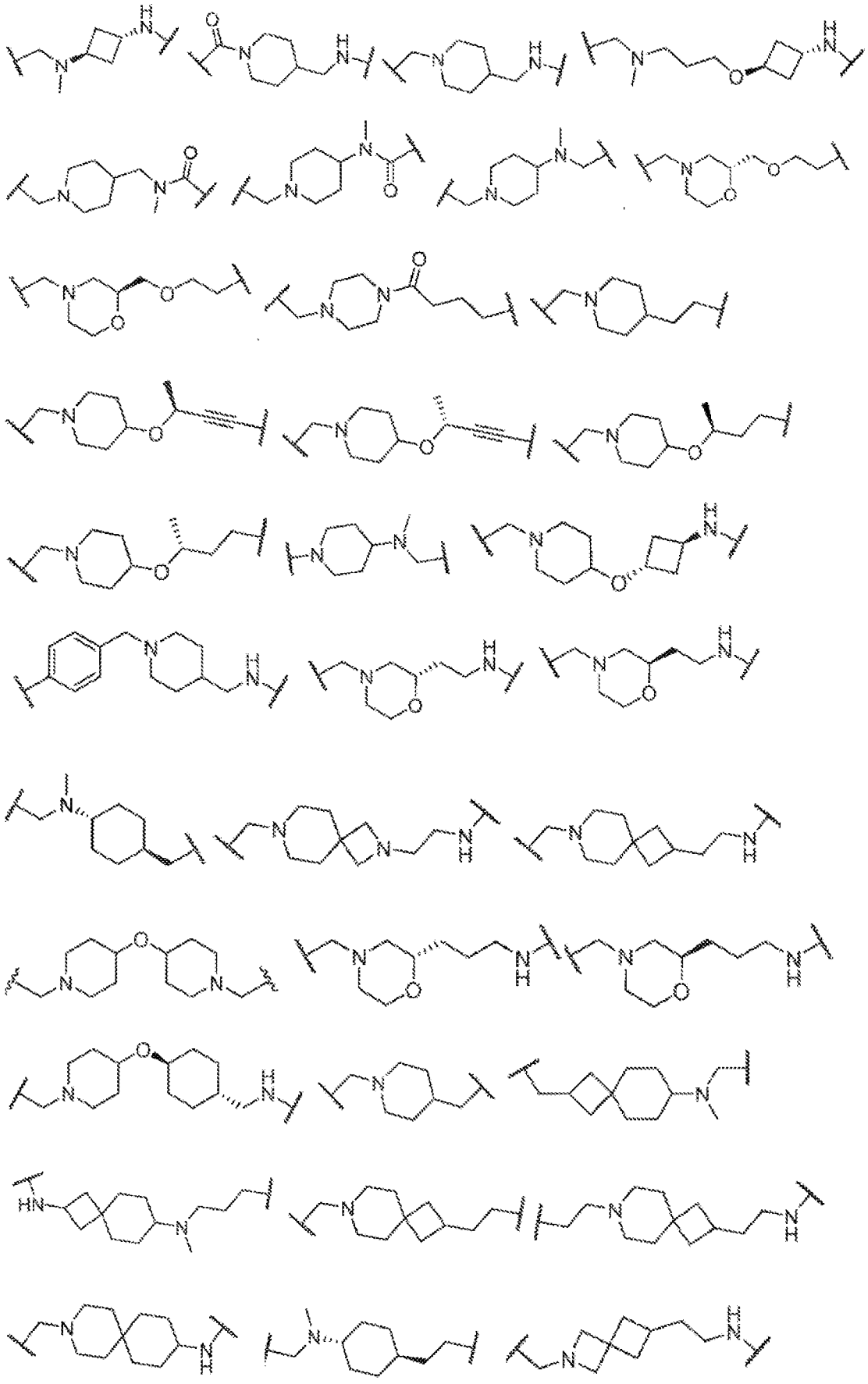


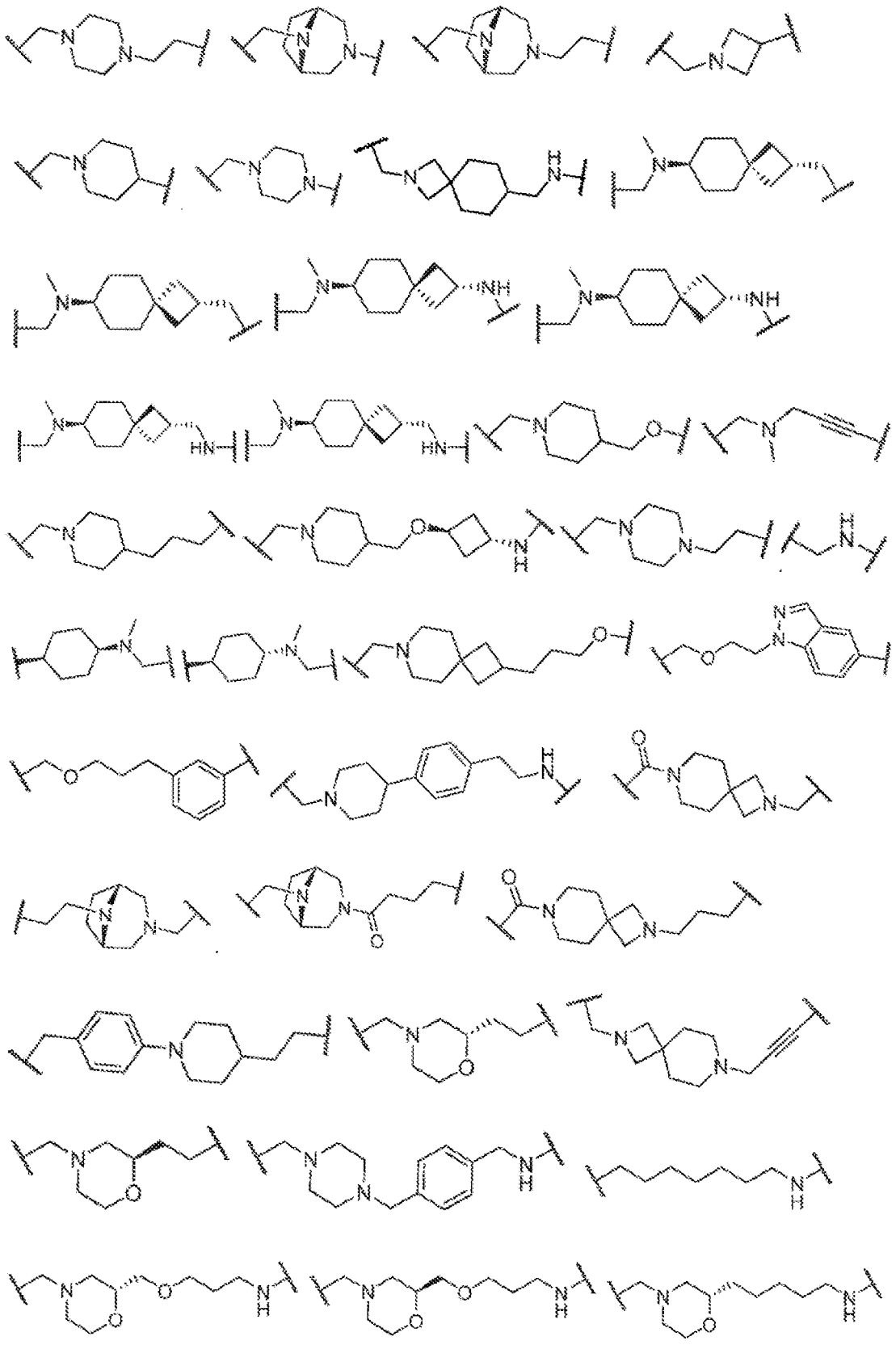


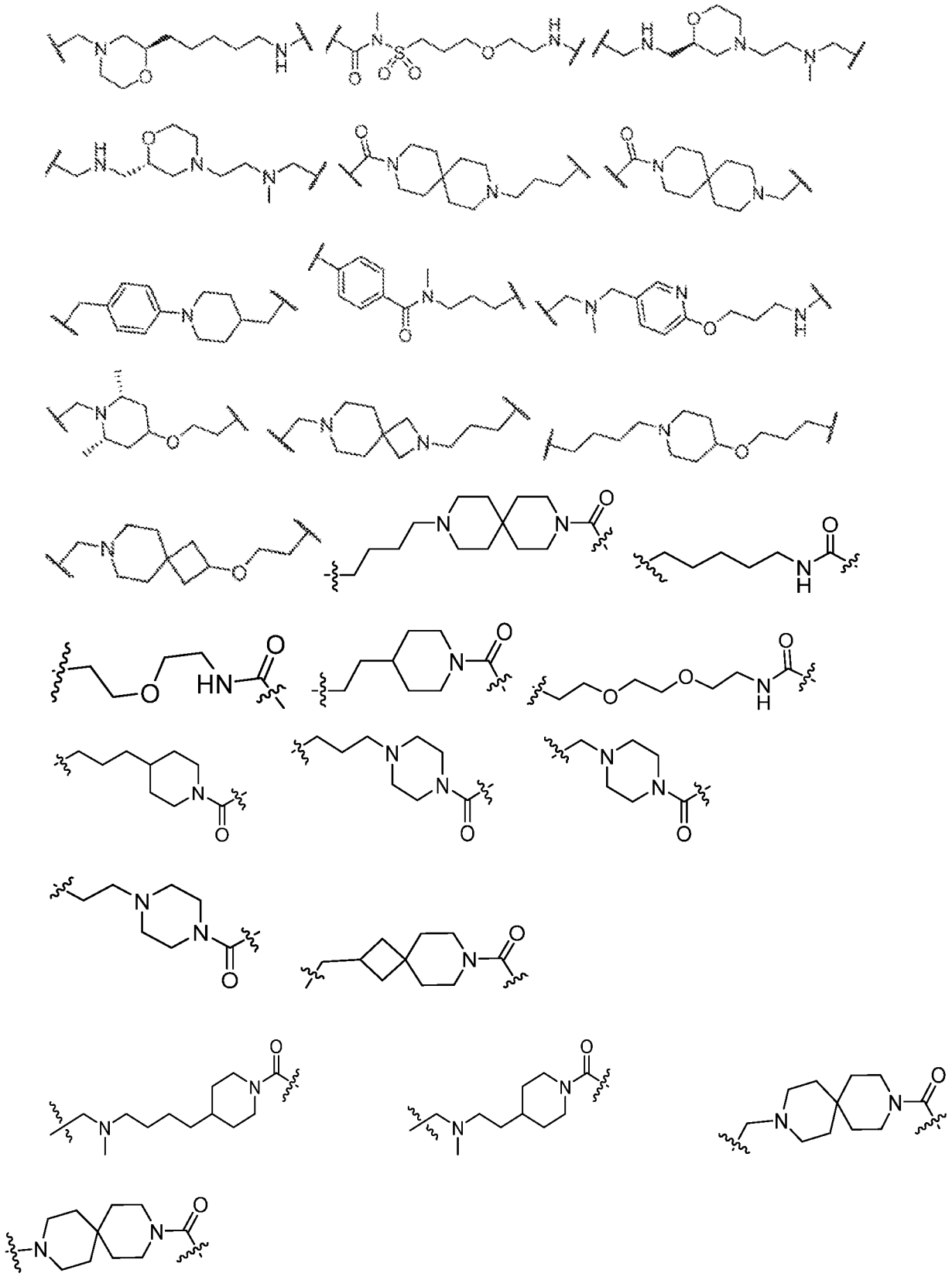


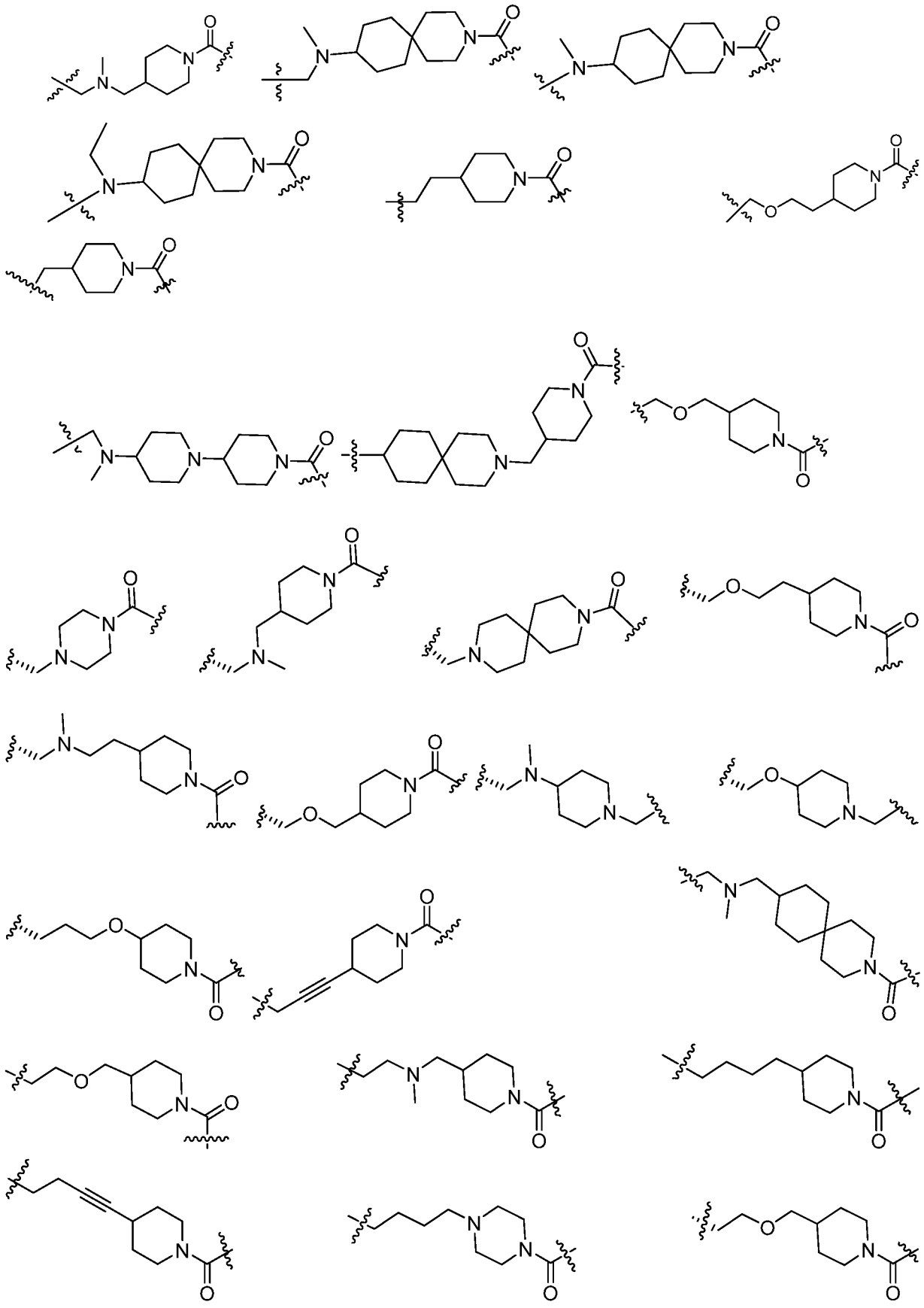


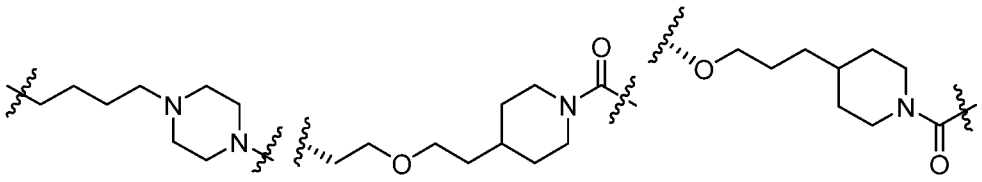












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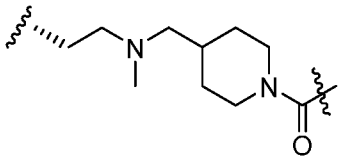
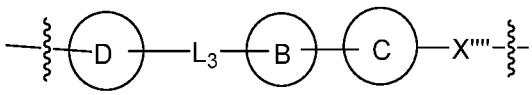


。

17. 如权利要求 12 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 为 LA，



LA

其中所述 LA 中：

环 D 不存在、6-10 元芳基、5-10 元杂芳基或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

环 B 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

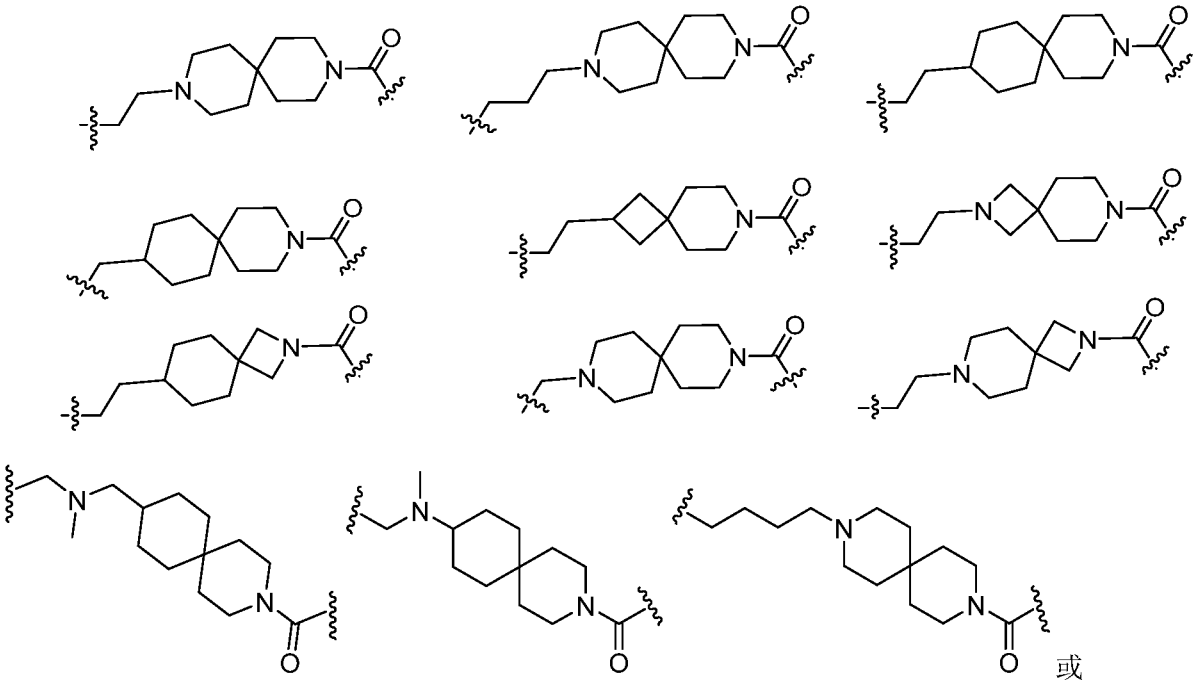
环 C 为不存在、C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

X""为 键 、-NH-、-NCH_3-、-O-、-$C(CH_3)_2$-、-S-、-C=C-、-C≡C-、-CHF-、-$CHCF_3$-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(O)O-、-OC(O)-、-C(O)NH-、-$C(O)NCH_3$-、-NHC(O)-、-$(CH_2)_t$-或-$NCH_3C(O)$-；所述-$(CH_2)_t$-中的一个或多个亚甲基任选地被选自-O-、-NH-、-C≡C-、-N(C_1-C_6 烷基)-、-C(O)-替代，t 为 0、1、2、3、4、5、6 或 7；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或多个亚甲基任选地被选自-O-、-NH-、-N(C_1-C_6 烷基)-、-N(C_1-C_6 卤代烷基)-、-N(C_1-C_6 羟基烷基)-、-C≡C-、-C(O)-或-N(C_3-C_8 环烷基)-替代，k 为 0、1、2、3、4、5、6、7、8、9 或 10。

18. 如权利要求 17 所述的式 I 化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 为 LA，所述 LA 中环 D 和环 B 不存在，环 C 为含有 1 个或者 2 个氮杂原子的的 7-11 元的亚螺杂环烷基；X""为-C(O)-；L_3 为-$(CH_2)_k$-；k 为 1、2、3、4 或者 5。

19. 如权利要求 18 所述的式 I 化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 选自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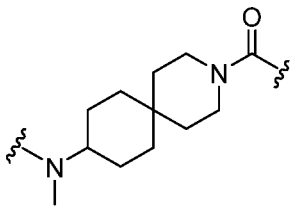
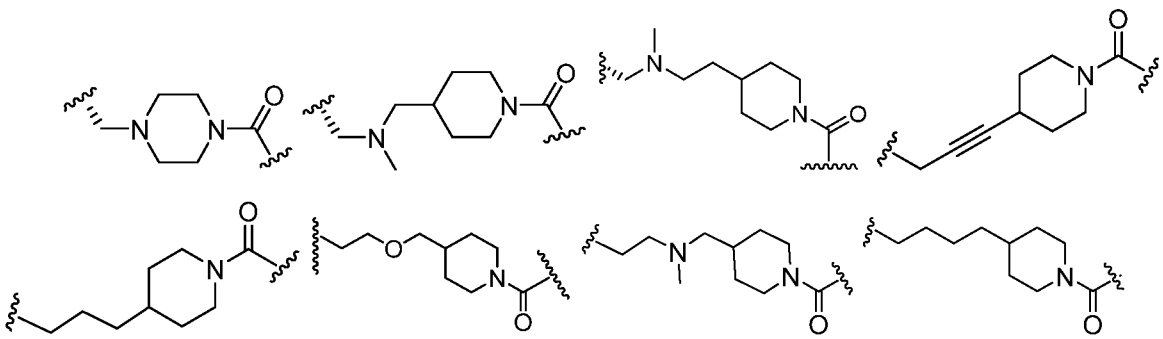
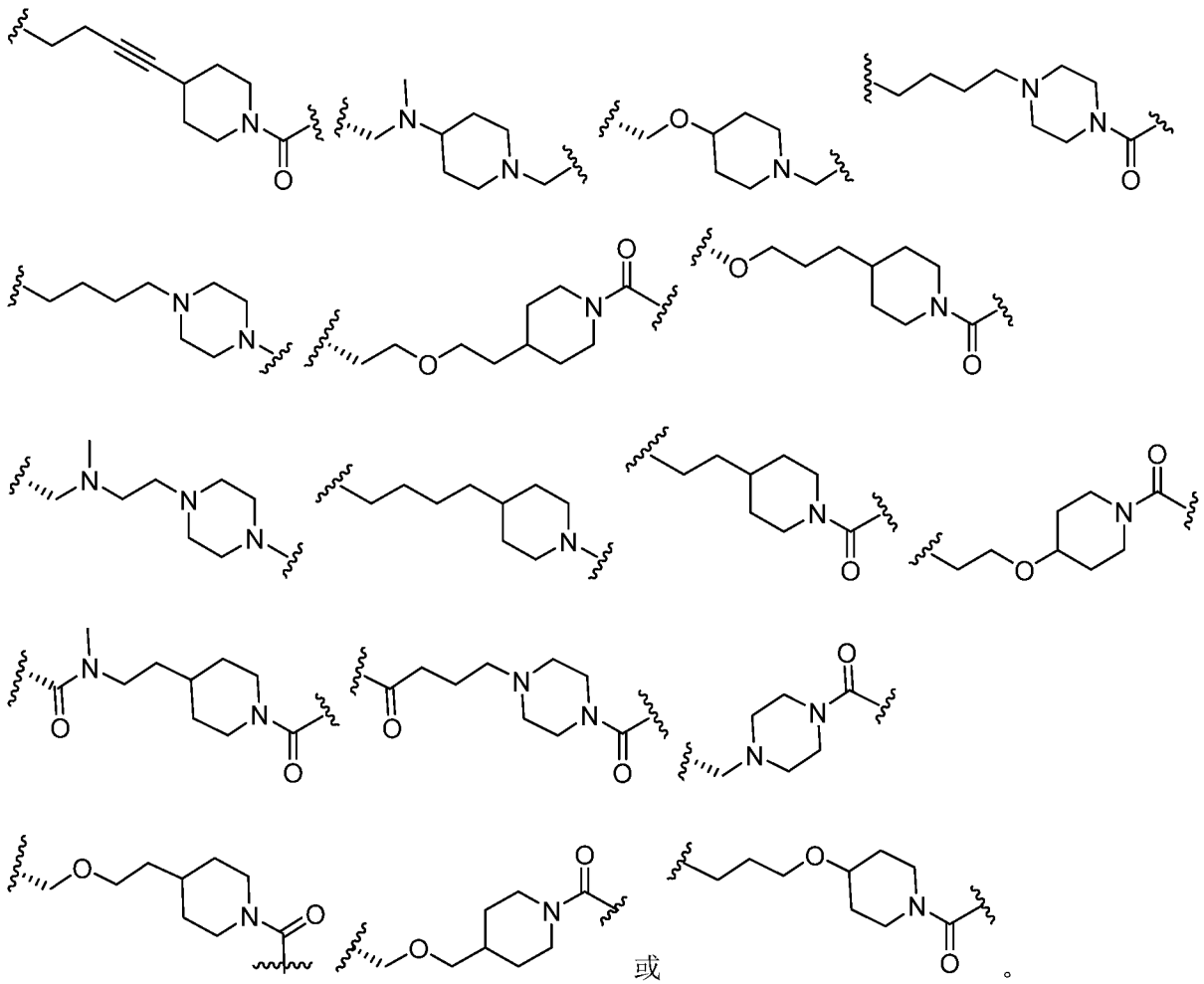

。

20. 如权利要求 17 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 为 LA，所述 LA 中环 D 和环 B 不存在，环 C 为含有 1 个或者 2 个氮杂原子的 4-7 元的杂环烷基；X""为-C(O)-、键或-CH_2-；L_3 为-$(CH_2)_k$-；k 为 1、2、3、4 或者 5。

21. 如权利要求 20 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 选自

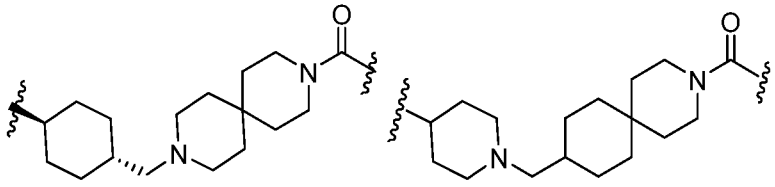


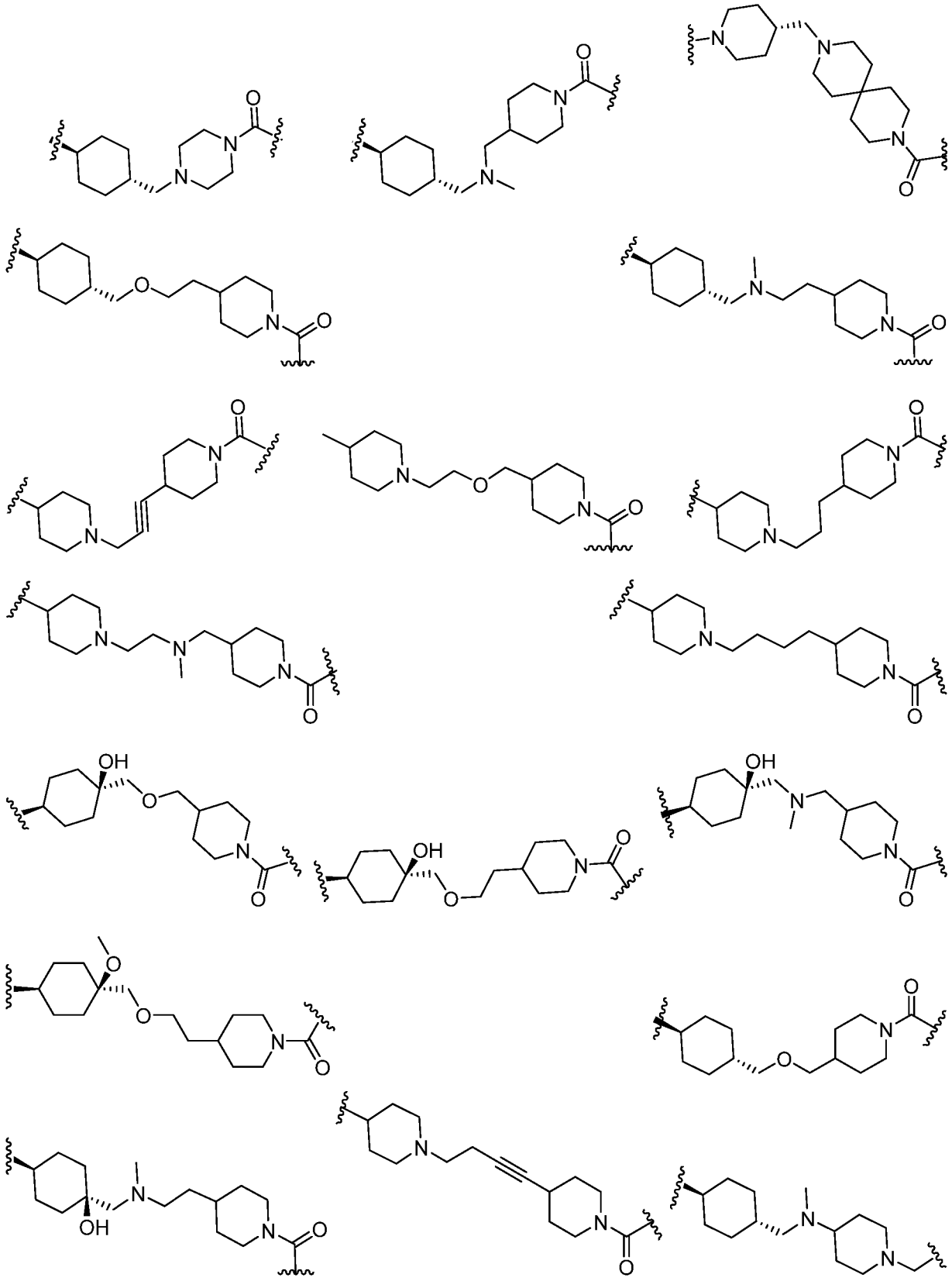


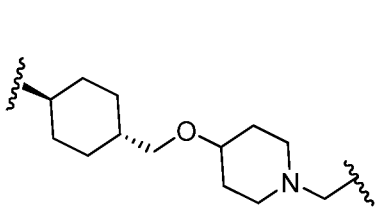
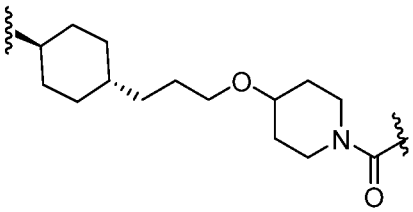
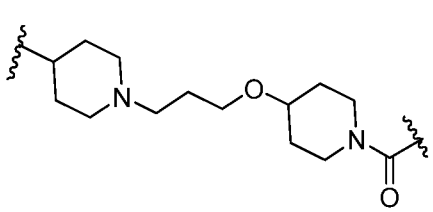
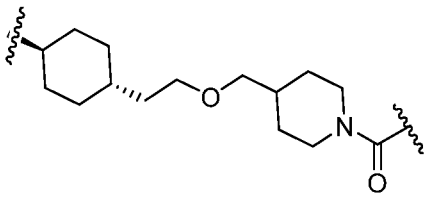
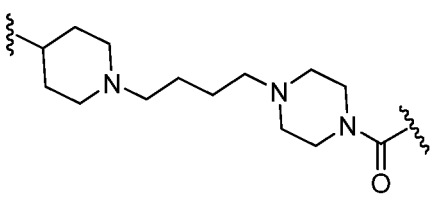
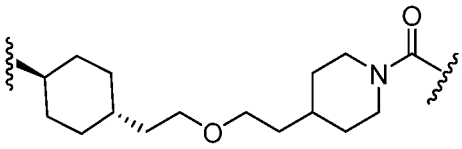
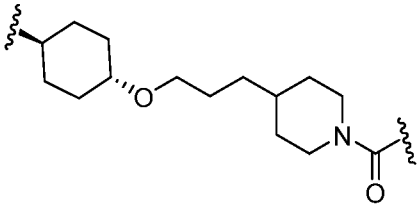
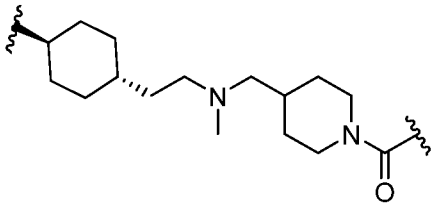
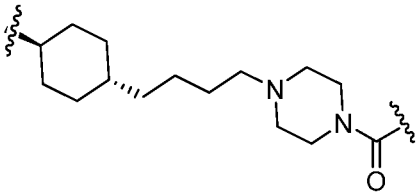
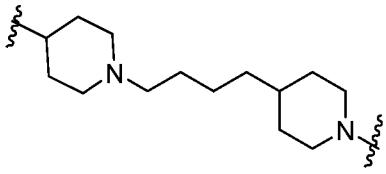
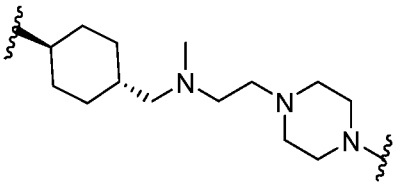
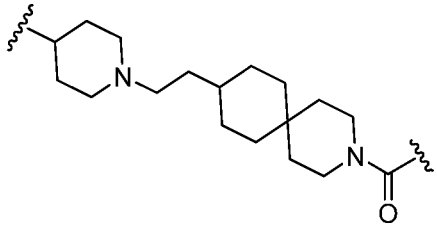
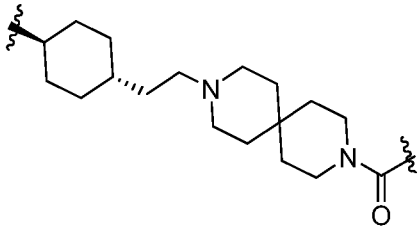
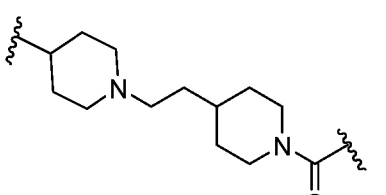
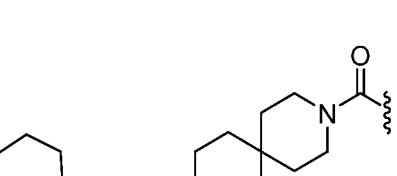
或 。

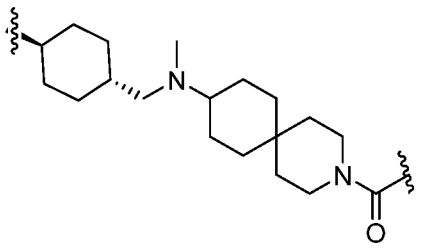
22. 如权利要求 17 所述的式 I 化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 为 LA，所述 LA 中环 D 为 C_4-C_7 元环烷基或 4-7 元杂环烷基；环 B、环 C 为不存在或为含有 1 个或者 2 个氮杂原子的的 5-11 元的亚杂环烷基；X""为-C(O)-或-$(CH_2)_t$-，t 为 0、1、2、3、4 或 5；L_3 为-$(CH_2)_k$-，k 为 1、2、3、4 或者 5。

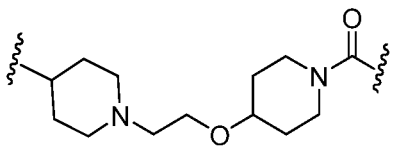
23. 如权利要求 22 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述 L 选自

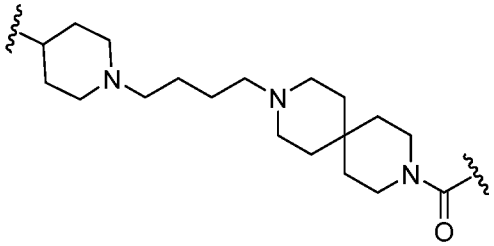


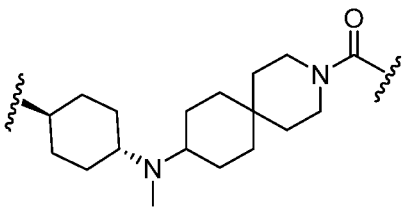


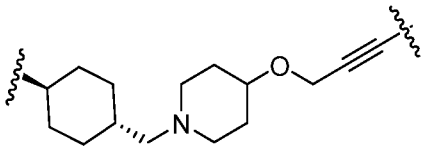
















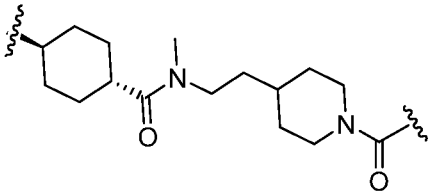


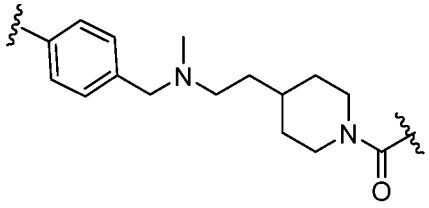


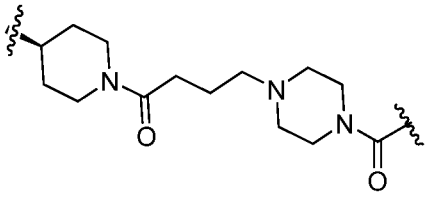


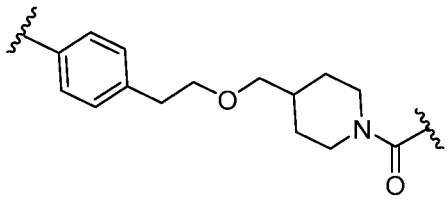


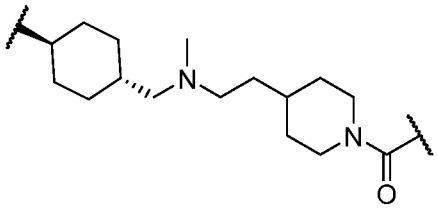


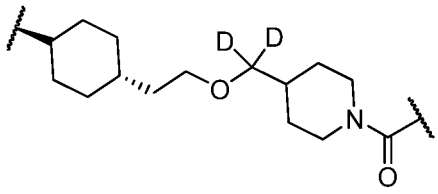


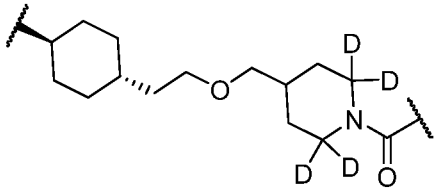


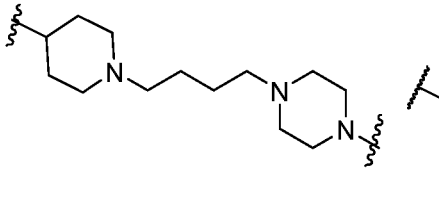


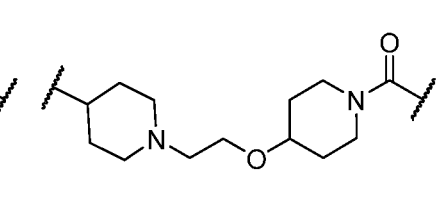


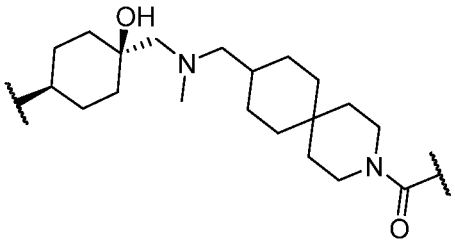
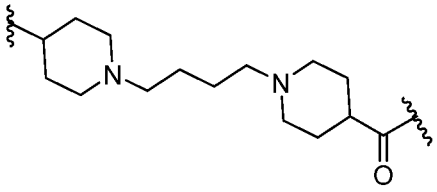








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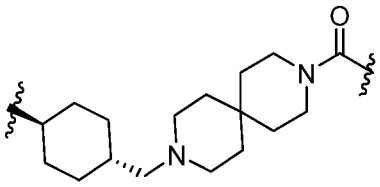
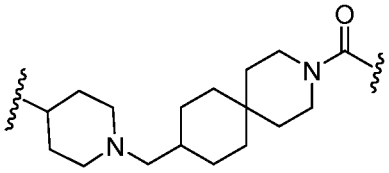
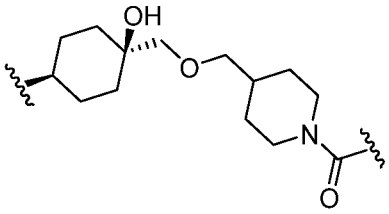
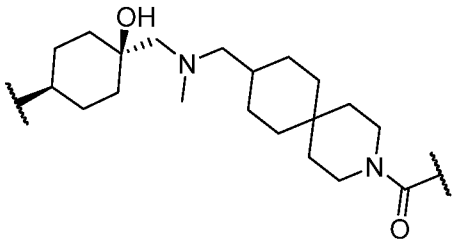
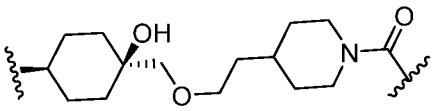
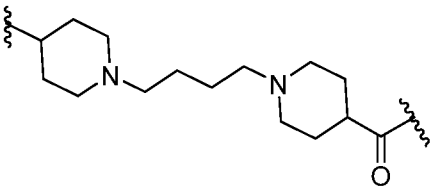
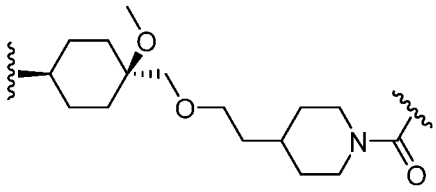
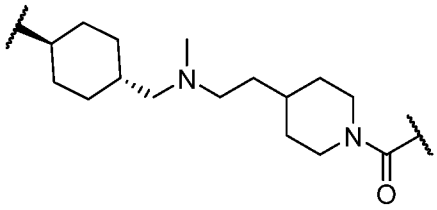
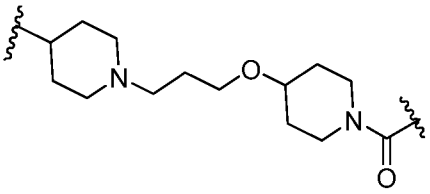
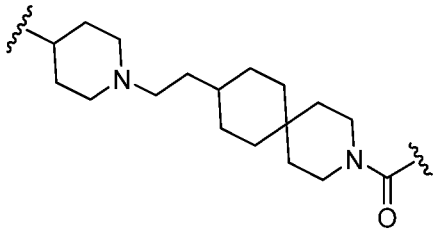
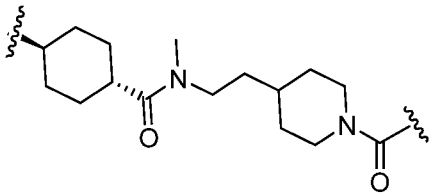
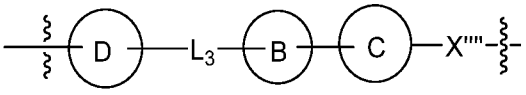











。

24. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，

所述 L 为 LA，



LA

其中所述 LA 中：

环 D 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

环 B 不存在或者为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

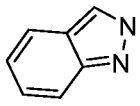
环 C 为不存在、C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

X""为键、-NH-、-NCH_3-、-O-、-$C(CH_3)_2$-、-S-、-C=C-、-C≡C-、-CHF-、-$CHCF_3$-、-C(O)-、-S(O)-、-$S(O)_2$-、-C(O)O-、-OC(O)-、-C(O)NH-、-$C(O)NCH_3$-、-NHC(O)-或-$NCH_3C(O)$-；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基任选地被选自氘、-O-、-NH-、-N(C_1-C_6 烷基)-、-N(C_1-C_6 卤代烷基)、-C≡C-、-C(O)-、-N(C_1-C_6 羟基烷基)-或-N(C_3-C_8 环烷基)-替代，k 为 0、1、2、3、4、5、 6、7、8、9 或 10；

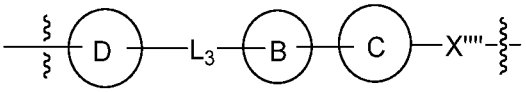
和或，当环 A"为含有 1 个、2 个或者 3 个选自 N、O 或 S 杂原子的 5-11 元双环杂芳基，环 D 为 6-10 元芳基、5-10 元杂芳基、C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基和-O-(C_1-C_6 烷基)的取代基取代。

25. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，

当环 A"为  时，所述环 D 为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基独立地被 1 个、2 个或 3 个羟基或被 1 个、2 个或 3 个-O-(C_1-C_6 烷基)取代。

26. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，

所述 L 为 LA，



LA

其中所述 LA 为方案 1、方案 2、方案 3 或方案 4

方案 1、

环 D 为 C_3-C_{12} 亚环烷基或含有 1-2 个 N 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、羟基或-O-(C_1-C_6 烷基)取代；

环 B 为 C_3-C_{12} 亚环烷基或含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基或-O-(C_1-C_6 烷基)的取代基取代；

环 C 为不存在；

X""为-C(O)-；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基被选自-O-、-NH-、-N(C_1-C_6 烷基)-、-N(C_1-C_6 卤代烷基)-、-C(O)-、-N(C_1-C_6 羟基烷基)-或-N(C_3-C_8 环烷基)-替代，k 为 0、1、2、3、4、5、 6、7、8、9 或 10；

方案 2、

环 D 为 C_3-C_{12} 亚环烷基或含有 1-2 个 N 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、羟基或甲氧基取代；

环 B 为含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基；

环 C 为不存在；

X""为-C(O)-；

L_3 为-$(CH_2)_k$-，k 为 1、2、3、4、5、 6、7、8、9 或 10；

方案 3、

环 D 为 C_3-C_{12} 亚环烷基或含有 1-2 个 N 杂原子的 3-12 元亚杂环烷基，所述亚环烷基和亚杂环烷基任选被选自卤素、羟基或甲氧基取代；

环 B 为含有 1-2 个选自 N、O 或 S 杂原子的 3-12 元亚杂环烷基；

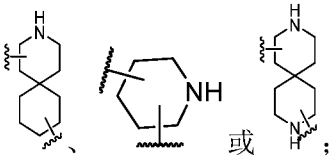
环 C 为不存在；

X""为-C(O)-；

L_3 为-$(CH_2)_k$-，k 为 1、2、3 或 4；

方案 4、

环 D 为亚环己基或含有 1-2 个 N 杂原子的 6 元亚杂环烷基，所述亚环己基和 6 元亚杂环烷基任选被选自卤素、羟基或甲氧基取代；

环 B 为  、、或；

环 C 为不存在；

X""为-C(O)-；

L_3 为-$(CH_2)_k$-，所述 L_3 中的一个或两个亚甲基被选自-O-、-NH-、-N(C_1-C_6 烷基)-、-N(C_1-C_6 卤代烷基)-、-C(O)-、-N(C_1-C_6 羟基烷基)-或-N(C_3-C_8 环烷基)-替代，k 为 1、2、3 或 4。

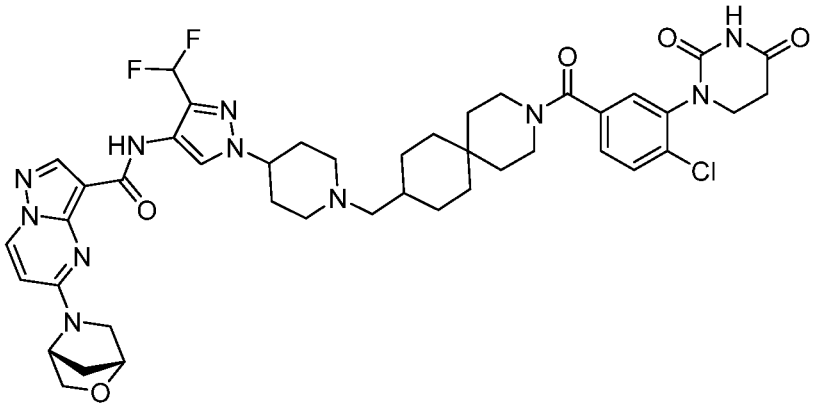
27. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，

所述 LA 中，环 D 为 6-10 元芳基、含有 1 个或者 2 个氮杂原子的 4-7 元饱和的单环亚杂环烷基、含有 1 个或者 2 个氮杂原子的 7-11 元的亚螺杂环烷基或者亚稠杂环烷基；

和或，环 C 为 4-11 元的饱和或部分不饱和的亚螺环烷基、4-11 元的饱和或部分不饱和的亚稠环烷基、8-10 元双环饱和或部分不饱和的亚环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-7 元饱和或部分不饱和的亚杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和或部分不饱和的亚螺杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 4-11 元饱和/或部分不饱和的亚稠杂环烷基、具有 1-2 个独立地选自氮、氧或硫杂原子的 8-10 元双环饱和/或部分不饱和的亚杂环烷基，所述环烷基和杂环烷基任选被选自氘、卤素、氧代、氰基、氨基、羟基、C_1-C_6 烷基、C_1-C_6 卤代烷基、C_1-C_6 羟基烷基和-O-(C_1-C_6 烷基)的取代基取代；

和或，所述 LA 中，L_3 为-$(CH_2)_k$-，所述 L_3 中一个或两个亚甲基任选地被选自氘、-C(O)-、-C≡C-、-O-、-NH-、-NCH_3-或-NCH_2CH_3-的基团替代；k 为 1、2、3 或者 4。

28. 如权利要求 1 所述的式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，其特征在于，所述式I化合物为



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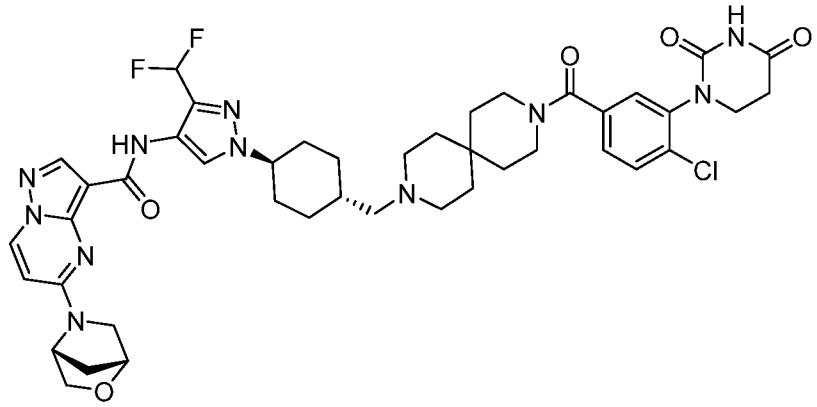

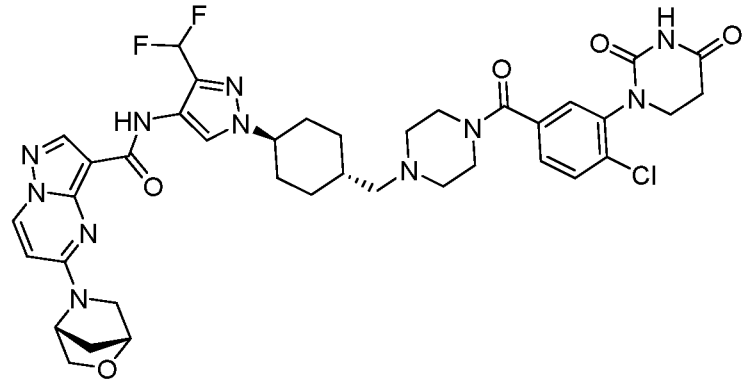

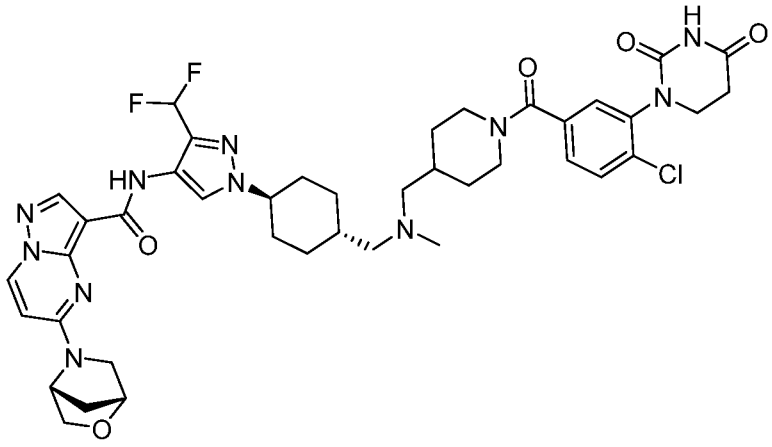

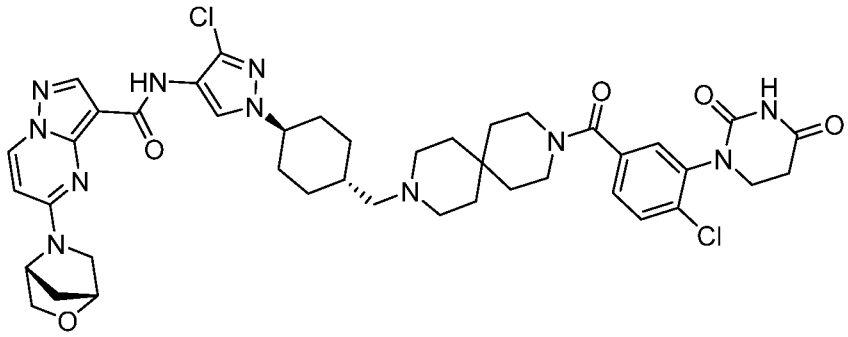

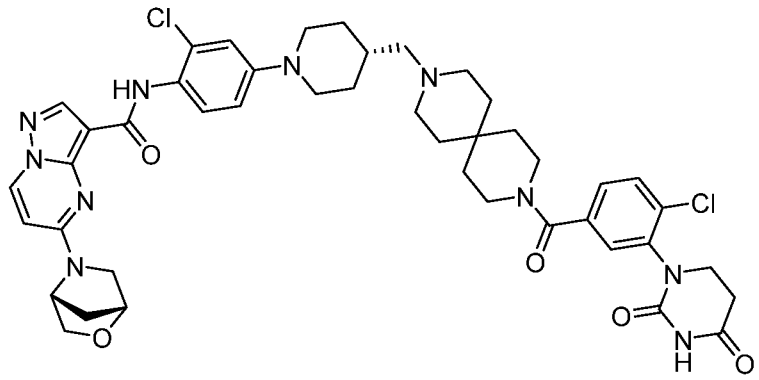

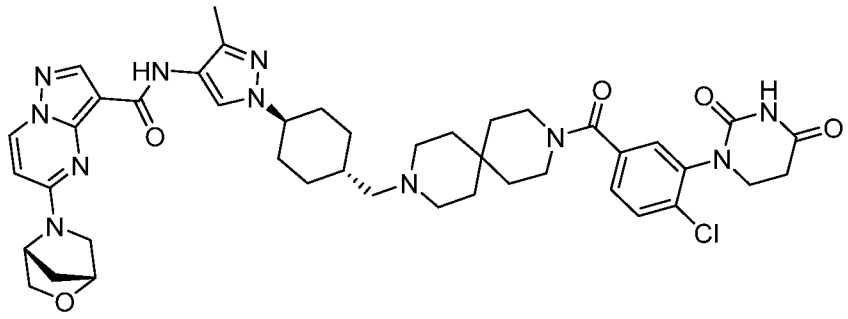

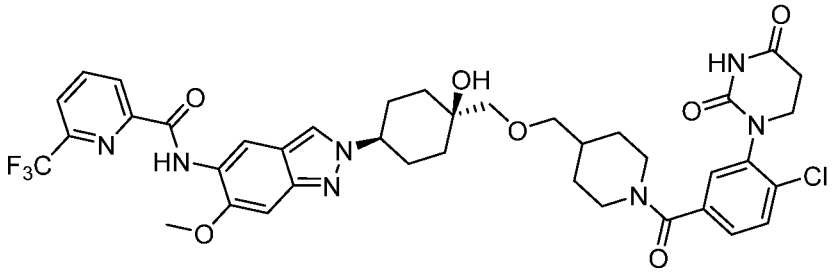

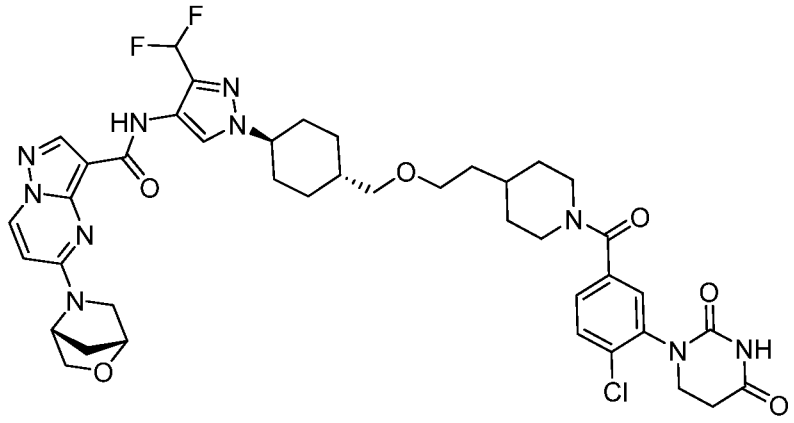

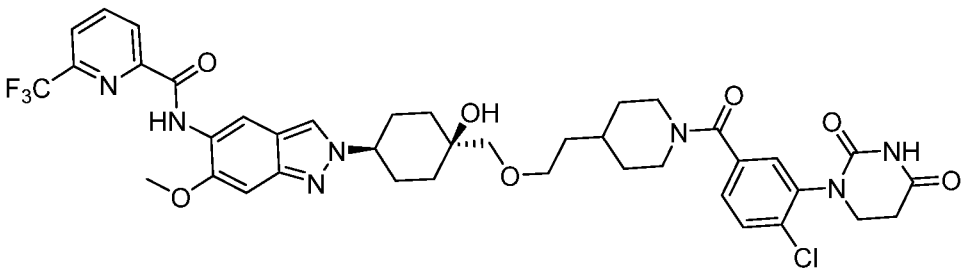

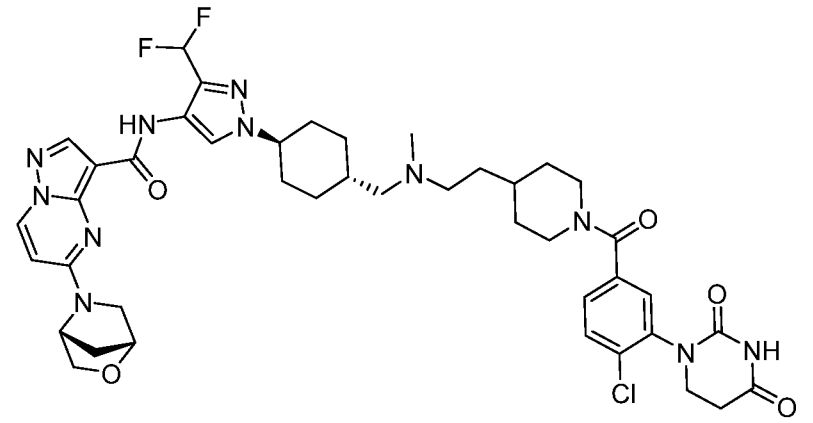

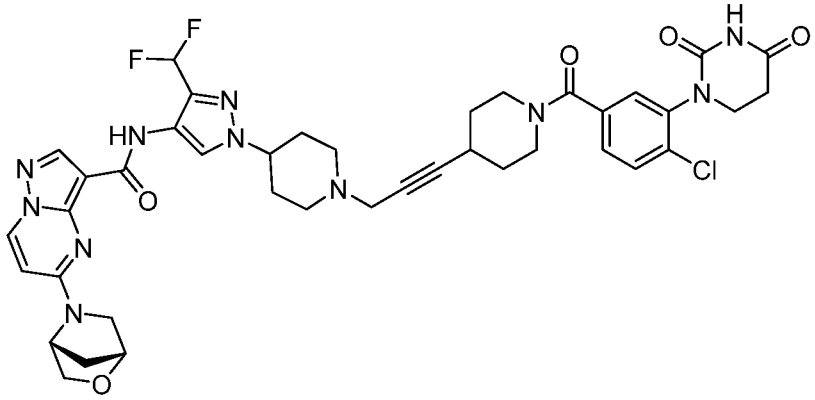

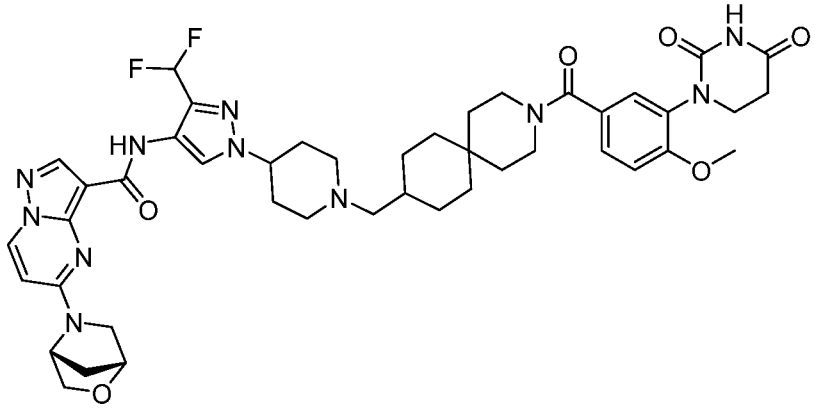

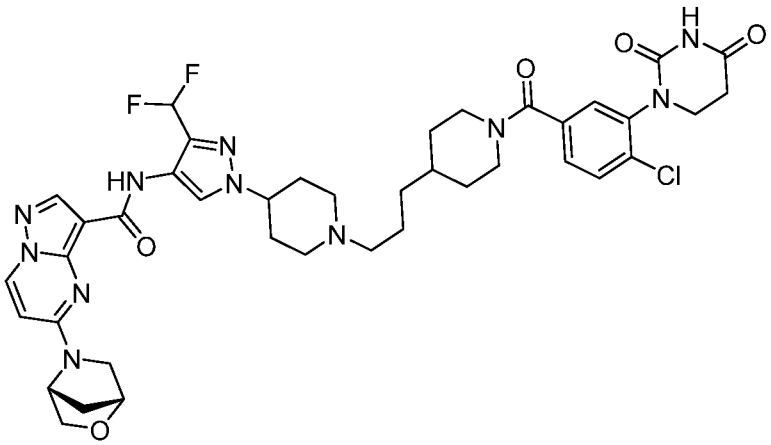

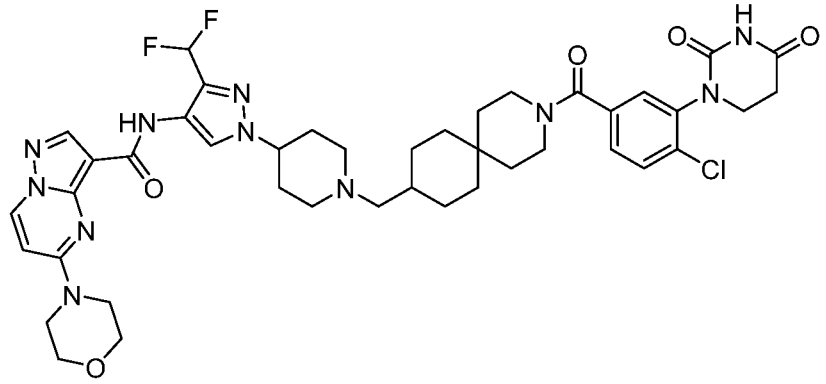

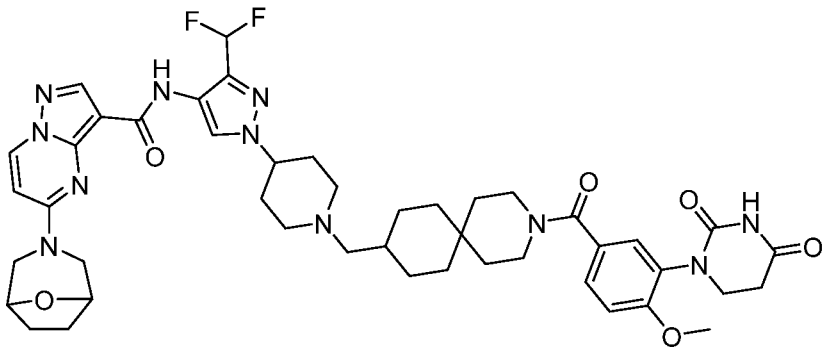

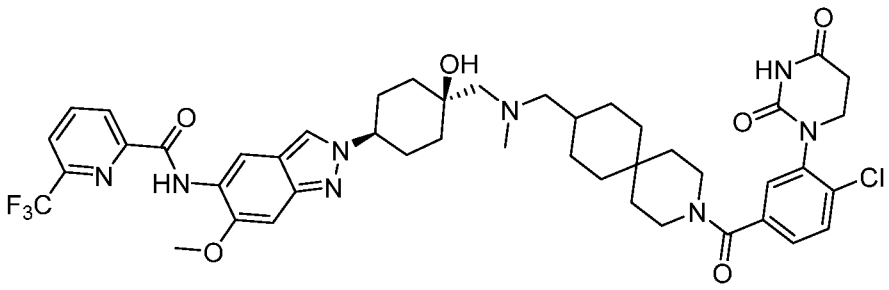

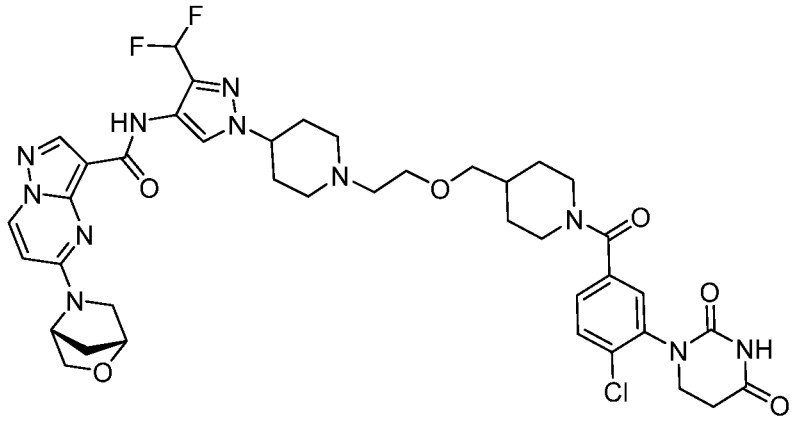

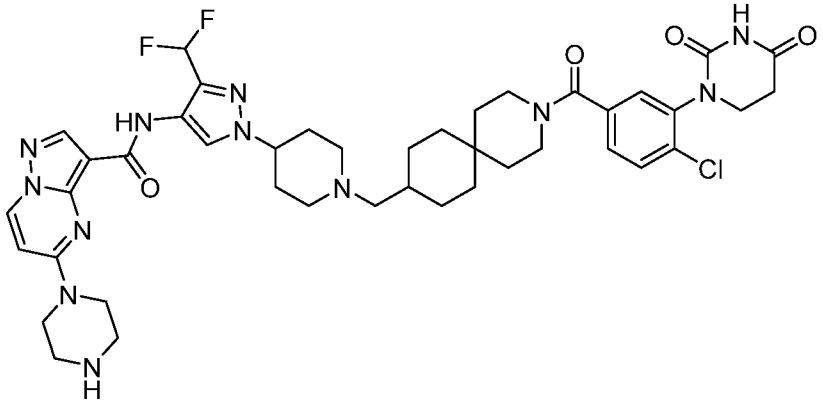

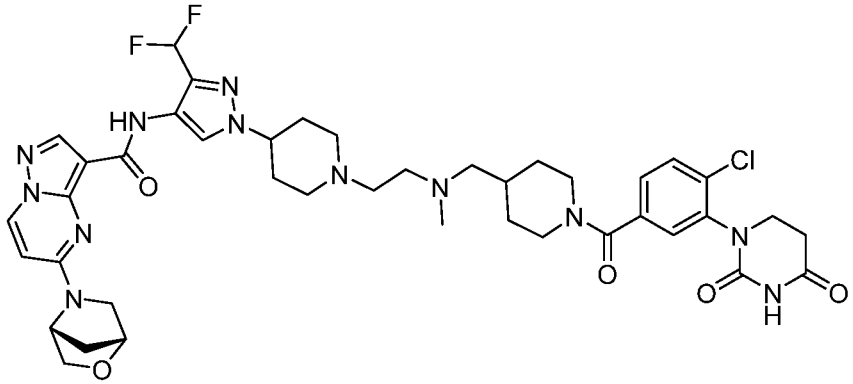

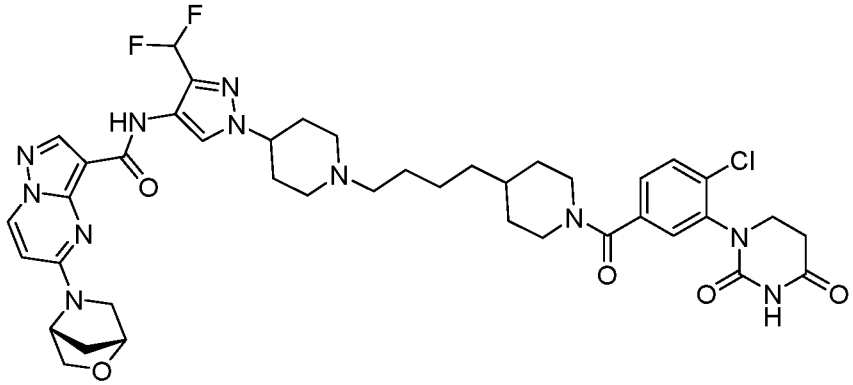

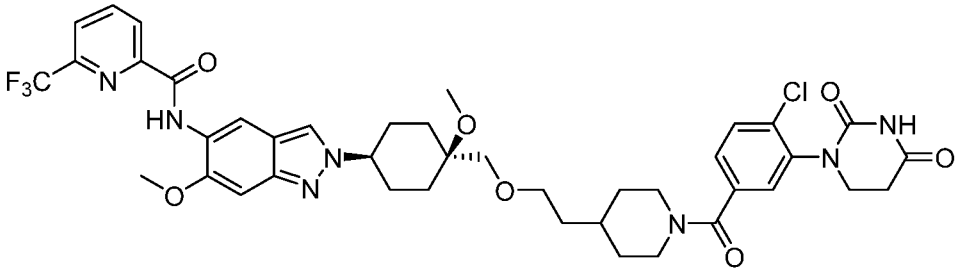

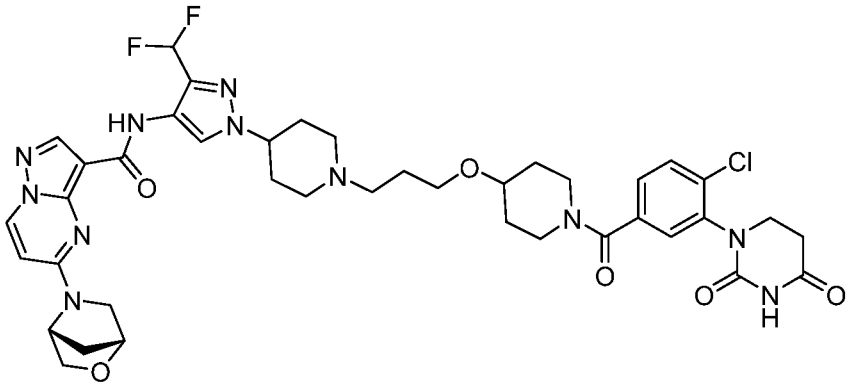

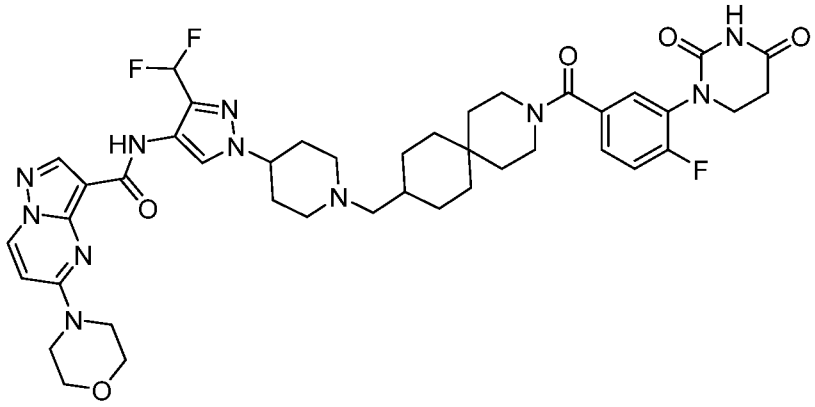

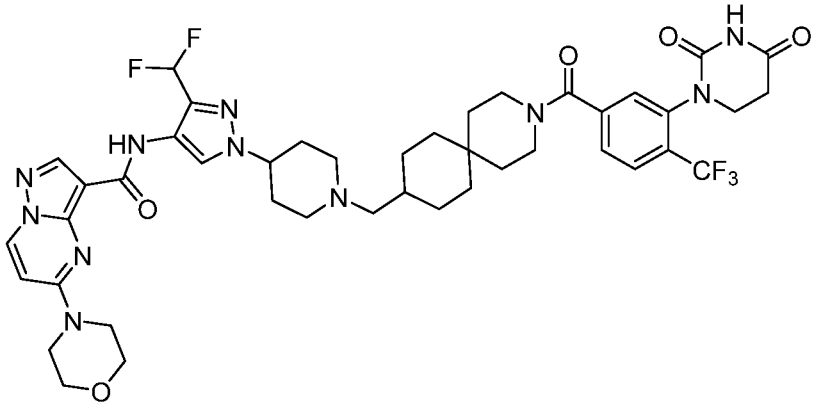

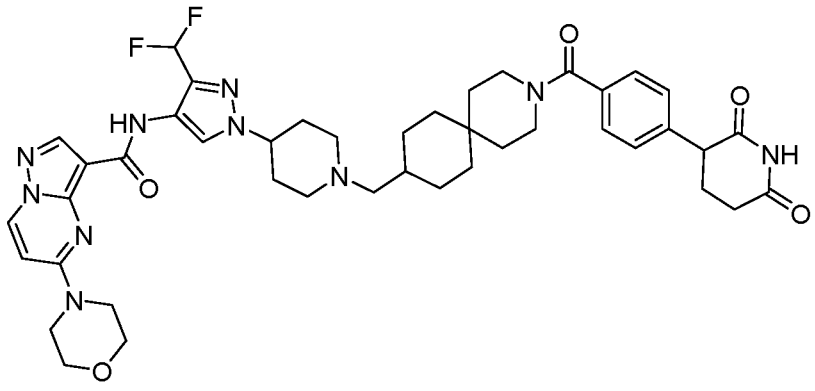

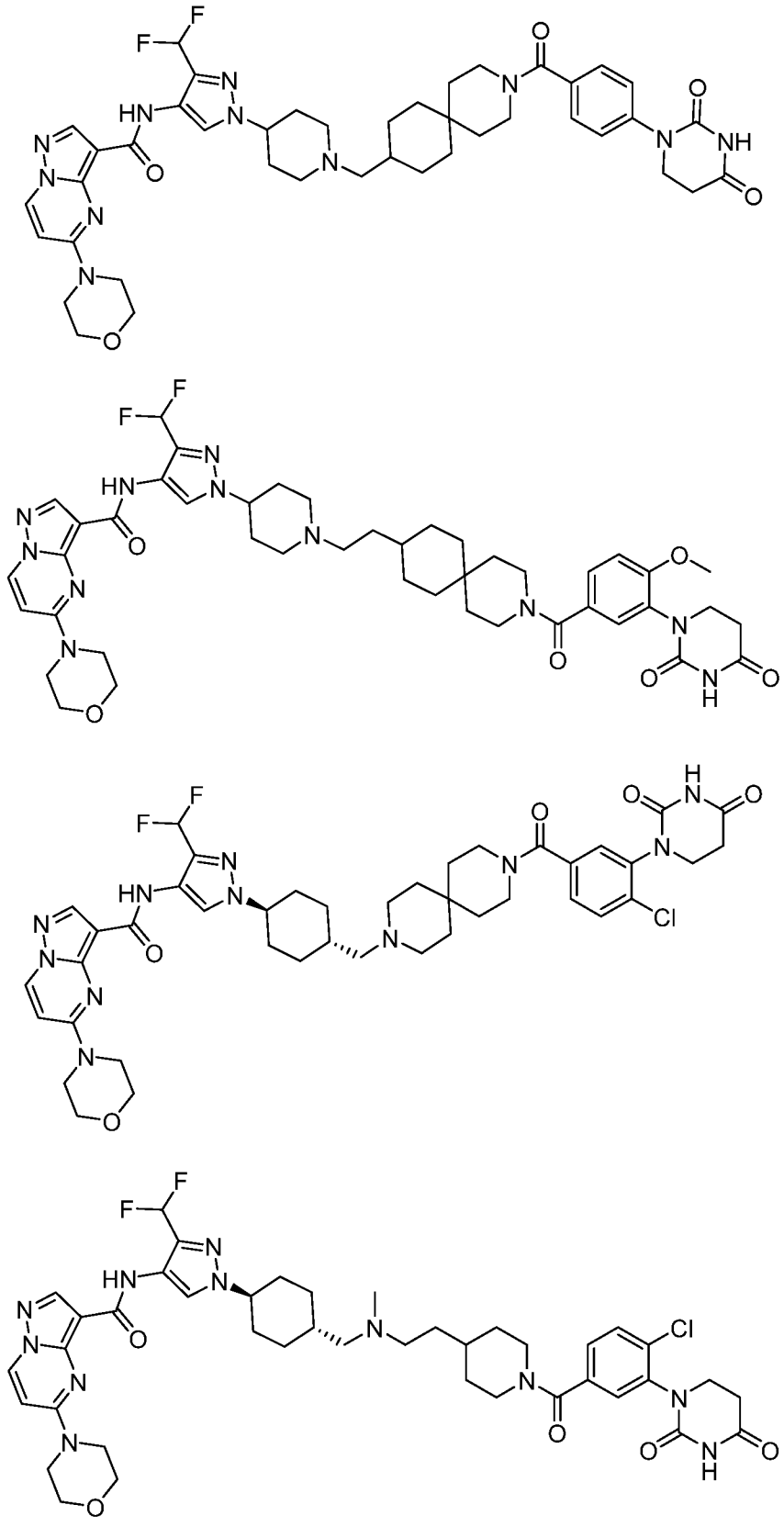

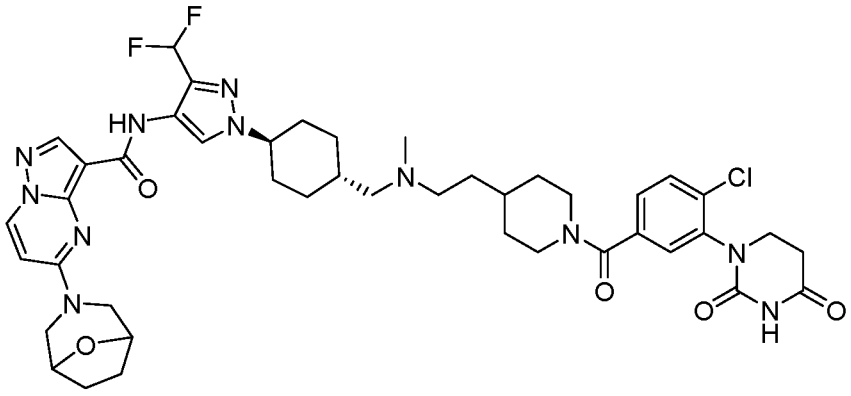

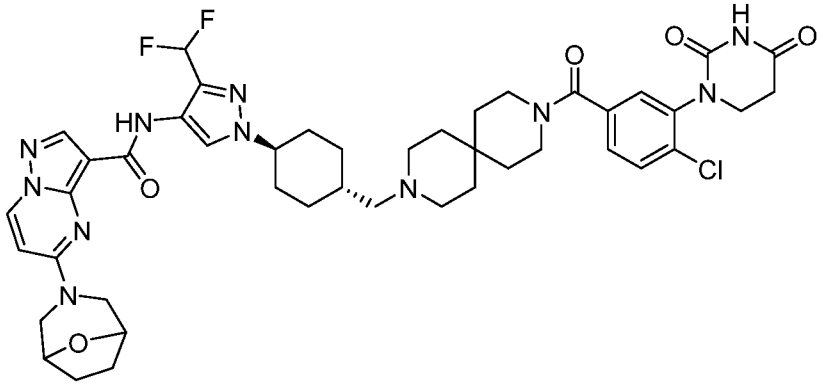

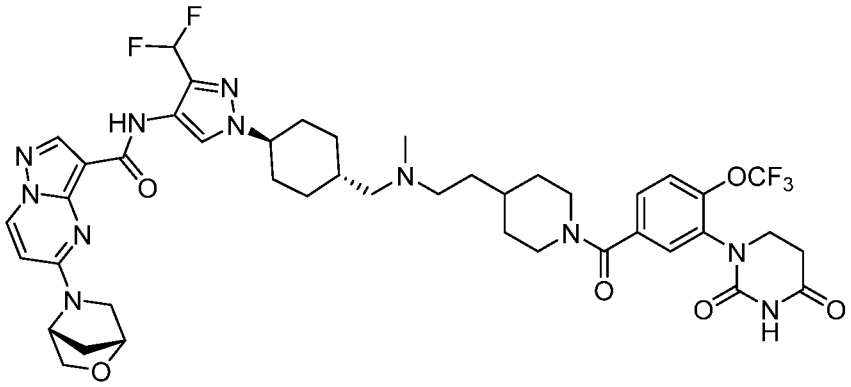

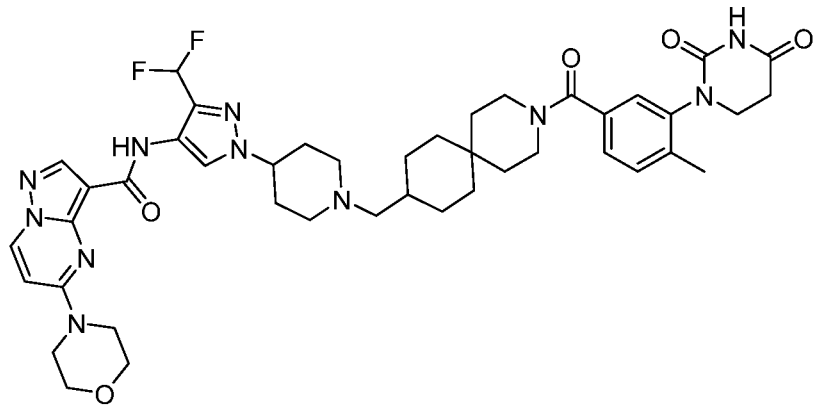

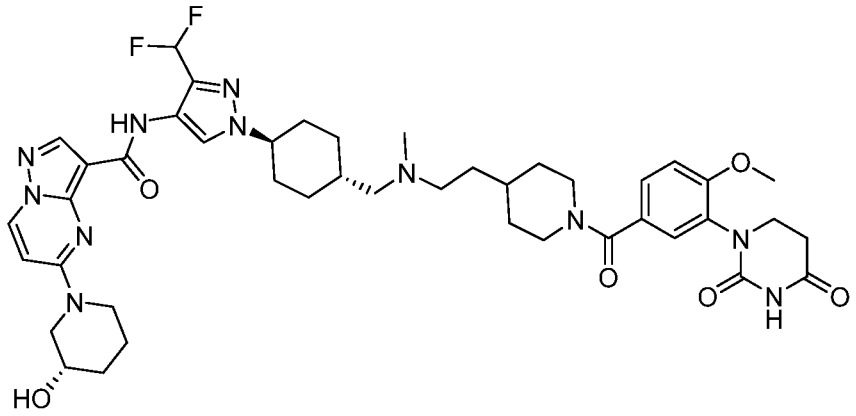

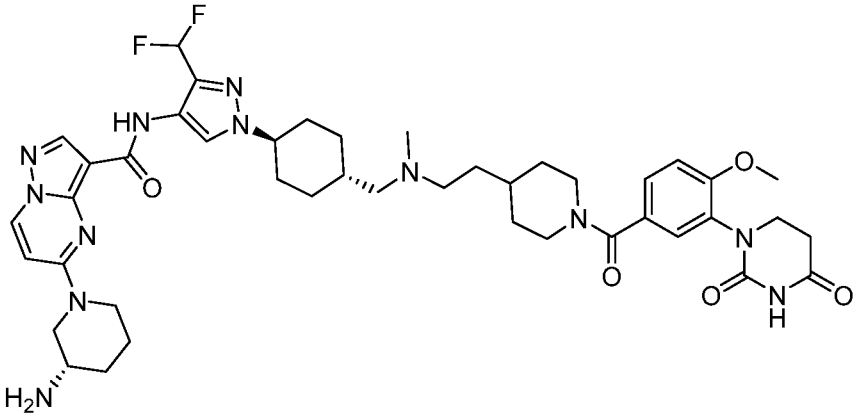

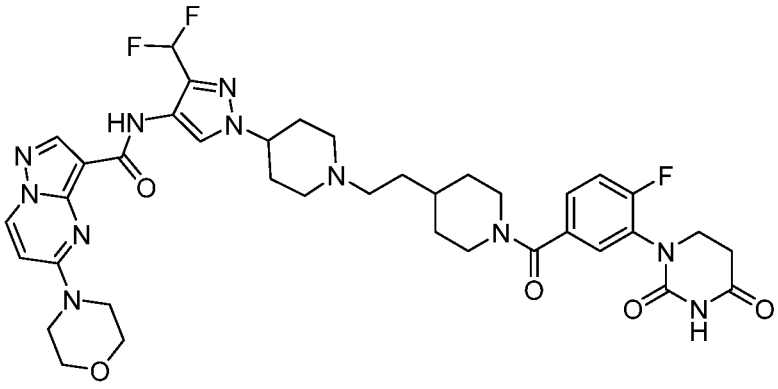

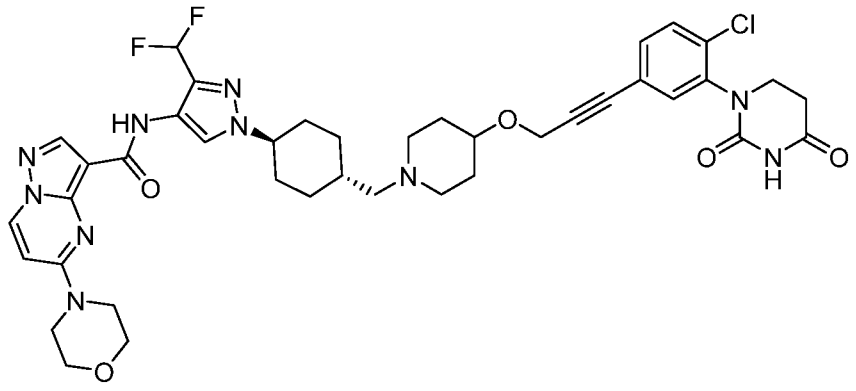

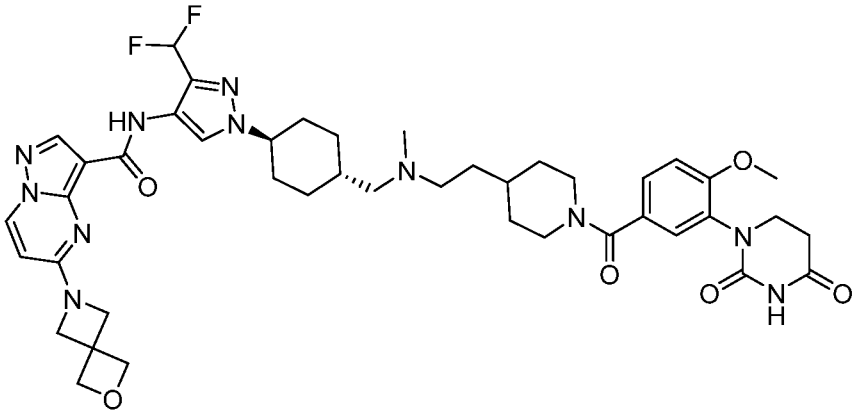

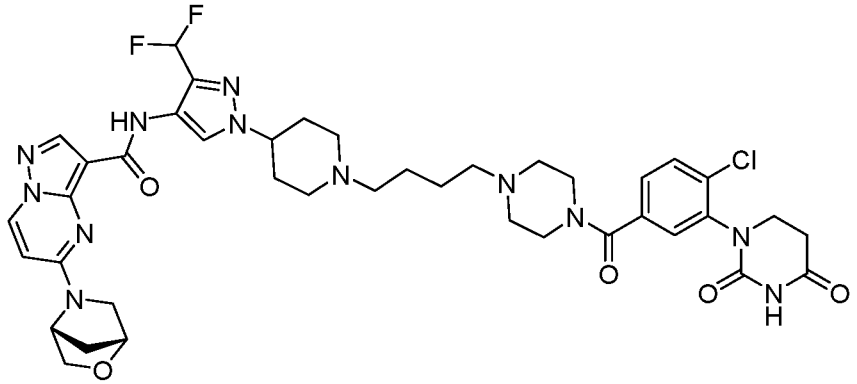

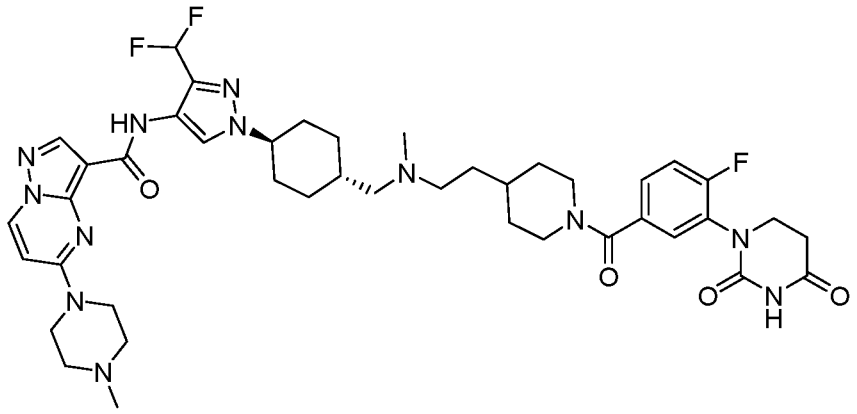

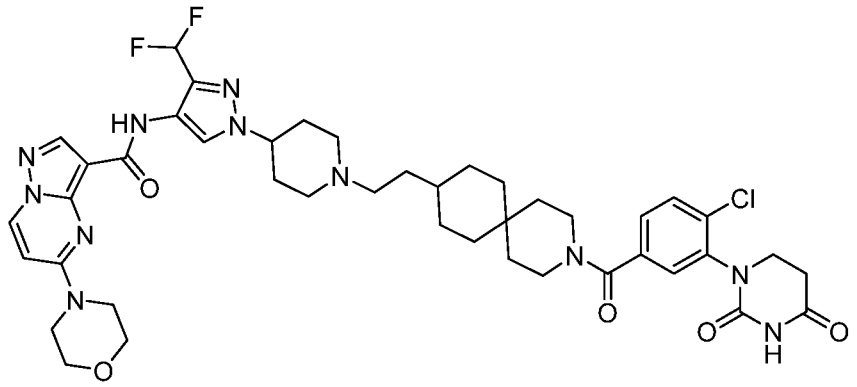

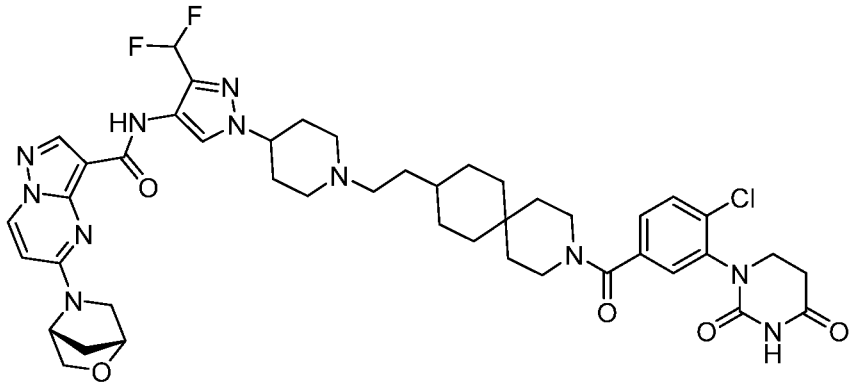

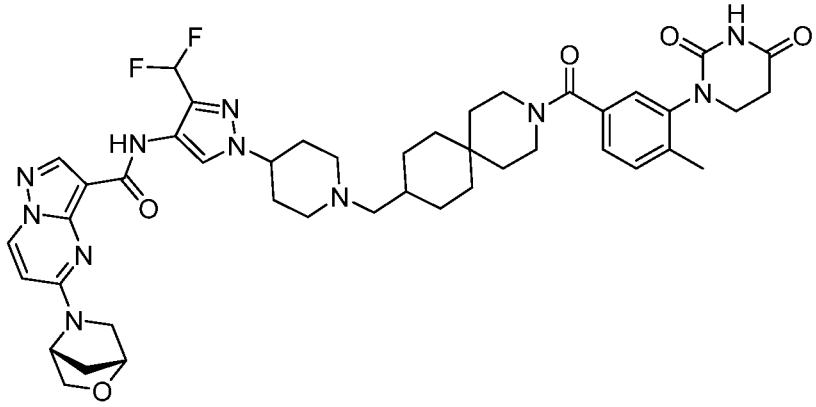

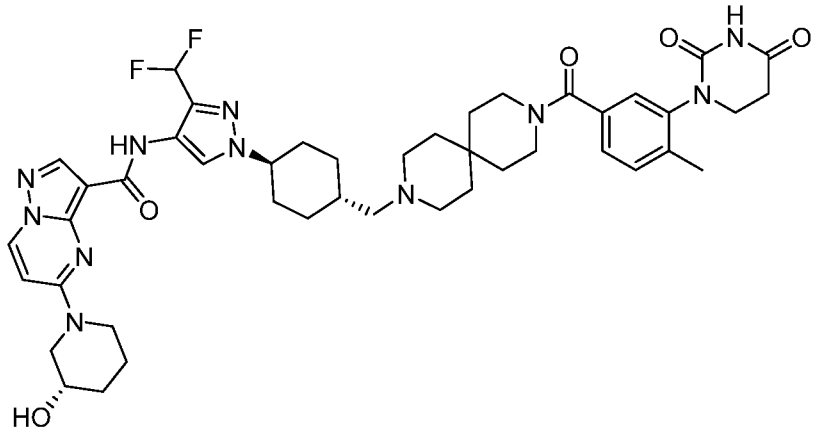

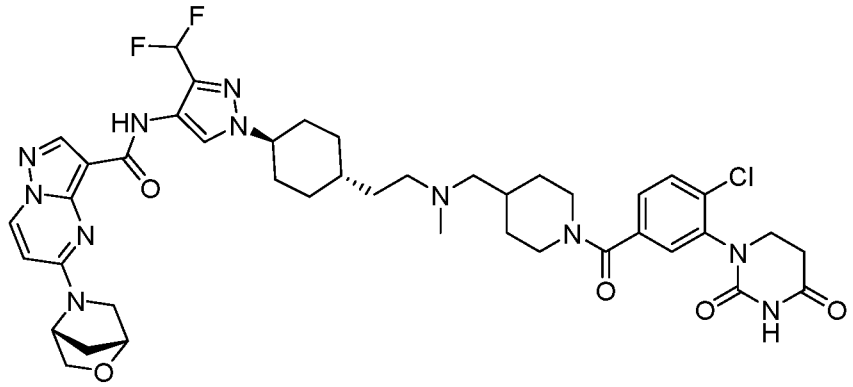

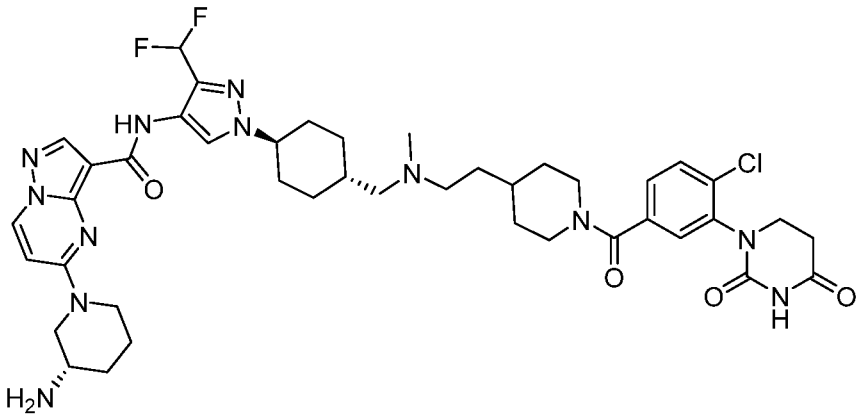

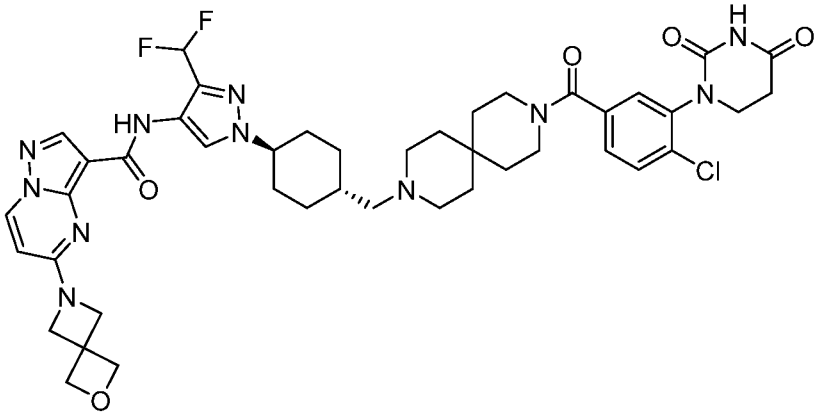

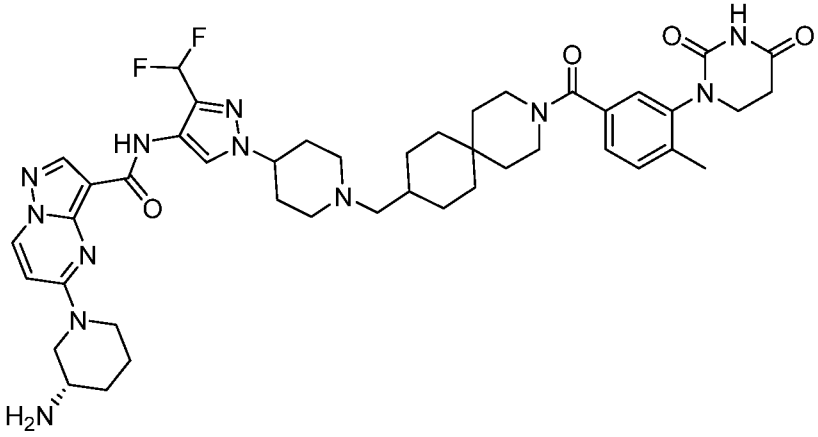

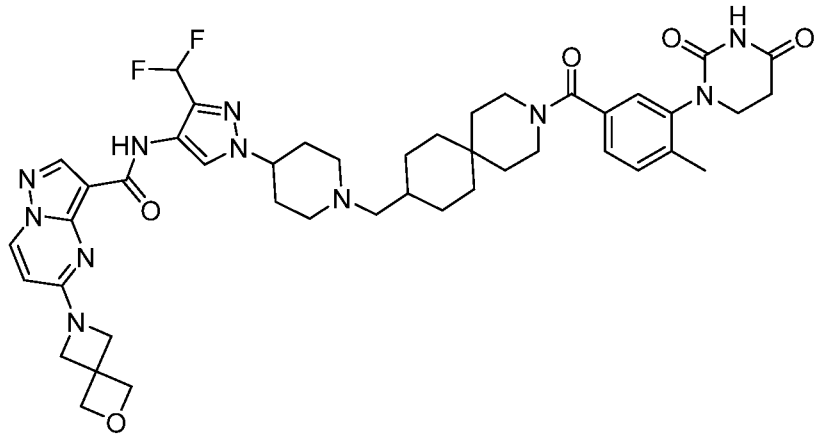

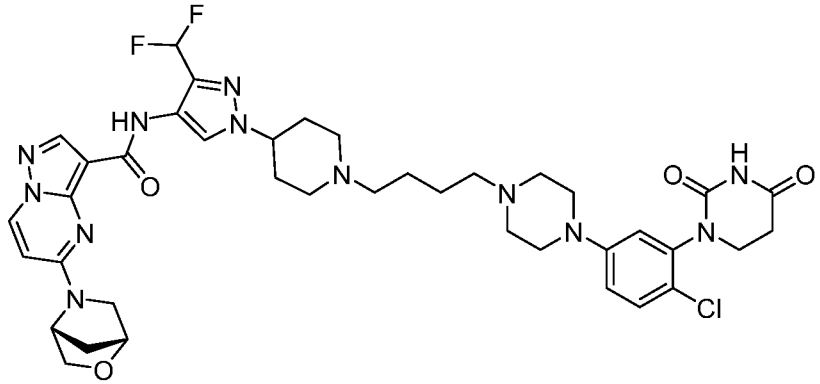

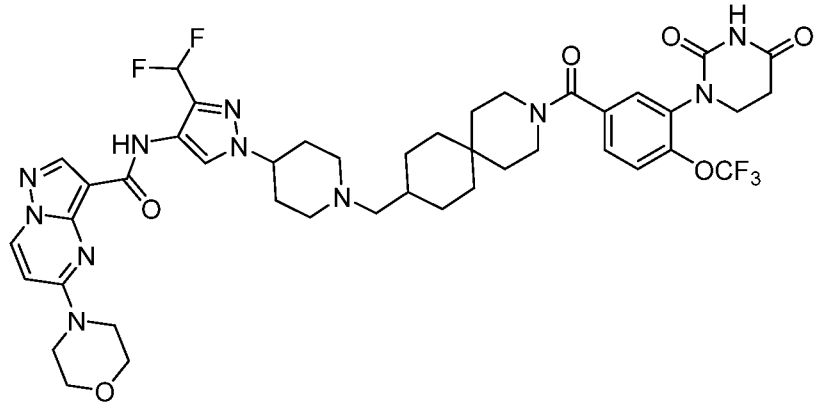

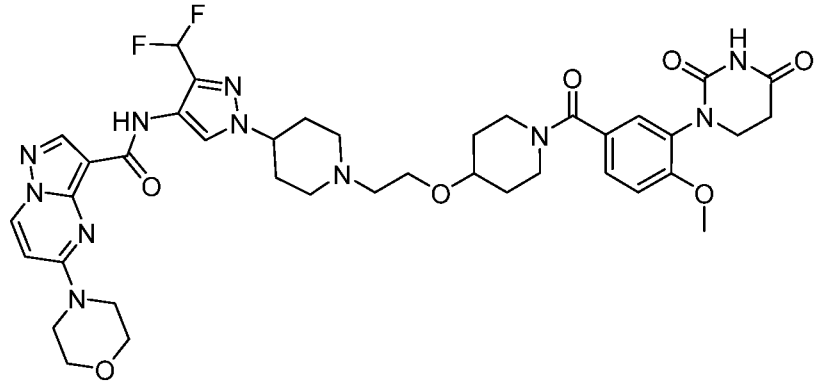

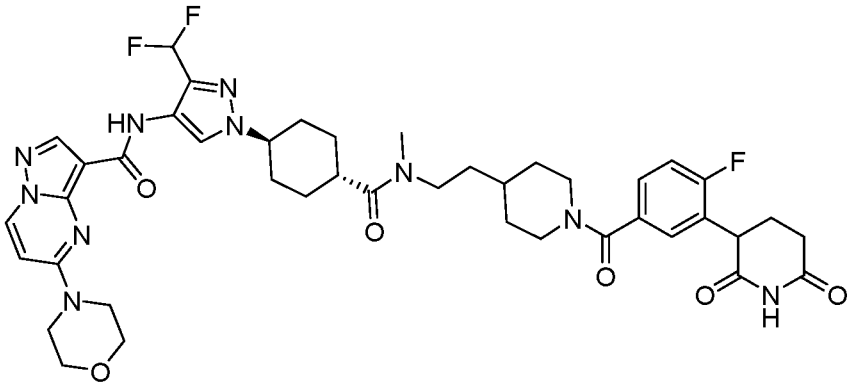

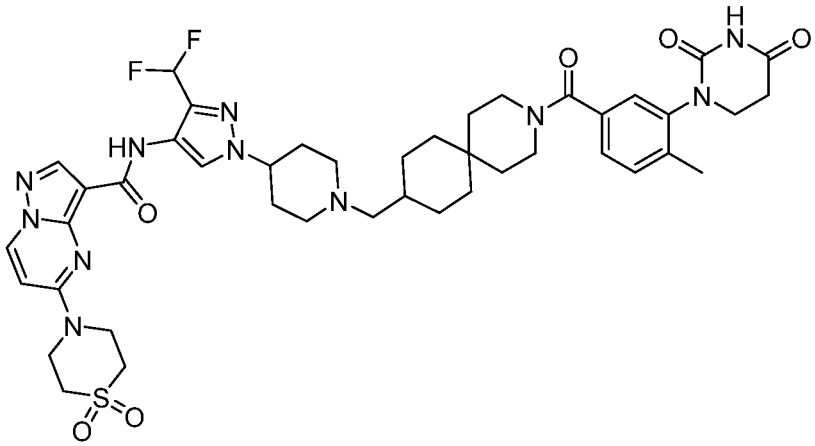

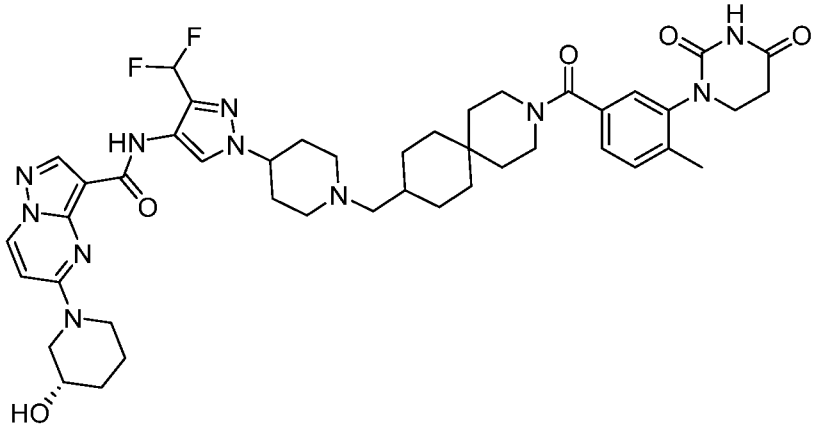

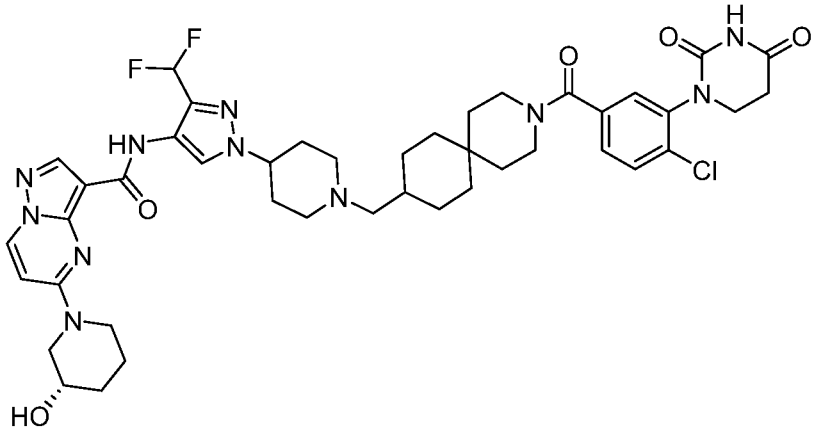

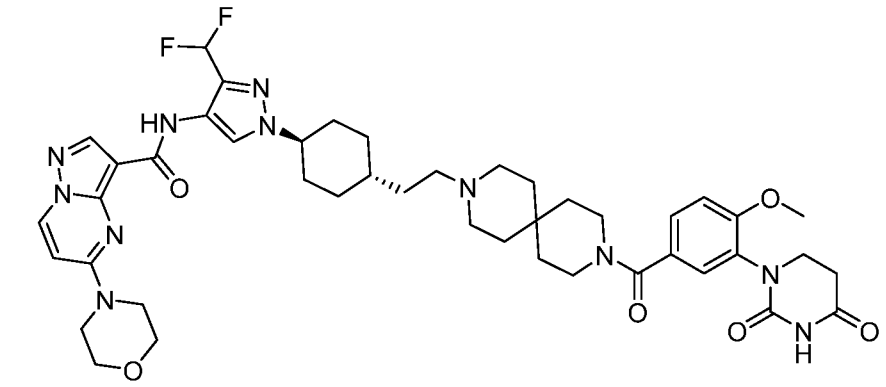

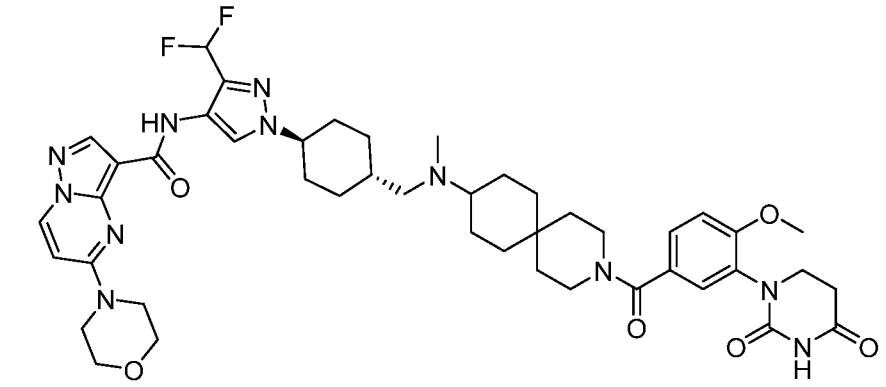

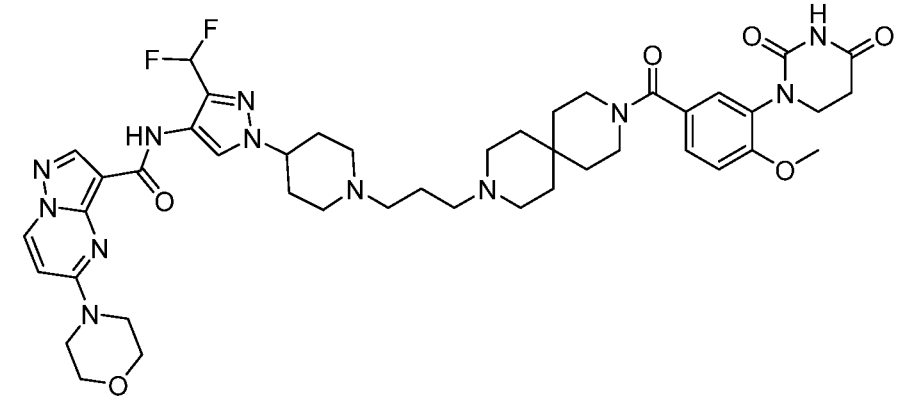

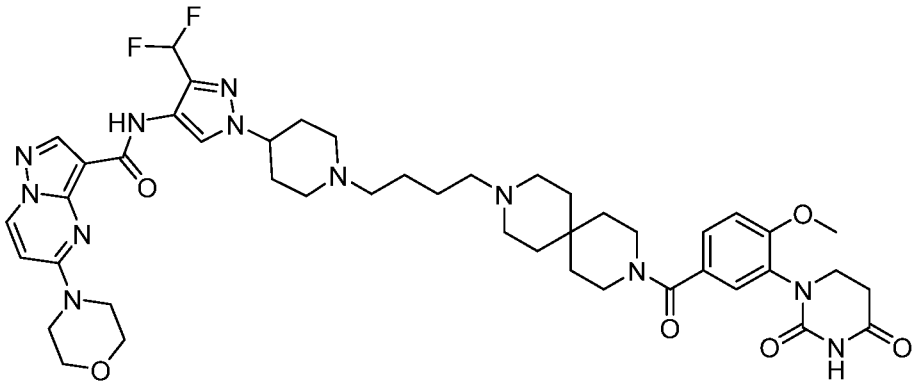

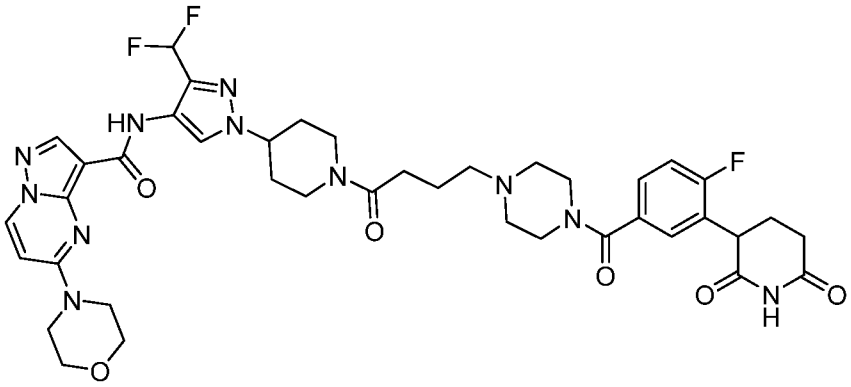

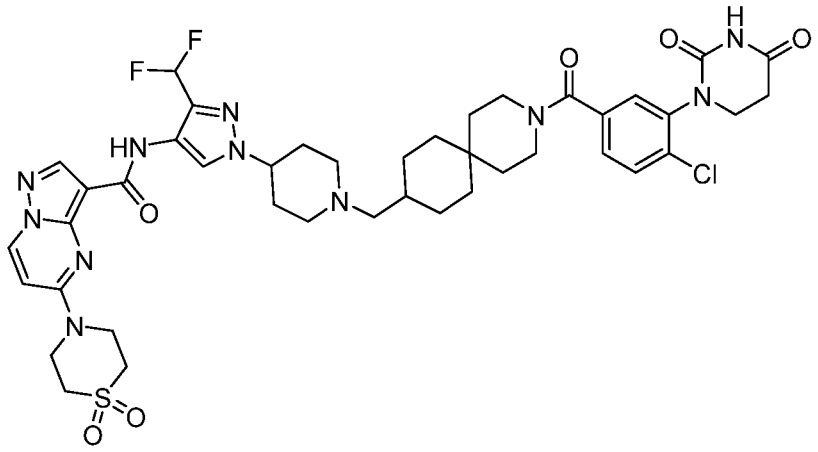

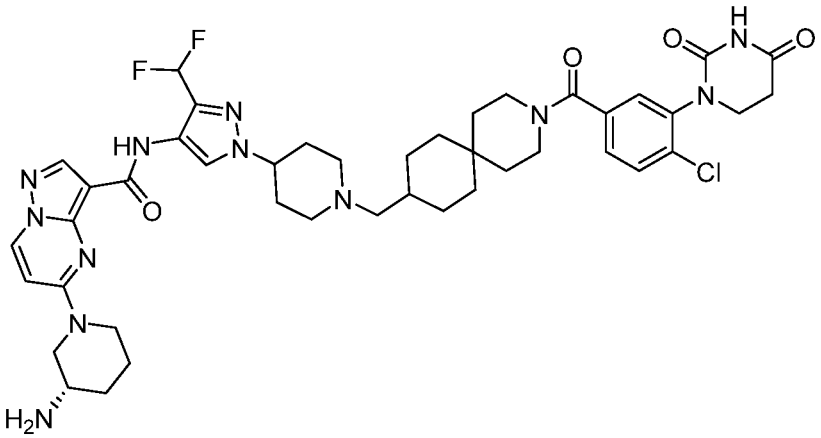

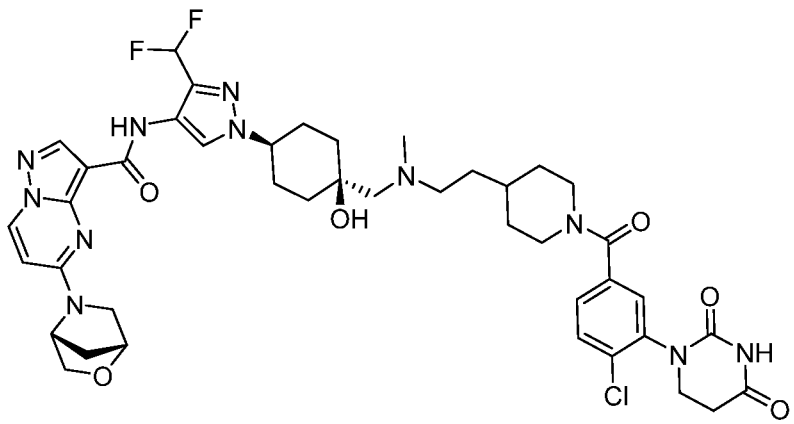

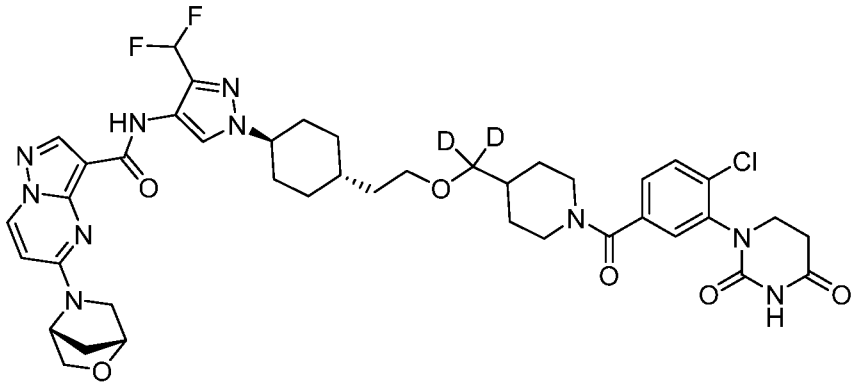

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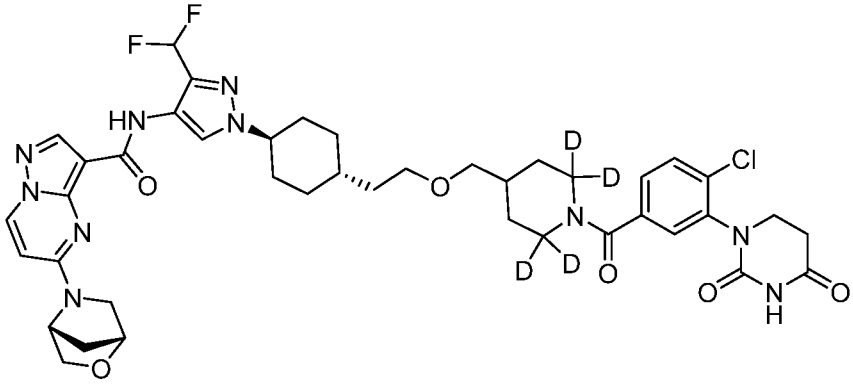

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29. 一种药物组合物，其包含权利要求 1-28 任一项所述式I化合物，或其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐，以及药学上可接受的载体、稀释剂或赋形剂。

30. 权利要求 1-28 任一项所述式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐在制备治疗和/预防 IRAK4 介导的疾病或病症的药物中的应用，或者 TLR (除 TLR3R 以外)、IL-1α 或 IL-1β 受体家族介导的疾病或病症的药物中的应用。

31. 权利要求 1-28 任一项所述式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐在制备治疗和/预防癌症、神经退化性病症、病毒性疾病、自身免疫性疾病、炎性疾病、遗传性病症、激素相关疾病、代谢病症、与器官移植相关疾病、免疫缺陷病症、破坏性骨病、增生性病症、感染性疾病、与细胞死亡相关的病况、凝血酶诱发的血小板凝集、肝病、涉及 T 细胞活化的病理性免疫病况、心血管病症或 CNS 病症疾病的药物中的应用。

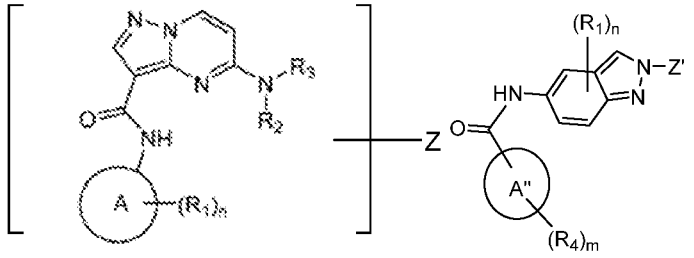
32.权利要求 1-28 任一项所述式I化合物，其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、前药或其药学上可接受的盐在制备治疗和/预防脑癌、肾癌、肝癌、肾上腺癌、膀胱癌、乳癌、胃癌、卵巢癌、结肠癌、直肠癌、前列腺癌、胰腺癌、肺癌、阴道癌、宫颈癌、睾丸癌、泌尿生殖道癌、食道癌、喉癌、皮肤癌、骨癌、甲状腺癌、肉瘤、神经胶母细胞瘤、神经母细胞瘤、多发性骨髓瘤、胃肠癌、颈部或头部肿瘤、表皮过度增生、牛皮藓、前列腺增生、腺瘤、

腺癌、角化棘皮瘤、表皮样癌、大细胞癌、非小细胞肺癌、淋巴瘤、霍奇金氏和非霍奇金氏、乳腺癌、滤泡癌、未分化性瘤、乳头装瘤、精原细胞瘤、黑素瘤、ABC DLBCL、霍奇金氏淋巴瘤、原发性皮肤 T 细胞淋巴瘤、慢性淋巴细胞性白血病、冒烟型惰性多发性骨髓瘤、白血病、弥漫性大 B 细胞淋巴瘤 DLBCL、慢性淋巴细胞性白血病 CLL、慢性淋巴细胞性淋巴瘤、原发性渗出性淋巴瘤、伯基特淋巴瘤 (Burkitt's Lymphoma)/白血病、急性淋巴细胞性白血病、B 细胞前淋巴细胞白血病、淋巴浆细胞淋巴瘤、瓦尔登斯特伦氏巨球蛋白血症 (Waldenstroms's macroglobulinemia WM)脾边缘区淋巴瘤、多发性骨髓瘤、或浆细胞瘤或血管内大 B 细胞淋巴瘤、阿尔茨海默症、帕金森氏病、肌肉萎缩性侧索硬化、亨廷顿氏病 (Huntington's disease)、大脑缺血或有创伤性损伤、谷氨酸神经毒性、低氧症、癫痫症、糖尿病治疗、代谢综合症、肥胖、器官移植或移植物抗宿主疾病造成的神经退化性疾病、眼病，如眼过敏、结膜炎、干眼症或春季结膜炎、影响鼻部的疾病，包括过敏性鼻炎；自身免疫性血液病症，如溶血性贫血、再生不全性贫血、纯红细胞贫血和特发性血小板减少、全身性红斑性狼疮症、类风湿性关节炎、多软骨炎、硬皮病、皮肌炎、多肌炎、慢性活性肝炎、重症肌无力、史蒂芬－约翰逊综合症、特发性口炎性腹泻、字体免疫性发炎性肠病、肠易综合症、乳糜泻、齿根骨膜炎、肺透明膜病、肾病、肾小球疾病、酒精性肝病、多发性硬化症、内分泌性眼病、格雷弗氏病 (Grave's disease)、肉瘤病、干眼症、春季结膜角膜炎、间质性肺纤维化、牛皮藓性关节炎、全身性幼年型特发性关节炎、肾炎、血管炎、间质性膀胱炎、憩室炎、肾小球肾炎、慢性肉芽肿性疾病、子宫内膜异位、钩端螺旋体病肾病、青光眼、视网膜疾病、老化、头痛、疼痛、复杂区域疼痛综合症、心肥大、肌肉萎缩、分解代谢症、肥胖、胎儿生长缓慢、高胆固醇血症、心脏病、慢性心脏衰竭、间皮瘤、无汗性外胚层发育不良、白塞氏病、色素失禁症、佩吉特氏病 (Paget's disease)、胰脏炎、遗传性周期性发热综合症、哮喘、急性肺损伤、急性呼吸窘迫综合症、嗜伊红血球增多、过敏反应、全身性过敏反应、鼻窦炎、眼过敏、二氧化硅诱发的疾病、COPD、肺病、囊肿性纤维化、酸诱发的肺损伤、肺动脉高压、多发性神经病、白内障、与全身性硬化症结合的肌肉炎症、包涵体肌炎、重症肌无力、甲状腺炎、阿狄森氏病 (Addison's disease)、扁平苔藓、1 型糖尿病、2 型糖尿病、阑尾炎、异位性皮炎、哮喘、过敏、细支气管炎、支气管炎、滑囊炎、子宫颈炎、胆管炎、胆囊炎、慢性移植排斥反应、结肠炎、结膜炎、膀胱炎、泪腺炎、皮炎、皮肌炎、多肌炎、脑炎、心内膜炎、子宫内膜炎、肠炎、小肠结肠炎、上踝炎、附睾炎、筋膜炎、纤维组织炎、胃炎、胃肠炎、亨诺-许兰紫斑病 (Henoch-Schonlein purpura)、肝炎、化脓性汗腺炎、免疫球蛋白 A 肾病、间质性肺病、喉炎、乳腺炎、脑膜炎、脊髓炎、心肌炎、肌炎、肾炎、肝纤维化、肾纤维化、酒精性脂肪肝、非酒精性脂肪肝、心脏纤维化、银屑病、克罗恩病、炎症性肠病、卵巢炎、睾丸炎、骨炎、耳炎、胰脏炎、腮腺炎、心包炎、腹膜炎、咽炎、胸膜炎、静脉炎、局部肺炎、肺炎、多发性肌炎、直肠炎、前列腺炎、肾盂肾炎、鼻炎、输卵管炎、窦炎、口腔炎、关节膜炎、肌腱炎、扁桃腺炎、溃疡性结肠炎、葡萄膜炎、阴道炎、血管炎、外阴炎、斑秃、多形性红斑、疱疹样皮炎、硬化病、白斑病、超敏性血管炎、荨麻疹、大疱性类天疱疮、寻常天疱疮、落叶型天疱疮、副肿瘤性天疱疮、获得性大疱性表皮松懈、急性和慢性痛风、慢性痛风性关节炎、牛皮藓、牛皮藓性关节炎、类风湿性关节

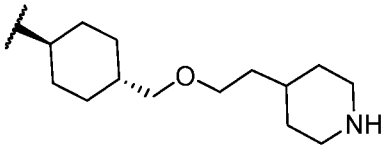
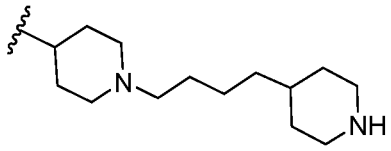
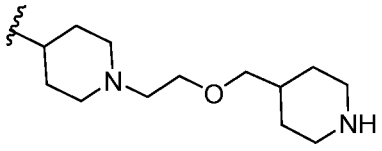
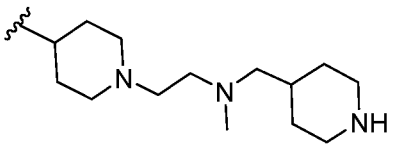
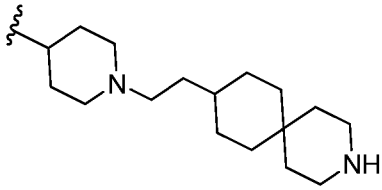
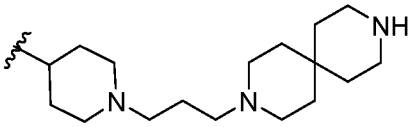
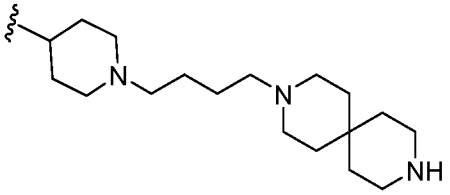
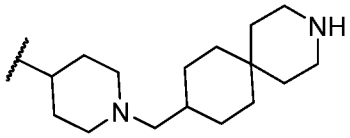
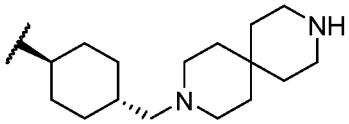
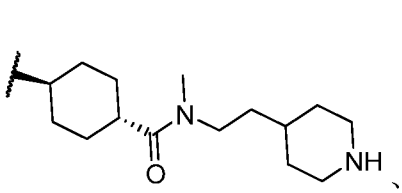
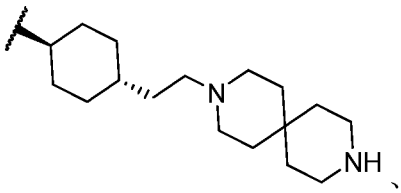
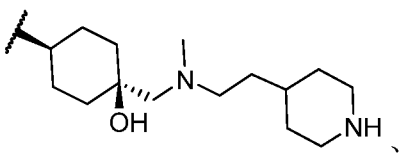
炎、幼年型类风湿性关节炎、隐热蛋白相关周其综合症或骨关节炎病症疾病的药物中的应用。

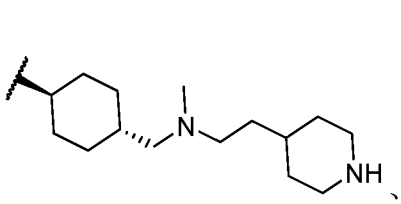
33. 一种物质 A 在制备 IRAK4 蛋白降解剂中的应用，所述物质 A 包括如权利要求 1-28 任一项所述式I化合物、其立体异构体、对映异构体、非对映异构体、氘代化物、水合物、溶剂化物、代谢物、前药或其药学上可接受的盐，或如权利要求 29 所述药物组合物。

34. 一种式VII或VIII化合物，其立体异构体、对映异构体、非对映异构体、氘代化物或其盐：



VII VIII

Z 为  、  、  、  、  、  、  、  、  、  、  、  。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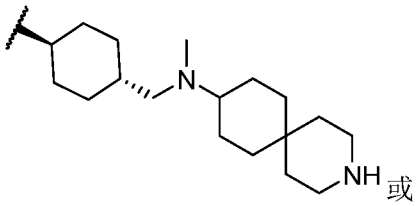
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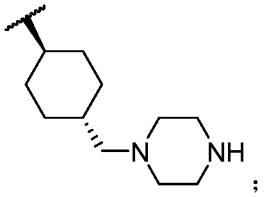
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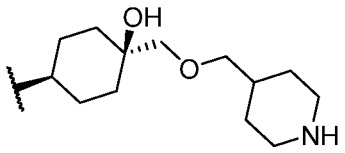
Z’为

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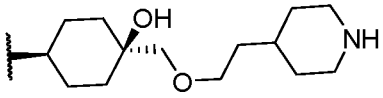
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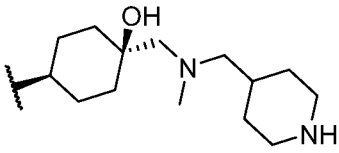
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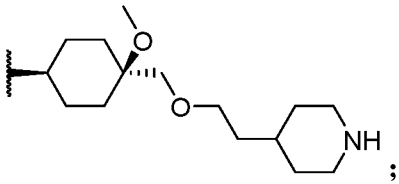
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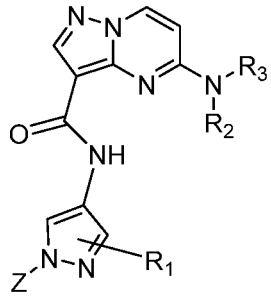
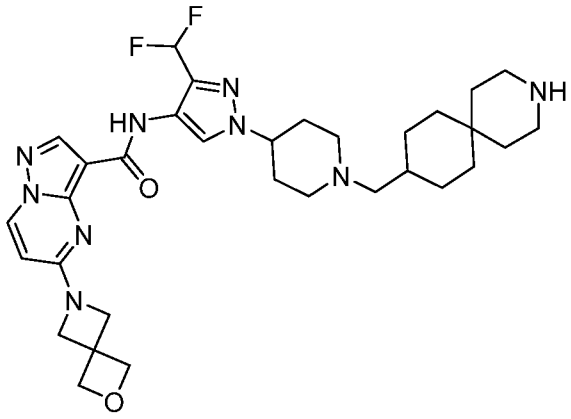
其中，m、n、A、A’、R_1、R_2、R_3和R_4如权利要求 1-28 任一项；



VII-1

较佳地，所述式VII化合物为式VII-1 所示化合物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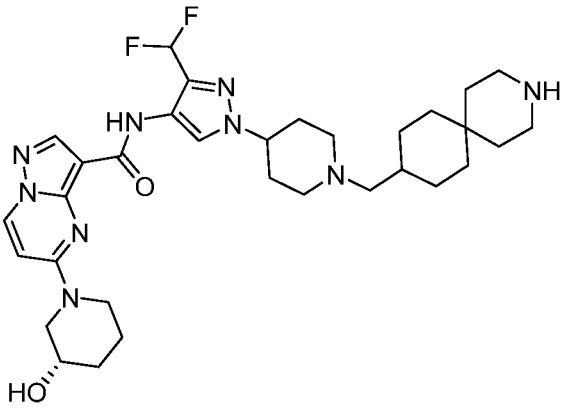
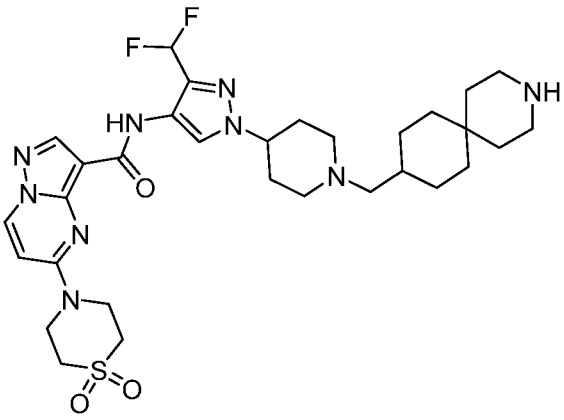
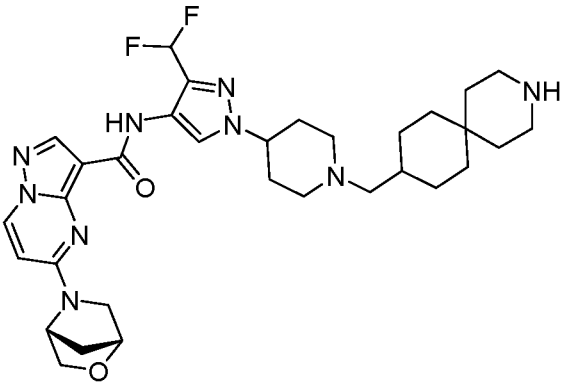
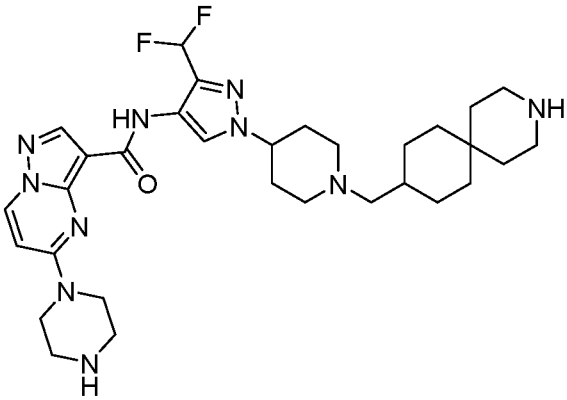
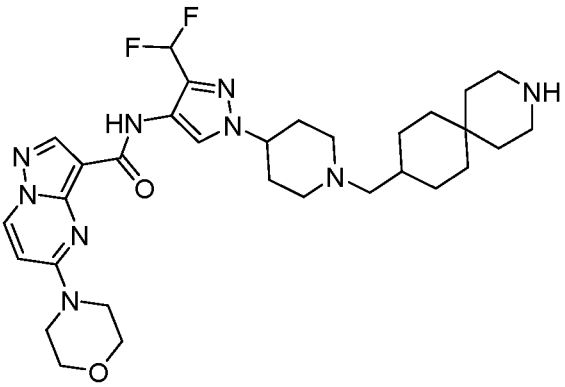
更佳地，所述式VII化合物为如下任一化合物：

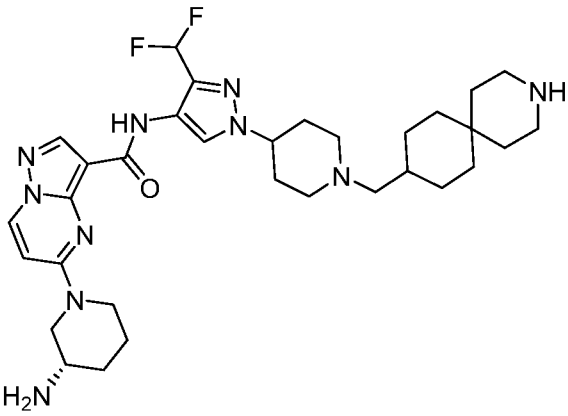


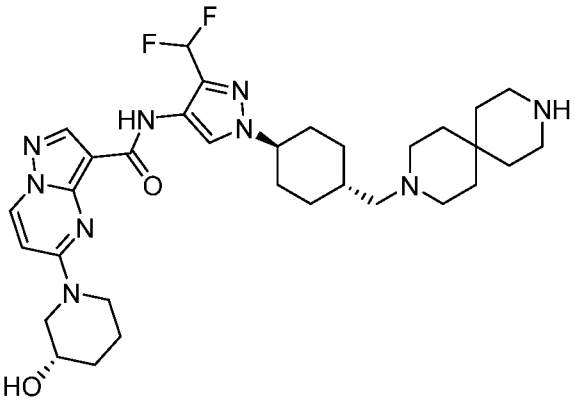


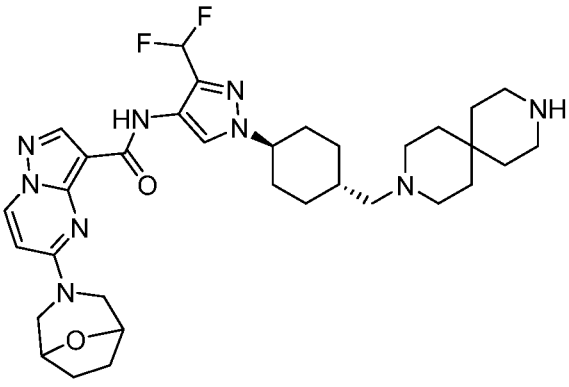


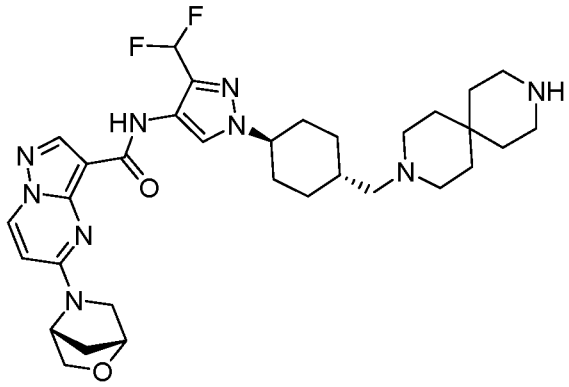


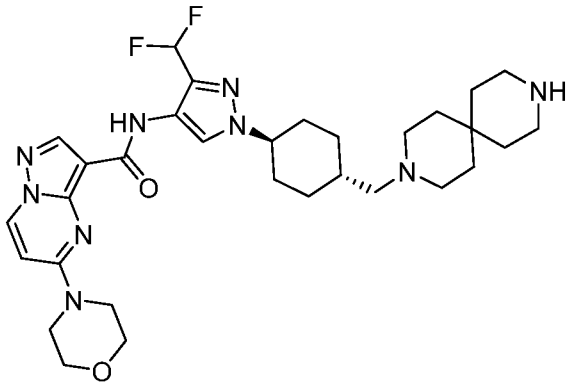


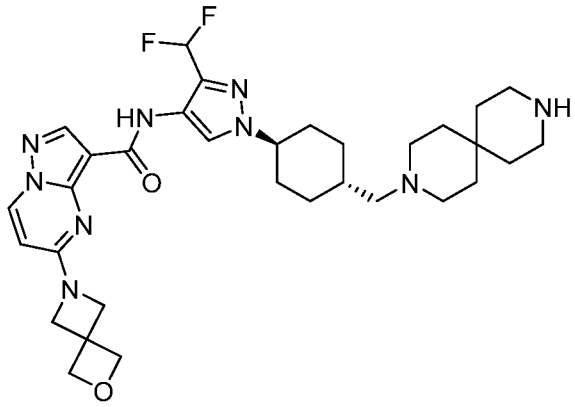


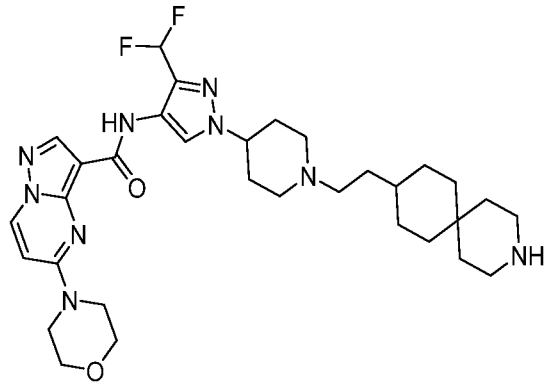


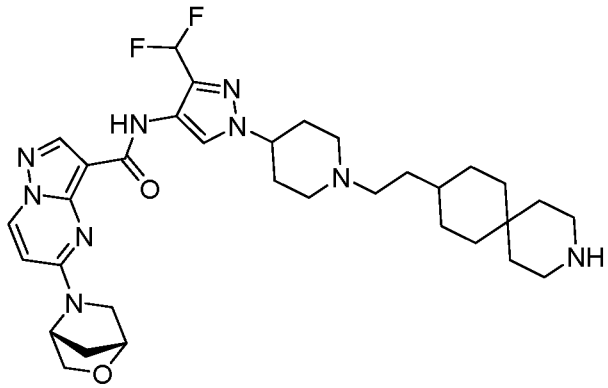


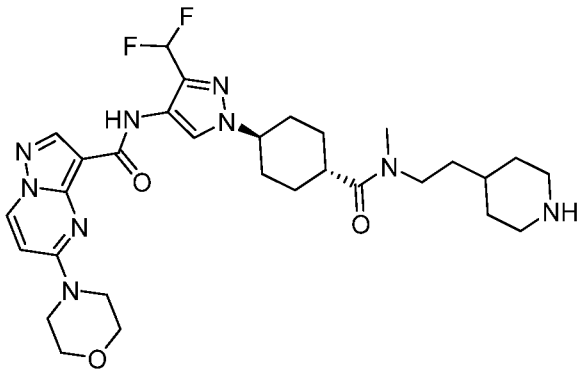


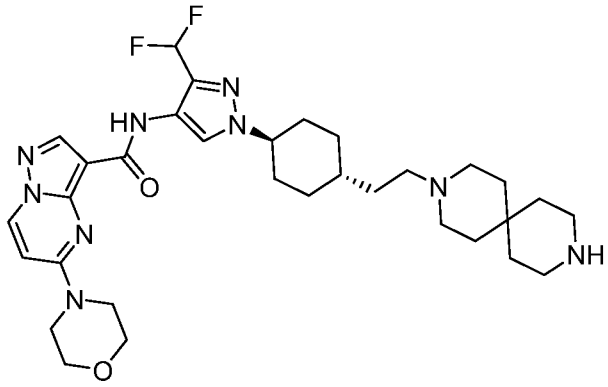


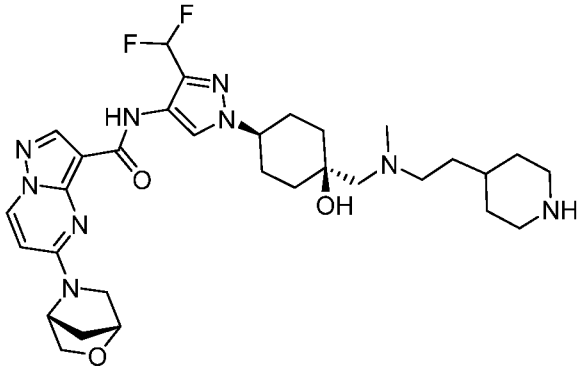


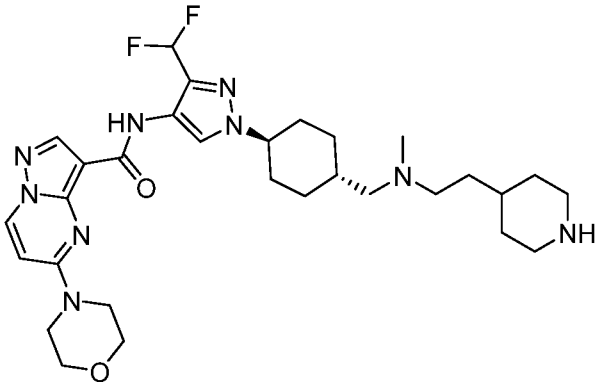


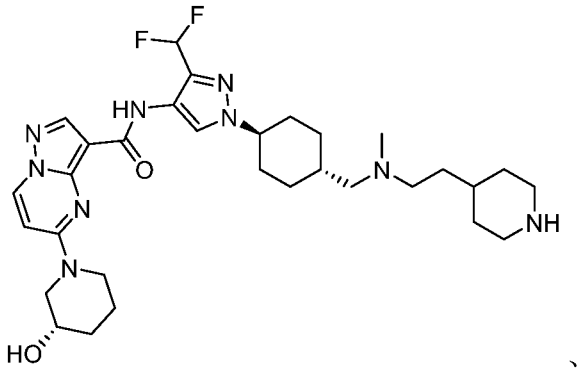


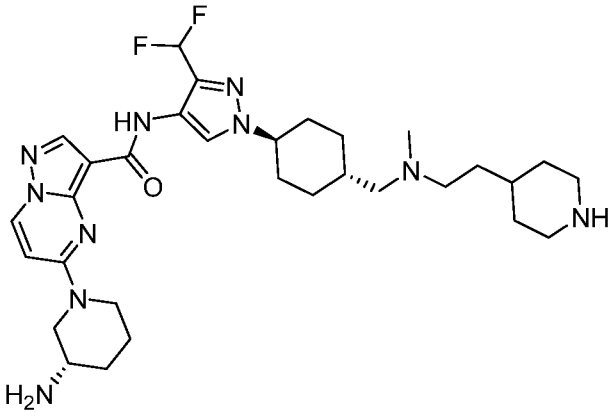


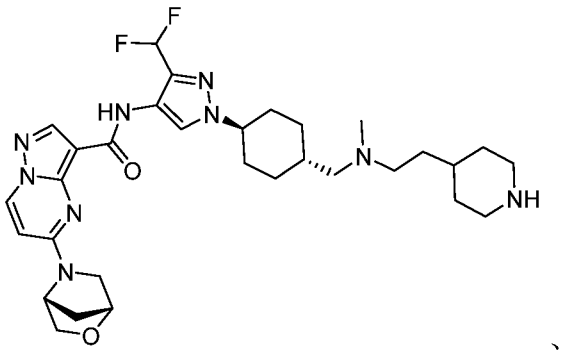


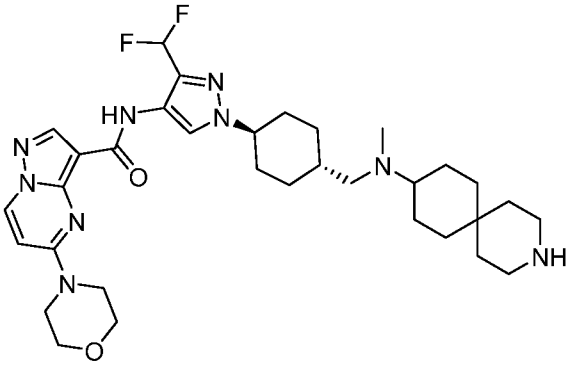


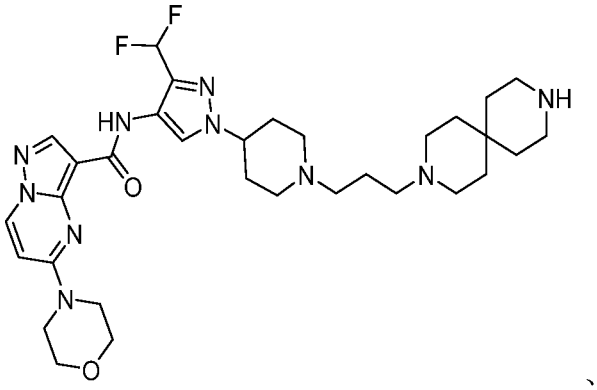


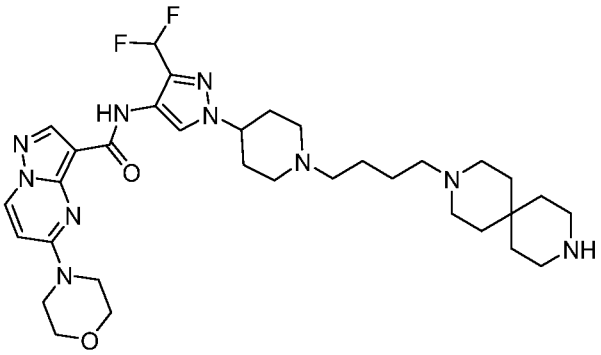


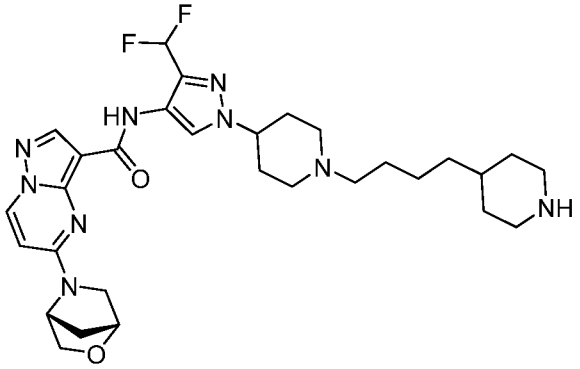


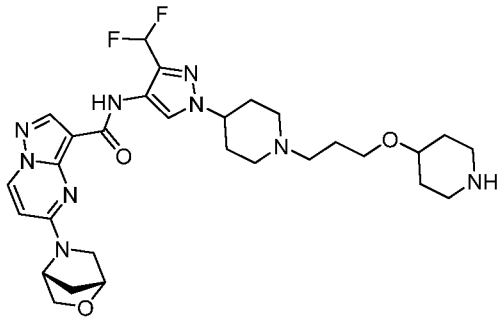
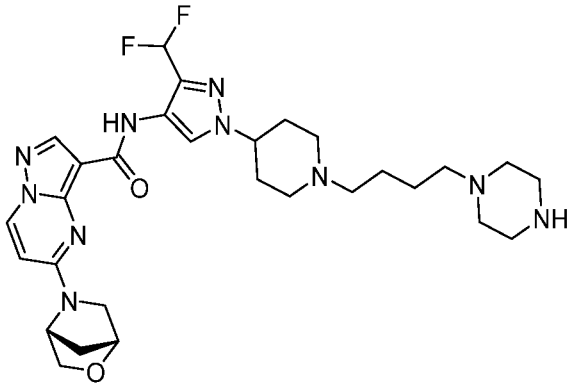











、

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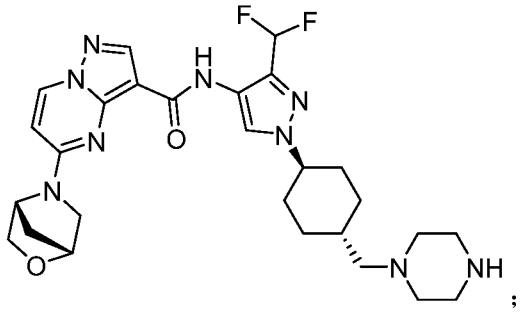
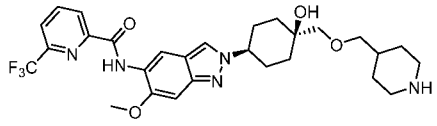
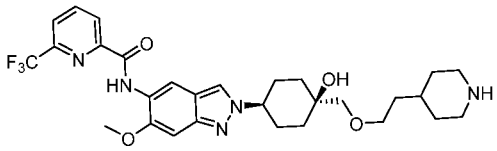
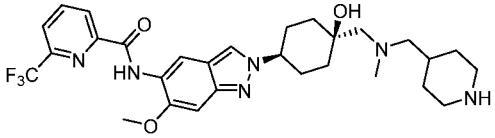
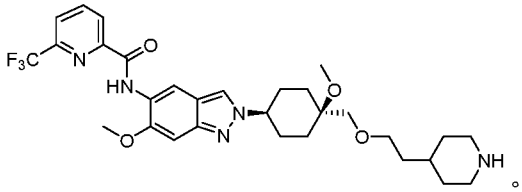

；

和/或，所述式VIII化合物为如下任一化合物：

、

、

或

。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/114323

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/10(2006.01)i; C07D 403/12(2006.01)i; C07D 401/14(2006.01)i; A61K 31/513(2006.01)i; A61P 35/00(2006.01)i; A61P 35/02(2006.01)i; A61P 25/08(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)

WPI, EPODOC, CNPAT, CAPLUS(STN), REGISTRY(STN), CNKI, 万方, WANFANG, 百度, BAIDU: IRAK, 白介素-1-受体激酶, 免疫, 白细胞介素, 吲哚, 哌啶, 上海领泰, 叶正清, 冯焱, 李世强, piperidinyl indole, inhibitor, 结构通式检索, structural general formula search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2022028547 A1 (SHANGHAI LEADINGTAC PHARMACEUTICAL CO., LTD.) 10 February 2022 (2022-02-10) description, p. 1, paragraph 1, p. 3, line 6 to p. 5, line 7, description, pp. 11-14, 23-24, 29-30, and 143-167, and description, pp. 213-223, intermediate table	1-34
PX	WO 2022147465 A1 (KYMERA THERAPEUTICS INC) 07 July 2022 (2022-07-07) description, p. 316, table, and claims 1-27	1-34
X	WO 2019099926 A1 (ARVINAS INC.) 23 May 2019 (2019-05-23) embodiment 59, claims 1-45, and description, paragraph [0003]	1-34
X	WO 2020113233 A1 (KYMERA THERAPEUTICS INC) 04 June 2020 (2020-06-04) description, table 1, description, paragraph [002956], and claims 1-28	1-34
X	WO 2020264499 A1 (KYMERA THERAPEUTICS INC) 30 December 2020 (2020-12-30) description, table 1, and claims 1-26	1-34
A	WO 2019160915 A1 (DANA-FARBER CANCER INSTITUTE, INC.) 22 August 2019 (2019-08-22) entire description	1-34

☑ 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	Date of mailing of the international search report
07 November 2022	**23 November 2022**
Name and mailing address of the ISA/CN **China National Intellectual Property Administration (ISA/CN)** **No. 6, Xitucheng Road, Jimenqiao, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/114323

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 110612294 A (ARVINAS INC.) 24 December 2019 (2019-12-24) embodiment	1-34
PA	WO 2022088551 A1 (SHANGHAI LEADINGTAC PHARMACEUTICAL CO., LTD.) 05 May 2022 (2022-05-05)	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/114323

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☑ Claims Nos.: **1-27,29-33**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

[1] The compound of formula (I) involved in claims 1-27 and 29-33 comprises three parts, i.e., PTM, L, and ULM. The PTM, L, and ULM each cover a large scope of substituents, such that it is difficult to exhaust searches of the prior art for the scopes of current claims. Moreover, the layer-by-layer substitution of the described three parts of substituents causes claims 1-27 and 29-33 to cover a large scope of protection. However, the description of the present application only verifies the biological activity of a small number of specific compounds. According to the content disclosed in the present application, a person skilled in the art cannot determine that claims 1-27 and 29-33, as a whole, can also solve the technical problem of the present application. Claims 1-27 and 29-33 are not supported by the description. The present report relates to conducting a search according to a scope reasonably generalized by the content fully disclosed in the description, and a search was conducted for the following general formula scopes in claims 1-27 and 29-33: PTM is defined as PTM-3 and PTM-3' shown in claim 4, ULM is defined as the structural fragment shown in claim 11, and L is defined as a compound shown in PTM-L-ULM composed of the groups shown in claim 12.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2022/114323

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2022028547	A1	10 February 2022	TW	202210470	A	16 March 2022
WO	2022147465	A1	07 July 2022		None		
WO	2019099926	A1	23 May 2019	US	2019151295	A1	23 May 2019
				EP	3710443	A1	23 September 2020
WO	2020113233	A1	04 June 2020	BR	112021010484	A2	24 August 2021
				JP	2022516401	A	28 February 2022
				CO	2021007068	A2	30 September 2021
				IL	283471	A	29 July 2021
				CA	3119773	A1	04 June 2020
				US	2021323952	A1	21 October 2021
				KR	20210111252	A	10 September 2021
				EP	3886904	A1	06 October 2021
				US	2022324854	A1	13 October 2022
				US	11117889	B1	14 September 2021
				AU	2019389174	A1	01 July 2021
				SG	11202105424P	A	29 June 2021
				CN	113423427	A	21 September 2021
WO	2020264499	A1	30 December 2020	EP	3989966	A1	04 May 2022
				JP	2022538192	A	31 August 2022
				BR	112021026517	A2	10 May 2022
				CO	2021017893	A2	17 January 2022
				KR	20220032063	A	15 March 2022
				CA	3144805	A1	30 December 2020
				CN	114502158	A	13 May 2022
				IL	289267	A	01 February 2022
				AU	2020302118	A1	24 February 2022
WO	2019160915	A1	22 August 2019	CA	3090275	A1	22 August 2019
				AU	2019220632	A1	23 July 2020
				EP	3752504	A1	23 December 2020
				US	2021230144	A1	29 July 2021
CN	110612294	A	24 December 2019	KR	20190116315	A	14 October 2019
				CO	2019009424	A2	28 February 2020
				JP	2020506922	A	05 March 2020
				BR	112019015484	A2	28 April 2020
				AU	2022221386	A1	15 September 2022
				EP	3577109	A1	11 December 2019
				CA	3050309	A1	09 August 2018
				IL	268069	A	26 September 2019
				RU	2019123462	A	27 January 2021
				MX	2019009046	A	30 October 2019
				AU	2018215212	A1	11 July 2019
				WO	2018144649	A1	09 August 2018
				US	2018215731	A1	02 August 2018
WO	2022088551	A1	05 May 2022		None		

国际检索报告

国际申请号
PCT/CN2022/114323

A. 主题的分类

C07D 471/10(2006.01)i; C07D 403/12(2006.01)i; C07D 401/14(2006.01)i; A61K 31/513(2006.01)i; A61P 35/00(2006.01)i; A61P 35/02(2006.01)i; A61P 25/08(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）)

WPI,EPODOC,CNPAT,CAPLUS(STN),REGISTRY(STN),CNKI,万方,百度:IRAK，白介素-1-受体激酶，免疫，白细胞介素，吲哚，哌啶，上海领泰，叶正清，冯焱，李世强，piperidinyl indole，inhibitor，结构通式检索

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
PX	WO 2022028547 A1 (SHANGHAI LEADINGTAC PHARMACEUTICAL CO LTD) 2022年2月10日 (2022-02-10) 说明书第1页第1段，第3页第6行-第5页第7行，说明书第11-14，23-24，29-30，143-167页，说明书第213-223页中间体表格	1-34
PX	WO 2022147465 A1 (KYMERA THERAPEUTICS INC) 2022年7月7日 (2022-07-07) 说明书第316页表格，权利要求1-27	1-34
X	WO 2019099926 A1 (ARVINAS INC) 2019年5月23日 (2019-05-23) 实施例59，权利要求1-45，说明书第[0003]段	1-34
X	WO 2020113233 A1 (KYMERA THERAPEUTICS INC) 2020年6月4日 (2020-06-04) 说明书表1，说明书第[002956]段，权利要求1-28	1-34
X	WO 2020264499 A1 (KYMERA THERAPEUTICS INC) 2020年12月30日 (2020-12-30) 说明书表1，权利要求1-26	1-34
A	WO 2019160915 A1 (DANA FARBER CANCER INST INC) 2019年8月22日 (2019-08-22) 说明书全文	1-34
A	CN 110612294 A (阿尔维纳斯运营股份有限公司) 2019年12月24日 (2019-12-24) 实施例部分	1-34

☑ 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	国际检索报告邮寄日期
2022年11月7日	2022年11月23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 王超 电话号码 86-(10)-53962337

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
PA	WO 2022088551 A1 (SHANGHAI LEADINGTAC PHARMACEUTICAL CO LTD) 2022年5月5日 (2022 - 05 - 05)	1-34

国际检索报告

国际申请号
PCT/CN2022/114323

第II栏　某些权利要求被认为是不能检索的意见(续第1页第2项)

根据条约第17条(2)(a)，对某些权利要求未做国际检索报告的理由如下：

1. ☐ 权利要求：
因为它们涉及不要求本单位进行检索的主题，即：

2. ☑ 权利要求： 1-27,29-33
因为它们涉及国际申请中不符合规定的要求的部分，以致不能进行任何有意义的国际检索， 具体地说：

[1] 权利要求1-27，29-33中涉及的式（I）化合物包括PTM，L以及ULM三部分， PTM，L以及ULM每个部分均覆盖了较大的取代基范围，致使难以针对目前权利要求的范围进行穷尽现有技术的检索。同时，前述三部分取代基的层层取代致使上述权利要求覆盖了较大保护范围，但本申请说明书仅验证了少量具体化合物的生物活性，根据本申请公开的内容，本领域技术人员不能确定权利要求1-27，29-33作为一个整体也能解决本申请的技术问题。权利要求1-27，29-33得不到说明书的支持。本报告根据说明书充分公开的内容合理概括的范围进行检索，针对权利要求1-27，29-33中以下通式范围进行检索：PTM限定为权利要求4所示的PTM-3和PTM-3’，ULM限定为权利要求11所示的结构片段以及L限定为权利要求12所示基团组成的PTM-L-ULM所示的化合物。

3. ☐ 权利要求：
因为它们是从属权利要求，并且没有按照细则6.4(a)第2句和第3句的要求撰写。

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2022/114323

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	2022028547	A1	2022年2月10日	TW	202210470	A	2022年3月16日
WO	2022147465	A1	2022年7月7日		无		
WO	2019099926	A1	2019年5月23日	US	2019151295	A1	2019年5月23日
				EP	3710443	A1	2020年9月23日
WO	2020113233	A1	2020年6月4日	BR	112021010484	A2	2021年8月24日
				JP	2022516401	A	2022年2月28日
				CO	2021007068	A2	2021年9月30日
				IL	283471	A	2021年7月29日
				CA	3119773	A1	2020年6月4日
				US	2021323952	A1	2021年10月21日
				KR	20210111252	A	2021年9月10日
				EP	3886904	A1	2021年10月6日
				US	2022324854	A1	2022年10月13日
				US	11117889	B1	2021年9月14日
				AU	2019389174	A1	2021年7月1日
				SG	11202105424P	A	2021年6月29日
				CN	113423427	A	2021年9月21日
WO	2020264499	A1	2020年12月30日	EP	3989966	A1	2022年5月4日
				JP	2022538192	A	2022年8月31日
				BR	112021026517	A2	2022年5月10日
				CO	2021017893	A2	2022年1月17日
				KR	20220032063	A	2022年3月15日
				CA	3144805	A1	2020年12月30日
				CN	114502158	A	2022年5月13日
				IL	289267	A	2022年2月1日
				AU	2020302118	A1	2022年2月24日
WO	2019160915	A1	2019年8月22日	CA	3090275	A1	2019年8月22日
				AU	2019220632	A1	2020年7月23日
				EP	3752504	A1	2020年12月23日
				US	2021230144	A1	2021年7月29日
CN	110612294	A	2019年12月24日	KR	20190116315	A	2019年10月14日
				CO	2019009424	A2	2020年2月28日
				JP	2020506922	A	2020年3月5日
				BR	112019015484	A2	2020年4月28日
				AU	2022221386	A1	2022年9月15日
				EP	3577109	A1	2019年12月11日
				CA	3050309	A1	2018年8月9日
				IL	268069	A	2019年9月26日
				RU	2019123462	A	2021年1月27日
				MX	2019009046	A	2019年10月30日
				AU	2018215212	A1	2019年7月11日
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(54) IRAK4 DEGRADATION AGENT, AND PREPARATION METHOD THEREFOR AND USE THEREOF

(57) An IRAK4 degradation agent as represented by structural formula PTM-L-ULM (I), and a preparation method therefor and the use thereof. The provided compound can effectively inhibit and/or degrade IRAK4 kinase protein in a cell and inhibit an immune cell from producing IL-6.

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Description

[0001] The present application claims priority to the Chinese Patent Application 202110966608X filed on Aug. 23, 2021, the Chinese Patent Application 2022105581585 filed on May 19, 2022, and the Chinese Patent Application 2022109894485 filed on Aug. 17, 2022, which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

[0002] The present invention relates to the field of pharmaceuticals and particularly to an IRAK4-targeting protein-degrading compound, a pharmaceutical composition, a preparation method therefor, and use thereof in the preparation of a medicament for treating and/or preventing IRAK4-mediated related diseases or disorders, such as cancer, immune diseases and inflammatory diseases.

BACKGROUND

[0003] Interleukin-1 receptor kinase 4 (IRAK4) is a serine/threonine-specific protein kinase, which has biologically important kinase activity and plays an important role in activating the immune system. Studies have shown that IRAK4 is a key factor in the signaling pathways of the receptors of the interleukin (IL)-1β family (including IL-1R, IL-18R, IL-33R and IL-36R) and Toll-like receptors (TLRs), and that both IRAK4-deficient mice and IRAK4-deficient patients are non-responsive to stimulation by TLRs (except TLR3) and the IL-1β family.

[0004] According to whether MyD88 is involved or not, the TLR/IL-1β-mediated signaling pathways are classified into two categories: MyD88-dependent signaling pathways and MyD88-independent signaling pathways. The signaling pathways mediated by IL-1R and TLR2, TLR4, TLR7/8 and TLR9 all rely on MyD88 as a regulatory factor to activate downstream inflammatory signaling pathways. Upon binding to the ligand, TLR/IL-1β recruits MyD88 molecules. Further, MyD88 recruits IRAK4 into the TLR/IL-1β complex through its N-terminal death domain, and interacts with IRAK1 or IRAK2 and activates them, thereby signaling downstream to the E3 ubiquitin ligase TNF receptor associated factor (TRAF6), activating the serine/threonine kinase TAK1 and further the NF-κB and MAPK signaling pathways, resulting in the release of various inflammatory cytokines and anti-apoptotic molecules. The IRAK4-dependent TLR/IL-1β signaling pathway has been shown to be associated with a variety of diseases such as multiple sclerosis, atherosclerosis, myocardial infarction, myocarditis, Vogt-Koyanagi-Harada syndrome, systemic lupus erythematosus (SLE), obesity, type 1 diabetes, rheumatoid arthritis, spondyloarthritis (especially psoriatic spondyloarthritis and Bekhterev's disease), lupus erythematosus, psoriasis, vitiligo, giant cell arteritis, chronic inflammatory intestinal diseases and viral diseases, for example, HIV (human immunodeficiency virus), hepatitis viruses; skin diseases such as psoriasis, atopic dermatitis, Kindler's syndrome, bullous pemphigoid, allergic contact dermatitis, alopecia areata, acneinversa and acne vulgaris; other inflammatory diseases such as allergy, Bechet's disease, gout, adult-onset Still's disease, pericarditis and chronic inflammatory intestinal diseases such as ulcerative colitis and Crohn's disease, transplant rejection and graft-versus-host reactions; gynecological diseases such as adenomyosis, dysmenorrhea, dyspareunia and endometriosis, especially pain related to adenomyosis and other symptoms related to adenomyosis such as dysmenorrhea, dyspareunia, dysuria and difficulty defecating; eye diseases such as retinal ischemia, keratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration and ocular pigment layer inflammation; fibrotic diseases such as liver fibrosis, myocarditis, primary biliary cirrhosis, cystic fibrosis; chronic liver diseases such as fatty liver hepatitis, especially non-alcoholic fatty liver disease (NAFLD) and/or non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH); cardiovascular diseases and neurological disorders such as myocardial reperfusion injury, myocardial infarction, hypertension, and Alzheimer's disease, stroke, craniocerebral trauma, amyotrophic lateral sclerosis (ALS) and Parkinson's disease; pruritus and pain (including acute, chronic, inflammatory and neuropathic pain) such as hyperalgesia, allodynia, premenstrual pain, pain related to adenomyosis, postoperative pain, interstitial cystitis, CRPS (complex local pain syndrome), trigeminal neuralgia, prostatitis, pain caused by spinal cord injury, pain caused by inflammation, lower back pain, cancer pain, chemotherapy-related pain, HIV treatment-induced neuropathy, pain caused by burns and chronic pain; tumor diseases such as certain lymphomas: ABC-DLBCL (activated B-cell diffuse large cell B-cell lymphoma), mantle cell lymphoma and Waldenstrom disease, as well as chronic lymphocytic leukemia, melanoma, pancreatic tumors and hepatocellular carcinoma, ras-dependent tumors, breast cancer, ovarian cancer, colorectal cancer, head and neck cancer, lung cancer, and prostate cancer.

[0005] Modulation of IRAK4-mediated signaling pathways is primarily associated with its kinase function. However, there are also reports that signal modulation by IRAK4 of downstream processes is associated with the non-kinase function of IRAK4 in certain cell types. Cushing et al. have indicated that despite reduced levels of IRAK4 phosphorylation in IL-1β-stimulated human skin fibroblasts, pharmacological inhibition of IRAK4 does not result in inhibition of IL-6 and TNF-α. Supporting these results, the scaffolding function of IRAK4 is important for IL1 signaling, but its kinase activity is redundant in IRAK4-deficient fibroblasts compared to wild-type cells. Chiang et al. have also indicated that the kinase

activity of IRAK4 is not essential in human B cells and T cells, dendritic cells and monocytes, and siRNA gene excision also shows that IRAK4 can function as a scaffold in these cells. A variety of potent selective inhibitors against IRAK4 have been reported, such as CA-4948, BAY-1834845, BMS-986126 and PF-06650833. These inhibitors can selectively inhibit the kinase activity of IRAK4 and are mainly used for the prevention and treatment of autoimmune diseases, inflammatory diseases and tumor diseases. However, since IRAK4 can function as a scaffold protein and an active kinase, and traditional small-molecule inhibitors easily lead to drug resistance, inhibiting only the kinase activity of IRAK4 may not be sufficient to produce a therapeutic effect.

[0006] Proteolysis targeting chimera (PROTAC) is a technology different from the traditional small-molecule inhibitors. The traditional small-molecule inhibitors usually need to act on the active site of a target protein to inhibit the activity of the target protein, while the PROTAC is a heterogeneous bifunctional molecule, one end of which is a small-molecule inhibitor capable of recognizing the target protein, and the other end of which is an E3 ubiquitin ligase ligand capable of recognizing E3 ubiquitin ligase via a linking chain. Such a bifunctional molecule recognizes the target protein and the E3 ubiquitin ligase *in vivo,* draws the target protein and the E3 ubiquitin ligase closer to form a ternary complex, and degrades the target protein *in vivo* through a ubiquitin-proteasome pathway after ubiquitinating the target protein. Compared with the traditional small-molecule inhibitors, in one aspect, the PROTAC only needs to draw the target protein and the E3 ubiquitin ligase closer to degrade the substrate, and the action mode enables the technology to be applied to some non-druggable targets; in another aspect, the PROTAC molecules can be released to continue to participate in the degradation process of the next protein after the target protein is degraded, so that the degradation effect with a catalytic effect can realize efficient degradation with less dosage of the PROTAC medicament; in yet another aspect, the traditional small-molecule inhibitors easily generate drug resistance often because a point mutation occurs, so that the small-molecule inhibitors lose the inhibition effect on the target point, while the PROTAC can directly degrade the target protein, so that the drug resistance generated by the point mutation can be avoided to a certain extent. Therefore, compared with the traditional small-molecule inhibitors, the PROTAC technology has high advantages and feasibility in the research and development of small-molecule new drugs, and these drugs are expected to become next-generation promising new drugs. PROTAC technology has also been applied to the modification of various target drugs, such as the androgen receptor, the estrogen protein receptor, and BTK. Several types of IRAK4-targeting degraders are disclosed in US2019/0151295, US2019/0192688, WO2019/160915 and WO2020/113233. There is an urgent need to develop more IRAK4-targeting degraders.

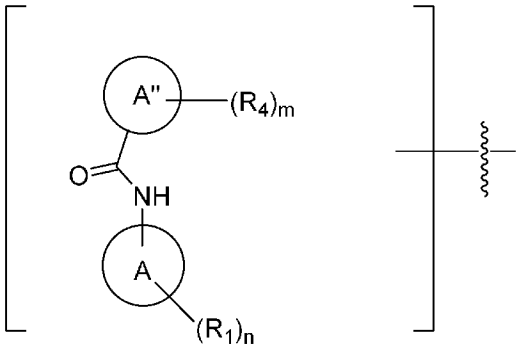
SUMMARY

[0007] The present invention provides a compound of formula I, a stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or a pharmaceutically acceptable salt thereof;

PTM-L-ULM I

wherein:

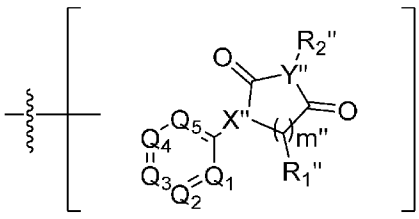
the PTM has a structure of the following formula:



PTM-1

wherein in the PTM-1:
m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;
ring A'' is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S;
ring A is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S;
each R_1 is independently selected from: C_1-C_4 alkyl, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_{1-2}$, C_3-C_8 cycloalkyl, -O(C_3-C_8 cycloalkyl), -NH(C_3-C_8 cycloalkyl), 3-8 membered heterocycloalkyl, -O(3-8 membered heterocycloalkyl), -NH(3-8 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), - NH(6-10 membered aryl), 5-6 membered heteroaryl, -O(5-6 membered heteroaryl), -NH(5-6 membered heteroaryl), CN, halogen, -OH, -NH_2, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, -C(O)NH_2, -S(O)$_2$H, -S(O)$_2NH_2$, -C(O)(C_1-C_4 alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$ or -S(O)NH(C_1-C_4 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, -OH, C_1-C_4 alkyl, -O(C_1-C_4 allcyl), methylpiperidine, - S(O)$_2$H, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$ and C(O)O(C_1-C_4 alkyl);
or the R_1, together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
each R_4 is independently hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-6 membered heteroaryl, CN, halogen, -OH, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, -C(O)NH_2, -S(O)$_2$H, -S(O)$_2NH_2$, -C(O)(C_1-C_4 alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$, -S(O)NH(C_1-C_4 alkyl) or X(R_2)(R_3), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, -OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, -S(O)$_2$H, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$, and -C(O)O(C_1-C_4 alkyl);
X is O, S, CH_2 or N;
R_2 and R_3 are independently selected from: hydrogen, C_1-C_6, alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl or 5-6 membered heteroaryl, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, OH, oxo, N(R_b)$_2$, oxopyrrolidinyl and morpholinyl, or R_2 and R_3, together with the atom to which they are attached, form C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with one or more substituents selected from R_a;
R_a is independently selected from oxo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_3-C_6 cycloalkyl or CF_3; and
R_b is independently selected from H or C_1-C_4 alkyl;
L is a linking chain, which links PTM and ULM by covalent bonds;
the ULM has a structure of the following formula:



ULM-1

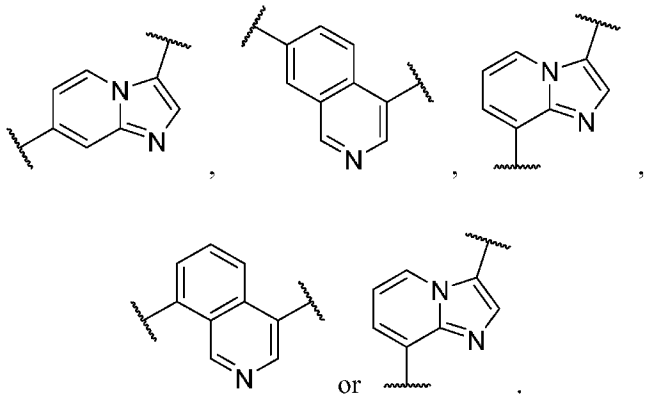
wherein in the ULM-1:
X'' is C or N;
Y'' is C, N, O or S;
Q_1, Q_2, Q_3, Q_4 and Q_5 are each independently CR_3'' or N;
each R_3'' is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkl, 6-10 membered aryl, 5-10 membered heteroaryl, -O(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(3-8 membered heterocycloalkyl), N(C_1-C_6 alkyl)$_{1-2}$, NH(C_3-C_8 cycloalkyl), NH(3-8 membered heterocycloalkyl), -O-(6-10 aryl) or -0-(5-10 membered heteroaryl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino; or R_3'', together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, heteroaryl or aryl;
m'' is 1, 2 or 3;
each R_1'' is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8

membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl or -O(C_1-C_6 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino;

R_2" is hydrogen, deuterium, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl and C_3-C_6 cycloalkyl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano, amino and -OC(O)(C_1-C_6 alkyl).

[0008] Preferably, in certain embodiments of the present invention, each R_3" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, -O(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(3-8 membered heterocycloalkyl), N(C_1-C_6 alkyl)$_{1-2}$, NH(C_3-C_8 cycloalkyl), NH(3-8 membered heterocycloalkyl), -0-(6-10 aryl) or -0-(5-10 membered heteroaryl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino; or R_3", together with the atom to which it is attached, forms cycloalkyl or heterocycloalkyl.

[0009] Preferably, in certain embodiments of the present invention, R_3", together with the atom to which it is attached, forms heteroaryl, which is not



[0010] Preferably, in certain embodiments of the present invention,

in the PTM-1:

m is 0 or 1;

n is 0, 1 or 2;

ring A" is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S;

ring A is 6-10 membered aryl or 5-6 membered heteroaryl;

R_1 is independently selected from: C_1-C_4 alkyl, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_{1-2}$, C_3-C_8 cycloalkyl, -O(C_3-C_8 cycloalkyl), -NH(C_3-C_8 cycloalkyl), 3-8 membered heterocycloalkyl, -O(3-8 membered heterocycloalkyl), -NH(3-8 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), - NH(6-10 membered aryl), 5-6 membered heteroaryl, -O(5-6 membered heteroaryl), -NH(5-6 membered heteroaryl), CN, halogen, -OH, -NH_2, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(Ci-Ca alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, -C(O)NH_2, -S(O)$_2$H, -S(O)$_2$$NH_2$, -C(O)($C_1$-$C_4$ alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$ or -S(O)NH(C_1-C_4 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, -OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, - S(O)$_2$H, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$, or -C(O)O(C_1-C_4 alkyl);

or the R_1, together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

R_4 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-6 membered heteroaryl, CN, halogen, -OH, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, -C(O)NH_2, -S(O)$_2$H, -S(O)$_2$$NH_2$, -C(O)($C_1$-$C_4$ alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$, -S(O)NH(C_1-C_4 alkyl) or -X(R_2)(R_3), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, - OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, -S(O)$_2$H, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$, or -C(O)O(C_1-C_4 alkyl); or

X is O, S, CH_2 or N;

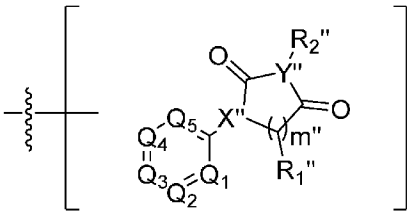
R_2 and R_3 are independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 aryl or 5-6 membered heteroaryl, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, OH, oxo, $N(R_b)_2$, oxopyrrolidinyl or morpholinyl, or R_2 and R_3, together with the atom to which they are attached, form C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from oxo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_3-C_6 cycloalkyl or CF_3; and

R_b is independently selected from H or C_1-C_4 alkyl;

L is a linking chain, which links PTM and ULM by covalent bonds;

the ULM has a structure of the following formula:



ULM-1

wherein in the ULM-1:

X" is C or N;

Y" is C, N, O or S;

Q_1, Q_2, Q_3, Q_4 and Q_5 are each independently CR_3" or N;

each R_3" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, -O(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(3-8 membered heterocycloalkyl), N(C_1-C_6 alkyl)$_{1-2}$, NH(C_3-C_8 cycloalkyl), NH(3-8 membered heterocycloalkyl), -0-(6-10 aryl) or -0-(5-10 membered heteroaryl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino; or R_3", together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, heteroaryl or aryl;

m" is 1, 2 or 3;

each R_1" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl or -O(C1-C6 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino;

R_2" is hydrogen, deuterium, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl and C_3-C_6 cycloalkyl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano, amino or -OC(O)(C_1-C_6 alkyl).

Preferably, in certain embodiments of the present invention,

in the PTM-1:

m is 0, 1, 2, 3 or 4;

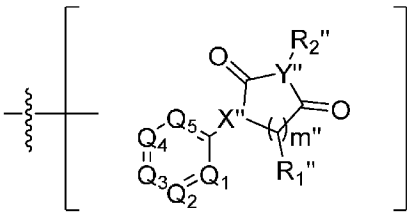
n is 0, 1, 2, 3 or 4;

ring A" is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S;

ring A is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S;

R_1 is independently selected from: C_1-C_4 alkyl, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_{1-2}$, C_3-C_8 cycloalkyl, -O(C_3-C_8 cycloalkyl), -NH(C_3-C_8 cycloalkyl), 3-8 membered heterocycloalkyl, -O(3-8 membered heterocycloalkyl), -NH(3-8 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), - NH(6-10 membered aryl), 5-6 membered heteroaryl, -O(5-6 membered heteroaryl), -NH(5-6 membered heteroaryl), CN, halogen, -OH, -NH_2, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, -C(O)NH_2, -S(O)$_2$H, -S(O)$_2NH_2$, -C(O)(C_1-C_4 alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$ or -S(O)NH(C_1-C_4 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, -OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, - S(O)$_2$H, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$, or -C(O)O(C_1-C_4 alkyl);

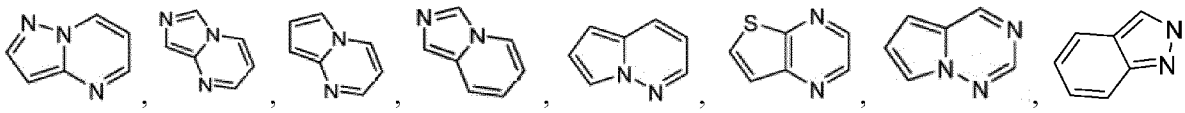
or the R_1, together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
R_4 is hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-6 membered heteroaryl, CN, halogen, -OH, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, -C(O)NH_2, -S(O)$_2$H, -S(O)$_2NH_2$, -C(O)(C_1-C_4 alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$, -S(O)NH(C_1-C_4 alkyl) or -X(R_2)(R_2), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, - OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, -S(O)$_2$H, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1\text{-}2}$, or -C(O)O(C_1-C_4 alkyl);
X is O, S, CH_2 or N;
R_2 and R_3 are independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl or 5-6 membered heteroaryl, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, OH, oxo, N(R_b)$_2$, oxopyrrolidinyl or morpholinyl, or R_2 and R_3, together with the atom to which they are attached, form C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents selected from R_a;
R_a is independently selected from oxo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_3-C_6 cycloalkyl or CF_3; and
R_b is independently selected from H or C_1-C_4 alkyl;
L is a linking chain, which links PTM and ULM by covalent bonds;
the ULM has a structure of the following formula:



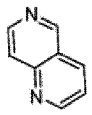
ULM-1

wherein in the ULM-1:
X" is C or N;
Y" is C, N, O or S;
Q_1, Q_2, Q_3, Q_4 and Q_5 are each independently CR_3" or N;
each R_3" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, -O(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(3-8 membered heterocycloalkyl), N(C_1-C_6 alkyl)$_{1\text{-}2}$, NH(C_3-C_8 cycloalkyl), NH(3-8 membered heterocycloalkyl), -O-(6-10 aryl) or -O-(5-10 membered heteroaryl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino; or R_3", together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, heteroaryl or aryl;
m" is 1, 2 or 3;
each R_1" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl or -O(C_1-C_6 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino;
R_2" is hydrogen, deuterium, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl and C_3-C_6 cycloalkyl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano, amino or -OC(O)(C_1-C_6 alkyl).

[0011] Preferably, in certain embodiments of the present invention, in the PTM-1, ring A" is 9-10 membered bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S; preferably, ring A" is



or



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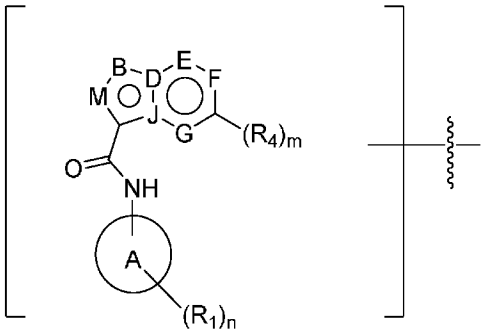
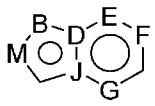
[0012] Preferably, in certain embodiments of the present invention, the PTM is



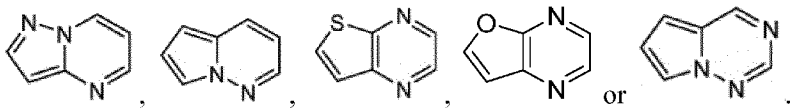
PTM-2

wherein in the PTM-2:
B is CH, N, O or S;
M is CH, N, O or S;
D is CH or N;
E is CH or N;
F is CH or N;
G is CH or N;
J is CH or N;
when B or M is S or O, D is CH, E is N, F is CH, G is N, and J is CH; and B and M are not simultaneously S and/or O;
the ring A, R_1, n, R_4 and m are as defined and described in PTM-1.

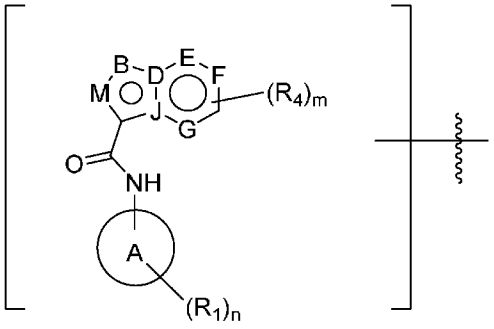
[0013] Preferably, in certain embodiments of the present invention, the



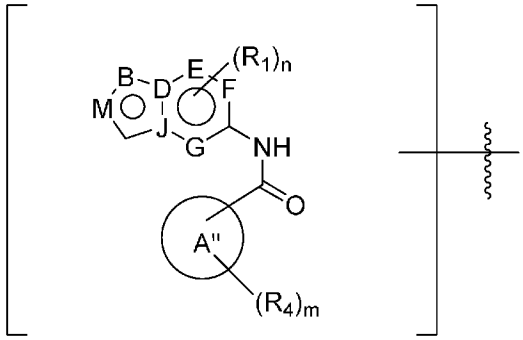
in the PTM-2 is



[0014] Preferably, in certain embodiments of the present invention, the PTM is



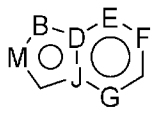
PTM-2'



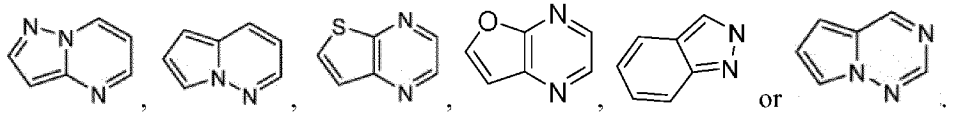
PTM-2"

wherein in the PTM-2' or PTM-2":
B is CH, N, O or S;
M is CH, N, O or S;
D is CH or N;
E is CH or N;
F is CH or N;
G is CH or N;
J is CH or N;
when B or M is S or O, D is CH, E is N, F is CH, G is N, and J is CH; and B and M are not simultaneously S and/or O;
the ring A, ring A", R_1, n, R_4 and m are as defined and described in PTM-1.

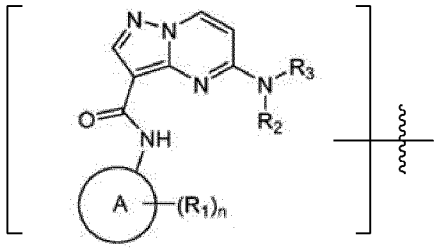
[0015] Preferably, in certain embodiments of the present invention, the



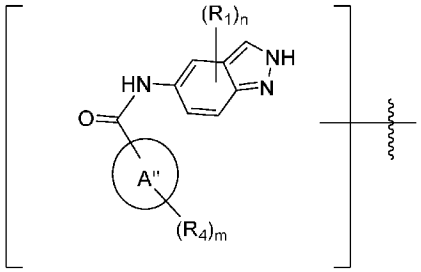
in the PTM-2' is



[0016] Preferably, in certain embodiments of the present invention, the PTM is:



PTM-3



PTM-3'

wherein the ring A, ring A", R_1, R_2, R_3, R_4, m and n are as defined and described in PTM-1.

[0017] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2, PTM-2' and PTM-3:
ring A is phenyl or is 5-6 membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N or O; preferably, ring A is phenyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, pyrimidinyl, triazolyl, tetrazolyl, thienyl, thiazolyl, furanyl, oxazolyl,

isoxazolyl or isothiazolyl; further preferably, ring A is pyrazolyl or thienyl.

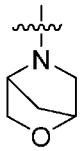
[0018] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2, PTM-2' and PTM-3, n is 1 or 2; preferably n is 2.

[0019] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2, PTM-2' and PTM-3, R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, CH_3 or OCH_3; preferably, R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl containing 1 or 2 heteroatoms selected from N, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, CH_3 or OCH_3; further preferably, the R_1 is CHF_2, CF_3, cyclohexyl, piperidinyl, methyl, cyano or piperazinyl.

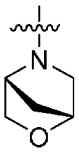
[0020] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2 and PTM-3, R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, CH_3 or OCH_3; preferably, R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl containing 1 or 2 heteroatoms selected from N, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, CH_3 or OCH_3; further preferably, the R_1 is CHF_2, CF_3, cyclohexyl, piperidinyl or piperazinyl.

[0021] In certain embodiments of the present invention, R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl containing 1 or 2 heteroatoms selected from N, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, C_1-C_4 alkyl or C_1-C_4 alkoxy.

[0022] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2 and PTM-3, R_2 and R_3 are each independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, and are each optionally substituted with one or more halogens, OH, $N(R_b)_2$ or morpholinyl groups, or R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; R_a is independently selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl or CF_3; and R_b is independently selected from H or C_1-C_4 alkyl; more preferably, R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl containing, in addition to the N atom to which they are attached, 1 additional heteroatom selected from N or O, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; the R_a is independently selected from C_1-C_4 alkyl, CF_3, CHF_2, OH, halogen or NH_2; further preferably, the R_2 and R_3, together with the nitrogen atom to which they are attached, form



; still further preferably, the R_2 and R_3, together with the nitrogen atom to which they are attached, form



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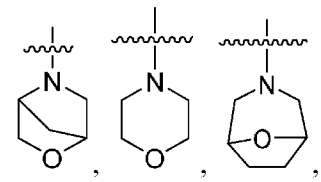
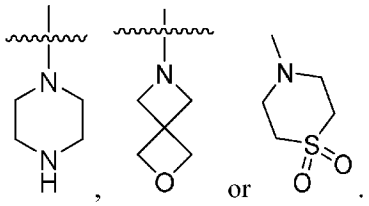
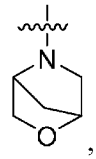
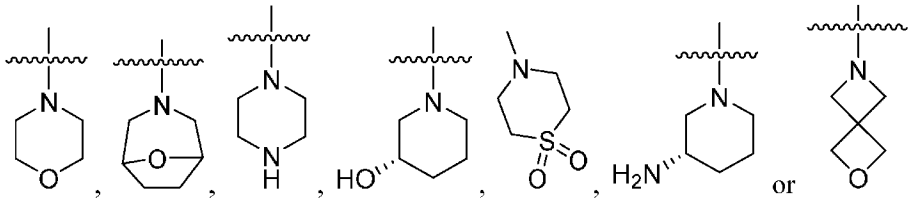
[0023] Preferably, in certain embodiments of the present invention, R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl containing, in addition to the N atom to which they are attached, 1 additional heteroatom selected from N, S or O, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; the R_a is independently selected from C_1-C_4 alkyl, C_1-C_4 alkyl substituted with 1, 2 or 3 halogens (preferably C_1-C_4 alkyl substituted with 1, 2 or 3 fluorines, and more preferably methyl substituted with 1, 2 or 3 fluorines), OH, halogen or NH_2; preferably, the R_2 and R_3, together with the nitrogen atom to which they are attached, form



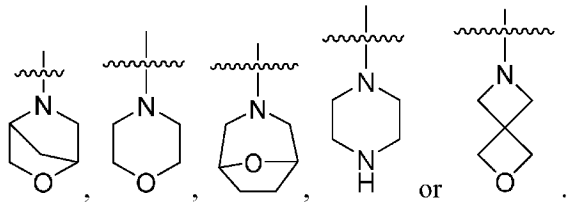


[0024] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2' and PTM-3, R_2 and R_3 are each independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, and are each optionally substituted with one or more halogens, OH, $N(R_b)_2$ or morpholinyl groups, or R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; R_a is independently selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_3-C_6 cycloalkyl or CF_3; and R_b is independently selected from H or C_1-C_4 alkyl; preferably, R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl containing, in addition to the N atom to which they are attached, 1 additional heteroatom selected from N or O, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; the R_a is independently selected from C_1-C_4 alkyl, CF_3, CHF_2, OH, halogen or NH_2; preferably, the R_2 and R_3, together with the nitrogen atom to which they are attached, form

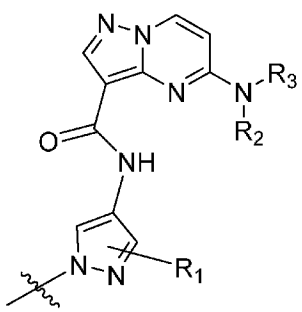




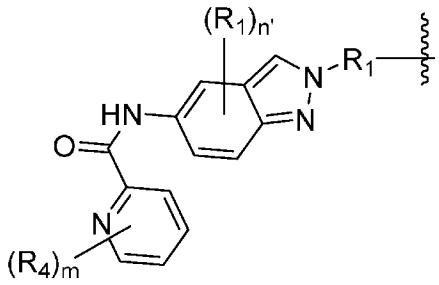
[0025] Preferably, in certain embodiments of the present invention, in the PTM-1, PTM-2' and PTM-3, R_2 and R_3 are each independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl and 3-8 membered heterocycloalkyl, and are each optionally substituted with one or more halogens, OH, $N(R_b)_2$ and morpholinyl groups, or R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; R_a is independently selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl and CF_3; and R_b is independently selected from H and C_1-C_4 alkyl; preferably, R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl containing, in addition to the N atom to which they are attached, 1 additional heteroatom selected from N or O, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; the R_a is independently selected from C_1-C_4 alkyl, CF_3, CHF_2, OH, halogen and NH_2; preferably, the R_2 and R_3, together with the nitrogen atom to which they are attached, form



[0026] Preferably, in certain embodiments of the present invention, the PTM has a structure of the following formula:



PTM-3a

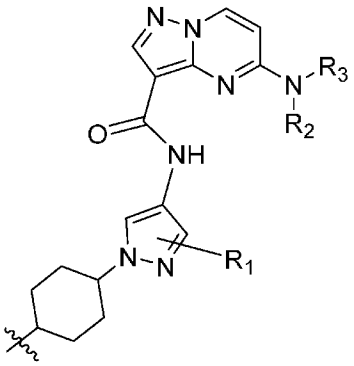


PTM-3a'

wherein,

n' is 0, 1, 2 or 3;
the R_1, R_2, R_3, R_4, m and n are as described and defined in PTM-1, PTM-2, PTM-2' and PTM-3.

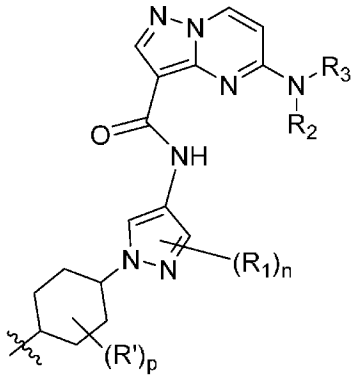
[0027] Preferably, in certain embodiments of the present invention, the PTM has a structure of the following formula:



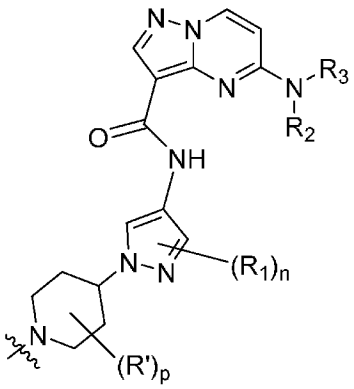
PTM-3b

wherein R_1, R_2, R_3, R_4, m and n are as described and defined in PTM-1, PTM-2, PTM-2' and PTM-3.

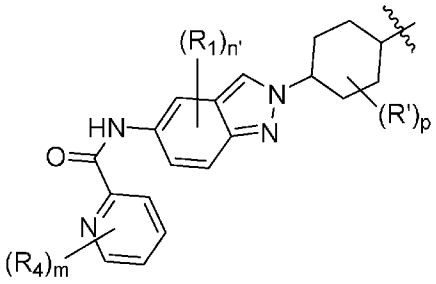
[0028] Preferably, in certain embodiments of the present invention, the PTM has a structure of the following formula:



PTM-3b'



PTM-3c'



PTM-3d'

wherein,

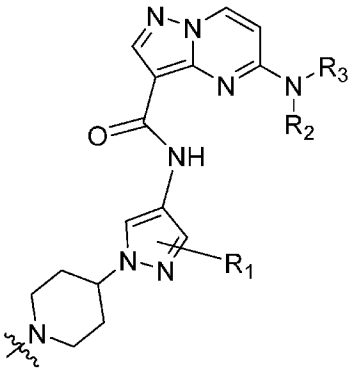
n' is 0, 1, 2 or 3;

each R is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl or - O(C_1-C_6 alkyl), wherein the alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8 or 9;

the R_1, R_2, R_3, R_4, m and n are as described and defined in PTM-1, PTM-2' and PTM-3.

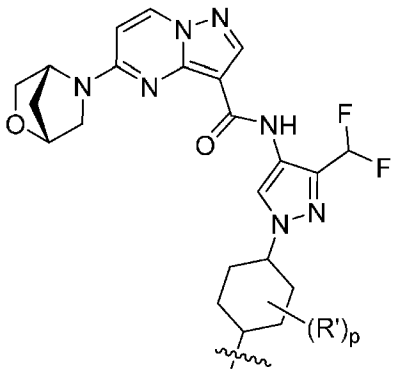
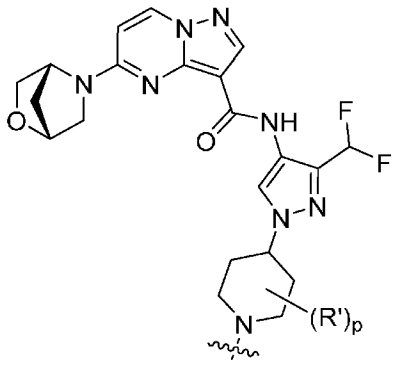
[0029] Preferably, in certain embodiments of the present invention, the PTM has a structure of the following formula:



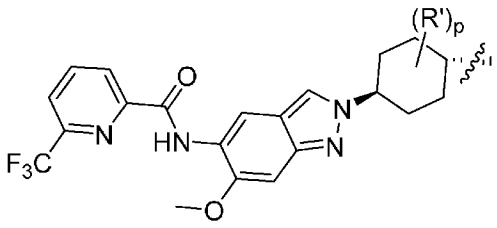
PTM-3c

wherein the R_1, R_2 and R_3 are as described and defined in PTM-1, PTM-2' and PTM-3.

[0030] Preferably, in certain embodiments of the present invention, the PTM has a structure of the following formula:

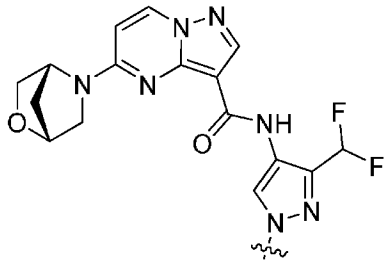
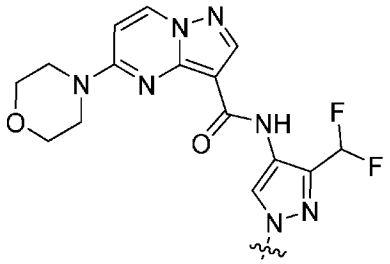
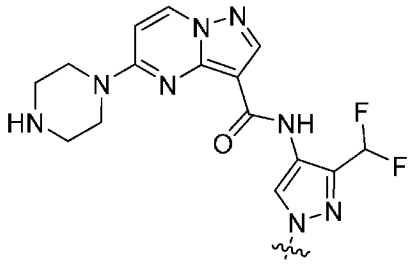
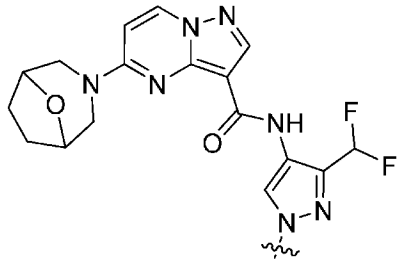
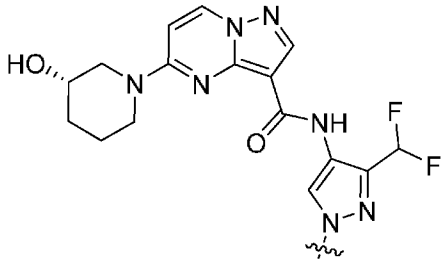
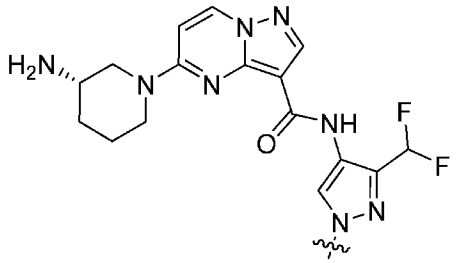
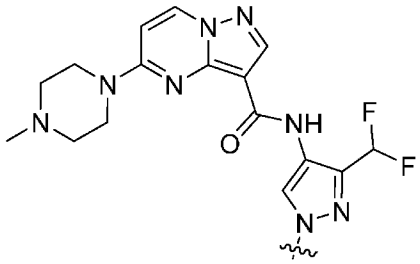



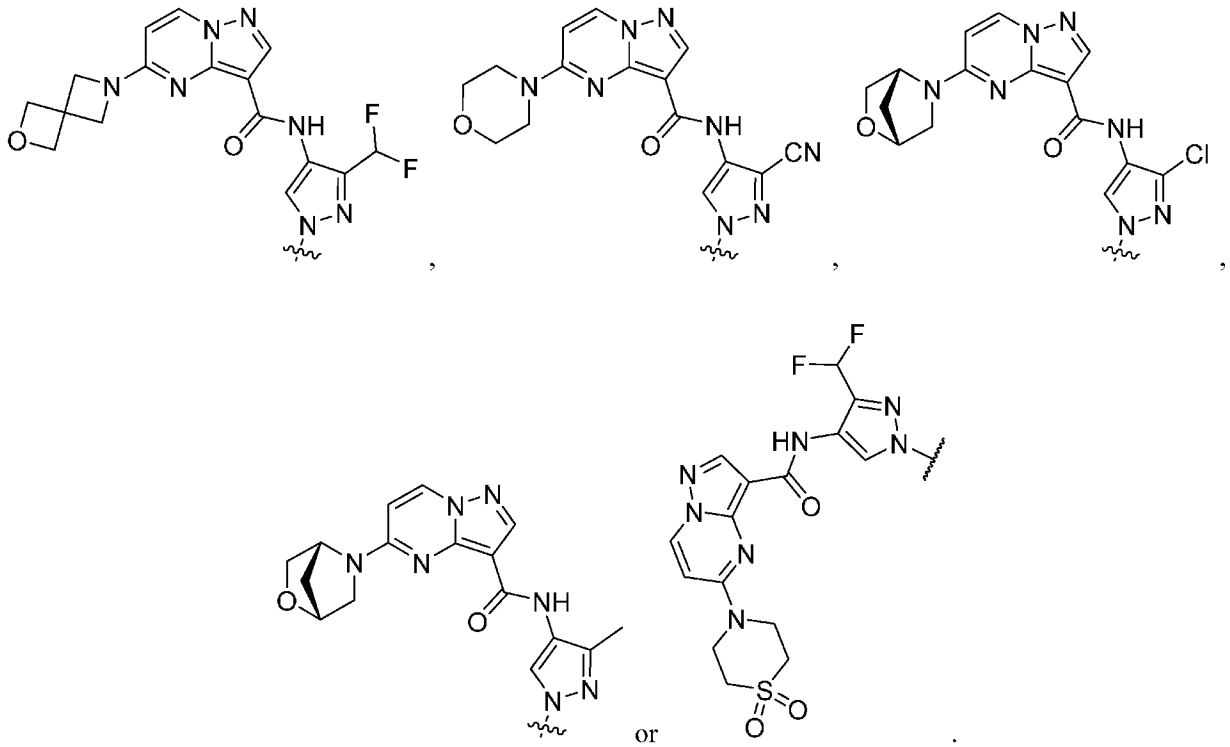
or



wherein the R' and p are as defined and described in PTM-3b', PTM-3c' and PTM-3d'.

[0031] Preferably, in certain embodiments of the present invention, the PTM has a structure of the following formula:



[0032] In certain embodiments of the present invention, 1 or 2 of Q_1, Q_2, Q_3, Q_4 and Q_5 in the ULM-1 are N, and the rest are each independently CR_3".

[0033] In certain embodiments of the present invention, Q_1, Q_2, Q_3, Q_4 and Q_5 in the ULM-1 are each independently CR_3".

[0034] In certain embodiments of the present invention, X" in the ULM-1 is N.

[0035] In certain embodiments of the present invention, X" in the ULM-1 is C.

[0036] In certain embodiments of the present invention, Y" in the ULM-1 is N.

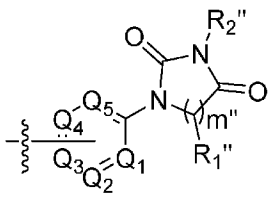
[0037] In certain embodiments of the present invention, each R_1" in the ULM-1 is independently hydrogen, deuterium, -F, -Cl or C_1-C_6 alkyl, wherein the alkyl is optionally substituted with 1-3 halogens; preferably, R_1" is hydrogen.

[0038] In certain embodiments of the present invention, R_2" in the ULM-1 is hydrogen or C_1-C_6 alkyl, wherein the alkyl is optionally substituted with 1-3 halogens; preferably, R_2" is hydrogen.

[0039] In certain embodiments of the present invention, each R_3" in the ULM-1 is independently hydrogen, deuterium, halogen, -O(C_1-C_6 alkyl) or C_1-C_6 alkyl, wherein the alkyl is optionally substituted with 1-3 halogens; preferably, each R_3" is independently hydrogen, deuterium, F, Cl, methyl, methoxy, ethoxy, trifluoromethoxy, 2-hydroxypropan-2-yl or trifluoromethyl.

[0040] In certain embodiments of the present invention, each R_3" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl or -O(C_1-C_6 alkyl); the alkyl is optionally substituted with 1-3 groups independently selected from hydroxy and halogen.

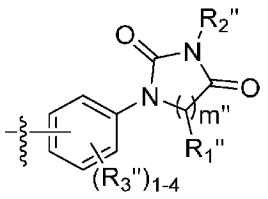
[0041] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1a

wherein the Q_1, Q_2, Q_3, Q_4, Q_5, R_1", R_2" and m" are as defined in the ULM-1 described above.

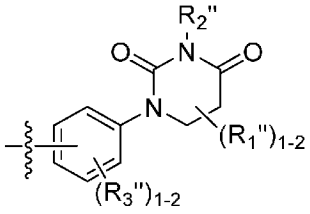
[0042] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1b

wherein the R_1", R_2", R_3" and m" are as defined in the ULM-1 described above.

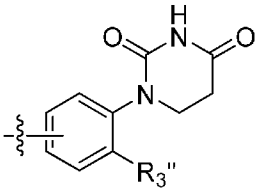
[0043] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1c

wherein the R_1", R_2" and R_3" are as defined in the ULM-1 described above.

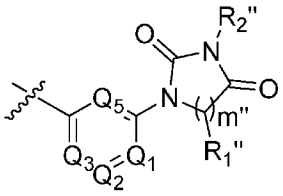
[0044] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1d

wherein the R_3" is as defined in the ULM-1 described above.

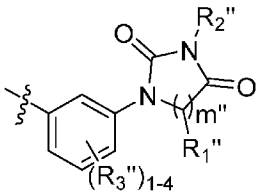
[0045] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1e

wherein the Q_1, Q_2, Q_3, Q_5, R_1", R_2" and m" are as defined in the ULM-1 described above.

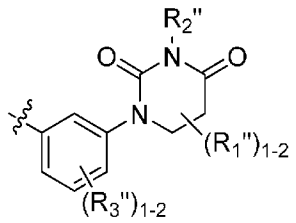
[0046] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1f

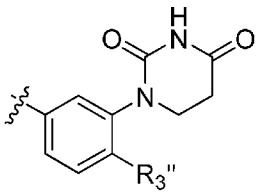
wherein the R_1", R_2", R_3" and m" are as defined in the ULM-1 described above.

[0047] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1g

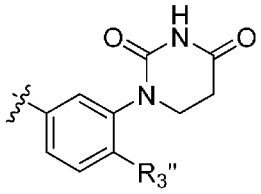
wherein the R_1", R_2" and R_3" are as defined in the ULM-1 described above.



ULM-1h

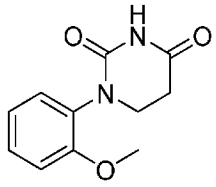
wherein the R_3" is as defined in the ULM-1 described above.

[0048] In certain embodiments of the present invention, the ULM has a structure of the following formula:



; R_3" is halogen, C_1-C_6 alkyl or -O(C_1-C_6 alkyl).

[0049] In certain embodiments of the present invention, the ULM is selected from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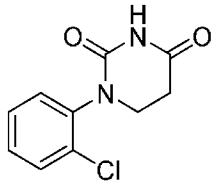
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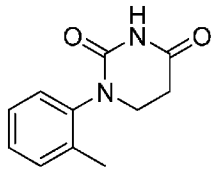
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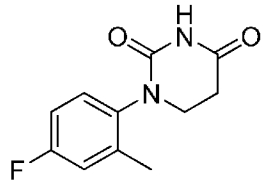
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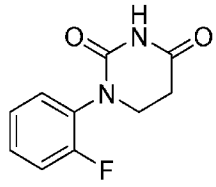
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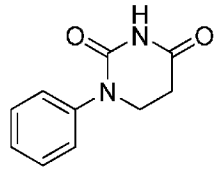
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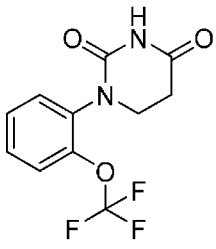
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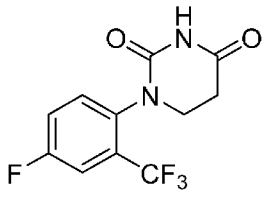
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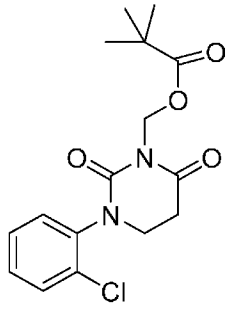
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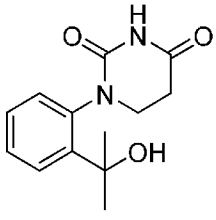
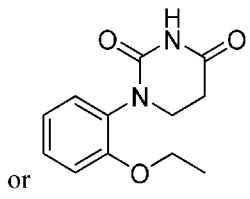
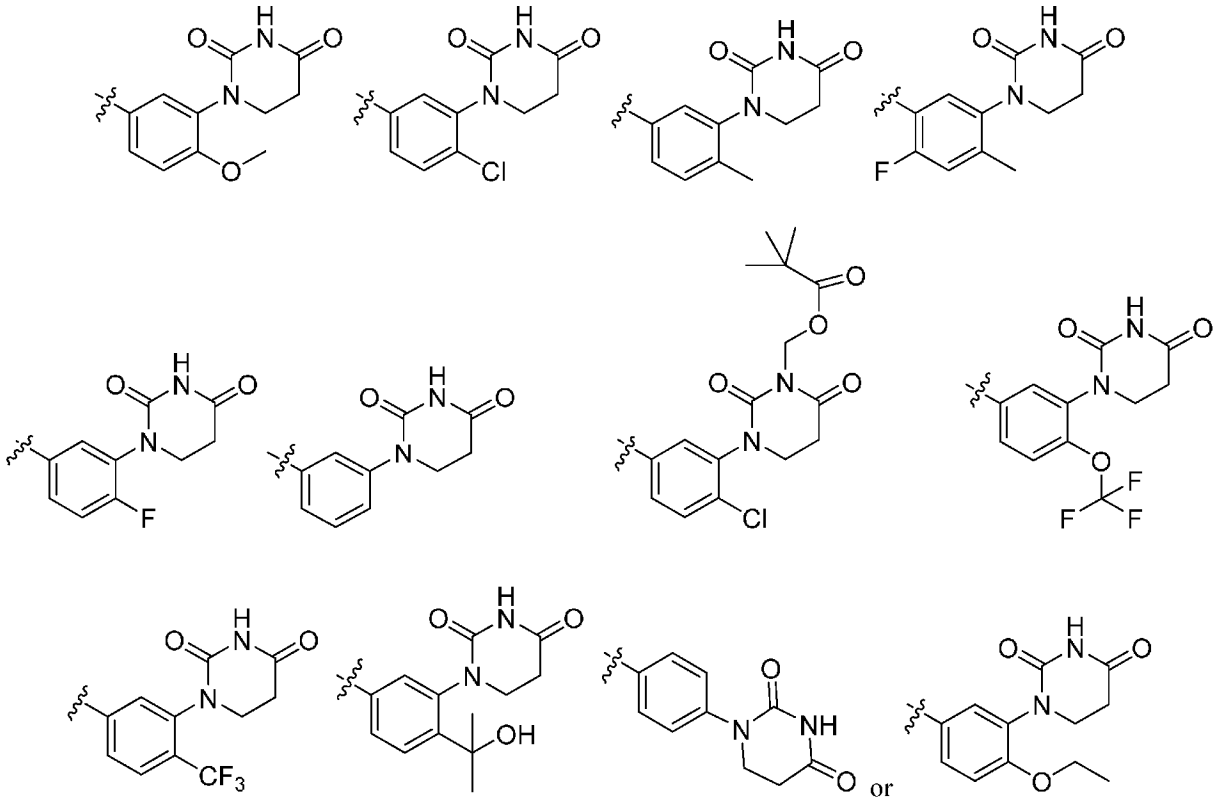
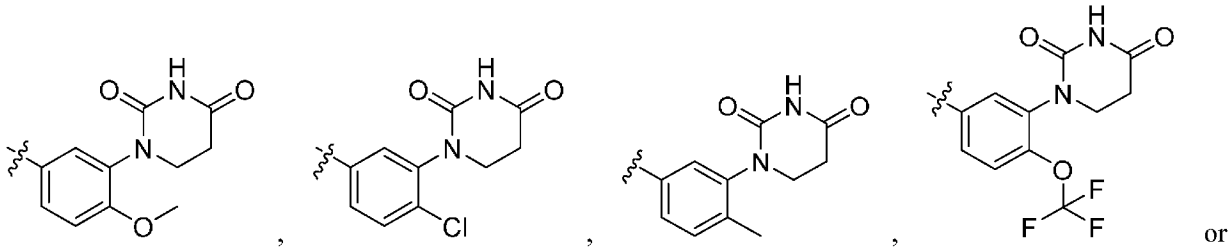


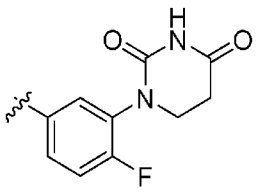

or .

[0050] In certain embodiments of the present invention, the ULM is selected from

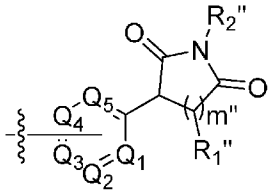

or

, preferably


or


.

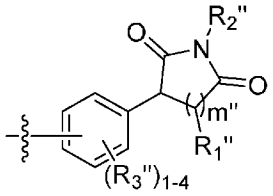
[0051] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1aa

wherein the Q_1, Q_2, Q_3, Q_4, Q_5, R_1", R_2" and m" are as defined in the ULM-1 described above.

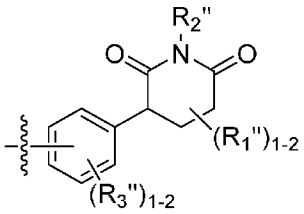
[0052] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1bb

wherein the R_1", R_2", R_3" and m" are as defined in the ULM-1 described above.

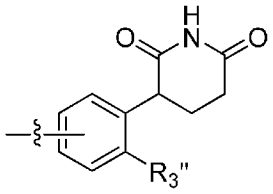
[0053] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1cc

wherein the R_1", R_2" and R_3" are as defined in the ULM-1 described above.

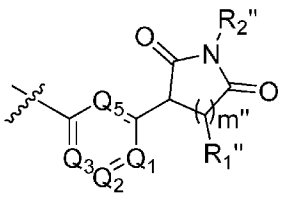
[0054] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1dd

wherein the R_3" is as defined in the ULM-1 described above.

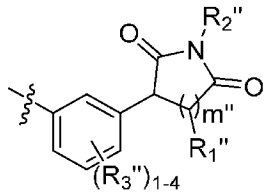
[0055] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1ee

wherein the Q_1, Q_2, Q_3, Q_5, R_1", R_2" and m" are as defined in the ULM-1 described above.

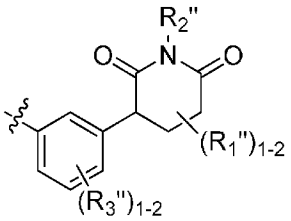
[0056] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1ff

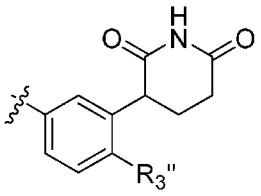
wherein the R_1", R_2", R_3" and m" are as defined in the ULM-1 described above.

[0057] In certain embodiments of the present invention, the ULM has a structure of the following formula:



ULM-1gg

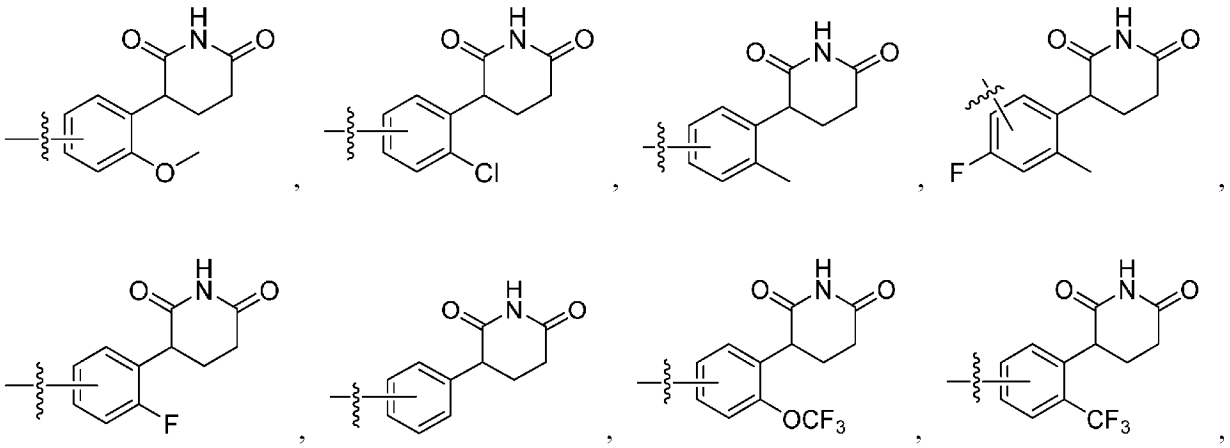
wherein the R_1", R_2" and R_3" are as defined in the ULM-1 described above.

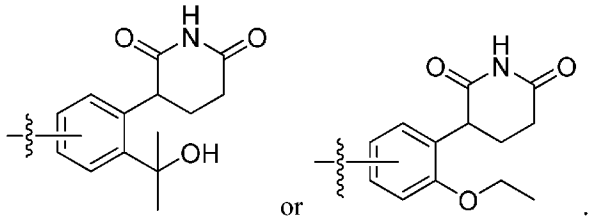


ULM-1hh

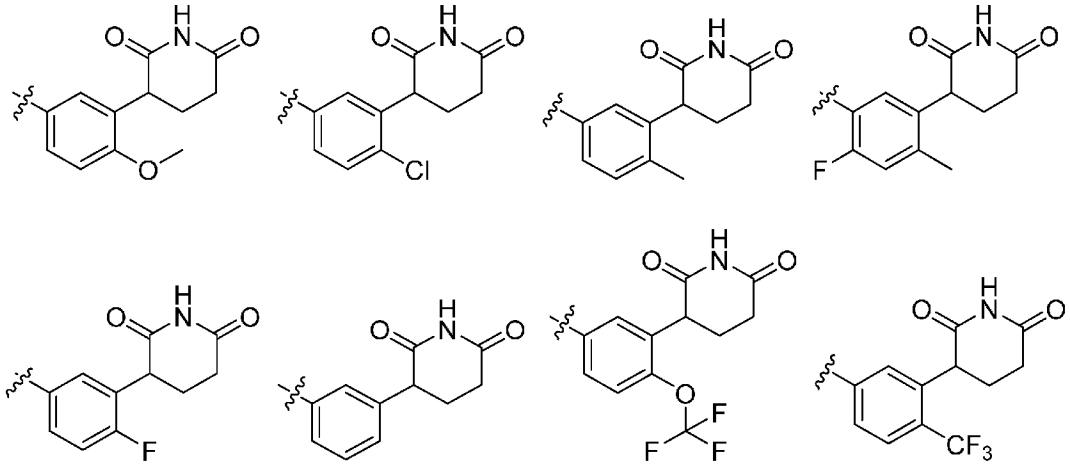
wherein the R_3" is as defined in the ULM-1 described above.

[0058] In certain embodiments of the present invention, the ULM is selected from





[0059] In certain embodiments of the present invention, the ULM is selected from



[0060] In certain embodiments of the present invention, L is a bond.

[0061] In certain embodiments of the present invention, L is $-(CH_2)_j-$, wherein 1 or more methylene groups in the $-(CH_2)_j-$ are optionally substituted with groups selected from $-NR^{3'}-$, -O-, -S-, -S(O)-, $-S(O)NR^{3'}-$, $-NR^{3'}S(O)-$, $-S(O)_2-$, $-S(O)_2NR^{3'}-$, $-NR^{3'}S(O)_2-$, $-NR^{4'}S(O)_2NR^{3'}-$, $-CR^{1'}R^{2'}-$, -C(O)-, -C(O)O-, -OC(O)-, $-NR^{3'}C(O)O-$, $-OC(O)NR^{3'}-$, $-C(O)NR^{3'}-$, $-NR^{3'}C(O)-$, $-NR^{4'}C(O)NR^{3'}-$, -P(O)-, -P(O)O-, -OP(O)-, -OP(O)O-, ethenylene, ethynylene, C_3-C_{12} cycloalkylene, 3-12 membered heterocycloalkylene containing 1 or more heteroatoms selected from N, O or S, 6-10 membered arylene or 5-10 membered heteroarylene, wherein the ethenylene, cycloalkylene, heterocycloalkylene, arylene and heteroarylene are each independently optionally substituted with 1 or more substituents selected from halogen, $-OR^{3'}$, $-NR^{3'}R^{4'}$, oxo, nitro, cyano, C1-C6 alkyl, -S(C1-C6 alkyl), C3-C10 cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, $-C(O)R^{1'}$, $-C(O)OR^{3'}$, $-OC(O)R^{1'}$, $-C(O)NR^{3'}$, $-NR^{3'}C(O)R^{1'}$, $-S(O)R^{1'}$, $-S(O)NR^{3'}$, $-S(O)_2R^{1'}$, $-S(O)_2NR^{3'}$, $-NR^{3'}S(O)_2R^{1'}$, $-NR^{4'}S(O)_2NR^{3'}$, $-OC(O)NR^{3'}$ and $NR^{4'}C(O)NR^{3'}$, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with 1 or more substituents selected from halogen, -OH, $-NR^{3'}R^{4'}$, oxo, nitro, cyano, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl, and 5-10 membered heteroaryl; $R^{1'}$ and $R^{2'}$ are each independently halogen, -OH, $-NR^{3'}R^{4'}$, C_1-C_6 alkyl, C_1-C_6 chloroalkyl, hydroxy C_1-C_6 alkyl, $-O(C_1$-C_6 alkyl), $-NH(C_1$-C_6 alkyl), $-NH(C_1$-C_6 alkyl)$_2$, C_3-C_{10} cycloalkyl, $-O(C_3$-C_{10} cycloalkyl), $-NH(C_3$-C_{10} cycloalkyl), 3-10 membered heterocycloalkyl, -0(3-10 membered heterocycloalkyl), -NH(3-10 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), -NH(6-10 membered aryl), 5-10 membered heteroaryl, -0(5-10 membered heteroaryl) or -NH(5-10 membered heteroaryl), wherein $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl; j is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25.

[0062] In certain embodiments of the present invention, L is $-(CH_2)_j-$, wherein 1 or more methylene groups in the

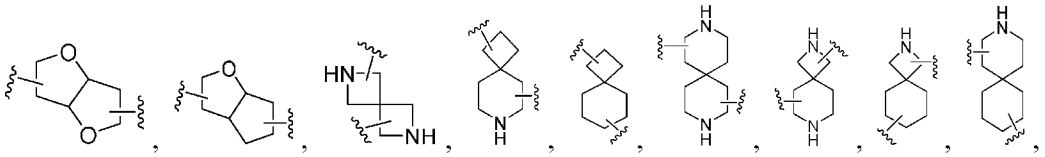
$-(CH_2)_j-$ are optionally substituted with groups selected from $-NR^{3'}-$, -O-, -S-, -S(O)-, $-S(O)NR^{3'}-$, $-NR^{3'}S(O)-$, $-S(O)_2-$, $-S(O)_2NR^{3'}-$, $-NR^{3'}S(O)_2-$, $-NR^{4'}S(O)_2NR^{3'}-$, $-CR^{1'}R^{2'}-$, -C(O)-, -C(O)O-, -OC(O)-, $-NR^{3'}C(O)O-$, $-OC(O)NR^{3'}-$, $-C(O)NR^{3'}-$, $-NR^{3'}C(O)-$, $-NR^{4'}C(O)NR^{3'}-$, -P(O)-, -P(O)O-, -OP(O)-, -OP(O)O-, ethenylene, ethynylene, C_3-C_{12} cycloalkylene, 3-12 membered heterocycloalkylene containing 1 or more heteroatoms selected from N, O or S, 6-10 membered arylene or 5-10 membered heteroarylene, wherein the ethenylene, cycloalkylene, heterocycloalkylene, arylene and heteroarylene are each independently optionally substituted with 1 or more substituents selected from halogen, $-OR^{3'}$, $-NR^{3'}R^{4'}$, oxo, nitro, cyano, C1-C6 alkyl, -S(C1-C6 alkyl), C3-C10 cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, $-C(O)R^{1'}$, $-C(O)OR^{3'}$, $-OC(O)R^{1'}$, $-C(O)NR^{3'}$, $-NR^{3'}C(O)R^{1'}$, $-S(O)R^{1'}$, $-S(O)NR^{3'}$, $-S(O)_2R^{1'}$, $-S(O)_2NR^{3'}$, $-NR^{3'}S(O)_2R^{1'}$, $-NR^{4'}S(O)_2NR^{3'}$, $-OC(O)NR^{3'}$ and $NR^{4'}C(O)NR^{3'}$, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with 1 or more substituents selected from halogen, -OH, $-NR^{3'}R^{4'}$, oxo, nitro, cyano, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl, and 5-10 membered heteroaryl; $R^{1'}$ and $R^{2'}$ are each independently halogen, -OH, $-NR^{3'}R^{4'}$, C_1-C_6 alkyl, C_1-C_6 chloroalkyl, hydroxy C_1-C_6 alkyl, $-O(C_1$-C_6 alkyl), $-NH(C_1$-C_6 alkyl), $-NH(C_1$-C_6 alkyl)$_2$, C_3-C_{10} cycloalkyl, $-O(C_3$-C_{10} cycloalkyl), $-NH(C_3$-C_{10} cycloalkyl), 3-10 membered heterocycloalkyl, -0(3-10 membered heterocycloalkyl), -NH(3-10 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), -NH(6-10 membered aryl), 5-10 membered heteroaryl, -0(5-10 membered heteroaryl) or -NH(5-10 membered heteroaryl), wherein $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl; j is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25.

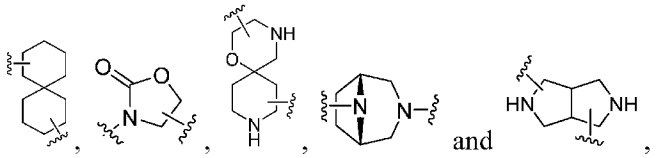
[0063] Preferably, in certain embodiments of the present invention, L is $-(CH_2)_j-$, wherein 1 or more methylene groups in the $-(CH_2)_j-$ are optionally replaced by groups selected from $-NR^{3'}-$, -O-, $-CR^{1'}R^{2'}-$, -C(O)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -OC(O)-, $-C(O)NR^{3'}-$, $-NR^{3'}C(O)-$, $-S(O)_2NR^{3'}-$, $-NR^{3'}S(O)_2-$, ethenylene, ethynylene, phenyl, 8-10 membered bicyclic arylene, 3-7 membered saturated and/or partially unsaturated cycloalkylene, 4-11 membered saturated and/or partially unsaturated spirocycloalkylene, 4-11 membered saturated and/or partially unsaturated fused cycloalkylene, 8-10 membered bicyclic saturated and/or partially unsaturated cycloalkylene, 4-7 membered saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated and/or partially unsaturated spiroheterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated and/or partially unsaturated fused heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 8-10 membered bicyclic saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 8-10 membered bicyclic heteroaryl having 1-5 heteroatoms selected from nitrogen, oxygen or sulfur, wherein the ethenylene, ethynylene, cycloalkylene, heterocycloalkylene, phenyl, spiroheterocycloalkylene, fused heterocycloalkylene, spirocycloalkylene, fused cycloalkylene and heteroarylene are each independently optionally substituted with 1 or more substituents selected from halogen, oxo, $-NR^{3'}R^{4'}$, $-OR^{3'}$, nitro, -CN, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl and 3-10 membered heterocycloalkyl, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with 1 or more substituents selected from halogen, -OH, $-NH_2$, -CN, C_1-C_4 alkyl and C_3-C_6 cycloalkyl; $R^{1'}$ and $R^{2'}$ are each independently halogen, -OH, $-NH_2$, C_1-C_4 alkyl, C_1-C_4 chloroalkyl, C_1-C_4 hydroxyalkyl, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), C_3-C_6 cycloalkyl, $-O(C_3$-C_6 cycloalkyl), $-NH(C_3$-C_6 cycloalkyl), 3-6 membered heterocycloalkyl, -O(3-6 membered heterocycloalkyl) or $-NH(C_3$-C_6 cycloalkyl); $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium, C_1-C_4 alkyl, C_3-C_6 cycloalkyl or 3-6 membered heterocycloalkyl; j is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

[0064] Preferably, in certain embodiments of the present invention, L is $-(CH_2)_j-$, wherein 1 or more methylene groups in the $-(CH_2)_j-$ are optionally replaced by groups selected from $-NR^{3'}-$, -O-, $-CR^{1'}R^{2'}-$, -C(O)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -OC(O)-, $-C(O)NR^{3'}-$, $-NR^{3'}C(O)-$, $-S(O)_2NR^{3'}-$, $-NR^{3'}S(O)_2-$, ethenylene, ethynylene, phenyl, 8-10 membered bicyclic arylene, 3-7 membered saturated and/or partially unsaturated monocyclic cycloalkylene, 4-11 membered saturated and/or partially unsaturated spirocycloalkylene, 4-11 membered saturated and/or partially unsaturated fused cycloalkylene, 8-10 membered bicyclic saturated and/or partially unsaturated cycloalkylene, 4-7 membered saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen or oxygen, 4-11 membered saturated and/or partially unsaturated spiroheterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen or oxygen, 4-11 membered saturated and/or partially unsaturated fused heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen or oxygen, 8-10 membered bicyclic saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen or oxygen, 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen or oxygen, or 8-10 membered bicyclic heteroaryl having 1-5 heteroatoms selected from nitrogen or oxygen, wherein the ethenylene, ethynylene, cycloalkylene, heterocycloalkylene, phenyl, spiroheterocycloalkylene, fused heterocycloalkylene, fused cycloalkylene, spirocycloalkylene and heteroarylene are each independently optionally substituted with 1 or more substituents selected from halogen, oxo, $-NR^{3'}R^{4'}$, $-OR^{3'}$, nitro, -CN, C_1-C_6 alkyl, C_3-C_6 cycloalkyl and 3-6 membered heterocycloalkyl, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with 1 or more substituents selected from halogen,

-OH, -NH_2, - CN, C_1-C_4 alkyl and C_3-C_6 cycloalkyl; $R^{1'}$ and $R^{2'}$ are each independently halogen, -OH, -NH_2, C_1-C_4 alkyl, C_1-C_4 chloroalkyl, C_1-C_4 hydroxyalkyl, -O(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), C_3-C_6 cycloalkyl, -O(C_3-C_6 cycloalkyl), -NH(C_3-C_6 cycloalkyl), 3-6 membered heterocycloalkyl, -O(3-6 membered heterocycloalkyl) or -NH(C_3-C_6 cycloalkyl); $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium, C_1-C_4 alkyl, C_3-C_6 cycloalkyl or 3-6 membered heterocycloalkyl; j is 2, 3, 4, 5, 6, 7, 8, 9 or 10.

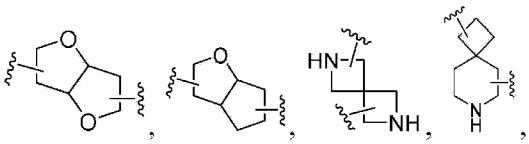
[0065] Preferably, in certain embodiments of the present invention, L is -$(CH_2)_j$-, wherein 1, 2, 3 or 4 methylene groups in the -$(CH_2)_j$- are optionally replaced by groups selected from -NH-, -NCH_3-, -NCH_2CH_3-, -O-, -$C(CH_3)_2$-, -CHF-, -$CHCF_3$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -C(O)NCH_3-, -NHC(O)-, - $NCH_3C(O)$-, ethenylene, ethynylene, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, oxiranylidene, oxetanylidene, oxolanylidene, oxanylidene, aziridinylidene, azetidinylidene, azolidinylidene, piperidinylidene, piperazinylidene, morpholinylidene, homomorpholinylidene, phenylene, pyrrolylidene, thienylidene, furylidene, imidazolylidene, pyrazolylidene, triazolylidene, tetrazolylidene, oxazolylidene, isoxazolylidene, thiazolylidene, isothiazolylidene, pyridinylidene, pyrimidinylidene, pyridazinylidene, pyrazinylidene,

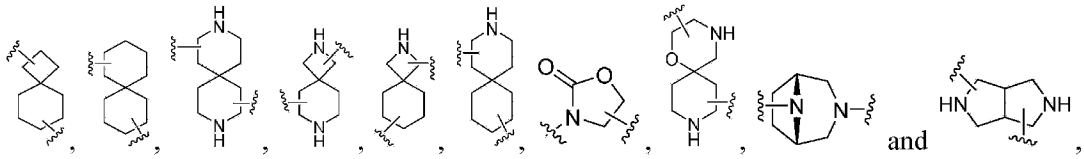




wherein the group for replacement is optionally substituted with 1 or more substituents selected from halogen, oxo, -$NR^{3'}R^{4'}$, -$OR^{3'}$ and C_1-C_4 alkyl, wherein the alkyl is optionally substituted with 1 or more substituents selected from halogen, -OH and -NH_2; $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium or C_1-C_4 alkyl; j is 2, 3, 4, 5, 6, 7 or 8.

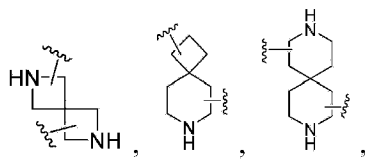
[0066] Preferably, in certain embodiments of the present invention, L is -$(CH_2)_j$-, wherein 1, 2 or 3 methylene groups in the -$(CH_2)_j$- are optionally replaced by groups selected from -NH-, -NCH_3-, -NCH_2CH_3-, -O-, -$C(CH_3)_2$-, -CHF-, -$CHCF_3$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, -C(O)NCH_3-, -NHC(O)-, - $NCH_3C(O)$-, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, oxiranylidene, oxetanylidene, oxolanylidene, oxanylidene, aziridinylidene, azetidinylidene, azolidinylidene, piperidinylidene, piperazinylidene, morpholinylidene, homomorpholinylidene,

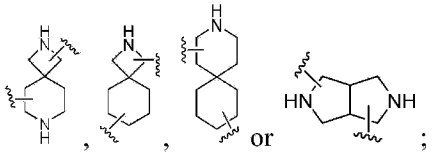




wherein the group for replacement is optionally substituted with 1 or more substituents selected from F, Cl, oxo, -$NR^{3'}R^{4'}$, -$OR^{3'}$ and C_1-C_4 alkyl, wherein the alkyl is optionally substituted with 1 or more substituents selected from halogen, -OH and -NH_2; $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium, methyl, ethyl and propyl; j is 2, 3, 4, 5, 6, 7 or 8.

[0067] Preferably, in certain embodiments of the present invention, L is -$(CH_2)_j$-, wherein 1, 2 or 3 methylene groups in the -$(CH_2)_j$- are optionally replaced by groups selected from -O-, -NH-, -NCH_3-, - NCH_2CH_3-, -C(O)-, -C(O)NH-, -NHC(O)-, -$NCH_3C(O)$-, -C(O)NCH_3-,

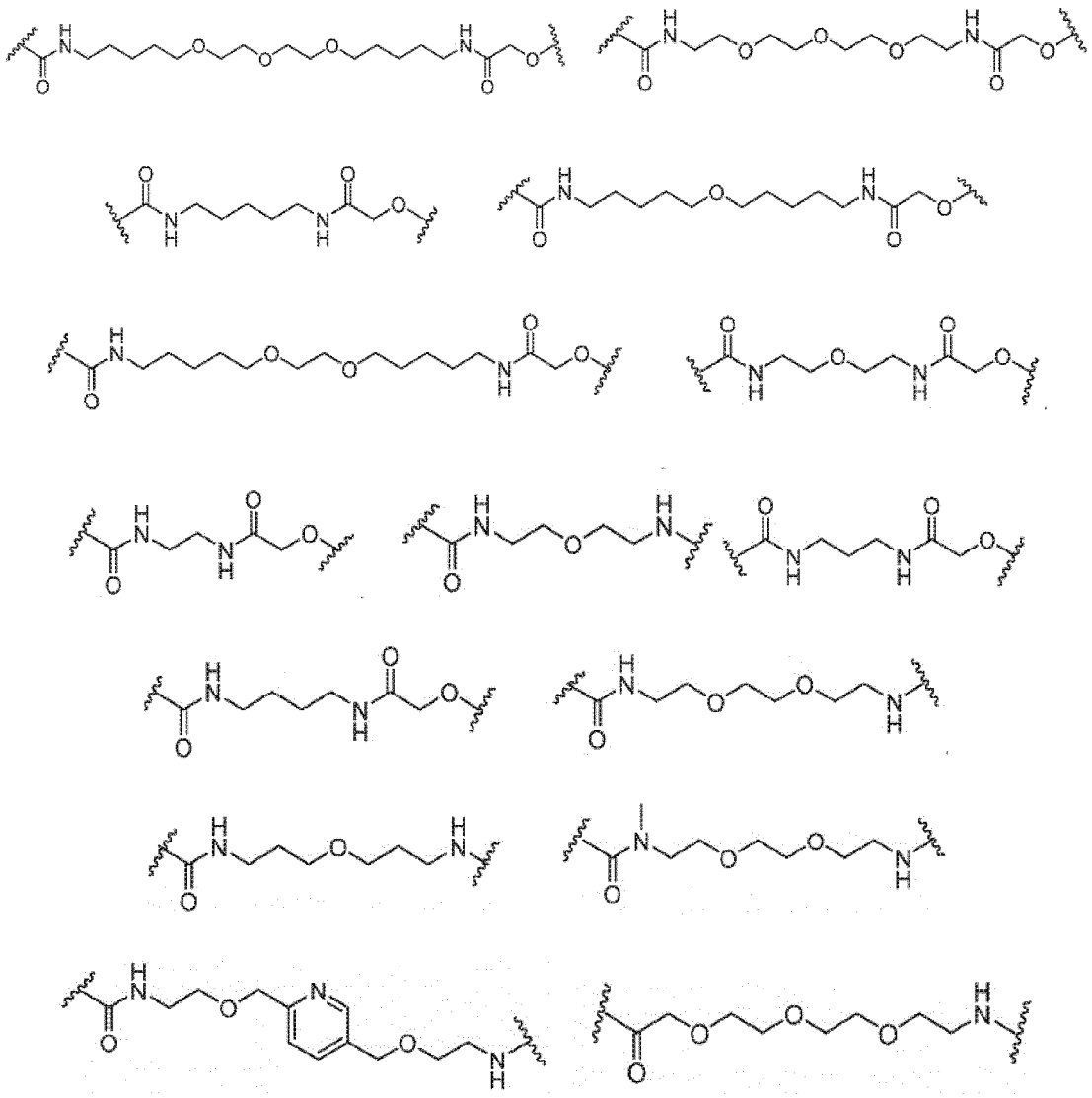


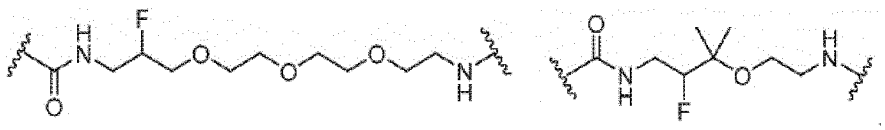


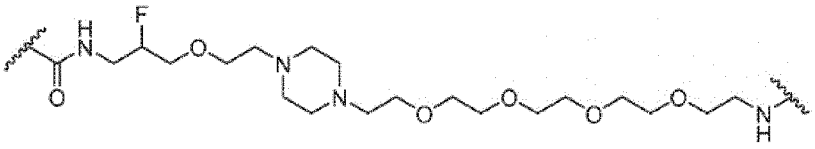
j is 2, 3, 4, 5, 6, 7 or 8.

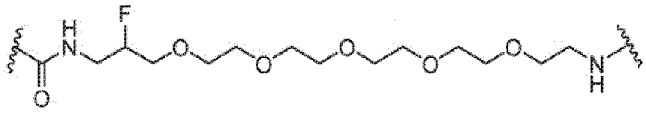
[0068] Preferably, in certain embodiments of the present invention, L is selected from $-(CH_2)_{j-1}-C(O)-$, wherein the methylene in the $-(CH_2)_{j-1}-C(O)-$ is as defined in the L described above, and is optionally replaced by 1 or more groups, and j is as defined in the L described above.

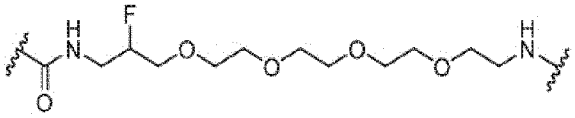
[0069] Preferably, in certain embodiments of the present invention, L is selected from

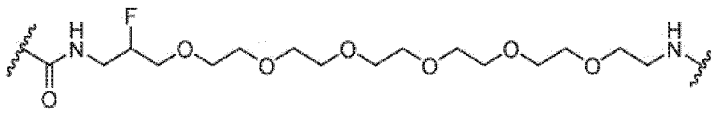


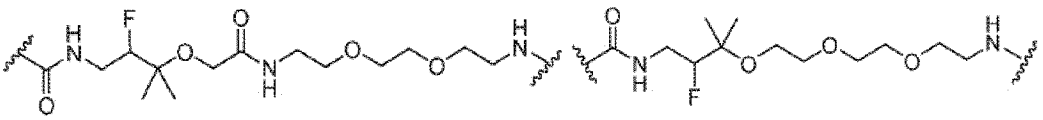


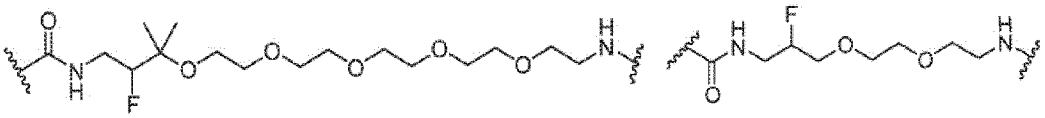


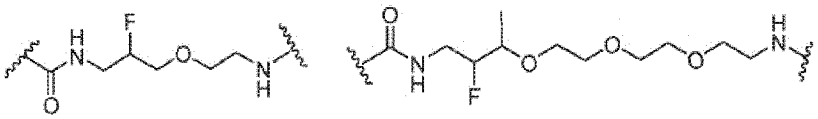


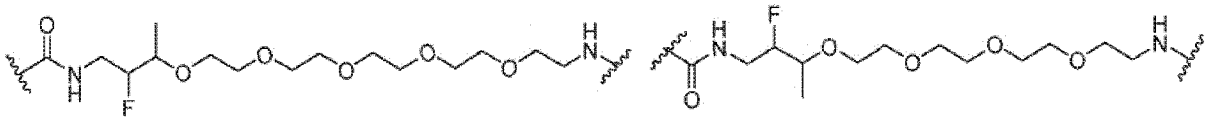


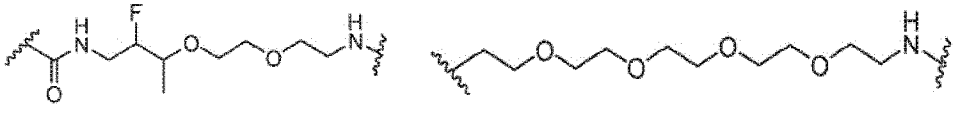


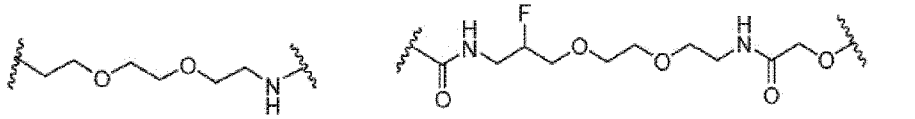


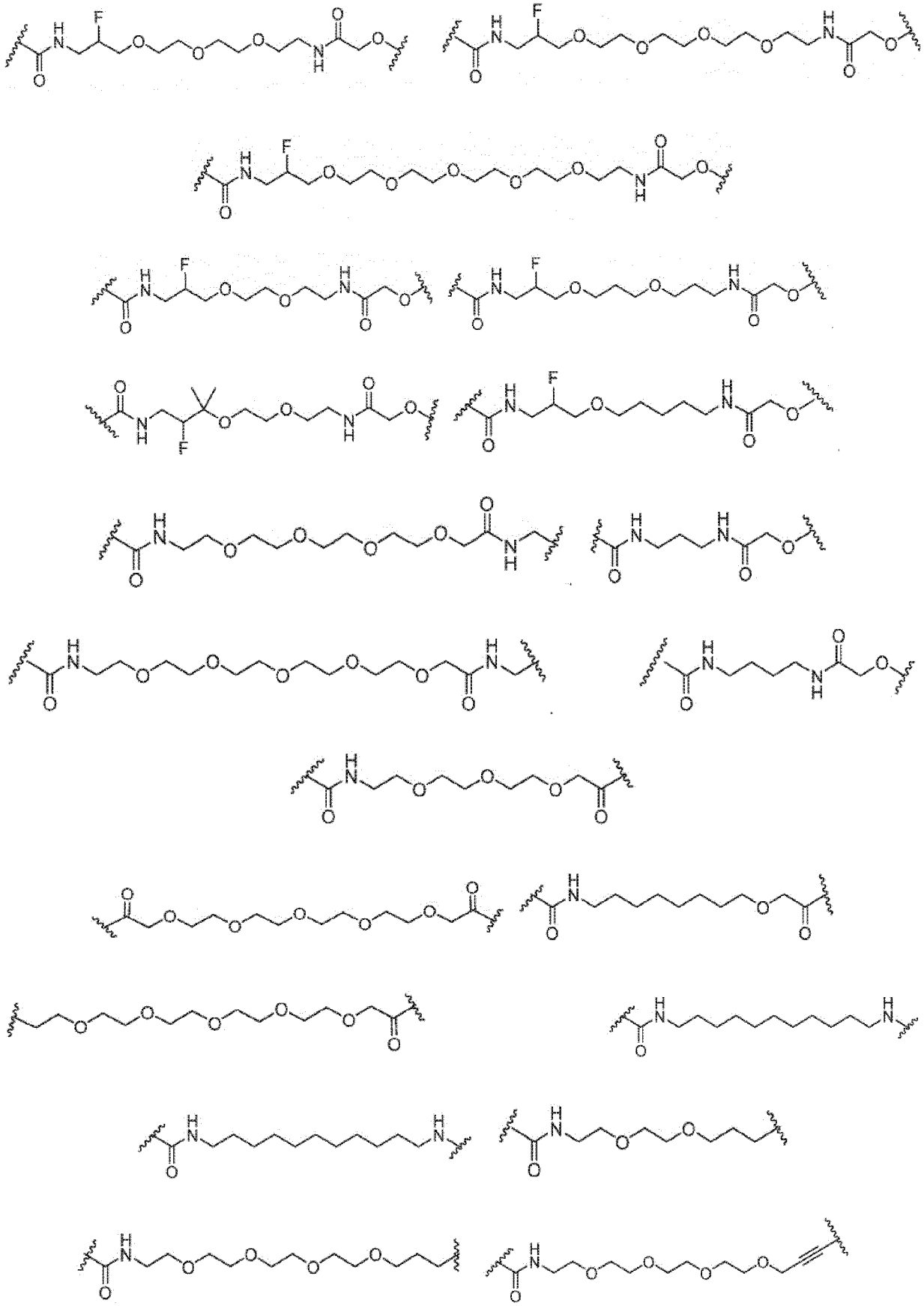


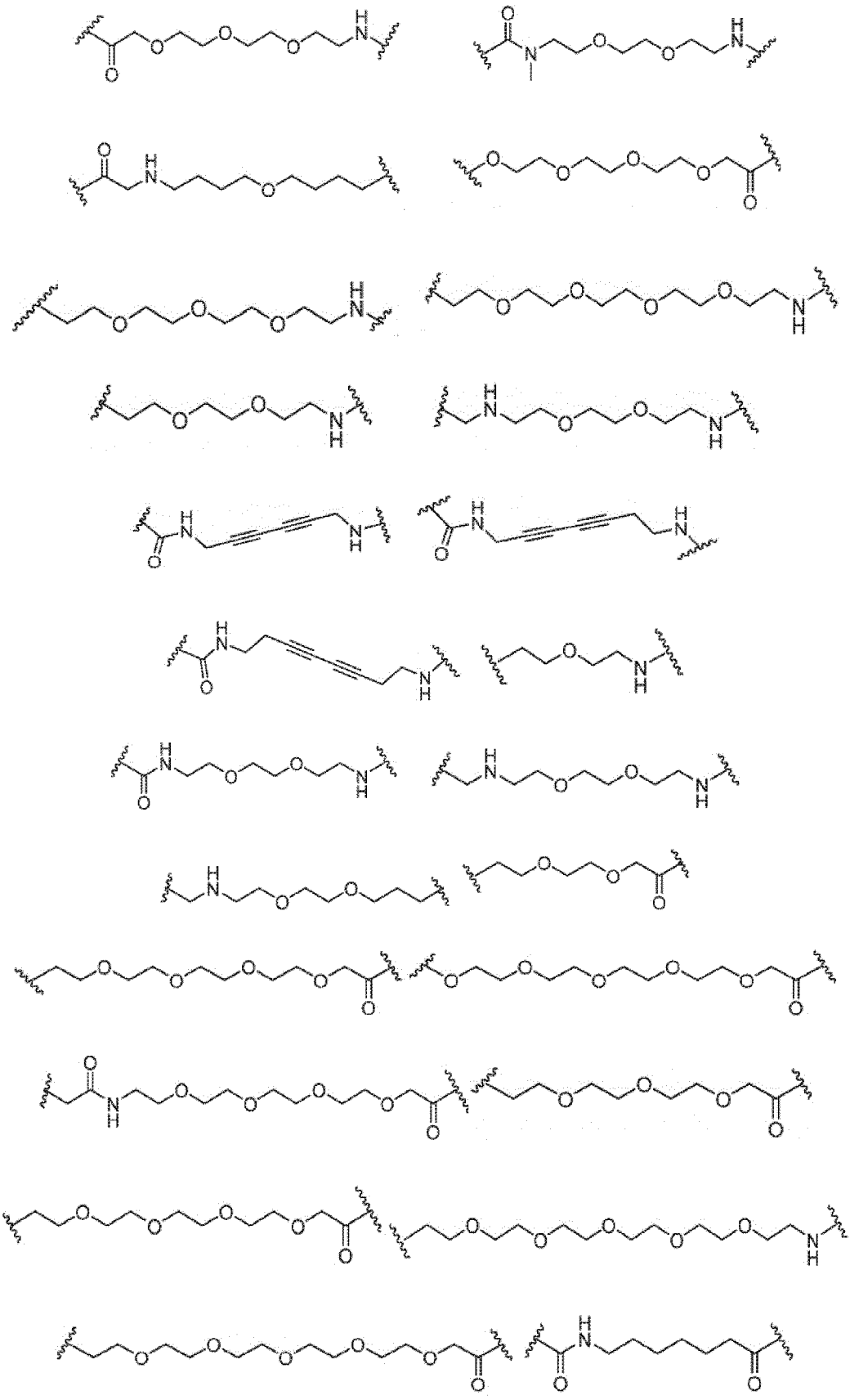


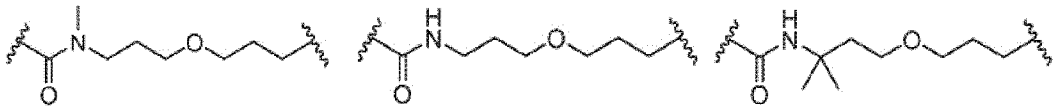


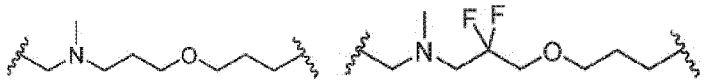


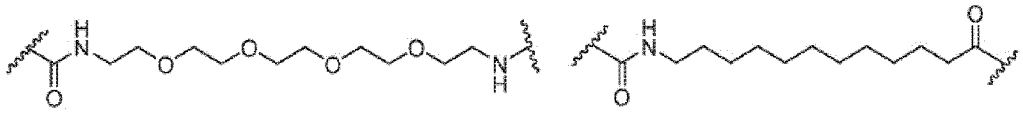


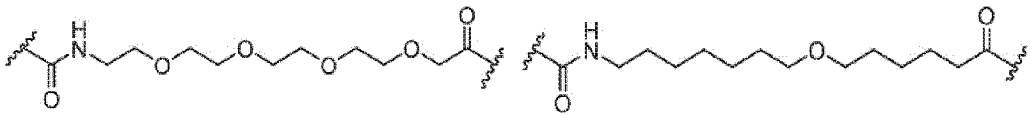


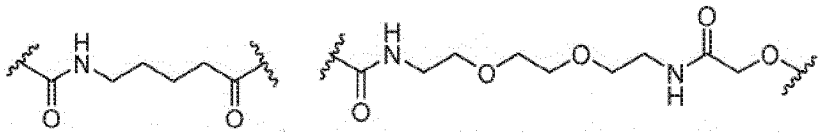


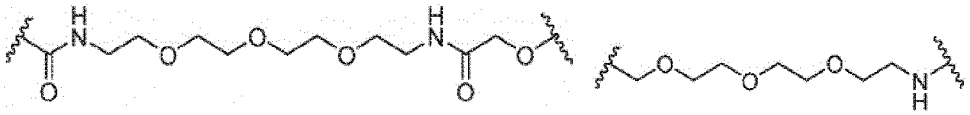


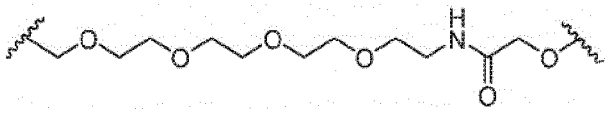


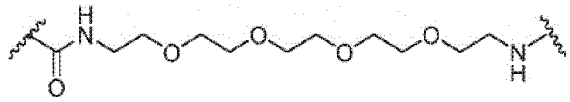


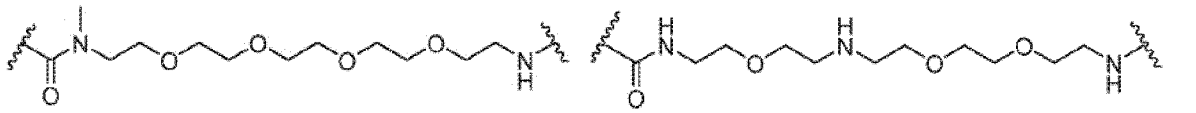


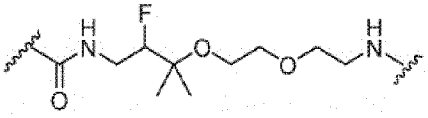


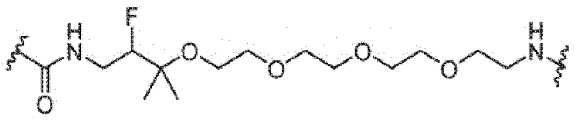


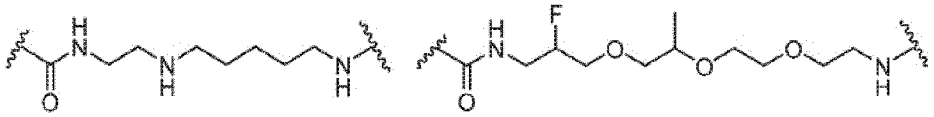


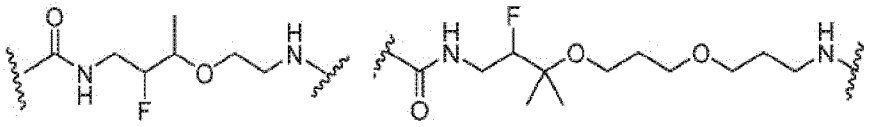


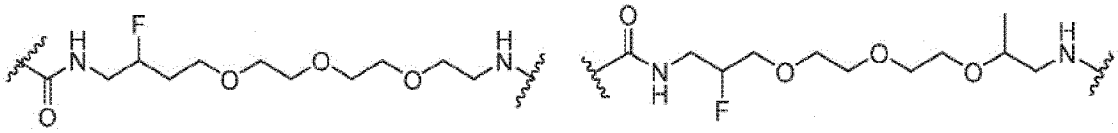


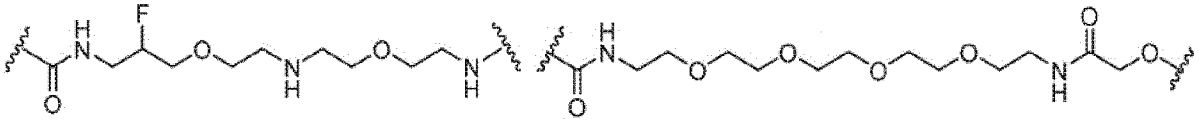


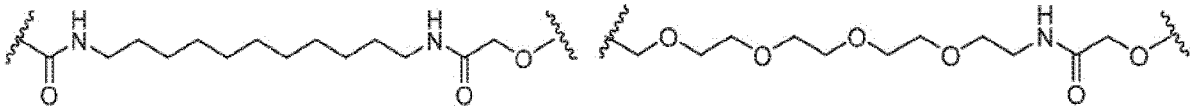


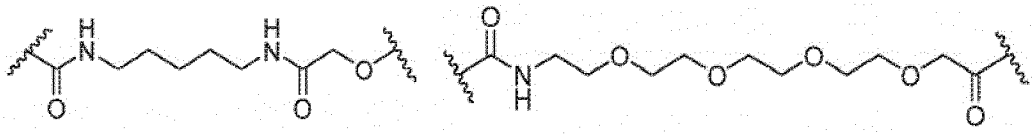


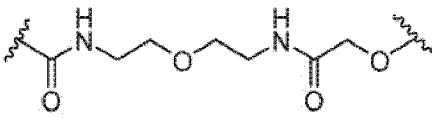


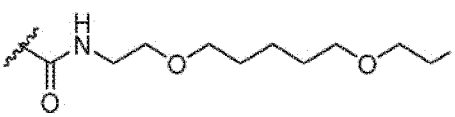


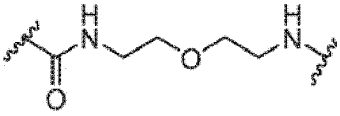


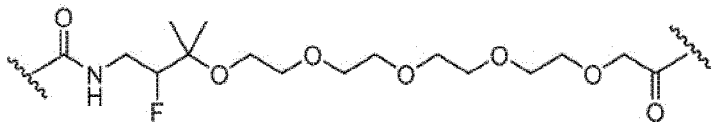


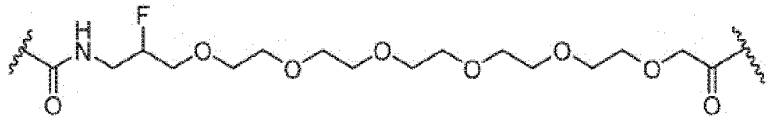


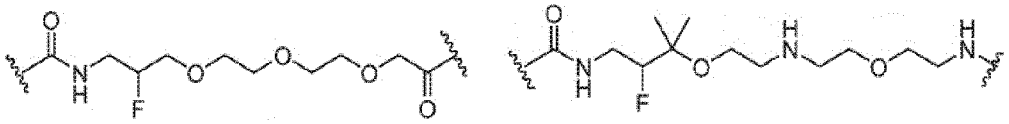


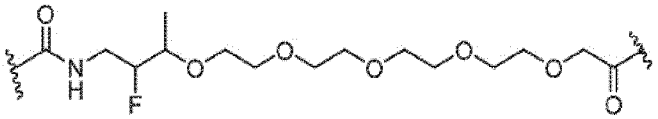


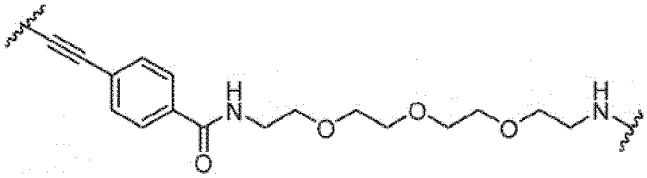


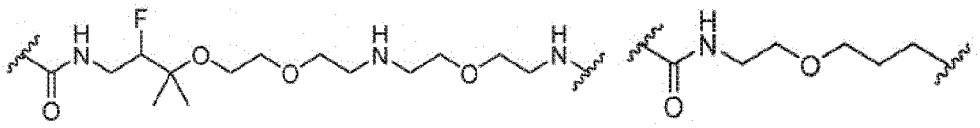


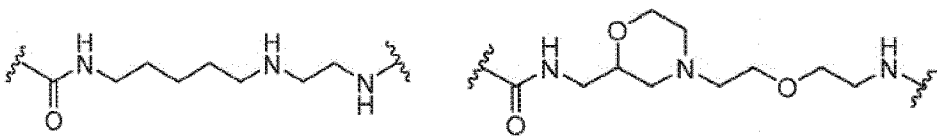


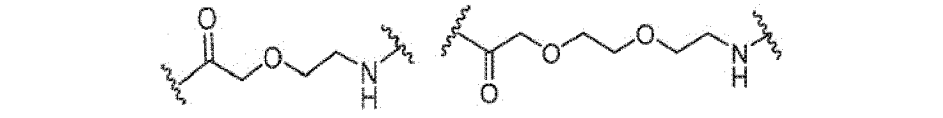


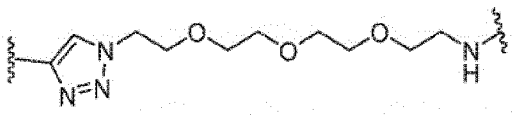


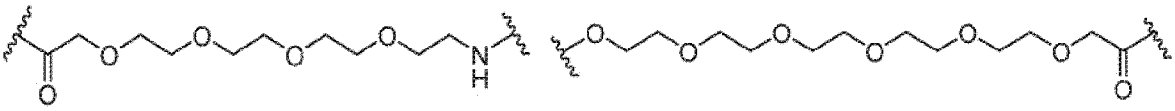


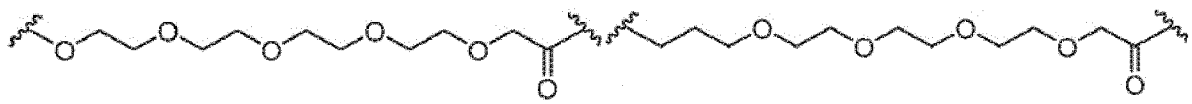


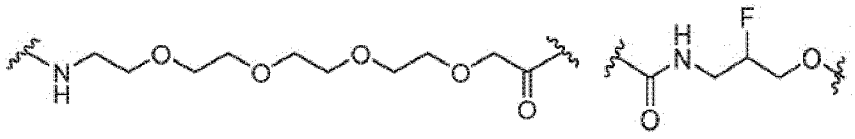


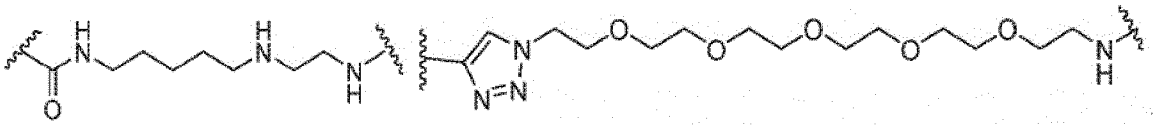


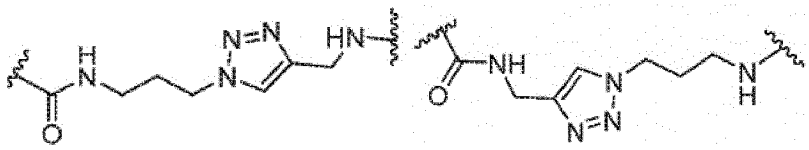


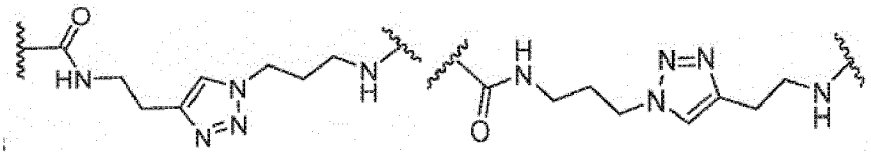


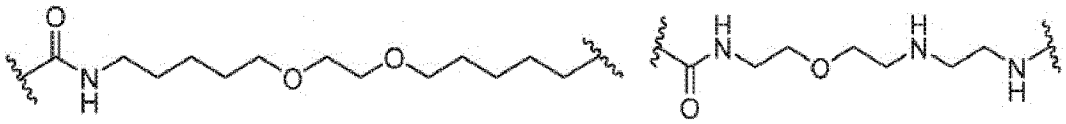


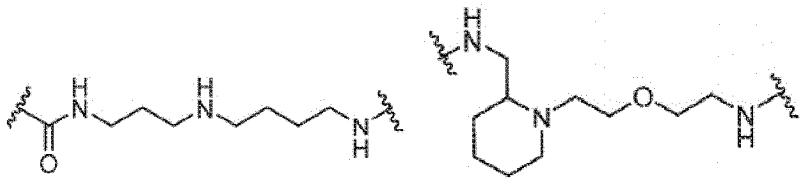


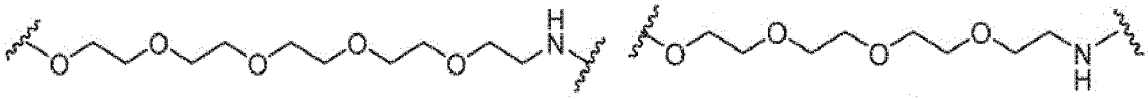


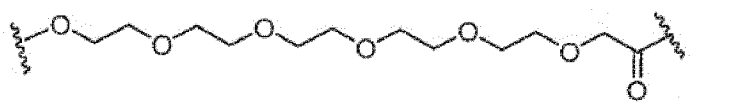


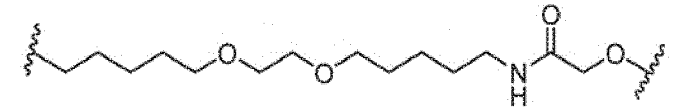


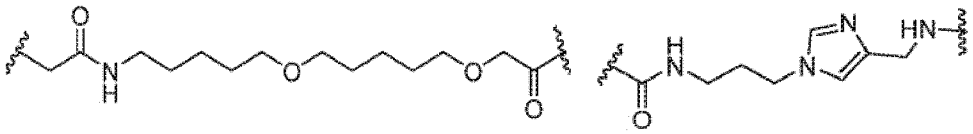


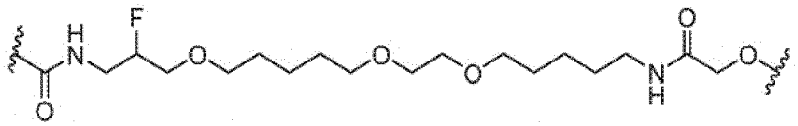


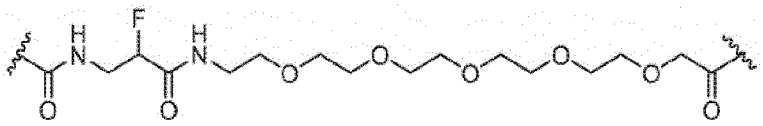


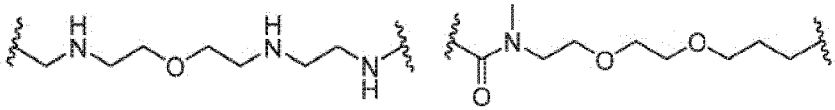


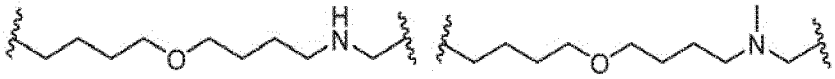


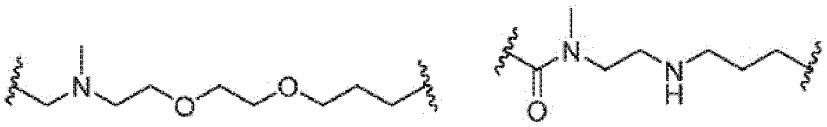


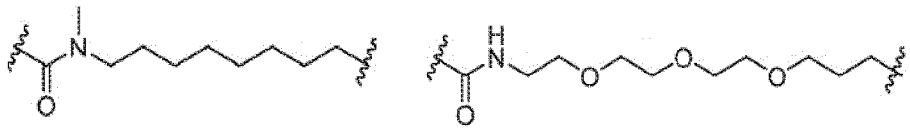


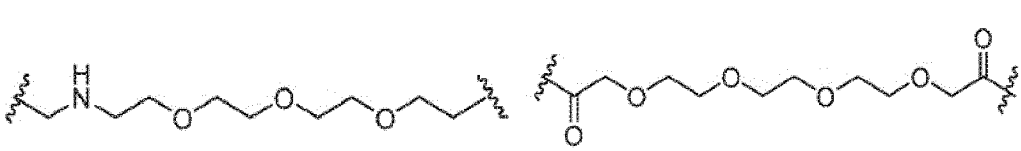


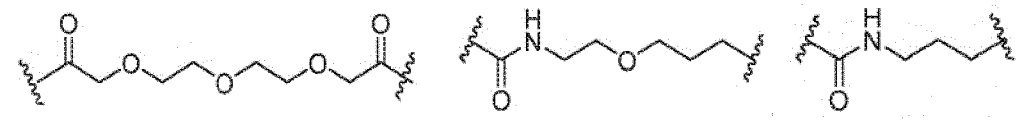


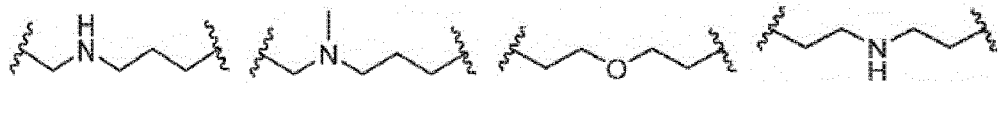


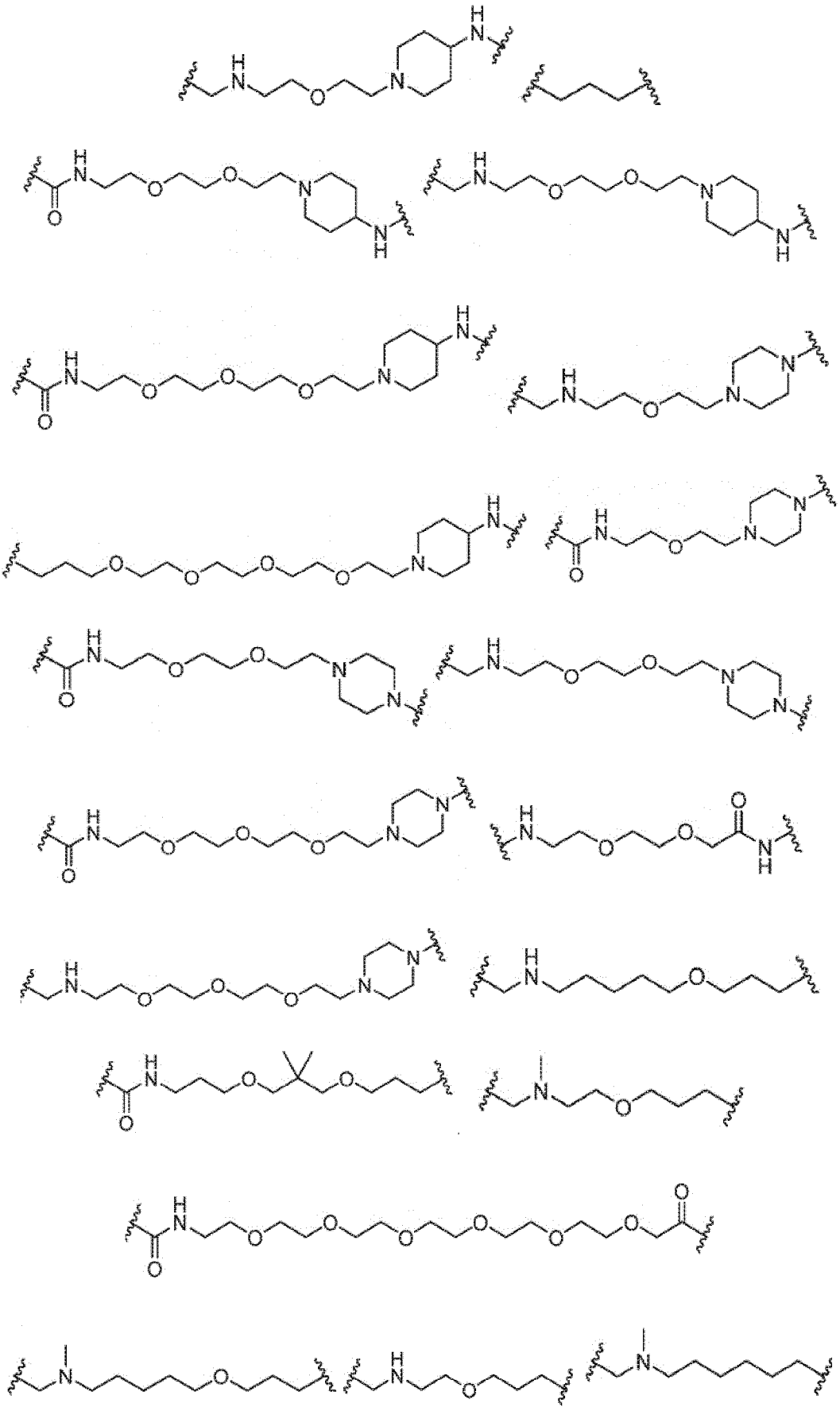


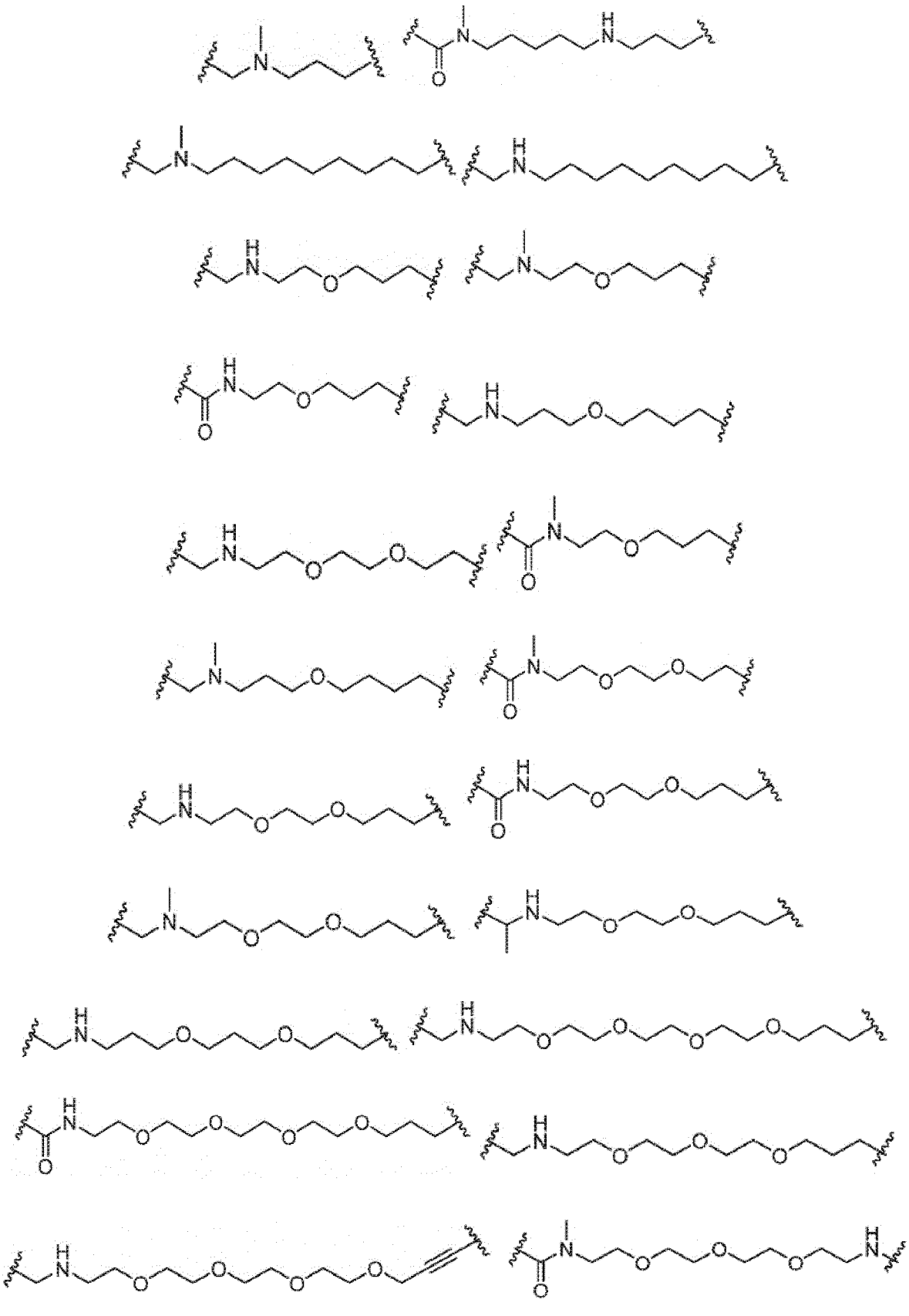


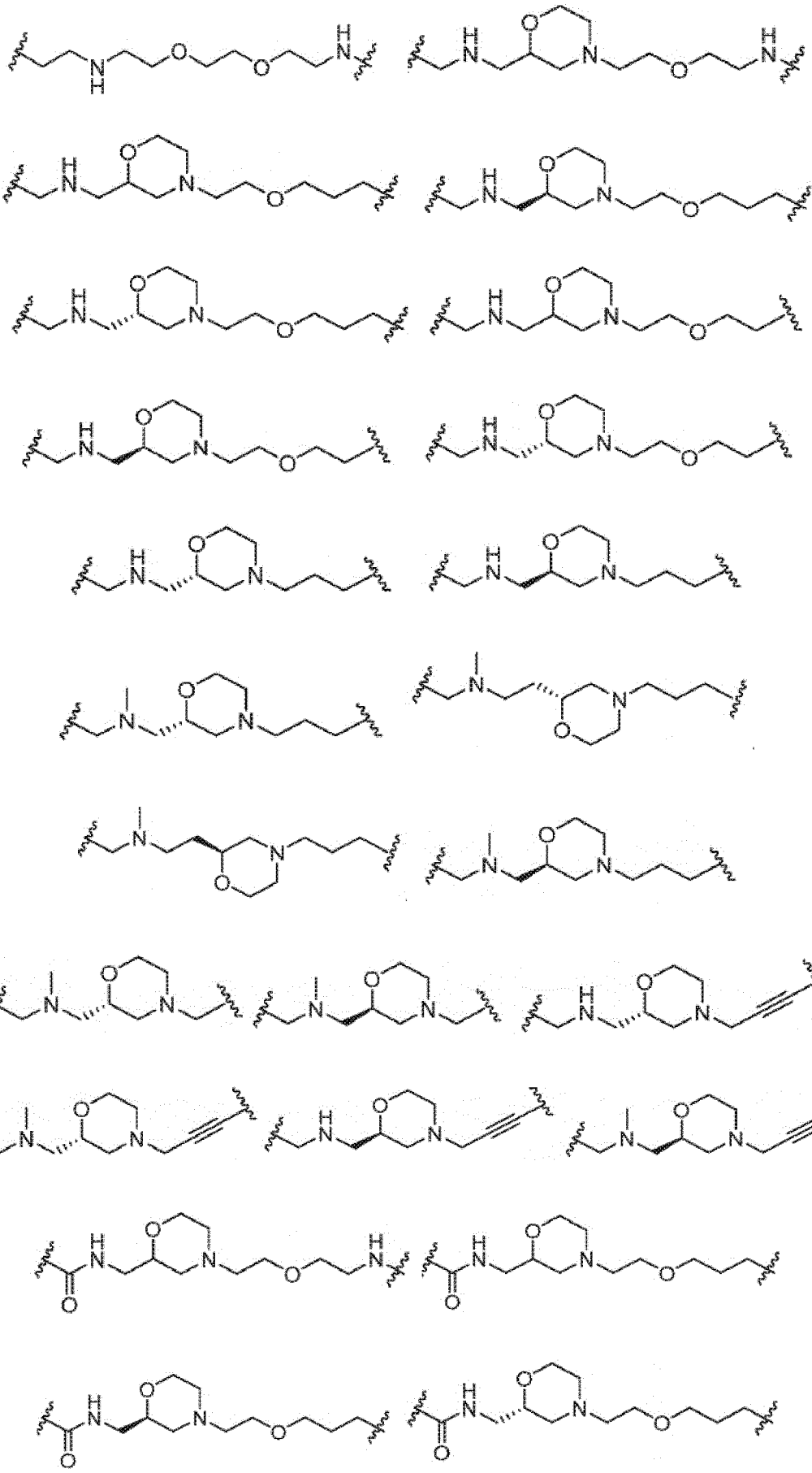


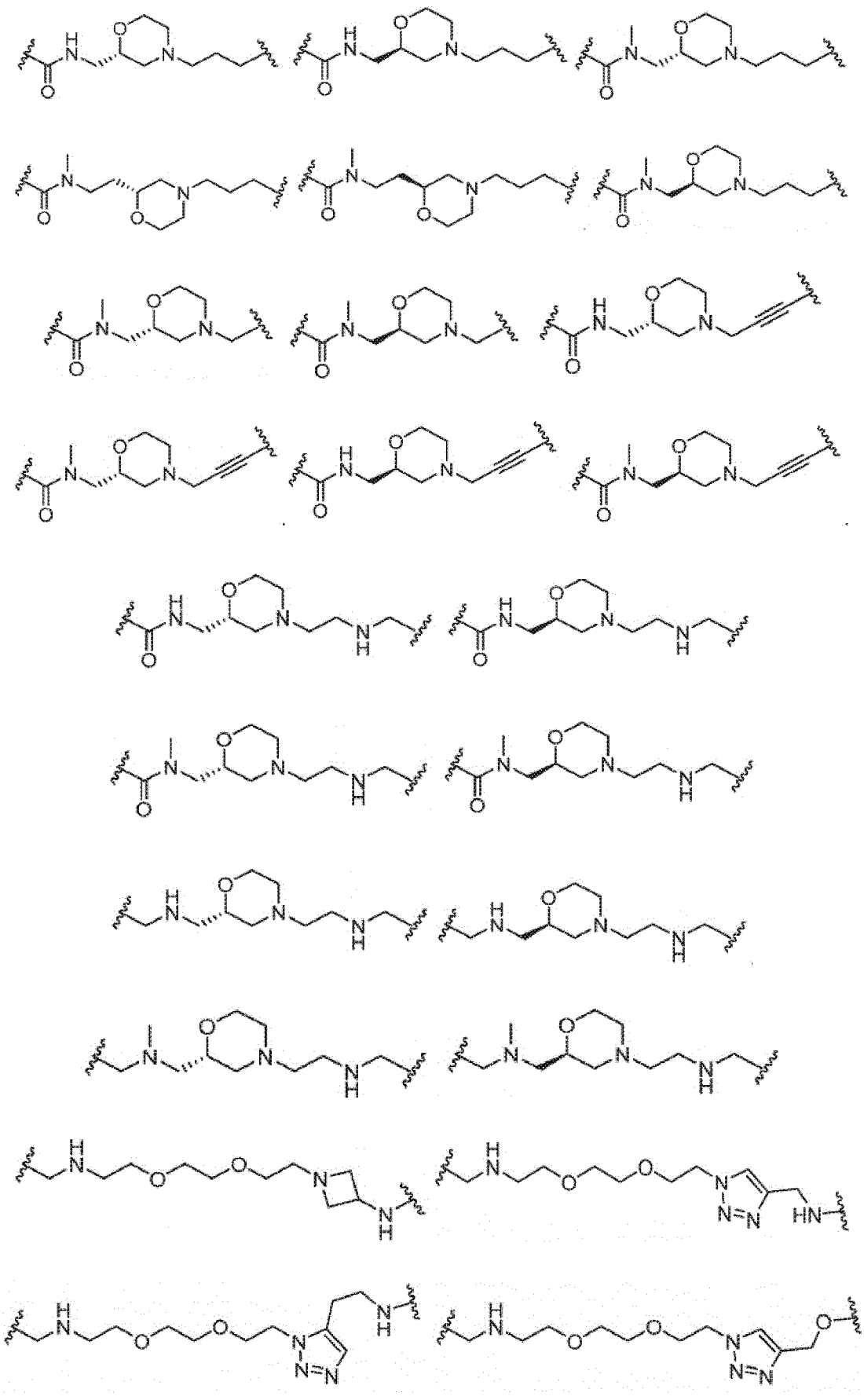


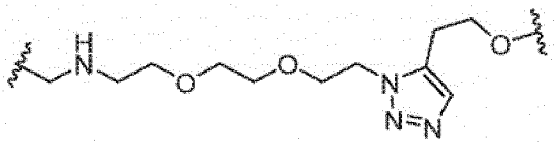


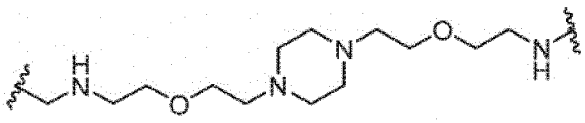


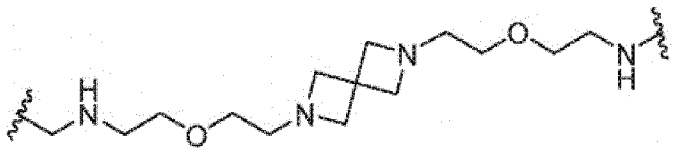


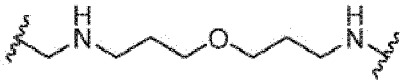


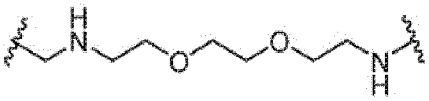


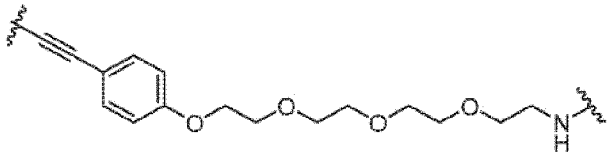


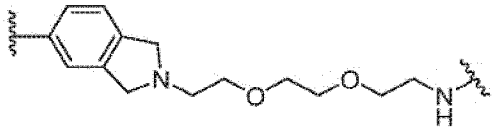


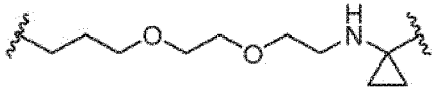


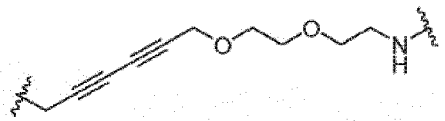


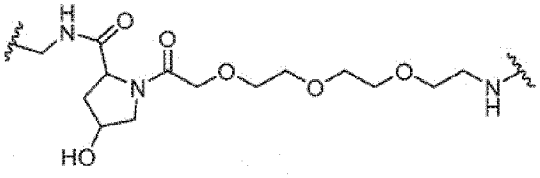


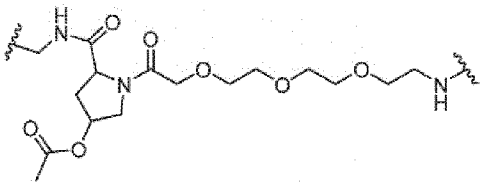


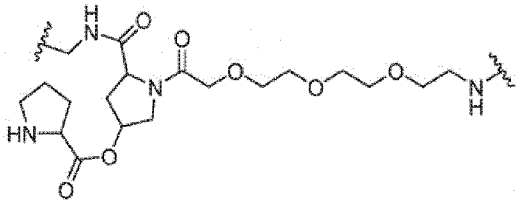


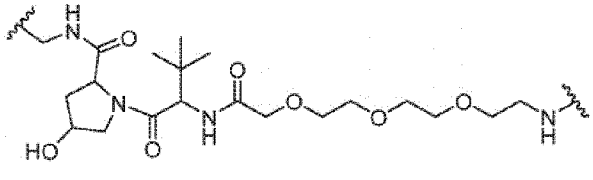


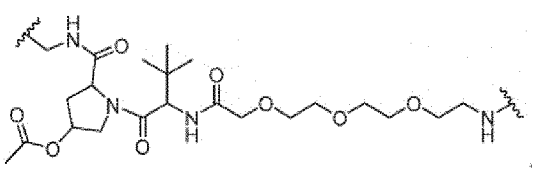


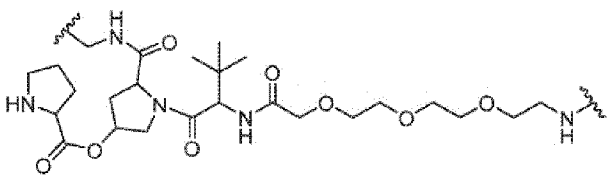


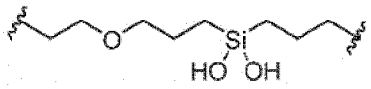


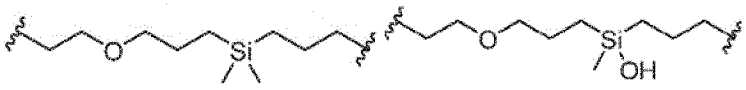


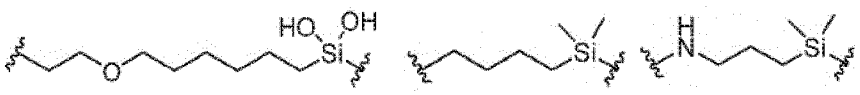


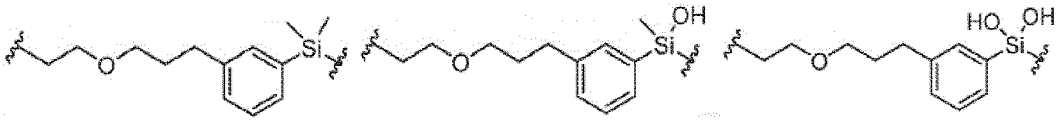


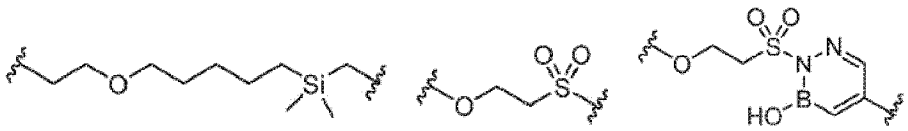


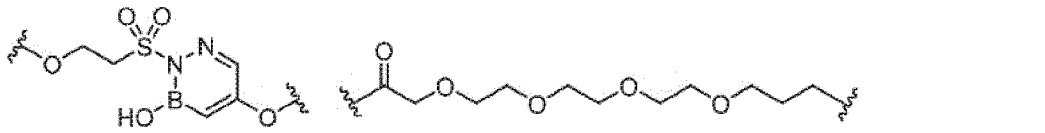


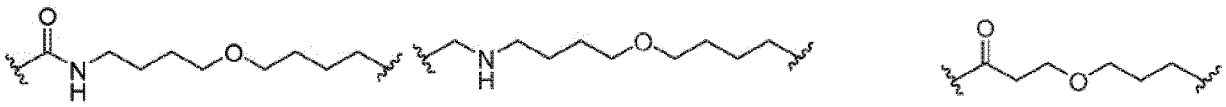


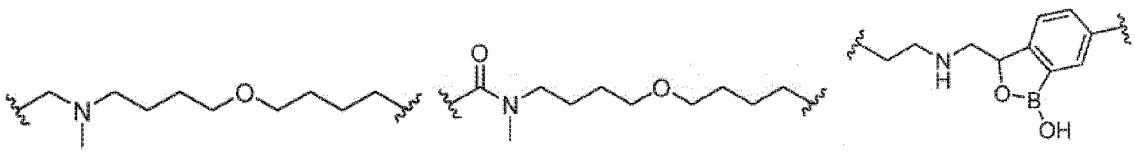


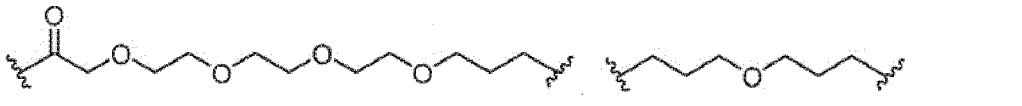


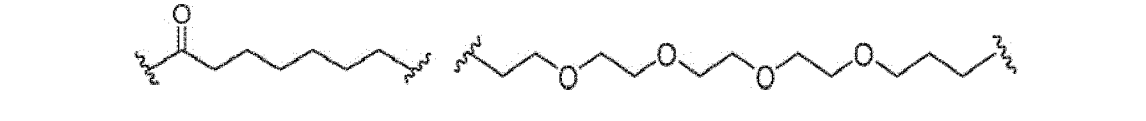


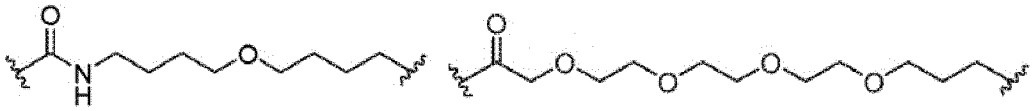


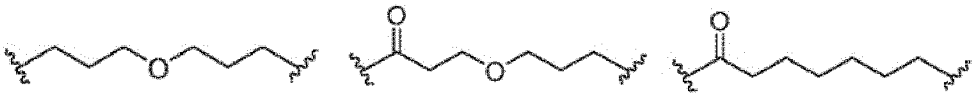


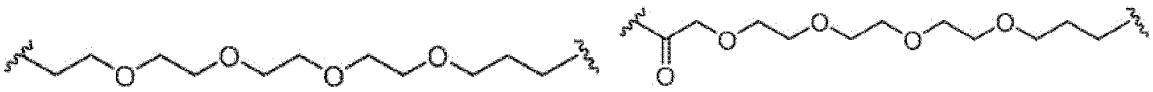


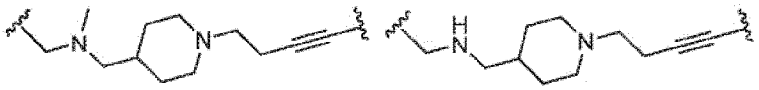


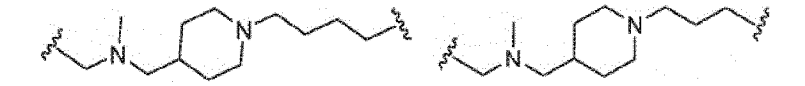


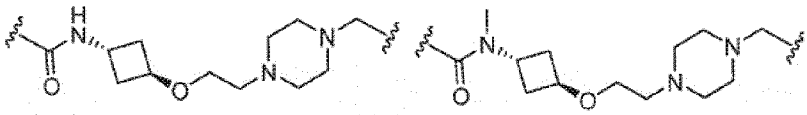


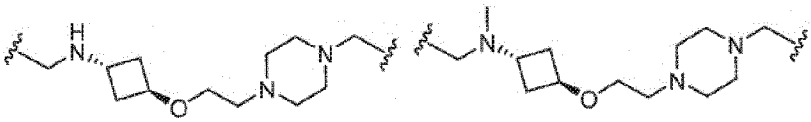


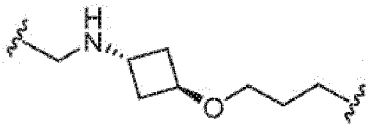


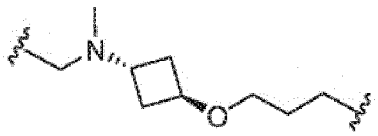


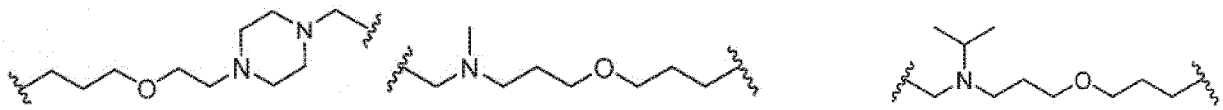


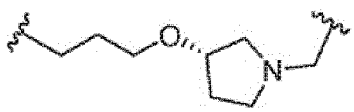


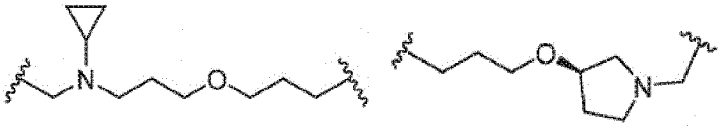


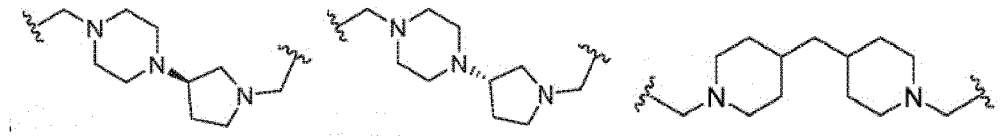


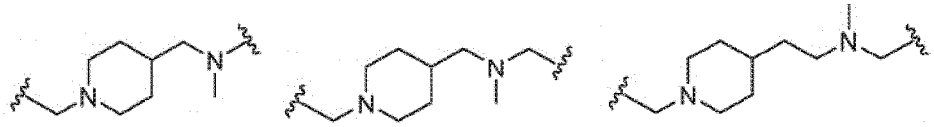


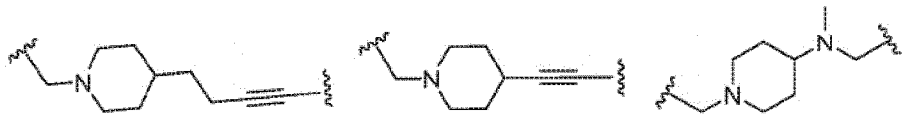


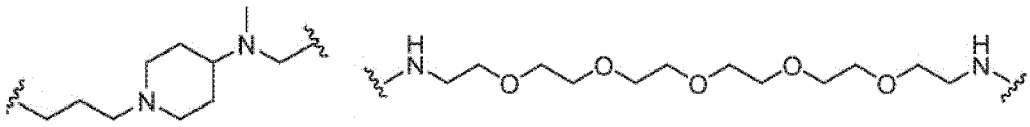


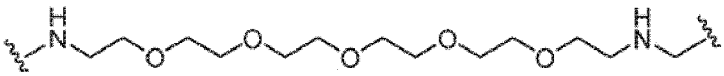


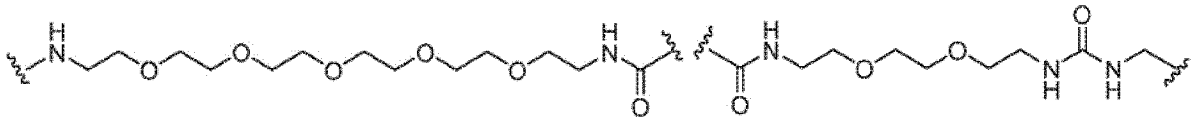


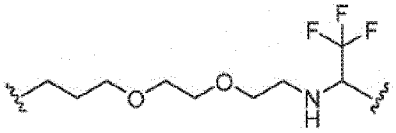


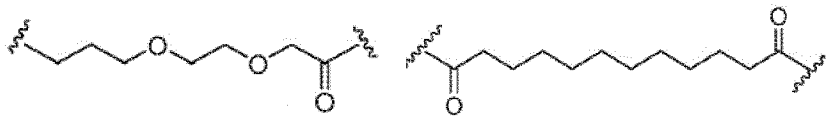


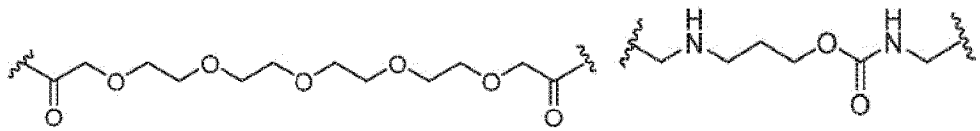


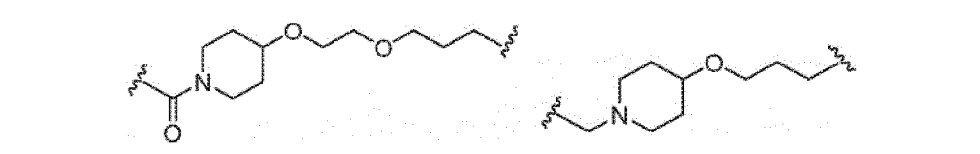


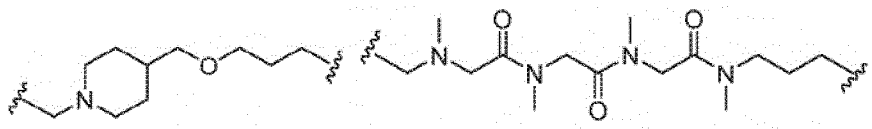


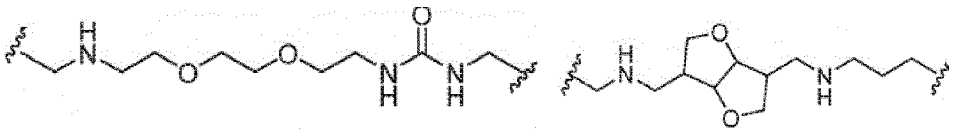


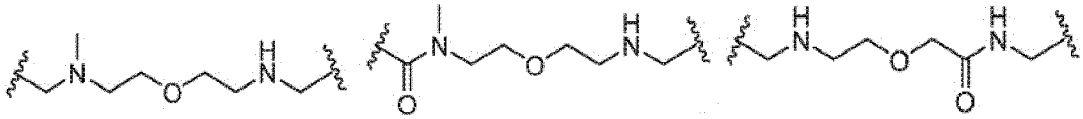


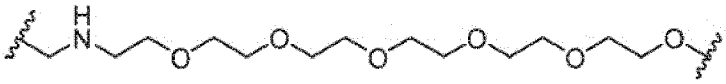


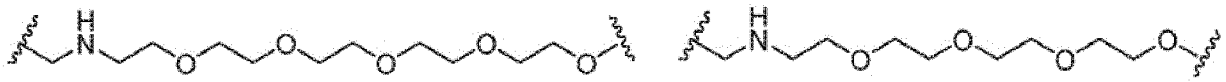


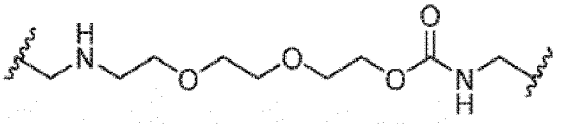


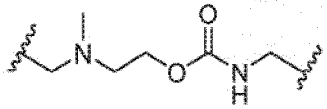


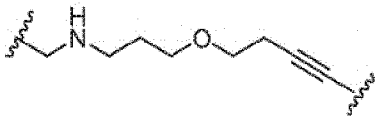


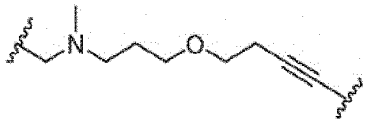


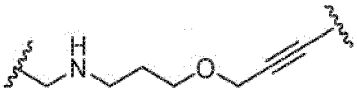


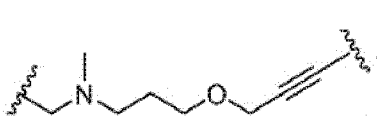


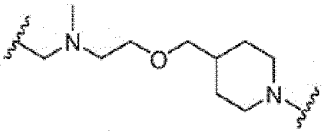


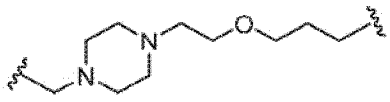


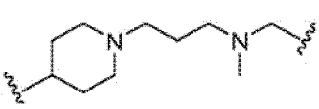


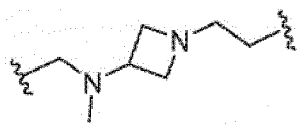


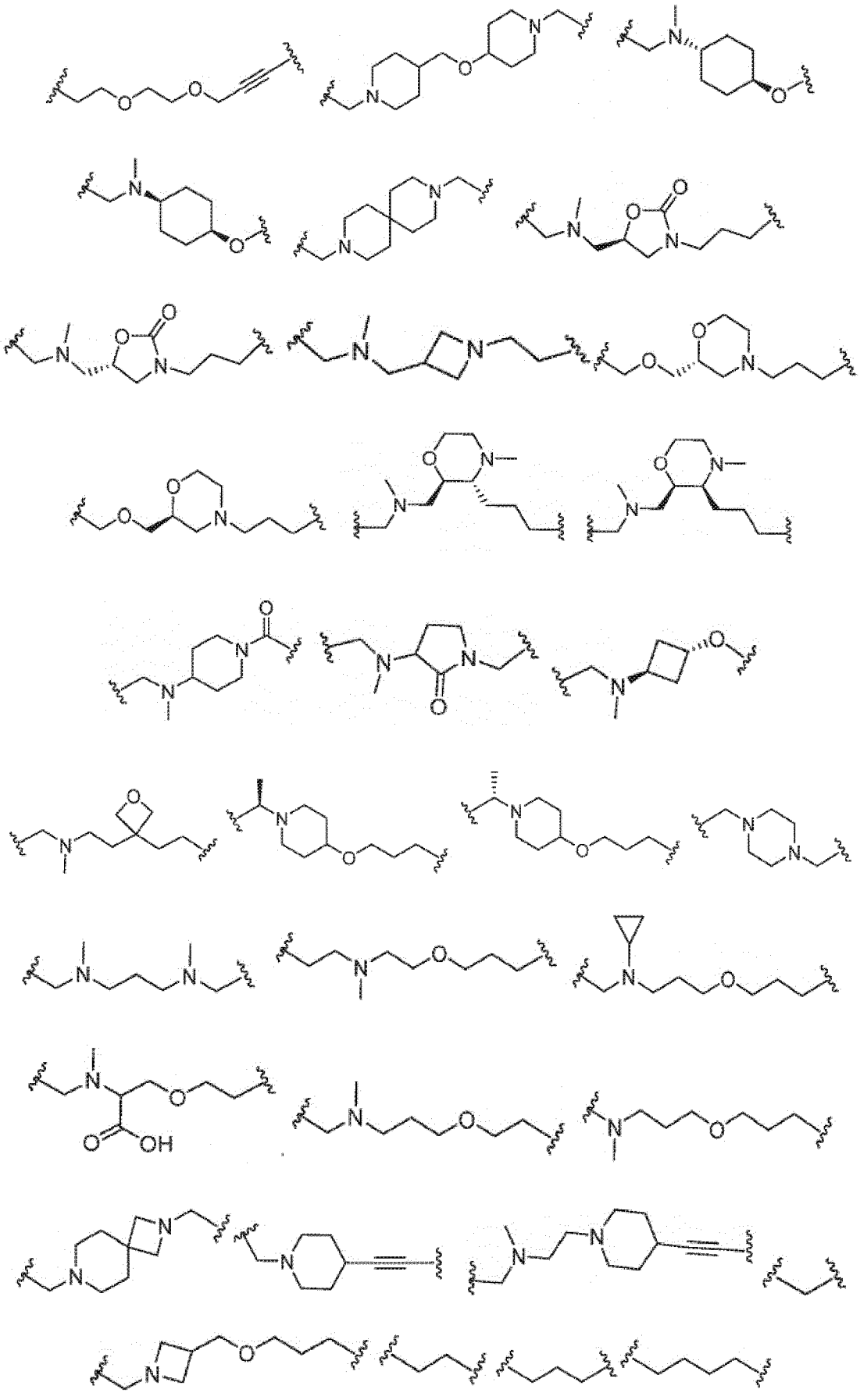


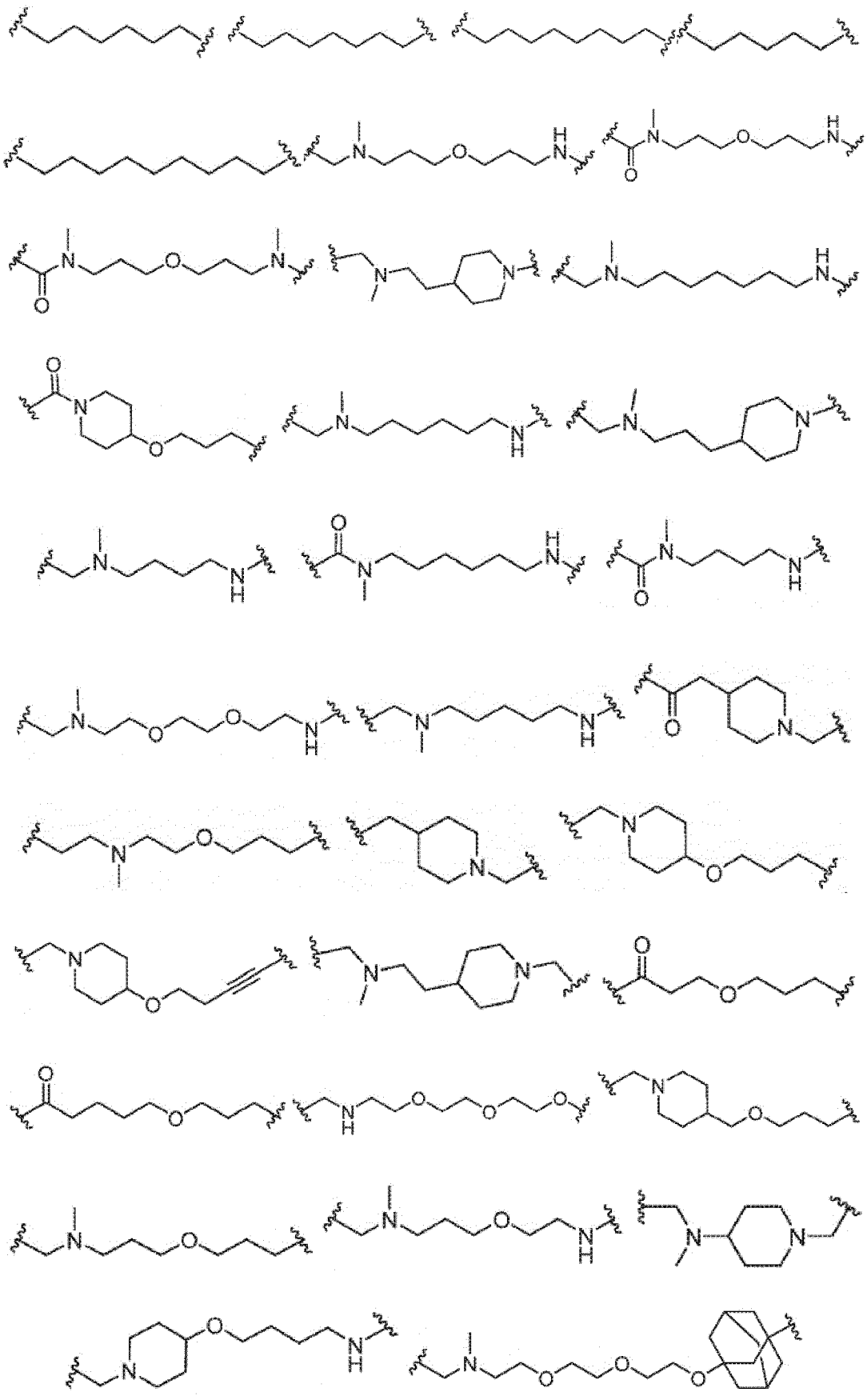


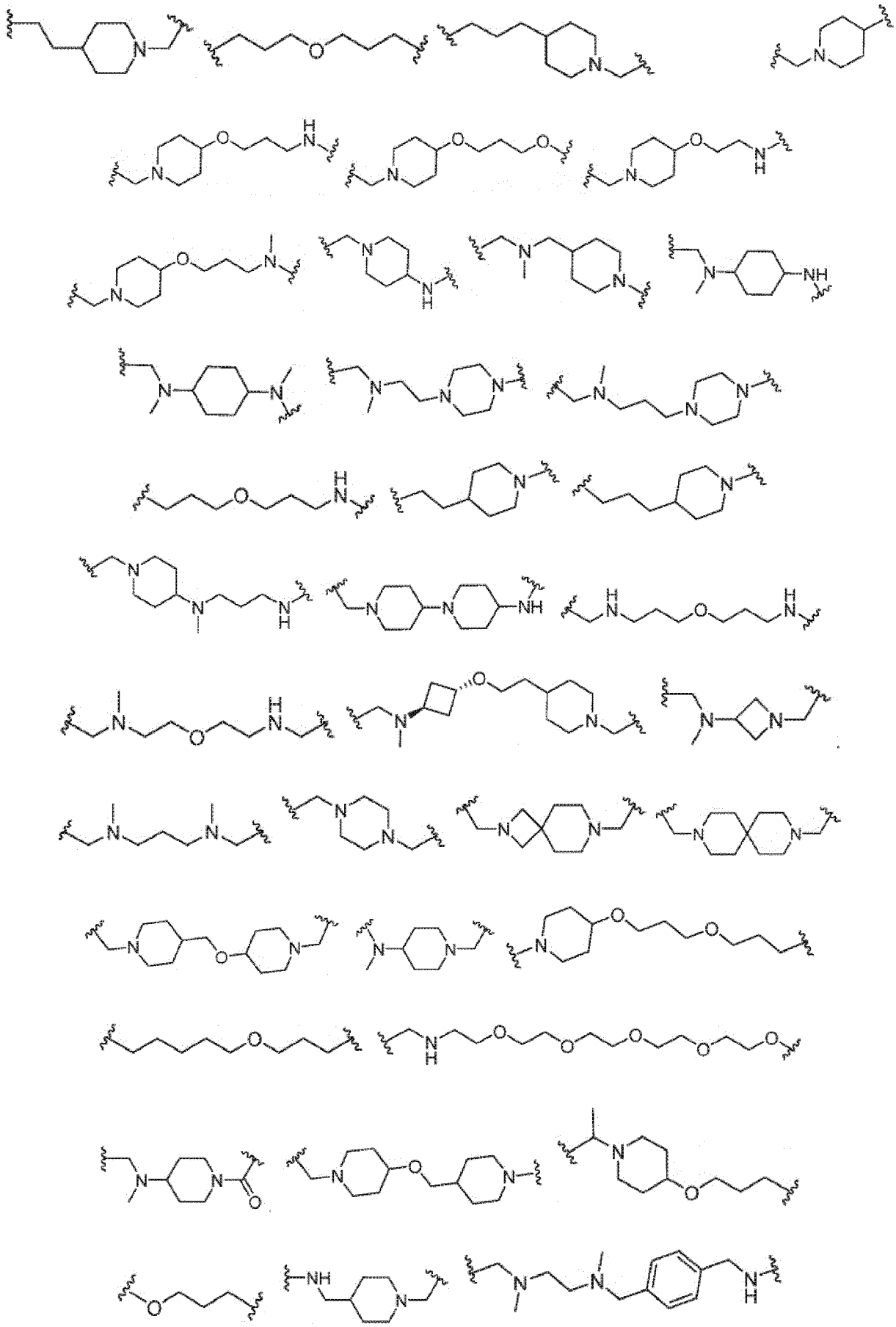


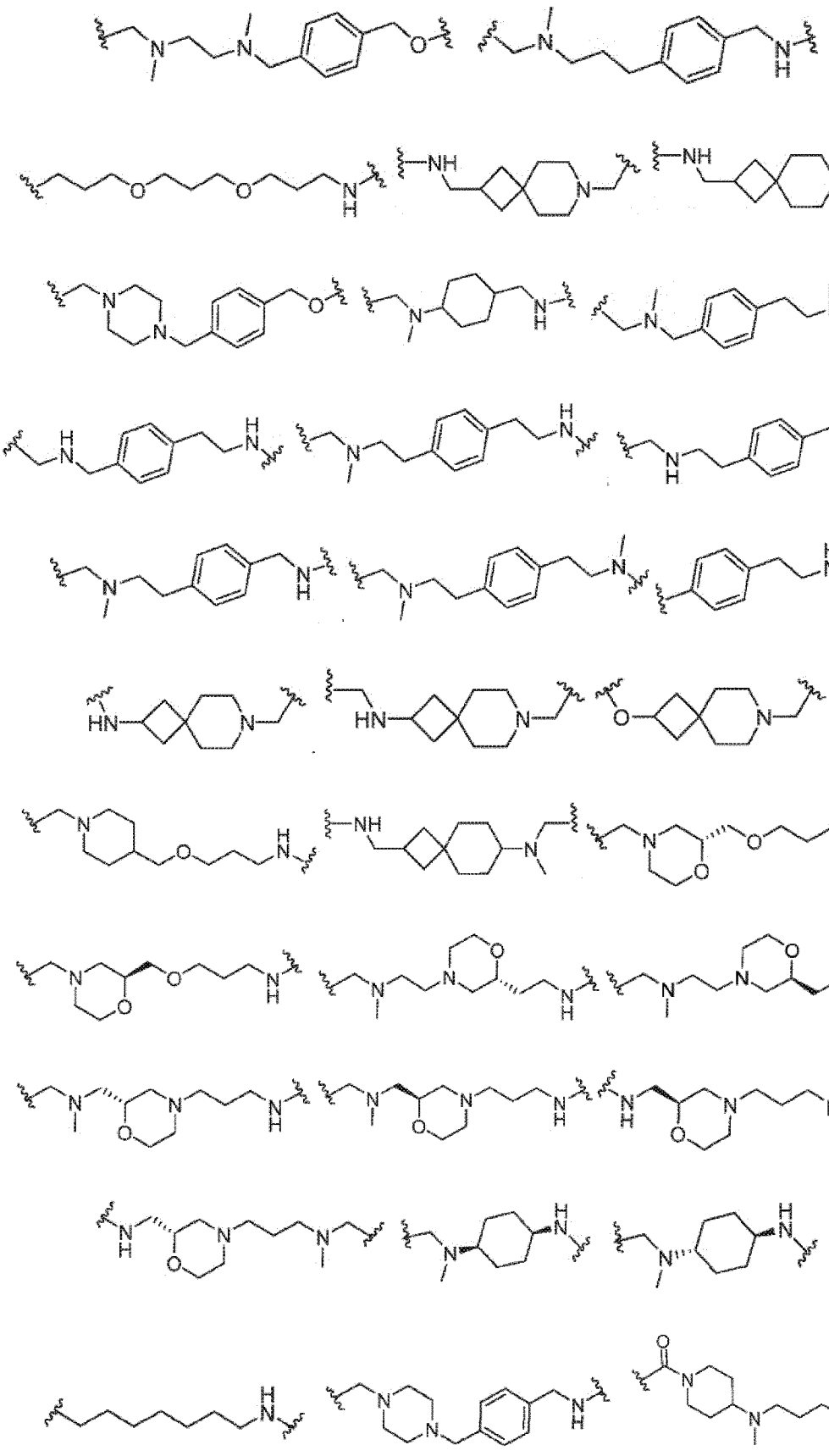


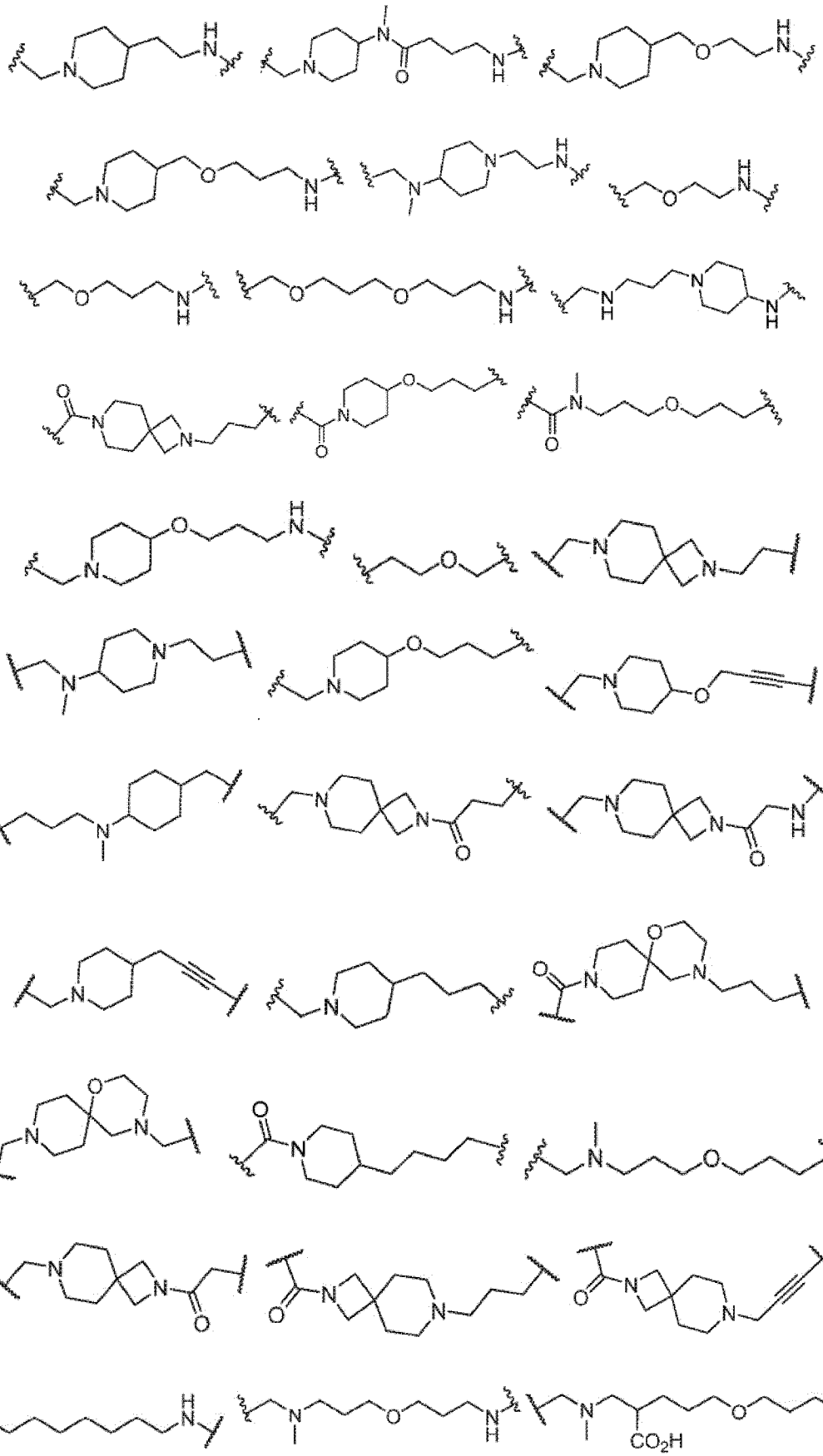


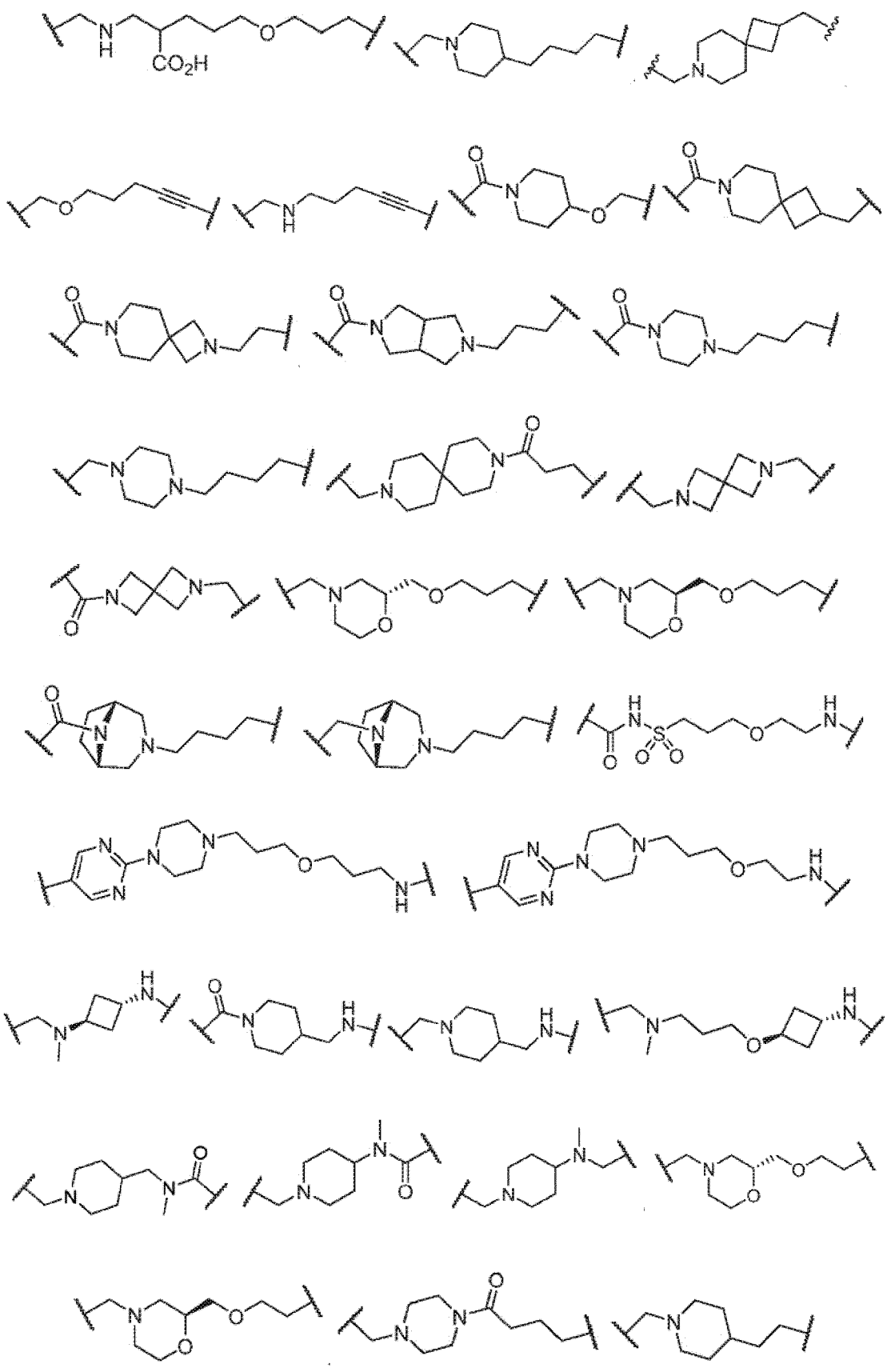


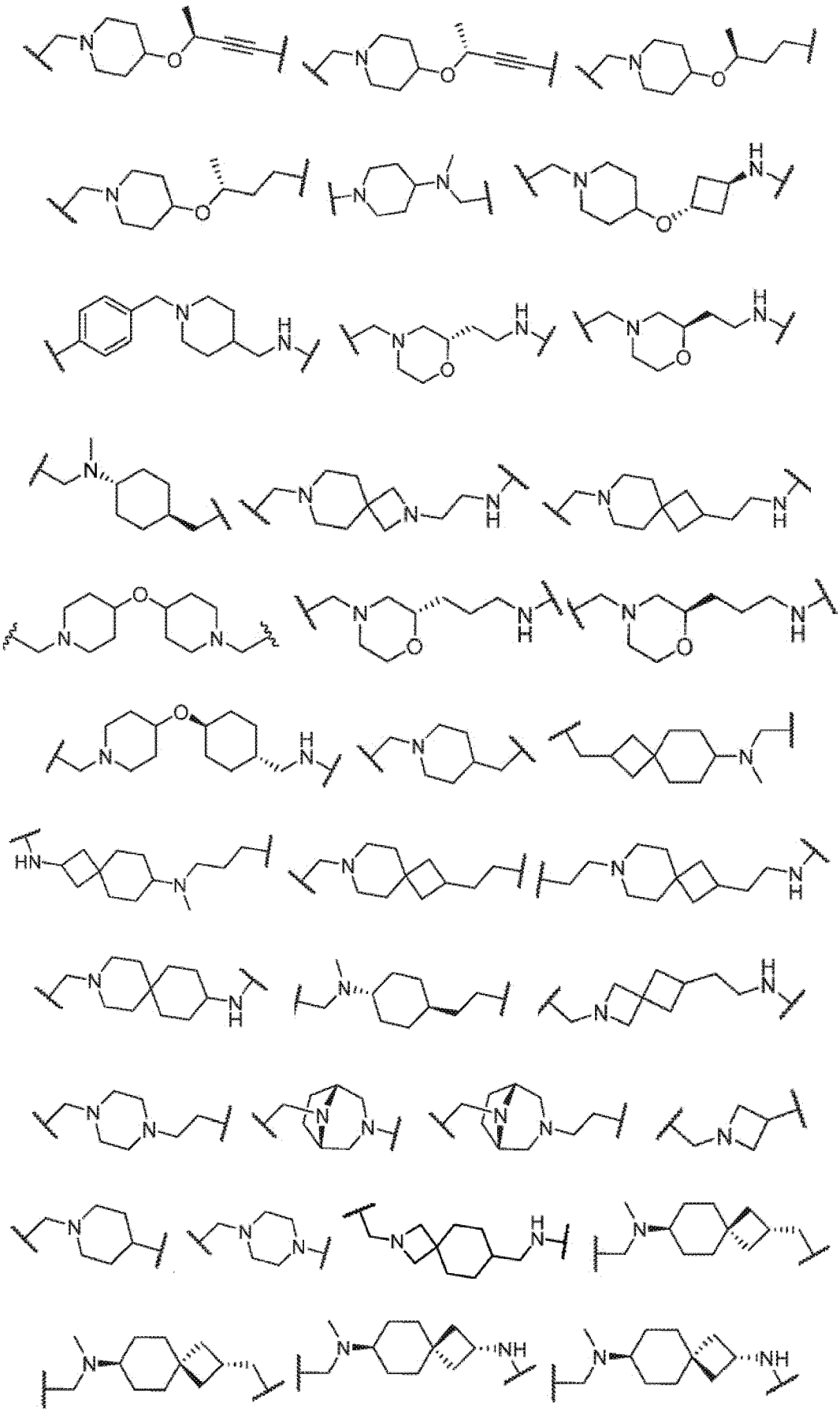


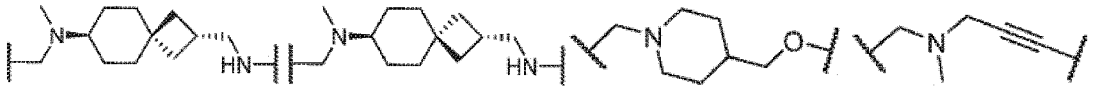


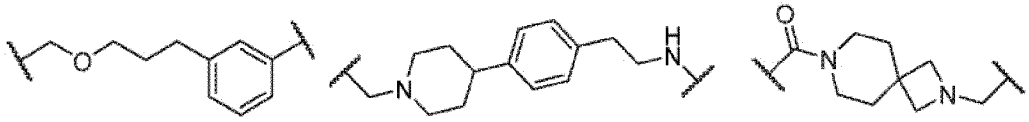


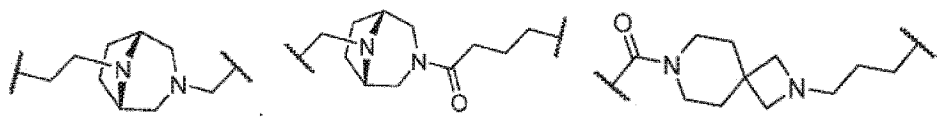


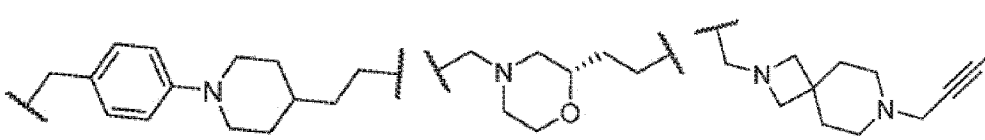


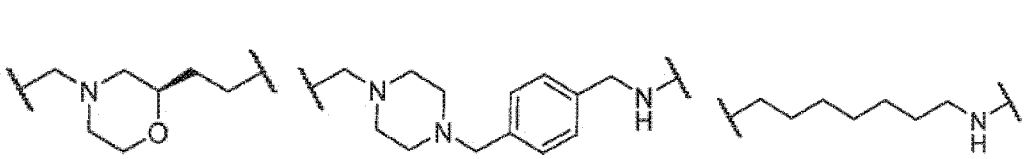


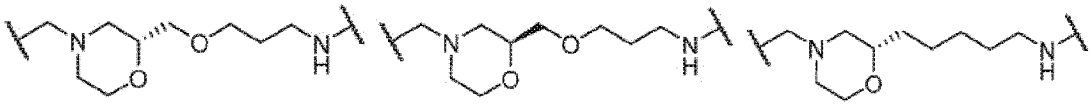


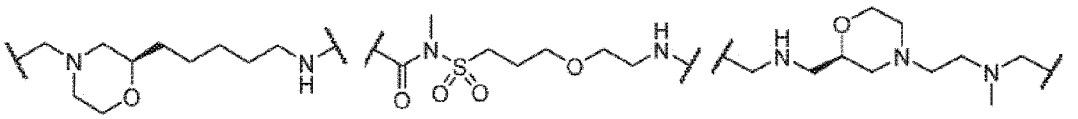


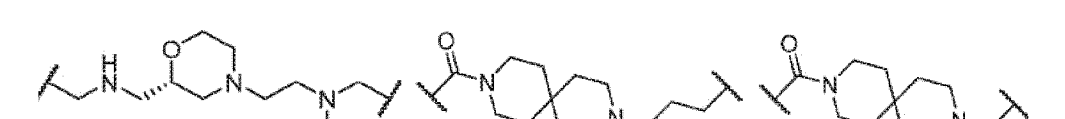


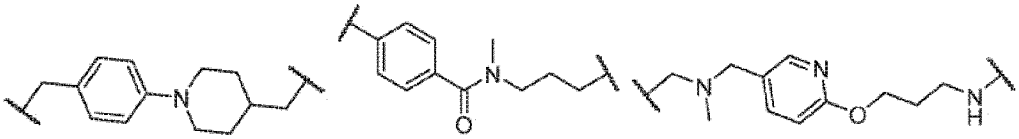


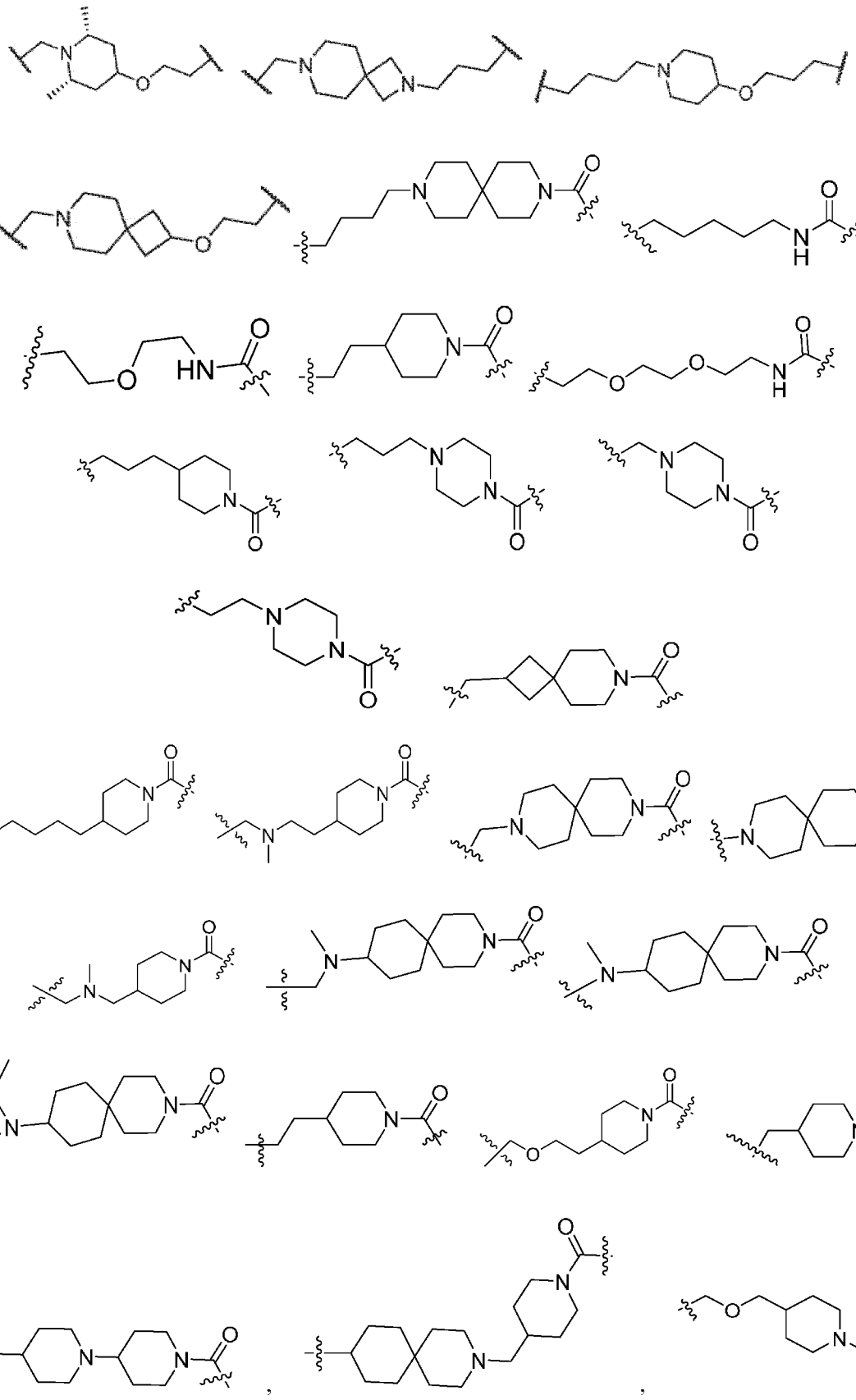


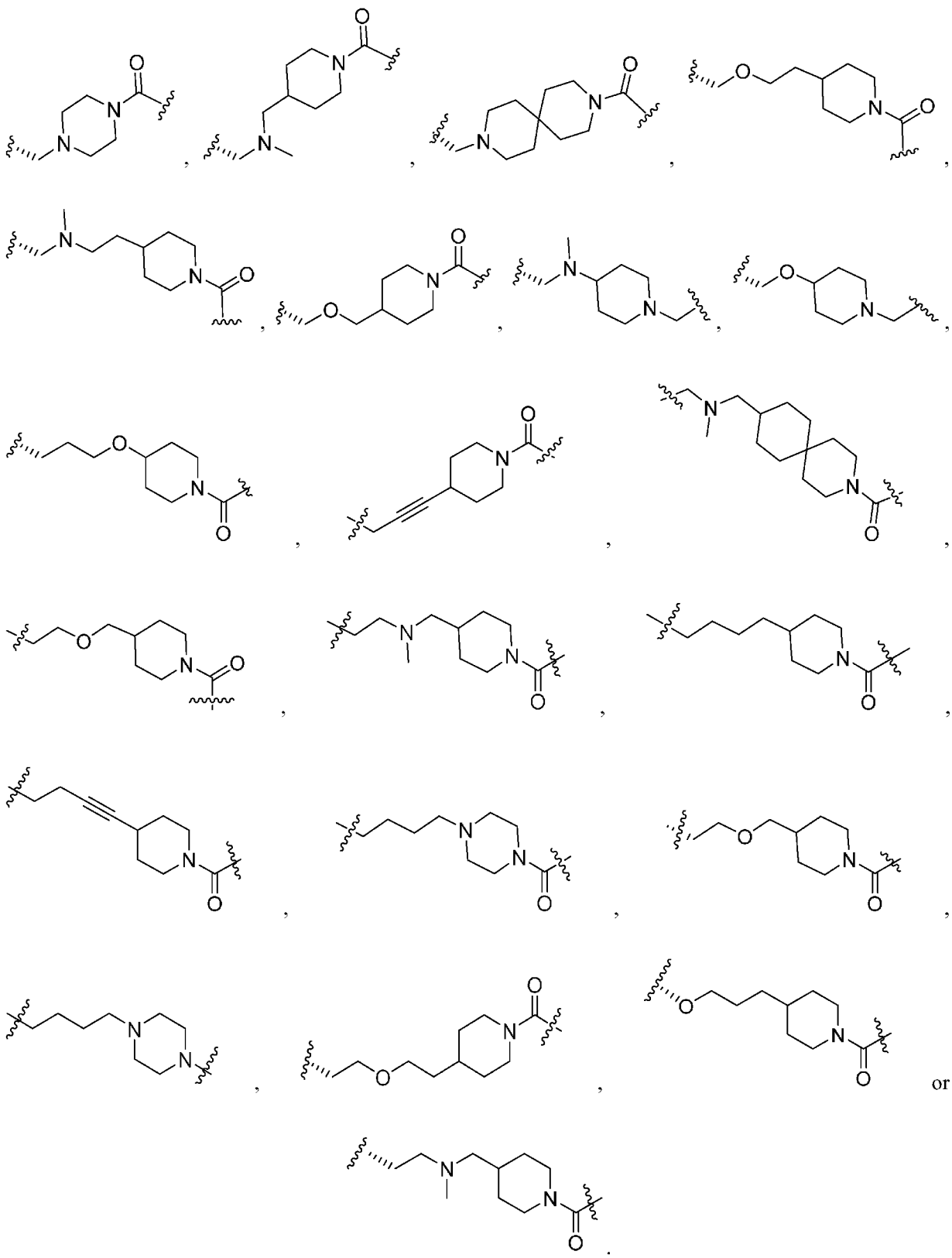




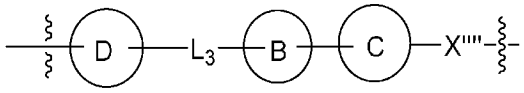








[0070] Preferably, in certain embodiments of the present invention, L is LA,

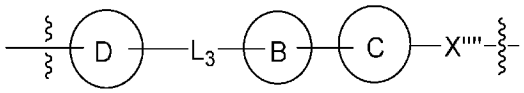


LA

wherein in the LA:

ring D is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring B is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring C is absent, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
X"" is a bond, -NH-, -NCH_3-, -O-, -$C(CH_3)_2$-, -S-, -C=C-, -C=C-, -CHF-, -$CHCF_3$-, -C(O)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -C(O)NH-, -$C(O)NCH_3$-, -NHC(O)- or -$NCH_3C(O)$-;
L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from deuterium, -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -N(C_1-C_6 hydroxyalkyl)- or - N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0071] Preferably, in certain embodiments of the present invention, L is LA,

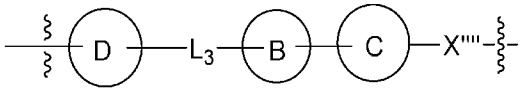


LA

wherein in the LA:

ring D is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring B is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring C is absent, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
X"" is a bond, -NH-, -NCH_3-, -O-, -$C(CH_3)_2$-, -S-, -C=C-, -C≡C-, -CHF-, -$CHCF_3$-, -C(O)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -C(O)NH-, -$C(O)NCH_3$-, -NHC(O)- or -$NCH_3C(O)$-;
L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -N(C_1-C_6 hydroxyalkyl)- or -N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0072] Preferably, in certain embodiments of the present invention, L is LA,

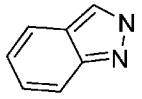


LA

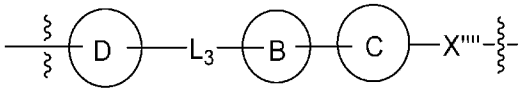
wherein in the LA:

ring D is absent, 6-10 membered aryl or 5-10 membered heteroaryl or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring B is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring C is absent, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
X"" is a bond, -NH-, -NCH_3-, -O-, -$C(CH_3)_2$-, -S-, -C=C-, -C≡C-, -CHF-, -$CHCF_3$-, -C(O)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -C(O)NH-, -$C(O)NCH_3$-, -NHC(O)-, -$(CH_2)_t$- or -$NCH_3C(O)$-; one or more methylene groups in the -$(CH_2)_t$- are optionally replaced by groups selected from -O-, -NH-, -C≡C-, -N(C_1-C_6 alkyl)- and -C(O)-, and t is 0, 1, 2, 3, 4, 5, 6 or 7.

[0073] L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -N(C_1-C_6 hydroxyalkyl)-, -C≡C-, -C(O)- or -N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. Preferably, in certain embodiments of the present invention, when ring A" is 5-11 membered bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S, ring D is 6-10 membered aryl, 5-10 membered heteroaryl, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl and -O-(C_1-C_6 alkyl).
[0074] Preferably, in certain embodiments of the present invention, when ring A" is



, the ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are independently substituted with 1, 2 or 3 hydroxy groups or with 1, 2 or 3 -O-(C_1-C_6 alkyl) groups.
[0075] In certain embodiments of the present invention, the L is LA,



LA

wherein the LA is scheme 1, scheme 2, scheme 3 or scheme 4;

scheme 1:

ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, -O-(C_1-C_6 alkyl) or hydroxy;
ring B is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected

from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring C is absent;
X‴ is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -C(O)-, -N(C_1-C_6 hydroxyalkyl)- or -N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

scheme 2:

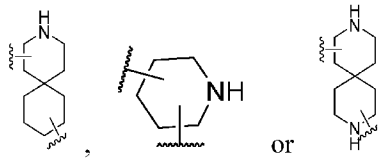
ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, methoxy or hydroxy;
ring B is 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms;
ring C is absent;
X‴ is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein k is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

scheme 3:

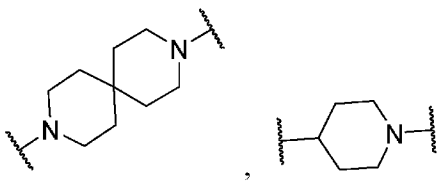
ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, hydroxy or methoxy;
ring B is 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S;
ring C is absent;
X‴ is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein k is 1, 2, 3 or 4;

scheme 4:

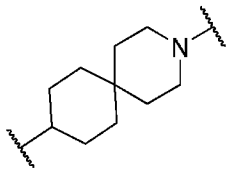
ring D is cyclohexylene or is 6-membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cyclohexylene and 6-membered heterocycloalkylene are optionally substituted with substituents selected from halogen, hydroxy or methoxy;
ring B is



(e.g.,



or



);

ring C is absent;

X"" is -C(O)-;

L_3 is $-(CH_2)_k-$, wherein one or two methylene groups in the L_3 are replaced by groups selected from -O-, -NH-, $-N(C_1-C_6$ alkyl)-, $-N(C_1-C_6$ haloalkyl)-, -C(O)-, $-N(C_1-C_6$ hydroxyalkyl)- or $-N(C_3-C_8$ cycloalkyl)-, and k is 1, 2, 3 or 4.

[0076] Preferably, in certain embodiments of the present invention, in the LA, ring D is absent.

[0077] Preferably, in certain embodiments of the present invention, in the LA, ring D is 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms, or 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

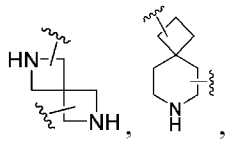
[0078] Preferably, in certain embodiments of the present invention, in the LA, ring D is 6-10 membered aryl, 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms, or 7-11 membered spiro-heterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

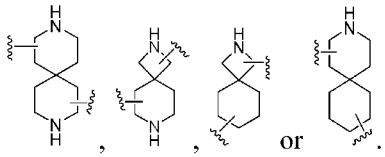
[0079] Preferably, in certain embodiments of the present invention, in the LA, ring D is 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms, or 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

[0080] Preferably, in certain embodiments of the present invention, in the LA, ring D is 7-11 membered spiroheterocycloalkylene containing 1 or 1 nitrogen heteroatom.

[0081] Preferably, in certain embodiments of the present invention, in the LA, ring D is 7-11 membered spiroheterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

[0082] Preferably, in certain embodiments of the present invention, in the LA, ring D is



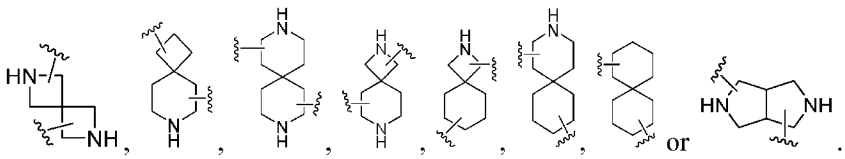


[0083] Preferably, in certain embodiments of the present invention, in the LA, ring B is absent.

[0084] Preferably, in certain embodiments of the present invention, in the LA, ring B is 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms, or 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

[0085] Preferably, in certain embodiments of the present invention, in the LA, ring B is 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

[0086] Preferably, in certain embodiments of the present invention, in the LA, ring B is piperidinylidene, piperazinylidene,



[0087] Preferably, in certain embodiments of the present invention, ring C is 4-11 membered saturated or partially

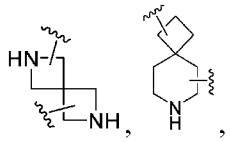
unsaturated spirocycloalkylene, 4-11 membered saturated or partially unsaturated fused cycloalkylene, 8-10 membered bicyclic saturated or partially unsaturated cycloalkylene, 4-7 membered saturated or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated or partially unsaturated spiroheterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated and/or partially unsaturated fused heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 8-10 membered bicyclic saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl and -O-(C_1-C_6 alkyl).

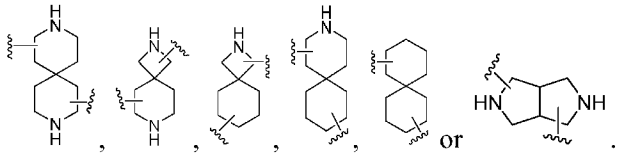
[0088] Preferably, in certain embodiments of the present invention, in the LA, ring C is 3-7 membered saturated or partially unsaturated cycloalkylene, 4-11 membered saturated or partially unsaturated spirocycloalkylene, 4-11 membered saturated or partially unsaturated fused cycloalkylene, 8-10 membered bicyclic saturated or partially unsaturated cycloalkylene, 4-7 membered saturated or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated or partially unsaturated spiroheterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated and/or partially unsaturated fused heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 8-10 membered bicyclic saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur.

[0089] Preferably, in certain embodiments of the present invention, in the LA, ring C is 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms, or 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

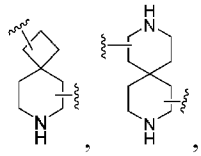
[0090] Preferably, in certain embodiments of the present invention, in the LA, ring C is 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms.

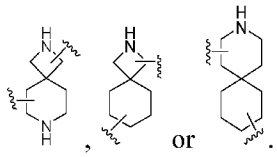
[0091] Preferably, in certain embodiments of the present invention, in the LA, ring C is





[0092] Preferably, in certain embodiments of the present invention, in the LA, ring C is





[0093] Preferably, in certain embodiments of the present invention, in the LA, X"" is a bond, -CH_2- or - C(O)-.

[0094] Preferably, in certain embodiments of the present invention, in the LA, X"" is a bond or -C(O)-.

[0095] Preferably, in certain embodiments of the present invention, in the LA, X"" is -C(O)-.

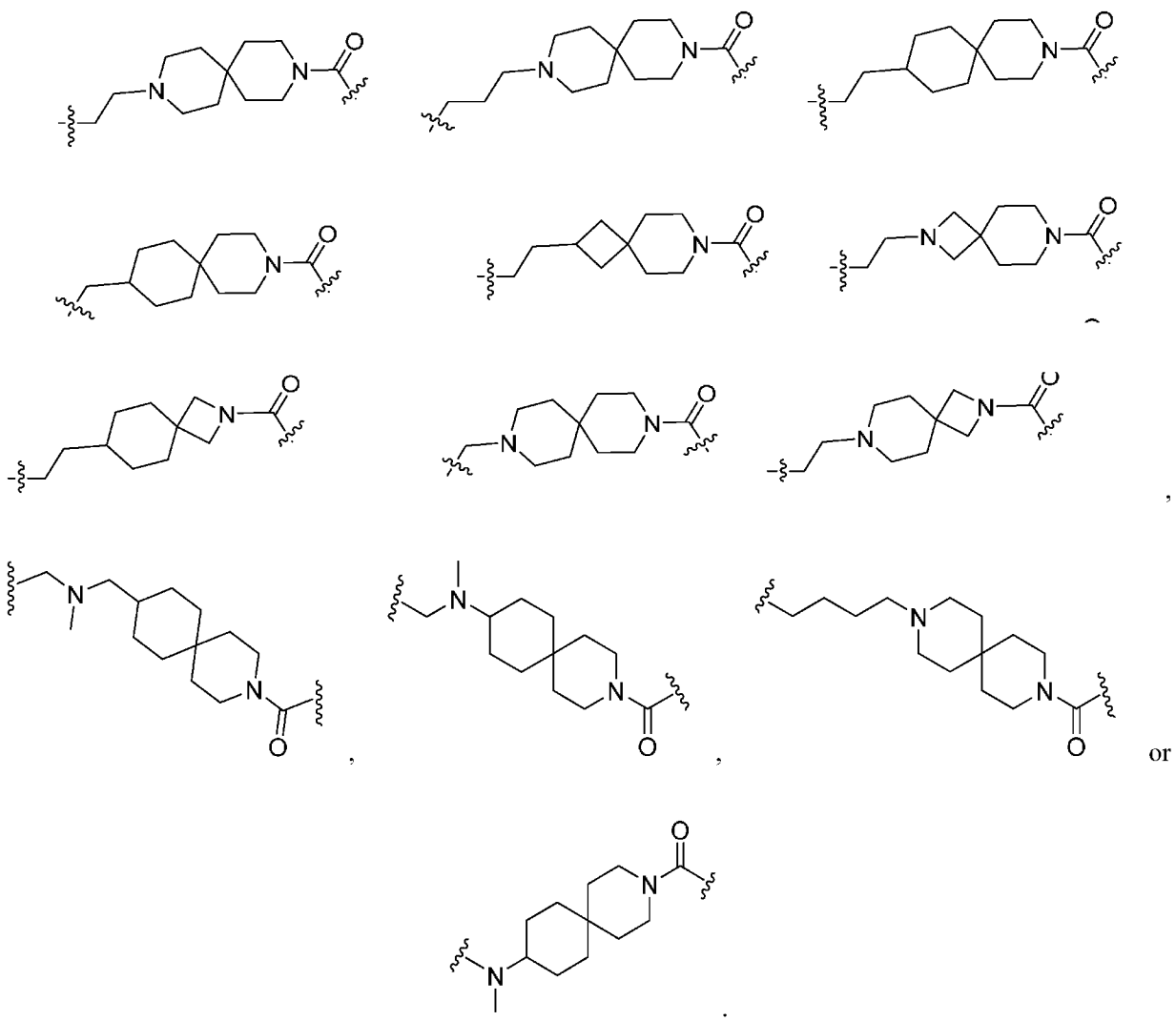
[0096] Preferably, in certain embodiments of the present invention, in the LA, L_3 is -$(CH_2)_k$-, wherein one methylene

group in the L_3 is optionally replaced by a group selected from -O-, -NH-, $-NCH_3-$ or $-NCH_2CH_3-$; k is 1, 2, 3 or 4.

[0097] Preferably, in certain embodiments of the present invention, in the LA, L_3 is $-(CH_2)_k-$, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from deuterium-C(O)-, -O-, - NH-, $-NCH_3-$ or $-NCH_2CH_3-$; k is 1, 2, 3 or 4.

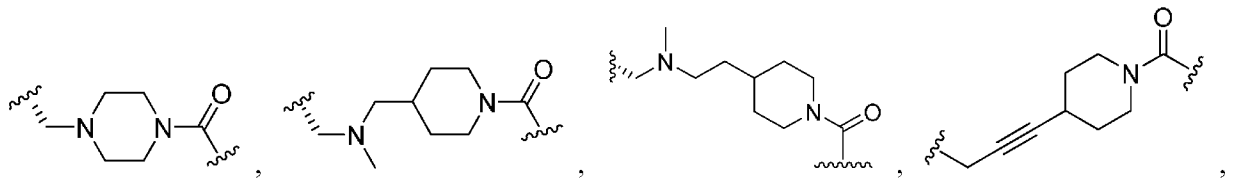
[0098] Preferably, in certain embodiments of the present invention, in the LA, ring D and ring B are absent, and ring C is 7-11 membered spiroheterocycloalkylene containing 1 or 2 nitrogen heteroatoms; X‴ is -C(O)-; L_3 is $-(CH_2)_k-$; k is 1, 2, 3, 4 or 5.

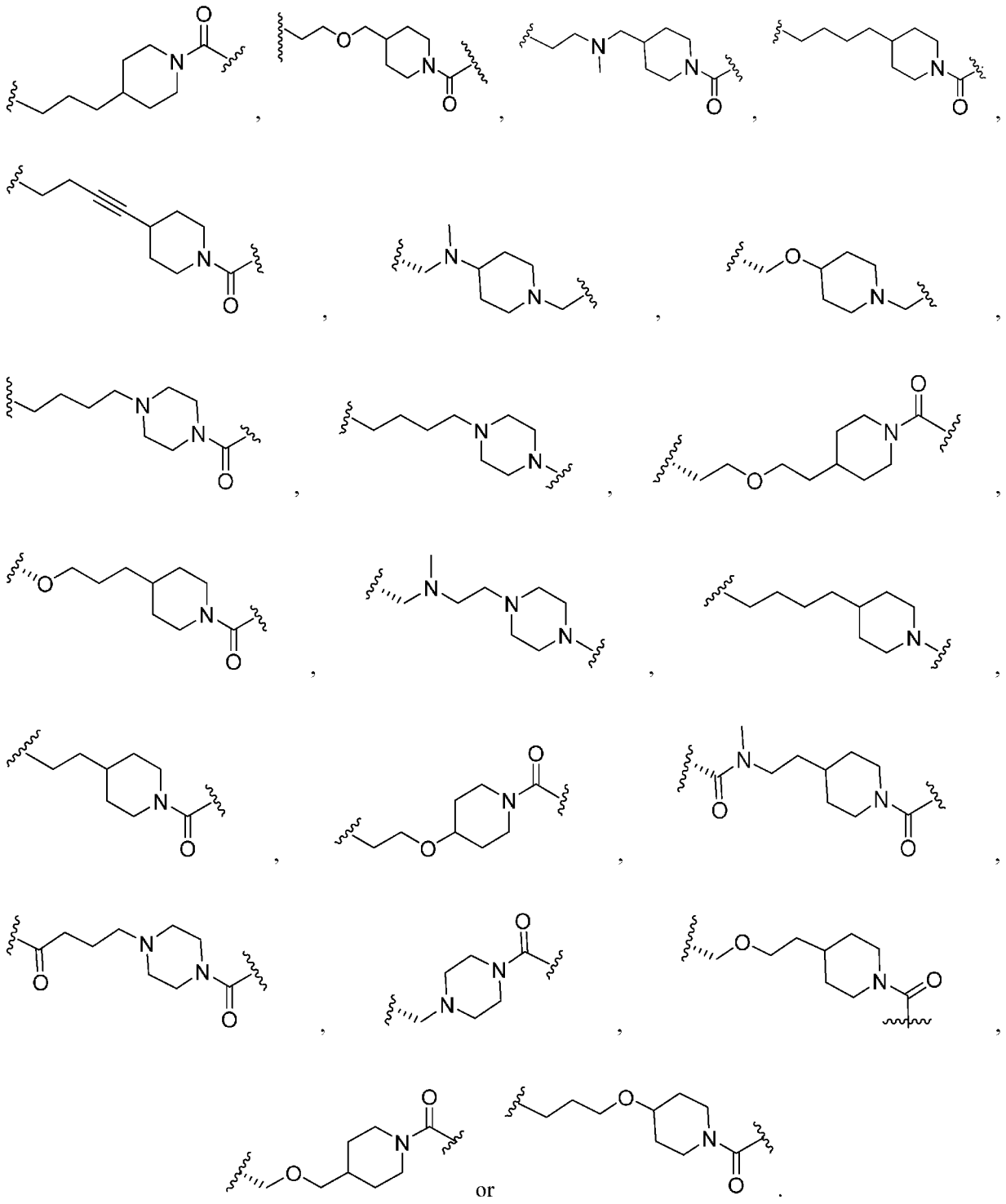
[0099] Preferably, in certain embodiments of the present invention, formula L is selected from



[0100] Preferably, in certain embodiments of the present invention, in the LA, ring D and ring B are absent, and ring C is 4-7 membered heterocycloalkyl containing 1 or 2 nitrogen heteroatoms; X"" is -C(O)-, a bond or $-CH_2-$; L_3 is $-(CH_2)_k-$; k is 1, 2, 3, 4 or 5.

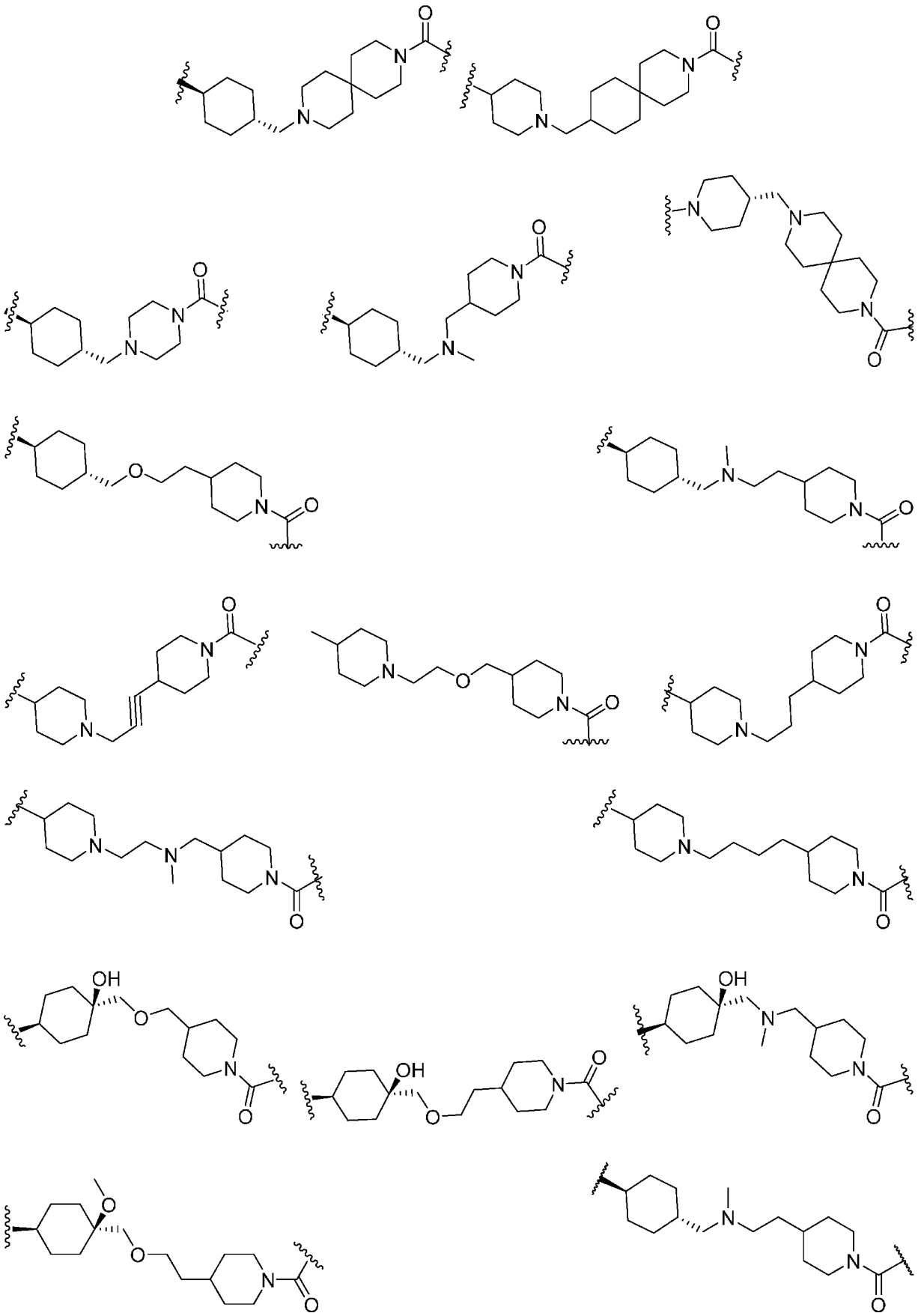
[0101] Preferably, in certain embodiments of the present invention, formula L is selected from

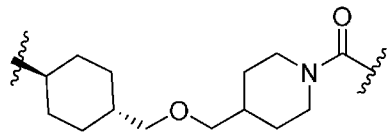


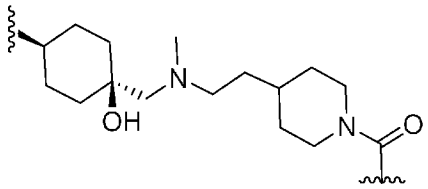


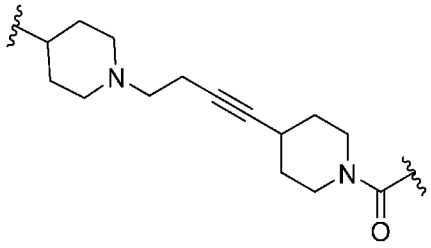
[0102] Preferably, in certain embodiments of the present invention, in the LA, ring D is C_4-C_7 membered cycloalkyl or 4-7 membered heterocycloalkyl; ring B and ring C are absent or are 5-11 membered heterocycloalkylene containing 1 or 2 nitrogen heteroatoms; X"" is -C(O)- or -$(CH2)_t$-, t is 0, 1, 2, 3, 4 or 5; L_3 is -$(CH_2)_k$-, wherein k is 1, 2, 3, 4 or 5.

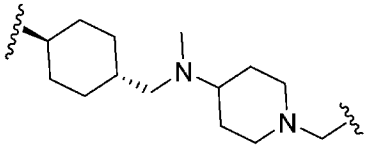
[0103] Preferably, in certain embodiments of the present invention, formula L is selected from

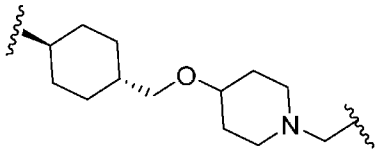


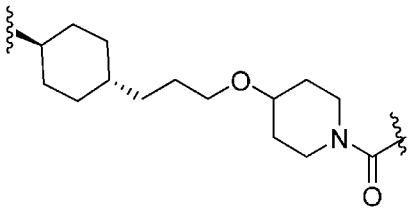


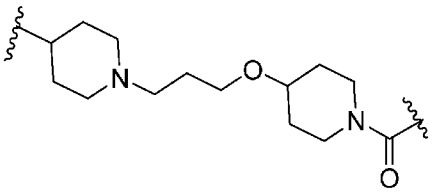


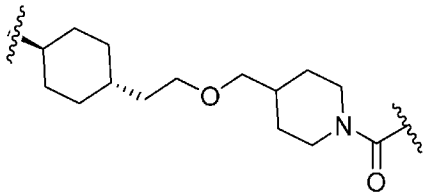


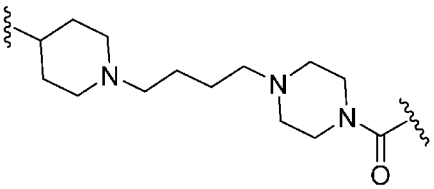


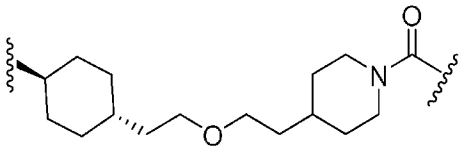


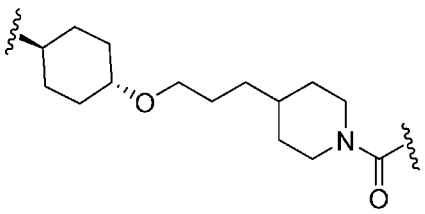


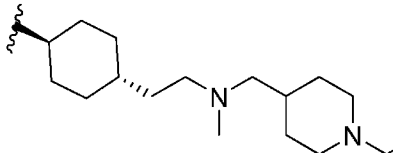


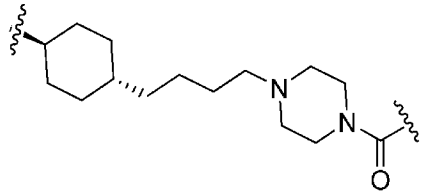


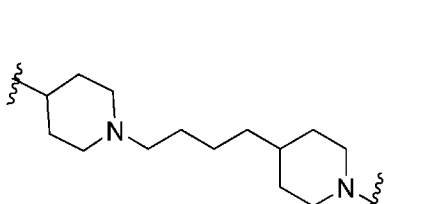


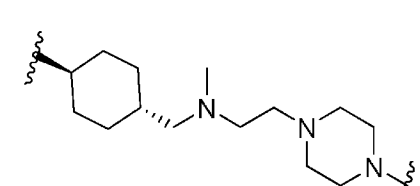


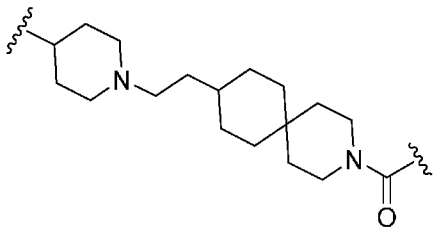


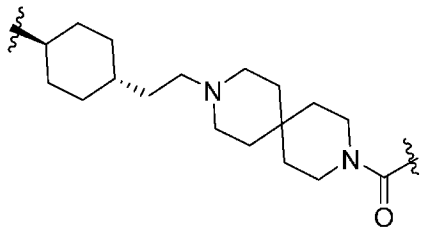


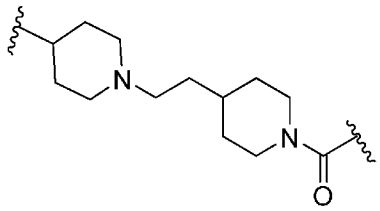


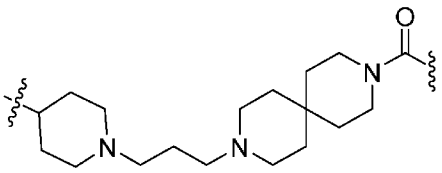


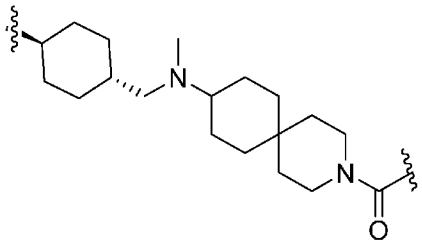


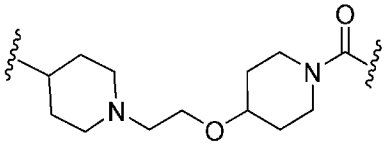


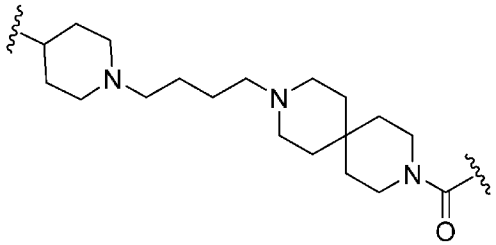


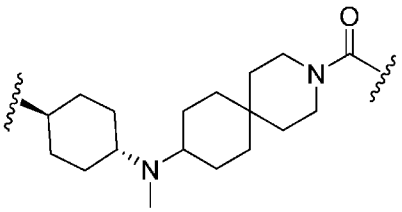


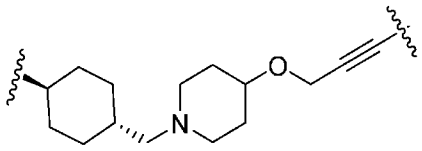


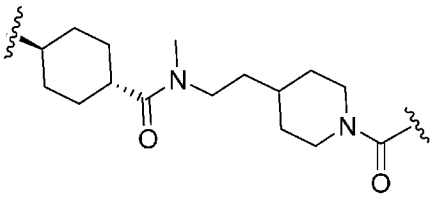


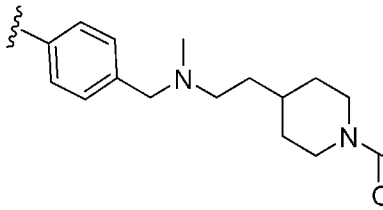


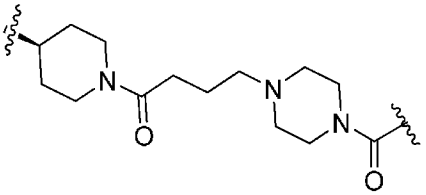


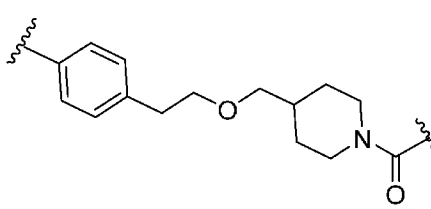


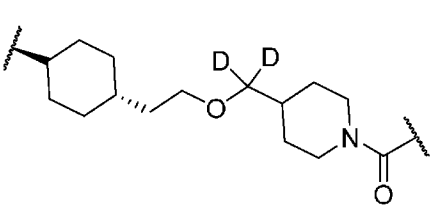


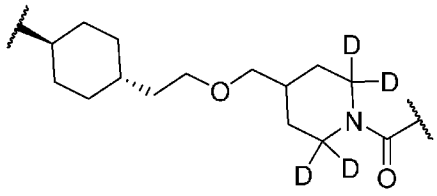
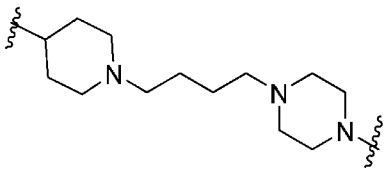
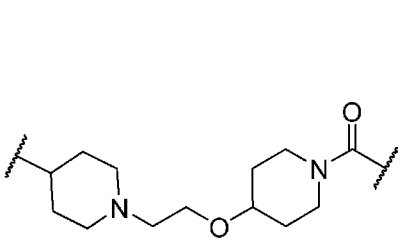
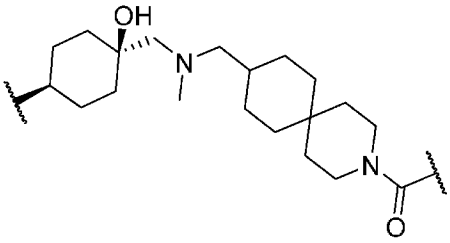










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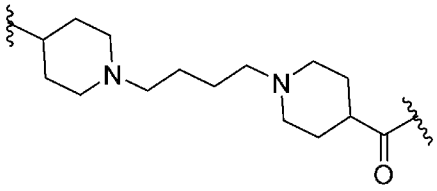
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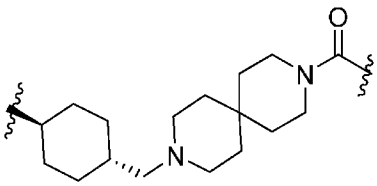
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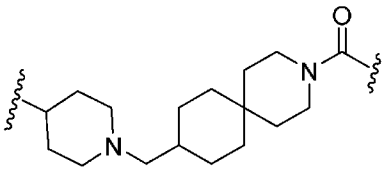
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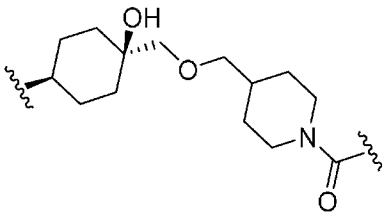
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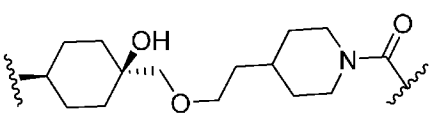
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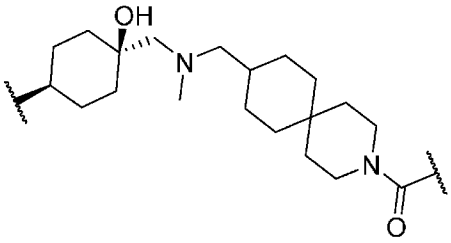
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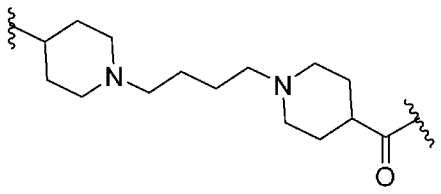
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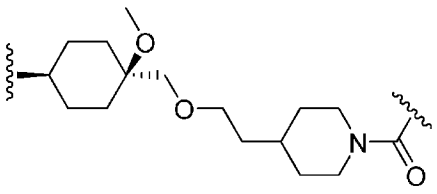
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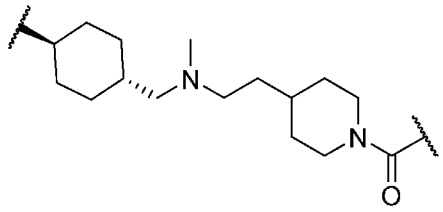
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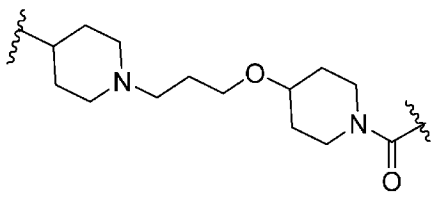
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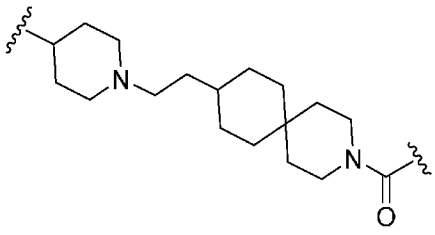
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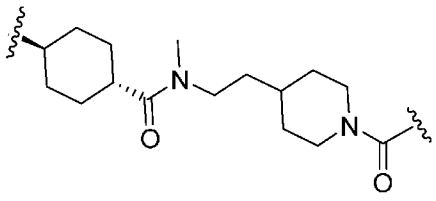
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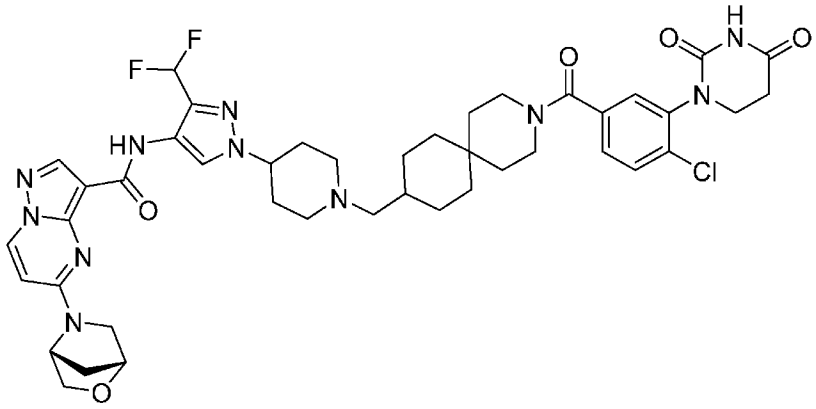
[0104] In certain embodiments of the present invention, the pharmaceutically acceptable salt may be a formate.

[0105] Preferably, in certain embodiments of the present invention, the compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is: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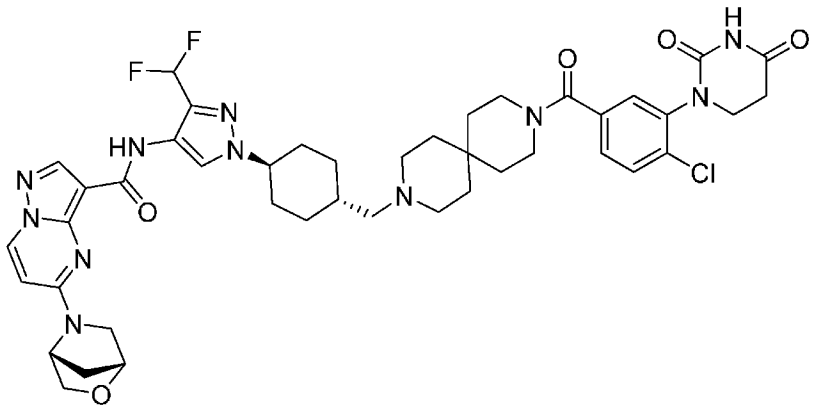

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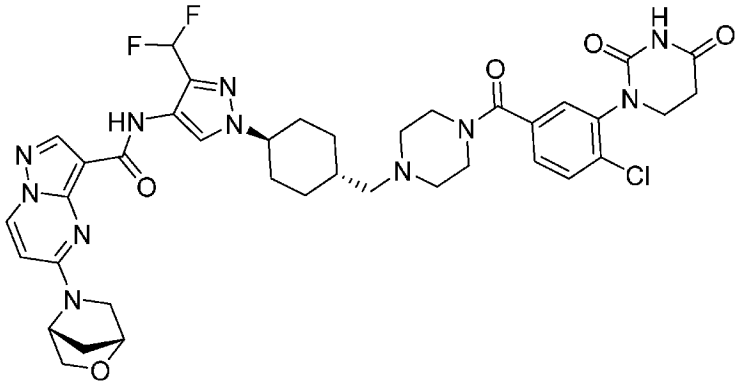

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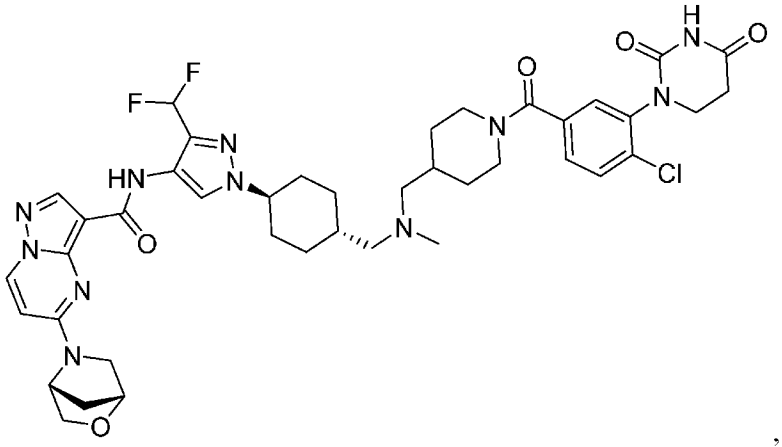

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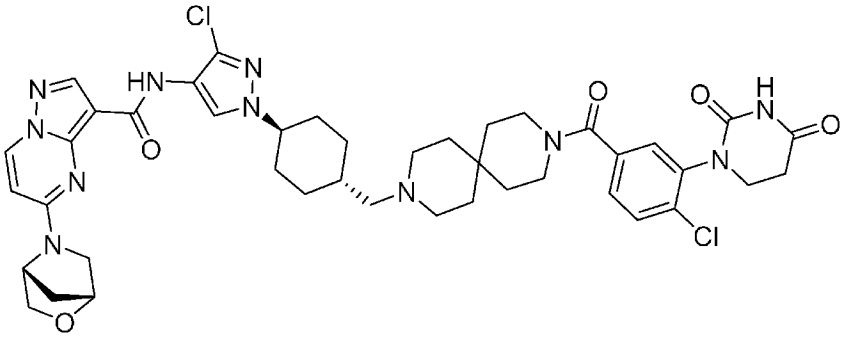

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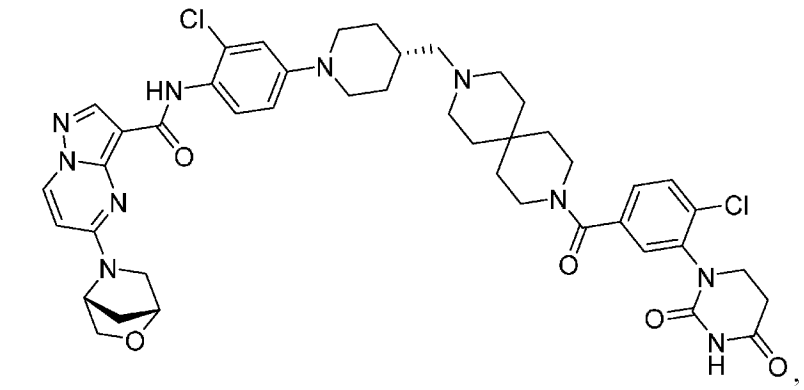

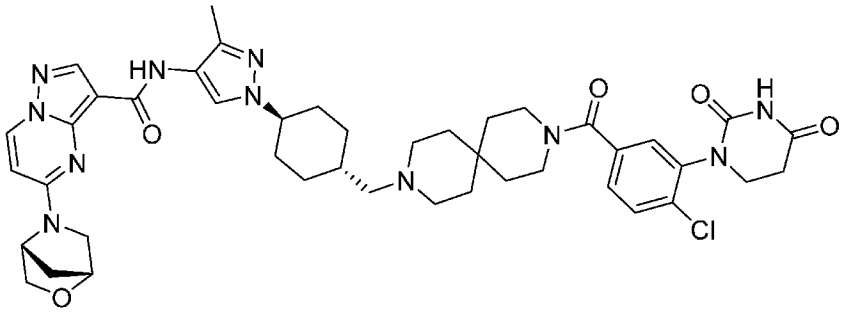

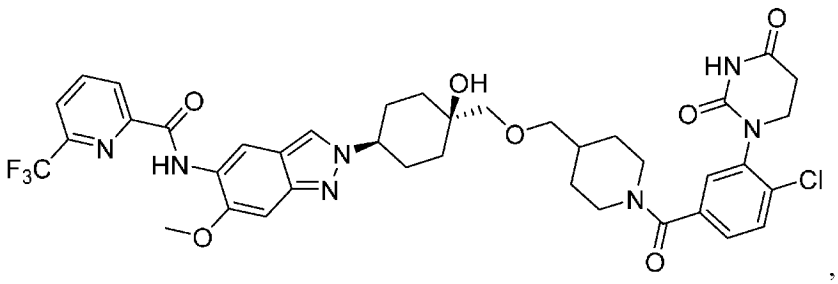

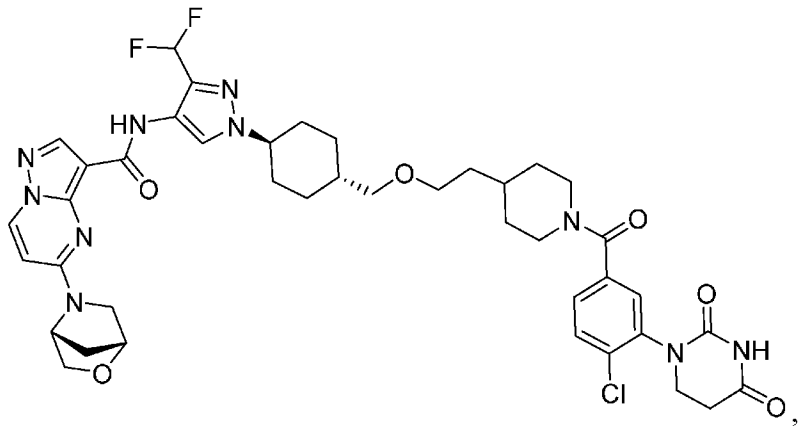

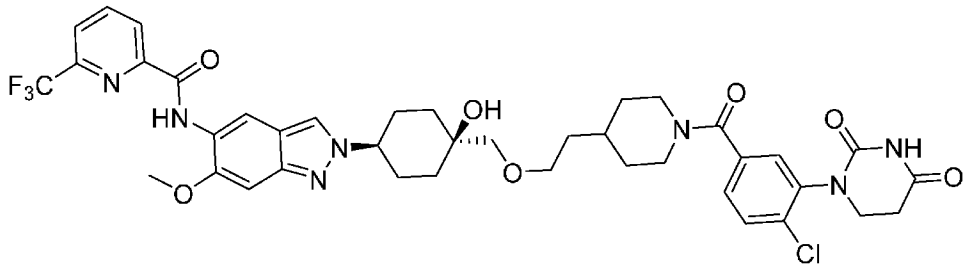

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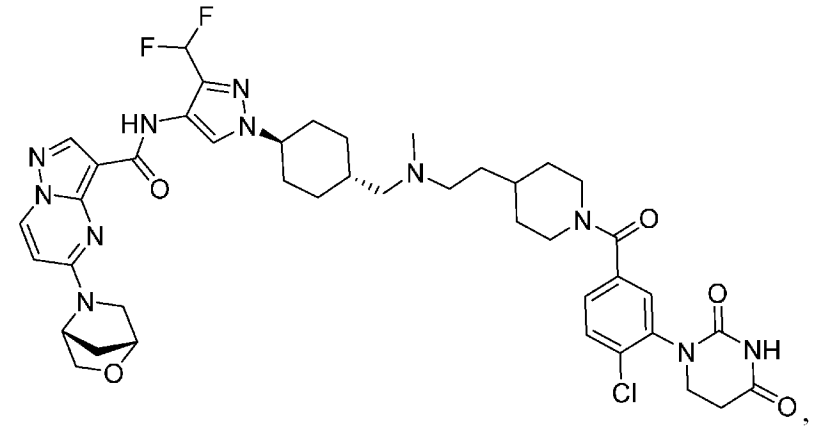

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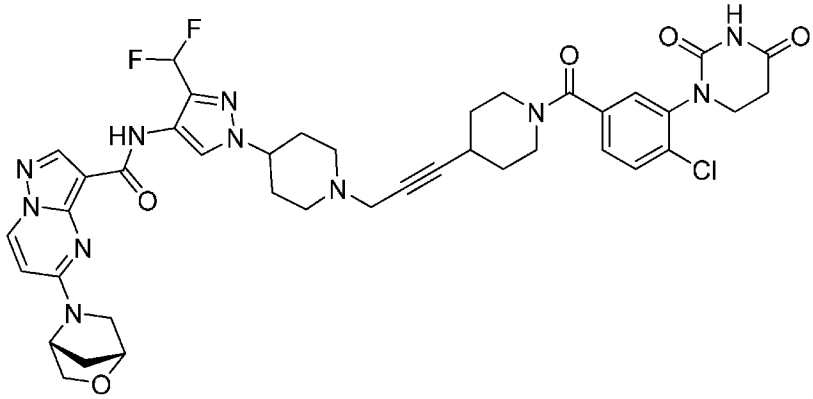

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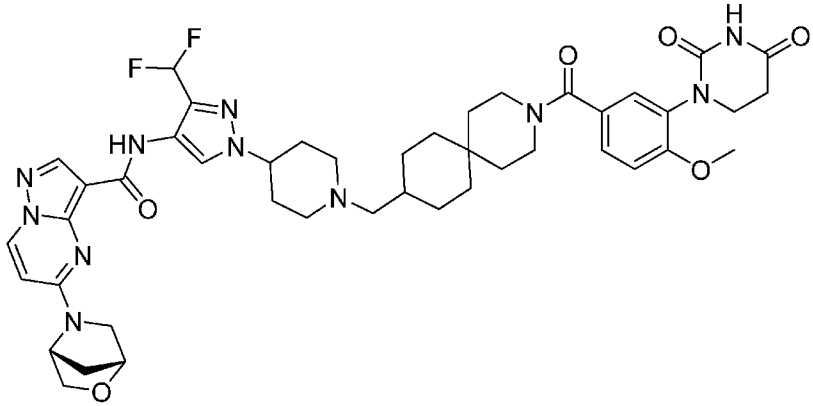

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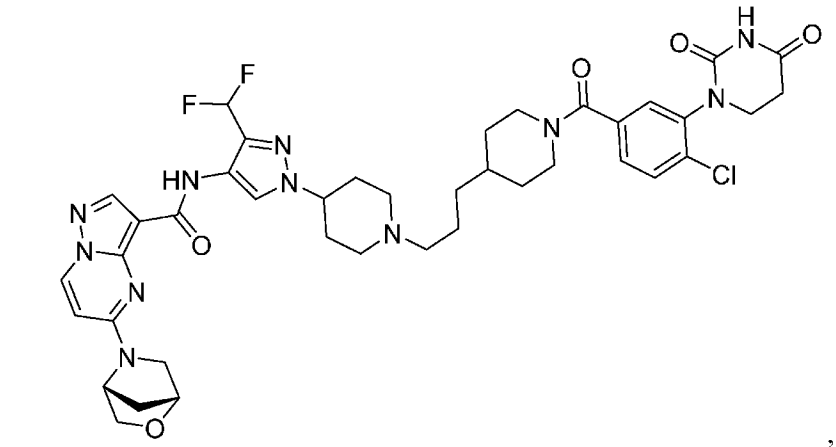

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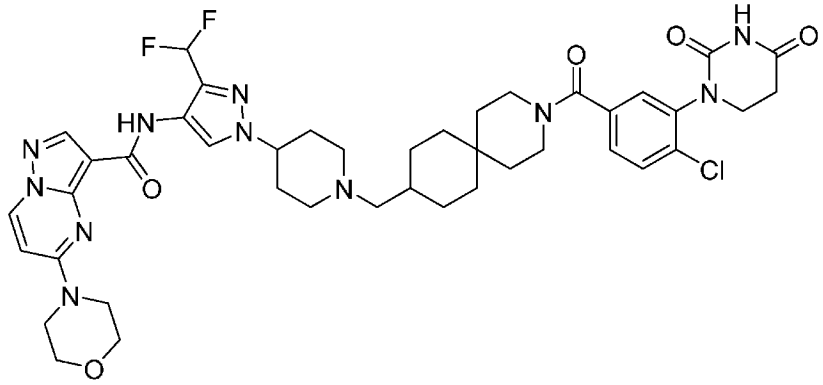

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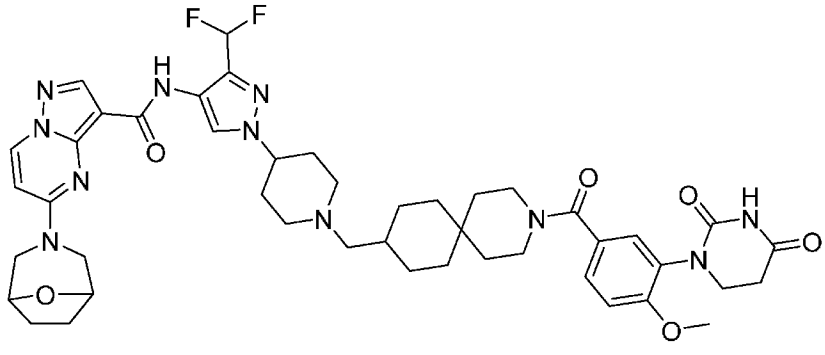

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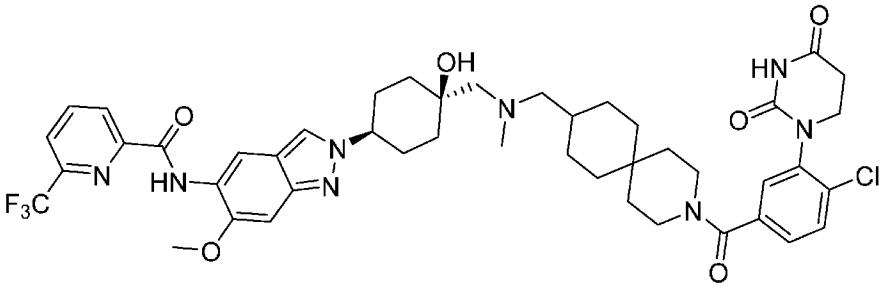

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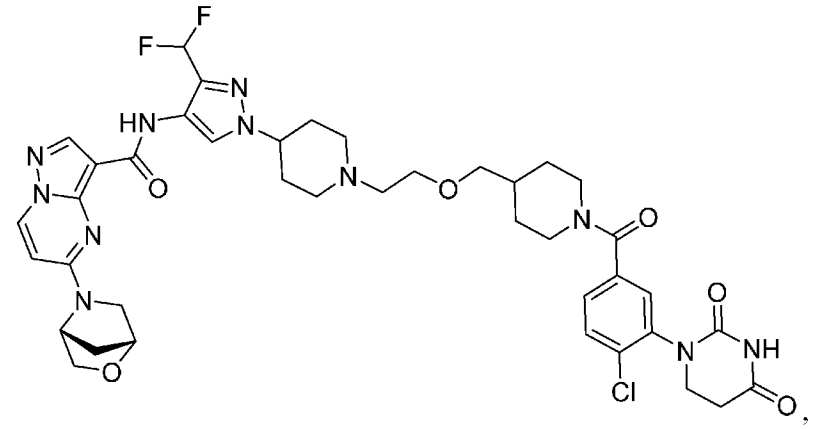

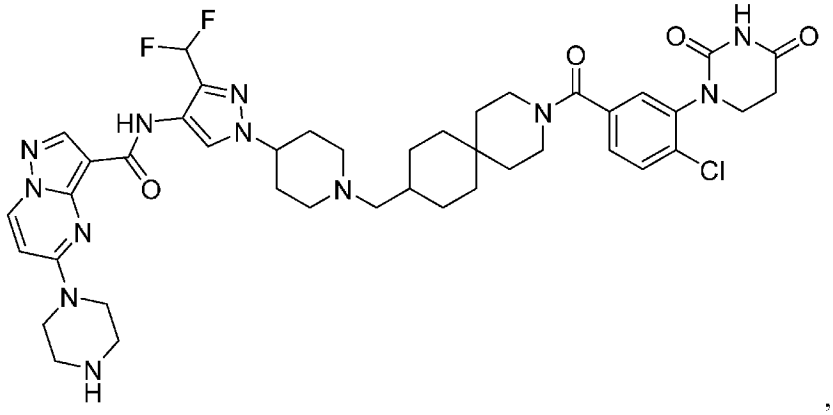

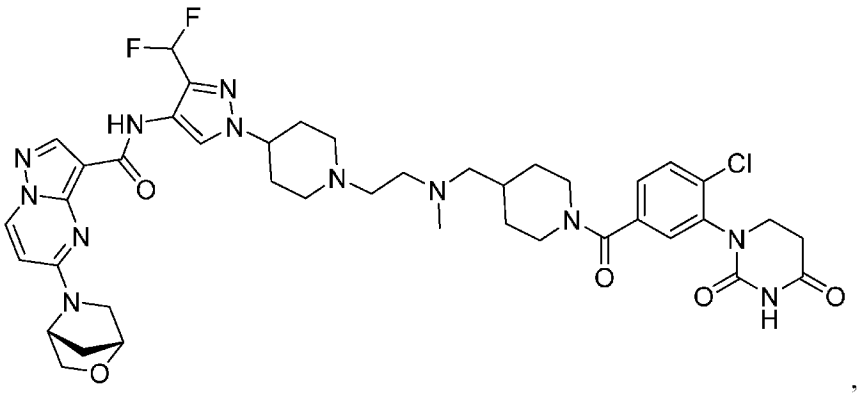

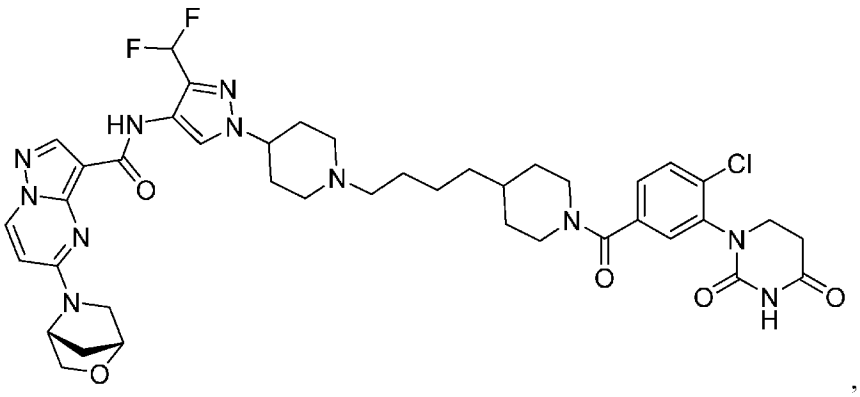

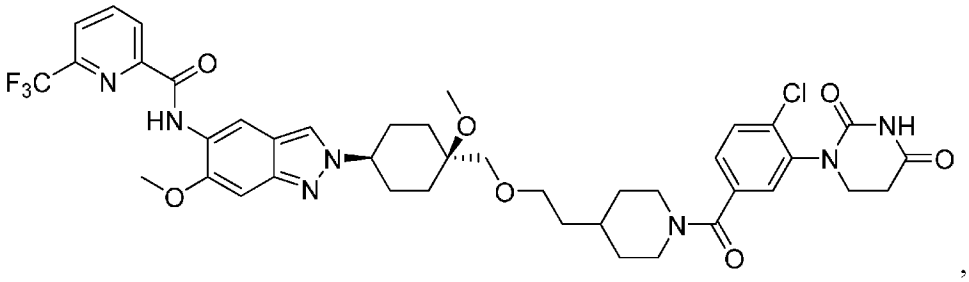

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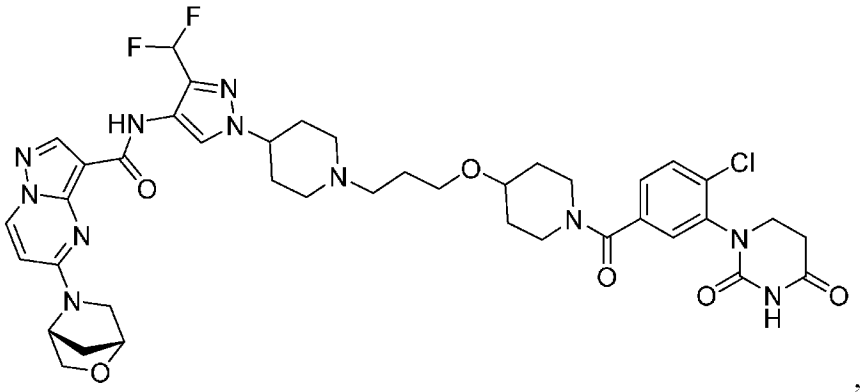

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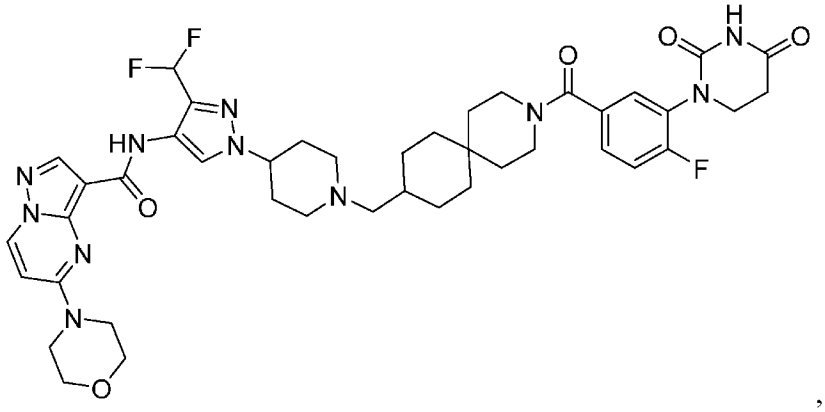

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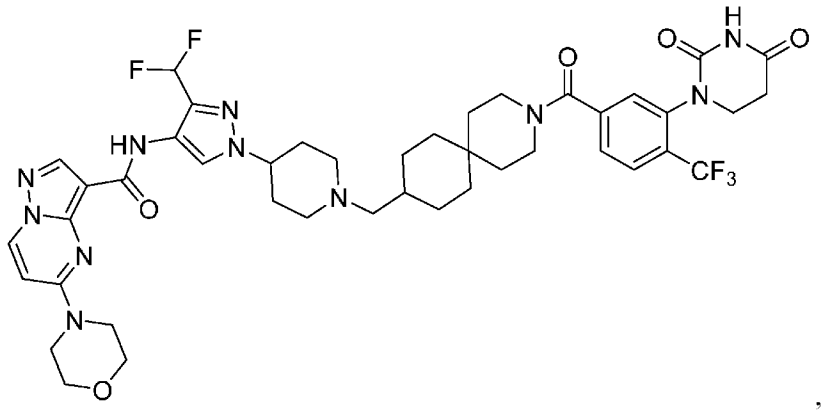

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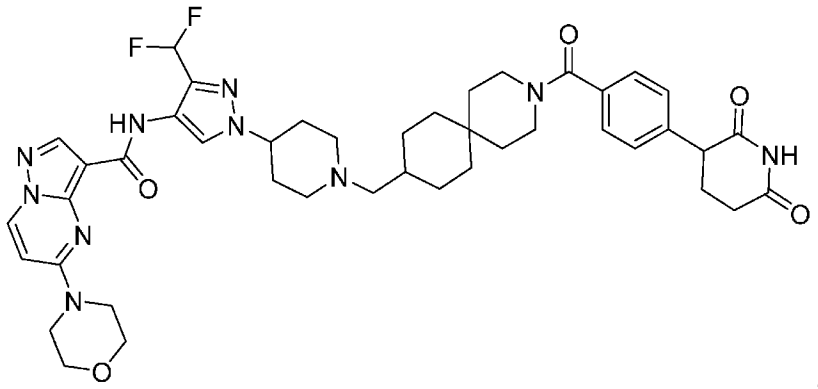

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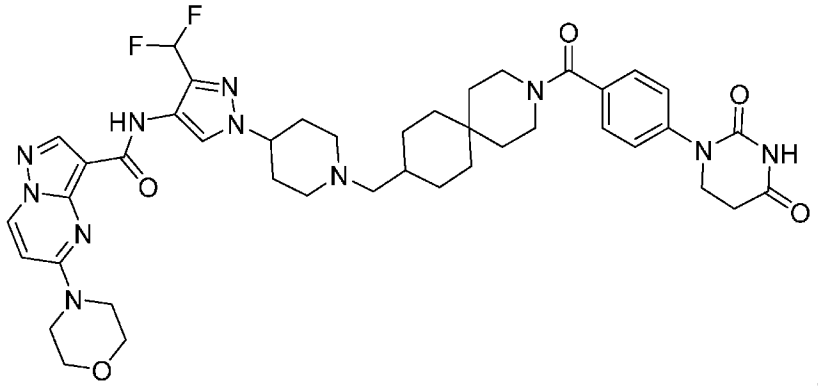

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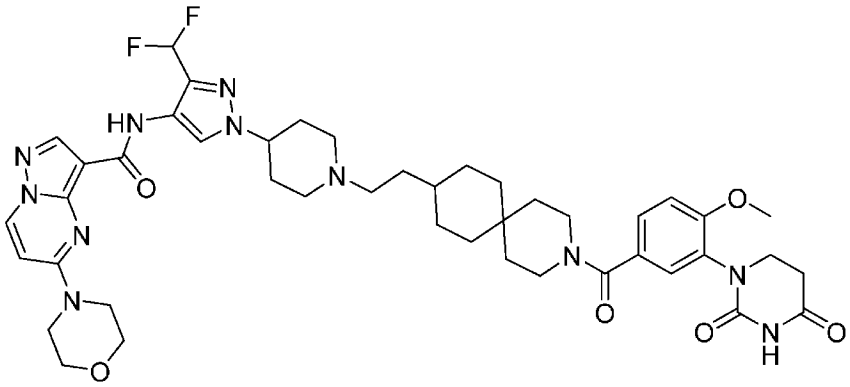

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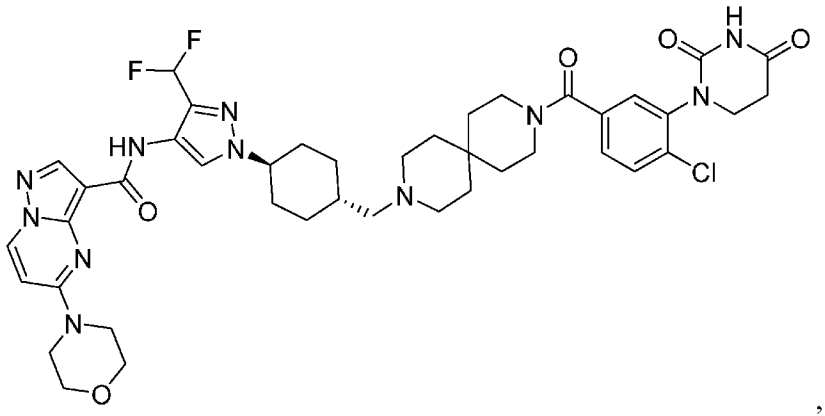

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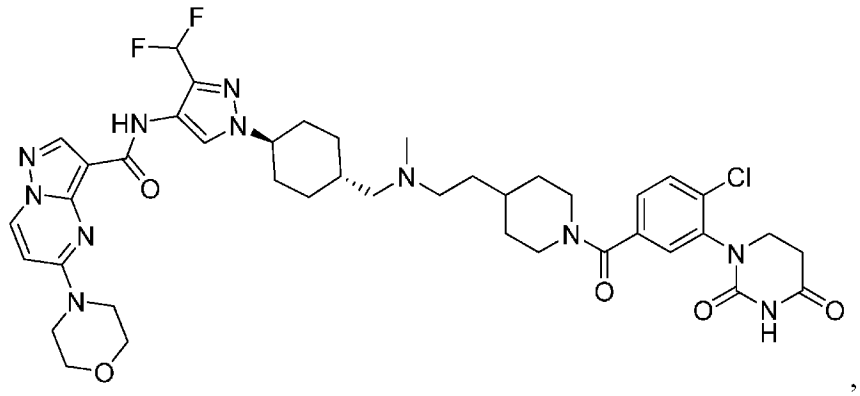

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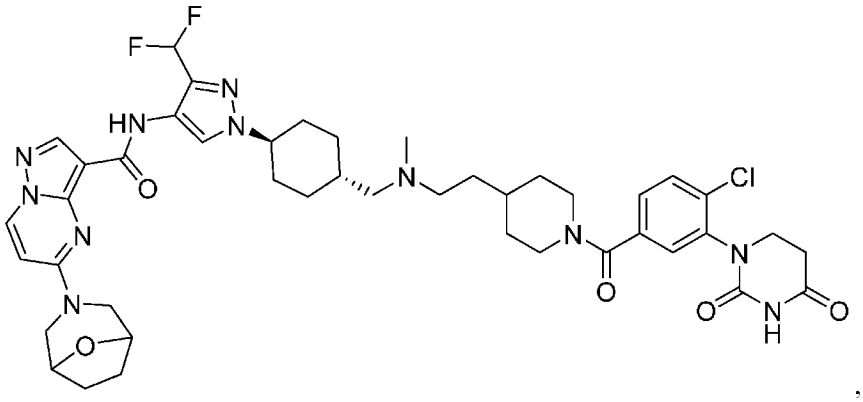

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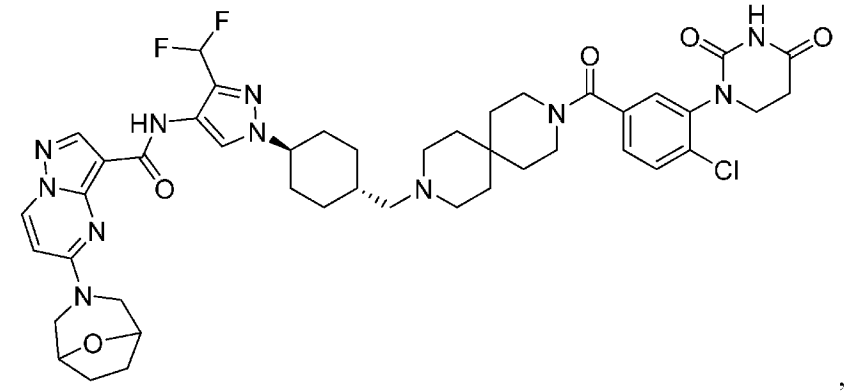

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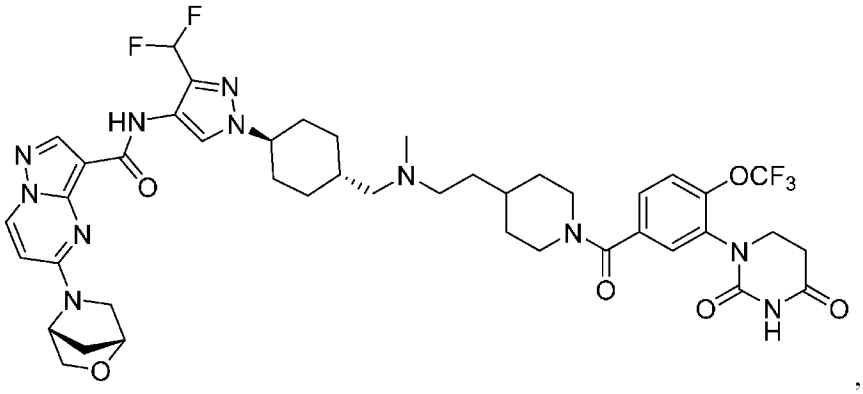

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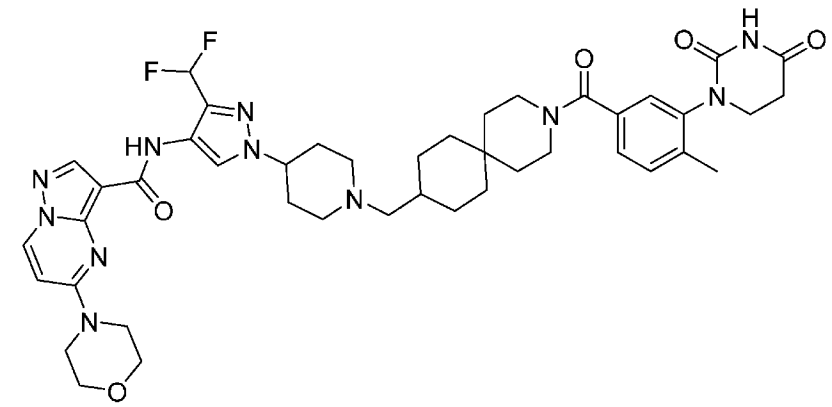

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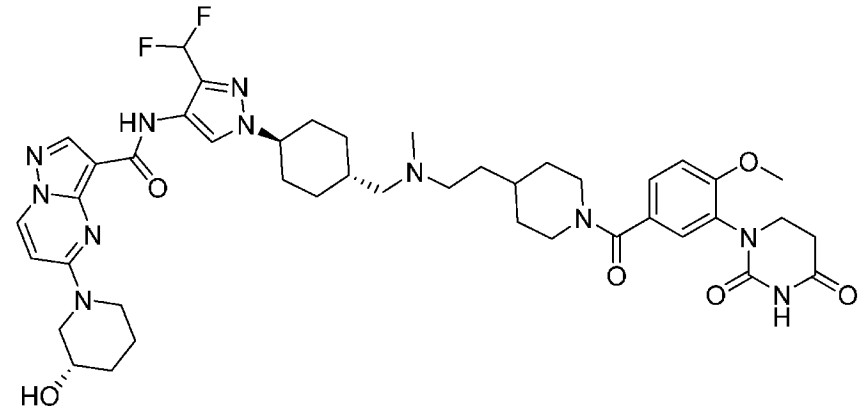

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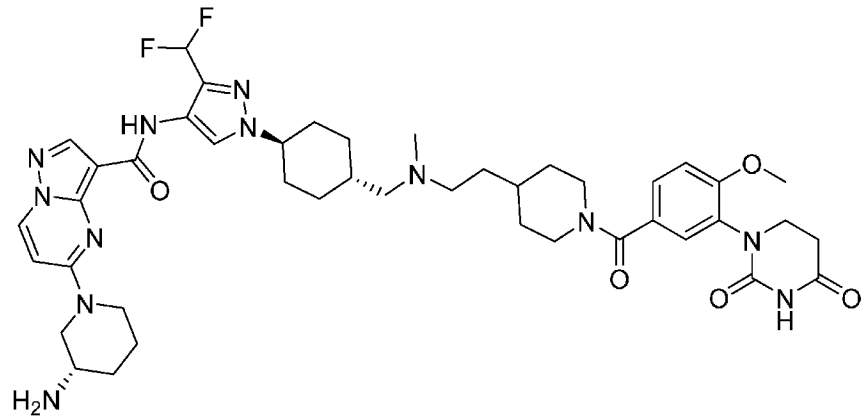

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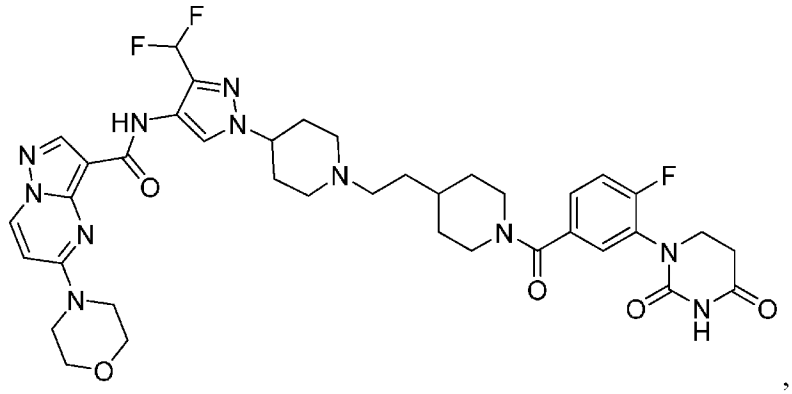

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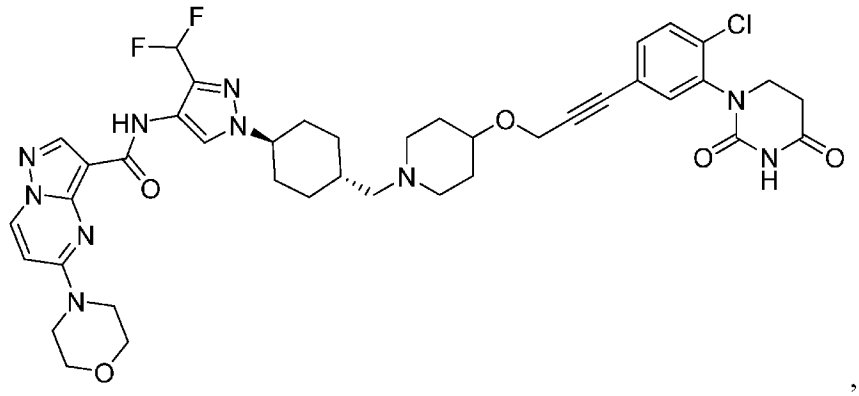

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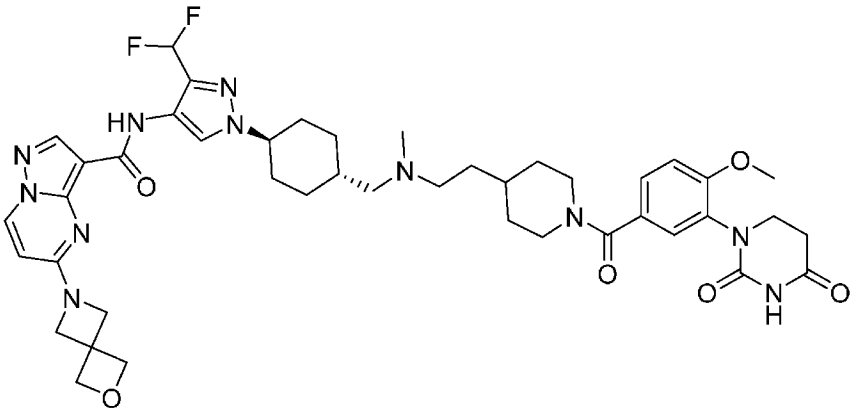

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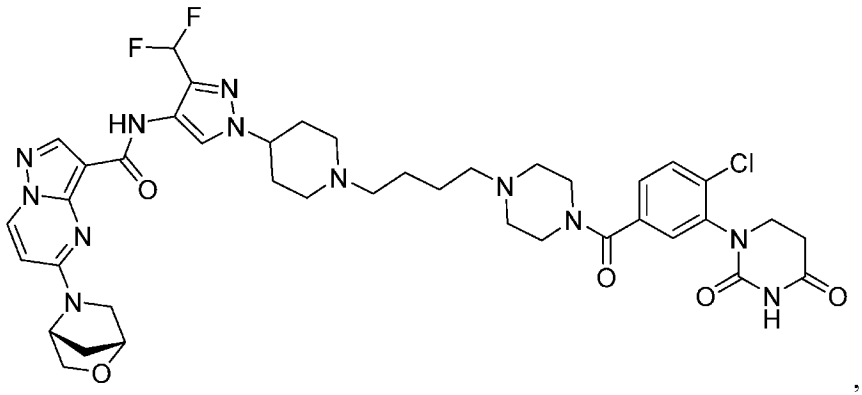

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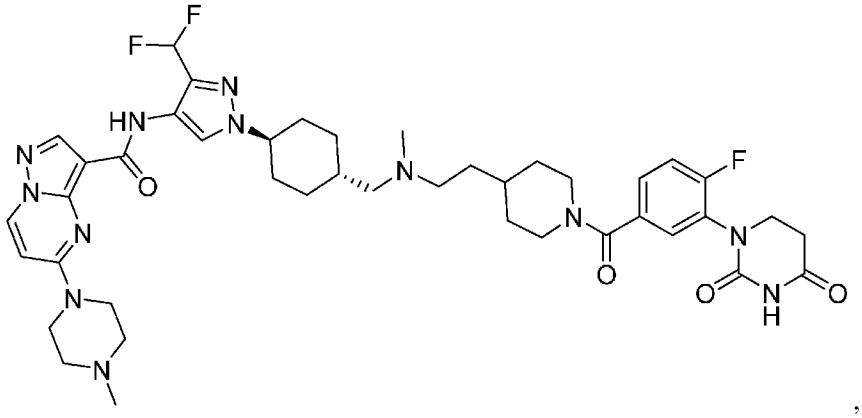

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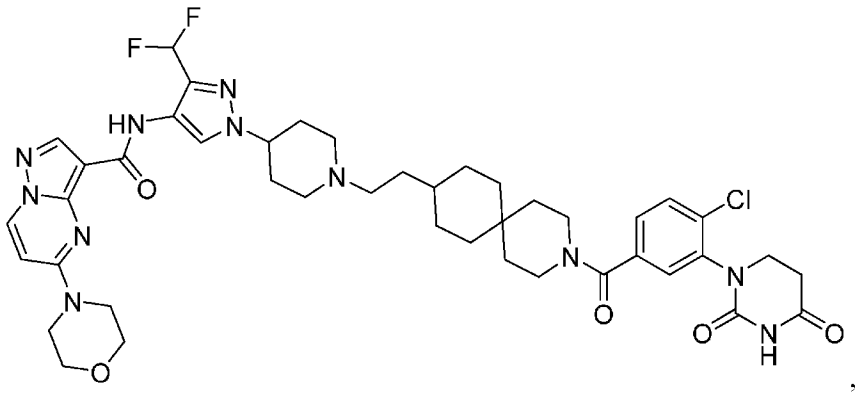

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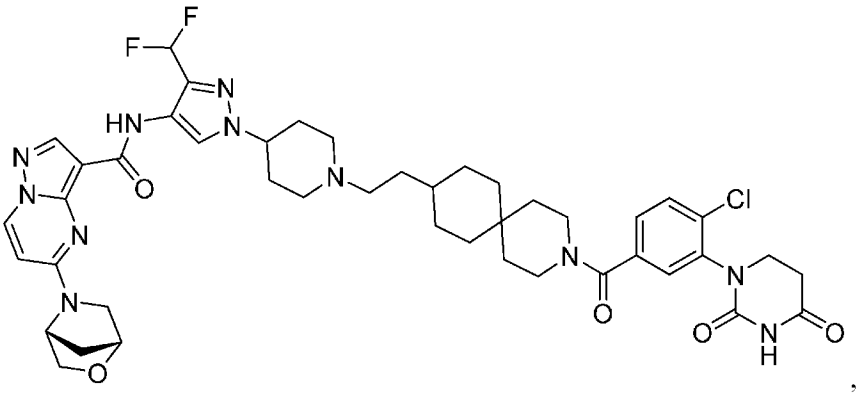

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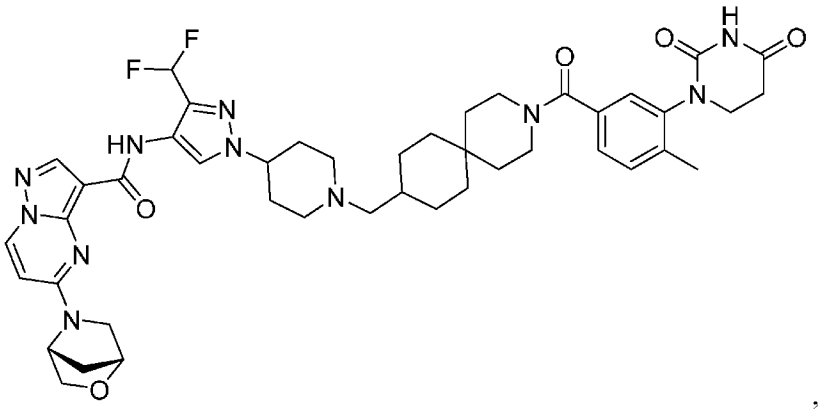

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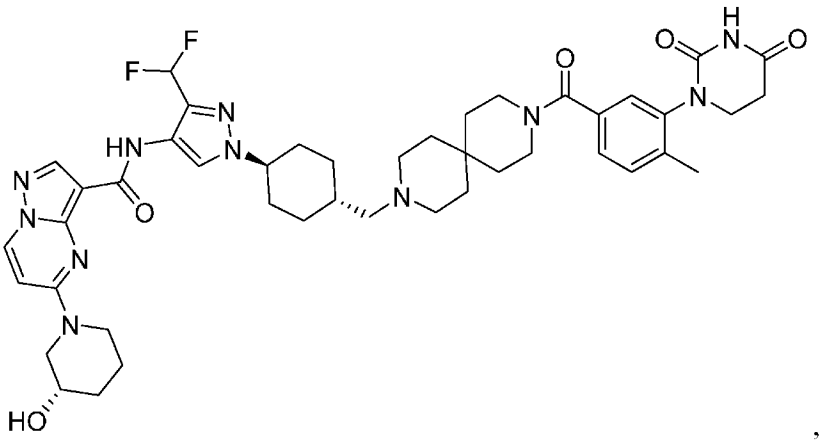

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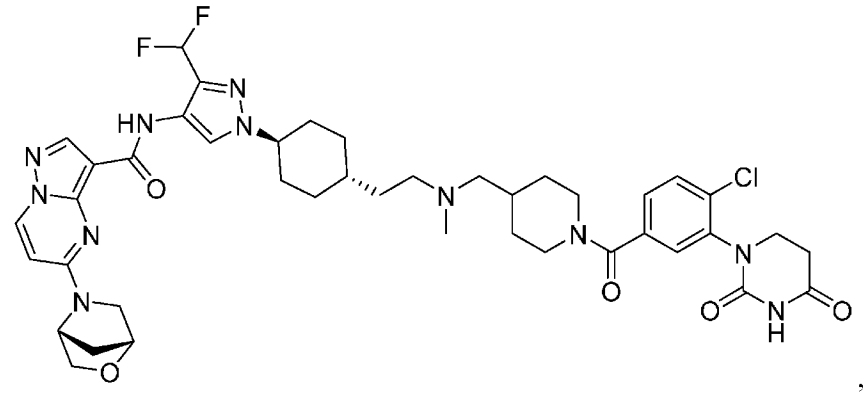

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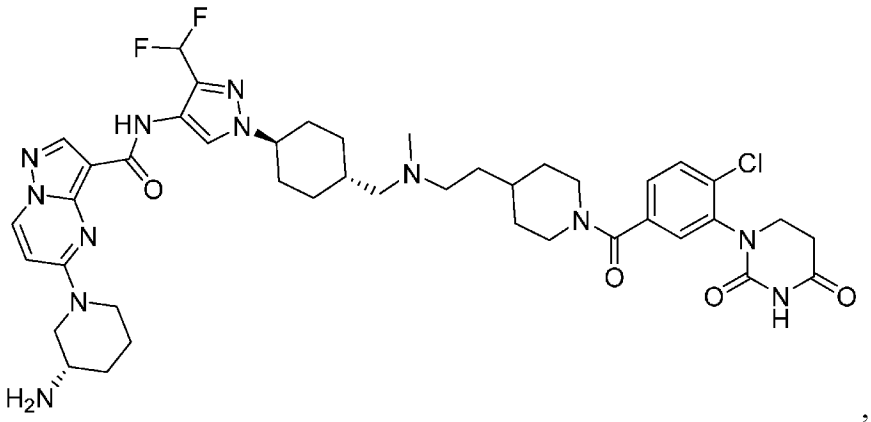

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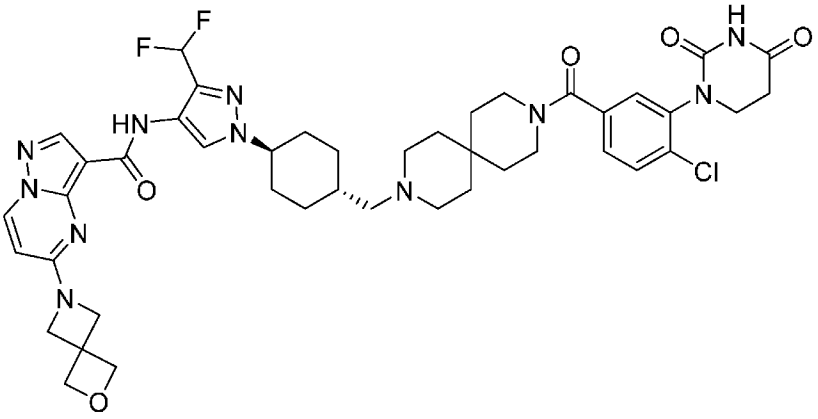

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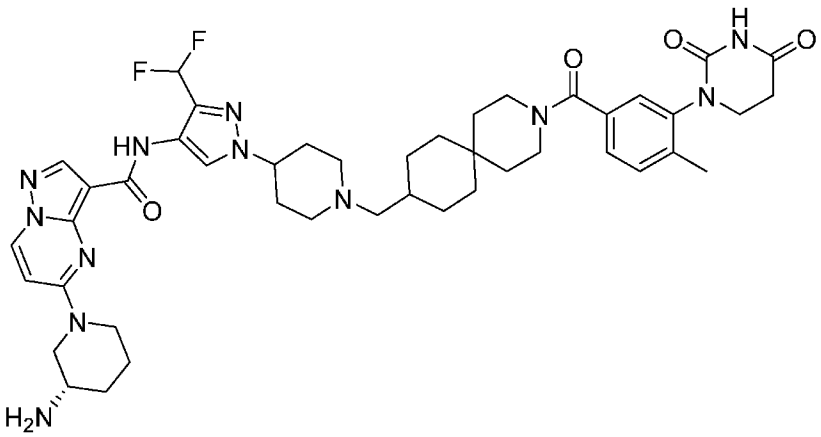

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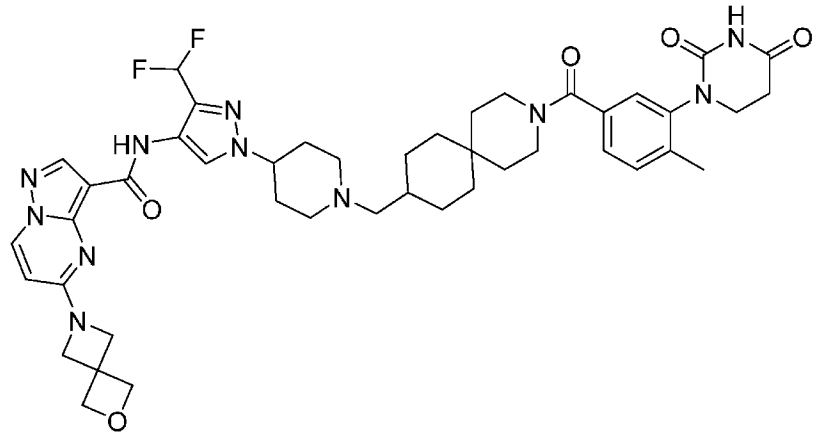

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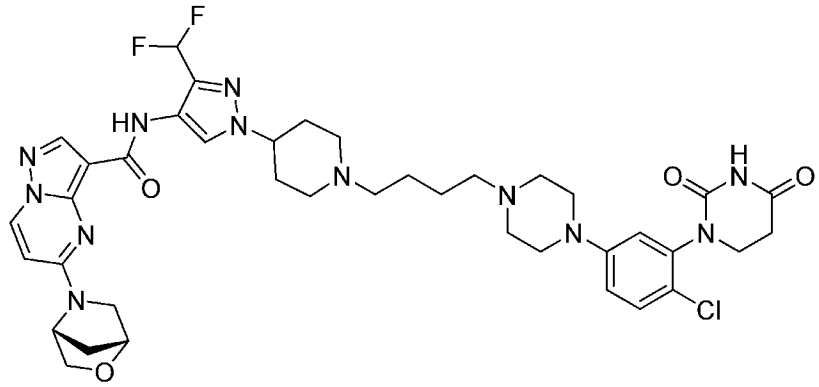

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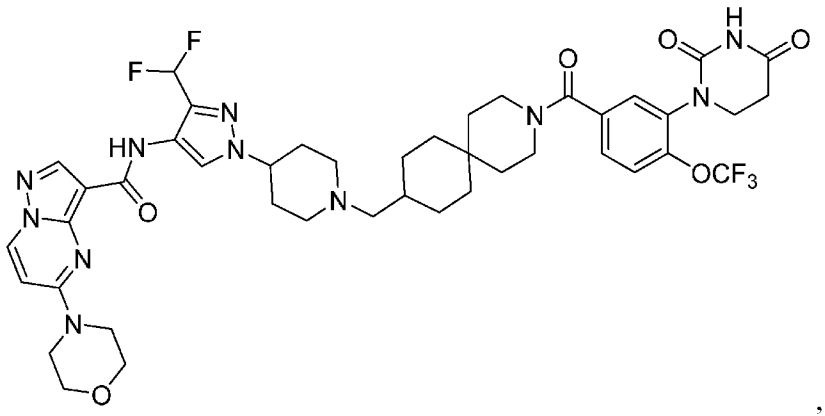

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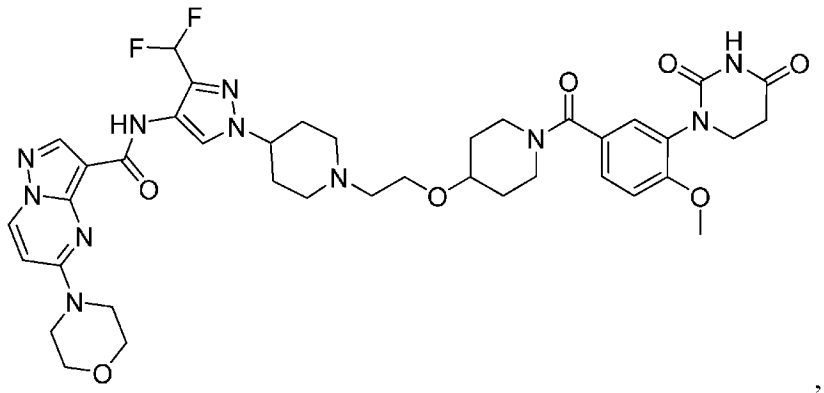

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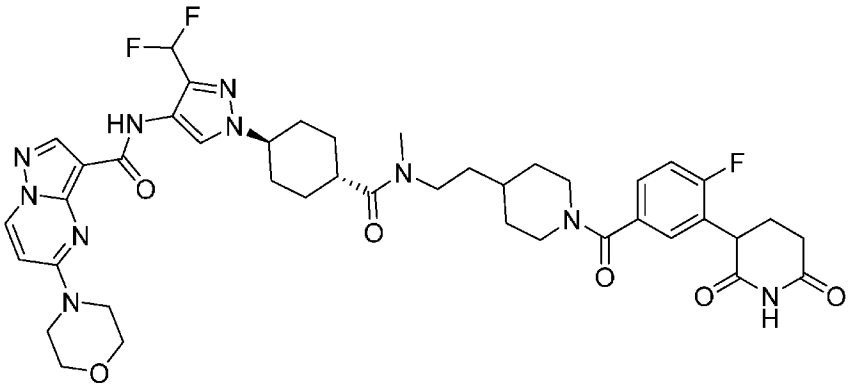

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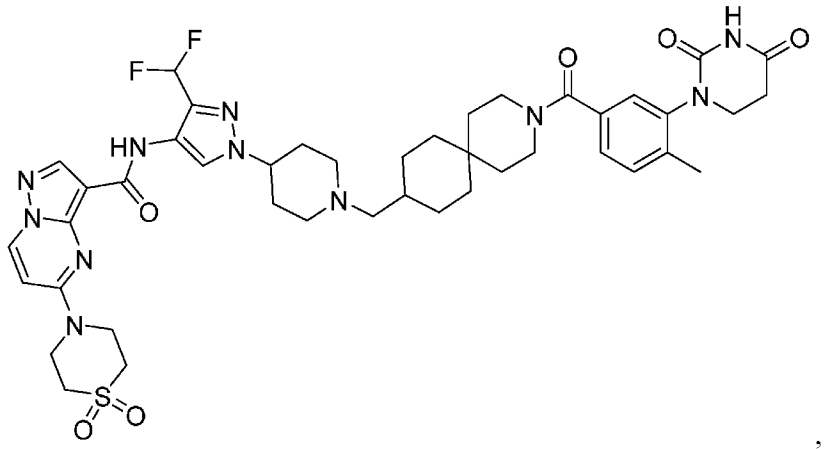

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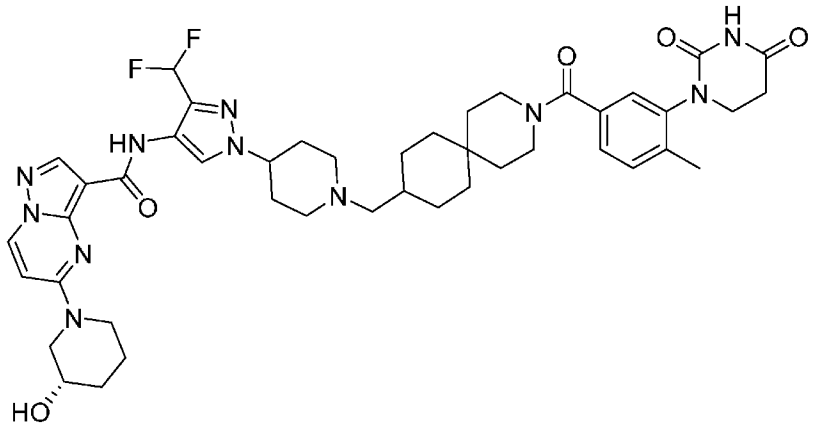

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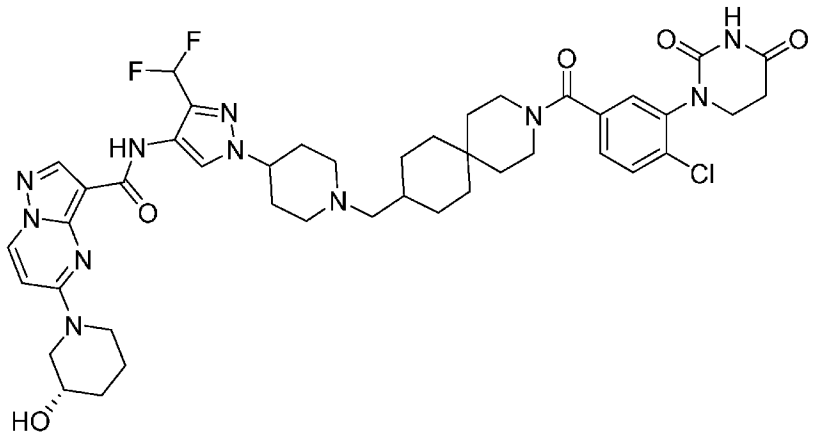

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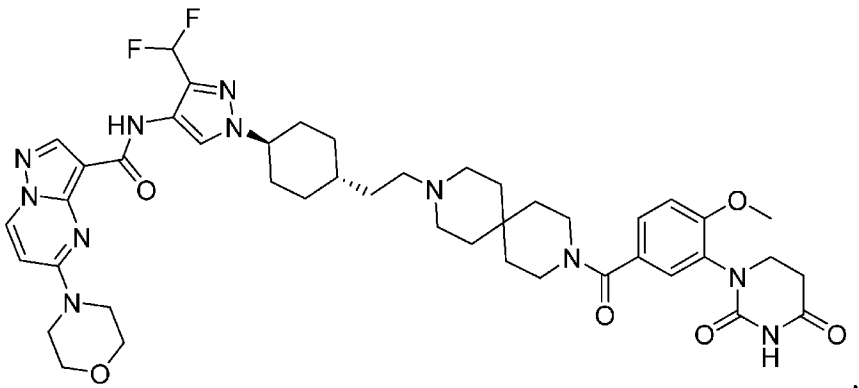

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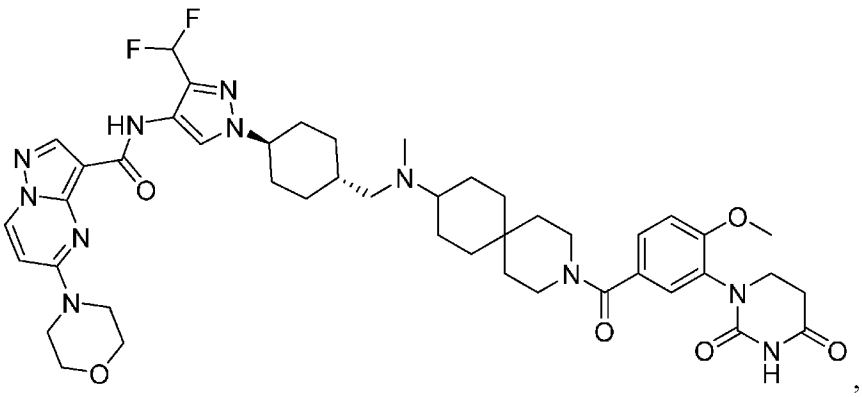

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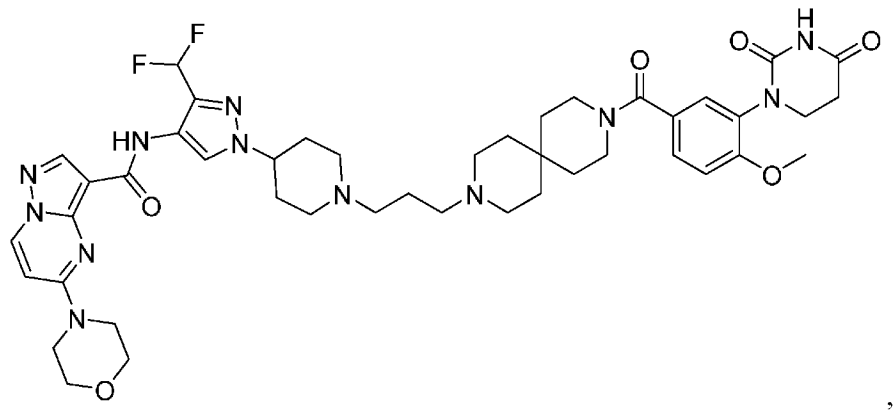

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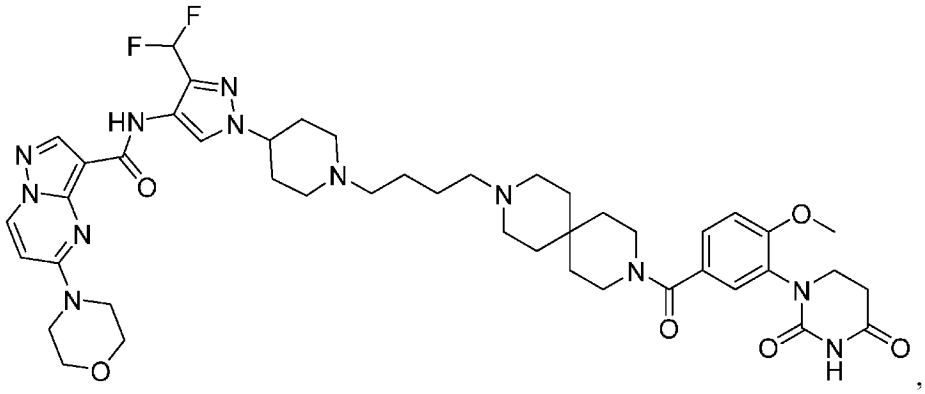

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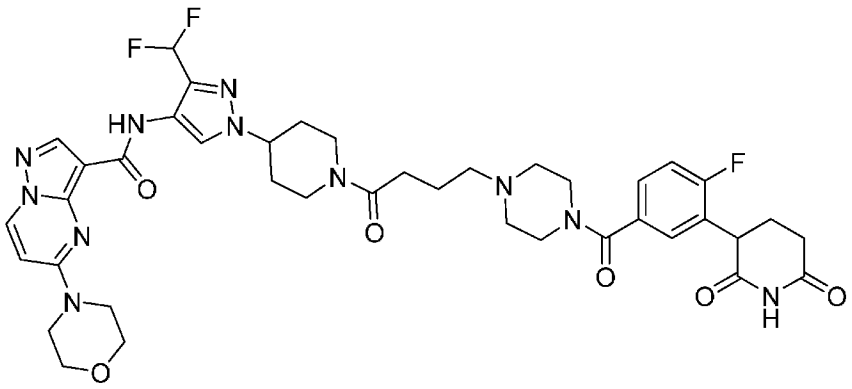

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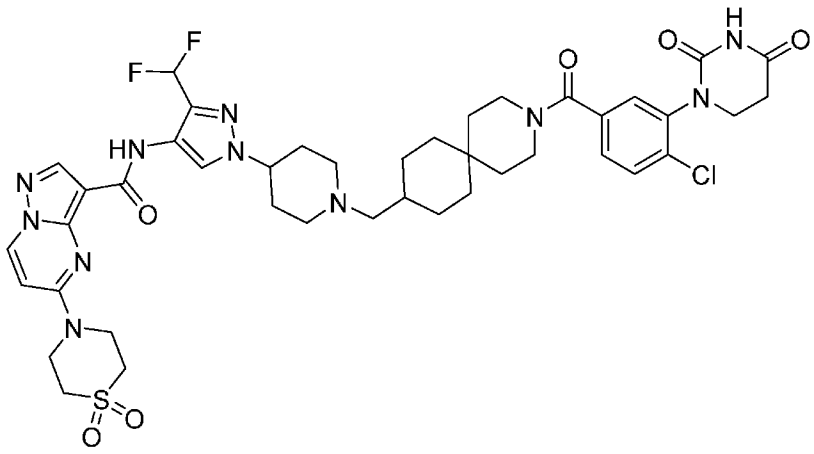

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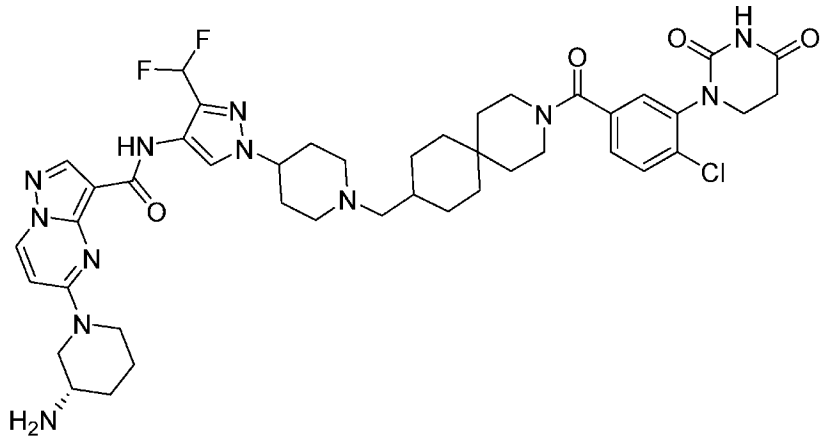

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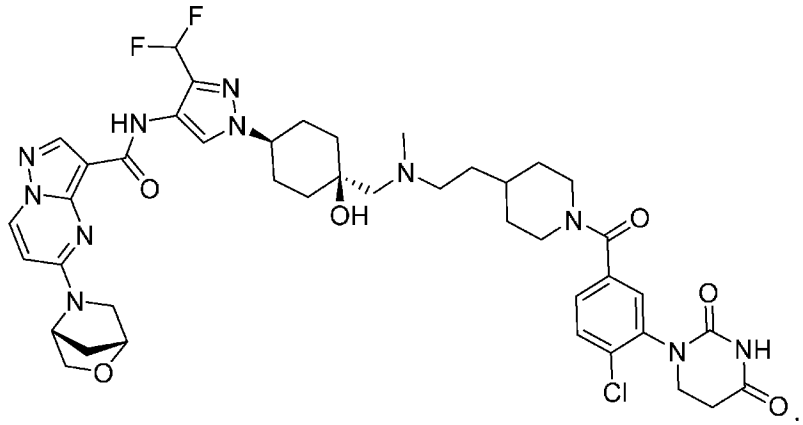
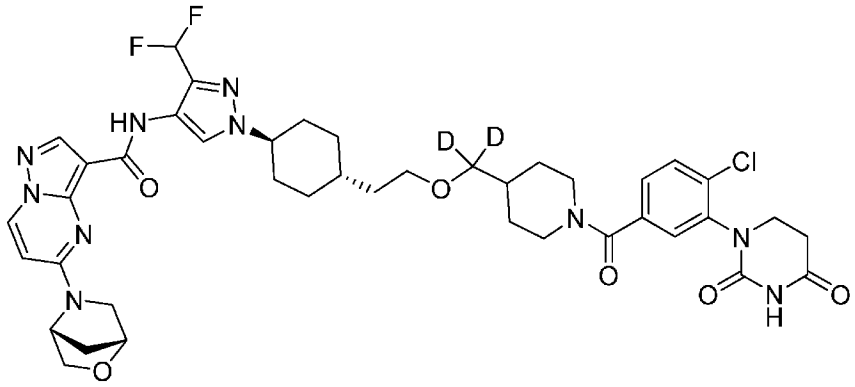


[0106] Preferably, in certain embodiments of the present invention, the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is



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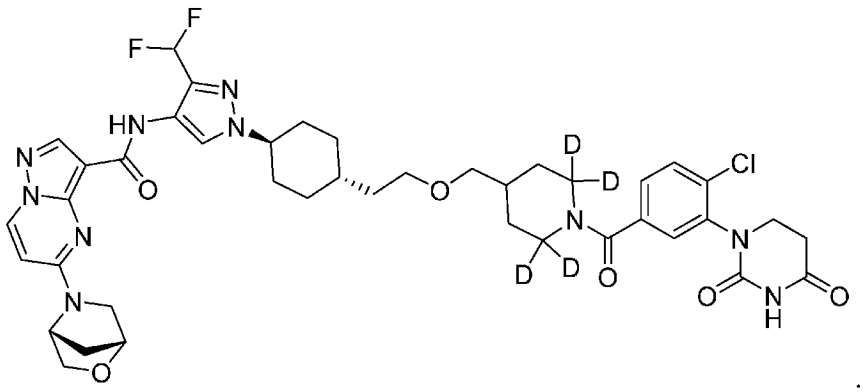
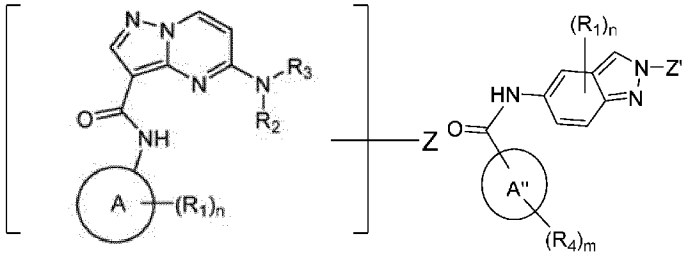
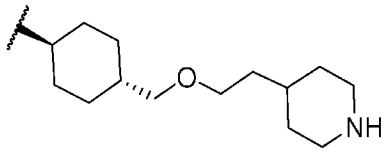


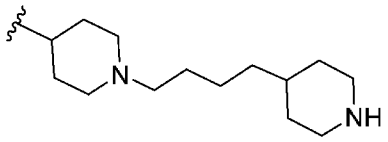
[0107] The present invention further discloses a compound of formula VII or VIII, a stereoisomer, enantiomer, diastereomer or deuteride thereof or a salt thereof:

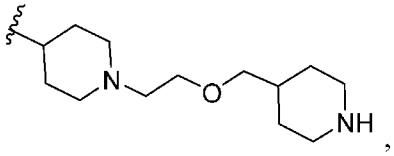


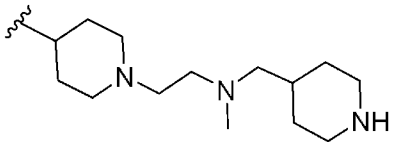
VII VIII

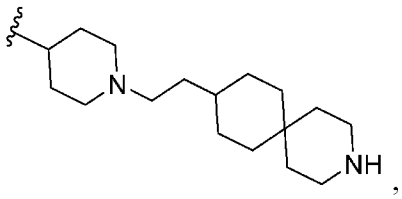
Z is

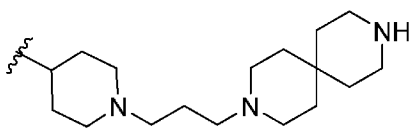


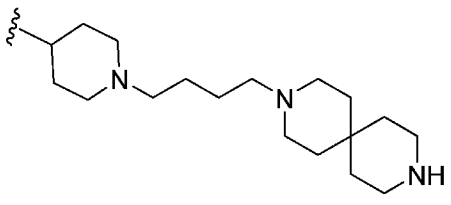


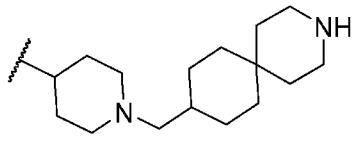
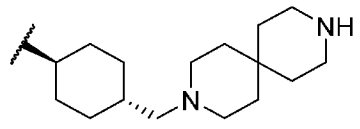
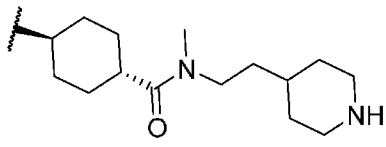
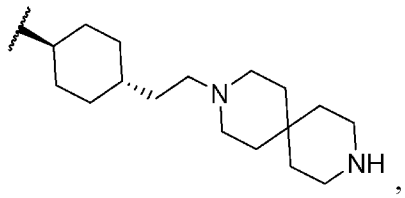
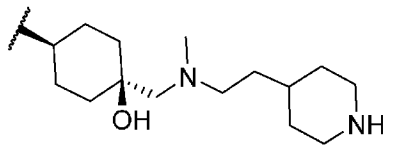
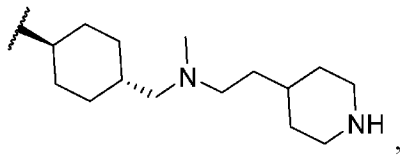
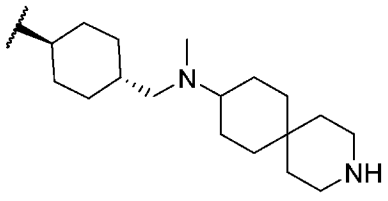
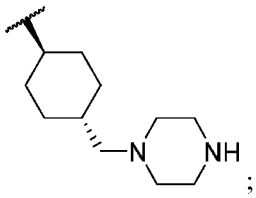










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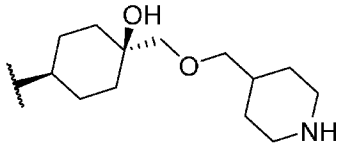
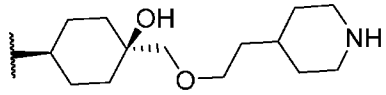
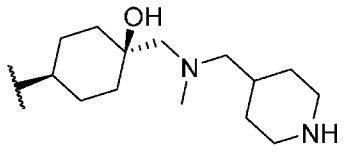
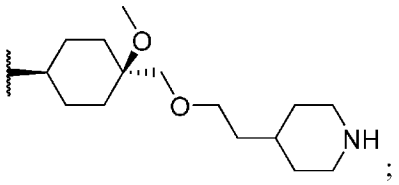
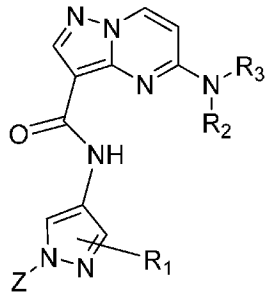





wherein m, n, A, A', R_1, R_2, R_3 and R_4 are as previously described.

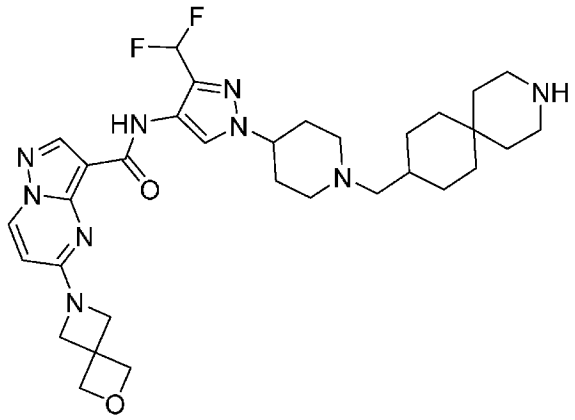
[0108] In certain embodiments of the present invention, the compound of formula VII is a compound of



formula VII-1 **VII-1** .

[0109] In certain embodiments of the present invention,

[0110] The compound of formula VII is any of the following compounds: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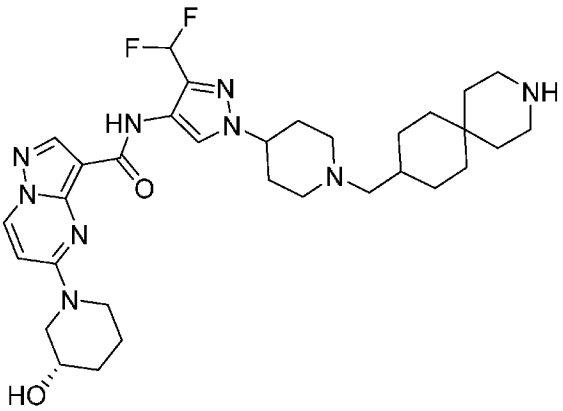
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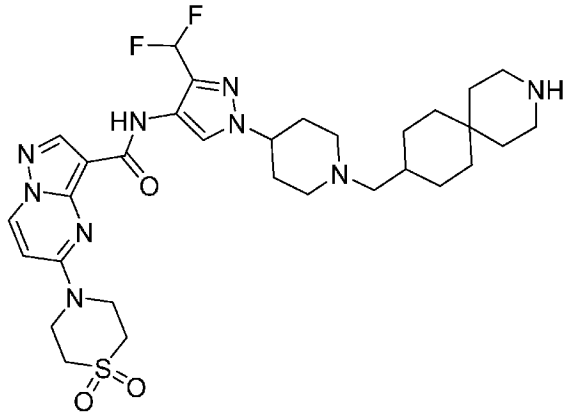
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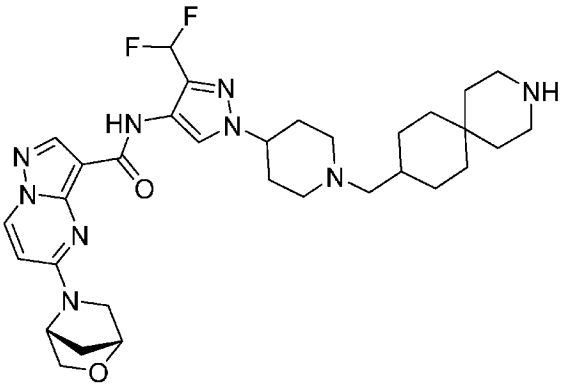
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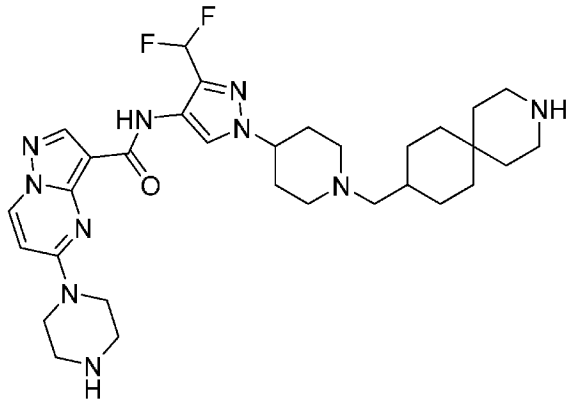
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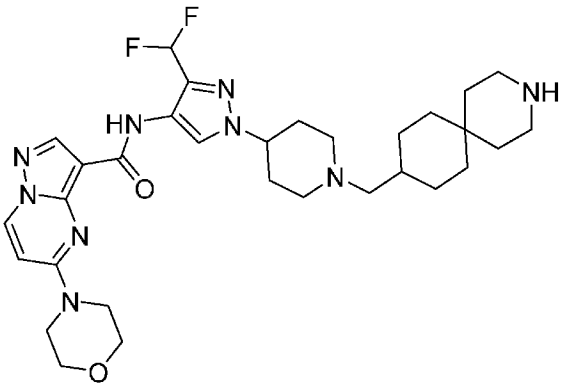
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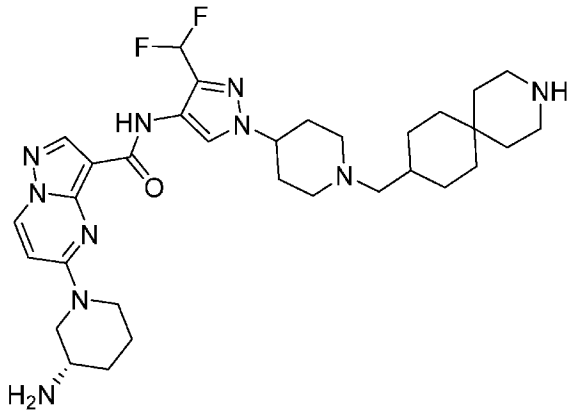

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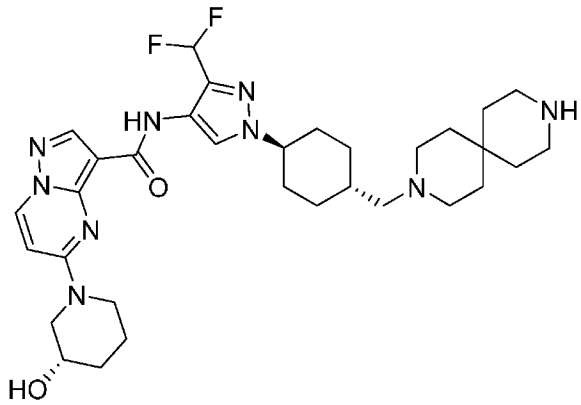

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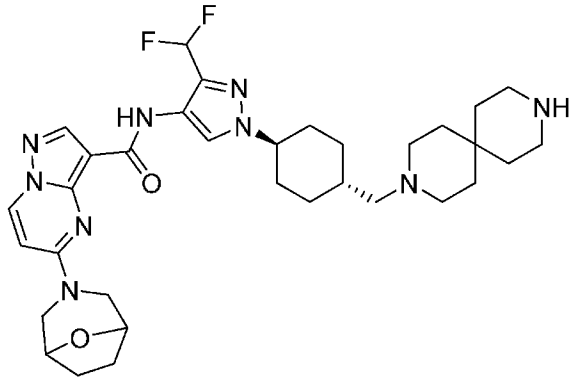

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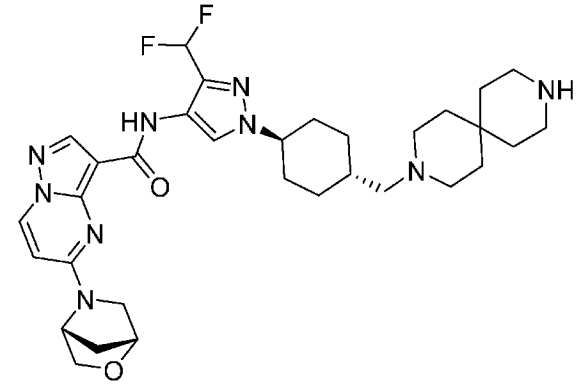

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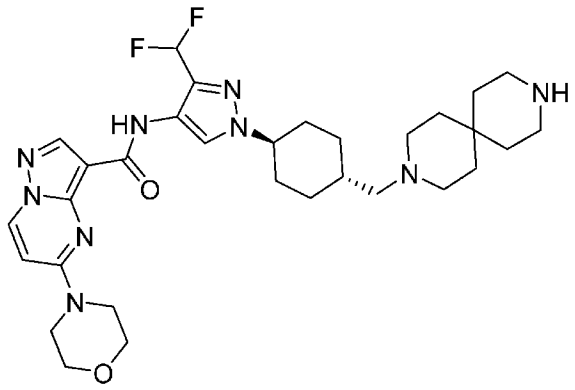

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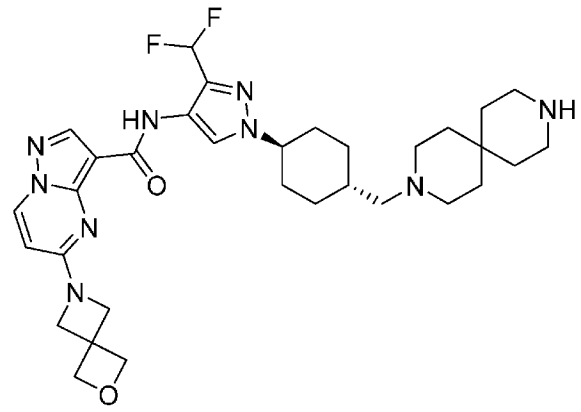

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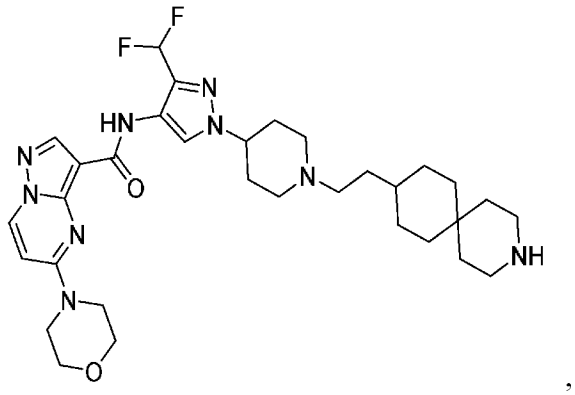

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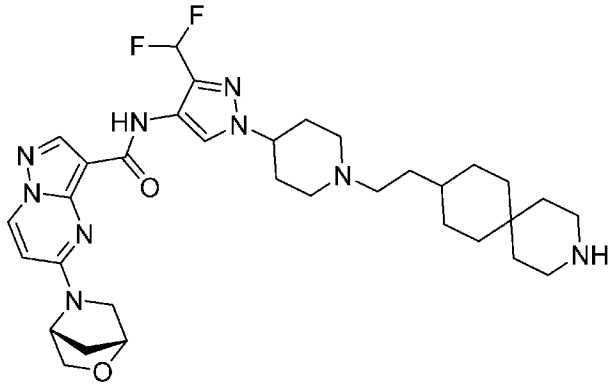

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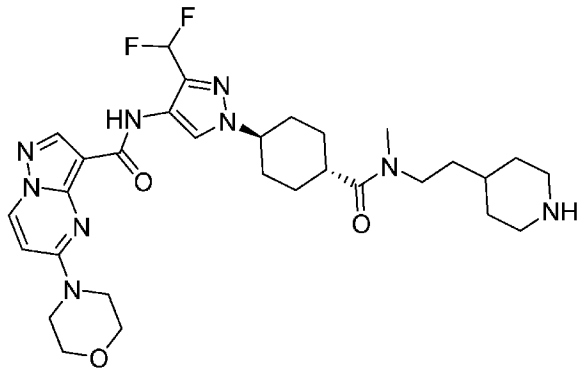

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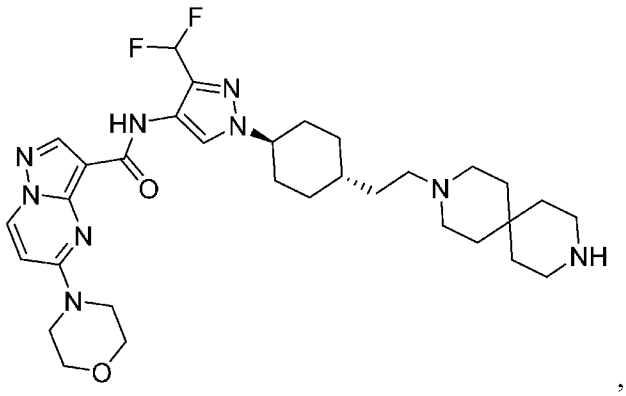

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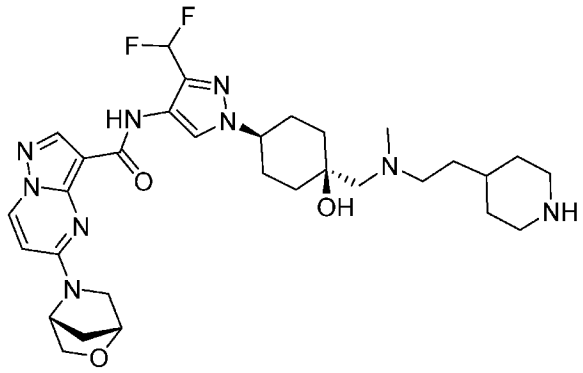

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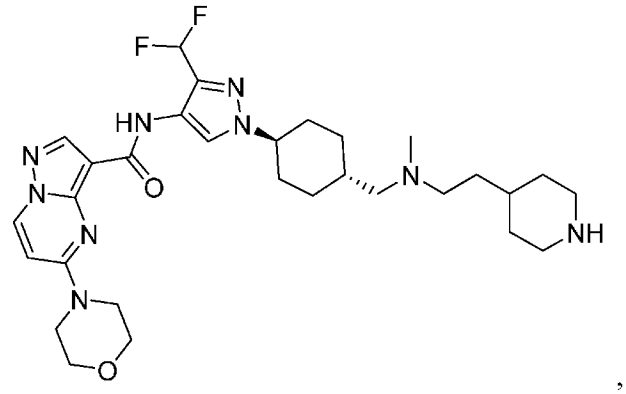

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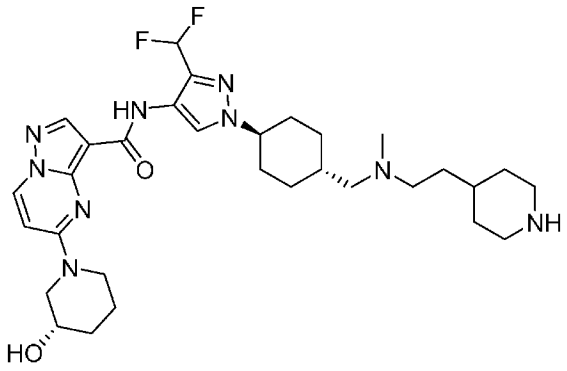

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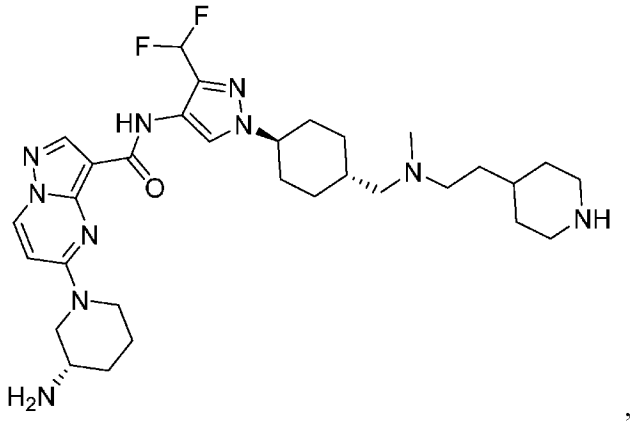

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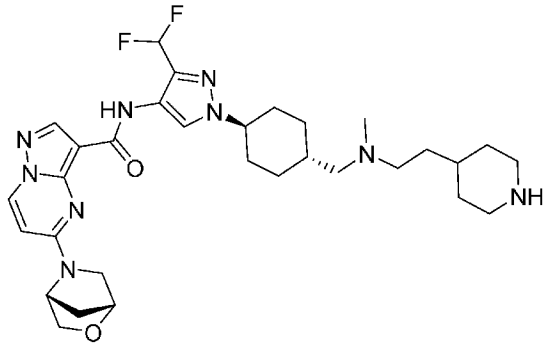

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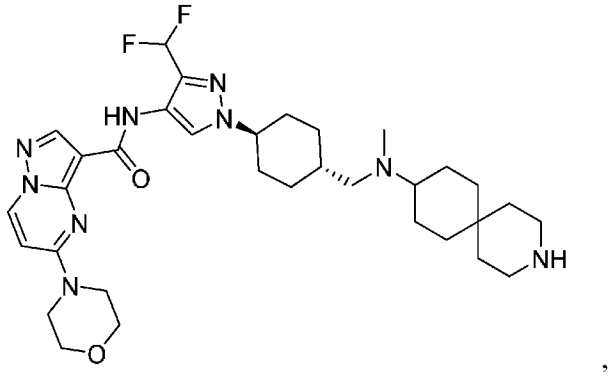

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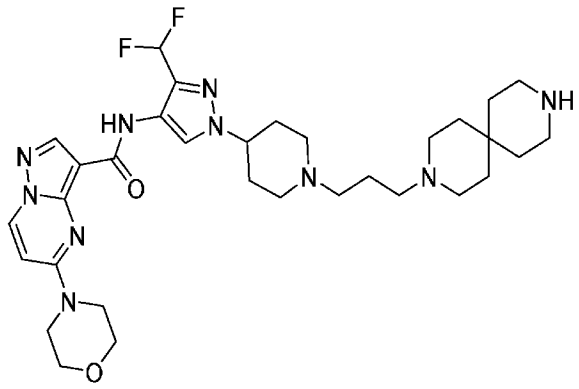
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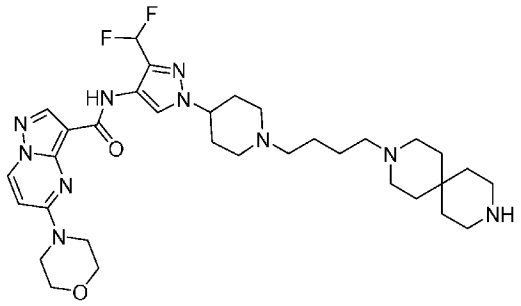
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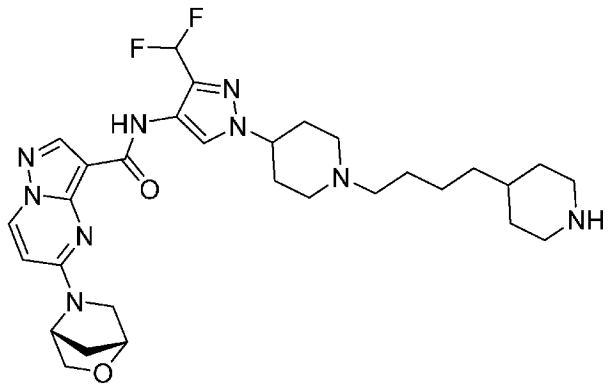
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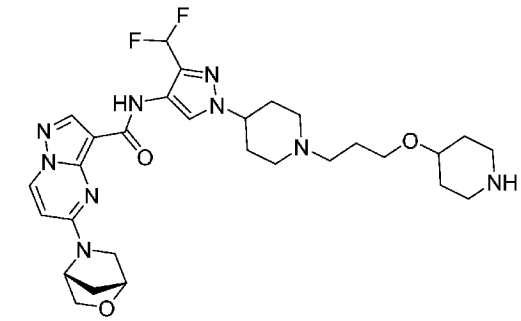
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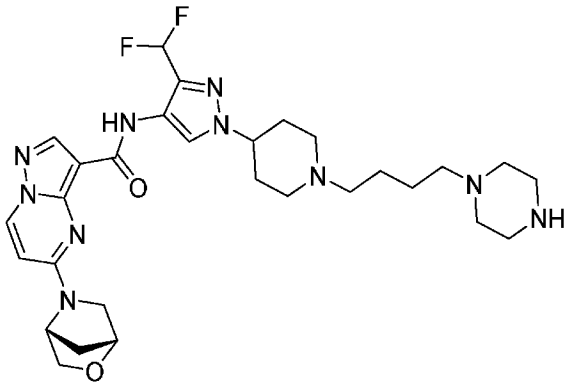
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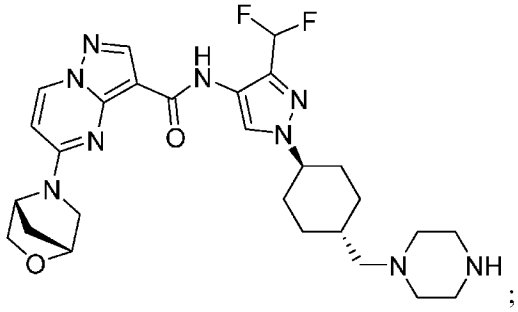
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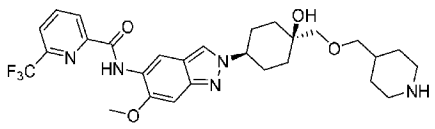
and/or, the compound of formula VIII is any of the following compounds: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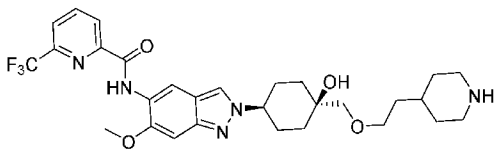
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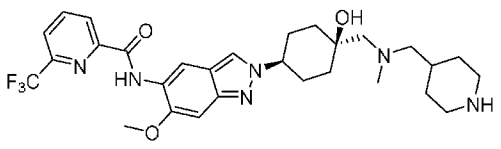
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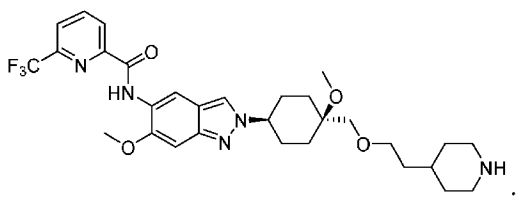
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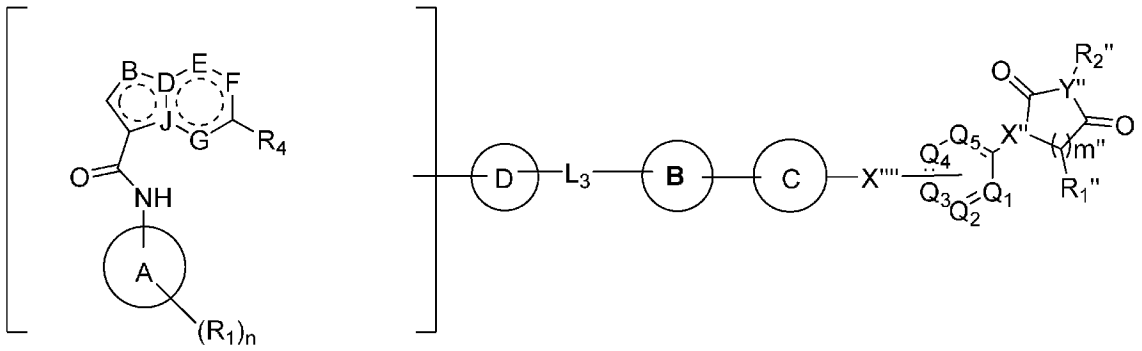
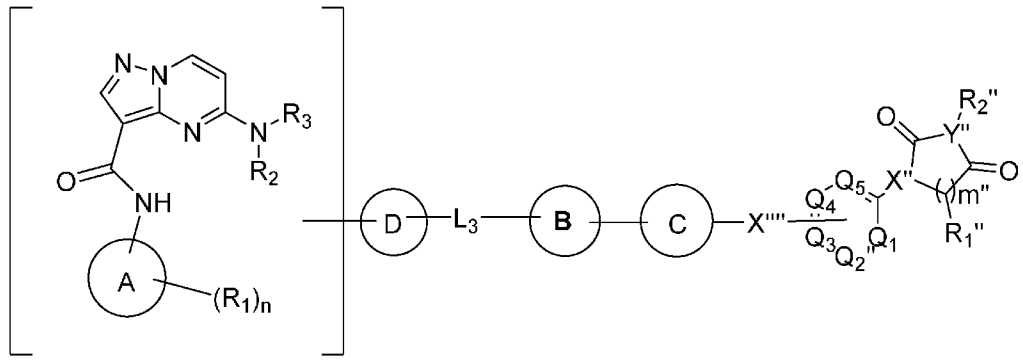
[0111] Preferably, in certain embodiments of the present invention, the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is a compound of formula II, and/or a stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or a pharmaceutically acceptable salt thereof,



II

wherein the R_1, n, R_4, B, D, E, F, G, J and ring A are as defined and described in PTM-2'; the Q_1, Q_2, Q_3, Q_4, Q_5, X", Y", m", R_1" and R_2" are as defined and described in the ULM-1 herein; the L_3, ring D, ring B, ring C and X"" are as defined and described in the LA herein.

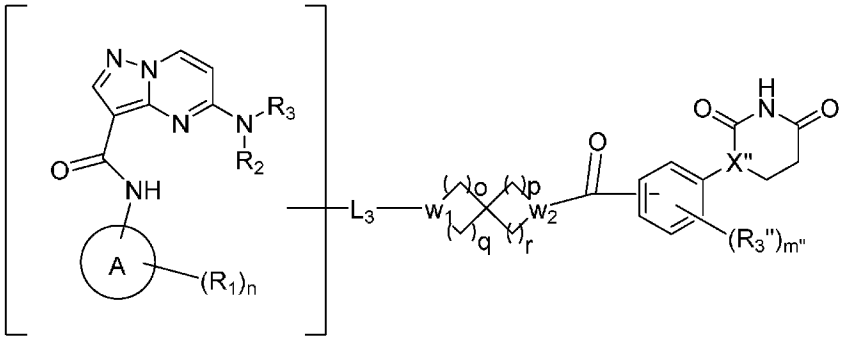
[0112] Preferably, in certain embodiments of the present invention, the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is a compound of formula III, and/or a stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or a pharmaceutically acceptable salt thereof,



III

wherein the R_1, n, R_2, R_3 and ring A are as defined and described in PTM-3; the Q_1, Q_2, Q_3, Q_4, Q_5, X", Y", m", R_1" and R_2" are as defined and described in the ULM-1 herein; the L_3, ring D, ring B, ring C and X"" are as defined and described in the LA herein.

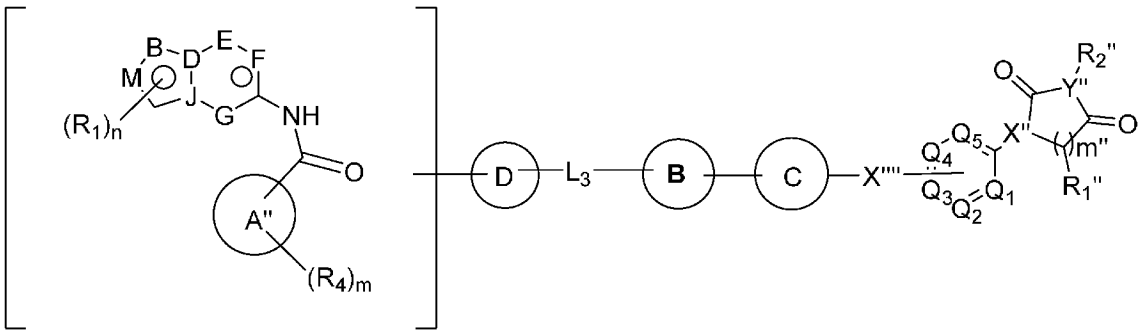
[0113] Preferably, in certain embodiments of the present invention, the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is a compound of formula IV, and/or a stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or a pharmaceutically acceptable salt thereof,



IV

wherein the R_1, n, R_2, R_3, ring A are as defined and described in PTM-3; the X", m" and R_3" are as defined and described in the ULM-1 herein; the L_3 is as defined and described in the LA herein; o, p, q and r are each independently 1 or 2; w_1 and w_2 are each independently CH or N, and at least one of them is N.

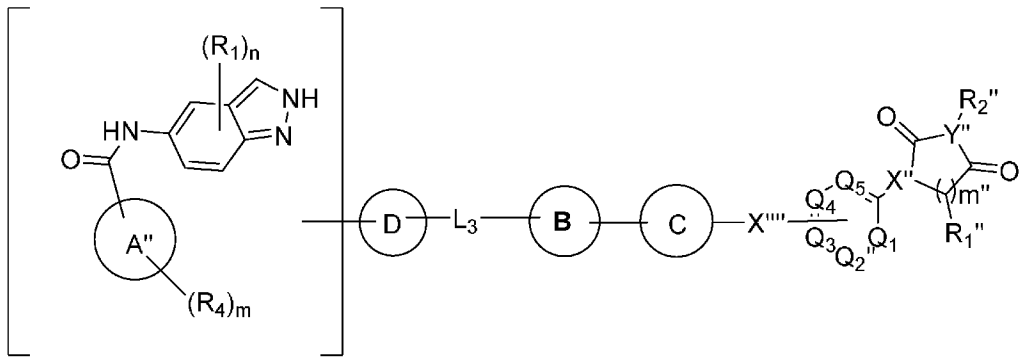
[0114] Preferably, in certain embodiments of the present invention, the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is a compound of formula V, and/or a stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or a pharmaceutically acceptable salt thereof,



V

wherein the R_1, n, R_4, B, D, E, F, G, J and ring A" are as defined and described in PTM-2'; the Q_1, Q_2, Q_3, Q_4, Q_5, X", Y", m", R_1" and R_2" are as defined and described in the ULM-1 herein; the L_3, ring D, ring B, ring C and X"" are as defined and described in the LA herein.

[0115] Preferably, in certain embodiments of the present invention, the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof are/is a compound of formula VI, and/or a stereoisomer, enantiomer, diastereomer, deuteride, metabolite, hydrate, solvate and/or prodrug thereof and/or a pharmaceutically acceptable salt thereof,



VI

wherein the R_1, n, R_2, R_3 and ring A" are as defined and described in PTM-3; the Q_1, Q_2, Q_3, Q_4, Q_5, X", Y", m", R_1" and R_2" are as defined and described in the ULM-1 herein; the L_3, ring D, ring B, ring C and X"" are as defined and described in the LA herein.

[0116] The present invention provides a method for preparing the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof.

[0117] The present invention provides a pharmaceutical composition, comprising a therapeutically effective amount of the compound of formula 1, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

[0118] The present invention provides a pharmaceutical composition, comprising a therapeutically effective amount of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0119] The present invention provides a method for degrading the IRAK4 protein, comprising contacting the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof with the IRAK4 protein.

[0120] The present invention provides use of a substance A in the preparation of a degrader for the IRAK4 protein, the substance A comprising the previously described compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the previously described pharmaceutical composition thereof.

[0121] The compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof of the present invention is used as a medicament for treating or preventing IRAK4-mediated diseases or disorders.

[0122] The compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof of the present invention is used as a medicament for treating or preventing diseases or disorders mediated by TLR (except TLR3R) or the IL-1β receptor family (including IL-1R, IL-18R, IL-33R and IL-36R).

[0123] The compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof of the present invention is used as a medicament for treating or preventing IRAK4-mediated diseases or disorders, wherein the IRAK4-mediated diseases or disorders are MyD88-driven diseases or disorders.

[0124] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing IRAK4-mediated diseases or disorders.

[0125] In the present invention, the IRAK4-mediated diseases or disorders are MyD88-driven diseases or disorders.

[0126] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing diseases or disorders mediated by TLR (except TLR3R) or the IL-1β receptor family (including IL-1R, IL-18R, IL-33R and IL-36R).

[0127] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing IRAK4-regulated diseases or disorders, wherein the IRAK4-mediated diseases or disorders are MyD88-driven diseases or disorders.

[0128] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing disorders or diseases including cancer, neurodegenerative disorders, viral diseases, autoimmune diseases, inflammatory diseases, genetic disorders, hormone-associated diseases, metabolic disorders, diseases associated with organ transplantation, immunodeficiency disorders, destructive bone diseases,

proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver diseases, pathological immune conditions involving T cell activation, cardiovascular disorders or CNS.

[0129] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing a cancer or proliferative disease, wherein the cancer or proliferative disease is brain cancer, kidney cancer, liver cancer, adrenal cancer, bladder cancer, breast cancer, stomach cancer, ovarian cancer, colon cancer, rectal cancer, prostate cancer, pancreatic cancer, lung cancer, vaginal cancer, cervical cancer, testicular cancer, genitourinary tract cancer, esophageal cancer, laryngeal cancer, skin cancer, bone cancer, thyroid cancer, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, neck or head tumor, epidermal hyperplasia, psoriasis, prostate hyperplasia, adenoma, adenocarcinoma, keratoacanthoma, squamous cell carcinoma, large cell carcinoma, non-small cell lung cancer, lymphoma, Hodgkin's and non-Hodgkin's, breast cancer, follicular carcinoma, undifferentiated carcinoma, papillary tumor, seminoma, melanoma, ABC DLBCL, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, chronic lymphocytic leukemia, smoldering indolent multiple myeloma, leukemia, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary exudative lymphoma, Burkitt's lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenstroms's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, or plasmacytoma or intravascular large B-cell lymphoma.

[0130] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing a neurodegenerative disease, wherein the neurodegenerative disease is a neurodegenerative disease caused by Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, diabetes therapy, metabolic syndrome, obesity, organ transplantation or graft-versus-host disease.

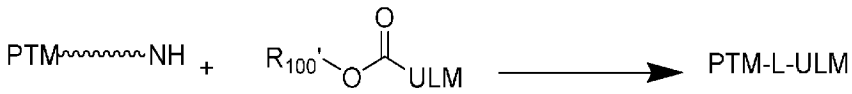
[0131] The present invention provides use of the compound of formula I, formula II, formula III, formula IV, formula V or formula VI, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing an inflammatory disease, wherein the inflammatory disease is an eye disease, such as eye allergy, conjunctivitis, dry eye or spring conjunctivitis, a disease affecting the nose, including allergic rhinitis; an autoimmune hematological disorder, such as hemolytic anemia, aplastic anemia, pure red blood cell anemia and idiopathic thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stephen-Johnson syndrome, idiopathic stomatitis diarrhea, autoimmune inflammatory bowel disease, irritable bowel syndrome, celiac disease, tooth root periostitis, lung hyaline membrane disease, nephropathy, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcomatosis, dry eye, spring conjunctival keratitis, interstitial pulmonary fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, interstitial cystitis, diverticulitis, glomerulonephritis, chronic granulomatous disease, adenomyosis, leptospirosis nephropathy, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle atrophy, catabolism, obesity, slow fetal growth, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, pigment incontinence, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, allergic reaction, systemic allergic reaction, sinusitis, eye allergy, silica-induced disease, COPD, lung disease, cystic fibrosis, liver fibrosis, renal fibrosis, alcoholic fatty liver, non-alcoholic fatty liver, heart fibrosis, psoriasis, Crohn's disease, inflammatory bowel disease, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataract, muscle inflammation combined with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, type 1 diabetes, type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic transplant rejection, colitis, conjunctivitis, cystitis, lacrimal gland inflammation, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, upper ankle inflammation, epididymitis, fasciitis, fibrous tissue inflammation, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, suppurative sweat inflammation, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, mumps, pericarditis, peritonitis, pharyngitis, pleurisy, phlebitis, local pneumonia, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, articular membrane inflammation, tendinitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, sclerosis, vitiligo, hypersensitivity vasculitis, urticaria, bullous pemphigoid, pemphigus vulgaris, deciduous pemphigus, paraneoplastic pemphigus, acquired bullous epidermal laxity, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, cryopyrin-associated periodic syndrome or osteoarthritis.

[0132] The present invention provides a method for treating or preventing IRAK4-mediated diseases or disorders, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula I, formula II, formula III or formula IV, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof.

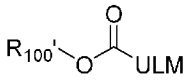
[0133] The present invention provides a method for treating or preventing IRAK4-mediated diseases or disorders, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula I, formula II, formula III or formula IV, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof, wherein the IRAK4-mediated diseases or disorders are MyD88-driven diseases or disorders.

[0134] The present invention provides a method for treating or preventing diseases or disorders mediated by TLRs (except TLR3R) or the IL-1 receptor family (including IL-1R, IL-18R, IL-33R and IL-36R), comprising administering to a patient in need thereof a therapeutically effective amount of the compound of formula I, formula II, formula III or formula IV, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof.

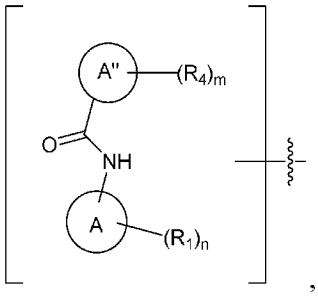
[0135] The present invention provides a method for preparing the compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof,



[0136] wherein the ~~~ is a portion of linking chain L; the NH may be a primary or secondary amine; the NH group undergoes a substitution reaction with an ester group in

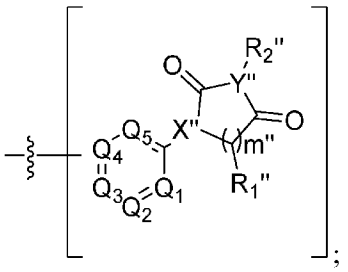


under alkaline conditions to prepare the compound of formula I, wherein the R_{100}' is pentafluorophenyl or *p*-nitrophenyl; the PTM is



,

wherein the ring A, ring A", n, R_1, R_4 and m are as defined and described in PTM-1; the ULM is



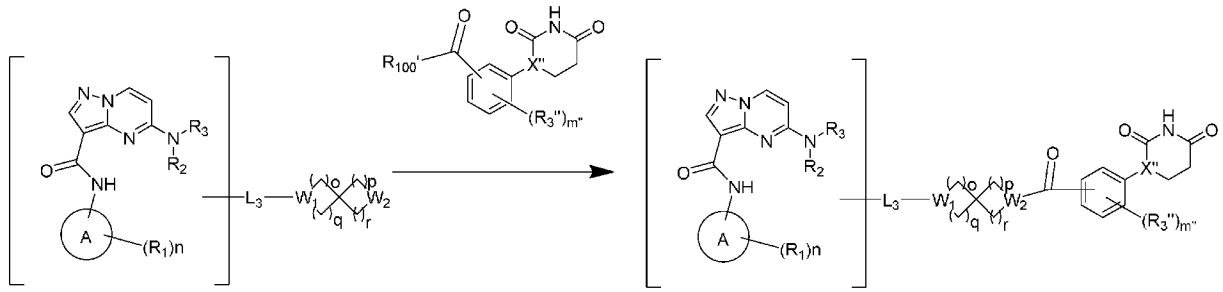
;

the Q_1, Q_2, Q_3, Q_4, Q_5, X", Y", m", R_1" and R_2" are as defined in the ULM-1 herein; the alkali in the substitution reaction includes, but is not limited to, triethylamine, *N,N*-diisopropylethylamine, potassium carbonate, sodium carbonate and

sodium bicarbonate.

[0137] The present invention provides a method for preparing the compound of formula II, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof.

[0138] The present invention provides a method for preparing the compound of formula IV, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof,



IVa IVb IV

[0139] wherein the ring A, n, R_1, R_2 and R_3 are as defined and described in PTM-3; L_3 is as defined and described in LA; W_2 is NH; W_1 is CH or N; o, p, q and r are each independently 1 or 2; X" is CH or N; R3" and m" are as defined and described in ULM-1; R_{100}' is pentafluorophenyl or *p*-nitrophenyl; the formula IVa undergoes a substitution reaction with formula IVb to give the compound of formula IV; the alkali in the substitution reaction includes, but is not limited to, triethylamine, *N,N*-diisopropylethylamine, potassium carbonate, sodium carbonate and sodium bicarbonate.

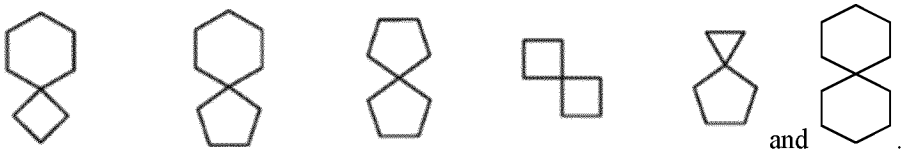
[0140] Detailed description: Unless otherwise stated, the following terms used in the specification and claims have the following meanings.

[0141] "Alkyl" refers to a saturated aliphatic hydrocarbon group, including linear or branched alkyl; C_1-C_8 alkyl refers to an alkyl group containing 1-8 carbon atoms, e.g., methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, *n*-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, *n*-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, *n*-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl or various branched isomers thereof, preferably C_1-C_6 alkyl, and further preferably, C_1-C_4 alkyl. The alkyl groups may be substituted or unsubstituted.

[0142] "Cycloalkyl" refers to a saturated or partially unsaturated, monocyclic or polycyclic hydrocarbon substituent; "C_3-C_{12} cycloalkyl" refers to a cycloalkyl group containing 3 to 12 carbon atoms; "C_3-C_8 cycloalkyl" refers to a cycloalkyl group containing 3 to 8 carbon atoms; "C_5-C_{10} cycloalkyl" refers to a cycloalkyl group containing 5 to 10 carbon atoms.

[0143] Non-limiting examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl and the like, preferably cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, preferably C_3-C_8 cycloalkyl, and further preferably C_3-C_6 cycloalkyl.

[0144] Polycyclic cycloalkyl groups include spiro, fused and bridged cycloalkyl groups. "Spirocycloalkyl" refers to a polycyclic group in which monocyclic rings share a carbon atom (called spiro atom), and they may contain one or more double bonds, but none of the rings has a fully conjugated π-electron system. According to the number of spiro atoms shared among the rings, a spirocycloalkyl group may be a monospirocycloalkyl group, a bispirocycloalkyl group or a polyspirocycloalkyl, preferably a bispirocycloalkyl group. Non-limiting examples of spirocycloalkyl groups include:



and .

[0145] "Fused cycloalkyl" refers to an all-carbon polycyclic group in which each ring shares a pair of adjacent carbon atoms with other rings in the system, wherein one or more of the rings may contain one or more double bonds, but none of the rings has a fully conjugated π-electron system. According to the number of constituent rings, a fused cycloalkyl

group may be a bicyclic, tricyclic, tetracyclic or polycyclic fused cycloalkyl group, preferably a bicyclic fused cycloalkyl group. Non-limiting examples of fused cycloalkyl groups include:

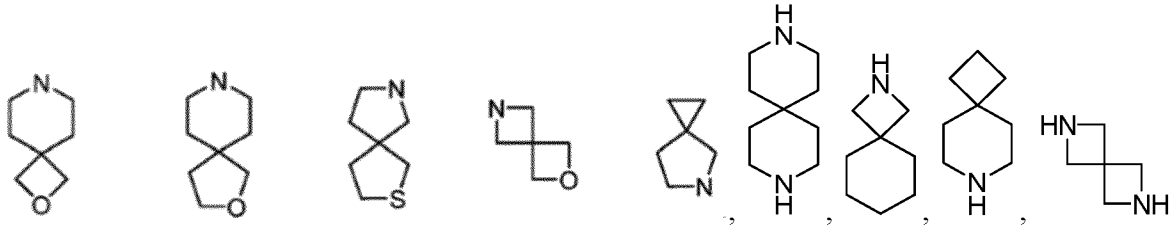
[0146] "Bridged cycloalkyl" refers to an all-carbon polycyclic group in which any two rings share two carbon atoms not directly connected, and they may contain one or more double bonds, but none of the rings has a fully conjugated π-electron system. According to the number of constituent rings, a bridged cycloalkyl group may be a bicyclic, tricyclic, tetracyclic or polycyclic bridged cycloalkyl group. Non-limiting examples of bridged cycloalkyl groups include:

[0147] The cycloalkyl ring may be fused to an aryl, heteroaryl or heterocycloalkyl ring, wherein the ring attached to the parent structure is a cycloalkyl group; non-limiting examples include indanyl, tetrahydronaphthyl, benzocycloheptyl, and the like. The cycloalkyl groups may be optionally substituted or unsubstituted.

[0148] "Heterocycloalkyl" refers to a saturated or partially unsaturated, monocyclic or polycyclic hydrocarbon substituent, wherein one or more of the ring atoms are selected from nitrogen, oxygen or $S(O)_r$ (wherein r is an integer of 0, 1 or 2), but a ring portion of -O-O-, -O-S- or -S-S- is not included, and the other ring atoms are carbon atoms. "3-12 membered heterocycloalkyl" refers to a cyclic group containing 3 to 12 ring atoms, "5-10 membered heterocycloalkyl" refers to a cyclic group containing 5 to 10 ring atoms, and "3-8 membered heterocycloalkyl" refers to a cyclic group containing 3 to 8 ring atoms. A "3-12 membered heterocycloalkyl" group containing 1-3 heteroatoms selected from N, O or S is preferred. A 3-12 membered heterocycloalkyl group containing 1 or 2 N atoms is further preferred.

[0149] Non-limiting examples of monocyclic heterocycloalkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, homopiperazinyl and the like, preferably piperidinyl and piperazinyl.

[0150] Polycyclic heterocycloalkyl groups include spiro, fused and bridged heterocycloalkyl groups. "Spiroheterocycloalkyl" refers to a polycyclic heterocycloalkyl group in which monocyclic rings share an atom (called spiro atom), wherein one or more of the ring atoms are selected from nitrogen, oxygen or S(O)r (wherein r is an integer of 0, 1 or 2), and the other ring atoms are carbon atoms. They may contain one or more double bonds, but none of the rings has a fully conjugated π-electron system. According to the number of spiro atoms shared among the rings, a spirocycloalkyl group may be a monospiroheterocycloalkyl group, a bispiroheterocycloalkyl group or a polyspiroheterocycloalkyl group, preferably a saturated "3-12 membered bispiroheterocycloalkyl" group containing 1-3 heteroatoms selected from N, O or S, and further preferably a saturated "3-12 membered bispiroheterocycloalkyl" group containing 1 or 2 N atoms. Non-limiting examples of spiroheterocycloalkyl groups include:



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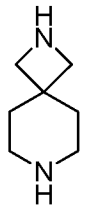
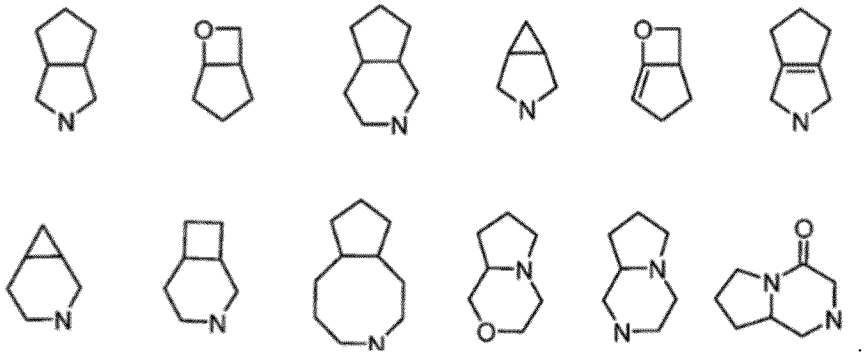
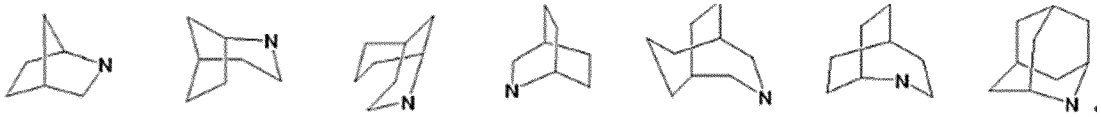


[0151] "Fused heterocycloalkyl" refers to a polycyclic heterocycloalkyl group in which each ring shares a pair of adjacent atoms with the other rings in the system, and one or more of the rings may contain one or more double bonds, but none of the rings has a fully conjugated π-electron system, wherein one or more of the ring atoms are selected from nitrogen, oxygen or S(O)r (wherein r is an integer of 0, 1 or 2), and the other ring atoms are carbon atoms. According to the number of constituent rings, a fused heterocycloalkyl group may be a bicyclic, tricyclic, tetracyclic or polycyclic fused heterocycloalkyl group, preferably a "3-12 membered bicyclic fused heterocycloalkyl" group containing 1-3 heteroatoms selected from N, O or S, and further preferably a saturated "3-12 membered bicyclic fused heterocycloalkyl" group containing 1 or 2 N atoms. Non-limiting examples of fused heterocycloalkyl groups include:



[0152] "Bridged heterocycloalkyl" refers to a polycyclic heterocycloalkyl group in which any two rings share two atoms not directly connected, and they may contain one or more double bonds, but none of the rings has a fully conjugated π-electron system, wherein one or more of the ring atoms are selected from nitrogen, oxygen or $S(O)_r$ (wherein r is an integer of 0, 1 or 2), and the other ring atoms are carbon atoms. According to the number of constituent rings, a bridged heterocycloalkyl group may be a bicyclic, tricyclic, tetracyclic or polycyclic bridged cycloalkyl group; non-limiting examples of bridged heterocycloalkyl groups include:



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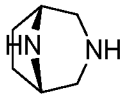
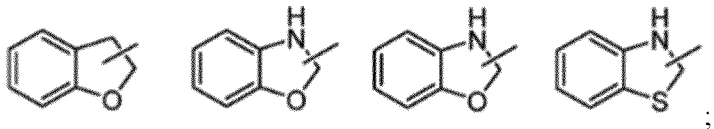
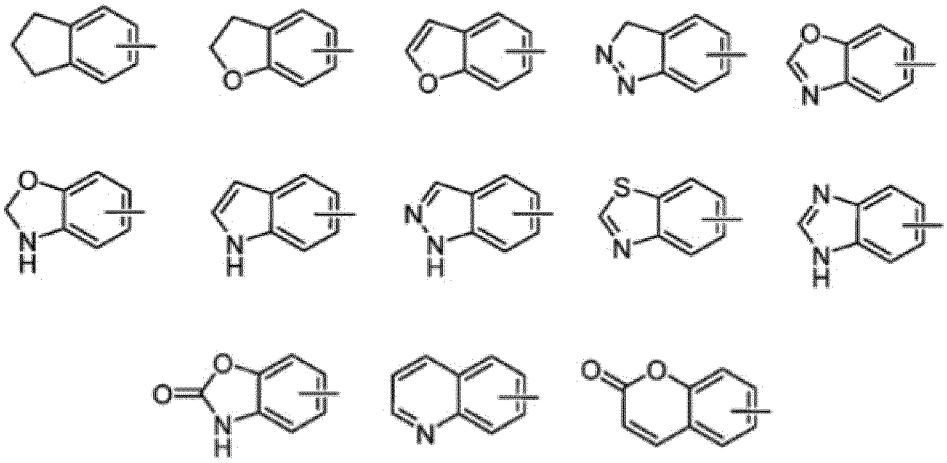


[0153] The heterocycloalkyl ring may be fused to an aryl, heteroaryl or cycloalkyl ring, wherein the ring attached to the parent structure is a heterocycloalkyl group; non-limiting examples include:



the heterocycloalkyl groups may be optionally substituted or unsubstituted.

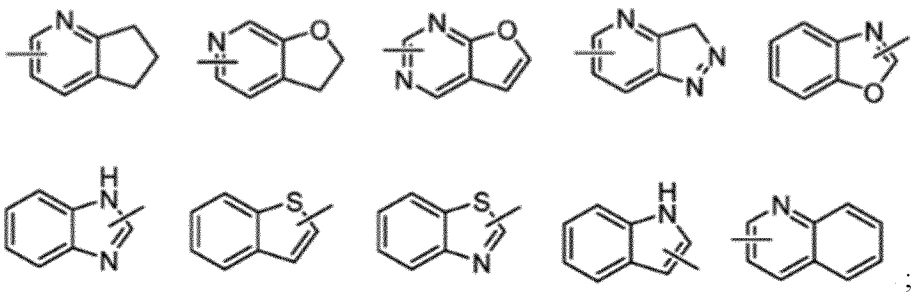
[0154] "Aryl" refers to an all-carbon monocyclic or fused polycyclic group (i.e., rings that share pairs of adjacent carbon atoms) and a polycyclic group having a conjugated π-electron system; "6-10 membered aryl" refers to an all-carbon aryl group containing 6-10 carbon atoms, such as phenyl and naphthyl, preferably phenyl. The aryl ring may be fused to a heteroaryl, heterocycloalkyl or cycloalkyl ring, wherein the ring attached to the parent structure is an aryl ring; non-limiting examples include:



;

the aryl groups may be optionally substituted or unsubstituted.

[0155] "Heteroaryl" refers to a heteroaromatic system containing 1 to 4 heteroatoms, and the heteroatoms include nitrogen, oxygen or $S(O)_r$ (wherein r is an integer of 0, 1 or 2); 5-6 membered heteroaryl refers to a heteroaromatic system containing 5-6 ring atoms; 5-10 membered heteroaryl refers to a heteroaromatic system containing 5-10 ring atoms; a 5-6 membered heteroaryl group is preferred; a 5-6 membered heteroaryl group containing 1 or 2 N atoms is further preferred; non-limiting examples include furanyl, thienyl, pyridyl, pyrrolyl, *N*-alkylpyrrolyl, pyrimidinyl, pyrazinyl, pyrazole, imidazolyl, triazolyl, tetrazolyl and the like, preferably pyridyl. The heteroaryl ring may be fused to an aryl, heterocycloalkyl or cycloalkyl ring, wherein the ring attached to the parent structure is a heteroaryl ring; non-limiting examples include:



;

the heteroaryl groups may be optionally substituted or unsubstituted.

[0156] "Alkenyl" refers to an alkyl group as defined above, which consists of at least two carbon atoms and at least one carbon-carbon double bond; "C_{2-8} alkenyl" refers to a linear or branched alkenyl group containing 2-8 carbon atoms, including but not limited to ethenyl, 1-propenyl, 2-propenyl, 1-, 2- or 3-butenyl and the like, preferably a "C_{2-6} alkenyl" group, and further preferably a "C_{2-4} alkenyl" group. The alkenyl groups may be substituted or unsubstituted.

[0157] "Alkynyl" refers to an alkyl group as defined above, which consists of at least two carbon atoms and at least one carbon-carbon triple bond; "C_{2-8} alkynyl" refers to a linear or branched alkynyl group containing 2-8 carbon atoms, including but not limited to ethynyl, 1-propynyl, 2-propynyl, 1-, 2- or 3-butynyl, preferably a "C_{2-6} alkynyl" group, and further preferably a "C_{2-4} alkynyl" group. The alkynyl groups may be substituted or unsubstituted.

[0158] "-ylene" refers to a divalent group. For example, alkylene refers to a divalent alkyl group; alkenylene refers to a divalent alkenyl group; alkynylene refers to a divalent alkynyl group; cycloalkylene refers to a divalent cycloalkyl group; heterocycloalkylene refers to a divalent heterocycloalkyl group; arylene refers to a divalent aryl group; heteroarylene refers to a divalent heteroaryl group; the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are as

defined above; the "-ylene" groups may be optionally substituted or unsubstituted.

[0159] "Alkoxy" refers to -O-(alkyl), wherein the alkyl group is as defined above. "Ci-Cs alkoxy" refers to an alkyloxy group containing 1-8 carbon atoms; non-limiting examples include methoxy, ethoxy, propoxy, butoxy and the like. The alkoxy groups may be substituted or unsubstituted.

[0160] "Cycloalkoxy" refers to -O-(unsubstituted cycloalkyl), wherein the cycloalkyl group is as defined above. C_3-C_8 cycloalkoxy refers to a cycloalkyloxy group containing 3-8 carbon atoms; non-limiting examples include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like. The cycloalkoxy groups may be optionally substituted or unsubstituted.

[0161] "Haloalkyl" refers to an alkyl group optionally substituted with one or more fluorine, chlorine, bromine or iodine atoms, wherein the alkyl group is as defined above; non-limiting examples include difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, tribromomethyl and the like.

[0162] "Haloalkoxy" refers to a group in which the hydrogen on the alkyl group is substituted with one or more fluorine, chlorine, bromine or iodine atoms, wherein the alkoxy group is as defined above. Examples include difluoromethoxy, dichloromethoxy, dibromomethoxy, trifluoromethoxy, trichloromethoxy, tribromomethoxy and the like.

[0163] "Hydroxyalkyl" refers to an alkyl group optionally substituted with one or more -OH groups, wherein the alkyl group is as defined above; non-limiting examples include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxyisopropyl.

[0164] "Aminoalkyl" refers to an alkyl group optionally substituted with one or more $-NH_2$ groups, wherein the alkyl group is as defined above; non-limiting examples include aminomethyl, aminoethyl, aminopropyl and aminoisopropyl.

[0165] "Ammonia" and "amine" are recognized in the art and refer to substituted or unsubstituted ammonia.

[0166] "Oxo" refers to the =O group.

[0167] "Halogen" refers to fluorine, chlorine, bromine or iodine.

[0168] "Cyano" refers to -CN.

[0169] "Hydroxy" refers to -OH.

[0170] "Raney-Ni" refers to Raney nickel (a hydrogen active catalytic reducing agent).

[0171] "HATU" refers to 2-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate.

[0172] "DIEA" refers to diisopropylethylamine.

[0173] "MeOH" refers to methanol.

[0174] "$NaBH_3CN$" refers to sodium cyanoborohydride.

[0175] "$LiAlH_4$" refers to aluminum lithium hydride.

[0176] "THF" refers to tetrahydrofuran.

[0177] "DMF" refers to dimethylformamide.

[0178] "Py-BOP" refers to benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate.

[0179] "HATU" refers to 2-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate.

[0180] "TFA" refers to triethylamine.

[0181] "EA" refers to ethyl acetate.

[0182] "CbzCl" refers to benzyl chloroformate.

[0183] "Cs_2CO_3" refers to cesium carbonate.

[0184] "$NaHCO_3$" refers to sodium bicarbonate.

[0185] "IBX" refers to 2-iodoxybenzoic acid.

[0186] "STAB" refers to sodium triacetoxyborohydride.

[0187] "DMSO" refers to dimethyl sulfoxide.

[0188] "K_2CO_3" refers to potassium carbonate.

[0189] "DCM" refers to dichloromethane.

[0190] "KI" refers to potassium iodide.

[0191] "NH_4Cl" refers to ammonium chloride.

[0192] "NazSOa" refers to sodium sulfate.

[0193] "$LiBH_4$" refers to lithium borohydride.

[0194] "NMP" refers to N-methylpyrrolidone.

[0195] "*i*-PrOH" refers to isopropanol.

[0196] "EtOH" refers to ethanol.

[0197] "$Pd(OH)_2/C$" refers to palladium hydroxide/carbon.

[0198] "DCE" refers to 1,2-dichloroethane.

[0199] "PE" refers to petroleum ether.

[0200] "Sat." refers to a saturated solution.

[0201] "PCC" refers to pyridinium chlorochromate.

[0202] "CuI" refers to cuprous iodide.

[0203] "TsCl" refers to 4-toluenesulfonyl chloride.

[0204] "HNO_3" refers to nitric acid.

[0205] "$NaBH(OAc)_3$" refers to sodium triacetoxyborohydride.

[0206] "Dess-Martin" refers to (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

[0207] "DMP" refers to dimethyl phthalate.

[0208] "TEA" refers to triethylamine.

[0209] "DAST" refers to diethylaminosulfur trifluoride.

[0210] "NBS" refers to N-bromosuccinimide.

[0211] "$(Ph)_2NH$" refers to diphenylamine.

[0212] "$Pd_2(dba)_3$" refers to tris(dibenzylideneacetone)dipalladium.

[0213] "Xantphos" refers to 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

[0214] "NaOt-Bu" refers to sodium tert-butoxide.

[0215] "DPBS" refers to Dulbecco's phosphate-buffered saline.

[0216] "PBS" refers to phosphate-buffered saline.

[0217] "SDS-PAGE" refers to sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

[0218] "PVDF" refers to polyvinylidene fluoride.

[0219] "More" independently means 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0220] "Optional" or "optionally" means that the event or circumstance subsequently described may, but does not necessarily, occur, and that the description includes instances where the event or circumstance occurs or does not occur. For example, "a heterocycloalkyl group optionally substituted with alkyl" means that the alkyl may, but does not necessarily, exist, and that the description includes cases where the heterocycloalkyl group is or is not substituted with the alkyl group.

[0221] "Substituted" means that one or more, preferably up to 5, further preferably 1-3 hydrogen atoms in the group are independently substituted with a corresponding number of substituents. It goes without saying that a substituent is only in its possible chemical position, and those skilled in the art will be able to determine (experimentally or theoretically) possible or impossible substitution without undue effort. For example, it may be unstable when an amino or hydroxy group having free hydrogen is bound to a carbon atom having an unsaturated (such as olefin) bond.

[0222] "Pharmaceutical composition" refers to a mixture containing one or more of the compounds or the physiologically/pharmaceutically acceptable salts or pro-drugs thereof described herein, and other chemical components, for example, physiologically/pharmaceutically acceptable carriers and excipients. The pharmaceutical composition is intended to promote the administration to an organism, so as to facilitate the absorption of the active ingredient, thereby exerting biological activity.

[0223] The present invention also provides a pharmaceutically acceptable salt of the compound of formula I, formula II, formula III or formula IV The term "pharmaceutically acceptable salt" refers to a relatively nontoxic acid addition salt or base addition salt of the compound of the present invention. The acid addition salt is a salt formed from the compound of formula (I) of the present invention and a suitable inorganic acid or organic acid. These salts may be prepared during the final isolation and purification of the compound or by reacting the purified compound of formula (I) in its free base form with a suitable organic acid or inorganic acid. The representative acid addition salt includes hydrobromide, hydrochloride, sulfate, bisulfate, sulfite, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, biphosphate, carbonate, bicarbonate, toluate, citrate, maleate, fumarate, succinate, tartrate, benzoate, methanesulfonate, p-toluenesulfonate, gluconate, lactobionate, lauryl sulfonate and the like. The base addition salt is a salt formed from the compound of formula (I) and a suitable inorganic base or organic base, including, for example, a salt formed with alkali metal, alkaline earth metal and quaternary ammonium cations, such as sodium salts, lithium salts, potassium salts, calcium salts, magnesium salts, tetramethyl quaternary ammonium salts, tetraethyl quaternary ammonium salts and the like; the amine salt includes salts formed with ammonia (NH_3) and primary, secondary or tertiary amines, such as methylamine salts, dimethylamine salts, trimethylamine salts, triethylamine salts, ethylamine salts and the like.

[0224] The compound of the present invention or the pharmaceutically acceptable salt thereof may be administered to mammals including humans, and may be administered orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), topically (powders, ointments or drops) or intratumorally.

[0225] The compound of the present invention may be administered at a dose of about 0.05-300 mg/kg body weight/day, preferably 10-300 mg/kg body weight/day, and preferably 10-150 mg/kg body weight/day.

[0226] The compound of the present invention or the pharmaceutically acceptable salt thereof may be formulated into a solid dosage form for oral administration, including but not limited to capsules, tablets, pills, pulvis, granules and the like. In these solid dosage forms, the compound of formula (I) of the present invention, as an active ingredient, is mixed with at least one conventional inert excipient (or carrier), such as sodium citrate or dicalcium phosphate, or with the following ingredients: (1) fillers or extenders, such as starch, lactose, sucrose, glucose, mannitol, silicic acid and the like; (2) binders, such as hydroxymethyl cellulose, alginate, gelatin, polyvinylpyrrolidone, sucrose, acacia and the like; (3) humectants, such as glycerol and the like; (4) disintegrants, such as agar, calcium carbonate, potato or tapioca

starch, alginic acid, certain complex silicates, sodium carbonate and the like; (5) solution retarders, such as paraffin and the like; (6) absorption accelerators, such as quaternary ammonium compounds and the like; (7) wetting agents, such as cetyl alcohol, glycerol monostearate and the like; (8) adsorbents, such as kaolin and the like; and (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycol, sodium lauryl sulfate and the like, or mixtures thereof. Capsules, tablets and pills may further comprise buffers.

[0227] The solid dosage forms such as tablets, dragees, capsules, pills and granules may be coated or microencapsulated using coatings and shells such as enteric coatings and other materials well known in the art. They may comprise opacifying agents, and the active ingredient in such a composition may be released in a certain part of the digestive tract in a delayed manner. Examples of embedding components that can be used are polymeric substances and wax-based substances. If necessary, the active ingredient can also be in microcapsule form with one or more of the above-mentioned excipients.

[0228] The compound of the present invention or the pharmaceutically acceptable salt thereof may be formulated into a liquid dosage form for oral administration, including but not limited to pharmaceutically acceptable emulsions, solutions, suspensions, syrups, tinctures and the like. In addition to the compound of formula (I) or the pharmaceutically acceptable salt thereof as an active ingredient, the liquid dosage form may comprise inert diluents commonly used in the art, such as water and other solvents, solubilizers and emulsifiers, for example, ethanol, isopropanol, ethyl carbonate, ethyl acetate, propylene glycol, 1,3-butanediol, dimethylformamide, and oils, especially cottonseed oil, peanut oil, corn germ oil, olive oil, castor oil, sesame oil and the like, or mixtures of these substances. In addition to such inert diluents, the liquid dosage form in the present invention may further comprise conventional adjuvants, such as wetting agents, emulsifiers, suspending agents, sweeteners, flavoring agents, perfuming agents and the like.

[0229] The suspending agents include, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum methylate, agar and the like, or mixtures of these substances.

[0230] The compound of the present invention or the pharmaceutically acceptable salt thereof may be formulated into a dosage form for parenteral injection, including but not limited to physiologically acceptable sterile aqueous or anhydrous solutions, dispersions, suspensions or emulsions, and sterile powders for redissolving into sterile injectable solutions or dispersions. Suitable carriers, diluents, solvents or excipients include water, ethanol, polyols and suitable mixtures thereof.

[0231] The compound of the present invention or the pharmaceutically acceptable salt thereof may also be formulated into a dosage form for topical administration, including, for example, ointments, pulvis, suppositories, drops, sprays, inhalants and the like. The compound of formula (I) or the pharmaceutically acceptable salt thereof in the present invention as an active ingredient is mixed under sterile conditions with a physiologically acceptable carrier and optional preservatives, buffers or propellants that may be required if necessary.

[0232] The present invention also provides a pharmaceutical composition comprising the compound of formula (I) or the pharmaceutically acceptable salt thereof as an active ingredient, and a pharmaceutically acceptable carrier, excipient or diluent. In the preparation of the pharmaceutical composition, the compound of formula (I) or the pharmaceutically acceptable salt thereof in the present invention is typically mixed with the pharmaceutically acceptable carrier, excipient or diluent.

[0233] The composition in the present invention may be formulated into a conventional pharmaceutical formulation according to a conventional preparation method. For example, tablets, pills, capsules, pulvis, granules, emulsions, suspensions, dispersions, solutions, syrups, elixirs, ointments, drops, suppositories, inhalants, sprays and the like.

[0234] The compound or the pharmaceutically acceptable salt thereof described in the present invention may be administered alone or, if desired, in combination with other pharmaceutically acceptable therapeutic agents, such as other anti-tumor drugs, anti-inflammatory drugs or autoimmune drugs. The ingredients to be combined may be administered simultaneously or sequentially, and administered in a single formulation or in different formulations. The combination may include not only a combination of the compound in the present invention and one additional active agent, but also a combination of the compound in the present invention and two or more additional active agents.

[0235] The present invention uses an IRAK4 kinase activity test experiment to prove that the compounds of the present invention can effectively bind to the IRAK4 target protein or produce inhibitory effects; uses Western-Blot to prove that the compounds of the present invention can effectively specifically degrade the IRAK4 protein in THP-1 cells; uses an LPS-induced normal human whole blood PBMC-secreted cytokine concentration determination experiment to prove that the compounds of the present invention can effectively inhibit the production of immune cell IL-6; and uses Western-Blot to prove that the compounds of the present invention have significant degradation effects on both the IRAK4 long chain (IRAK4-L) and the IRAK4 short chain (IRAK4-S) in human PBMCs. The compound of formula I, formula II, formula III or formula IV, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof can effectively degrade the IRAK4 protein, thereby achieving a preventing or treating effect on IRAK4-related diseases or disorders.

DETAILED DESCRIPTION

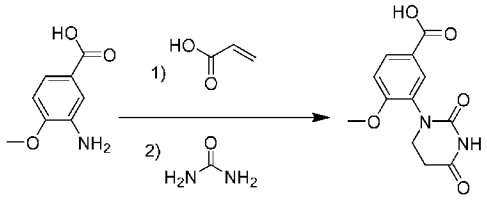
[0236] The present invention will be further explained in detail below with reference to examples, which are not intended to limit the present invention, and the present invention is not merely limited to the contents of the examples. Starting materials in the examples of the present invention are known and commercially available, or may be synthesized by using or according to methods known in the art. Unless otherwise stated, experimental procedures without specific conditions indicated in the examples of the present invention are generally conducted according to conventional conditions, or according to conditions recommended by the manufacturers of the starting materials or commercial products.

I. Compound preparation examples

Intermediate 1: 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoic acid

Step 1: preparation of 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoic acid

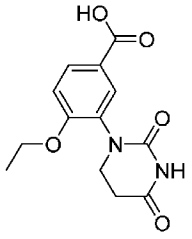
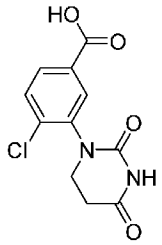
[0237]



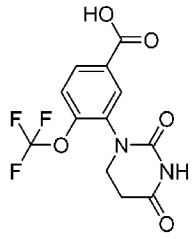
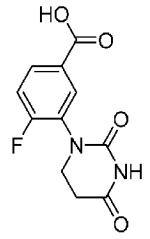
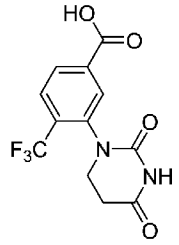
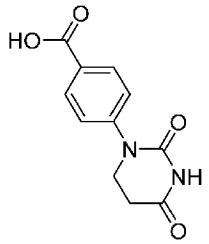
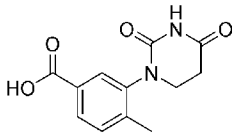
[0238] 3-Amino-4-methoxybenzoic acid (5.0 g, 2.93 mmol) was suspended in acrylic acid (8.05 mL, 117 mmol), and the suspension was stirred at 100 °C for 3 h. The reaction liquid was then cooled to room temperature with stirring. Acetic acid (33 mL) was added, and the stirred suspension was heated at 100 °C for 10 min. Urea (11.00 g, 183 mmol) was added, and the reaction liquid was stirred overnight at 120 °C. The reaction liquid was added to a mixture of ice water and concentrated hydrochloric acid (37%), and the mixture was stirred. The resulting suspension was stored in a refrigerator at 5 °C overnight and then filtered, and the solid was washed with water and dried to give a solid. The solid was triturated in a hydrochloric acid solution (0.05 M), filtered, washed with methyl *tert*-butyl ether, and dried under reduced pressure at 40 °C to give the target product, 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoic acid.

[0239] 1H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 10.34 (s, 1H), 7.92 (dd, J = 8.6, 2.2 Hz, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.94-3.82 (m, 3H), 3.60 (t, J = 6.7 Hz, 2H), 2.69 (s, 2H).

[0240] The following intermediates were prepared by referring to the method for intermediate 1:

Intermediate	Structure	Name	LC-MS
Intermediate 2		3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-ethoxybenzoic acid	(ESI, *m/z*): $[M+H]^+$ = 279.1
Intermediate 3		4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl) benzoic acid	(ESI, *m/z*): $[M+H]^+$ = 269.0

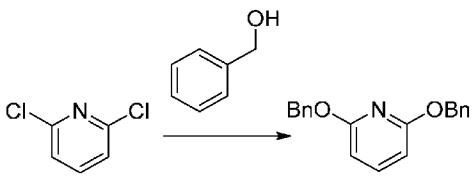
(continued)

Intermediate	Structure	Name	LC-MS
Intermediate 4		3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoic acid	(ESI, *m/z*): $[M+H]^+$ = 319.1
Intermediate 5		3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoic acid	(ESI, *m/z*): $[M+H]^+$ = 253.0
Intermediate 6		3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethyl)benzoic acid	(ESI, *m/z):* $[M+H]^+$ = 303.0
Intermediate 7		4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoic acid	(ESI, *m/z*): $[M+H]^+$ = 235.1
Intermediate 35		3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoic acid	(ESI, *m/z*): $[M+H]^+$ = 249.1

Intermediate 8: 3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoic acid

Step 1: preparation of 2,6-bis(benzyloxy)pyridine

[0241]



[0242] Benzyl alcohol (109.6 g, 1.01 mol) was added to a solution of sodium hydride (60% in mineral oil, 54.0 g, 1.35

mol) in *N,N*-dimethylformamide (600 mL) at 0 °C. After 30 min of stirring, 2,6-dichloropyridine (50.0 g, 0.338 mol) was then added. The reaction mixture was heated to 80 °C and stirred overnight. After the reaction mixture was cooled to room temperature, it was quenched with ice water (1000 mL). The solid was collected by filtration and dried to give the target product, 2,6-bis(benzyloxy)pyridine.

[0243] ^{1}H NMR (DMSO-d_6, 400 MHz): δ7.68 (t, J = 8.4 Hz, 1H), 7.48-7.36 (m, 10H), 6.45 (d, J = 8.4 Hz, 2H), 5.38 (s, 4H).

[0244] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 292.2.

Step 2: preparation of 2,6-bis(benzyloxy)-3-bromopyridine

[0245]

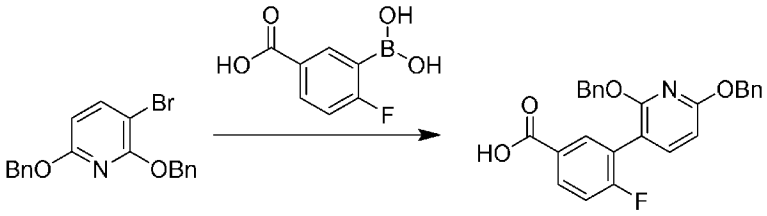
[0246] *N*-Bromosuccinimide (41.7 g, 0.23 mol) was added to a solution of 2,6-bis(benzyloxy)pyridine (75.9 g, 0.26 mol) in acetonitrile (600 mL). The reaction mixture was stirred at 80 °C for 2 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate (500 mL) and washed with water and saturated brine. The organic layer was collected, dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by silica gel column chromatography to give the target product, 2,6-bis(benzyloxy)-3-bromopyridine.

[0247] ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.88 (d, J = 8.4 Hz, 1H), 7.45-7.37 (m, 10H), 6.44 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H), 5.33 (s, 2H).

[0248] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 372.1.

Step 3: preparation of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-4-fluorobenzoic acid

[0249]

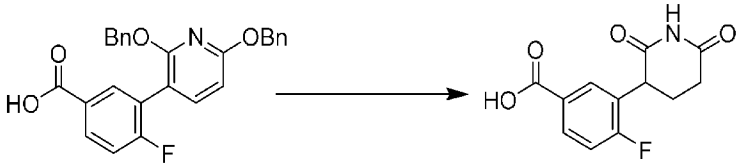


[0250] The $PdCl_2$(dppf)-chloroform complex (612 mg, 0.84 mmol) and sodium carbonate (1.77 g, 16.74 mmol) were added to a mixture of 2,6-bis(benzyloxy)-3-bromopyridine (3.1 g, 8.37 mmol) and 3-borono-4-fluorobenzoic acid (1.85 g, 10.05 mmol) in dioxane (31 mL) and water (7.5 mL). The reaction mixture was heated at 90 °C for 16 h under nitrogen atmosphere. After the reaction was complete, 15% hydrochloric acid solution (20 mL) was added. The mixture was extracted with ethyl acetate (100 mL × 3), washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and then concentrated under reduced pressure, and the concentrate was purified by silica gel column chromatography to give the target product, 3-(2,6-bis(benzyloxy)pyridin-3-yl)-4-fluorobenzoic acid.

[0251] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 430.2

Step 4: preparation of 3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoic acid

[0252]



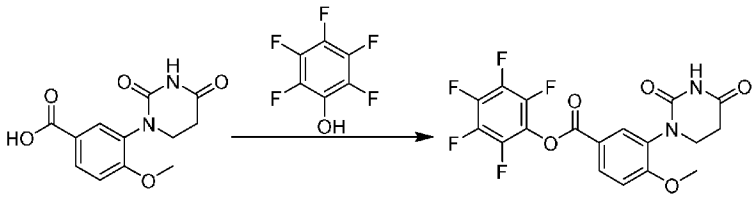
[0253] Palladium/carbon (10%, 120 mg) was added to a solution of 3-(2,6-bis(benzyloxy)pyridin-3-yl)-4-fluorobenzoic acid (1.50 g, 3.49 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 48 h under hydrogen atmosphere. After the reaction was complete, the reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography to give the target product, 3-(2,6-dioxopiperidine-3-yl)-4-fluorobenzoic acid.

[0254] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 252.1

[0255] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 10.92 (s, 1H), 7.91-7.95 (m, 2H), 7.30-7.34 (m, 1H), 4.15-4.19 (m, 1H), 2.70-2.79 (m, 1H), 2.53-2.57 (m, 1H), 2.23-2.27 (m, 1H), 2.01-2.07 (m, 1H).

Intermediate 9: pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate

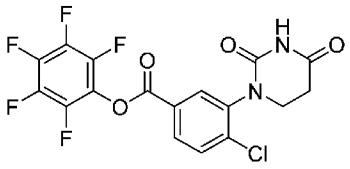
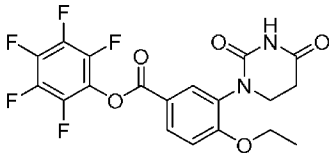
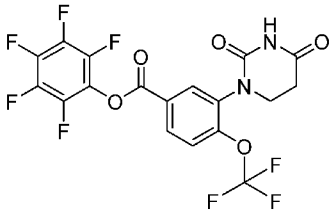
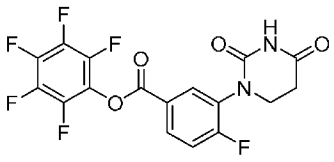
[0256]



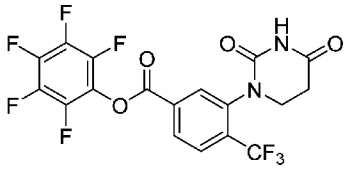
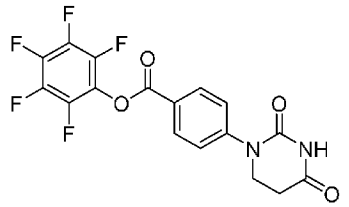
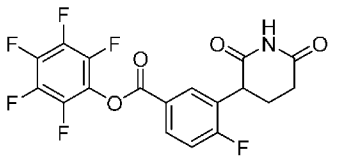
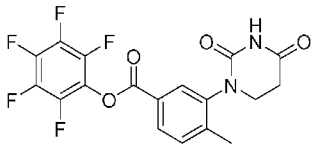
[0257] A mixture of 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoic acid (2.0 g, 7.58 mmol), 2,3,4,5,6-pentafluorophenol (1.67 g, 9.09 mmol) and *N,N'*-dicyclohexylcarbodiimide (1.87 g, 9.09 mmol) in *N,N*-dimethylformamide (20 mL) was stirred at room temperature for 3 h. The reaction liquid was poured into water (200 mL), and the resulting solution was stirred for 0.5 h and extracted with ethyl acetate (200 mL × 3). The organic phase was collected, washed with water (500 mL × 2) and saturated brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by silica gel column chromatography to give the target product, pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate.

[0258] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 431.1

[0259] The following intermediates were prepared by referring to the method for intermediate 9:

Intermediate	Structure	Name	LC-MS
Intermediate 10		pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl) benzoate	(ESI, *m/z*): $[M+H]^1$ = 435.0
Intermediate 11		pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-ethoxybenzoate	(ESI, *m/z*): $[M+H]^1$ = 445.1
Intermediate 12		pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoate	(ESI, *m/z*): $[M+H]^+$ = 485.0
Intermediate 13		pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoate	(ESI, *m/z*): $[M+H]^+$ = 419.0

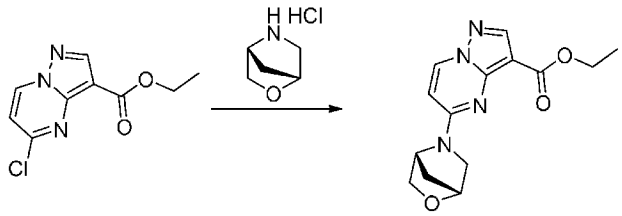
(continued)

Intermediate	Structure	Name	LC-MS
Intermediate 14		pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethyl)benzoate	(ESI, *m/z*): $[M+H]^+$ = 469.0
Intermediate 15		pentafluorophenyl 4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl) benzoate	(ESI, *m/z*): $[M+H]^1$ = 401.0
Intermediate 16		pentafluorophenyl 3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoate	(ESI, *m/z*): $[M+H]^+$ = 418.0
Intermediate 36		pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoate	(ESI, *m/z*): $[M+H]^+$ = 415.0

Intermediate 17: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

Step 1: preparation of ethyl 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[0260]

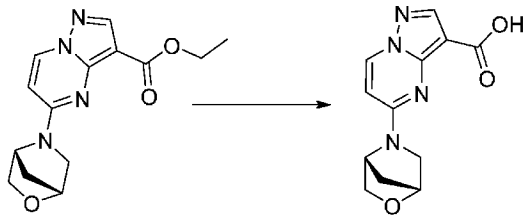


[0261] Ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (5.0 g, 22.1 mmol) and (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (3.0 g, 22.1 mmol) were dissolved in acetonitrile (60 mL), and *N,N*-diisopropylethylamine (11.4 g, 88.5 mmol) was added. The mixture was stirred at 60 °C for 2 h and concentrated by rotary evaporation under reduced pressure to remove the solvent, and water (100 mL) was then added. The mixture was extracted with ethyl acetate (100 mL × 3), and the organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the target product (crude), ethyl 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[0262] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 289.0.

Step 2: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

[0263]



[0264] Ethyl 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (5.5 g, 19.0 mmol) was added to ethanol (50 mL) and tetrahydrofuran (25 mL), and a saturated aqueous solution of lithium hydroxide (an aqueous solution prepared from 912 mg of lithium hydroxide and 0.75 mL of water) was added. The reaction mixture was stirred overnight at room temperature and concentrated under reduced pressure, and the concentrate was directly purified by reversed-phase chromatography (0.05% formic acid, 15% acetonitrile) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0265] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 261.0.

[0266] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.76 (dd, *J* = 7.6, 3.8 Hz, 1H), 8.22 (d, *J* = 3.8 Hz, 1H), 6.90-6.30 (m, 1H), 5.30-5.00 (m, 1H), 4.85-4.74 (m, 1H), 3.93-3.70 (m, 2H), 3.65-3.50 (m, 2H), 1.90-2.05 (m, 2H).

Intermediate 18: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of benzyl 4-(tosyloxy)piperidine-1-carboxylate

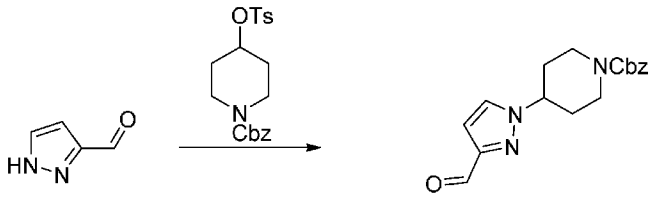
[0267]

[0268] A mixture of benzyl 4-hydroxypiperidine-1-carboxylate (8.0 g, 34 mmol), *p*-toluenesulfonyl chloride (7.8 g, 40.1 mmol), triethylamine (10.3 g, 102 mmol) and 4-dimethylaminopyridine (0.41 g, 3.4 mmol) in dichloromethane (100 mL) was stirred overnight at room temperature. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (100 mL × 3). The organic layer was collected, washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by column chromatography to give the target product, benzyl 4-(tosyloxy)piperidine-1-carboxylate.

[0269] LC-MS: (ESI, m/z): $[M+Na]^+$ = 412.1.

Step 2: preparation of benzyl 4-(3-formyl-1*H*-pyrrol-1-yl)piperidine-1-carboxylate

[0270]



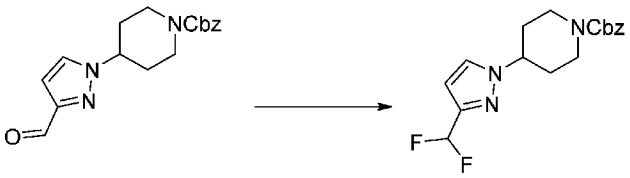
[0271] A mixture of 1*H*-pyrazole-3-carbaldehyde (2.5 g, 26 mmol), benzyl 4-(tosyloxy)piperidine-1-carboxylate (12.5 g, 32.1 mmol), cesium carbonate (25.4 g, 78 mmol) and potassium iodide (5.33 g, 32.1 mmol) in *N*,*N*-dimethylformamide (50 mL) was stirred overnight at 50 °C. The reaction mixture was diluted with water (250 mL) and extracted with ethyl acetate (250 mL × 3). The organic layer was collected, washed with saturated brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by column chromatography to give the target

product, benzyl 4-(3-formyl-1*H*-pyrrol-1-yl)piperidine-1-carboxylate.

[0272] LC-MS: (ESI, *m/z):* $[M+Na]^{l}$ = 336.3.

Step 3: preparation of benzyl 4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0273]

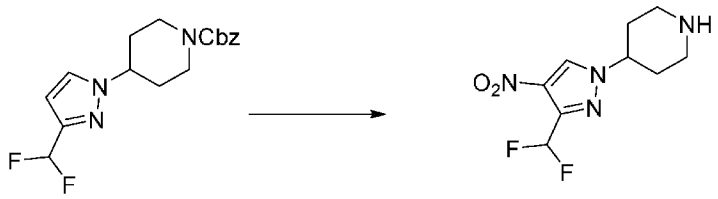


[0274] Diethylaminosulfur trifluoride (4.62 g, 28.7 mmol) was added to a mixture of benzyl 4-(3-formyl-1*H*-pyrrol-1-yl)piperidine-1-carboxylate (1.5 g, 4.8 mmol) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the concentrate was purified by column chromatography to give the target product, benzyl 4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0275] LC-MS: (ESI, *m/z):* $[M+H]^{+}$ = 336.1.

Step 4: preparation of 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine

[0276]

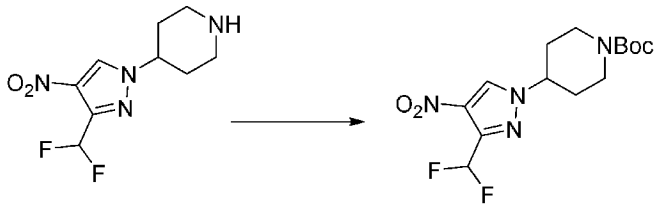


[0277] Nitric acid (1 mL) was added to a mixture of benzyl 4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (1.0 g, 3.0 mmol) in sulfuric acid (5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into ice water (30 mL) and extracted with methanol/dichloromethane (10%, 50 mL × 3). The organic layer was collected, washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the target product, 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine. The resulting crude product was directly used in the next step.

[0278] LC-MS: (ESI, *m/z):* $[M+H]^{+}$ = 247.1.

Step 5: preparation of tert-butyl 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0279]



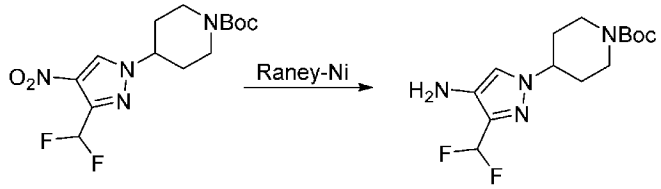
[0280] A mixture of 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine (650 mg, 2.6 mmol), *di-tert*-butyl dicarbonate (680 mg, 3.1 mmol), triethylamine (788 mg, 7.8 mmol) and 4-dimethylaminopyridine (32 mg, 0.26 mmol) in dichloromethane (10 mL) was stirred overnight at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL × 3). The organic layer was collected, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by chromatography to

give the target product, *tert*-butyl 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0281] LC-MS: (ESI, *m/z*): $[M-57+2H]^+$ = 291.1.

Step 6: preparation of tert-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0282]

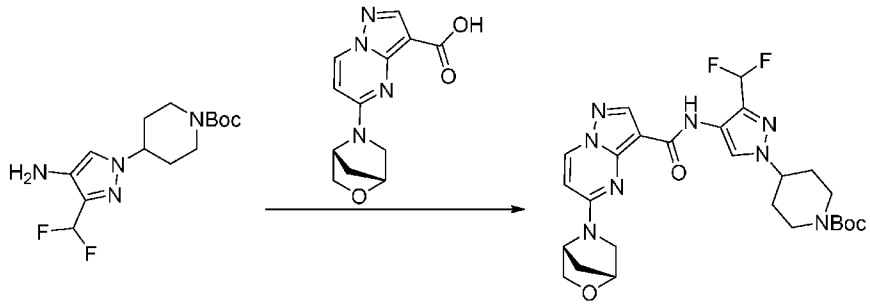


[0283] Raney-Ni (70 mg) and hydrazine hydrate (85%, 1.0 mL) were added to a solution of tert-butyl 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (710 mg, 2.052 mmol) in ethanol (20 mL). The reaction mixture was stirred at room temperature for 2 h and filtered, and the filtrate was concentrated under reduced pressure to give the target product, *tert*-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate. The resulting crude product was used in the next step without further purification.

[0284] LC-MS: (ESI, *m/z*): $[M-57+2H]^+$ = 261.3.

Step 7: preparation of *tert*-butyl 4-(4-(5-((1*R*,4*R*)-2-oxa-5-aza[2.2.1]heptan-5-yl)pyrazolo[1,5-α]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0285]

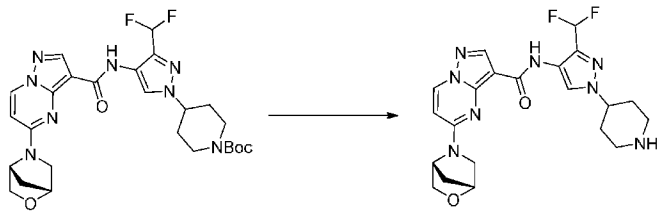


[0286] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (461 mg, 1.77 mmol), HATU (874 mg, 2.3 mmol) and *N,N*-diisopropylethylamine (685 mg, 5.1 mmol) were added to a mixture of tert-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (560 mg, 1.77 mmol) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (100 mL). The resulting solution was extracted with ethyl acetate (50 mL × 3). The organic layer was collected, washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by column chromatography to give the target product, *tert*-butyl 4-(4-(5-((1*R*,4*R*)-2-oxa-5-aza[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(diffuoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0287] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 559.2.

Step 8: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0288]



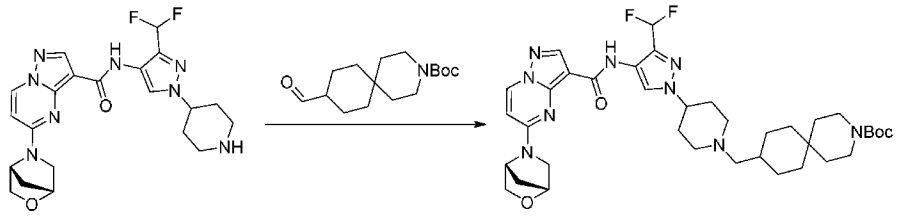
[0289] A solution of *tert*-butyl 4-(4-(5-((1*R*,4*R*)-2-oxa-5-aza[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyraaol-1-yl)piperidine-1-carboxylate (540 mg, 0.97 mmol) in trifluoroacetic acid/dichloromethane (8 mL, 1:3) was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude product of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The crude product was directly used in the next step.

[0290] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 459.2.

Intermediate 19: *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-((4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro [5.5]undecane-3-carboxylate

[0291]

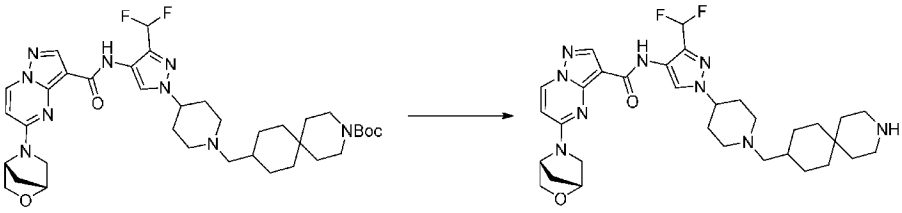


[0292] *N,N*-Diisopropylethylamine (0.5 mL) and *tert*-butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (94 mg, 0.334 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200 mg, crude, 0.334 mmol) in methanol (10 mL). After the mixture was stirred for 30 min, sodium cyanoborohydride (106 mg, 1.67 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL × 3). The organic layer was collected, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by column chromatography to give the target product, *tert-butyl* 9-((4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0293] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 724.4.

Step 2: preparation of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0294]



[0295] A mixture of *tert*-butyl 9-((4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (130 mg, 0.18 mmol) in trifluoroacetic acid/dichloromethane (6 mL, 1:2) was stirred at room temperature for 1 h. The reaction

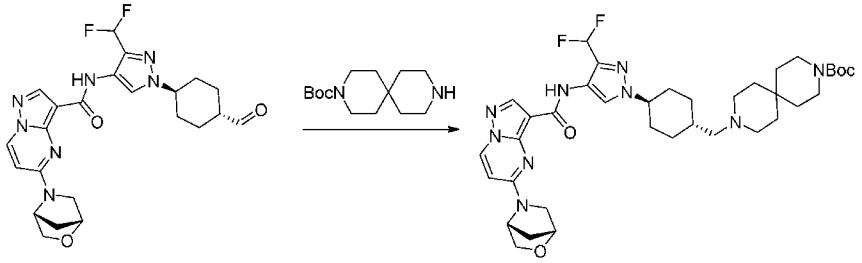
mixture was concentrated under reduced pressure to give a crude product of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The crude product was directly used in the next step.

[0296] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 624.4.

Intermediate 20: *N*-(1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-aaabicyclo[2.2.1]heptan-5-yl)pyraaolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0297]

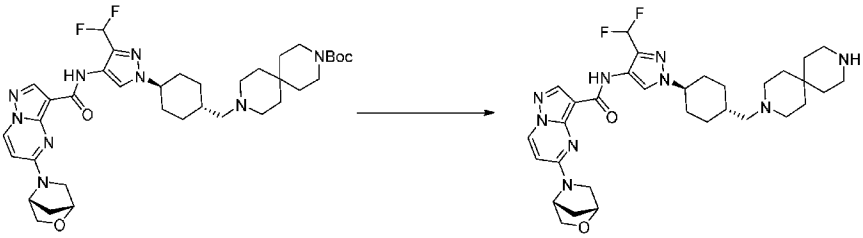


[0298] A reaction mixture of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.31 mmol), *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (86 mg, 0.34 mmol) and sodium triacetoxyborohydride (326 mg, 1.55 mmol) in tetrahydrofuran (15 mL) was stirred overnight at room temperature. The reaction mixture was quenched with water (50 mL). The resulting solution was extracted with dichloromethane (20 mL × 3). The organic layer was collected, washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrate was purified by column chromatography to give *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[0299] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 724.3.

Step 2: preparation of *N*-(1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0300]



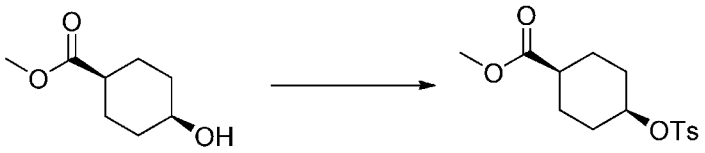
[0301] Trifluoroacetic acid (2 mL) was added to a stirred solution of *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (200 mg, 0.27 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to give a crude product of *N*-(1-((1R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The crude product was directly used in the next step.

[0302] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 624.3.

Intermediate 21: ((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol

Step 1: preparation of methyl (1*S*,4*S*)-4-(*p*-toluenesulfonyloxy)cyclohexane-1-carboxylate

[0303]



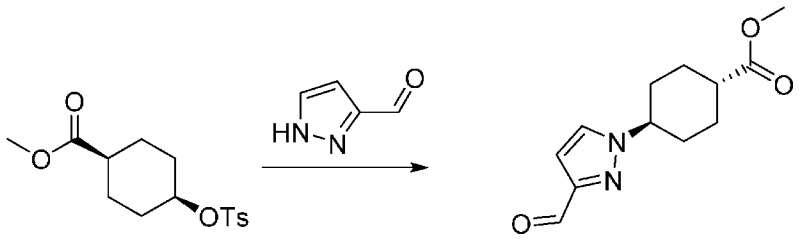
[0304] The compound methyl (1*S*,4*S*)-4-hydroxycyclohexane-1-carboxylate (5.0 g, 31.6 mmol) was dissolved in DCM (50 mL), and DMAP (1.9 g, 15.8 mmol), TEA (16.0 g, 158 mmol) and TsCl (9.1 g, 47.5 mmol) were added. The mixture was stirred overnight at room temperature. Water (100 mL) was added to the reaction liquid, and the resulting mixture was extracted with DCM (100 mL × 3). The organic phase was washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, and filtered. The crude product was purified by column chromatography (EA/PE = 1:1) to give methyl (1*S*,4*S*)-4-(*p*-toluenesulfonyloxy)cyclohexane-1 -carboxylate.

[0305] LC-MS: (ES, *m/z*): $[M+NH_4^+]^+$ = 330.0.

[0306] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83-7.76 (m, 2H), 7.47 (d, *J*= 7.9 Hz, 2H), 4.66 (s, 1H), 3.59 (s, 3H), 2.42 (s, 3H), 1.67-1.53 (m, 8H).

Step 2: preparation of methyl (1*R*,4*R*)-4-(3-formyl-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0307]



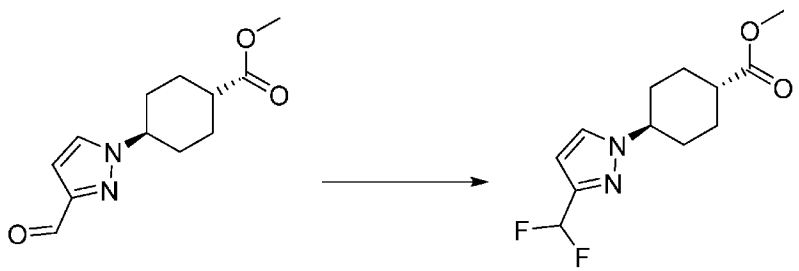
[0308] 1*H*-Pyrazole-3-carbaldehyde (2.4 g, 25.0 mmol) was dissolved in DMF (50 mL), and methyl (1*S*,4*S*)-4-(*p*-toluenesulfonyloxy)cyclohexane-1-carboxylate (9.4 g, 30.0 mmol), Cs_2CO_3 (24.5 g, 75 mmol) and KI (5.0 g, 30.0 mmol) were added. The mixture was stirred overnight at 50 °C, and water (500 mL) was added. After 5 min of stirring, the mixture was extracted with EA (500 mL × 3). The organic phase was washed with saturated brine (500 mL), dried over anhydrous sodium sulfate, and filtered. The crude product was purified by column chromatography (EA:PE = 7:13) to give methyl (1*R*,4*R*)-4-(3-formyl-1*H*-pyrazol-1-yl)cyclohexane-1 -carboxylate.

[0309] LC-MS: (ES, *m/z):* $[M+H]^+$ = 237.1.

[0310] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.39-4.29 (m, 1H), 3.62 (s, 3H), 2.47-2.38 (m, 1H), 2.14-2.01 (m, 4H), 1.91-1.77 (m, 2H), 1.62-1.48 (m, 2H).

Step 3: preparation of methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0311]



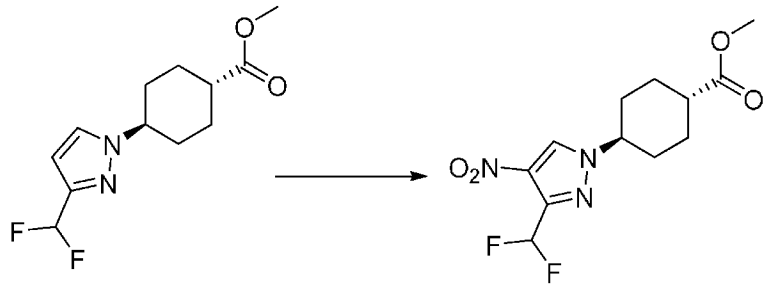
[0312] Methyl (1*R*,4*R*)-4-(3-formyl-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (1.0 g, 4.2 mmol) was dissolved in anhydrous DCM (20 mL), and DAST (4.1 g, 25.4 mmol) was added at 0 °C. The mixture was slowly warmed to room temperature and stirred overnight. A saturated aqueous solution of sodium bicarbonate was added dropwise to the reaction mixture in an ice bath to quench the reaction. The aqueous phase was separated and extracted twice with dichloromethane. After concentration under reduced pressure, the resulting crude product was purified by column chromatography (EA:PE = 1:4) to give methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-1*H*-pyrazol-1 -yl)cyclohexane-1-carboxylate.

[0313] LC-MS: (ES, *m/z*): $[M+H]^+$ = 259.1.

[0314] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.08-6.85 (m, 1H), 6.49 (s, 1H), 4.28-4.17 (m, 1H), 3.62 (s, 3H), 2.47-2.36 (m, 1H), 2.15-1.95 (m, 4H), 1.86-1.73 (m, 2H), 1.61-1.48 (m, 2H).

Step 4: preparation of methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1 -carboxylate

[0315]

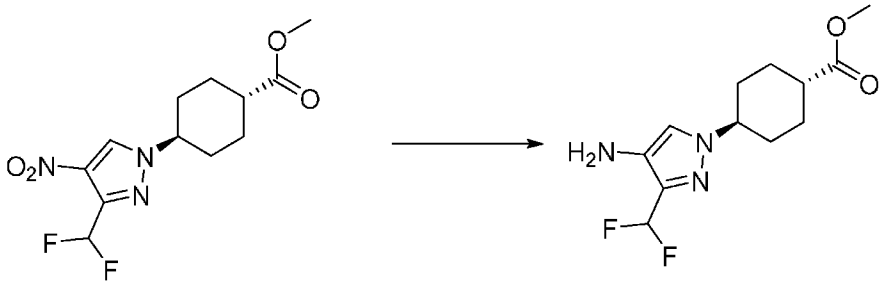


[0316] Methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl(cyclohexane-1-carboxylate (1.0 g, 3.9 mmol) was dissolved in concentrated H_2SO_4 (5 mL), and concentrated HNO_3 (1 mL) was added dropwise at 0 °C. The mixture was slowly warmed to room temperature and stirred overnight. The reaction liquid was slowly poured into an ice water mixture (20 mL). The resulting mixture was filtered, and the filter cake was washed with water 3 times and then dried under vacuum to give methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1 -carboxylate. The resulting product was directly used in the next step.

[0317] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 7.39-7.20 (m, 1H), 4.42-4.30 (m, 1H), 3.62 (s, 3H), 2.46-2.37 (m, 1H), 2.16-2.00 (m, 4H), 1.93-1.72 (m, 2H), 1.59-1.40 (m, 2H).

Step 5: preparation of methyl (1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0318]

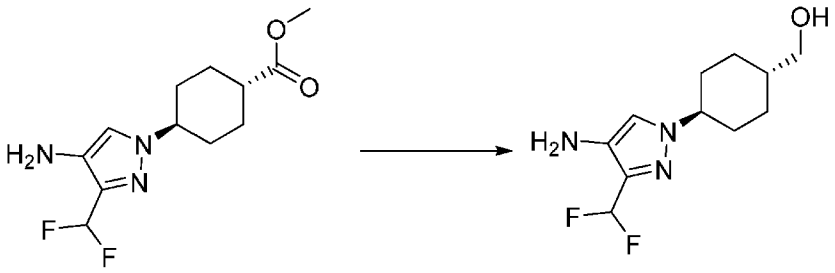


[0319] Methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (880 mg, 2.9 mmol) was dissolved in THF (10 mL), and Pd/C (440 mg, 50%) was added. The mixture was purged with H_2 3 times and stirred at room temperature for 4 h under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give methyl (1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1 -yl)cyclohexane-1-carboxylate. The resulting crude product was directly used in the next step.

[0320] LC-MS: (ES, *m/z):* $[M+H]^+$ = 274.1.

Step 6: preparation of ((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol

[0321]



[0322] Methyl (1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (750 mg, 2.7 mmol) was dissolved in anhydrous THF (5 mL), and BH_3/THF (27.5 mL, 1 M/THF, 27.5 mmol) was added at 0 °C. The mixture was slowly warmed to room temperature and stirred overnight. MeOH was added dropwise to the reaction liquid in an ice bath until no visible bubbles were generated, and the resulting mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give ((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol.

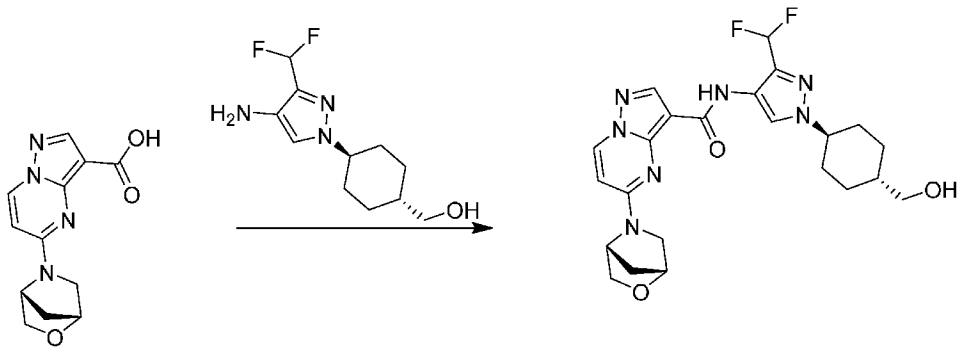
[0323] LC-MS: (ES, *m/z*): $[M+H]^+$ = 246.1.

[0324] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17 (d, *J* = 14.3 Hz, 1H), 7.06-6.68 (m, 1H), 4.46 (t, *J* = 5.3 Hz, 1H), 4.03 (s, 2H), 3.94 (td, *J* = 8.2, 4.0 Hz, 1H), 3.27-3.22 (m, 2H), 1.97 (d, *J* = 9.5 Hz, 2H), 1.83 (d, *J* = 11.4 Hz, 2H), 1.69-1.57 (m, 2H), 1.39 (d, *J* = 2.9 Hz, 1H), 1.12-0.97 (m, 2H).

Intermediate 22: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0325]



[0326] ((1*R*,4*R*)-4-(4-Amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol (360 mg, 1.5 mmol) was dissolved in DMF (10 mL), and 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (380 mg, 1.5 mmol), DIEA (566 mg, 4.4 mmol) and HATU (726 g, 1.9 mmol) were added. The mixture was stirred overnight at room temperature, and water (50 mL) was added. After 5 min of stirring, the mixture was extracted with EA (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

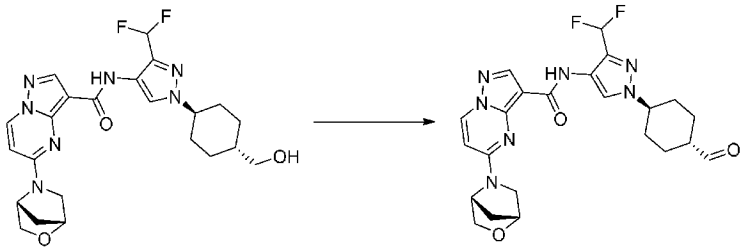
[0327] LC-MS: (ES, *m/z*): $[M+H]^+$ = 488.2.

[0328] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (d, *J* = 5.4 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.2 Hz, 1H), 8.23 (d, *J* = 5.4 Hz, 1H), 7.30-6.94 (m, 1H), 6.90-6.34 (m, 1H), 5.33-5.03 (m, 1H), 4.77 (d, *J* = 16.7 Hz, 1H), 4.52-4.30 (m, 1H), 4.22-4.05 (m, 1H), 3.89-3.69 (m, 2H), 3.67-3.42 (m, 2H), 3.17-2.97 (m, 2H), 2.12-1.80 (m, 6H), 1.80-1.61 (m,

2H), 1.48-1.36 (m, 1H), 1.19-1.01 (m, 2H).

Step 2: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0329]



[0330] IBX (460 mg, 1.64 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (400 mg, 0.82 mmol) in ACN (20 mL), and the reaction liquid was stirred at 85 °C for 1 h. After the reaction liquid was concentrated under reduced pressure, water (50 mL) was added, and the resulting mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, and then concentrated. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

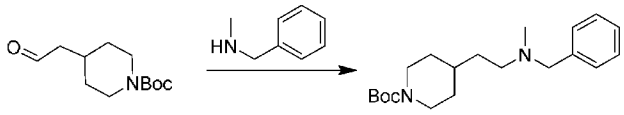
[0331] LC-MS: (ES, *m/z*): $[M+H]^+$ = 486.2.

[0332] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 9.51 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.44-8.35 (m, 1H), 8.26 (d, *J* = 5.2 Hz, 1H), 7.27-6.98 (m, 1H), 6.93-6.40 (m 1H), 5.30-5.05 (m, 1H), 4.77 (d, *J* = 16.6 Hz, 1H), 4.26-4.15 (m, 1H), 3.84-3.72 (m, 2H), 3.67-3.59 (m, 2H), 3.45 (d, *J* = 9.9 Hz, 1H), 2.45-2.35 (m, 1H), 2.18-1.74 (m, 8H), 1.45-1.28 (m, 2H).

Intermediate 23: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-α]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(2-(phenyl(methyl)amino)ethyl)piperidine-1-carboxylate

[0333]



[0334] *N*-Methyl-1-phenylmethylamine (1.067 g, 8.82 mmol) andAcOH (0.79 g, 13.23 mmol) were added to a solution of *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1 g, 4.41 mmol) in DCE (3 mL) under N_2 atmosphere. After the mixture was stirred at room temperature for 30 min, STAB (2.8 g, 13.23 mmol) was added, and then the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL), and the mixture was extracted with EA (30 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:20) to give tert-butyl 4-(2-(phenyl(methyl)amino)ethyl)piperidine-1 -carboxylate.

[0335] LC-MS: (ESI, m/z): $[M+H]^+$ = 333.2.

Step 2: preparation of tert-butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate

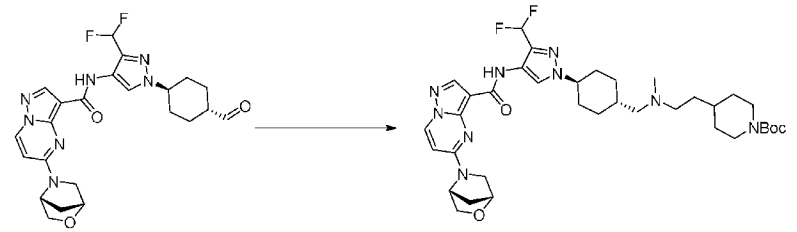
[0336]

[0337] $Pd(OH)_2/C$ (250 mg) was added to a solution of *tert*-butyl 4-(2-(phenyl(methyl)amino)ethyl)piperidine-1-carboxylate (1 g, 3.01 mmol) in THF (3 mL), and the reaction liquid was then stirred at room temperature for 2 h under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give tert-butyl 4-(2-(methylamino)ethyl)piperidine-1 -carboxylate.

[0338] LC-MS: (ESI, m/z): $[M+H]^+$ = 243.2.

Step 3: preparation of *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[0339]

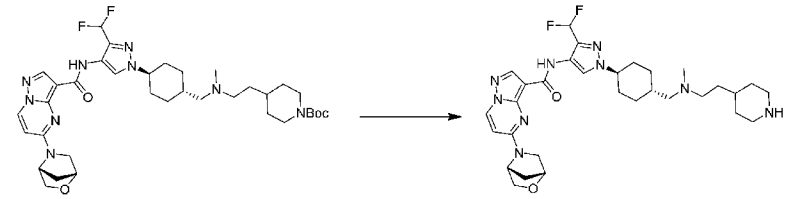


[0340] *tert*-Butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (329 mg, 0.928 mmol) and STAB (419 mg, 1.862 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (300 mg, 0.618 mmol) in THF (3 mL), and the reaction was stirred at room temperature for 2 h under N2 atmosphere. Water (20 mL) was added to quench the reaction, and the mixture was extracted with DCM (20 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[0341] LC-MS: (ESI, m/z): $[M+H]^+$ = 712.4.

Step 4: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-α]pyrimidine-3-carboxamide

[0342]



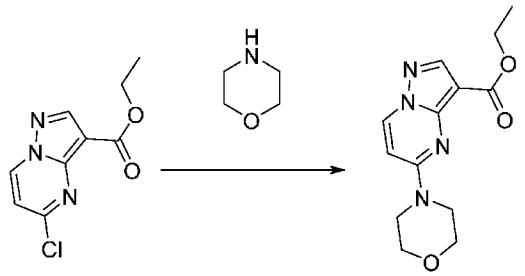
[0343] TFA (1 mL) was added to a solution of *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (200 mg, 0.281 mmol) in DCM (3 mL), and the reaction liquid was stirred at room temperature for 2 h under N2 atmosphere. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0344] LC-MS: (ESI, m/z): $[M+H]^+$ = 612.4.

Intermediate 24: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[0345]

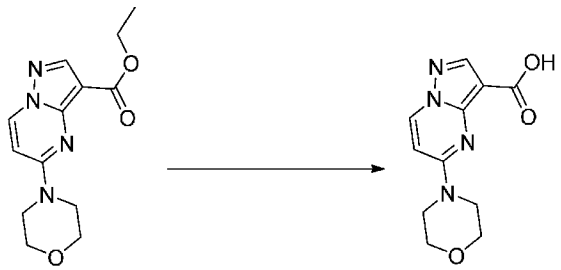


[0346] *tert*-Butyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6 g, 27 mmol), morpholine (2.3 g, 27 mmol) and *N,N*-diisopropylethylamine (10.4 g, 81 mmol) were dissolved in acetonitrile (60 mL), and the mixture was heated to 60 °C and stirred overnight. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate) to give ethyl 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3 -carboxylate.

[0347] LC-MS: (ESI, m/z): $[M+H]^+$ = 277.3.

Step 2: preparation of 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

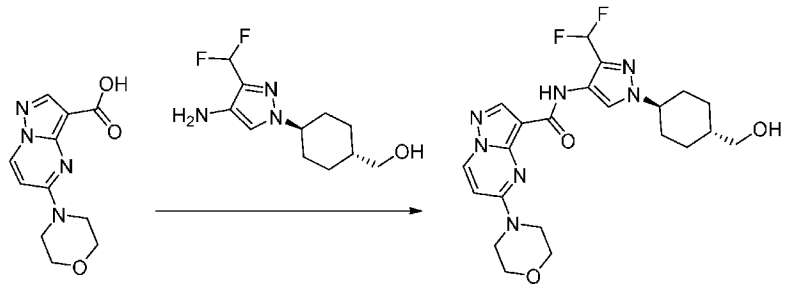
[0348]



[0349] Ethyl 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4.3 g, 16 mmol) was dissolved in a mixed solution (methanol/water = 5:1, 40 mL), and lithium hydroxide (2.6 g, 64 mmol) was added. The mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 2 with dilute hydrochloric acid (2 mol/L) and filtered, and the solid was dried under vacuum to give 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0350]

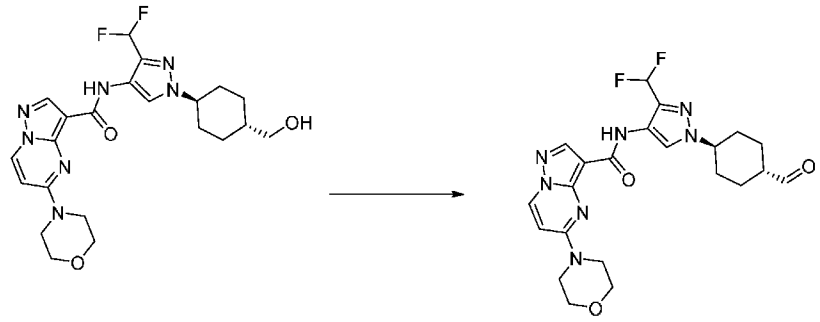


[0351] 5-Morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (248 mg, 1.0 mmol), ((1R,4R)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol (245 mg, 1.0 mmol) and HATU (494 mg, 1.3 mmol) were dissolved in DMF (5 mL), and DIEA (387 mg, 3.0 mmol) was added. The reaction liquid was stirred at room temperature for 16 h. After the reaction was complete, the reaction liquid was diluted with water (50 mL), stirred, and filtered. The filter cake was washed with water (5 mL × 3) and dried under vacuum to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0352] LC-MS: (ESI, m/z): $[M+H]^+$ = 476.1.

Step 4: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0353]



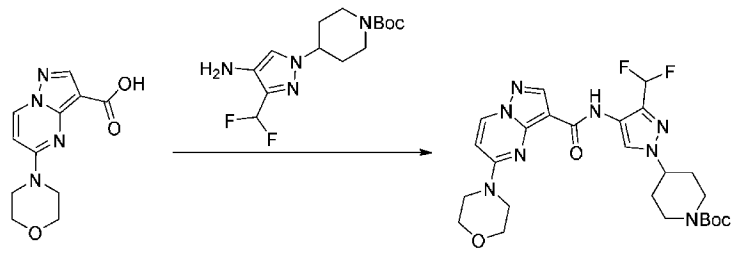
[0354] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.17 mmol) was dissolved in DCM (4 mL), and the Dess-Martin (144 mg, 0.34 mmol) reagent was added. The reaction liquid was stirred overnight at room temperature. After filtration, the solid was washed with DCM (10 mL × 3). The organic phase was concentrated under reduced pressure, and the crude product was purified by normal-phase column chromatography to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0355] LC-MS: (ESI, m/z): $[M+H]^+$ = 474.1.

Intermediate 25: *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0356]



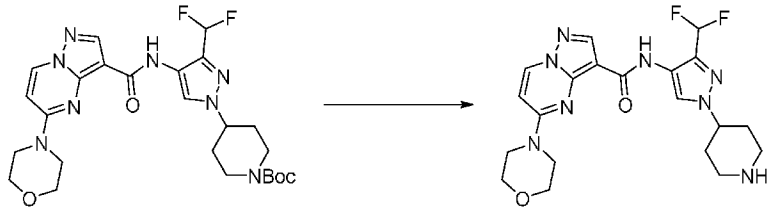
[0357] HATU (900 mg, 2.4 mmol) was added to a solution of 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (470 mg, 1.9 mmol) and DIEA (1 mL, 4.7 mmol) in DMF (20 mL) at 25 °C. After the mixture was stirred at 25 °C for 2 h, *tert*-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (0.5 g, 1.5 mmol) was added, and the reaction liquid was then stirred overnight at 25 °C. Water (30 mL) was added to the reaction liquid, and the mixture was then extracted with EA (50 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA) to give *tert*-butyl 4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-

carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0358] LC-MS: (ESI, m/z): $[M+H]^+$ = 547.4.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0359]

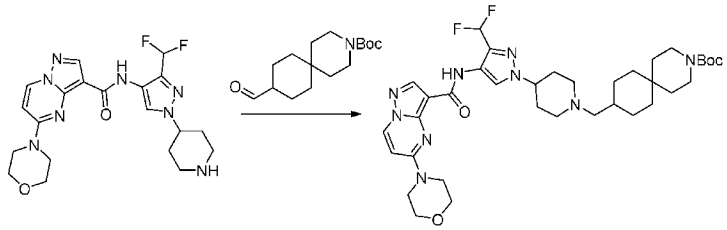


[0360] TFA (1 mL) was added to a solution of *tert*-butyl 4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (0.2 g, 0.366 mmol) in DCM (3 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0361] LC-MS: (ESI, m/z): $[M+H]^l$ = 447.2.

Step 3: preparation of *tert*-butyl 9-((4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate

[0362]

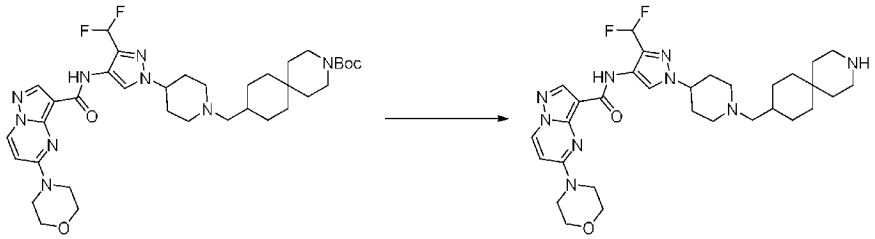


[0363] *tert*-Butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (150 mg, 0.45 mmol) and $NaBH_3CN$ (100 mg, 2.25 mmol) were added to a solution of *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200 mg, 0.45 mmol) andDIEA(0.5 mL, 1.35 mmol) in MeOH (5 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 16 h. After filtration and concentration under reduced pressure, the resulting crude product was purified by flash column chromatography (MeOH:DCM = 3:97) to give *tert*-butyl 9-((4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0364] LC-MS: (ESI, m/z): $[M+H]^+$ = 712.4.

Step 4: preparation of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0365]

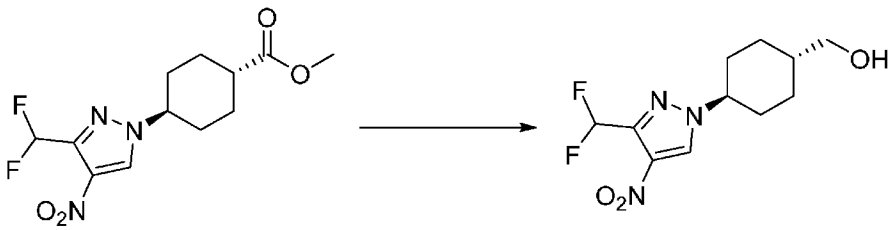


[0366] TFA (1 mL) was added to a solution of *tert*-butyl 9-((4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (0.14 g, 0.2 mmol) in DCM (3 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(diffuoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting product was directly used in the next step.

[0367] LC-MS: (ESI, m/z): $[M+H]^+$ = 612.5.

Intermediate 26: ((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)methanol

[0368]



[0369] A solution of methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (4.0 g, 13.2 mmol) in THF (50 mL) was cooled to -20 °C, and $LiAlH_4$ (1 M in THF, 16 mL) was added dropwise. After the reaction liquid was stirred at room temperature for 0.5 h, a 15% sodium hydroxide solution (8 mL) was slowly added, and water (50 mL) was added. The mixture was extracted with a MeOH/DCM mixed solution (V/V = 1:9, 50 mL × 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give ((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)methanol.

[0370] LC-MS: (ESI, m/z): $[M-56]^l$ = 276.0.

Intermediate 27: *N*-(1-(1-(2-(3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(2-oxoethyl)-3-azaspiro[5.5]undecane-3-carboxylate

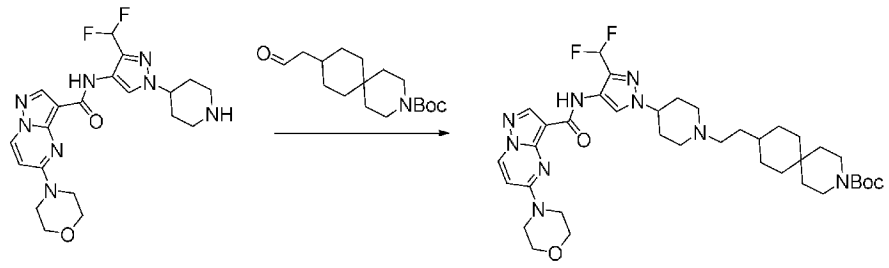
[0371]

[0372] *tert*-Butyl 9-(2-hydroxyethyl)-3-azaspiro[5.5]undecane-3-carboxylate (250 mg, 0.842 mmol) and PCC (543.8 mg, 2.523 mmol) were added to DCM (5 mL). The mixture was stirred at room temperature for 2 h and then filtered. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product of *tert*-butyl 9-(2-oxoethyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0373] LC-MS: (ESI, m/z): $[M-56]^+$ = 240.1.

Step 2: preparation of *tert*-butyl 9-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)-3-azaspiro[5.5]undecane-3-carboxylate

[0374]

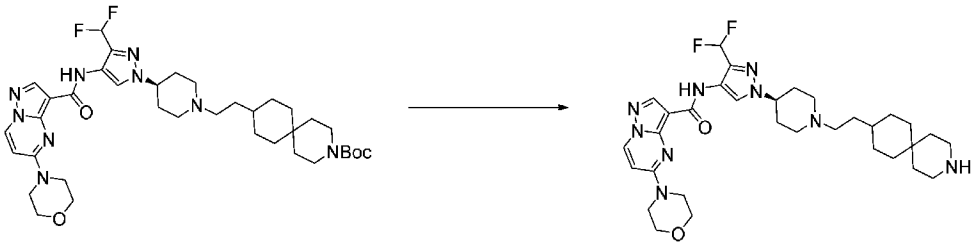


[0375] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (140 mg, 0.314 mmol) and tert-butyl 9-(2-oxoethyl)-3-azaspiro[5.5]undecane-3-carboxylate (185 mg, 0.628 mmol) were added to THF, and sodium triacetoxyborohydride (133 mg, 0.628 mmol) was then added. The mixture was stirred at room temperature for 2 h, and water (20 mL) was added. The mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal-phase column chromatography (MeOH:DCM = 1:19) to give *tert*-butyl 9-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0376] LC-MS: (ESI, m/z): $[M+H]^+$ = 726.4.

Step 3: preparation of *N*-(1-(1-(2-(3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0377]



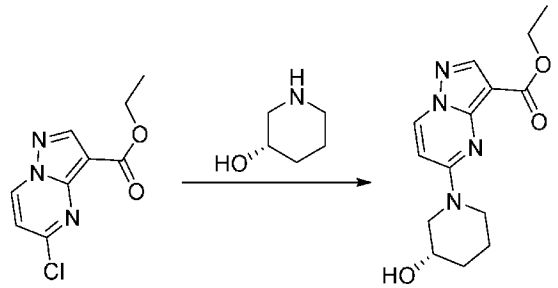
[0378] *tert*-Butyl 9-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)-3-azaspiro[5.5]undecane-3-carboxylate (121 mg, 0.167 mmol) was added to TFA (0.5 mL) and DCM (2.5 mL), and the mixture was stirred at room temperature for 2 h. The reaction liquid was concentrated under reduced pressure to give a crude product of *N*-(1-(1-(2-(3-azaspiro[5.5]undecane-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0379] LC-MS: (ESI, m/z): $[M+H]^+$ = 626.4.

Intermediate 28: *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl (*S*)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[0380]

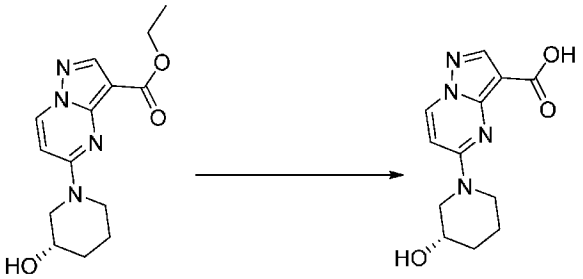


[0381] Ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.0 g, 4.4 mmol), (*S*)-piperidin-3-ol (445 mg, 4.4 mmol) and *N,N*-diisopropylethylamine (1.7 g, 13.3 mmol) were dissolved in acetonitrile (10 mL), and the reaction liquid was heated to 60 °C and stirred overnight. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate:petroleum ether = 87:13) to give ethyl (*S*)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[0382] LC-MS: (ESI, m/z): $[M+H]^+$ = 291.1.

Step 2: preparation of (*S*)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

[0383]

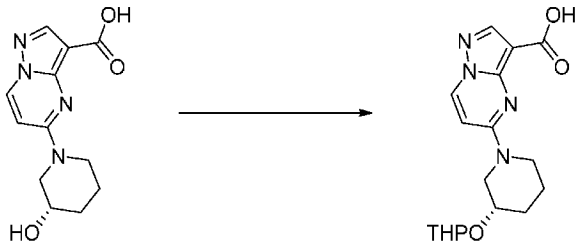


[0384] Ethyl (*S*)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.1 g, 3.9 mmol) was dissolved in a mixed solution (methanol/water = 5:1, 10 mL), and lithium hydroxide (643 mg, 16 mmol) was added. The mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 2 with dilute hydrochloric acid (2 mol/L) and filtered, and the filter cake was dried under vacuum to give (5)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0385] LC-MS: (ESI, m/z): $[M+H]^+$ = 263.1.

Step 3: preparation of 5-((3S)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

[0386]

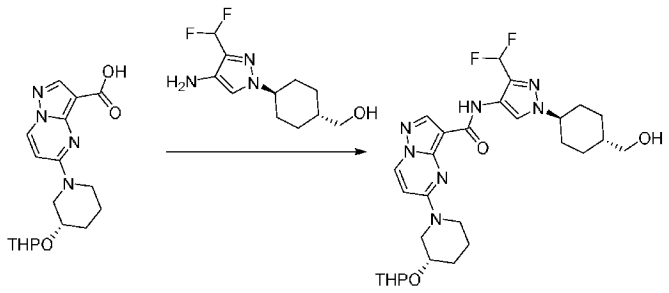


[0387] (*S*)-5-(3-Hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (300 mg, 1.14 mmol) was dissolved in tetrahydrofuran (15 mL), and 3,4-dihydro-2*H*-pyran (962 mg, 11.4 mmol) and tetrabutylammonium tribromide (111 mg, 0.23 mmol) were added. The mixture was heated to 60 °C and stirred overnight. The reaction liquid was concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate) to give 5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0388] LC-MS: (ESI, m/z): $[M+H]^+$ = 347.2.

Step 4: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0389]

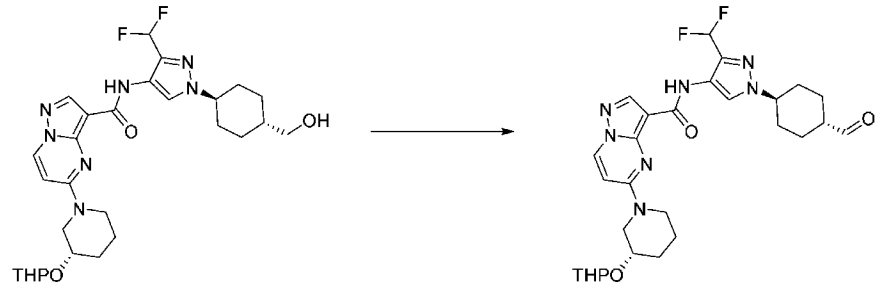


[0390] 5-((3*S*)-3-((Tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (180 mg, 0.52 mmol) and ((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol (137 mg, 0.52 mmol) were dissolved in DMF (10 mL), and *N,N*-diisopropylethylamine (201 mg, 1.56 mmol) and py-BOP (348 mg, 0.67 mmol) were added with stirring. The mixture was stirred overnight at 60 °C. The reaction liquid was cooled to room temperature, and water (100 mL) was added. The mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0391] LC-MS: (ESI, m/z): $[M+H]^+$ = 574.3.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0392]



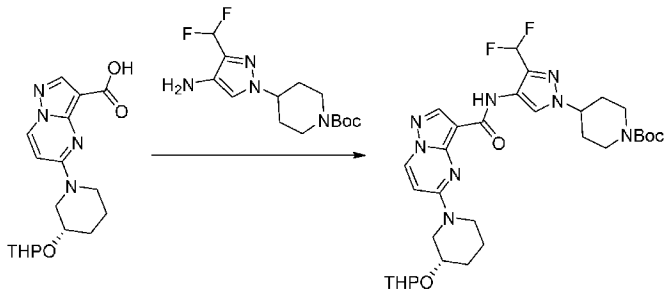
[0393] *N*-(3-(Difluoromethyl)-1-((1*R*,4*S*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200 mg, 0.35 mmol) was dissolved in acetonitrile (20 mL), and IBX (196 mg, 0.70 mmol) was added. The mixture was stirred at 80 °C for 2 h. The reaction liquid was concentrated under reduced pressure, and the crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give N (3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0394] LC-MS: (ESI, m/z): $[M+H]^+$ = 572.3.

Intermediate 29: preparation of (*S*)-*N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0395]

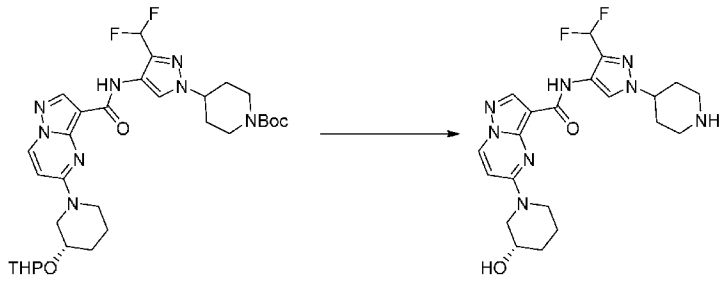


[0396] 5-((3*S*)-3-((Tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (210 mg, 0.61 mmol) and tert-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (191 mg, 0.61 mmol) were dissolved in DMF (10 mL), and *N,N*-diisopropylethylamine (236 mg, 1.83 mmol) and Py-BOP (475 mg, 0.91 mmol) were added with stirring. The mixture was heated to 60 °C and stirred overnight. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give *tert*-butyl 4-(3-(difluoromethyl)-4-(5-((3S)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0397] LC-MS: (ESI, m/z): $[M+H]^+$ = 645.3.

Step 2: preparation of (*S*)-*N*-(3-(-difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0398]

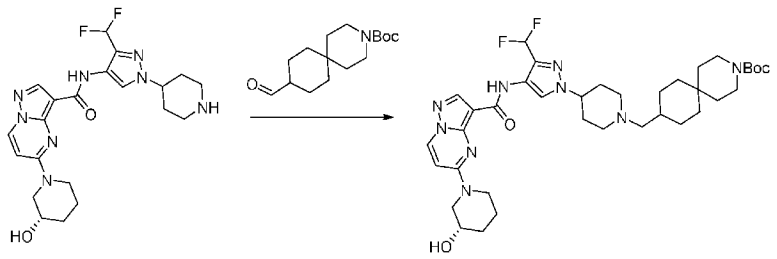


[0399] *tert*-Butyl 4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (180 mg, 0.28 mmol) was dissolved in dichloromethane (3 mL), and trifluoroacetic acid (1 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give (*S*)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[0400] LC-MS: (ESI, m/z): $[M+H]^+$ = 461.2.

Step 3: preparation of *tert*-butyl (*S*)-9-((4-(3-(difluoromethyl)-4-(5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro [5.5]undecane-3-carboxylate

[0401]

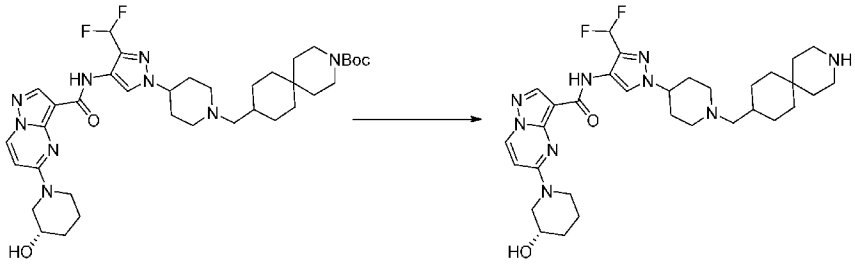


[0402] (*S*)-*N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (180 mg, crude, 0.28 mmol) and tert-butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (87 mg, 0.31 mmol) were dissolved in tetrahydrofuran (10 mL), and sodium triacetoxyborohydride (180 mg, 0.84 mmol) was added with stirring. The mixture was stirred overnight at room temperature. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give tert-butyl (*S*)-9-((4-(3-(difluoromethyl)-4-(5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0403] LC-MS: (ESI, m/z): $[M+H]^+$ = 726.3.

Step 4: preparation of (*S*)-*N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0404]



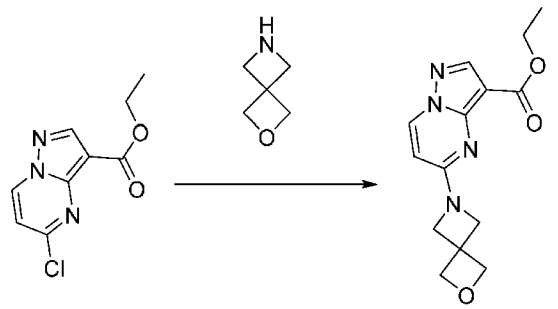
[0405] tert-Butyl (*S*)-9-((4-(3-(difluoromethyl)-4-(5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (160 mg, 0.22 mmol) was dissolved in dichloromethane (3 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give (*S*)-*N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[0406] LC-MS: (ESI, m/z): $[M+H]^+$ = 626.4.

Intermediate 30: *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[0407]

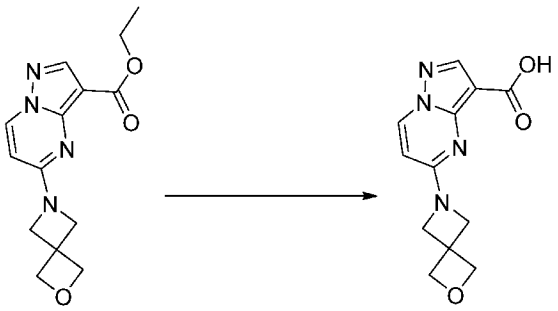


[0408] Ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.0 g, 4.4 mmol), 2-oxa-6-azaspiro[3.3]heptane (439 mg, 4.4 mmol), and *N,N*-diisopropylethylamine (1.7 g, 13.3 mmol) were dissolved in acetonitrile (10 mL), and the reaction liquid was heated to 60 °C and stirred overnight. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate) to give ethyl 5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[0409] LC-MS: (ESI, m/z): $[M+H]^+$ = 289.2.

Step 2: preparation of 5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

[0410]

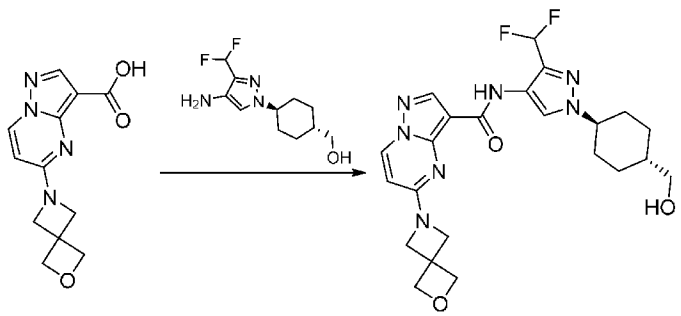


[0411] Ethyl 5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.1 g, 3.8 mmol) was dissolved in 10 mL of a mixed solution (methanol/water = 5:1), lithium hydroxide (639 mg, 15 mmol) was added, and the mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 2 with 2 mol/L dilute hydrochloric acid and filtered. The solid was dried under vacuum to give 5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0412] LC-MS: (ESI, m/z): $[M+H]^+$ = 261.1.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0413]



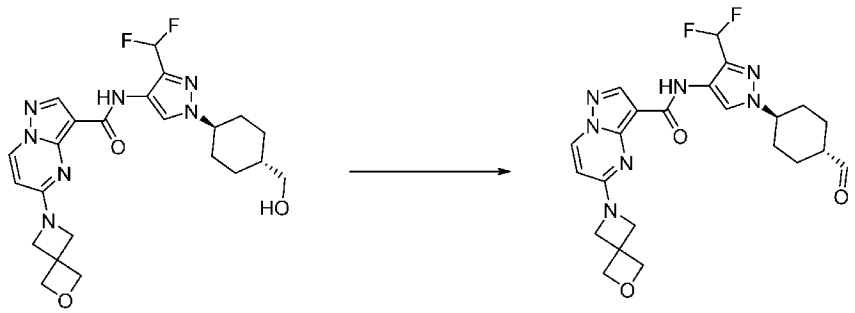
[0414] 5-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (110 mg, 0.41 mmol) and ((1*R*,4*R*)-4-(4-amino-3-(diffuoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol (100 mg, 0.41 mmol) were dissolved in

DMF (3 mL). HATU (202 mg, 0.53 mmol) and DIEA (212 mg, 1.6 mmol) were added. The reaction liquid was heated to 90 °C, stirred overnight, diluted with water (80 mL), extracted with ethyl acetate (100 mL × 2), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 1:9) to give the compound *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

[0415] LC-MS: (ESI, m/z): $[M+H]^+$ = 488.2.

Step 4: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0416]



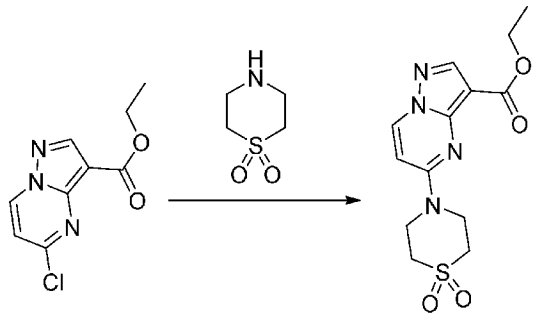
[0417] The compound *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1H-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.246 mmol) was dissolved in DCM (3 mL), then PCC (107 mg, 0.493 mmol) was added, and the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL) and extracted with dichloromethane (25 mL × 4). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MEOH = 1:10) to give the compound *N*-(3-(difluoromethyl)-1-((*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0418] LC-MS: (ESI, m/z): $[M+H]^+$ = 486.3.

Intermediate 31: *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[0419]

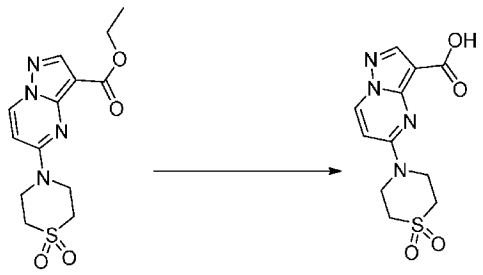


[0420] Ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.0 g, 4.4 mmol), thiomorpholine 1,1-dioxide (906 mg, 5.3 mmol), and *N,N*-diisopropylethylamine (2.3 g, 18 mmol) were dissolved in acetonitrile (10 mL), and the mixture was heated to 60 °C and stirred overnight. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate:petroleum ether = 9:1) to give ethyl 5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[0421] LC-MS: (ESI, m/z): $[M+H]^+$ = 325.0.

Step 2: preparation of 5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

[0422]

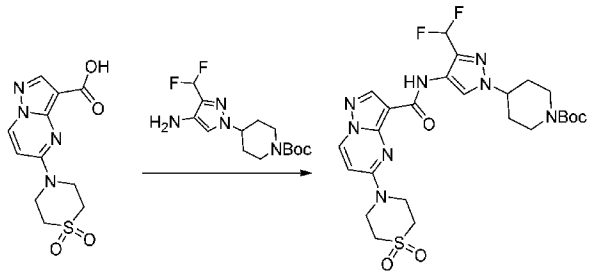


[0423] Ethyl 5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (900 mg, 2.8 mmol) was dissolved in a mixed solution (methanol/water = 5:1, 10 mL), lithium hydroxide (470 mg, 11.2 mmol) was added, and the mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 3 with dilute hydrochloric acid (2 mol/L) and filtered, and the filter cake was dried under vacuum to give 5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0424] LC-MS: (ESI, m/z): $[M+H]^+$ = 297.0.

Step 3: preparation of *tert*-butyl 4-(3-(difluoromethyl)-4-(5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0425]

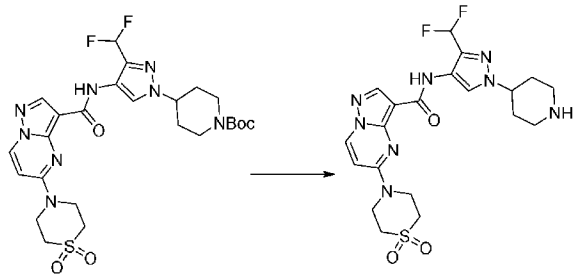


[0426] 5-(1,1-Dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (150 mg, 0.51 mmol) and tert-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (161 mg, 0.51 mmol) were dissolved in DMF (5 mL), DIEA (271 mg, 2.1 mmol) and HATU (251 mg, 0.66 mmol) were added while stirring, and the reaction liquid was stirred at room temperature for 12 h. The reaction liquid was diluted with water (60 mL) and extracted with ethyl acetate (60 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 7:3) to give tert-butyl 4-(3-(difluoromethyl)-4-(5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1H-pyrazol-1-yl)piperidine-1-carboxylate.

[0427] LC-MS: (ESI, m/z): $[M+Na]^+$= 617. 1.

Step 4: preparation of *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0428]



[0429] *tert*-Butyl 4-(3-(difluoromethyl)-4-(5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-α]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (80 mg, 0.13 mmol) was dissolved in dichloromethane (2 mL), trifluoroacetic acid (0.4 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[0430] LC-MS: (ESI, m/z): $[M+H]^+$ = 495.2.

Intermediate 32: 3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde

Step 1: preparation of 3-azaspiro[5.5]undecane-9-carbaldehyde

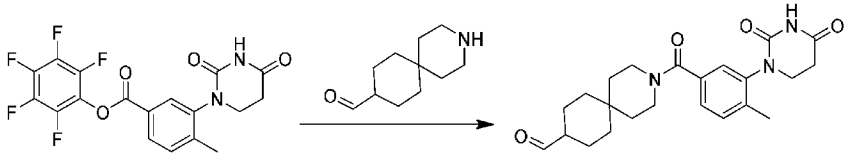
[0431]

[0432] tert-Butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (200 mg, 0.71 mmol) was dissolved in DCM (2 mL), TFA (0.4 mL) was added, and the reaction liquid was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 3-azaspiro[5.5]undecane-9-carbaldehyde.

[0433] LC-MS: (ESI, m/z): $[M+H]^+$ = 182.2.

Step 2: preparation of 3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde

[0434]

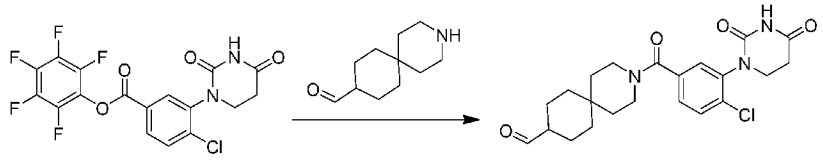


[0435] 3-Azaspiro[5.5]undecane-9-carbaldehyde (345 mg, 0.71 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoate (295 mg, 0.71 mmol) were dissolved in DMSO (5 mL), and the mixture was stirred at room temperature for 1 h. Water (50 mL) was added to the reaction liquid. The mixture was extracted with EA (30 mL $\times$ 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to give 3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde.

[0436] LC-MS: (ESI, m/z): $[M+H]^+$ = 412.2.

Intermediate 33: 3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde

[0437]



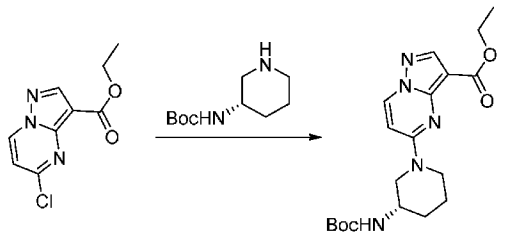
[0438] Intermediate 33 was prepared by referring to the method for intermediate 32.

[0439] LC-MS: (ESI, m/z): $[M+H]^+$ = 432.1.

Intermediate 34: tert-butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate

Step 1: preparation of ethyl (S)-5-(3-((tert-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-α]pyrimidine-3-carboxylate

[0440]

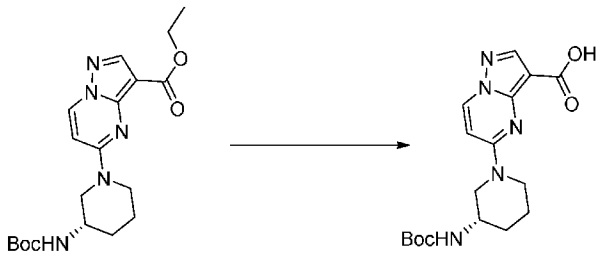


[0441] Ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2.0 g, 8.9 mmol), tert-butyl (*S*)-piperidin-3-ylcarboxylate (1.8 g, 8.9 mmol), and *N,N*-diisopropylethylamine (3.5 g, 27 mmol) were dissolved in acetonitrile (20 mL). The reaction liquid was heated to 60 °C, stirred overnight, and directly concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 9:1) to give ethyl (*S*)-5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[0442] LC-MS: (ESI, m/z): $[M+H]^+$= 390.0.

Step 2: preparation of (*S*)-5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

[0443]

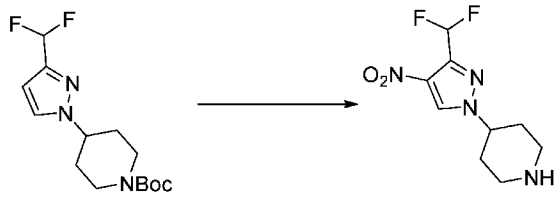


[0444] Ethyl (*S*)-5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (3.2 g, 8.2 mmol) was dissolved in a mixed solution (methanol/water = 5:1, 30 mL), lithium hydroxide (787 mg, 32.8 mmol) was added, and the mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 2 with dilute hydrochloric acid (2 mol/L) and filtered, and the filter cake was dried under vacuum to give (*S*)-5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0445] LC-MS: (ESI, m/z): $[M+H]^+$ = 362.5.

Step 3: preparation of 4-(3-(difluoromethyl)-4-nitro- l H-pyrazol- l -yl)piperidine

[0446]

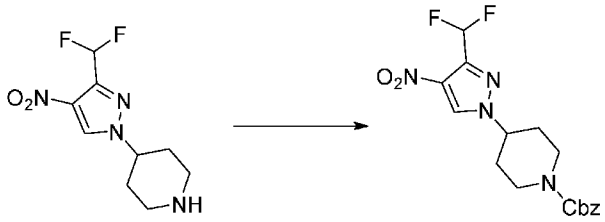


[0447] tert-Butyl 4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (1 g, 3 mmol) was dissolved in concentrated sulfuric acid (10 mL) and cooled to zero. Concentrated nitric acid (1 mL) was slowly added dropwise, and the reaction liquid was stirred at room temperature overnight. The reaction liquid was slowly poured into ice water (300 mL). The aqueous phase was adjusted to pH = 8 with sodium carbonate, extracted with a mixed solution of methanol/dichloromethane (10/1, 60 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 4-(3-(difluoromethyl)-4-nitro-1 H-pyrazol-1 - yl)piperidine.

[0448] LC-MS: (ESI, m/z): $[M+H]^{l}$ = 247.0.

Step 4: preparation of benzyl 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0449]

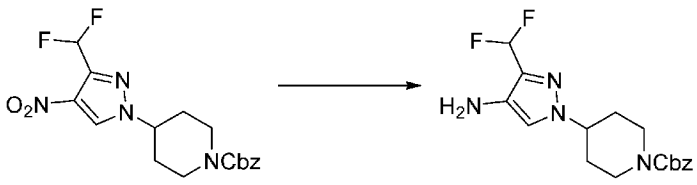


[0450] 4-(3-(Difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine (460 mg, 1.9 mmol) was dissolved in dichloromethane (6 mL), DIEA (735 mg, 5.7 mmol) and CbzCl (391 mg, 2.3 mmol) were added, and the mixture was stirred at room temperature for 2 h. Water (80 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (100 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:1) to give benzyl 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0451] LC-MS: (ESI, m/z): $[M+H]^{+}$= 381.2.

Step 5: preparation of benzyl 4-(4-amino-3-(difluoromethyl)-1*H*pyrazol-1-yl)piperidine-1-carboxylate

[0452]

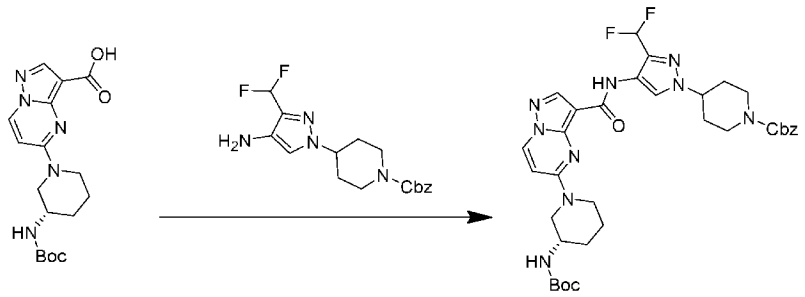


[0453] Benzyl 4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (500 mg, 1.3 mmol), iron powder (294 mg, 5.2 mmol), and NH_4Cl (418 mg, 7.9 mmol) were added to water (10 mL). The reaction liquid was heated to 90 °C, stirred for 2 h, filtered, diluted with water (80 mL), and extracted with ethyl acetate (100 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give benzyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0454] LC-MS: (ESI, m/z): $[M+H]^{+}$ = 351.2.

Step 6: preparation of benzyl (*S*)-4-(4-(5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1 -yl)piperidine-1 -carboxylate

[0455]

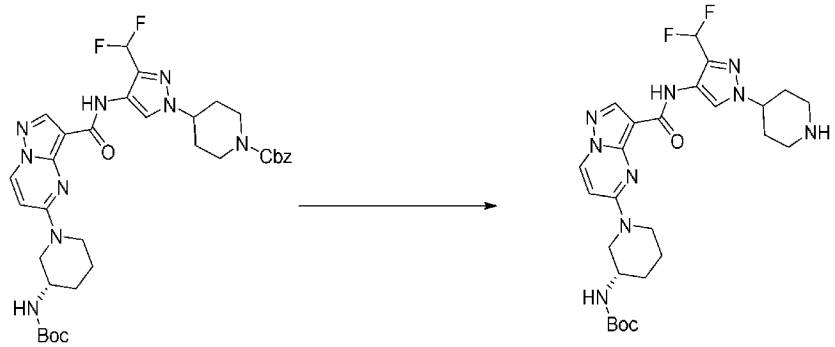


[0456] (*S*)-5-(3-((*tert*-Butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (56 mg, 0.15 mmol), benzyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboacylate (54 mg, 0.15 mmol), and PyBOP (240 mg, 0.45 mmol) were dissolved in DMF (5 mL), then DIEA (60 mg, 0.45 mmol) was added, and the mixture was stirred at room temperature for 16 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to give benzyl (*S*)-4-(4-(5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-α]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0457] LC-MS: (ESI, m/z): $[M+H]^{l}$ = 694.4.

Step 7: preparation of *tert-butyl* (*S*)-(1-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate

[0458]

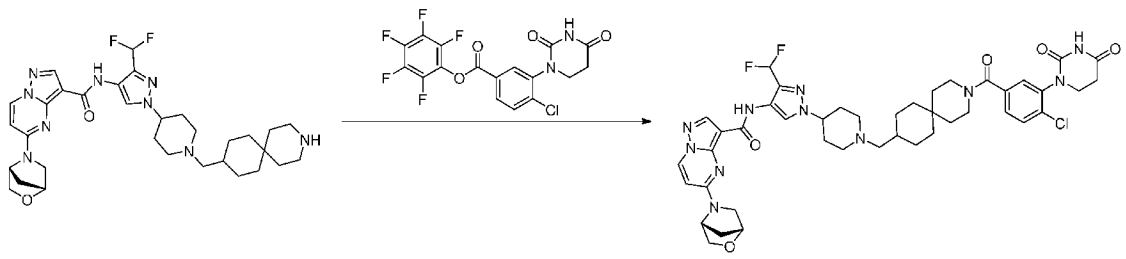


[0459] Benzyl (*S*)-4-(4-(5-(3-((*tert*-butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboacylate (90 mg, 0.13 mmol) was dissolved in THF (3 mL), and Pd/C (10%, 50 mg) was added. The mixture was purged three times with H_2 and stirred at room temperature for 1 h under hydrogen atmosphere. The reaction liquid was filtered through celite, the filter cake was washed with THF (10 mL × 3), and the filtrate was concentrated under reduced pressure to give a crude product of tert-butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate.

[0460] LC-MS: (ESI, m/z): $[M+H]^{+}$= 560.3.

Example 1: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0461]



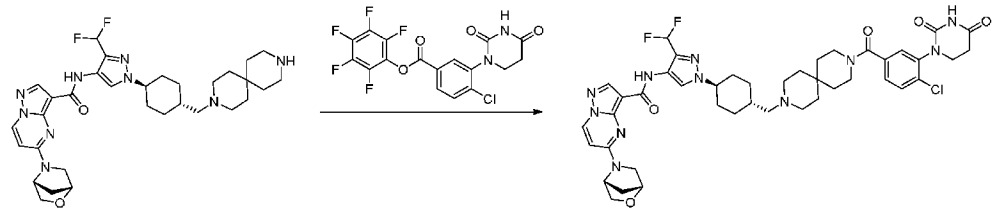
[0462] A solution of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, crude, 0.18 mmol), pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (78 mg, 0.18 mmol), and *N,N*-diisopropylethylamine (116 mg, 0.9 mmol) in dimethyl sulfoxide (5 mL) was stirred at room temperature overnight. The resulting mixture was poured into water (50 mL) and stirred for 10 min. The mixture was filtered, and the filter cake was purified by preparative HPLC to give the target product, 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1 (2H)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0463] LC-MS: (ESI, *m/z):* $[M+H]^+$= 874.5.

[0464] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.9 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J*= 4.0 Hz, 1H), 8.26 (d, *J*= 5.7 Hz, 1H), 7.63 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.9 Hz, 1H), 7.39 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.27-6.96 (m, 1H), 6.90-6.41 (m, 1H), 5.30-5.05 (m, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 4.26-4.14 (m, 1H), 3.86-3.70 (m, 3H), 3.66-3.41 (m, 5H), 3.30-3.25 (m, 2H), 2.96-2.84 (m, 2H), 2.79-2.70 (m, 2H), 2.22-2.08 (m, 2H), 2.06-1.83 (m, 8H), 1.75-1.65 (m, 2H), 1.63-1.24 (m, 7H), 1.19-0.91 (m, 4H).

Example 2: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*r*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0465]



[0466] Example 2 was prepared by referring to the method for Example 1.

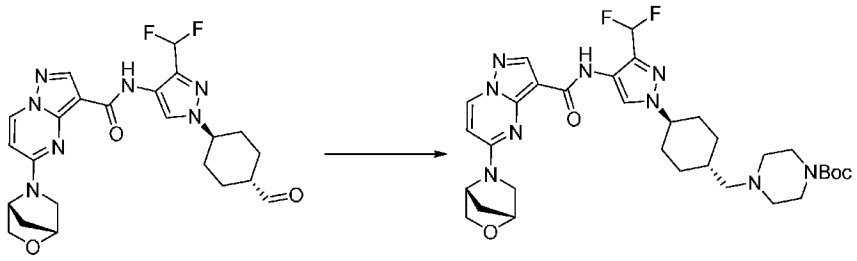
[0467] LC-MS: (ESI, m/z): $[M+H]^+$ = 874.4

[0468] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J*= 6.3 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.38 (d, *J*= 4.4 Hz, 1H), 8.25 (d, *J*= 5.7 Hz, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26-6.95 (m, 1H), 6.91-6.41 (m, 1H), 5.32-5.03 (m, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 4.17 (t, *J* = 12.9 Hz, 1H), 3.84-3.71 (m, 3H), 3.67-3.57 (m, 4H), 3.45 (d, *J* = 9.8 Hz, 1H), 3.30-3.25 (m, 2H), 2.79-2.71 (m, 2H), 2.38-2.24 (m, 4H), 2.13-1.77 (m, 8H), 1.79-1.66 (m, 2H), 1.60-1.35 (m, 9H), 1.12-0.92 (m, 2H).

Example 3: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1R,4R)-4-((4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(((1*R*,4R)-4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)piperazine-1-carboxylate

[0469]

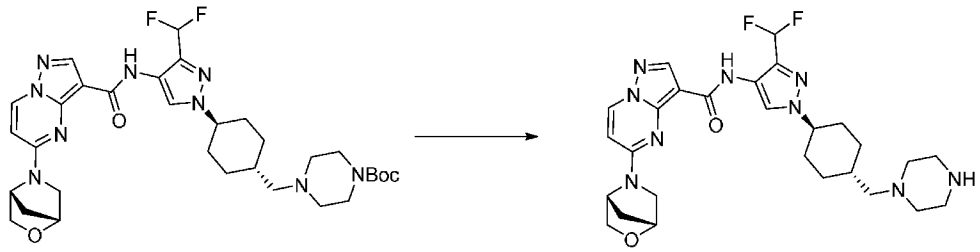


[0470] 5-((1*R*,4*R*)-2-Oxa-5-aaabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1R,4R)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (130 mg, 0.268 mmol) and *tert*-butyl piperazine-1-carboxylate (60 mg, 0.322 mmol) were dissolved in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature. Sodium triacetoxyborohydride (284 mg, 1.34 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give *tert-butyl4-(((1R,4R)-4-(4-(5-((1R,4R)*-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1 -yl)cyclohexyl)methyl)piperazine-1 -carboxylate.

[0471] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 656.3.

Step 2: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0472]

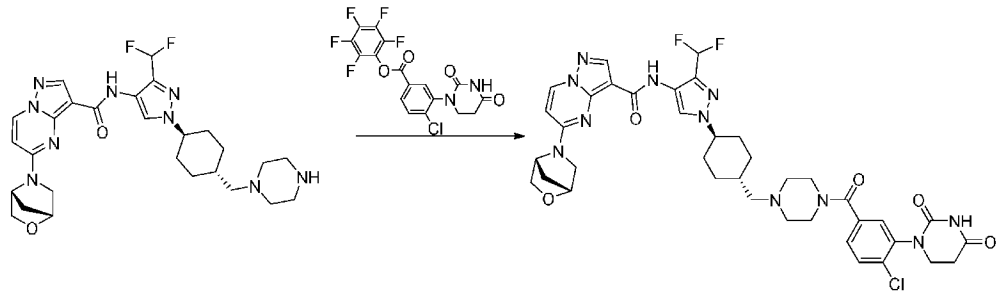


[0473] *tert-Butyl* 4-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)piperazine-1 - carboxylate (120 mg, 0.183 mmol) was dissolved in dichloromethane (5 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[0474] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 556.3

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-((4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[0475]



[0476] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(piperazin-1-ylmethyl)cyclohexyl)-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.185 mmol, trifluoroacetate) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (96 mg, 0.22 mmol) were dissolved in dimethyl sulfoxide (10 mL), and the mixture was stirred at room temperature. DIEA (0.5 mL) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by pre-HPLC to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-((4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

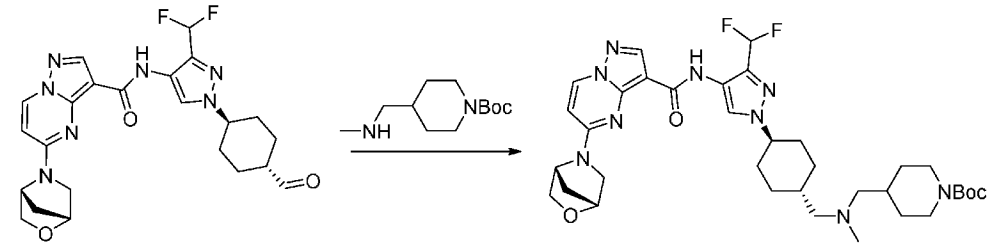
[0477] LC-MS: (ESI, *m/z*): $[M+H]^+$= 806.2.

[0478] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.49 (d, *J*= 6.0 Hz, 1H), 8.78 (d, *J*= 7.8 Hz, 1H), 8.38 (d, *J* = 4.3 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.65 (d, *J*= 8.2 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.27-6.94 (m, 1H), 6.89-6.38 (m, 1H), 5.32-5.02 (m, 1H), 4.77 (d, *J* = 17.6 Hz, 1H), 4.25-4.15 (m, 1H), 3.86-3.71 (m, 3H), 3.68-3.57 (m, 4H), 3.45 (d, *J*= 10.3 Hz, 2H), 2.80-2.70 (m, 2H), 2.45-2.25 (m, 4H), 2.16 (d, *J* = 7.0 Hz, 2H), 2.11-1.83 (m, 7H), 1.1-1.67 (m, 2H), 1.68-1.50 (m, 1H), 1.16-0.98 (m, 2H).

Example 4: 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-((1R,4R)-4-((((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)methyl)piperidine-1-carboxylate

[0479]

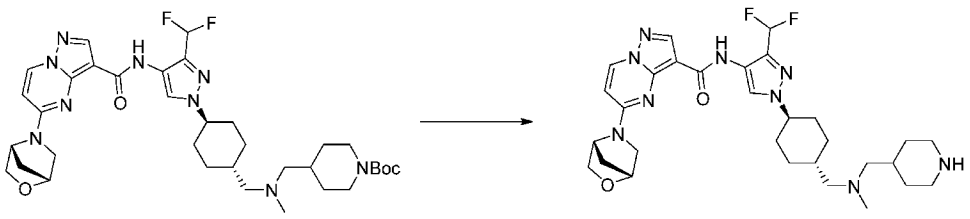


[0480] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (130 mg, 0.268 mmol) and tert-butyl 4-((methylamino)methyl)piperidine-1-carboxylate (73 mg, 0.320 mmol) were dissolved in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature. Sodium triacetoxyborohydride (284 mg, 1.34 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give tert-butyl 4-(((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)methyl)piperidine-1-carboxylate.

[0481] LC-MS: (ESI, m/z): $[M+H]^+$= 698.4.

Step 2: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(piperidin-4-ylmethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0482]

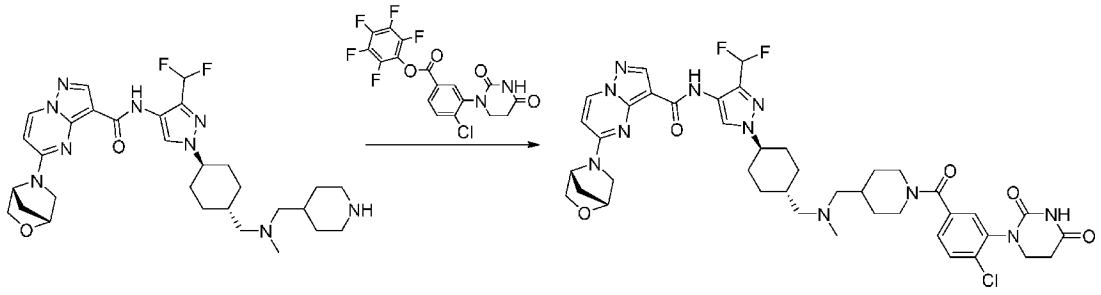


[0483] tert-Butyl 4-(((((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)methyl)piperidine-1-carboxylate (150 mg, 0.215 mmol) was dissolved in dichloromethane (5 mL), trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 2 h and directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(piperidin-4-ylmethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[0484] LC-MS: (ESI, m/z): $[M+H]^+$ = 598.3.

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*(1-((1*R*,4*R*)-4-((((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0485]



[0486] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(piperidin-4-ylmethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.251 mmol, trifluoroacetate) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (134 mg, 0.309 mmol) were dissolved in dimethyl sulfoxide (10 mL), and the mixture was stirred at room temperature. DIEA (0.5 mL) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by pre-HPLC to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-((((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

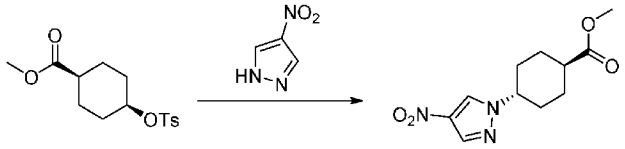
[0487] LC-MS: (ESI, m/z): $[M+H]^+$ = 848.3.

[0488] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J*= 5.8 Hz, 1H), 8.78 (d, *J*= 7.7 Hz, 1H), 8.38 (d, *J*= 4.4 Hz, 1H), 8.25 (d, *J*= 5.5 Hz, 1H), 8.17 (s, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.9 Hz, 1H), 7.38 (dd, J= 8.2, 2.0 Hz, 1H), 7.27-7.94 (m, 1H), 6.90-6.42 (m, 1H), 5.33-5.00 (m, 1H), 4.77 (d, *J*= 17.4 Hz, 1H), 4.52-4.33 (m, 1H), 4.17 (t, *J*= 10.6 Hz, 1H), 3.86-3.70 (m, 3H), 3.68-3.53 (m, 3H), 3.45 (d, *J*= 10.1 Hz, 1H), 3.14-2.96 (m, 1H), 2.90-2.68 (m, 3H), 2.25-1.46 (m, 19H), 1.18-0.88 (m, 4H).

Example 5: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of methyl (1*R*,4*R*)-4-(4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0489]



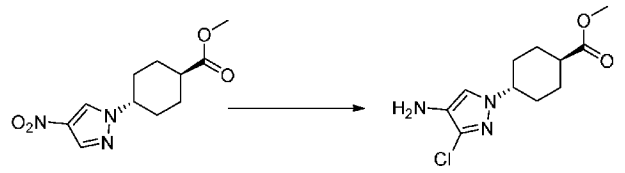
[0490] 4-Nitro-1*H*-pyrazole (1.8 g, 15.9 mmol) and methyl (1S,4S)-4-(p-toluenesulfonyl)cyclohexane-1-carboxylate (5.2 g, 16.7 mmol) were dissolved in DMF (50 mL). Cs_2CO_3 (15.6 g, 47.7 mmol) and KI (2.78 g, 16.7 mmol) were added, and the mixture was stirred at 50 °C overnight. Water (200 mL) was added, and the mixture was stirred for 10 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 7:11) to give methyl (1R,4R)-4-(4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate.

[0491] LC-MS: (ESI, *m/z):* $[M+H]^+$= 254.1.

[0492] ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.26 (s, 1H), 4.33-4.25 (m, 1H), 3.63 (s, 3H), 2.42-2.35 (m, 1H), 2.15-2.00 (m, 4H), 1.89-1.76 (m, 2H), 1.59-1.45 (m, 2H).

Step 2: preparation of methyl (1*R*,4*R*)-4-(4-amino-3-chloro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0493]

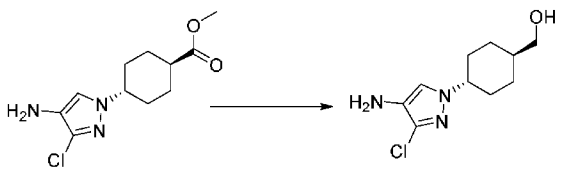


[0494] Methyl (1R,4R)-4-(4-nitro-1H-pyrazol-1-yl)cyclohexane-1-carboxylate (1.4 g, 5.5 mmol) was dissolved in ethanol (45 mL). HCl (4.6 mL, 55.3 mmol) and Pd (5%, alumina-supported, 140 mg) were added. Triethylsilane (3.85 g, 33.2 mmol) was added dropwise under N_2 atmosphere, and the mixture was stirred at room temperature overnight. The pH was adjusted to 8 with a saturated $NaHCO_3$ solution, and the mixture was extracted with ethyl acetate (150 mL × 3). The organic phase was washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:19) to give methyl (1R,4R)-4-(4-amino-3-chloro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate.

[0495] LC-MS: (ESI, *m/z*): $[M+H]^+$ =258.1 and $[M+14]^+$ =272.1.

Step 3: preparation of ((1*R*,4*R*)-4-(4-amino-3-chloro-1*H*-pyrazol-1-yl)cyclohexyl)methanol

[0496]



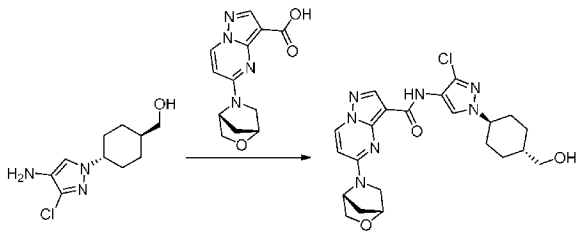
[0497] Methyl (1*R*,4*R*)-4-(4-amino-3-chloro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (1.0 g, 3.9 mmol) was dissolved in THF (20 mL), BH_3/THF (1 M, 39 mL, 39 mmol) was added, and the mixture was reacted at room temperature overnight. After the reaction was quenched with MeOH (10 mL), the mixture was concentrated under reduced pressure.

The crude product was purified by column chromatography (MeOH:DCM = 1:19) to give ((1*R*,4*R*)-4-(4-amino-3-chloro-1*H*-pyrazol-1-yl)cyclohexyl)methanol.

[0498] LC-MS: (ESI, *m/z):* $[M+H]^+$= 230.2.

Step 4: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0499]

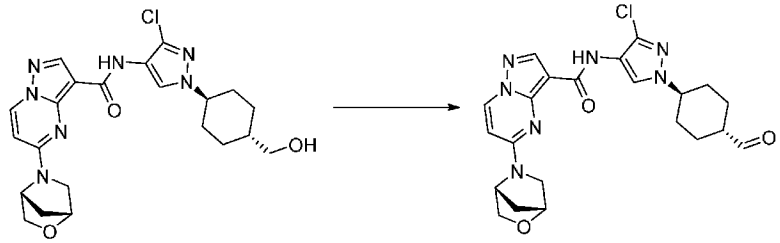


[0500] ((1*R*,4*R*)-4-(4-Amino-3-chloro-1*H*-pyrazol-1-yl)cyclohexyl)methanol (300 mg, 1.3 mmol), HATU (570 mg, 1.5 mmol), and DIEA (387 mg, 3.0 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (260 mg, 1.0 mmol) in DMF (10 mL), and the mixture was stirred at room temperature overnight. Water (100 mL) was added, and the mixture was stirred for 10 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-y1)-*N*-(3-chloro-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0501] LC-MS: (ESI, *m/z):* $[M+H]^+$= 472.0.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxo-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0502]

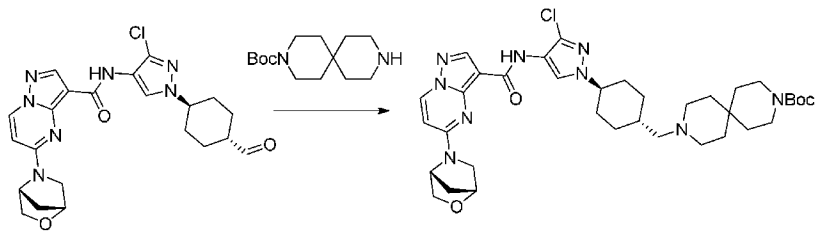


[0503] IBX (297 mg, 1.06 mmol) was added to a solution of 5-((1 *R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (250 mg, 0.53 mmol) in ACN (20 mL), and the mixture was stirred at 85 °C for 1.5 h and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give 5-((1*R*,4*R*)-2-oxo-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0504] LC-MS: (ESI, m/z): $[M+H]^+$= 470.2.

Step 6: preparation of *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-chloro-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0505]

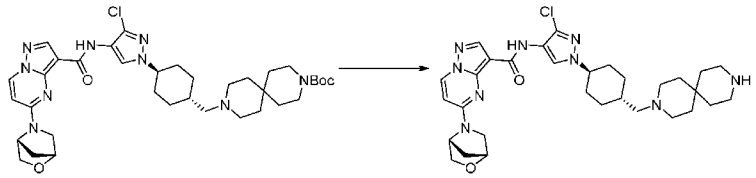


[0506] STAB (285 mg, 1.34 mmol) was added to a solution of 5-((1 *R*,4*R*)-2-oxo-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (210 mg, 0.45 mmol) and tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (114 mg, 0.45 mmol) in THF (10 mL), and the mixture was stirred at room temperature overnight and concentrated under reduced pressure. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give *tert-butyl* 9-(((1R,4R)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-chloro-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[0507] LC-MS: (ESI, *m/z*): $[M+Na]^+$ = 708.2.

Step 7: preparation of *N*-(1-((1R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-chloro-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0508]

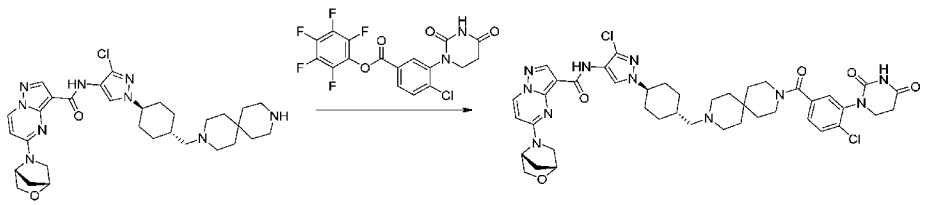


[0509] TFA (1 mL) was added to a solution of *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-chloro-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (190 mg, 0.27 mmol) in DCM (5 mL), and the mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give *N*-(1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-chloro-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0510] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 608.3.

Step 8: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-chloro-1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0511]



[0512] *N*-(1-((1*R*,4*R*)-4-((3,9-Diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-chloro-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (190mg, 0.31 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (136 mg, 0.31 mmol) were dissolved in DMSO (5 mL), then DIEA (202 mg, 1.6 mmol) was added, and the reaction liquid was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was stirred for 10 min and filtered. The solid was purified by

preparative reversed-phase chromatography to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-chloro-1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

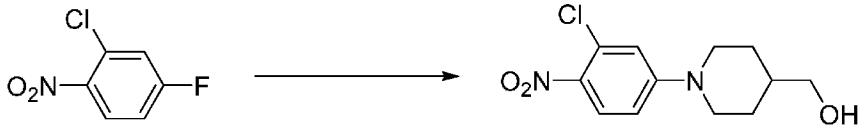
[0513] LC-MS: (ESI, *m/z*): $[M+H]^+$= 858.2.

[0514] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.44 (d, *J*= 8.7 Hz, 1H), 8.80 (d, *J*= 7.7 Hz, 1H), 8.24 (d, *J* = 3.5 Hz, 1H), 8.06 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 6.95-6.39 (m, 1H), 5.30-5.00 (m, 1H), 4.79 (s, 1H), 4.25-4.15 (m, 1H), 3.92-3.38 (m, 9H), 2.80-2.68 (m, 2H), 2.40-2.20 (m, 4H), 2.11 (d, *J* = 6.5 Hz, 2H), 2.06-1.95 (m, 2H), 1.94-1.76 (m, 6H), 1.70-1.30 (m, 9H), 1.10-0.95 (m, 2H).

Example 6: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of (1-(3-chloro-4-nitrophenyl)piperidin-4-yl)methanol

[0515]

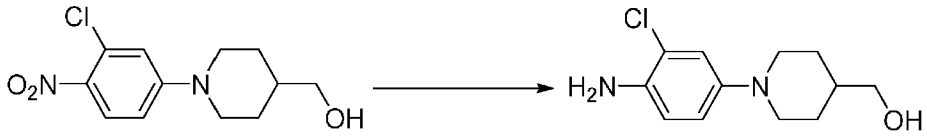


[0516] K_2CO_3 (1.57 g, 11.4 mmol) and 2-(piperidin-4-yl)ethan-1-ol (0.78 g, 6.8 mmol) were added to a solution of 2-chloro-4-fluoro-1-nitrobenzene (1.0 g, 5.7 mmol) in DMF (20 mL), and the mixture was stirred at 100 °C for 1 h. Water (200 mL) was added, and the mixture was stirred for 10 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 1:1) to give (1-(3-chloro-4-nitrophenyl)piperidin-4-yl)methanol.

[0517] LC-MS: (ESI, *m/z):* $[M+H]^+$= 271.0.

Step 2: preparation of (1-(4-amino-3-chlorophenyl)piperidin-4-yl)methanol

[0518]

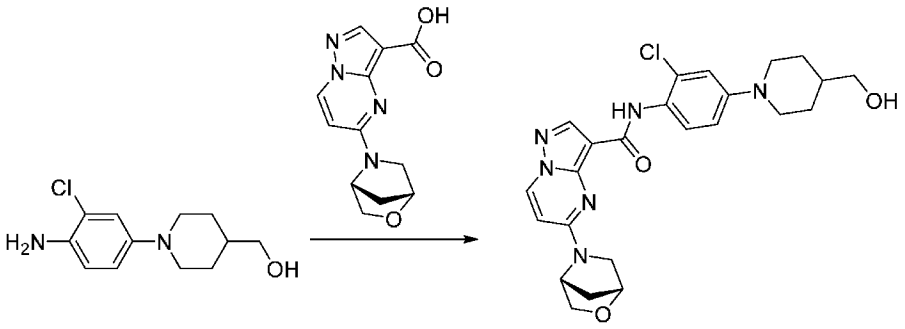


[0519] (1-(3-Chloro-4-nitrophenyl)piperidin-4-yl)methanol (1.3 g, 4.8 mmol) was dissolved in ethanol (30 mL), Raney-Ni (1 mL) and N_2H_4-H_2O (1 mL) were added, and the mixture was stirred at room temperature for 1 h, filtered, concentrated, and dried to give (1-(4-amino-3-chlorophenyl)piperidin-4-yl)methanol.

[0520] LC-MS: (ESI, *m/z*): $[M+H]^+$= 241.1.

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0521]

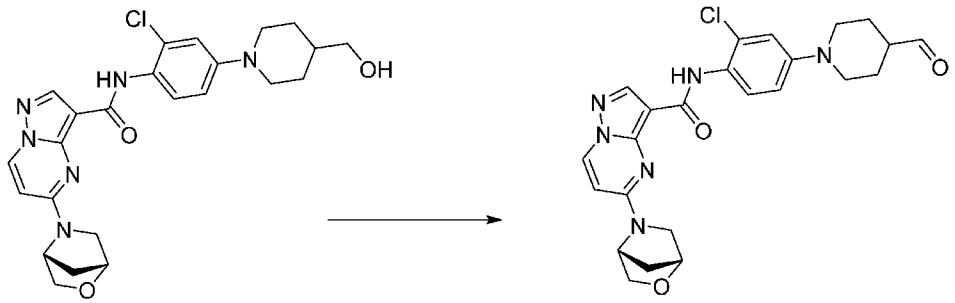


[0522] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (0.6 g, 2.3 mmol), HATU (1.33 g, 3.5 mmol), and DIEA (0.89 g, 6.9 mmol) were added to a solution of (1-(4-amino-3-chlorophenyl)piperidin-4-yl)methanol (1.0 g, 4.2 mmol) in DMF (20 mL), and the mixture was stirred at room temperature overnight. Water (200 mL) was added, and the mixture was stirred for 10 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(2-chloro-4-(4-(hydroacymethyl)piperidin-1 -yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0523] LC-MS: (ESI, *m/z):* $[M+H]^{l}$ = 483.1.

Step 4: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-formylpiperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0524]

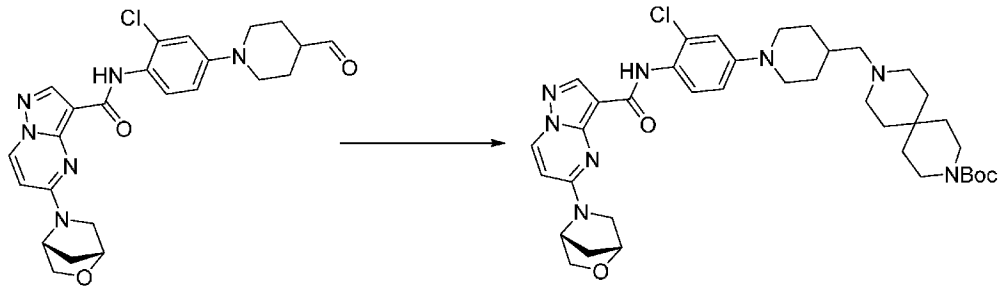


[0525] IBX (560 mg, 2.0 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide(500 mg, 1.0 mmol) in CAN (20 mL), and the mixture was stirred at 100 °C for 1.5 h. The reaction liquid was directly concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(2-chloro-4-(4-formylpiperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0526] LC-MS: (ESI, *m/z):* $[M+H]^{+}$= 481.1.

Step 5: preparation of *tert*-butyl 9-((1-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-chlorophenyl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0527]

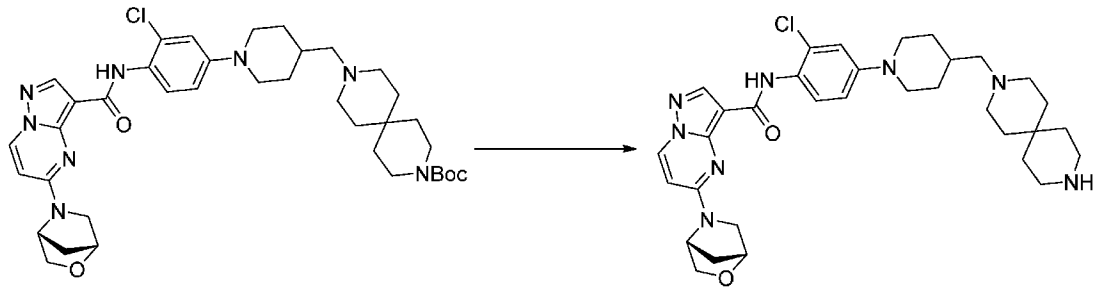


[0528] STAB (528 mg, 2.49 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-formylpiperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (400 mg, 0.83 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (232 mg, 0.91 mmol) in THF (10 mL), and the mixture was stirred at room temperature overnight and concentrated under reduced pressure. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:9) to give *tert-butyl* 9-((1-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-chlorophenyl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[0529] LC-MS: (ESI, *m/z):* $[M+Na]^+$ = 719.3.

Step 6: preparation of *N*-(4-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-2-chlorophenyl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]undecan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0530]

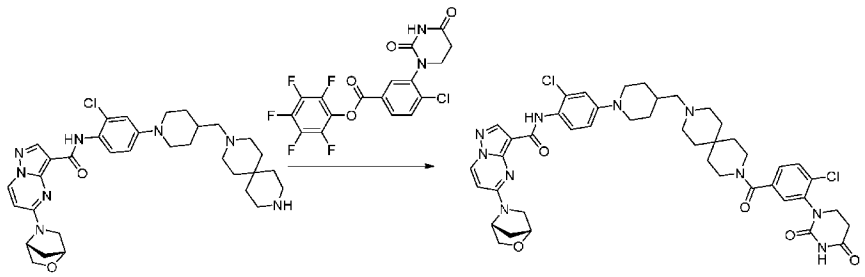


[0531] TFA (1 mL) was added to a solution of *tert*-butyl 9-((1-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-chlorophenyl)piperidin-4-yl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (150 mg, 0.21 mmol) in DCM (5 mL), and the mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to give N-(4-(4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-2-chlorophenyl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]undecan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0532] LC-MS: (ESI, *m/z):* $[M+H]^+$= 619.2.

Step 7: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0533]



[0534] *N*-(4-(4-((3,9-Diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)-2-chlorophenyl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]undecan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.24 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (105 mg, 0.24 mmol) were dissolved in DMSO (5 mL), DIEA (155 mg, 1.2 mmol) was added, and then the reaction liquid was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was stirred for 2 min and filtered. The solid was purified by preparative reversed-phase chromatography to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(2-chloro-4-(4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)piperidin-1-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

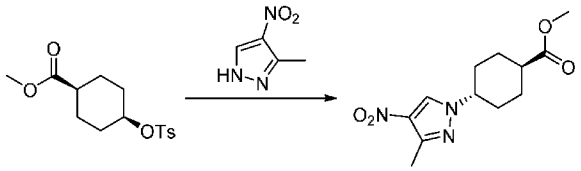
[0535] LC-MS: (ESI, *m/z):* $[M+H]^+$= 869.3.

[0536] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.60 (d, *J*= 11.9 Hz, 1H), 8.80 (d, *J*= 7.7 Hz, 1H), 8.26 (d, *J*= 3.3 Hz, 1H), 8.08 (dd, *J*= 15.0, 9.1 Hz, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 2.0 Hz, 1H), 7.39 (dd, *J*= 8.2, 2.0 Hz, 1H), 7.00 (d, *J*= 2.4 Hz, 1H), 6.99-6.92 (m, 1H), 6.90-6.44 (m, 1H), 5.34-5.04 (m, 1H), 4.77 (d, *J*= 12.1 Hz, 1H), 3.84-3.70 (m, 3H), 3.68-3.43 (m, 7H), 3.30-3.20 (m, 2H), 2.78-2.70 (m, 2H), 2.64 (t, *J*= 11.6 Hz, 2H), 2.39-2.21 (m, 4H), 2.14 (d, *J*= 6.9 Hz, 2H), 2.07-1.92 (m, 2H), 1.82-1.30 (m, 11H), 1.23-1.08 (m, 2H).

Example 7: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

Step 1: preparation of methyl (1*R*,4*R*)-4-(3-methyl-4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0537]



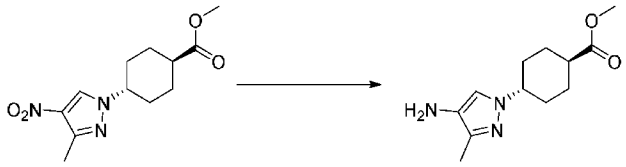
[0538] A solution of methyl (1*S*,4*S*)-4-(*p*-toluenesulfonyl)cyclohexane-1-carboxylate (2.0 g, 15.7 mmol), 3-methyl-4-nitro-1*H*-pyrazole (5.9 g, 18.8 mmol), Cs_2CO_3 (15.4 g, 47.1 mmol), and KI (3.1 g, 18.8 mmol) in DMF (30.0 mL) was stirred at 120 °C for 2 h. Water (200 mL) was added to the reaction liquid, and then the mixture was extracted with EA (200 mL × 2). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (EA:PE = 0-1:5) to give methyl (1*R*,4*R*)-4-(3-methyl-4-nitro-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate.

[0539] LC-MS: (ESI, *m/z*): $[M+H]^+$= 268.0.

[0540] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 4.24-4.14 (m, 1H), 3.61 (s, 3H), 2.42 (s, 3H), 2.44-2.34 (m, 1H), 2.14-1.96 (m, 4H), 1.87-1.71 (m, 2H), 1.62-1.41 (m, 2H).

Step 2: preparation of methyl (1*R*,4*R*)-4-(4-amino-3-methyl-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[0541]

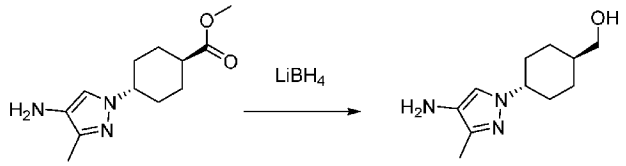


[0542] A solution of methyl (1R,4R)-4-(3-methyl-4-nitro-1H-pyrazol-1-yl)cyclohexane-1-carboxylate (2.0 g, 7.4 mmol), Fe (2.5 g, 37.0 mmol), and NH_4Cl (4.8 g, 74.0 mmol) in MeOH (50.0 mL) was stirred at 80 °C for 3 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (acetonitrile/0.05% aqueous NH_4OH solution, 5%-95%) to give methyl (1*R*,4*R*)-4-(4-amino-3-methyl-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate.

[0543] LC-MS: (ESI, m/z): $[M+H]^l$ = 238.3.

Step 3: preparation of ((1*R*,4*R*)-4-(4-amino-3-methyl-1*H*-pyrazol-1-yl)cyclohexyl)methanol

[0544]

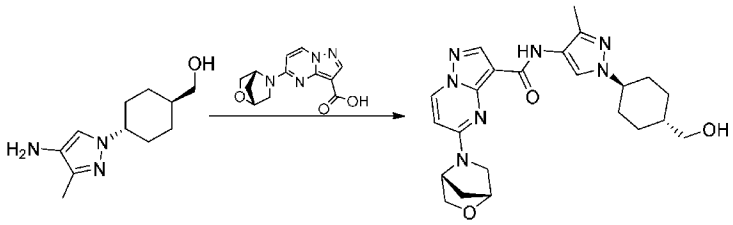


[0545] A solution of methyl (1*R*,4*R*)-4-(4-amino-3-methyl-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (300.0 mg, 1.3 mmol) and $LiBH_4$ (111.0 mg, 4.0 mmol) in THF/MeOH (10.0 mL/2.0 mL) was stirred at 60 °C for 1 h. Water (20.0 mL) was added to quench the reaction, and then the mixture was extracted with DCM (50 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give ((1*R*,4*R*)-4-(4-amino-3-methyl-1*H*-pyrazol-1-yl)cyclohexyl)methanol.

[0546] LC-MS: (ESI, *m/z*): $[M+H]^+$= 210.1.

Step 4: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N (1-((1R,4R)-4-(hydroxymethyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0547]

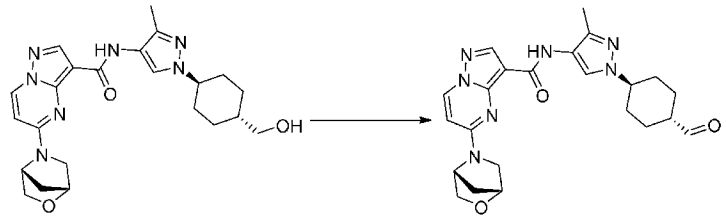


[0548] ((1*R*,4*R*)-4-(4-Amino-3-methyl-1*H*-pyrazol-1-yl)cyclohexyl)methanol (230.0 mg, 1.1 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (260.0 mg, 1.0 mmol),HATU(418.0 mg, 1.1 mmol), andDIEA(387.0 mg, 3.0 mmol) in DMF (500.0 mL). The reaction liquid was stirred at room temperature for 1.0 h. Cold water (250.0 mL) was added to the reaction liquid. The resulting suspension was filtered, and the filter cake was washed with water and dried under vacuum to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting crude product was directly used in the next step without purification.

[0549] LC-MS: (ESI, m/z): $[M+H]^+$= 452.1.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-formylcyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0550]

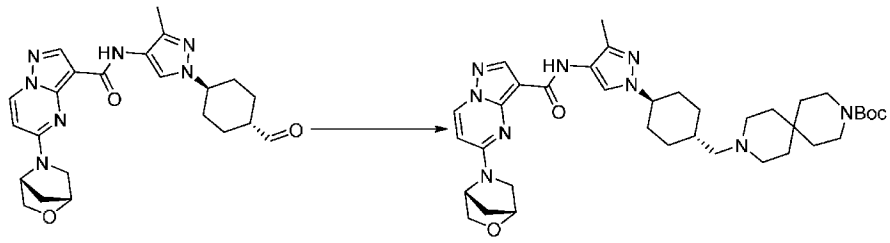


[0551] A mixture of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (320.0 mg, 0.7 mmol) and IBX (392 mg, 1.4 mmol) in ACN (10 mL) was stirred at 60 °C for 1 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1R,4R)-4-formylcyclohexyl)-3-methyl-1 *H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

[0552] LC-MS: (ESI, *m/z):* $[M+H]^+$= 450.1.

Step 6: preparation of *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-methyl-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0553]

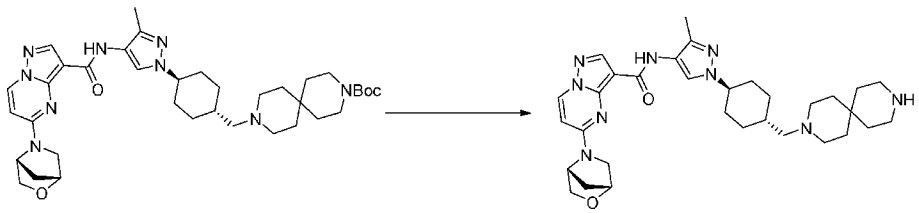


[0554] STAB (381.6 mg, 1.8 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-formylcyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (250.0 mg, 0.6 mmol) and tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (203.0 mg, 0.8 mmol) in THF (10 mL). The reaction liquid was then stirred at 25 °C for 1.0 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-methyl-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5] undecane-3-carboxylate.

[0555] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 688.3.

Step 7: preparation of N (1-((1R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0556]

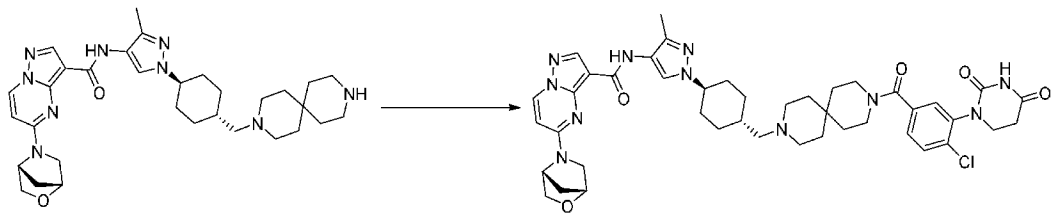


[0557] A solution of tert-butyl 9-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-methyl-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (300.0 mg, 0.4 mmol) in TFA/DCM (1.0 mL/3.0 mL) was stirred at room temperature for 1.0 h. The reaction liquid was directly concentrated under vacuum under reduced pressure to give *N*-(1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting crude product was directly used in the next step.

[0558] LC-MS: (ESI, *m/z*): $[M+H]^+$= 588.6.

Step 8: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-((1R,4R)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0559]



[0560] DIEA (54.20 mg, 0.42 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (143.2 mg, 0.33 mmol) were added to a solution of N-(1-((1R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200.0 mg, 0.3 mmol) in DMSO (5.0 mL), and the reaction mixture was stirred at room temperature for 2 h. Water (15.0 mL) was added to the reaction liquid, and then the mixture was extracted with DCM (30.0 mL × 2). The organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (acetonitrile/0.05% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-((1R,4R)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

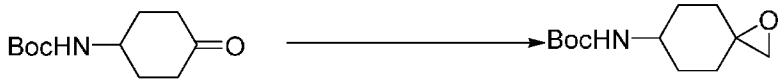
[0561] LC-MS: (ESI, m/z): $[M+H]^+$ = 838.4.

[0562] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.21 (d, J= 7.6 Hz, 1H), 8.80 (d, *J* = 7.8 Hz, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.9 Hz, 1H), 7.39 (dd, *J*= 8.2, 1.9 Hz, 1H), 6.92-6.43 (m, 1H), 5.25-5.05 (m, 1H), 4.78 (s, 1H), 4.05-3.88 (m, 1H), 3.88-3.57 (m, 7H), 3.45 (d, *J*= 10.1 Hz, 1H), 3.30-3.26 (m, 2H), 2.78-2.68 (m, 2H), 2.41-1.93 (m, 12H), 1.86 (d, *J* = 11.5 Hz, 2H), 1.77-1.62 (m, 2H), 1.60-1.31 (m, 10H), 1.11-0.95 (m, 2H).

Example 8: *N*-(2-((1*S*,4*S*)-4-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methoxy)methyl)-4-hydroxycyclohexyl)-6-methoxy-2H-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

Step 1: preparation of tert-butyl (1-oxaspiro[2.5]octan-6-yl)carbamate

[0563]

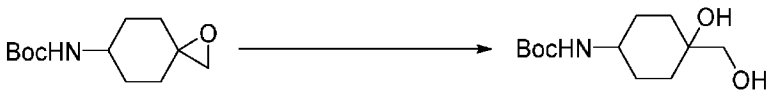


[0564] NaH (1.17 g, 29.3 mmol) was added to a solution of Me_3OS^{II-} (6.2 g, 28.2 mmol) in DMSO (50 mL) at 0 °C under stirring, and the reaction mixture was stirred at room temperature for 1 h. Then a solution of tert-butyl (4-oxocyclohexyl)carbamate (5.0 g, 23.5 mmol) in DMSO (20 mL) was added dropwise. After the addition, the reaction liquid was stirred at room temperature for another 1 h. Water (700 mL) was added to the reaction liquid, and the mixture was extracted with EtOAc (100 mL × 3). The organic phase was washed with saturated brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 0-1:1) to give tert-butyl (1-oxaspiro [2.5] octan-6-yl)carbamate.

[0565] ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, *J*= 7.2 Hz, 1H), 3.37 (m, 1H), 2.57 (s, 2H), 1.83 (td, *J*= 13.3, 4.1 Hz, 2H), 1.77-1.64 (m, 2H), 1.48-1.40 (m, 2H), 1.38 (s, 9H), 1.20 (d, *J*= 13.1 Hz, 2H).

Step 2: preparation of tert-butyl (4-hydroxy-4-(hydroxymethyl)cyclohexyl)carbamate

[0566]

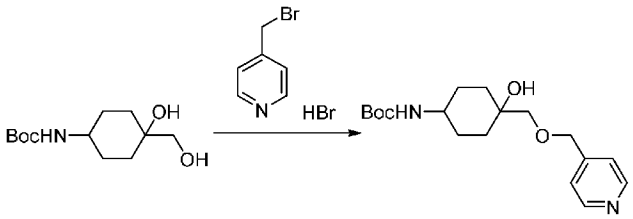


[0567] 2 N NaOH (47 mL) was added to a solution of tert-butyl (1-oxaspiro[2.5]octan-6-yl)carbamate (4.7 g, 20.7 mmol) in NMP (50 mL) while stirring, and then the reaction liquid was stirred at 100 °C for 2 h. Water (500 mL) was added to the reaction liquid, and the mixture was extracted with EA (100 mL × 3). The organic phase was washed with saturated brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give *tert*-butyl (4-hydroxy-4-(hydroxymethyl)cyclohexyl)carbamate.

[0568] ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (d, *J*= 7.9 Hz, 1H), 4.46 (t, *J*= 5.8 Hz, 1H), 3.81 (s, 1H), 3.11 (t, *J* = 6.8 Hz, 3H), 1.56-1.45 (m, 4H), 1.44-1.34 (m, 13H).

Step 3: preparation of tert-butyl (4-hydroxy-4-((pyridin-4-ylmethoxy)methyl)cyclohexyl)carbamate

[0569]



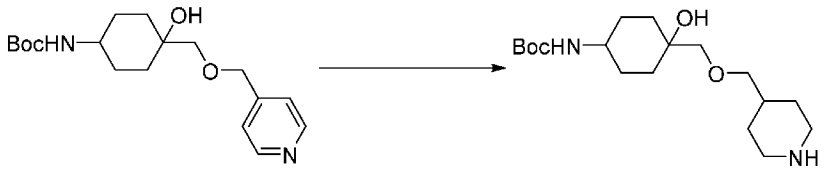
[0570] NaH (292 mg, 7.3 mmol) was added to a solution of *tert-butyl* (4-hydroxy-4-(hydroxymethyl)cyclohexyl)carbamate (600 mg, 2.4 mmol) in THF (20 mL) at 0 °C, the reaction mixture was stirred at 0 °C for 20 min and then stirred at room temperature for another 30 min, and 4-(bromomethyl)pyridine hydrogen bromide salt (617 mg, 2.4 mmol) was added. The reaction liquid was stirred at room temperature overnight. Water (30 mL) was added to the reaction liquid, and the mixture was extracted with EA (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-4:1) to give *tert-butyl* (4-hydroxy-4-((pyridin-4-ylmethoxy)methyl)cyclohexyl)carbamate.

[0571] LC-MS: (ESI, *m/z):* $[M+H]^l$ = 337.1.

[0572] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J*= 5.8 Hz, 2H), 7.34 (d, *J*= 5.6 Hz, 2H), 6.69 (d, *J*= 7.6 Hz, 1H), 4.55 (s, 2H), 4.19 (s, 1H), 3.23 (s, 2H), 3.18-3.07 (m, 1H), 1.60-1.48 (m, 6H), 1.42-1.35 (m, *J*= 9.2 Hz, 11H).

Step 4: preparation of *tert-butyl* (4-hydroxy-4-((piperidin-4-ylmethoxy)methyl)cyclohexyl)carbamate

[0573]

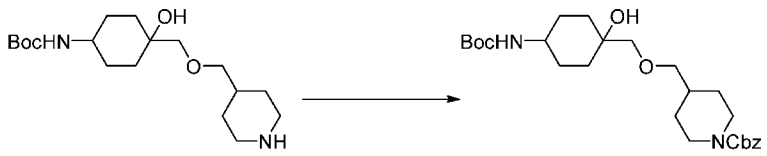


[0574] A mixture of tert-butyl (4-hydroxy-4-((pyridin-4-ylmethoxy)methyl)cyclohexyl)carbamate (700 mg, 2.07 mmol) and Pd/C (400 mg) in *i*-PrOH/H_2O (18 mL/21 mL) was stirred at 75 °C overnight under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give tert-butyl (4-hydroxy-4-((piperidin-4-ylmethoxy)methyl)cyclohexyl)carbamate. The resulting crude product was directly used in the next step.

[0575] LC-MS: (ESI, *m/z*): $[M+H]^+$= 343.2.

Step 5: preparation of benzyl 4-(((4-((tert-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate

[0576]

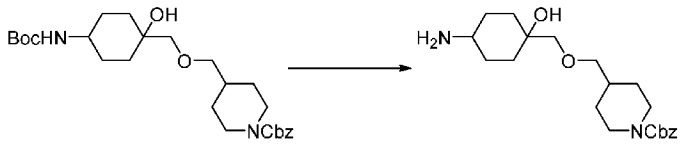


[0577] A solution of tert-butyl (4-hydroxy-4-((piperidin-4-ylmethoxy)methyl)cyclohexyl)carbamate (630 mg, 1.83 mmol) and CbzCl (376 mg, 2.20 mmol) inACN (10 mL) and a saturated aqueous $NaHCO_3$ solution (10 mL) were stirred at room temperature overnight. The reaction liquid was concentrated under reduced pressure and extracted with DCM (50 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EA:PE = 0-7:3) to give benzyl *4-((((4-((tert*-butoacycarbonyl)amino)-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate.

[0578] LC-MS: (ESI, *m/z*): [M+Na] '= 499.3.

Step 6: preparation of benzyl 4-(((4-amino-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate

[0579]

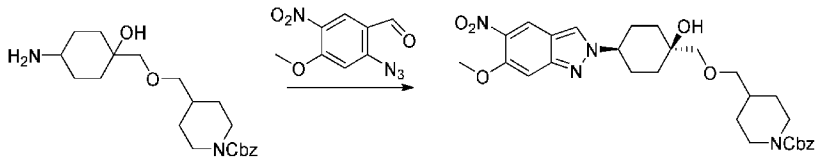


[0580] TFA (3 mL) was added to a solution of benzyl 4-(((4-((tert-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate (300 mg, 0.63 mmol) in DCM (12 mL) at -10 to 0 °C while stirring, and then the reaction liquid was stirred at room temperature for 2 h. The pH of the reaction mixture was adjusted to 9.0 with DIEA, and then the mixture was directly concentrated under reduced pressure to give benzyl 4-(((4-amino-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate. The resulting crude product was directly used in the next step without purification.

[0581] LC-MS: (ESI, m/z): $[M+H]^+$= 377.2.

Step 7: preparation of benzyl 4-((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2*H*-indol-2-yl)cyclohexyl)methoxy)methyl)piperidine-1 -carboxylate

[0582]



[0583] 2-Azido-4-methoxy-5-nitrobenzaldehyde (170 mg, 0.76 mmol) was added to a solution of benzyl 4-(((4-amino-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate (237 mg, 0.63 mmol) in toluene (10 mL) while stirring. The reaction liquid was stirred at 100 °C for 3 h. The reaction liquid was directly concentrated under reduced pressure. The crude product was purified by flash column chromatography (EA:PE = 0-4:1) and then purified by Prep-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give benzyl 4-((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2*H*-indol-2-yl)cyclohexyl)methoxy)methyl)piperidine-1-carboxylate.

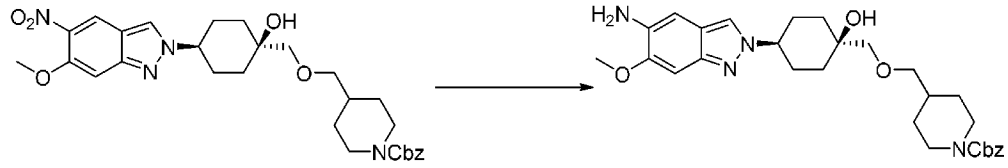
[0584] LC-MS: (ESI, m/z): $[M+H]^l$ = 553.2.

[0585] ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.37 (s, 1H), 7.40-7.29 (m, 5H), 7.26 (s, 1H), 5.07 (s, 2H), 4.45 (t, *J*= 12.0 Hz, 1H), 4.36 (s, 1H), 4.06-3.99 (m, 2H), 3.90 (s, 3H), 3.29 (d, *J*= 6.2 Hz, 2H), 3.20 (s, 2H), 2.85-2.75 (m,

2H), 2.35-2.20 (m, 2H), 1.89 (d, *J* = 11.8 Hz, 2H), 1.76-1.61 (m, 7H), 1.15-1.02 (m, 2H).

Step 8: preparation of *tert-butyl* 4-((((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate

[0586]

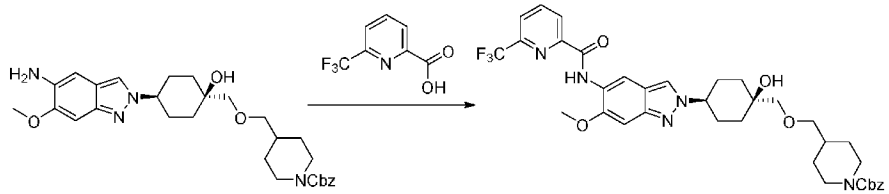


[0587] Raney-Ni (0.3 mL) and N_2H_4 H_2O (0.3 mL) were added to a solution of benzyl 4-((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2*H*-indol-2-yl)cyclohexyl)methoxy)methyl)piperidine-1-carboxylate (200 mg, 0.36 mmol) in EtOH (20 mL). The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was filtered through celite, and the filtrate was directly concentrated under reduced pressure to give *tert-butyl* 4-((((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate. The resulting crude product was directly used in the next step.

[0588] LC-MS: (ESI, m/z): $[M+H]^+$ = 523.2.

Step 9: preparation of benzyl 4-((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methoxy)methyl)piperidine-1-carboxylate

[0589]



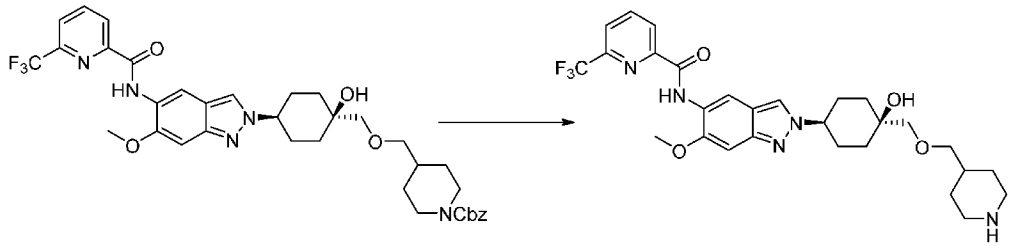
[0590] 6-(Trifluoromethyl)picolinic acid (90 mg, 0.47 mmol), HATU (178 mg, 0.47 mmol), and DIEA (140 mg, 1.08 mmol) were added to a solution of tert-butyl 4-((((1S,4S)-4-(5-amino-6-methoxy-2H-indol-2-yl)-1-hydroxycyclohexyl)methoxy)methyl)piperidine-1-carboxylate (190 mg, 0.36 mmol) in DMF (5 mL) while stirring. Then the reaction liquid was stirred at room temperature for 2 h. Water (30 mL) was added to the reaction liquid, and the mixture was extracted with EA (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-4:1) to give benzyl 4-((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methoxy)methyl)piperidine-1 -carboxylate.

[0591] LC-MS: (ESI, m/z): $[M+H]^+$= 696.3.

[0592] ^1H NMR (400 MHz, DMSO-d6) δ 10.51 (s, 1H), 8.69 (s, 1H), 8.47 (d, *J*= 7.7 Hz, 1H), 8.41 (t, *J*= 7.8 Hz, 1H), 8.32 (s, 1H), 8.22 (d, *J*= 7.7 Hz, 1H), 7.41-7.29 (m, 5H), 7.16 (s, 1H), 5.08 (s, 2H), 4.40-4.29 (m, 2H), 4.15-3.95 (m 5H), 3.29 (d, *J*= 6.2 Hz, 2H), 3.21 (s, 2H), 2.91-2.70 (m, 2H), 2.35-2.15 (m, 2H), 1.90 (d, *J*= 9.5 Hz, 2H), 1.85-1.60 (m, 7H), 1.12-.1.02 (m, 2H).

Step 10: preparation of *N*-(2-((1*S*,4*S*)-4-hydroxy-4-((piperidin-4-ylmethoxy)methyl)cyclohexyl)-6-methoxy-2H-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0593]

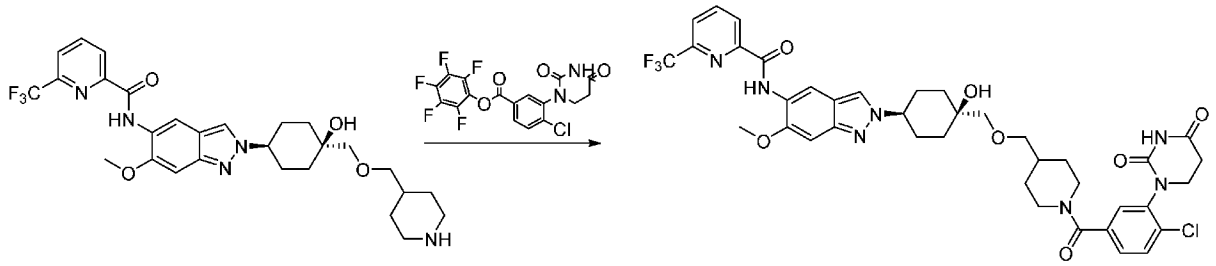


[0594] $Pd(OH)_2/C$ (80 mg) was added to a solution of benzyl 4-((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methoxy)methyl)piperidine-1-carboxylate (170 mg, 0.24 mmol) in EA (20 mL). Then the reaction liquid was stirred at 70 °C overnight under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was directly concentrated under reduced pressure to give *N*-(2-((1*S*,4*S*)-4-hydroxy-4-((piperidin-4-ylmethoxy)methyl)cyclohexyl)-6-methoxy-277-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide.

[0595] LC-MS: (ESI, m/z): $[M+H]^+$= 562.3.

Step 11: preparation of *N*-(2-((1*S*,4*S*)-4-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methoxy)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0596]



[0597] A mixture of *N*-(2-((1*S*,4*S*)-4-hydroxy-4-((piperidin-4-ylmethoxy)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide (130 mg, 0.23 mmol), pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (121 mg, 0.28 mmol), and DIEA (89 mg, 0.69 mmol) in DMSO (6 mL) was stirred at room temperature overnight. The reaction liquid was diluted with water (50 mL) and extracted with DCM (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(2-((1*S*,4*S*)-4-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)piperidin-4-yl)methoxy)methyl)-4-hydroxycyclohexyl)-6-methoxy-277-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide.

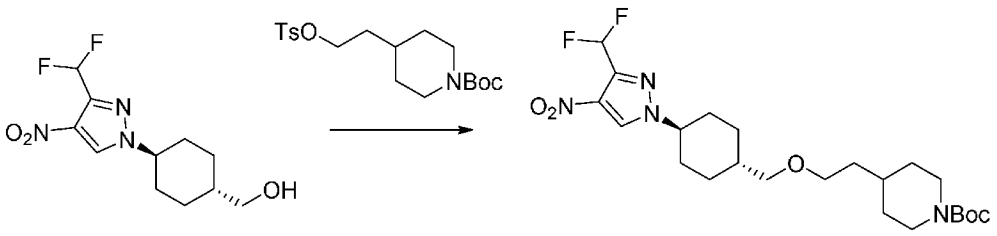
[0598] LC-MS: (ESI, *m/z*): $[M+H]^+$= 812.1.

[0599] ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* = 7.5 Hz, 2H), 8.69 (s, 1H), 8.46 (d, *J* = 7.7 Hz, 1H), 8.40 (t, *J*= 7.8 Hz, 1H), 8.32 (s, 1H), 8.21 (d, *J*= 7.6 Hz, 1H), 7.65 (d, *J*= 8.2 Hz, 1H), 7.57 (d, *J*= 1.4 Hz, 1H), 7.40 (dd, *J*= 8.2, 1.5 Hz, 1H), 7.16 (s, 1H), 4.58-4.29 (m, 3H), 3.99 (s, 3H), 3.84-3.55 (m, 3H), 3.33-3.28 (m, 2H), 3.22 (s, 2H), 3.13-3.03 (m, 1H), 2.88-2.70 (m, 3H), 2.35-2.20 (m, 2H), 1.94-1.59 (m, 9H), 1.21-1.15 (m, 2H).

Example 9: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(2-(((1*R*,4*R*)-4-(3-(diffuoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0600]

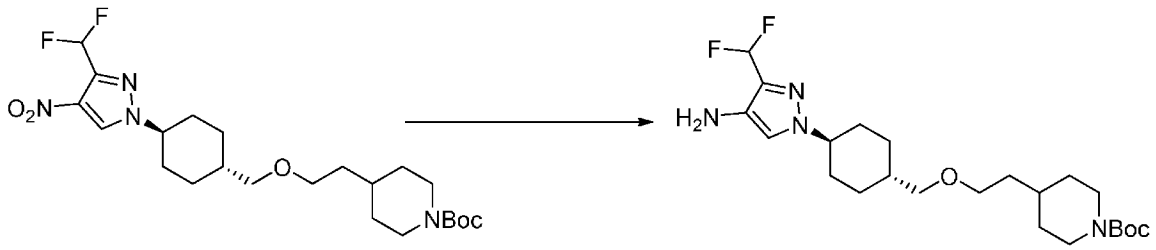


[0601] NaH (60%, 580 mg, 14.5 mmol) was added to a solution of ((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)methanol (1.0 g, 3.64 mmol) in anhydrous THF (30 mL) at 0 °C, and then the mixture was stirred at room temperature for 1 h. *tert-Butyl* 4-(2-(p-toluenesulfonyl)ethyl)piperidine-1-carboxylate (2.79 g, 7.28 mmol) and KI (1.21 g, 7.28 mmol) were added, and the reaction liquid was stirred at 70 °C overnight. Water (50 mL) was slowly added to the reaction liquid, and the mixture was extracted with EtOAc (100 mL × 3). The combined organic phases were washed with saturated brine (50 mL) and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-7:13) to give tert-butyl 4-(2-(((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0602] LC-MS: (ESI, *m/z):* $[M+Na]^+$ = 509.2.

Step 2: preparation of tert-butyl 4-(2-(((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0603]

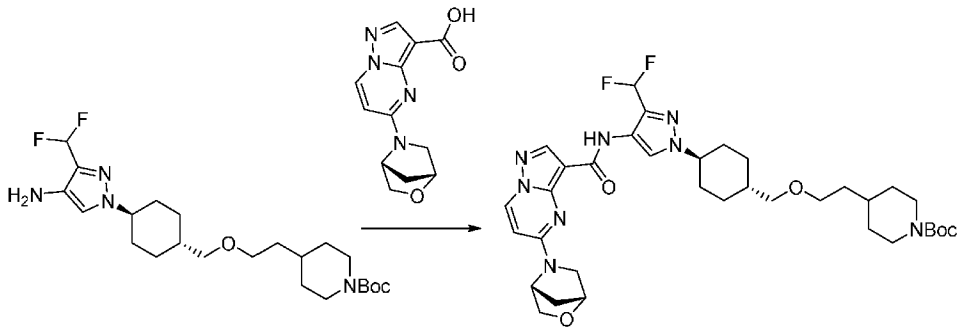


[0604] Raney-Ni (0.4 mL) and hydrazine hydrate (85%, 0.4 mL) were added to a solution of tert-butyl 4-(2-(((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (185 mg, 0.38 mmol) in ethanol (10 mL), and then the reaction liquid was stirred at room temperature for 1 h. The mixture was filtered, and the filtrate was directly concentrated under reduced pressure to give *tert-butyl* 4-(2-(((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1 -carboxylate.

[0605] LC-MS: (ESI, m/z): $[M+H]^+$= 457.2.

Step 3: preparation of tert-butyl 4-(2-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0606]



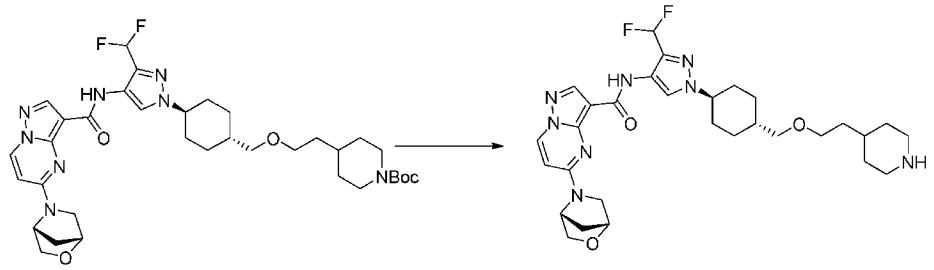
[0607] 5-((1*R*,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (86 mg, 0.33

mmol), HATU (188 mg, 0.50 mmol), and DIEA (128 mg, 0.99 mmol) were added to a solution of *tert-butyl* 4-(2-(((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (150 mg, 0.33 mmol) in DMF (5 mL). The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (50 mL) and then extracted with EA (50 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by reversed-phase chromatography (CH_3CN/H_2O (0.5% FA), 5%-95%) to give tert-butyl 4-(2-(((1R,4R)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1 -yl)cyclohexyl)methoxy)ethyl)piperidine-1 -carboxylate.

[0608] LC-MS: (ESI, *m/z):* $[M+Na]^+$ = 721.2.

Step 4: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0609]

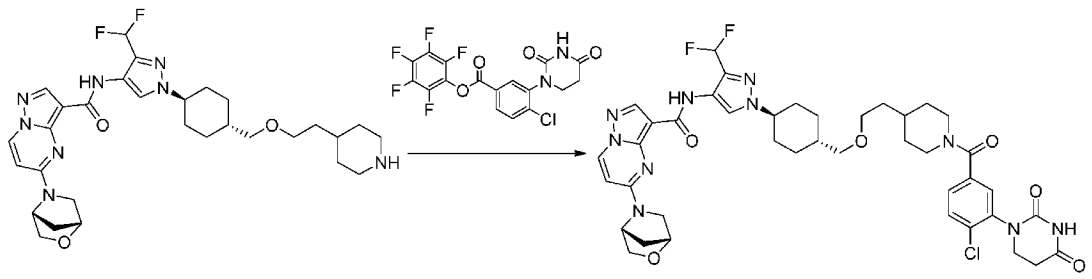


[0610] A reaction liquid of tert-butyl 4-(2-(((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (80 mg, 0.11 mmol) in TFA/DCM (3 mL, 1/5) was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting product was directly used in the next step.

[0611] LC-MS: (ESI, *m/z*): $[M+H]^+$= 599.3

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0612]



[0613] A solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.13 mmol), pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (58 mg, 0.13 mmol), and DIEA (86 mg, 0.66 mmol) in DMSO (5 mL) was stirred at room temperature overnight. The reaction liquid was poured into water (50 mL) and stirred for 10 min. The mixture was filtered, and the filter cake was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-(1*R*,4*R*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

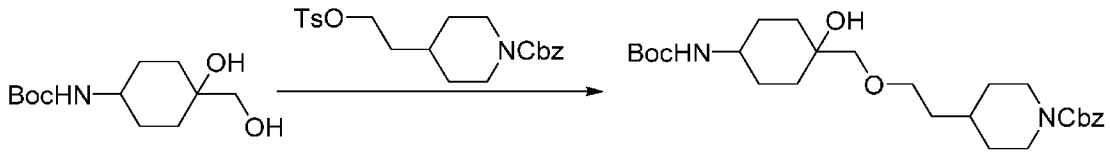
[0614] LC-MS: (ESI, *m/z):* $[M+H]^+$= 849.1.

[0615] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J*= 4.3 Hz, 1H), 8.25 (d, *J*= 5.6 Hz, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.29-6.93 (m, 1H), 6.90-6.40 (m, 1H), 5.30-5.03 (m, 1H), 4.77 (d, *J*= 17.2 Hz, 1H), 4.50-4.35 (m, 1H), 4.24-4.11 (m, 1H), 3.86-3.70 (m, 3H), 3.66-3.52 (m, 3H), 3.50-3.40 (m, 3H), 3.22 (d, *J*= 6.4 Hz, 2H), 3.12-2.95 (m, 1H), 2.83-2.70 (m, 3H), 2.08-1.91 (m, 4H), 1.88-1.54 (m, 8H), 1.55-1.44 (m, 2H), 1.19-1.04 (m, 4H).

Example 10: *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

Step 1: preparation of benzyl 4-(2-((4-((tert-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0616]



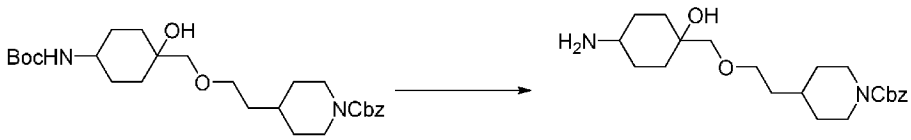
[0617] NaH (376 mg, 9.4 mmol) was added to a solution of tert-butyl (4-hydroxy-4-(hydroxymethyl)cyclohexyl)carbamate (770 mg, 3.13 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Then benzyl 4-(2-(p-toluenesulfonyl)ethyl)piperidine-1 -carboxylate (2.62 g, 6.26 mmol) and KI (1.04 g, 6.26 mmol) were added. The reaction liquid was stirred at 70 °C overnight. The reaction liquid was diluted with water (50 mL) and extracted with EA (30 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-3:2) to give benzyl 4-(2-((4-((*tert*-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0618] LC-MS: (ESI, *m/z*): $[M+Na]^+$ = 513.1.

[0619] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41-7.29 (m, 5H), 6.67 (d, *J*= 7.5 Hz, 1H), 5.06 (s, 2H), 4.05-3.90 (m, 3H), 3.42 (t, *J* = 6.4 Hz, 2H), 3.10 (s, 3H), 2.88-2.68 (m, 2H), 1.65 (d, *J* = 12.6 Hz, 2H), 1.55-1.32 (m, 20H), 1.13-0.92 (m, 2H).

Step 2: preparation of benzyl 4-(2-((4-amino-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0620]

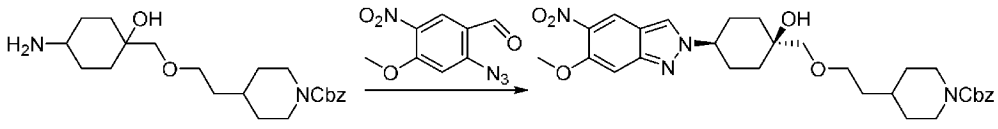


[0621] TFA (1.2 mL) was added to a solution of benzyl 4-(2-((4-((tert-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (270 mg, 0.55 mmol) in DCM (3 mL) at -10 to 0 °C while stirring, and then the reaction liquid was stirred at room temperature for 2 h. DIEA was added to the reaction liquid to adjust the pH to 9.0, and the mixture was concentrated under reduced pressure to give benzyl 4-(2-((4-amino-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0622] LC-MS: (ESI, *m/z*): $[M+H]^+$= 391.2.

Step 3: preparation of benzyl 4-(2-(((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2*H*-indol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0623]



[0624] 2-Azido-4-methoxy-5-nitrobenzaldehyde (150 mg, 0.66 mmol) was added to a solution of benzyl 4-(2-((4-amino-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (400 mg, 0.55 mmol) in toluene (15 mL) while stirring. The reaction liquid was stirred at 100 °C for 3 h. The reaction liquid was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (EA:PE = 0-9:1) to give benzyl 4-(2-(((1S,4S)-1-hydroxy-4-(6-methoxy-5-nitro-2H-indol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0625] LC-MS: (ESI, *m/z*): $[M+H]^+$= 567.3.

[0626] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.38 (s, 1H), 7.41-7.29 (m, 5H), 7.27 (s, 1H), 5.07 (s, 2H), 4.50-4.40 (m, 1H), 4.34 (s, 1H), 4.05-3.95 (m, 2H), 3.91 (s, 3H), 3.47 (t, *J*= 6.4 Hz, 2H), 3.21 (s, 2H), 2.90-2.70 (m, 2H), 2.35-2.19 (m, 2H), 1.90 (d, *J*= 9.7 Hz, 2H), 1.75-1.50 (m, 7H), 1.50-1.40 (m, 2H), 1.11-0.98 (m, 2H).

Step 4: preparation of benzyl 4-(2-(((1*S*,4*S*-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

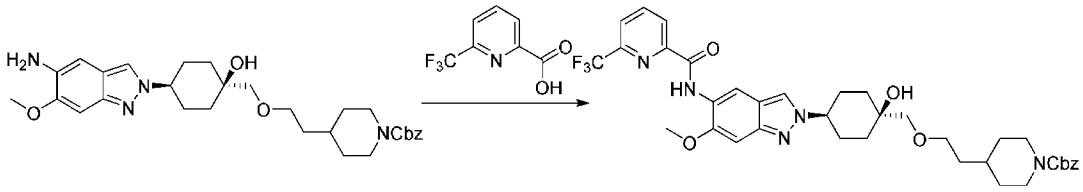
[0627]

[0628] Raney-Ni (0.5 mL) and N_2H_4 H_2O (0.5 mL) were added to a solution of benzyl 4-(2-(((1S,4S)-1-hydroxy-4-(6-methoxy-5-nitro-2H-indol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (250 mg, 0.44 mmol) in EtOH (20 mL). The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give benzyl 4-(2-(((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate. The resulting product was directly used in the next step.

[0629] LC-MS: (ESI, *m/z*): $[M+H]^+$= 537.3

Step 5: preparation of benzyl 4-(2-(((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0630]



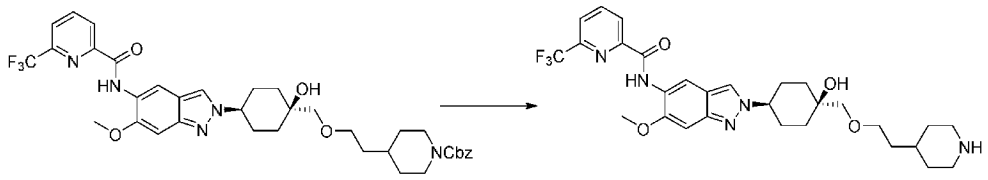
[0631] 6-(Trifluoromethyl)picolinic acid (101 mg, 0.53 mmol), HATU (217 mg, 0.57 mmol), and DIEA (170 mg, 1.32 mmol) were added to a solution of benzyl 4-(2-(((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (236 mg, 0.44 mmol) in DMF (5 mL) while stirring. Then the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (50 mL) and extracted with EA (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-4:1) to give benzyl 4-(2-(((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2H-indol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0632] LC-MS: (ESI, *m/z*): $[M+H]^+$= 710.2.

[0633] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.69 (s, 1H), 8.46 (d, *J*= 7.7 Hz, 1H), 8.40 (t, *J*= 7.8 Hz, 1H), 8.32 (s, 1H), 8.21 (d, *J*= 7.7 Hz, 1H), 7.41-7.28 (m, 5H), 7.16 (s, 1H), 5.06 (s, 2H), 4.40-4.20 (m, 2H), 4.10-3.90 (m, 5H), 3.47 (t, *J*= 6.4 Hz, 2H), 3.21 (s, 2H), 2.90-2.70 (m, 2H), 2.32-2.18 (m, 2H), 1.90 (d, *J*= 10.4 Hz, 2H), 1.72-1.53 (m, 7H), 1.52-1.40 (m, 2H), 1.15-1.00 (m, 2H).

Step 6: preparation of N-(2-((1S,4S)-4-hydroxy-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0634]

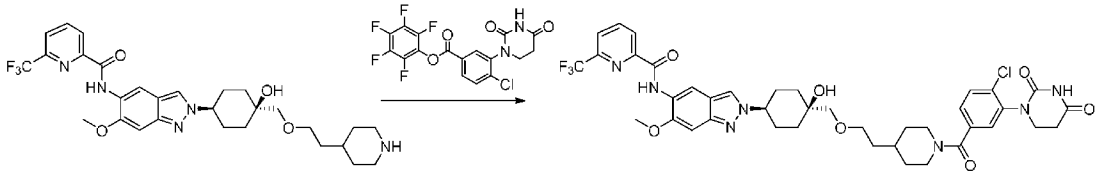


[0635] $Pd(OH)_2/C$ (100 mg) was added to a solution of benzyl 4-(2-(((1*S*,4*S*)-1 -hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (200 mg, 0.28 mmol) in EA (20 mL). Then the reaction liquid was stirred at 70 °C overnight under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was concentrated to give *N*-(2-((1*S*,4*S*)-4-hydroxy-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide. The resulting product was directly used in the next step.

[0636] LC-MS: (ESI, *m/z):* $[M+H]^+$= 576.2.

Step 7: preparation of *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0637]



[0638] A solution of *N*-(2-((1*S*,4*S*)-4-hydroxy-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide (130 mg, 0.22 mmol), pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (118 mg, 0.27 mmol), and DIEA (87 mg, 0.68 mmol) in DMSO (3 mL) was stirred at room temperature overnight. The reaction liquid was diluted with water (30 mL) and extracted with DCM (10 mL × 3). The organic phase was washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide.

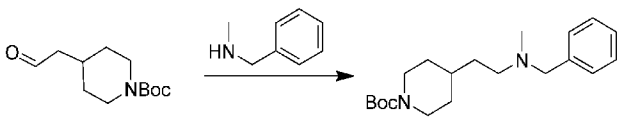
[0639] LC-MS: (ESI, *m/z):* $[M+H]^+$= 826.1.

[0640] ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* = 5.7 Hz, 2H), 8.69 (s, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 8.41 (t, *J*= 7.8 Hz, 1H), 8.33 (s, 1H), 8.22 (d, *J*= 7.7 Hz, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.16 (s, 1H), 4.50-4.26 (m, 3H), 3.98 (s, 3H), 3.83-3.53 (m, 3H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.21 (s, 2H), 3.13-2.97 (m, 1H), 2.86-2.71 (m, 3H), 2.32-2.18 (m, 2H), 1.90 (d, *J* = 9.8 Hz, 2H), 1.85-1.45 (m, 9H), 1.15-1.05 (m, 2H).

Example 11: 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-((1R,4R)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(2-(phenyl(methyl)amino)ethyl)piperidine-1-carboxylate

[0641]



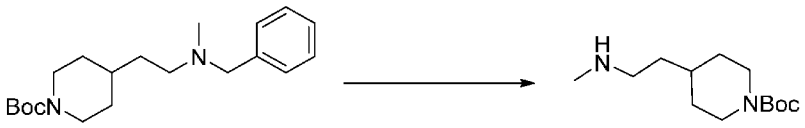
[0642] *N*-Methyl-1-phenylmethylamine (1.067 g, 8.82 mmol) andAcOH (0.79 g, 13.23 mmol) were added to a solution of tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1 g, 4.41 mmol) in DCE (3 mL) under N_2 atmosphere. After the mixture was stirred at room temperature for 30 min, STAB (2.8 g, 13.23 mmol) was added, and then the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL), and the mixture was extracted

with EA (30 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:20) to give *tert-butyl* 4-(2-(phenyl(methyl)amino)ethyl)piperidine-1 -carboxylate.

[0643] LC-MS: (ESI, *m/z*): $[M+H]^+$= 333.2.

Step 2: preparation of tert-butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate

[0644]

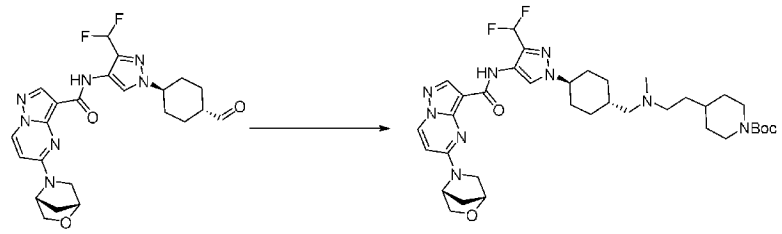


[0645] $Pd(OH)_2$/C (250 mg) was added to a solution of *tert-butyl* 4-(2-(phenyl(methyl)amino)ethyl)piperidine-1-carboxylate (1 g, 3.01 mmol) in THF (3 mL), and the reaction liquid was then stirred at room temperature for 2 h under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give tert-butyl 4-(2-(methylamino)ethyl)piperidine-1 -carboxylate.

[0646] LC-MS: (ESI, m/z): $[M+H]^+$= 243.2.

Step 3: preparation of tert-butyl 4-(2-((((1R,4R)-4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[0647]

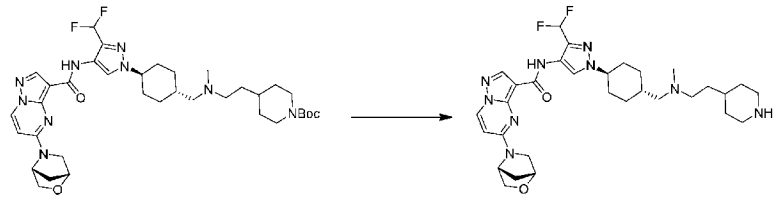


[0648] tert-Butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (329 mg, 0.928 mmol) and STAB (419 mg, 1.862 mmol) were added to a solution of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (300 mg, 0.618 mmol) in THF (3 mL), and the reaction was stirred at room temperature for 2 h under N2 atmosphere. Water (20 mL) was added to quench the reaction, and the mixture was extracted with DCM (20 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl 4-(2-((((1*R*,4R)-4-(4-(5-((1R,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[0649] LC-MS: (ESI, m/z): $[M+H]^l$ = 712.4.

Step 4: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[0650]

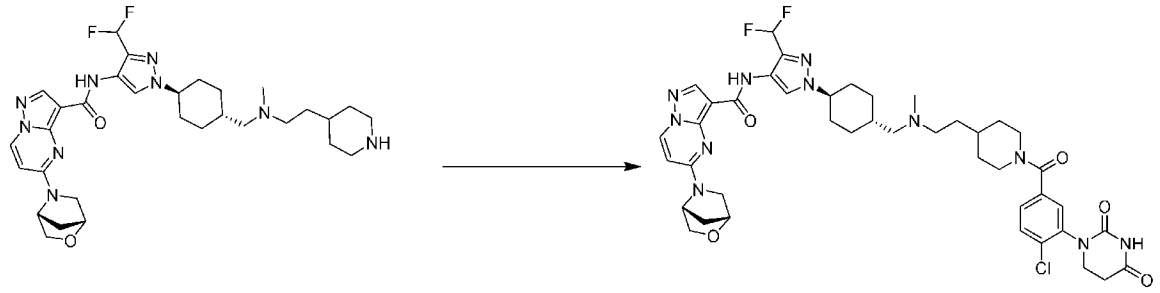


[0651] TFA (1 mL) was added to a solution of tert-butyl 4-(2-((((1R,4R)-4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (200 mg, 0.281 mmol) in DCM (3 mL), and the reaction liquid was stirred at room temperature for 2 h under N2 atmosphere. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0652] LC-MS: (ESI, m/z): $[M+H]^+$= 612.4.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*(1-((1*R*,4*R*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0653]



[0654] DIEA (109 mg, 1.564 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (134 mg, 1.043 mmol) were added to a solution of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-((1R,4R)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (175mg, 0.521 mmol) in DMSO (3 mL), and then the reaction liquid was stirred at room temperature for 3 h. Water (15 mL) was added to the reaction liquid, and the mixture was extracted with DCM (30 mL × 2) and dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure, and the resulting crude product was purified by Prep-HPLC (acetonitrile/0.05% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

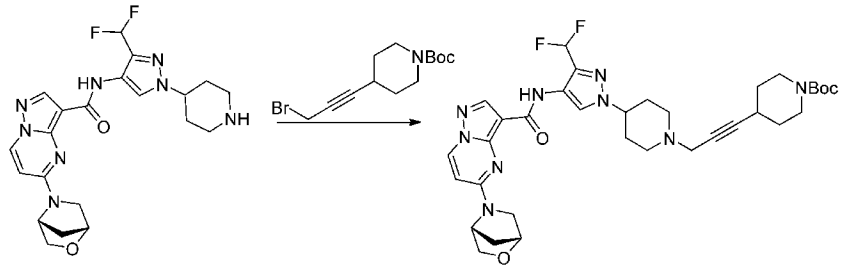
[0655] LC-MS: (ESI, *m/z*): $[M+H]^+$= 862.1.

[0656] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J*= 6.0 Hz, 1H), 8.78 (d, J= 7.7 Hz, 1H), 8.38 (d, *J*= 4.4 Hz, 1H), 8.25 (d, *J*= 5.6 Hz, 1H), 7.62 (t, *J*= 7.7 Hz, 1H), 7.54 (d, *J*= 1.9 Hz, 1H), 7.38 (dd, *J*= 8.2, 2.0 Hz, 1H), 7.26-6.95 (m, 1H), 6.90-6.42 (m, 1H), 5.31-5.05 (m, 1H), 4.77 (d, J= 17.3 Hz, 1H), 4.52-4.34 (m, 1H), 4.24-4.12 (m, 1H), 3.86-3.70 (m, 3H), 3.65-3.53 (m, 3H), 3.45 (d, *J*= 10.0 Hz, 1H), 3.11-2.94 (m, 1H), 2.77-2.65 (m, 3H), 2.29 (t, *J*= 7.0 Hz, 2H), 2.15-2.07 (m, 5H), 2.05-1.82 (m, 6H), 1.80-1.68 (m, 3H), 1.66-1.46 (m, 3H), 1.41-1.32 (m, 2H), 1.18-0.95 (m, 4H).

Example 12: 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N (1-(1-(3-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)prop-2-yn-1-yl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(3-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)prop-1-yn-1-yl)piperidine-1-carboxylate

[0657]

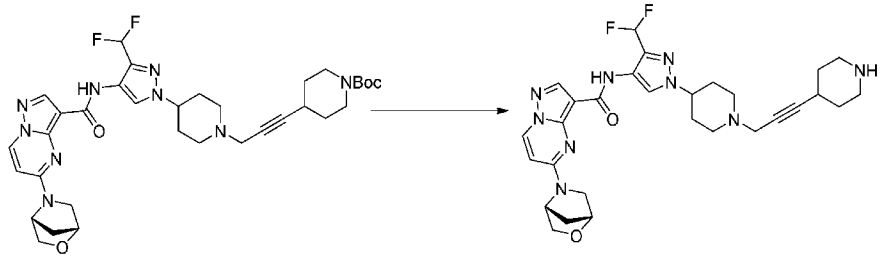


[0658] A mixture of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, TFA salt, 0.33 mmol), tert-butyl 4-(3-bromoprop-1-yn-1-yl)piperidine-1-carboxylate (99 mg, 0.33 mmol), and K_2CO_3 (227 mg, 1.65 mmol) in THF (20 mL) was stirred at 70 °C overnight. The reaction liquid was diluted with water (20 mL), extracted with DCM (20 mL × 3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-1) to give tert-butyl 4-(3-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)- 177-pyrazol-1 -yl)piperidin-1 -yl)prop-1 -yn-1 -yl)piperidine-1 -carboxylate.

[0659] LC-MS: (ESI, *m/z):* $[M+H]^+$= 680.3.

Step 2: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-(1-(3-(piperidin-4-yl)prop-2-yn-1-yl)piperidin-4-yl)-1*H*pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0660]

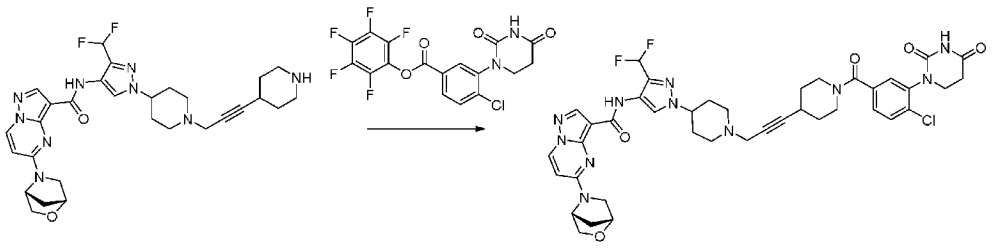


[0661] A mixture of tert-butyl 4-(3-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)prop-1-yn-1-yl)piperidine-1-carboxylate (70 mg, 0.10 mmol) in TFA/DCM (3 mL, 1/5) was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(3-(piperidin-4-yl)prop-2-yn-1-yl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting product was directly used in the next step.

[0662] LC-MS: (ESI, *m/z):* $[M+H]^+$= 580.2.

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)prop-2-yn-1-yl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0663]



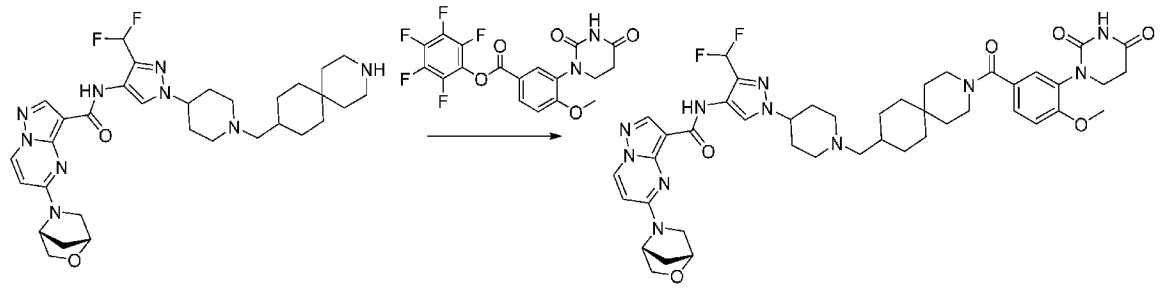
[0664] A mixture of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N (3-(difluoromethyl)-1-(1-(3-(piperidin-4-yl)prop-2-yn-1-yl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, crude, 0.12 mmol), pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (52 mg, 0.12 mmol), and DIEA (774 mg, 0.60 mmol) in DMSO (5 mL) was stirred at room temperature overnight. The reaction liquid was poured into water (50 mL) and stirred for 10 min. The mixture was filtered, and the filter cake was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)prop-2-yn-1-yl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0665] LC-MS: (ESI, *m/z):* $[M+H]^{l}$ = 830.3.

[0666] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.51 (d, J= 5.8 Hz, 1H), 8.79 (d, J= 7.7 Hz, 1H), 8.42 (s, 1H), 8.26 (d, J= 5.6 Hz, 1H),7.64 (d, J= 8.2 Hz, 1H), 7.58 (d, *J*= 1.9 Hz, 1H), 7.41 (dd, J= 8.2, 2.0 Hz, 1H), 7.28-6.97 (m, 1H), 6.90-6.43 (m, 1H), 5.30-5.02 (m, 1H), 4.77 (d, *J*= 18.9 Hz, 1H), 4.30-4.20 (m, 1H), 4.18-3.90 (m, 1H), 3.88-3.70 (m, 3H), 3.68-3.56 (m, 3H), 3.54-3.36 (m, 3H), 3.30-3.21 (m, 2H), 3.00-2.64 (m, 5H), 2.40-2.20 (m, 2H), 2.12-1.73 (m, 8H), 1.62-1.42 (m, 2H).

Example 13: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0667]



[0668] A mixture of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (160 mg, 0.26 mmol), pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (110 mg, 0.26 mmol), and DIEA (168 mg, 1.3 mmol) in DMSO (5 mL) was stirred at room temperature overnight. The reaction liquid was poured into water (50 mL) and stirred for 10 min. The mixture was filtered, and the filter cake was purified by Prep-HPLC to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

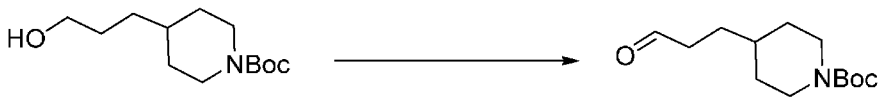
[0669] LC-MS: (ESI, *m/z*): $[M+H]^{+}$= 870.3.

[0670] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J*= 4.0 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.41-7.29 (m, 2H), 7.27-6.95 (m, 2H), 6.91-6.40 (m, 1H), 5.31-5.00 (m, 1H), 4.77 (d, *J*= 17.5 Hz, 1H), 4.27-4.15 (m, 1H), 3.86-3.71 (m, 5H), 3.65-3.39 (m, 8H), 2.89 (d, *J*= 10.4 Hz, 2H), 2.68 (t, *J*= 6.5 Hz, 2H), 2.15 (d, *J* = 6.1 Hz, 2H), 2.08-1.87 (m, 8H), 1.76-1.65 (m, 2H), 1.63-1.38 (m, 5H), 1.36-1.21 (m, 2H), 1.19-0.95 (m, 4H).

Example 14: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)propyl)piperidin-4-yl)-3-(difluoromethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(3-oxopropyl)piperidine-1-carboxylate

[0671]

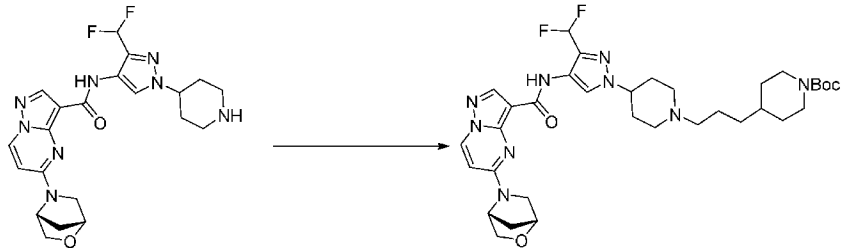


[0672] IBX (2.88 g, 10.285 mmol) was added to a solution of tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (1.0 g, 4.115 mmol) in ACN (30 mL), and the mixture was stirred at 80 °C for 2 h. After the reaction was complete, the mixture was extracted with ethyl acetate (50 mL × 3), and the organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 1:1) to give tert-butyl 4-(3-oxopropyl)piperidine-1-carboxylate.

[0673] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (t, *J* = 1.5 Hz, 1H), 3.96-3.86 (m, 2H), 2.70-2.60 (m, 2H), 2.46 (td, *J* = 7.5, 1.4 Hz, 2H), 1.66-1.56 (m, 3H), 1.56-1.36 (m, 4H), 1.39 (s, 9H).

Step 2: preparation of tert-butyl 4-(3-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)propyl)piperidine-1-carboxylate

[0674]

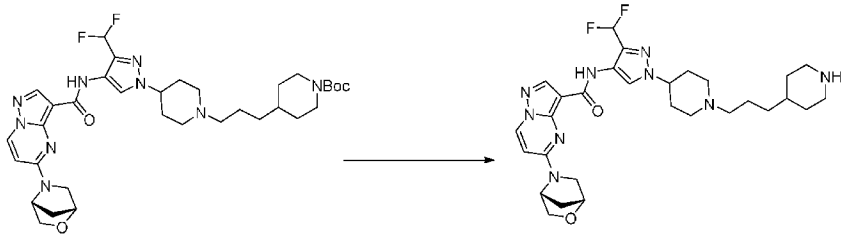


[0675] tert-Butyl 4-(3-oxopropyl)piperidine-1-carboxylate (95 mg, 0.394 mmol) and STAB (208 mg, 0.981 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.327 mmol) in THF (30 mL), and the mixture was stirred at room temperature for 2 h and extracted with ethyl acetate (40 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 3:7) to give tert-butyl 4-(3-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)propyl)piperidine-1-carboxylate.

[0676] LC-MS: (ESI, *m/z*): $[M+H]^+$= 684.2.

Step 3: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-(1-(3-(piperidin-4-yl)propyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0677]



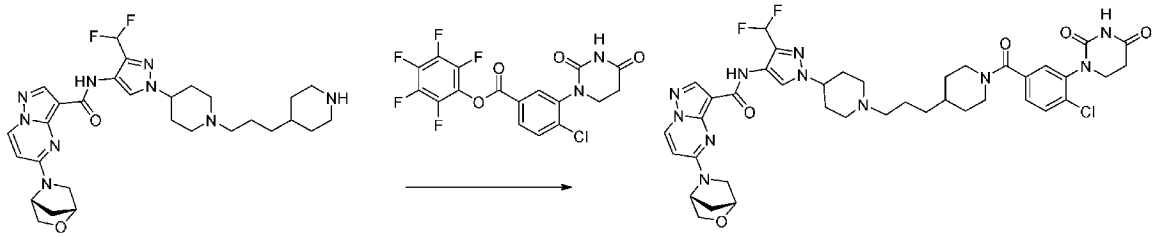
[0678] TFA (5 mL) was added to a solution of tert-butyl 4-(3-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)propyl)piperidine-1-carboxylate (200 mg, 0.293 mmol) in DCM (20 mL), and the mixture was stirred at room temperature for 2 h, made basic with a saturated $NaHCO_3$ solution, and extracted with ethyl acetate (60 mL × 3). The organic phase was washed with saturated brine (150 mL) and concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(3-(piperidin-4-yl)propyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-

carboxamide.

[0679] LC-MS: (ESI, *m/z*): $[M+H]^+$= 584.2.

Step 4: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N**(1-(1-(3-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)propyl)piperidin-4-yl)-3-(difluoromethyl)-1 *H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0680]



[0681] 5-((1 *R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(3-(piperidin-4-yl)propyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.257 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (134 mg, 0.308 mmol) were dissolved in DMSO (5 mL). DIEA (100 mg, 0.775 mmol) was added, and then the mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was stirred for 2 min and filtered. The filter cake was purified by preparative reversed-phase chromatography to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)propyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

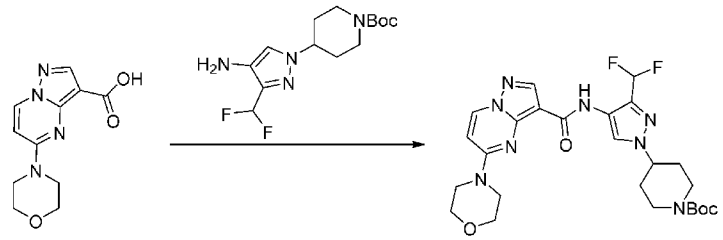
[0682] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 834.0.

[0683] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.40 (d, *J*= 3.7 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.64 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.27-6.96 (m, 1H), 6.90-6.40 (m, 1H), 5.30-5.05 (m, 1H), 4.77 (d,J= 17.5 Hz, 1H), 4.52-4.33 (m, 1H), 4.26-4.14 (m, 1H), 3.85-3.72 (m, 3H), 3.66-3.57 (m, 3H), 3.45 (d, *J*= 10.2 Hz, 1H), 3.11-2.89 (m, 3H), 2.79-2.66 (m, 3H), 2.30 (t, *J*= 6.9 Hz, 2H), 2.09-1.84 (m, 9H), 1.82-1.69 (m, 1H), 1.68-1.58 (m, 1H), 1.56-1.40 (m, 3H), 1.30-1.20 (m, 2H), 1.16-1.02 (m, 2H).

Example 15: *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5 -*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0684]

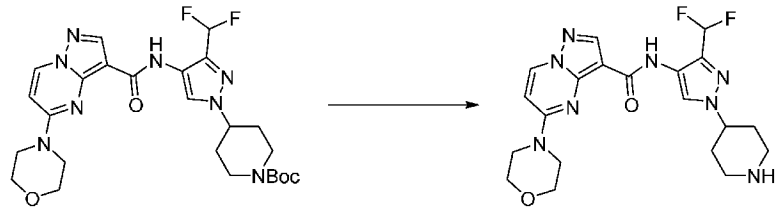


[0685] HATU (900 mg, 2.4 mmol) was added to a solution of 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (470 mg, 1.9 mmol) and DIEA (1 mL, 4.7 mmol) in DMF (20 mL) at 25 °C. After the mixture was stirred at 25 °C for 2 h, tert-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (0.5 g, 1.5 mmol) was added, and the reaction liquid was then stirred overnight at 25 °C. Water (30 mL) was added to the reaction liquid, and the mixture was then extracted with EA (50 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA) to give *tert-butyl* 4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0686] LC-MS: (ESI, m/z): $[M+H]^+$ = 547.4.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1H-pyrazol-4-yl)-5-morpholinopyrazolo[1,5 -*a*]pyrimidine-3-carboxamide

[0687]

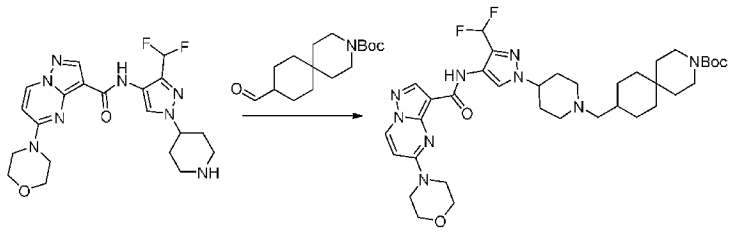


[0688] TFA (1 mL) was added to a solution of tert-butyl 4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamido)-1H-pyrazol-1 -yl)piperidine-1-carboxylate (0.2 g, 0.366 mmol) in DCM (3 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0689] LC-MS: (ESI, m/z): $[M+H]^+$ = 447.2.

Step 3: preparation of tert-butyl 9-((4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-α]pyrimidine-3-carboxamido)-1 H-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate

[0690]

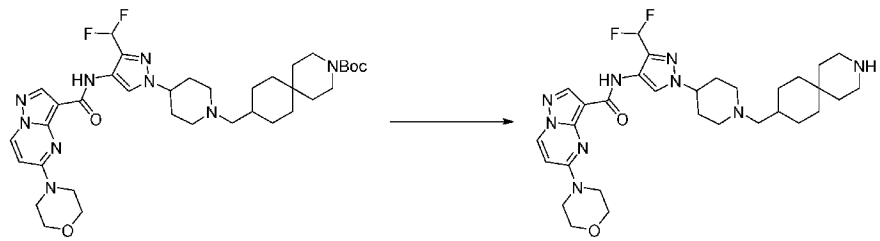


[0691] tert-Butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (150 mg, 0.45 mmol) and $NaBH_3CN$ (100 mg, 2.25 mmol) were added to a solution of N-(3-(difluoromethyl)-1-(piperidin-4-yl)-1H-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*] pyrimidine-3-carboxamide (200 mg, 0.45 mmol) andDIEA(0.5 mL, 1.35 mmol) in MeOH (5 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 16 h. After filtration and concentration under reduced pressure, the resulting crude product was purified by flash column chromatography (MeOH:DCM = 3:97) to give tert-butyl 9-((4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0692] LC-MS: (ESI, m/z): $[M+H]^+$= 712.4.

Step 4: preparation of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1 *H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide

[0693]

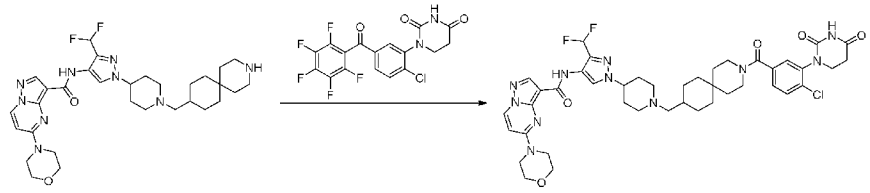


[0694] TFA (1 mL) was added to a solution of tert-butyl 9-((4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (0.14 g, 0.2 mmol) in DCM (3 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 1 h. The reaction liquid was directly concentrated under reduced pressure to give N (1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting product was directly used in the next step.

[0695] LC-MS: (ESI, m/z): $[M+H]^{l}$ = 612.5.

Step 5: preparation of *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0696]



[0697] DIEA (0.1 mL, 0.54 mmol) was added to a solution of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.18 mmol) and 1-(2-chloro-5-pentafluorobenzoyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (90 mg, 0.19 mmol) in DMSO (2 mL) at 25 °C. The reaction liquid was stirred at 25 °C for 16 h. The reaction liquid was poured into water (10 mL) and filtered, and the filter cake was purified by Prep-HPLC to give *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3 -carboxamide.

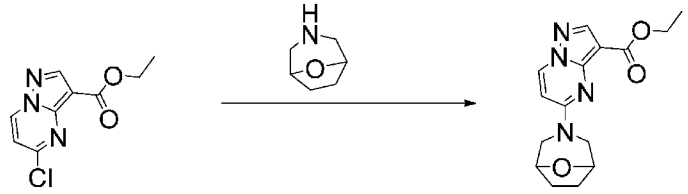
[0698] LC-MS: (ESI, *m/z):* $[M+H]^{+}$= 862.4.

[0699] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J*= 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.63 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.25-6.95 (m, 1H), 6.91 (d, *J*= 8.0 Hz, 1H), 4.26-4.14 (m, 1H), 3.87-3.68 (m, 9H), 3.66-3.50 (m, 3H), 3.31-3.20 (m, 2H), 2.95-2.83 (m, 2H), 2.80-2.68 (m, 2H), 2.21-2.08 (m, 2H), 2.07-1.87 (m, 6H), 1.70 (d, *J*= 8.7 Hz, 2H), 1.63-1.41 (m, 5H), 1.38-1.25 (m, 2H), 1.16-1.02 (m, 4H).

Example 16: 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[0700]

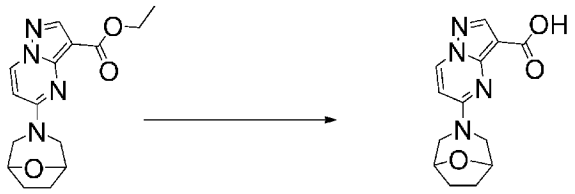


[0701] 8-Oxa-3-azabicyclo[3.2.1]octane (1.3 g, 8.9 mmol) and DIEA (3.4 g, 26 mmol) were added to a solution of ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2.0 g, 8.9 mmol) inACN (20 mL), and the reaction liquid was heated to 60 °C and reacted for 2 h. Water (200 mL) was added to quench the reaction, and the mixture was extracted with EA (200 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (PE:EA = 1-5:1) to give ethyl 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-α]pyrimidine-3-carboxylate.

[0702] LC-MS: (ESI, *m/z):* $[M+H]^{l}$ = 303.2.

Step 2: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-α]pyrimidine-3-carboxylic acid

[0703]

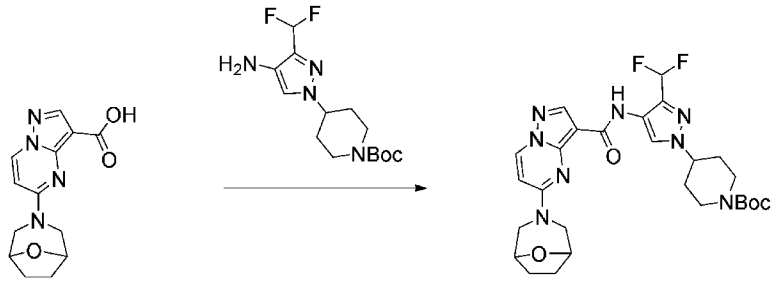


[0704] LiOH (1.4 g, 34 mmol) was added to a mixture of ethyl 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (2.6 g, 8.6 mmol) in H_2O/MeOH (3 mL/26 mL), and then the reaction liquid was heated to 60 °C and reacted for 12 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (acetonitrile/0.05% aqueous NH_4OH solution, 5%-95%) to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0705] LC-MS: (ESI, *m/z):* $[M+H]^+$= 275.3.

Step 3: preparation of tert-butyl 4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[0706]

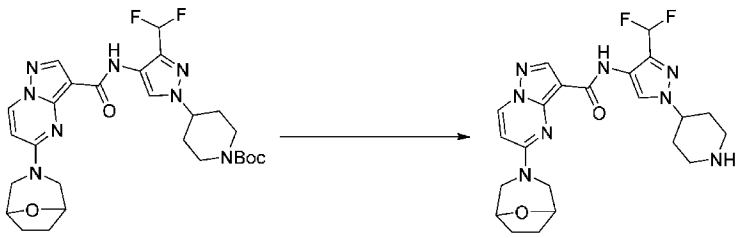


[0707] tert-Butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (316 mg, 1 mmol), HATU (456 mg, 1.2 mmol), and DIEA (387 mg, 3 mmol) were added to a solution of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (274 mg, 1 mmol) in DMF (5 mL), and then the reaction liquid was reacted at 25 °C for 12 h. The reaction liquid was poured into water and then extracted with EA (50 mL × 2), and the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl 4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[0708] LC-MS: (ESI, *m/z):* $[M+H]^+$= 573.4.

Step 4: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0709]

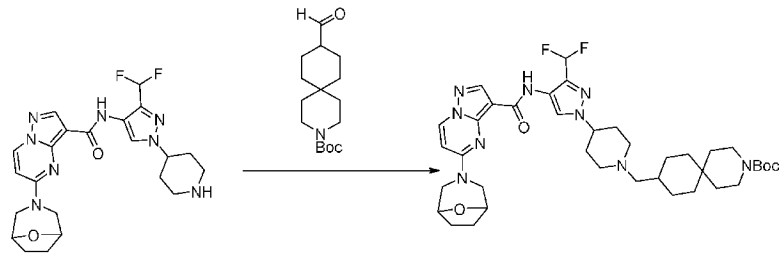


[0710] A solution of *tert*-butyl 4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (240 mg, 0.42 mmol) in HCl/1,4-dioxane (5 mL) was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0711] LC-MS: (ESI, *m/z):* $[M+H]^+$= 473.4.

Step 5: preparation of tert-butyl 9-((4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(-difluoromethyl)-1H-pyrazol-1-yl)piperidin-1-yl)methyl)-3 azaspiro [5.5]undecane-3-carboxylate

[0712]

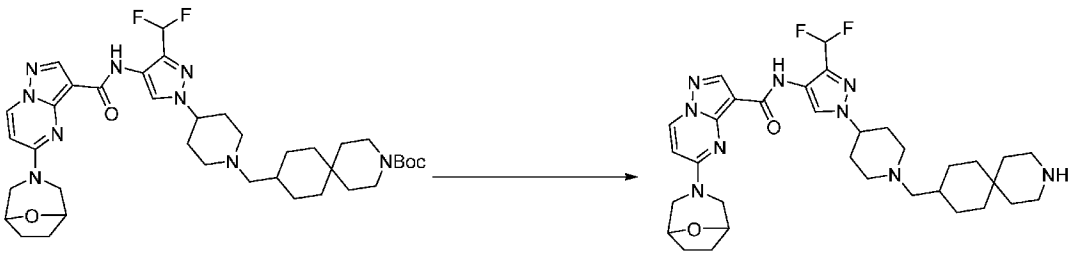


[0713] tert-Butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (77 mg, 0.27 mmol) and STAB (175 mg, 0.8 mmol) were added to a solution of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N (3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (130 mg, 0.27 mmol) in THF (10 mL). The reaction liquid was then stirred at 25 °C for 12 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl 9-((4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5] undecane-3-carboxylate.

[0714] LC-MS: (ESI, m/z): $[M+H]^+$ = 738.3.

Step 6: preparation of *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0715]

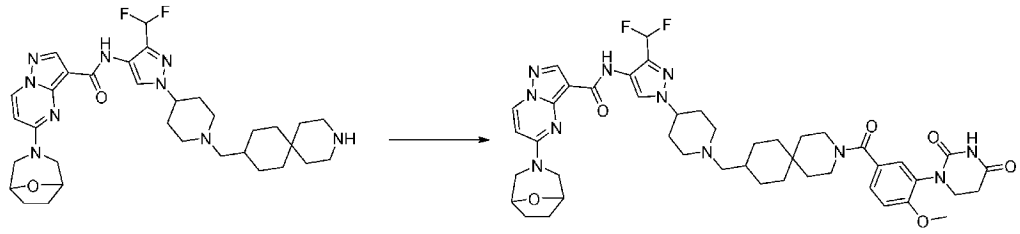


[0716] A solution of *tert-butyl* 9-((4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-α]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1 H-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (100 mg, 0.14 mmol) in HCl/1,4-dioxane (4 mL) was stirred at 25 °C for 1 h. Then the reaction liquid was directly concentrated under reduced pressure to give *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0717] LC-MS: (ESI, m/z): $[M+H]^+$= 638.3.

Step 7: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0718]



[0719] Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (123 mg, 0.28 mmol) and DIEA (93 mg, 0.72 mmol) were added to a solution of N-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-177-pyrazol-4-yl)-5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150.0 mg, 0.24 mmol) in DMSO (2 mL), and then the reaction liquid was stirred at room temperature for 12 h. The reaction liquid was poured into water (20 mL) and extracted with EA (30 mL × 2), and the organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (acetonitrile/0.05% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N (3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

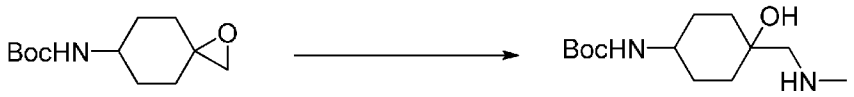
[0720] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 884.5.

[0721] ^1H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.41 (s, 1H), 8.81 (d, *J* = 7.8 Hz, 1H), 8.39 (s, 1H), 8.28 (d, J= 1.3 Hz, 1H), 7.37 (d, J= 8.4 Hz, 1H), 7.32 (s, 1H), 7.27-6.95 (m, 2H), 6.82 (d, *J*= 7.9 Hz, 1H), 4.50-4.37 (m, 2H), 4.30-4.00 (m, 2H), 3.84 (s, 3H), 3.68-3.34 (m, 6H), 3.28-3.11 (m, 2H), 2.98-2.78 (m, 2H), 2.73-2.60 (m, 2H), 2.22-1.63 (m, 14H), 1.61-1.17 (m, 8H), 1.18-0.93 (m, 4H).

Example 17: *N*-(2-((1*S*,4*S*)-4-((((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

Step 1: preparation of tert-butyl (4-hydroxy-4-(methylamino)methyl)cyclohexyl)carbamate

[0722]

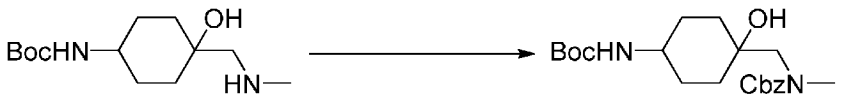


[0723] Methylamine (40 mL, 25%-30% aqueous solution) was added to a mixture of tert-butyl (1-oxaspiro[2.5]octan-6-yl)carbamate (4.2 g, 18.42 mmol) in EtOH/H_2O (90 mL/15 mL). Then the reaction liquid was stirred at 25 °C overnight. The reaction liquid was directly concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-1:1) to give *tert*-butyl (4-hydroxy-4-(methylamino)methyl)cyclohexyl)carbamate.

[0724] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 259.2.

Step 2: preparation of benzyl ((4-((tert-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methyl)(methyl)carbamate

[0725]



[0726] A mixture of tert-butyl (4-hydroxy-4-(methylamino)methyl)cyclohexyl)carbamate (1.2 g, 4.61 mmol) and benzyl chloroformate (941 mg, 5.53 mmol) in ACN/sat. $NaHCO_3$ (20 mL/20 mL) was stirred at room temperature overnight. The reaction liquid was diluted with water (50 mL) and then extracted with EA (50 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-7:3) to give benzyl ((4-((tert-

butoxycarbonyl)amino)-1-hydroxycyclohexyl)methyl)(methyl)carbamate.

[0727] LC-MS: (ESI, *m/z*): $[M+Na]^+$ = 415.2.

Step 3: preparation of benzyl ((4-amino-1-hydroxycyclohexyl)methyl)(methyl)carbamate

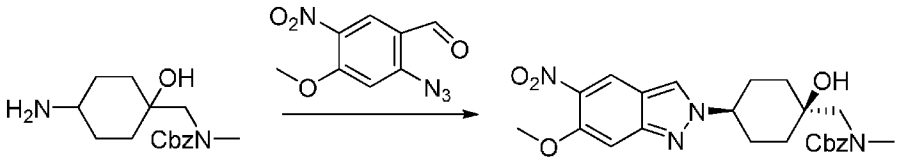
[0728]

[0729] TFA (5 mL) was added to a solution of benzyl ((4-((tert-butoxycarbonyl)amino)-1-hydroxycyclohexyl)methyl)(methyl)carbamate (1.5 g, 3.81 mmol) in DCM (15 mL) at 0 °C while stirring, and then the reaction liquid was stirred at 0 °C for 2 h. The pH of the reaction liquid was adjusted to 9.0 with DIEA, and then the mixture was directly concentrated under reduced pressure to give benzyl ((4-amino-1-hydroxycyclohexyl)methyl)(methyl)carbamate. The resulting crude product was directly used in the next step.

[0730] LC-MS: (ESI, m/z): $[M+H]^+$= 293.1.

Step 4: preparation of benzyl (((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)carbamate

[0731]



[0732] 2-Azido-4-methoxy-5-nitrobenzaldehyde (1.2 g, 5.7 mmol) was added to a solution of benzyl ((4-amino-1-hydroxycyclohexyl)methyl)(methyl)carbamate (1.5 g, 3.8 mmol) in toluene (40 mL) while stirring. The reaction liquid was stirred at 100 °C for 3 h. The reaction liquid was directly concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-1) to give benzyl (((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)carbamate.

[0733] LC-MS: (ESI, m/z): $[M+H]^+$= 469.2

[0734] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.38 (s, 1H), 7.45-7.23 (m, 6H), 5.09 (s, 2H), 4.66-4.36 (m, 2H), 3.91 (s, 3H), 3.28 (s, 2H), 3.10-2.95 (m, 3H), 2.30-2.20 (m, 2H), 1.95-1.60 (m, 2H), 1.78-1.63 (m, 2H), 1.59-1.41 (m, 2H).

Step 5: preparation of benzyl (((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexylmethyl)(methyl)carbamate

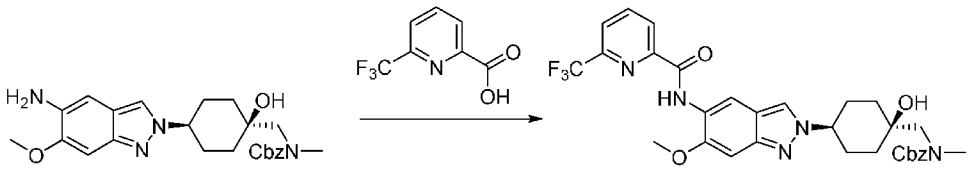
[0735]

[0736] $N_2H_4H_2O$ (1.2 mL) and Raney-Ni (0.5 mL) were added to a solution of benzyl (((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2H-indol-2-yl)cyclohexyl)methyl)(methyl)carbamate (1.1 g, 2.34 mmol) in EtOH (20 mL). The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give benzyl (((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexylmethyl)(methyl)carbamate. The resulting crude product was directly used in the next step.

[0737] LC-MS: (ESI, m/z): $[M+H]^+$= 439.2

Step 6: preparation of benzyl (((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridineformyl)-2H-indol-2-yl)cyclohexyl)methyl)(methyl)carbamate

[0738]



[0739] 6-(Trifluoromethyl)picolinic acid (538 mg, 2.78 mmol), HATU (1.06 g, 2.78 mmol), and DIEA (828 mg, 6.42 mmol) were added to a solution of benzyl (((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indol-2-yl)-1-hydroxycyclohexylmethyl)(methyl)carbamate (940 mg, 2.14 mmol) in DMF (10 mL) while stirring. Then the reaction liquid was stirred at room temperature overnight. The reaction liquid was diluted with water (100 mL) and extracted with EA (30 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EA:PE = 0-9:1) to give benzyl (((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridineformyl)-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)carbamate.

[0740] LC-MS: (ESI, *m/z*): $[M+H]^+$= 612.2.

[0741] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.69 (s, 1H), 8.46 (d, *J*= 7.5 Hz, 1H), 8.40 (t, *J*= 7.8 Hz, 1H), 8.31 (s, 1H), 8.21 (dd, *J*= 7.7, 1.0 Hz, 1H), 7.42-7.28 (m, 5H), 7.16 (s, 1H), 5.09 (s, 2H), 4.60-4.31 (m, 2H), 3.98 (s, 3H), 3.28 (s, 2H), 3.10-2.95 (m, 3H), 2.30-2.15 (m, 2H), 1.95-1.60 (m, 2H), 1.67 (t, *J*= 14.9 Hz, 2H), 1.57-1.40 (m, 2H).

Step 7: preparation of *N*-(2-((1*S*,4*S*)-4-hydroxy-4-((methylamino)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

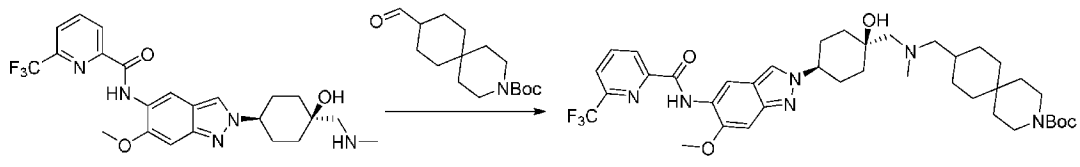
[0742]

[0743] $Pd(OH)_2$/C (200 mg) was added to a solution of benzyl (((1S,4S)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridineformyl)-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)carbamate (500 mg, 0.81 mmol) in EA (20 mL). Then the reaction liquid was stirred at 70 °C overnight under H_2 atmosphere. The reaction liquid was filtered through celite, and the filtrate was concentrated under reduced pressure to give N-(2-((1*S*,4*S*)-4-hydroxy-4-((methylamino)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide. The resulting crude product was directly used in the next step.

[0744] LC-MS: (ESI, *m/z):* $[M+H]^l$ = 478.1.

Step 8: preparation of *tert-butyl* 9-(((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)amino)methyl)-3-azaspiro[5.5]undecane-3-carboxylate

[0745]



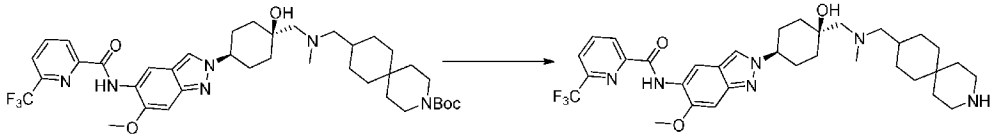
[0746] A mixture of N-(2-((1*S*,4*S*)-4-hydroxy-4-((methylamino)methyl)cyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluor-

omethyl)pyridinecarboxamide (200 mg, 0.41 mmol), tert-butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (141 mg, 0.50 mmol), and STAB (434 mg, 2.05 mmol) in THF (10 mL) was stirred at room temperature overnight. The reaction liquid was diluted with water (30 mL), and then the mixture was extracted with DCM (10 mL × 3). The organic phase was washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl 9-(((((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)amino)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0747] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 743.3.

Step 9: preparation of *N*-(2-((1*S*,4*S*)-4-((((3-azaspiro[5.5]undecan-9-yl)methyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0748]

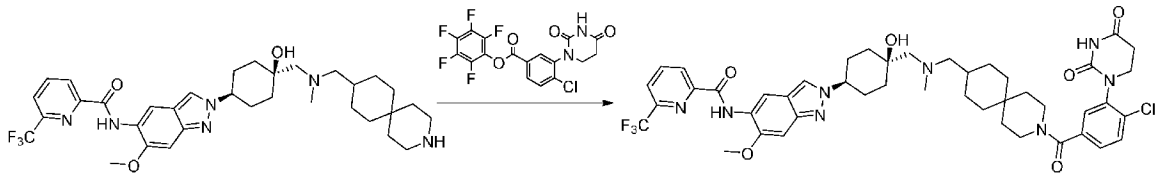


[0749] TFA (2 mL) was added to a solution of tert-butyl 9-(((((1S,4S)-1-hydroxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indol-2-yl)cyclohexyl)methyl)(methyl)amino)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (200 mg, 0.27 mmol) in DCM (5 mL) at 0 °C. Then the reaction liquid was stirred at room temperature for 2 h. The pH of the reaction liquid was adjusted to 9.0 with DIE. The organic phase was washed with water (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give *N*-(2-((1*S*,4*S*)-4-((((3-azaspiro[5.5]undecan-9-yl)methyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide. The resulting crude product was directly used in the next step.

[0750] LC-MS: (ESI, *m/z*): $[M+H]^+$= 643.3.

Step 10: preparation of *N*-(2-((1*S*,4*S*)-4-((((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0751]



[0752] A mixture of *N*-(2-((1*S*,4*S*)-4-((((3-azaspiro[5.5]undecan-9-yl)methyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide (130 mg, 0.20 mmol), pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (105 mg, 0.24 mmol), and DIEA (77 mg, 0.60 mmol) in DMSO (5 mL) was stirred at room temperature overnight. The reaction liquid was diluted with water (50 mL), and then the mixture was extracted with DCM (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give A-(2-((15,45)-4-((((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide.

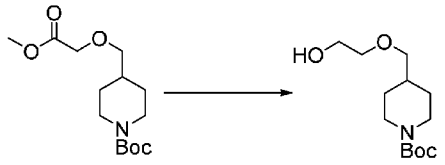
[0753] LC-MS: (ESI, *m/z):* $[M+H]^+$= 893.1.

[0754] ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 2H), 8.69 (s, 1H), 8.47 (d, *J*= 7.8 Hz, 1H), 8.41 (t, *J*= 7.8 Hz, 1H), 8.32 (s, 1H), 8.22 (d, *J*= 7.8 Hz, 1H), 7.63 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 1.7 Hz, 1H), 7.39 (d, *J*= 8.3 Hz, 1H), 7.15 (s, 1H), 4.37-4.27 (m, 1H), 4.10-3.90 (m, 4H), 3.82-3.49 (m, 4H), 3.35-3.25 (m, 1H), 2.80-2.70 (m, 2H), 2.36-2.15 (m, 9H), 1.95-1.85 (m, 2H), 1.78-1.22 (m, 14H), 1.18-0.98 (m, 4H).

Example 18: 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-(1-(2-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methoxy)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-((2-hydroxyethoxy)methyl)piperidine-1-carboxylate

[0755]



[0756] $LiAlH_4$ (1.0 mol/L, 5.8 mL) was added dropwise to a solution of methyl 4-((2-methoxy-2-oxoethoxy)methyl)piperidine-1-carboxylate (1.1 g, 3.83 mmol) in anhydrous THF (30 mL) at 0 °C under N_2 atmosphere, and then the reaction liquid was stirred at room temperature for 3 h. A 15% NaOH solution was slowly added dropwise to the reaction liquid while stirring. The mixture was filtered, and the filtrate was extracted with EA (30 mL × 2). The organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-3:97) to give tert-butyl 4-((2-hydroxyethoxy)methyl)piperidine-1-carboxylate.

[0757] LC-MS: (ESI, *m/z):* $[M+H]^l$ = 260.1.

Step 2: preparation of tert-butyl 4-((2-oxoethoxy)methyl)piperidine-1-carboxylate

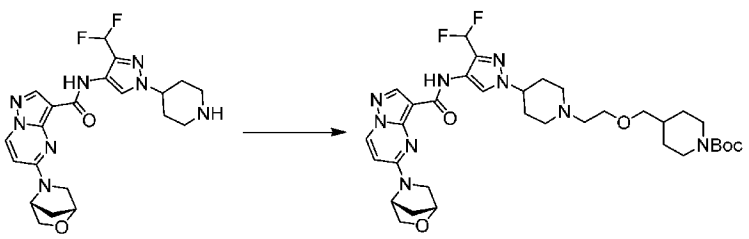
[0758]

[0759] A mixture of tert-butyl 4-((2-hydroxyethoxy)methyl)piperidine-1-carboxylate (700 mg, 2.7 mmol) and IBX (1.5 g, 5.4 mmol) in acetonitrile (15 mL) was stirred at 80 °C for 2 h. The mixture was filtered, diluted with water (30 mL), and extracted with EA (30 mL × 2). The organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (EA:PE = 0-2:3) to give *tert-butyl* 4-((2-oxoethoxy)methyl)piperidine-1-carboxylate.

[0760] LC-MS: (ESI, *m/z*): $[M\text{-}t\text{-}Bu]^+$ = 202.1.

Step 3: preparation of *tert*-butyl 4-((2-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethoxy)methyl)piperidine-1 -carboxylate

[0761]



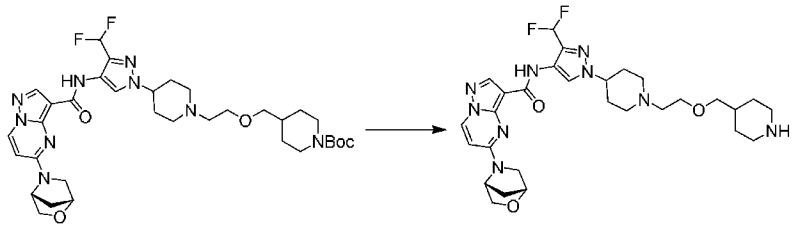
[0762] STAB (277.8 mg, 1.44 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (220.0 mg, 0.48 mmol) and tert-butyl 4-((2-oxoethoxy)methyl)piperidine-1-carboxylate (185.2 mg, 0.72 mmol) in THF (5 mL). Then the reaction liquid was

stirred at room temperature for 4 h. Water (20 mL) was added to quench the reaction, and then the mixture was extracted with DCM (20 mL × 2). The organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give *tert-butyl* 4-((2-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethoxy)methyl)piperidine-1 -carboxylate.

[0763] LC-MS: (ESI, *m/z):* $[M+H]^+$= 700.2.

Step 4: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-ylmethoxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0764]

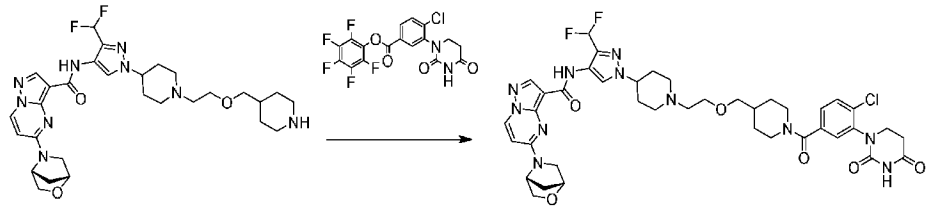


[0765] TFA (1.0 mL) was added to a solution of tert-butyl 4-((2-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethoxy)methyl)piperidine-1-carboxylate (150.0 mg, 0.214 mmol) in DCM (3.0 mL), and the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-ylmethoxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0766] LC-MS: (ESI, m/z): $[M+H]^+$= 600.4.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methoxy)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0767]



[0768] DIEA (77.5 mg, 0.6 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (95.6 mg, 0.22 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-ylmethoxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120.0 mg, 0.2 mmol) in DMSO (5.0 mL), and then the reaction liquid was stirred at room temperature for 2 h. Water (15 mL) was added to quench the reaction, and then the mixture was extracted with DCM (30 mL × 2). The organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC (acetonitrile/0.05% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methoxy)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0769] LC-MS: (ESI, *m/z*): $[M+H]^+$= 850.3.

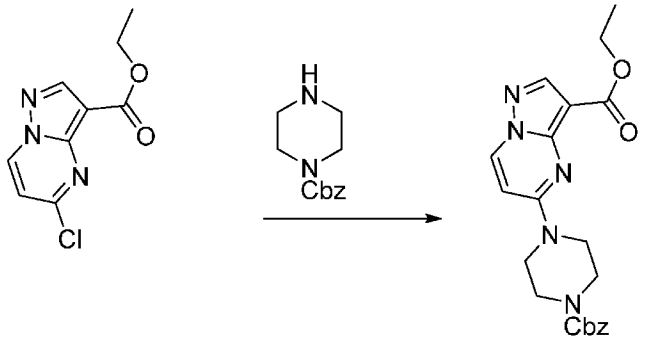
[0770] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.6 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 3.8 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.25-6.95 (m, 1H), 6.91-6.40 (m, 1H), 5.30-5.05 (m, 1H), 4.77 (d, J = 17.6 Hz, 1H), 4.55-4.35 (m, 1H), 4.28-4.10 (m, 1H), 3.83-3.75 (m, 3H), 3.66-3.57 (m, 3H), 3.53-3.42 (m, 3H), 3.30-3.26 (m, 2H), 3.06-2.96 (m, 3H), 2.77-2.66 (m, 3H),

2.34-2.20 (m, 3H), 2.06-1.85 (m, 10H), 1.14-1.08(m, 2H).

Example 19: *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate

[0771]



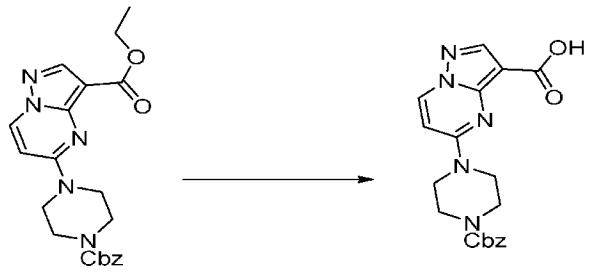
[0772] Ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (3.0 g, 13.3 mmol) and benzyl piperazine-1-carboxylate (2.9 g, 13.3 mmol) were dissolved in a solution of ACN (30 mL). DIEA (5.2 g, 40 mmol) was added, and the reaction liquid was heated to 60 °C, stirred for 2 h, and concentrated under reduced pressure. The crude product was dissolved in ethyl acetate (100 mL), washed with saturated brine, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 2:1) to give ethyl 5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[0773] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 410.2.

[0774] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 7.9 Hz, 1H), 8.22 (s, 1H), 7.41-7.33 (m, 5H), 6.86 (d, J = 7.9 Hz, 1H), 5.13 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.88-3.74 (m, 4H), 3.62-3.49 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H).

Step 2: preparation of 5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

[0775]

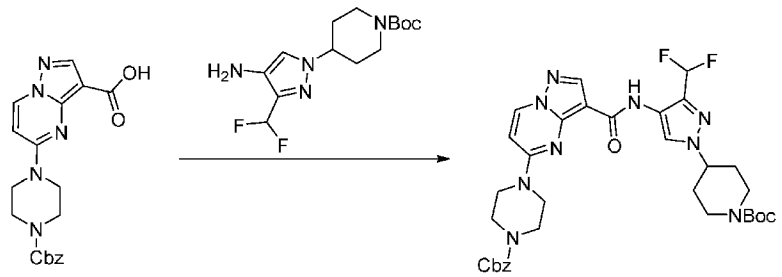


[0776] Ethyl 5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (2.6 g, 6.3 mmol) was dissolved in methanol (26 mL), lithium hydroxide (1.0 g, 25.2 mmol) was added, and the reaction liquid was stirred at 60 °C for 2 h. After the reaction was complete, dilute hydrochloric acid (2 mol/L) was added to the reaction liquid to adjust the pH of the reaction liquid to 2. Then the mixture was filtered, and the resulting filter cake was washed with water and dried under vacuum to give 5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid.

[0777] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 382.2.

Step 3: preparation of benzyl 4-(3-((1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate

[0778]

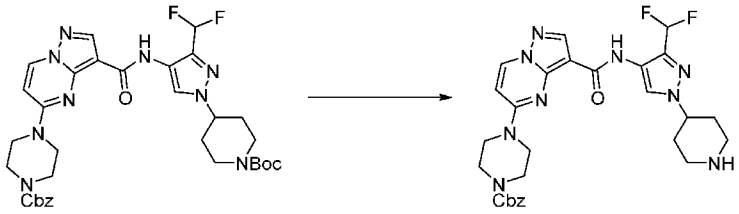


[0779] HATU (380 mg, 0.50 mmol) was added to a solution of 5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (270 mg, 0.4 mmol) and DIEA (0.5 mL, 1.0 mmol) in DMF (5 mL) at 25 °C. After the mixture was stirred at room temperature for 2 h, tert-butyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (0.21 g, 0.3 mmol) was added, and the reaction liquid was stirred at 25 °C overnight. Water (30 mL) was added to quench the reaction, and the mixture was extracted with EA (50 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (MeOH:DCM = 0-3:97) to give benzyl 4-(3-((1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate.

[0780] LC-MS: (ESI, m/z): $[M+H]^+$ = 680.4.

Step 4: preparation of benzyl 4-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate

[0781]

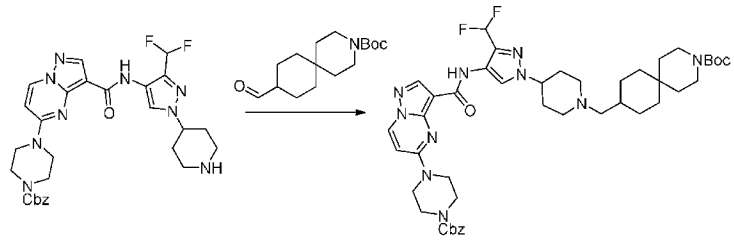


[0782] TFA (1 mL) was added to a solution of benzyl 4-(3-((1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-3-(difluoromethyl)-1Hpyrazol-4-yl)carbamoyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperazine-1-carboaylate (0.29 g, 0.42 mmol) in DCM (5 mL), and then the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give benzyl 4-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate.

[0783] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 580.5.

Step 5: preparation of *tert*-butyl 9-((4-(4-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1H-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro [5.5]undecane-3-carboxylate

[0784]



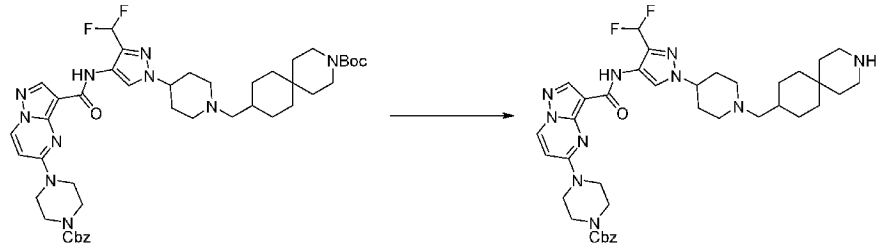
[0785] tert-Butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (144 mg, 0.45 mmol) and $NaBH_3CN$ (138 mg, 1.2 mmol) were added to a solution of benzyl 4-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1H-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate (230 mg, 0.4 mmol) and DIEA (0.35 mL, 2.0 mmol) in MeOH (10 mL). The reaction liquid was stirred at 25 °C overnight. Water (30 mL) was added to quench the reaction, and then the mixture

was extracted with EA (50 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-3:97) to give *tert*-butyl 9-((4-(4-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[0786] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 845.5.

Step 6: preparation of benzyl 4-(3-((1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate

[0787]

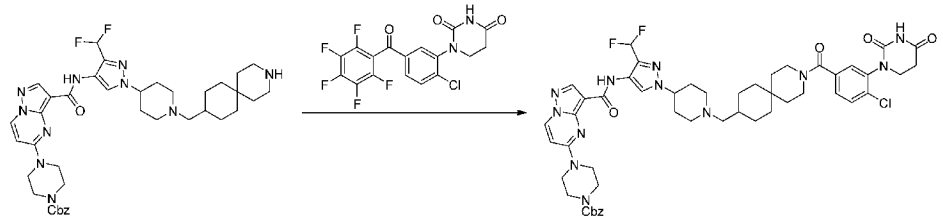


[0788] TFA (1 mL) was added to a solution of tert-butyl 9-((4-(4-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (0.29 g, 0.34 mmol) in DCM (3 mL), and the mixture was stirred at 25 °C for 1 h. The reaction liquid was directly concentrated under reduced pressure to give benzyl 4-(3-((1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate.

[0789] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 745.4.

Step 7: preparation of benzyl 4-(3-((1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1H-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate

[0790]

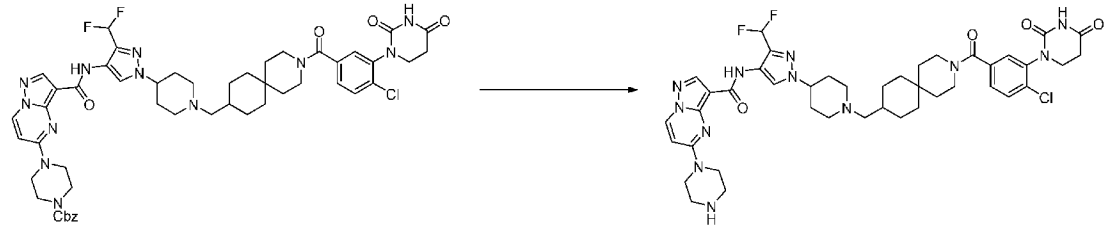


[0791] DIEA (0.1 mL, 0.6 mmol) was added to a solution of benzyl 4-(3-((1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate (240 mg, 0.32 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (144 mg, 0.33 mmol) in DMSO (5 mL). The reaction liquid was then stirred at 25 °C for 16 h. Water (30 mL) was added to the reaction liquid, and the mixture was extracted with EA (50 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-3:97) to give benzyl 4-(3-((1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate.

[0792] LC-MS: (ESI, m/z): $[M+H]^+$ = 995.0.

Step 8: preparation of *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1H pyrazol-4-yl)-5-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[0793]



[0794] Iodotrimethylsilane (0.85 mL, 0.6 mmol) was added to a solution of benzyl 4-(3-((1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperazine-1-carboxylate (290 mg, 0.29 mmol) in DCM (15 mL) at 0 °C, and then the reaction liquid was stirred at 25 °C for 16 h. The reaction liquid was poured into water, extracted with DCM (20 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC to give *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(piperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

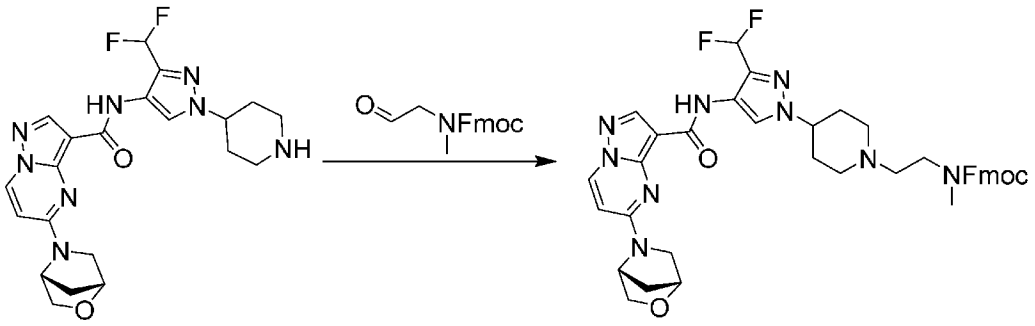
[0795] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 861.1.

[0796] ^{1}H NMR (400 MHz, MeOD) δ 8.62 (d, J = 7.9 Hz, 1H), 8.43 (brs, 2.67H, FA), 8.35 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.08-6.77 (m, 2H), 4.57-4.43 (m, 1H), 4.15-4.03 (m, 4H), 3.79 (t, J = 6.4 Hz, 2H), 3.75-3.65 (m, 2H), 3.63-3.48 (m, 2H), 3.47-3.37 (m, 2H), 3.37-3.30 (m, 2H), 3.05-2.95 (m, 2H), 2.95-2.77 (m, 4H), 2.43-2.27 (m, 4H), 1.92-1.75 (m, 3H), 1.74-1.65 (m, 3H), 1.65-1.45 (m, 2H), 1.39-1.12 (m, 5H).

Example 20: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of (9*H*-fluoren-9-yl)methyl (2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1H-pyrazol-1-yl)piperidin-1-yl)ethyl)(methyl)carbamate

[0797]

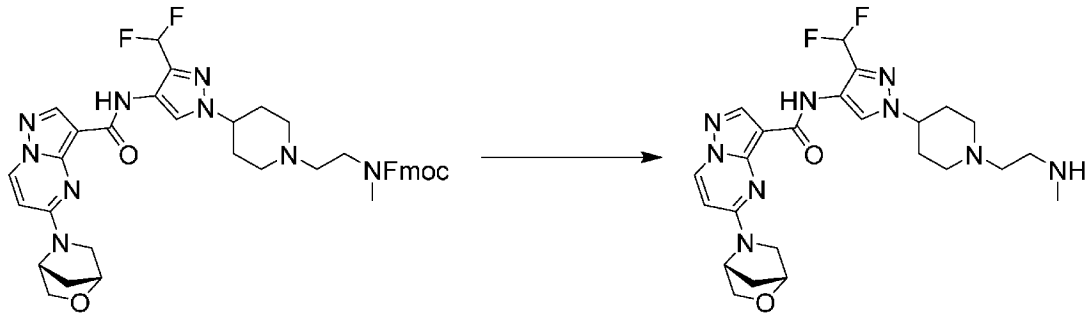


[0798] (9*H*-Fluoren-9-yl)methyl methyl(2-oxoethyl)carboxylate (91 mg, 0.31 mmol) and STAB (165 mg, 0.78 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (120 mg, 0.26 mmol) in THF (10 mL). The reaction liquid was stirred at room temperature for 16 h. Water (50 mL) was added to quench the reaction, and the mixture was extracted with DCM (20 mL × 3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give (9H-fluoren-9-yl)methyl (2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)(methyl)carbamate.

[0799] LC-MS: (ESI, *m/z*): $[M+H]^1$ = 738.5.

Step 2: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0800]

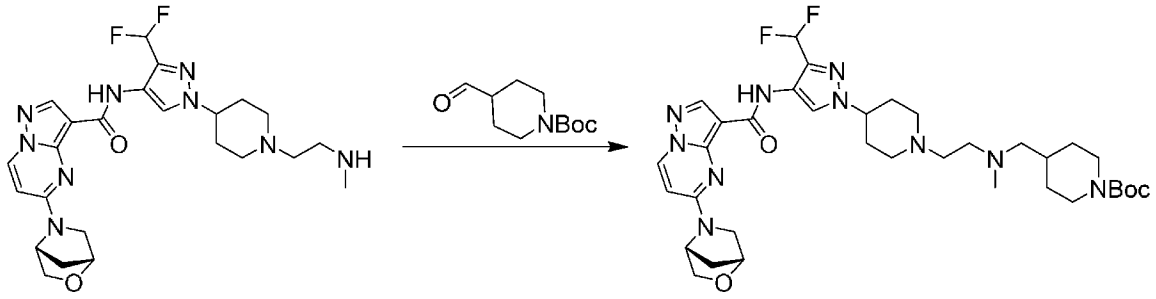


[0801] Pyridine (0.1 mL) was added to a solution of (9*H*-fluoren-9-yl)methyl (2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)(methyl)carbamate (120 mg, 0.16 mmol) in DCM (5 mL). The reaction liquid was stirred at room temperature for 16 h. The reaction liquid was directly concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0802] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 516.6.

Step 3: preparation of tert-butyl 4-(((2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)(methyl)amino)methyl)piperidine-1-carboxylate

[0803]

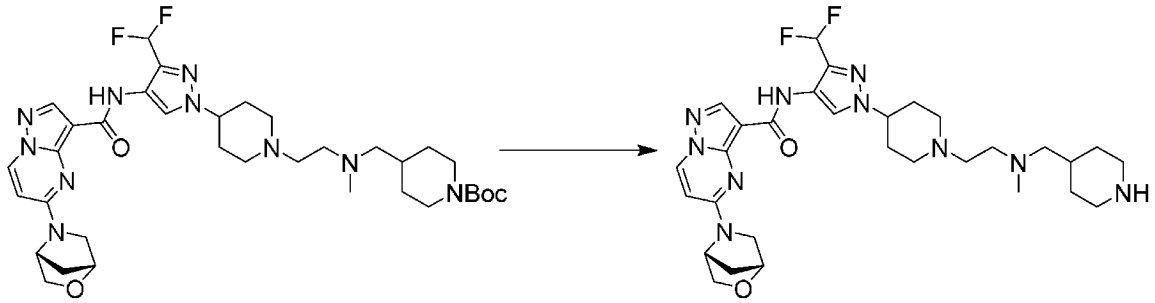


[0804] *tert*-Butyl 4-formylpiperidine-1-carboxylate (54 mg, 0.26 mmol) and STAB (108 mg, 0.51 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(methylamino)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.17 mmol) in THF (10 mL). The reaction liquid was stirred at room temperature for 16 h. Water (50 mL) was added to quench the reaction, and the mixture was extracted with DCM (20 mL × 3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-1:4) to give tert-butyl 4-(((2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)(methyl)amino)methyl)piperidine-1-carboxylate.

[0805] LC-MS: (ESI, *m/z):* $[M+H]^+$ = 713.4.

Step 4: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(methyl(piperidin-4-ylmethyl)amino)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0806]

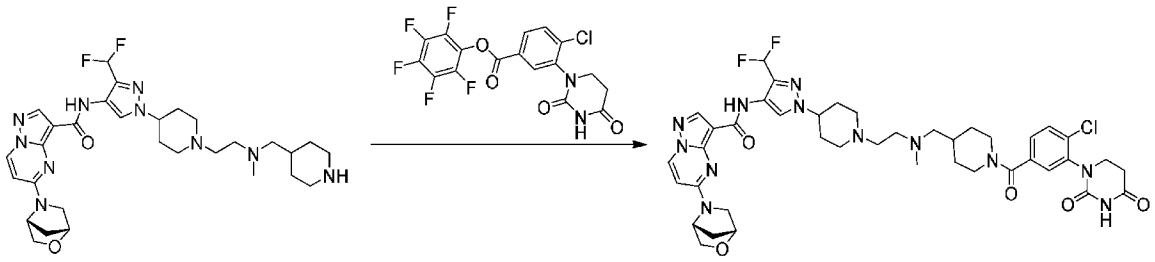


[0807] TFA (1 mL) was added to a solution of tert-butyl 4-(((2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)(methyl)amino)methyl)piperidine-1-carboxylate (100 mg, 0.14 mmol) in DCM (5 mL). The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(methyl(piperidin-4-ylmethyl)amino)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide. The resulting product was directly used in the next step.

[0808] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 613.3.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0809]



[0810] DIEA (52 mg, 0.4 mmol) was added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(2-(methyl(piperidin-4-ylmethyl)amino)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (80 mg, 0.13 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (67 mg, 0.156 mmol) in DMSO (2 mL). Then the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was poured into water and filtered, and the filter cake was purified by Prep-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

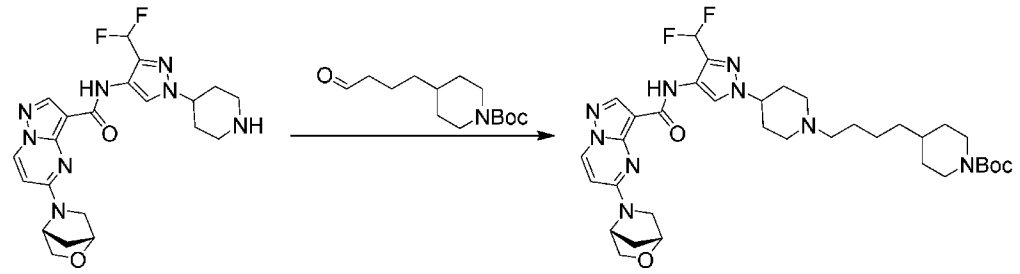
[0811] LC-MS: (ESI, m/z): $[M+H]^+$ = 863.3.

[0812] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 3.6 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.25-6.95 (m, 1H), 6.92-6.43 (m, 1H), 5.40-5.06 (m, 1H), 4.77 (d, *J* = 17.3 Hz, 1H), 4.60-4.40 (m, 1H), 4.30-4.10 (m, 1H), 3.92-3.75 (m 3H), 3.68-3.56 (m, 3H), 3.55-3.45 (m, 1H), 3.10-2.90 (m, 3H), 2.84-2.68 (m, 3H), 2.48-2.40 (m, 4H), 2.24-1.55 (m, 16H),

Example 21: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(4-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)butyl)piperidine-1-carboxylate

[0813]

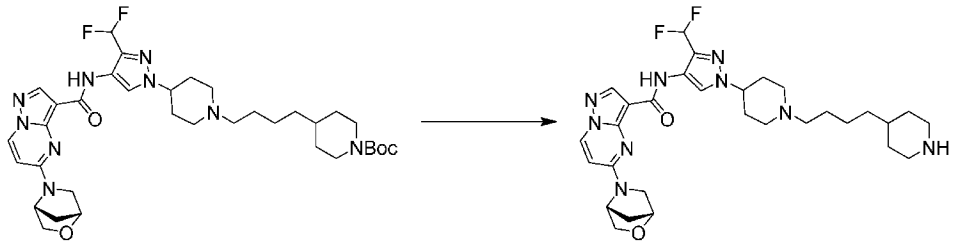


[0814] *tert*-Butyl 4-(4-oxobutyl)piperidine-1-carboxylate (100 mg, 0.36 mmol) and STAB (170 mg, 0.71 mmol) were added to a solution of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.24 mmol) in THF (5 mL). The reaction liquid was stirred at 25 °C for 2 h. Water (30 mL) was added to quench the reaction, and the mixture was extracted with DCM (30 mL × 3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (MeOH:DCM = 0-3:97) to give tert-butyl 4-(4-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)butyl)piperidine-1-carboxylate.

[0815] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 698.0.

Step 2: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(3-(difluoromethyl)-1-(1-(4-(piperidin-4-yl)butyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0816]

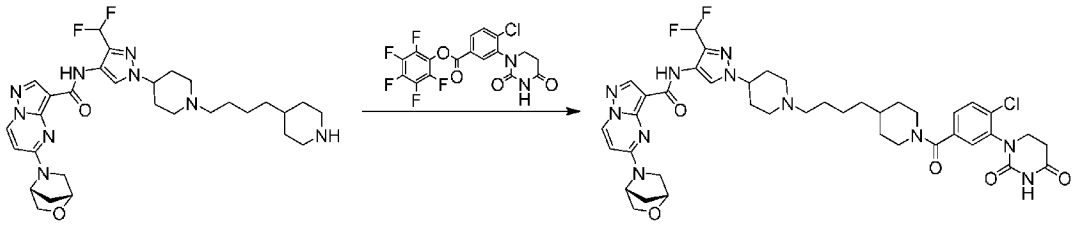


[0817] TFA (1 mL) was added to a solution of tert-butyl 4-(4-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-y)butyl)piperidine-1-carboxylate (0.2 g, 0.26 mmol) in DCM (5 mL). The reaction liquid was stirred at 25 °C for 2 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(4-(piperidin-4-yl)butyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0818] LC-MS: (ESI, *m/z*): $[M+H]^+$ = 598.1.

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0819]



[0820] DIEA (0.14 mL, 0.78 mmol) was added to a solution of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-(4-(piperidin-4-yl)butyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-car-

boxamide (160 mg, 0.26 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (130 mg, 0.26 mmol) in DMSO (4 mL). The reaction liquid was stirred at 25 °C for 2 h. Water (10 mL) was added to quench the reaction, and the mixture was extracted with DCM (20 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by Prep-HPLC to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

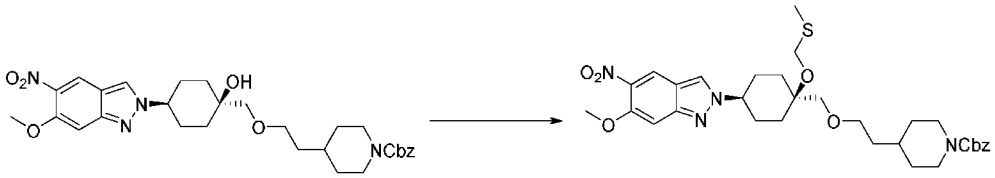
[0821] LC-MS: (ESI, m/z): $[M+H]^+$ = 848.3.

[0822] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.50 (d, J = 5.3 Hz, 1H), 8.78 (d, J = 7.7 Hz, 1H), 8.40 (s, 1H), 8.25 (d, J = 5.0 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.20-7.00 (m, 1H), 6.98-6.45 (m, 1H), 5.40-5.05 (m, 1H), 4.77 (d, J = 17.3 Hz, 1H), 4.54-4.34 (m, 1H), 4.28-4.12 (m, 1H), 3.83-3.72 (m, 3H), 3.67-3.57 (m, 3H), 3.45 (d, J = 9.6 Hz, 1H), 3.02-2.85 (m, 3H), 2.80-2.70 (m, 2H), 2.36-2.26 (m, 2H), 2.08-1.88 (m, 8H), 1.76-1.47 (m, 4H), 1.47-1.22 (m, 6H), 1.18-1.02 (m, 2H).

Example 22: *N*-(2-((1S,4S)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-l(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)-4-methoxycyclohexyl)-6-methoxy-2*H*-indol-5-yl)-6-(trifluoromethyl)pyridineamide

Step 1: preparation of benzyl 4-(2-(((1*S*,4*S*)-4-(6-methoxy-5-nitro-2*H*-indazol-2-yl)-1-((methylthio)methoxy)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate

[0823]

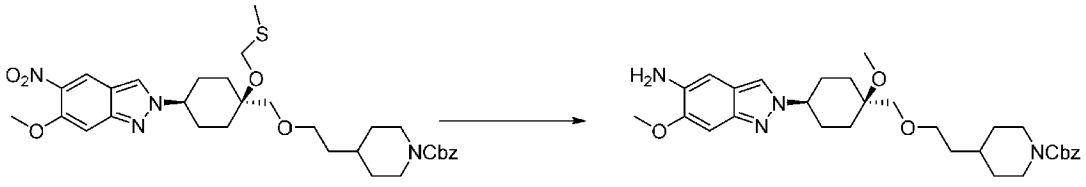


[0824] The compound benzyl 4-(2-(((1*S*,4*S*)-1-hydroxy-4-(6-methoxy-5-nitro-2H-indazol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (700 mg, 1.24 mmol) and AczO (151 mg, 1.48 mmol) were dissolved in anhydrous DMSO (20 mL), and the mixture was stirred at room temperature for 16 h under nitrogen atmosphere. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:9) to give benzyl 4-(2-(((1*S*,4*S*)-4-(6-methoxy-5-nitro-2*H*-indazol-2-yl)-1-((methylthio)methoxy)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0825] LC-MS: (ESI, m/z): $[M+H]^+$ = 627.2.

Step 2: preparation of benzyl 4-(2-(((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indazol-2-yl)-1-methoxycyclohexyl)methoxy)ethyl)piperidine-1 -carboxylate

[0826]

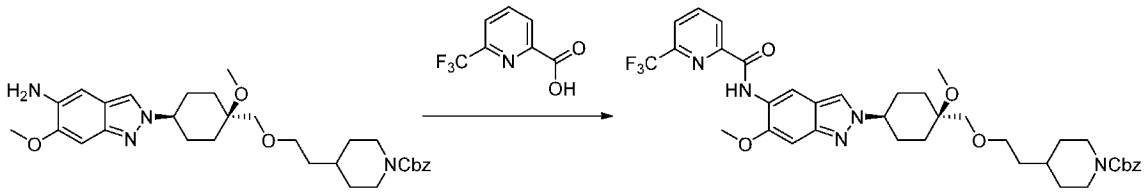


[0827] The compound benzyl 4-(2-(((1*S*,4*S*)-4-(6-methoxy-5-nitro-2*H*-indazol-2-yl)-1-((methylthio)methoxy)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (600 mg, 0.96 mmol) and pretreated Raney-Ni (200 mg) (pretreatment method: washing with water 3 times, then washing with acetone 3 times, and finally washing with ethanol 3 times) were dissolved in anhydrous ethanol (50 mL), and the mixture was stirred at room temperature for 3 h under hydrogen atmosphere and filtered. The filtrate was directly concentrated under reduced pressure, and the crude product was purified by reversed-phase silica gel column chromatography (ACN:H_2O = 1:1, flow rate 40 mL/min) to give benzyl 4-(2-(((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indazol-2-yl)-1-methoxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0828] LC-MS: (ESI, m/z): $[M+H]^l$ = 551.3.

Step 3: preparation of benzyl 4-(2-(((1*S*,4*S*)-1-methoxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indazol-2-yl)cycloheacyl)methoxy)ethyl)piperidine-1-carboxylate

[0829]

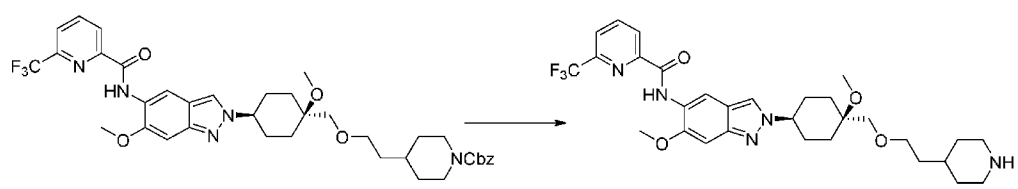


[0830] The compound 6-(trifluoromethyl)picolinic acid (60 mg, 0.3 mmol), HATU (114 mg, 0.3 mmol), and DIEA (100 mg, 0.78 mmol) were dissolved in DMF (10 mL), and the mixture was stirred at room temperature for 20 min. Benzyl 4-(2-(((1*S*,4*S*)-4-(5-amino-6-methoxy-2*H*-indazol-2-yl)-1-methoxycyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (150 mg, 0.26 mmol) was added, and the mixture was reacted at room temperature for 1 h. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:1) to give benzyl 4-(2-(((1*S*,4*S*)-1-methoxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indazol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate.

[0831] LC-MS: (ESI, m/z): $[M+H]^+$ = 724.4.

Step 4: preparation of *N*-(6-methoxy-2-((1*S*,4*S*)-4-methoxy-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-2*H*-indazol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0832]

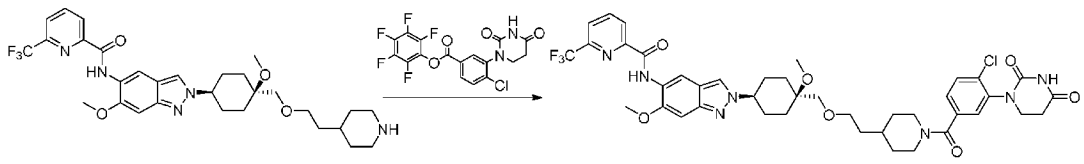


[0833] Benzyl 4-(2-(((1*S*,4*S*)-1-methoxy-4-(6-methoxy-5-(6-(trifluoromethyl)pyridinecarboxamido)-2*H*-indazol-2-yl)cyclohexyl)methoxy)ethyl)piperidine-1-carboxylate (70 mg, 0.097 mmol) was dissolved in trifluoroacetic acid (3 mL), and the mixture was heated to 90 °C and stirred for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(6-methoxy-2-((1*S*,4*S*)-4-methoxy-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-2*H*-indazol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide, which was directly used in the next step without purification.

[0834] LC-MS: (ESI, m/z): $[M+H]^l$ = 590.4.

Step 5: preparation of *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)-4-methoxycyclohexyl)-6-methoxy-2*H*-indazol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide

[0835]



[0836] *N*-(6-Methoxy-2-((1*S*,4*S*)-4-methoxy-4-((2-(piperidin-4-yl)ethoxy)methyl)cyclohexyl)-2*H*-indazol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide (70 mg, 0.097 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (48 mg, 0.11 mmol) and *N*,*N*-diisopropylethylamine (37 mg,

0.29 mmol) were added while stirring. After the mixture was stirred at room temperature for 2 h, water (50 mL) was added, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated brine (3 × 60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude product. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(2-((1*S*,4*S*)-4-((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethoxy)methyl)-4-methoxycyclohexyl)-6-methoxy-2*H*-indazol-5-yl)-6-(trifluoromethyl)pyridinecarboxamide.

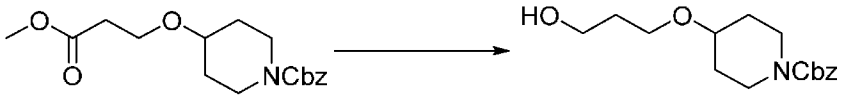
[0837] LC-MS: (ESI, m/z): $[M+H]^+$ = 840.3.

[0838] ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (d, *J* = 4.5 Hz, 2H), 8.68 (s, 1H), 8.49-8.37 (m, 2H), 8.32 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.18 (s, 1H), 4.52-4.30 (m, 2H), 3.98 (s, 3H), 3.80-3.52 (m, 3H), 3.47 (t, *J*= 6.2 Hz, 2H), 3.34 (s, 2H), 3.19 (s, 3H), 3.15-2.95 (m, 1H), 2.85-2.70 (m, 3H), 2.19-1.97 (m, 2H),-1.96-1.85 (m, 4H), 1.85-1.55 (m, 3H), 1.55-1.45 (m, 4H), 1.25-1.05 (m, 2H).

Example 23: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)oxy)propyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

Step 1: preparation of benzyl 4-(3-hydroxypropoxy)piperidine-1-carboxylate

[0839]

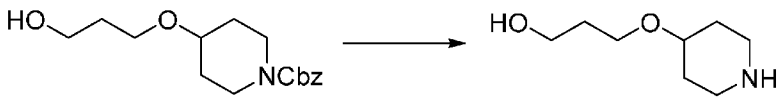


[0840] Benzyl 4-(3-methoxy-3-oxopropyl)piperidine-1-carboxylate (500 mg, 1.49 mmol) was dissolved in anhydrous THF (10 mL). A BH_3/THF solution (15 mL, 14.9 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 16 h. Methanol was added to quench the reaction liquid, and the mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 9:1) to give benzyl 4-(3-hydroxypropoxy)piperidine-1-carboxylate.

[0841] LC-MS: (ESI, m/z): $[M+H]^+$ = 294.2.

Step 2: preparation of 3-(piperidin-4-yloxy)propan-1-ol

[0842]

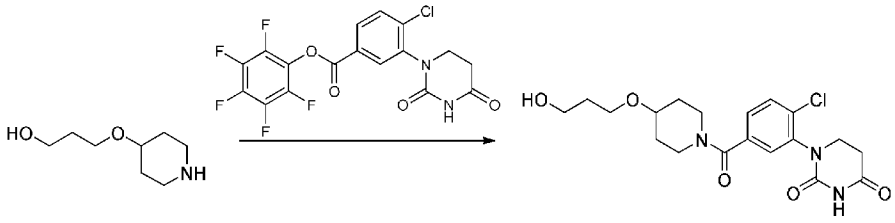


[0843] Benzyl 4-(3-hydroxypropoxy)piperidine-1-carboxylate (200 mg, 0.68 mmol) was dissolved in ethyl acetate (10 mL). $Pd(OH)_2$/C (80 mg) was added, and the mixture was heated to 70 °C under hydrogen atmosphere and stirred overnight. The reaction liquid was cooled to room temperature and filtered, and the filtrate was concentrated under reduced pressure to give 3-(piperidin-4-yloxy)propan-1-ol. The crude product was directly used in the next step without purification.

[0844] LC-MS: (ESI, m/z): $[M+H]^+$ = 160.2.

Step 3: preparation of 1-(2-chloro-5-(4-(3-hydroxypropoxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0845]



[0846] 3-(Piperidin-4-yloxy)propan-1-ol (100 mg, 0.62 mmol) was dissolved in DMSO (10 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (300 mg, 0.69 mmol) and DIEA (240 mg, 1.86 mmol) were added, and the mixture was stirred at room temperature for 2 h. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (30 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give 1-(2-chloro-5-(4-(3-hydroxypropoxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[0847] LC-MS: (ESI, m/z): $[M+H]^+$ = 410.1.

Step 4: preparation of 3-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)oxy)propionaldehyde

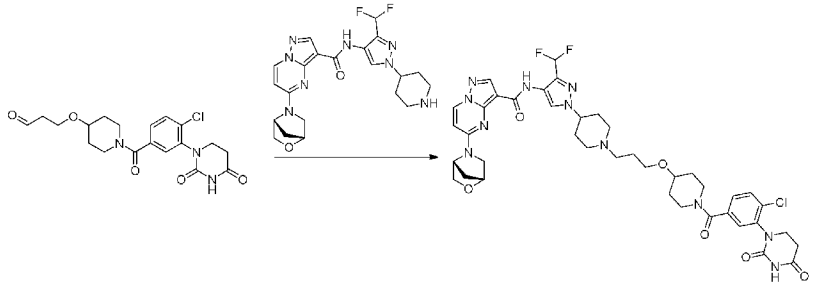
[0848]

[0849] 1-(2-Chloro-5-(4-(3-hydroxypropoxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (60 mg, 0.147 mmol) was dissolved in DCM (5 mL). PCC (63 mg, 0.294 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction liquid was concentrated under reduced pressure, and the crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give 3-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)oxy)propionaldehyde.

[0850] LC-MS: (ESI, m/z): $[M+H]^+$ = 408.1.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)piperidin-4-yl)oxy)propyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0851]



[0852] 3-((1-(4-Chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)oxy)propionaldehyde (55 mg, 0.135 mmol) was dissolved in THF (5 mL). 5-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (crude: 70 mg, 0.135 mmol) and STAB (86 mg, 0.405 mmol) were added, and the mixture was stirred at room temperature for 2 h. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with a saturated aqueous sodium chloride solution (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated

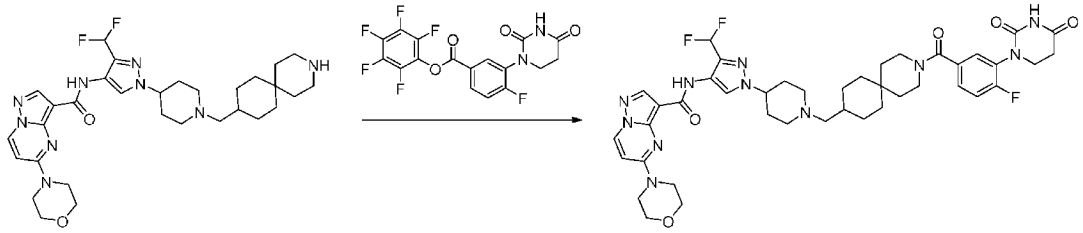
under reduced pressure to give a crude product. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(3-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)oxy)propyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0853] LC-MS: (ESI, m/z): $[M+H]^+$ = 850.4.

[0854] ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 3.2 Hz, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 7.67-7.55 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.30-6.92 (m, 1H), 6.88-6.45 (m, 1H), 5.28-5.08 (m, 1H), 4.77 (d, *J* = 17.7 Hz, 1H), 4.30-4.10 (m, 1H), 4.02-3.68 (m, 4H), 3.62-3.47 (m, 7H), 3.30-3.10 (m, 2H), 3.00-2.85 (m, 2H), 2.78-2.69 (m, 2H), 2.45-2.31 (m, 2H), 2.10-1.55 (m, 12H), 1.52-1.37 (m, 2H).

Example 24: *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1H-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide

[0855]



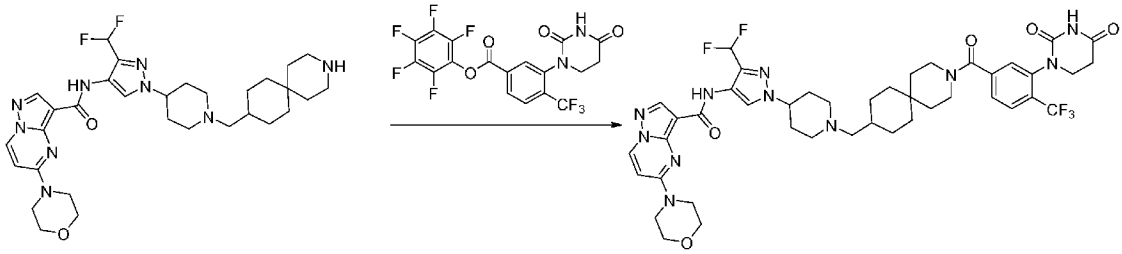
[0856] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.14 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-fluorobenzoate (58 mg, 0.14 mmol) and *N*,*N*-diisopropylethylamine (54 mg, 0.42 mmol) were added while stirring. After the mixture was stirred at room temperature for 2 h, water (50 mL) was added. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give N-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide.

[0857] LC-MS: (ESI, m/z): $[M+H]^+$ = 846.4.

[0858] ^1H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 2H), 7.23-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.25-4.15 (m, 1H), 3.84-3.69 (m, 10H), 3.65-3.49 (m, 2H), 3.31-3.24 (m, 2H), 2.89 (d, *J* = 10.3 Hz, 2H), 2.73 (t, *J* = 6.6 Hz, 2H), 2.20-2.04 (m, 2H), 2.04-1.80 (m, 6H), 1.70-1.43 (m, 7H), 1.43-1.20 (m, 2H), 1.20-0.96 (m, 4H).

Example 25: *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethyl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0859]



[0860] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide (100 mg, 0.14 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethyl)benzoate (65 mg, 0.14 mmol) and *N*,*N*-diisopropylethylamine (54 mg, 0.42 mmol) were added while stirring. After the mixture was stirred at room temperature for

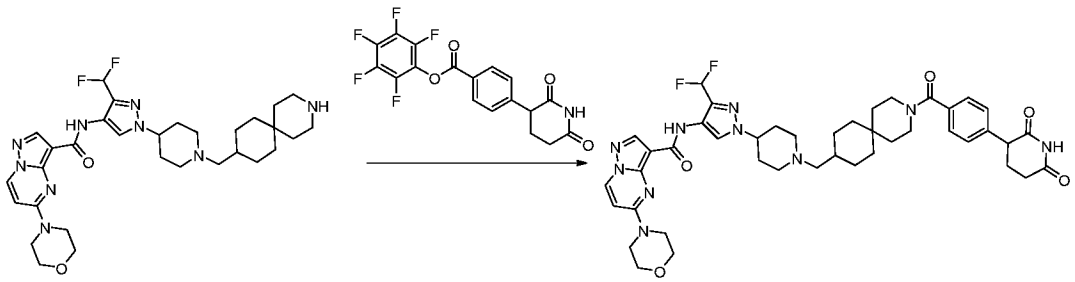
2 h, water (50 mL) was added. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethyl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1H-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0861] LC-MS: (ESI, m/z): $[M+H]^+$ = 896.4.

[0862] ^1H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.40 (s, 1H), 8.83 (d, J= 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.23-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.28-4.12 (m, 1H), 3.94-3.80 (m, 1H), 3.80-3.70 (m, 8H), 3.65-3.55 (m, 2H), 3.51-3.41 (m, 1H), 3.30-3.20 (m, 2H), 2.94-2.80 (m, 2H), 2.75-2.60 (m, 2H), 2.24-2.06 (m, 2H), 2.06-1.90 (m, 6H), 1.80-1.60 (m, 2H), 1.60-1.30 (m, 6H), 1.30-1.20 (m, 1H), 1.17-0.92 (m, 4H).

Example 26: *N*-(3-(difluoromethyl)-1-(1-((3-(4-(2,6-oxopiperidin-3-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0863]



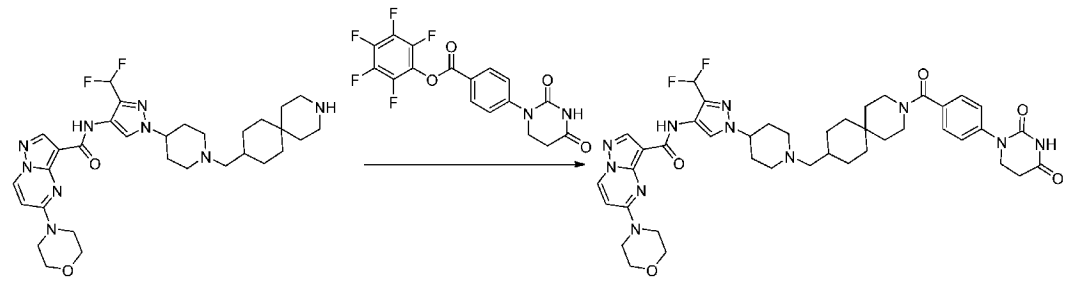
[0864] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.14 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-(2,6-dioxopiperidin-3-yl)benzoate (56 mg, 0.14 mmol) and *N*,*N*-diisopropylethylamine (54 mg, 0.42 mmol) were added while stirring. After the mixture was stirred at room temperature for 2 h, water (50 mL) was added, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated brine (60 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude product. The filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give N-(3-(difluoromethyl)-1-(1-((3-(4-(2,6-oxopiperidin-3-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1H-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0865] LC-MS: (ESI, m/z): $[M+H]^+$ = 827.4.

[0866] ^1H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 9.40 (s, 1H), 8.83 (d, J= 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.40-7.25 (m, 4H), 7.23-6.95 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.35-4.06 (m, 1H), 3.97-3.88 (m, 1H), 3.84-3.73 (m, 8H), 3.64-3.50 (m, 2H), 3.31-3.22 (m, 2H), 2.92-2.80 (m, 2H), 2.75-2.62 (m, 1H), 2.56-2.51 (m, 1H), 2.30-1.90 (m, 10H), 1.76-1.25 (m, 9H), 1.20-0.93 (m, 4H).

Example 27: *N*-(3-(difluoromethyl)-1-(1-((3-(4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0867]



[0868] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.14 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pen-

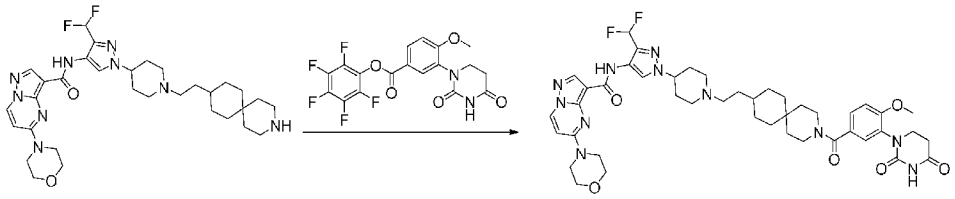
tafluorophenyl 4-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (56 mg, 0.14 mmol) and *N*,*N*-diisopropylethylamine (54 mg, 0.42 mmol) were added while stirring. After the mixture was stirred at room temperature for 2 h, water (50 mL) was added. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(3-(difluoromethyl)-1-(1-((3-(4-(2,4-dioxotetrahydropyrimidin-l(2*H*)-yl)benzoyl)-3-aza-spiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0869] LC-MS: (ESI, m/z): $[M+H]^1$ = 828.4.

[0870] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J*= 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.39 (s, 4H), 7.23-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.26-4.15 (m, 1H), 3.92-3.70 (m, 10H), 3.68-3.50 (m, 2H), 3.31-3.22 (m, 2H), 2.89 (d, *J*= 10.1 Hz, 2H), 2.72 (t, *J*= 6.6 Hz, 2H), 2.24-2.09 (m, 2H), 2.07-1.84 (m, 6H), 1.75-1.29 (m, 9H), 1.18-0.92 (m, 4H).

Example 28: *N*-(3-(difluoromethyl)-1-(1-(2-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3-aza-spiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-1H pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0871]



[0872] *N*-(1-(1-(2-(3-Azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (103 mg, 0.165 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (85 mg, 0.198 mmol) were added to DMSO (3 mL). Then DIEA (63.8 mg, 0.495 mmol) was added. The mixture was stirred at room temperature for 16 h, and then water (20 mL) was added. The mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (acetonitrile/0.5% aqueous formic acid solution, 5%-95%) to give the product of formate of *N*-(3-(difluoromethyl)-1-(1-(2-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

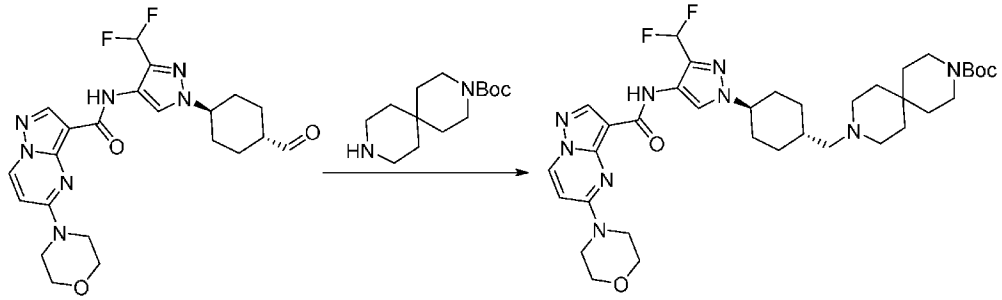
[0873] LC-MS: (ESI, m/z): $[M+H]^+$ = 872.5.

[0874] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 8.27 (s, 0.62H, HCOOH), 7.42-7.28 (m, 2H), 7.26-6.94 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.30-4.10 (m, 1H), 3.84 (s, 3H), 3.79-3.61(m, 8H), 3.62-3.54 (m, 6H), 2.97-2.91 (m, 2H), 2.71-2.65 (m, 2H), 2.37-2.17 (m, 2H), 2.05-1.85 (m, 6H), 1.75-1.62 (m, 2H), 1.55-1.17 (m, 9H), 1.17-0.93 (m, 4H).

Example 29: *N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(((1R,4R)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0875]

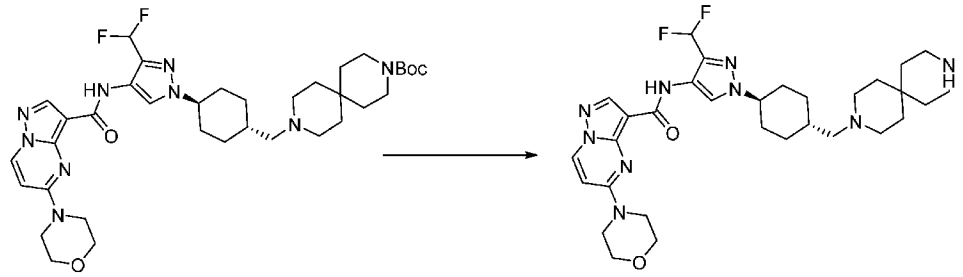


[0876] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.10 mmol) and tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (24 mg, 0.10 mmol) were dissolved in THF (3 mL). Sodium triacetoxyborohydride (67 mg, 0.32 mmol) was added to the reaction liquid while stirring, and the reaction liquid was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to give *tert*-butyl 9-(((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[0877] LC-MS: (ESI, m/z): $[M+H]^+$ = 712.3.

Step 2: preparation of N (1-((1R,4R)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0878]

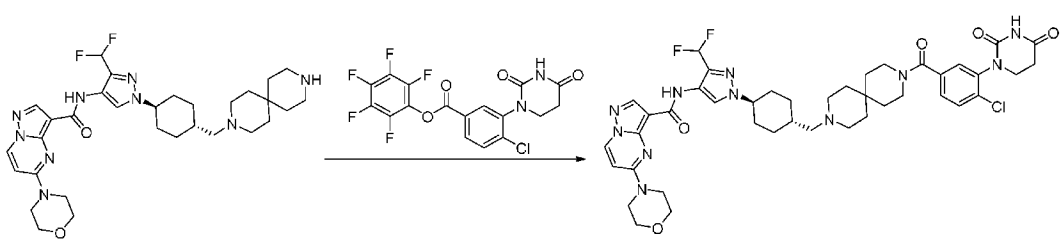


[0879] *tert*-Butyl 9-(((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1H-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboacylate (95 mg, 0.13 mmol) was dissolved in DCM (3 mL). TFA (1 mL) was added, and the reaction liquid was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give N (1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cycloheacyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide (crude), which was directly used in the next step.

[0880] LC-MS: (ESI, m/z): $[M+H]^+$ = 612.3.

Step 3: preparation of *N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0881]



[0882] *N*-(1-((1*R*,4*R*)-4-((3,9-Diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide (130 mg, 0.13 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (57 mg, 0.13 mmol) were dissolved in DMSO (5 mL). DIEA (84 mg, 0.65 mmol) was added to the reaction liquid while stirring, and the reaction liquid was stirred at room temperature for 1 h. After the reaction was complete, the reaction liquid was poured into water (50 mL), and the mixture was extracted with EA (30 mL × 3). The organic phases were combined, washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and separated and purified by prep-HPLC to give *N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

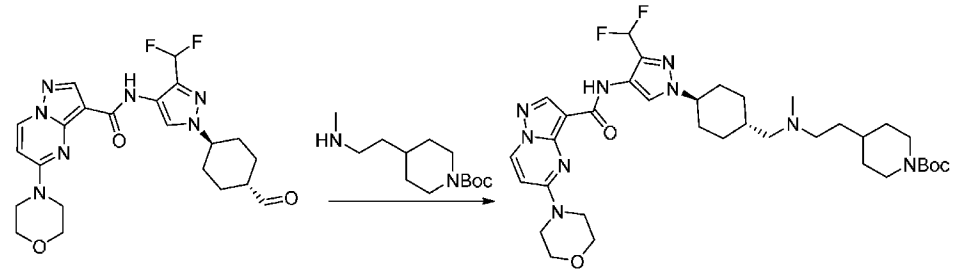
[0883] LC-MS: (ESI, m/z): $[M+H]^+$ = 862.3.

[0884] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.39 (s, 1H), 8.82 (d, J = 6.3 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.25-6.95 (m, 1H), 6.90 (d, J = 7.6 Hz, 1H), 4.27-4.07 (m, 1H), 3.90-3.50 (m, 12H), 3.40-3.30 (m, 2H), 2.79-2.70 (m, 2H), 2.43-2.23 (m, 4H), 2.20-1.95 (m, 4H), 1.93-1.83 (m, 2H), 1.82-1.30 (m, 11H), 1.09-0.94 (m, 2H).

Example 30: *N*-(1-((1R,4R)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[0885]

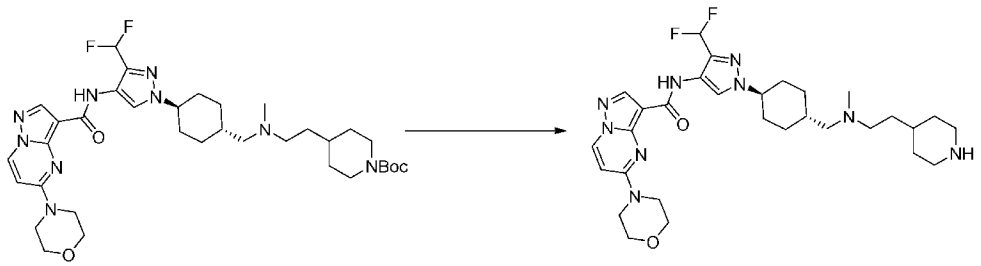


[0886] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.23 mmol) was dissolved in THF (10 mL). *tert*-Butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (56 mg, 0.23 mmol) and STAB (146 mg, 0.69 mmol) were added, and the mixture was reacted at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:11) to give *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[0887] LC-MS: (ESI, m/z): $[M+H]^+$ = 700.4.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0888]

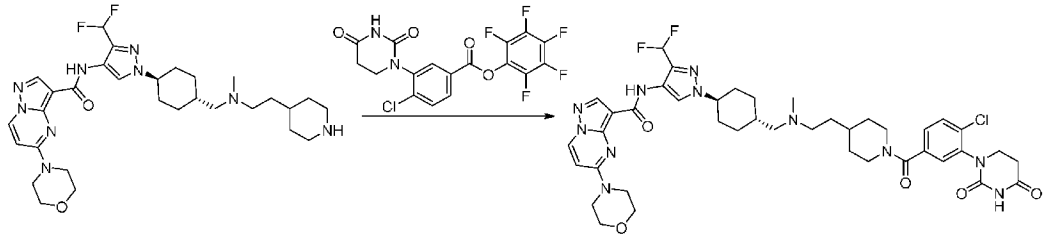


[0889] *tert*-Butyl 4-(2-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (95 mg, 0.14 mmol) was dissolved in DCM (3 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step.

[0890] LC-MS: (ESI, m/z): $[M+H]^+$ = 600.3.

Step 3: preparation of *N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0891]



[0892] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (95 mg, 0.14 mmol) was dissolved in DMSO (5 mL). DIEA (77 mg, 0.60 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (61 mg, 0.14 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (50 mL) was added, and the mixture was stirred for 5 min and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give *N*-(1-((1R,4R)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

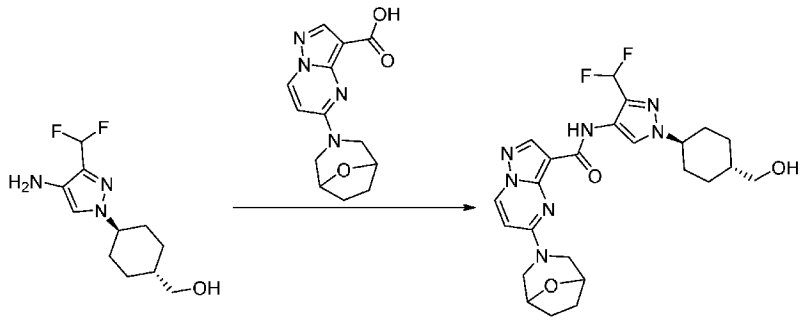
[0893] LC-MS: (ESI, m/z): $[M+H]^+$ = 850.4.

[0894] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.39 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.24-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.49-4.38 (m, 1H), 4.23-4.13 (m, 1H), 3.83-3.76 (m, 4H), 3.75-3.70 (m, 4H), 3.66-3.52 (m, 2H), 3.10-2.95 (m, 1H), 2.84-2.67 (m, 3H), 2.29 (t, *J* = 7.0 Hz, 2H), 2.14-2.01 (m, 7H), 1.93-1.84 (m, 2H), 1.82-1.46 (m, 7H), 1.41-1.32 (m, 2H), 1.17-0.95 (m, 4H).

Example 31: 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0895]



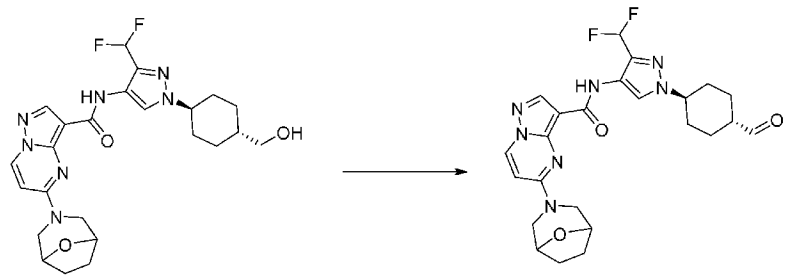
[0896] ((1*R*,4*R*)-4-(4-Amino-3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanol (410 mg, 1.67 mmol) was dissolved in DMF (10 mL). 5-(8-Oxa-3-azaspirobicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (459 mg, 1.67 mmol), HATU (825 mg, 2.17 mmol), and DIEA (646 mg, 5.01 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (50 mL) was added, and the mixture was stirred for 5 min and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography

to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0897] LC-MS: (ESI, m/z): $[M+H]^+$ = 502.3.

Step 2: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1R,4R)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0898]

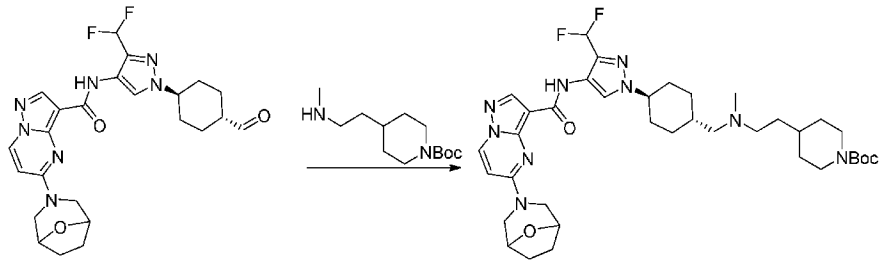


[0899] 5-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-A-(3-(difluoromethyl)-1-((1R,4R)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (290 mg, 0.58 mmol) was dissolved in ACN (10 mL). IBX (324 mg, 1.16 mmol) was added, and the mixture was reacted at 85 °C for 1.5 h and concentrated under reduced pressure to remove ACN. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0900] LC-MS: (ESI, m/z): $[M+H]^+$ = 500.3.

Step 3: preparation of *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[0901]

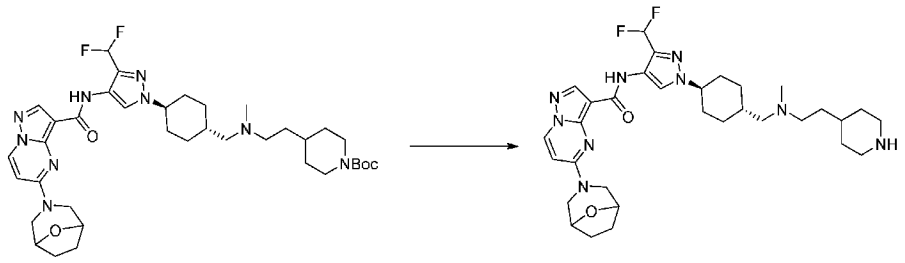


[0902] 5-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1R,4R)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.20 mmol) was dissolved in THF (10 mL). *tert*-Butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (48 mg, 0.20 mmol) and STAB (127 mg, 0.6 mmol) were added, and the mixture was reacted at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:11) to give *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[0903] LC-MS: (ESI, m/z): $[M+H]^+$ = 726.4.

Step 4: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0904]

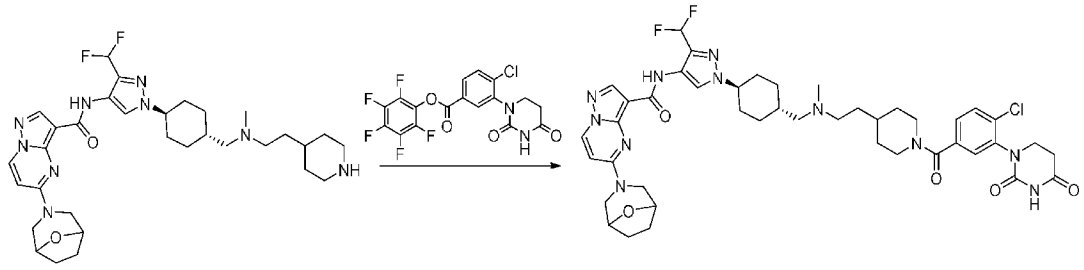


[0905] *tert*-Butyl 4-(2-((((1*R*,4*R*)-4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (110 mg, 0.15 mmol) was dissolved in DCM (3 mL). TFA (1 mL) was added, and the reaction liquid was reacted at room temperature for 1 h and concentrated under reduced pressure to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide, which was directly used in the next step.

[0906] LC-MS: (ESI, m/z): $[M+H]^+$ = 626.3.

Step 5: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(1-((1*R*,4*R*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0907]



[0908] 5-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1R,4R)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.15 mmol) was dissolved in DMSO (5 mL). DIEA (97 mg, 0.75 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (65 mg, 0.15 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (50 mL) was added, and the mixture was stirred for 5 min and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(1-((1*R*,4*R*)-4-(((2-(1 -(4-chloro-3 -(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

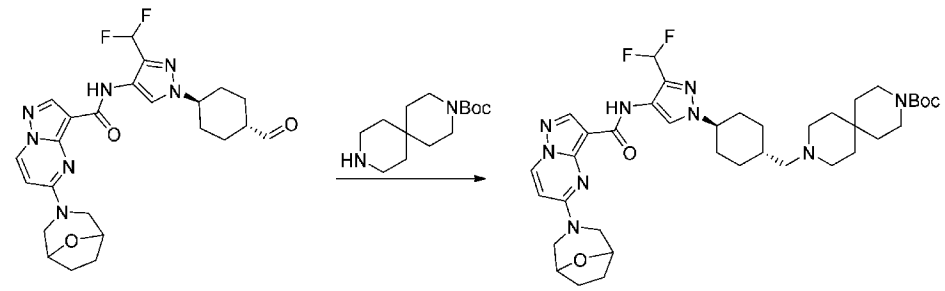
[0909] LC-MS: (ESI, m/z): $[M+H]^+$ = 876.2.

[0910] ^{1}H NMR(400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.41 (s, 1H), 8.82 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.30-6.95 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.48-4.42 (m, 2H), 4.26-4.09 (m, 2H), 3.79-3.50 (m, 4H), 3.27-3.17 (m, 2H), 3.10-2.90 (m, 1H), 2.85-2.70 (m, 3H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.15-2.07 (m, 5H), 2.07-2.01 (m, 2H), 1.95-1.83 (m, 4H), 1.82-1.47 (m, 9H), 1.41-1.31 (m, 2H), 1.17-0.96 (m, 4H).

Example 32: 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0911]

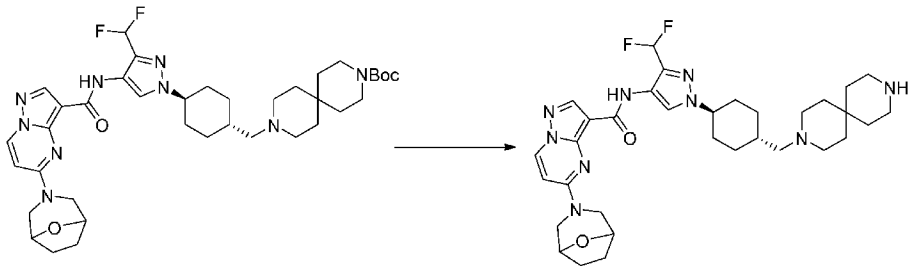


[0912] 5-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(3-(difluoromethyl)-1-((1R,4R)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.20 mmol) was dissolved in THF (10 mL). *tert*-Butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (48 mg, 0.20 mmol) and STAB (127 mg, 0.6 mmol) were added, and the mixture was reacted at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 1:11) to give *tert*-butyl 9-(((1*R*,4*R*)-4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[0913] LC-MS: (ESI, m/z): $[M+H]^+$ = 738.5.

Step 2: preparation of *N*-(1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

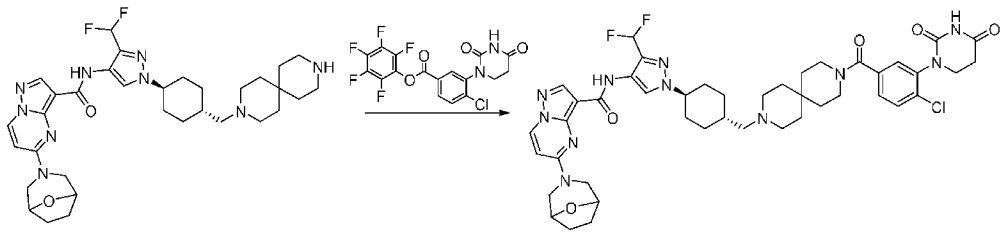
[0914]



[0915] *tert*-Butyl 9-(((1*R*,4*R*)-4-(4-(5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (105 mg, 0.14 mmol) was dissolved in DCM (3 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The mixture was concentrated under reduced pressure to give *N*-(1-((1*R*,4*R*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step.

Step 3: preparation of 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(1-((1R,4R)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0916]



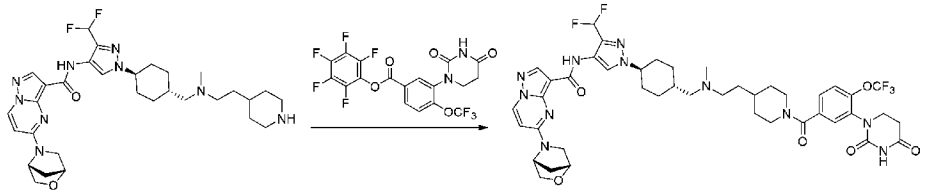
[0917] *N*-(1-((1*R*,4*R*)-4-((3,9-Diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(diffuoromethyl)-1*H*-pyrazol-4-yl)-5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.14 mmol) was dissolved in DMSO (5 mL). DIEA (90 mg, 0.70 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (61 mg, 0.14 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (50 mL) was added, and the mixture was stirred for 5 min and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give 5-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-*N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(diffuoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0918] LC-MS: (ESI, m/z): $[M+H]^+$ = 888.2.

[0919] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.41 (s, 1H), 8.81 (d, *J* = 7.9 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.24-6.97 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.47-4.41 (m, 2H), 4.31-3.93 (m, 3H), 3.81-3.72 (m, 1H), 3.67-3.51 (m, 3H), 3.25-3.15 (m, 2H), 2.77-2.72 (m, 2H), 2.35-2.25 (m, 4H), 2.15-2.07 (m, 2H), 2.16-2.98 (m, 2H), 1.96-1.29 (m, 19H), 1.10-0.92 (m, 2H).

Example 33: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0920]



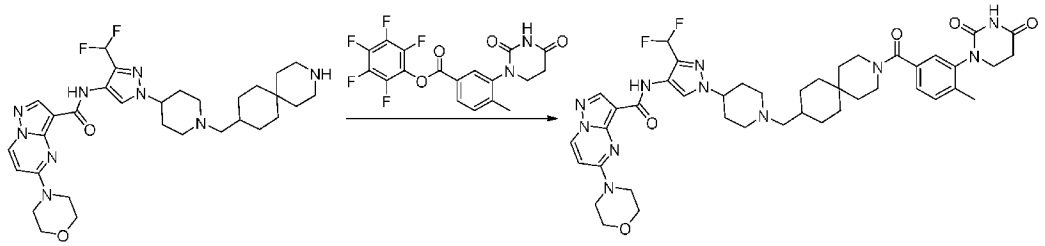
[0921] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.12 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-(trifluoromethoxy)benzoate (68 mg, 0.14 mmol) and *N,N*-diisopropylethylamine (46 mg, 0.36 mmol) were added while stirring. After the mixture was stirred at room temperature for 2 h, water (50 mL) was added. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((IR,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0922] LC-MS: (ESI, m/z): $[M+H]^+$ = 912.4.

[0923] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.50 (d, *J* = 6.1 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 4.2 Hz, 1H), 8.25 (t, *J* = 4.6 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.54-7.43 (m, 2H), 7.28-6.95 (m, 1H), 6.88-6.44 (m, 1H), 5.28-5.08 (m, 1H), 4.77 (d, *J* = 18.1 Hz, 1H), 4.52-4.40 (m, 1H), 4.24-4.15 (m, 1H), 3.86-3.42 (m, 7H), 3.10-2.95 (m, 1H), 2.80-2.60 (m, 3H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.14-1.48 (m, 17H), 1.43-1.30 (m, 2H), 1.20-0.93 (m, 4H).

Example 34: *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0924]



[0925] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamide (100 mg, 0.12 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoate (58 mg, 0.14 mmol) and *N*,*N*-diisopropylethylamine (46 mg, 0.36 mmol) were added while stirring. After the mixture was stirred at room temperature for 2 h, water (50 mL) was added. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give N-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

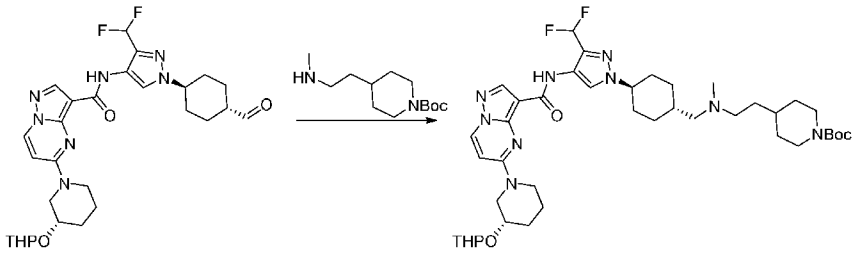
[0926] LC-MS: (ESI, m/z): $[M+H]^+$ = 842.4.

[0927] ^1H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.37-7.29 (m, 2H), 7.28-6.96 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.25-4.15 (m, 1H), 3.83-3.63 (m, 9H), 3.61-3.47 (m, 3H), 3.32-3.24 (m, 2H), 2.95-2.65 (m, 4H), 2.25-1.85 (m, 11H), 1.70 (d, J = 9.3 Hz, 2H), 1.58-1.15 (m, 7H), 1.12-0.91 (m, 4H).

Example 35: *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 4-(2-((((1*S*,4*R*)-4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[0928]

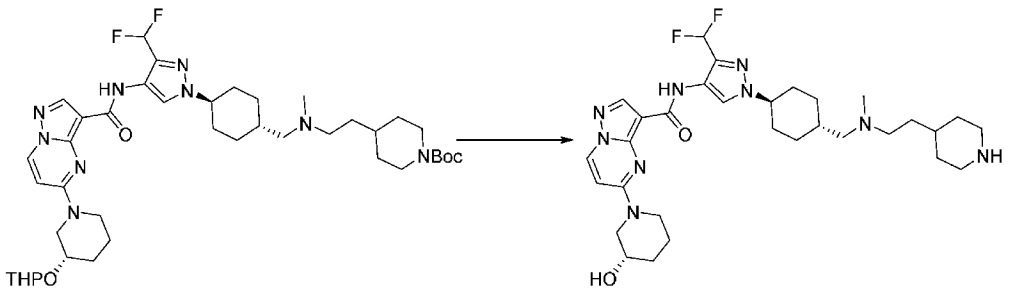


[0929] *N*-(3-(Difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.21 mmol) and *tert*-butyl 4-(2-(methylamino)ethyl)piperidine-1-carboaylate (51 mg, 0.21 mmol) were dissolved in tetrahydrofuran (10 mL). Sodium triacetoxyborohydride (222 mg, 1.05 mmol) was added while stirring. The mixture was stirred at room temperature overnight. Water (50 mL) was added, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give tert-butyl 4-(2-((((1S,4R)-4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[0930] LC-MS: (ESI, m/z): $[M+H]^+$ = 798.5.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[0931]

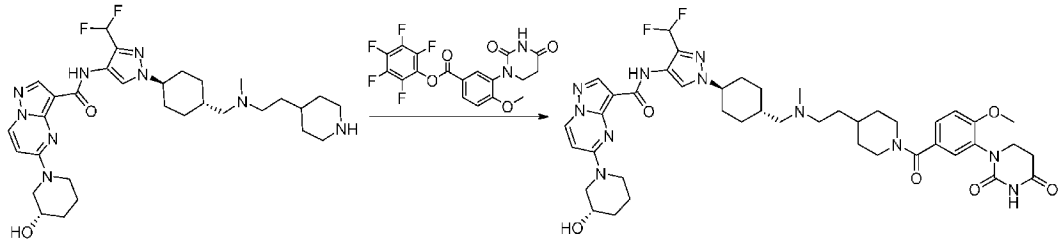


[0932] *tert*-Butyl 4-(2-((((1*S*,4*R*)-4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (80 mg, 0.10 mmol) was dissolved in dichloromethane (3 mL). Trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[0933] LC-MS: (ESI, m/z): $[M+H]^+$ = 614.3.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0934]



[0935] *N*-(3-(Difluoromethyl)-1-((1*R*,4*S*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.10 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (47 mg, 0.11 mmol) and *N*,*N*-diisopropylethylamine (38 mg, 0.30 mmol) were added while stirring. The mixture was stirred at room temperature overnight. Water (50 mL) was added. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide.

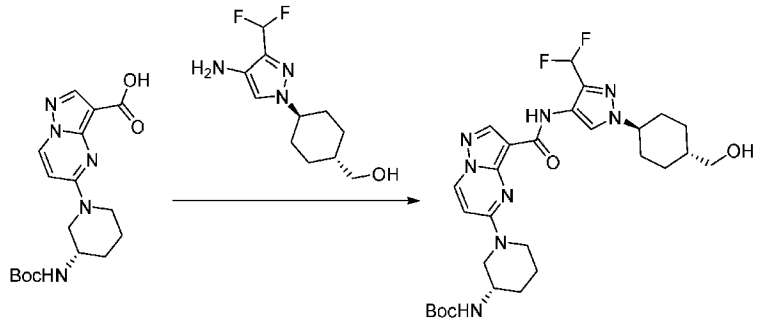
[0936] LC-MS: (ESI, m/z): $[M+H]^+$ = 860.4.

[0937] ^1H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.37 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 8.24 (d, *J* = 5.1 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.24-6.94 (m, 2H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.89 (d, *J* = 4.1 Hz, 1H), 4.50-4.15 (m, 2H), 4.03-3.80 (m, 5H), 3.72-3.53 (m, 4H), 3.51-3.40 (m, 1H), 3.10-2.65 (m, 4H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.15-1.95 (m, 7H), 1.92-1.25 (m, 15H), 1.17-0.95 (m, 4H).

Example 36: 5-((*S*)-3-aminopiperidin-1-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate

[0938]

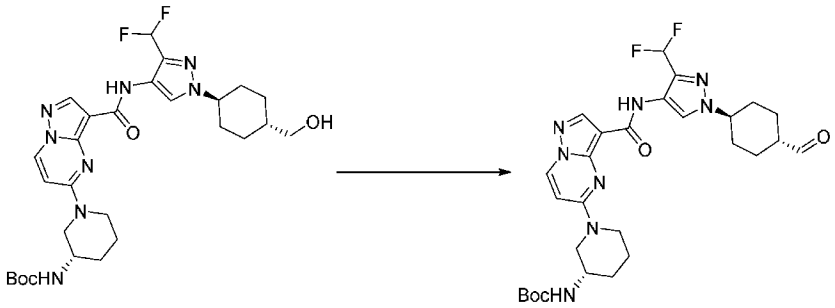


[0939] (S)-5-(3-((*tert*-Butoxycarbonyl)amino)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (150 mg, 0.42 mmol) was dissolved in DMF (10 mL). ((1*R*,4*R*)-4-(4-Amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)methanol (112 mg, 0.46 mmol), DIEA (163 mg, 1.26 mmol), and py-BOP (284 mg, 0.55 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (50 mL) was added, and the mixture was stirred for 5 min and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 0-1) to give *tert-butyl* ((S)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-(hydroxymethyl)cyclohexyl)-1H-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperidin-3-yl)carboxylate.

[0940] LC-MS: (ESI, m/z): $[M+H]^+$ = 589.3.

Step 2: preparation of *tert*-butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate

[0941]



[0942] *tert*-Butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate (190 mg, 0.32 mmol) was dissolved in ACN (10 mL). IBX (181 mg, 0.65 mmol) was added, and the mixture was reacted at 85 °C for 1.5 h. Water (30 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 0-1) to give *tert*-butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate.

[0943] LC-MS: (ESI, m/z): $[M+H]^+$ = 586.6.

Step 3: preparation of N-benzyl-N-methyl-2-(piperidin-4-yl)ethan-l-amine

[0944]

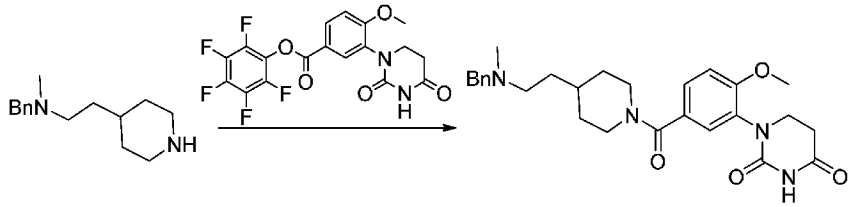
[0945] *tert*-Butyl 4-(2-(benzyl(methyl)amino)ethyl)piperidine-1-carboxylate (345 mg, 1.04 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly

concentrated under reduced pressure to give *N*-benzyl-*N*-methyl-2-(piperidin-4-yl)ethan-1-amine, which was directly used in the next step.

[0946] LC-MS: (ESI, m/z): $[M+H]^+$ = 233.2.

Step 5: preparation of 1-(5-(4-(2-(benzyl(methyl)amino)ethyl)piperidine-1-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0947]

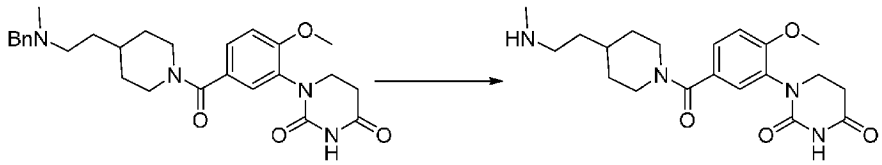


[0948] *N*-Benzyl-*N*-methyl-2-(piperidin-4-yl)ethan-1-amine (250 mg, 1.04 mmol) was dissolved in DMSO (10 mL). DIEA (671 mg, 5.2 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (451 mg, 1.04 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (100 mL) was added to the reaction liquid, and the mixture was stirred for 5 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give 1-(5-(4-(2-(benzyl(methyl)amino)ethyl)piperidine-1-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[0949] LC-MS: (ESI, m/z): $[M+H]^1$ = 479.2.

Step 6: preparation of 1-(2-methoxy-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

[0950]

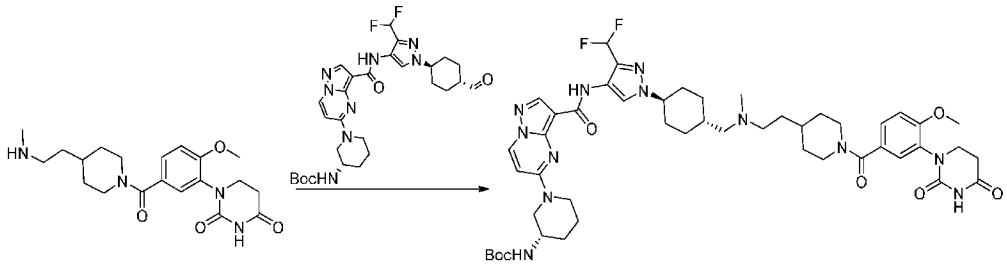


[0951] 1-(5-(4-(2-(Benzyl(methyl)amino)ethyl)piperidine-1-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (240 mg, 0.5 mmol) was dissolved in MeOH (10 mL). Pd/C (72 mg, 30%) was added, and the mixture was reacted at room temperature for 2 h. The mixture was filtered and concentrated under reduced pressure to give 1-(2-methoxy-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, which was directly used in the next step.

[0952] LC-MS: (ESI, m/z): $[M+Na]^+$ = 411.1.

Step 7: preparation of tert-butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate

[0953]

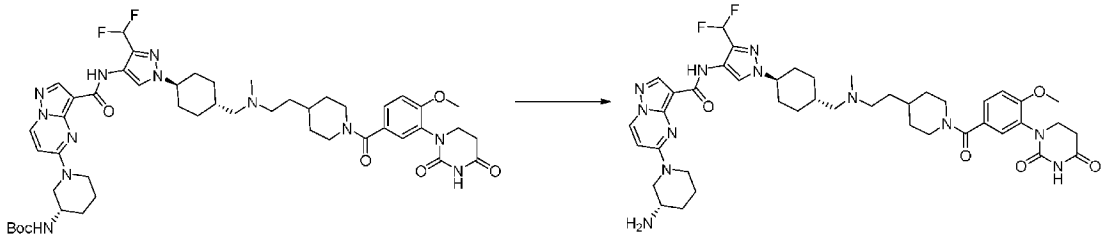


[0954] 1-(2-Methoxy-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (95 mg, 0.24 mmol) was dissolved in THF (10 mL). *tert*-Butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate (120 mg, 0.20 mmol) and STAB (127 mg, 0.60 mmol) were added, and the mixture was reacted at room temperature for 2 h. The reaction liquid was diluted with water (50 mL), and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1H-pyrazol-4-yl)carbonyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate.

[0955] LC-MS: (ESI, m/z): $[M+H]^+$ = 959.4.

Step 8: preparation of 5-((*S*)-3-aminopiperidin-1-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0956]



[0957] *tert*-Butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)carbonyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperidin-3-yl)carboxylate (100 mg, 0.10 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by preparative reversed-phase chromatography to give 5-((*S*)-3-aminopiperidin-1-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

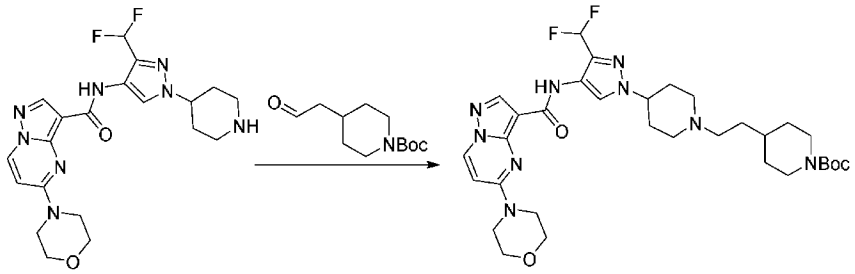
[0958] LC-MS: (ESI, m/z): $[M+H]^+$ = 859.4.

[0959] ^{1}H NMR(400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.36 (s, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.36 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.27-6.97 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 4.52-4.15 (m, 4H), 3.84 (s, 3H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.24-2.93 (m, 3H), 2.80-2.60 (m, 4H), 2.40-2.25 (m, 2H), 2.16-1.99 (m, 8H), 1.95-1.80 (m, 3H), 1.80-1.29 (m, 13H), 1.17-0.96 (m, 4H).

Example 37: *N*-(3-(difluoromethyl)-1-(1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate

[0960]

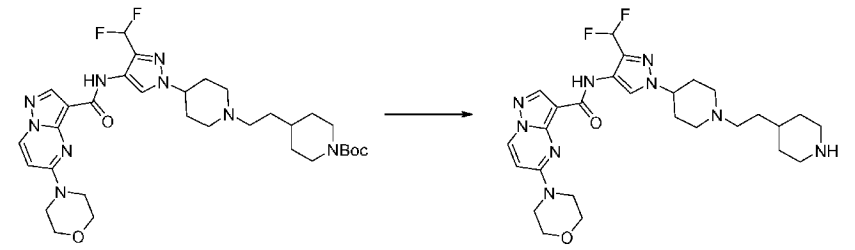


[0961] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (125 mg, 0.280 mmol) was added to a solution of *tert-butyl* 4-(2-oxoethyl)piperidine-1-carboxylate (95.466 mg, 0.421 mmol) in THF (3 mL). STAB (178.5 mg, 0.842 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL), and the mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 3:7) to give *tert-butyl* 4-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate.

[0962] LC-MS: (ESI, m/z): $[M+H]^+$ = 658.5.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0963]

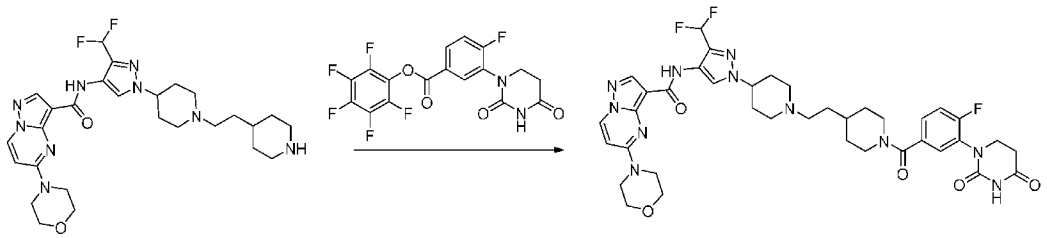


[0964] *tert*-Butyl 4-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)piperidine-1-carboxylate (160 mg, 0.347 mmol) was added to TFA (1 mL) and DCM (3 mL), and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give a crude product of *N*-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[0965] LC-MS: (ESI, m/z): $[M+H]^+$ = 558.4.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-(1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0966]



[0967] *N*-(3-(Difluoromethyl)-1-(1-(2-(piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (121 mg, 0.217 mmol) was added to a solution of pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoate (90.8 mg, 0.217 mmol) in DMSO (5 mL). DIEA (84.1 mg, 0.652 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction liquid was diluted with water (40 mL),

and the mixture was extracted with ethyl acetate (40 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography (acetonitrile-0.05% aqueous NH_4HCO_3 solution, 5%-95%) to give the product *N*-(3-(difluoromethyl)-1-(1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

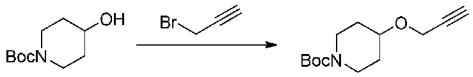
[0968] LC-MS: (ESI, m/z): $[M+H]^+$ = 792.3.

[0969] ^1H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.40 (s, 1H), 8.82 (s, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.59-7.27 (m, 3H), 7.24-6.83 (m, 2H), 4.51-4.15 (m, 2H), 3.83-3.55 (m, 11H), 3.12-2.85 (m, 3H), 2.81-2.64 (m, 3H), 2.38-2.30 (m, 2H), 2.08-1.55 (m, 9H), 1.46-1.31 (m, 2H), 1.20-0.99 (m, 2H).

Example 38: *N*(1-((1*R*,4*R*)-4-((4-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(prop-2-yn-1-yloxy)piperidine-1-carboxylate

[0970]

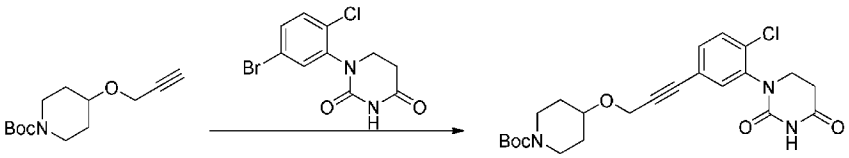


[0971] NaH (2.98 g, 124.2 mmol) was slowly added to tert-butyl 4-hydroxypiperidine-1-carboxylate (5 g, 24.84 mmol) in anhydrous THF (60 mL) at 0 °C, and the mixture was stirred for 30 min. Then 3-bromoprop-1-yne (5.91 g, 49.68 mmol) was added. The reaction liquid was slowly heated to room temperature, stirred for 5 h, and then filtered. Water (100 mL) was added, and the mixture was extracted with ethyl acetate (60 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 1:9) to give tert-butyl 4-(prop-2-yn-1-yloxy)piperidine-1-carboxylate.

[0972] LC-MS: (ESI, m/z): $[M-56]^+$ = 184. 1.

Step 2: preparation of tert-butyl 4-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)oxy)piperidine-1-carboxylate

[0973]

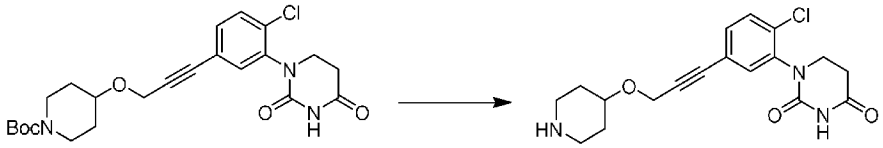


[0974] tert-Butyl 4-(prop-2-yn-1-yloacy)piperidine-1-carboxylate (232 mg, 0.971 mmol) was added to 1-(5-bromo-2-chlorophenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (350 mg, 1.164 mmol) in anhydrous DMF (10 mL). CuI (47.5 mg, 0.146 mmol), $CsCO_3$ (948 mg, 2.913 mmol), and $Pd(PPh_3)_2Cl_2$ (102.1 mg, 0.146 mmol) were added, and the reaction liquid was stirred at 80 °C for 4 h under N_2 atmosphere. Water (40 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (40 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 2:3) to give tert-butyl 4-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)prop-2-yn-1-yl)oxy)piperidine-1 -carboxylate.

[0975] LC-MS: (ESI, m/z): $[M+H]^+$ = 462.2.

Step 3: preparation of 1-(2-chloro-5-(3-(piperidin-4-yloxy)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0976]

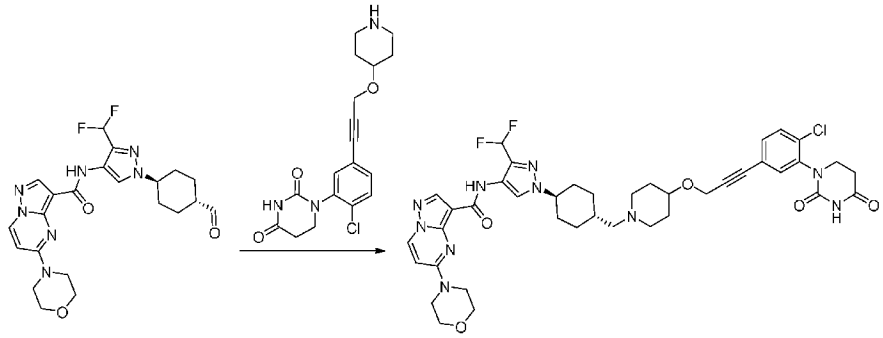


[0977] *tert*-Butyl 4-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)prop-2-yn-1-y))oxy)piperidine-1-carboxylate (160 mg, 0.347 mmol) was added to TFA (1 mL) and DCM (3 mL), and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give a crude product of 1-(2-chloro-5-(3-(piperidin-4-yloxy)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[0978] LC-MS: (ESI, m/z): $[M+H]^+$ = 362.1.

Step 4: preparation of *N*(1-((1*R*,4*R*)-4-((4-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0979]



[0980] 1-(2-Chloro-5-(3-(piperidin-4-yloxy)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (137.4 mg, 0.381 mmol) and DIEA (73.6 mg, 0.570 mmol) were added to THF (5 mL), and the mixture was stirred at room temperature for 10 min. Then *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.190 mmol) was added, and the mixture was stirred for 10 min. Then STAB (120.9 mg, 0.914 mmol) was added, and the reaction liquid was stirred at room temperature for 2 h. Water (20 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography (acetonitrile-0.05% aqueous FA solution, 5%-95%) to give *N*-(1-((1R,4R)-4-((4-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)prop-2-yn-1-yl)oxy)piperidin-1-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

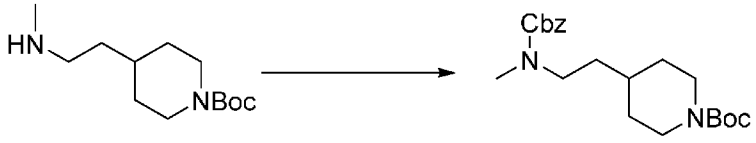
[0981] LC-MS: (ESI, m/z): $[M+H]^+$ = 819.3.

[0982] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.29 (s, 1H), 7.67-7.54 (m, 2H), 7.48-7.41 (m, 1H), 7.27-6.94 (m, 1H), 6.92-6.86 (m, 1H), 4.43 (s, 2H), 4.23-4.13 (m, 1H), 3.86-3.65 (m, 10H), 3.64-3.54 (m, 2H), 2.77-2.65 (m, 4H), 2.10-1.66 (m, 11H), 1.63-1.40 (m, 3H), 1.13-0.93 (m, 2H).

Example 39: *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1H-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[0983]

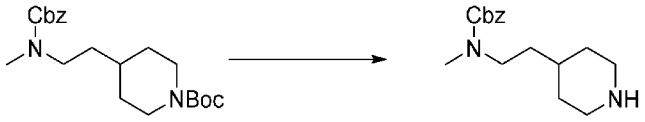


[0984] tert-Butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (200 mg, 0.82 mmol) was dissolved in dichloromethane (4 mL). Triethylamine (249, 2.46 mmol) and CbzCl (139 mg, 0.82 mmol) were added, and the reaction liquid was stirred at room temperature for 1 h. The reaction liquid was diluted with water (50 mL), and the mixture was extracted with dichloromethane (80 mL × 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 3:7) to give the compound *tert*-butyl 4-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[0985] LC-MS: (ESI, m/z): $[M+H-100]^+$ = 277.2.

Step 2: preparation of benzyl methyl(2-(piperidin-4-yl)ethyl)carbamate

[0986]

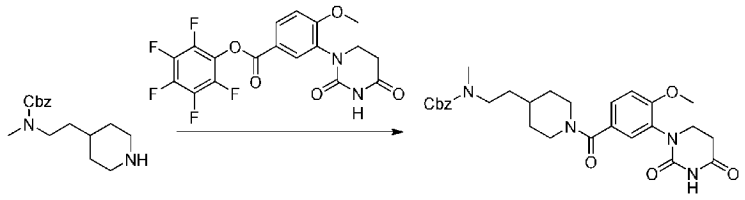


[0987] The compound *tert*-butyl 4-(2-(((benzyloxy)carbonyl)(methyl)amino)ethyl)piperidine-1-carboxylate (200 mg, 0.53 mmol) was dissolved in a hydrogen chloride/1,4-dioxane (4 mL) solution, and the reaction liquid was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give benzyl methyl(2-(piperidin-4-yl)ethyl)carbamate.

[0988] LC-MS: (ESI, m/z): $[M+H]^+$ = 277.2.

Step 3: preparation of benzyl (2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)carbamate

[0989]

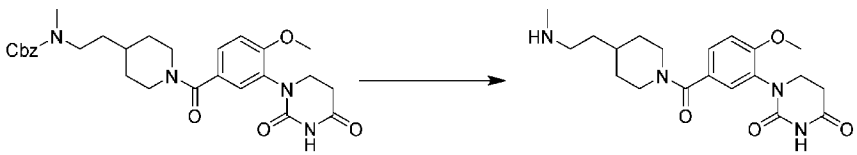


[0990] The compounds benzyl methyl(2-(piperidin-4-yl)ethyl)carbamate (200 mg, 0.72 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (309 mg, 0.72 mmol) were added to a DMSO (4 mL) solution. Then DIEA (278 mg, 2.1 mmol) was added, and the reaction liquid was stirred at room temperature for 3 h. The reaction liquid was diluted with water (50 mL), and the mixture was extracted with ethyl acetate (70 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 1:3) to give the compound benzyl (2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)carbamate.

[0991] LC-MS: (ESI, m/z): $[M+H]^+$ = 523.2.

Step 4: preparation of 1-(2-methoxy-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[0992]



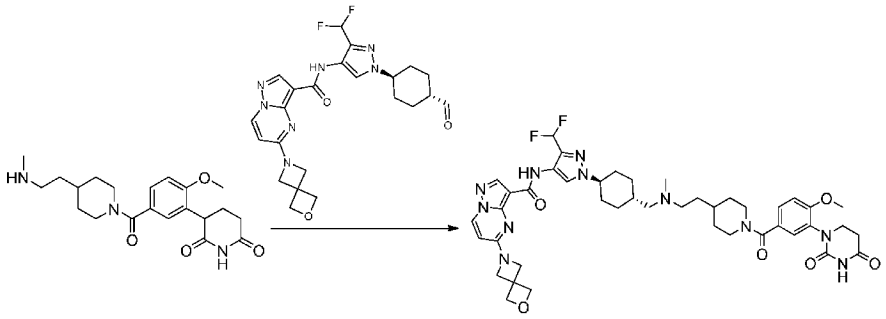
[0993] The compound benzyl (2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)carbamate (120 mg, 0.23 mmol) was dissolved in a methanol (3 mL) solution. Palladium on carbon

(10%, 24 mg) was added, and the reaction liquid was stirred at room temperature for 1 h. The reaction liquid was filtered under vacuum through celite, and the filtrate was concentrated under reduced pressure to give the compound 1-(2-methoxy-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione.

[0994] LC-MS: (ESI, m/z): $[M+H]^+$ = 389.2.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[0995]



[0996] The compounds *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (80 mg, 0.165 mmol) and 1-(2-methoxy-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (64 mg, 0.165 mmol) were dissolved in DCE (3 mL). STAB (70 mg, 0.330 mmol) was added, and the reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL), and the mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give the compound *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1H-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

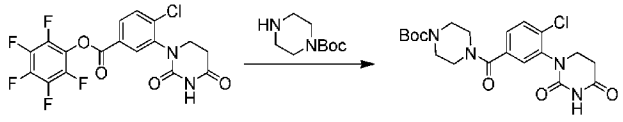
[0997] LC-MS: (ESI, m/z): $[M+H]^+$ = 858.4.

[0998] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.69 (s, 1H), 8.76 (d, *J* = 7.6 Hz, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.35 (s, 1H), 7.42-7.00 (m, 3H), 6.38 (d, *J* = 7.6 Hz, 1H), 4.78-4.70 (m, 4H), 4.48-4.35 (m, 4H), 4.25-4.10 (m, 1H), 3.84 (s, 3H), 3.59 (t, *J* = 5.0 Hz, 2H), 3.30-3.10 (m, 3H), 2.75-2.63 (m, 2H), 2.36-2.25 (m, 2H), 2.20-1.99 (m, 7H), 1.93-1.83 (m, 2H), 1.77-1.50 (m, 7H), 1.44-1.30 (m, 2H), 1.20-0.96 (m, 4H).

Example 40: 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-(1-(4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)$_n$-butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazine-1-carboxylate

[0999]

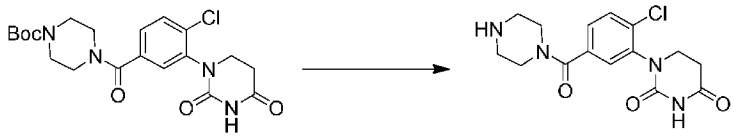


[1000] Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (450 mg, 1.037 mmol) and tert-butyl piperazine-1-carboxylate (386.28 mg, 2.074 mmol) were added to DMSO (5 mL). Then DIEA (401.31 mg, 3.111 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (20 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (25 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (MeOH:DCM = 1:19) to give *tert*-butyl 4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazine-1-carboxylate.

[1001] LC-MS: (ESI, m/z): $[M+Na]^+$ = 459.1

Step 2: preparation of 1-(2-chloro-5-(piperazine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1002]

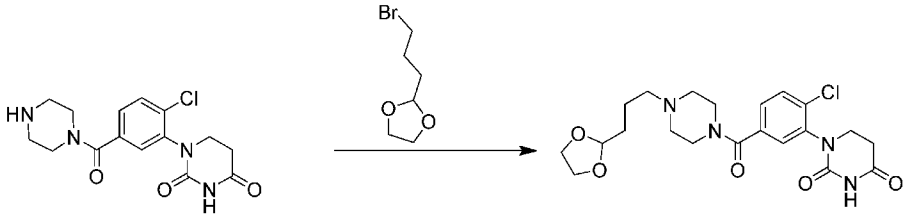


[1003] *tert*-Butyl 4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazine-1-carboxylate (402 mg, 0.922 mmol) was added to TFA (0.5 mL) and DCM (2.5 mL), and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give a crude product of 1-(2-chloro-5-(piperazine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1004] LC-MS: (ESI, m/z): $[M+H]^+$ = 337.0.

Step 3: preparation of 1-(5-(4-(3-(1,3-dioxolan-2-yl)propyl)piperazine-1-carbonyl)-2-chlorophenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1005]

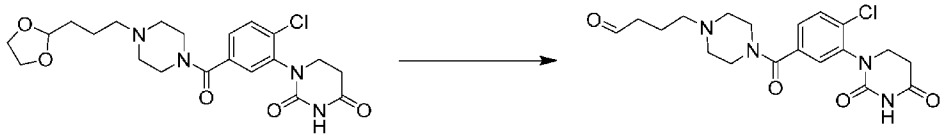


[1006] 1-(2-Chloro-5-(piperazine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (295 mg, 0.878 mmol) and 2-(3-bromopropyl)-1,3-dioxolane (256.9 mg, 1.316 mmol) were added to DMF (5 mL). Then $CsCO_3$ (858.2 mg, 2.634 mmol) was added, and the reaction liquid was stirred at 100 °C for 16 h. Water (40 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (MeOH:DCM = 1:11) to give 1-(5-(4-(3-(1,3-dioxolan-2-yl)propyl)piperazine-1-carbonyl)-2-chlorophenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1007] LC-MS: (ESI, m/z): $[M+H]^+$ = 451.1.

Step 4: preparation of 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)$_n$-butyraldehyde

[1008]

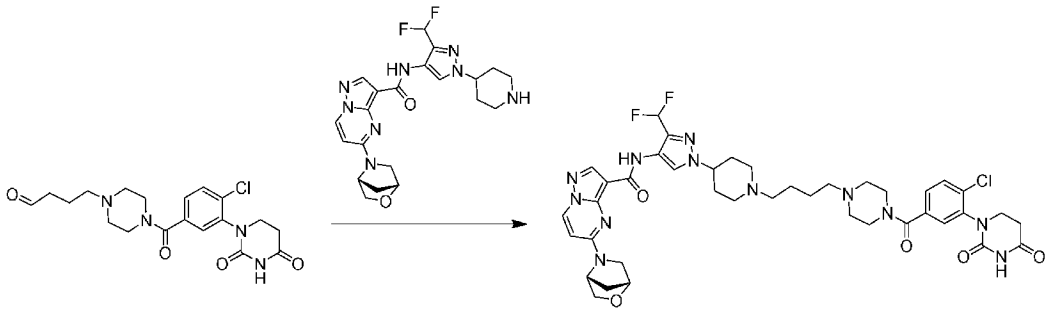


[1009] 1-(5-(4-(3-(1,3-Dioxolan-2-yl)propyl)piperazine-1-carbonyl)-2-chlorophenyl)dihydropyrimidine-2,4(1H,3H)-dione (100 mg, 0.22 mmol) was dissolved in DCM (0.5 mL). TFA (0.5 mL) was added, and the mixture was reacted at room temperature for 48 h. DCE (10 mL) and DIEA (1 mL) were added to the reaction liquid, and the mixture was concentrated under reduced pressure at room temperature to give 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)$_n$-butyraldehyde, which was directly used in the next step.

[1010] LC-MS: (ESI, m/z): $[M+H]^+$ = 407.1.

Step 5: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)*n*-butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1011]



[1012] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (40 mg, 0.087 mmol) was added to a solution of 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)*n*-butyraldehyde (crude) in DCE, and the mixture was stirred at room temperature for 0.5 h. STAB (55 mg, 0.26 mmol) was added, and the mixture was reacted at room temperature for 2 h, diluted with water (30 mL), and extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperazin-1-yl)*n*-butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

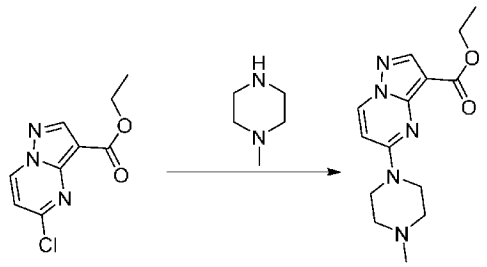
[1013] LC-MS: (ESI, m/z): $[M+H]^+$ = 849.2.

[1014] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.39 (d, *J* = 3.9 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.40 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.26-6.95 (m, 1H), 6.87-6.44 (m, 1H), 5.28-5.07 (m, 1H), 4.77 (d, *J* = 16.2 Hz, 1H), 4.25-4.12 (m, 1H), 3.84-3.70 (m, 3H), 3.67-3.55 (m, 4H), 3.45 (d, *J* = 10.2 Hz, 1H), 2.93 (d, *J* = 10.9 Hz, 2H), 2.82-2.70 (m, 2H), 2.45-2.25 (m, 9H), 2.12-1.78 (m, 9H), 1.51-1.38 (m, 4H).

Example 41: *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate

[1015]

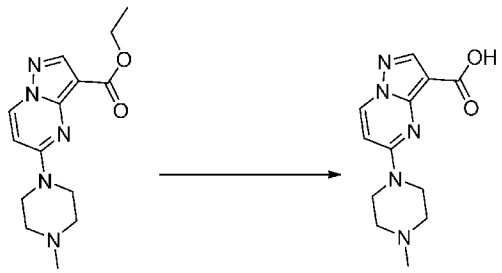


[1016] Ethyl 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1 g, 4.4 mmol), 1-methylpiperazine (445 mg, 4.4 mmol), and *N*,*N*-diisopropylethylamine (1.7 g, 13.3 mmol) were dissolved in acetonitrile (10 mL), and the mixture was heated to 60 °C and stirred overnight. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give ethyl 5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

[1017] LC-MS: (ESI, m/z): [M+H]' = 290.3.

Step 2: preparation of 5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

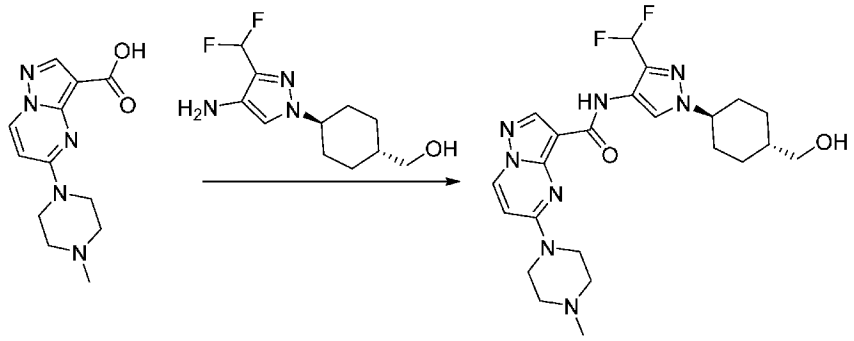
[1018]



[1019] Ethyl 5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (900 mg, 3.1 mmol) was dissolved in a mixed solution (methanol/water = 5:1, 10 mL), lithium hydroxide (520 mg, 12.4 mmol) was added, and the mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 3 with hydrochloric acid (2 mol/L) and filtered, and the filter cake was dried under vacuum to give 5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[1020]

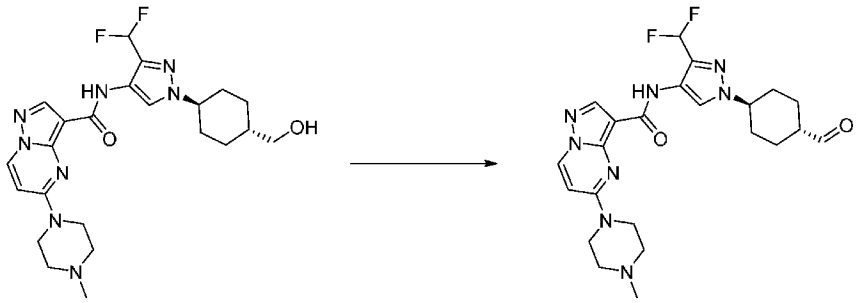


[1021] 5-(4-Methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (265 mg, 1.02 mmol) was dissolved in DMF (10 mL). ((1R,4R)-4-(4-Amino-3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanol (250 mg, 1.02 mmol), DIEA (395 mg, 3.06 mmol), and pyBOP (690 mg, 1.33 mmol) were added, and the mixture was reacted at 50 °C overnight. Water (50 mL) was added to the reaction liquid, and the mixture was stirred for 5 min, extracted with ethyl acetate (50 mL × 3), washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1022] LC-MS: (ESI, m/z): $[M+H]^+$ = 489.2.

Step 4: preparation of N (3-(difluoromethyl)-1-((1R,4R)-4-formylcyclohexyl)-1H pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

[1023]

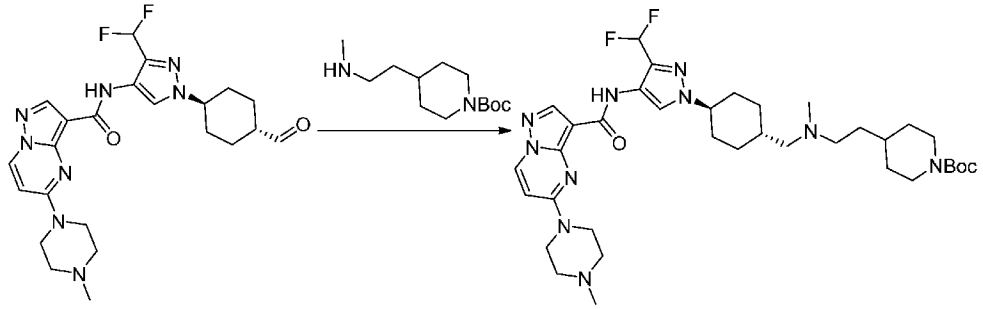


[1024] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(hydroxymethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (350 mg, 0.72 mmol) was dissolved inACN (10 mL). IBX (402 mg, 1.43 mmol) was added, and the mixture was reacted at 85 °C for 1.5 h. The reaction liquid was concentrated under reduced pressure to remove ACN, then water (30 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1025] LC-MS: (ESI, m/z): $[M+H]^+$ = 487.3.

Step 5: preparation of *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[1026]

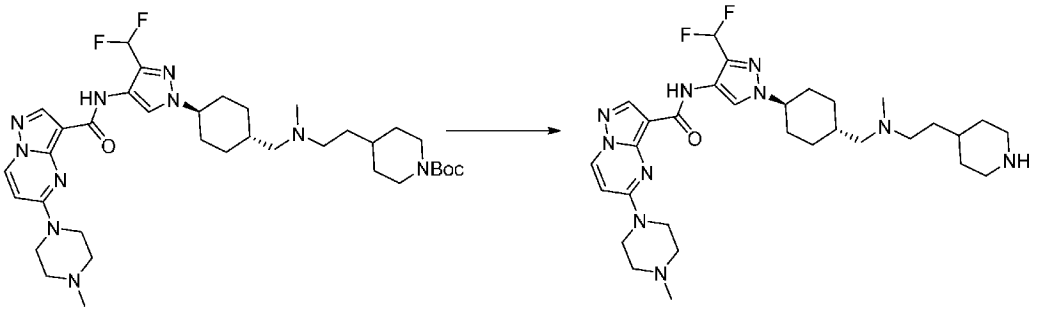


[1027] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (180 mg, 0.37 mmol) and tert-butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (107 mg, 0.44 mmol) were dissolved in tetrahydrofuran (10 mL). STAB (235 mg, 1.11 mmol) was added, and the mixture was reacted at room temperature for 2 h. The reaction liquid was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give *tert*-butyl 4-(2-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[1028] LC-MS: (ESI, m/z): $[M+H]^+$ = 713.4.

Step 6: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1029]

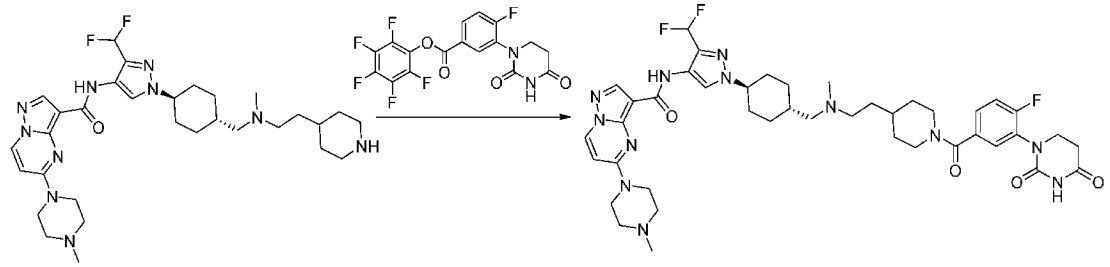


[1030] *tert*-Butyl 4-(2-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (220 mg, 0.31 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. The resulting product was directly used in the next step.

[1031] LC-MS: (ESI, m/z): $[M+H]^+$ = 613.3.

Step 7: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1032]



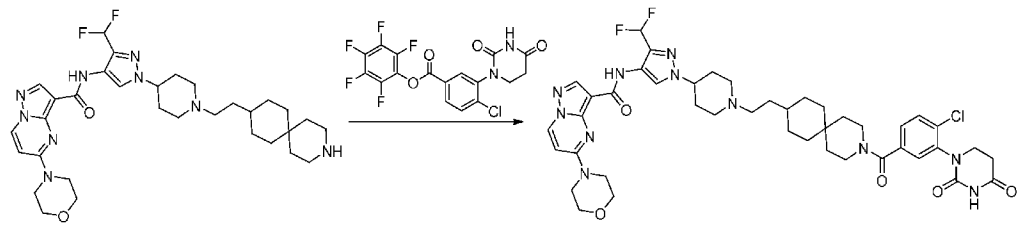
[1033] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (220 mg, 0.31 mmol) was dissolved in DMSO (10 mL). DIEA (200 mg, 1.55 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoate (130 mg, 0.31 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (100 mL) was added to the reaction liquid, and the mixture was stirred for 5 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give N (3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-(4-methylpiperazin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1034] LC-MS: (ESI, m/z): $[M+H]^+$ = 847.8.

[1035] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.41 (s, 1H), 8.79 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.27 (s, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.26-6.97 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.50-4.37 (m, 1H), 4.22-4.10 (m, 1H), 3.85-3.75 (m, 6H), 3.70-3.50 (m, 2H), 3.10-2.95 (m, 1H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.45-2.38 (m, 4H), 2.32-2.25 (m, 2H), 2.24 (s, 3H), 2.11-1.97 (m, 7H), 1.93-1.85 (m, 2H), 1.81-1.45 (m, 6H), 1.41-1.31 (m, 2H), 1.18-0.95 (m, 4H).

Example 42: *N*-(1-(1-(2-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1036]



[1037] *N*-(1-(1-(2-(3-Azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (23 mg, 0.03 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoate (14 mg, 0.03 mmol) and *N*,*N*-diisopropylethylamine (38 mg, 0.30 mmol) were added while stirring, and the mixture was stirred at room temperature for 2 h. Water (20 mL) was added to the reaction liquid. The mixture was filtered, and the filter cake was purified by p-TLC (methanol:dichloromethane = 1:9) to give *N*-(1-(1-(2-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

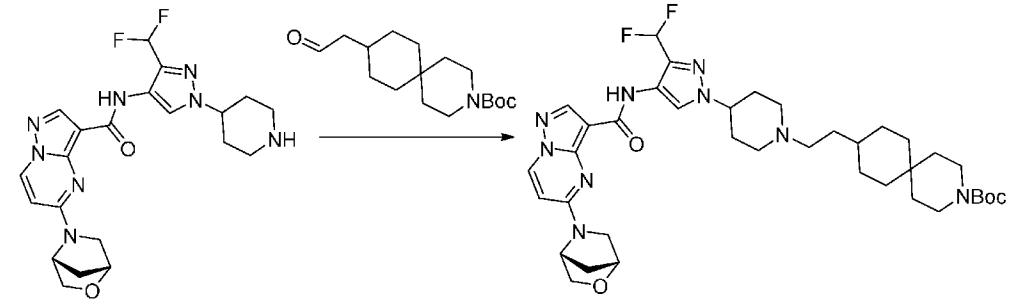
[1038] LC-MS: (ESI, m/z): $[M+H]^+$ = 876.3.

[1039] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.42-7.35 (m, 1H), 7.26-6.97 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.31-4.11 (m, 1H), 3.86-3.66 (m, 9H), 3.61-3.50 (m, 3H), 3.29-3.24 (m, 1H), 2.99-2.90 (m, 2H), 2.80-2.71 (m, 2H), 2.43-2.30 (m, 2H), 2.15-1.84 (m, 6H), 1.73-1.60 (m, 2H), 1.55-1.23 (m, 10H), 1.16-1.01 (m, 4H).

Example 43: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 9-(2-(4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)-3-azaspiro[5.5]undecane-3-carboxylate

[1040]

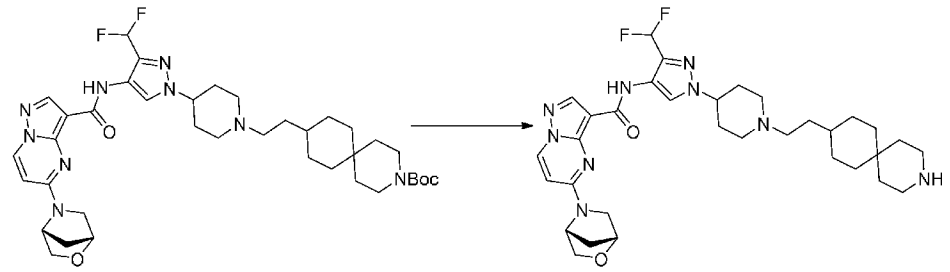


[1041] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.11 mmol) and *tert*-butyl 9-(2-oxoethyl)-3-azaspiro[5.5]undecane-3-carboxylate (40 mg, 0.13 mmol) were dissolved in tetrahydrofuran (10 mL). Sodium triacetoxyborohydride (70 mg, 0.33 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by p-TLC (methanol:dichloromethane = 1:9) to give *tert*-butyl 9-(2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[1042] LC-MS: (ESI, m/z): $[M+H]^+$ = 738.4.

Step 2: preparation of *N*-(1-(1-(2-(3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1043]

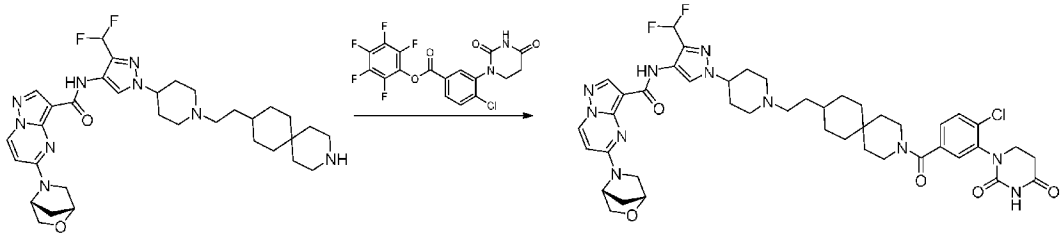


[1044] *tert*-Butyl 9-(2-(4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethyl)-3-azaspiro[5.5]undecane-3-carboxylate (40 mg, 0.05 mmol) was dissolved in dichloromethane (3 mL). Trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(1-(1-(2-(3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide. The resulting product was directly used in the next step without purification.

[1045] LC-MS: (ESI, m/z): $[M+H]^+$ = 638.3.

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1046]



[1047] *N*-(1-(1-(2-(3-Azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (40 mg, 0.05 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (24 mg, 0.05 mmol) and *N*,*N*-diisopropylethylamine (64 mg, 0.50 mmol) were added while stirring, and the mixture was stirred at room temperature overnight. Water (30 mL) was added to the reaction liquid. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(2-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)ethyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

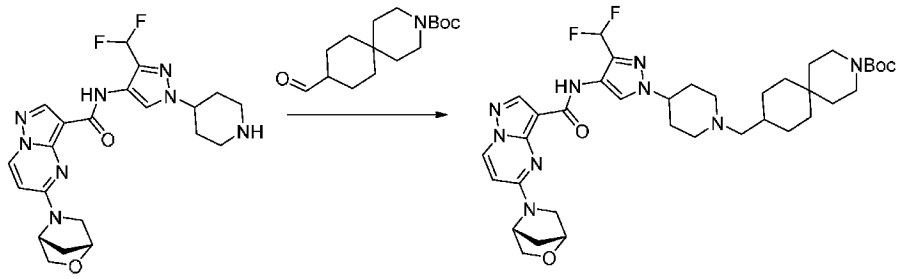
[1048] LC-MS: (ESI, m/z): $[M+H]^+$ = 888.3.

[1049] ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 3.9 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26-6.97 (m, 1H), 6.88-6.47 (m, 1H), 5.28-5,07 (m, 1H), 4.77 (d, *J* = 17.8 Hz, 1H), 4.30-4.10 (m, 1H), 3.85-3.72 (m, 3H), 3.67-3.41 (m, 5H), 3.30-3.24 (m, 2H), 2.97-2.88 (m, 2H), 2.80-2.70 (m, 2H), 2.35-2.27 (m, 2H), 2.03-1.80 (m, 8H), 1.72-1.65 (m, 2H), 1.55-1.26 (m, 9H), 1.24-0.97 (m, 4H).

Example 44: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(diffuoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 9-((4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate

[1050]

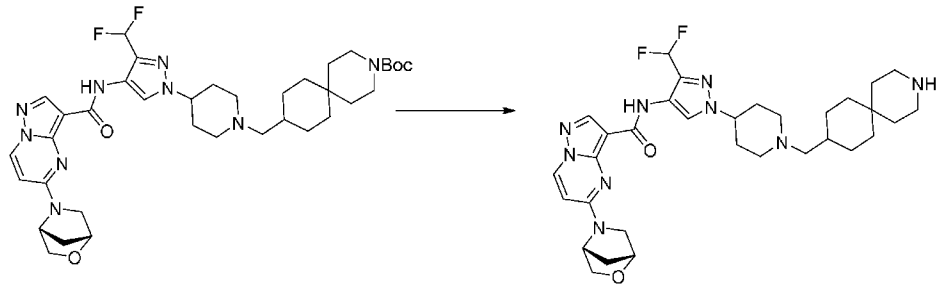


[1051] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, crude) was dissolved in THF (10 mL). *tert*-Butyl 9-formyl-3-azaspiro[5.5]undecane-3-carboxylate (50 mg, 0.18 mmol) and STAB (115 mg, 0.54 mmol) were added, and the mixture was reacted at room temperature for 2 h. The reaction liquid was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give tert-butyl 9-((4-(4-(5-(((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate.

[1052] LC-MS: (ESI, m/z): $[M+H]^+$ = 724.3.

Step 2: preparation of N-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-aaabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1053]

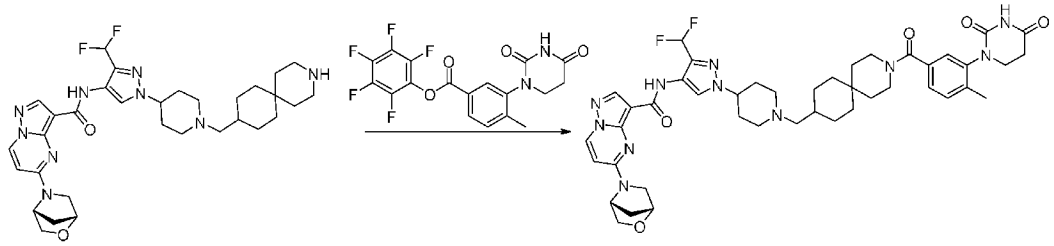


[1054] *tert*-Butyl 9-((4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidin-1-yl)methyl)-3-azaspiro[5.5]undecane-3-carboxylate (100 mg, 0.14 mmol) was dissolved in DCM (4 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(1-(1-((3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step.

[1055] LC-MS: (ESI, m/z): $[M+H]^+$ = 624.4.

Step 3: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1Hpyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1056]



[1057] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.14 mmol) was dissolved in DMSO (10 mL). DIEA (90 mg, 0.70 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoate (58 mg, 0.14 mmol) were added, and the mixture was reacted at room temperature for 2 h. Water (100 mL) was added to the reaction liquid, and the mixture was stirred for 5 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

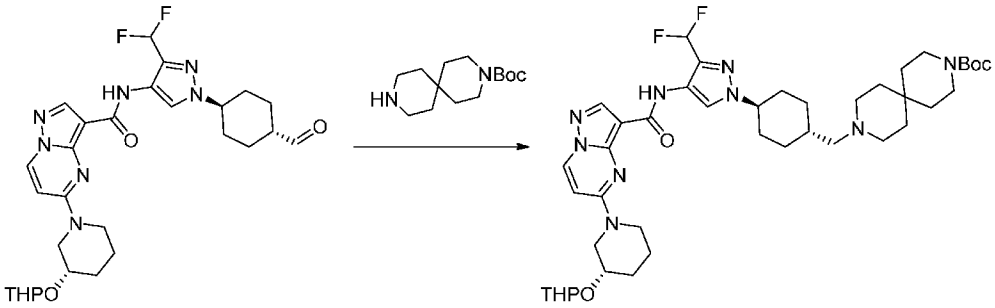
[1058] LC-MS: (ESI, m/z): $[M+H]^+$ = 854.4.

[1059] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 9.50 (d, *J* = 5.7 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 3.6 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 7.36-7.29 (m, 2H), 7.26-6.96 (m, 2H), 6.88-6.44 (m, 1H), 5.28-5.07 (m, 1H), 4.77 (d, *J* = 17.6 Hz, 1H), 4.31-4.11 (m, 1H), 3.88-3.71 (m, 3H), 3.63-3.45 (m, 5H), 2.95-2.85 (m, 2H), 2.81-2.65 (m, 2H), 2.25-2.10 (m, 5H), 2.07-1.87 (m, 8H),

Example 45: *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(((1*S*,4*R*)-4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[1060]

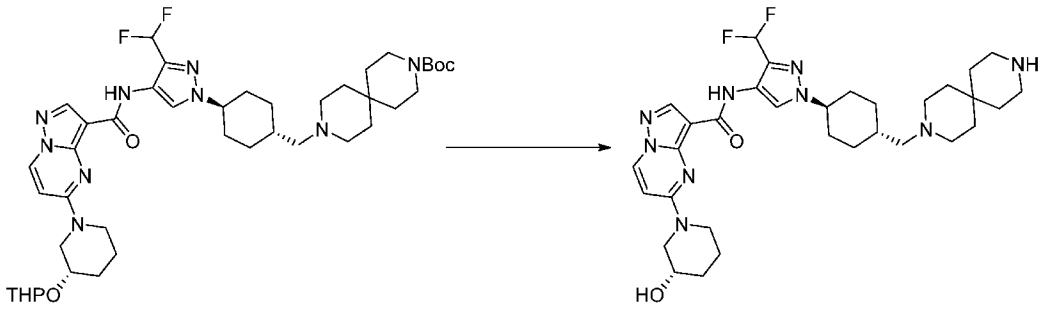


[1061] *N*-(3-(Difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.15 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (40 mg, 0.15 mmol) were dissolved in tetrahydrofuran (10 mL). Sodium triacetoxyborohydride (95 mg, 0.45 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give tert-butyl 9-(((1*S*,4*R*)-4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[1062] LC-MS: (ESI, m/z): $[M+H]^+$ = 810.4.

Step 2: preparation of *N*-(1-((1*R*,4*S*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1063]

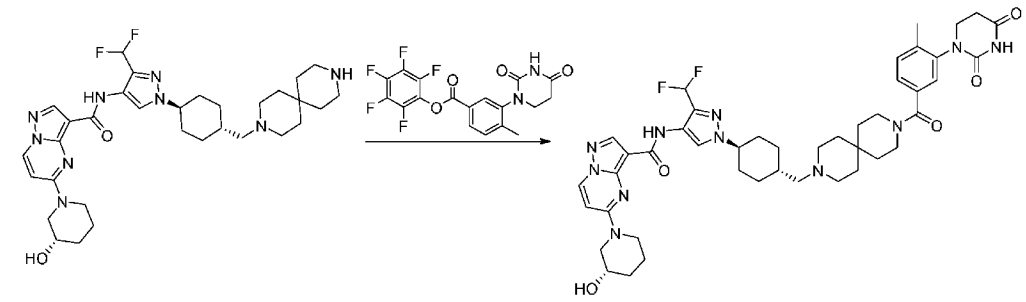


[1064] tert-Butyl 9-(((1*S*,4*R*)-4-(3-(difluoromethyl)-4-(5-((3*S*)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)piperidin-1-yl)pyrazolo[1.5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (100 mg, 0.12 mmol) was dissolved in dichloromethane (3 mL). Trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(1-((1*R*,4*S*)-4-((3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[1065] LC-MS: (ESI, m/z): $[M+H]^+$ = 626.3.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*S*)-4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1066]



[1067] *N*-(1-((1*R*,4*S*)-4-((3,9-Diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.12 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoate (55 mg, 0.13 mmol) and *N*,*N*-diisopropylethylamine (155 mg, 1.2 mmol) were added, and the mixture was stirred at room temperature overnight. Water (30 mL) was added to the reaction liquid. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(3-(diffuoromethyl)-1-((1*R*,4*S*)-4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-((*S*)-3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

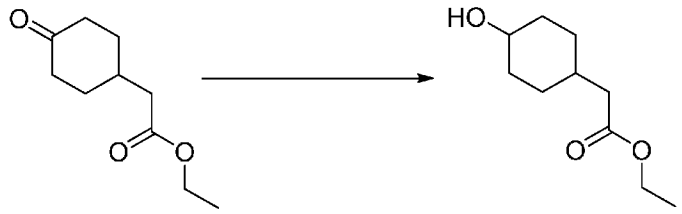
[1068] LC-MS: (ESI, m/z): $[M+H]^+$ = 856.4.

[1069] ^1H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 9.38 (s, 1H), 8.72 (d, *J* = 8.0 Hz, lH), 8.36 (s, 1H), 8.24 (s, 1H), 7.36-7.29 (m, 2H), 7.27-6.94 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.93-4.88 (m, 1H), 4.20-4.10 (m, 1H), 4.01-3.74 (m, 3H), 3.70-3.44 (m, 6H), 3.33-3.25 (m, 2H), 2.84-2.64 (m, 2H), 2.40-2.21 (m, 4H), 2.21 (s, 3H), 2.15-1.96 (m, 4H), 1.87-1.70 (m, 6H), 1.65-1.26 (m, 11H), 1.10-0.95 (m, 2H).

Example 46: 5-((1*R*,4*R*)-2-oxa-5-aza[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-(2-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)ethyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of ethyl 2-(4-hydroxycyclohexyl)acetate

[1070]

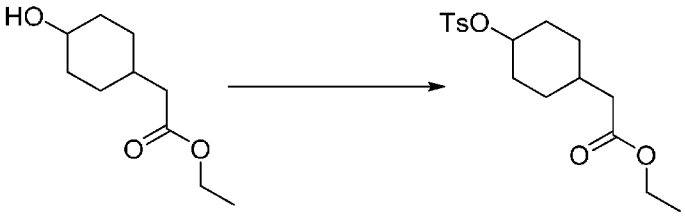


[1071] $NaBH_4$ (3.28 g, 86.96 mmol) was slowly added to a solution of ethyl 2-(4-oxocyclohexyl)acetate (8 g, 43.48 mmol) in anhydrous methanol (100 mL) at 0 °C, and the mixture was stirred for 2 h. Then a 10% aqueous NH_4Cl solution was added to quench the reaction. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (150 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product of ethyl 2-(4-hydroxycyclohexyl)acetate.

[1072] ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 3.60-3.47 (m, 1H), 2.25-2.14 (m, 2H), 2.05-1.93 (m, 2H), 1.81-1.69 (m, 3H), 1.35-1.20 (m, 5H), 1.11-0.97 (m, 2H).

Step 2: preparation of ethyl 2-(4-(*p*-toluenesulfonyloxy)cyclohexyl)acetate

[1073]



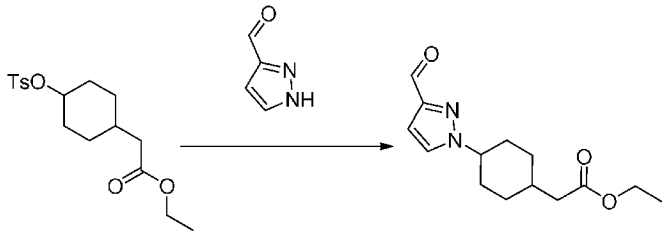
[1074] TsCl (11.55 g, 60.48 mmol) was added to a solution of ethyl 2-(4-hydroxycyclohexyl)acetate (7.5 g, 40.32 mmol) in DCM (120 mL). DMAP (1.49 g, 12.10 mmol) and TEA (12.3 g, 120.96 mmol) were added, and the mixture was stirred at room temperature for 16 h under N_2 atmosphere, diluted with water (100 mL), and extracted with ethyl acetate (80 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 3:7) to give ethyl 2-(4-(p-toluenesulfonyloxy)cyclohexyl)acetate.

[1075] LC-MS: (ESI, m/z): $[M+18]^+$ = 358.1.

[1076] ^1H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 4.41-4.30 (m, 1H), 4.04-4.01 (m, 2H), 2.42 (s, 3H), 2.16 (dd, *J* = 23.3, 6.9 Hz, 2H), 1.81-1.73 (m, 2H), 1.70-1.55 (m, 3H), 1.48-1.36 (m, 2H), 1.17-1.13 (m, 3H), 1.09-0.94 (m, 2H).

Step 3: preparation of ethyl 2-(4-(3-formyl-1*H*-pyrazol-1-yl)cyclohexyl)acetate

[1077]



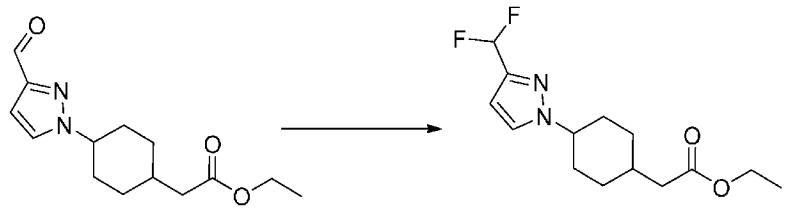
[1078] Ethyl 2-(4-(*p*-toluenesulfonyloxy)cyclohexyl)acetate (9.1 g, 26.76 mmol) was added to a solution of 1*H*-pyrazole-3-carbaldehyde (2.98 g, 26.76 mmol) in DMF (120 mL). Then $CsCO_3$ (14.4 g, 36.49 mmol) and KI (5.85 g, 29.19 mmol) were added, and the mixture was stirred at 50 °C for 16 h under N_2 atmosphere. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (80 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 1:4) to give ethyl 2-(4-(3-formyl-1*H*-pyrazol-1-yl)cyclohexyl)acetate.

[1079] LC-MS: (ESI, m/z): $[M+H]^+$ = 265.3.

[1080] ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.54 (s, 1H), 6.81 (s, 1H), 4.35-4.28 (m, 1H), 4.18-4.08 (m, 2H), 2.64-2.34 (m, 2H), 2.28-2.15 (m, 4H), 2.06-1.81 (m, 3H), 1.79-1.65 (m, 2H), 1.30-1.21 (m, 3H).

Step 4: preparation of ethyl 2-(4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)acetate

[1081]

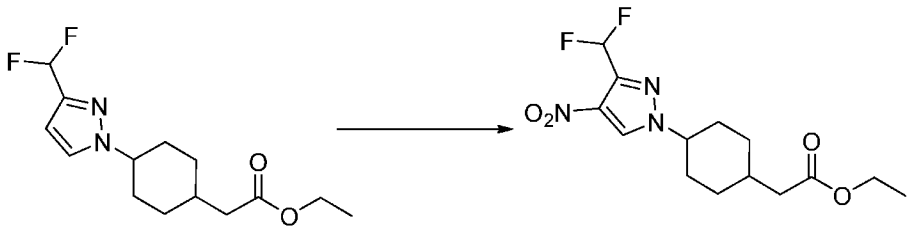


[1082] Ethyl 2-(4-(3-formyl-1*H*-pyrazol-1-yl)cyclohexyl)acetate (7.2 g, 27.27 mmol) was dissolved in anhydrous dichloromethane (100 mL). DAST (17.58 g, 109.08 mmol) was slowly added at 0 °C, and the mixture was stirred at room temperature for 16 h under N_2 atmosphere. Methanol (50 mL) was slowly added to the reaction liquid, and the mixture was diluted with water (100 mL) and extracted with ethyl acetate (80 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 3:17) to give ethyl 2-(4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)acetate.

[1083] LC-MS: (ESI, m/z): $[M+H]^+$ = 287.0.

Step 5: preparation of ethyl 2-(4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)acetate

[1084]

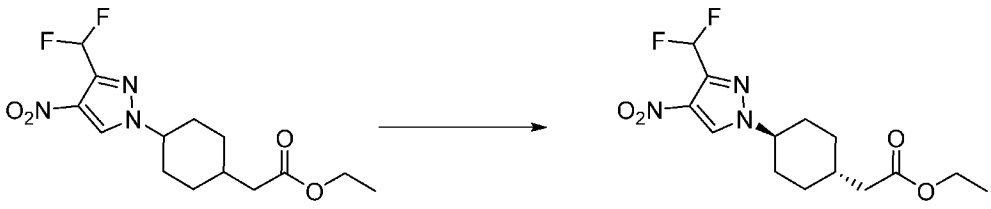


[1085] Ethyl 2-(4-(3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)acetate (2.7 g, 9.44 mmol) was added to a solution of HNO_3 (2.9 g, 47.2 mmol) in acetic acid (30 mL). Acetic anhydride (1.9 g, 18.9 mmol) was added, and the mixture was stirred at 50 °C for 16 h under N_2 atmosphere. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (80 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal phase column chromatography (EA:PE = 1:9) to give ethyl 2-(4-(3-(difluoromethyl)-4-nitro-1H-pyrazol-1 -yl)cyclohexyl)acetate.

[1086] LC-MS: (ESI, m/z): $[M+H]^+$ = 332.2.

Step 6: preparation of ethyl 2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)acetate

[1087]



[1088] Ethyl 2-(4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-pyrazol-1-yl)cyclohexyl)acetate (1.45 g, 4.38 mmol) was pu-

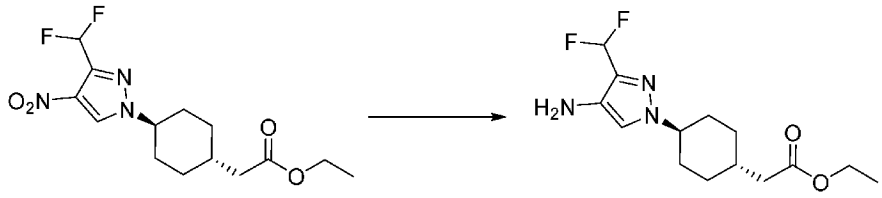
rified by preparative SFC (acetonitrile-0.1% aqueous FA solution, 5%-95%) to give the product of ethyl 2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)acetate.

[1089] LC-MS: (ESI, m/z): $[M+H]^+$ = 332.2.

[1090] ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.24-6.98 (m, 1H), 4.32-4.28 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.35 (d, *J* = 7.5 Hz, 2H), 2.28-2.13 (m, 3H), 2.02-1.98 (m, 2H), 1.76-1.74 (m, 2H), 1.57-1.49 (m, 2H), 1.26 (t, *J* = 5.2 Hz, 3H).

Step 7: preparation of ethyl 2-((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)acetate

[1091]

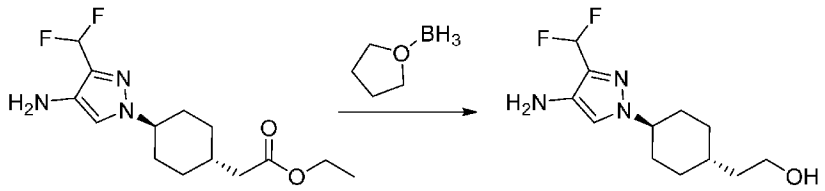


[1092] Ethyl 2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-nitro-1*H*-pyrazol-1-yl)cyclohexyl)acetate (850 mg, 2.56 mmol) was added to a solution of anhydrous ethanol (4 mL). A Raney-Ni solid-water mixture (1 mL) and hydrazine hydrate (0.8 mL) were added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was filtered, the filter cake was washed with ethanol, and the filtrate was directly concentrated under reduced pressure to give ethyl 2-((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)acetate.

[1093] LC-MS: (ESI, m/z): $[M+H]^+$ = 302.5.

Step 8: preparation of 2-((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl-1 -ol

[1094]

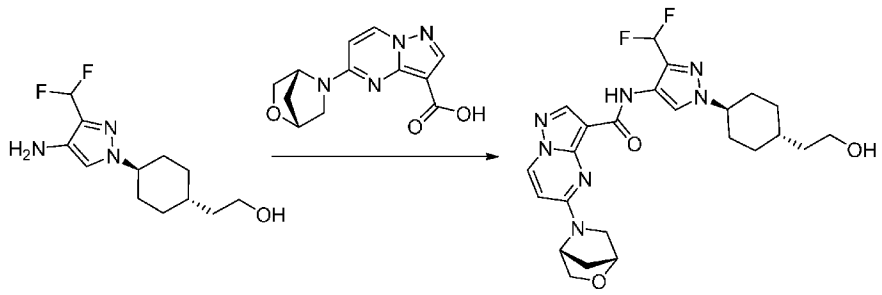


[1095] Ethyl 2-((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)acetate (100 mg, 0.33 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL). A solution of borane in tetrahydrofuran (4.98 mL, 4.98 mmol) was slowly added to the solution under nitrogen atmosphere, and the reaction liquid was heated to 50 °C and stirred for 3 h. The reaction liquid was cooled to room temperature. Methanol was slowly added dropwise until no bubbles were generated, and the resulting solution was concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give 2-((1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl-1-ol.

[1096] LC-MS: (ESI, m/z): $[M+H]^+$ = 260.2.

Step 9: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-hydroxyethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1097]

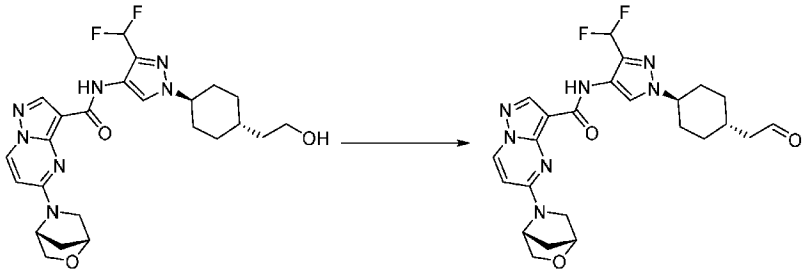


[1098] 2-((1*R*,4*R*)-4-(4-Amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl-1-ol (80 mg, 0.30 mmol) and 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (156 mg, 0.60 mmol) were dissolved in DMF (5 mL). *N,N*-Diisopropylethylamine (116 mg, 0.90 mmol) and Py-BOP (203 mg, 0.39 mmol) were added while stirring, and the mixture was stirred at 60 °C overnight. The reaction liquid was cooled to room temperature. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by p-TLC (methanol:dichloromethane = 1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-hydroxyethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1099] LC-MS: (ESI, m/z): $[M+H]^+$ = 502.2.

Step 10: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-oxoethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1100]

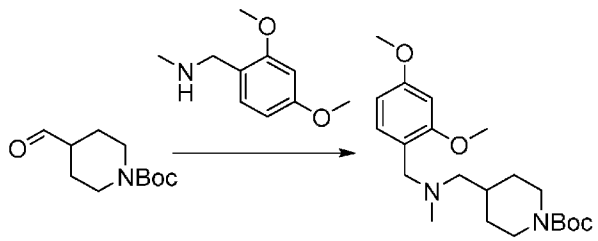


[1101] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-hydroxyethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.20 mmol) was dissolved in acetonitrile (10 mL). IBX (112 mg, 0.40 mmol) was added, and the mixture was stirred at 80 °C for 2 h. The reaction liquid was concentrated under reduced pressure, and the crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-oxoethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1102] LC-MS: (ESI, m/z): $[M+H]^+$ = 500.2.

Step 11: preparation of tert-butyl 4-(((2,4-dimethoxyphenyl)(methyl)amino)methyl)piperidine-1-carboxylate

[1103]

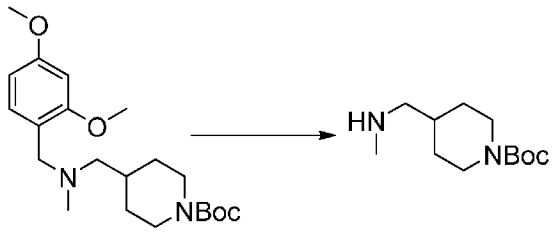


[1104] tert-Butyl 4-formylpiperidine-1-carboxylate (200 mg, 1.0 mmol) and 1-(2,4-dimethoxyphenyl)-N-methylmethanamine (190 mg, 1.1 mmol) were dissolved in tetrahydrofuran (10 mL). Then sodium triacetoxyborohydride (636 mg, 3.0 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 4:1) to give tert-butyl 4-(((2,4-dimethoxyphenyl)(methyl)amino)methyl)piperidine-1-carboxylate.

[1105] LC-MS: (ESI, m/z): $[M+H]^+$ = 379.2.

Step 12: preparation of *tert*-butyl 4-((methylamino)methyl)piperidine-1-carboxylate

[1106]

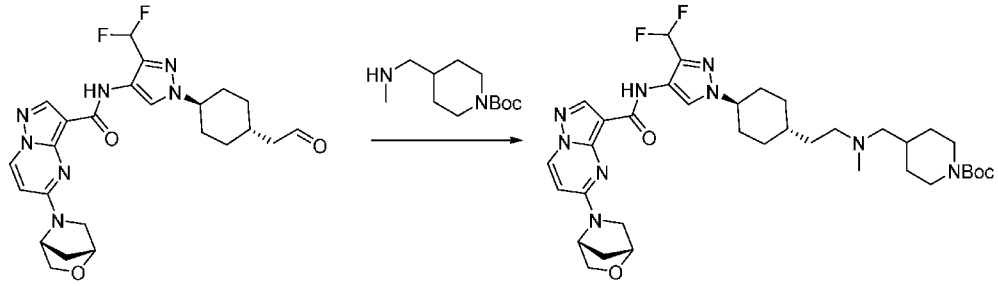


[1107] tert-Butyl 4-(((2,4-dimethoxyphenyl)(methyl)amino)methyl)piperidine-1-carboxylate (100 mg, 0.26 mmol) was dissolved in ethyl acetate (10 mL), 10% palladium on carbon (32 mg, 0.03 mmol) was added, and the resulting mixture was heated to 70 °C under hydrogen atmosphere and stirred overnight. After the reaction liquid was cooled to room temperature, the reaction liquid was filtered through celite, and the filtrate was directly concentrated under reduced pressure to give tert-butyl 4-((methylamino)methyl)piperidine-1-carboxylate.

[1108] LC-MS: (ESI, m/z): $[M+H]^+$ = 229.2.

Step 13: preparation of *tert*-butyl 4-(((2-((1R,4R)-4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamino)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl)(methyl)amino)methyl)piperidine-1-carboxylate

[1109]

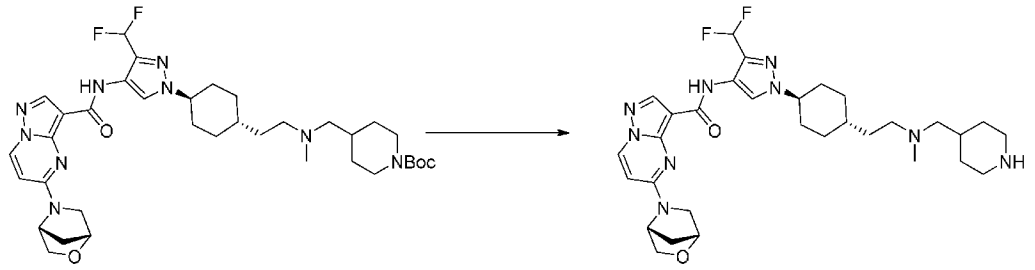


[1110] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-oxoethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.12 mmol) and tert-butyl 4-((methylamino)methyl)piperidine-1-carboxylate (60 mg, 0.26 mmol) were dissolved in tetrahydrofuran (10 mL). Sodium triacetoxyborohydride (127 mg, 0.6 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:9) to give tert-butyl 4-(((2-((1R,4R)-4-(4-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamino)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl)(methyl)amino)methyl)piperidine-1-carboxylate.

[1111] LC-MS: (ESI, m/z): $[M+H]^+$ = 712.4.

Step 14: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-(methyl(piperidin-4-ylmethyl)amino)ethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1112]

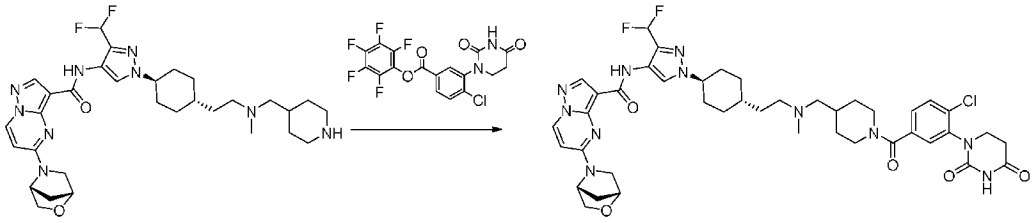


[1113] *tert*-Butyl 4-(((2-((1*R*,4*R*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamino)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl)(methyl)amino)methyl)piperidine-1-carboxylate (70 mg, 0.10 mmol) was dissolved in dichloromethane (3 mL). Then trifluoroacetic acid (1 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-(methyl(piperidin-4-ylmethyl)amino)ethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[1114] LC-MS: (ESI, m/z): $[M+H]^+$ = 612.3.

Step 15: preparation of 5-((1*R*,4*R*)-2-oxa-5-aza[2.2.1]heptan-5-yl)-*N*-(1-((1R,4R)-4-(2-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)ethyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1115]



[1116] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-(methyl(piperidin-4-ylmethyl)amino)ethyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.10 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (43 mg, 0.10 mmol) and *N*,*N*-diisopropylethylamine (130 mg, 1.0 mmol) were added while stirring, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid. The mixture was filtered, and the filter cake was purified by pre-HPLC (CH_3CN/0.10% aqueous FA solution, 5%-95%) to give 5-((1*R*,4*R*)-2-oxa-5-aza[2.2.1]heptan-5-yl)-*N*-(1-((1*R*,4*R*)-4-(2-(((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)methyl)(methyl)amino)ethyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

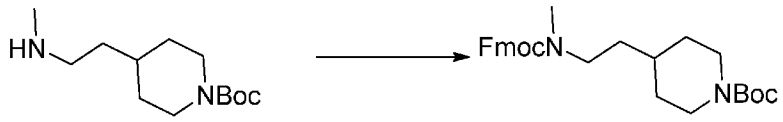
[1117] LC-MS: (ESI, m/z): $[M+H]^+$ = 862.3.

[1118] ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.50 (d, *J* = 6.3 Hz, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.42 (d, *J* = 4.0 Hz, 1H), 8.25 (d, *J* = 5.5 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.38 (d, *J* = 8.3,1.9 Hz, 1H), 7.26-6.97 (m, 1H), 6.88-6.45 (m, 1H), 5.28-5.08 (m, 1H), 4.77 (d, *J* = 16.7 Hz, 1H), 4.50-4.38 (m, 1H), 4.30-4.22 (m, 1H), 3.84-3.71 (m, 3H), 3.66-3.58 (m, 3H), 3.48-3.43 (m, 1H), 3.10-3.02 (m, 1H), 2.84-2.69 (m, 3H), 2.35-2.25 (m, 2H), 2.18-2.08 (m, 5H), 2.08-1.91 (m, 4H), 1.85-1.70 (m, 4H), 1.70-1.55 (m, 4H), 1.49-1.40 (m, 4H), 1.20-1.04 (m, 2H).

Example 47: 5-((*S*)-3-aminopiperidin-1-yl)-*N*-(1-((1*R*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[1119]

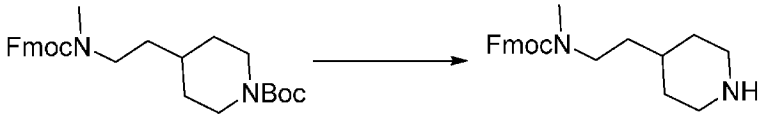


[1120] tert-Butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (240 mg, 1.0 mmol) was dissolved in DCM (20 mL). FmocCl (311 mg, 1.2 mmol) and pyridine (237 mg, 3.0 mmol) were added, and the mixture was reacted at room temperature overnight. The reaction liquid was diluted with water (50 mL) and extracted with DCM (30 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 0-4:1) to give tert-butyl 4-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[1121] LC-MS: (ESI, m/z): $[M+Na]^+$ = 487.3.

Step 2: preparation of (9*H*-fluoren-9-yl)methyl methyl(2-(piperidin-4-yl)ethyl)carbamate

[1122]

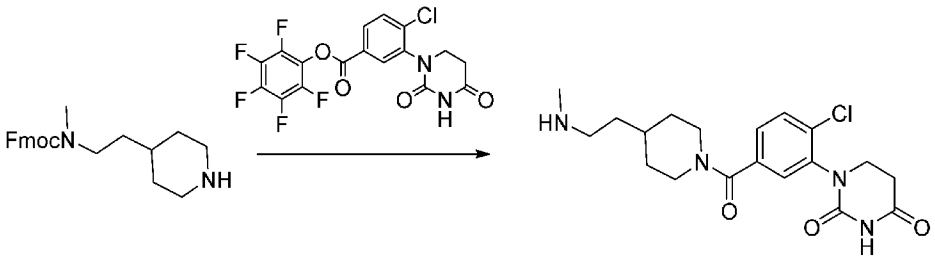


[1123] *tert*-Butyl 4-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)ethyl)piperidine-1-carboxylate (210 mg, 0.45 mmol) was dissolved in DCM (4 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give (9H-fluoren-9-yl)methyl methyl(2-(piperidin-4-yl)ethyl)carbamate, which was directly used in the next step.

[1124] LC-MS: (ESI, m/z): $[M+H]^+$ = 365.2.

Step 3: preparation of 1-(2-chloro-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1125]

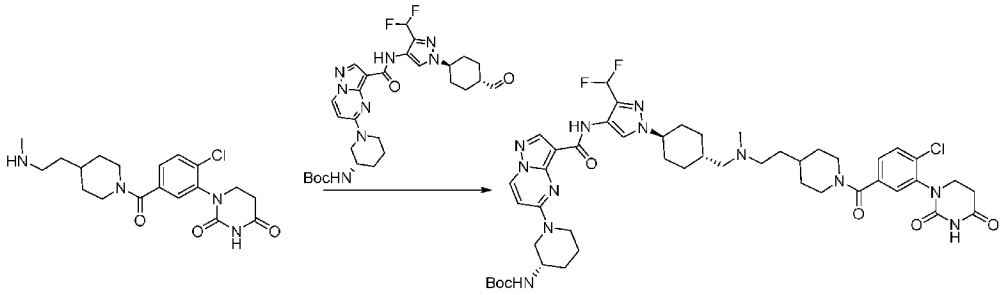


[1126] (9*H*-Fluoren-9-yl)methyl methyl(2-(piperidin-4-yl)ethyl)carbamate (210 mg, 0.45 mmol) was dissolved in DMSO (5 mL). DIEA (264 mg, 2.05 mmol) and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (178 mg, 0.41 mmol) were added, and the mixture was reacted at room temperature overnight. The reaction solution was purified by reversed-phase chromatography (45% ACN/0.1% aqueous NH_4HCO_3 solution) to give 1-(2-chloro-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1127] LC-MS: (ESI, m/z): $[M+H]^+$ = 393.1.

Step 4: preparation of *tert*-butyl ((*S*)-1-(3-((1-((1*R*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate

[1128]

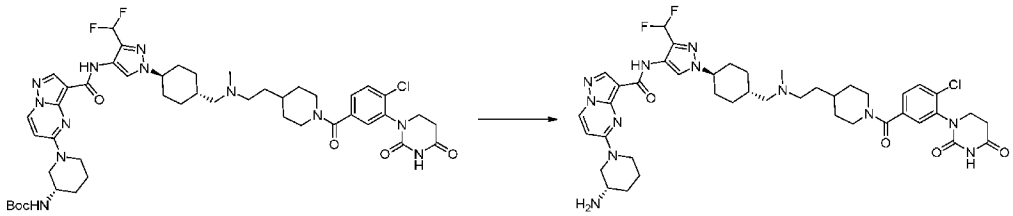


[1129] 1-(2-Chloro-5-(4-(2-(methylamino)ethyl)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (50 mg, 0.13 mmol) was dissolved in THF (10 mL). *tert*-Butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate (30 mg, 0.05 mmol) and STAB (83 mg, 0.39 mmol) were added. After the mixture was reacted for 0.5 h, tert-butyl ((*S*)-1-(3-((3-(difluoromethyl)-1-((1*R*,4*S*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate (60 mg, 0.10 mmol) was added in two portions within 1 h, and the mixture was reacted at room temperature for 2 h. The reaction liquid was diluted with water (50 mL), and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM = 0-1:9) to give *tert*-butyl ((*S*)-1-(3-((1-((1*R*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate.

[1130] LC-MS: (ESI, m/z): $[M+H]^+$ = 963.3.

Step 5: preparation of 5-((*S*)-3-aminopiperidin-1-yl)-*N*-(1-((1*R*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1131]



[1132] *tert*-Butyl ((*S*)-1-(3-((1-((1*R*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate (100 mg, 0.10 mmol) was dissolved in DCM (5 mL). TFA (1 mL) was added, and the mixture was reacted at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure. Then a saturated $NaHCO_3$ solution was added to adjust the pH to 8-9, and the mixture was extracted with MeOH/DCM (10%, 20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative reversed-phase chromatography to give 5-((*S*)-3-aminopiperidin-1-yl)-*N*-(1-((1*R*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1133] LC-MS: (ESI, m/z): $[M+H]^+$ = 863.1.

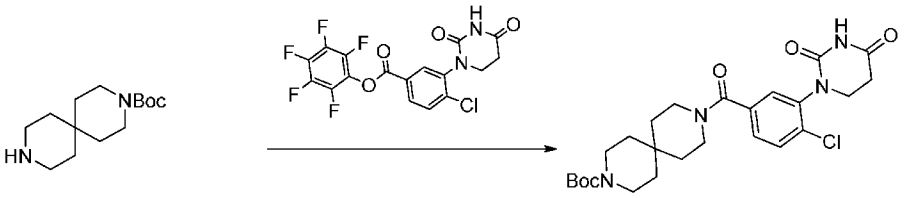
[1134] ^1H NMR (400 MHz, DMSO-d_6) δ 11.18-9.87 (s, 1H), 9.36 (s, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.26-6.97 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.50-4.25 (m, 2H), 4.18 (t, *J* = 11.9 Hz, 2H), 3.80-3.70 (m, 1H), 3.70-3.51 (m, 2H), 3.26-3.18 (m, 1H),

3.08-2.97 (m, 2H), 2.85-2.64 (m, 5H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.14-2.07 (m, 5H), 2.07-1.97 (m, 2H), 1.95-1.83 (m, 3H), 1.80-1.30 (m, 12H), 1.18-0.95 (m, 4H).

Example 48: *N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[1135]

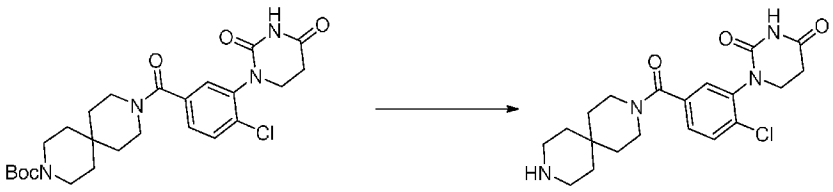


[1136] *tert*-Butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (100 mg, 0.39 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*-yl)benzoate (205 mg, 0.47 mmol) and *N*,*N*-diisopropylethylamine (153 mg, 1.18 mmol) were added while stirring, and the mixture was stirred at room temperature overnight. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) to give tert-butyl 9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[1137] LC-MS: (ESI, m/z): $[M\text{-Boc}]^+$ = 405.1.

Step 2: preparation of 1-(2-chloro-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1138]

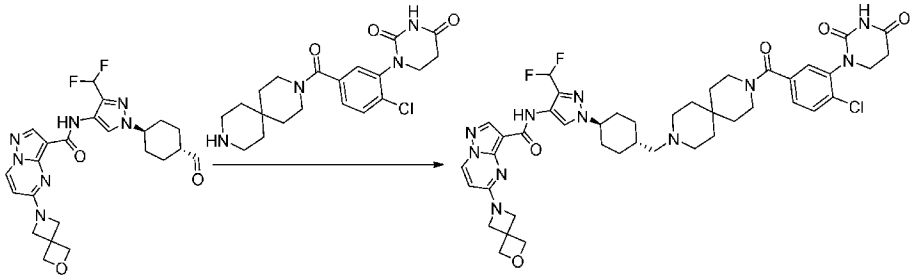


[1139] *tert*-Butyl 9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (170 mg, 0.34 mmol) was dissolved in dichloromethane (2.5 mL). Trifluoroacetic acid (0.5 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give 1-(2-chloro-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, which was directly used in the next step without purification.

[1140] LC-MS: (ESI, m/z): $[M+H]^+$ = 405.1.

Step 3: preparation of *N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1141]



[1142] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-formylcyclohexyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.10 mmol) and 1-(2-chloro-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (42 mg, 0.10 mmol) were dissolved in dichloroethane (10 mL). Sodium triacetoxyborohydride (44 mg, 0.20 mmol) was added, and the mixture was heated to 70 °C and stirred overnight. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(1-((1*R*,4*R*)-4-((9-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

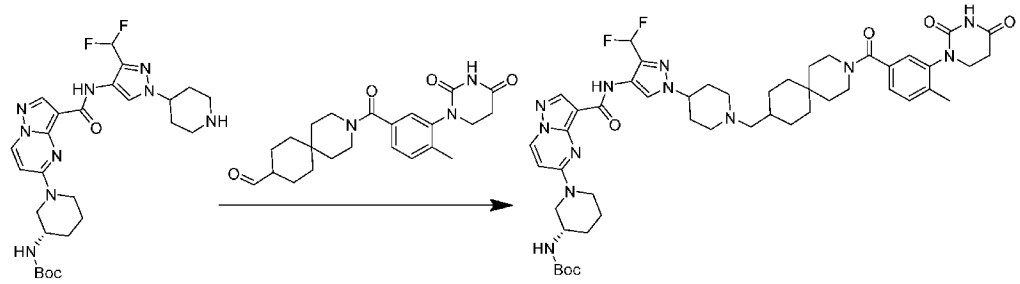
[1143] LC-MS: (ESI, m/z): $[M+H]^+$ = 874.2.

[1144] ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.44 (s, 1H), 8.39 (d, *J* = 5.3 Hz, 2H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.58-7.48 (m, 2H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.38-7.34 (m, 1H), 6.97-6.65 (m, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 4.98-4.85 (m, 4H), 4.47-4.37 (m, 4H), 4.13-4.06 (m, 1H), 3.86-3.74 (m, 4H), 3.46-3.38 (m, 2H), 3.00-2.74 (m, 3H), 2.39-2.29 (m, 3H), 2.29-2.10 (m, 3H), 2.10-2.00 (m, 2H), 1.92-1.76 (m, 3H), 1.40-1.10 (m, 10H), 0.95-0.85 (m, 1H).

Example 49: (*S*)-5-(3-aminopiperidin-1-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate

[1145]

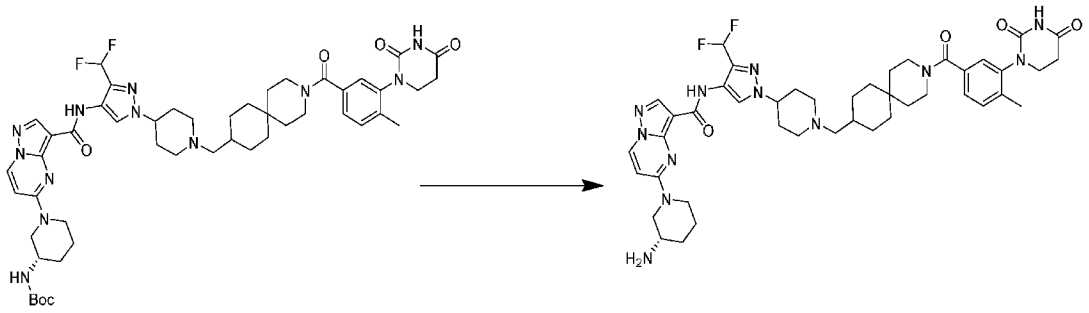


[1146] *tert*-Butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-a]pyrimidin-5-yl)piperidin-3-yl)carbamate (45 mg, 0.08 mmol) and 3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde (33 mg, 0.08 mmol) were dissolved in DMF (2 mL). $NaBH(OAc)_3$ (51 mg, 0.24 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The upper organic phases were combined and washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to give tert-butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate.

[1147] LC-MS: (ESI, m/z): $[M+H]^+$ = 955.5.

Step 2: preparation of (*S*)-5-(3-aminopiperidin-1-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1148]



[1149] *tert*-Butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate (30 mg, 0.03 mmol) was dissolved in DCM (0.5 mL). Then TFA (0.1 mL) was added, and the mixture was stirred at room temperature for 1 h. A saturated aqueous $NaHCO_3$ solution was added to the reaction liquid until the pH of the solution became slightly basic, and the mixture was extracted with a mixed organic solvent (MeOH:DCM = 1:10, 30 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by p-HPLC to give (*S*)-5-(3-aminopiperidin-1-yl)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

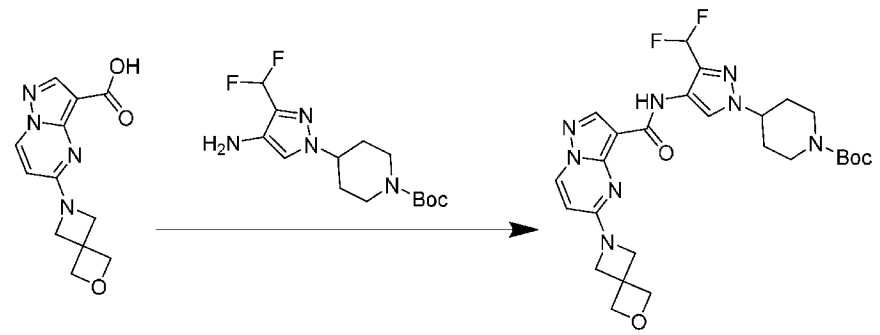
[1150] LC-MS: (ESI, m/z): $[M+H]^+$ = 855.7.

[1151] ^1H NMR (400 MHz, MeOD) δ 8.49 (d, *J* = 8.0 Hz, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.35-7.29 (m, 2H), 7.04-6.74 (m, 2H), 4.60-4.50 (m, 1H), 4.50-4.25 (m, 2H), 4.25-4.15 (m, 1H), 3.97-3.79 (m, 1H), 3.80-3.63 (m, 3H), 3.50-3.38 (m, 3H), 3.15-3.08 (m, 1H), 3.06-3.01 (m, 2H), 2.94-2.79 (m, 3H), 2.31 (s, 3H), 2.27-2.21 (m, 2H), 2.21-2.04 (m, 7H), 1.93-1.83 (m, 1H), 1.83-1.76 (m, 2H), 1.70-1.44 (m, 8H), 1.22-1.02 (m, 4H).

Example 50: *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(4-(5-(2-oxa-6-azaspiro[33]heptan-6-yl)pyrazolo[1,5-α]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

[1152]



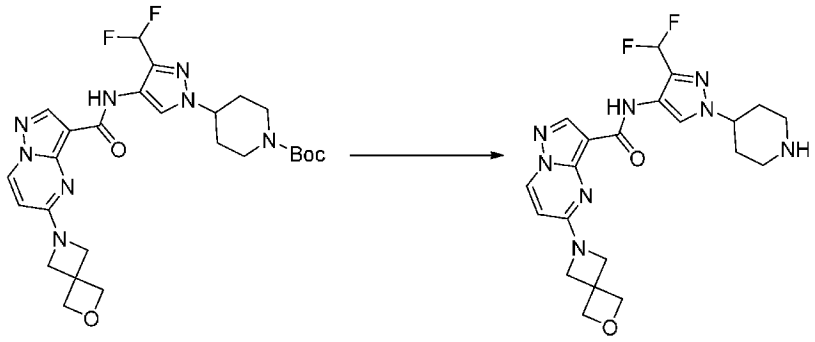
[1153] 5-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (130 mg, 0.5 mmol), benzyl 4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-pyrazol-1-yl)piperidine-1-carboxylate (158 mg, 0.5 mmol), and Py-BOP (780 mg, 1.5 mmol) were dissolved in DMF (6 mL), then DIEA (780 mg, 1.5 mmol) was added, and the mixture was stirred at room temperature for 16 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The upper organic phases were combined, washed with saturated brine (50 mL), dried over

anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal phase column chromatography to give tert-butyl 4-(4-(5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

[1154] LC-MS: (ESI, m/z): $[M+H]^+$ = 559.2.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1155]

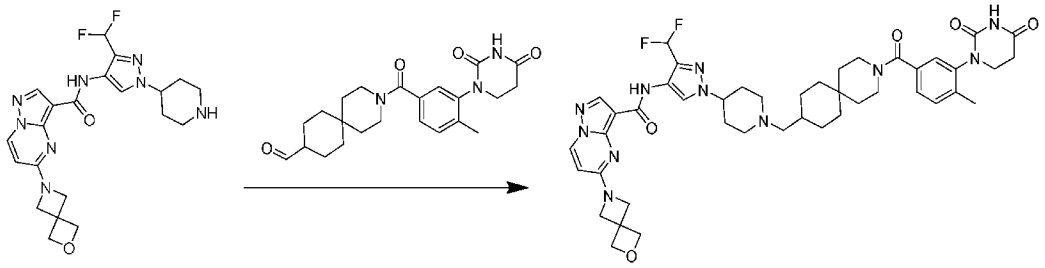


[1156] *tert*-Butyl 4-(4-(5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (250 mg, 0.45 mmol) was dissolved in DCM (4 mL). Then TFA (1 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give a crude product of *N*-(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1157] LC-MS: (ESI, m/z): $[M+H]^+$ = 459.3.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1158]



[1159] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (114 mg, 0.25 mmol) and 3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde (102 mg, 0.25 mmol) were dissolved in THF (5 mL). Sodium triacetoxyborohydride (160 mg, 0.75 mmol) was added, and the mixture was stirred at room temperature for 16 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The upper organic phases were combined and washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by prep-HPLC to give *N*-(3-(-difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin 1(2*H*-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a white solid.

[1160] LC-MS: (ESI, m/z): $[M+H]^+$ = 854.6.

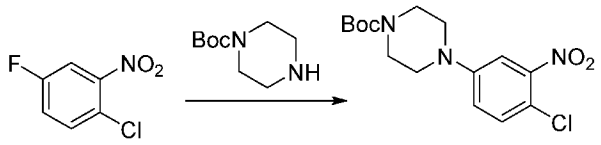
[1161] ^{1}H NMR (400 MHz, MeOD) δ 8.47 (d, *J* = 7.8 Hz, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.36-7.27 (m, 2H), 7.05-6.95 (m, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 4.62-4.50 (m, 2H), 4.50-4.39 (m, 4H), 4.26-4.11 (m, 1H), 3.95-3.82 (m, 1H), 3.77-3.60 (m, 3H), 3.49-3.40 (m, 2H), 3.05-2.97 (m, 2H), 2.89-2.79 (m, 2H), 2.37-2.20 (m, 5H),

2.20-2.09 (m, 6H), 1.83-1.75 (m, 2H), 1.71-1.41 (m, 7H), 1.37-1.27 (m, 2H), 1.24-1.08 (m, 4H).

Example 51: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 4-(4-chloro-3-nitrophenyl)piperazine-1-carboxylate

[1162]

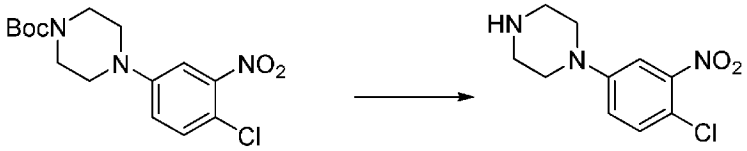


1- Chloro-4-fluoro-2-nitrobenzene (10.0 g, 56.81 mmol) was dissolved in DMSO (100 mL). Then *tert*-butyl piperazine-1-carboxylate (21 g, 85.27 mmol) and DIEA (52 mL) were added, and the mixture was heated to 110 °C and reacted for 48 h. Water (1000 mL) was added to the reaction liquid, and the mixture was stirred for 10 min and extracted with ethyl acetate (600 mL × 3). The organic phase was washed with saturated brine (1000 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (PE:EA = 5:1) to give tert-butyl 4-(4-chloro-3-nitrophenyl)piperazine-1-carboxylate.

[1163] LC-MS: (ESI, m/z): $[M\text{-}t\text{-}Bu]^+$ = 286.0.

Step 2: preparation of 1-(4-chloro-3-nitrophenyl)piperazine

[1164]

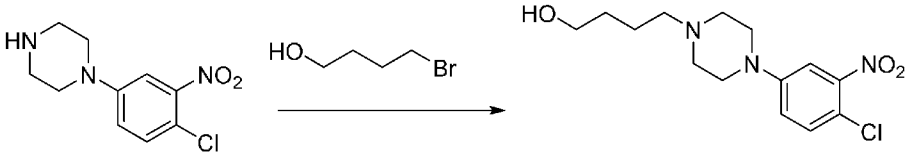


[1165] tert-Butyl 4-(4-chloro-3-nitrophenyl)piperazine-1-carboxylate (3.73 g, 10.9 mmol) was dissolved in DCM (30 mL). Then TFA (10 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 1-(4-chlorine-3-nitrophenyl)piperazine.

[1166] LC-MS: (ESI, m/z): $[M+H]^+$ = 242.0.

Step 3: preparation of 4-(4-(4-chloro-3-nitrophenyl)piperazin-1-yl)butyl-1-ol

[1167]

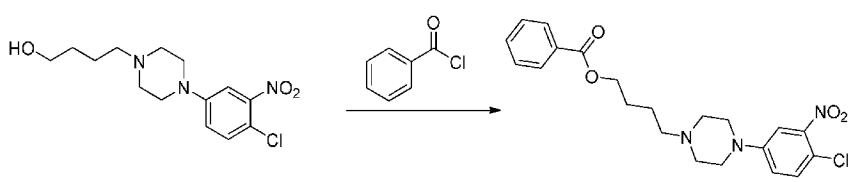


[1168] 1-(4-Chloro-3-nitrophenyl)piperazine (4.0 g, 10.9 mmol) was dissolved in DMF (25 mL). Then 4-bromobutyl-1-ol (1.75 g, 11.4 mmol), potassium carbonate (4.51 g, 32.7 mmol), and KI (1.89 g, 11.4 mmol) were added, and the reaction liquid was heated to 60 °C and stirred overnight. The reaction liquid was diluted with water (200 mL), and the mixture was stirred for 10 min and extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH = 1:19) to give 4-(4-(4-chloro-3-nitrophenyl)piperazin-1-yl)butyl-1-ol.

[1169] LC-MS: (ESI, m/z): $[M+H]^+$ = 314.1.

Step 4: preparation of 4-(4-(4-chloro-3-nitrophenyl)piperazin-1-yl)butylbenzoate

[1170]



[1171] 4-(4-(4-Chloro-3-nitrophenyl)piperazin-1-yl)butyl-1-ol (1.0 g, 3.19 mmol) was dissolved in THF (15 mL). Then benzoyl chloride (0.58 g, 4.15 mmol) and TEA (0.97 g, 9.57 mmol) were added, and the reaction liquid was heated to 70 °C and stirred overnight. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH = 1:13) to give 4-(4-(4-chloro-3-nitrophenyl)piperazin-1-yl)butylbenzoate.

[1172] LC-MS: (ESI, m/z): $[M+H]^+$ = 418.1.

Step 5: preparation of 4-(4-(3-amino-4-chlorophenyl)piperazin-1-yl)butylbenzoate

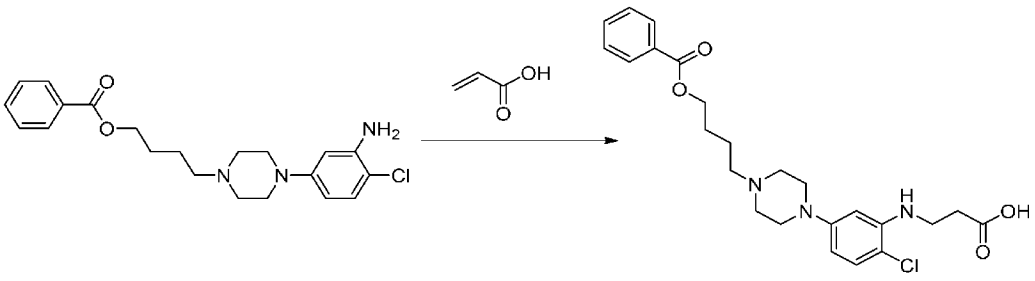
[1173]

[1174] 4-(4-(4-Chloro-3-nitrophenyl)piperazin-1-yl)butylbenzoate (1.2 g, 2.87 mmol) was dissolved in ethanol (15 mL). Hydrazine hydrate (1.5 mL) and Raney-Ni (solid-liquid mixture, 1.5 mL) were added, and the mixture was reacted at room temperature for 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give 4-(4-(3-amino-4-chlorphenyl)piperazin-1-yl)butylbenzoate.

[1175] LC-MS: (ESI, m/z): $[M+H]^+$ = 388.1.

Step 6: preparation of 3-((5-(4-(4-(benzoyloxy)butyl)piperazin-1-yl)-2-chlorophenyl)amino)propionic acid

[1176]

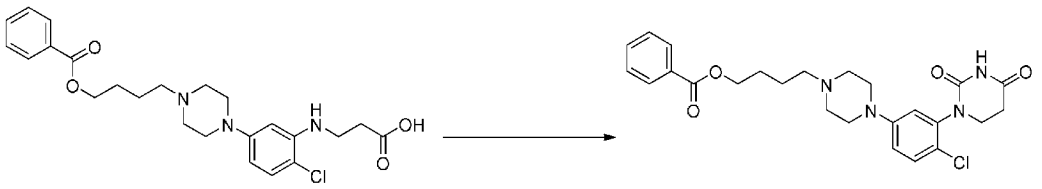


[1177] 4-(4-(3-Amino-4-chlorophenyl)piperazin-1-yl)butylbenzoate (1.0 g, 2.6 mmol) was dissolved in an acetic acid/water mixture (1/5, 12 mL). Then acrylic acid (0.558 g, 7.75 mmol) was added, and the reaction liquid was heated to 110 °C and stirred overnight. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 12%) to give 3-((5-(4-(4-(benzoyloxy)butyl)piperazin-1-yl)-2-chlorophenyl)amino)propionic acid.

[1178] LC-MS: (ESI, m/z): $[M+H]^+$ = 460.1.

Step 7: preparation of 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)butylbenzoate

[1179]

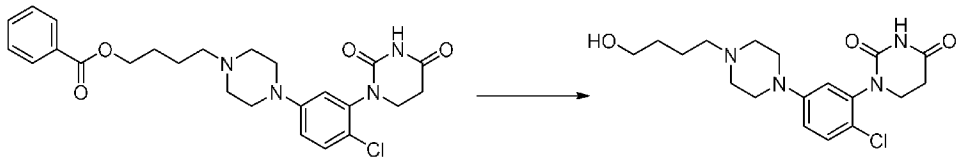


[1180] 3-((5-(4-(4-(Benzoyloxy)butyl)piperazin-1-yl)-2-chlorophenyl)amino)propionic acid (1.12 g, 2.44 mmol) was dissolved in acetic acid (15 mL). Then urea (2.92 g, 48.8 mmol) was added, and the reaction liquid was heated to 110 °C and stirred for 48 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with a MeOH/DCM mixed organic solvent (10%, 50 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH = 1:9) to give 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)butylbenzoate.

[1181] LC-MS: (ESI, m/z): $[M+H]^+$ = 485.1.

Step 8: preparation of 1-(2-chloro-5-(4-(4-hydroxybutyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1182]

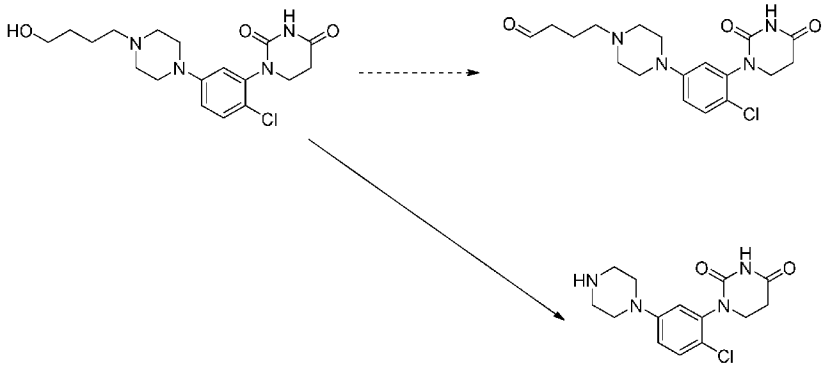


[1183] 4-(4-(4-Chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)butylbenzoate (0.74 g, 1.5 mmol) was added to concentrated hydrochloric acid (15 mL), and the mixture was heated to 70 °C and stirred overnight. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by reversed-phase column chromatography (ACN/H_2O = 16%, 0.1% aqueous FA solution) to give 1-(2-chloro-5-(4-(4-hydroxybutyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1184] LC-MS: (ESI, m/z): $[M+H]^+$ = 381.1.

Step 9: preparation of 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)n-butyraldehyde

[1185]



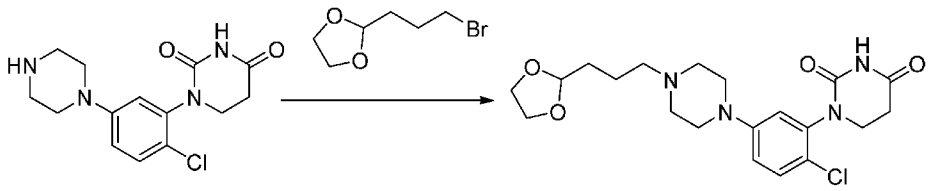
[1186] 1-(2-Chloro-5-(4-(4-hydroxybutyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (280 mg, 0.74 mmol) was dissolved in DCM (10 mL). Then Dess-Martin (628 mg, 1.48 mmol) was added, and the reaction liquid was stirred at room temperature overnight. The reaction liquid was directly concentrated under reduced pressure, and the

crude product was purified by reversed-phase column chromatography (ACN/H_2O = 16%, 0.1% aqueous FA solution). After analysis, the resulting product was not 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)*n*-butyraldehyde, but actually 1-(2-chloro-5-(piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione was obtained.

[1187] LC-MS: (ESI, m/z): $[M+H]^+$ = 309.2.

Step 10: preparation of 1-(5-(4-(3-(1,3-dioxolan-2-yl)propyl)piperazin-1-yl)-2-chlorophenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1188]

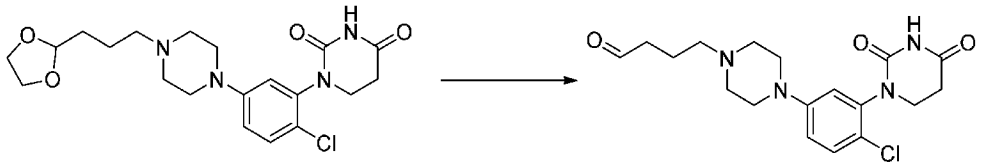


[1189] 1-(2-Chloro-5-(piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (65 mg, 0.21 mmol) was dissolved in ACN (10 mL). Then 2-(3-bromopropyl)-1,3-dioxolane (41 mg, 0.21 mmol), K_2CO_3 (87 mg, 0.63 mmol), and KI (18 mg, 0.21 mmol) were added, and the reaction liquid was heated to 80 °C and stirred overnight. The reaction liquid was concentrated under reduced pressure to remove ACN. Then water (50 mL) was added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH = 1:9) to give 1-(5-(4-(3-(1,3-dioxolan-2-yl)propyl)piperazin-1-yl)-2-chlorophenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1190] LC-MS: (ESI, m/z): $[M+H]^+$ = 423.1.

Step 11: preparation of 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)n-butyraldehyde

[1191]

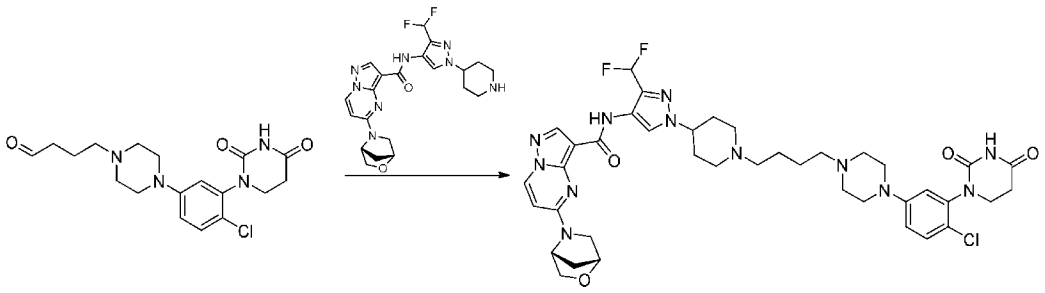


[1192] 1-(5-(4-(3-(1,3-Dioxolan-2-yl)propyl)piperazin-1-yl)-2-chlorophenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (20 mg, 0.047 mmol) was dissolved in DCM (1 mL). Then TFA (1 mL) was added. After the mixture was reacted at room temperature for 48 h, DCE (10 mL) and DIEA (1 mL) were added, and the mixture was concentrated under reduced pressure at room temperature to give 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)*n*-butyraldehyde (crude, in dichloroethane), which was directly used in the next step.

[1193] LC-MS: (ESI, m/z): $[M+H]^+$ = 379.1.

Step 12: preparation of 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(1-(1-(4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)butyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1194]



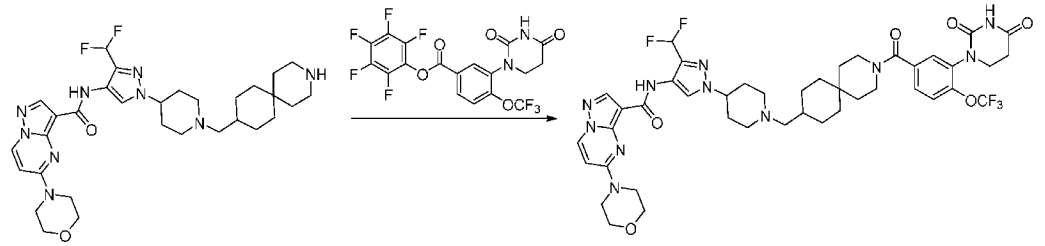
[1195] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*(3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (20 mg, 0.044 mmol) was added to a solution of 4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)*n*-butyraldehyde (crude) in DCE, and the mixture was stirred at room temperature for 0.5 h. STAB (28 mg, 0.13 mmol) was added, and the mixture was reacted at room temperature for 2 h. The reaction liquid was diluted with water (30 mL), and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give 5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-(1-(4-(4-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)phenyl)piperazin-1-yl)butyl)piperidin-4-yl)-3-(diffuoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1196] LC-MS: (ESI, m/z): $[M+H]^+$ = 821.3.

[1197] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H), 9.50 (d, *J* = 5.8 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H), 8.40 (d, *J* = 3.9 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.27-6.96 (m, 2H), 6.92 (dd, J = 9.0, 2.9 Hz, 1H), 6.88-6.44 (m, 1H), 5.28-5.07 (m, 1H), 4.77 (d, J = 17.3 Hz, 1H), 4.26-4.15 (m, 1H), 3.85-3.42 (m, 6H), 3.23-3.10 (m, 4H), 2.94 (d, J = 11.9 Hz, 2H), 2.80-2.62 (m, 2H), 2.49-2.46 (m, 4H), 2.40-2.25 (m, 4H), 2.05-1.80 (m, 8H), 1.53-1.41 (m, 4H).

Example 52: *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3 -carboxamide

[1198]



[1199] *N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.164 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoate (87 mg, 0.180 mmol) were dissolved in DMSO (5 mL). DIEA (65 mg, 0.492 mmol) was added, and the reaction liquid was stirred at room temperature overnight. The reaction liquid was diluted with water (20 mL), and the mixture was extracted with ethyl acetate (25 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give the compound N-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-(trifluoromethoxy)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

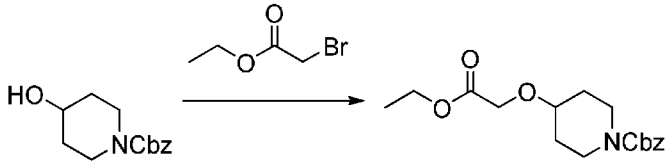
[1200] LC-MS: (ESI, m/z): $[M+H]^+$ = 912.4.

[1201] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, lH), 8.39 (s, 1H), 8.29 (s, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.24-6.87 (m, 2H), 4.24-4.17 (m, 1H), 3.83-3.50 (m, 13H), 3.30-3.26 (m, 1H), 2.93-2.85 (m, 2H), 2.75-2.65 (m, 2H), 2.18-2.10 (m, 2H), 2.05-1.88 (m, 6H), 1.70 (d, *J* = 9.0 Hz, 2H), 1.61-1.42 (m, 5H), 1.35-1.20 (m, 2H), 1.12-0.95 (m, 4H).

Example 53: *N*-(3-(diffuoromethyl)-1-(1-(2-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of benzyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate

[1202]



[1203] Benzyl 4-hydroxypiperidine-1-carboxylate (3 g, 12.8 mmol) was dissolved in anhydrous tetrahydrofuran (30 mL). Sodium hydride (1.1 g, 25.6 mmol) was added at zero, and the mixture was stirred for 60 min. Ethyl 2-bromoacetate (2.6 g, 15.4 mmol) was added, and the reaction liquid was stirred at room temperature overnight. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (150 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:1) to give benzyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate.

[1204] LC-MS: (ESI, m/z): $[M+Na]^+$ = 344.1.

Step 2: preparation of benzyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate

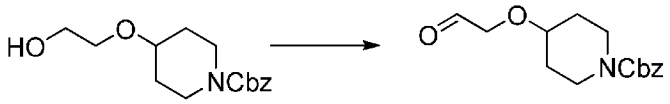
[1205]

[1206] Benzyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate (1.1 g, 3.4 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL). A solution of borane in tetrahydrofuran (2.9 g, 34 mmol) was added at zero, and the reaction liquid was stirred at room temperature overnight. Water (100 mL) was slowly added at zero, and the mixture was extracted with ethyl acetate (100 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 7:3) to give benzyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate.

[1207] LC-MS: (ESI, m/z): $[M+Na]^+$ = 302.1.

Step 3: preparation of benzyl 4-(2-oxoethoxy)piperidine-1-carboxylate

[1208]

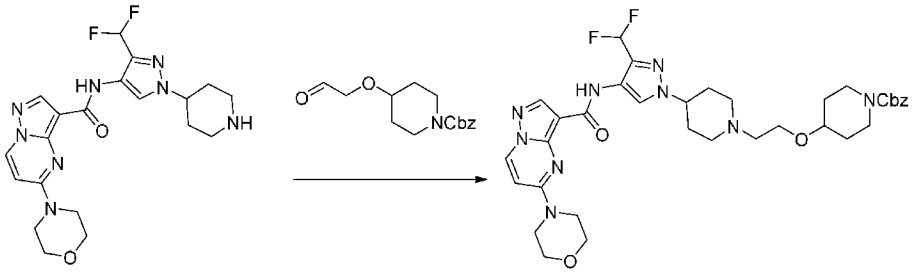


[1209] Benzyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate (400 mg, 1.4 mmol) was dissolved in DCM (4 mL). PCC (602 mg, 2.8 mmol) was added, and the reaction liquid was stirred at room temperature for 3 h. The mixture was filtered and directly concentrated under reduced pressure to give benzyl 4-(2-oxoethoxy)piperidine-1-carboxylate, which was directly used in the next step without purification.

[1210] LC-MS: (ESI, m/z): $[M+H]^+$ = 278.1.

Step 4: preparation of benzyl 4-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethoxy)piperidine-1-carboxylate

[1211]

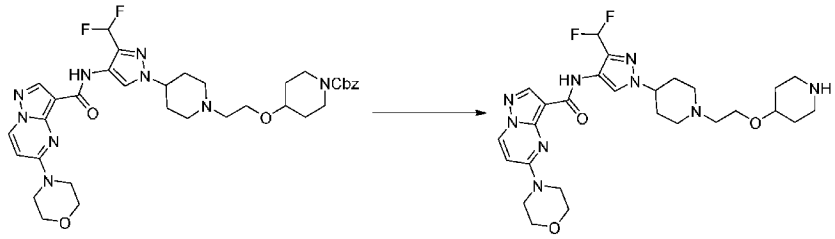


[1212] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.27 mmol) and benzyl 4-(2-oxoethoxy)piperidine-1-carboxylate (75 mg, 0.27 mmol) were dissolved in tetrahydrofuran (5 mL). Sodium triacetoxyborohydride (172 mg, 0.81 mmol) was added while stirring, and the mixture was stirred at room temperature for 3 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (60 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloroethane = 1:7) to give benzyl 4-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethoxy)piperidine-1 -carboxylate.

[1213] LC-MS: (ESI, m/z): $[M+H]^+$ = 708.3.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-yloxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1214]

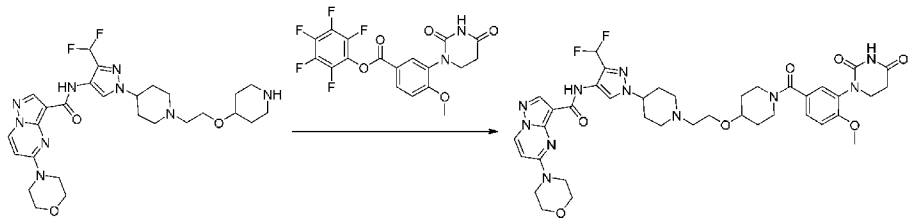


[1215] Benzyl 4-(2-(4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)piperidin-1-yl)ethoxy)piperidine-1-carboxylate (50 mg, 0.07 mmol) was dissolved in tetrahydrofuran (3 mL). Then palladium on carbon (10%, 10 mg) was added, and the mixture was stirred at room temperature for 1 h. The reaction liquid was filtered through celite, and the filtrate was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-(1-(2-(piperidin-4-yloxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide,which was directly used in the next step without purification.

[1216] LC-MS: (ESI, m/z): $[M+H]^+$ = 574.4.

Step 6: preparation of *N*-(3-(difluoromethyl)-1-(1-(2-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morphofinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1217]



[1218] *N*-(3-(Difluoromethyl)-1-(1-(2-(piperidin-4-yloxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (26 mg, 0.045 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (20 mg, 0.045 mmol) were dissolved in DMSO (2 mL). *N*,*N*-diisopropylethylamine (18 mg, 0.14 mmol) was added while stirring, and the mixture was stirred at room temperature for 3 h. Water (20 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give N-(3-(difluoromethyl)-1-(1-(2-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)ethyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

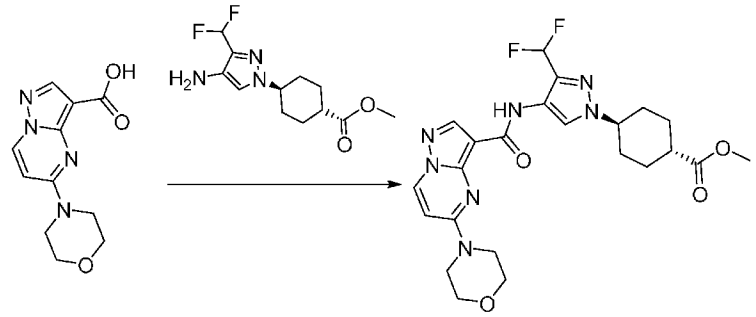
[1219] LC-MS: (ESI, m/z): $[M+H]^+$ = 820.6.

[1220] ^1H NMR (400 MHz, CD_3OD) δ 8.54 (d, J = 8.0 Hz, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.47-7.38 (m, 2H), 7.19 (d, J = 8.6 Hz, 1H), 7.00-6.72 (m, 2H), 3.92 (s, 3H), 3.89-3.77 (m, 8H), 3.70-3.67 (m, 3H), 3.15-3.10 (m, 1H), 2.80 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 5.5 Hz, 2H), 2.40-2.28 (m, 2H), 2.19 (t, J = 7.6 Hz, 1H), 2.14-2.08 (m, 2H), 2.04-1.90 (m, 3H), 1.64-1.55 (m, 2H), 1.34-1.26 (m, 8H).

Example 54: *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((2-(1-(3-(2,6-dioxopyridin-3-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)(methyl)carbamoyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate

[1221]

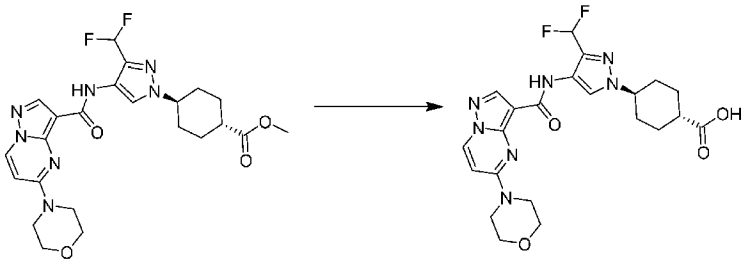


[1222] 5-Morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (200 mg, 0.73 mmol) was dissolved in DMF (4 mL). Methyl (1*R*,4*R*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (182 mg, 0.73 mmol), HATU (139 mg, 0.95 mmol), and DIEA (377 mg, 2.92 mmol) were added, and the reaction liquid was stirred at room temperature overnight. The reaction liquid was diluted with water (50 mL) and extracted with ethyl acetate (40 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA:PE = 9:1) to give methyl (1R,4R)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate.

[1223] LC-MS: (ESI, m/z): $[M+H]^+$ = 504.1.

Step 2: preparation of (1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexane-1 -carboxylic acid

[1224]

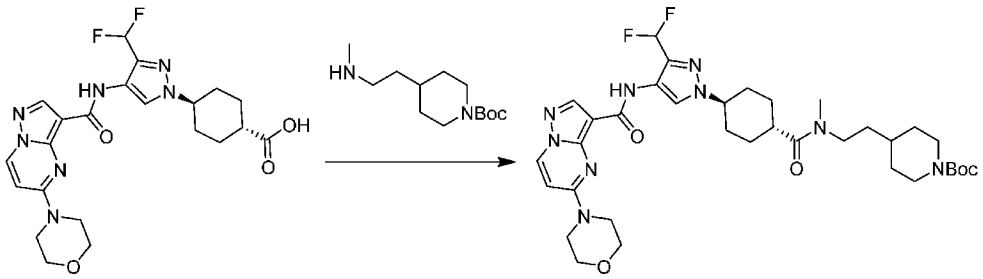


[1225] Methyl (1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylate (230 mg, 0.46 mmol) was dissolved in a mixed solution of methanol/water (5 mL, V/V = 5/1). Lithium hydroxide (44 mg, 1.84 mmol) was added, and the reaction liquid was heated to 60 °C and stirred for 2 h. The reaction liquid was adjusted to pH = 4 with dilute hydrochloric acid (2 mol/L), and the mixture was extracted with ethyl acetate (40 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylic acid, which was directly used in the next step.

[1226] LC-MS: (ESI, m/z): $[M+H]^+$ = 490.6.

Step 3: preparation of *tert*-butyl 4-(2-((1R,4R)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)-*N*-methylcyclohexane-1-carboxamido)ethyl)piperidine-1-carboxylate

[1227]

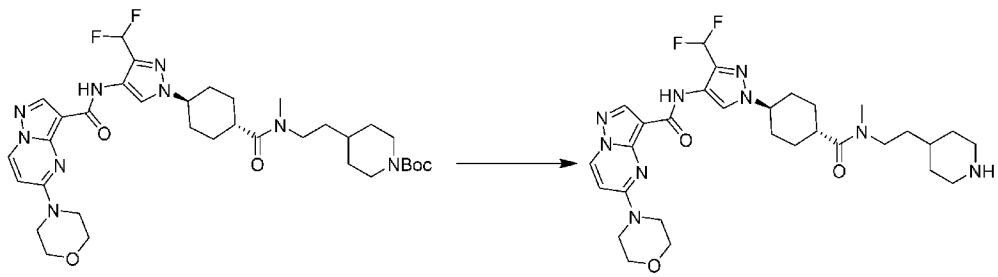


[1228] (1*R*,4*R*)-4-(3-(Difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexane-1-carboxylic acid (140 mg, 0.29 mmol) and *tert*-butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (70 mg, 0.29 mmol) were dissolved in DMF (4 mL). HATU (144 mg, 0.38 mmol) and DIEA (155 mg, 1.2 mmol) were added, and the reaction liquid was stirred at room temperature overnight. The reaction liquid was diluted with water (40 mL) and extracted with ethyl acetate (40 mL × 4). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (EA) to give *tert*-butyl 4-(2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)-*N*-methylcyclohexane-1 -carboxamido)ethyl)piperidine-1 -carboxylate.

[1229] LC-MS: (ESI, m/z): $[M+H]^+$ = 714.8.

Step 4: preparation of N-(3-(difluoromethyl)-1-((1R,4R)-4-(methyl(2-(piperidin-4-yl)ethyl)carbamoyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1230]

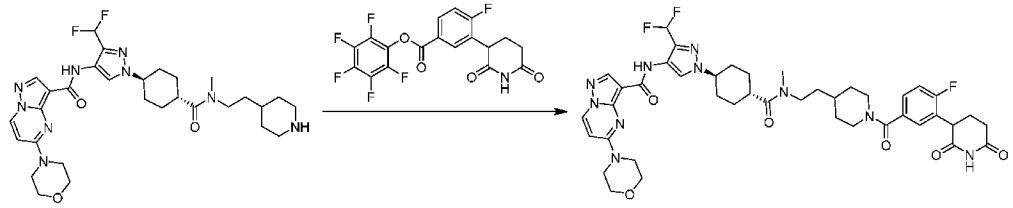


[1231] *tert*-Butyl 4-(2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-a]pyrimidine-3-carboxamido-1*H*-pyrazol-1-yl)-*N*-methylcyclohexane-1-carboxamido)ethyl)piperidine-1-carboxylate (130 mg, 0.18 mmol) was dissolved in dichloromethane (3 mL). Trifluoroacetic acid (0.3 mL) was added, and the mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(methyl(2-(piperidin-4-yl)ethyl)carbamoyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[1232] LC-MS: (ESI, m/z): $[M+H]^+$ = 614.2.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((2-(1-(3-(2,6-dioxopyridin-3-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)(methyl)carbamoyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1233]



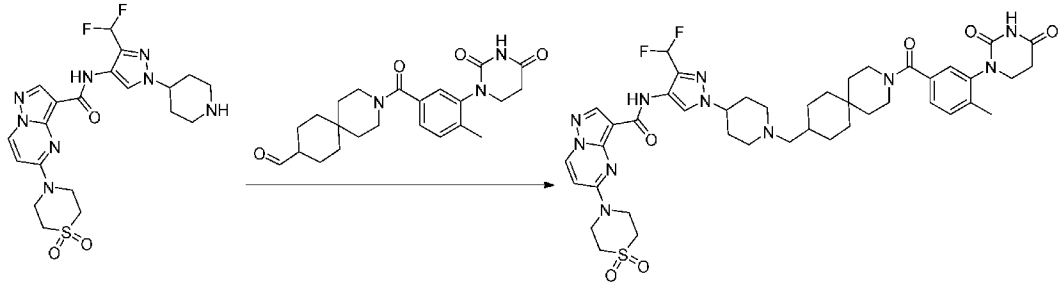
[1234] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(methyl(2-(piperidin-4-yl)ethyl)carbamoyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (130 mg, 0.18 mmol) and pentafluorophenyl 3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoate (75.3 mg, 0.18 mmol) were dissolved in DMSO (2 mL). DIEA (93 mg, 0.72 mmol) was added, and the reaction liquid was stirred at room temperature for 3 h. The reaction liquid was diluted with water (20 mL), and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((2-(1-(3-(2,6-dioxopyridin-3-yl)-4-fluorobenaoyl)piperidin-4-yl)ethyl)(methyl)carbamoyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1235] LC-MS: (ESI, m/z): $[M+H]^+$ = 847.4.

[1236] ^1H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.29 (s, 1H), 7.40-7.33 (m, 2H), 7.31-7.23 (m, 1H), 7.23-6.96 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.52-4.20 (m, 2H), 4.12 (dd, *J* = 12.7, 4.9 Hz, 1H), 3.88-3.66 (m, 8H), 3.62-3.48 (m, 1H), 3.433.34 (m, 1H), 3.01 (s, 3H), 2.82-2.62 (m, 4H), 2.60-2.54 (m, 1H), 2.29-2.17 (m, 1H), 2.08-1.98 (m, 3H), 1.95-1.67 (m, 6H), 1.66-1.35 (m, 6H), 1.21-1.02 (m, 2H).

Example 55: preparation of *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1237]



[1238] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.1 mmol) and 3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde (41 mg, 0.1 mmol) were dissolved in tetrahydrofuran (2 mL). Sodium triacetoxyborohydride (84 mg, 0.4 mmol) was added while stirring, and the mixture was stirred at room temperature for 3 h. The reaction liquid was diluted with water (50 mL), and the mixture was extracted with ethyl acetate (50 mL × 3). The organic

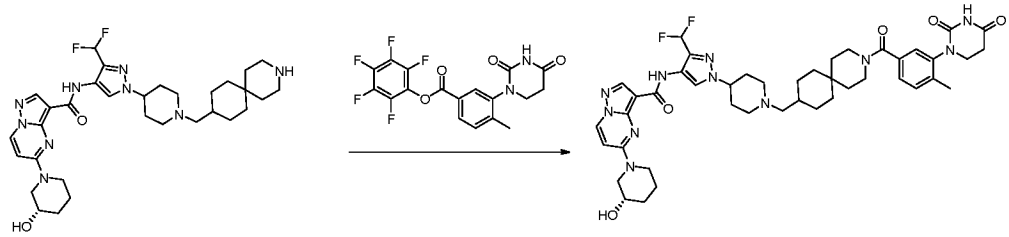
phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give *N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1239] LC-MS: (ESI, m/z): $[M+H]^+$ = 890.1

[1240] ^1H NMR (400 MHz, CD_3OD-d_4) δ 8.64 (d, J = 7.9 Hz, 1H), 8.37 (d, *J* = 5.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.36-7.29 (m, 2H), 7.06-6.77 (m, 2H), 4.60-4.52 (m, 2H), 4.42-4.34 (m, 4H), 4.25-4.14 (m, 1H), 3.92-3.82 (m, 1H), 3.77-3.62 (m, 3H), 3.49-3.40 (m, 2H), 3.30-3.22 (m, 4H), 3.06-3.00 (m, 2H), 2.92-2.82 (m, 2H), 2.31 (s, 3H), 2.28-2.22 (m, 2H), 2.20-2.06 (m, 6H), 1.82-1.72 (m, 2H), 1.70-1.63 (m, 2H), 1.55-1.39 (m, 2H), 1.33-1.25 (m, 2H), 1.24-1.12 (m, 3H).

Example 56: (*S*)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1241]



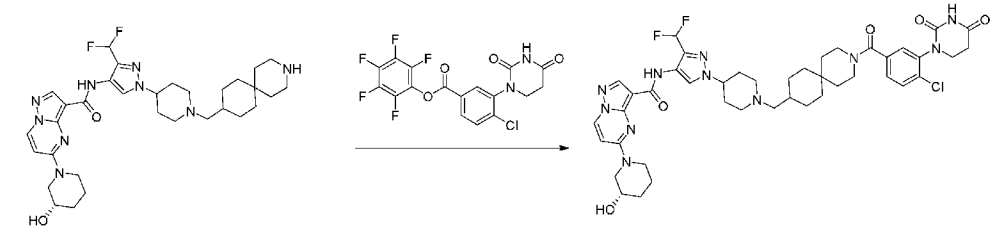
[1242] (*S*)-*N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, crude, 0.11 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoate (46 mg, 0.11 mmol) and *N*,*N*-diisopropylethylamine (142 mg, 1.1 mmol) were added while stirring, and the mixture was stirred at room temperature overnight. Water (50 mL) was added to the reaction liquid. The mixture was filtered, and the filter cake was purified by Pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give (*S*)-*N*-(3-(difluoromethyl)-1-(1-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methylbenzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo [1,5-*a*]pyrimidine-3-carboxamide.

[1243] LC-MS: (ESI, m/z): $[M+H]^+$ = 856.3.

[1244] ^1H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 9.38 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.37-7.29 (m, 2H), 7.26-6.96 (m, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J* = 2.0 Hz, 1H), 4.26-4.14 (m, 1H), 4.00-3.75 (m, 3H), 3.70-3.39 (m, 6H), 3.30-3.24 (m, 2H), 2.93-2.64 (m, 4H), 2.21 (s, 3H), 2.18-2.10 (m, 2H), 2.06-1.65 (m, 10H), 1.61-1.22 (m, 9H), 1.16-0.95 (m, 4H).

Example 57: (*S*)-*N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo [1,5-*a*]pyrimidine-3-carboxamide

[1245]



[1246] (*S*)-*N*-(1-(1-((3-Azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, crude, 0.11 mmol) was dissolved in dimethyl sulfoxide (3 mL). Pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (48 mg, 0.11 mmol) and *N*,*N*-diisopropylethylamine (142 mg, 1.1 mmol) were added while stirring, and the mixture was stirred at room temperature

overnight. Water (30 mL) was added to the reaction liquid. The mixture was filtered, and the filter cake was purified by Pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3 solution, 5%-95%) to give (*S*)-*N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5] undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(3-hydroxypiperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

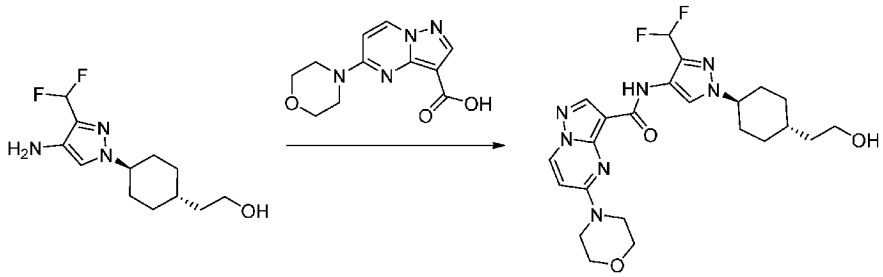
[1247] LC-MS: (ESI, m/z): $[M+H]^+$ = 876.3.

[1248] ^1H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.38 (s, 1H), 8.72 (d, *J* = 7.9 Hz, lH), 8.38 (s, 1H), 8.24 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.26-6.97 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 4.25-4.15 (m, 1H), 3.97-3.40 (m, 9H), 3.30-3.18 (m, 2H), 2.93-2.85 (m, 2H), 2.78-2.72 (m, 2H), 2.20-2.10 (m, 2H), 2.05-1.65 (m, 10H), 1.60-1.31 (m, 9H), 1.20-0.94 (m, 4H).

Example 58: *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-hydroxyethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1249]

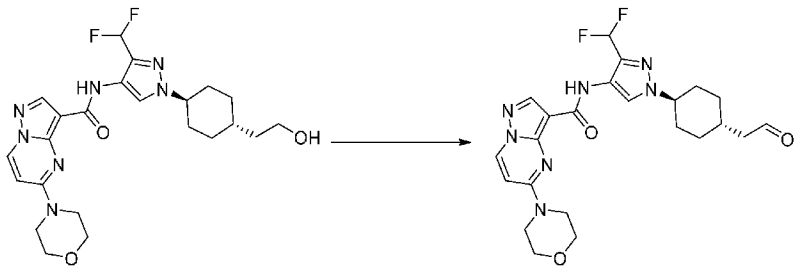


[1250] 2-((1*R*,4*R*)-4-(4-Amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl-1-ol (70 mg, 0.27 mmol) and 5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (74 mg, 0.30 mmol) were dissolved in DMF (10 mL). *N*,*N*-Diisopropylethylamine (104 mg, 0.81 mmol) and Py-BOP (210 mg, 0.40 mmol) were added while stirring, and the reaction liquid was heated to 60 °C and stirred overnight. Water (100 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by p-TLC (methanol:dichloromethane = 1:9) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-hydroxyethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1251] LC-MS: (ESI, m/z): $[M+H]^+$ = 490.2.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-oxoethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1252]



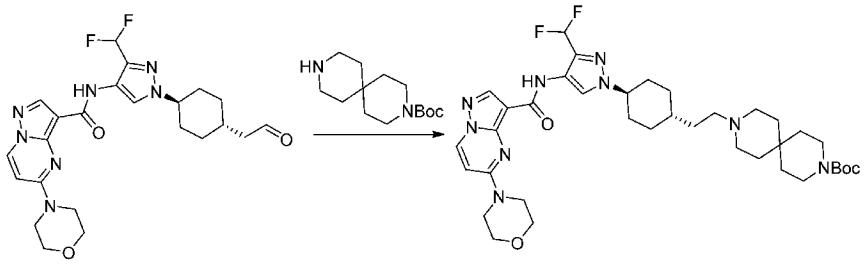
[1253] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(2-hydroxyethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.14 mmol) was dissolved in dichloromethane (5 mL). The Dess-Martin reagent (118 mg, 0.28 mmol) was added, and the mixture was stirred at room temperature for 1 h. Water (20 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was dried over

anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by p-TLC (methanol:dichloromethane = 1:9) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-oxoethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1254] LC-MS: (ESI, m/z): $[M+H]^+$ = 488.1.

Step 3: preparation of *tert*-butyl 9-(2-((1R,4R)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cycloheacyl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[1255]

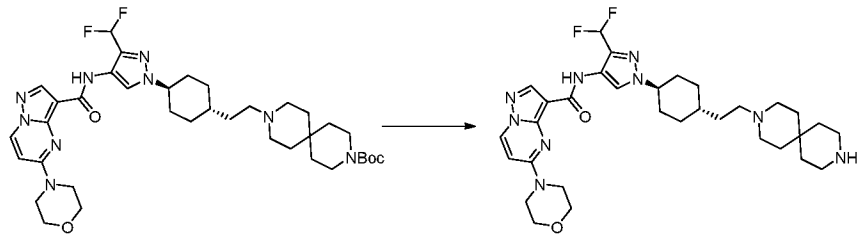


[1256] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(2-oxoethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.10 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (30 mg, 0.12 mmol) were dissolved in tetrahydrofuran (10 mL). Sodium triacetoxyborohydride (64 mg, 0.30 mmol) was added while stirring, and the mixture was stirred at room temperature for 2 h. Water (20 mL) was added to the reaction liquid, and the mixture was extracted with dichloromethane (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by p-TLC (methanol:dichloromethane = 1:9) to give tert-butyl 9-(2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate.

[1257] LC-MS: (ESI, m/z): $[M+H]^+$ = 726.6.

Step 4: preparation of *N*-(1-((1*R*,4*R*)-4-(2-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1258]

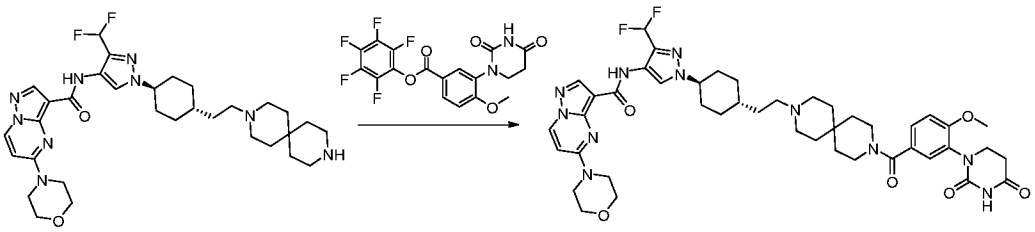


[1259] *tert*-Butyl 9-(2-((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morphofinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (60 mg, 0.08 mmol) was dissolved in dichloromethane (3 mL), and trifluoroacetic acid (1 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(1-((1*R*,4*R*)-4-(2-(3,9-diazaspiro[5.5]undecan-3-yl)ethyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[1260] LC-MS: (ESI, m/z): $[M+H]^+$ = 626.4.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1261]



[1262] *N*-(1-((1*R*,4*R*)-4-(2-(3,9-Diazaspiro[5.5]undecan-3-yl)ethyl)cyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, crude, 0.08 mmol) was dissolved in dimethyl sulfoxide (3 mL), and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (39 mg, 0.09 mmol) and *N*,*N*-diisopropylethylamine (103 mg, 0.8 mmol) were added with stirring. The mixture was stirred at room temperature for 2 h. Water (30 mL) was added to the reaction liquid, and the mixture was filtered. The filter cake was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3, 5%-95%) to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1263] LC-MS: (ESI, m/z): $[M+H]^+$ = 872.3.

[1264] ^1H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.40 (s, 1H), 8.82 (d, *J* = 7.9 Hz, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.25-6.95 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.30-4.20 (m, 1H), 3.84 (s, 3H), 3.82-3.70 (m, 8H), 3.62-3.30 (m, 6H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.36-2.22 (m, 6H), 2.10-1.98 (m, 2H), 1.87-1.73 (m, 2H), 1.70-1.30 (m, 15H).

[1265] Example 59: *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of tert-butyl 9-(benzylamino)-3-azaspiro[5.5]undecane-3-carboxylate

[1266]

[1267] Benzylamine (0.267 g, 2.5 mmol) and tert-butyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (0.66 g, 2.5 mmol) were dissolved in THF (10 mL), and $NaBH(OAc)_3$ (1.58 g, 7.48 mmol) was added. The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:24) to give *tert*-butyl 9-(benzylamino)-3-azaspiro[5.5]undecane-3-carboxylate.

[1268] LC-MS: (ESI, m/z): $[M+H]^+$ = 359.3.

Step 2: preparation of *tert*-butyl 9-amino-3-azaspiro[5.5]undecane-3-carboxylate

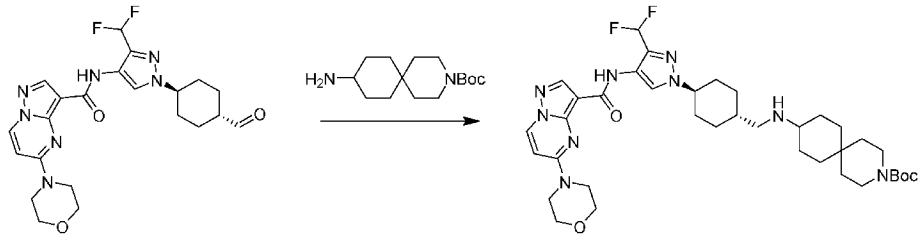
[1269]

[1270] tert-Butyl 9-(benzylamino)-3-azaspiro[5.5]undecane-3-carboxylate (330 mg, 0.92 mmol), Pd/C (100 mg) and $Pd(OH)_2$ (100 mg) were added to methanol (10 mL), and the mixture was purged with hydrogen 3 times and stirred at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give *tert*-butyl 9-amino-3-azaspiro[5.5]undecane-3-carboxylate.

[1271] LC-MS: (ESI, m/z): $[M+H]^+$ = 269.2.

Step 3: preparation of *tert*-butyl 9-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)amino)-3-azaspiro[5.5]undecane-3-carboxylate

[1272]

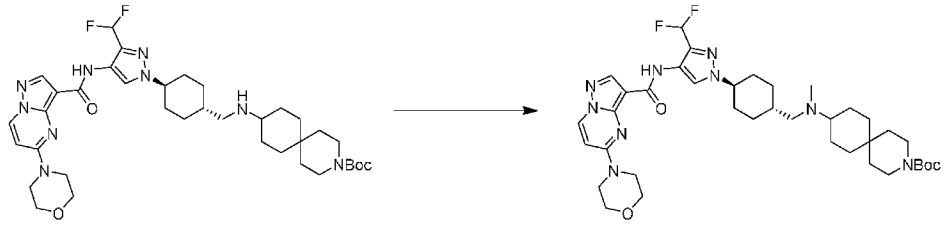


[1273] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-(formyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.21 mmol) and *tert*-butyl 9-amino-3-azaspiro[5.5]undecane-3-carboxylate (70 mg, 0.23 mmol) were dissolved in THF (4 mL), and $NaBH(OAc)_3$ (135 mg, 0.63 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction liquid was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:24) to give *tert*-butyl 9-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)amino)-3-azaspiro[5.5]undecane-3-carboxylate.

[1274] LC-MS: (ESI, m/z): $[M+H]^+$ = 726.5.

Step 4: preparation of *tert*-butyl 9-((((1R,4R)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)-3-azaspiro[5.5]undecane-3-carboxylate

[1275]

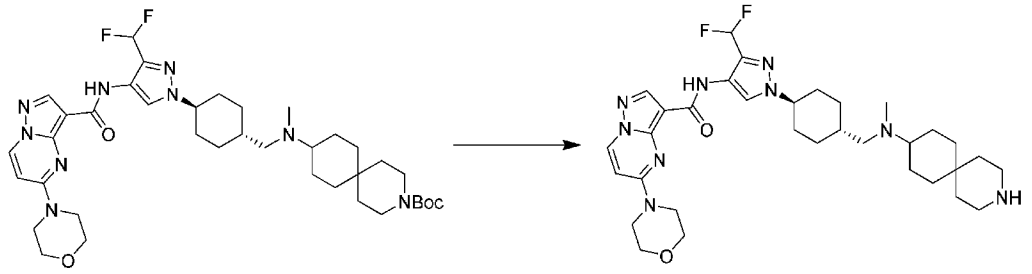


[1276] $NaBH(OAc)_3$ (100 mg, 0.47 mmol) was added to *tert*-butyl 9-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)amino)-3-azaspiro[5.5]undecane-3-carboxylate (100 mg, 0.13 mmol) and aqueous formaldehyde (37%, 1 mL) in THF (10 mL), and the mixture was heated to 60 °C and stirred for 2 h. The reaction liquid was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:19) to give tert-butyl 9-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)-3-azaspiro[5.5]undecane-3-carboxylate.

[1277] LC-MS: (ESI, m/z): $[M+H]^+$ = 740.4.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(3-azaspiro[5.5]undecan-9-yl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1278]

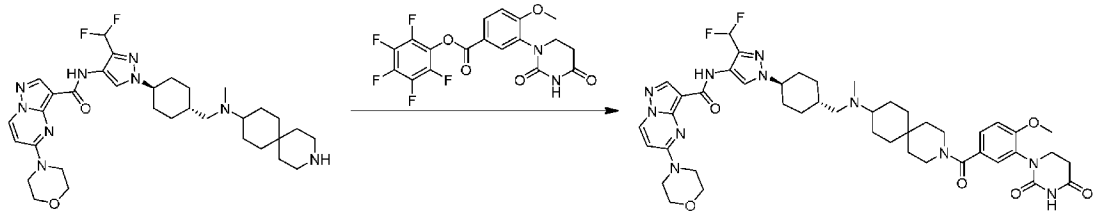


[1279] *tert*-Butyl 9-((((1*R*,4*R*)-4-(3-(difluoromethyl)-4-(5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-1*H*-pyrazol-1-yl)cyclohexyl)methyl)(methyl)amino)-3-azaspiro[5.5]undecane-3-carboxylate (0.10 g, 0.13 mmol) was dissolved in DCM (5 mL), and TFA (1 mL) was added. The mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(3-azaspiro[5.5]undecan-9-yl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[1280] LC-MS: (ESI, m/z): $[M+H]^+$ = 640.4.

Step 6: preparation of *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1281]



[1282] *N*-(3-(Difluoromethyl)-1-((1*R*,4*R*)-4-((methyl(3-azaspiro[5.5]undecan-9-yl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.1 mmol) and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoate (51 mg, 0.12 mmol) were dissolved in DMSO (1 mL), and DIEA (130 mg, 1 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction liquid was diluted with water (10 mL) and filtered, and the filter cake was purified by Prep-HPLC to give *N*-(3-(difluoromethyl)-1-((1*R*,4*R*)-4-(((3-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3-azaspiro[5.5]undecan-9-yl)(methyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

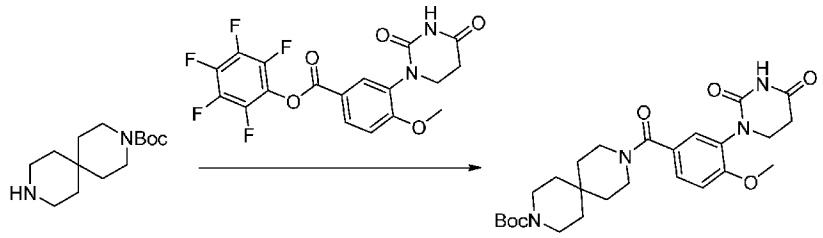
[1283] LC-MS: (ESI, m/z): $[M+H]^+$ = 886.4.

[1284] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.39 (s, 1H), 8.82 (d, *J* = 7.9 Hz, 1H), 8.38 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.32 (s, 1H), 7.22-6.95 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.22-4.12 (m, 1H), 3.84 (s, 3H), 3.81-3.75 (m, 4H), 3.74-3.70 (m, 4H), 3.62- 3.55 (m, 5H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.37-2.26 (m, 2H), 2.25-2.23 (m, 2H), 2.21 (s, 3H), 2.06-2.00 (m, 2H), 1.95-1.85 (m, 2H), 1.78-1.70 (m, 4H), 1.56-1.24 (m, 9H), 1.14-0.97 (m, 4H).

Example 60: *N*-(3-(difluoromethyl)-1-(1-(3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl 9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[1285]

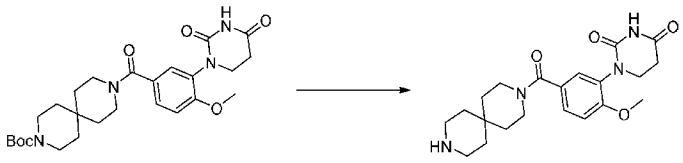


[1286] *tert*-Butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (200 mg, 0.79 mmol) was dissolved in dimethyl sulfoxide (4 mL), and pentafluorophenyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoate (340 mg, 0.79 mmol) and *N*,*N*-diisopropylethylamine (413 mg, 3.24 mmol) were added with stirring. The reaction liquid was stirred at room temperature for 3 h. The reaction liquid was diluted with water (40 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 9:1) to give *tert*-butyl 9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*-yl)-4-methoxybenzoyl)-3,9-diazasprio[5.5]undecane-3-carboxylate.

[1287] LC-MS: (ESI, m/z): $[M+H]^+$ = 501.2.

Step 2: preparation of 1-(2-methoxy-5-(3,9-azaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1288]

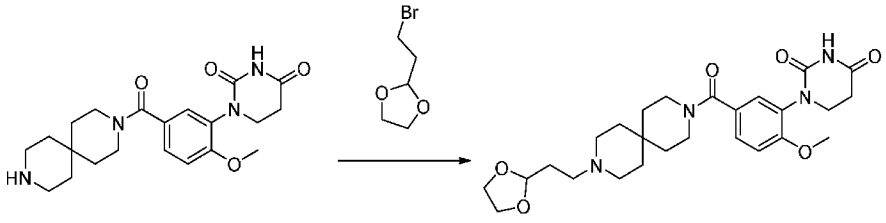


[1289] *tert*-Butyl 9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (230 mg, 0.46 mmol) was dissolved in dichloromethane (3 mL), and trifluoroacetic acid (0.3 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure to give 1-(2-methoxy-5-(3,9-azaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione, which was directly used in the next step without purification.

[1290] LC-MS: (ESI, m/z): $[M+H]^+$ = 401.1.

Step 3: preparation of 1-(5-(9-(2-(1,3-dioxolan-2-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1291]



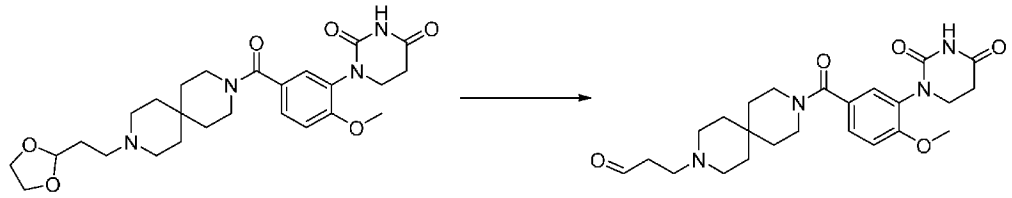
[1292] 1-(2-Methoxy-5-(3,9-azaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (180 mg, 0.45 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (121 mg, 0.67 mmol) were dissolved in DMF (5 mL), and K_2CO_3 (186 mg,1.3 mmol) was added with stirring. The reaction liquid was heated to 80 °C and stirred for 12 h. The reaction liquid was diluted with water (80 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:7) to give 1-(5-(9-(2-(1,3-dioxolan-

2-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1293] LC-MS: (ESI, m/z): $[M+H]^+$ = 501.7.

Step 4: preparation of 3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propanal

[1294]

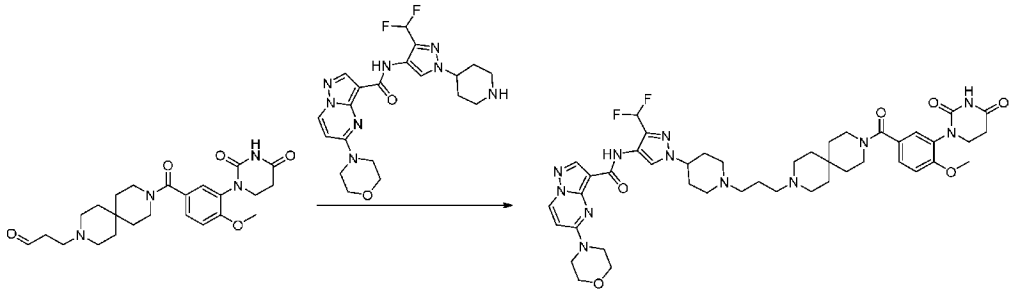


[1295] 1-(5-(9-(2-(1,3-Dioxolan-2-yl)ethyl)-3,9-diazaspiro[5.5]undecane-3-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (200 mg, 0.5 mmol) was dissolved in acetone (5 mL), and hydrochloric acid (2 mol/L, 10 mL) was added. The mixture was stirred at room temperature for 6 h. The reaction liquid was adjusted to pH = 8 with sodium bicarbonate and extracted with ethyl acetate (50 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propanal, which was used in the next step without purification.

[1296] LC-MS: (ESI, m/z): $[M+H]^+$ = 457.7.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-(1-(3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1297]



[1298] 3-(9-(3-(2,4-Dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propanal (70 mg, 0.15 mmol) and *N*-(3-(difluoromethyl)-l-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (67 mg, 0.15 mmol) were dissolved in dichloroethane (5 mL), and sodium triacetoxyborohydride (126 mg, 0.6 mmol) was added with stirring. The reaction liquid was stirred at room temperature for 3 h. The reaction liquid was diluted with water (50 mL) and extracted with dichloromethane (60 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by pre-HPLC (CH_3CN/0.08% aqueous NH_4HCO_3, 5%-95%) to give *N*-(3-(difluoromethyl)-1-(1-(3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

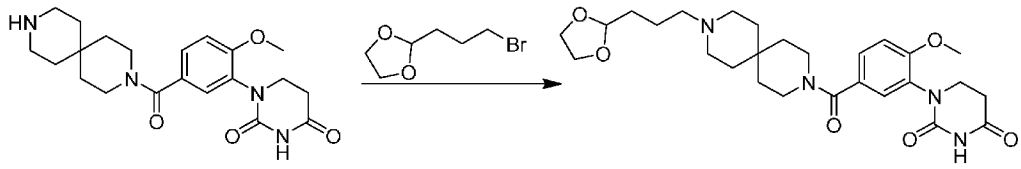
[1299] LC-MS: (ESI, m/z): $[M+H]^+$ = 887.2.

[1300] ^1H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.40 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.26-6.97 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 4.25-4.15 (m, 1H), 3.84 (s, 3H), 3.82-3.70 (m, 8H), 3.62-3.33 (m, 6H), 2.95-2.89 (m, 2H), 2.72-2.62 (m, 2H), 2.36-2.23 (m, 8H), 2.05-1.80 (m, 6H), 1.60-1.24 (m, 10H).

Example 61: *N*-(3-(difluoromethyl)-1-(1-(4-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)butyl)piperidin-4-yl)-177-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of 1-(5-(9-(3-(1,3-dioxolan-2-yl)propyl)-3,9-diazaspiro[5.5]undecane-3-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione

[1301]

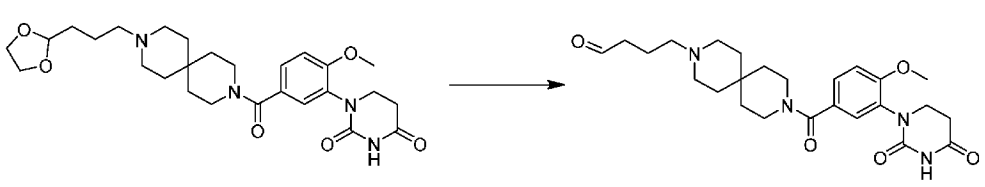


[1302] 1-(2-Methoxy-5-(3,9-azaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (151 mg, 0.377 mmol) and 2-(3-bromopropyl)-1,3-dioxolane (110.5 mg, 0.566 mmol) were added to acetonitrile (5 mL), and K_2CO_3 (518.3 mg,1.132 mmol) was added. The reaction liquid was heated to 80 °C and stirred for 16 h. The reaction liquid was diluted with water (40 mL), extracted with ethyl acetate (30 mL × 4), washed with saturated brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by normal-phase column chromatography (MeOH:DCM = 1:7) to give 1-(5-(9-(3-(1,3-dioxolan-2-yl)propyl)-3,9-diazaspiro[5.5]undecane-3-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione.

[1303] LC-MS: (ESI, m/z): $[M+H]^+$ = 515.3.

Step 2: preparation of 4-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro [5.5]undecan-3-yl)butanal

[1304]

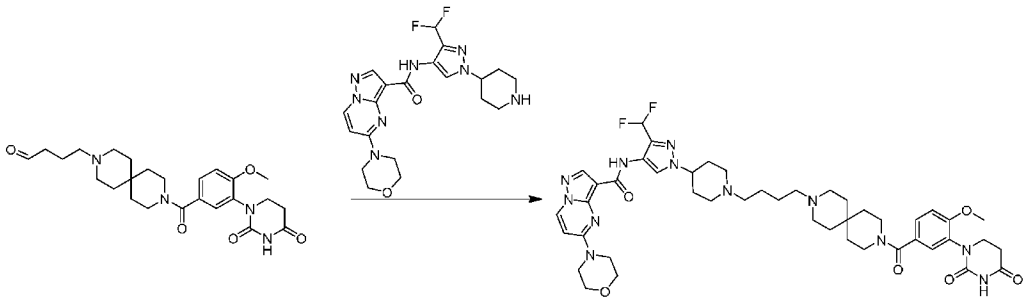


[1305] 1-(5-(9-(3-(1,3-Dioxolan-2-yl)propyl)-3,9-diazaspiro[5.5]undecane-3-carbonyl)-2-methoxyphenyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (80 mg, 0.16 mmol) was dissolved in DCM (2 mL), and TFA (0.5 mL) was added. The mixture was stirred overnight at room temperature. DCE (10 mL) and DIEA (1 mL) were added to the reaction liquid, and the mixture was directly concentrated under reduced pressure at room temperature for 10 min to give 4-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)butanal, which was directly used in the next step.

[1306] LC-MS: (ESI, m/z): $[M+H]^+$ = 471.5.

Step 3: preparation of *N*-(3-(difluoromethyl)-1-(1-(4-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)butyl)piperidin-4-yl)-177-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1307]



[1308] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.15 mmol) was added to 4-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)butanal (crude, in DCE). The mixture was stirred at room temperature for 0.5 h, and STAB (97 mg, 0.46 mmol) was then added. The mixture was stirred at room temperature for 2 h. The reaction liquid was diluted with water (30 mL) and extracted with ethyl acetate (30 mL × 3). The organic phase was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography to give *N*-(3-(difluoromethyl)-1-(1-(4-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)butyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

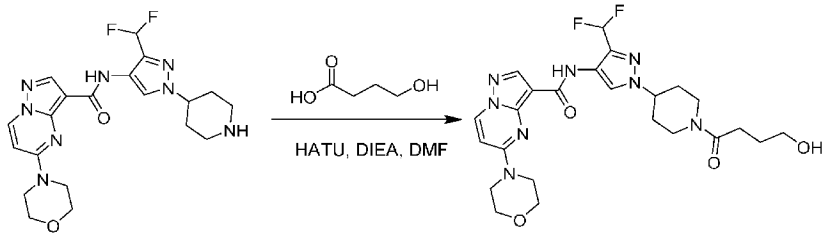
[1309] LC-MS: (ESI, m/z): $[M+H]^+$ = 901.4.

[1310] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.41 (s, 1H), 8.83 (d, *J* = 7.9 Hz, 1H), 8.28 (s, 1H), 8.15 (s, 1H), 7.38 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.33 (d, *J* = 1.9 Hz, 1H), 7.24-6.95 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.33-4.23 (m, 1H), 3.85 (s, 3H), 3.83-3.75 (m, 4H), 3.74-3.68 (m, 4H), 3.64-3.52 (m, 6H), 3.07-2.95 (m, 6H), 2.95-2.86 (m, 2H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.18 (t, *J* = 11.2 Hz, 2H), 2.05-1.93 (m, 4H), 1.73-1.57 (m, 6H), 1.56-1.42 (m, 6H).

Example 62: *N*-(3-(difluoromethyl)-1-(1-(4-(4-(3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoyl)piperazin-1-yl)butanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *N*-(3-(difluoromethyl)-1-(1-(4-hydroxybutanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1311]

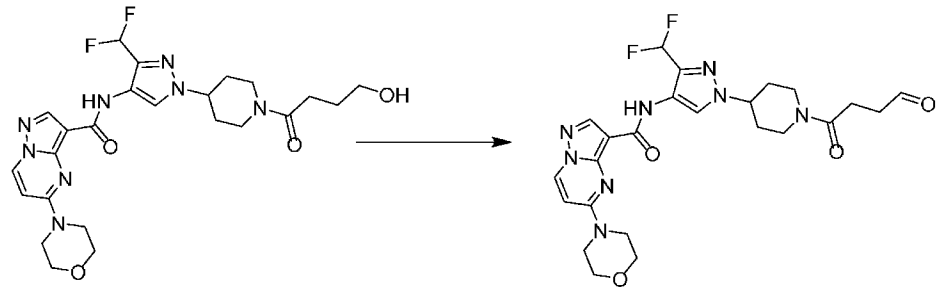


[1312] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (160 mg, 0.35 mmol), 4-hydroxybutyric acid (36 mg, 0.35 mmol) and HATU (130 mg, 0.42 mmol) were dissolved in DMF (5 mL), and DIEA (135 mg, 1.35 mmol) was then added. The reaction liquid was heated to 90 °C and stirred for 16 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal-phase column chromatography to give N-(3-(difluoromethyl)-1-(1-(4-hydroxybutanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1313] LC-MS: (ESI, m/z): $[M+H]^+$ = 533.4.

Step 2: preparation of *N*-(3-(difluoromethyl)-1-(1-(4-oxobutanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1314]

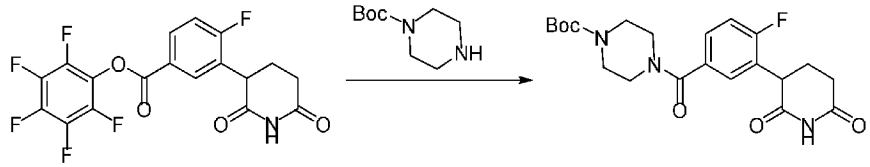


[1315] *N*-(3-(Difluoromethyl)-1-(1-(4-hydroxybutanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (26 mg, 0.05 mmol) was dissolved in DCM (2 mL), and DMP (42 mg, 0.10 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered. The filter cake was washed with THF (10 mL × 3), and the filtrate was concentrated under reduced pressure to give *N*-(3-(difluoromethyl)-1-(1-(4-oxobutanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1316] LC-MS: (ESI, m/z): $[M+H]^+$ = 531.5.

Step 3: preparation of tert-butyl 4-(3-(2,6-oxopiperidin-3-yl)-4-fluorobenzoyl)piperazine-1-carboxylate

[1317]

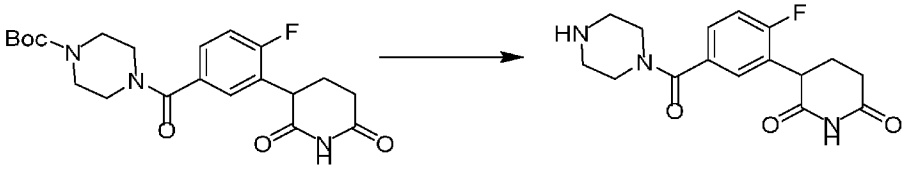


[1318] Pentafluorophenyl 3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoate (56 mg, 0.30 mmol) and tert-butyl piperazine-1-carboxylate (125 mg, 0.30 mmol) were dissolved in DMSO (2 mL), and DIEA (112 mg, 0.90 mmol) was added. The mixture was stirred at room temperature for 2 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (30 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal-phase column chromatography to give tert-butyl 4-(3-(2,6-oxopiperidin-3-yl)-4-fluorobenzoyl)piperazine-1-carboxylate.

[1319] LC-MS: (ESI, m/z): $[M-Boc]^+$ = 320.2.

Step 4: preparation of 3-(2-fluoro-5-(piperazine-1 -carbonyl)phenyl)piperidine-2,6-dione

[1320]

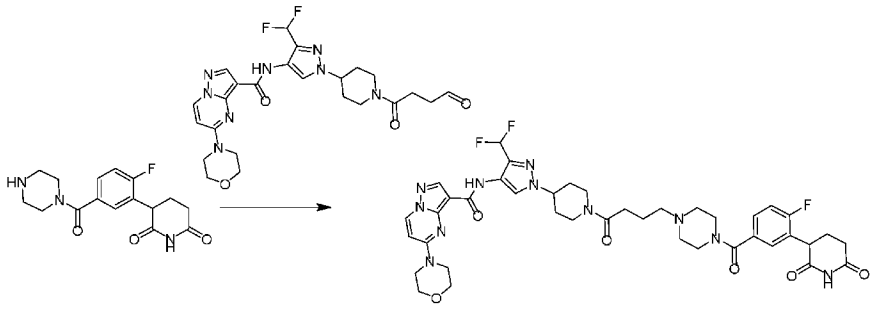


[1321] *tert*-Butyl 4-(3-(2,6-oxopiperidin-3-yl)-4-fluorobenzoyl)piperazine-1-carboxylate (80 mg, 0.19 mmol) was dissolved in DCM (0.5 mL), and TFA (0.1 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction liquid was concentrated under reduced pressure to give 3-(2-fluoro-5-(piperazine-1 -carbonyl)phenyl)piperidine-2,6-dione.

[1322] LC-MS: (ESI, m/z): $[M+H]^+$ = 320.2.

Step 5: preparation of *N*-(3-(difluoromethyl)-1-(1-(4-(4-(3-(2,6-dioxopiperidin-3-yl)-4-fluorobenzoyl)piperazin-1-yl)butanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1323]



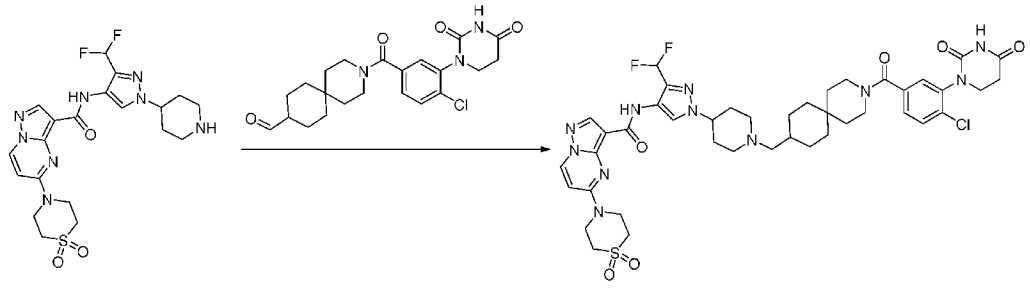
[1324] *N*-(3-(Difluoromethyl)-1-(1-(4-oxobutanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide (55 mg, 0.10 mmol) and 3-(2-fluoro-5-(piperazine-1-carbonyl)phenyl)piperidine-2,6-dione (32 mg, 0.10 mmol) were dissolved in DCE (2 mL), and $NaBH(OAc)_3$ (63 mg, 0.30 mmol) was added. The mixture was stirred at room temperature for 2 h. Water (20 mL) was added to the reaction liquid, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC to give N-(3-(difluoromethyl)-1-(1-(4-(4-(3-(2,6-dioxopiperidin-3-yl)-4-ffuorobenzoyl)piperazin-1-yl)butanoyl)piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1325] LC-MS: (ESI, m/z): $[M+H]^+$ = 834.1.

[1326] ^1H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 9.40 (s, 1H), 8.82 (d, J = 4.3 Hz, 1H), 8.42 (s, 1H), 8.29 (s, 1H), 7.37 (s, 2H), 7.29-6.87 (m, 3H), 4.55-4.49 (m, 2H), 4.14-4.07 (m, 1H), 4.02-3.95 (m, 1H), 3.89-3.65 (m, 10H), 3.20-3.13 (m, 2H), 2.88-2.53 (m, 4H), 2.46-2.16 (m, 9H), 2.10-1.95 (m, 3H), 1.90-1.83 (m, 1H), 1.83-1.56 (m, 3H).

Example 63: *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H* pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1327]



[1328] *N*-(3-(Difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.16 mmol) and 3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecane-9-carbaldehyde (70 mg, 0.16 mmol) were dissolved in THF (3 mL), and sodium triacetoxyborohydride (102 mg, 0.48 mmol) was added. The mixture was stirred at room temperature for 16 h. Water (50 mL) was added to the reaction liquid, and the mixture was extracted with EA (30 mL × 3). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was isolated and purified by Prep-HPLC to give *N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-(1,1-dioxothiomorpholinyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1329] LC-MS: (ESI, m/z): $[M+H]^+$ = 910.4.

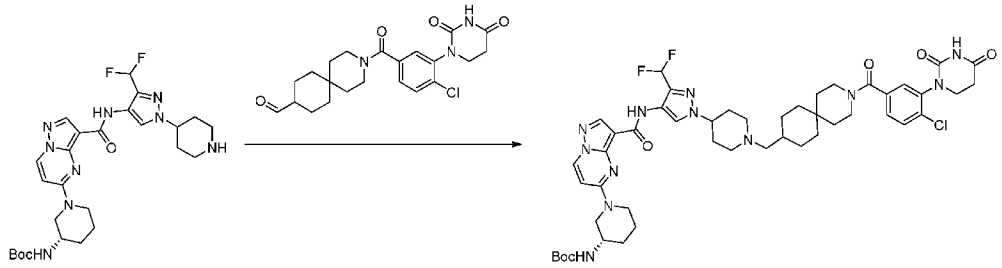
[1330] ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.25 (s, 1H), 8.92 (d, *J* = 7.9 Hz, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.25-6.97 (m, 2H), 4.31-4.20 (m, 5H), 3.77-3.70

(m, 1H), 3.67-3.57 (m, 3H), 3.33-3.23 (m, 5H), 2.90 (d, *J*= 9.3 Hz, 2H), 2.75-2.67 (m, 3H), 2.18-2.11 (m, 2H), 2.07-1.87 (m, 6H), 1.73-1.65 (m, 2H), 1.62-1.23 (m, 7H), 1.15-0.92 (m, 4H).

Example 64: (*S*)-5-(3-aminopiperidin-1-yl)-*N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of *tert*-butyl (*S*)-(1-(3-((1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate

[1331]

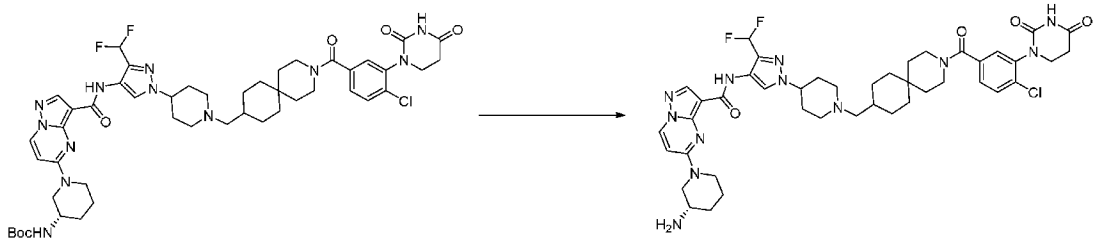


[1332] *tert*-Butyl (*S*)-(1-(3-((3-(difluoromethyl)-1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carbamate (70 mg, 0.12 mmol) and 3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5,5]undecane-9-carbaldehyde (70 mg, 0.15 mmol) were dissolved in THF (2 mL), and $NaBH(OAc)_3$ (56 mg, 0.37 mmol) was added. The reaction liquid was stirred for 2 h. The reaction liquid was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (methanol:dichloromethane = 1:24) to give tert-butyl (*S*)-(1-(3-((1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate.

[1333] LC-MS: (ESI, m/z): $[M+H]^+$ = 975.4.

Step 2: preparation of (*S*)-5-(3-aminopiperidin-1-yl)-*N*-(1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1334]



[1335] *tert*-Butyl (*S*)-(1-(3-((1-(1-((3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)piperidin-3-yl)carboxylate (30 mg, 0.03 mmol) was dissolved in DCM (5 mL), and TFA (1 mL) was added. The reaction liquid was stirred at room temperature for 1 h. The reaction liquid was directly concentrated under reduced pressure, and the crude product was purified by Prep-HPLC to give (*S*)-5-(3-aminopiperidin-1-yl)-*N*-(1-(1-((3 -(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)piperidin-4-yl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide.

[1336] LC-MS: (ESI, m/z): $[M+H]^+$ = 875.3.

[1337] ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 7.9 Hz, 1H), 8.37 (s, 1H), 8.34-8.30 (m, 2H), 7.65 (d, *J* = 8.2 Hz,

1H), 7.53 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.26-6.95 (m, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 4.23-4.13 (m, 2H), 3.82-3.74 (m, 1H), 3.70-3.40 (m, 7H), 3.30-3.10 (m, 3H), 2.97-2.92 (m, 2H), 2.77-2.73 (m, 2H), 2.25-1.75 (m, 11H), 1.75- 1.15 (m, 12H), 1.15-0.96 (m, 4H).

Example 65: 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*S*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

Step 1: preparation of 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate

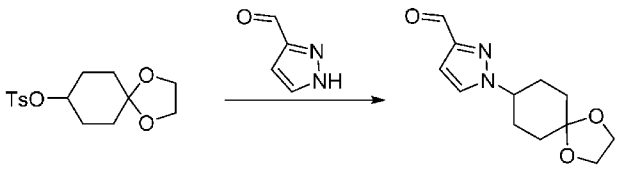
[1338]

[1339] 1,4-Dioxaspiro[4.5]decan-8-ol (25.7 g, 163 mmol) was dissolved in dichloromethane (100 mL), and TsCl (46.6 g, 244 mmol), TEA (49.3 g, 488 mmol) and DMAP (4.0 g, 33.0 mmol) were added with stirring. The reaction liquid was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and water (200 mL) was added. The mixture was extracted with ethyl acetate (100 mL × 3). The organic phase was washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 3:7) to give 1,4-dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate.

[1340] LC-MS: (ESI, m/z): $[M+Na]^+$ = 335.1.

Step 2: preparation of 1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole-3-carbaldehyde

[1341]



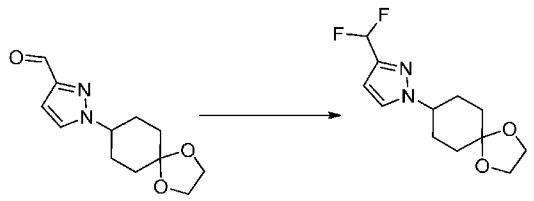
[1342] 1,4-Dioxaspiro[4.5]decan-8-yl 4-methylbenzenesulfonate (48.5 g, 156.25 mmol) and 1*H*-pyrazole-3-carbaldehyde (12.5 g, 130.21 mmol) were dissolved in DMF (200 mL), and cesium carbonate (127.0 g, 390.63 mmol) and KI (25.9 g, 156.25 mmol) were added with stirring. The reaction liquid was heated to 50 °C and stirred overnight. The reaction liquid was diluted with water (2000 mL) and extracted with ethyl acetate (200 mL × 4). The organic phase was washed with saturated brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:4) to give 1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole-3-carbaldehyde.

[1343] LC-MS: (ESI, m/z): $[M+H]^+$ = 237.2.

[1344] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 7.99 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.49-4.39 (m, 1H), 3.96-3.86 (m, 4H), 2.08-1.99 (m, 4H), 1.84-1.75 (m, 2H), 1.75-1.64 (m, 2H).

Step 3: preparation of 3-(difluoromethyl)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole

[1345]

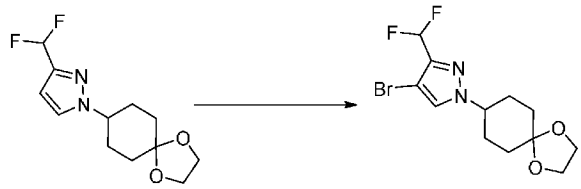


[1346] 1-(1,4-Oxaspiro[4.5]decan-8-yl)-1*H*-pyrazole-3-carbaldehyde (13.3 g, 56.36 mmol) was dissolved in anhydrous dichloromethane (50 mL), and DAST (54.4 g, 338.14 mmol) was added slowly at 0 °C. The reaction liquid was stirred overnight at room temperature. The reaction liquid was quenched by slow addition of methanol and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 3:7) to give 3-(difluoromethyl)-1 -(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole.

[1347] LC-MS: (ESI, m/z): $[M+H]^+$ = 259.1.

Step 4: preparation of 4-bromo-3-(difluoromethyl)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole

[1348]



[1349] 3-(Difluoromethyl)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole (8.6 g, 33.33 mmol) was dissolved in DMF (50 mL), and NBS (7.12 g, 40.00 mmol) was added with stirring. The reaction liquid was heated to 60 °C and stirred for 2 h. The reaction liquid was diluted with water (500 mL) and extracted with ethyl acetate (100 mL × 4). The organic phase was washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 3:7) to give 4-bromo-3-(difluoromethyl)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole.

[1350] LC-MS: (ESI, m/z): $[M+H]^+$ = 337.0.

Step 5: preparation of 4-(4-bromo-3-(difluoromethyl)-1*H*-pyrazol-1 -yl)cyclohexan-1 -one

[1351]

[1352] 4-Bromo-3-(difluoromethyl)-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1*H*-pyrazole (10.4 g, 30.95 mmol) was dissolved in acetone (40 mL), and HCl (2 mol/L, 60 mL) was added with stirring. The reaction liquid was stirred at 0 °C for 1 h. The reaction liquid was made weakly basic with saturated sodium bicarbonate solution and extracted with ethyl acetate (100 mL × 4). The organic phase was washed with saturated brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:4) to give 4-(4-bromo-3-(difluoromethyl)-1*H*-pyrpyrazol-1-yl)cyclohexan-1-one.

[1353] LC-MS: (ESI, m/z): $[M+H]^+$ = 293.0.

Step 6: preparation of 4-bromo-3-(difluoromethyl)-1-(1-oxaspiro[2.5]octan-6-yl)-1*H*-pyrazole

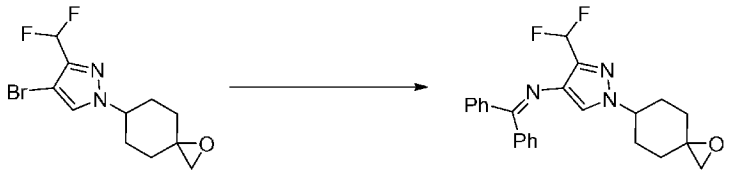
[1354]

[1355] Trimethylsulfoxonium iodide (1.36 g, 6.16 mmol) was dissolved in dimethyl sulfoxide (20 mL), and NaH (246 mg, 10.27 mmol) was added at 0 °C. After the reaction liquid was stirred at room temperature for 1 h, 4-(4-bromo-3-(difluoromethyl)-1*H*-pyrazol-1-yl)cyclohexan-1-one (1.2 g, 5.14 mmol) was added, and the mixture was then stirred overnight at room temperature. The reaction liquid was diluted with water (100 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:4) to give 4-bromo-3-(difluoromethyl)-1-(1-oxaspiro[2.5]octan-6-yl)-1*H*-pyrazole.

[1356] LC-MS: (ESI, m/z): $[M+H]^+$ = 307.0.

Step 7: preparation of *N*-(3-(difluoromethyl)-1-(1-oxaspiro[2.5]octan-6-yl)-1*H*-pyrazol-4-yl)-1,1-diphenylmethanimine

[1357]

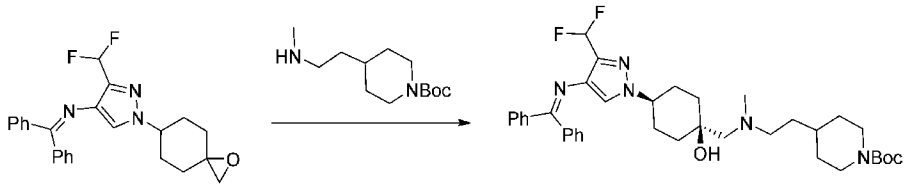


[1358] 4-Bromo-3-(difluoromethyl)-1-(1-oxaspiro[2.5]octan-6-yl)-1*H*-pyrazole (800 mg, 3.104 mmol) and $(Ph)_2NH$ (618 mg, 3.415 mmol) were dissolved in 1,4-dioxane (40 mL), and $Pd_2(dba)_3$ (568 mg, 0.62 mmol), Xantphos (717 mg, 1.24 mmol) and NaOt-Bu (894 mg, 9.31 mmol) were added with stirring. The reaction liquid was heated to 90 °C and stirred overnight under nitrogen atmosphere. The reaction liquid was directly concentrated under reduced pressure, diluted with water (100 mL), and extracted with ethyl acetate (50 mL × 3). The organic phase was washed with saturated brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate:petroleum ether = 1:3) to give *N*-(3-(difluoromethyl)-1-(1-oxaspiro[2.5]octan-6-yl)-1*H*-pyrazol-4-yl)-1,1-diphenylmethanimine.

[1359] LC-MS: (ESI, m/z): $[M+H]^+$ = 408.1.

Step 8: preparation of *tert*-butyl 4-(2-((((1*S*,4*S*)-4-(3-(difluoromethyl)-4-((diphenylmethylene)amino)-1*H*-pyrazol-1-yl)-1-hydroxycyclohexyl)methyl)(methyl)amino-1-carboxylate

[1360]



[1361] *N*-(3-(Difluoromethyl)-1-(1-oxaspiro[2.5]octan-6-yl)-1*H*pyrazol-4-yl)-1,1-diphenylmethanimine (180 mg, 0.44 mmol) and *tert*-butyl 4-(2-(methylamino)ethyl)piperidine-1-carboxylate (128 mg, 0.53 mmol) were dissolved in ethanol (4 mL). Water (2 mL) was then added, and K_2CO_3 (122 mg, 0.88 mmol) was added. After the reaction liquid was microwaved at 110 °C for half an hour, water (10 mL) was added, and the mixture was extracted with a methanol/dichloromethane solution (V/V = 1/9, 25 mL × 4). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane:methanol = 1:9) to give tert-butyl 4-(2-((((1*S*,4*S*)-4-(3-(difluoromethyl)-4-((diphenylmethylene)amino)-1*H*-pyrazol-1 -yl)-1-hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate.

[1362] LC-MS: (ESI, m/z): $[M+H]^+$ = 650.5.

Step 9: preparation of *tert*-butyl 4-(2-((((1*S*,4*S*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

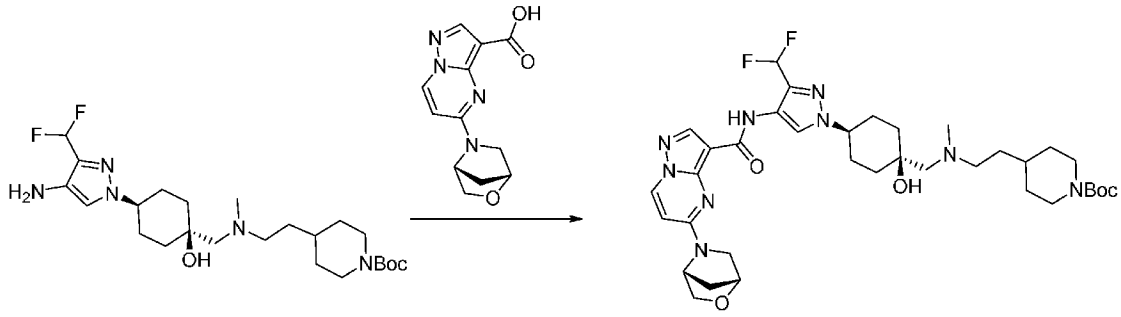
[1363]

[1364] *tert*-Butyl 4-(2-((((1*S*,4*S*)-4-(3-(difluoromethyl)-4-((diphenylmethylene)amino)-1*H*-pyrazol-1-yl)-1-hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (150 mg, 0.23 mmol) was dissolved in tetrahydrofuran (2 mL), and HCl (2 mol/L, 1 mL) was added. The reaction liquid was stirred at room temperature for 30 min. The reaction liquid was diluted with water (10 mL) and extracted with ethyl acetate (25 mL x 2). The aqueous phase was made weakly basic with saturated sodium bicarbonate solution and extracted with a mixed solution of methanol and dichloromethane (V/V = 1/9, 25 mL x 3). The organic phase was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give *tert*-butyl 4-(2-((((1*S*,4*S*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1 -yl)-1 -hydroxy cyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1 -carboxylate.

[1365] LC-MS: (ESI, m/z): $[M+H]^+$=486.2.

Step 10: preparation of *tert*-butyl 4-(2-((((1*S*,4*S*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)-1 -hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate

[1366]

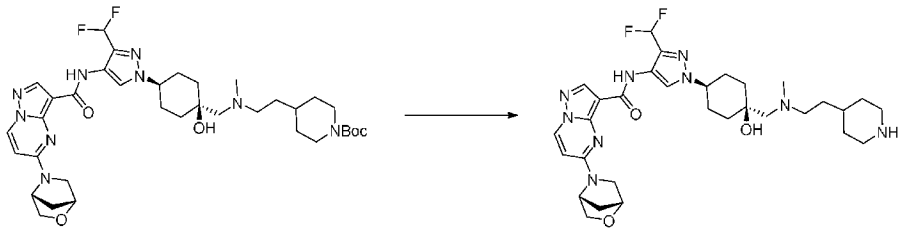


[1367] *tert-Butyl* 4-(2-((((1*S*,4*S*)-4-(4-amino-3-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (85 mg, 0.17 mmol) and 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (91 mg, 0.34 mmol) were dissolved in DMF (5 mL), and *N*,*N*-diisopropylethylamine (68 mg, 0.51 mmol) and HATU (158 mg, 0.26 mmol) were added with stirring. The reaction liquid was stirred overnight at room temperature. The reaction liquid was diluted with water (50 mL) and extracted with a mixed solution of methanol and dichloromethane (V/V = 1/9, 25 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane: methanol = 1:9) to give *tert*-butyl 4-(2-((((1*S*,4*S*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)-1 -hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1 -carboxylate.

[1368] LC-MS: (ESI, m/z): $[M+H]^+$=728.3.

Step 11: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*S*,4*S*)-4-hydroxy-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1369]

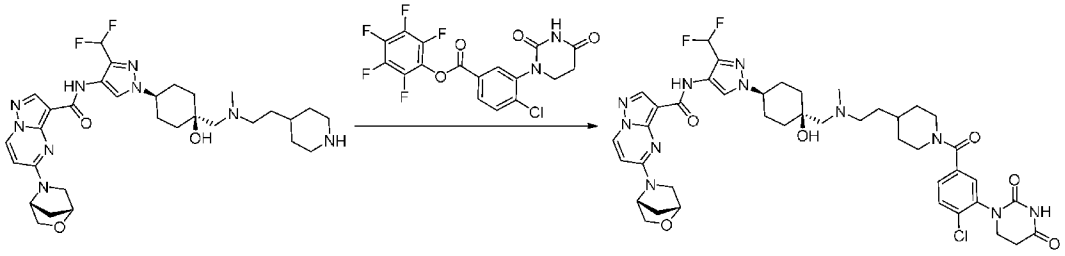


[1370] *tert-Butyl* 4-(2-((((1*S*,4*S*)-4-(4-(5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-3-(difluoromethyl)-1*H*-pyrazol-1-yl)-1-hydroxycyclohexyl)methyl)(methyl)amino)ethyl)piperidine-1-carboxylate (120 mg, 0.16 mmol) was dissolved in dichloromethane (2.5 mL), and trifluoroacetic acid (0.5 mL) was added. The mixture was stirred at room temperature for 2 h. The reaction liquid was directly concentrated under reduced pressure to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*S*,4*S*)-4-hydroxy-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide, which was directly used in the next step without purification.

[1371] LC-MS: (ESI, m/z): $[M+H]^+$=628.3.

Step 12: preparation of 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*S*,4*S*)-4-(((2-(1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-3-(difluoromethyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

[1372]



[1373] 5-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(3-(difluoromethyl)-1-((1*S*,4*S*)-4-hydroxy-4-((methyl(2-(piperidin-4-yl)ethyl)amino)methyl)cyclohexyl)-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.19 mmol) was dissolved in dimethyl sulfoxide (3 mL), and pentafluorophenyl 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoate (100 mg, 0.23 mmol) and *N,N*-diisopropylethylamine (148 mg, 1.14 mmol) were added with stirring. The reaction liquid was stirred at room temperature for 2 h. The reaction liquid was diluted with water (5 mL) and filtered, and the solid was purified by p-TLC (dichloromethane:methanol = 10:1) to give 5-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-*N*-(1-((1*S*,4*S*)-4-(((2-(1-(4-chloro-3 -(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)benzoyl)piperidin-4-yl)ethyl)(methyl)amino)methyl)-4-hydroxycyclohexyl)-3 -(difluoromethyl)- 1*H*-pyrazol-4-yl)pyrazolo [1,5-*a*]pyrimidine-3-carboxamide.

[1374] LC-MS: (ESI, m/z): $[M+H]^+$=878.2.

[1375] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.51 (s, 1H), 8.78 (d, *J*= 7.7 Hz, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 7.63 (d, *J*= 8.3 Hz, 1H), 7.55 (s, 1H), 7.38 (d, *J*= 7.9 Hz, 1H), 7.26-6.96 (m, 1H), 6.90-6.42 (m, 1H), 5.33-5.05 (m, 1H), 4.77 (d, *J*= 17.1 Hz, 1H), 4.50-4.39 (m, 1H), 4.20-3.97 (m, 2H), 3.87-3.70 (m, 3H), 3.64-3.40 (m, 4H), 3.12-2.92 (m, 1H), 2.82-2.67 (m, 3H), 2.46-2.38 (m, 2H), 2.32-2.21 (m, 5H), 2.12- 1.92 (m, 4H), 1.86-1.55 (m, 7H), 1.52-1.32 (m, 4H), 1.18-1.04 (m, 2H).

II. Biological Activity Test Examples

Test Example 1: IRAK4 Kinase Activity Test

[1376] The KinEASE-STK S1 serine/threonine kinase kit (Cisbio) was used to test the inhibitory effect of the compounds on the IRAK4 kinase activity, and the method is specifically as follows: A compound was dissolved in dimethyl sulfoxide, and the solution was diluted in the buffer of the kit with an equal gradient, such that the final concentration range of the test compound in the reaction systems was 10,000 nM-0.038nM. Then 2.5 nM IRAK4 kinase (Carna), 1 μM biotinylated polypeptide substrate (Cisbio) and 7 μM adenosine triphosphate (Sigma-Aldrich) were sequentially added, and the mixtures were incubated at 37 °C for 120 min. Subsequently, an anti-phosphoserine/threonine antibody (Cisbio) conjugated with a europium element compound and conjugated modified XL665 streptavidin (Cisbio) were added to the reaction systems to stop the reactions. After 1 h of incubation at room temperature, the fluorescence intensity of each well was measured at the excitation wavelength of 337 nm and the emission wavelengths of 620 nm and 665 nm with a microplate reader EnVision (PerkinElmer) in the HTRF mode, and Ratio values were calculated using the formula Ratio = (665 nm/620 nm) × 10^4. The inhibition rate of the compound at each concentration was calculated by comparing the fluorescence intensity ratio with that of the control group. Then a non-linear curve fitting of logarithmic concentration-inhibition rate was performed using GraphPad Prism 7, and the IC_{50} value of the compound was obtained.

Table 1:

Example	IC_{50} (nM)
Example 1	30.3
Example 2	15.5
Example 3	67.2
Example 4	37.0
Example 5	359.7
Example 6	524.4
Example 7	313.4
Example 8	10.6
Example 9	131
Example 10	12.92
Example 11	18.5
Example 12	270.4
Example 13	19.3
Example 14	124.3
Example 15	14.2
Example 16	8.8
Example 17	15.1
Example 18	66.9
Example 19	3.8
Example 20	89.2
Example 21	9.9
Example 22	9.29
Example 23	22.96
Example 24	6.08
Example 25	14.13

(continued)

Example	IC_{50} (nM)
Example 26	14.30
Example 27	13.50
Example 28	12.87
Example 29	17.04
Example 30	4.64
Example 31	8.05
Example 32	7.74
Example 33	23.90
Example 34	11.03
Example 35	3.36
Example 36	3.86
Example 37	13.08
Example 38	19.97
Example 39	17.04
Example 40	34.50
Example 41	25.52
Example 42	18.64
Example 43	45.01
Example 44	13.45
Example 45	2.98
Example 46	277.70
Example 47	7.86
Example 48	36.07
Example 49	7.05
Example 50	36.74
Example 51	27.10
Example 52	23.83
Example 54	9.82
Example 55	21.31
Example 56	3.87
Example 57	4.57
Example 59	8.71
Example 60	21.94
Example 61	9.06
Example 62	28.86
Example 63	36.24
Example 64	5.93

(continued)

Example	IC_{50} (nM)
Example 65	52.15
"-" represents not detected.	

[1377] Experimental results: The compounds of the present invention can bind efficiently to the target protein and inhibit the IRAK4 kinase activity.

Test Example 2: Degradation of IRAK4 in THP-1 Cells by Compounds

[1378] THP-1 cells (Stem Cell Bank, Chinese Academy of Sciences) were inoculated onto a 24-well cell culture plate at 0.95 mL/well, with a cell density of 5×10^5 cells/well. The cell plate was incubated overnight in a 37 °C, 5% carbon dioxide incubator, and 50 μL of a solution of a compound in dimethyl sulfoxide was added, such that the final concentration of the compound fell within the range of 0.03-3000 nM. After another 24 h of incubation, cells were collected into 1.5 mL centrifuge tubes and centrifuged at 1000 rpm at 4 °C for 5 min. The cell pellets were washed twice with 1× DPBS. The resuspended cells were lysed with 200 μL of lysis buffer (Western and IP cell lysis buffer (Beyotime), supplemented with 1 mM phenylmethylsulfonyl fluoride and protease inhibitor cocktail (Beyotime)), left to stand on ice for 30 min, and then centrifuged at 14,000 g at 4 °C for 10 min. The supernatant samples were assayed by Western Blot for IRAK4 protein levels.

Human IRAK4 AlphaLISA Assay

[1379] The above cell lysates were also tested for IRAK4 degradation using a human IRAK4 AlphaLISA assay kit (PerkinElmer, AL3117C). The method is specifically as follows: 2-μL test samples of cell lysate supernatant were transferred to a white 384-well plate (PerkinElmer, 6007299), and 4 μL of 5x anti-IRAK4 receptor beads (PerkinElmer, final concentration of 10 μg/mL) was then added. The plate was incubated at 23 °C for 30 min. Then 4 μL of 5x biotin-labeled anti-IRAK4 antibody (PerkinElmer, final concentration of 1 nM) was added, and the plate was incubated at 23 °C for 60 min. Finally, 10 μL of 2x streptavidin-labeled donor beads (final concentration of 40 μg/mL) was added to each well, and the plate was incubated in the dark at 23 °C for 30 min. After the incubation was complete, AlphaLISA signal values were measured on a microplate reader EnVision (PerkinElmer, 2105) in the AlphaScreen standard mode, and IRAK4 concentrations were calculated from these signal values. Then a non-linear curve fitting of logarithmic concentration-inhibition rate was performed using GraphPad Prism 7, and the DC_{50} and D_{max} values of the compound were obtained.

Table 2:

Example	DC_{50} (nM)	D_{max} (%)
Example 1	3.7	90.0
Example 2	1.8	95.8
Example 3	-	-
Example 4	-	-
Example 5	-	-
Example 6	-	-
Example 7	148.5	76.4
Example 8	8.8	86.8
Example 9	128.6	81.0
Example 10	2.8	99.3
Example 11	12.7	90.7
Example 12	-	-
Example 13	5.5	84.4

(continued)

Example	DC_{50} (nM)	D_{max} (%)
Example 14	-	-
Example 15	2.5	92.1
Example 16	6.4	87.9
Example 17	10.37	99.4
Example 18	54.3	62.5
Example 19	5.1	97.7
Example 20	78.6	86.96
Example 21	9.6	95.5
Example 22	3.42	96.53
Example 23	10.10	93.65
Example 24	6.16	96.32
Example 25	62.13	97.82
Example 28	3.18	89.42
Example 29	2.75	98.48
Example 30	5.23	90.09
Example 31	6.10	91.10
Example 32	3.46	90.53
Example 34	3.55	87.11
Example 35	0.78	100
Example 36	3.45	96.02
Example 37	41.96	81.07
Example 39	10.86	93.89
Example 40	32.75	79.18
Example 42	3.66	91.70
Example 43	15.08	79.51
Example 44	6.30	80.45
Example 45	0.82	96.16
Example 47	4.84	99.01
Example 48	5.55	94.41
Example 49	3.22	97.07
Example 50	5.94	82.09
Example 52	18.45	95.43
Example 54	8.13	88.18
Example 55	7.52	79.18
Example 56	0.41	96.44
Example 57	0.58	96.57
Example 59	7.92	70.81
Example 60	9.36	96.59

(continued)

Example	DC_{50} (nM)	D_{max} (%)
Example 61	28.96	87.91
Example 63	9.18	79.3
Example 64	7.47	96.06
Example 65	14.26	87.24
"-" represents not detected.		

[1380] Experimental results: The compounds of the present invention can effectively degrade the IRAK4 kinase protein in cells, and have excellent degradation activity.

[1381] Test Example 3: Determination of Concentration of Cytokines Secreted by LPS-Induced Normal Human Whole Blood PBMCs

(1) Determination of concentration of cytokines secreted by LPS-induced normal human whole blood PBMCs

[1382] Fresh normal human whole blood (healthy people from 22-50 years of age, freshly collected blood) anticoagulated with heparin sodium was plated onto a 96-well clear cell plate (Labserv, 310109008) at 190 μL/well, and 10 μL of diluted compound solution was then added to corresponding wells, such that the final concentration of the compound fell within the range of 10-20,000 nM. The final concentration of dimethyl sulfoxide was 0.1%. The compound-treated cell plate was sealed with a plate-sealing membrane. After the plate was incubated in a 37 °C, 5% carbon dioxide incubator for 20 h, 10 μL of LPS (0111:B4) (Sigma, L4391) was added, making a final concentration of 100 ng/mL. The cell plate was sealed with a plate-sealing membrane. After the plate was incubated in a 37 °C, 5% carbon dioxide incubator for another 5 h, the plate was centrifuged at 2000 rpm for 10 min, and 30 μL of supernatant plasma was transferred from each well to a new 96-well clear cell plate for cytokine concentration testing and stored at -80 °C before testing.

Interleukin-6 (IL-6) AlphaLISA assay

[1383] Supernatant plasma samples of LPS-induced human whole blood (healthy people from 22-50 years of age, freshly collected blood) were assayed for IL-6 concentrations using an interleukin-6 (IL-6) AlphaLISA assay kit (PerkinElmer, AL223 C).

[1384] IL-6 standard solutions with different concentrations, ranging from 0 to 100,000 pg/mL, were prepared by following the instructions for use of the product. 2 μL of each of the IL-6 standard solutions and test samples of cell supernatant were added to a white 384-well plate (PerkinElmer, 6007299), and 8 μL of a mixed solution of 5x anti-IL-6 receptor beads (PerminElmer, final concentration of 10 μg/mL) and biotin-labeled anti-IL-6 antibody (PerminElmer, final concentration of 1 nM) was then added to each well. The plate was incubated at 23 °C for 60 min. Finally, 10 μL of 2x streptavidin-labeled donor beads (final concentration of 40 μg/mL) was added to each well, and the plate was incubated in the dark at 23 °C for another 30 min. After the incubation was complete, AlphaLISA signal values were measured on a microplate reader EnVision (PerkinElmer, 2105) in the AlphaScreen standard mode. A standard curve was plotted from the AlphaLISA signal values of the IL-6 standard solutions, and the IL-6 concentration in each cell lysate supernatant was determined from the standard curve according to the AlphaLISA signal value of the test sample. The inhibition rate of the compound at each concentration was calculated by comparing the IL-6 concentration with that of the control group. Then a non-linear curve fitting of logarithmic concentration-inhibition rate was performed using GraphPad Prism 7, and the IC_{50} value of the compound was calculated.

(2) Determination of concentration of cytokines secreted by LPS-induced human PBMCs

[1385] Frozen human PBMCs (Milestone, PB010C) were thawed and resuspended in RPMI 1640 medium (Gibco, A1049101) supplemented with 10% fetal bovine serum (Gibco, 10099141), 100 U/mL penicillin and 100 μg/mL streptomycin (Gibco, 15140122). On the same day, PBMCs were plated onto a 96-well clear cell plate (Labserv, 310109008) at 150 μL/well, with a cell density of 2 x 105 cells/well. Then 50 μL of diluted compound solution was added to corresponding wells with cells, such that the final concentration of the compound fell within the range of 0.026-10,000 nM. The final concentration of DMSO was 0.25%. After the compound-treated cell plate was incubated in a 37 °C, 5% CO2 incubator for 1 h or 20 h, 10 μL of LPS (0111:B4) (Sigma, L4391) was added, making a final concentration of 100 ng/mL.

After the cell plate was incubated in a 37 °C, 5% CO2 incubator for another 5 h, the plate was centrifuged at 2000 rpm for 10 min, and 100 μL of cell supernatant was transferred from each well to a new 96-well clear cell plate for cytokine concentration testing and stored at -80 °C before testing.

Interleukin-6 (IL-6) AlphaLISA assay

[1386] The LPS-induced human PBMC cell supernatants were assayed for IL-6 concentrations using an interleukin-6 (IL-6) AlphaLISA assay kit (PerkinElmer, AL223 C).

[1387] IL-6 standard solutions with different concentrations, ranging from 0 to 100,000 pg/mL, were prepared by following the instructions for use of the product. 2 μL of each of the IL-6 standard solutions and test samples of cell supernatant were added to a white 384-well plate (PerkinElmer, 6007299), and 8 μL of a mixed solution of 5x anti-IL-6 receptor beads (final concentration of 10 μg/mL) and biotin-labeled anti-IL-6 antibody (final concentration of 1 nM) was then added to each well. The plate was incubated at 23 °C for 60 min. Finally, 10 μL of 2x streptavidin-labeled donor beads (final concentration of 40 μg/mL) was added to each well, and the plate was incubated in the dark at 23 °C for another 30 min. After the incubation was complete, AlphaLISA signal values were measured on a microplate reader EnVision (PerkinElmer, 2105) in the AlphaScreen standard mode. A standard curve was plotted from the AlphaLISA signal values of the IL-6 standard solutions, and the IL-6 concentration in each cell lysate supernatant was determined from the standard curve according to the AlphaLISA signal value of the test sample. The inhibition rate of the compound at each concentration was calculated by comparing the IL-6 concentration with that of the control group. Then a non-linear curve fitting of logarithmic concentration-inhibition rate was performed using GraphPad Prism 7, and the IC_{50} value of the compound was calculated.

Table 3:

Example	Human whole blood IC_{50} (nM)	hPBMC IC_{50} (nM)
Example 1	287	3.1
Example 2	246	2.2

[1388] Experimental results: The compounds of the present invention have good inhibitory effects on IL-6 production by immune cells.

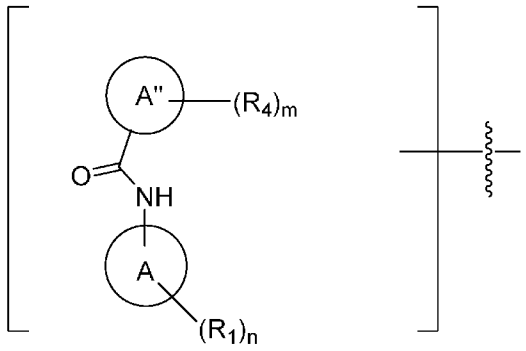
Claims

1. A compound of formula I, a stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or a pharmaceutically acceptable salt thereof:

PTM-L-ULM I

wherein:

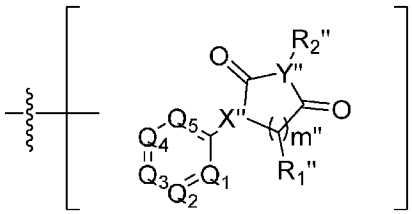
the PTM has a structure of the following formula:



PTM-1

wherein in the PTM-1:

m is 0, 1, 2, 3 or 4;
n is 0, 1, 2, 3 or 4;
ring A'' is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or/and 3 heteroatoms selected from N, O or S;
ring A is 6-10 membered aryl or is 5-11 membered monocyclic or bicyclic heteroaryl containing 1, 2 or/and 3 heteroatoms selected from N, O or S;
each R_1 is independently selected from: C_1-C_4 alkyl, -O(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_{1-2}$, C_3-C_8 cycloalkyl, -O(C_3-C_8 cycloalkyl), -NH(C_3-C_8 cycloalkyl), 3-8 membered heterocycloalkyl, -O(3-8 membered heterocycloalkyl), -NH(3-8 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), -NH(6-10 membered aryl), 5-6 membered heteroaryl, -O(5-6 membered heteroaryl), -NH(5-6 membered heteroaryl), CN, halogen, -OH, $-NH_2$, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, $-C(O)NH_2$, $-S(O)_2H$, $-S(O)_2NH_2$, -C(O)(C_1-C_4 alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$ or -S(O)NH(C_1-C_4 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, -OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, $-S(O)_2H$, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$ and -C(O)O(C_1-C_4 alkyl);
or the R_1, together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
each R_4 is independently hydrogen, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-6 membered heteroaryl, CN, halogen, -OH, -NHC(O)(C_1-C_4 alkyl), -NHS(O)(C_1-C_4 alkyl), -NHS(O)$_2$(C_1-C_4 alkyl), -COOH, $-C(O)NH_2$, $-S(O)_2H$, $-S(O)_2NH_2$, -C(O)(C_1-C_4 alkyl), -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -C(O)O(C_1-C_4 alkyl), -S(O)(C_1-C_4 alkyl), -S(O)$_2$(C_1-C_4 alkyl), -S(O)$_2$NH(C_1-C_4 alkyl), -S(O)$_2$N(C_1-C_4 alkyl)$_2$, -S(O)NH(C_1-C_4 alkyl) or X(R_2)(R_3), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with groups selected from halogen, cyano, -OH, C_1-C_4 alkyl, -O(C_1-C_4 alkyl), methylpiperidine, $-S(O)_2H$, -S(O)$_2$(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_{1-2}$, and -C(O)O(C_1-C_4 alkyl); X is O, S, CH_2 or N;
R_2 and R_3 are independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl or 5-6 membered heteroaryl, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, OH, oxo, N(R_b)$_2$, oxopyrrolidinyl and morpholinyl, or R_2 and R_3, together with the atom to which they are attached, form C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with one or more substituents selected from R_a;
R_a is independently selected from oxo, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_3-C_6 cycloalkyl or CF_3; and
R_b is independently selected from H or C_1-C_4 alkyl;
L is a linking chain, which links PTM and ULM by covalent bonds;
the ULM has a structure of the following formula:

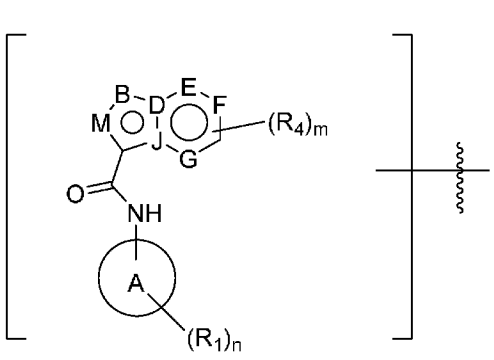


ULM-1

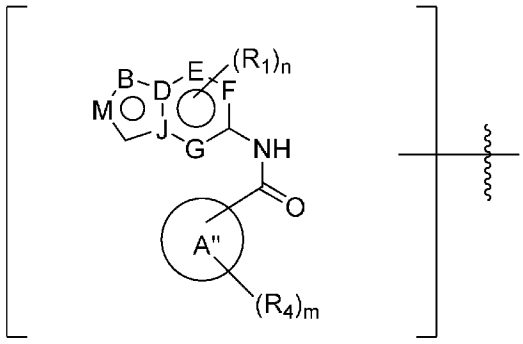
wherein in the ULM-1:

X" is C or N;
Y" is C, N, O or S;
Q_1, Q_2, Q_3, Q_4 and Q_5 are each independently CR_3" or N;
each R_3" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, -O(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(3-8 membered heterocycloalkyl), N(C_1-C_6 alkyl)$_{1-2}$, NH(C_3-C_8 cycloalkyl), NH(3-8 membered heterocycloalkyl), -0-(6-10 aryl) or -0-(5-10 membered heteroaryl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino; or R_3", together with the atom to which it is attached, forms cycloalkyl, heterocycloalkyl, heteroaryl or aryl;
m" is 1, 2 or 3;
each R_1" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl or -O(C_1-C_6 alkyl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino;
R_2" is hydrogen, deuterium, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl and C_3-C_6 cycloalkyl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano, amino and - OC(O)(C_1-C_6 alkyl).

2. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein the PTM is



PTM-2'

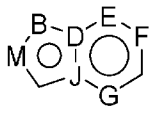


PTM-2"

wherein in the PTM-2' and PTM-2":
B is CH, N, O or S;
M is CH, N, O or S;
D is CH or N;
E is CH or N;
F is CH or N;
G is CH or N;
J is CH or N;
when B or M is S or O, D is CH, E is N, F is CH, G is N, and J is CH; and B and M are not simultaneously S and/or O;

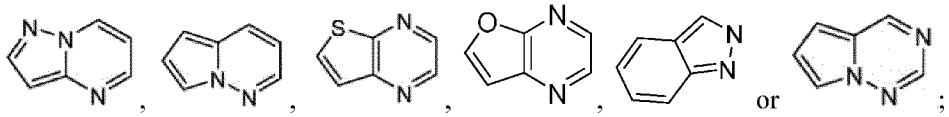
the ring A, ring A", R_1, n, R_4 and m are as defined and described in PTM-1 in claim 1.

3. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 2, wherein



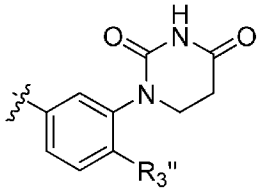
in

the PTM-2' is



;

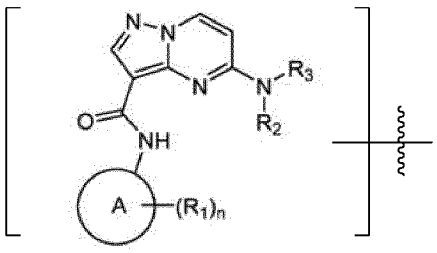
and/or, the ULM has a structure of the following formula:



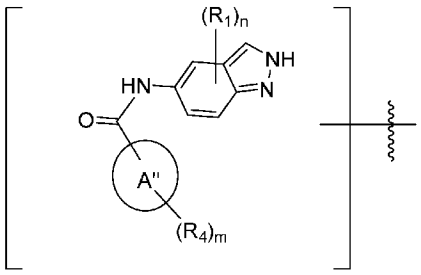
;

R_3" is halogen, C_1-C_6 alkyl or -O(C_1-C_6 alkyl);
and/or, the pharmaceutically acceptable salt is a formate.

4. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 2, wherein the PTM is



PTM-3

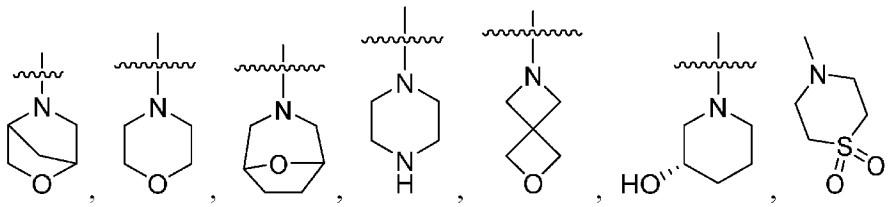


PTM-3'

wherein the ring A, ring A", R_1, R_2, R_3, R_4, m and n are as defined and described in PTM-1 in claim 1.

5. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1, 2 and 4, wherein ring A is phenyl or is 5-6 membered heteroaryl containing 1, 2 or 3 heteroatoms selected from N or O; preferably, ring A is phenyl, pyridyl, pyrrolyl, pyrazolyl, imidazolyl, pyrimidinyl, triazolyl, tetrazolyl, thienyl, thiazolyl, furanyl, oxazolyl, isoxazolyl or isothiazolyl; further preferably, ring A is pyrazolyl or thienyl; and/or, each R_3" is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, -O(C_1-C_6 alkyl), -O-(C_3-C_8 cycloalkyl), -O-(3-8 membered heterocycloalkyl), N(C_1-C_6 alkyl)$_{1-2}$, NH(C_3-C_8 cycloalkyl), NH(3-8 membered heterocycloalkyl), -O-(6-10 aryl) or -0-(5-10 membered heteroaryl), wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino; or R_3", together with the atom to which it is attached, forms cycloalkyl or heterocycloalkyl;

and/or, the R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, CH_3 or OCH_3; preferably, R_1 is independently selected from: C_1-C_4 alkyl, C_3-C_6 cycloalkyl, 3-6 membered heterocycloalkyl containing 1 or 2 heteroatoms selected from N, CN or halogen, wherein the alkyl, cycloalkyl and heterocycloalkyl are optionally substituted with halogen, OH, CH_3 or OCH_3; further preferably, the R_1 is CHF_2, CF_3, cyclohexyl, piperidinyl, methyl, cyano or piperazinyl;
and/or, the R_2 and R_3 are each independently selected from: hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 3-8 membered heterocycloalkyl, and are each optionally substituted with one or more halogens, OH, $N(R_b)_2$ or morpholinyl groups, or R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; R_a is independently selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl, CF_3, CHF_2, OH, halogen or NH_2, wherein the alkyl is optionally substituted with C_3-C_6 cycloalkyl or CF_3; and R_b is independently selected from H or C_1-C_4 alkyl; preferably, R_2 and R_3, together with the nitrogen atom to which they are attached, form 3-8 membered heterocycloalkyl containing, in addition to the N atom to which they are attached, 1 additional heteroatom selected from N or O, wherein the heterocycloalkyl is optionally substituted with one or more substituents selected from R_a; the R_a is independently selected from C_1-C_4 alkyl, CF_3, CHF_2, OH, halogen or NH_2; further preferably, the R_2 and R_3, together with the nitrogen atom to which they are attached, form



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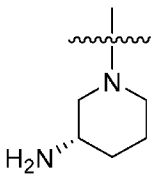
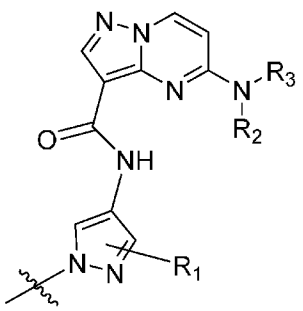
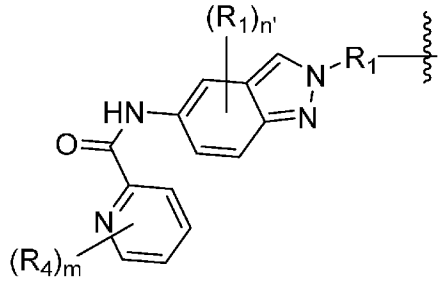


6. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1, 2 and 4, wherein the PTM has a structure of the following formula:



PTM-3a

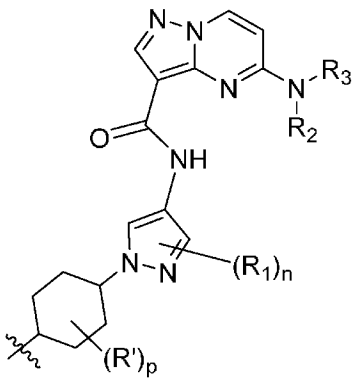


PTM-3a'

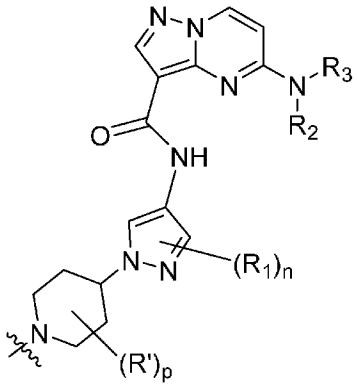
wherein,

n' is 0, 1, 2 or 3;
the R_1, R_2, R_3, R_4, m and n are as defined and described in PTM-1, PTM-2' and PTM-3 in claim 1.

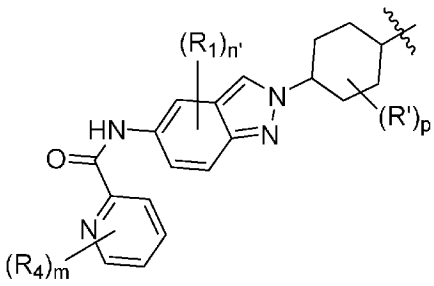
7. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1, 2 and 4, wherein the PTM has a structure of the following formula:



PTM-3b'



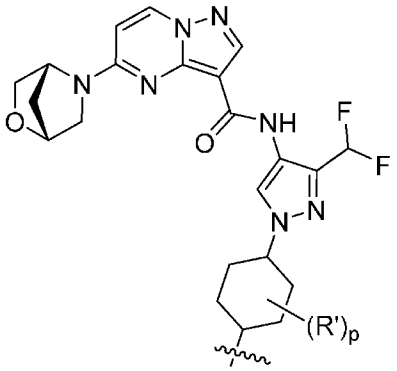
PTM-3c'



PTM-3d'

wherein,

n' is 0, 1, 2 or 3;
each R' is independently hydrogen, deuterium, hydroxy, amino, cyano, halogen, C_1-C_6 alkyl or -O(C_1-C_6 alkyl), wherein the alkyl is optionally substituted with 1-3 groups independently selected from hydroxy, halogen, cyano and amino;
p is 0, 1, 2, 3, 4, 5, 6, 7, 8 or 9;
the R_1, R_2, R_3, R_4, m and n are as defined and described in PTM-1, PTM-2' and PTM-3 in claim 1;
preferably, the PTM has a structure of the following formula:



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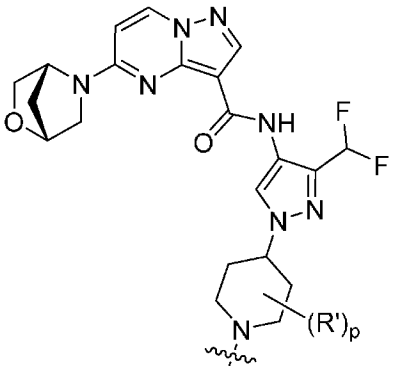

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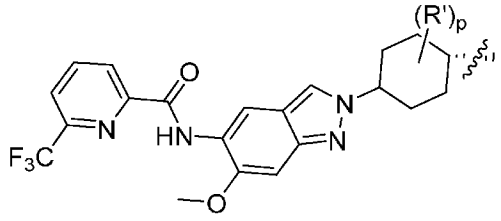
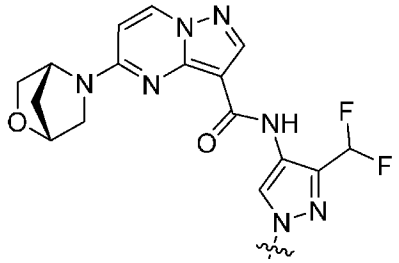


;

or, the PTM has a structure of the following formula: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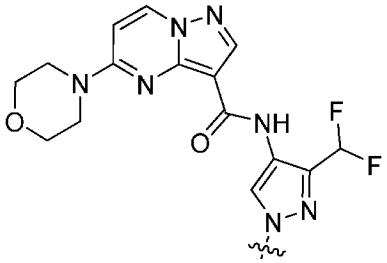
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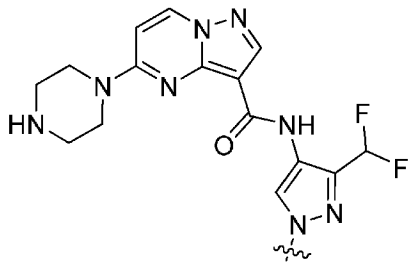
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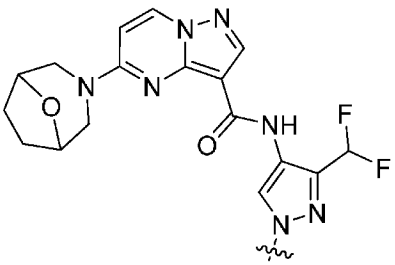
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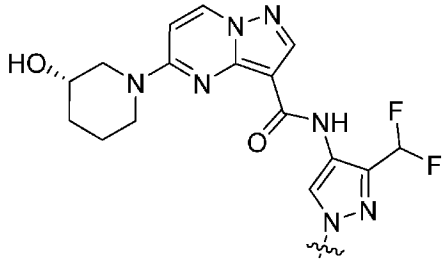
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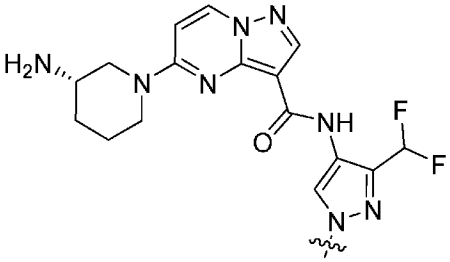
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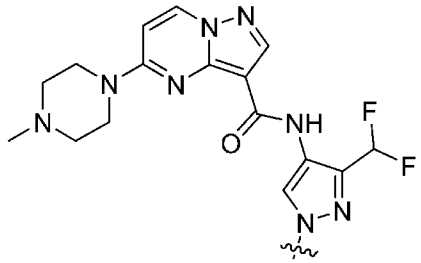
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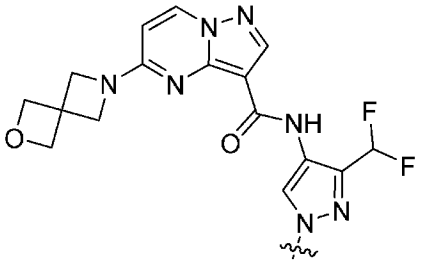
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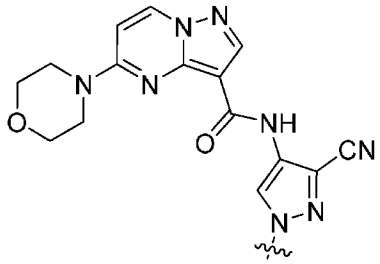
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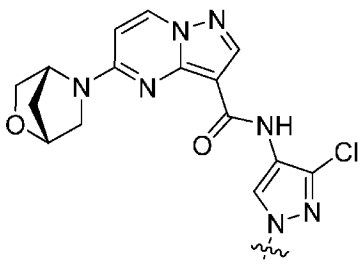
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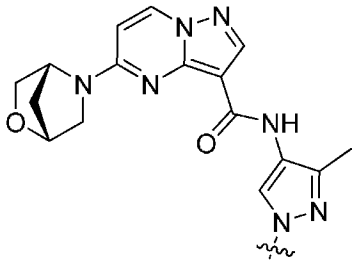
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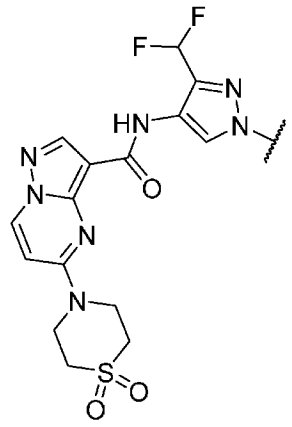


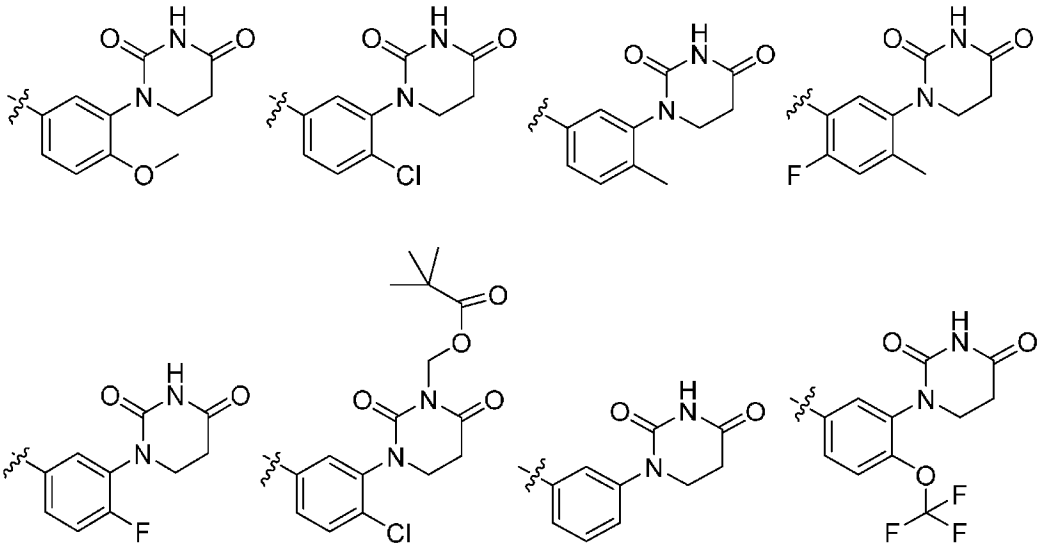
8. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein 1 or 2 of Q_1, Q_2, Q_3, Q_4 and Q_5 in the ULM-1 are N, and the rest are each independently CR_3".

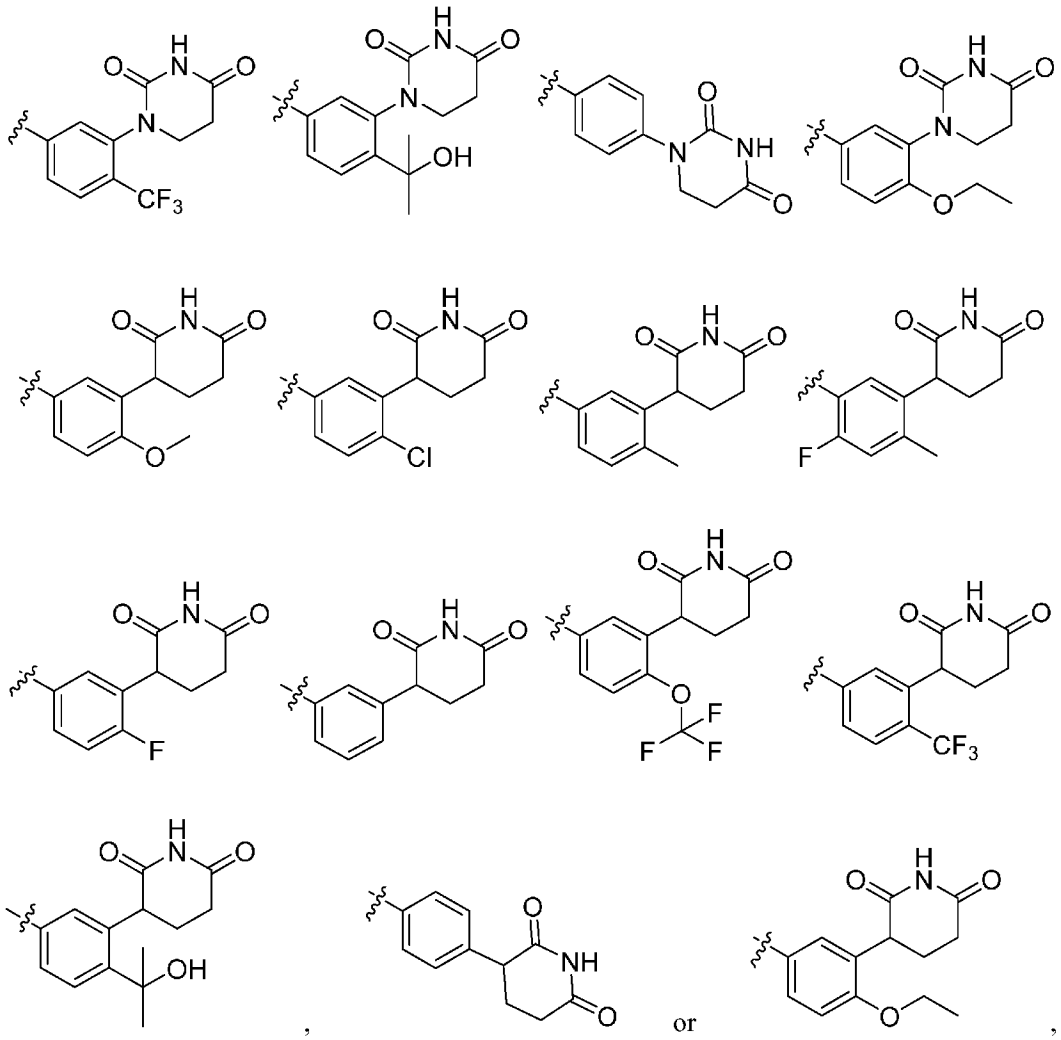
9. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein Q_1, Q_2, Q_3, Q_4 and Q_5 in the ULM-1 are each independently CR_3"; and/or, Y" in the ULM-1 is N;

and/or, each R_1" in the ULM-1 is independently hydrogen, deuterium, -F, -Cl or C_1-C_6 alkyl, wherein the alkyl is optionally substituted with 1-3 halogens; preferably, R_1" is hydrogen;
and/or, R_2" in the ULM-1 is hydrogen or C_1-C_6 alkyl, wherein the alkyl is optionally substituted with 1-3 halogens; preferably, R_2" is hydrogen.

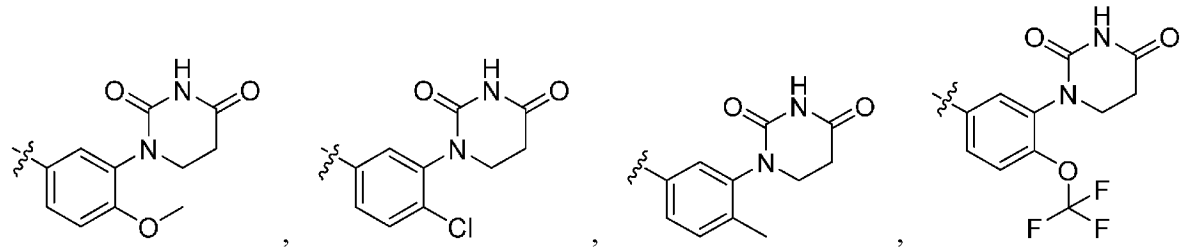
10. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein each R_3" in the ULM-1 is independently hydrogen, deuterium, halogen, -O(C_1-C_6 alkyl) or C_1-C_6 alkyl, wherein the alkyl is optionally substituted with 1-3 halogens; preferably, each R_3" is independently hydrogen, deuterium, F, Cl, methyl, methoxy, ethoxy, trifluoromethoxy, 2-hydroxypropan-2-yl or trifluoromethyl.

11. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein the ULM is selected from





preferably



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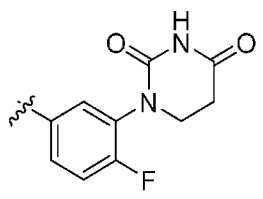
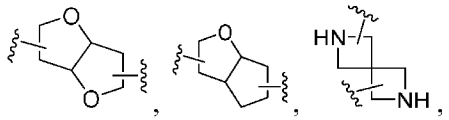


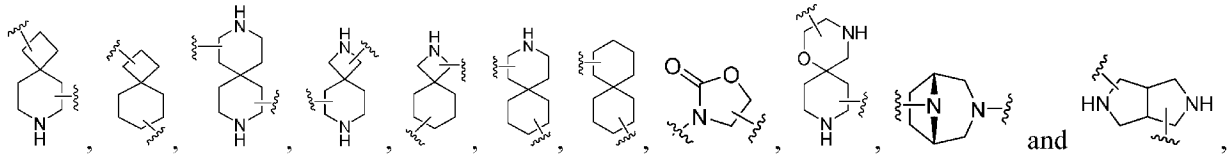
;

and/or, the L is a bond.

12. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein the L is -$(CH_2)_j$-, wherein 1 or more methylene groups in the $(CH_2)_j$- are optionally substituted with substituents selected from -$NR^{3'}$-, -O-, -S-, -S(O)-, -S(O)$NR^{3'}$-, -$NR^{3'}$S(O)-, -S$(O)_2$-, -S$(O)_2NR^{3'}$-, -$NR^{3'}S(O)_2$-, -$NR^{4'}S(O)_2NR^{3'}$-, - $CR^{1'}R^{2'}$-, -C(O)-, -C(O)O-, -OC(O)-, -$NR^{3'}$C(O)O-, -OC(O)$NR^{3'}$-, -C(O)$NR^{3'}$-, -$NR^{3'}$C(O)-, -$NR^{4'}$C(O)$NR^{3'}$-, - P(O)-, -P(O)O-, -OP(O)-, -OP(O)O-, ethenylene, ethynylene, C_3-C_{12} cycloalkylene, 3-12 membered heterocycloalkylene containing 1 or more heteroatoms selected from N, O or S, 6-10 membered arylene or 5-10 membered heteroarylene, wherein the ethenylene, cycloalkylene, heterocycloalkylene, arylene and heteroarylene are each independently optionally substituted with 1 or more substituents selected from halogen, -$OR^{3'}$, -$NR^{3'}R^{4'}$, oxo, nitro, cyano, C_1-C_6 alkyl, -S(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl, 5-10 membered heteroaryl, -C(O)$R^{1'}$, -C(O)$OR^{3'}$, -OC(O)$R^{1'}$, - C(O)$NR^{3'}$, -$NR^{3'}$C(O)$R^{1'}$, -S(O)$R^{1'}$, -S(O)$NR^{3'}$, -S$(O)_2R^{1'}$, -S$(O)_2NR^{3'}$, -$NR^{3'}S(O)_2R^{1'}$, -$NR^{4'}S(O)_2NR^{3'}$, - OC(O)$NR^{3'}$ and -$NR^{4'}$C(O)$NR^{3'}$, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently optionally substituted with 1 or more substituents selected from halogen, -OH, -$NR^{3'}R^{4'}$, oxo, nitro, cyano and C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl and 5-10 membered heteroaryl; $R^{1'}$ and $R^{2'}$ are each independently halogen, -OH, -$NR^{3'}R^{4'}$, C_1-C_6 alkyl, C_1-C_6 chloroalkyl, hydroxy C_1-C_6 alkyl, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, - O(C_3-C_{10} cycloalkyl), -NH(C_3-C_{10} cycloalkyl), 3-10 membered heterocycloalkyl, -0(3-10 membered heterocycloalkyl), -NH(3-10 membered heterocycloalkyl), 6-10 membered aryl, -0(6-10 membered aryl), - NH(6-10 membered aryl), 5-10 membered heteroaryl, -0(5-10 membered heteroaryl) or -NH(5-10 membered heteroaryl); $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, 6-10 membered aryl or 5-10 membered heteroaryl; j is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25.

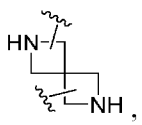
13. The compound of formula I, and/or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof according to claim 12, wherein the L is -$(CH_2)_j$-, wherein 1, 2, 3 or 4 methylene groups in the -$(CH_2)_j$- are optionally replaced by groups selected from -NH-, -NCH_3-, -NCH_2CH_3-, -O-, -$C(CH_3)_2$-, -CHF-, -$CHCF_3$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NH-, - C(O)NCH_3-, -NHC(O)-, -NCH_3C(O)-, ethenylene, ethynylene, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, oxiranylidene, oxetanylidene, oxolanylidene, oxanylidene, aziridinylidene, azetidinylidene, azolidinylidene, piperidinylidene, piperazinylidene, morpholinylidene, homomorpholinylidene, phenylene, pyrrolylidene, thienylidene, furylidene, imidazolylidene, pyrazolylidene, triazolylidene, tetrazolylidene, oxazolylidene, isoxazolylidene, thiazolylidene, isothiazolylidene, pyridinylidene, pyrimidinylidene, pyridazinylidene, pyrazinylidene,

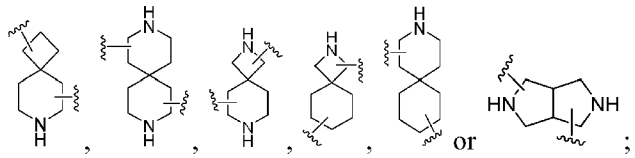




wherein the group for replacement is optionally substituted with 1 or more substituents selected from halogen, oxo, -$NR^{3'}R^{4'}$, -$OR^{3'}$ and C_1-C_4 alkyl, wherein the alkyl is optionally substituted with 1 or more substituents selected from halogen, -OH and -NH_2; $R^{3'}$ and $R^{4'}$ are each independently hydrogen, deuterium or C_1-C_4 alkyl; j is 2, 3, 4, 5, 6, 7 or 8.

14. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof according to claim 12, wherein the L is - $(CH_2)_j$-, wherein 1, 2 or 3 methylene groups in the -$(CH_2)_j$- are optionally replaced by groups selected from - O-, -NH-, -NCH_3-, -NCH_2CH_3-, -C(O)-, -C(O)NH-, -NHC(O)-, -NCH_3C(O)-, -C(O)NCH_3-,

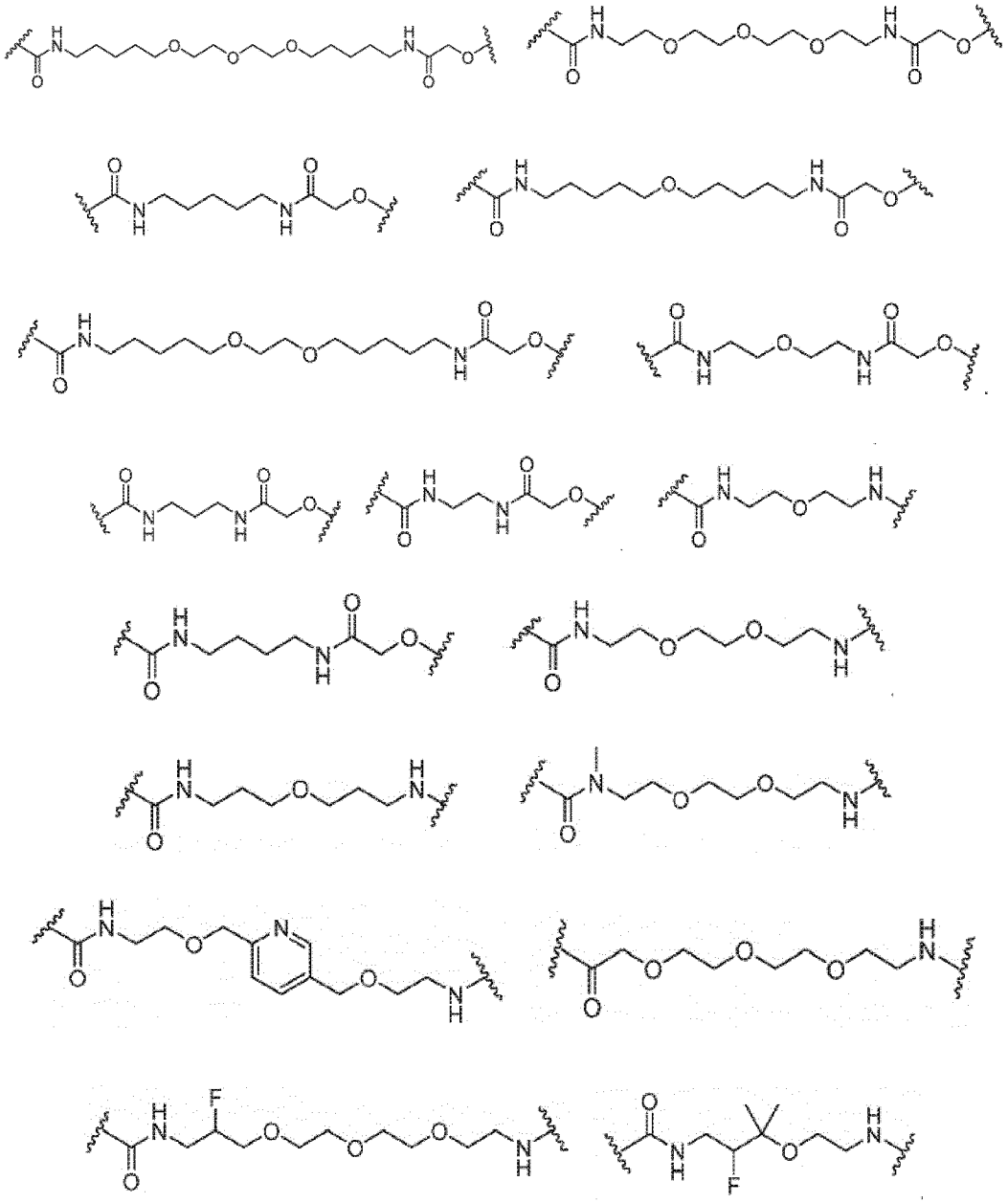


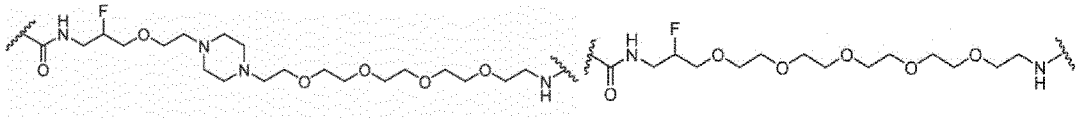


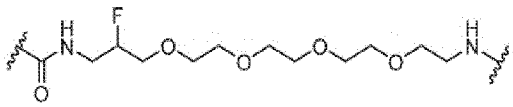
j is 2, 3, 4, 5, 6, 7 or 8.

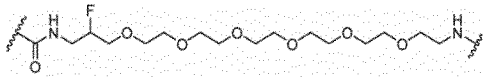
15. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof according to claim 12, wherein the L is - $(CH_2)_{j-1}$-C(O)-, wherein the methylene group in the -$(CH_2)_{j-1}$-C(O)- is as defined in claim 11 and optionally substituted with 1 or more groups, and j is as defined in claim 20.

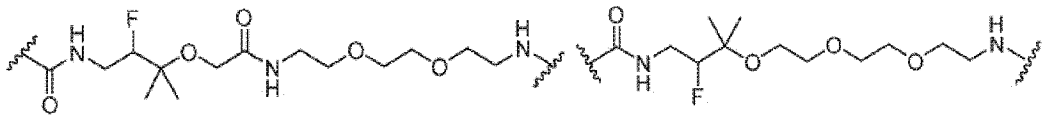
16. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate and/or prodrug thereof and/or the pharmaceutically acceptable salt thereof according to claim 12, wherein the L is

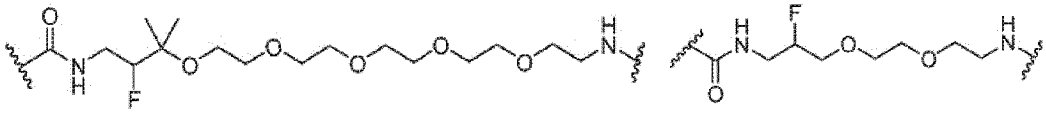


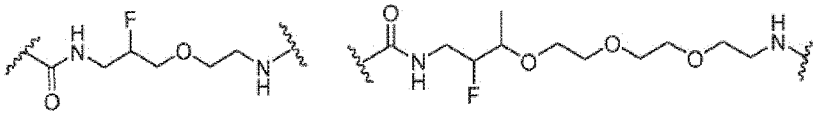


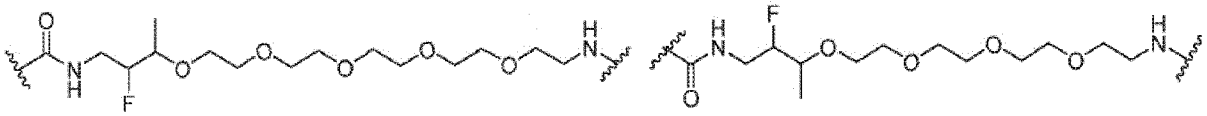


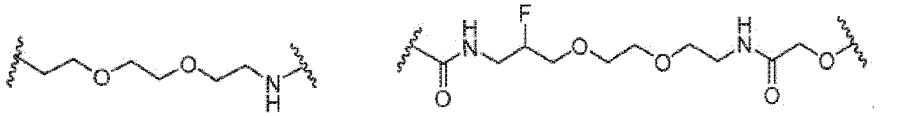


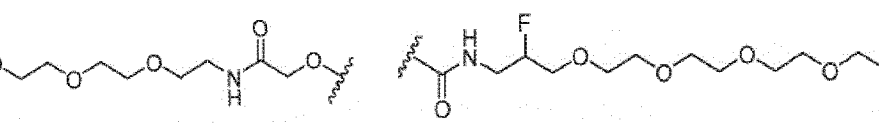


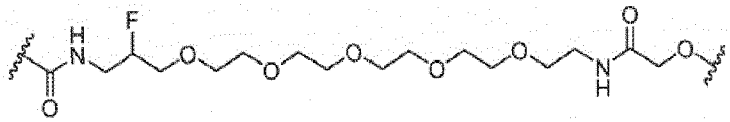


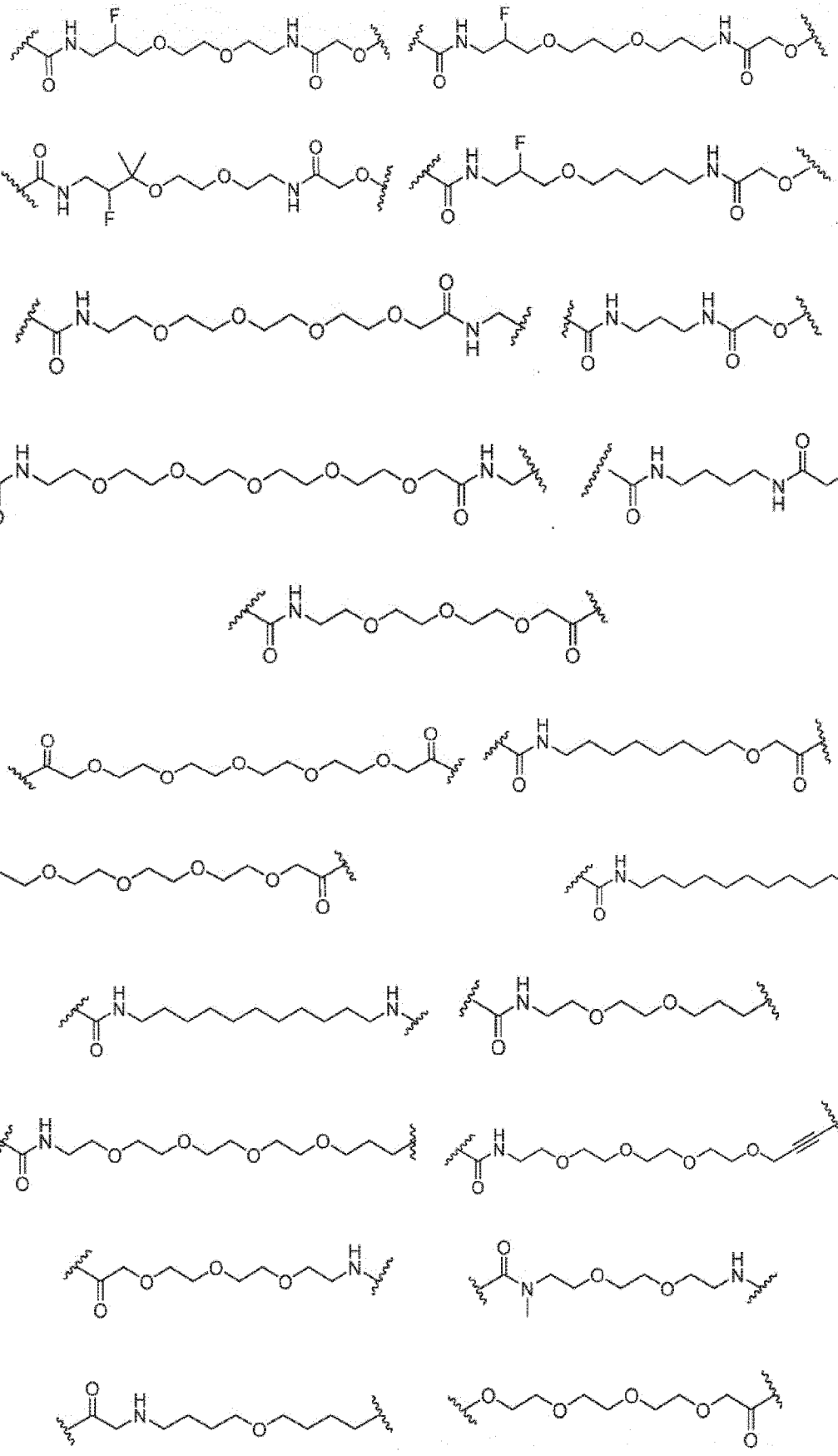


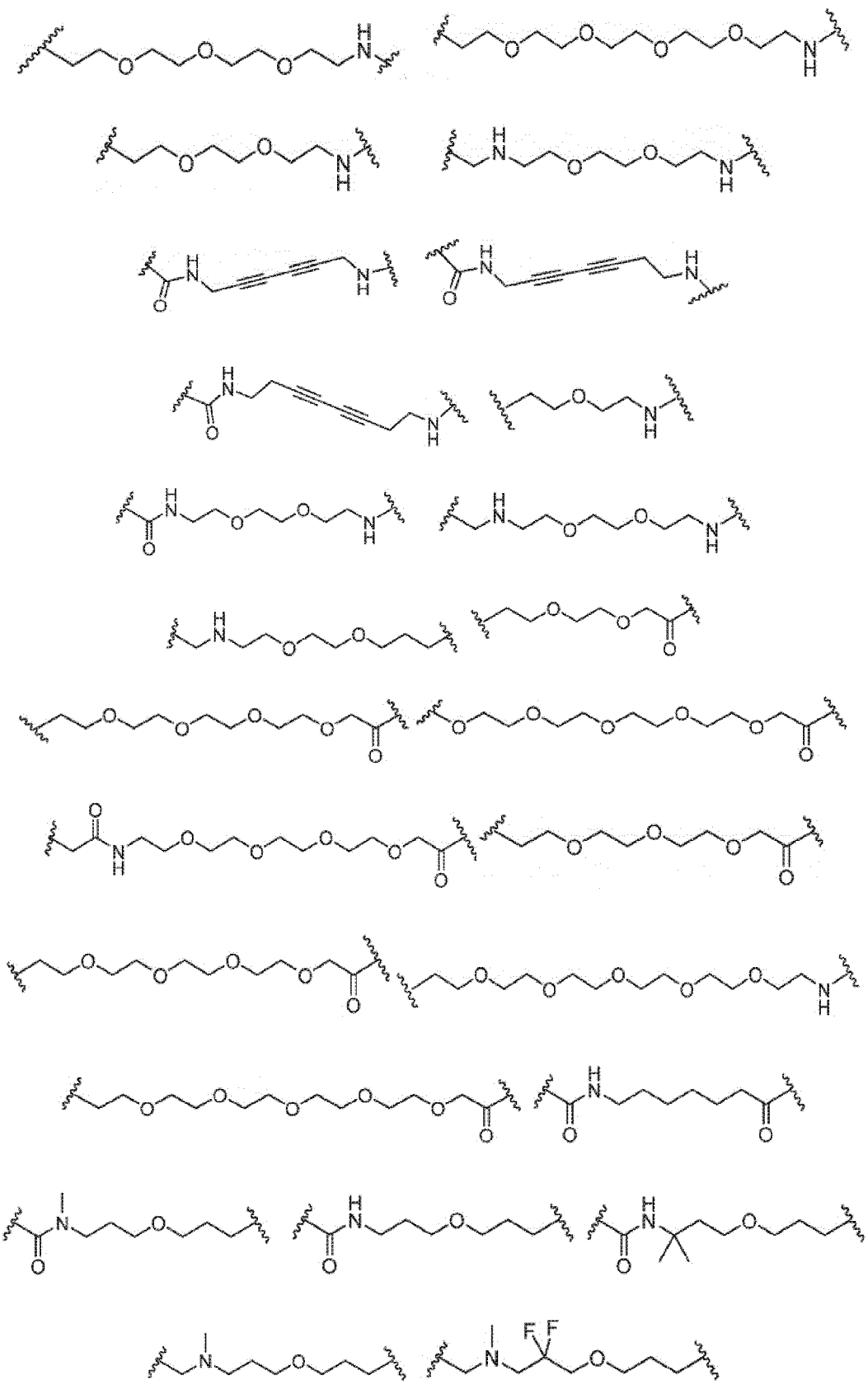


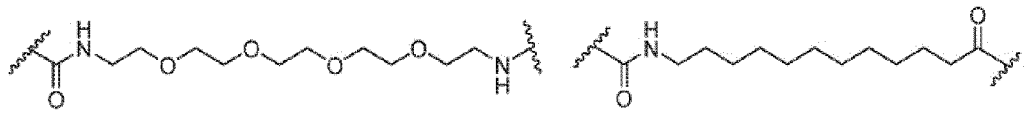


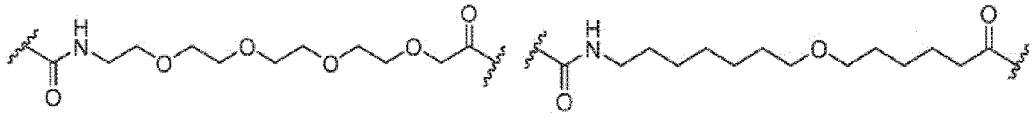


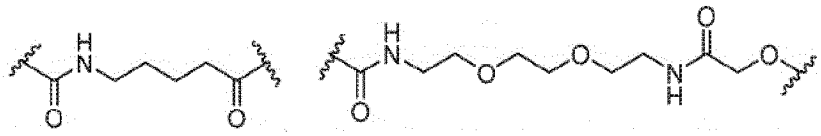


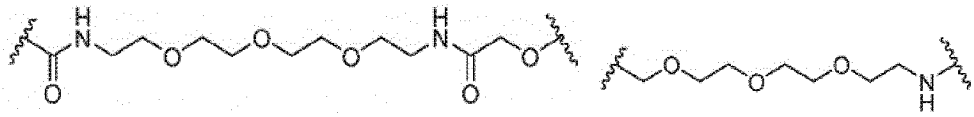


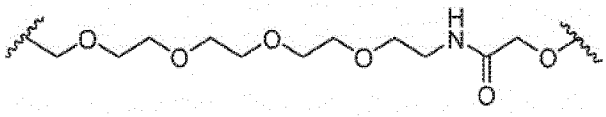


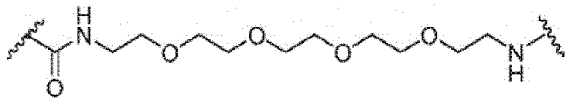


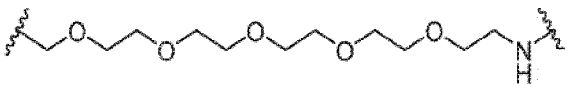


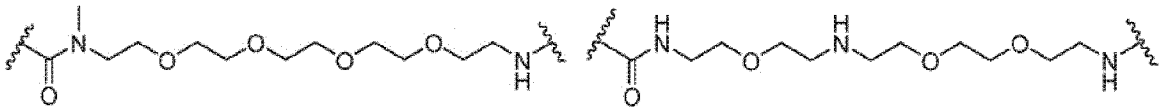


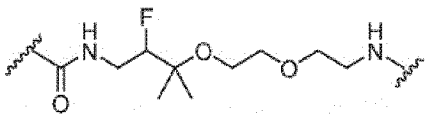


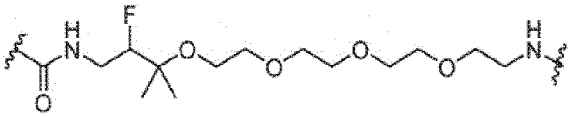


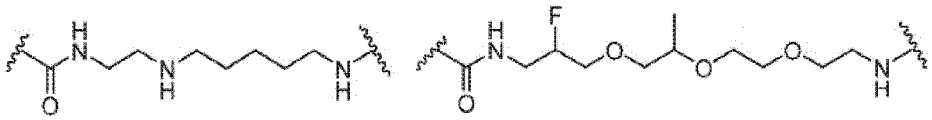


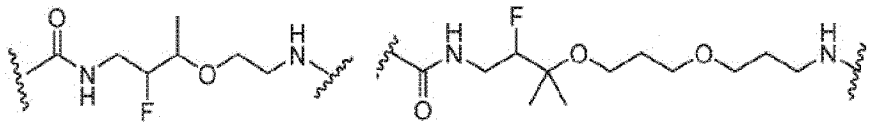


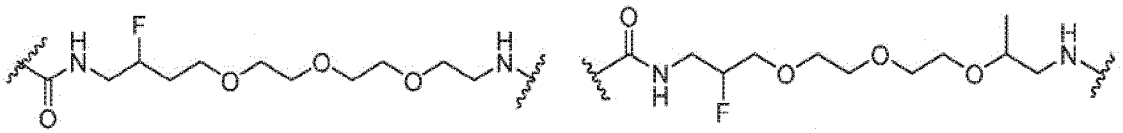


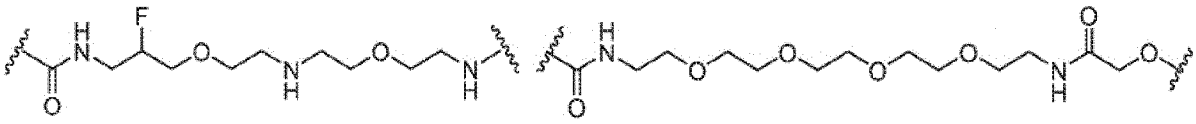


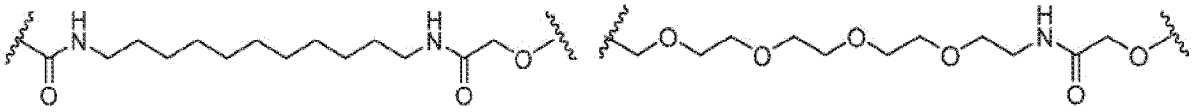


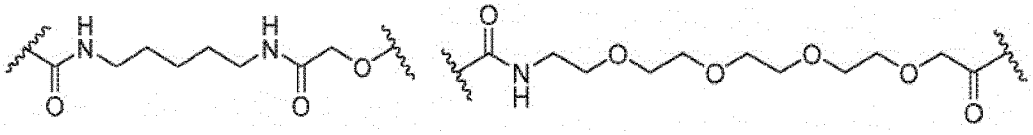


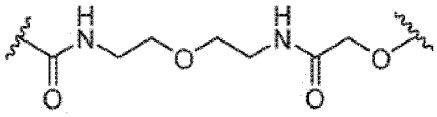


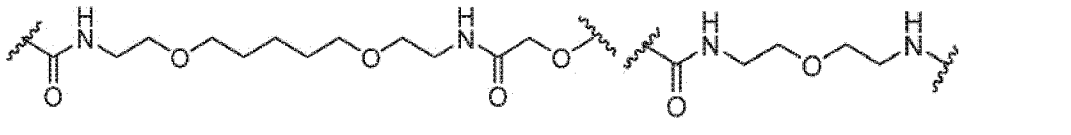


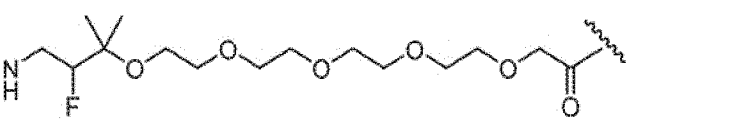


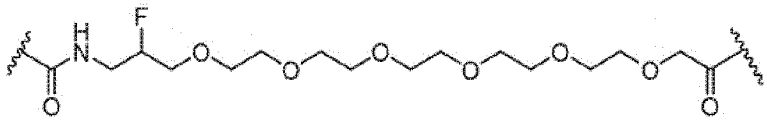


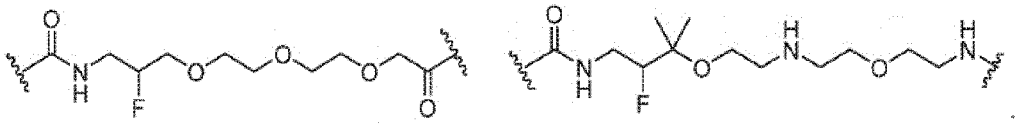


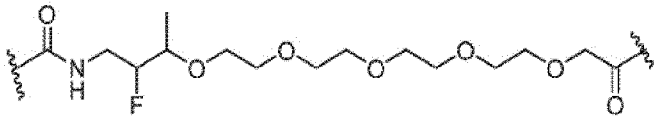


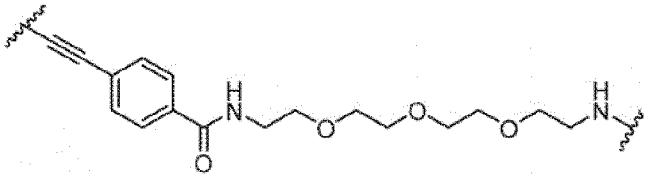


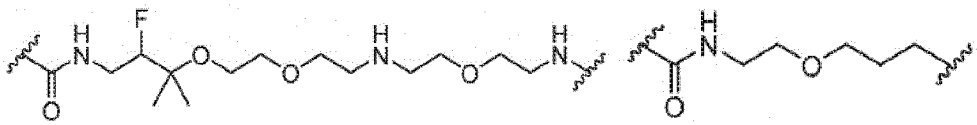


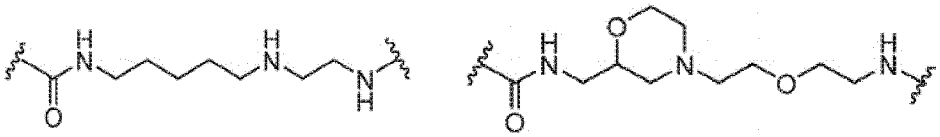


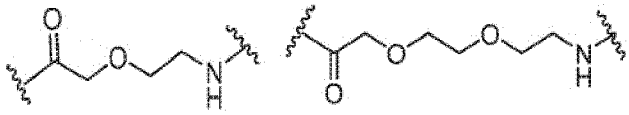


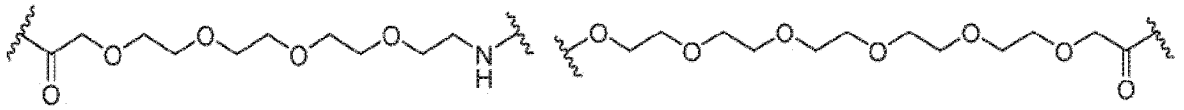


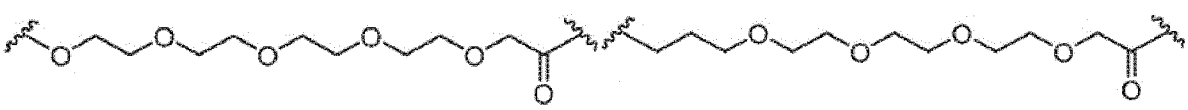


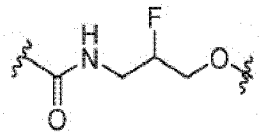


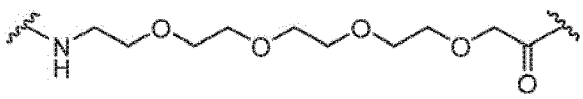


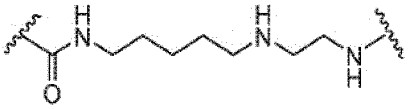


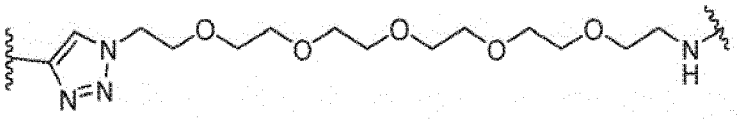


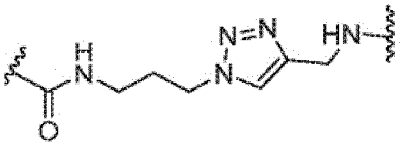


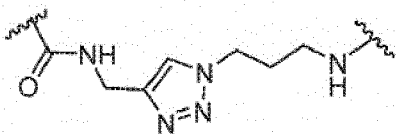


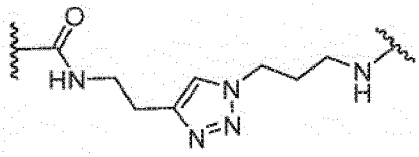


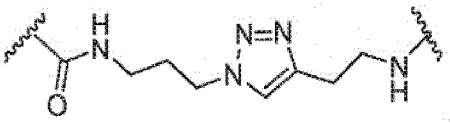


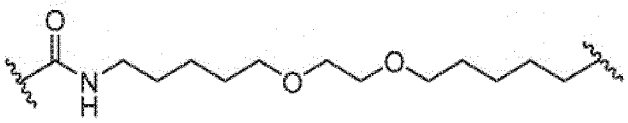


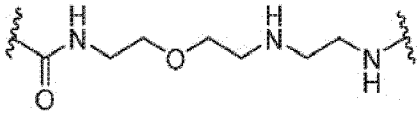


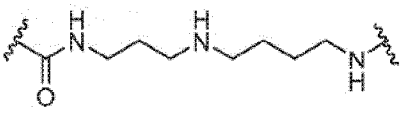


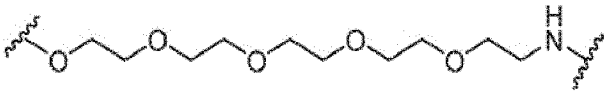


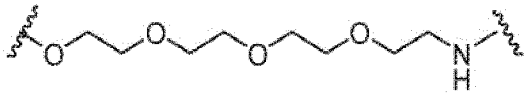


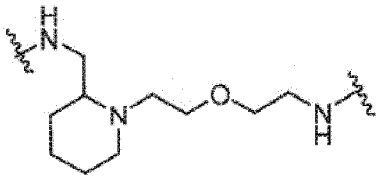


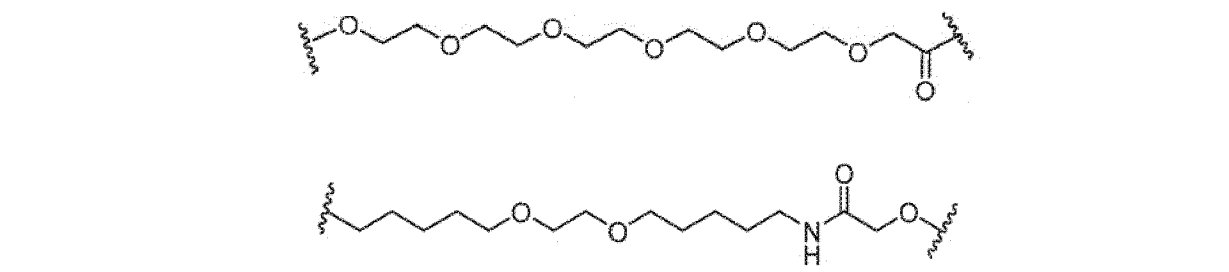


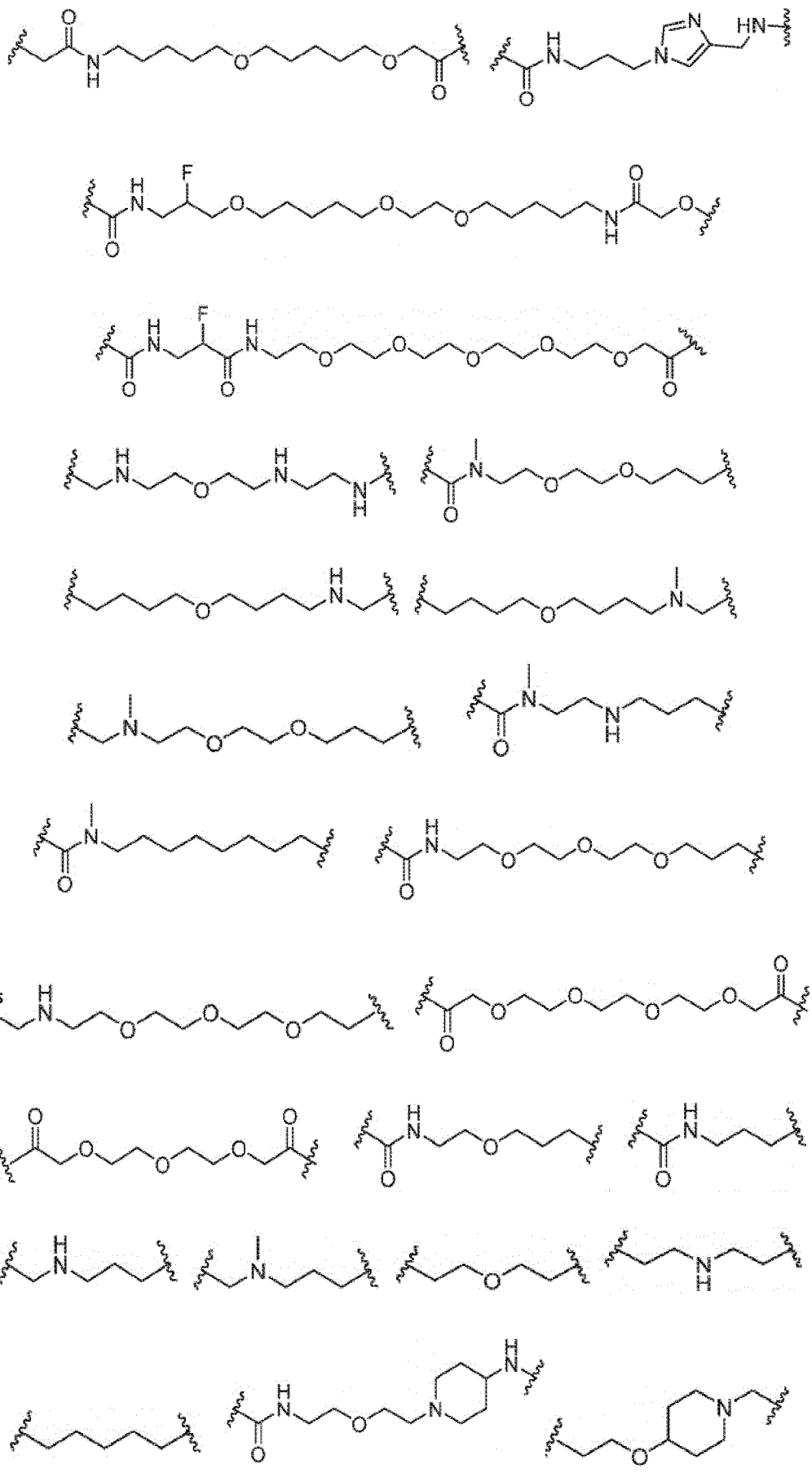


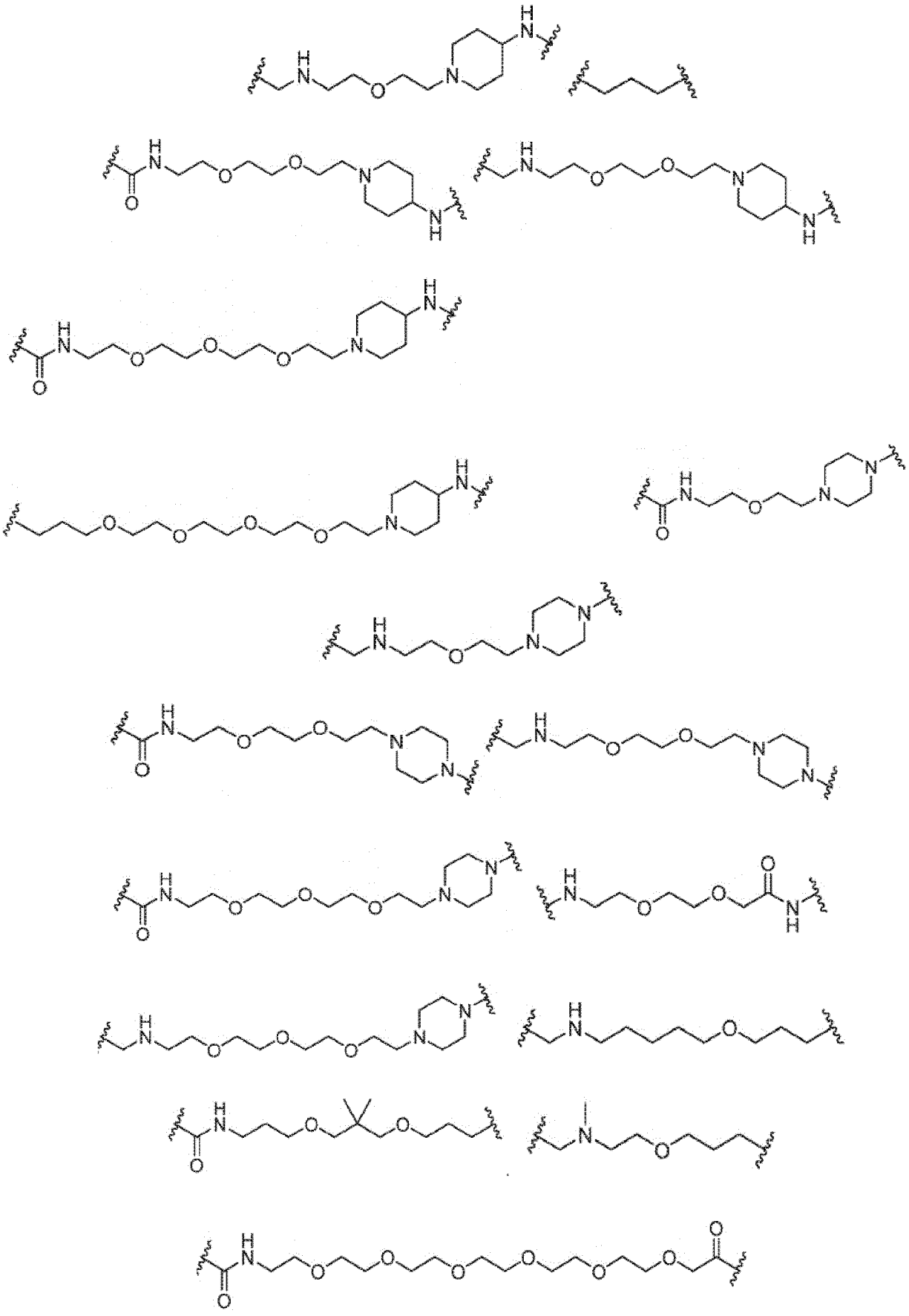


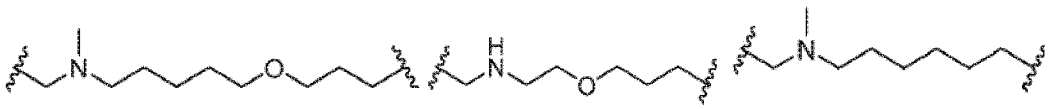


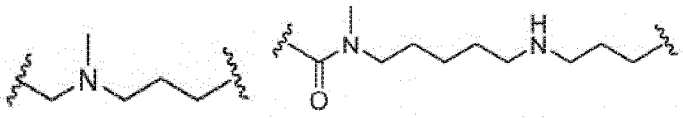


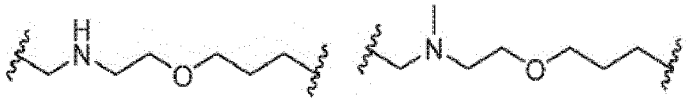


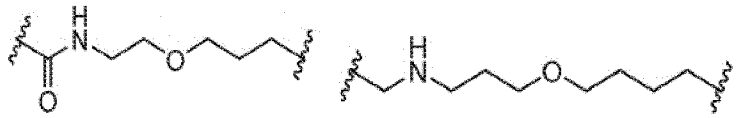


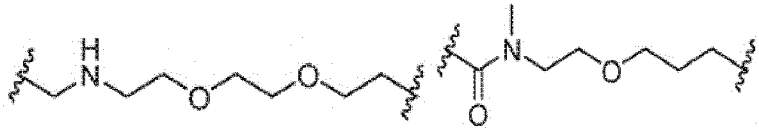


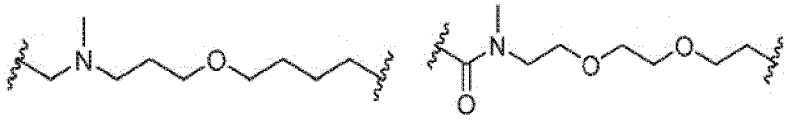


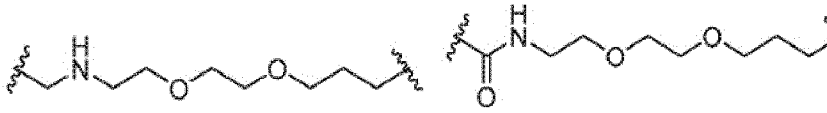


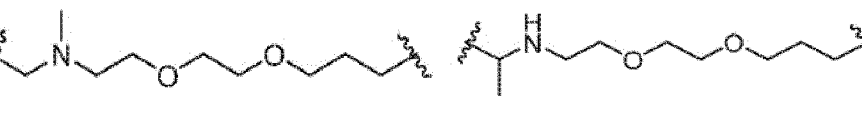


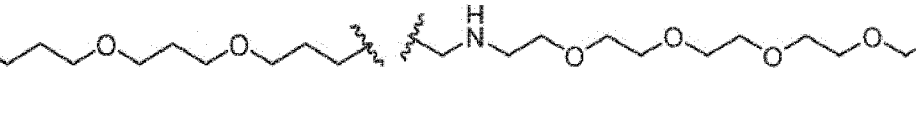


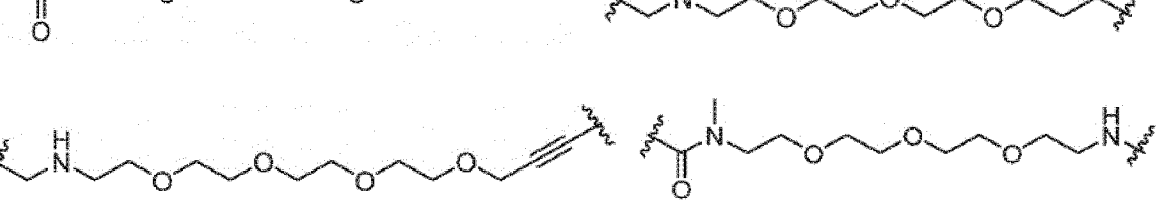


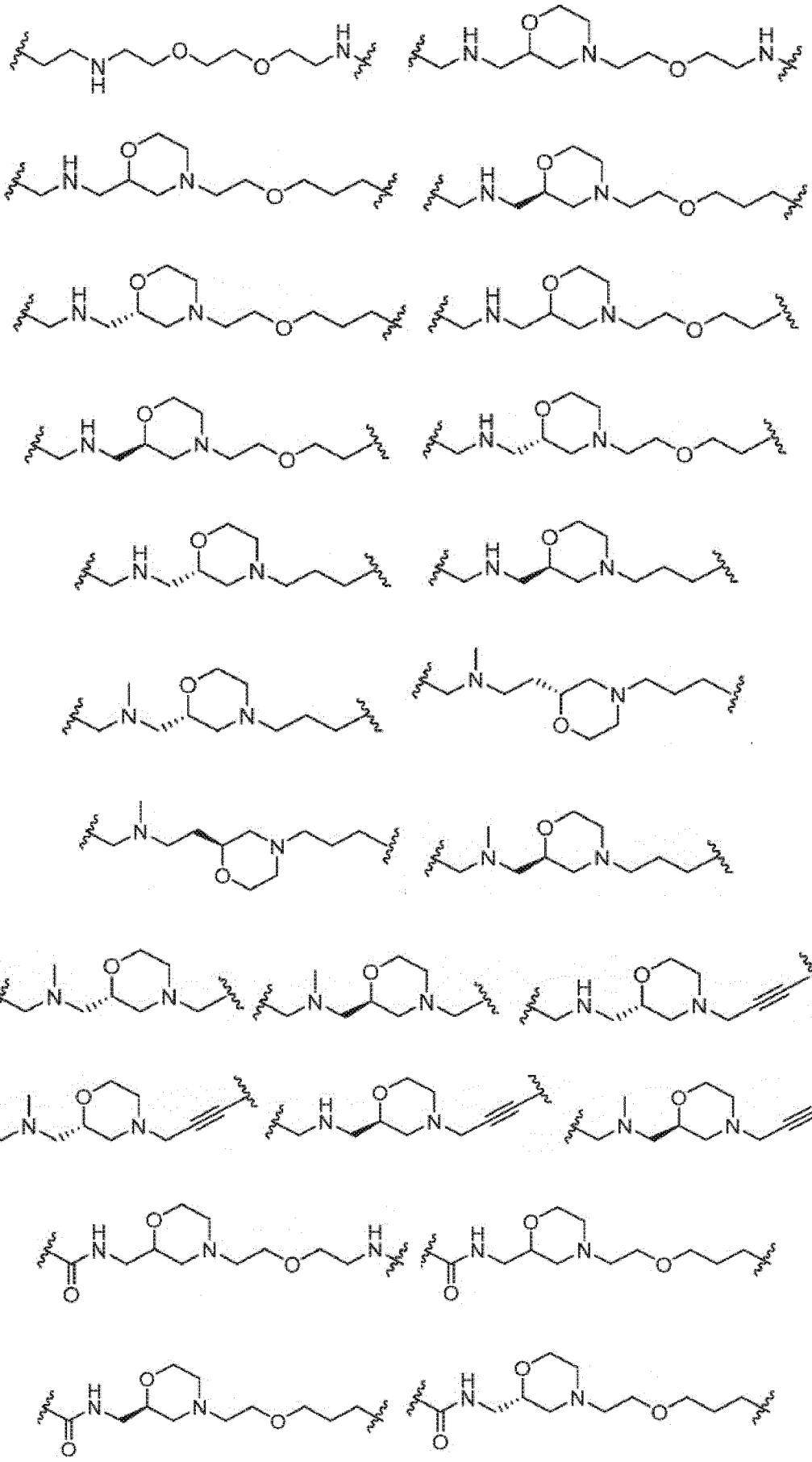


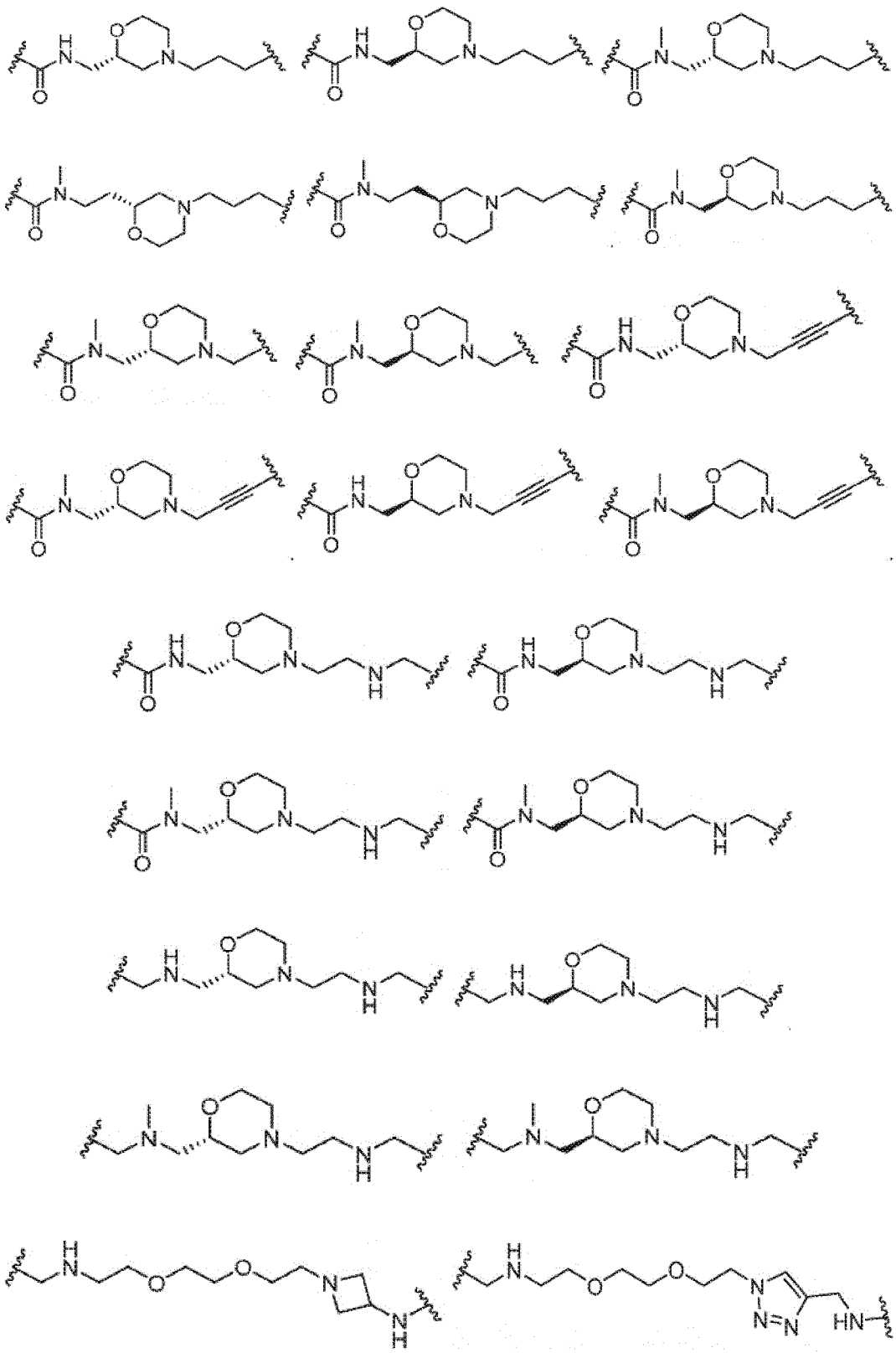


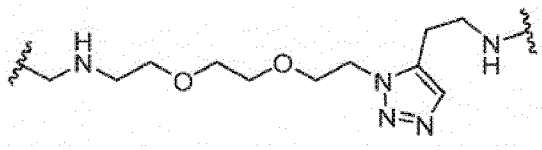


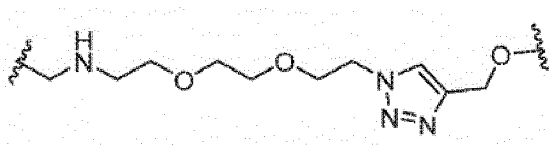


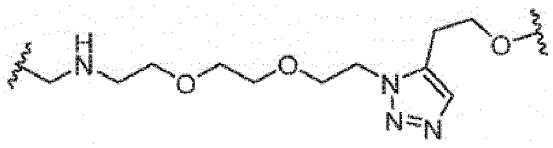


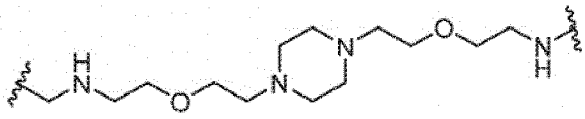


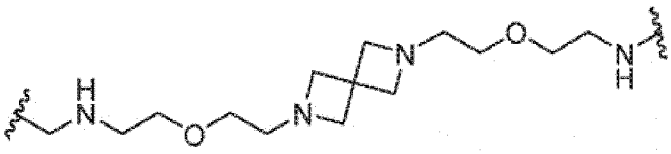


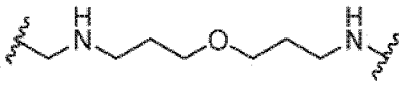


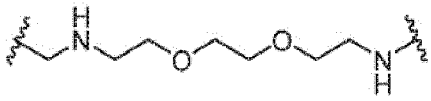


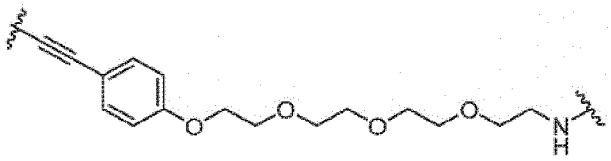


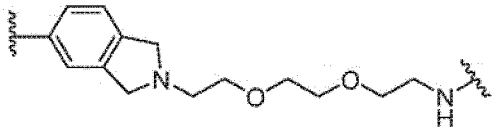


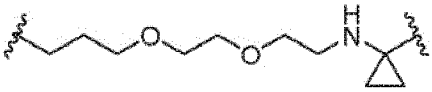


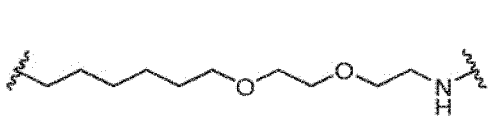


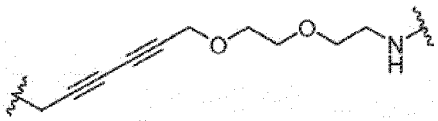


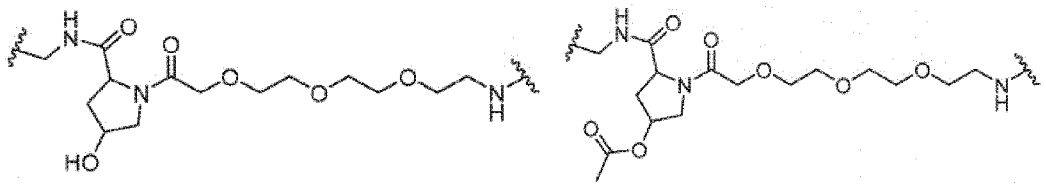


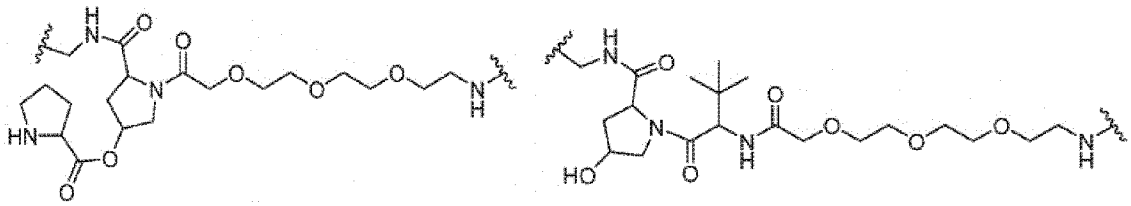


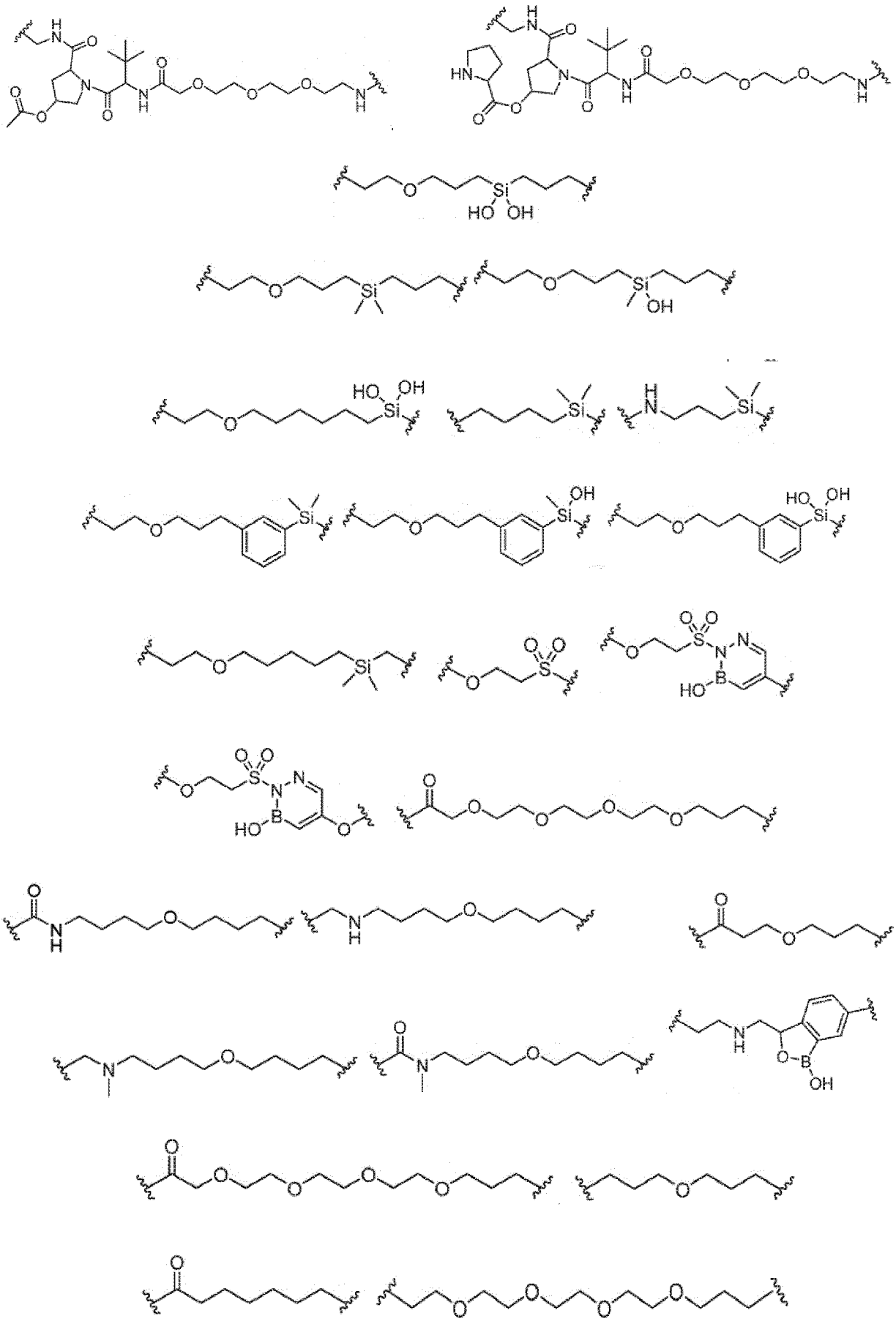


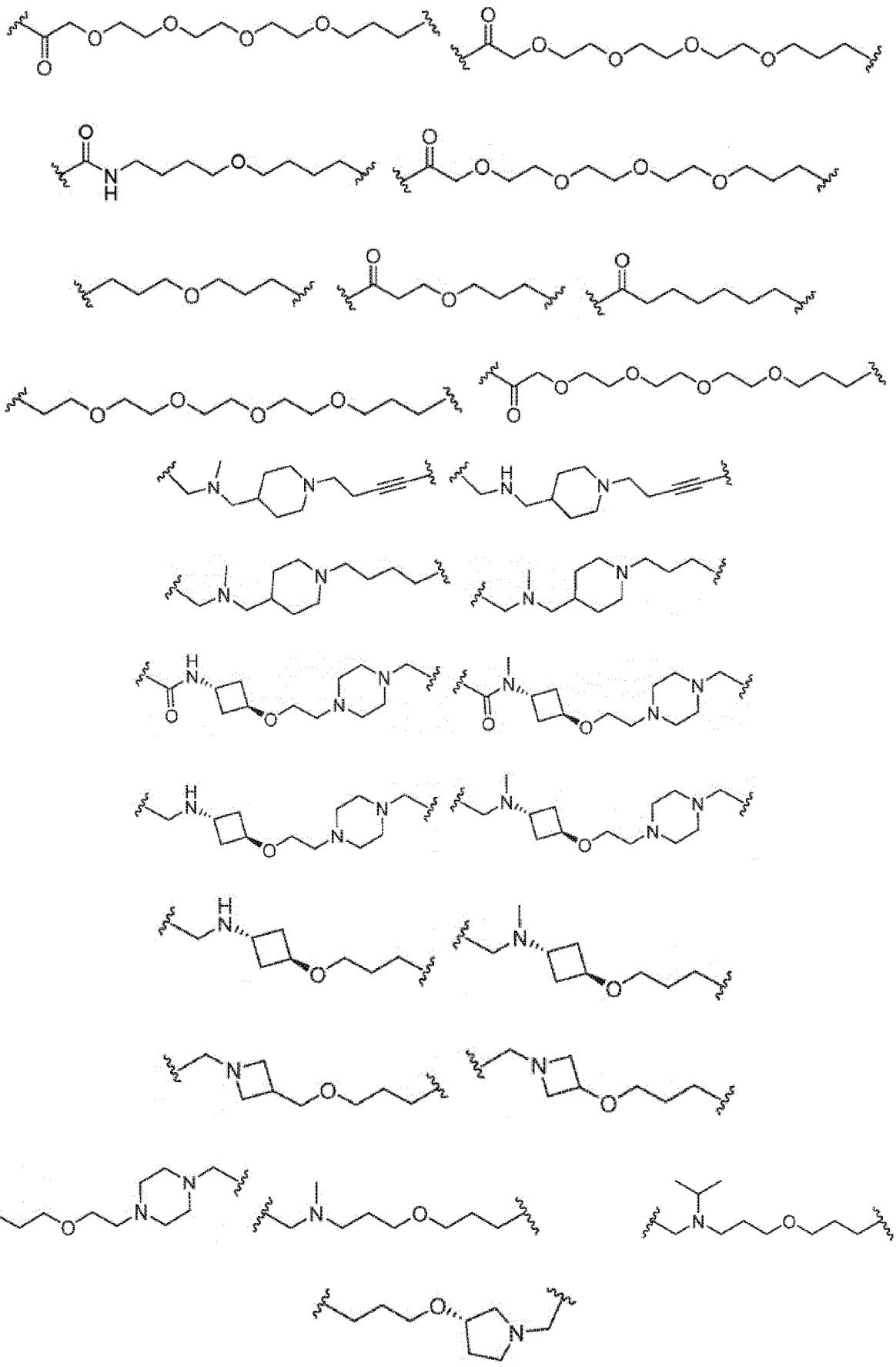


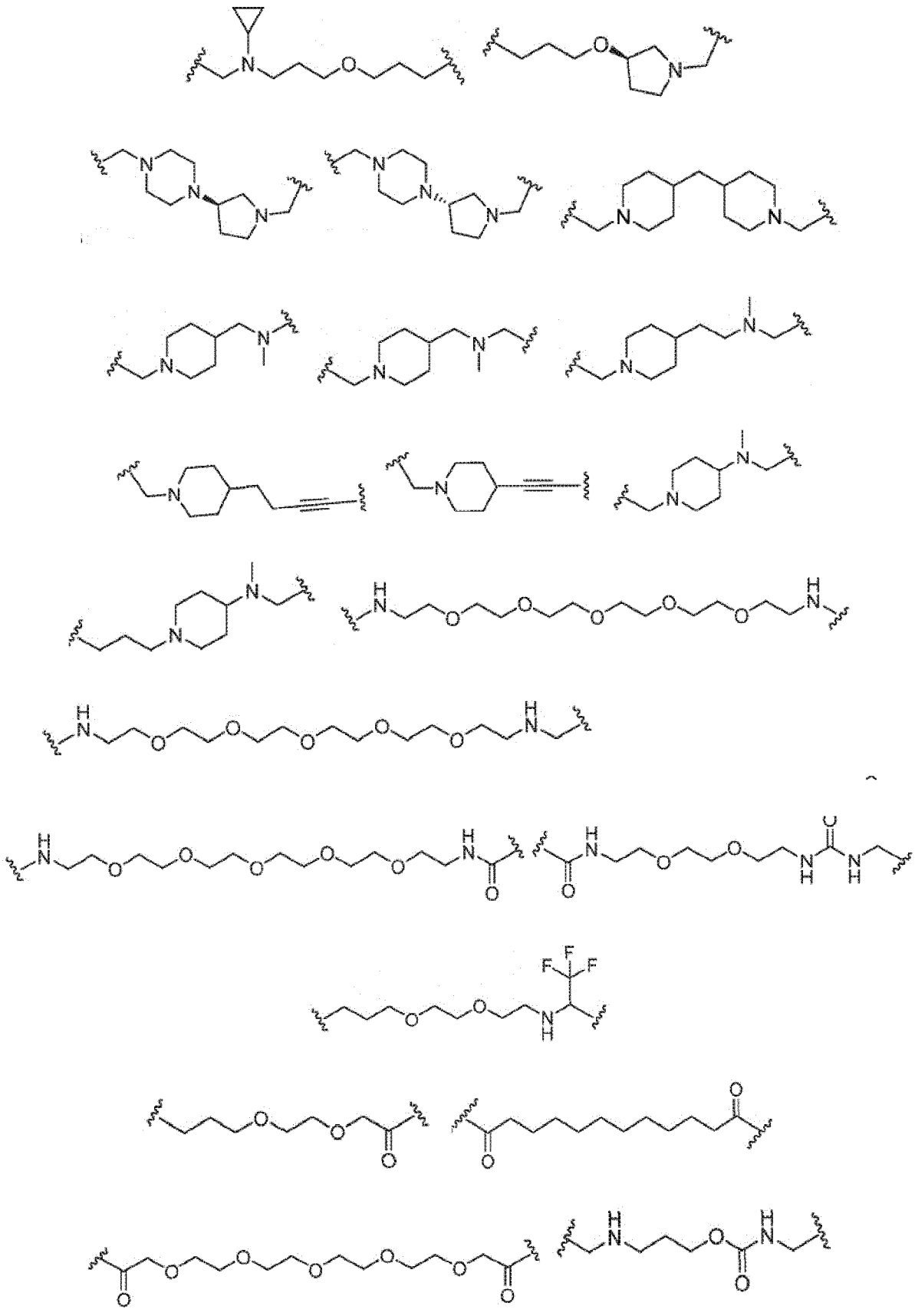


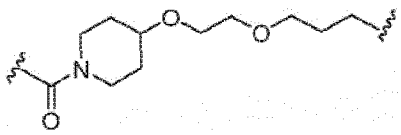


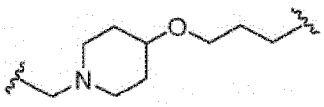


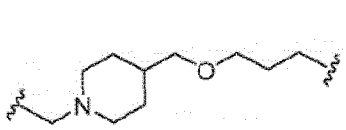


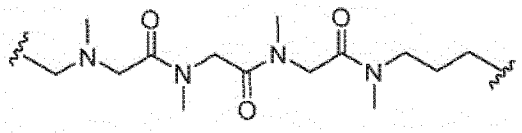


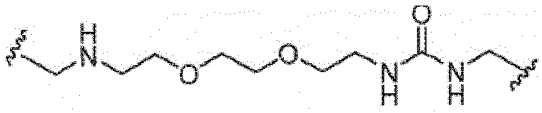


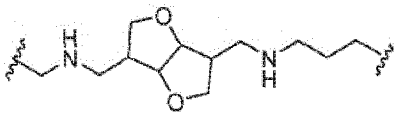


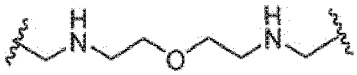


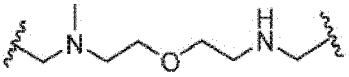


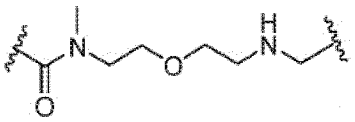


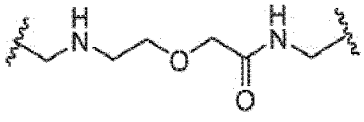


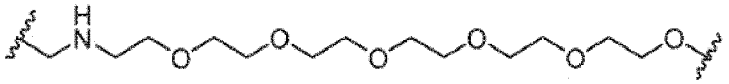


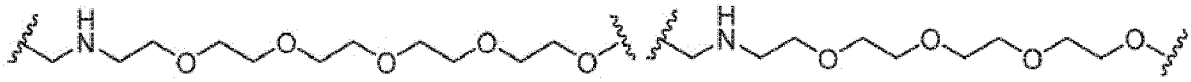


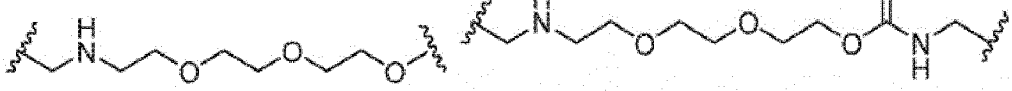


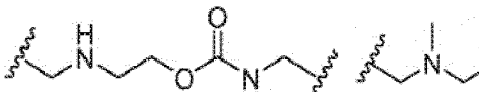


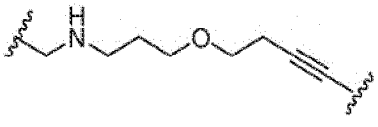


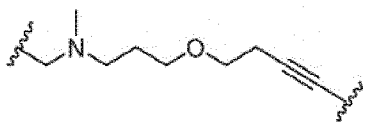


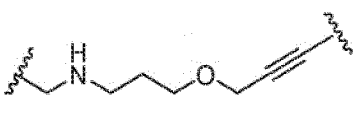


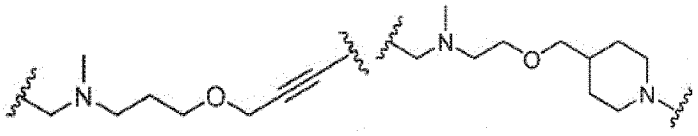


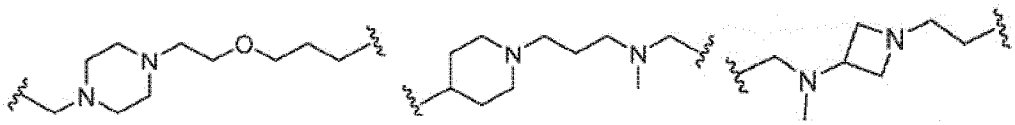


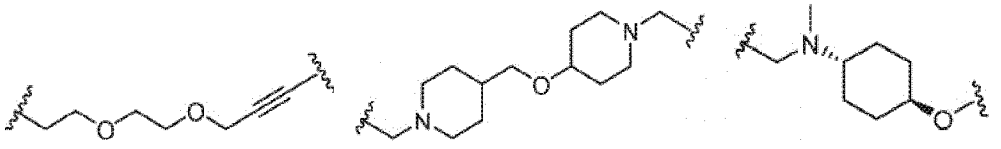


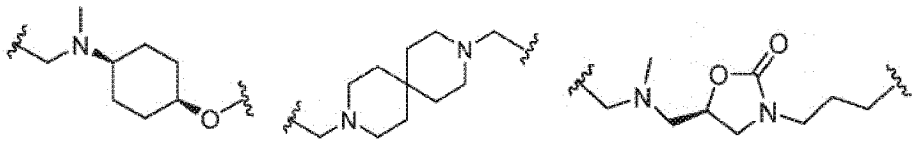


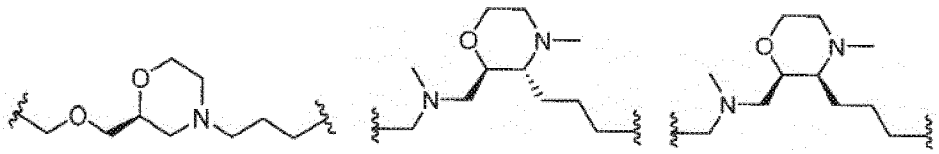


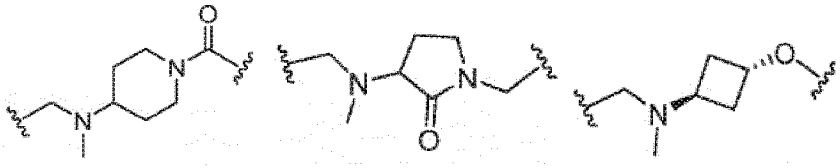


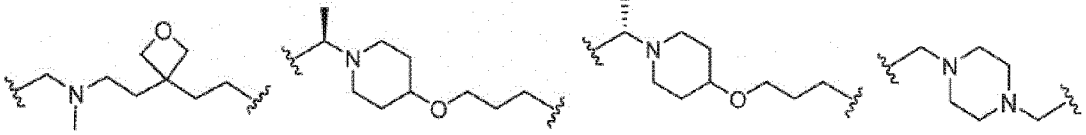


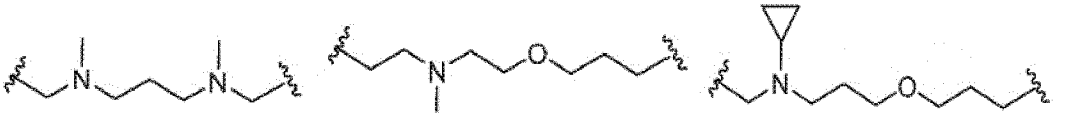


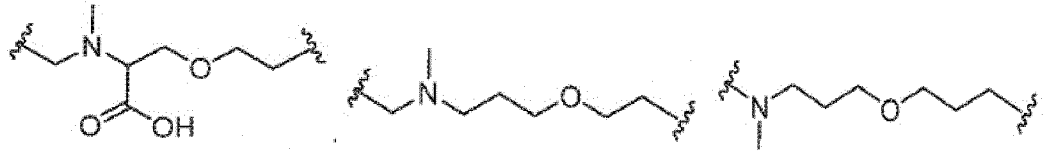


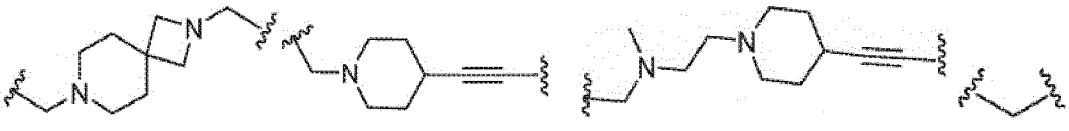


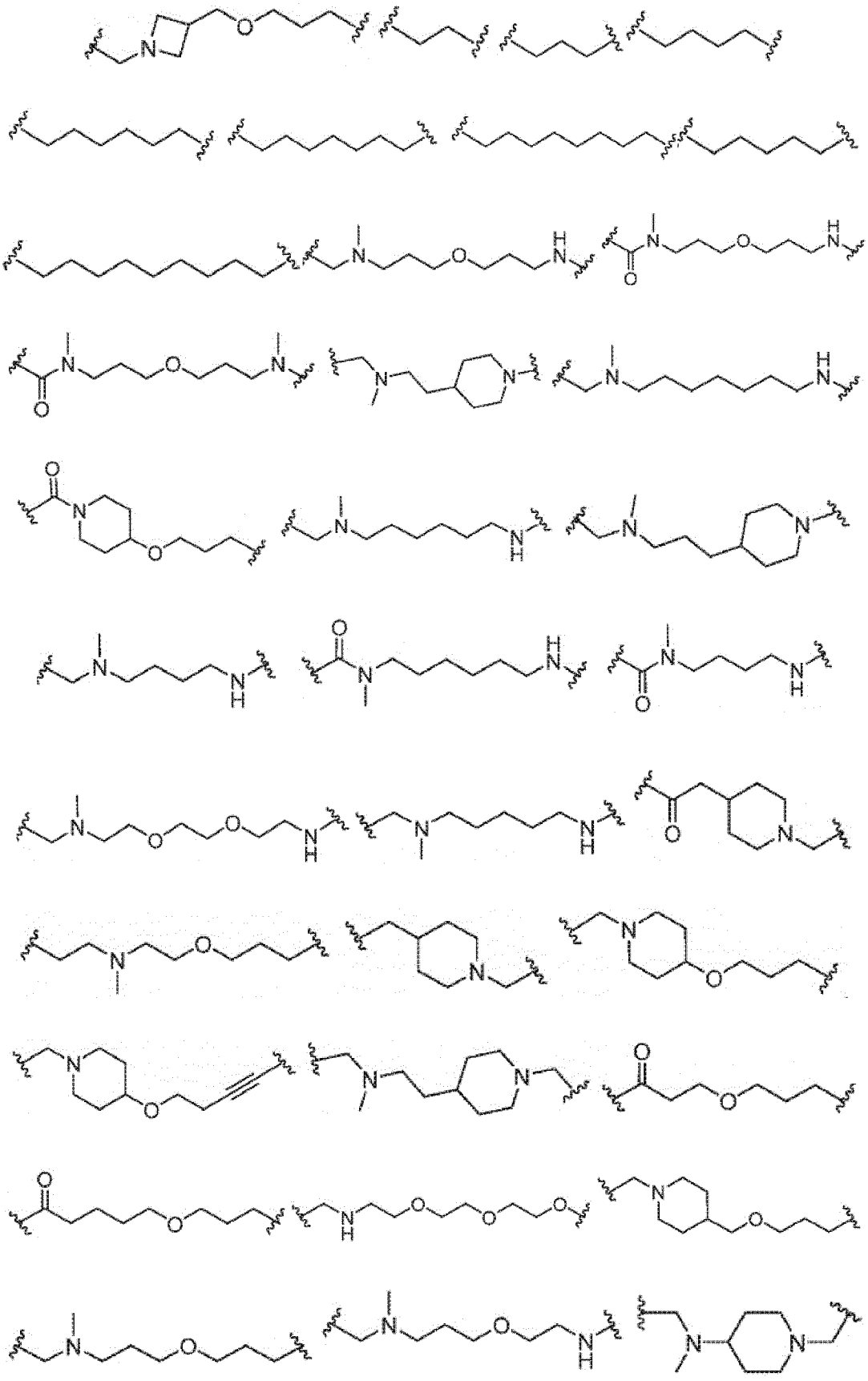


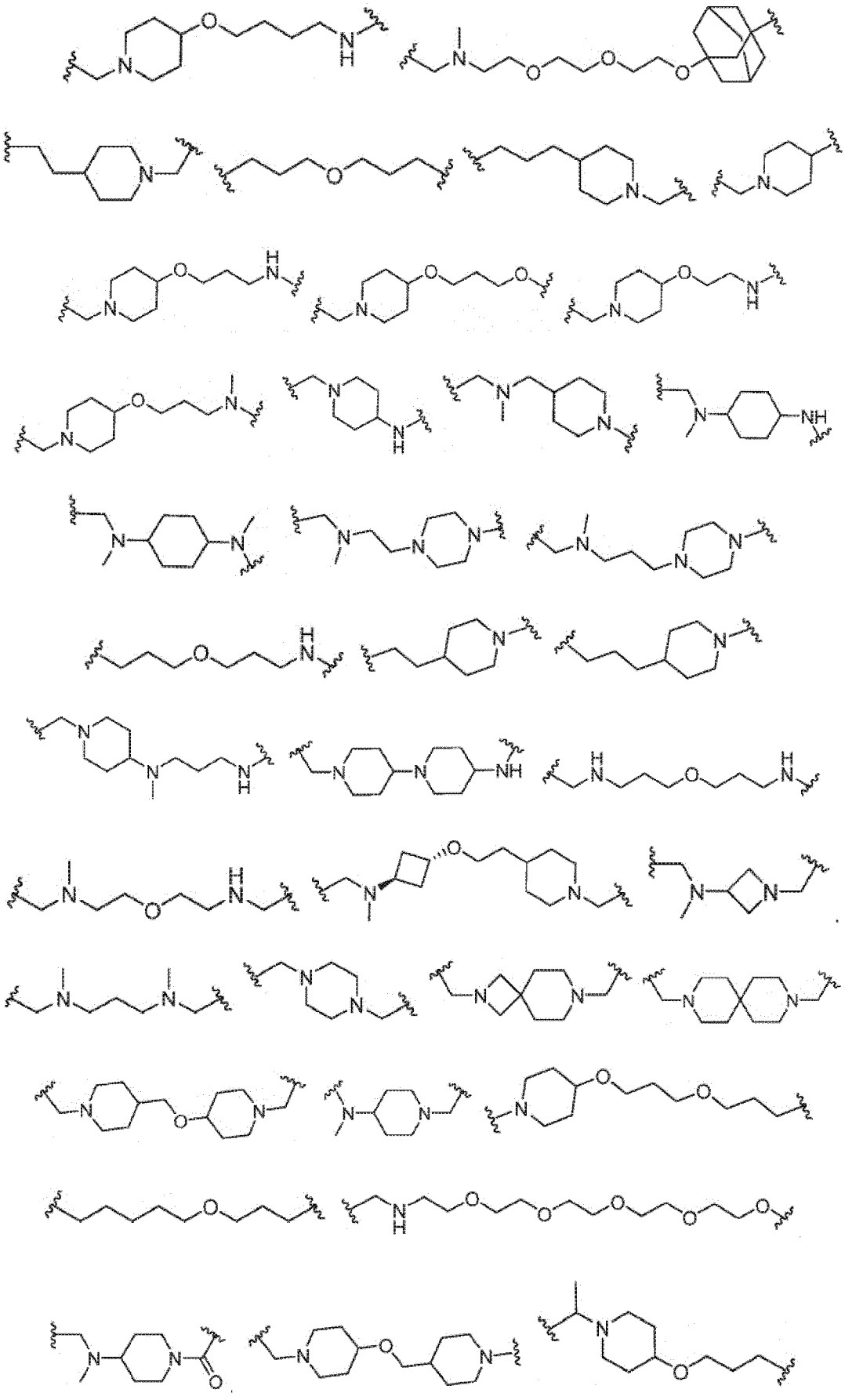


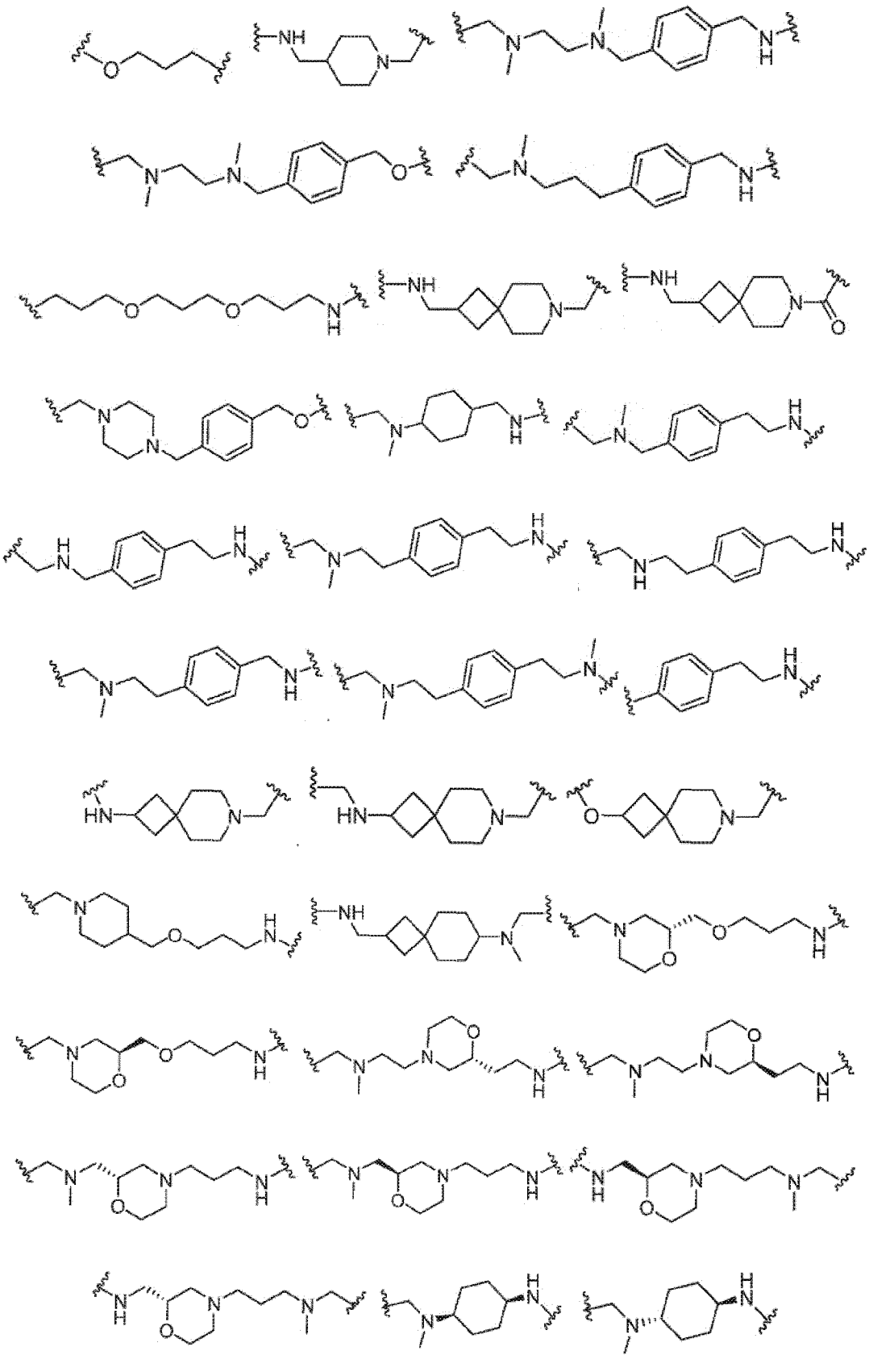


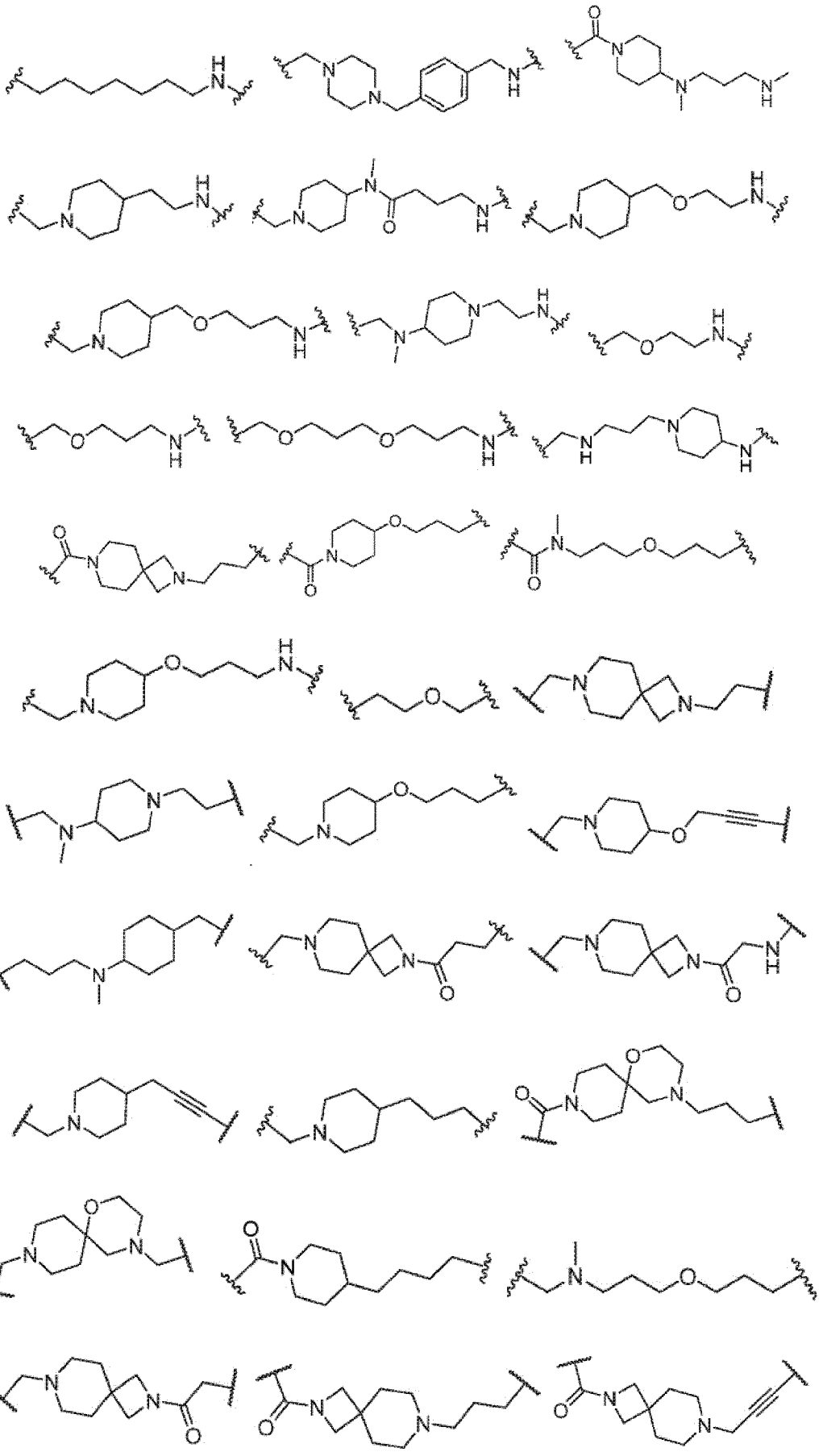


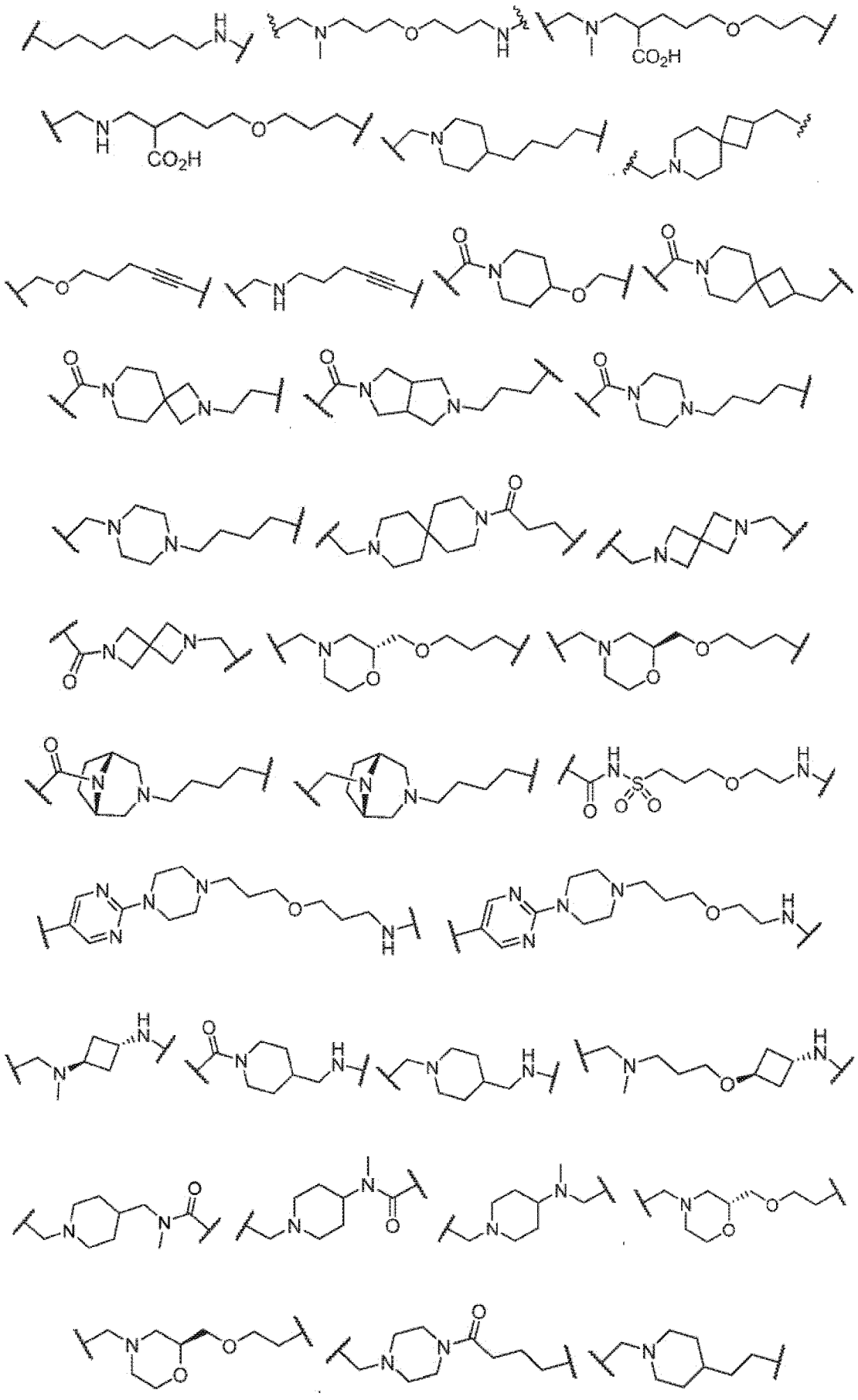


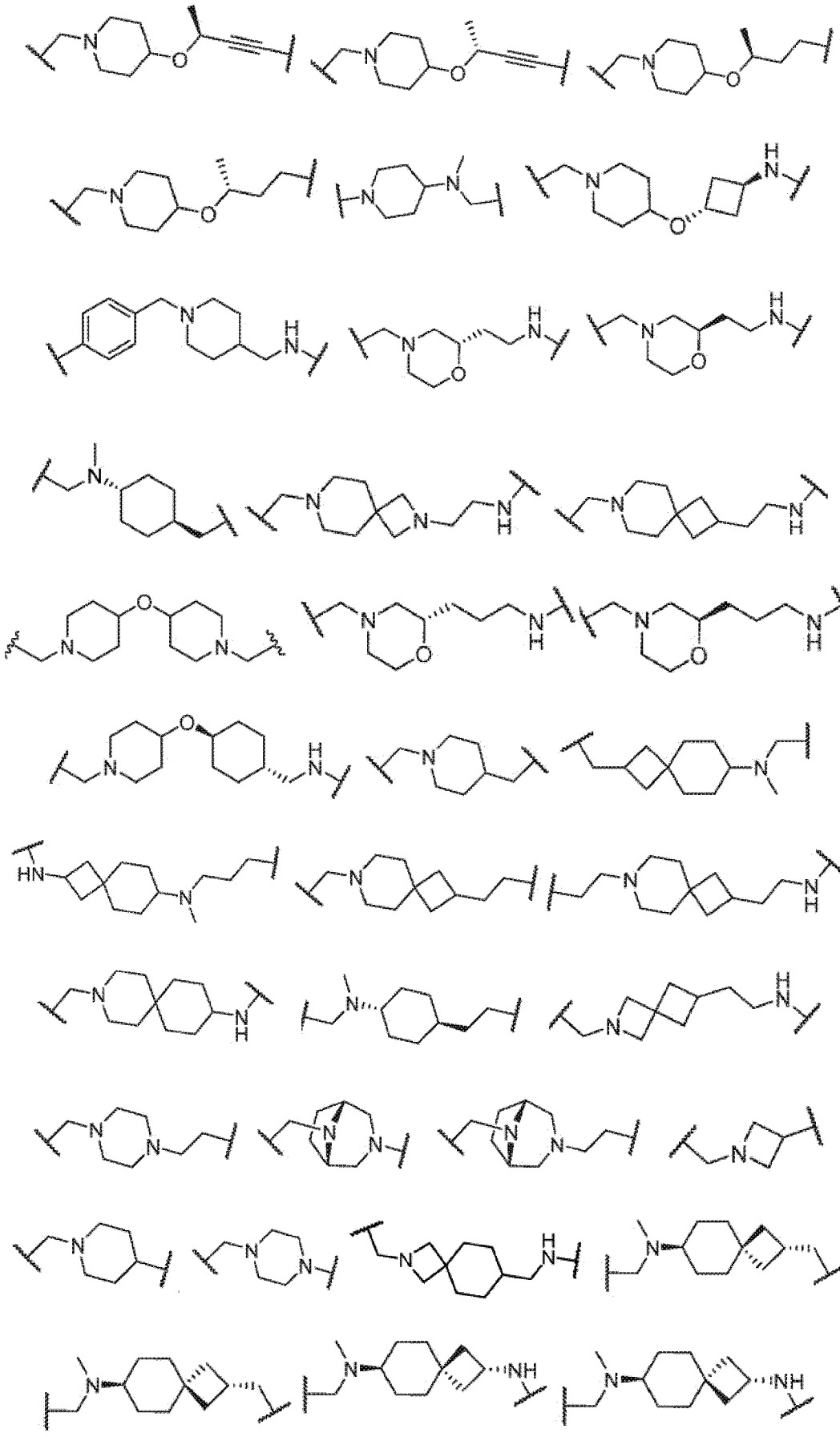


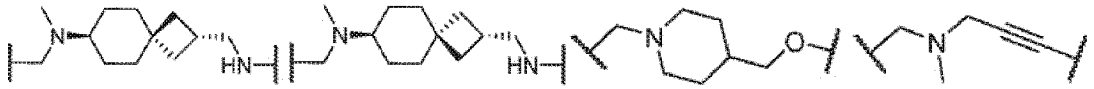


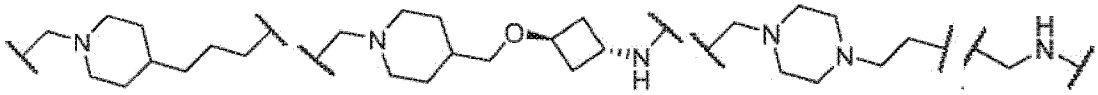


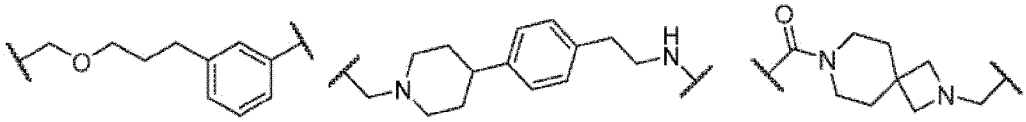


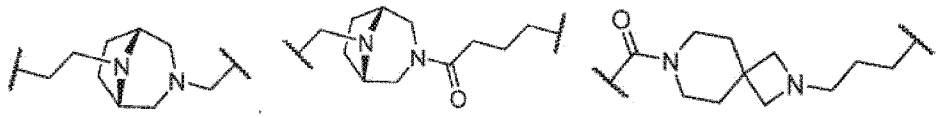


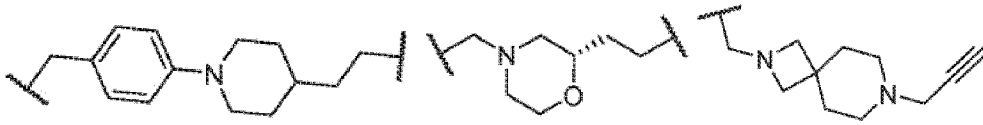


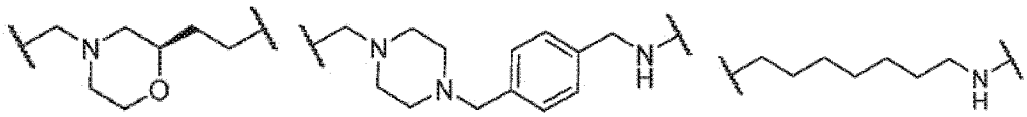


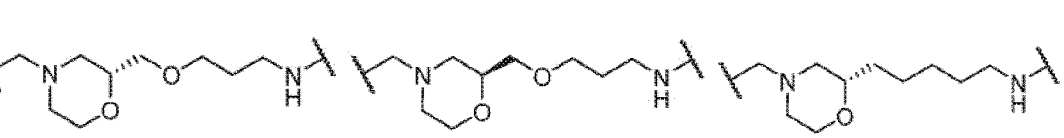


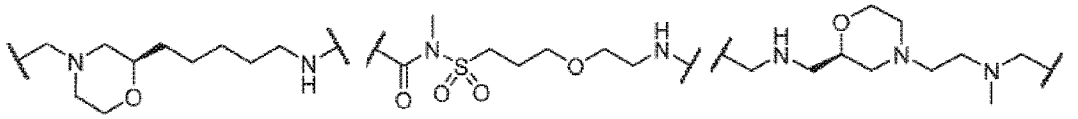


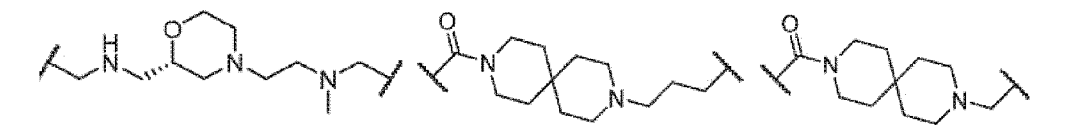


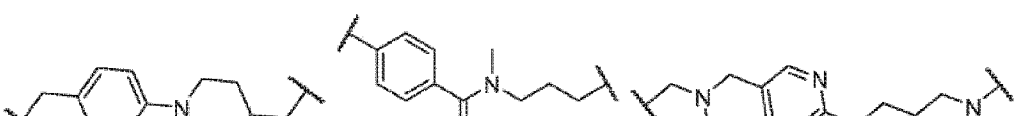


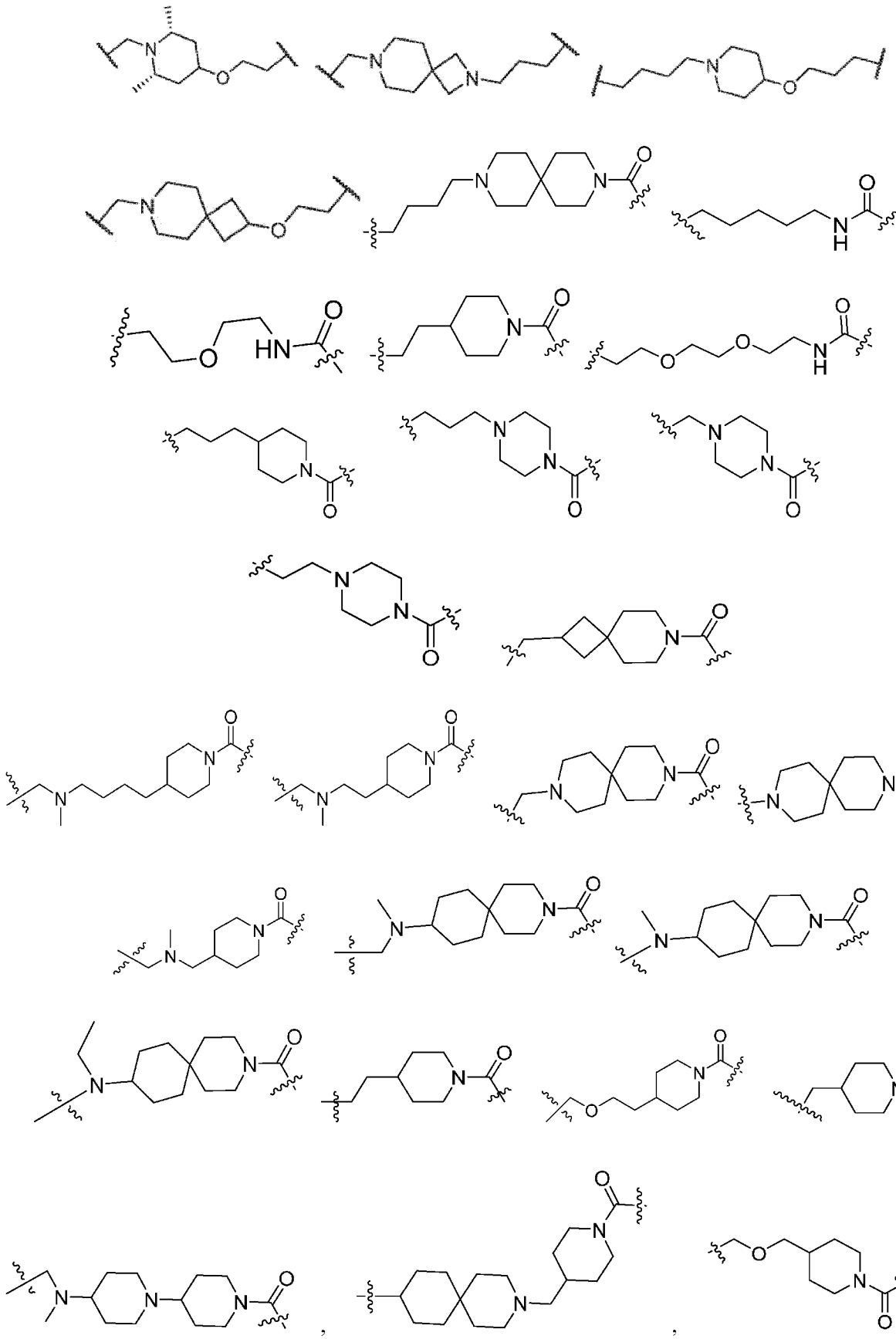


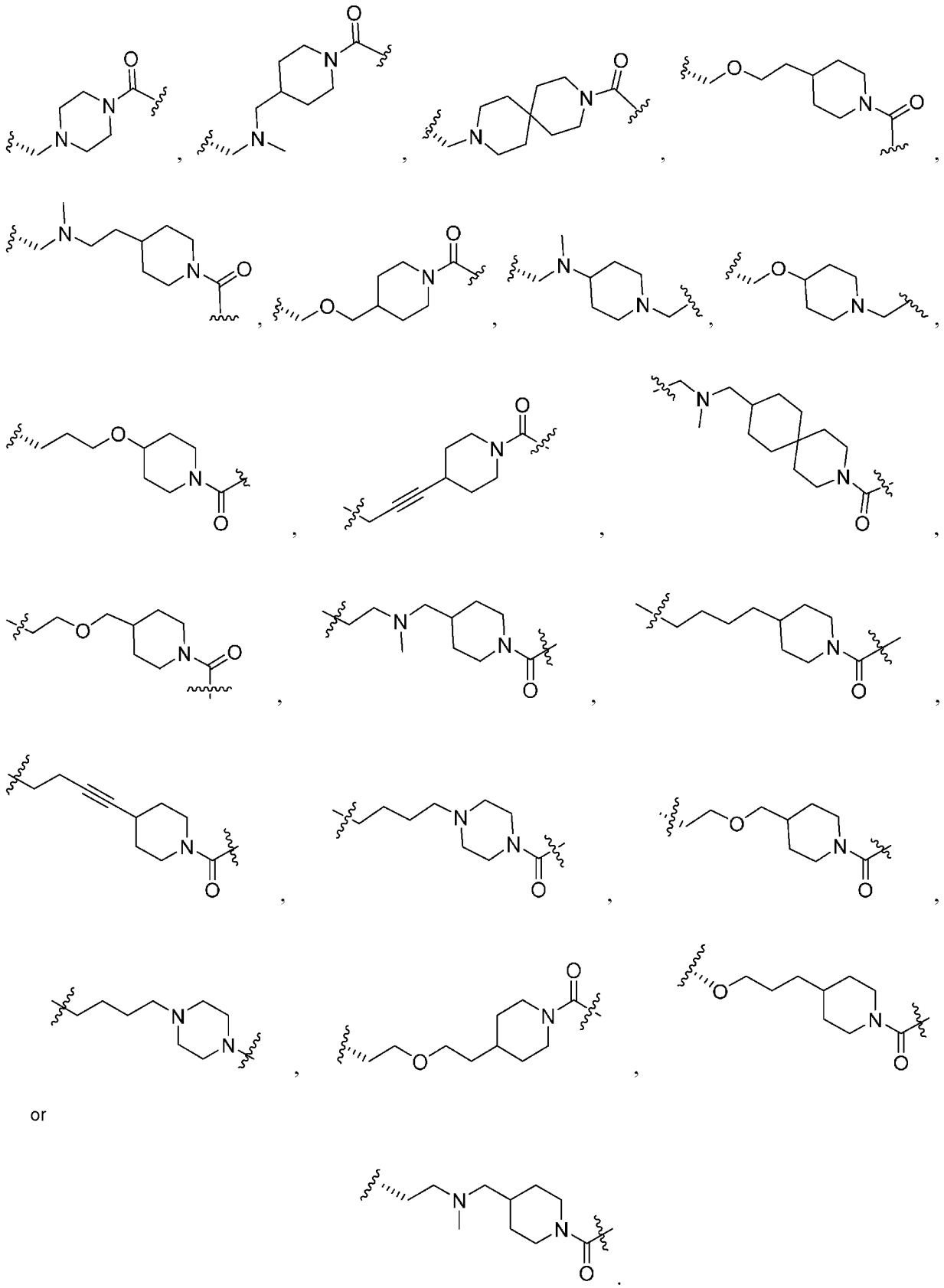






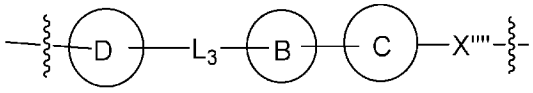






or

17. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 12, wherein the L is LA,



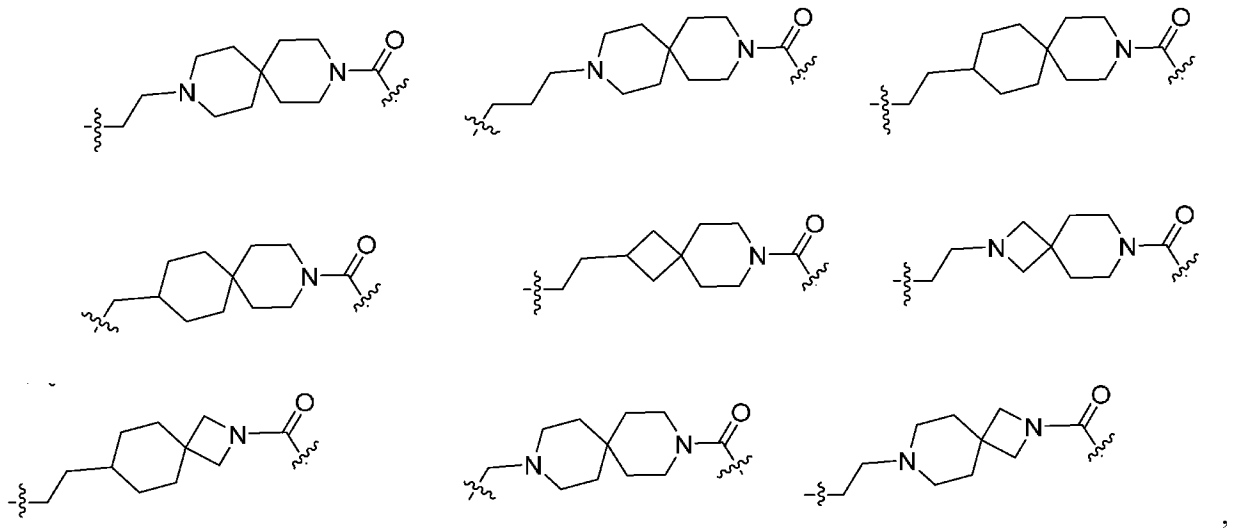
LA

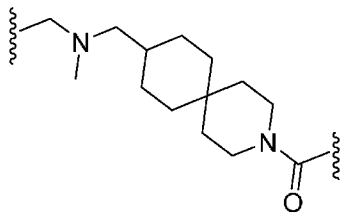
wherein in the LA:

ring D is absent, 6-10 membered aryl or 5-10 membered heteroaryl or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring B is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring C is absent, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
X"" is a bond, -NH-, -NCH_3-, -O-, -$C(CH_3)_2$-, -S-, -C=C-, -C≡C-, -CHF-, -$CHCF_3$-, -C(O)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -C(O)NH-, -$C(O)NCH_3$-, -NHC(O)-, -$(CH_2)_t$- or -$NCH_3C(O)$-; one or more methylene groups in the -$(CH_2)_t$- are optionally replaced by groups selected from -O-, -NH-, -C≡C-, -N(C_1-C_6 alkyl)- and -C(O)-, and t is 0, 1, 2, 3, 4, 5, 6 or 7;
L_3 is -$(CH_2)_k$-, wherein one or more methylene groups in the L_3 are optionally replaced by groups selected from -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -N(C_1-C_6 hydroxyalkyl)-, -C≡C-, -C(O)- or -N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

18. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 17, wherein the L is LA, and in the LA, ring D and ring B are absent, and ring C is 7-11 membered spiroheterocycloalkylene containing 1 or 2 nitrogen heteroatoms; X"" is -C(O)-; L_3 is -$(CH_2)_k$-; k is 1, 2, 3, 4 or 5.

19. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 18, wherein the L is selected from

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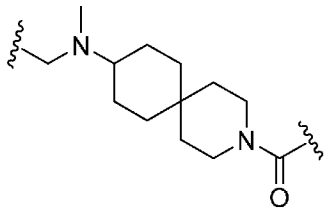
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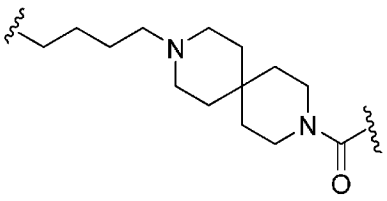

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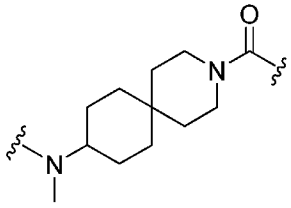
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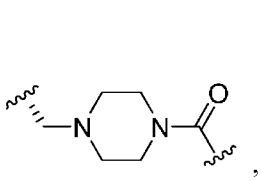
20. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 17, wherein the L is LA, and in the LA, ring D and ring B are absent, and ring C is 4-7 membered heterocycloalkyl containing 1 or 2 nitrogen heteroatoms; X'''' is -C(O)-, a bond or -CH_2-; L_3 is -$(CH_2)_k$-; k is 1, 2, 3, 4 or 5.

21. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 20, wherein the L is selected from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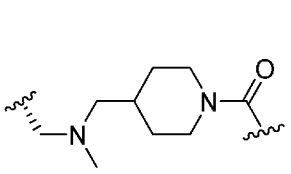
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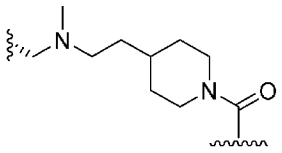
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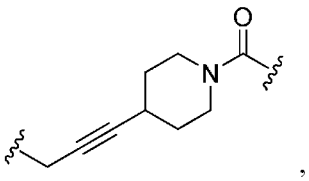
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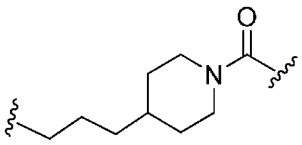
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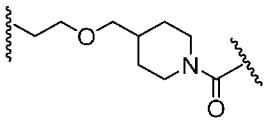
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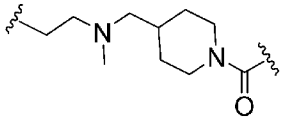
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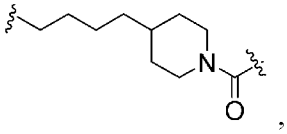
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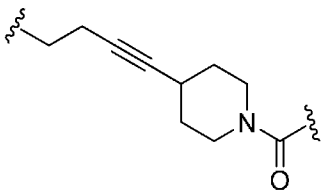
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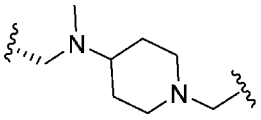
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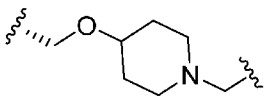
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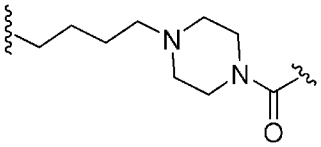
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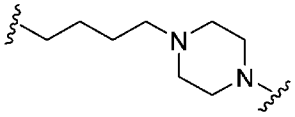
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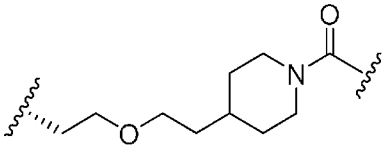
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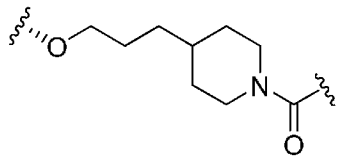
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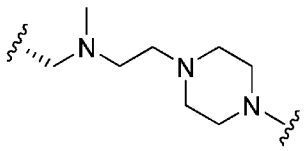
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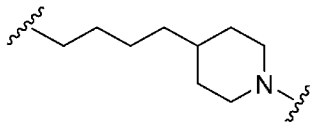
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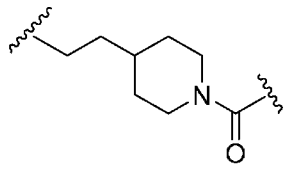
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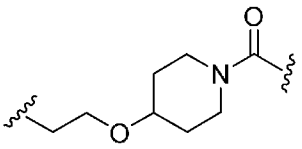
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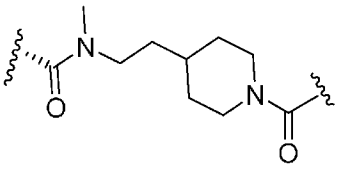
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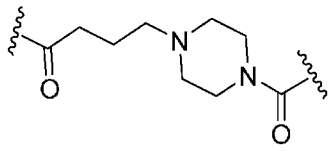
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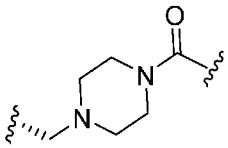
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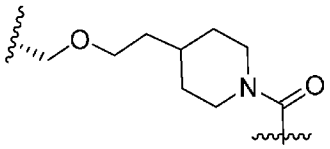
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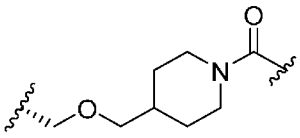
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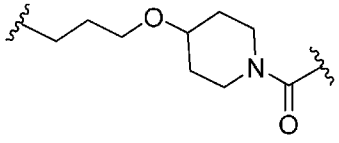
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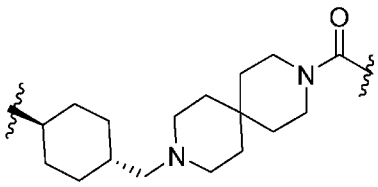
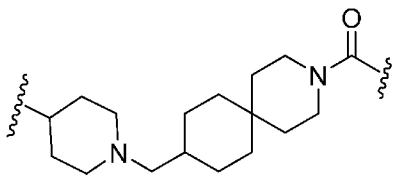
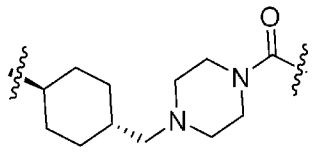
22. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 17, wherein the L is LA, and in the LA, ring D is C_4-C_7 membered cycloalkyl or 4-7 membered heterocycloalkyl, and ring B and ring C are absent or 5-11 membered heterocycloalkylene containing 1 or 2 nitrogen heteroatoms; X"" is -C(O)- or -$(CH_2)_t$-, and t is 0, 1, 2, 3, 4 or 5; L_3 is -$(CH_2)_k$-, and k is 1, 2, 3, 4 or 5.

23. The compound of formula 1, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 22, wherein the L is selected from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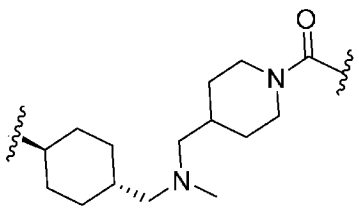
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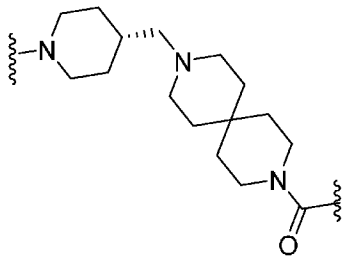
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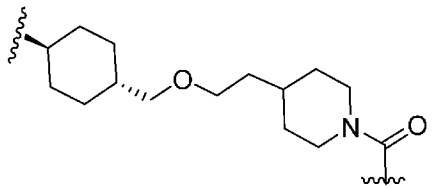
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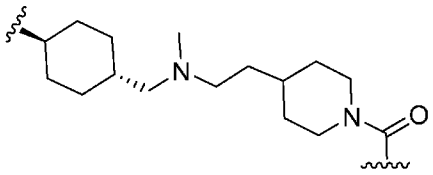
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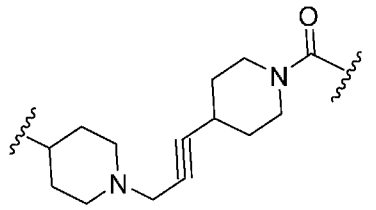
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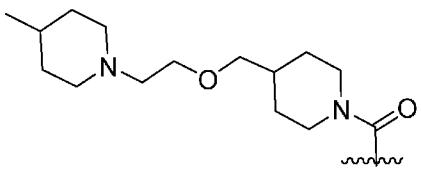
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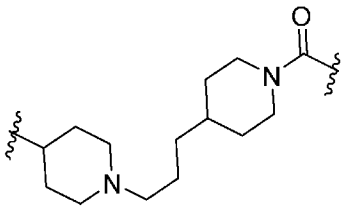
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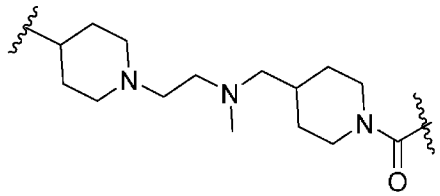
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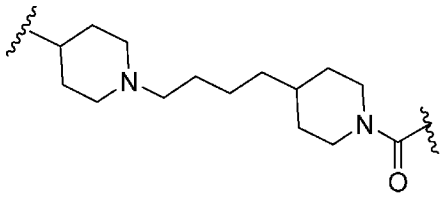
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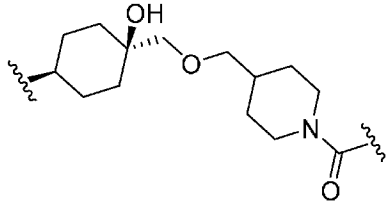
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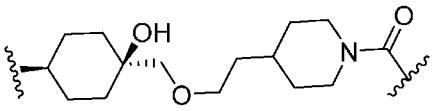
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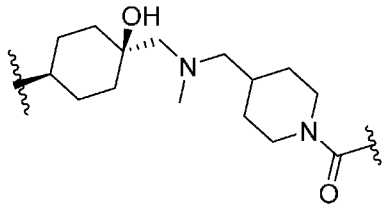
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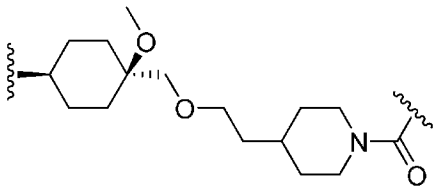
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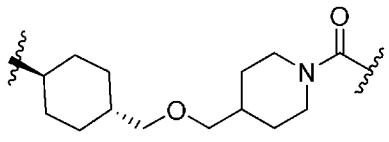
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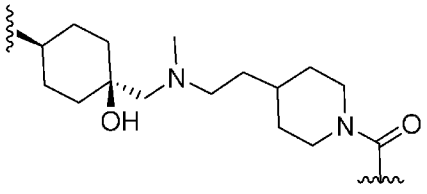
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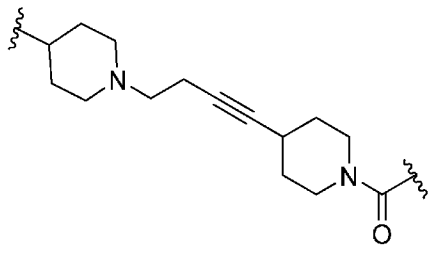
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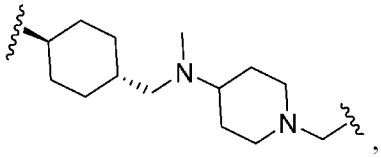
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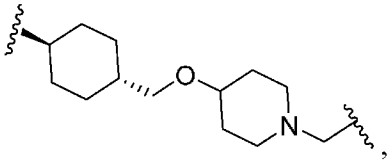
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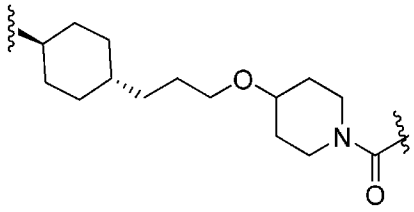
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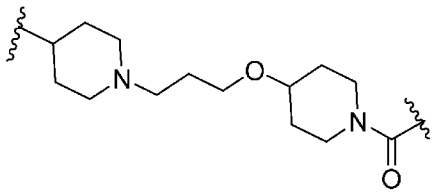
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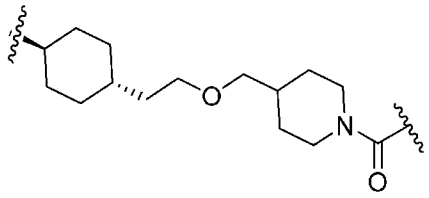
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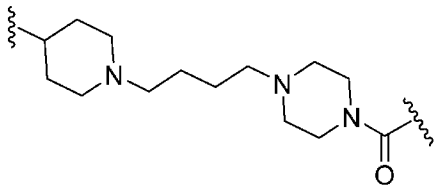
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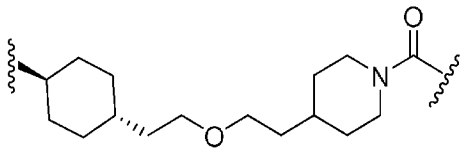
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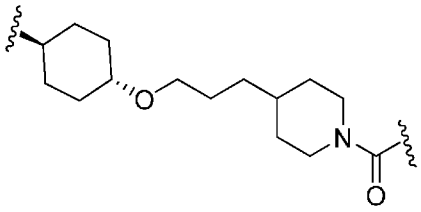
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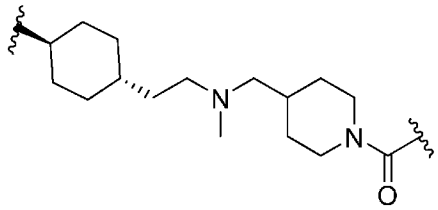
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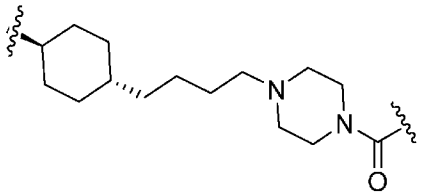
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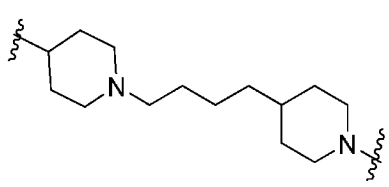
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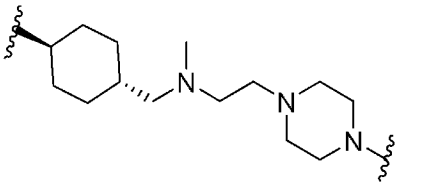
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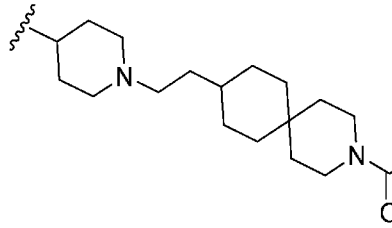
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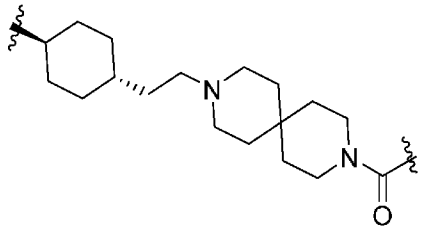
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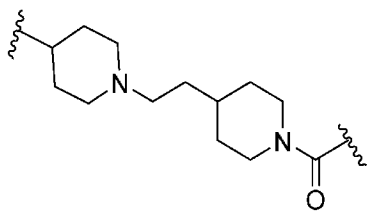

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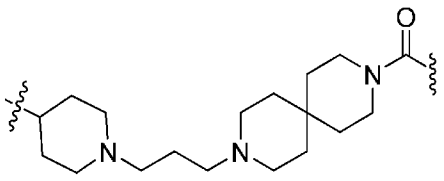

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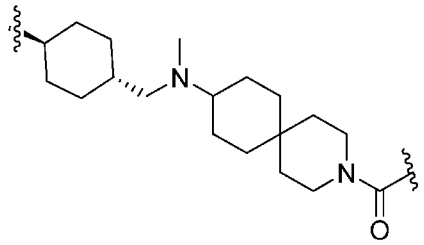

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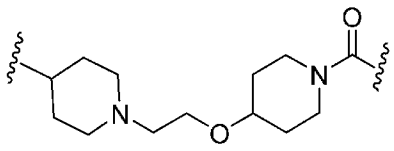

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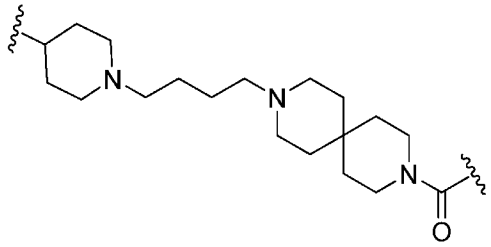

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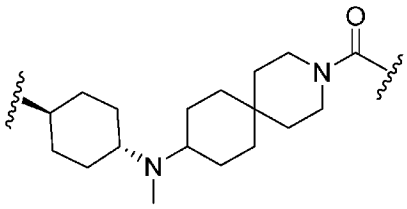

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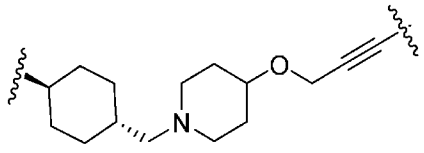

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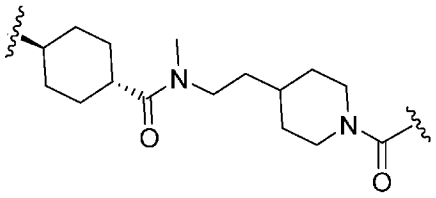

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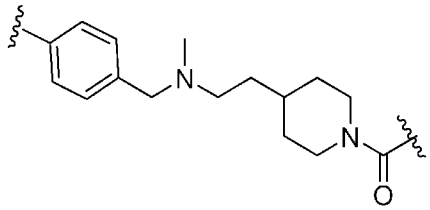

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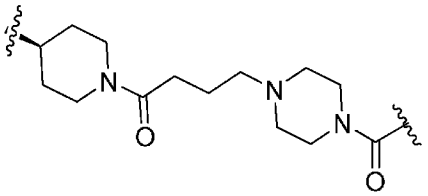

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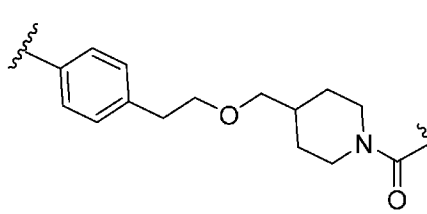

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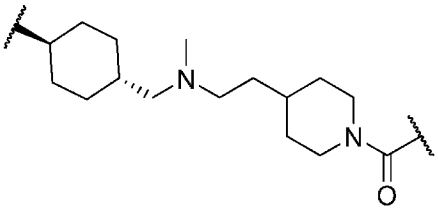

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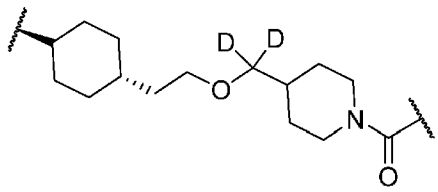
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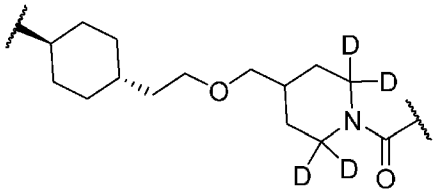
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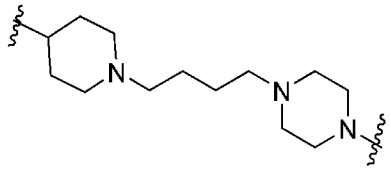
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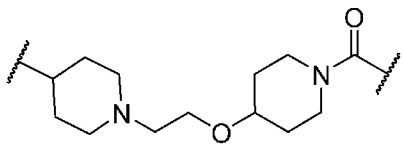
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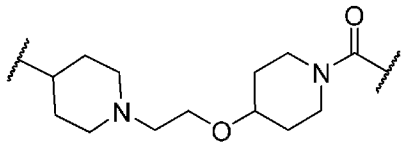
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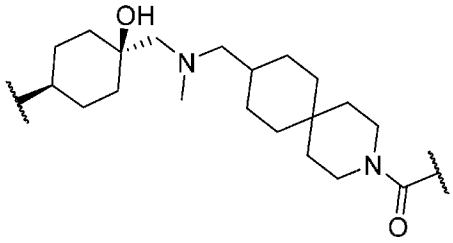

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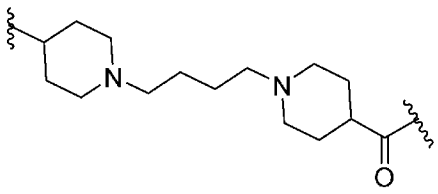
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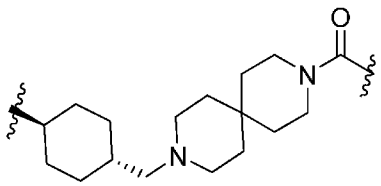
preferably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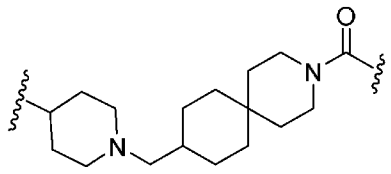
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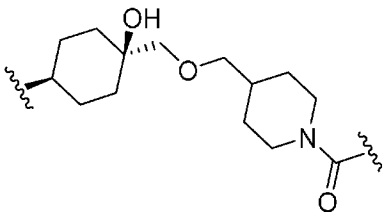
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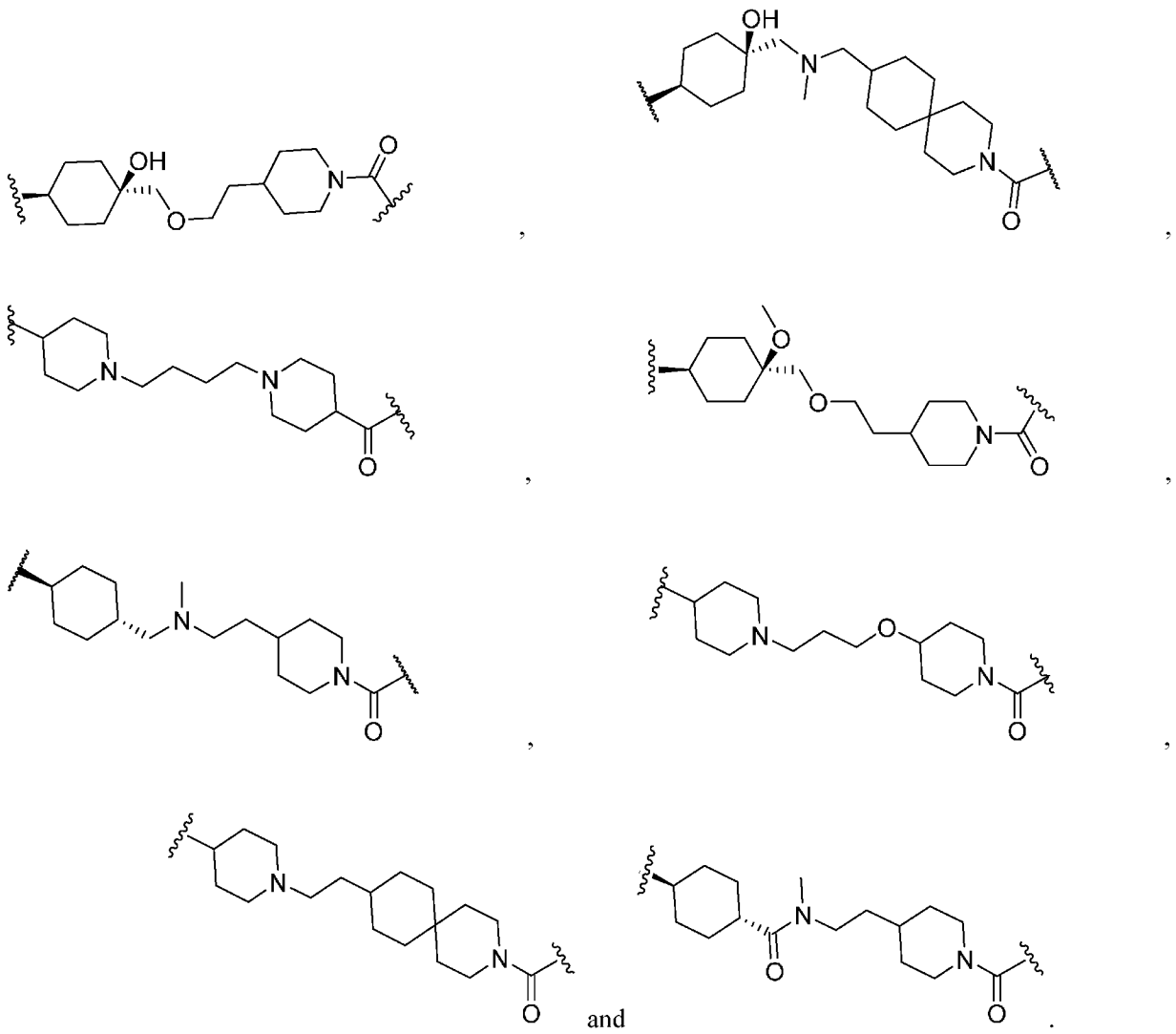
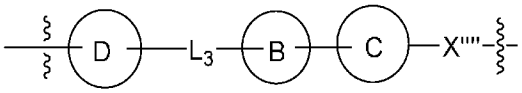


24. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein the L is the LA,



LA

wherein in the LA:

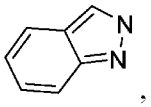
ring D is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);

ring B is absent or is C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl. Ci-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);

ring C is absent, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, Ci-

C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
X"" is a bond, -NH-, -NCH_3-, -O-, -$C(CH_3)_2$-, -S-, -C=C-, -C≡C-, -CHF-, -$CHCF_3$-, -C(O)-, -S(O)-, -$S(O)_2$-,-C(O)O-, -OC(O)-, -C(O)NH-, -$C(O)NCH_3$-, -NHC(O)- or -$NCH_3C(O)$-;
L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from deuterium, -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -C≡C-, -C(O)-, -N(C_1-C_6 hydroxyalkyl)- or -N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
and/or, when ring A" is 5-11 membered bicyclic heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O or S, ring D is 6-10 membered aryl, 5-10 membered heteroaryl, C_3-C_{12} cycloalkylene or 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, Ci-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl and -O-(C_1-C_6 alkyl).

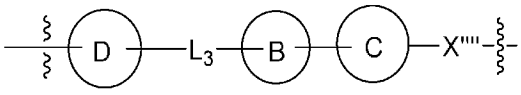
25. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein when ring A" is



the ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are independently substituted with 1, 2 or 3 hydroxy groups or with 1, 2 or 3 -O-(C_1-C_6 alkyl) groups.

26. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein

the L is LA,



LA

wherein the LA is scheme 1, scheme 2, scheme 3 or scheme 4;

scheme 1:

ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, hydroxy or -O-(C_1-C_6 alkyl);
ring B is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl or -O-(C_1-C_6 alkyl);
ring C is absent;
X"" is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are replaced by groups selected from -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -C(O)-, -N(C_1-C_6 hydroxyalkyl)- or -N(C_3-C_8 cycloalkyl)-, and k is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

scheme 2:

ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, hydroxy or methoxy;
ring B is 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 ni-

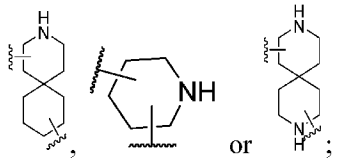
trogen heteroatoms;
ring C is absent;
X"" is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein k is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

scheme 3:

ring D is C_3-C_{12} cycloalkylene or is 3-12 membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cycloalkylene and heterocycloalkylene are optionally substituted with substituents selected from halogen, hydroxy or methoxy;
ring B is 3-12 membered heterocycloalkylene containing 1-2 heteroatoms selected from N, O or S;
ring C is absent;
X"" is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein k is 1, 2, 3 or 4;

scheme 4:

ring D is cyclohexylene or is 6-membered heterocycloalkylene containing 1-2 N heteroatoms, wherein the cyclohexylene and 6-membered heterocycloalkylene are optionally substituted with substituents selected from halogen, hydroxy or methoxy;
ring B is

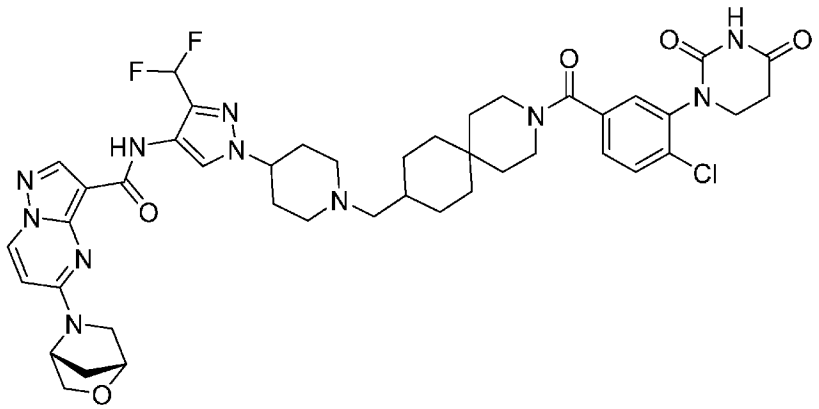


ring C is absent;
X"" is -C(O)-;
L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are replaced by groups selected from -O-, -NH-, -N(C_1-C_6 alkyl)-, -N(C_1-C_6 haloalkyl)-, -C(O)-, -N(C_1-C_6 hydroxyalkyl)- or -N(C_3-C_8 cycloalkyl)-, and k is 1, 2, 3 or 4.

27. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein

in the LA, ring D is 6-10 membered aryl, 4-7 membered saturated monocyclic heterocycloalkylene containing 1 or 2 nitrogen heteroatoms, or 7-11 membered spiroheterocycloalkylene or fused heterocycloalkylene containing 1 or 2 nitrogen heteroatoms;
and/or, ring C is 4-11 membered saturated or partially unsaturated spirocycloalkylene, 4-11 membered saturated or partially unsaturated fused cycloalkylene, 8-10 membered bicyclic saturated or partially unsaturated cycloalkylene, 4-7 membered saturated or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated or partially unsaturated spiroheterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 4-11 membered saturated and/or partially unsaturated fused heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, 8-10 membered bicyclic saturated and/or partially unsaturated heterocycloalkylene having 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with substituents selected from deuterium, halogen, oxo, cyano, amino, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl and -O-(C_1-C_6 alkyl);
and/or, in the LA, L_3 is -$(CH_2)_k$-, wherein one or two methylene groups in the L_3 are optionally replaced by groups selected from deuterium, -C(O)-, -C≡C-, -O-, -NH-, -NCH_3- or -NCH_2CH_3-; k is 1, 2, 3 or 4.

28. The compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of formula I is



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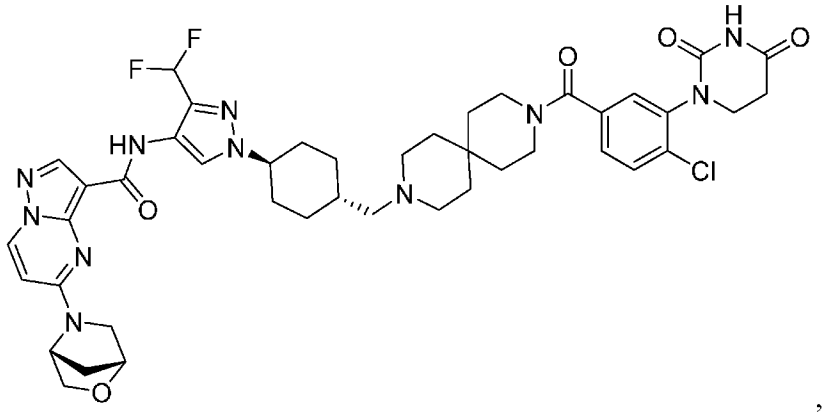

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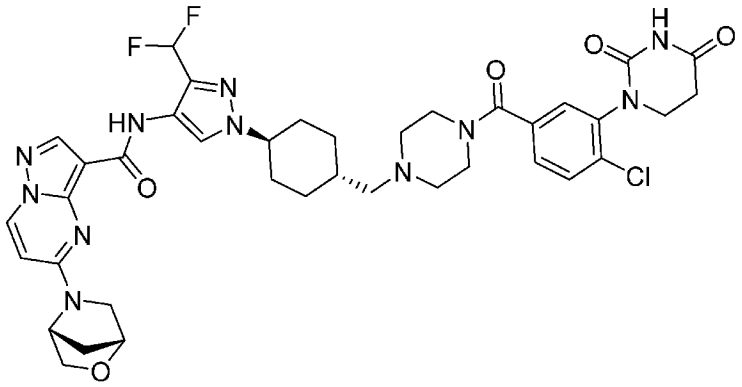

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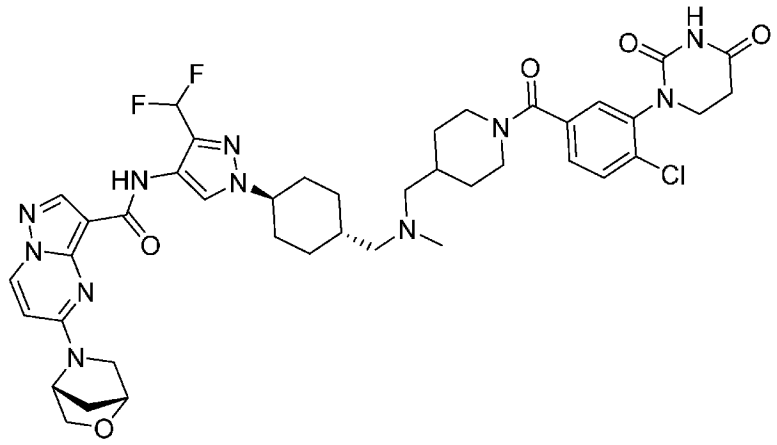

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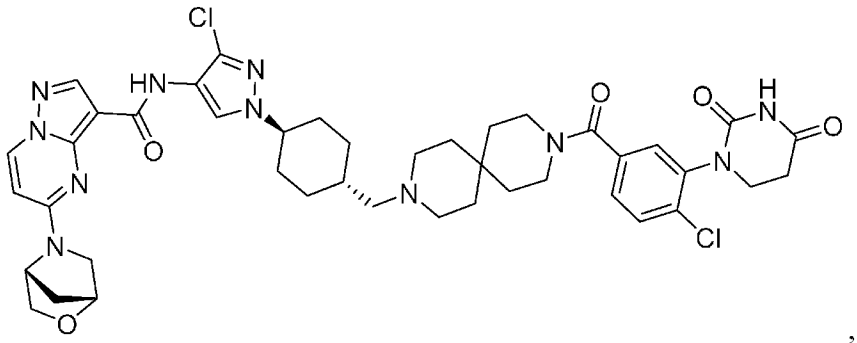

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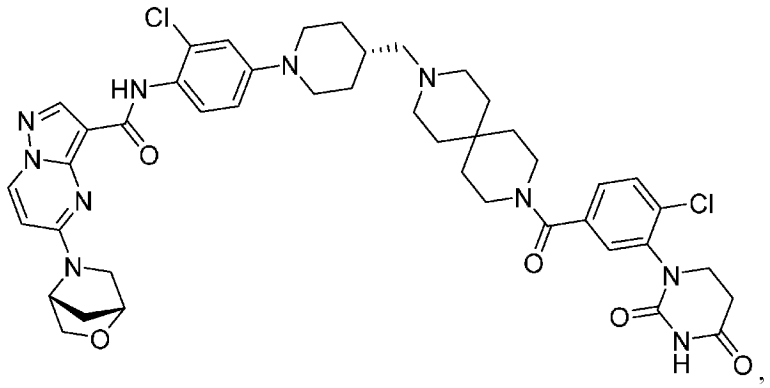

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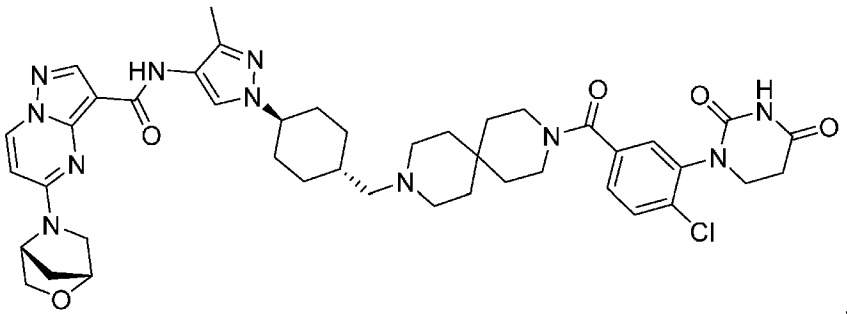

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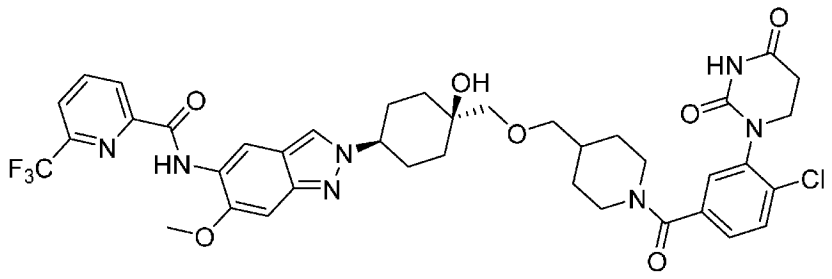

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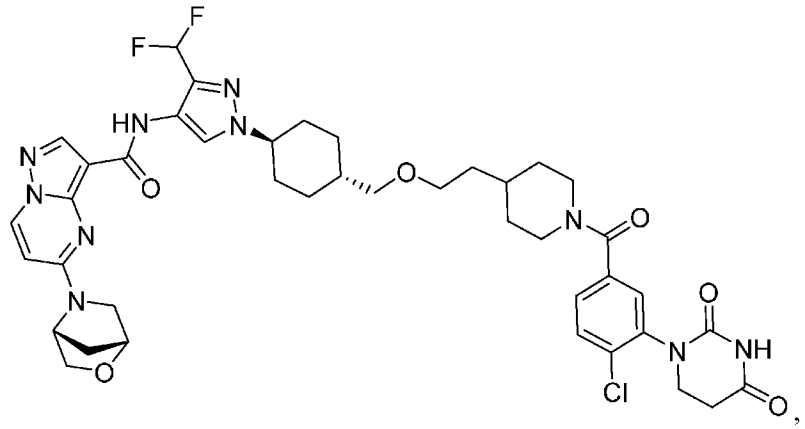

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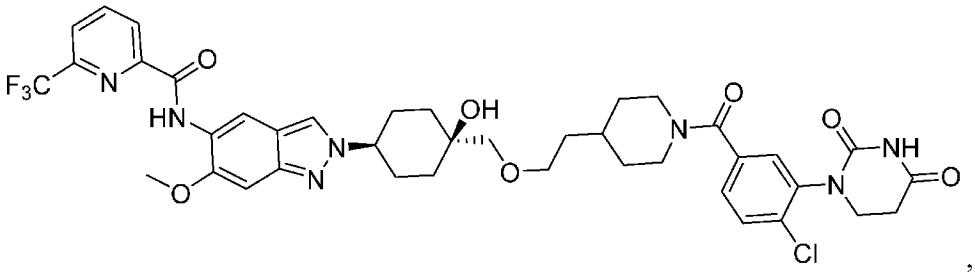

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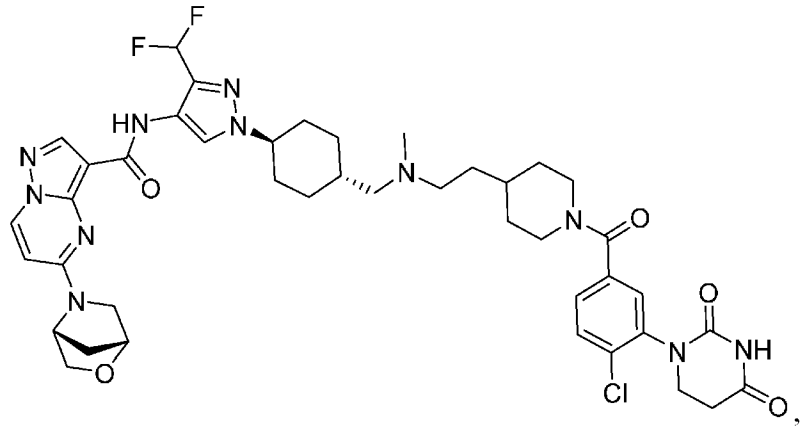

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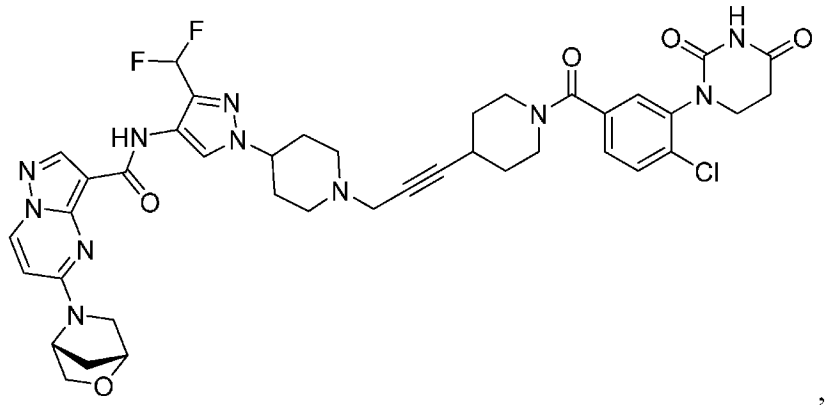

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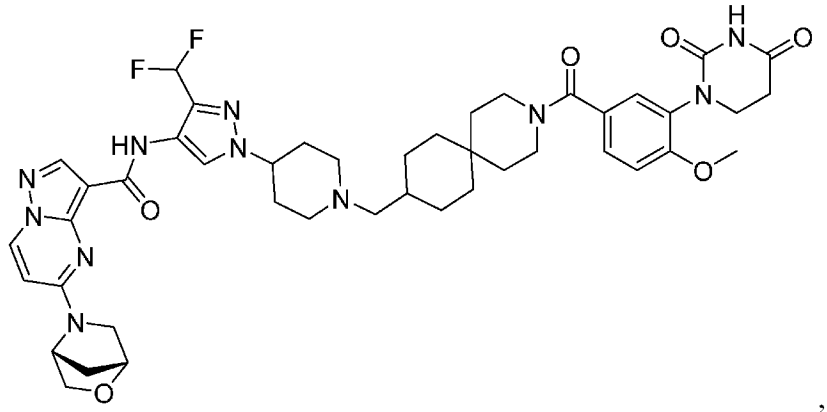

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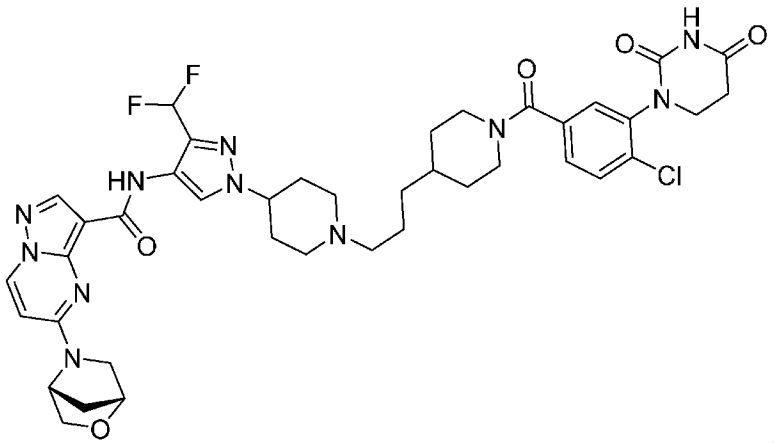

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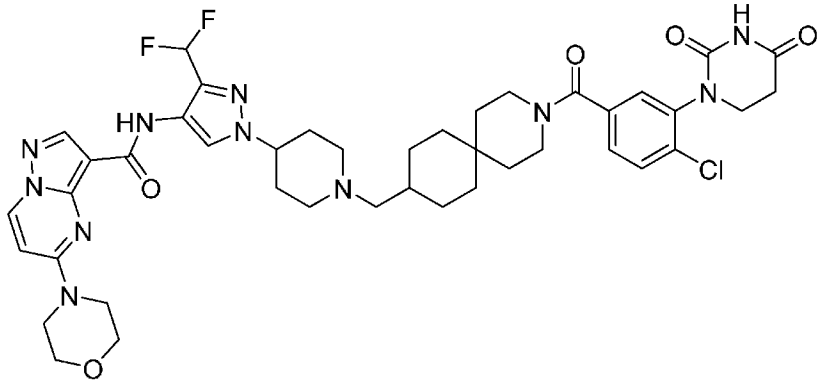

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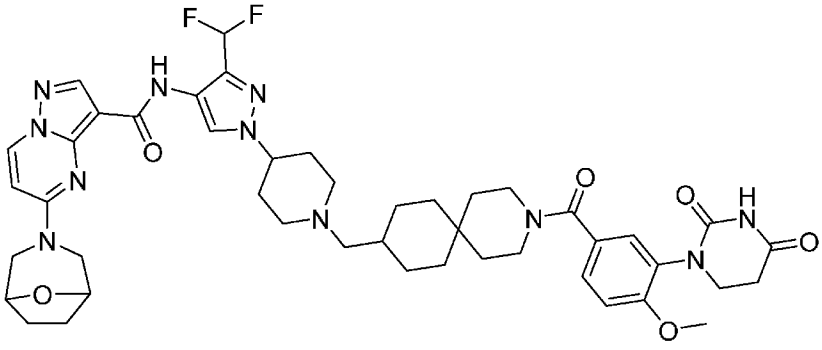

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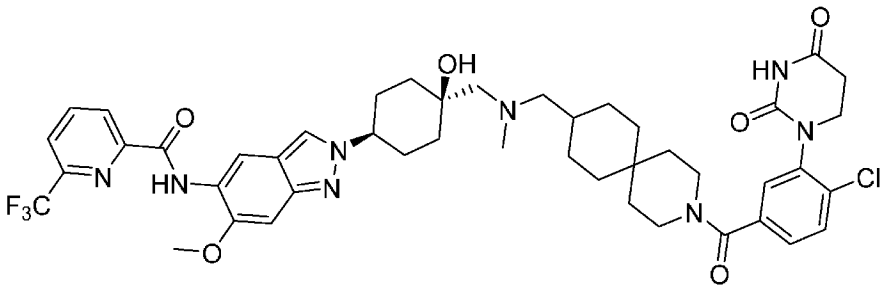

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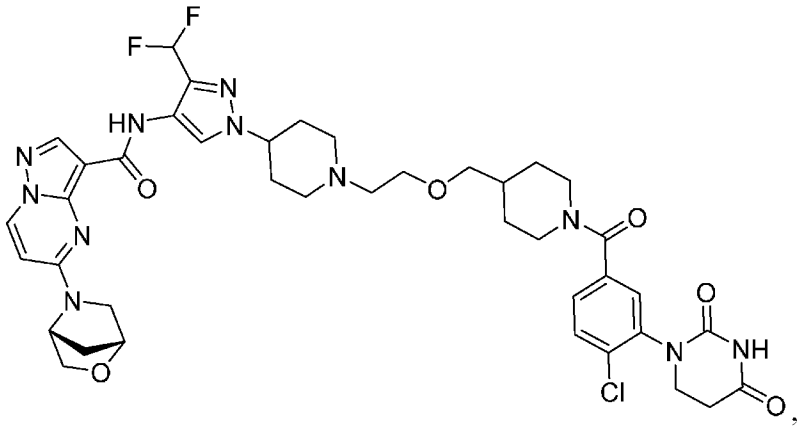

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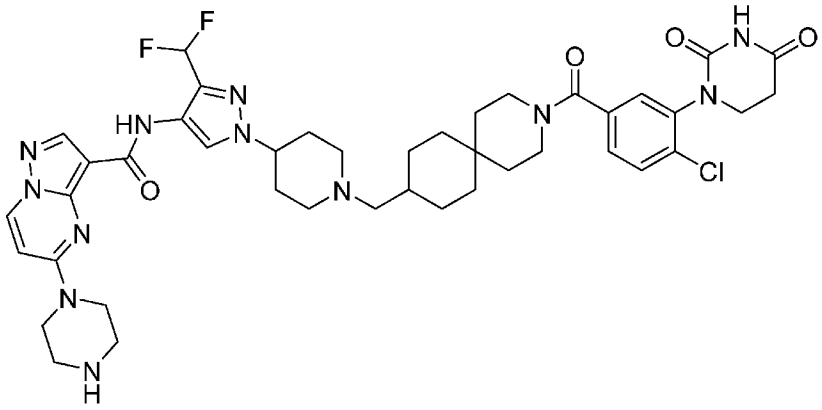

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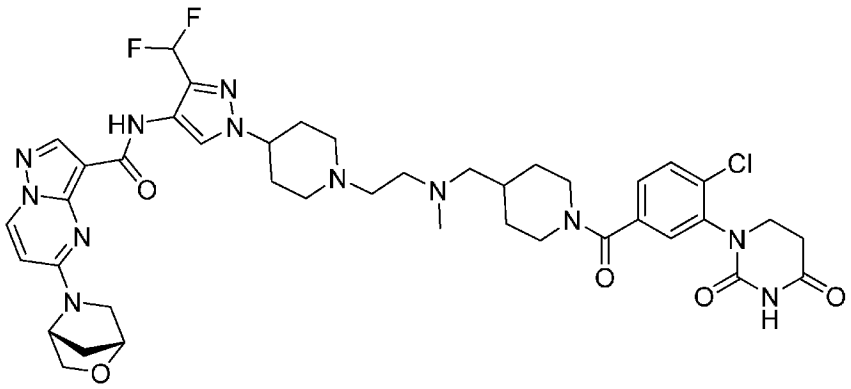

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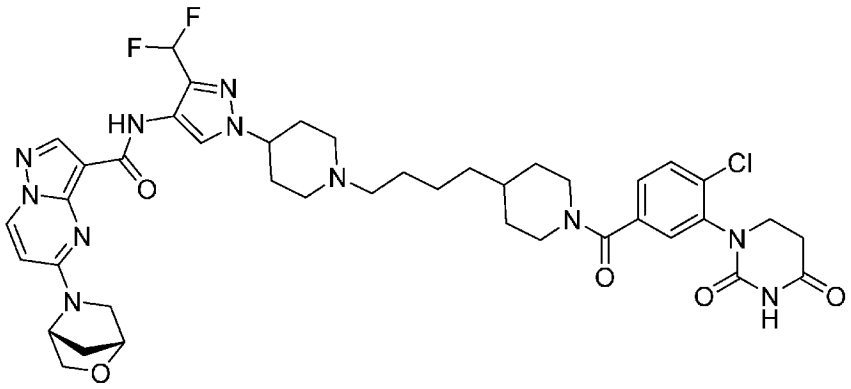

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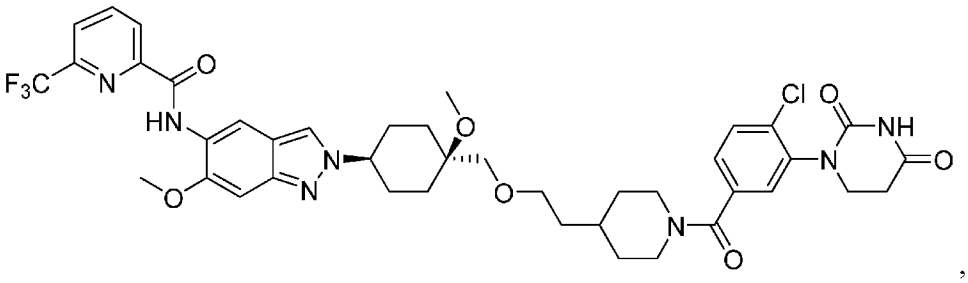

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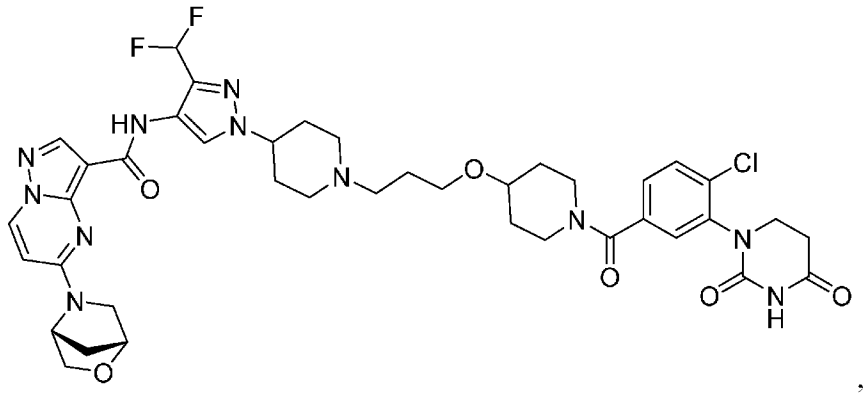

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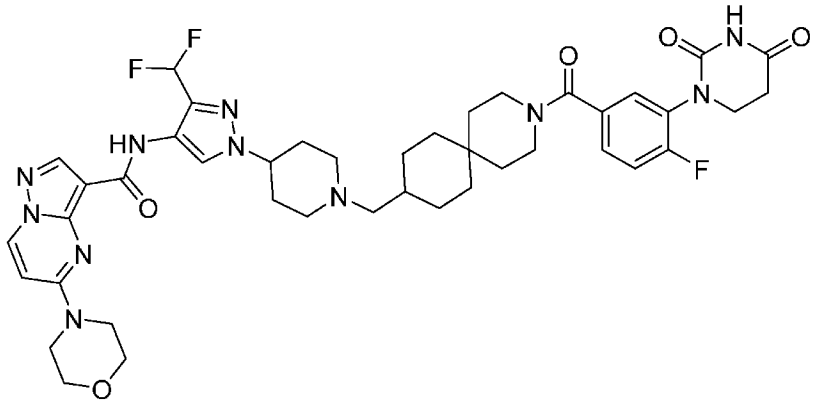

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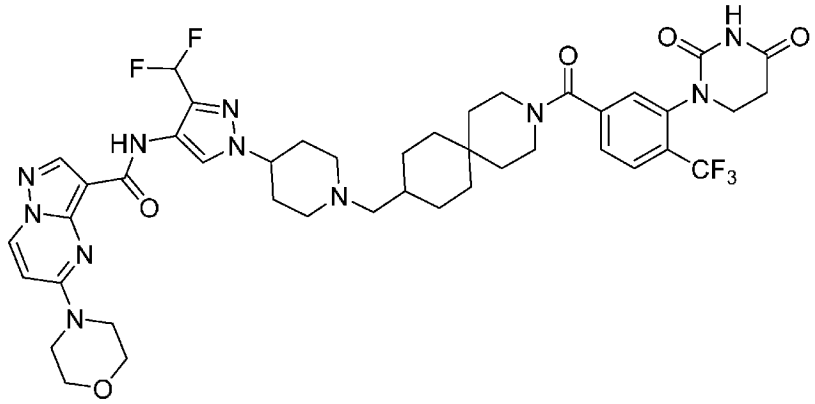

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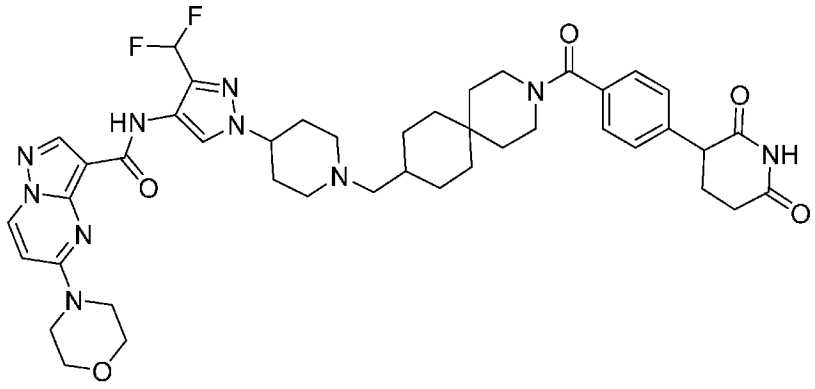

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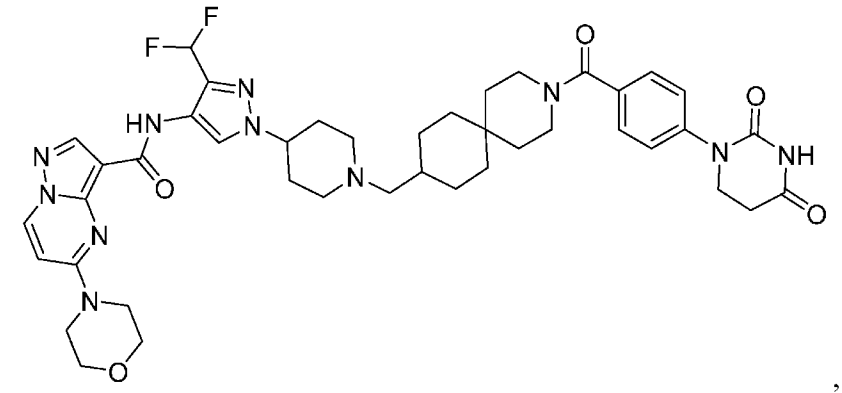

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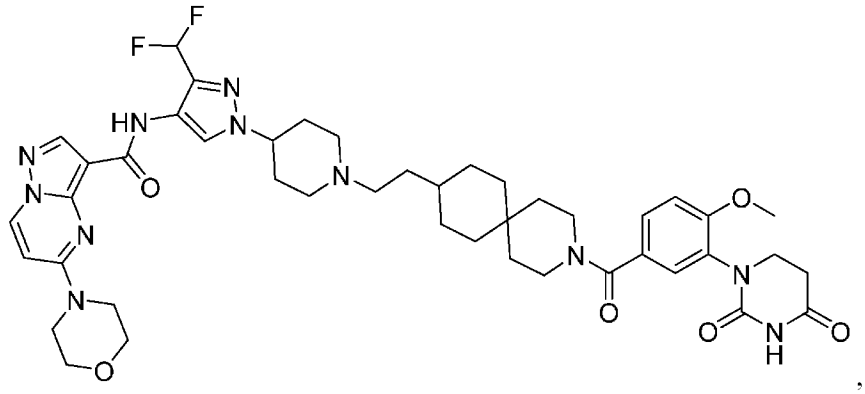

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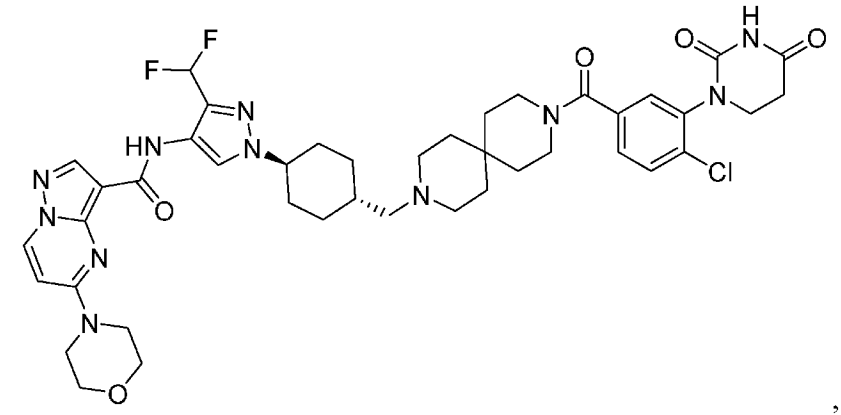

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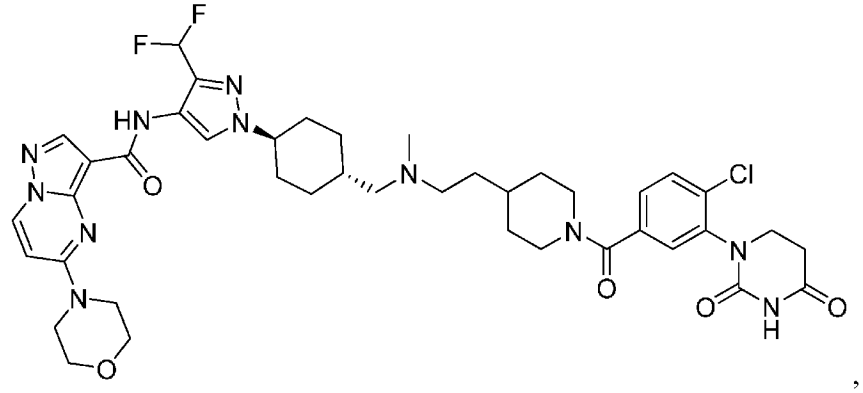

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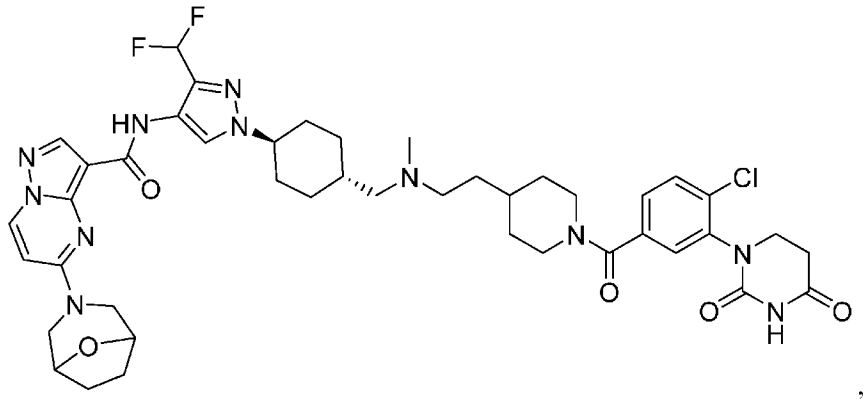

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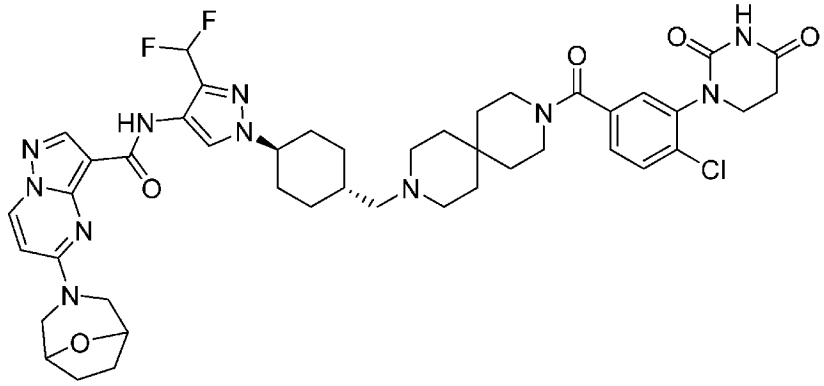

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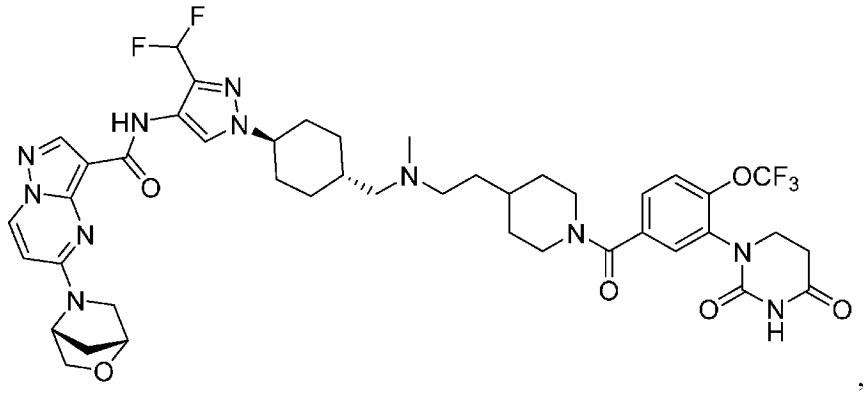

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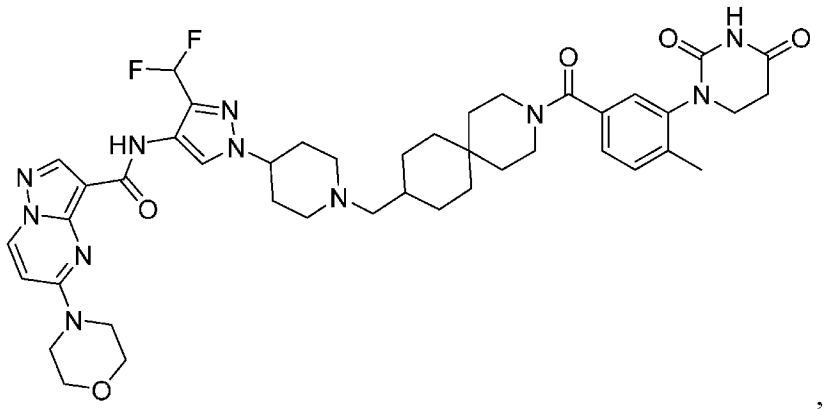

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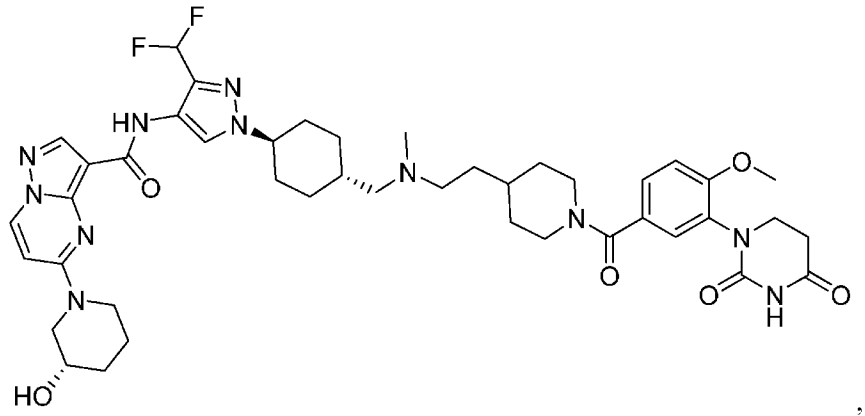

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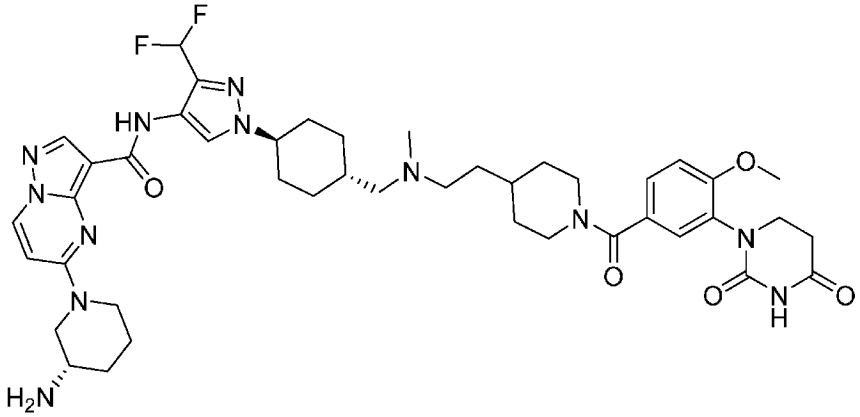

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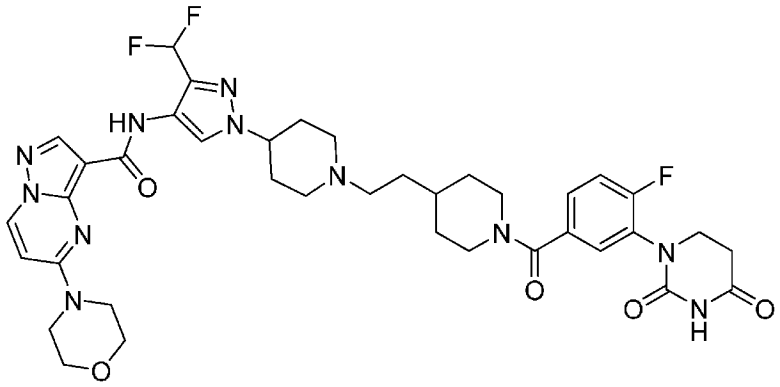

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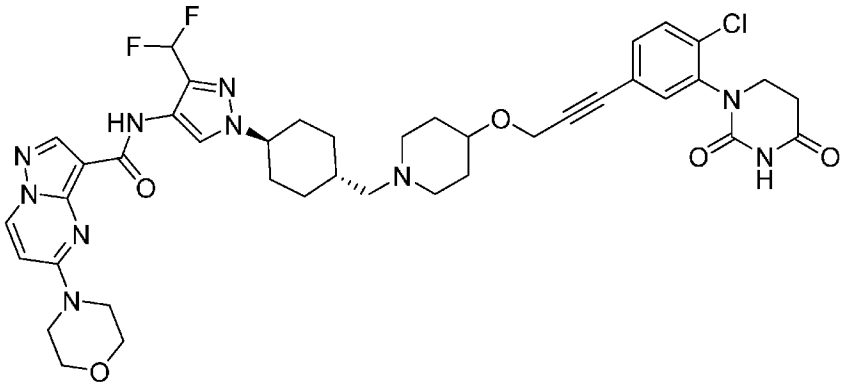

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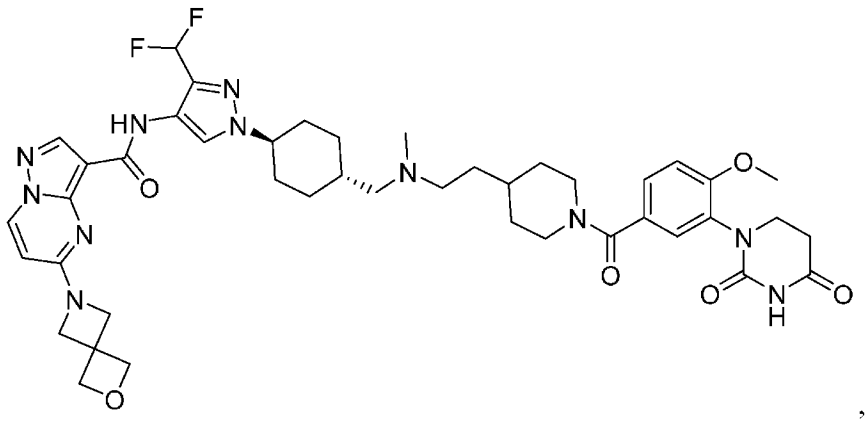

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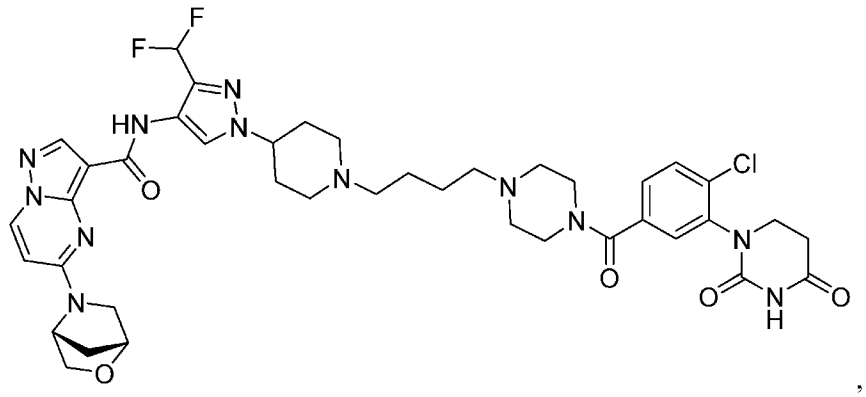

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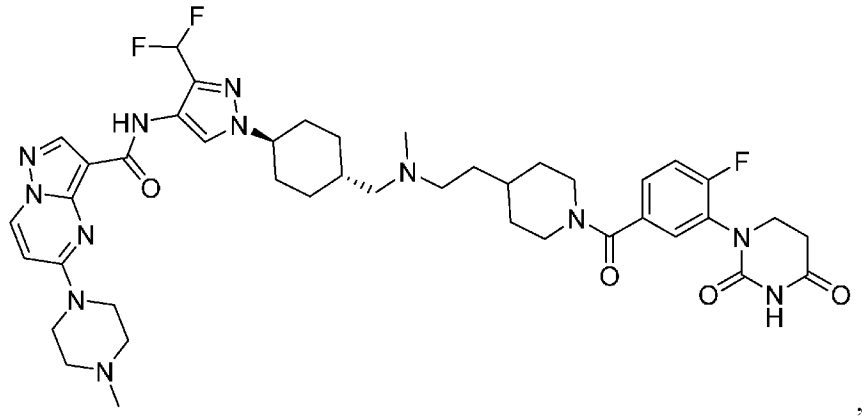

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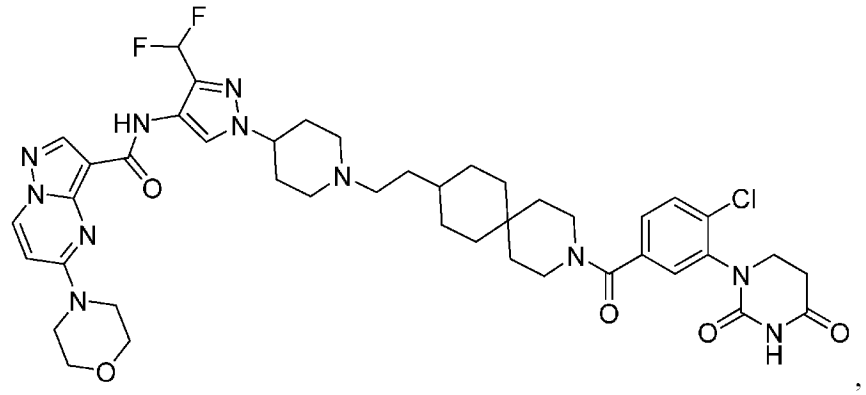

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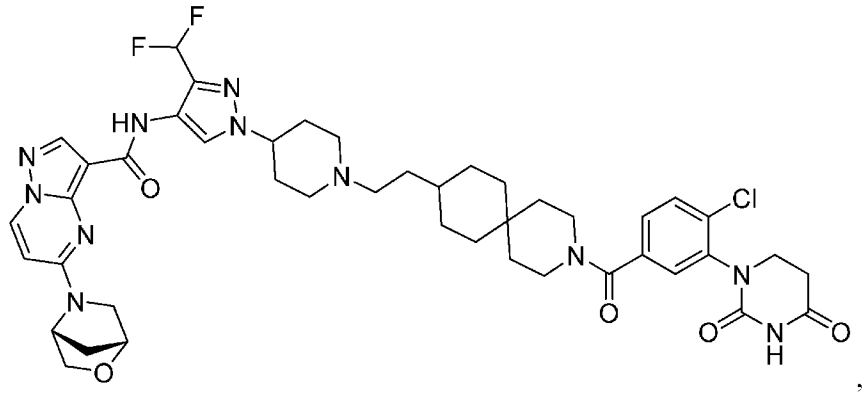

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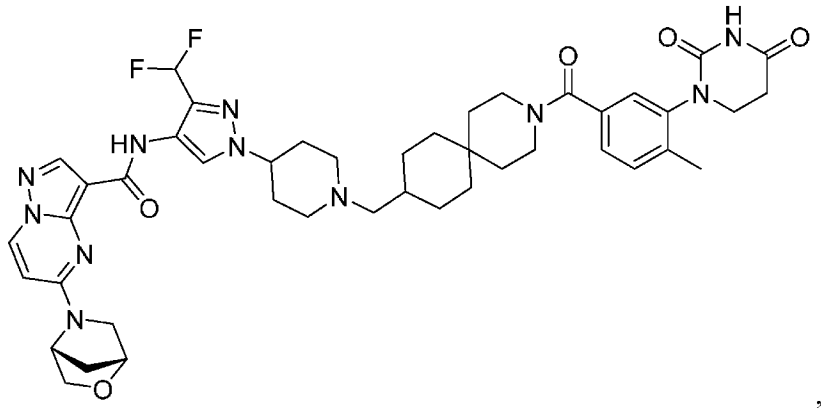

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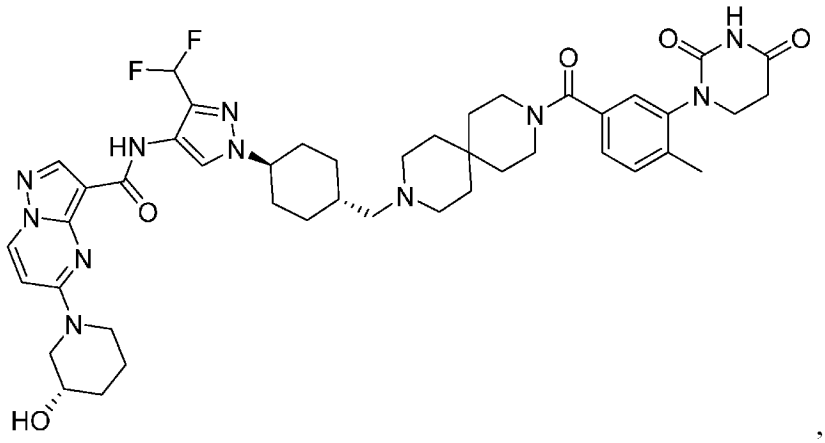

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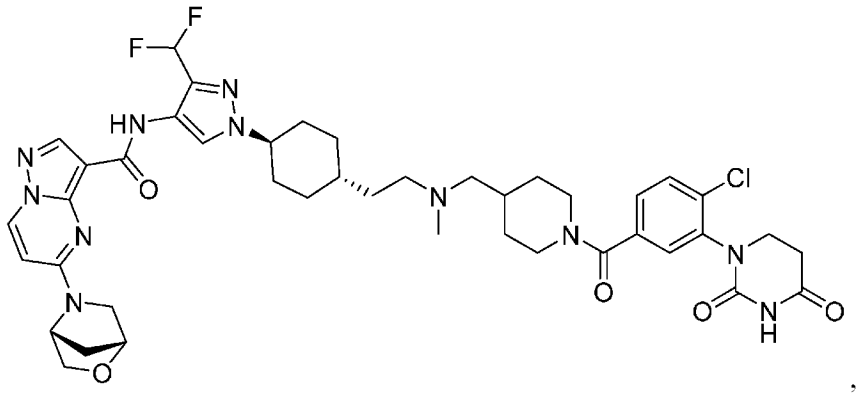

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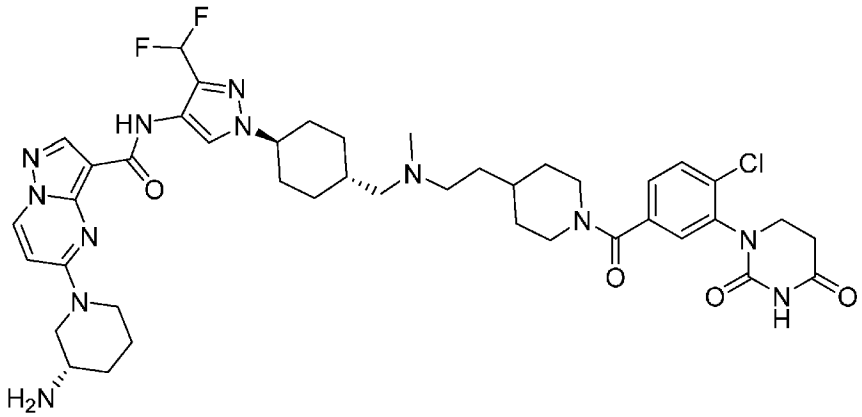

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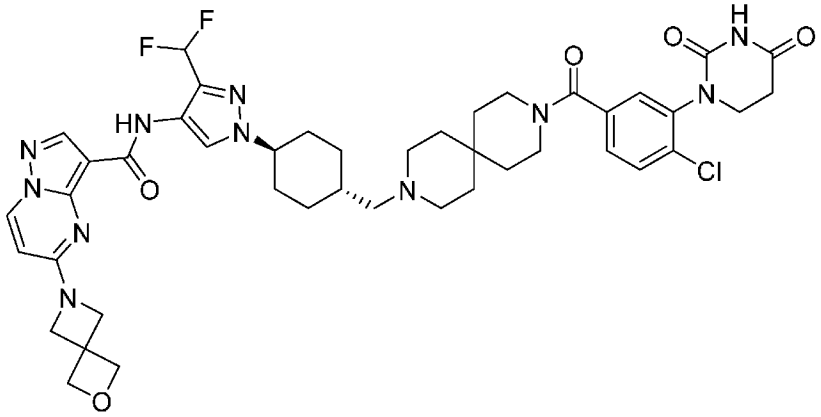

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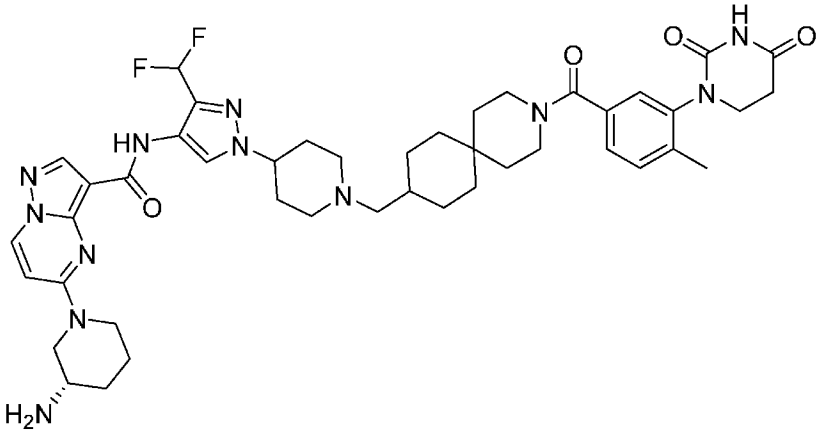

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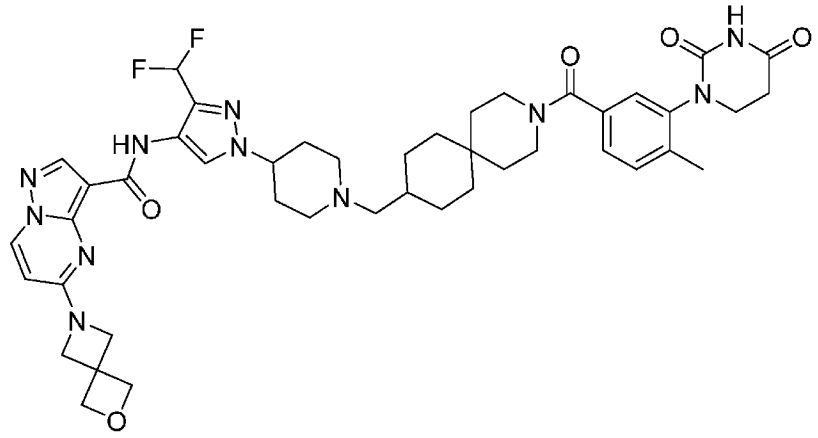

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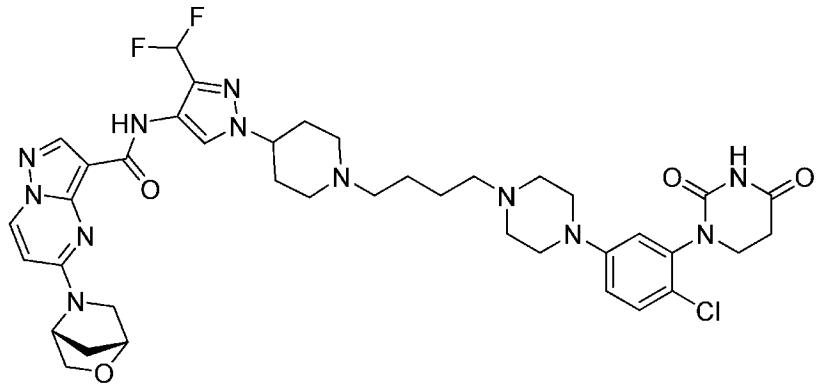

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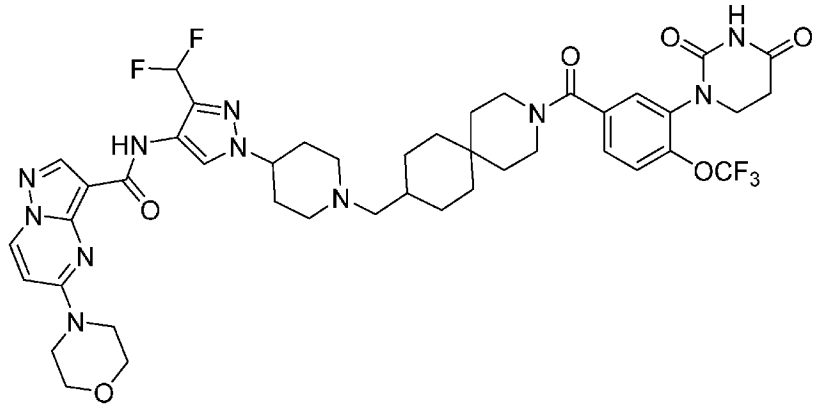

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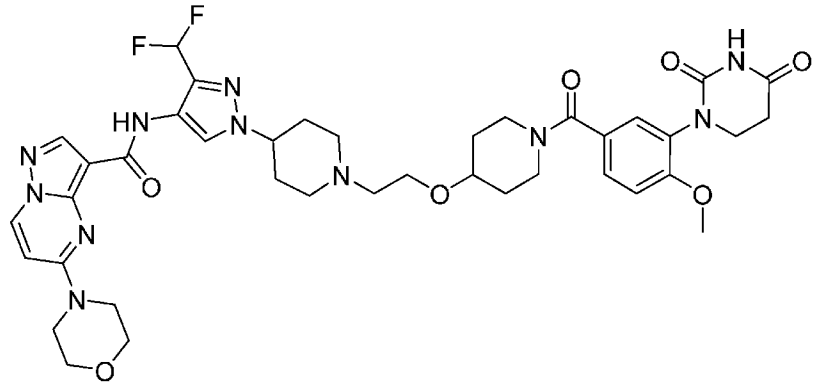

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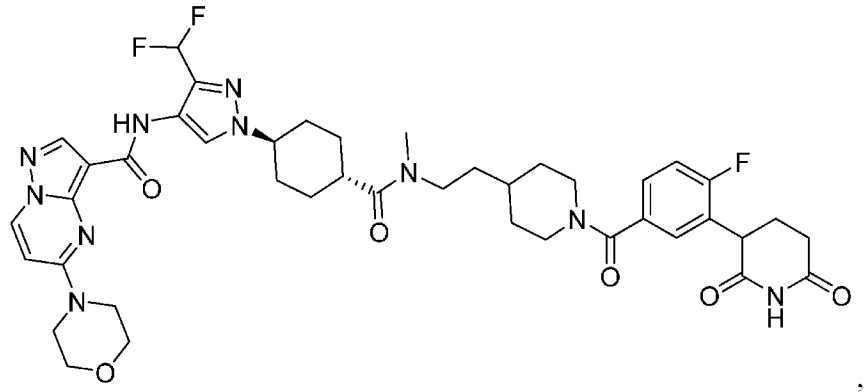

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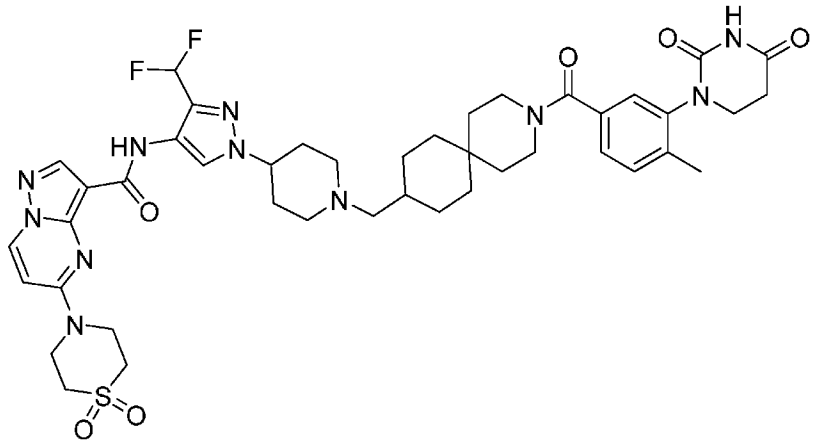

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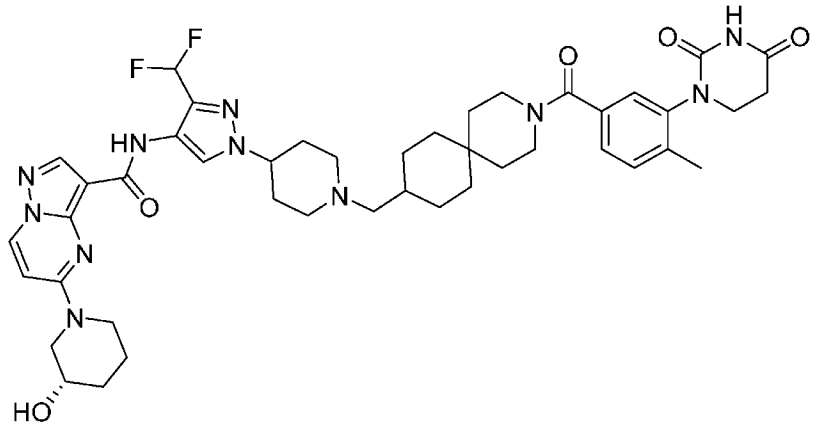

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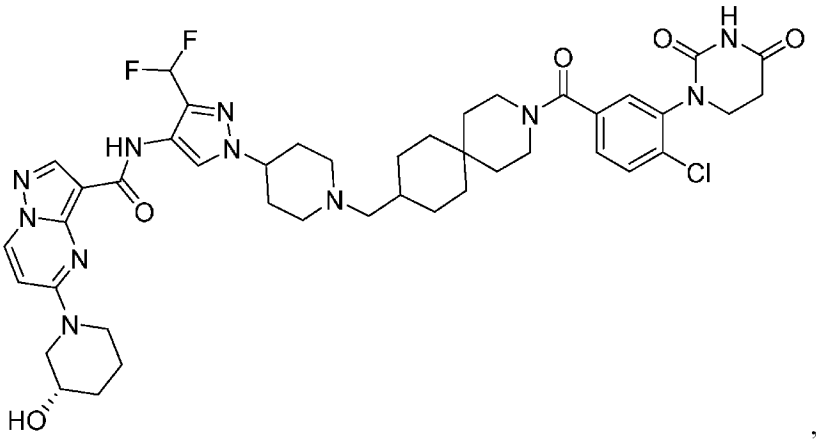

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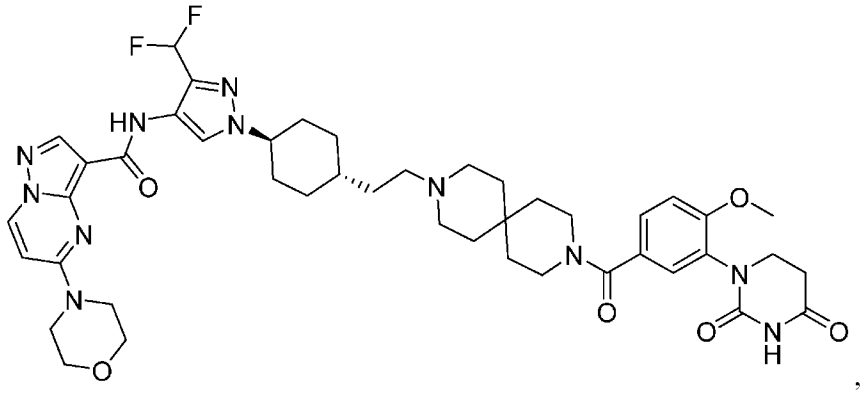

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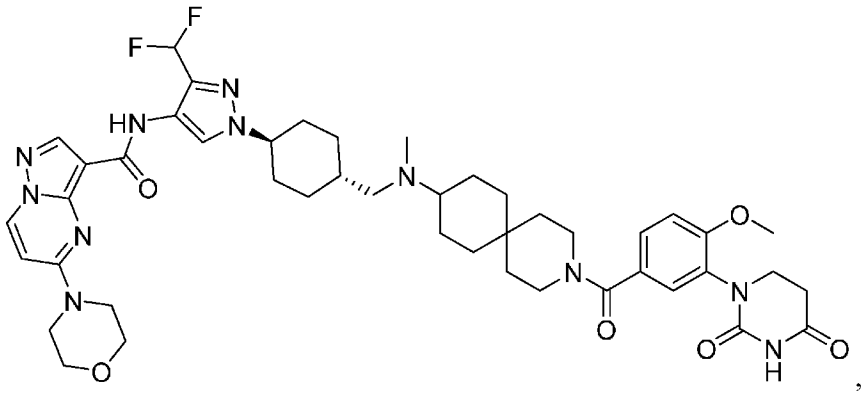

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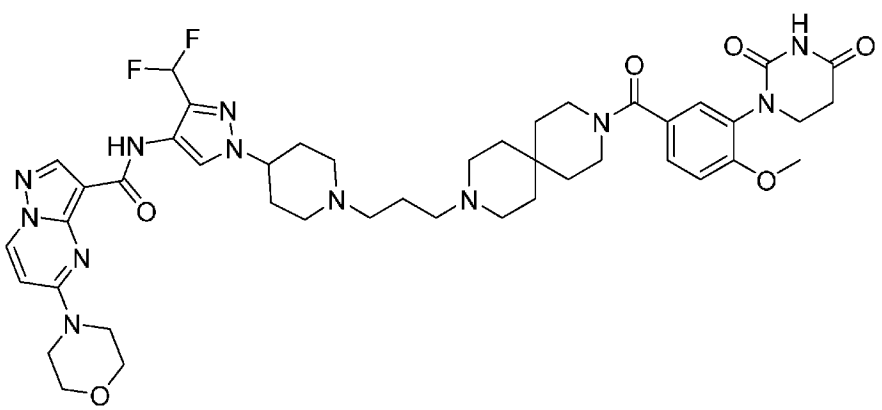

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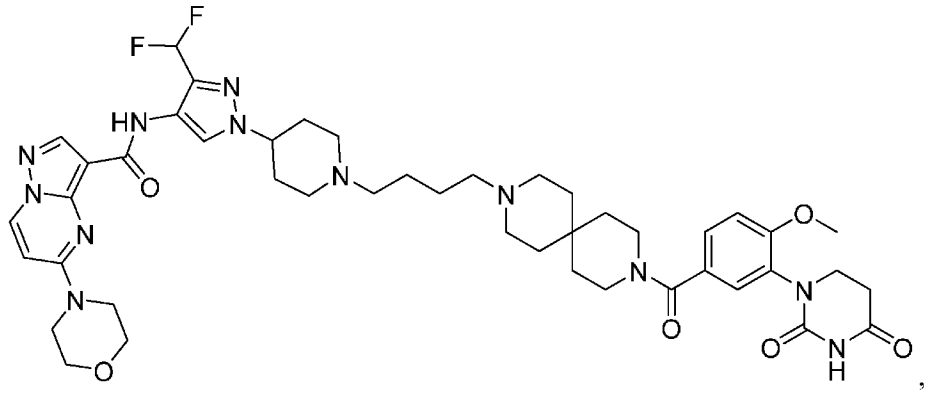

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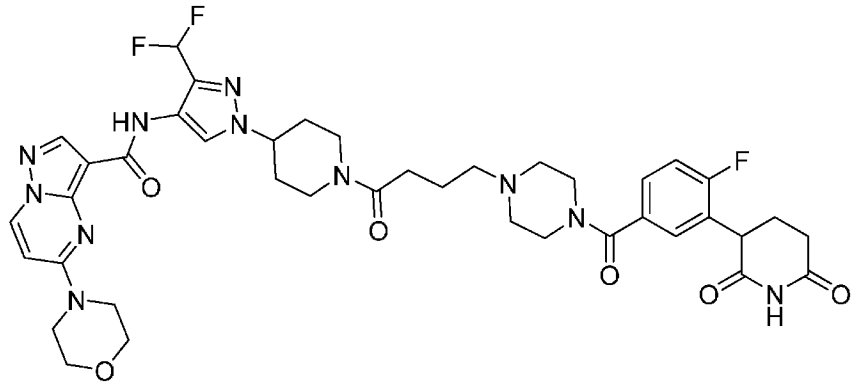

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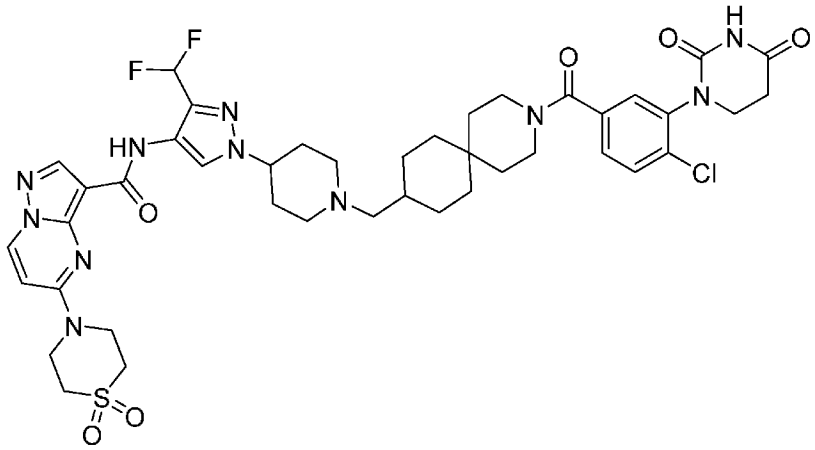

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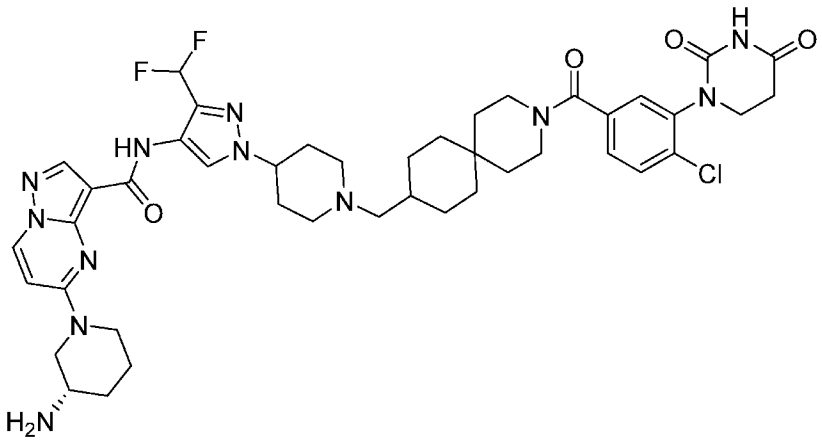

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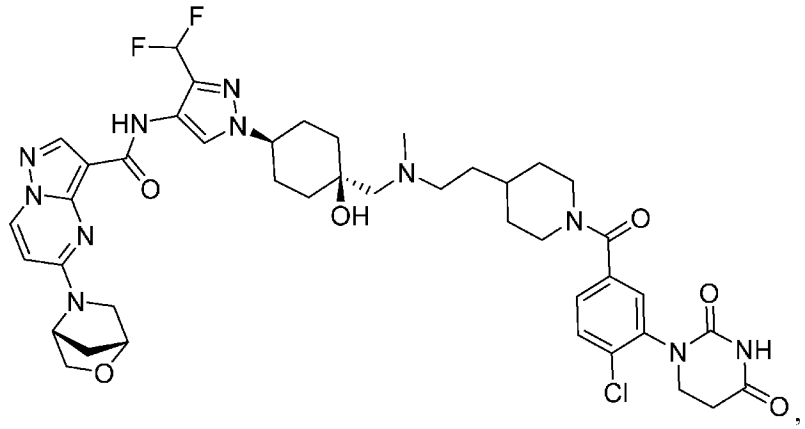

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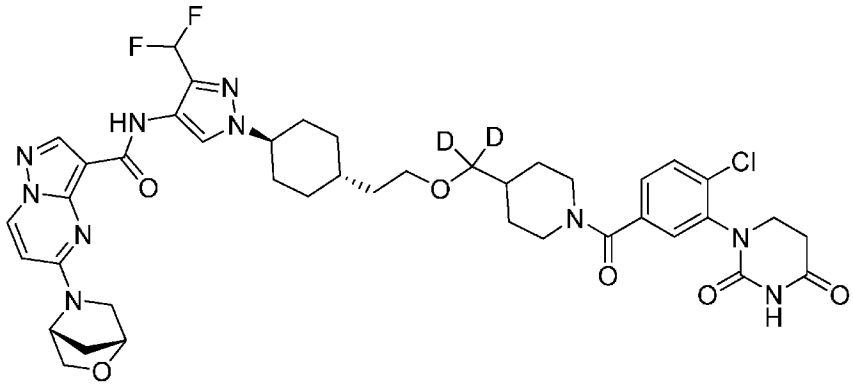

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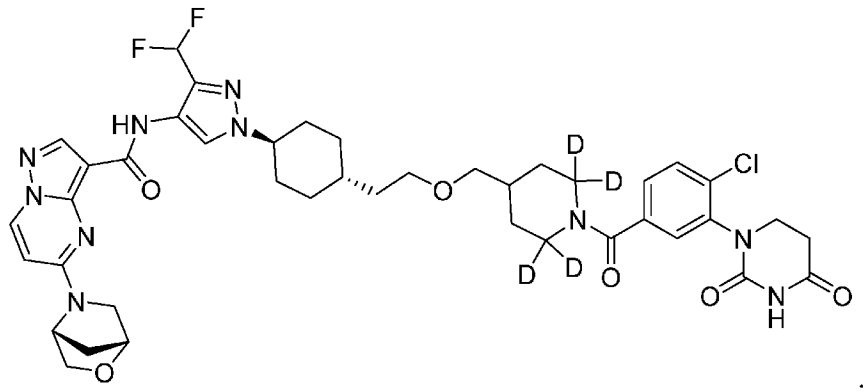


29. A pharmaceutical composition, comprising the compound of formula I, or the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1-28, and a pharmaceutically acceptable carrier, diluent or excipient.

30. Use of the compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1-28 in the preparation of a medicament for treating and/or preventing IRAK4-mediated diseases or disorders, or diseases or disorders mediated by TLRs (except TLR3R) or the IL-1α or IL-1β receptor family.

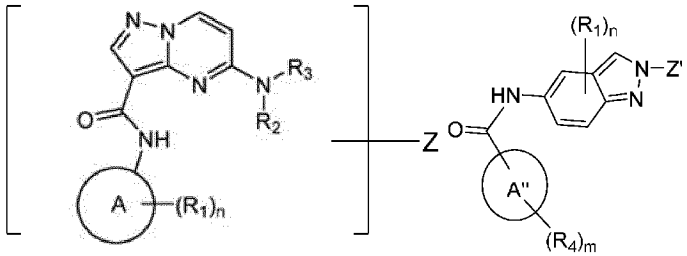
31. Use of the compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1-28 in the preparation of a medicament for treating and/or preventing disorders or diseases including cancer, neurodegenerative disorders, viral diseases, autoimmune diseases, inflammatory diseases, genetic disorders, hormone-associated diseases, metabolic disorders, diseases associated with organ transplantation, immunodeficiency disorders, destructive bone diseases, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver diseases, pathological immune conditions involving T cell activation, cardiovascular disorders or CNS.

32. Use of the compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1-28 in the preparation of a medicament for treating and/or preventing disorders or diseases including brain cancer, kidney cancer, liver cancer, adrenal cancer, bladder cancer, breast cancer, stomach cancer, ovarian cancer, colon cancer, rectal cancer, prostate cancer, pancreatic cancer, lung cancer, vaginal cancer, cervical cancer, testicular cancer, genitourinary tract cancer, esophageal cancer, laryngeal cancer, skin cancer, bone cancer, thyroid cancer, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, neck or head tumor, epidermal hyperplasia, psoriasis, prostate hyperplasia, adenoma, adenocarcinoma, keratoacanthoma, squamous cell carcinoma, large cell carcinoma, non-small cell lung cancer, lymphoma, Hodgkin's and non-Hodgkin's, breast cancer, follicular carcinoma, undifferentiated carcinoma, papillary tumor, seminoma, melanoma, ABC DLBCL, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, chronic lymphocytic leukemia, smoldering indolent multiple myeloma, leukemia, diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary exudative lymphoma, Burkitt's lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenstroms's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, or plasmacytoma or intravascular large B-cell lymphoma; neurodegenerative disease caused by Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, diabetes therapy, metabolic syndrome, obesity, organ transplantation or graft-versus-host disease; eye diseases, such as eye allergy, conjunctivitis, dry eye or spring conjunctivitis, diseases affecting the nose, including allergic rhinitis; autoimmune hematological disorders, such as hemolytic anemia, aplastic anemia, pure red blood cell anemia and idiopathic thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, dermatomyositis, polymyositis, chronic active hepatitis, myasthenia gravis, Stephen-Johnson syndrome, idiopathic stomatitis diarrhea, autoimmune inflammatory bowel disease, irritable bowel syndrome, celiac disease, tooth root periostitis, lung hyaline membrane disease, nephropathy, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine ophthalmopathy, Grave's disease, sarcomatosis, dry eye, spring conjunctival keratitis, interstitial pulmonary fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, vasculitis, interstitial cystitis, diverticulitis, glomerulonephritis, chronic granulomatous

disease, adenomyosis, leptospirosis nephropathy, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle atrophy, catabolism, obesity, slow fetal growth, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, pigment incontinence, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma, acute lung injury, acute respiratory distress syndrome, eosinophilia, allergic reaction, systemic allergic reaction, sinusitis, eye allergy, silica-induced disease, COPD, lung disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataract, muscle inflammation combined with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, type 1 diabetes, type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic transplant rejection, colitis, conjunctivitis, cystitis, lacrimal gland inflammation, dermatitis, dermatomyositis, polymyositis, encephalitis, endocarditis, Endometritis, enteritis, enterocolitis, upper ankle inflammation, epididymitis, fasciitis, fibrous tissue inflammation, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, suppurative sweat inflammation, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, liver fibrosis, renal fibrosis, alcoholic fatty liver, non-alcoholic fatty liver, heart fibrosis, psoriasis, Crohn's disease, inflammatory bowel disease, oophoritis, orchitis, osteitis, otitis, pancreatitis, mumps, pericarditis, peritonitis, pharyngitis, pleurisy, phlebitis, local pneumonia, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, articular membrane inflammation, tendinitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, sclerosis, vitiligo, hypersensitivity vasculitis, urticaria, bullous pemphigoid, pemphigus vulgaris, deciduous pemphigus, paraneoplastic pemphigus, acquired bullous epidermal laxity, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, cryopyrin-associated periodic syndrome or osteoarthritis.

33. Use of a substance A in the preparation of an IRAK4 protein degrader, wherein the substance A comprises the compound of formula I, the stereoisomer, enantiomer, diastereomer, deuteride, hydrate, solvate, metabolite or prodrug thereof or the pharmaceutically acceptable salt thereof according to any of claims 1-28, or the pharmaceutical composition according to claim 29.

34. A compound of formula VII or VIII, a stereoisomer, enantiomer, diastereomer or deuteride thereof or a salt thereof:



VII VIII

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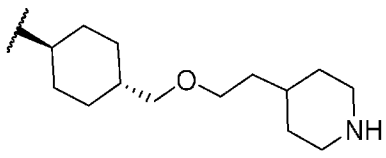

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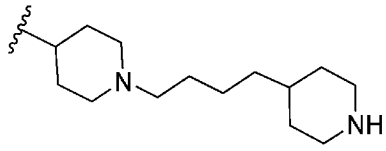

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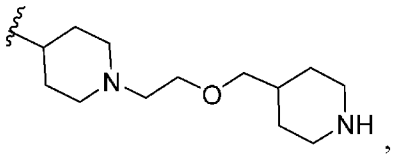

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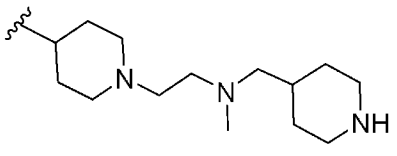

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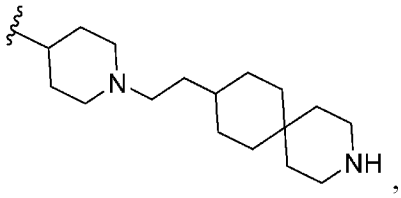

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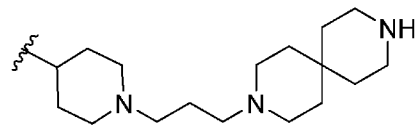
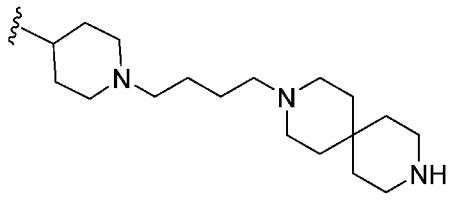
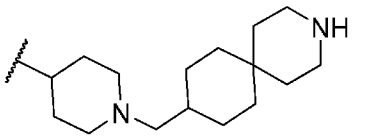
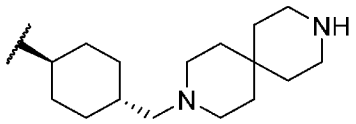
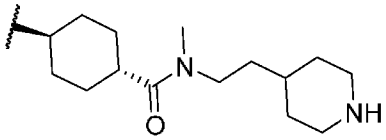
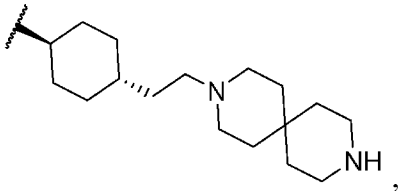
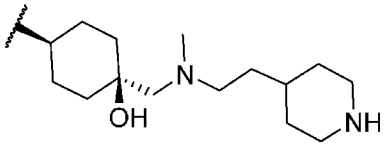
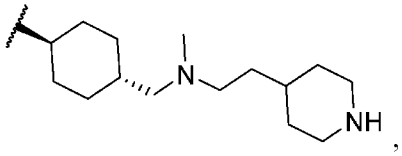
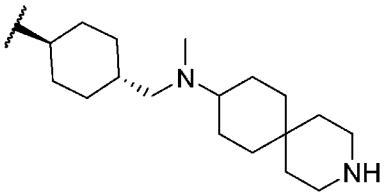
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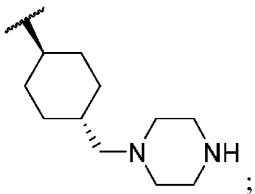
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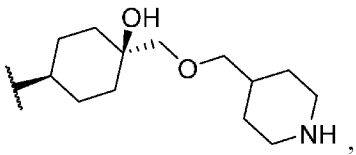
Z' is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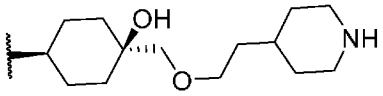
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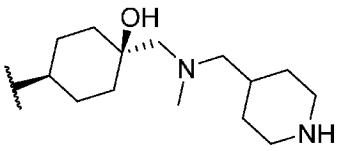

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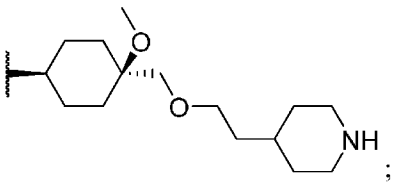
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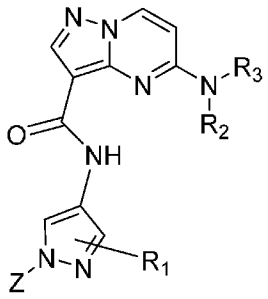
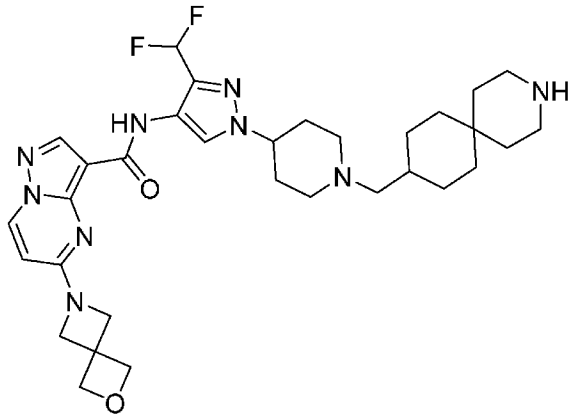
wherein m, n, A, A', R_1, R_2, R_3 and R_4 are as defined in any of claims 1-28;



preferably, the compound of formula VII is a compound of formula VII-1;
more preferably, the compound of formula VII is any of the following compounds: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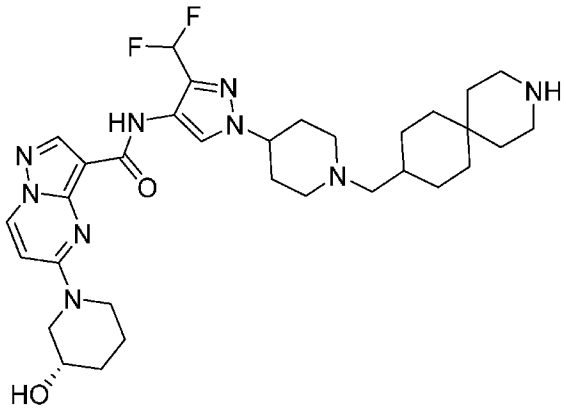
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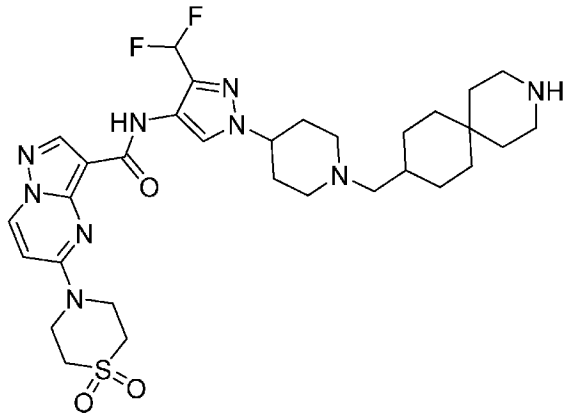
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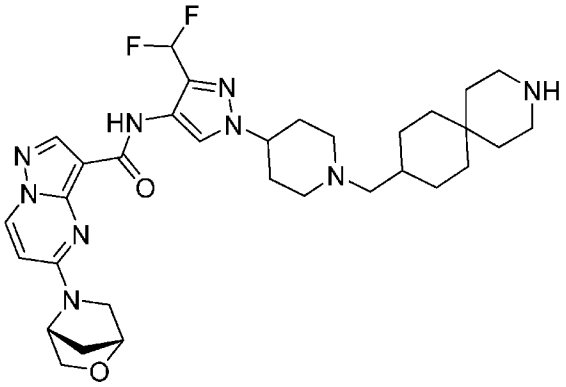
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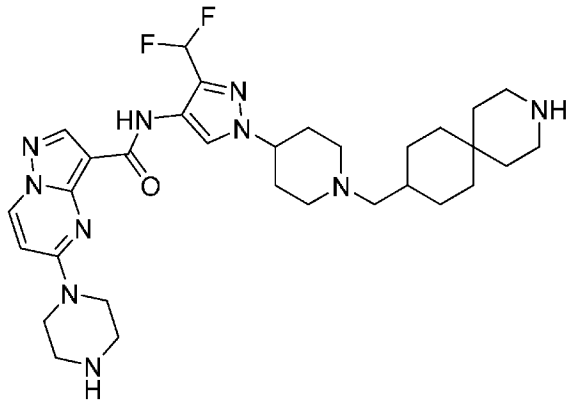
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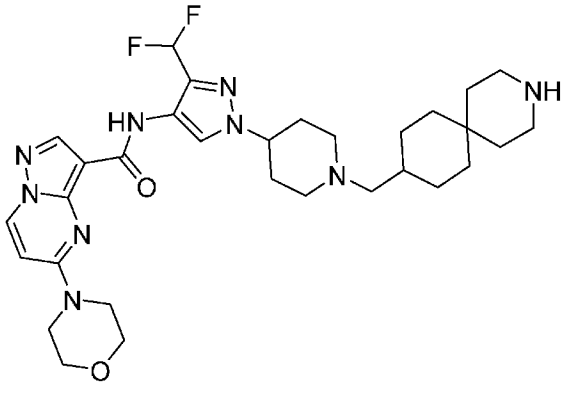
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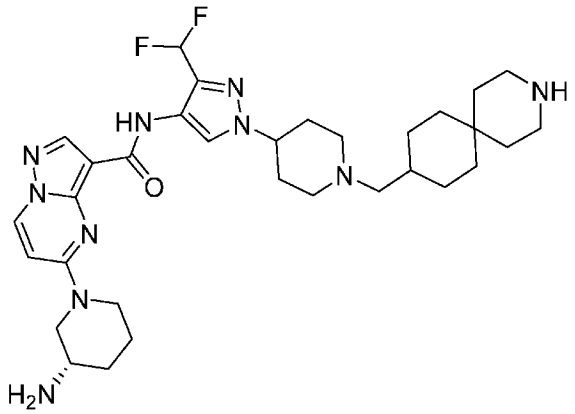
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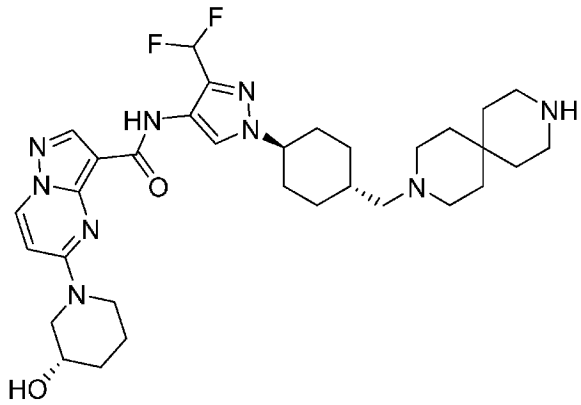
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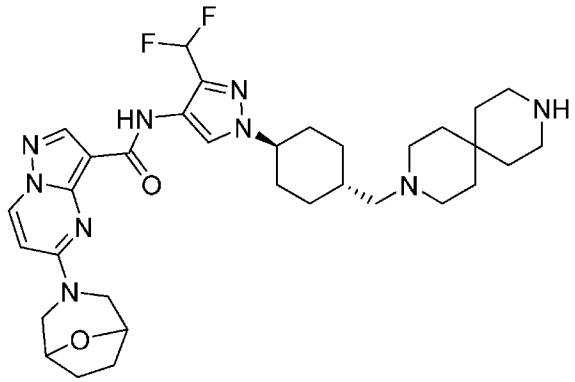
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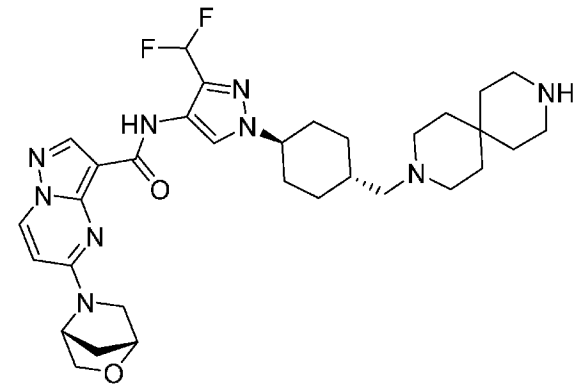
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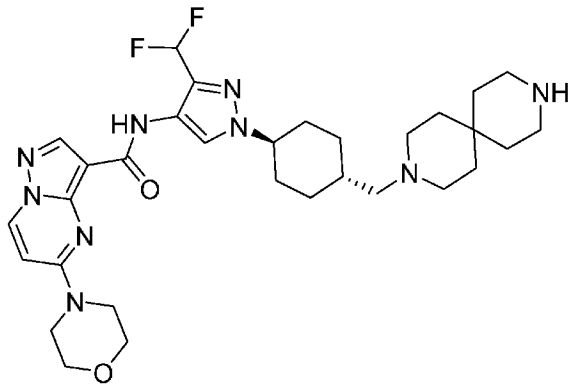
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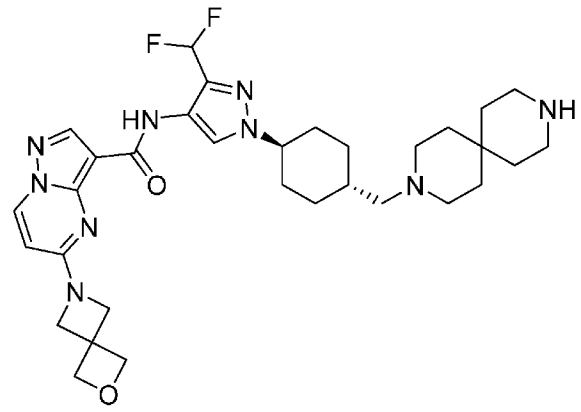
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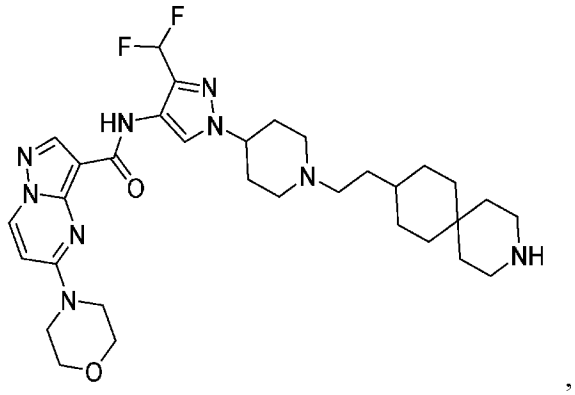
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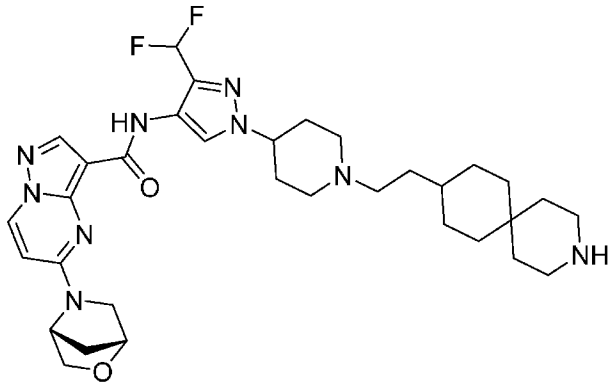
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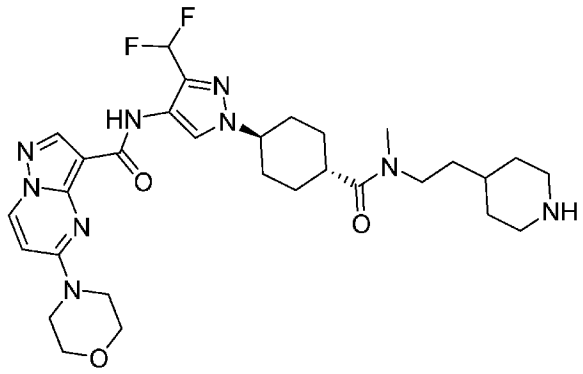
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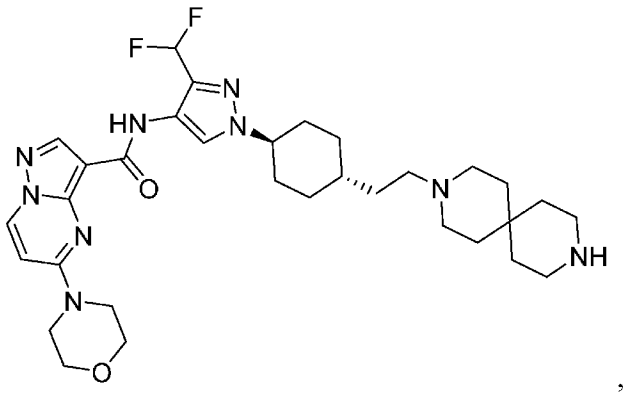
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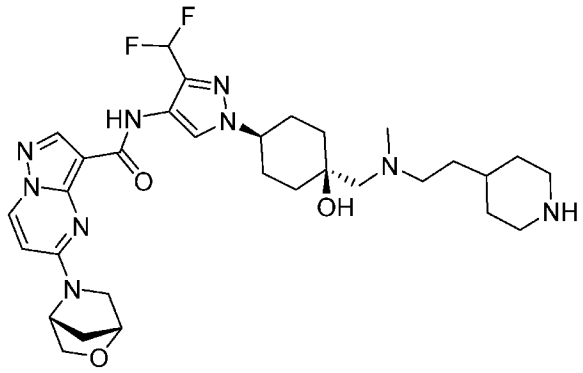
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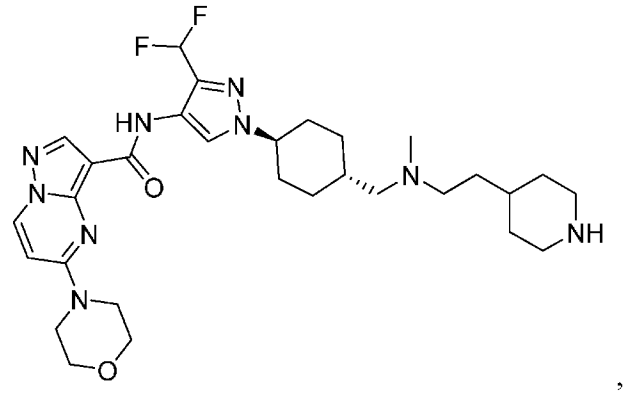
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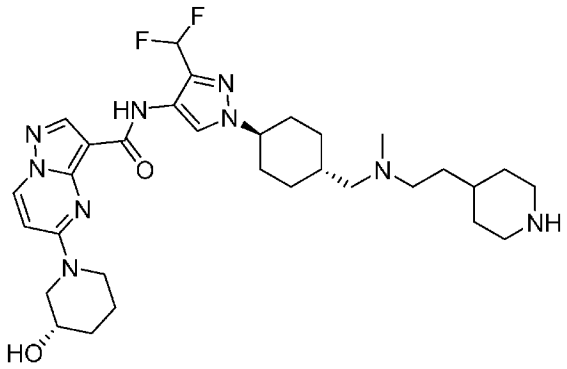
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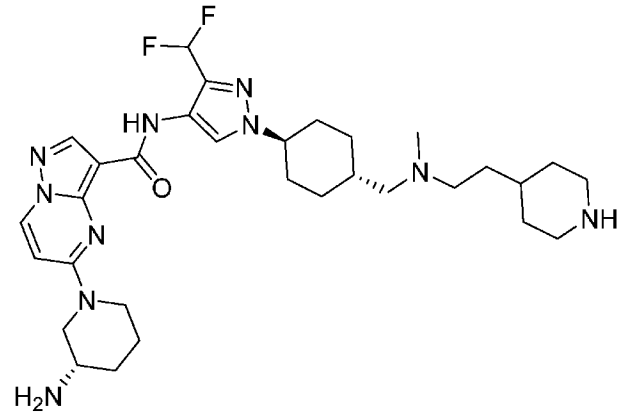
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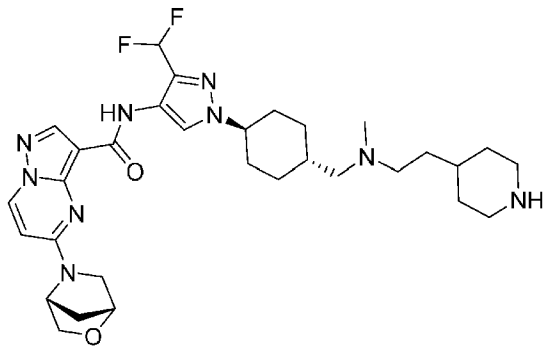
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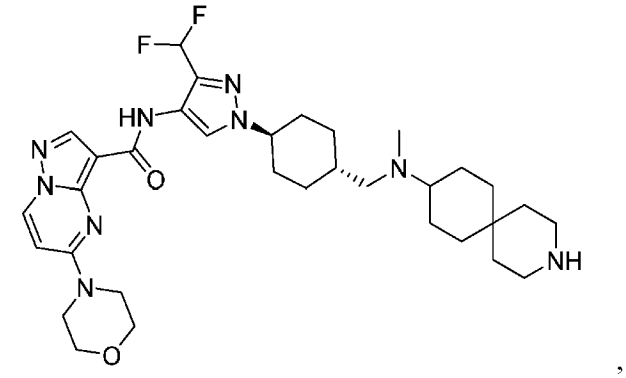
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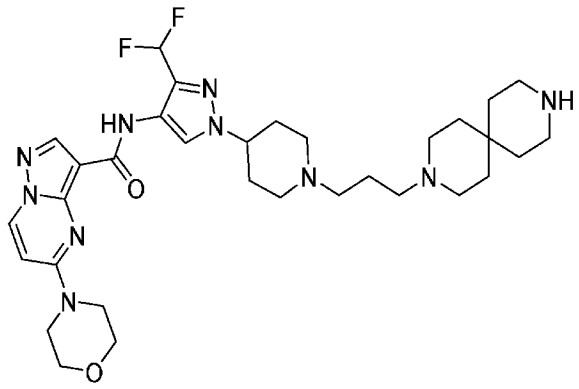
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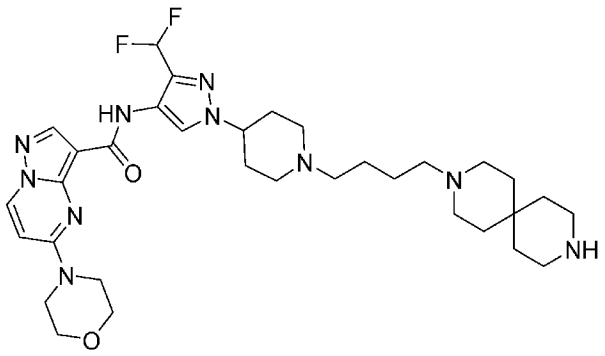
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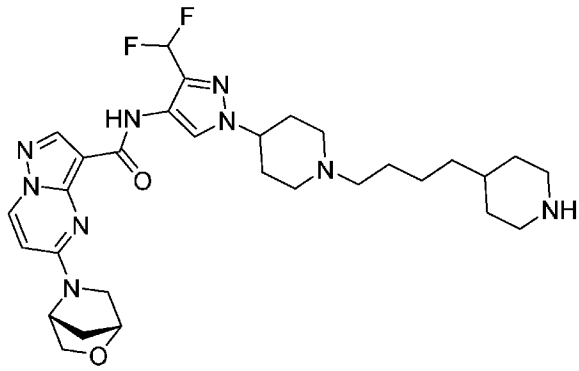
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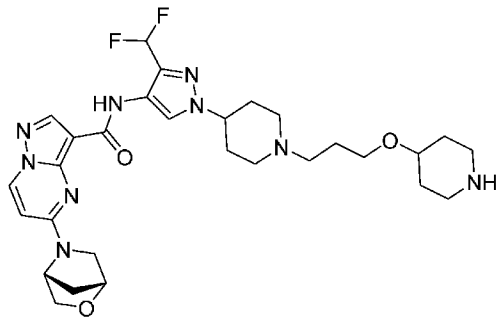
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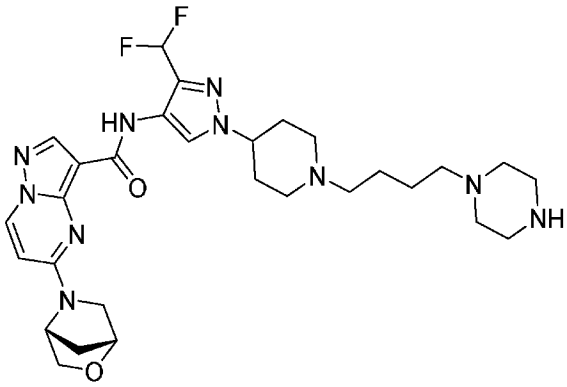
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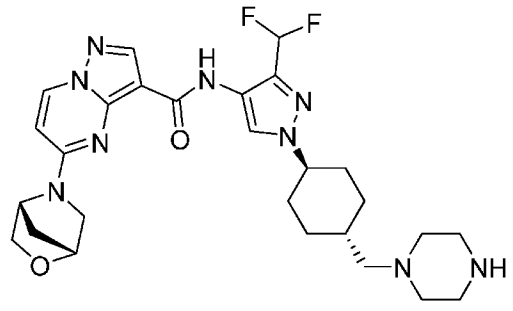
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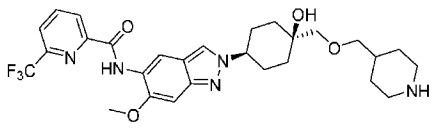
and/or, the compound of formula VIII is any of the following compounds: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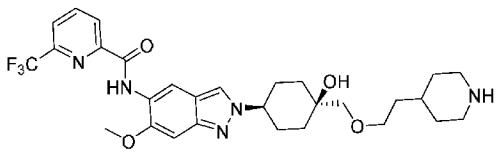
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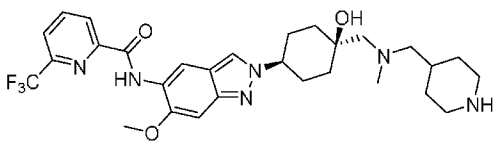
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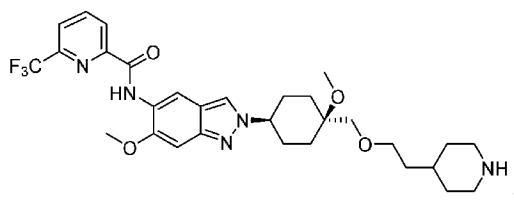
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/114323

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/10(2006.01)i; C07D 403/12(2006.01)i; C07D 401/14(2006.01)i; A61K 31/513(2006.01)i; A61P 35/00(2006.01)i; A61P 35/02(2006.01)i; A61P 25/08(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)

WPI, EPODOC, CNPAT, CAPLUS(STN), REGISTRY(STN), CNKI, 万方, WANFANG, 百度, BAIDU: IRAK, 白介素-1-受体激酶, 免疫, 白细胞介素, 哌啶, 哌啶, 上海领泰, 叶正清, 冯焱, 李世强, piperidinyl indole, inhibitor, 结构通式检索, structural general formula search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2022028547 A1 (SHANGHAI LEADINGTAC PHARMACEUTICAL CO., LTD.) 10 February 2022 (2022-02-10) description, p. 1, paragraph 1, p. 3, line 6 to p. 5, line 7, description, pp. 11-14, 23-24, 29-30, and 143-167, and description, pp. 213-223, intermediate table	1-34
PX	WO 2022147465 A1 (KYMERA THERAPEUTICS INC) 07 July 2022 (2022-07-07) description, p. 316, table, and claims 1-27	1-34
X	WO 2019099926 A1 (ARVINAS INC.) 23 May 2019 (2019-05-23) embodiment 59, claims 1-45, and description, paragraph [0003]	1-34
X	WO 2020113233 A1 (KYMERA THERAPEUTICS INC) 04 June 2020 (2020-06-04) description, table 1, description, paragraph [002956], and claims 1-28	1-34
X	WO 2020264499 A1 (KYMERA THERAPEUTICS INC) 30 December 2020 (2020-12-30) description, table 1, and claims 1-26	1-34
A	WO 2019160915 A1 (DANA-FARBER CANCER INSTITUTE, INC.) 22 August 2019 (2019-08-22) entire description	1-34

☑ 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	Date of mailing of the international search report
07 November 2022	**23 November 2022**
Name and mailing address of the ISA/CN **China National Intellectual Property Administration (ISA/CN)** **No. 6, Xitucheng Road, Jimenqiao, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/114323

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 110612294 A (ARVINAS INC.) 24 December 2019 (2019-12-24) embodiment	1-34
PA	WO 2022088551 A1 (SHANGHAI LEADINGTAC PHARMACEUTICAL CO., LTD.) 05 May 2022 (2022-05-05)	1-34

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2022/114323

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☑ Claims Nos.: **1-27,29-33**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

[1] The compound of formula (I) involved in claims 1-27 and 29-33 comprises three parts, i.e., PTM, L, and ULM. The PTM, L, and ULM each cover a large scope of substituents, such that it is difficult to exhaust searches of the prior art for the scopes of current claims. Moreover, the layer-by-layer substitution of the described three parts of substituents causes claims 1-27 and 29-33 to cover a large scope of protection. However, the description of the present application only verifies the biological activity of a small number of specific compounds. According to the content disclosed in the present application, a person skilled in the art cannot determine that claims 1-27 and 29-33, as a whole, can also solve the technical problem of the present application. Claims 1-27 and 29-33 are not supported by the description. The present report relates to conducting a search according to a scope reasonably generalized by the content fully disclosed in the description, and a search was conducted for the following general formula scopes in claims 1-27 and 29-33: PTM is defined as PTM-3 and PTM-3' shown in claim 4, ULM is defined as the structural fragment shown in claim 11, and L is defined as a compound shown in PTM-L-ULM composed of the groups shown in claim 12.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2022/114323

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