(12) 按照专利合作条约所公布的国际申请

(19) 世界知识产权组织
国 际 局

(43) 国际公布日
2018 年 6 月 28 日 (28.06.2018)

WIPO | PCT

(10) 国际公布号
WO 2018/113584 A1

(51) 国际专利分类号:
C07D 471/04 (2006.01) *A61K 31/506* (2006.01)
C07D 239/84 (2006.01) *A61K 31/517* (2006.01)
C07D 475/00 (2006.01) *A61K 31/519* (2006.01)
A61K 31/437 (2006.01) *A61P 35/00* (2006.01)
A61K 31/505 (2006.01)

(21) 国际申请号: PCT/CN2017/116186

(22) 国际申请日: 2017 年 12 月 14 日 (14.12.2017)

(25) 申请语言: 中文

(26) 公布语言: 中文

(30) 优先权:
201611177188.2 2016年12月19日 (19.12.2016) CN
201710453749.5 2017年6月15日 (15.06.2017) CN

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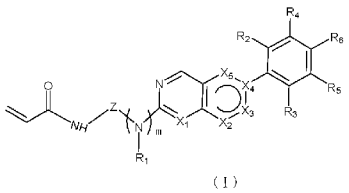
(81) 指定国 (除另有指明, 要求每一种可提供的国家保护): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW。

(84) 指定国 (除另有指明, 要求每一种可提供的地区保护): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), 欧亚 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 欧洲 (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG)。

(54) **Title:** FGFR4 INHIBITOR, PREPARATION METHOD THEREFOR AND PHARMACEUTICAL USE THEREOF

(54) 发明名称: FGFR4抑制剂、其制备方法与药学上的应用



(I)

(57) **Abstract:** Provided are an FGFR4 inhibitor having the structure of formula (I), and a preparation method therefor and the use thereof. The compound has a very strong inhibitory effect on FGFR4 kinase activity and has a very high selectivity, and can be widely used in the preparation of a drug for treating cancers, especially prostate cancer, liver cancer, pancreatic cancer, esophageal carcinomas, gastric cancer, lung cancer, breast cancer, ovarian carcinomas, colon cancer, skin cancer, glioblastomas or rhabdomyosarcomas, and is expected to be developed into a new generation of FGFR4 inhibitor drugs.

(57) 摘要: 提供一种具有式(Ⅰ)结构的FGFR4抑制剂及其制备方法和应用, 该化合物对FGFR4激酶活性具有很强的抑制作用, 并具有非常高的选择性, 可广泛应用于制备治疗癌症特别是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤的药物, 有望开发成新一代FGFR4抑制剂药物。

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本国际公布:

— 包括国际检索报告(条约第21条(3))。

FGFR4抑制剂、其制备方法与药学上的应用

技术领域

本发明属于药物合成领域，具体涉及一种FGFR4抑制剂、其制备方法与药学上的应用。

技术背景

成纤维细胞生长因子（FGF）是一个有 22 种具有不同生物学活性的结构相关多肽的一个家族，它们能调节细胞增殖，分化，迁移，并在肢体发育，血管生成，组织修复，以及肿瘤形成等过程中发挥主要作用（Eswarakumar et al., 2005 Cytokine Growth Factor Rev16:139-149;Ornitz and Itoh,2001 Genome Bio12:Reviews3005）。

FGF 的相应受体（FGFR）属于受体酪氨酸激酶的一个家族 RPTK。目前已经有 FGFR1，FGFR2，FGFR3 以及 FGFR4 四种受体被发现（Ullrich and Schlessinger, 1990 Cell 61:203）。它们与相应的配体 FGF 的相互作用会导致受体二聚化和自我磷酸化，从而启动下游包括 MAPK 和 AKT 在内多种信号传导级联反应（Powers et al., 2000 Endocr Relat Cancer7:165-197）。

FGFR1-3 已经被发现在多种肿瘤（包括骨髓瘤、乳腺癌、胃癌、结肠癌、膀胱癌、膜腺癌、和肝细胞癌等）中有过表达，突变，转位，并且被认为是驱动癌症的基因(Chesi et al., 2001 Blood 97:729-726; Gowardhan et al., 2005 Br J Cancer92:320-327 ;Jaakkola et al., 1993 Int J Cancer54:378-282 ;Jang et al., 2001 Cancer Res 61:3541-3543)，也已经有一些 FGFR 抑制剂在临床及临床前的研发过程中。但之前有研究表明 FGFR1 能调节细胞内磷酸化水平，因此泛 FGFR 抑制剂会带来安全性上的担忧。

肝细胞癌（HCC）是导致中国癌症相关死亡的主要起因之一，也是每年发病人数增长最快的癌症之一（Shariff et al., 2009 Expert Rev Gastroenterol Hepato13:353-367）。目前的一线治疗方案是索拉芬妮，且没有被批准的二线药物，仍然需要具有抗肿瘤剂的靶向药物。

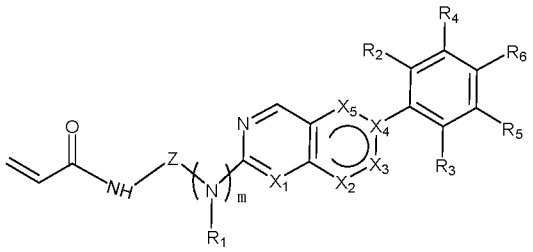
在 5～10%的肝细胞癌病人中带有 FGF19 的过表达，而 FGFR4 是人肝细胞中存在的优势 FGFR, 并且其在肝细胞中的高表达被认为与肝细胞肿瘤的侵袭性相关。因此 FGFR4 在肝癌中有非常重要的作用。另外，FGF19 以及 FGFR4 的相互作用也被认为与其他癌症类型（比如胃癌，前列腺癌，肺癌，结肠直肠癌，胰腺癌，卵巢癌）的侵袭性有关（Ye et al, 2011 Cancer 5304-5313; Xu et al, 2011 BMC Cancer 11:84; Fawdar et al, 2013 PNAS 110:12426-12431）。

目前已有一些 FGFR 抑制剂作为抗肿瘤药物进入临床研究阶段，但这些都主要是针对 FGFR1、2 和 3 的抑制剂，对 FGFR4 的活性抑制较弱，且 FGFR1-3 的抑制具有高血磷症等靶点相关副作用。FGFR4 高选择性抑制剂能有效治疗 FGFR4 信号通路异常导致的癌症疾病，并可避免 FGFR1-3 抑制导致的高血磷症等相关副作用，针对 FGFR4 的高选择性小分子抑制剂在肿瘤靶向治疗领域具有重大应用前景。因此，研发选择性靶向 FGFR4 的可以作为良好药物候选物的新型抗肿瘤试剂将可以满足国内肝癌及其他肿瘤靶向药物的需求，并带来安全性好和特异性更强的优点。

发明内容

本发明的目的在于提供一种 FGFR4 抑制剂、其制备方法与药学上的应用。

本发明第一方面提供一种式(I)化合物、其立体异构体或其药学上可接受盐：



（I）

其中，

X_1 选自-C(R_7)-或 N；

X_2、X_3、X_5 各自独立的选自-(CR_8)$_n$-、-C(O)-、-N(R_9)-、N、O 或 S；

X_4 选自 C 或 N；

Z 选自 C_{1-8} 亚烷基、C_{2-8} 亚链烯基、C_{2-8} 亚链炔基、C_{3-8} 环烷基、3-10 元杂环基、C_{5-10} 芳基或 5-10 元杂芳基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8} 烷基、C_{2-8} 链烯基、C_{2-8} 链炔基、C_{3-8} 环烷基、3-10 元杂环基、C_{5-10} 芳基、5-10 元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$ 或-C_{0-8}-N(R_{13})-C(O)OR_{11} 的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8} 烷基、C_{2-8} 链烯基、C_{2-8} 链炔基、卤取代 C_{1-8} 烷基、C_{3-8} 环烷基、3-10 元杂环基、C_{5-10} 芳基、5-10 元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$ 或-C_{0-8}-N(R_{13})-C(O)OR_{11} 的取代基所取代；

R_1 选自氢、氘、C_{1-8} 烷基、C_{1-8} 烷氧 C_{1-8} 烷基、C_{3-8} 环烷氧基 C_{1-8} 烷基、C_{3-8} 环烷基 C_{1-8} 烷基、C_{2-8} 链烯基、C_{2-8} 链炔基、C_{3-8} 环烷基、3-10 元杂环基、C_{5-10} 芳基、5-10 元杂芳基或 C_{1-8} 烷酰基；

R_2、R_3、R_4、R_5、R_6、R_7 各自独立的选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-8} 烷基、C_{2-8} 链烯基、C_{2-8} 链炔基、C_{3-8} 环烷基、3-10 元杂环基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-S(O)($NR_9$)$R_{10}$、-$C_{0-8}$-P(O)($R_{10}$)$_2$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$ 或-C_{0-8}-N(R_{13})-C(O)OR_{11}，或者，R_2 与 R_4、R_3 与 R_5、R_4 与 R_6、R_5 与 R_6 和其直接相连的碳原子一起形成 C_{5-10} 环烷基、5-10 元杂环基、5-10 元芳基或 5-10 元杂芳基，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8} 烷基、C_{2-8} 链烯基、C_{2-8} 链炔基、卤取代 C_{1-8} 烷基、C_{3-8} 环烷基、3-10 元杂环基、C_{5-10} 芳基、5-10 元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$ 或-C_{0-8}-N(R_{13})-C(O)OR_{11} 的取代基所取代；

R_8选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-S(O)(NR_9)R_{10}$、$-C_{0-8}-P(O)(R_{10})_2$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

R_9选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基或C_{1-8}烷酰基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

R_{10}选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{3-8}环烷基、3-10元杂环基、卤取代C_{1-8}烷基、C_{5-10}芳基、5-10元杂芳基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基或C_{1-8}烷酰氨基；

R_{11}选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基或5-10元杂芳基，上述基团任选地被以下基团单取代或多取代：氘、卤素、氰基、C_{1-8}烷基、C_{1-8}烷氧基、C_{1-8}烷硫基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基、C_{1-8}烷基磺酰胺基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基、=O或羟基；

R_{12}选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{1-8}烷氧基、C_{3-8}环烷基、C_{3-8}环烷氧基、3-10元杂环基、3-10元杂环氧基、C_{5-10}芳基、5-10元杂芳基、C_{5-10}芳氧基或5-10元杂芳氧基，上述基团任选地被以下基团单取代或多取代：氘、卤素、氰基、C_{1-8}烷基、C_{1-8}烷氧基、C_{1-8}烷硫基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基、C_{1-8}烷基磺酰胺基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基、=O或羟基；

R_{13}、R_{14}各自独立的选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基或C_{1-8}烷酰基，或者，R_{13}、R_{14}和其直接相连的氮原子一起形成4-10元杂环基，

上述基团任选地被以下基团单取代或多取代：氘、卤素、C_{1-8}烷基、C_{1-8}烷氧基、C_{1-8}烷硫基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基、C_{1-8}烷基磺酰胺基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基、=O或羟基；

m为0或1；

n 为 0、1 或 2；

r 为 0、1 或 2；

条件是，当 X_3 选自-$(CR_8)_n$-时，X_2 选自-C(O)-，X_4 选自 C，X_5 选自-$N(R_9)$-、N、O 或 S；当 X_3 选自-C(O)-时，X_2 选自-$N(R_9)$-，且 Z 选自 C_{1-8} 烷基、C_{2-8} 链烯基、C_{2-8} 链炔基或苯基。

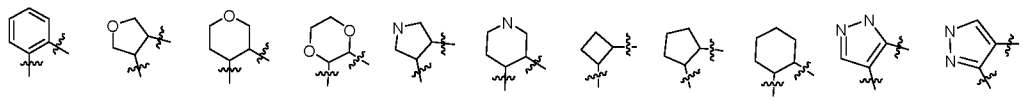
作为进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，Z 选自 C_{1-4} 亚烷基、C_{2-4} 亚链烯基、C_{2-4} 亚链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基或 5-8 元杂芳基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$ 或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$ 的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$ 或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$ 的取代基所取代；

R_1 选自氢、氘、C_{1-4} 烷基、C_{1-4} 烷氧 C_{1-4} 烷基、C_{3-6} 环烷氧基 C_{1-4} 烷基、C_{3-6} 环烷基 C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基或 C_{1-4} 烷酰基；

R_2、R_3、R_4、R_5、R_6、R_7 各自独立的选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-$S(O)(NR_9)R_{10}$、-C_{0-4}-$P(O)(R_{10})_2$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$ 或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$，或者，R_2 与 R_4、R_3 与 R_5、R_4 与 R_6、R_5 与 R_6 和其直接相连的碳原子一起形成 C_{5-8} 环烷基、5-8 元杂环基、5-8 元芳基或 5-8 元杂芳基，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-4} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$ 或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$ 的取代基所取代。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，Z 选自 C_{1-2} 亚烷基或如下结构：



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上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$ 或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$ 的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、

$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，R_1 选自氢、氘、甲基、异丙基、甲氧乙基、环丙氧甲基、环丙甲基、烯丙基、环丙基或乙酰基；

R_2、R_3、R_4、R_5 各自独立的选自氢、氘、卤素、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、$-C_{0-4}-O-R_{11}$ 或$-C_{0-4}-NR_{13}R_{14}$，或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 C_{5-8} 环烷基、5-8 元杂环基、5-8 元芳基或 5-8 元杂芳基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-4} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代；

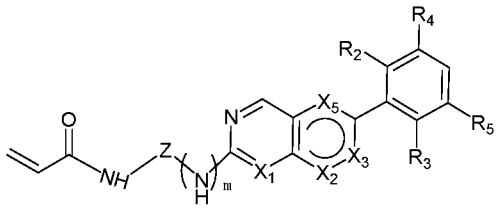
R_6 选自氢或氘。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，R_1 选自氢、氘、甲基或环丙甲基；

R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、甲基、异丙基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、$-C_{0-4}-O-R_{11}$ 或$-C_{0-4}-NR_{13}R_{14}$，或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮，所述 5-8 元杂环基任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-4} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代；

R_6 选自氢或氘。

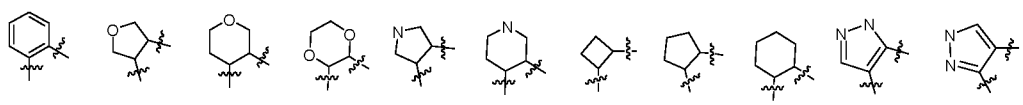
作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐选自如下式(Ⅱa)化合物：



（Ⅱa），

其中，X_3 选自$-N(R_9)-$、N、O 或 S；

Z 选自 C_{1-2} 亚烷基或如下结构：



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上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、

$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或 $-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或 $-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代；

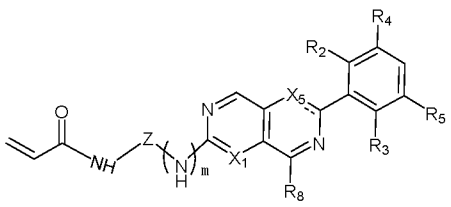
R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、甲基、异丙基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、$-C_{0-4}-O-R_{11}$ 或 $-C_{0-4}-NR_{13}R_{14}$，或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮，所述 5-8 元杂环基任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-4} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或 $-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代；

R_7 选自氢、氘、氯、氟、羟基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、$-C_{0-4}-O-R_{11}$ 或 $-C_{0-4}-NR_{13}R_{14}$；

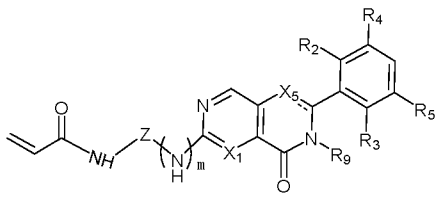
R_9 选自氢、氘、C_{1-4} 烷基、C_{3-6} 环烷基或 3-8 元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或 $-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代；

X_1、X_2、X_5、R_8、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r 如前所述。

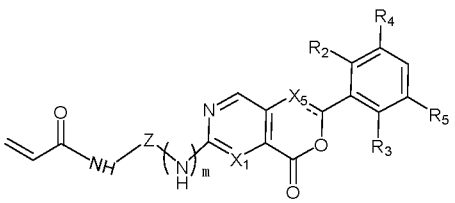
作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐选自如下式(IIIa-1)、(IIIa-2)、(IIIa-3)或(IIIa-4)化合物：



(IIIa-1)

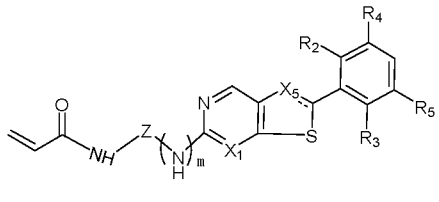


(IIIa-2)



(IIIa-3)

或



(IIIa-4)

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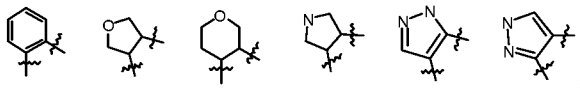
其中，Z 选自 C_{1-2} 亚烷基或如下结构：



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上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

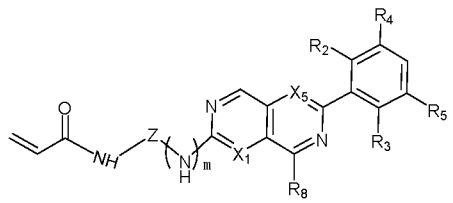
R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或$-O-R_{11}$，或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮；

R_7选自氢、氘、氯、氟、羟基、环丙基或$-O-R_{11}$；

R_9选自氢、氘、C_{1-4}烷基、C_{3-6}环烷基或3-8元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、C_{1-4}烷基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-NR_{13}R_{14}$或$-C_{0-4}-C(O)NR_{13}R_{14}$的取代基所取代；

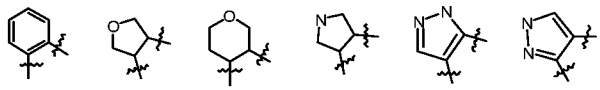
X_1、X_5、R_8、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r如权利要求1所述。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，选自式(Ⅳa-1)化合物：



(Ⅳa-1)

其中，X_5选自-CH-或N；

Z选自C_{1-2}亚烷基或如下结构：  ，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或$-O-R_{11}$，或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮；

R_7选自氢、氘、氯、氟、羟基、环丙基或-O-R_{11}；

R_8选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-S(O)($NR_9$)$R_{10}$、-$C_{0-8}$-P(O)($R_{10}$)$_2$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-$NR_{13}R_{14}$、-$C_{0-8}$-C(O)$NR_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-8}$-N($R_{13}$)-C(O)O$R_{11}$，

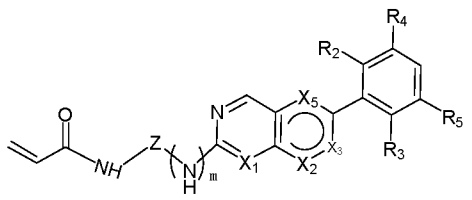
上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代；

X_1、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r如前所述。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，R_8选自氢、氘、卤素、氰基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-O-R_{11}、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-N(R_{13})-C(O)R_{12}或-C_{0-8}-N(R_{13})-C(O)OR_{11}，

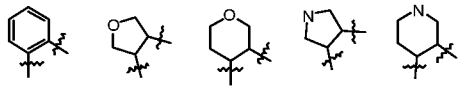
上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐，选自如下式（Ⅱb)化合物：



（Ⅱb)，

其中，X_3选自-(CR_8)$_n$-或-C(O)-；

Z选自C_{1-2}亚烷基或如下结构：  ，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、甲基、异丙基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、$-C_{0-4}-O-R_{11}$或$-C_{0-4}-NR_{13}R_{14}$，或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮，所述5-8元杂环基任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-4}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

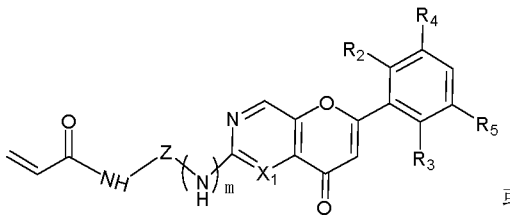
R_7选自氢、氘、氯、氟、羟基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、$-C_{0-4}-O-R_{11}$或$-C_{0-4}-NR_{13}R_{14}$；

R_9选自氢、氘、C_{1-4}烷基、C_{3-6}环烷基或3-8元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

X_1、X_2、X_5、R_8、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r如前所述；

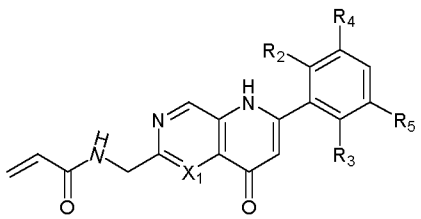
条件是，当X_3选自$-(CR_8)_n-$时，X_2选自-C(O)-，X_5选自$-N(R_9)-$、N、O或S；当X_3选自-C(O)-时，X_2选自$-N(R_9)-$，且Z选自C_{1-4}烷基或苯基。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐选自如下式(IIIb-1)或(IIIb-2)化合物：



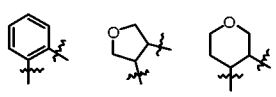
(IIIb-1)

或



(IIIb-2)

，

其中，Z选自C_{1-2}亚烷基或如下结构：  ，

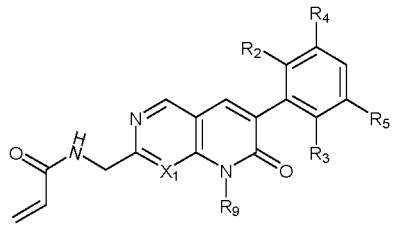
上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或-O-R_{11}，或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮；

R_7 选自氢、氘、氯、氟、羟基、环丙基或-O-R_{11}；

X_1、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、r 如前所述。

作为更进一步优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐选自如下式(IIIb-3)化合物：



(IIIb-3)，

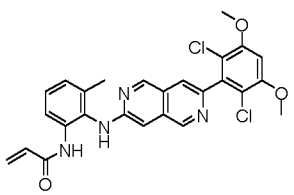
其中，R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或-O-R_{11}，或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮；

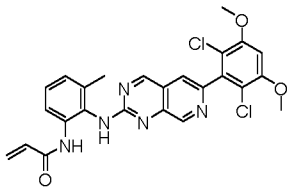
R_7 选自氢、氘、氯、氟、羟基、环丙基或-O-R_{11}；

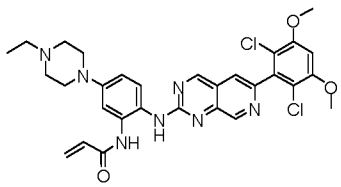
R_9 选自氢、氘、C_{1-4} 烷基、C_{3-6} 环烷基或 3-8 元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、C_{1-4} 烷基、卤取代 C_{1-4} 烷基、C_{3-6} 环烷基、3-8 元杂环基、-C_{0-4}-O-R_{11}、-C_{0-4}-N$R_{13}R_{14}$ 或-C_{0-4}-C(O)N$R_{13}R_{14}$ 的取代基所取代；

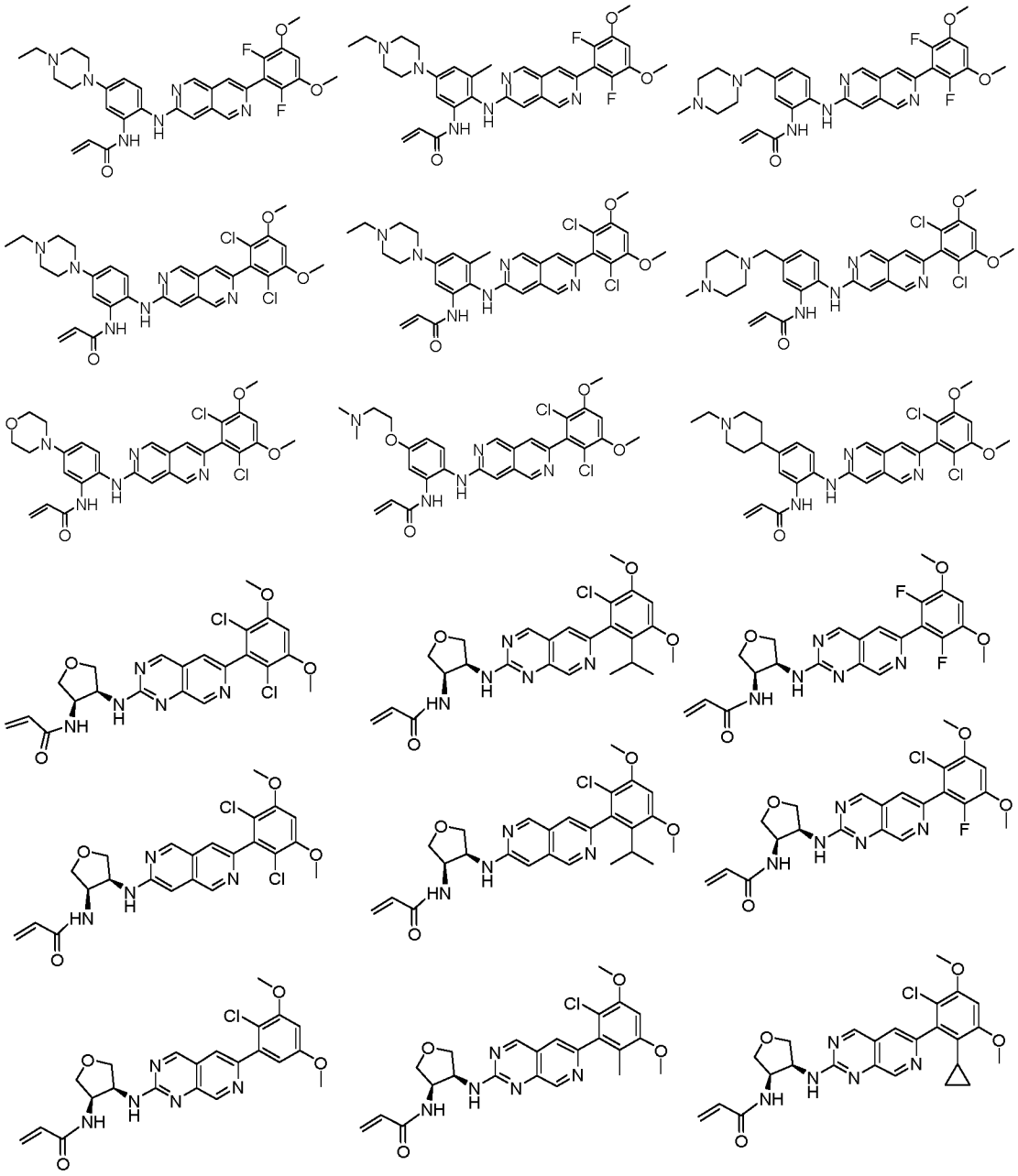
X_1、R_8、R_{10}、R_{11}、R_{13}、R_{14}、n 如前所述。

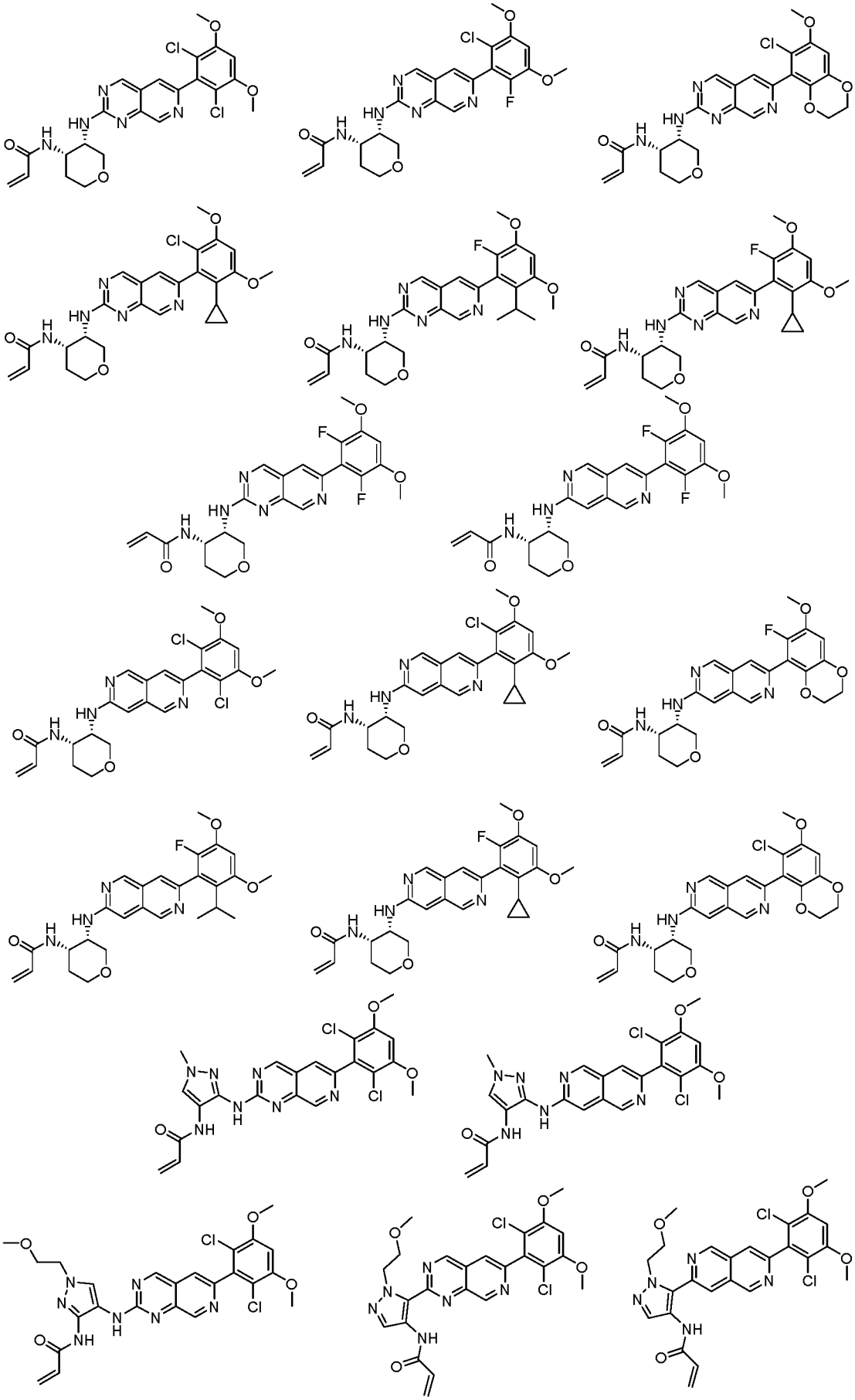
作为最优选的方案，所述的式(I)化合物、其立体异构体或其药学上可接受盐包括但不限于如下化合物：

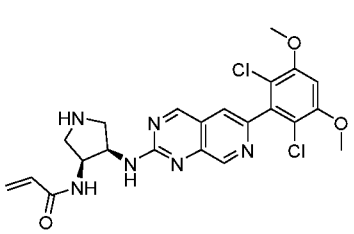
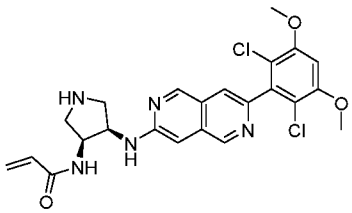
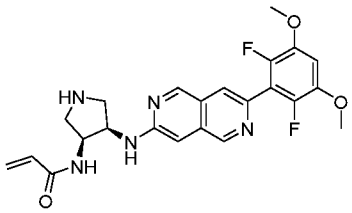
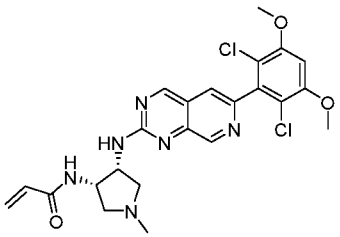
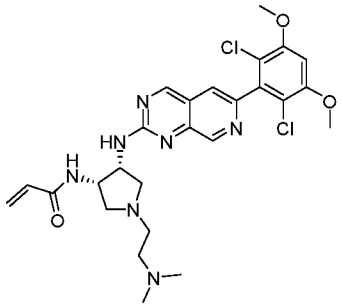
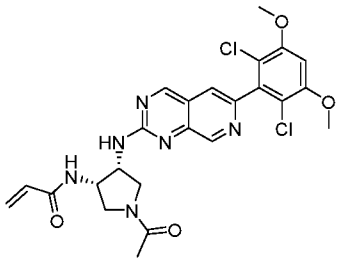
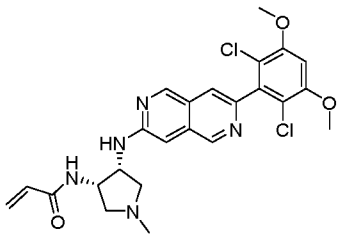
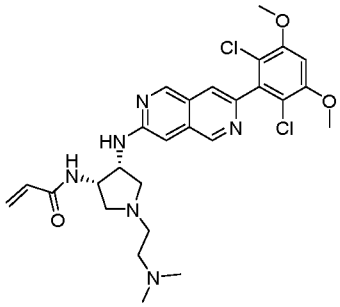
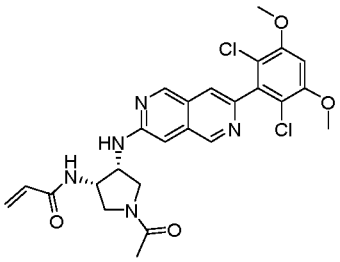
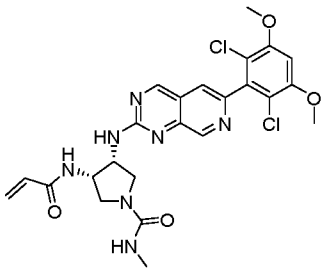
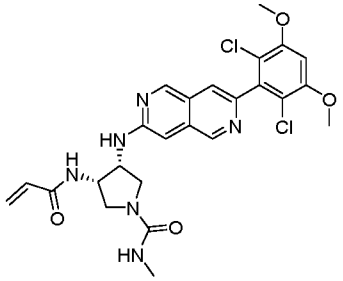
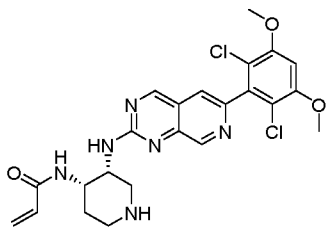
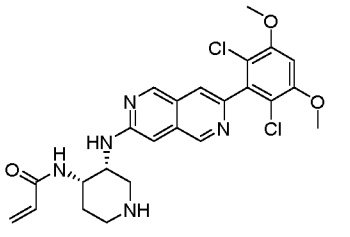
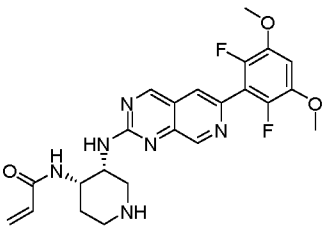


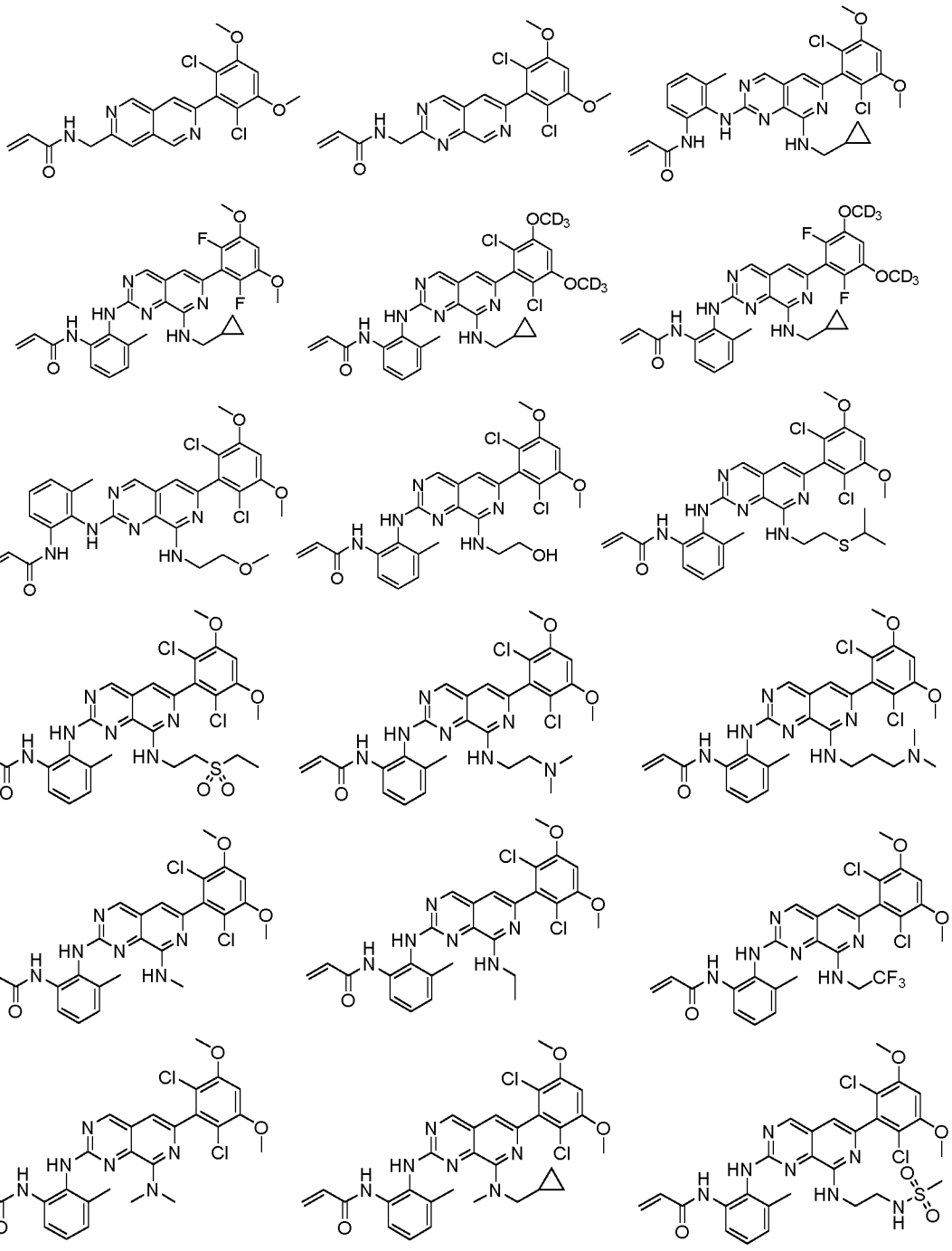


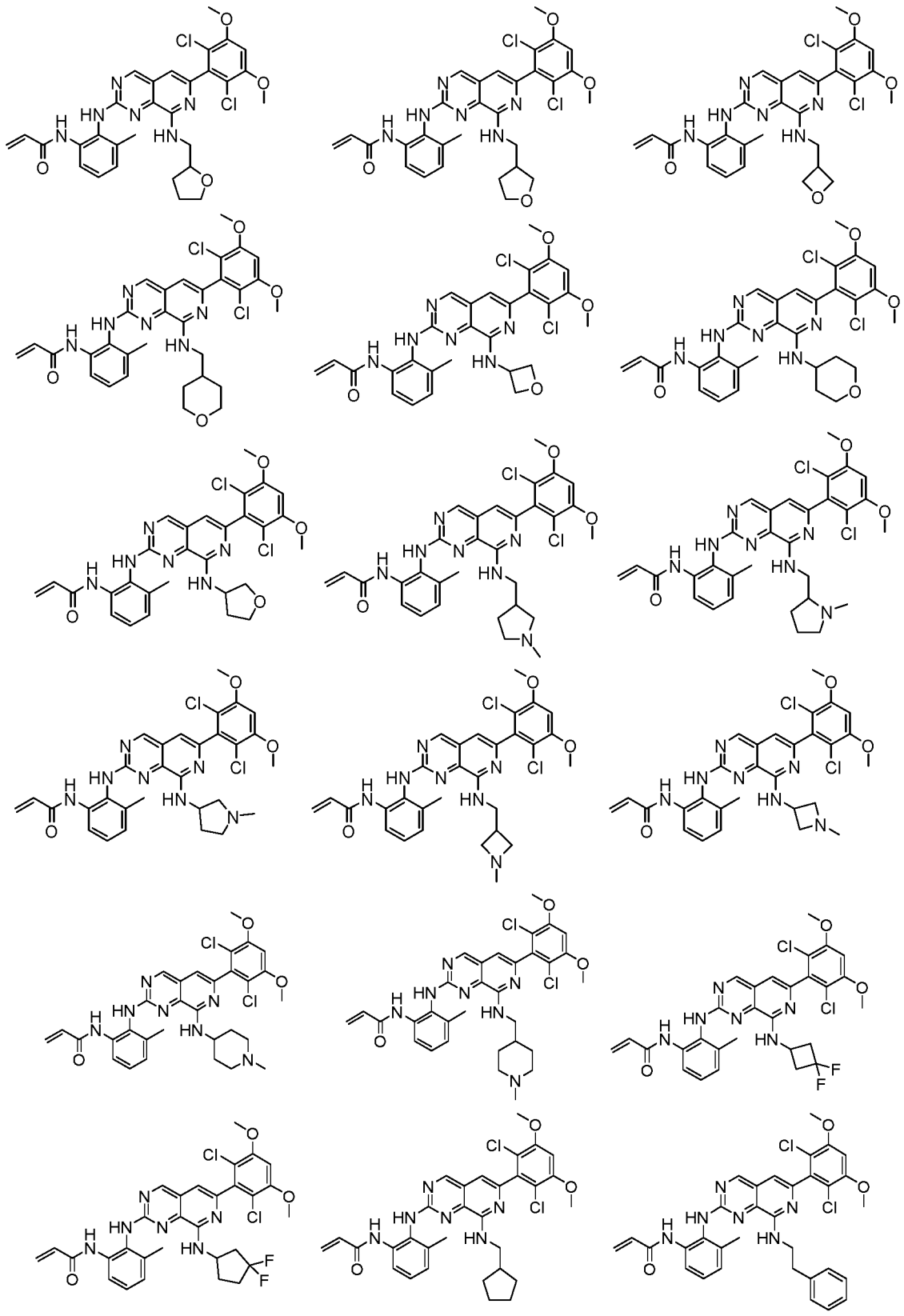


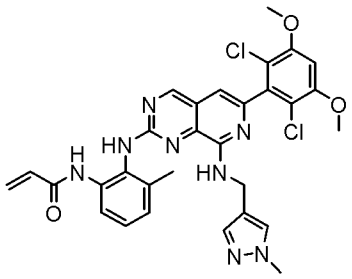
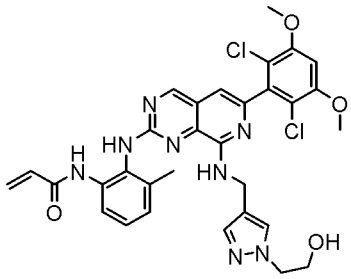
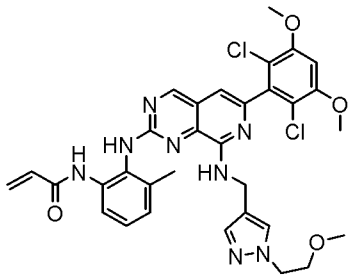
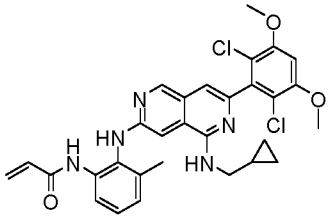
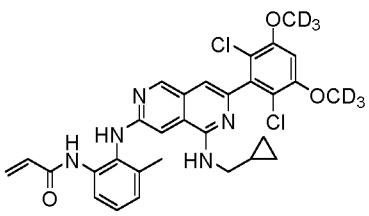
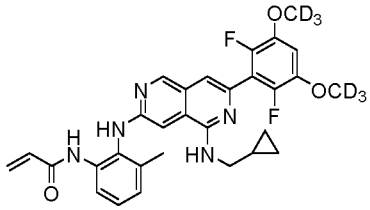
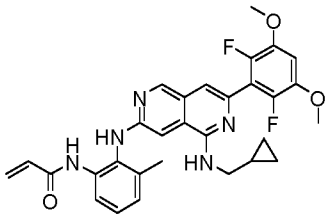
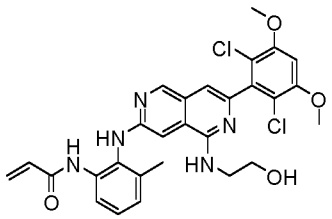
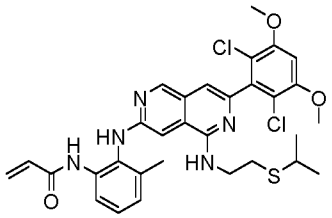
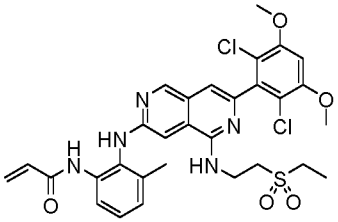
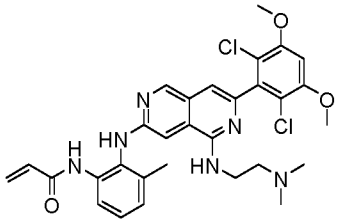
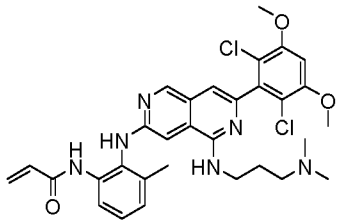
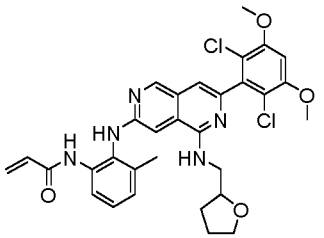
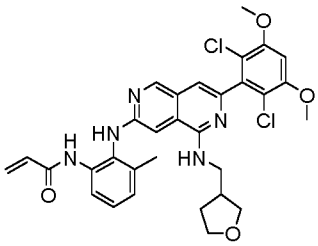
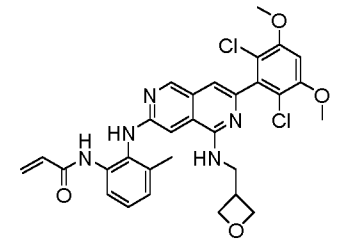
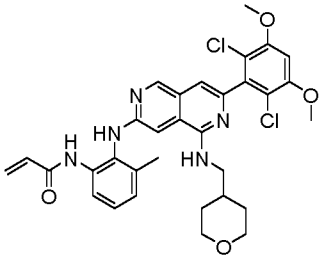
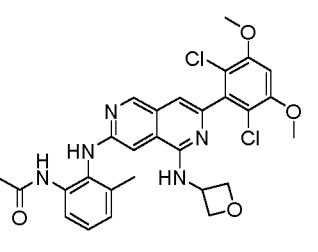
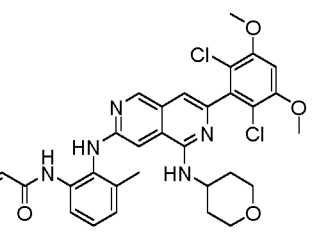


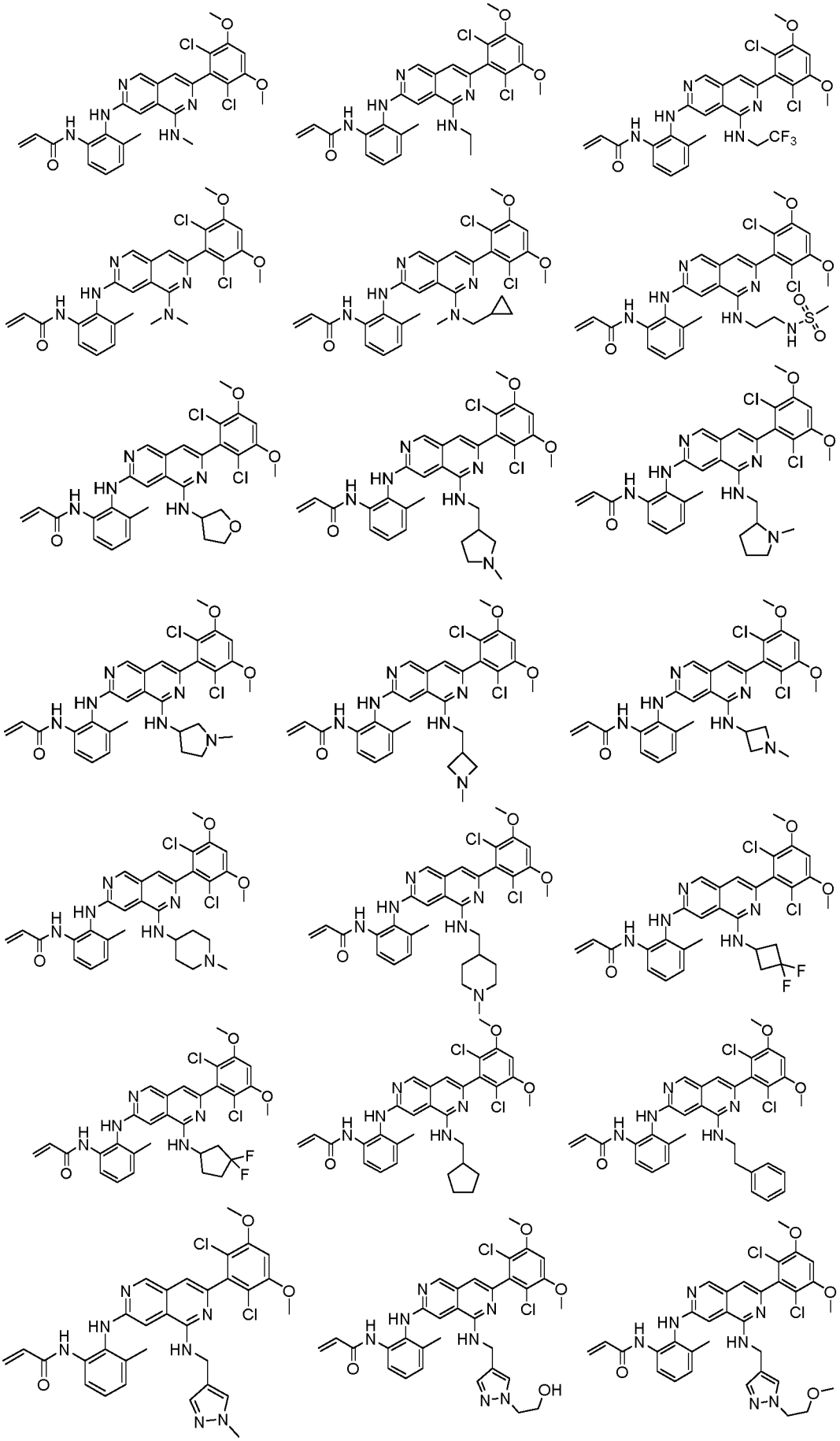


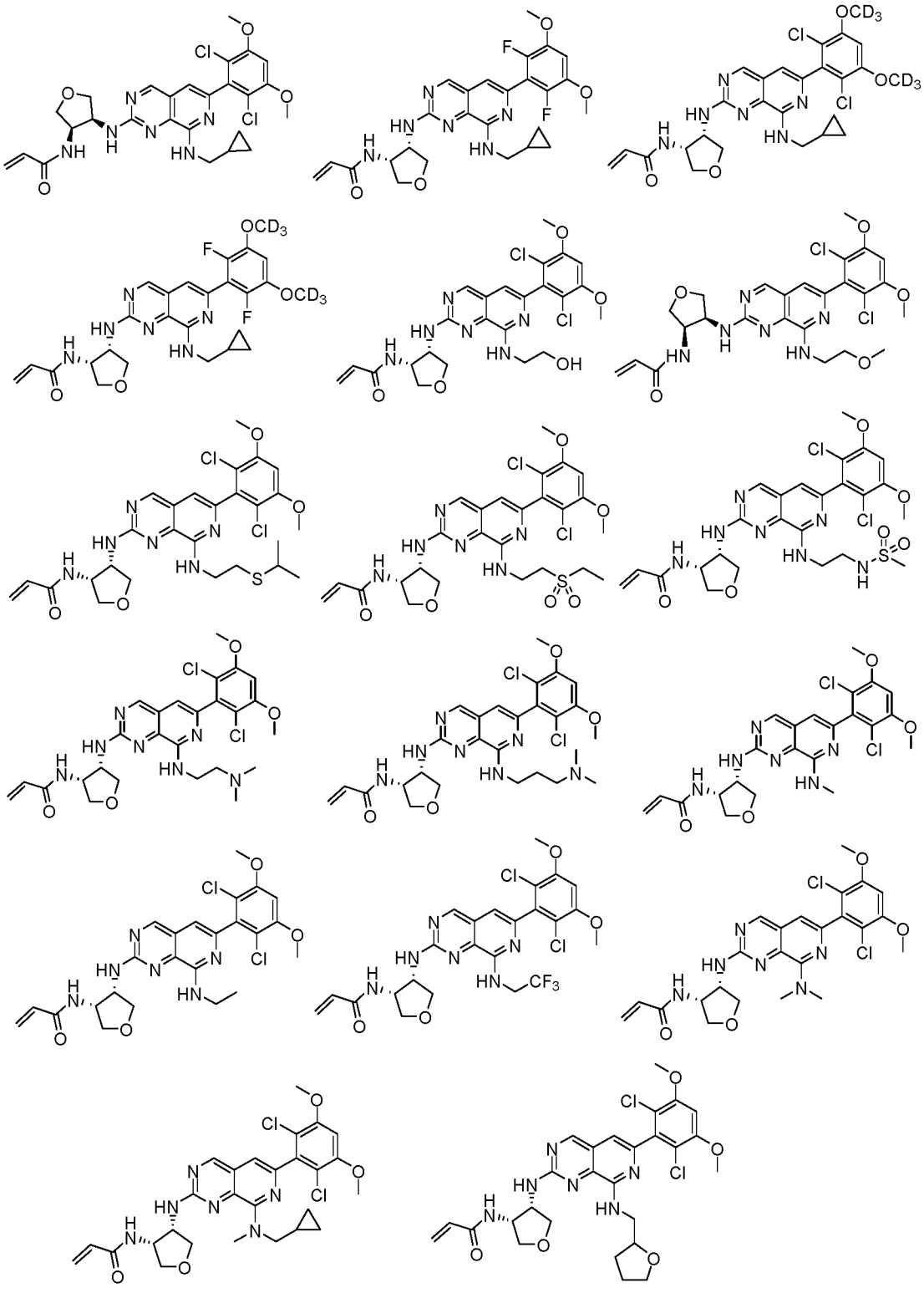















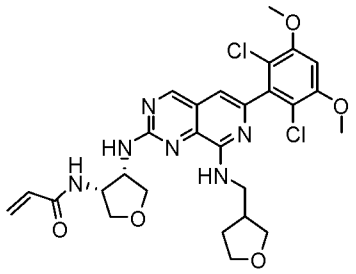
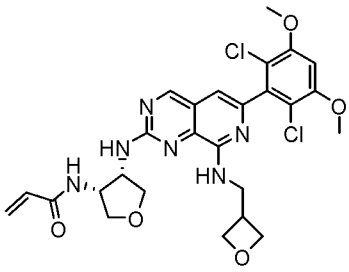
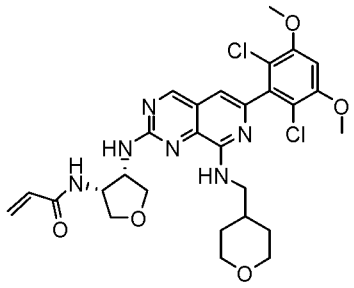
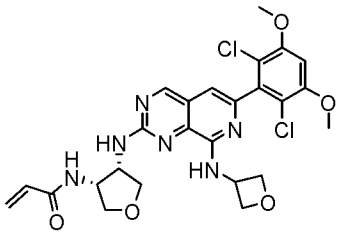
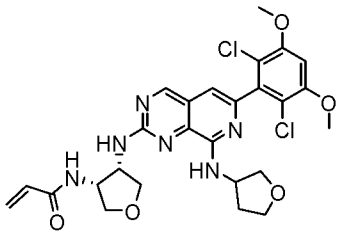
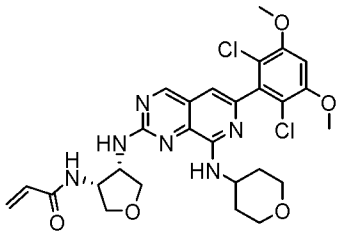
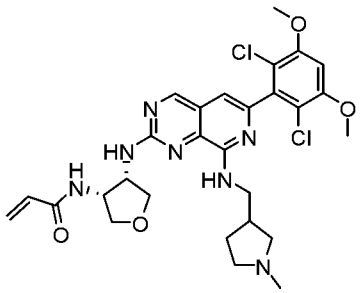
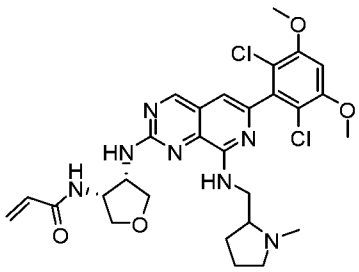
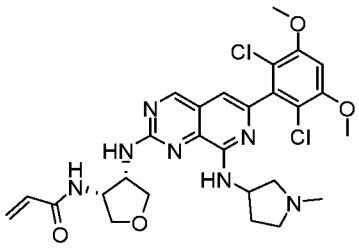
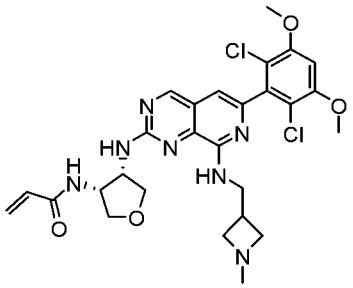
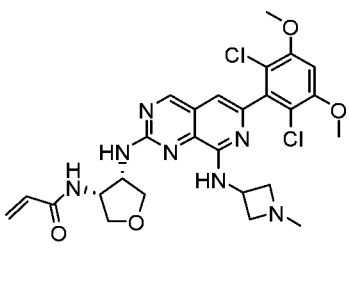
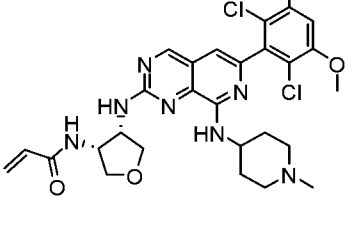


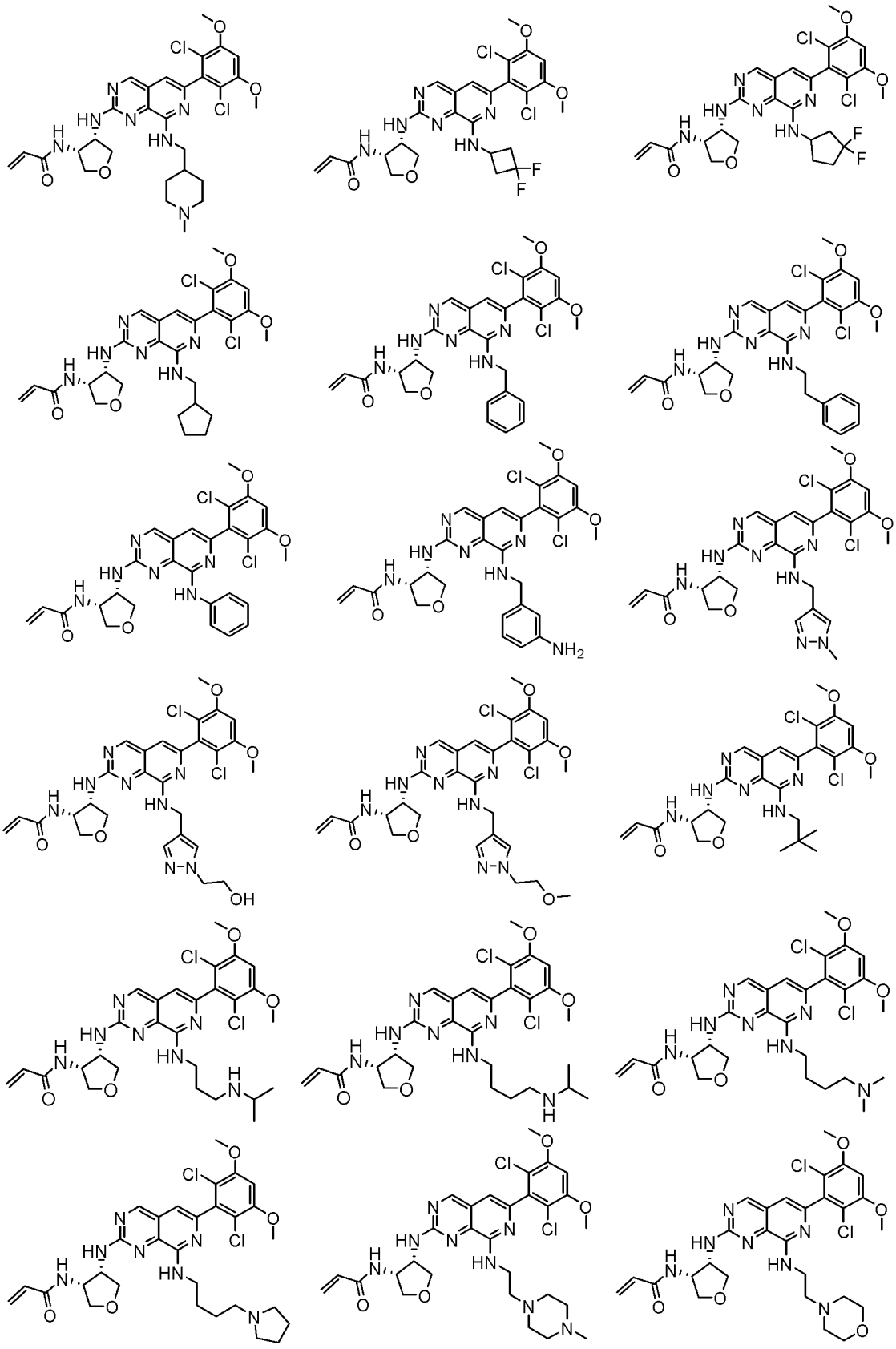


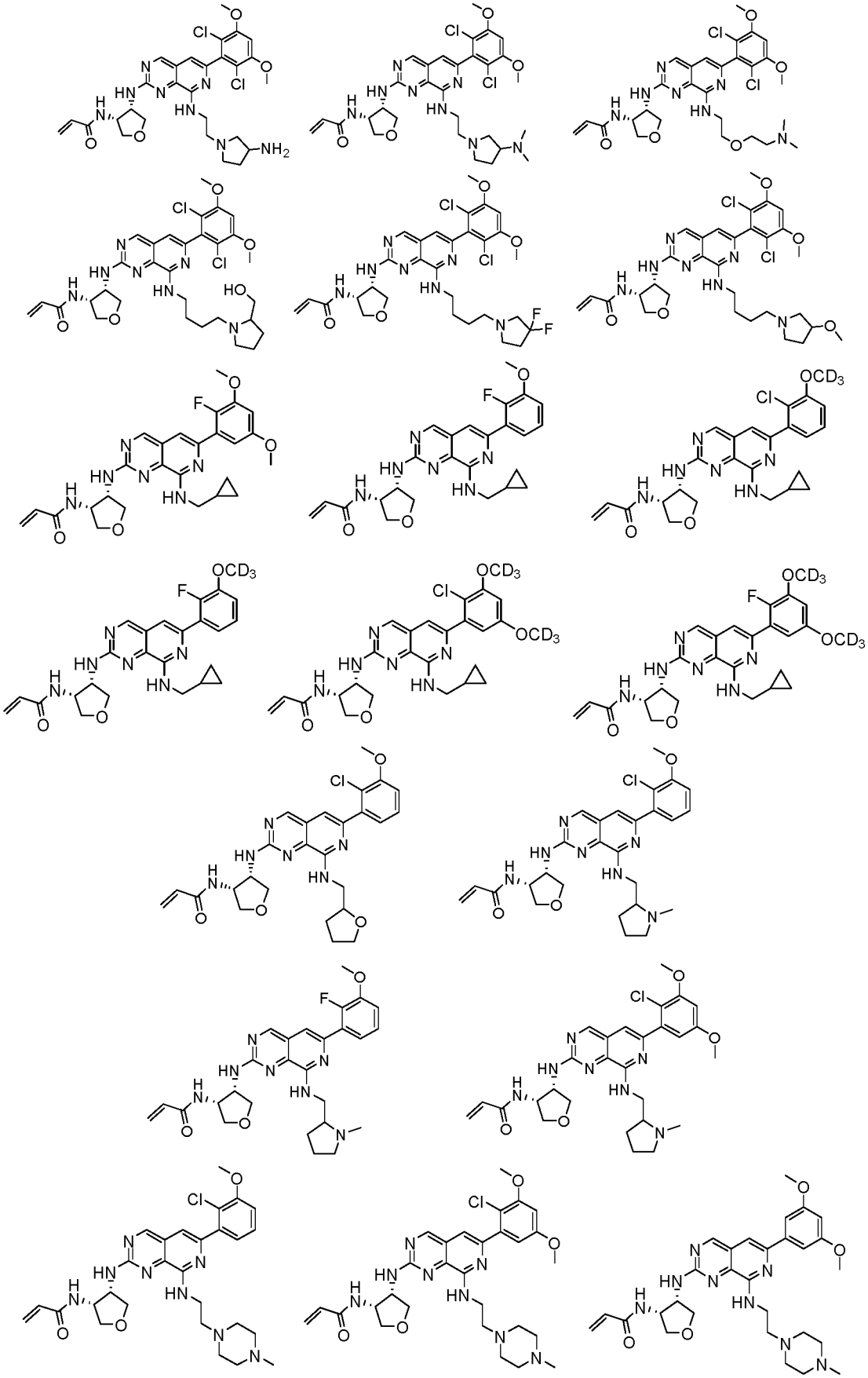



















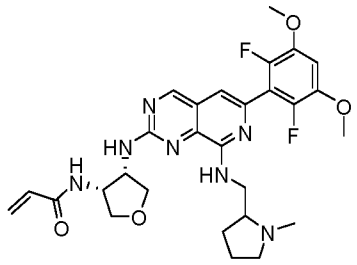
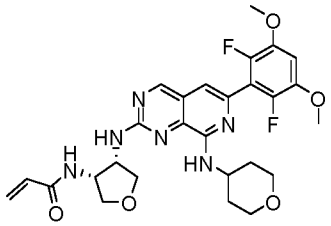
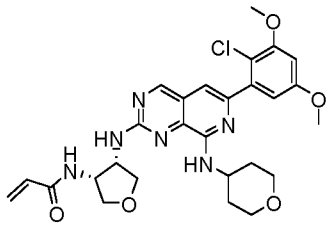
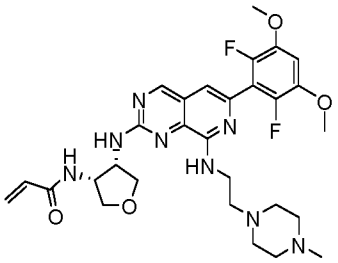
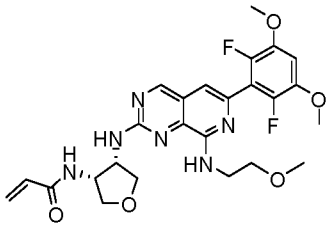
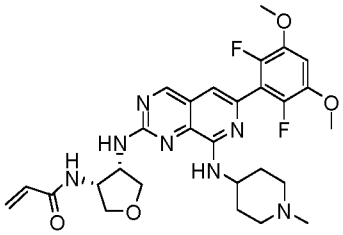
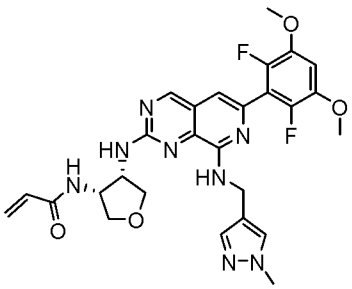
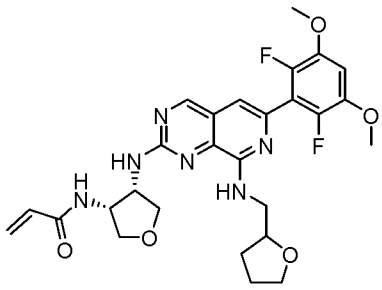
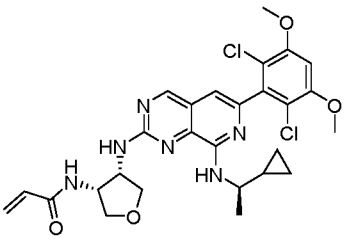
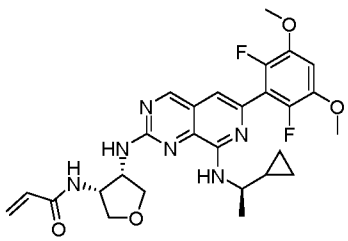
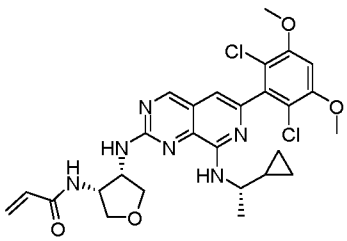
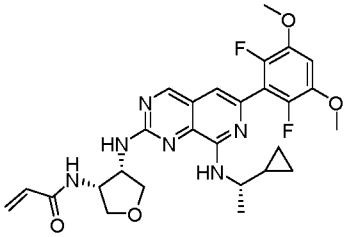
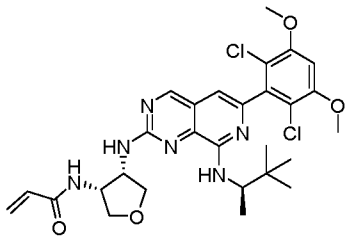
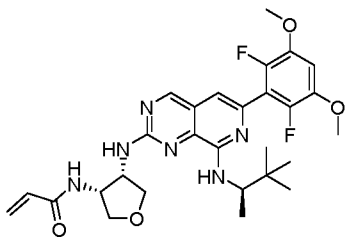
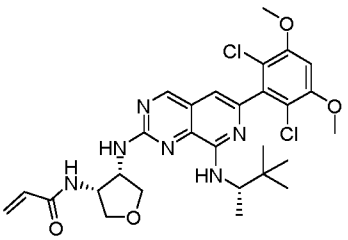
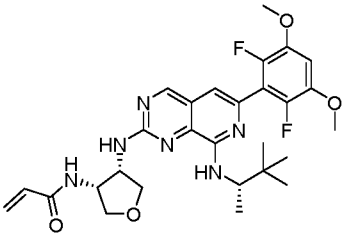


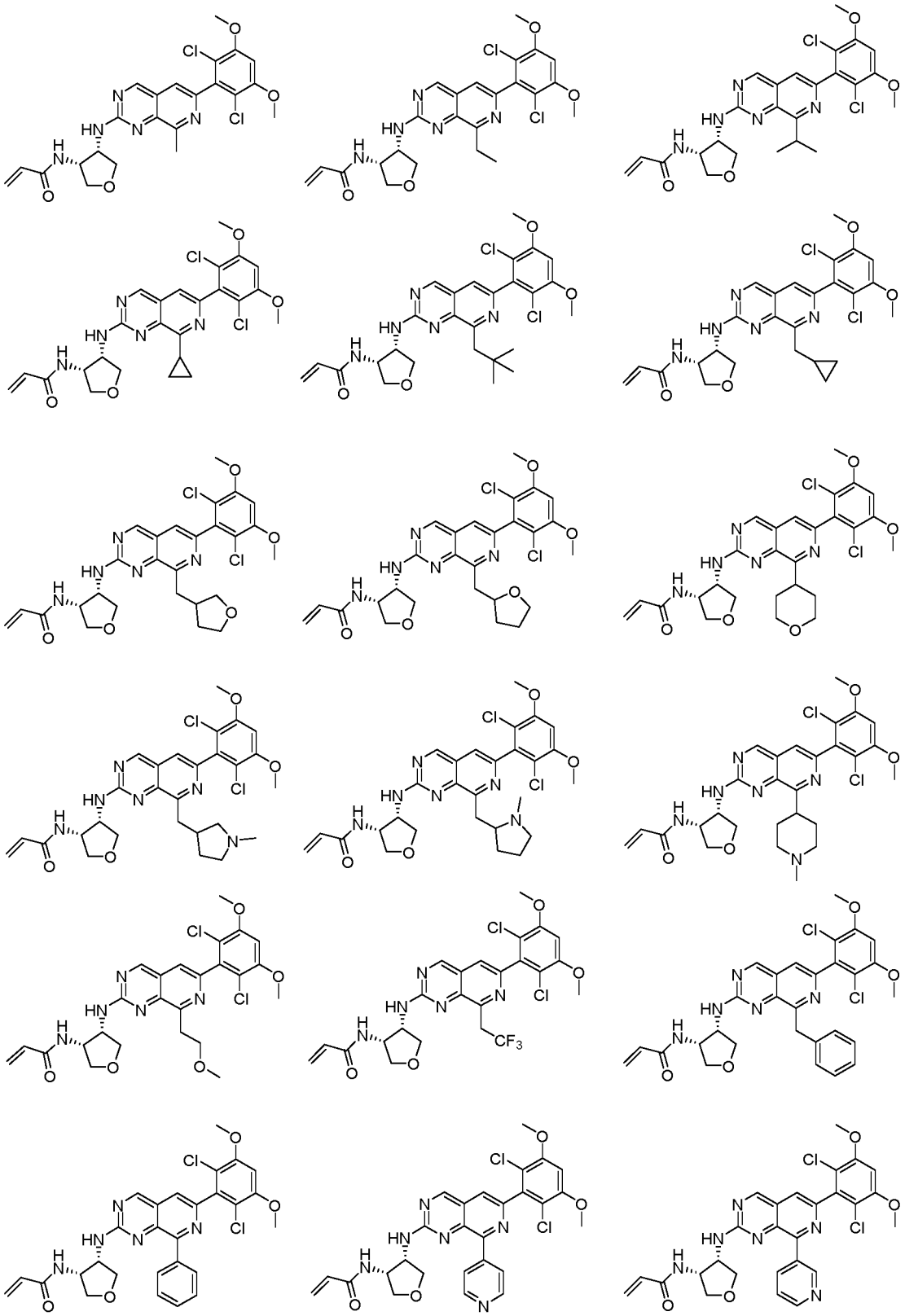


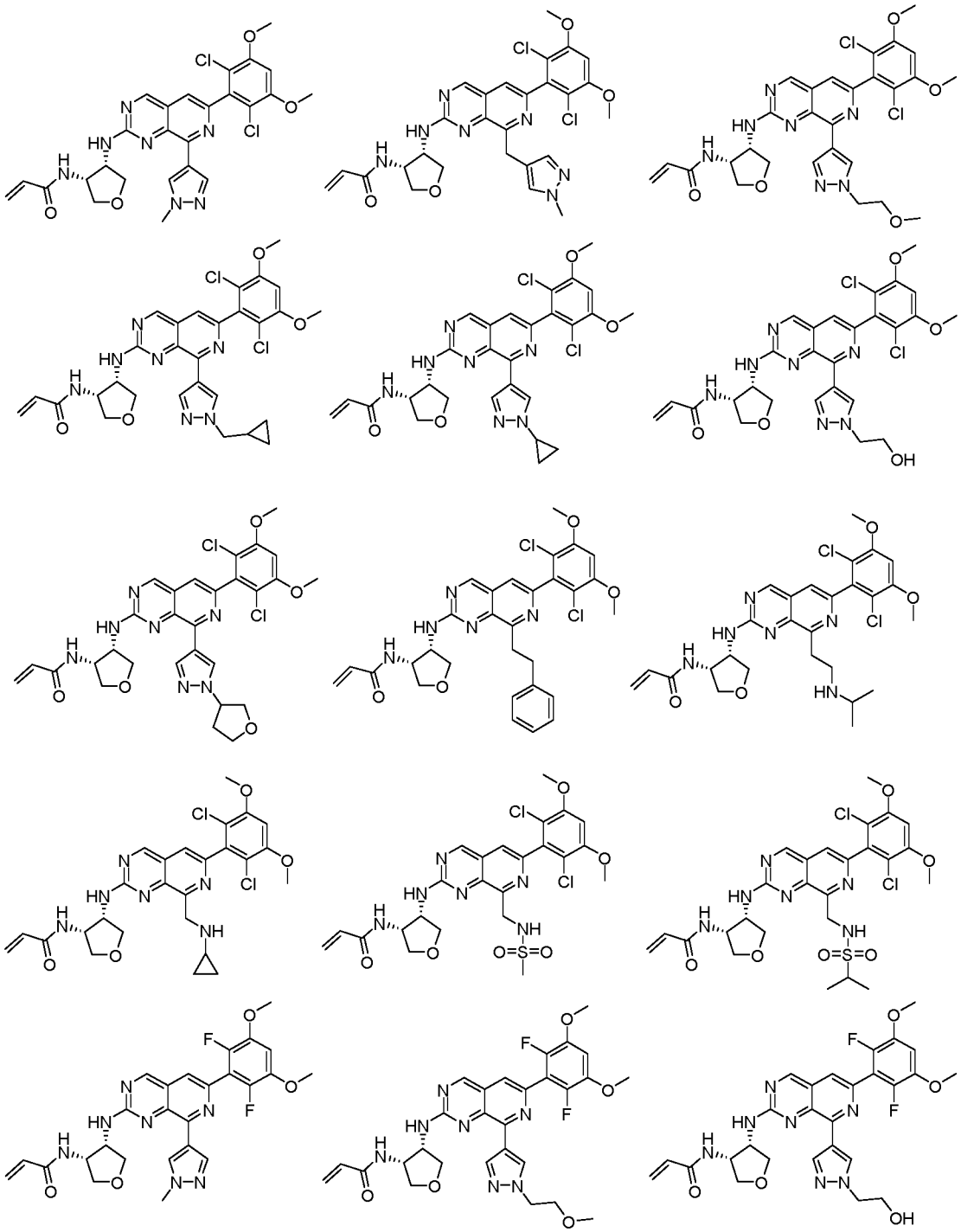













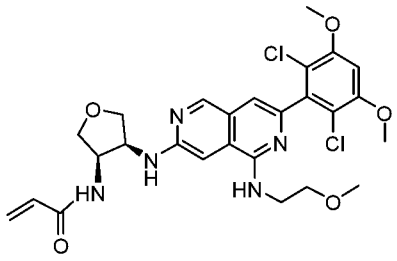
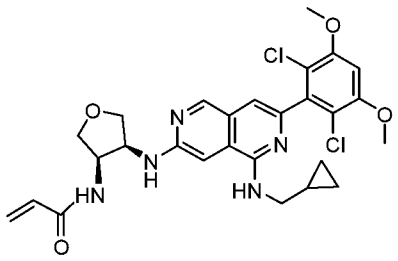
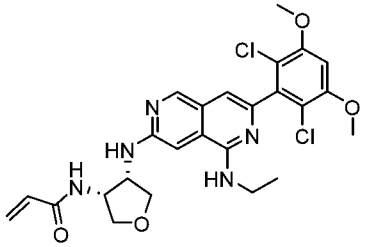
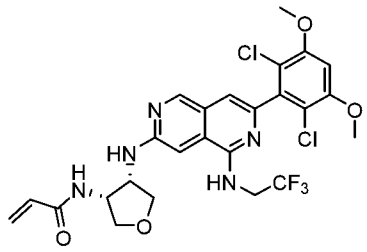
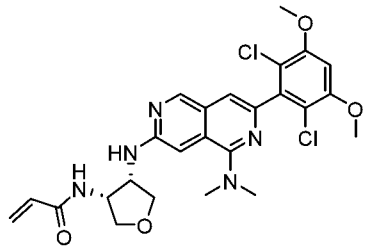
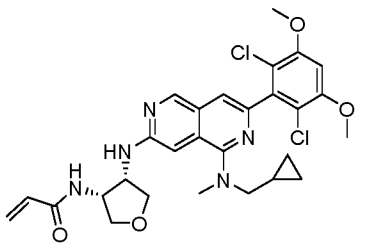
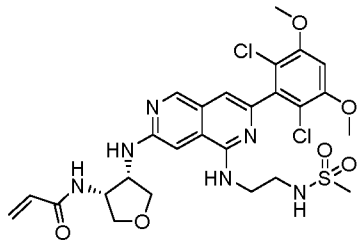
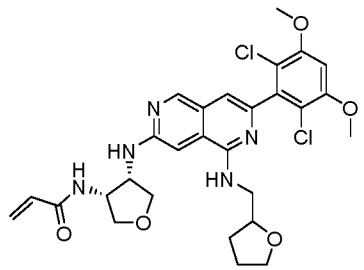
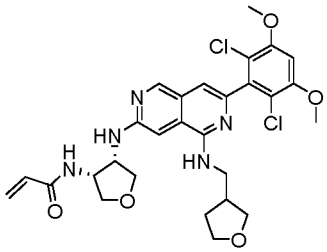
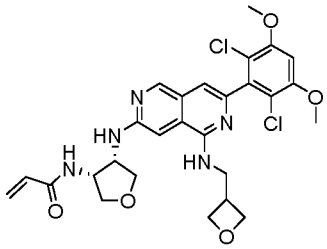
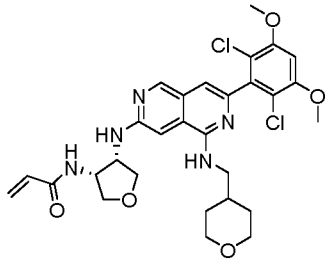
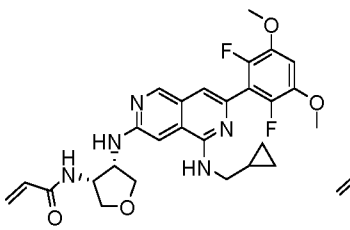
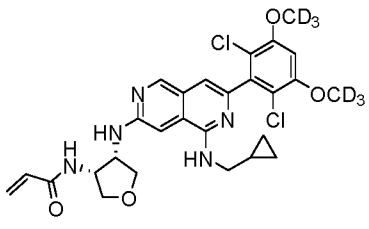
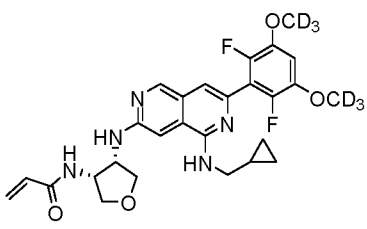
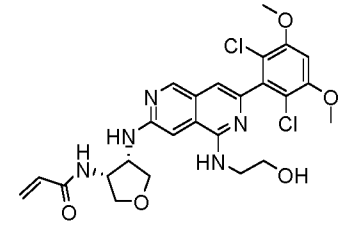
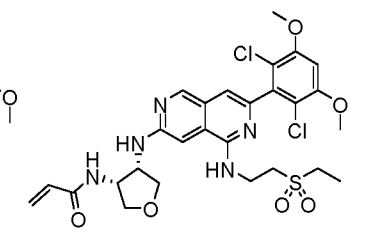
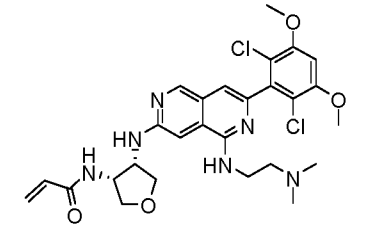


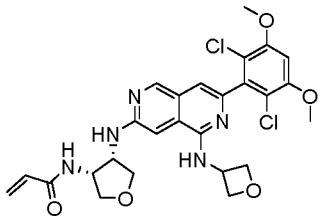
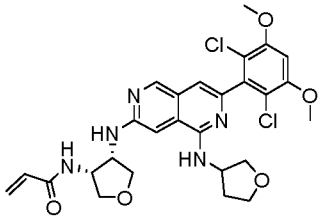
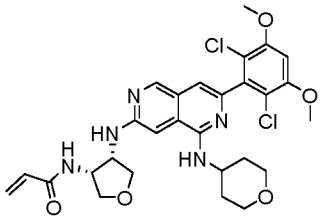
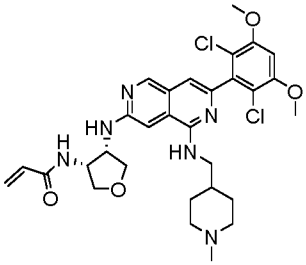
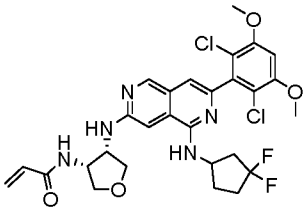
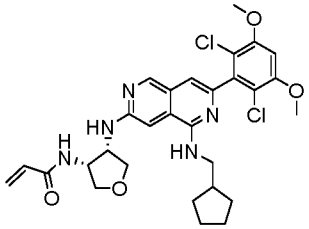
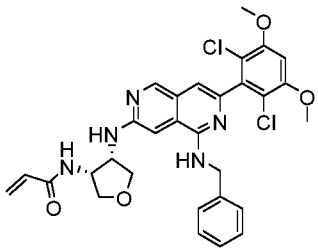
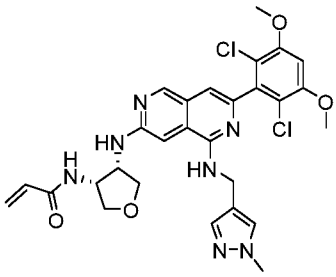
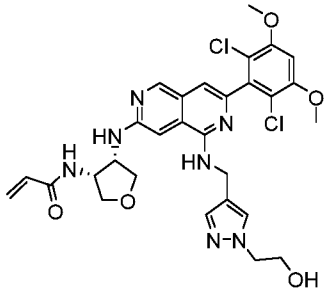
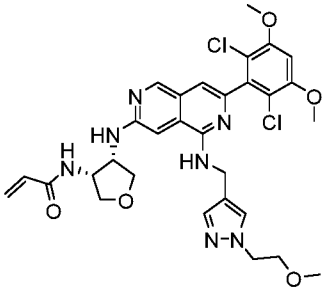
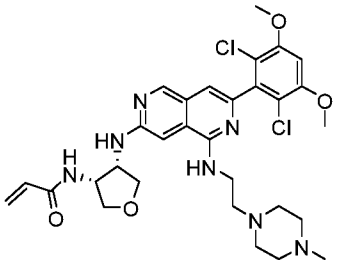
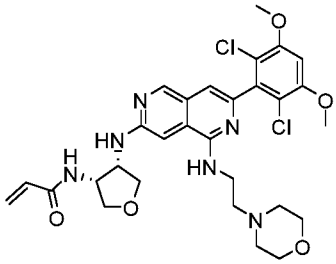
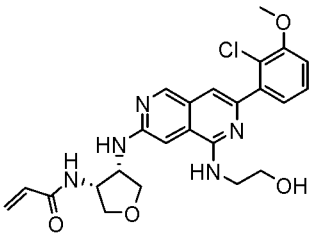
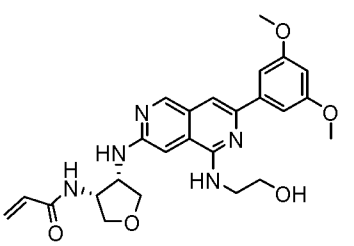
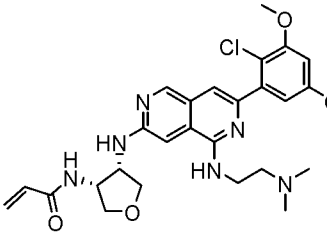
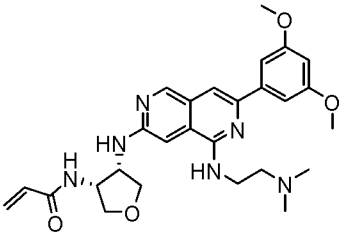
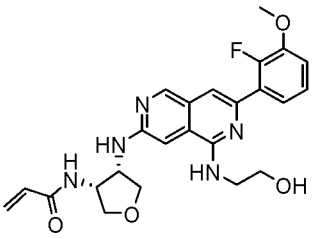


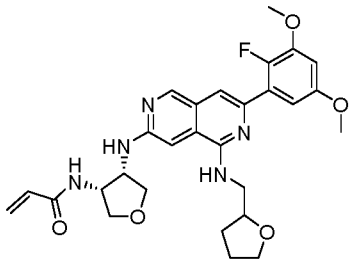
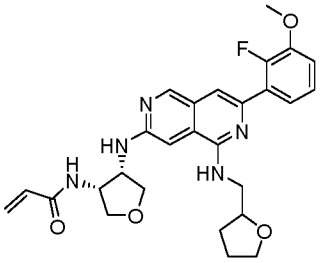
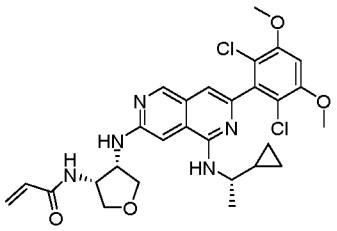
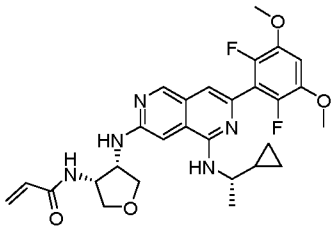
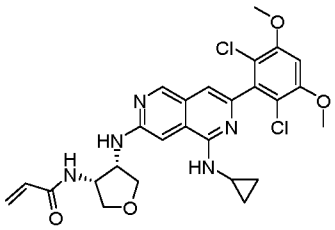
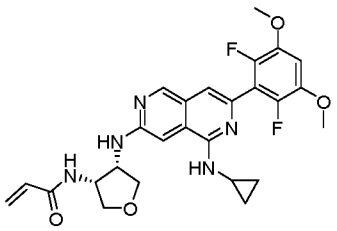
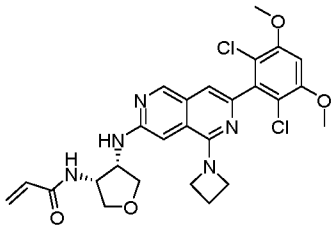
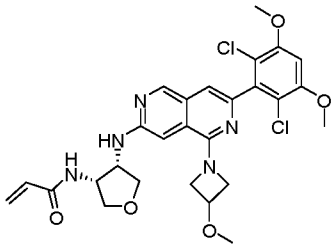
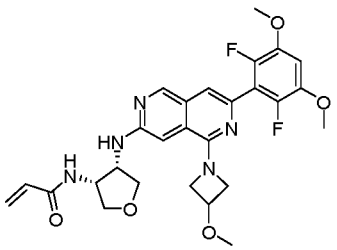
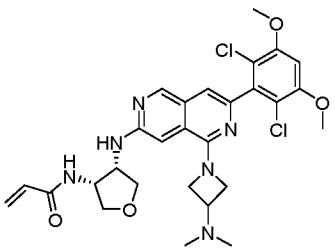
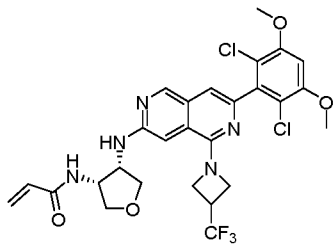
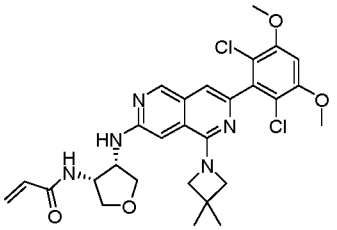
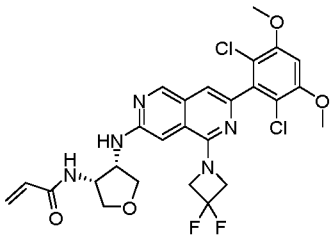
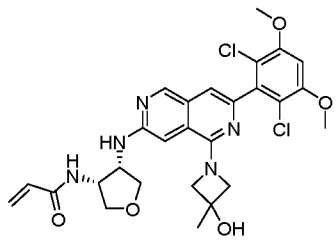
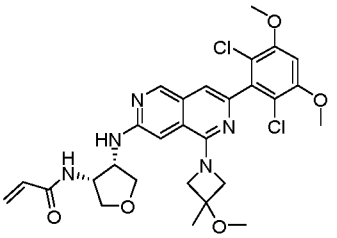
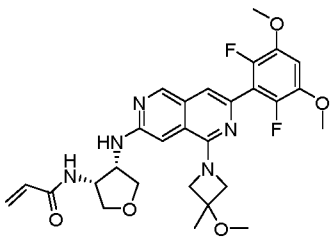
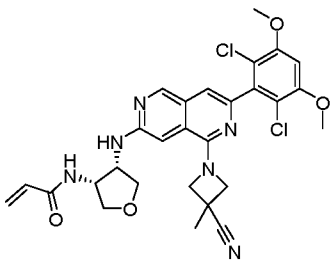

















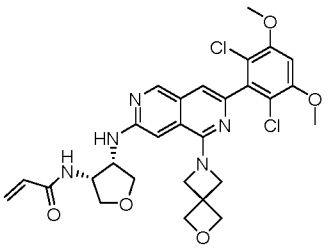
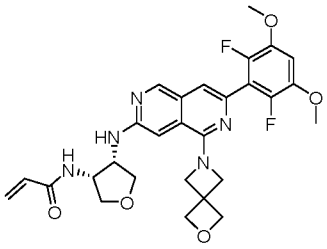
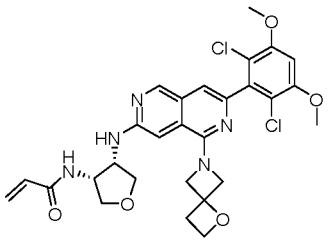
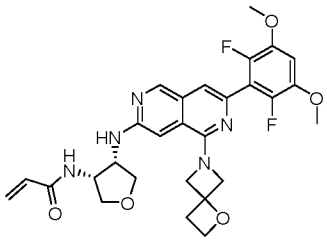
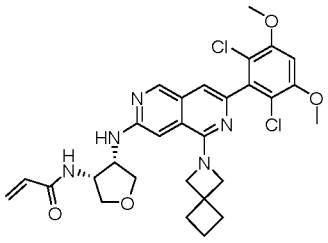
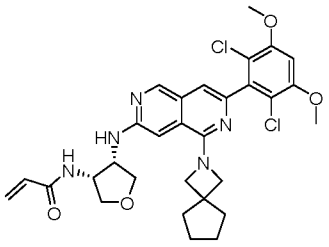
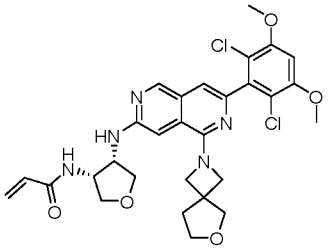
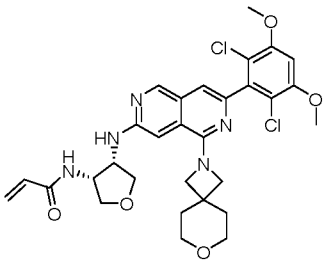
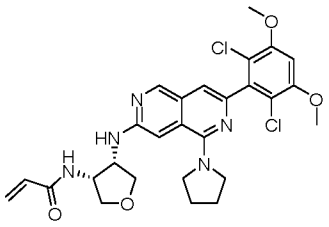
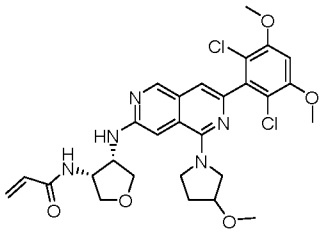
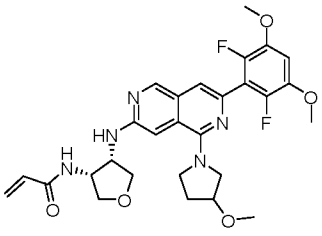
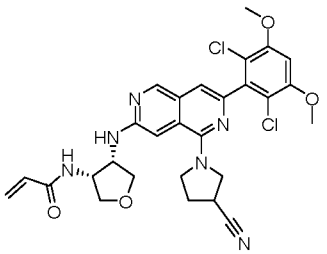
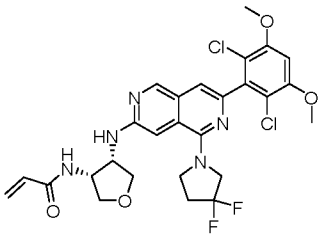
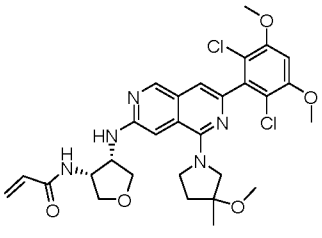
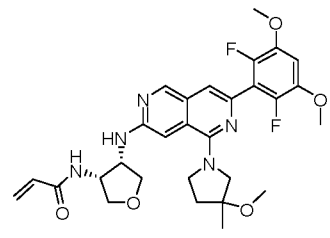
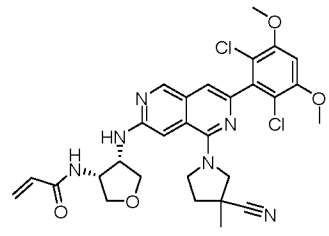
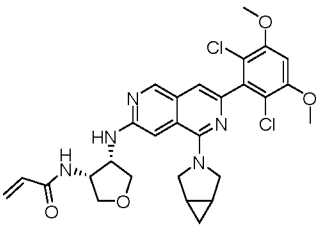


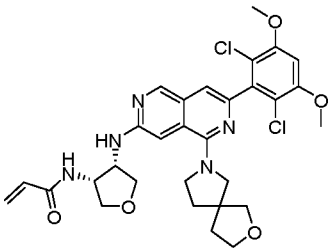
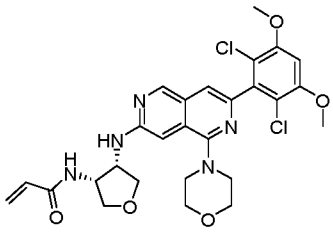
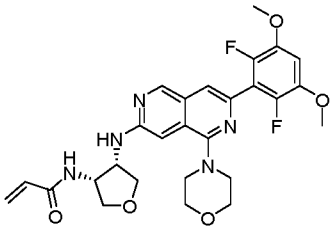
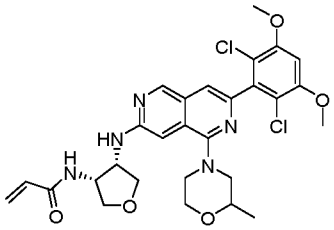
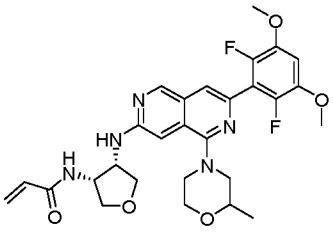
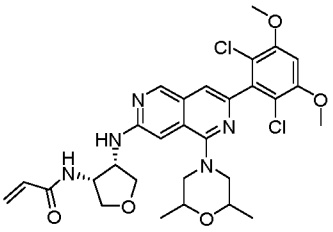
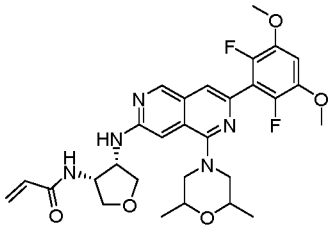
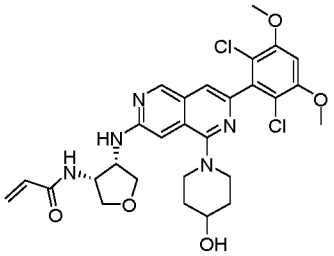
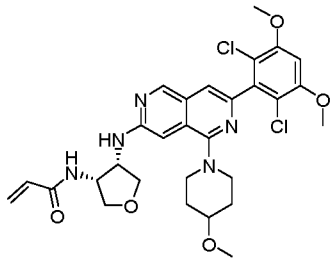
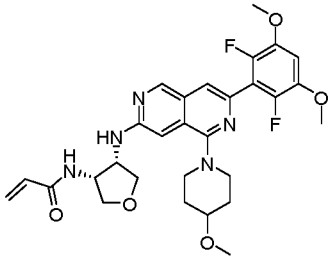
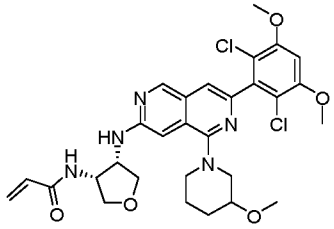
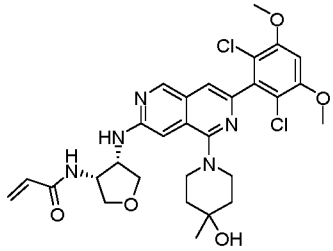
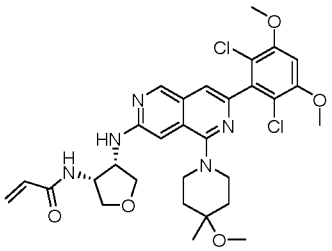
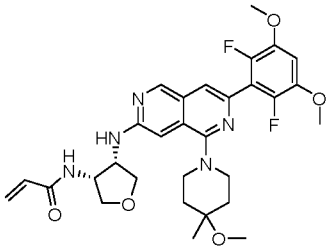
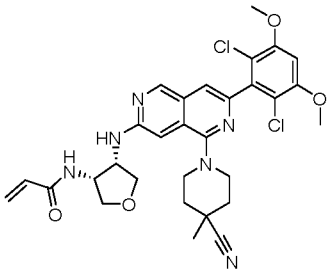
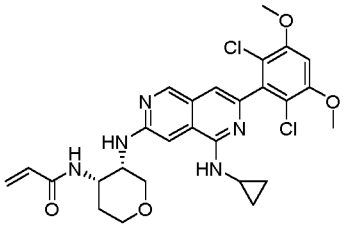
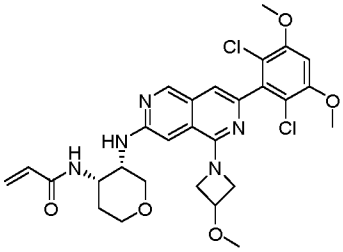
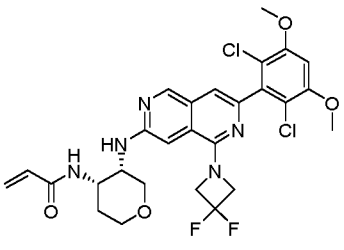


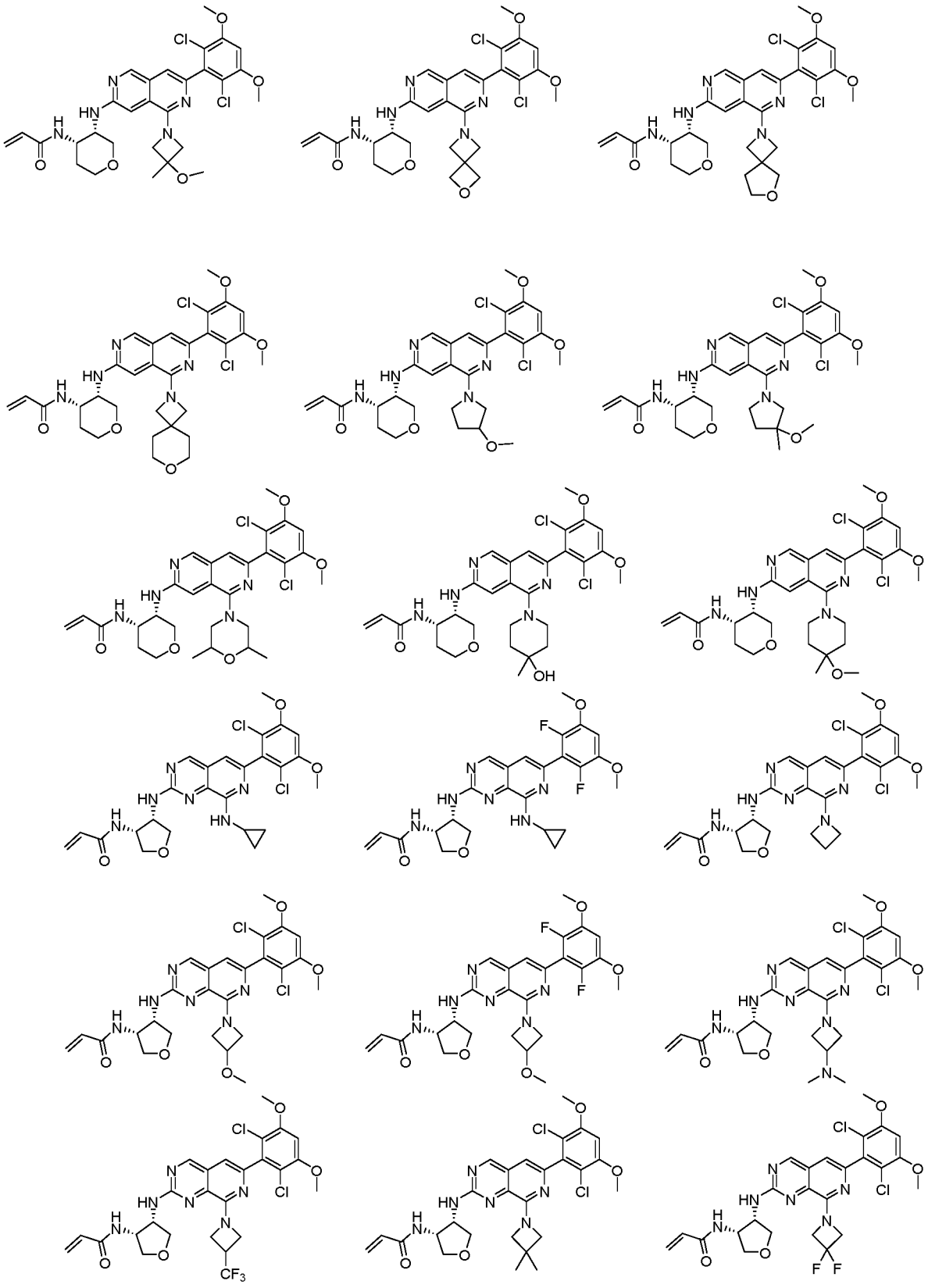


















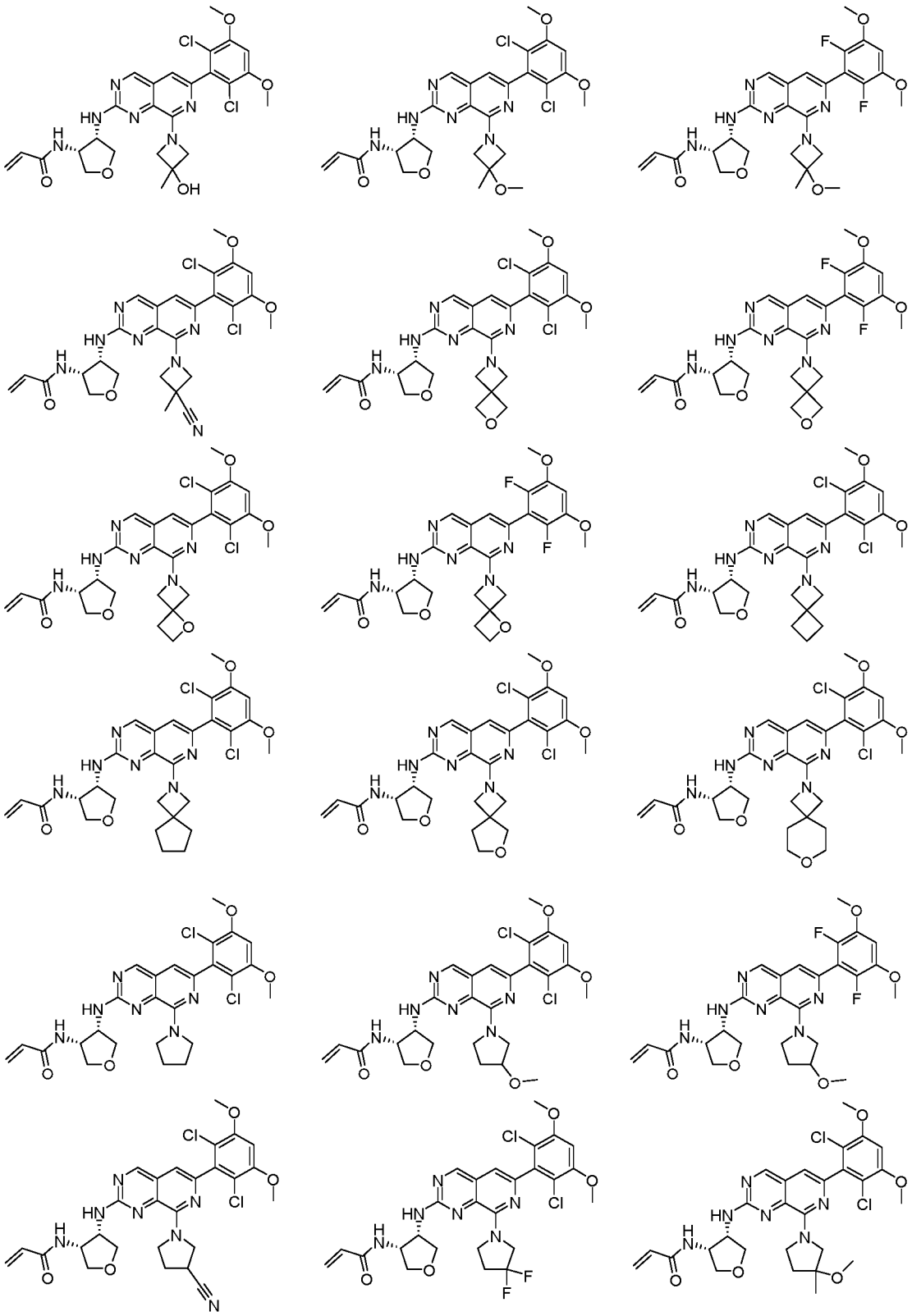


















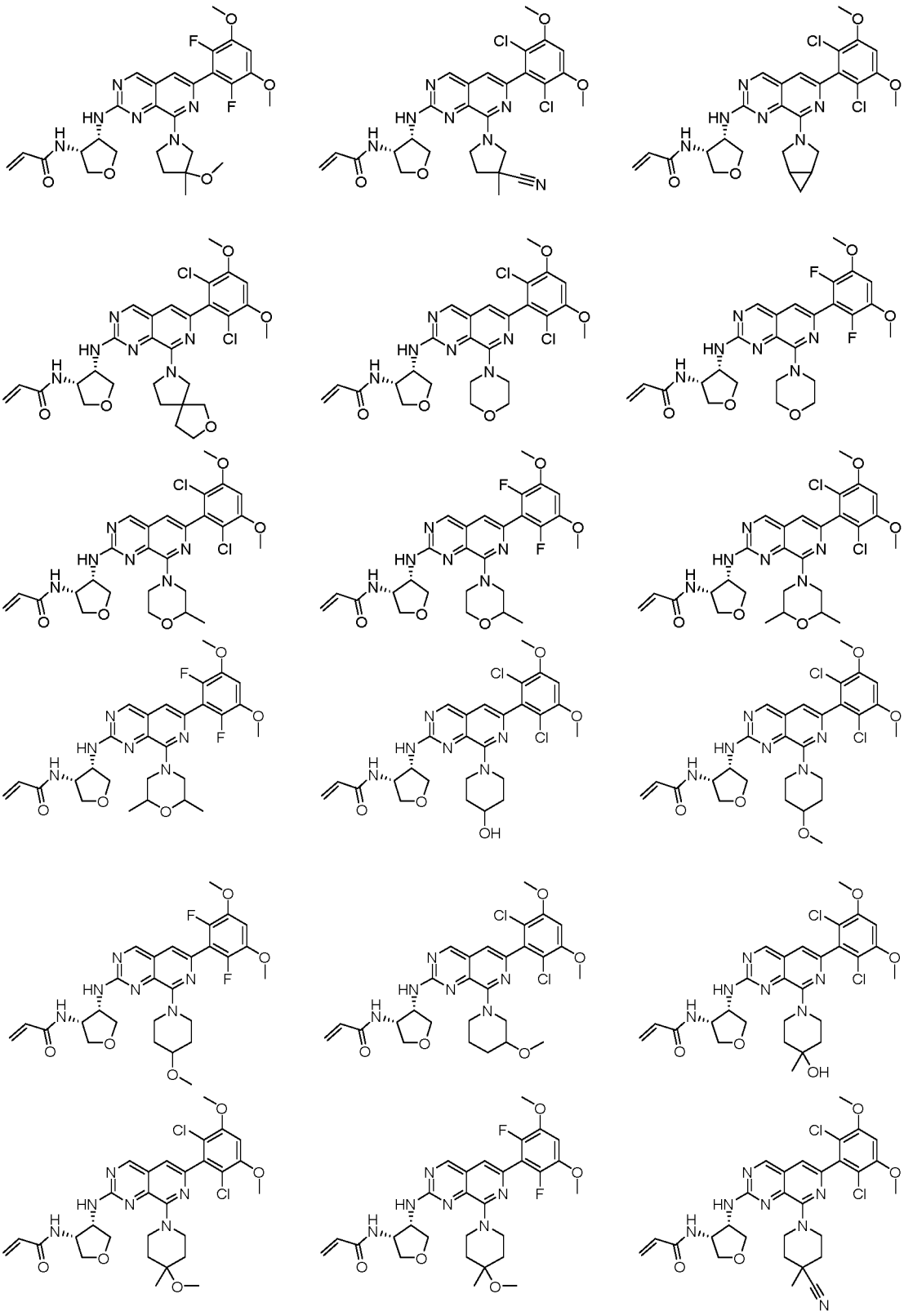


















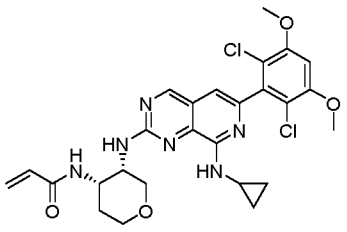
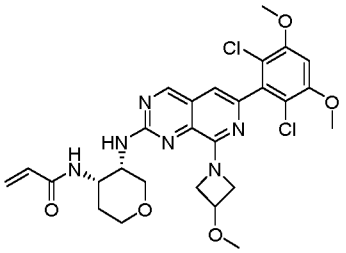
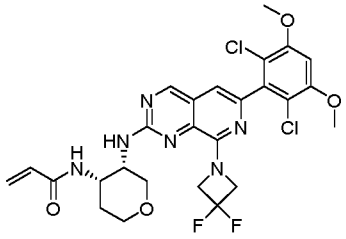
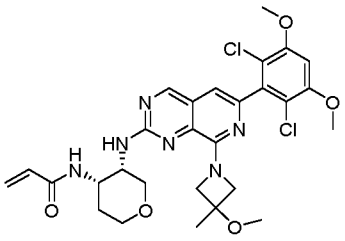
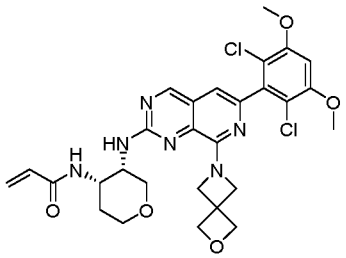
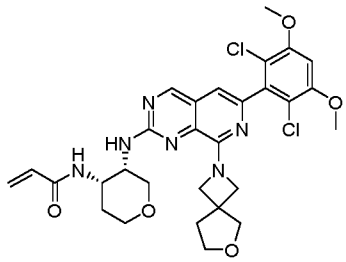
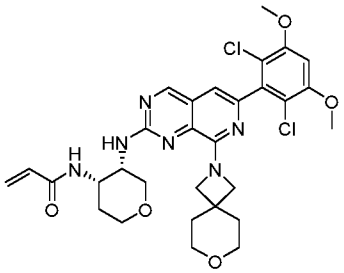
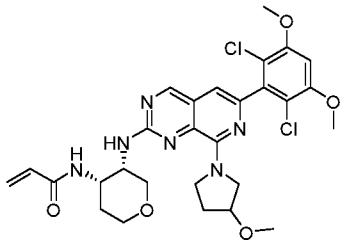
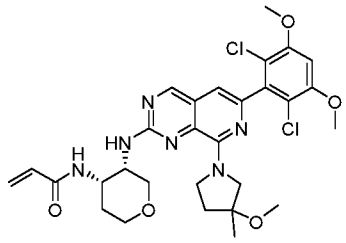
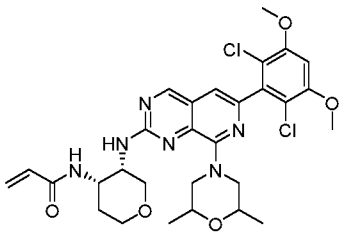
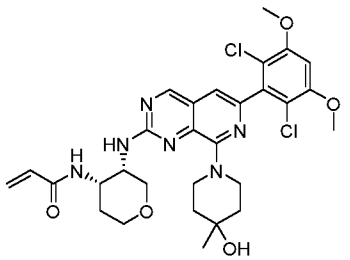
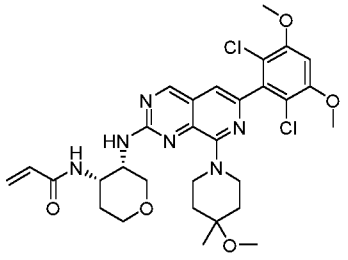


















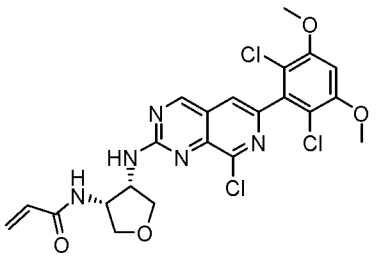
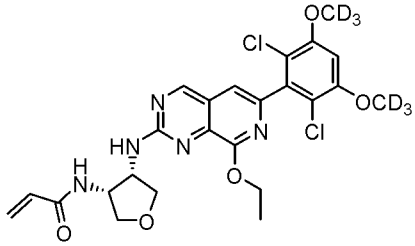
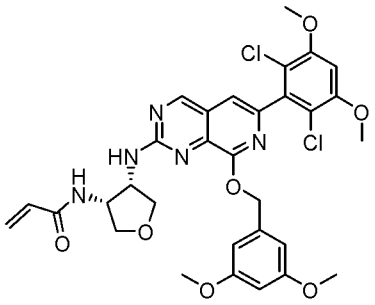
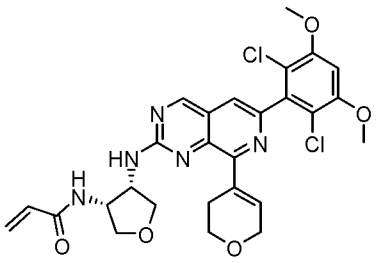
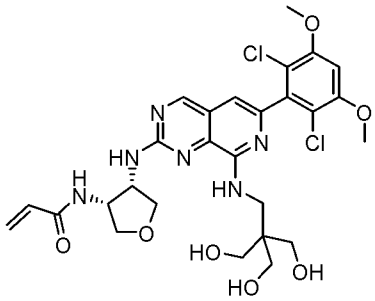
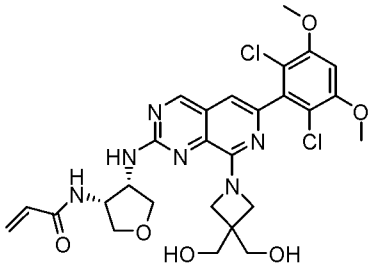
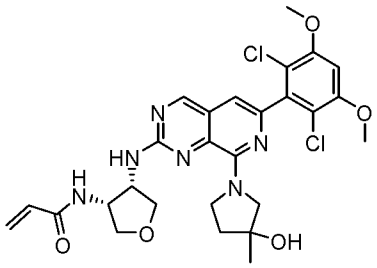
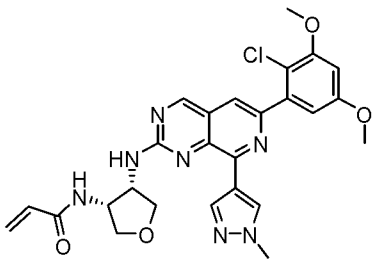
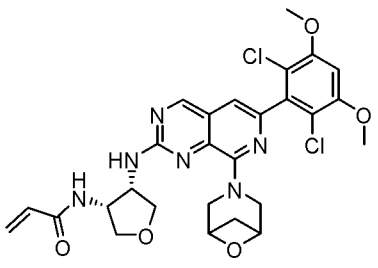
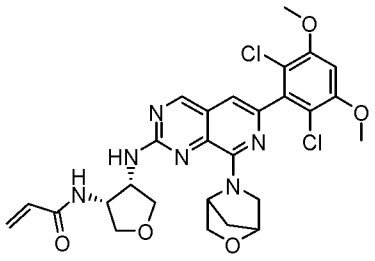
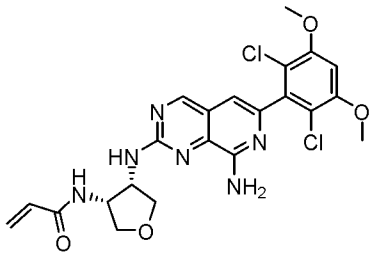
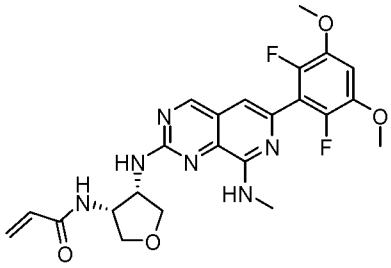
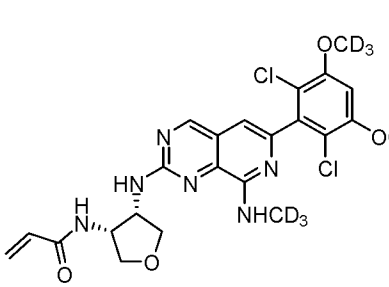
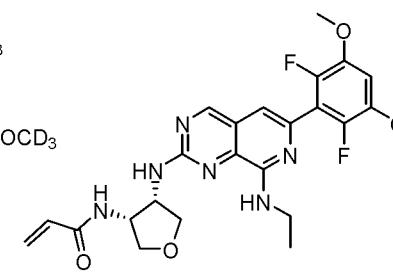
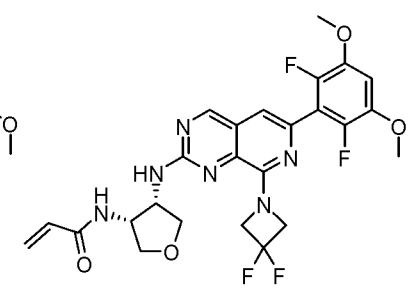



















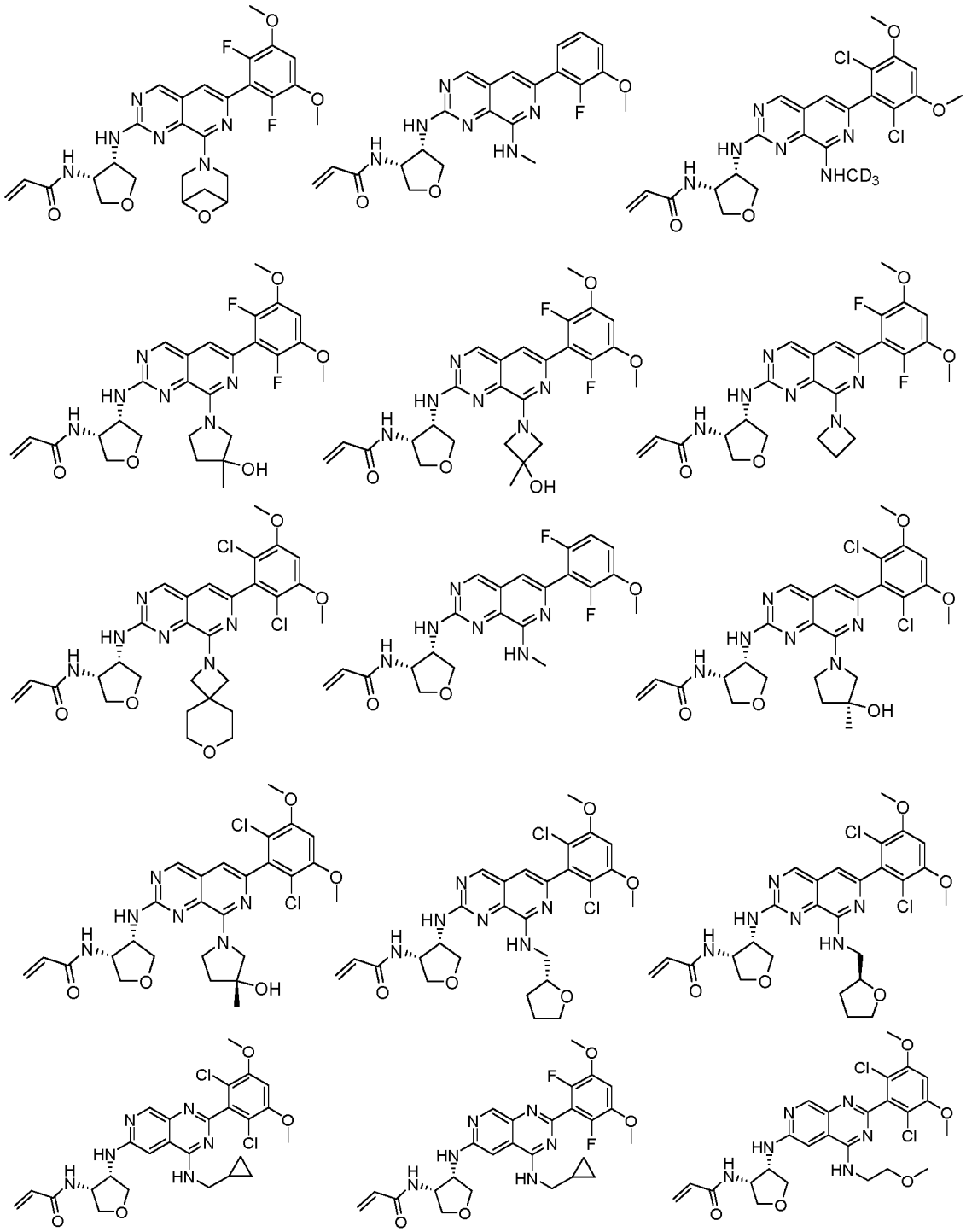


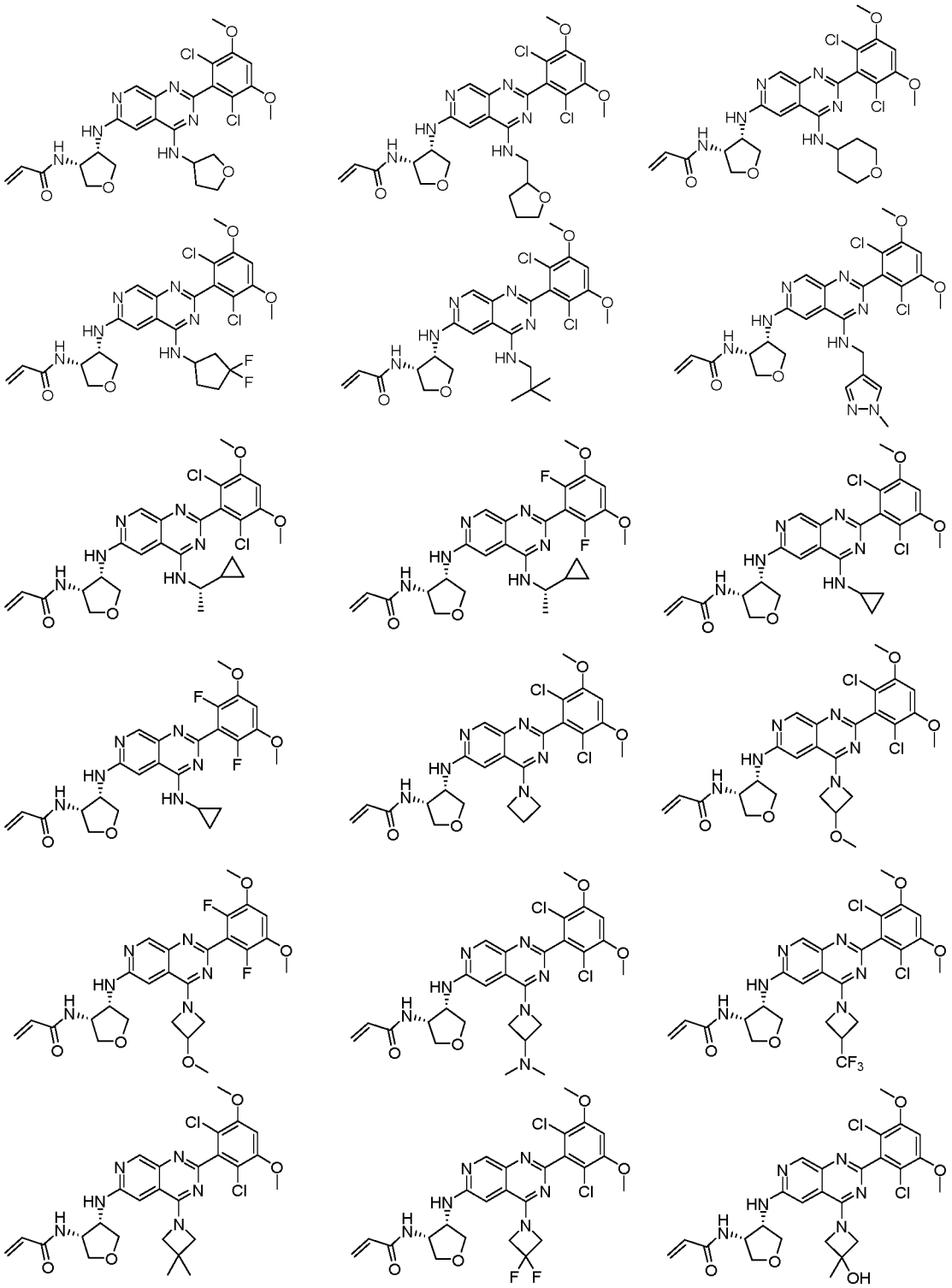


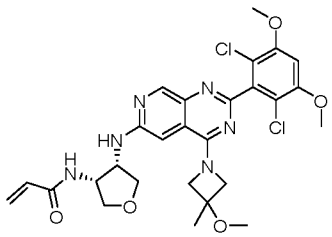
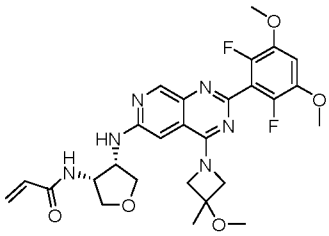
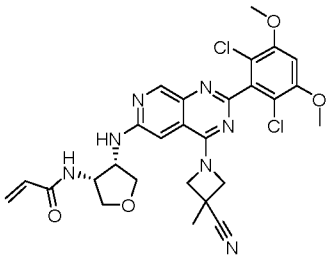
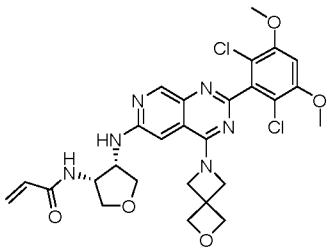
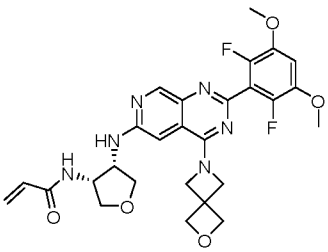
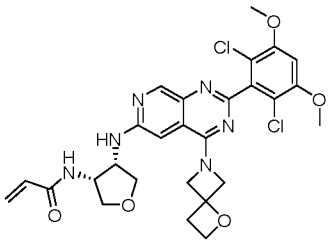
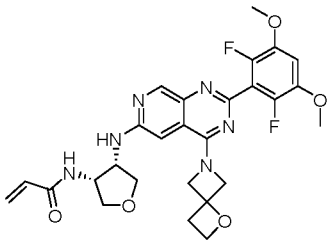
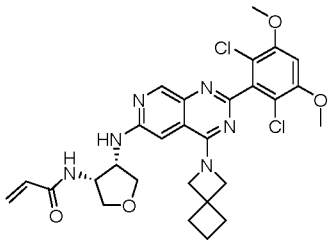
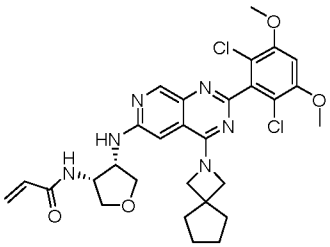
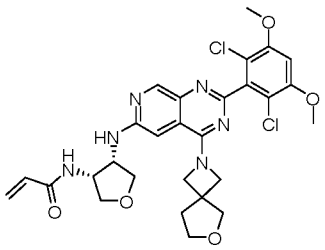
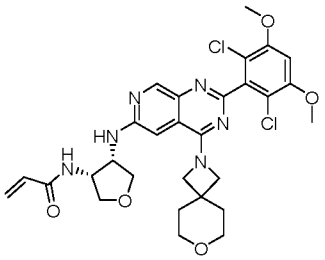
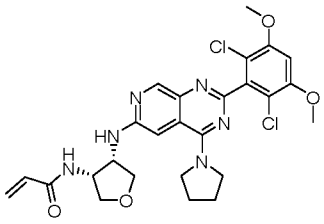
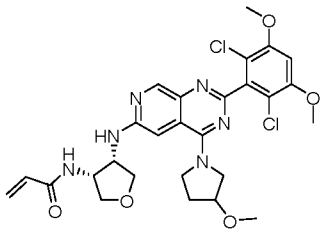
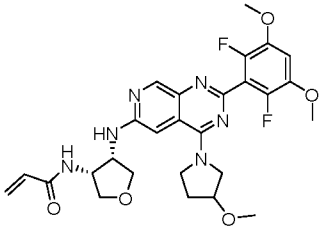
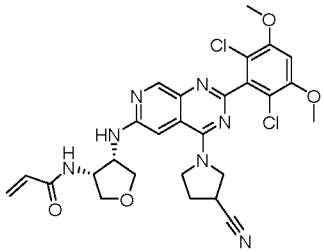
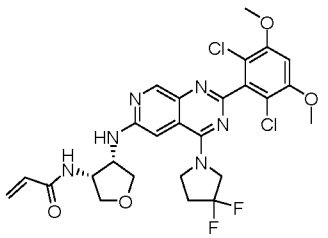
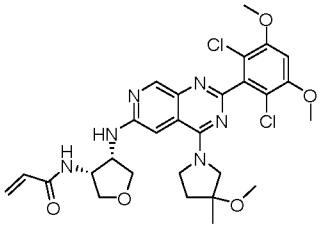
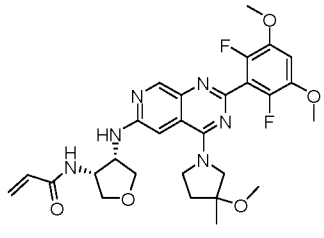
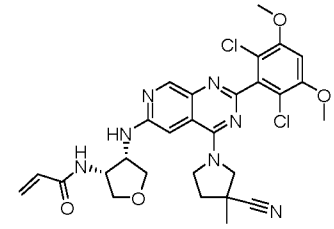
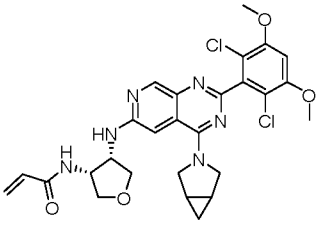


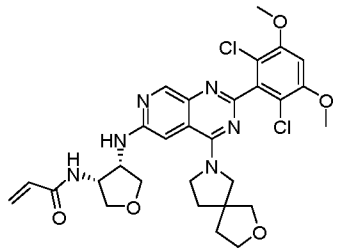
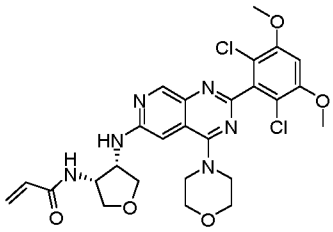
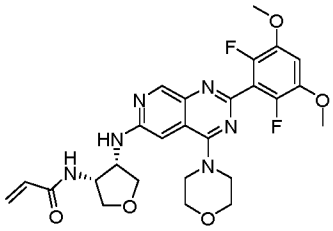
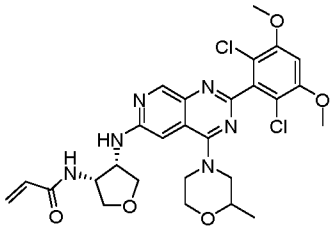
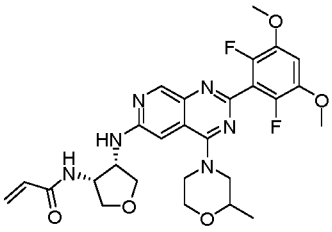
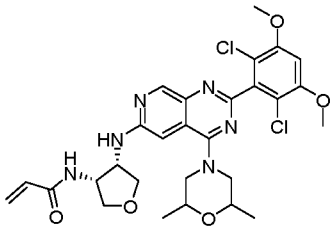
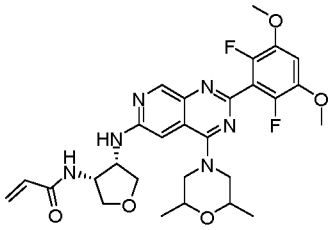
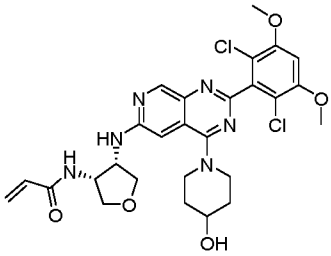
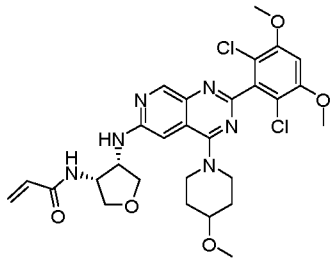
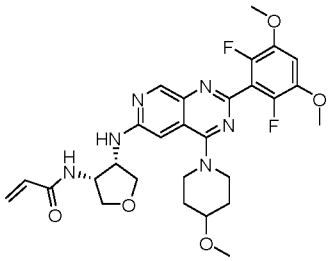
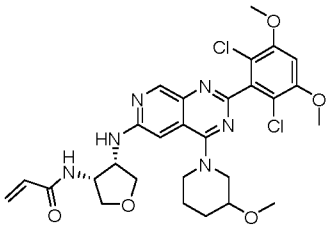
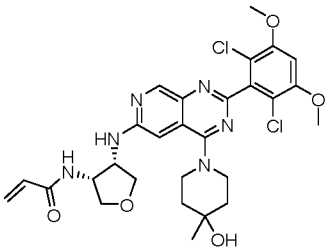
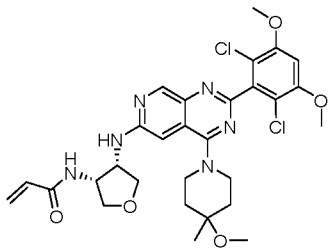
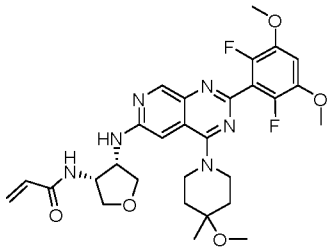
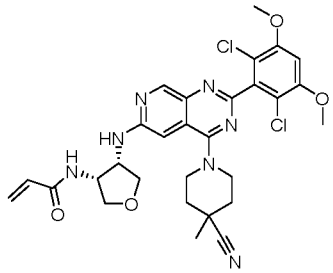
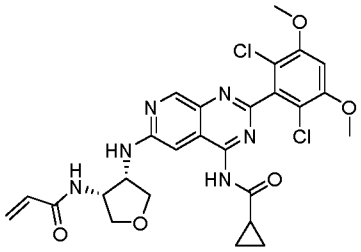
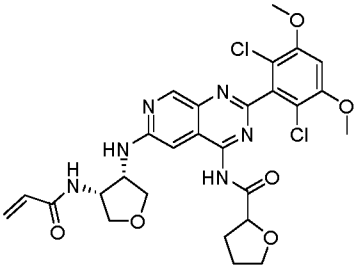
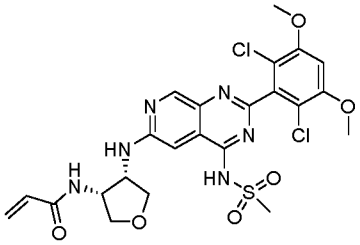













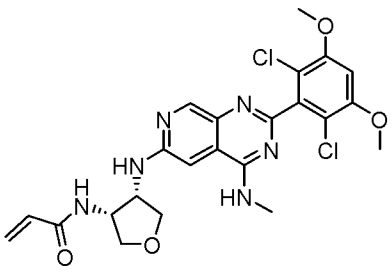
















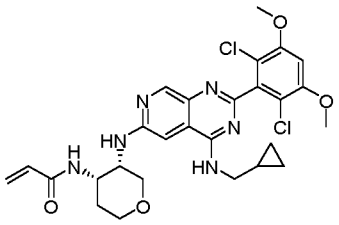


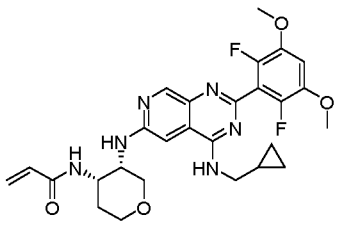


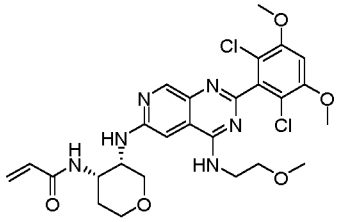





















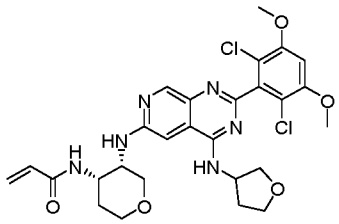



















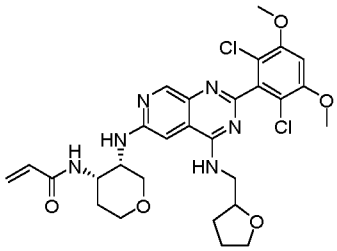


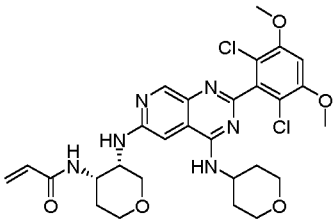


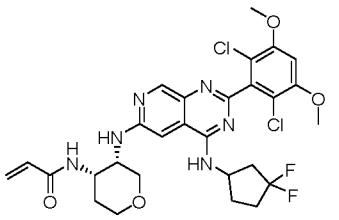


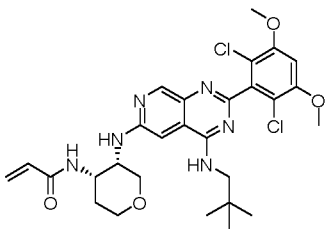


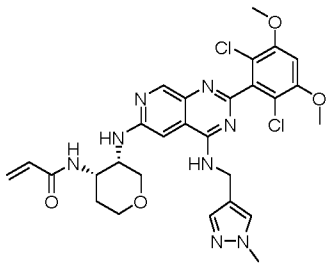


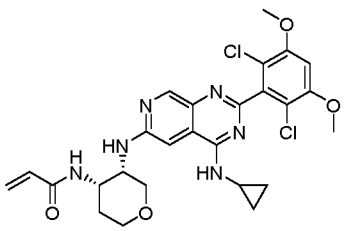


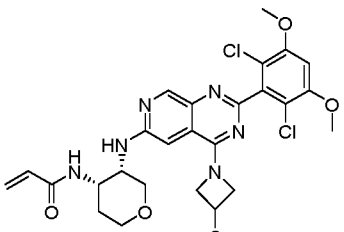


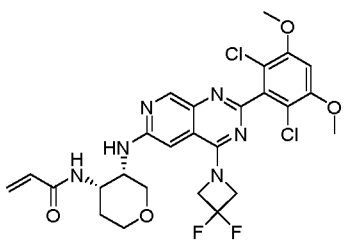


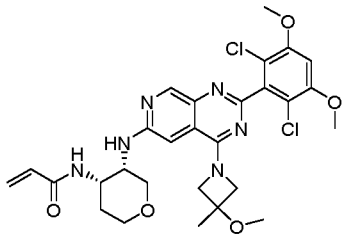


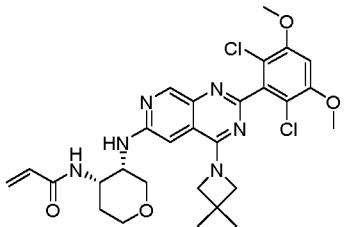


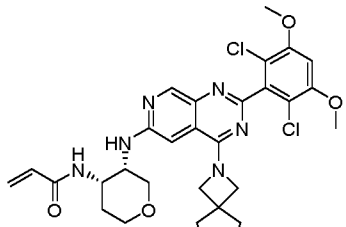


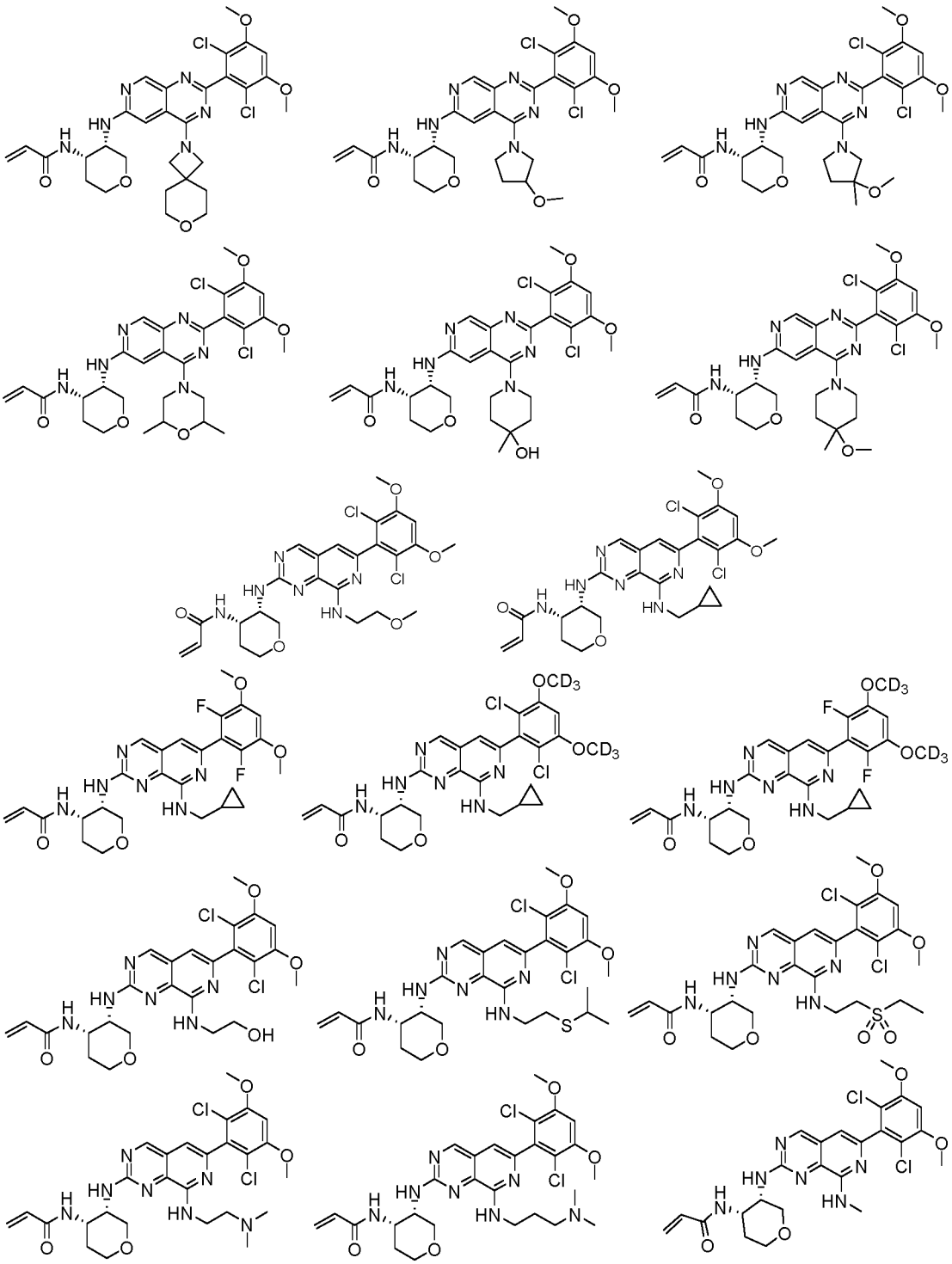


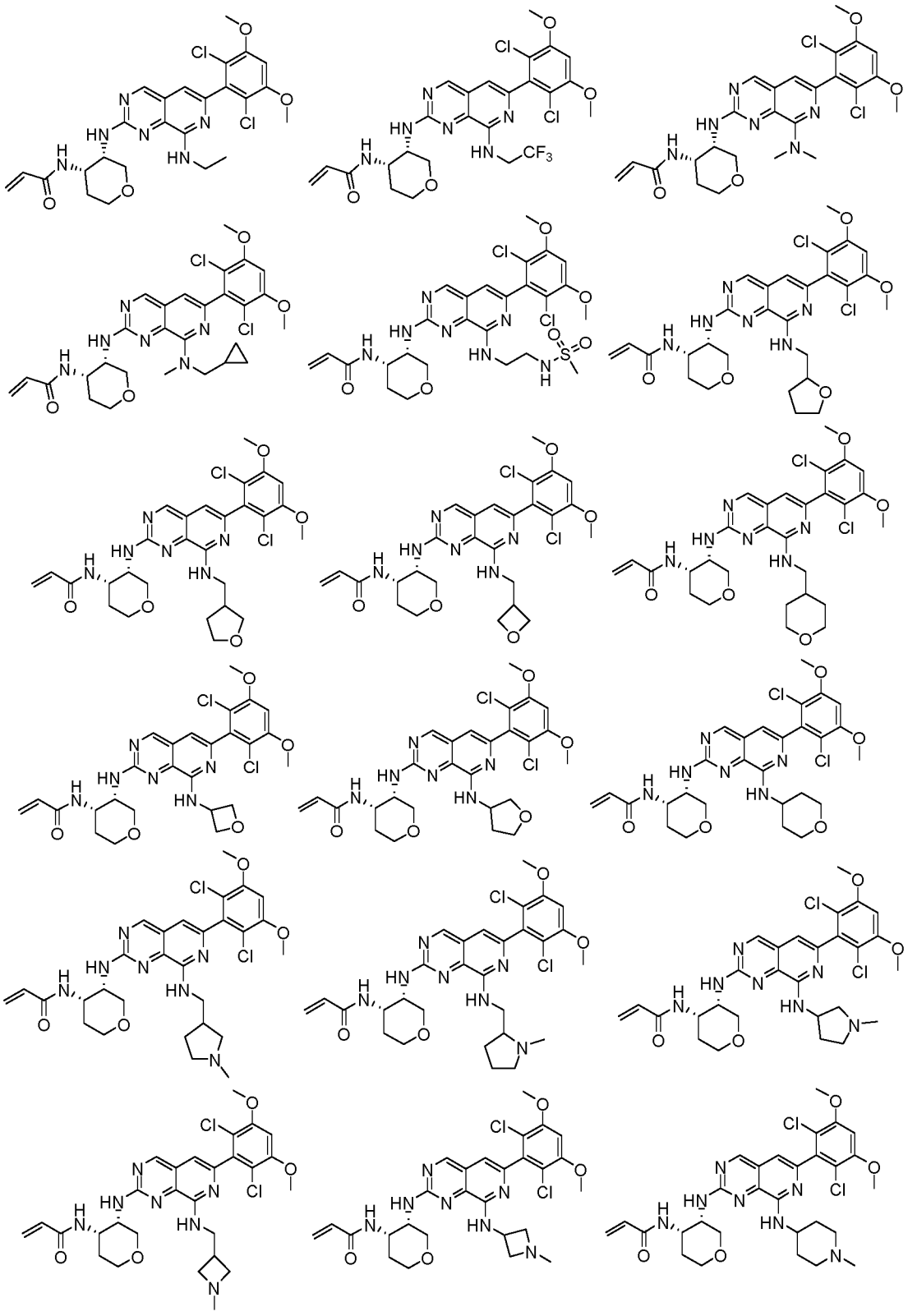


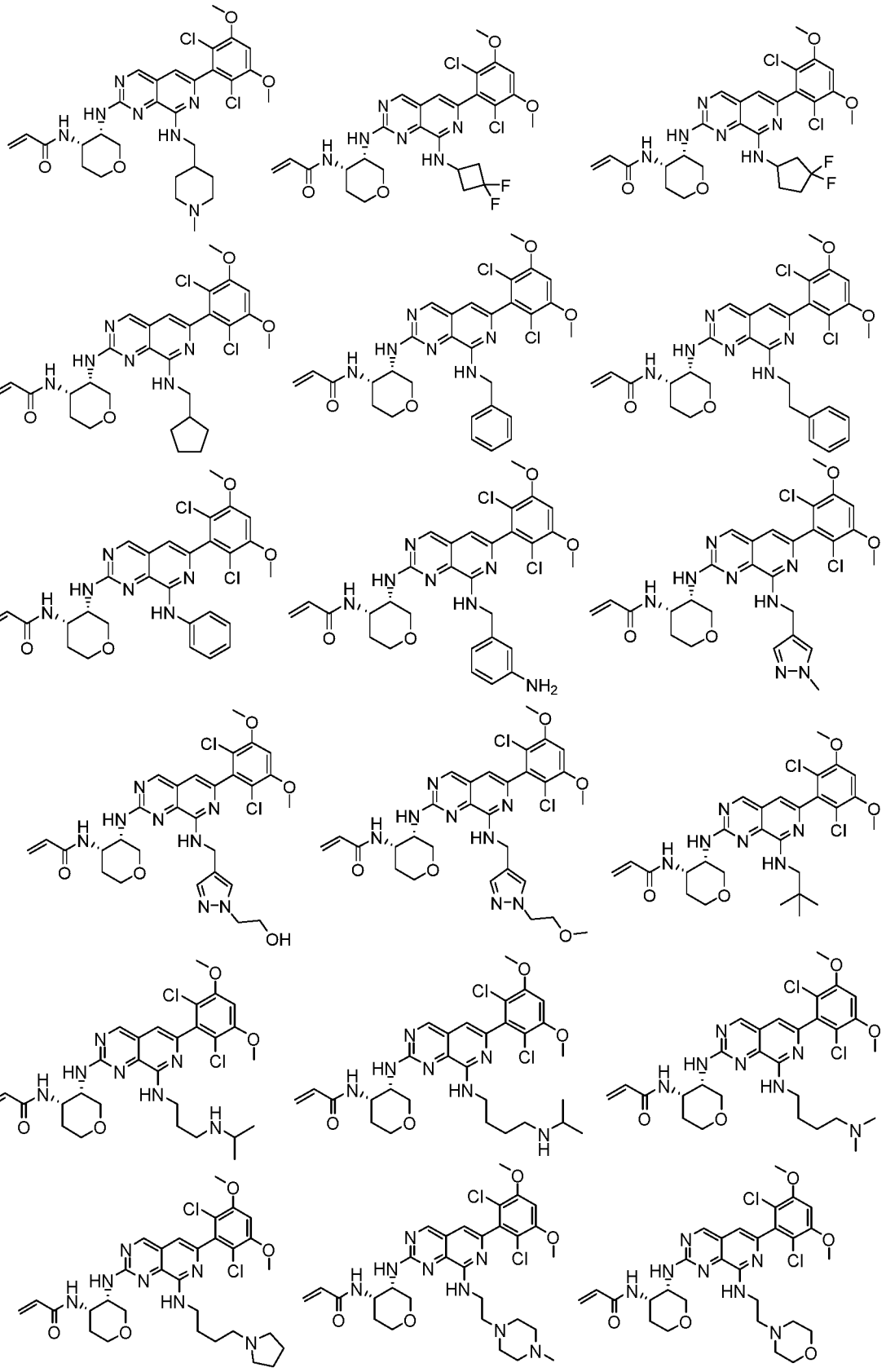


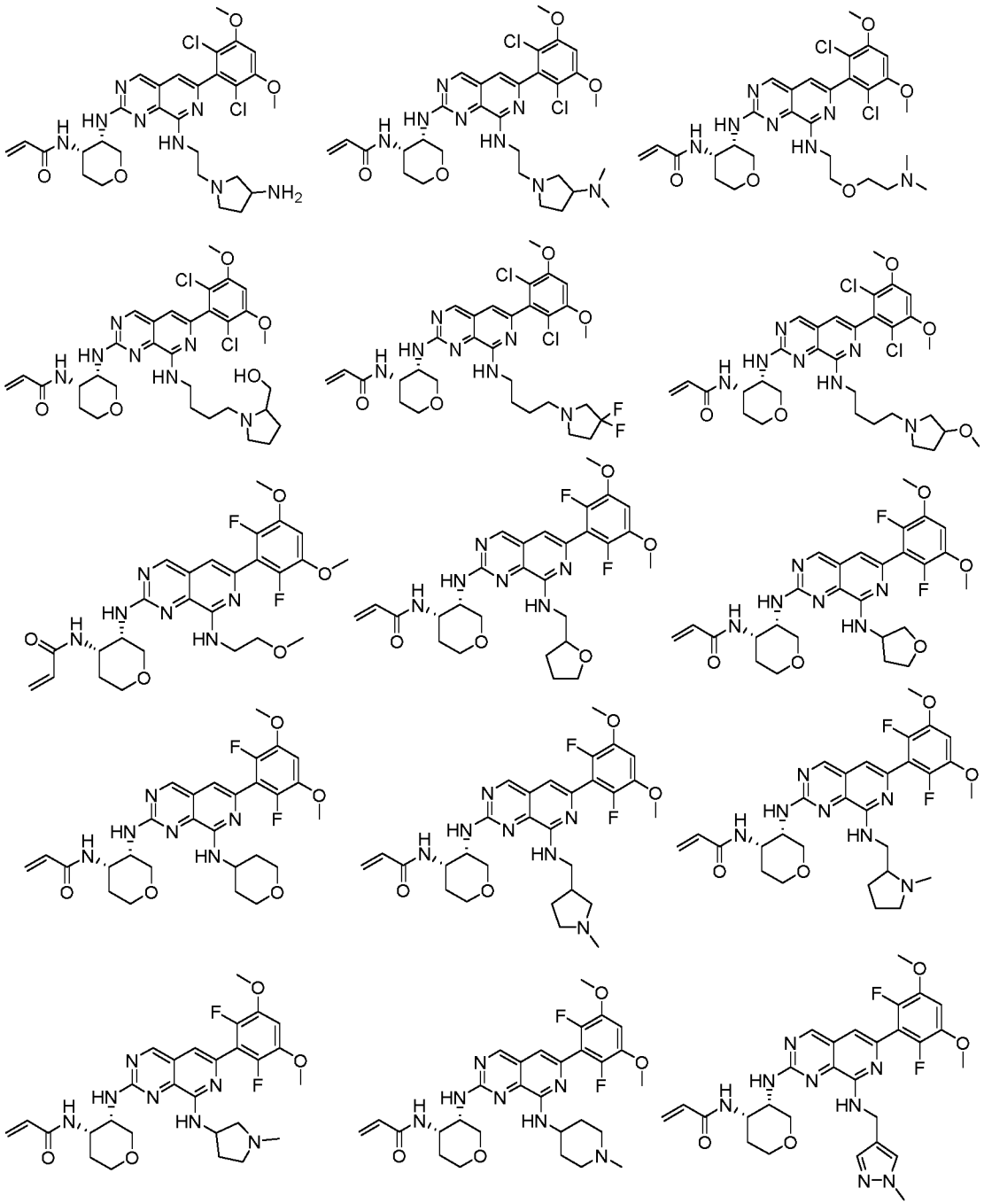


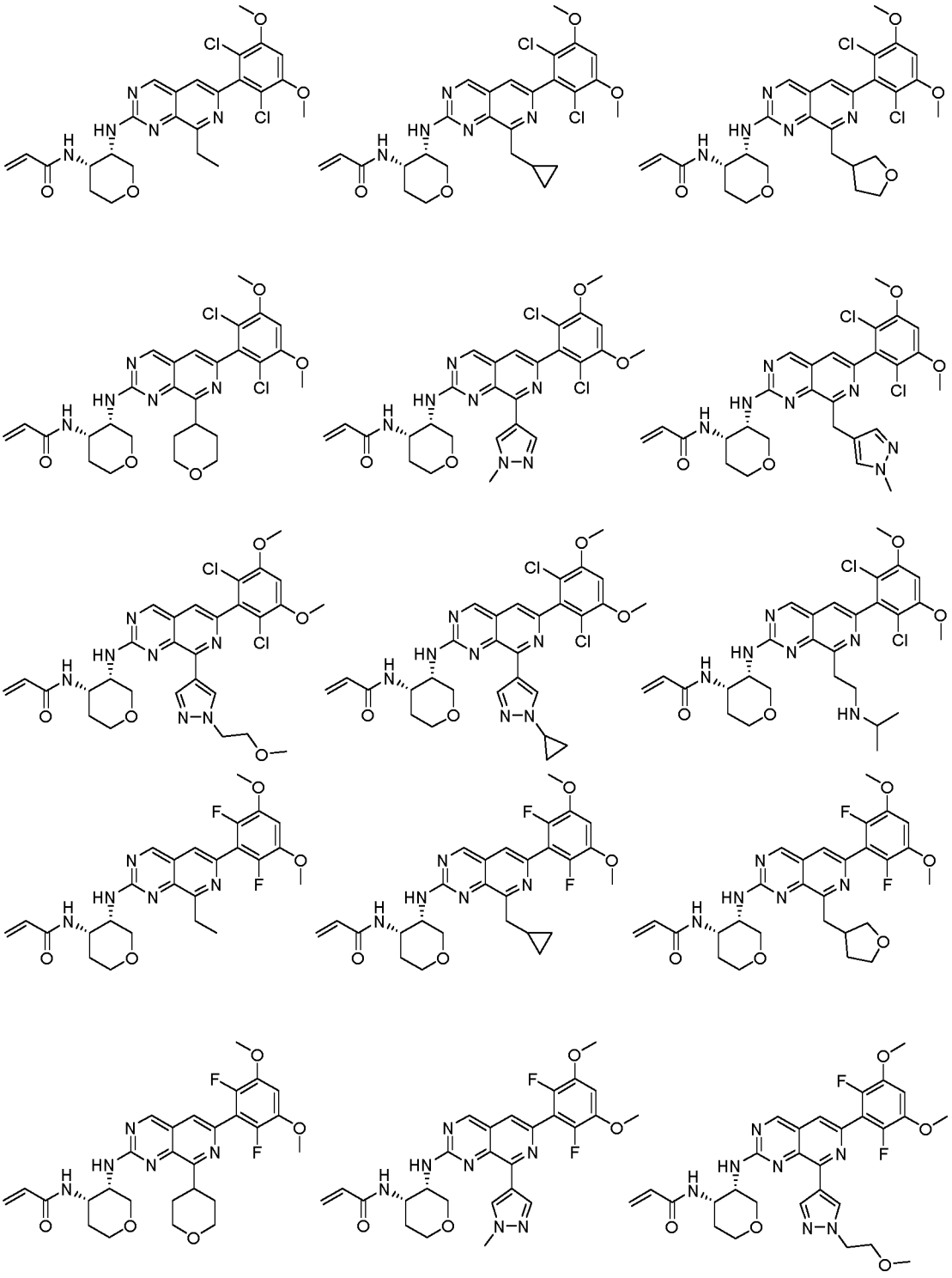


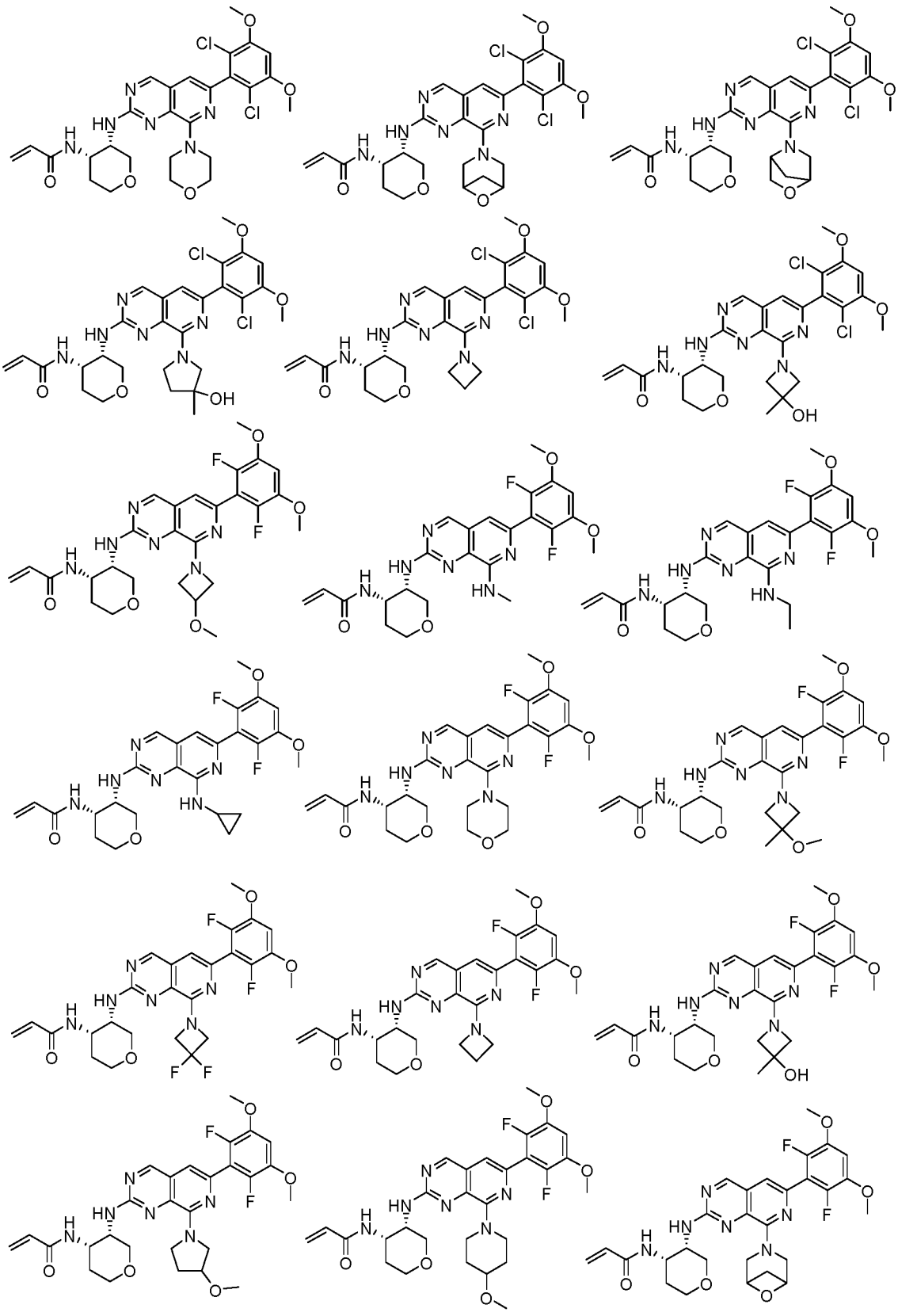


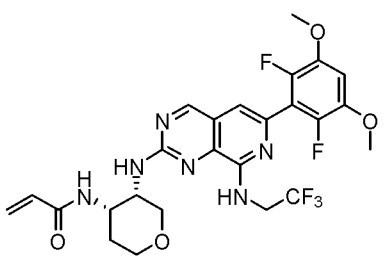


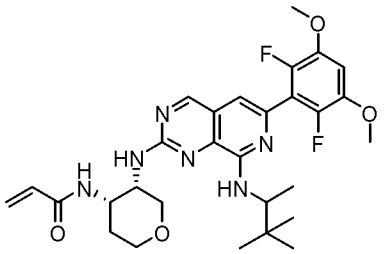


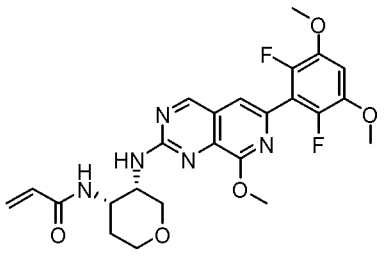


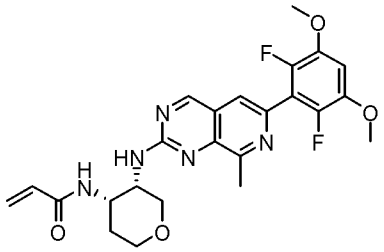


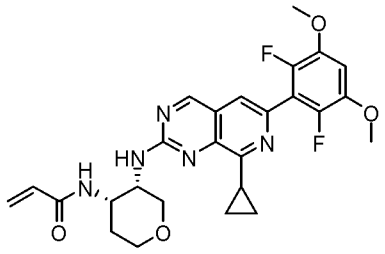


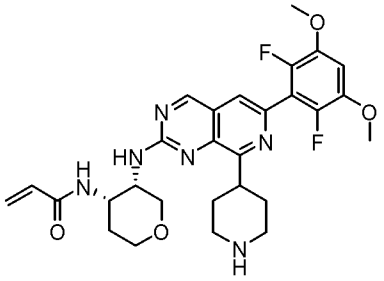


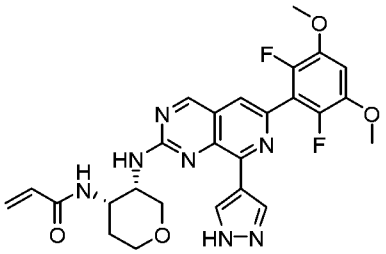


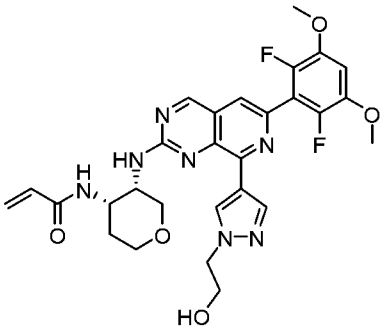


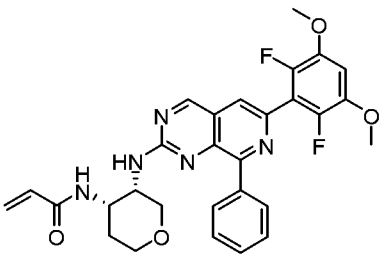


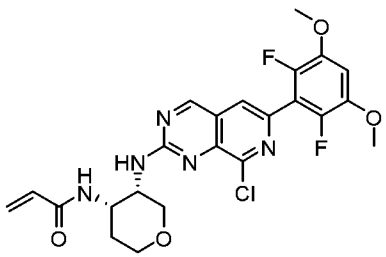


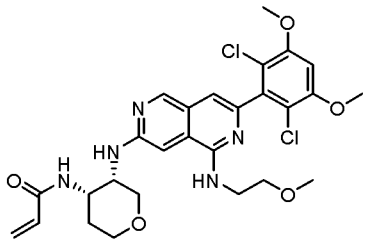


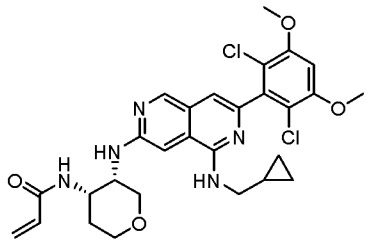


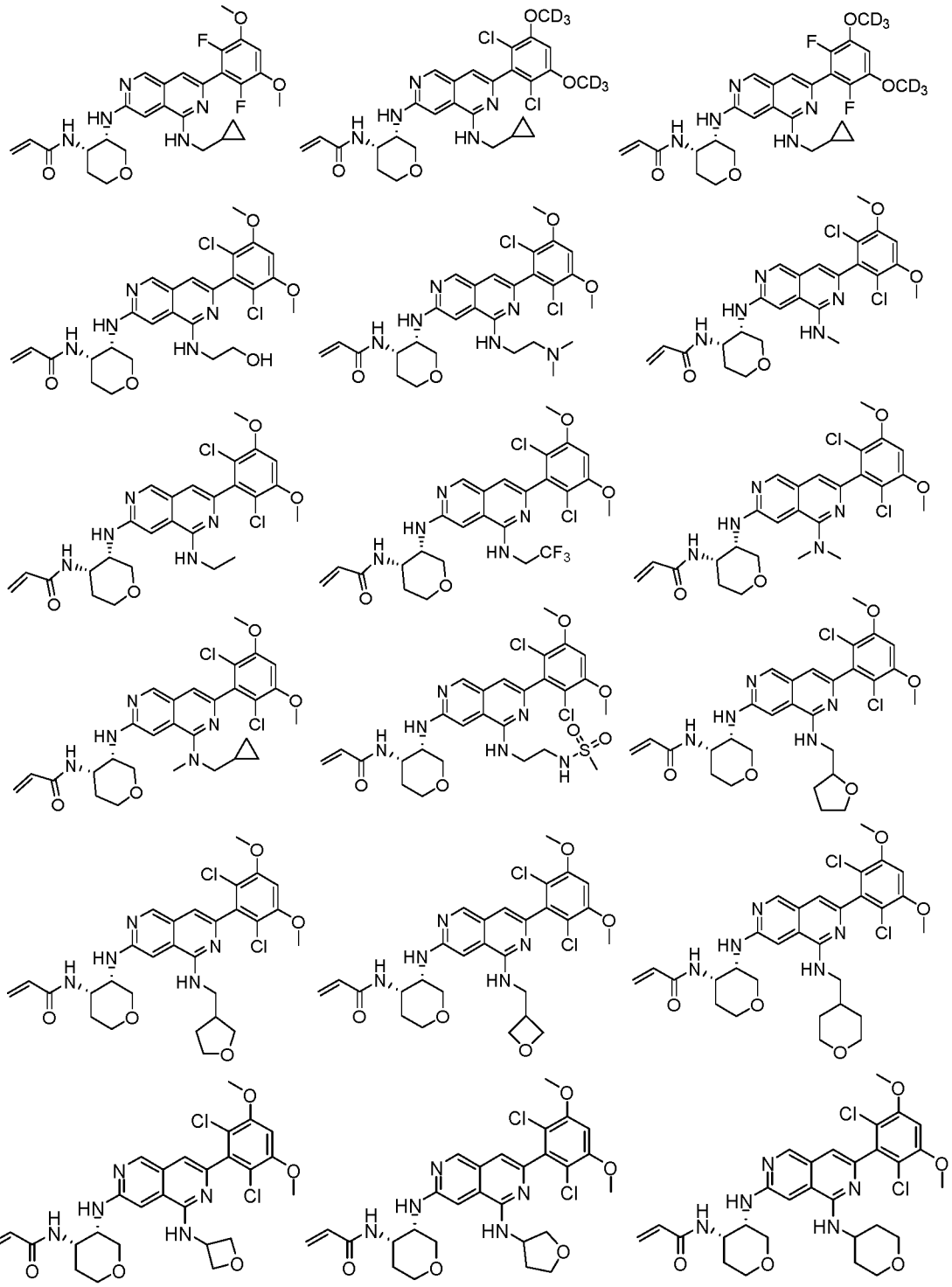


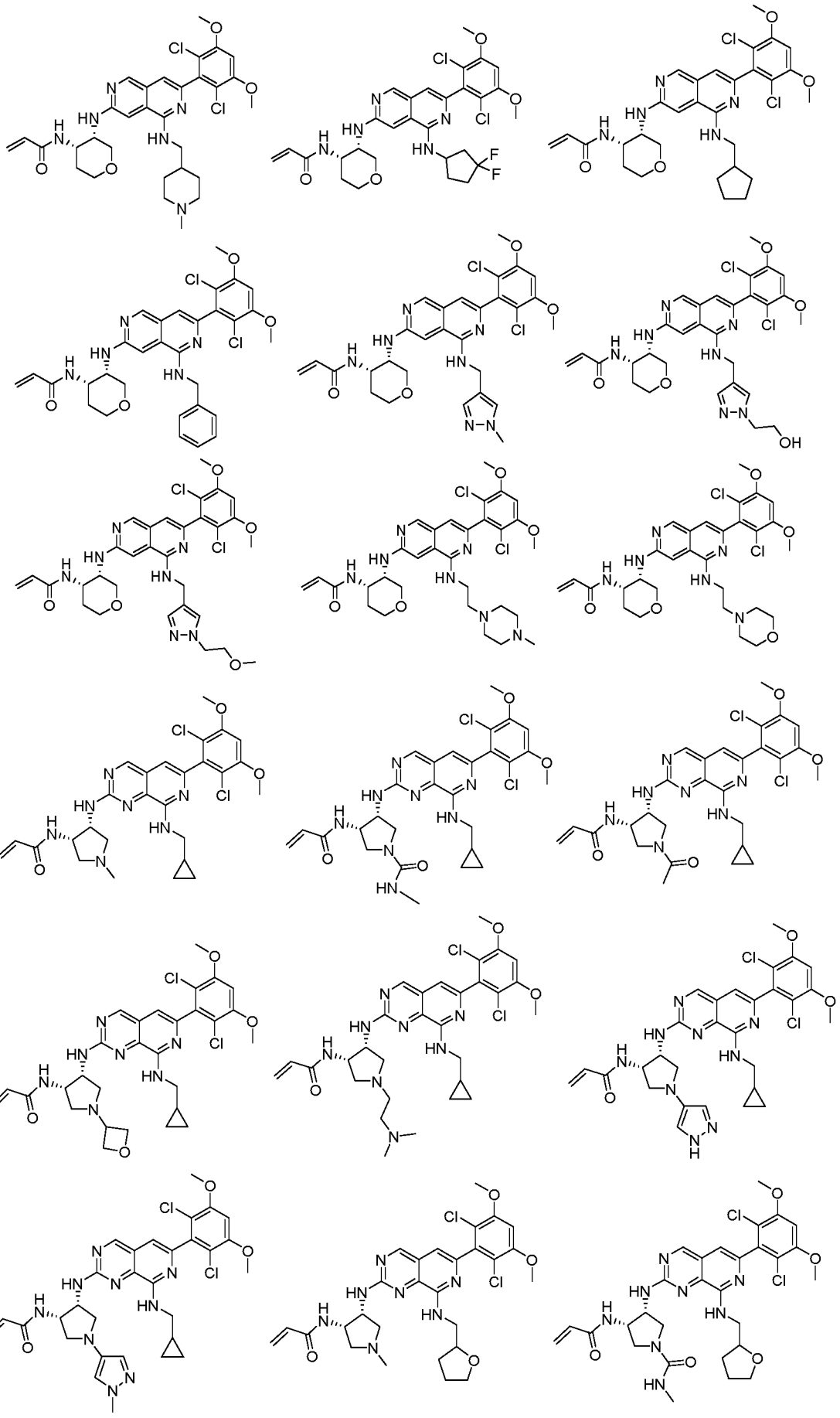


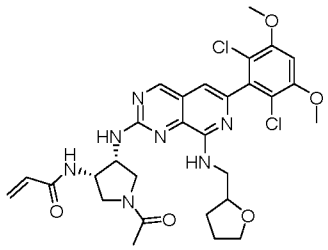
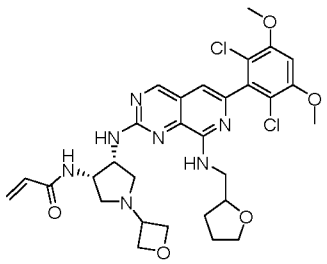
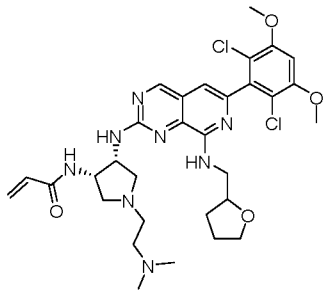
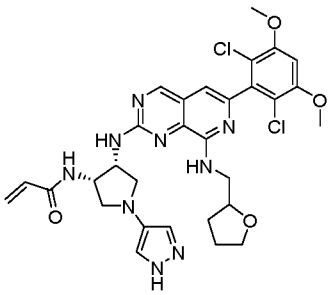
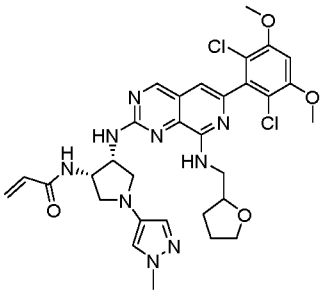
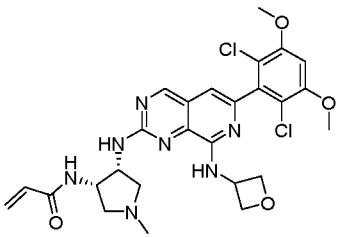
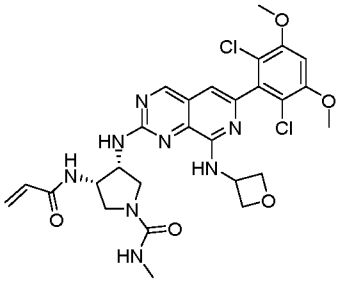
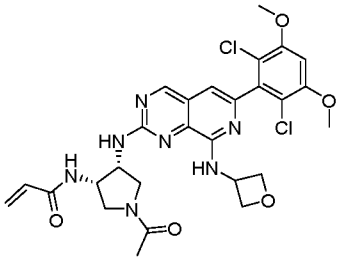
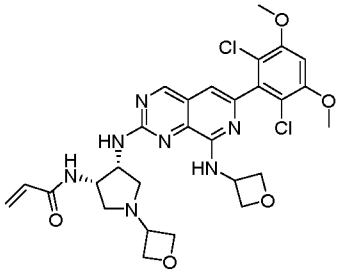
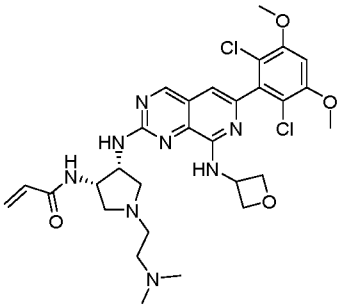
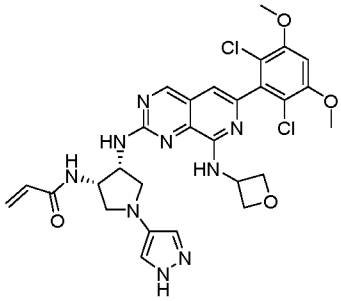
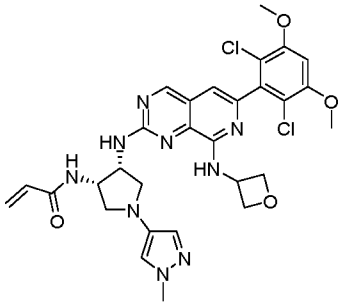
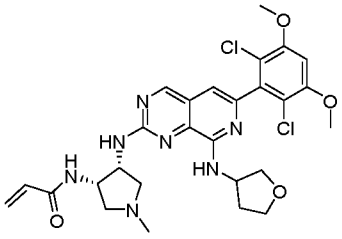
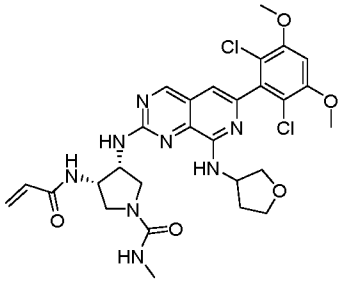
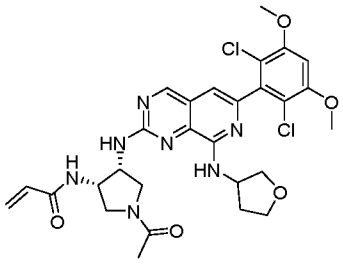
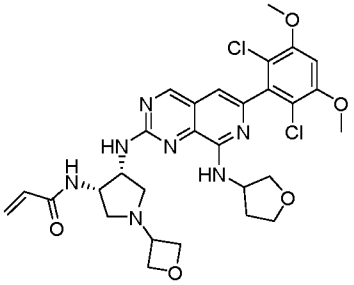
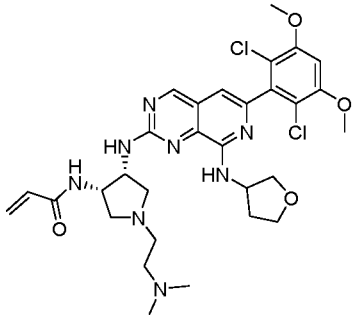
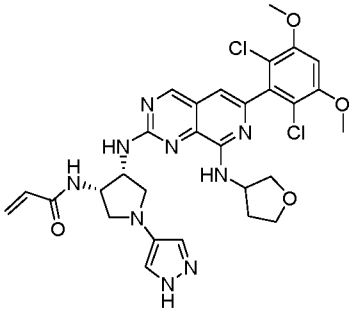


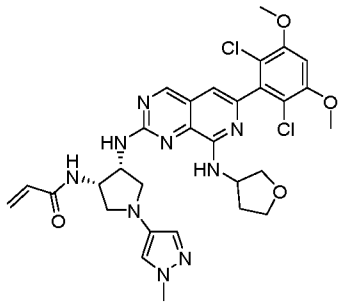
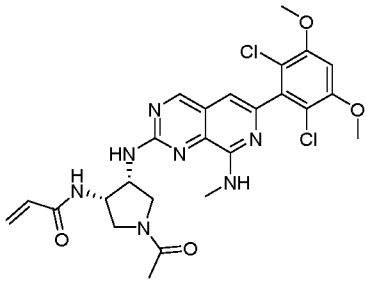
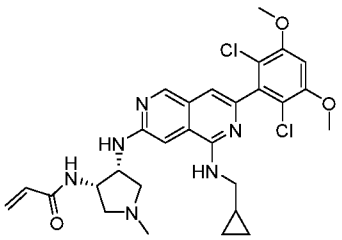
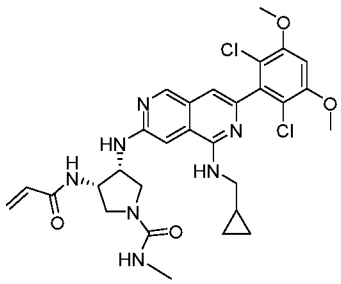
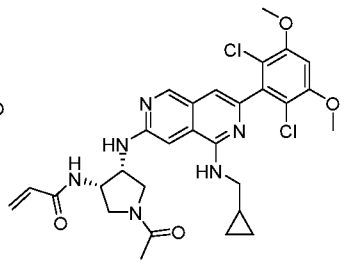
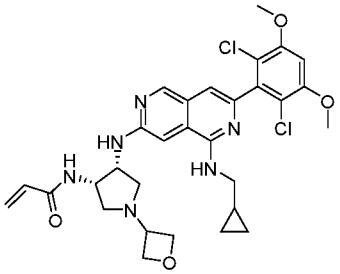
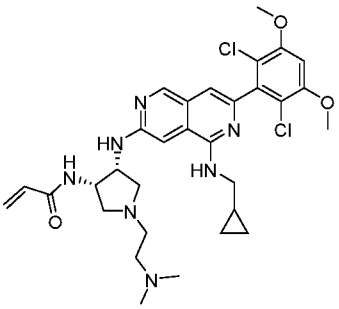
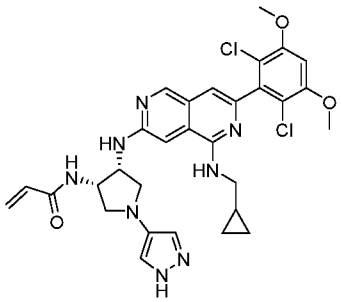
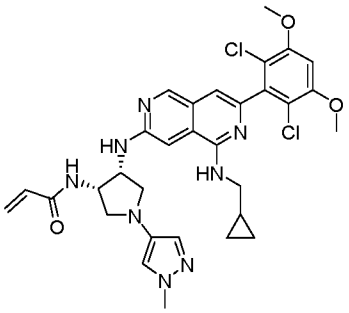
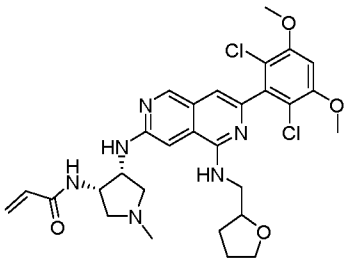
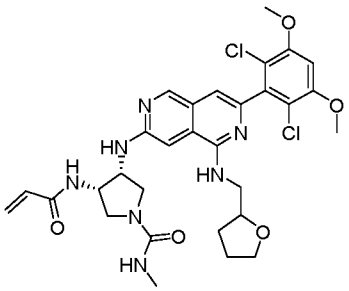
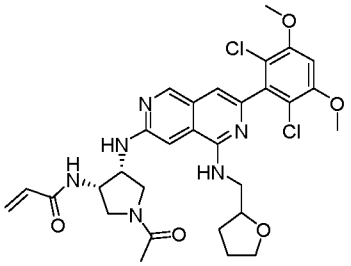
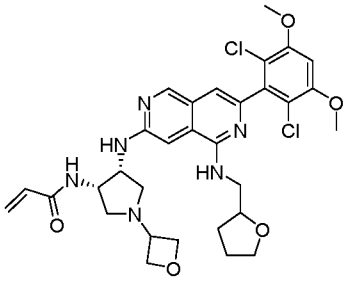
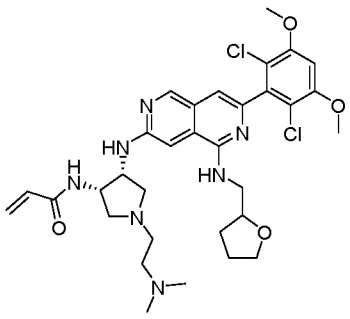
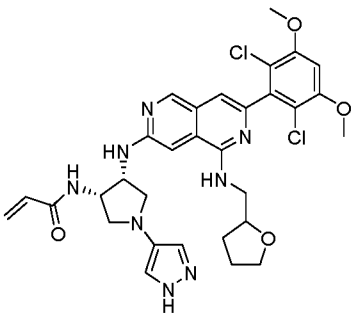
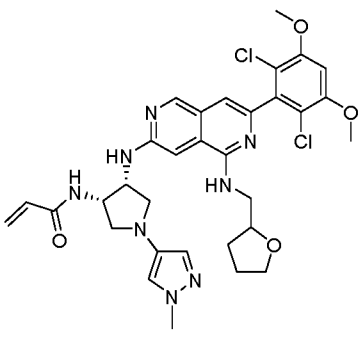
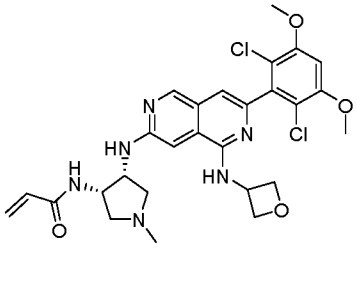


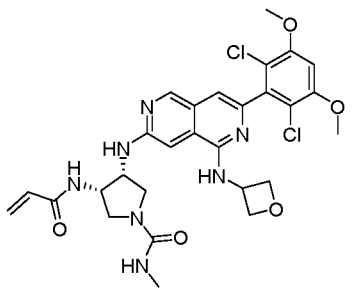
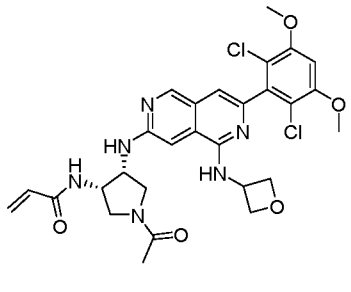
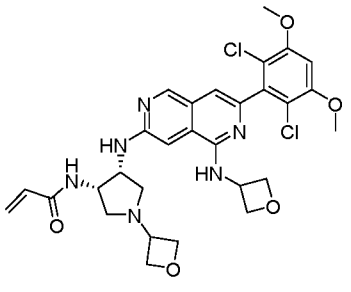
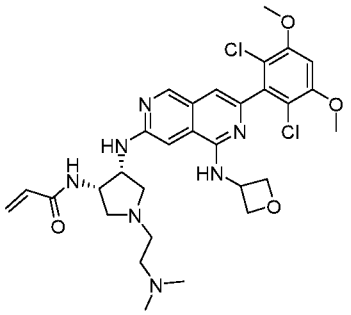
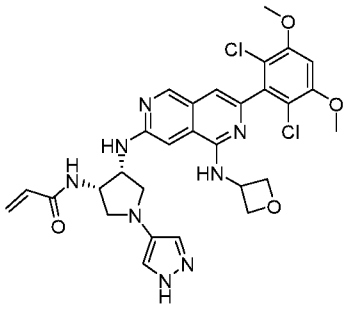
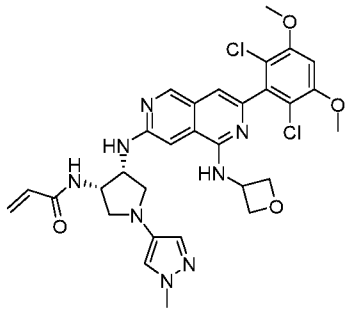
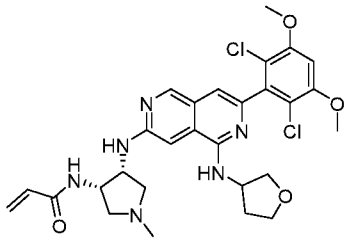
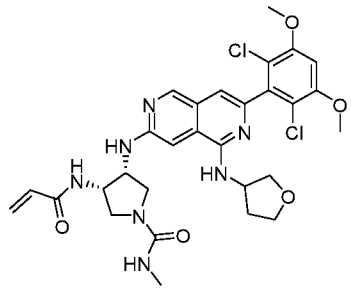
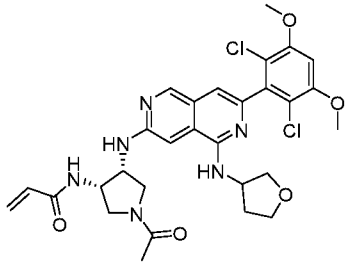
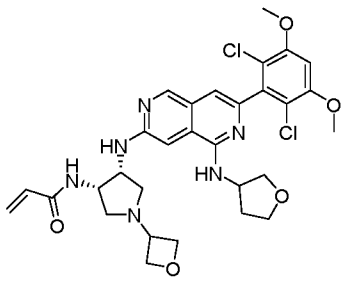
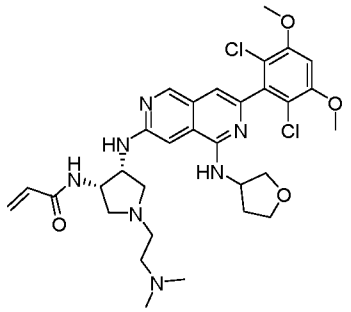
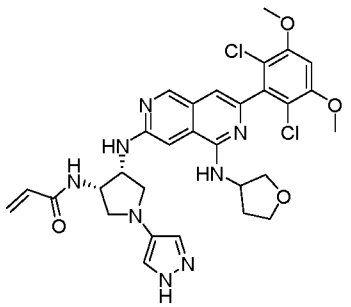
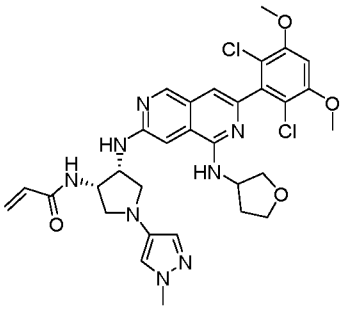
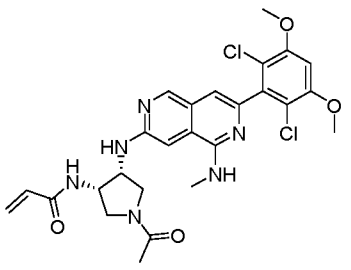
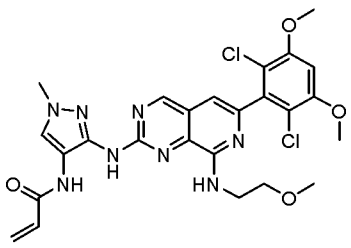
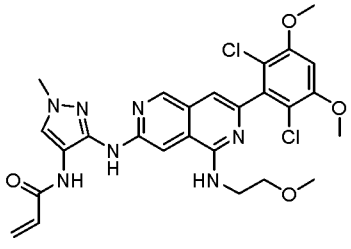


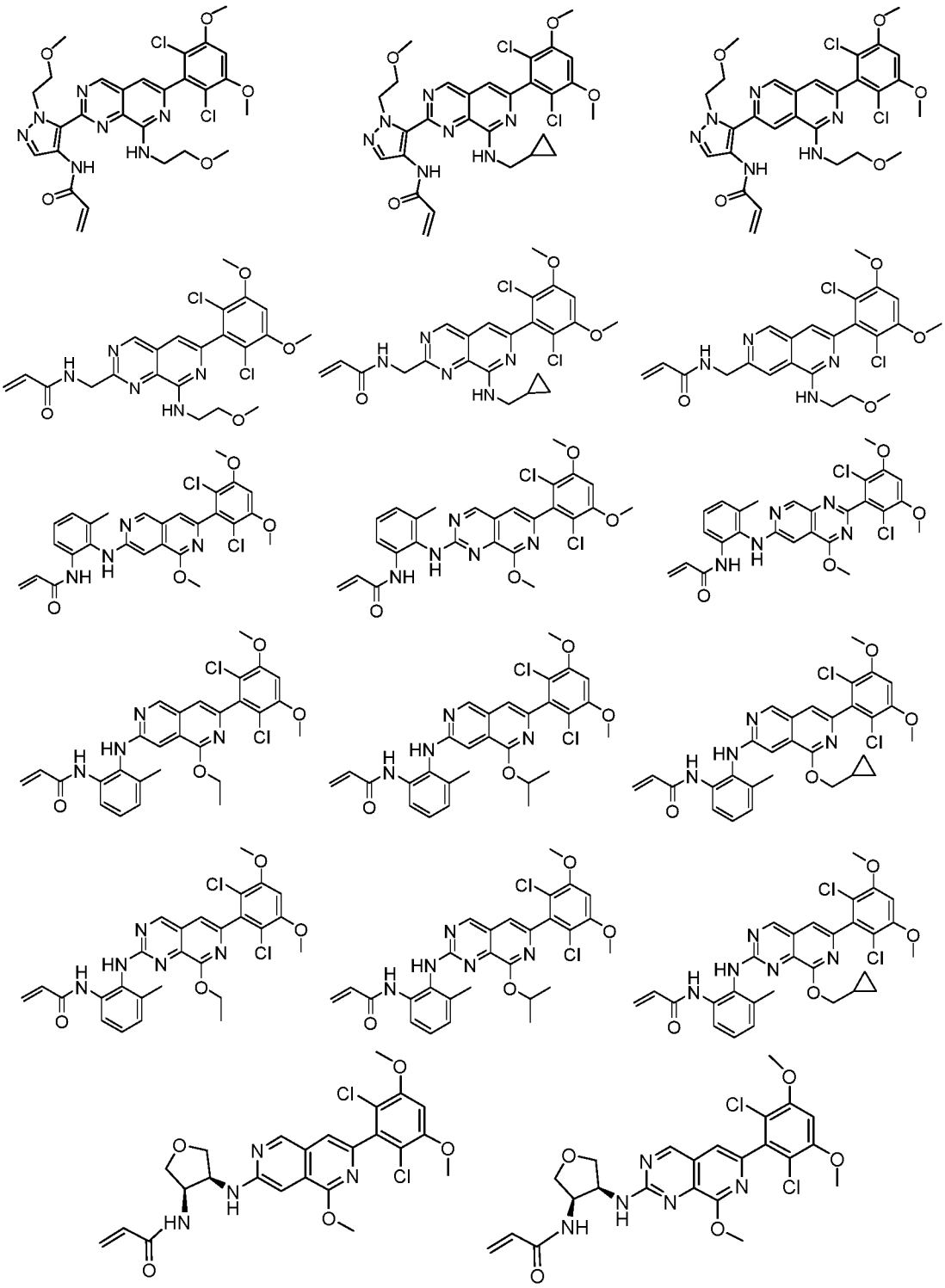


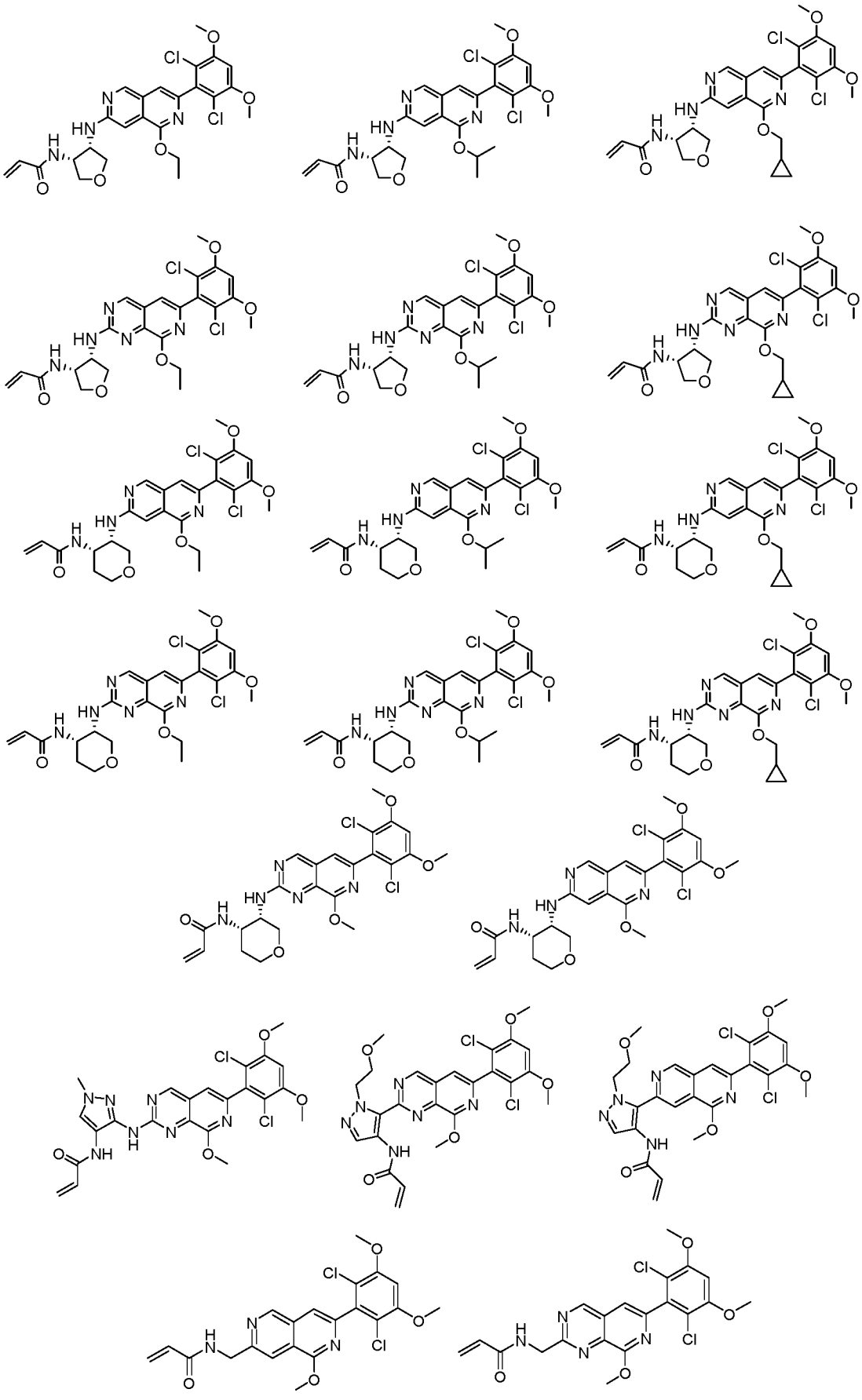


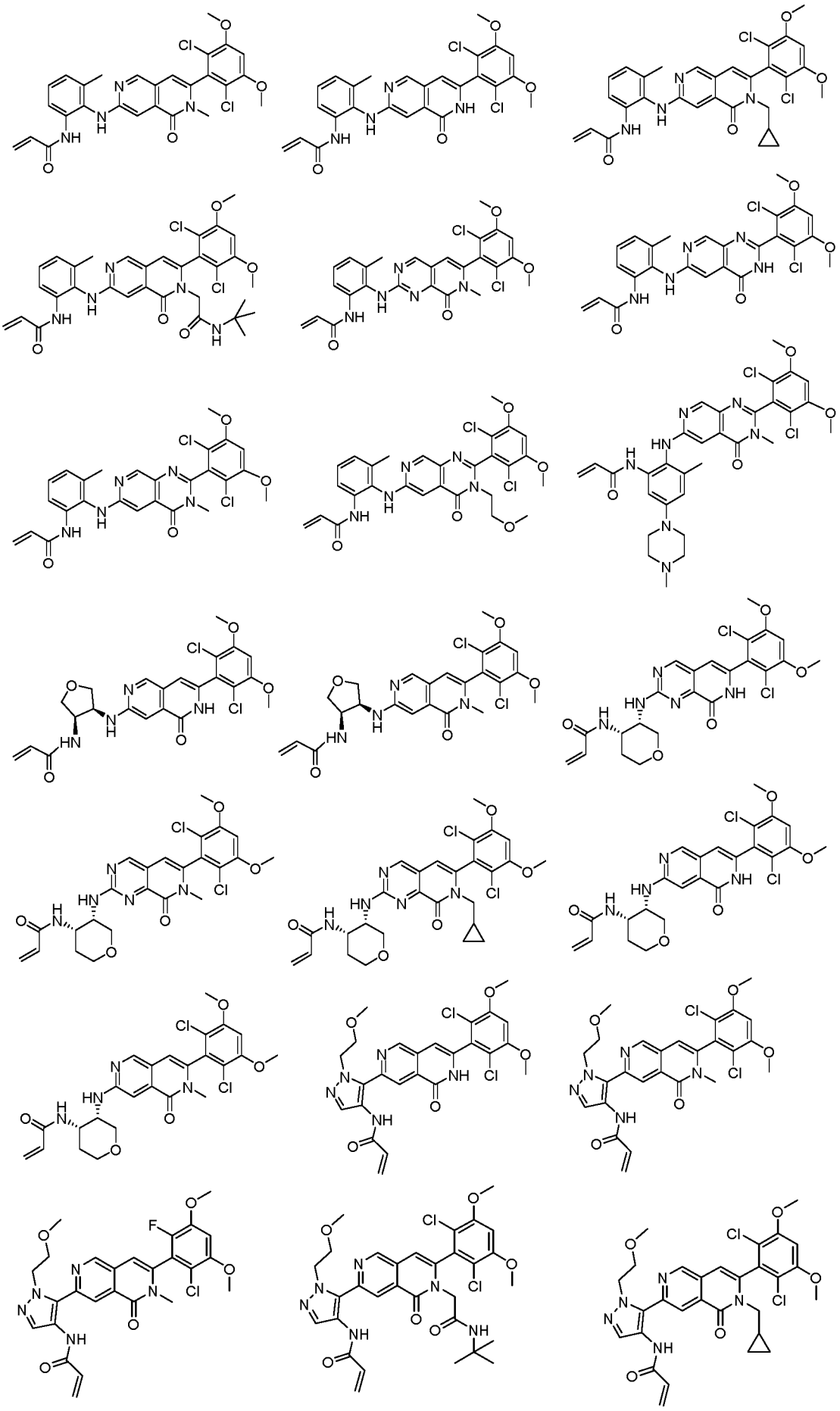



















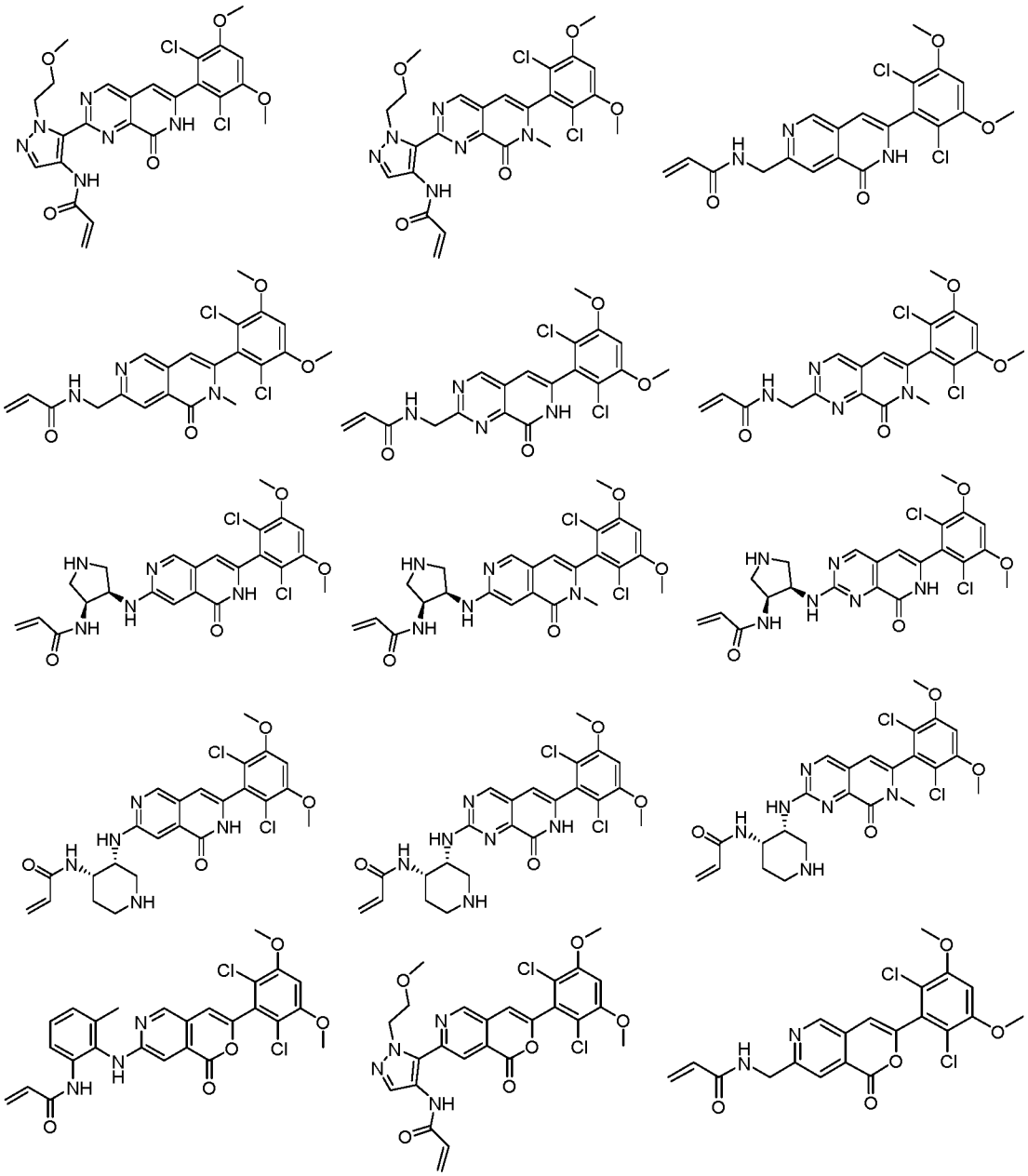


















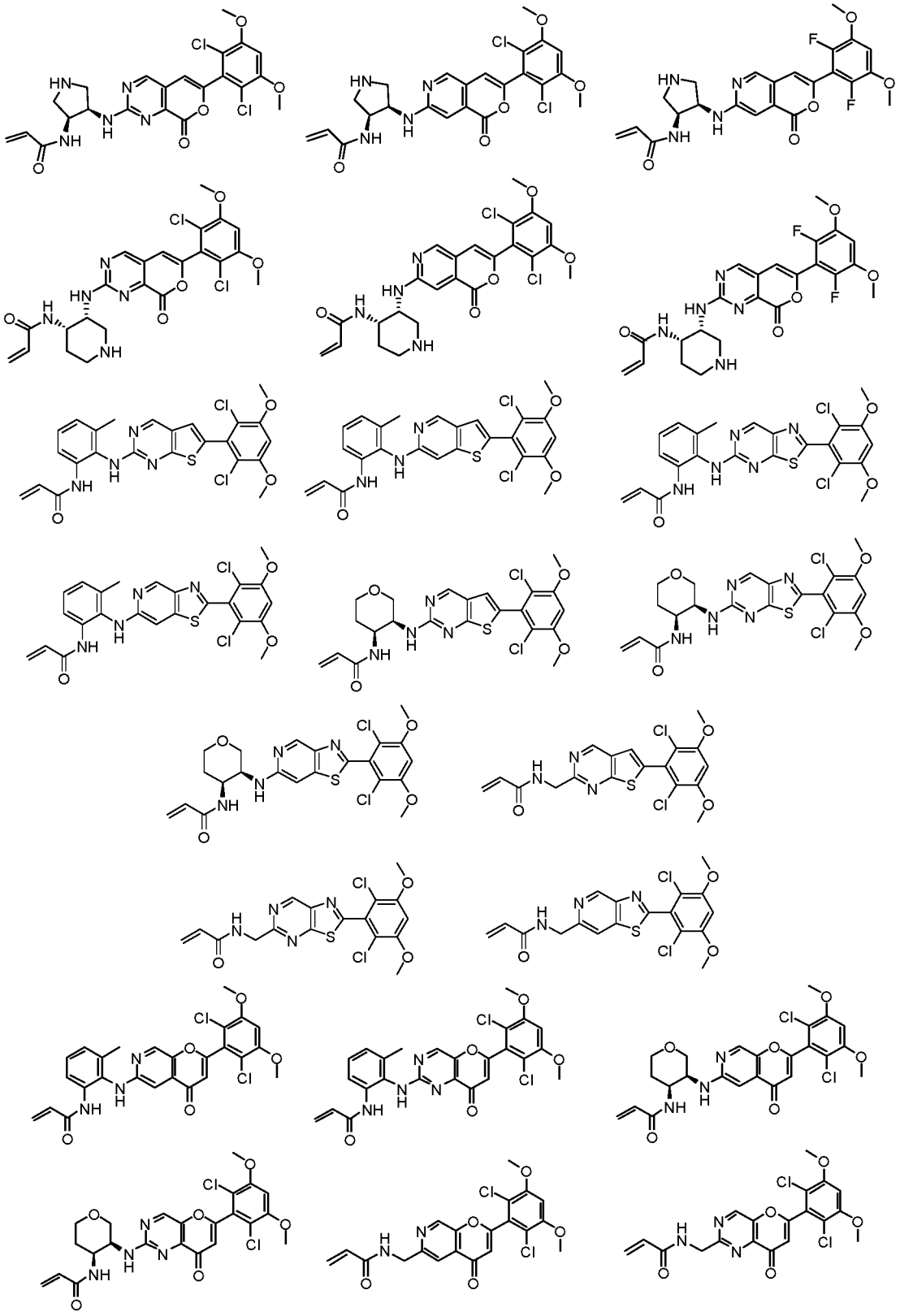

















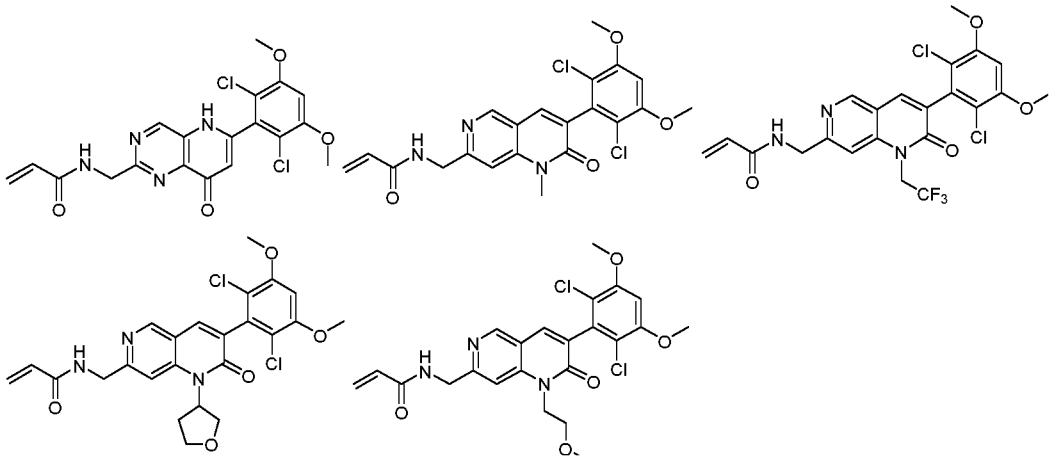












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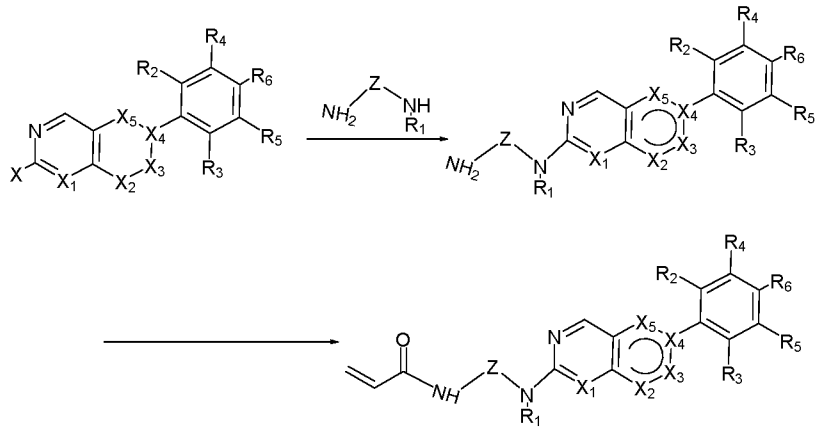
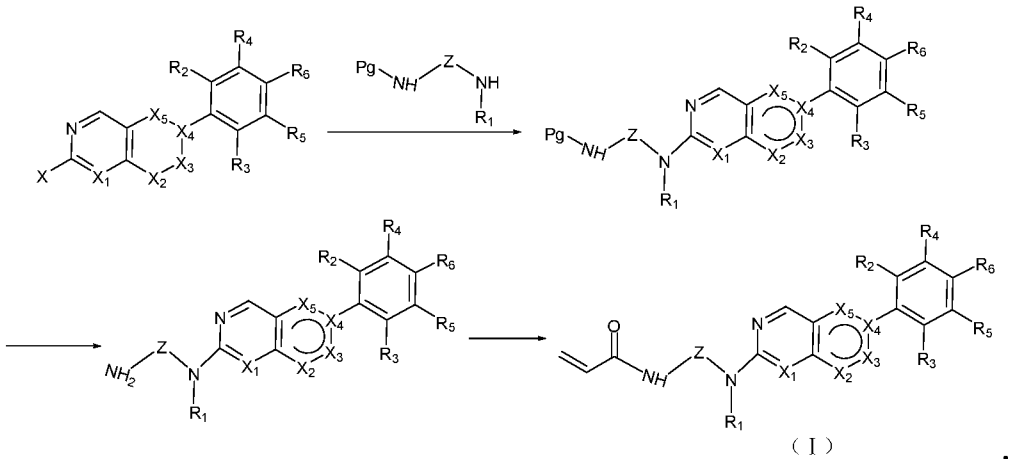
本发明第二方面提供一种前述式(I)化合物、其立体异构体或其药学上可接受盐的制备方法，当 m=1 时，根据烯丙酰胺基的反应顺序，可按如下方式进行制备：



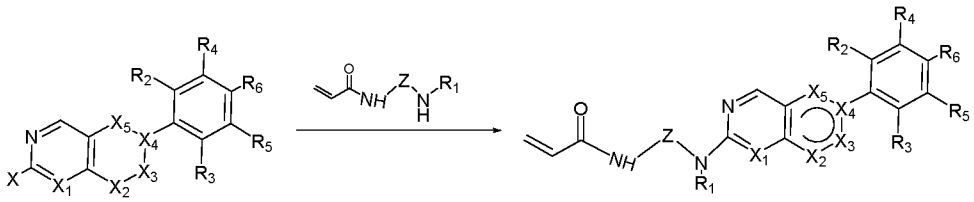
（I），

或者，



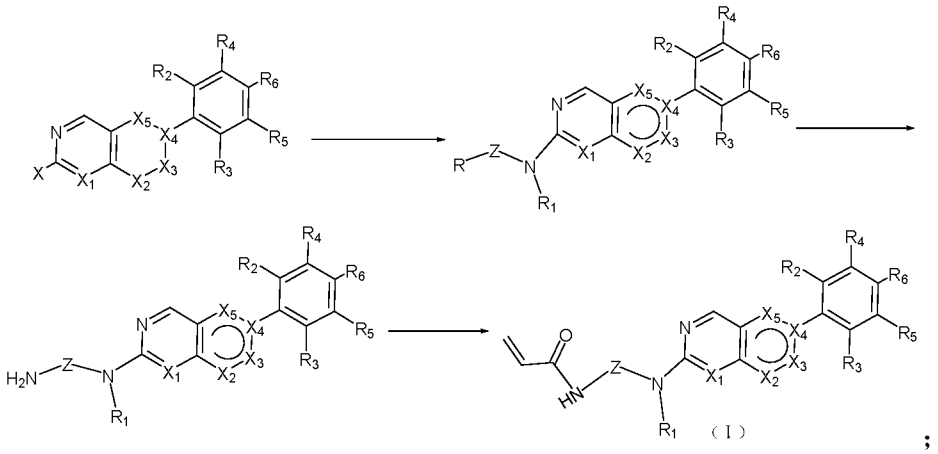
（I），

或者，



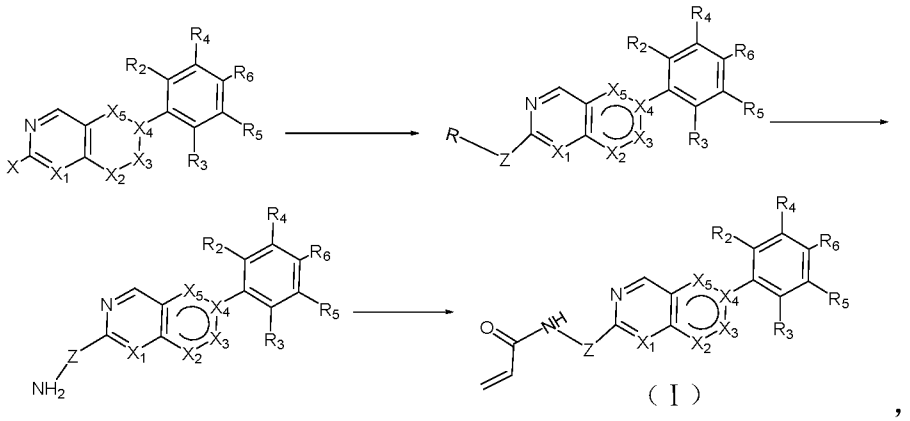
（Ⅰ）

或者，



（Ⅰ）；

或者，当 m=0 时，可按如下方式进行制备：



（Ⅰ），

任选的，根据取代基的不同，在不同的取代基之间进行转换反应；

其中：X 为离去基团，优选自氯、溴、甲硫基、甲磺酰基或甲氧基；R 选自硝基、氰基或叠氮基；Pg 为氨基保护基，优选自叔丁氧羰基、苄氧羰基、2-联苯基-2-丙氧羰基或对甲苯磺酰基；X_1、X_2、X_3、X_4、X_5、R_1、R_2、R_3、R_4、R_5、R_6、R_7、R_8、R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r 如前所述。

作为更进一步优选的方案，当 X 选自甲磺酰基时，其相应化合物可通过 R 为甲硫基时与氧化剂，例如 m-CPBA（间氯过氧苯甲酸）氧化反应制备得到。

作为更进一步优选的方案，所述任选的根据取代基的不同，在不同的取代基之间进行转换反应是指，在需要时，也可以在前述缩合反应之后，根据 X_1、X_2、X_3、X_4、X_5、R_1、R_2、R_3、R_4、R_5、R_6、R_7、R_8、R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14} 取代基定义的不同，在符合化学合成原理的条件下，通过本领域常规实验进行取代基的转换。

本发明第三方面提供一种药物组合物，其包括治疗有效剂量的前述式(I)化合物、其立体异构体或其药学上可接受盐及可药用的载体。

本发明第四方面提供一种前述式(I)化合物、其立体异构体或其药学上可接受盐，或前述药物组合物在制备 FGFR4 抑制剂药物中的应用。

本发明第五方面提供一种前述式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或前述药物组合物在制备治疗癌症的药物中的应用。

优选的，所述癌症是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤。

本发明第六方面提供一种前述式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或前述药物组合物，其用作 FGFR4 抑制剂。

本发明第七方面提供一种前述式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或前述药物组合物，其用于治疗癌症。

优选的，所述癌症是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤。

本发明第八方面提供一种抑制 FGFR4 的方法，所述方法包括给予需要治疗的患者有效治疗量的前述式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或前述药物组合物。

本发明第九方面提供一种治疗癌症的方法，所述方法包括给予需要治疗的患者有效治疗量的前述式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或前述药物组合物。

优选的，所述癌症是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤。

本发明所开发的系列化合物对 FGFR4 激酶活性具有很强的抑制作用，并具有非常高的选择性，可广泛应用于制备治疗癌症特别是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤的药物，有望开发成新一代 FGFR4 抑制剂药物。

应理解，在本发明范围内中，本发明的上述各技术特征和在下文(如实施例)中具体描述的各技术特征之间都可以互相组合，从而构成新的或优选的技术方案。限于篇幅，在此不再一一累述。

具体实施方式

本申请的发明人经过广泛而深入地研究，首次研发出一种具有式（Ⅰ）结构的FGFR4抑制剂，该系列化合物对FGFR4激酶活性具有很强的抑制作用，并具有非常高的选择性，可广泛应用于制备治疗癌症特别是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤的药物，有望开发成新一代FGFR4抑制剂药物。。在此基础上，完成了本发明。

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。

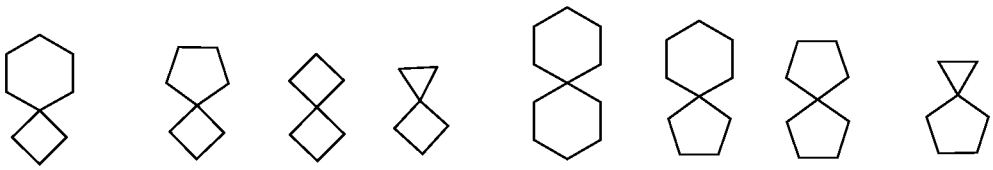
“烷基”指直链或含支链的饱和脂族烃基团，例如，“C_{1-8}烷基”指包括 1 至 8 个碳原子的直链烷基和含支链烷基，包括但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、仲丁基、正戊基、1，1-二甲基丙基、1，2-二甲基丙基、2，2-二甲基丙基、1-乙基丙基、2-甲基丁基、3-甲基丁基、正己基、1-乙基-2-甲基丙基、1，1，2-三甲基丙基、1，1-二甲基丁基、1，2-二甲基丁基、2，2-二甲基丁基、1，3-二甲基丁基、2-乙基丁基、2-甲基戊基、3-甲基戊基、4-甲基戊基、2，3-二甲基丁基、正庚基、2-甲基己基、3-甲基己基、4-甲基己基、5-甲基己基、2，3-二甲基戊基、2，4-二甲基戊基、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等。

烷基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代 C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10 元杂环基、C_{5-10}芳基、5-10 元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“环烷基”指饱和或部分不饱和单环或多环环状烃取代基，例如，“C_{3-8}环烷基”指包括 3 至 8 个碳原子的环烷基，分为单环环烷基、多环环烷基，其中：

单环环烷基包括但不限于环丙基、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。

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，这些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、双螺环烷基或多螺环烷基，螺环烷基包括但不限于：



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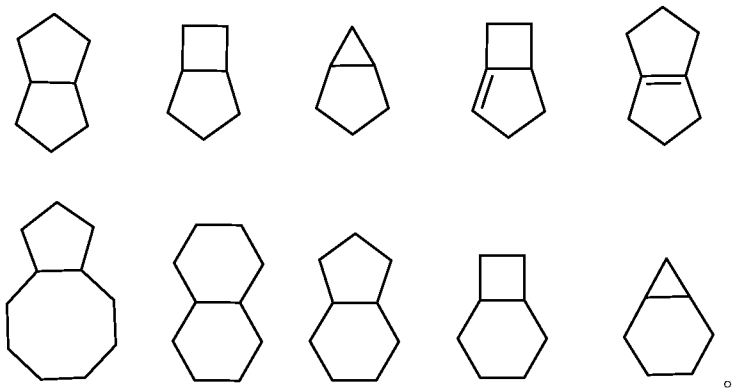
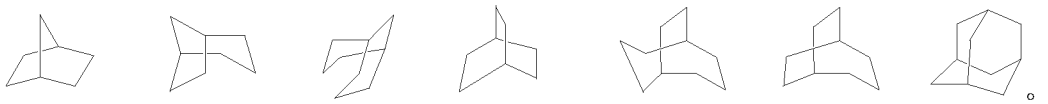
“稠环烷基”指系统中的每个环与体系中的其他环共享毗邻的一对碳原子的全碳多环基团，其中一个或多个环可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统。根据组成环的数目可以分为双环、三环、四环或多环稠环烷基，稠环烷基包括但不限于：



“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，这些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，桥环烷基包括但不限于：



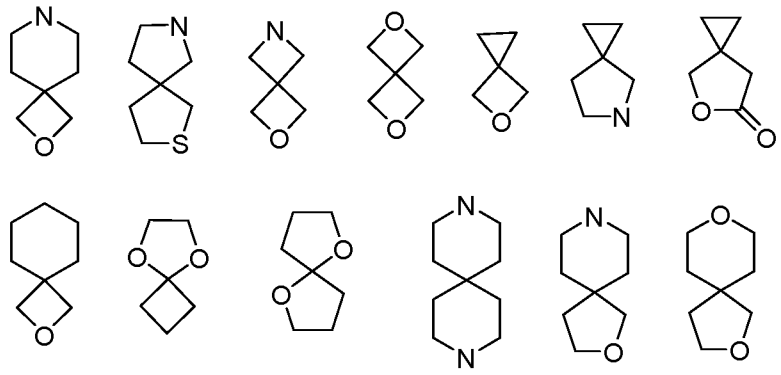
所述环烷基环可以稠合于芳基、杂芳基或杂环烷基环上，其中与母体结构连接在一起的环为环烷基，包括但不限于茚满基、四氢萘基、苯并环庚烷基等。

环烷基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代 C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10 元杂环基、C_{5-10}芳基、5-10 元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“杂环基”指饱和或部分不饱和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、2)的杂原子，但不包括-O-O-、-O-S-或-S-S-的环部分，其余环原子为碳。例如，“5-10元杂环基”指包含5至10个环原子的环基，“3-10元杂环基”指包含3至10个环原子的环基。

单环杂环基包括但不限于吡咯烷基、哌啶基、哌嗪基、吗啉基、硫代吗啉基、高哌嗪基等。

多环杂环基包括螺环、稠环和桥环的杂环基。“螺杂环基”指单环之间共用一个原子(称螺原子)的多环杂环基团，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)的杂原子，其余环原子为碳。这些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杂环基分为单螺杂环基、双螺杂环基或多螺杂环基。螺杂环基包括但不限于：



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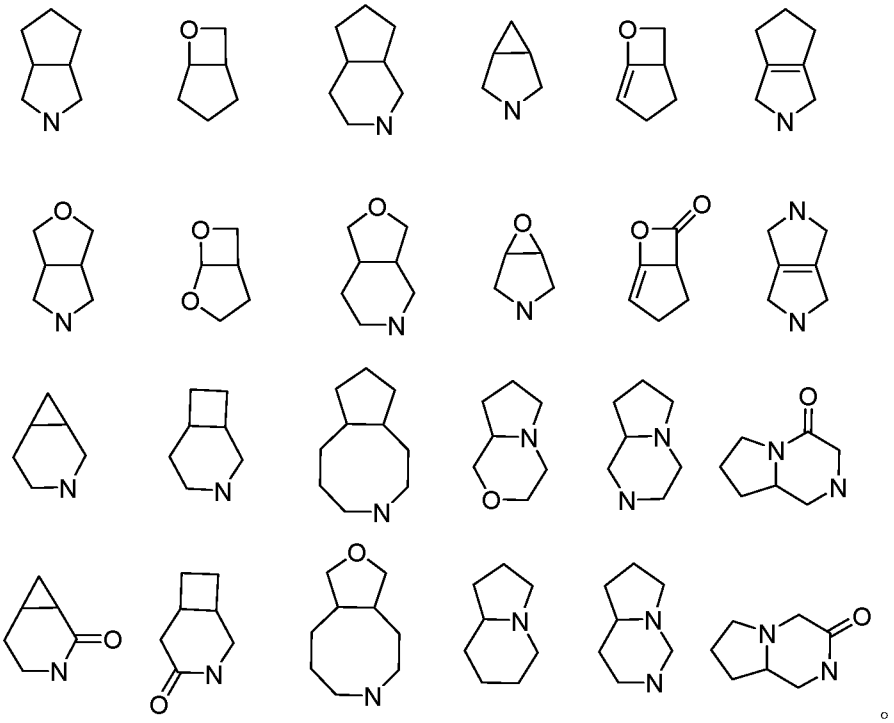
“稠杂环基”指系统中的每个环与体系中的其他环共享毗邻的一对原子的多环杂环基团，一个或多个环可以含有一个或多个双键，但没有一个环具有完全共轭的 π 电子系统，其中一个或多个环原子选自氮、氧或 $S(O)_r$(其中 r 是整数 0 、1、2) 的杂原子，其余环原子为碳。根据组成环的数目可以分为双环、三环、四环或多环稠杂环烷基，稠杂环基包括但不限于：



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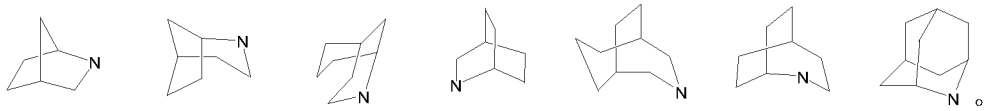
“桥杂环基”指任意两个环共用两个不直接连接的原子的多环杂环基团，这些可以含有一个或多个双键，但没有一个环具有完全共轭的π电子系统，其中一个或多个环原子选自氮、氧或 $S(O)_r$(其中 r 是整数 0、1、2) 的杂原子，其余环原子为碳。根据组成环的数目可以分为双环、三环、四环或多环桥杂环基，桥杂环基包括但不限于：



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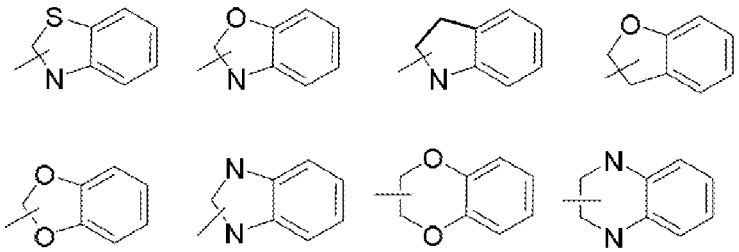
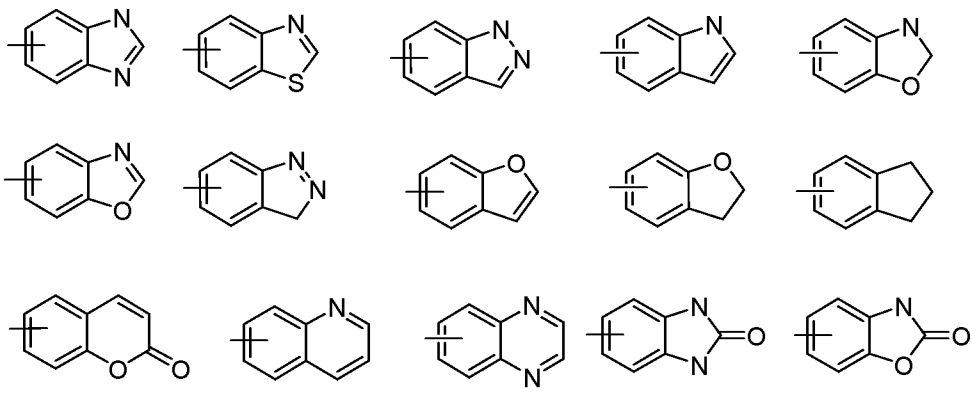
所述杂环基环可以稠合于芳基、杂芳基或环烷基环上，其中与母体结构连接在一起的环为杂环基，包括但不限于：



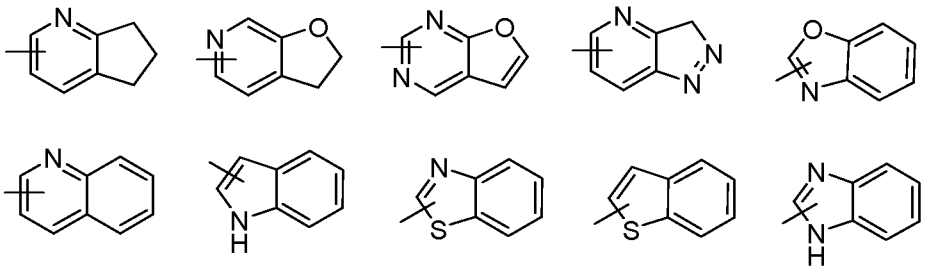
杂环基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“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)基团，具有共轭的 π 电子体系的多环 (即其带有相邻对碳原子的环) 基团，例如，“C_{5-10}芳基”指含有 5-10 个碳的全碳芳基，“5-10 元芳基”指含有 5-10 个碳的全碳芳基，包括但不限于苯基和萘基。所述芳基环可以稠合于杂芳基、杂环基或环烷基环上，其中与母体结构连接在一起的环为芳基环，包括但不限于：



芳基可以是取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“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、氧和S(O)r (其中r是整数0、1、2) 的杂原子，例如，5-7元杂芳基指含有5-7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，包括但不限于呋喃基、噻吩基、吡啶基、吡咯基、N-烷基吡咯基、嘧啶基、吡嗪基、咪唑基、四唑基等。所述杂芳基环可以稠合于芳基、杂环基或环烷基环上，其中与母体结构连接在一起的环为杂芳基环，包括但不限于：



杂芳基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“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定义的烷基，例如，C_{2-8}链烯基指含有2-8个碳的直链或含支链烯基。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。

烯基可以是取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“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，例如，C_{2-8}链炔基指含有2-8个碳的直链或含支链炔基。包括但不限于乙炔基、1-丙炔基、2-丙炔基、1-，2-或3-丁炔基等。

炔基可以是取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“烷氧基”指-O-(烷基)，其中烷基的定义如上所述，例如，“C_{1-8}烷氧基”指含1-8个碳的烷基氧基，包括但不限于甲氧基、乙氧基、丙氧基、丁氧基等。

烷氧基可以是任选取代的或未取代的，当被取代时，取代基，优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“环烷氧基”指和-O-(未取代的环烷基)，其中环烷基的定义如上所述，例如，“C_{3-8}环烷氧基”指含3-8个碳的环烷基氧基，包括但不限于环丙氧基、环丁氧基、环戊氧基、环己氧基等。

环烷氧基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代 C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10 元杂环基、C_{5-10}芳基、5-10 元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“3-10元杂环氧基”指和-O-(未取代的3-10元杂环基)，其中3-10元杂环基的定义如上所述，3-10元杂环氧基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“C_{5-10}芳氧基”指和-O-(未取代的C_{5-10}芳基)，其中C_{5-10}芳基的定义如上所述，C_{5-10}芳氧基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“5-10 元杂芳氧基”指和-O-(未取代的 5-10 元杂芳基)，其中 5-10 元杂芳基的定义如上所述，5-10 元杂芳氧基可以是任选取代的或未取代的，当被取代时，取代基优选为一个或多个以下基团，独立地选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、卤取代 C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10 元杂环基、C_{5-10}芳基、5-10 元杂芳基、$-C_{0-8}-S(O)_rR_{10}$、$-C_{0-8}-O-R_{11}$、$-C_{0-8}-C(O)OR_{11}$、$-C_{0-8}-C(O)R_{12}$、$-C_{0-8}-O-C(O)R_{12}$、$-C_{0-8}-NR_{13}R_{14}$、$-C_{0-8}-C(O)NR_{13}R_{14}$、$-C_{0-8}-N(R_{13})-C(O)R_{12}$或$-C_{0-8}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

“C_{1-8}烷酰基”指C_{1-8}烷基酸去掉羟基后剩下的一价原子团，通常也表示为“$C_{0-7}-C(O)-$”，例如，“$C_1-C(O)-$”是指乙酰基；“$C_2-C(O)-$” 是指丙酰基；“$C_3-C(O)-$” 是指丁酰基或异丁酰基。

“$-C_{0-8}-S(O)_rR_{10}$”指$-S(O)_rR_{10}$中的硫原子连接在 C_{0-8}烷基上，其中 C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“$-C_{0-8}-O-R_{11}$”指$-O-R_{11}$中的氧原子连接在C_{0-8}烷基上，其中C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“$-C_{0-8}-C(O)OR_{11}$”指$-C(O)OR_{11}$中的羰基连接在 C_{0-8}烷基上，其中 C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“$-C_{0-8}-C(O)R_{12}$”指$-C(O)R_{12}$中的羰基连接在C_{0-8}烷基上，其中C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“$-C_{0-8}-O-C(O)R_{12}$”指$-O-C(O)R_{12}$中的氧原子连接在 C_{0-8}烷基上，其中 C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“-C_{0-8}-$NR_{13}R_{14}$”指-$NR_{13}R_{14}$中的氮原子连接在C_{0-8}烷基上，其中C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“-C_{0-8}-$C(O)NR_{13}R_{14}$”指-$C(O)NR_{13}R_{14}$中的羰基连接在C_{0-8}烷基上，其中C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$”指-$N(R_{13})$-$C(O)R_{12}$中的氮原子连接在C_{0-8}烷基上，其中C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$”指-$N(R_{13})$-$C(O)OR_{11}$中的氮原子连接在C_{0-8}烷基上，其中C_0烷基是指键，C_{1-8}烷基的定义如上所述。

“卤取代C_{1-8}烷基”指烷基上的氢任选的被氟、氯、溴、碘原子取代的1-8个碳烷基基团，包括但不限于二氟甲基、二氯甲基、二溴甲基、三氟甲基、三氯甲基、三溴甲基等。

“卤取代C_{1-8}烷氧基” 烷基上的氢任选的被氟、氯、溴、碘原子取代的1-8个碳烷氧基基团。包括但不限于二氟甲氧基、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。

“卤素”指氟、氯、溴或碘。“THF”指四氢呋喃。“EA/EtOAc”指乙酸乙酯。“MeOH”指甲醇。“EtOH”指乙醇。“PivOH”指三甲基乙酸。“DMSO”指二甲亚砜。“DMF”指N、N-二甲基甲酰胺。“DIPEA”指二异丙基乙胺。“CH_3CN”指乙晴。“PE”指石油醚。“DCM / CH_2Cl_2”指二氯甲烷。“DCE”指二氯乙烷。“DMA”指二甲基乙酰胺。“Et_3N”指三乙胺。“NH_4Cl”指氯化铵。“NMP”指N-甲基吡咯烷酮。“HOAc”指乙酸。“TFA”指三氟乙酸。“MeI”指碘甲烷。“KI”指碘化钾。“MsCl”指甲磺酰氯。“SO_2Cl_2”指磺酰氯。“$POCl_3$”指三氯氧磷。“MeONa”指甲醇钠。“$NaHCO_3$”指碳酸氢钠。“Na_2SO_4”指硫酸钠。“K_2CO_3”指碳酸钾。“NaN_3”指叠氮化钠。“NaH”指氢化钠。“CuI”指碘化亚铜。“PPA”指多聚磷酸。“m-CPBA”指间氯过氧苯甲酸。“MnO_2”指二氧化锰。“$LiAlH_4$”指氢化铝锂。“LiOH”指氢氧化锂。“NaOAc”指乙酸钠。“$NaNO_2$”指亚硝酸钠。“$AgNO_3$”指硝酸银。“Boc_2O”指二碳酸二叔丁酯。“LiCl”指氯化锂。“$Zn(CN)_2$”指氰化锌。“IBX”指2-碘酰苯甲酸。“Pd/C”指钯碳。“$Pd(OAc)_2$”指醋酸钯。“PPh_3”指三苯基磷。“$Pd(PPh_3)_2Cl_2$”指双三苯基磷二氯化钯。“$Pd_2(dba)_3$”指三（二亚苄基丙酮）二钯。“Pd(dppf)Cl_2”指[1,1'-双（二苯基膦基）二茂铁]二氯化钯。“$Pd(PPh_3)_4$”指 四（三苯基膦）钯。“brett-phos”指二环己基[3,6-二甲氧基-2',4',6'-三异丙基[1,1'-联苯]-2-基]膦。

“任选”或“任选地”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基团”意味着烷基可以但不必须存在，该说明包括杂环基团被烷基取代的情形和杂环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键的碳原子（如烯烃）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。

下面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。

本发明的化合物结构是通过核磁共振 (NMR) 或/和液质联用色谱 (LC-MS)来确定的。NMR 化学位移(δ)以百万分之一 (ppm) 的单位给出。NMR 的测定是用 Bruker AVANCE-400 核磁仪，测定溶剂为氘代二甲基亚砜 (DMSO-d_6)，氘代甲醇 (CD_3OD) 和氘代氯仿 ($CDCl_3$)，内标为四甲基硅烷 (TMS)。

液质联用色谱 LC-MS 的测定用 Agilent 6120 质谱仪。HPLC 的测定使用安捷伦 1200DAD 高压液相色谱仪 (Sunfire C18 150 × 4.6 mm 色谱柱)和 Waters 2695-2996 高压液相色谱仪 (Gimini C18 150 × 4.6 mm 色谱柱)。

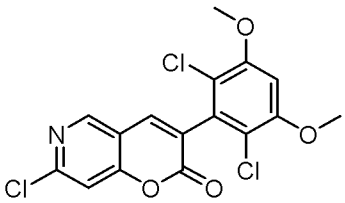
薄层层析硅胶板使用烟台黄海 HSGF254 或青岛 GF254 硅胶板，TLC 采用的规格是 0.15 mm～0.20 mm，薄层层析分离纯化产品采用的规格是 0.4 mm～0.5 mm。柱层析一般使用烟台黄海硅胶 200～300 目硅胶为载体。

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，本发明的所有反应均在连续的磁力搅拌下，在干燥氮气或氩气氛下进行，溶剂为干燥溶剂，反应温度单位为摄氏度。

中间体的制备

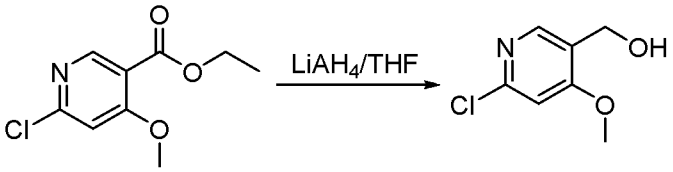
中间体 1　7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2H-吡喃并[3,2-c]吡啶-2-酮的制备



第一步：　6-氯-4-甲氧基尼古丁酸乙酯的制备

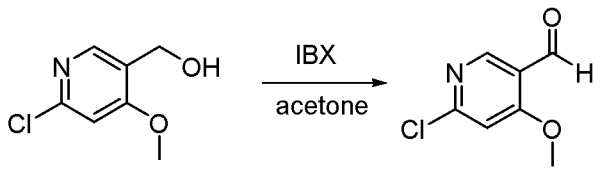
化合物 4,6-二氯尼古丁酸乙酯（10.0 g，45.4 mmol）加入无水 THF（100 mL），冰水浴冷却至 0 ℃，再加入 MeONa（2.8 g，51.8 mmol）。加完后室温搅拌，反应过夜。反应完全后浓缩，除去 THF，粗产品溶于乙酸乙酯（100 mL），水洗 2 次，无水 Na_2SO_4 干燥。过滤，浓缩，得化合物 6-氯-4-甲氧基尼古丁酸乙酯（8.2 g，收率：84%）。MS (ESI): *m/z* 216.3 $[M+1]^+$.

第二步：(6-氯-4-甲氧基吡啶-3-基)甲醇的制备



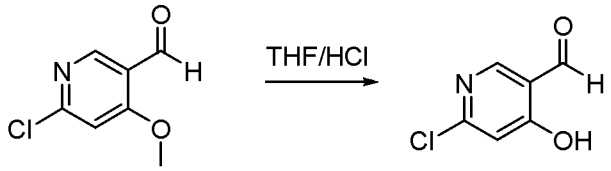
化合物 6-氯-4-甲氧基尼古丁酸乙酯（8.2 g，38.1 mmol）溶于无水 THF（200 mL），冰水浴冷却下加入 $LiAH_4$（3.0 g，81.1 mmol），加完后室温反应 2 小时。反应完全，加入 2N NaOH 水溶液（25 mL）萃取。过滤除去固体残渣，滤液经浓缩得化合物 6-氯-4-甲氧基吡啶-3-基)甲醇（6.0 g，收率：91%）。MS (ESI): *m/z* 174.2 $[M+1]^+$.

第三步：6-氯-4-甲氧基尼古丁醛的制备



化合物 6-氯-4-甲氧基吡啶-3-基)甲醇（6.0 g，34.6 mmol）溶于丙酮（100 mL），再加入 IBX（12.0 g，42.9 mmol），加热至回流，反应 18 小时。反应完全，过滤，浓缩，得化合物 6-氯-4-甲氧基尼古丁醛（4.2 g，收率：71%）。MS (ESI): *m/z* 172.2 $[M+1]^+$.

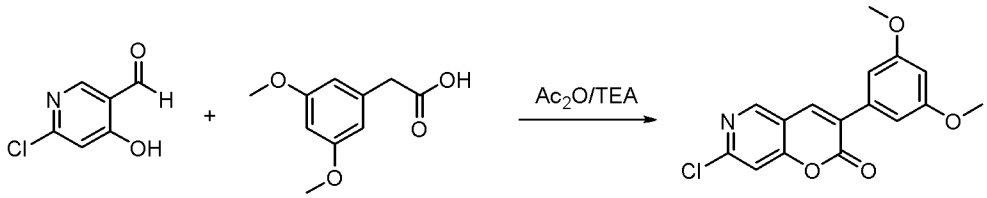
第四步：6-氯-4-羟基尼古丁醛的制备



化合物 6-氯-4-甲氧基尼古丁醛（4.2 g，24.5 mmol）溶于 1,4-二氧六环（30 ml），再加入浓盐酸（10 mL），加热至 90 ℃，反应 16 小时。反应完全后浓缩，粗产品经硅胶柱层析分离（PE：EA = 2 : 1），得化合物 6-氯-4-羟基尼古丁醛（1.5 g，收率：39%）。

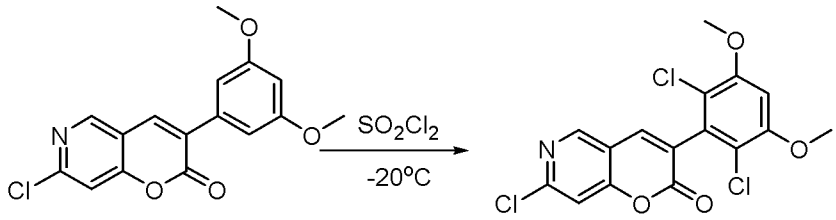
^{1}H NMR (400MHz, $CDCl_3$): δ ppm 11.37 (s, 1H), 9.99 (s, 1H), 8.57 (s, 1H), 6.99 (s, 1H).

第五步：7-氯-3-(3,5-二甲氧苯基)-2H-吡喃并[3,2-c]吡啶-2-酮的制备



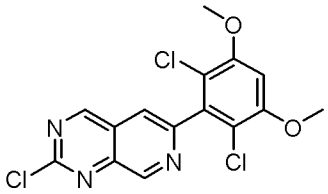
化合物 6-氯-4-羟基尼古丁醛（0.60 g，3.82 mmol）加入乙酸酐（10 mL），再加入 2-(3,5-二甲氧苯基)乙酸（0.80 g，4.08 mmol）和三乙胺（1.5 g，10.7 mmol），加热至 110 ℃，反应 40 分钟。反应完全，冷却至室温，浓缩，所得固体用石油醚/乙酸乙酯（3:1）洗涤，得化合物 7-氯-3-(3,5-二甲氧苯基)-2H-吡喃并[3,2-c]吡啶-2-酮（0.35 g，收率：29%）。MS (ESI): *m/z* 318.3 $[M+1]^+$.

第六步：7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2H-吡喃并[3,2-c]吡啶-2-酮的制备

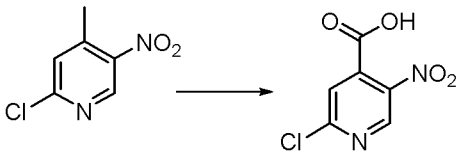


化合物 7-氯-3-(3,5-二甲氧苯基)-2H-吡喃并[3,2-c]吡啶-2-酮（0.35 g，1.1 mmol）溶于无水乙腈（10 mL）。冷却至-30 ℃，滴加 SO_2Cl_2（1.0 g，7.4 mmol），维持低温反应 1 小时。加入饱和 $NaHCO_3$ 水溶液淬灭，浓缩除去乙腈。过滤，固体再依次水洗和石油醚/乙酸乙酯（3:1）洗涤，得化合物 7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2H-吡喃并[3,2-c]吡啶-2-酮（0.21 g，收率：49%）。MS (ESI): *m/z* 386.3 $[M+1]^+$.

中间体 2　2-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶的制备

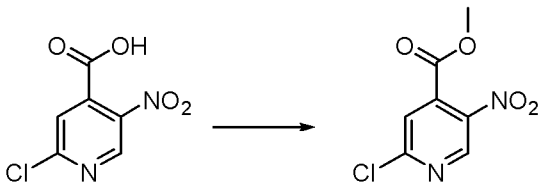


第一步：2-氯-5-硝基异尼古丁酸的制备



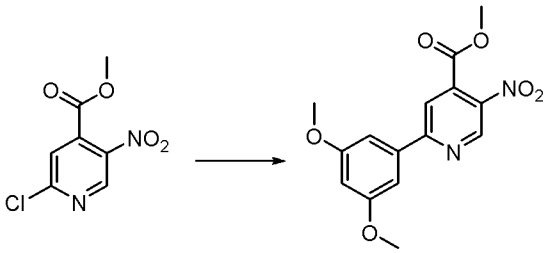
0 ℃下，在 2-氯-4-甲基-5-硝基吡啶 (20.0 g, 11.6mmol) 的硫酸 (200 mL) 溶液中加入三氧化铬 (40.0 g, 40 mmol)。加完后，混合物在 0 ℃下搅拌 1 小时，慢慢变到室温搅拌过夜，然后泼到冰水（1L）中。过滤得到 2-氯-5-硝基异尼古丁酸(18 g, 收率: 77 %)。MS (ESI): *m/z* 201.1 $[M-1]^-$.

第二步：　2-氯-5-硝基异尼古丁酸甲酯的制备



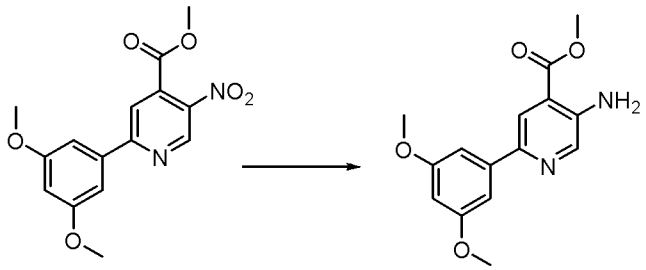
0 ℃下，在 2-氯-5-硝基异尼古丁酸 (16 g, 80 mmol) 的二氯甲烷 (150 mL) 混悬液中加入草酰氯 (12.7 g, 100 mmol)。加完后，反应液在室温下搅拌 3 小时。加入甲醇 (100 mL)，然后反应液在室温继续搅拌 4 小时，旋干。粗产品用二氯甲烷 (200 mL) 溶解，用碳酸氢钠溶液 (100 mL*2) 洗涤，并用无水硫酸钠干燥，浓缩得到化合物 2-氯-5-硝基异尼古丁酸甲酯(17.2 g, 收率: 98 %)。

第三步：　2-(3,5-二甲氧苯基)-5-硝基异尼古丁酸甲酯的制备



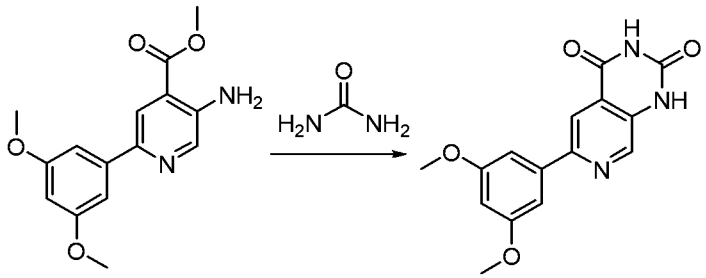
在 2-氯-5-硝基异尼古丁酸甲酯 (10.0 g, 46.0 mmol) 的二氧六环 (200 mL) 和水 (50 mL) 溶液中加入 3,5-二甲氧基苯硼酸 (8.47 g, 46 mmol)，四(三苯基膦)钯 (5 g,4.6 mmol) 和碳酸钠 (5 g, 16 mmol)。加完料后， 混合物在 110 ℃氮气环境下搅拌直到原料反应完。反应液浓缩后柱层析（洗脱剂: CH_2Cl_2/PE 20:1）分离，得到化合物 2-(3,5-二甲氧苯基)-5-硝基异尼古丁酸甲酯（6 g, 收率: 41%）。MS (ESI): *m/z* 318.9 $[M+1]^+$.

第四步：　5-氨基-2-(3,5-二甲氧苯基)异尼古丁酸甲酯的制备



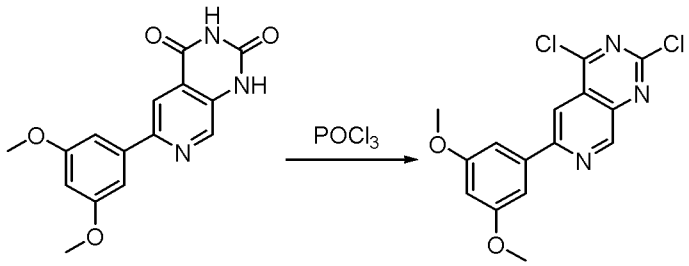
在 2-(3,5-二甲氧苯基)-5-硝基异尼古丁酸甲酯 (6 g, 18.8 mmol) 的甲醇 (100 mL) 溶液中加入钯/碳 (10%, 500 mg)，然后混合物在室温氢气环境下搅拌 4 小时。过滤并旋干，得到 5-氨基-2-(3,5-二甲氧苯基)异尼古丁酸甲酯 (5 g, 收率: 92.3 %)。MS (ESI): *m/z* 289.3[M+1]$^+$.

第五步：6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,4(1H,3H)-二酮的制备



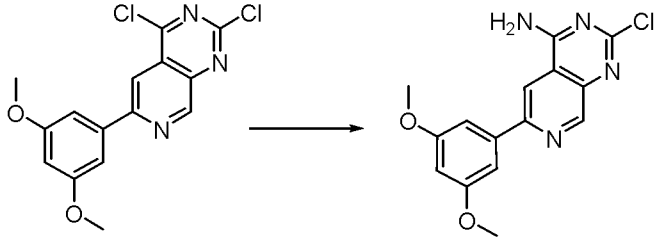
5-氨基-2-(3,5-二甲氧苯基)异尼古丁酸甲酯 (5 g, 17.4 mmol) 和脲 (12 g, 200 mmol)的混合物加热到 160 ℃，搅拌 4 小时。然后泼到冰水 (100 mL) 中，过滤，得到 6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,4(1H,3H)-二酮（6 g, 收率: 99 %）。MS (ESI): *m/z* 300.3 [M+1]$^+$.

第六步：2,4-二氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶的制备



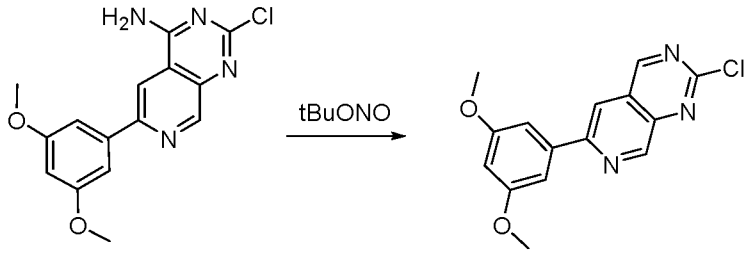
在 6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,4(1H,3H)-二酮 (5.0 g, 16.7 mmol) 的三氯氧磷 (50 mL) 混悬液中加入 N,N-二乙基苯胺 (3 mL)。然后混合物在 110 ℃下搅拌过夜。溶剂旋干，加入冰水 (200 mL)， 用碳酸氢钠水溶液调节 pH 到 7，水溶液用 EtOAc (50 mL)萃取 3 次。有机层用无水硫酸钠干燥，过滤，浓缩，柱层析分离[洗脱剂:（EA : PE = 1: 5）] 得到化合物 2,4-二氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶（2.5 g,收率: 44.5%）。MS (ESI): *m/z* 336.2 [M+1]$^+$.

第七步：2-氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺的制备



在 2,4-二氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶 (2.5 g, 7.5 mmol) 的甲醇 (100 mL) 溶液中加入浓氨水(2 g)。然后混合物在 25 ℃下搅拌 4 小时。用盐酸（1N）调节 pH 值到 7，甲醇在真空下旋掉，过滤得到 2-氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺 (2 g, 收率: 84 %)。MS (ESI): *m/z* 317.1[M+1]$^+$.

第八步：2-氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶的制备

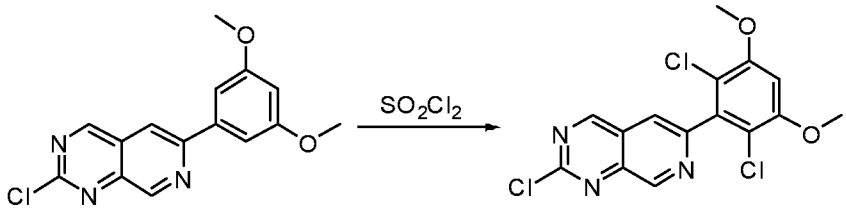


在 2-氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺 (1 g, 3.1 mmol) 的四氢呋喃 (100 mL) 溶液中加入叔丁基亚硝酸酯（720 mg, 6.2 mmol）。然后混合物加热到回流，搅拌 48 小时。反应液浓缩后柱层析 [洗脱剂: （EA:PE=1: 5 -1:2）] 得到化合物 2-氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶 (400 mg，收率: 41%)。

^{1}H NMR (400 MHz, DMSO-d_6): δ9.7(s, 1H), 9.53(s, 1H), 8.74(s, 1H), 7.4(s, 2H), 6.64(s, 1H), 3.88(S, 6H);

MS (ESI): *m/z* 302.0[M+1]$^+$.

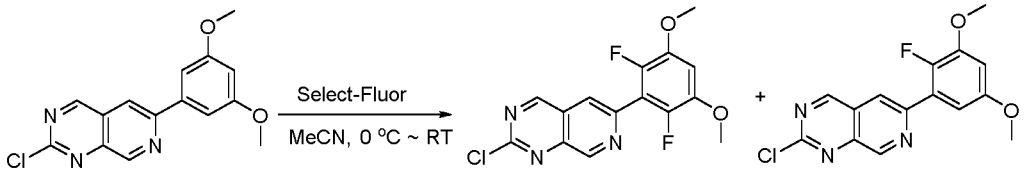
第九步：2-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶的制备



参照中间体 1 第六步的合成方法制备。

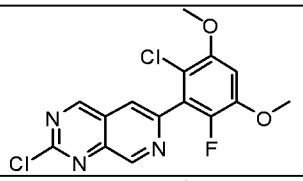
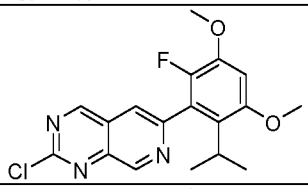
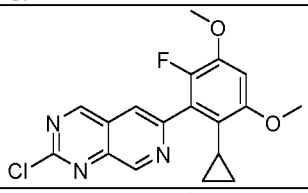
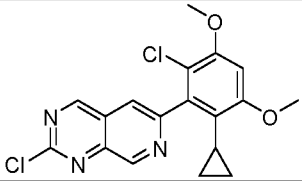
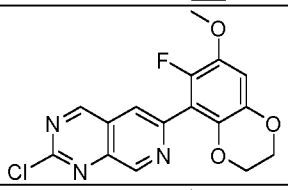
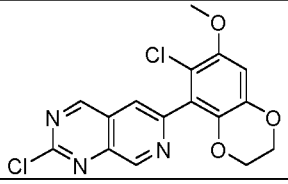
中间体 3　2-氯-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶和

中间体 4　2-氯-6-(2-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶的制备

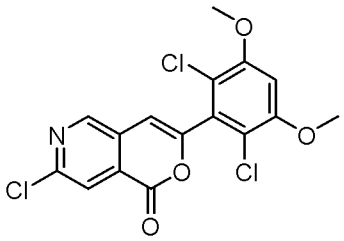


2-氯-6-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶（120 mg, 0.4 mmol）溶于干燥乙腈（20 mL），冰水浴冷却至 0 ℃，慢慢滴加 1-氯甲基-4-氟-1,4-重氮化二环 2.2.2 辛烷双(四氟硼酸盐)（select-fluor，283 mg, 0.8 mmol）。加完后升至室温反应 6 小时。TLC 监测，基本反应完全。用饱和 $NaHCO_3$ 淬灭，除去大部分乙腈，乙酸乙酯萃取。浓缩，硅胶柱层析(PE/EA=10/11，加 10% DCM 调节)，得到 2-氯-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶(20 mg，产率：15%)，MS m/z (ESI): 338 [M+H]+。同时得到 2-氯-6-(2-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶 (70 mg，产率 55%)，MS m/z (ESI): 320 [M+H]$^+$.

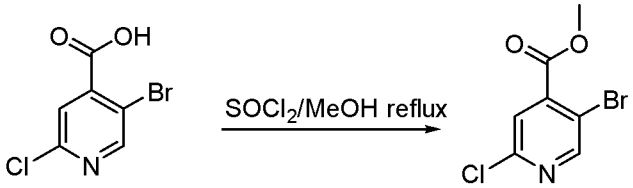
以下中间体 5-10 参照中间体 2 的合成方法制备：

中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
5		2-氯-6-(2-氯-6-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶	355
6		2-氯-6-(2-氟-6-异丙基-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶	362
7		2-氯-6-(2-环丙基-6-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶	360
8		2-氯-6-(2-氯-6-环丙基-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶	377
9		2-氯-6-(6-氟-7-甲氧基-2,3-二氢苯并[b][1,4]二噁英-5-基)吡啶并[3,4-d]嘧啶	348
10		2-氯-6-(6-氯-7-甲氧基-2,3-二氢苯并[b][1,4]二噁英-5-基)吡啶并[3,4-d]嘧啶	365

中间体 11　7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1H-吡喃并[4,3-c]吡啶-1-酮的制备



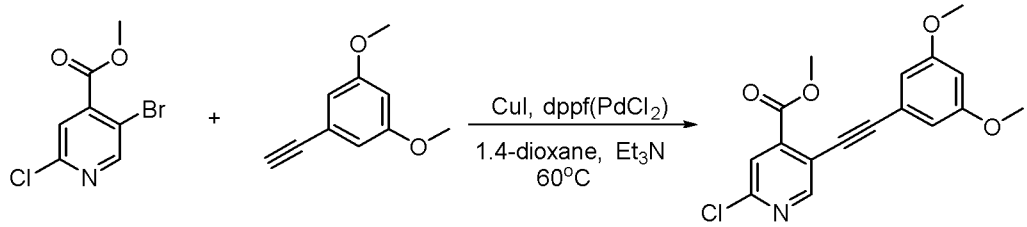
第一步：5-溴-2-氯异尼古丁酸甲酯的制备



5-溴-2-氯异尼古丁酸（30.0 g，12.6 mmol）溶于甲醇（300 mL），再加入 $SOCl_2$（18.0 g，15 mmol），加热至 75 ℃，反应 8 小时，LCMS 监测反应完全。冷却至室温，减压浓缩。所

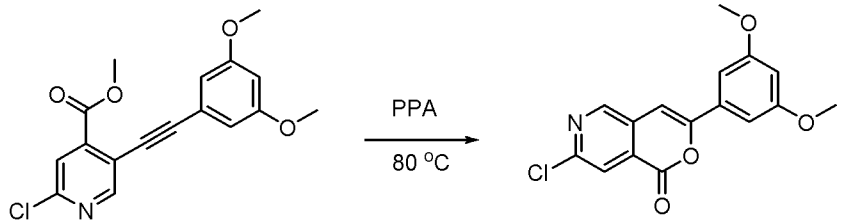
得粗品加入 EtOAc（300 mL），再用饱和 $NaHCO_3$ 水溶液洗涤，无水 Na_2SO_4 干燥。过滤，浓缩，得到 5-溴-2-氯异尼古丁酸甲酯（32.0 g，收率：99%）。MS (ESI): *m/z* 251.9 $[M+1]^+$.

第二步：2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁酸甲酯的制备



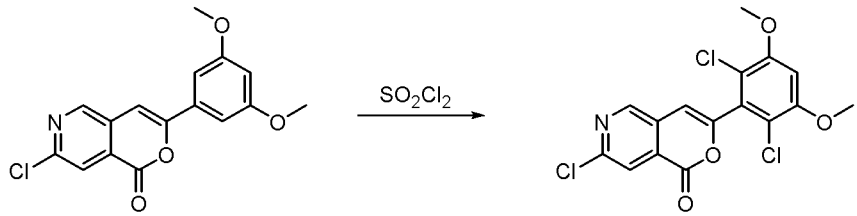
5-溴-2-氯异尼古丁酸甲酯（30 g, 120 mmol）溶于 1,4-二氧六环（300 mL），再加入 3,5-二甲氧基苯乙炔（20.4 g, 120 mmol），CuI（2.28 g,12 mmol），$Pd(dppf)Cl_2$ （4.2 g, 6 mmol）以及 Et_3N（12.0 g, 120 mmol），抽换气，N_2 保护, 加热至 60 ℃，反应 6 小时。反应完全，过滤，浓缩。粗品经硅胶柱层析分离（DCM: PE = 20: 1），得化合物 2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁酸甲酯（22 g, 收率：55%）。MS (ESI): *m/z* 332.1 $[M+1]^+$.

第三步：7-氯-3-(3,5-二甲氧苯基)-1H-吡喃并[4,3-c]吡啶-1-酮的制备



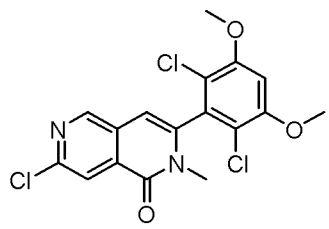
2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁酸甲酯（21.0 g，63 mmol）加入 PPA（200 mL），加热至 80 ℃，反应 8 小时。LCMS 监测反应完全，反应混合物倒入冰水（1000 mL）。过滤，得到固体化合物 7-氯-3-(3,5-二甲氧苯基)-1H-吡喃并[4,3-c]吡啶-1-酮（15.0 g，收率：75%）。MS (ESI): *m/z* 318.2 $[M+1]^+$.

第四步：7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1H-吡喃并[4,3-c]吡啶-1-酮的制备

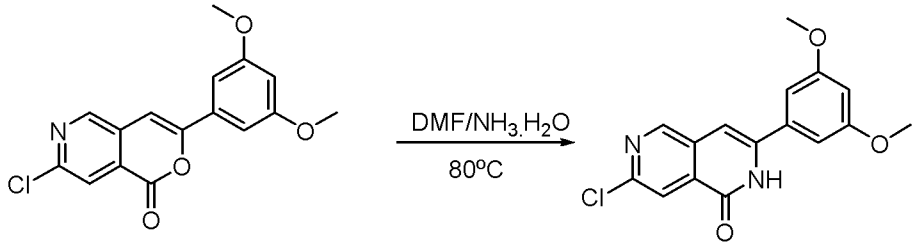


参照中间体 1 第六步的合成方法制备。

中间体 12　7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮的制备



第一步：7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1(2H)-酮的制备

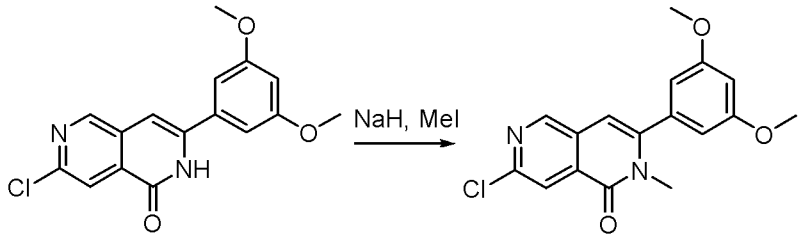


化合物 7-氯-3-(3,5-二甲氧苯基)-1H-吡喃并[4,3-c]吡啶-1-酮（15 g, 47.3 mmol）溶于 DMF（200 mL），加入浓氨水（150 mL）。反应混合物加热至 80 ℃反应 48 小时。LCMS 监测反应完全，过滤，得到固体化合物 7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1(2H)-酮（7.5 g，收率：50.5%）。

^{1}H NMR (400MHz, DMSO-d6): δ ppm11.7(m, 1H), 8.97(s, 1H), 8.01(s, 1H), 7.14(s, 1H), 6.97(s, 2H), 6.61(s,1H), 3.86(s, 6H);

MS (ESI): *m/z* 317.2 $[M+1]^+$.

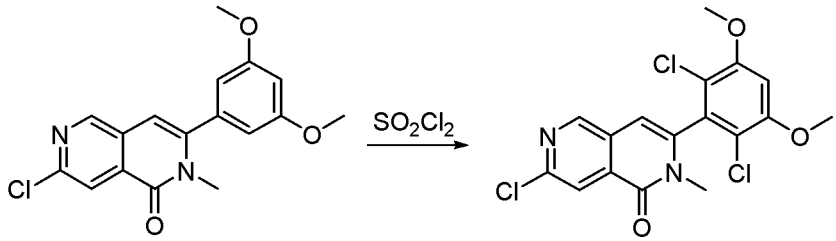
第二步：7-氯-3-(3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮的制备



7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1(2H)-酮（2g, 6.32 mmol）溶于 DMF（30 mL），冰水浴冷却下加入 NaH（758 mg, 18.95 mmol）。混合物在 0 ℃下搅拌 15 分钟，然后滴入 MeI（8.967g, 63.151 mmol），室温下搅拌反应 1 小时。反应完毕后，加水淬灭。乙酸乙酯萃取三次，合并有机相，水洗，饱和食盐水洗，无水硫酸钠干燥。过滤，浓缩后柱层析分离（洗脱剂: PE/EtOAc = 2:1），得到化合物 7-氯-3-(3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮（1.35g, 收率：65%）。

MS m/z (ESI): 331.0 $[M+H]^+$.

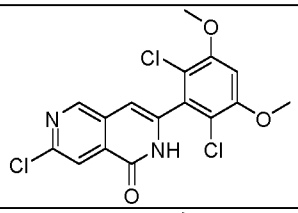
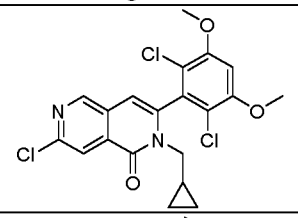
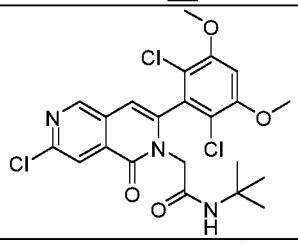
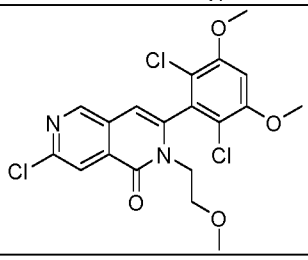
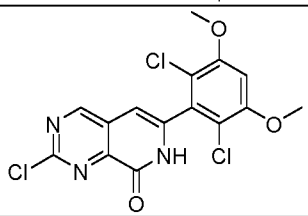
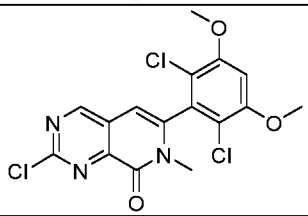
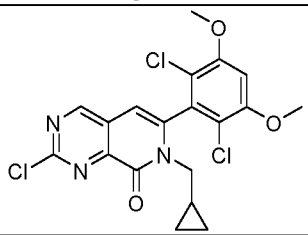
第三步：7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮的制备



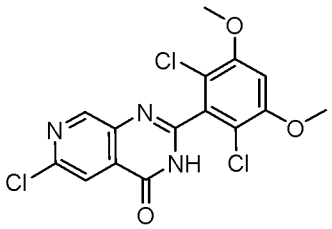
参照中间体 1 第六步的合成方法制备。MS m/z (ESI): 399.2 $[M+H]^+$.

以下中间体 13-19 参照中间体 12 的合成方法制备：

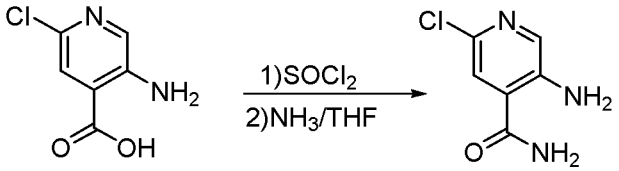
中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$

13		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1(2H)-酮	385
14		7-氯-2-(环丙基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1(2H)-酮	440
15		N-(叔-丁基)-2-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-羰基-2,6-二氮杂萘-2(1H)-基)乙酰胺	499
16		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2-(2-甲氧基乙基)-2,6-二氮杂萘-1(2H)-酮	444
17		2-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-8(7H)-酮	387
18		2-氯-6-(2,6-二氯-3,5-二甲氧苯基)-7-甲基吡啶并[3,4-d]嘧啶-8(7H)-酮	401
19		2-氯-7-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-8(7H)-酮	441

中间体 20　6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮的制备

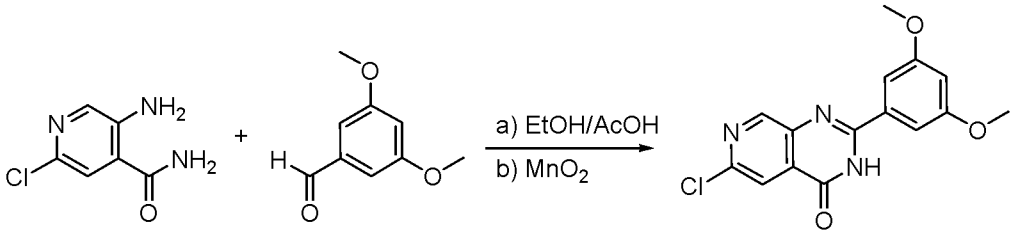


第一步：**5-氨基-2-氯异尼克酰胺的制备**



5-氨基-2-氯异尼古丁酸（4.0 g，23 mmol）加入 $SOCl_2$（50 mL），加热至 80 ℃，搅拌反应 4 小时。反应完全，冷却至室温。浓缩，所得粗产品溶于无水 THF（20 mL），冰水浴冷却，加入浓氨水（100 mL），反应完全。CH_2Cl_2（100 mL）萃取 5 次，合并有机相，无水 Na_2SO_4 干燥。过滤，浓缩，得化合物 5-氨基-2-氯异尼克酰胺（3.5 g, 收率：88%）。

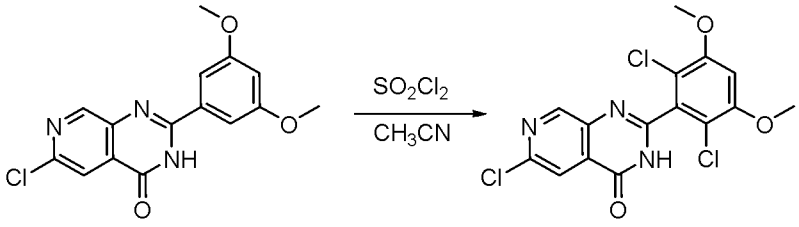
第二步：**6-氯-2-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮的制备**



化合物 5-氨基-2-氯异尼克酰胺（3.5 g，20.4 mmol）和 3,5-二甲氧基苯甲醛（3.7 g，22.3 mmol）溶于 EtOH（50 mL），加入 HOAc（10 mL），加热至 80 ℃，反应 2 天。反应液浓缩，粗产品溶于 CH_2Cl_2（100 mL）和 THF（100 mL）混合溶液，再加入 MnO_2（17.0 g，87.0 mmol），室温搅拌 4 天。反应完全，过滤，浓缩，粗品再加入 EtOAc（100 mL）打浆。过滤，得化合物 6-氯-2-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮（4.0 g，收率：63%）。

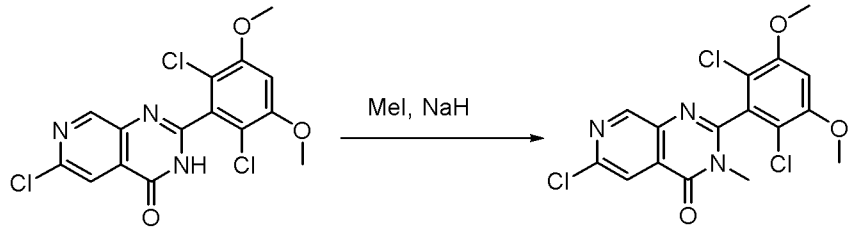
^{1}H NMR (400MHz, DMSO-d6): δ ppm 12.78 (s, 1H), 8.91 (s, 1H), 7.95 (s, 1H), 7.44 (s, 1H), 7.43 (s, 1H),3.84 (s, 6H).

第三步：**6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮的制备**



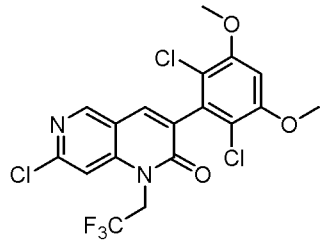
6-氯-2-(3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮（1.0 g，3.2 mmol）溶于 CH_3CN（50 mL），冷却至-20 ℃，再加入 SO_2Cl_2（0.85 g，6.3 mmol），维持低温反应 3 小时。反应完全，加入饱和 $NaHCO_3$ 水溶液淬灭。过滤，得化合物 6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮（1.1 g，92%）。MS (ESI): *m/z* 386 $[M+H]^+$.

中间体 **21** **6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-3-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮的制备**

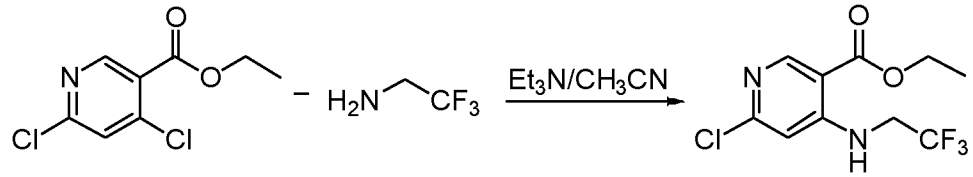


6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4(3H)-酮（0.65 g, 1.68 mmol）溶于DMF（20 mL），冰水浴冷却至 0 ℃，加入 NaH（134 mg, 3.36 mmol）。室温下搅拌反应 2 小时。反应完全，加入水（50 mL）淬灭。过滤，清水洗涤，干燥，得到化合物 6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-3-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮（0.65 g, 产率 96%）。MS m/z (ESI): 400 $[M+H]^+$.

中间体 22 7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(2,2,2-三氟乙基)-1,6-二氮杂萘-2(1H)-酮的制备

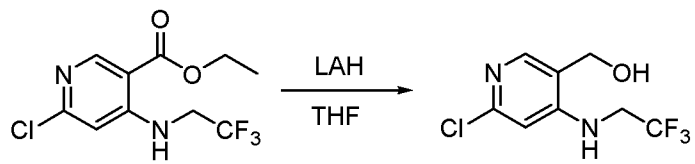


第一步：6-氯-4-((2,2,2-三氟乙基)氨基)尼古丁酸乙酯的制备



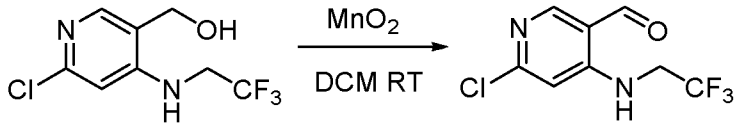
4,6-二氯尼古丁酸乙酯（4.0 g，18.18 mmol）和三氟乙氨（2.7 g，27.27 mmol）溶于 DMSO（50 mL），再加入 Et_3N（5.5 g，54.55 mmol）。加热至 120 ℃，反应 12 小时。反应完全，冷却至室温，加入水（200 mL），再用 EtOAc（50 mL）萃取 3 次，有机相用无水 Na_2SO_4 干燥。过滤，浓缩，粗品经硅胶柱层析分离（PE:EA=3:1），得化合物 6-氯-4-((2,2,2-三氟乙基)氨基)尼古丁酸乙酯（1.5 g，收率：29.1%）。MS (ESI): *m/z* 283.0 $[M+1]^+$.

第二步：(6-氯-4-((2,2,2-三氟乙基)氨基)吡啶-3-基)甲醇的制备



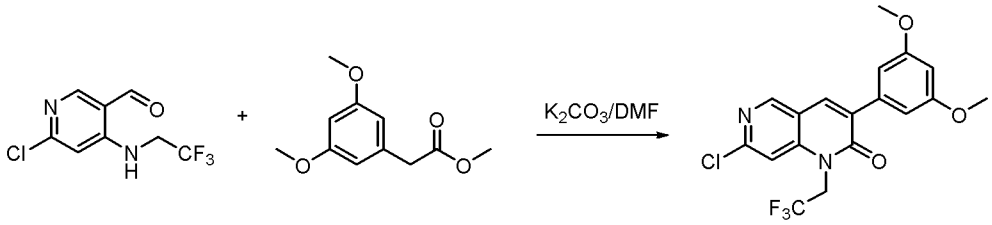
化合物 6-氯-4-((2,2,2-三氟乙基)氨基)尼古丁酸乙酯（1.5 g，5.32 mmol）溶于干燥 THF（30 mL），冰水浴冷却。缓慢加入 $LiAlH_4$（0.39 g，10.64 mmol ），0 ℃下反应 2 小时。反应完全，加入 $Na_2SO_4{\cdot}10H_2O$ 淬灭。过滤，滤液浓缩，得化合物(6-氯-4-((2,2,2-三氟乙基)氨基)吡啶-3-基)甲醇（1.1 g，收率：86%）。

第三步：6-氯-4-((2,2,2-三氟乙基)氨基)尼古丁醛的制备



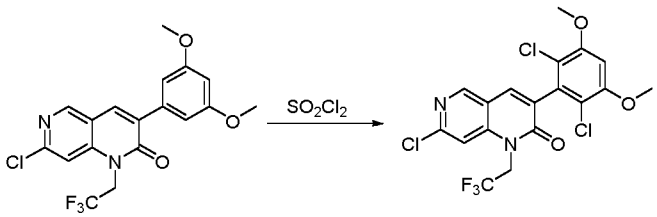
化合物(6-氯-4-((2,2,2-三氟乙基)氨基)吡啶-3-基)甲醇（1.1 g, 4.58 mmol）溶于 CH_2Cl_2/THF（30 mL/10 mL），再加入 MnO_2（4.78 g, 54.9 mmol），室温搅拌反应 12 小时。反应完全，过滤，滤液浓缩，得粗产品 6-氯-4-((2,2,2-三氟乙基)氨基)尼古丁醛（0.86 g，收率：79%）。

第四步：7-氯-3-(3,5-二甲氧苯基)-1-(2,2,2-三氟乙基)-1,6-二氮杂萘-2(1H)-酮的制备



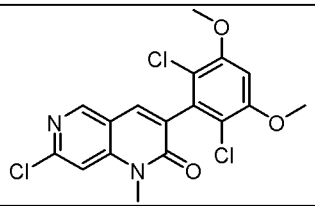
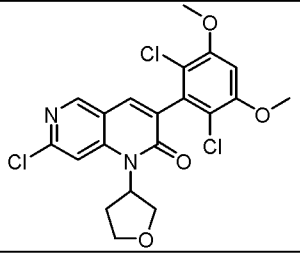
6-氯-4-((2,2,2-三氟乙基)氨基)尼古丁醛（0.86 g，3.61 mmol ）溶于 DMF（20 mL），再加入 3,5-二甲氧基苯乙酸甲酯（760 mg，3.61 mmol）和 K_2CO_3（1.5 g，10.84 mmol），加热至 110 ℃，反应 3 小时。反应完全，浓缩，粗产品经硅胶柱层析分离（PE:EA=10:1），得 7-氯-3-(3,5-二甲氧苯基)-1-(2,2,2-三氟乙基)-1,6-二氮杂萘-2(1H)-酮（960 mg，收率：67%）。MS (ESI): *m/z* 399.0 $[M+1]^+$.

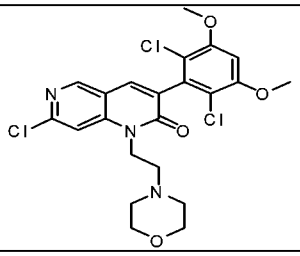
第五步：7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(2,2,2-三氟乙基)-1,6-二氮杂萘-2(1H)-酮的制备



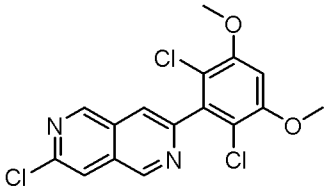
参照中间体 1 第六步的合成方法制备。

以下中间体 23-25 参照中间体 22 的合成方法制备：

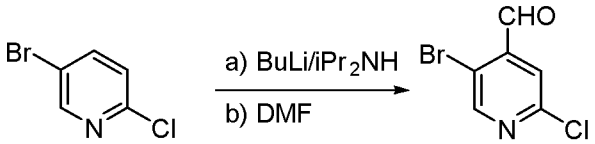
中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
23		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-1,6-二氮杂萘-2(1H)-酮	400
24		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(四氢呋喃-3-基)-1,6-二氮杂萘-2(1H)-酮	456

25		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(2-吗啉代乙基)-1,6-二氮杂萘-2(1H)-酮	499

中间体 26 3-氯-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘的制备



第一步：5-溴-2-氯异尼古丁醛的制备

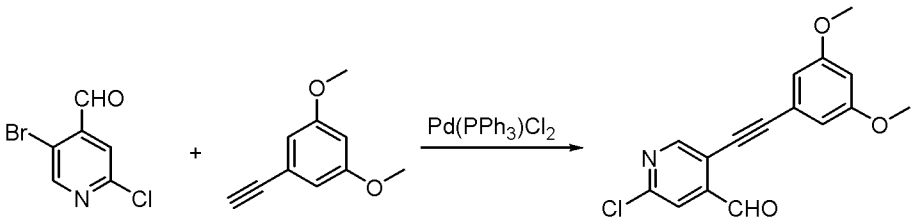


二异丙胺（8.95 g，88 mmol）溶于干燥 THF (100 mL) ，氮气保护，冷却至-78 ℃，滴加正丁基锂 (50 mL，78 mmol)，加完后在 0 ℃下搅拌反应 10 分钟。再冷却至-78 ℃，然后加入 2-氯-5-溴吡啶（10.0 g，52 mmol），在此温度下搅拌反应 1 小时，最后滴加干燥 DMF（11.4 g，0.16 mol），继续低温搅拌反应 1 小时。加入氯化铵溶液粹灭，然后用 EtOAc（300 mL）稀释，用水（50 mL）洗涤 3 次，再用饱和食盐水（100 mL）洗涤，无水硫酸钠干燥。过滤，浓缩后柱层析（洗脱剂: PE/EtOAc 9:1）分离，得到化合物 5-溴-2-氯异尼古丁醛（7.0 g, 产率：61%）。

^{1}H NMR (400 MHz, CDCl3): δ 10.3(s, 1H), 8.69 (s, 1H), 7.73 (s, 1H).

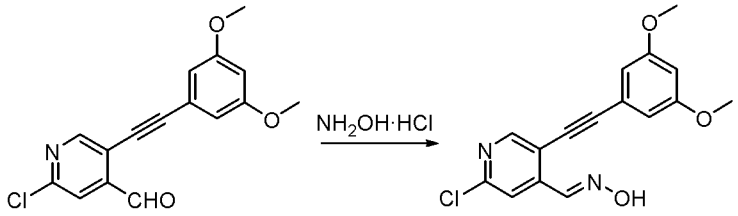
MS m/z (ESI): 252.0, 254.0, 256.0 $[M+MeOH+H]^+$。

第二步：2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁醛的制备



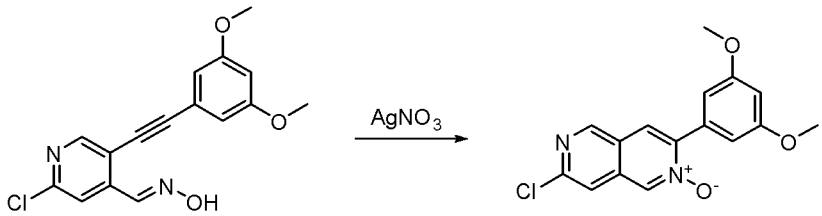
氮气保护下将 5-溴-2-氯异尼古丁醛（2.5 g，11.3 mmol），1-乙炔基-3,5-二甲氧基苯（1.93 g，11.9 mmol），DIPEA （3.66 g，28.4 mmol），CuI（108 mg，0.6 mmol），$Pd(PPh_3)_2Cl_2$（398 mg, 0.6 mmol）加入 1,4-二氧六环（50 mL）中，加热 50 ℃，搅拌反应 1 小时。反应完全，用 EtOAc（300 mL）稀释， 依次用水（50 mL * 3）和饱和食盐水（100 mL）洗涤，并用无水硫酸钠干燥，浓缩后柱层析（洗脱剂: PE/EtOAc 9:1）分离，得到化合物 2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁醛 (3.0 g, 产率：75%)。MS m/z (ESI): 302.2, 304.2 $[M+H]^+$.

第三步：2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁醛肟的制备



在氮气保护下 2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁醛（0.6 g, 2 mmol），NaOAc（245 mg, 3.0 mmol）以及盐酸羟胺（207 mg, 3.0 mmol）溶于乙醇/1,2-二氯乙烷（20 mL/11.2 mL），加热 50 ℃，搅拌反应 50 分钟。反应完全，加入 EtOAc（200 mL）稀释，依次用水 (50 mL * 2) 和饱和食盐水 (80 mL) 洗涤，并用无水硫酸钠干燥。过滤，浓缩，得到化合物 2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁醛肟（612 mg, 产率：100%）。

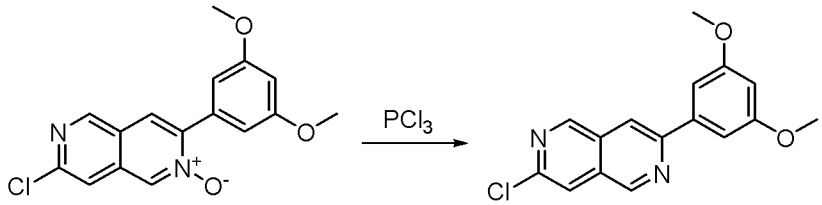
第四步：7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-2-氧化的制备



2-氯-5-((3,5-二甲氧苯基)乙炔基)异尼古丁醛肟（612 mg，1.9 mmol），$AgNO_3$（66 mg，0.38 mmol）加入氯仿（20 mL），加热至 60 ℃，搅拌反应 1 小时。反应完全，浓缩，柱层析（洗脱剂: CH_2Cl_2 /MeOH 35:1）分离，得到化合物 7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-2-氧化（580 mg，产率：95%）。

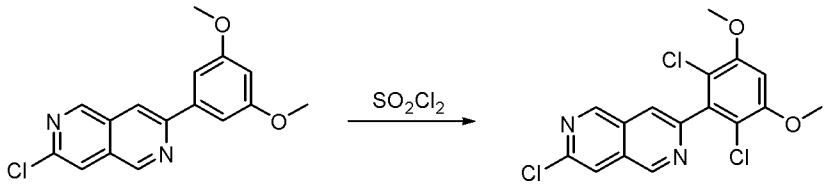
MS m/z (ESI): 317.2, 319.2 $[M+H]^+$.

第五步：3-氯-7-(3,5-二甲氧苯基)-2,6-二氮杂萘的制备



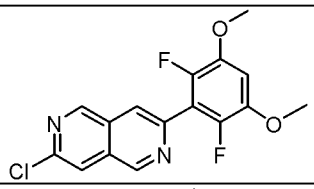
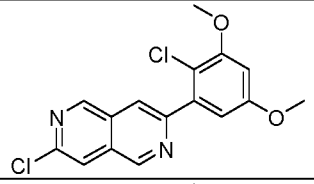
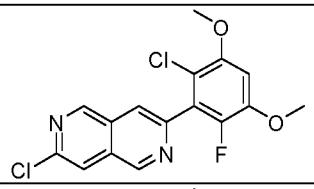
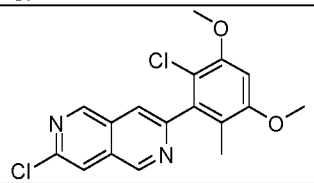
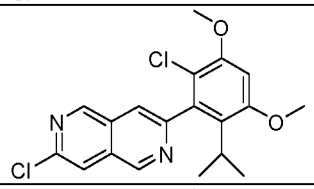
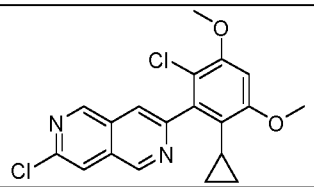
7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-2-氧化（200 mg, 0.63 mmol）溶于二氯甲烷（10 mL），冰水浴冷却，再加入三氯化磷（0.7 mL, 1.4 mmol）。室温下搅拌反应过夜。反应完全，加入饱和 $NaHCO_3$ 水溶液（20 ml），DCM（80 mL）萃取。饱和食盐水（50 mL）洗涤，无水硫酸钠干燥。过滤，浓缩，柱层析（洗脱剂：CH_2Cl_2 /MeOH 50:1）分离，得化合物 3-氯-7-(3,5-二甲氧苯基)-2,6-二氮杂萘（60 mg, 产率：32%）。MS m/z (ESI): 301.2, 303.2 $[M+H]^+$.

第六步：3-氯-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘的制备

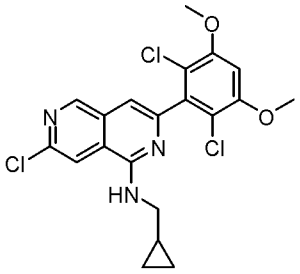


参照中间体 1 的合成方法制备。

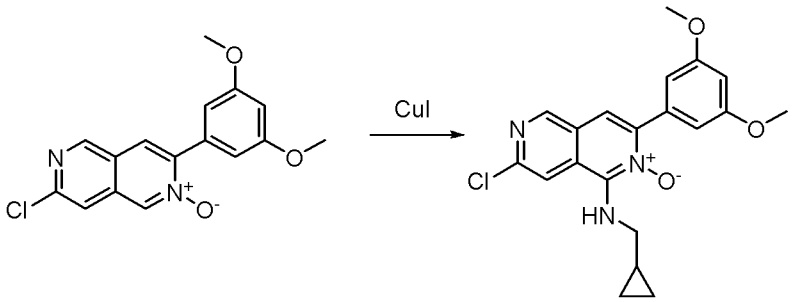
以下中间体 27-32 参照中间体 26 的合成方法制备：

中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
27		3-氯-7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘	337
28		3-氯-7-(2-氯-3,5-二甲氧苯基)-2,6-二氮杂萘	336
29		3-氯-7-(2-氯-6-氟-3,5-二甲氧苯基)-2,6-二氮杂萘	354
30		3-氯-7-(2-氯-3,5-二甲氧基-6-甲基苯基)-2,6-二氮杂萘	350
31		3-氯-7-(2-氯-6-异丙基-3,5-二甲氧苯基)-2,6-二氮杂萘	378
32		3-氯-7-(2-氯-6-环丙基-3,5-二甲氧苯基)-2,6-二氮杂萘	376

中间体 **33** 7-氯-N-(环丙基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺的制备



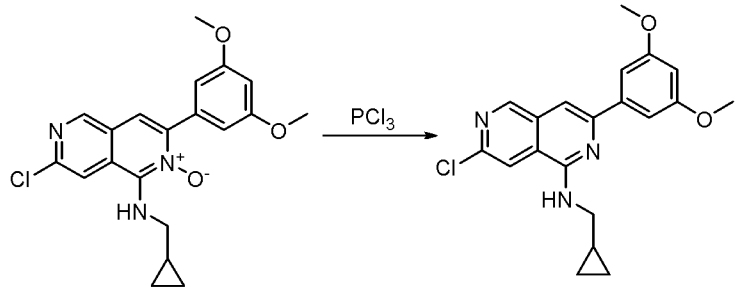
第一步：7-氯-1-((环丙基甲基)氨基)-3-(3,5-二甲氧苯基)-2,6-二氮杂萘 2-氧化的制备



将 7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘 2-氧化（4.0 g，12.6 mmol）溶于甲苯（80 mL），依次加入环丙基甲胺（7.19 g，0.1mol）和 CuI（241 mg,1.26 mmol）。在氧气氛围下加热 50 度反应过夜。反应完全，反应液过滤后浓缩。残留物柱层析（洗脱剂: 二氯甲烷/甲醇 25:1）分离，得到化合物 7-氯-1-((环丙基甲基)氨基)-3-(3,5-二甲氧苯基)-2,6-二氮杂萘 2-氧化（2.8g，57%）。

MS m/z (ESI): 386.4 $[M+H]^+$.

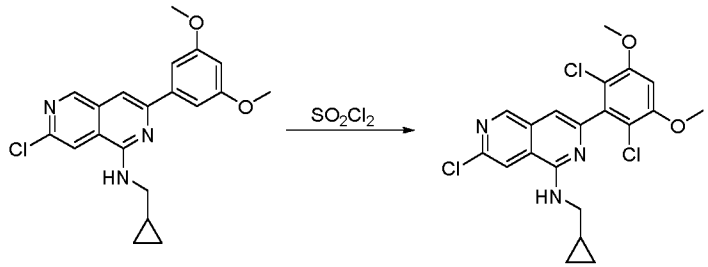
第二步：7-氯-N-(环丙基甲基)-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺的制备



将 7-氯-1-((环丙基甲基)氨基)-3-(3,5-二甲氧苯基)-2,6-二氮杂萘 2-氧化（2.8 g,5.1 mmol）溶于二氯甲烷（40 mL），冰水浴冷却下滴加 PCl_3（3 mL，6.1 mmol），室温搅拌反应 1 小时。将碳酸氢钠饱和溶液（50 mL）加入反应中，然后用二氯甲烷（100 mL * 3）萃取，合并有机相，用无水硫酸钠干燥浓缩。残留物柱层析（洗脱剂: 二氯甲烷/甲醇 50:1）分离，得到化合物 7-氯-N-(环丙基甲基)-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺（570 mg，21%）。

MS m/z (ESI): 370.4 $[M+H]^+$.

第三步：7-氯-N-(环丙基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺的制备

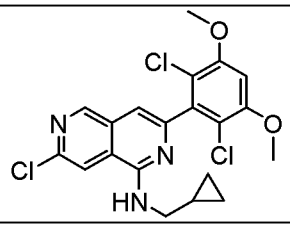
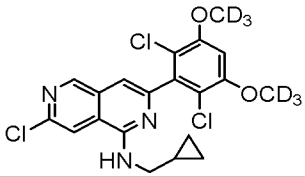
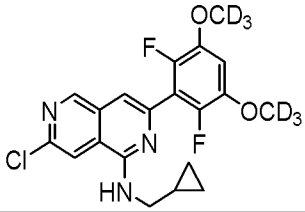
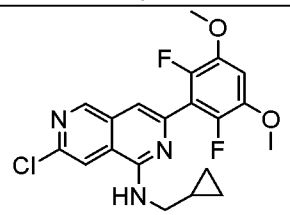
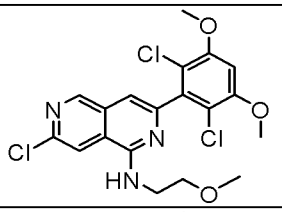
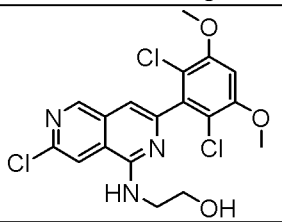
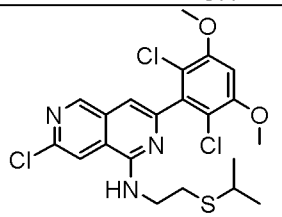


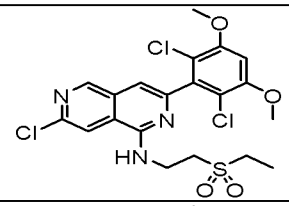
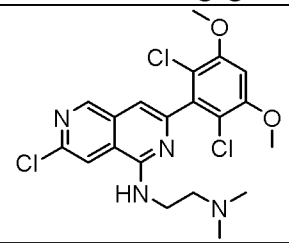
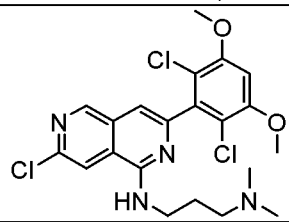
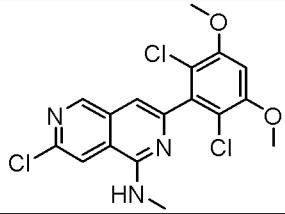
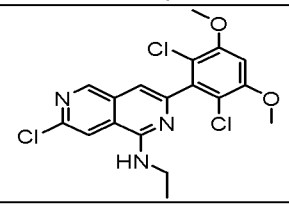
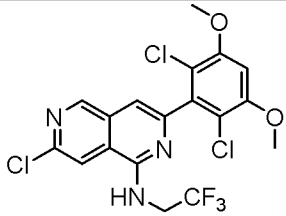
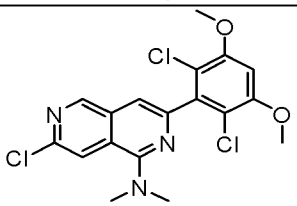
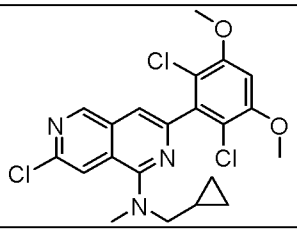
将 7-氯-N-(环丙基甲基)-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺（550 mg，0.27 mmol）加入乙腈（20 mL），然后在-30 度下滴加磺酰氯（73 mg，0.54 mmol），维持低温搅拌反应 1 小时。将碳酸氢钠饱和溶液（30 mL）加入反应液中，然后用乙酸乙酯（50 mL * 3）萃取。合并有机相，用无水硫酸钠干燥，过滤，浓缩。残留物柱层析（洗脱剂: 石油醚/

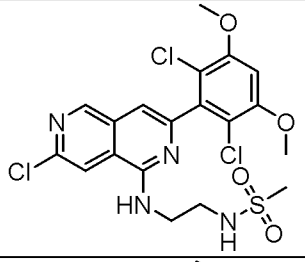
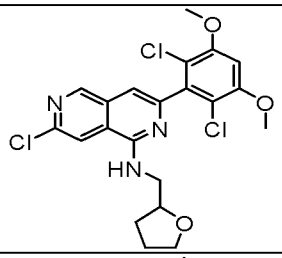
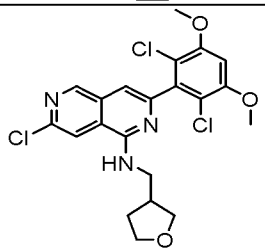
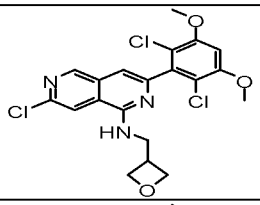
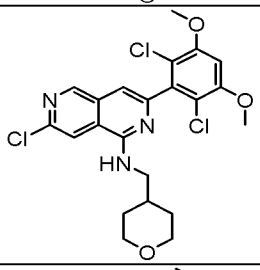
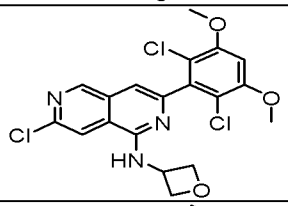
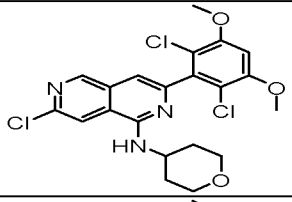
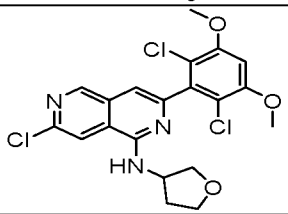
乙酸乙酯 10:1）分离，得到化合物 7-氯-N-(环丙基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺（337 mg，52%）。

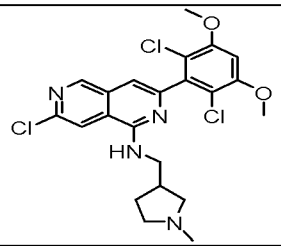
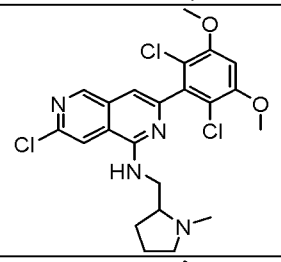
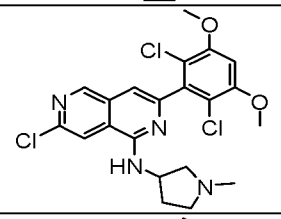
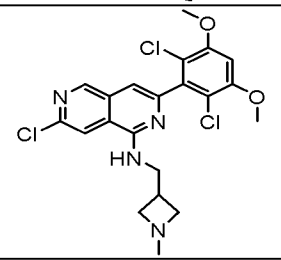
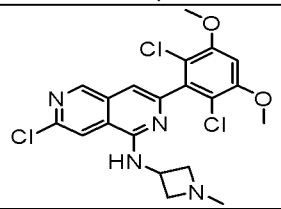
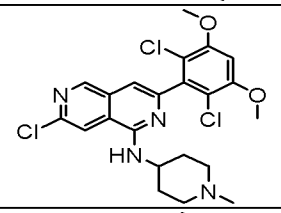
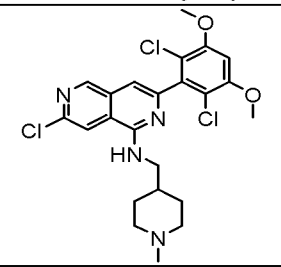
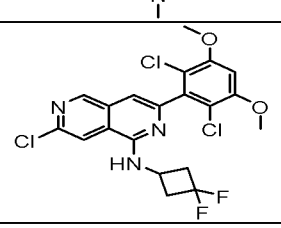
MS m/z (ESI+APCI): 438.2/440.2 $[M+H]^+$.

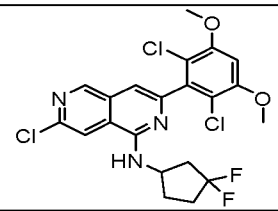
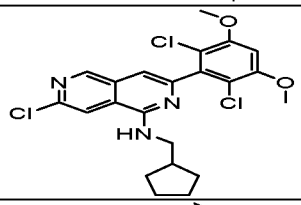
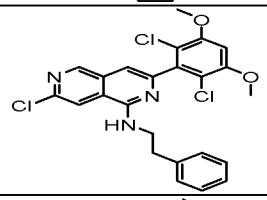
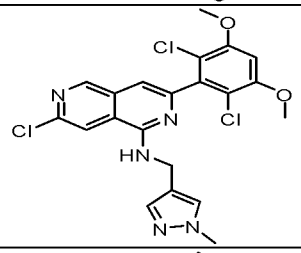
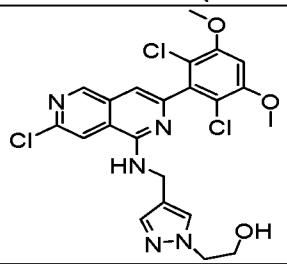
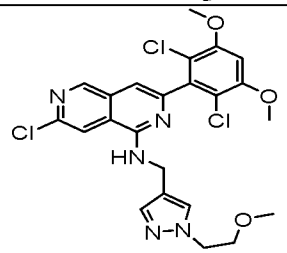
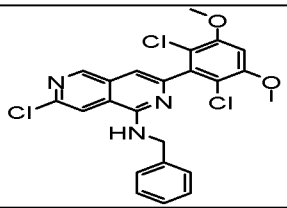
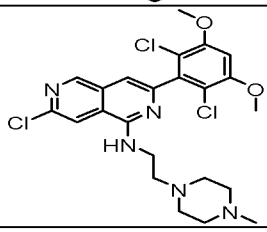
以下中间体 34-131 参照中间体 33 的合成方法制备：

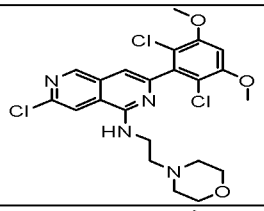
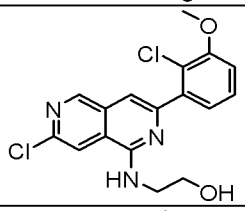
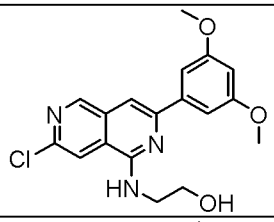
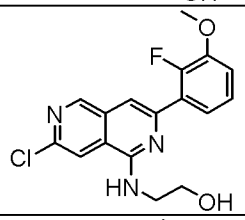
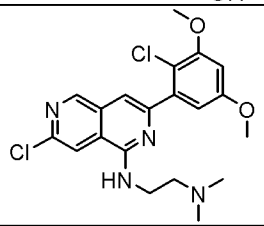
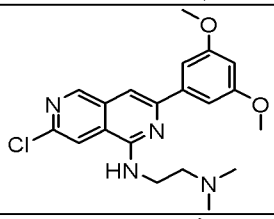
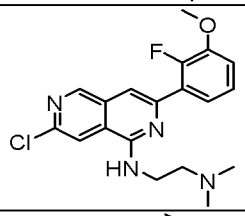
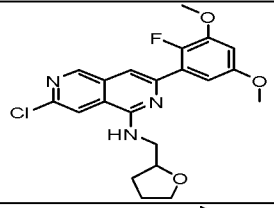
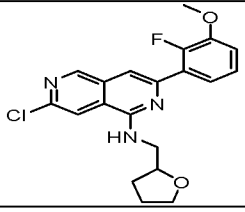
中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
34		7-氯-N-(环丙基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	438
35		7-氯-N-(环丙基甲基)-3-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-1-胺	444
36		7-氯-N-(环丙基甲基)-3-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-1-胺	412
37		7-氯-N-(环丙基甲基)-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	406
38		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(2-甲氧基乙基)-2,6-二氮杂萘-1-胺	442
39		2-((7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)氨基)乙烷-1-醇	428
40		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(异丙基硫代)乙基)-2,6-二氮杂萘-1-胺	486

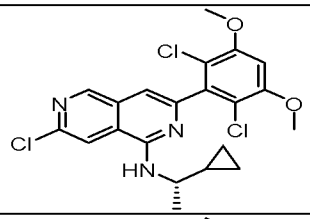
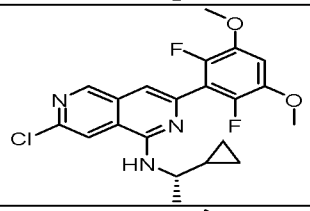
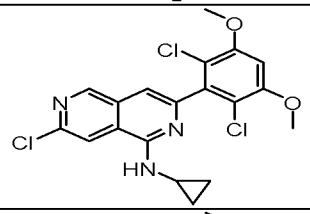
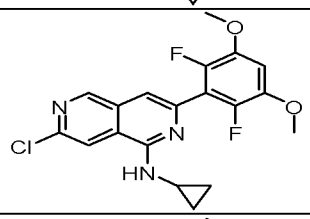
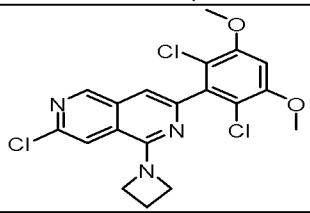
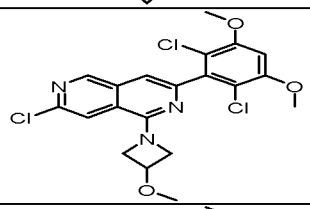
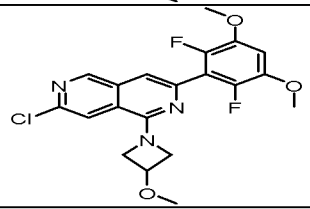
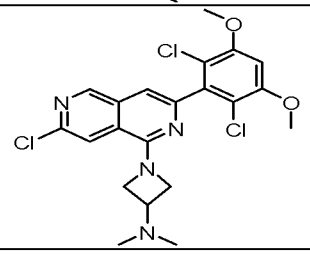
41		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(乙基磺酰)乙基)-2,6-二氮杂萘-1-胺	504
42		N^1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-N^2,N^2-二甲基乙烷-1,2-二胺	455
43		N^1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-N^3,N^3-二甲基丙烷-1,3-二胺	469
44		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-甲基-2,6-二氮杂萘-1-胺	398
45		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-乙基-2,6-二氮杂萘-1-胺	412
46		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(2,2,2-三氟乙基)-2,6-二氮杂萘-1-胺	466
47		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N,N-二甲基-2,6-二氮杂萘-1-胺	412
48		7-氯-N-(环丙基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-N-甲基-2,6-二氮杂萘-1-胺	452

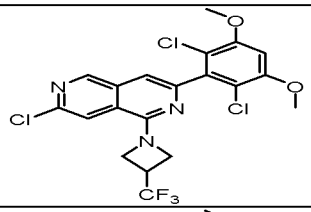
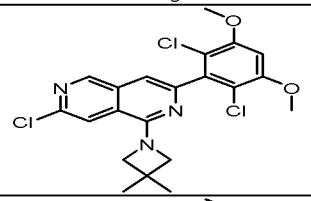
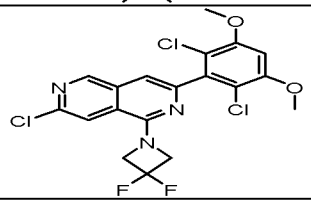
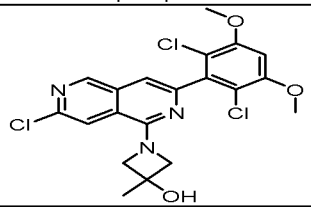
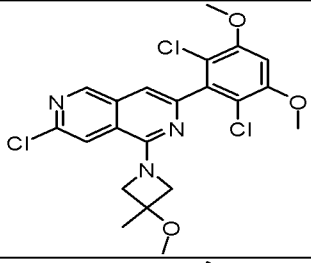
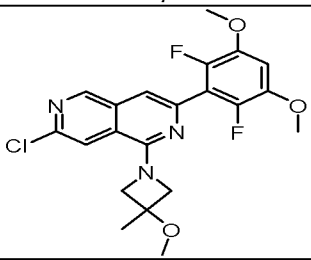
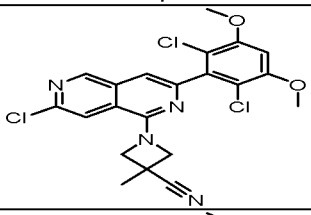
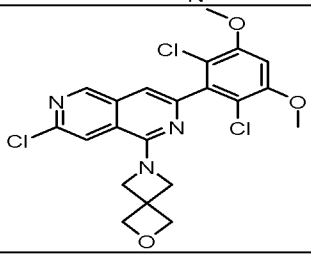
49		N-(2-((7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)氨基)乙基)甲磺酰胺	505
50		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((四氢呋喃-2-基)甲基)-2,6-二氮杂萘-1-胺	468
51		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((四氢呋喃-3-基)甲基)-2,6-二氮杂萘-1-胺	468
52		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(噁丁环-3-基甲基)-2,6-二氮杂萘-1-胺	454
53		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((四氢-2H-吡喃-4-基)甲基)-2,6-二氮杂萘-1-胺	482
54		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(噁丁环-3-基)-2,6-二氮杂萘-1-胺	440
55		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(四氢-2H-吡喃-4-基)-2,6-二氮杂萘-1-胺	468
56		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(四氢呋喃-3-基)-2,6-二氮杂萘-1-胺	454

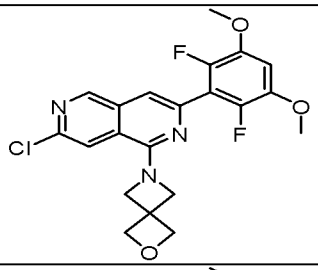
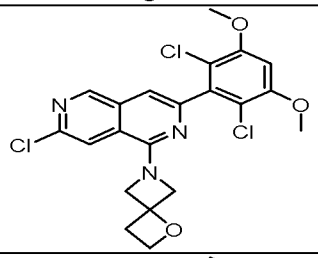
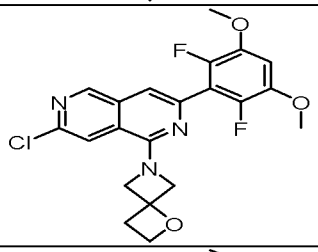
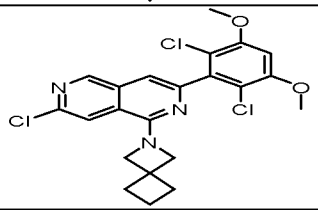
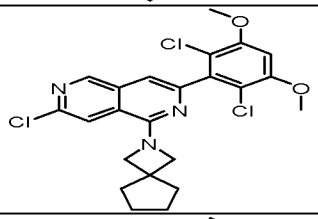
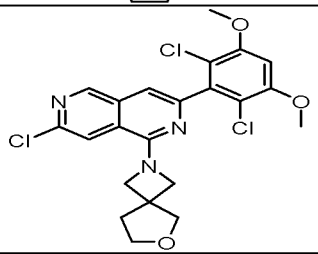
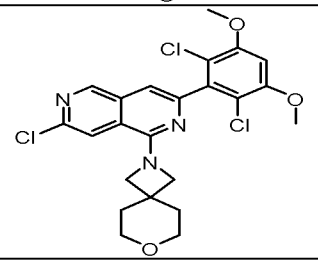
57		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-3-基)甲基)-2,6-二氮杂萘-1-胺	481
58		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-2-基)甲基)-2,6-二氮杂萘-1-胺	481
59		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(1-甲基吡咯烷-3-基)-2,6-二氮杂萘-1-胺	467
60		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基吖丁啶-3-基)甲基)-2,6-二氮杂萘-1-胺	467
61		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(1-甲基吖丁啶-3-基)-2,6-二氮杂萘-1-胺	453
62		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(1-甲基哌啶-4-基)-2,6-二氮杂萘-1-胺	481
63		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基哌啶-4-基)甲基)-2,6-二氮杂萘-1-胺	495
64		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二氟环丁基)-2,6-二氮杂萘-1-胺	474

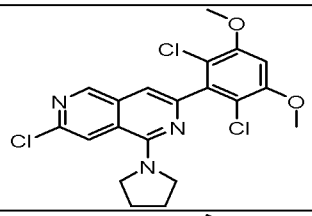
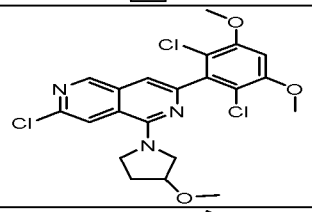
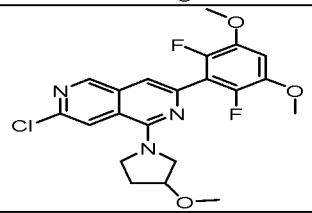
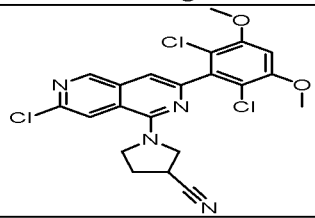
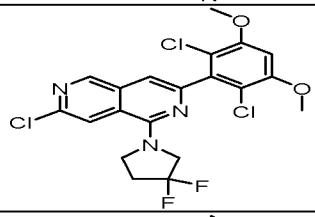
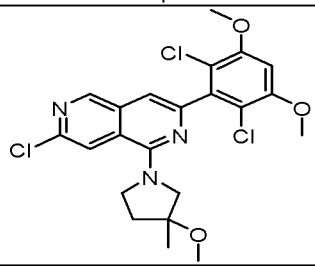
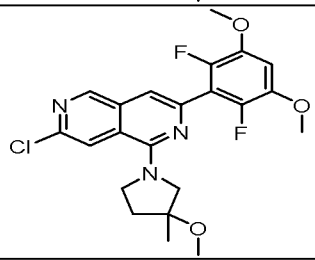
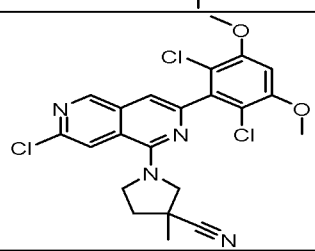
65		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二氟环戊基)-2,6-二氮杂萘-1-胺	488
66		7-氯-N-(环戊基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	466
67		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-苯乙基-2,6-二氮杂萘-1-胺	488
68		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基-1H-吡唑-4-基)甲基)-2,6-二氮杂萘-1-胺	478
69		2-(4-(((7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)氨基)甲基)-1H-吡唑-1-基)乙烷-1-醇	508
70		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)-2,6-二氮杂萘-1-胺	522
71		N-苯甲基-7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	474
72		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(4-甲基哌嗪-1-基)乙基)-2,6-二氮杂萘-1-胺	510

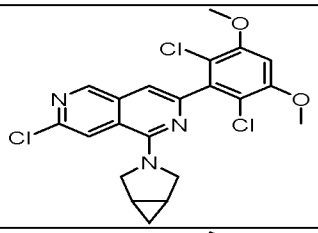
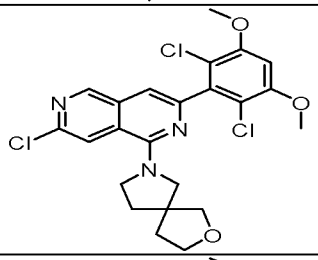
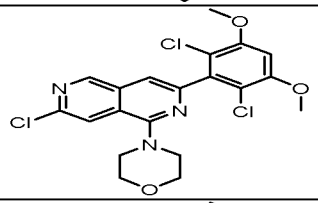
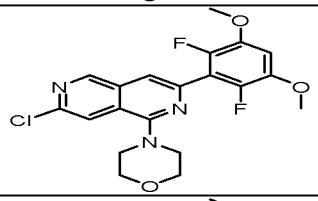
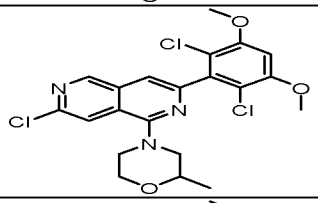
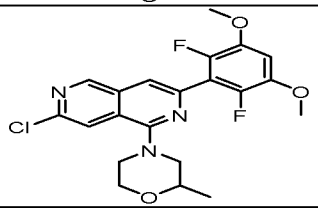
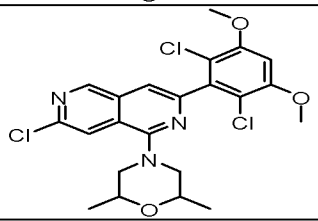
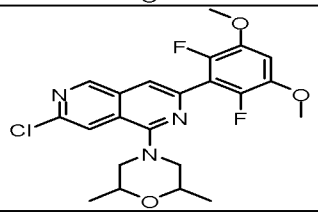
73		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-N-(2-吗啉代乙基)-2,6-二氮杂萘-1-胺	497
74		2-((7-氯-3-(2-氯-3-甲氧苯基)-2,6-二氮杂萘-1-基)氨基)乙烷-1-醇	364
75		2-((7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)氨基)乙烷-1-醇	360
76		2-((7-氯-3-(2-氟-3-甲氧苯基)-2,6-二氮杂萘-1-基)氨基)乙烷-1-醇	348
77		N^1-(7-氯-3-(2-氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-N^2,N^2-二甲基乙烷-1,2-二胺	421
78		N^1-(7-氯-3-(3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-N^2,N^2-二甲基乙烷-1,2-二胺	387
79		N^1-(7-氯-3-(2-氟-3-甲氧苯基)-2,6-二氮杂萘-1-基)-N^2,N^2-二甲基乙烷-1,2-二胺	375
80		7-氯-3-(2-氟-3,5-二甲氧苯基)-N-((四氢呋喃-2-基)甲基)-2,6-二氮杂萘-1-胺	418
81		7-氯-3-(2-氟-3-甲氧苯基)-N-((四氢呋喃-2-基)甲基)-2,6-二氮杂萘-1-胺	388

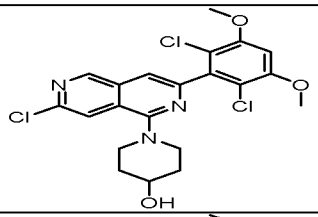
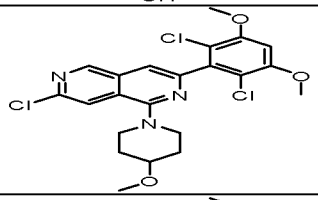
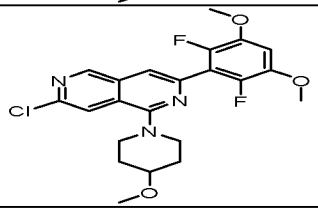
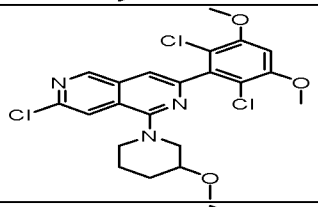
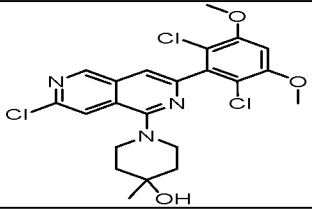
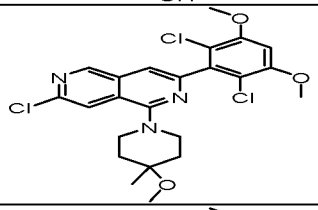
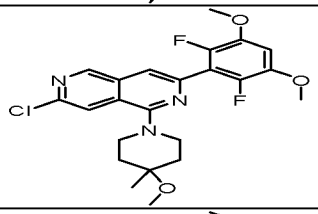
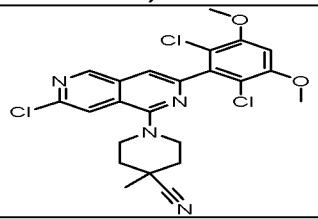
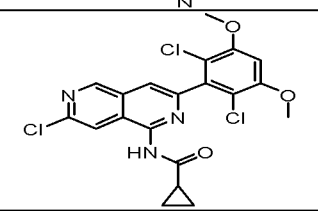
82		(S)-7-氯-N-(1-环丙基乙基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	452
83		(S)-7-氯-N-(1-环丙基乙基)-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	420
84		7-氯-N-环丙基-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	424
85		7-氯-N-环丙基-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-胺	392
86		1-(吖丁啶-1-基)-7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘	424
87		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3-甲氧基吖丁啶-1-基)-2,6-二氮杂萘	454
88		7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-1-(3-甲氧基吖丁啶-1-基)-2,6-二氮杂萘	422
89		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-N,N-二甲基吖丁啶-3-胺	467

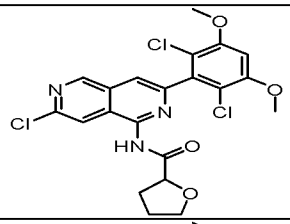
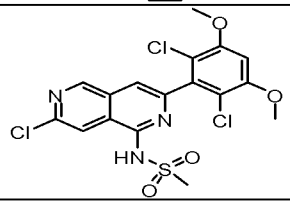
90		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3-(三氟甲基)吖丁啶-1-基)-2,6-二氮杂萘	492
91		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3,3-二甲基吖丁啶-1-基)-2,6-二氮杂萘	452
92		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3,3-二氟吖丁啶-1-基)-2,6-二氮杂萘	460
93		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-3-甲基吖丁啶-3-醇	454
94		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3-甲氧基-3-甲基吖丁啶-1-基)-2,6-二氮杂萘	468
95		7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-1-(3-甲氧基-3-甲基吖丁啶-1-基)-2,6-二氮杂萘	436
96		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-3-甲基吖丁啶-3-甲腈	463
97		6-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2-氧杂-6-氮杂螺[3.3]庚烷	466

98		6-(7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2-氧杂-6-氮杂螺[3.3]庚烷	434
99		6-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-1-氧杂-6-氮杂螺[3.3]庚烷	466
100		6-(7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-1-氧杂-6-氮杂螺[3.3]庚烷	434
101		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(2-氮杂螺[3.3]庚烷-2-基)-2,6-二氮杂萘	464
102		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(2-氮杂螺[3.4]辛烷-2-基)-2,6-二氮杂萘	478
103		2-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-6-氧杂-2-氮杂螺[3.4]辛烷	480
104		2-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-7-氧杂-2-氮杂螺[3.5]壬烷	494

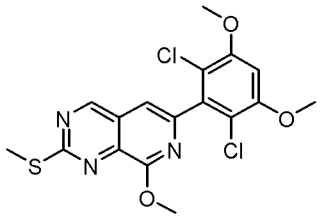
105		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(吡咯烷-1-基)-2,6-二氮杂萘	438
106		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3-甲氧基吡咯烷-1-基)-2,6-二氮杂萘	468
107		7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-1-(3-甲氧基吡咯烷-1-基)-2,6-二氮杂萘	436
108		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)吡咯烷-3-甲腈	463
109		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3,3-二氟吡咯烷-1-基)-2,6-二氮杂萘	474
110		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3-甲氧基-3-甲基吡咯烷-1-基)-2,6-二氮杂萘	482
111		7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-1-(3-甲氧基-3-甲基吡咯烷-1-基)-2,6-二氮杂萘	450
112		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-3-甲基吡咯烷-3-甲腈	477

113		1-(3-氮杂二环[3.1.0]已烷-3-基)-7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘	450
114		7-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2-氧杂-7-氮杂螺[4.4]壬烷	494
115		4-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)吗啉	454
116		4-(7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)吗啉	422
117		4-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2-甲基吗啉	468
118		4-(7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2-甲基吗啉	436
119		4-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2,6-二甲基吗啉	482
120		4-(7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-2,6-二甲基吗啉	450

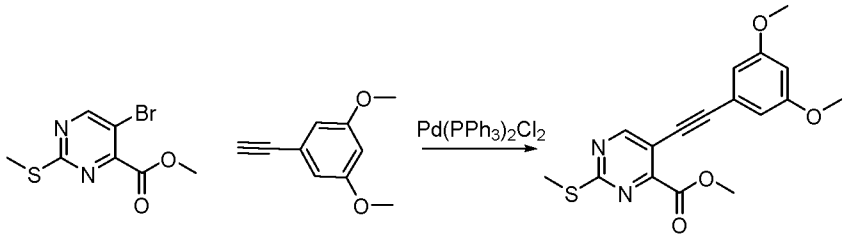
121		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)哌啶-4-醇	468
122		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(4-甲氧基哌啶-1-基)-2,6-二氮杂萘	482
123		7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-1-(4-甲氧基哌啶-1-基)-2,6-二氮杂萘	450
124		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(3-甲氧基哌啶-1-基)-2,6-二氮杂萘	482
125		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-4-甲基哌啶-4-醇	482
126		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-(4-甲氧基-4-甲基哌啶-1-基)-2,6-二氮杂萘	496
127		7-氯-3-(2,6-二氟-3,5-二甲氧苯基)-1-(4-甲氧基-4-甲基哌啶-1-基)-2,6-二氮杂萘	464
128		1-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)-4-甲基哌啶-4-甲腈	491
129		N-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)环丙甲酰胺	452

130		N-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)四氢呋喃-2-甲酰胺	482
131		N-(7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)甲磺酰胺	462

中间体 **132** **6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备**

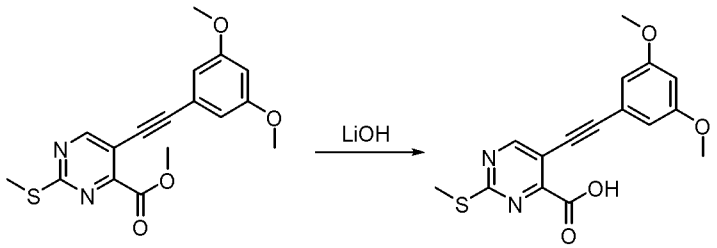


第一步：5-((3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸甲酯的制备



5-溴-2-(甲硫基)嘧啶-4-羧酸甲酯（2631 mg，10.0 mmol），1-乙炔基-3,5-二甲氧基苯（1622 mg，10.0 mmol）溶于干燥 THF（50 mL），抽换气，氮气保护。再依次加入 Et_3N（2.8 mL，20.0 mmol），$Pd(PPh_3)_2Cl_2$（702 mg，1.0 mmol），PPh_3（525 mg，2.0 mmol）以及 CuI（190 mg，1.0 mmol）。加热至 90 ℃，搅拌反应过夜。反应完全，冷却至室温，加入饱和 $NaHCO_3$ 水溶液（100 mL），EtOAc（100 mL）萃取 2 次。饱和食盐水洗涤，无水 Na_2SO_4 干燥。过滤，浓缩，硅胶柱层析（PE:EA 4:1）分离，得化合物 5-((3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸甲酯（2.5 g，收率：73%）。MS m/z (ESI): 345.2 $[M+H]^+$.

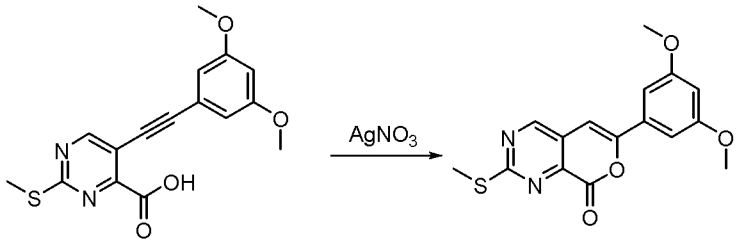
第二步：5-((3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸的制备



5-((3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸甲酯（600 mg，1.742 mmol）溶于甲醇（15 mL），加入一水合氢氧化锂（366 mg，8.711 mmol）的水溶液（5 mL）。室温搅拌过夜，反应完全。减压蒸发除去有机溶剂，水相中加入 EtOAc（30 mL），用 1 N 盐酸溶液调

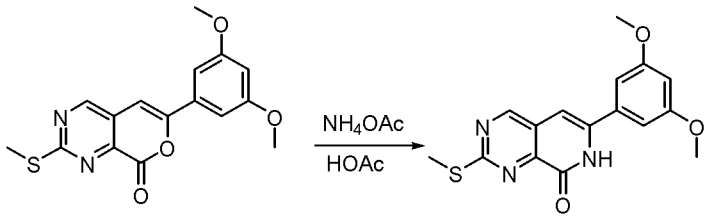
节 pH 值到 3 ~ 4。有机相分离后用饱和食盐水洗涤，无水硫酸钠干燥。过滤，浓缩，得到化合物 5-((3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸（584 mg, 定量收率）。MS m/z (ESI): 331.2 $[M+H]^+$.

第三步：6-(3,5-二甲氧苯基)-2-(甲硫基)-8H-吡喃并[3,4-d]嘧啶-8-酮的制备



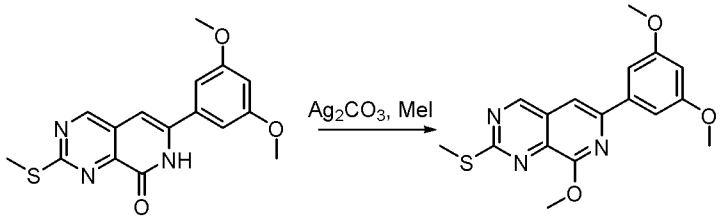
5-((3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸（584 mg, 1.768 mmol）加入丙酮（25 mL），再向此悬浊液中加入 $AgNO_3$（180 mg, 1.059 mmol）。室温搅拌反应 4 小时，并有绿色固体析出。过滤，得到化合物 6-(3,5-二甲氧苯基)-2-(甲硫基)-8H-吡喃并[3,4-d]嘧啶-8-酮（600 mg, 粗品）。MS m/z (ESI): 331.2 $[M+H]^+$.

第四步：6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8(7H)-酮的制备



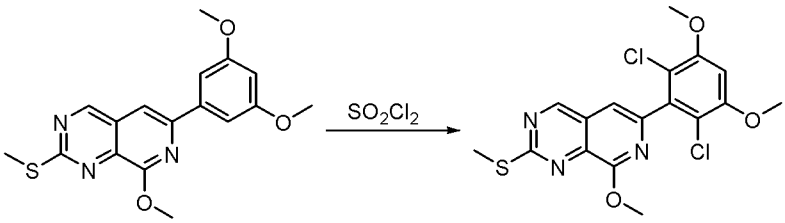
6-(3,5-二甲氧苯基)-2-(甲硫基)-8H-吡喃并[3,4-d]嘧啶-8-酮（600 mg，粗品）加入冰醋酸（50 mL），再加入醋酸铵（2.1 g，27.243 mmol)。加热至 115 ℃反应 16 小时。反应完全，冷却至室温，缓慢倒入饱和碳酸氢钠水溶液。EtOAc（100 mL）萃取。有机相分液后用饱和食盐水洗涤，无水硫酸钠干燥，浓缩后柱层析 （洗脱剂: CH_2Cl_2/MeOH 0 ~ 6%）分离，得到化合物 6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8(7H)-酮（298 mg，两步收率：50%）。MS m/z (ESI): 330.2 $[M+H]^+$.

第五步：6-(3,5-二甲氧苯基)-8-甲氧基-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备



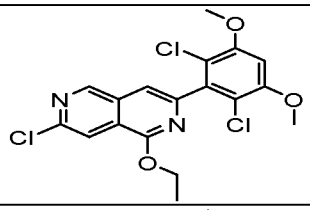
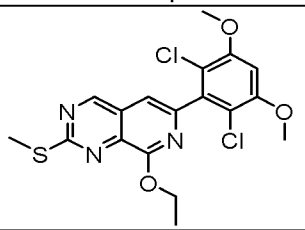
6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8(7H)-酮（100 mg，0.304 mmol）和碳酸银（109 mg，0.395 mmol）加入甲苯（3 mL），再加入碘甲烷（431 mg，3.036 mmol)。混合物在封管内加热至 100 ℃反应 3 小时。反应完全，冷却至室温，加入 EtOAc 稀释。过滤除去盐，滤液浓缩后柱层析（洗脱剂：PE/EtOAc 10 ~ 80%）分离，得到化合物 6-(3,5-二甲氧苯基)-8-甲氧基-2-(甲硫基)吡啶并[3,4-d]嘧啶（47 mg，收率：45 %)。MS m/z (ESI):344.3 $[M+H]^+$.

第六步：6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备

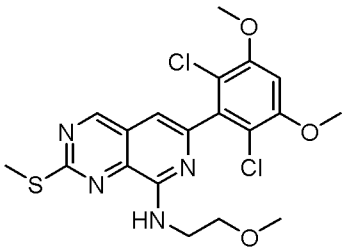


参照中间体 1 的合成方法制备。

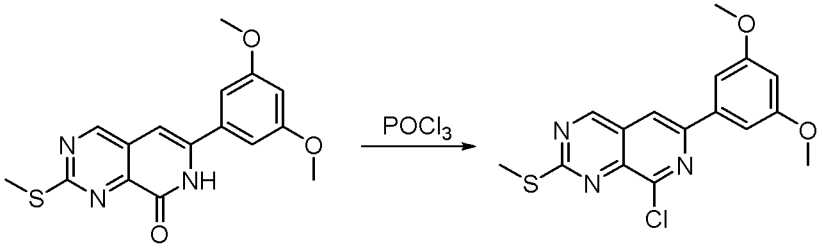
以下中间体 133-134 参照实施例 132 合成方法制备得到：

中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
133		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-乙氧基-2,6-二氮杂萘	413
134		6-(2,6-二氯-3,5-二甲氧苯基)-8-乙氧基-2-(甲硫基)吡啶并[3,4-d]嘧啶	426

中间体 135　6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-甲氧基乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺的制备



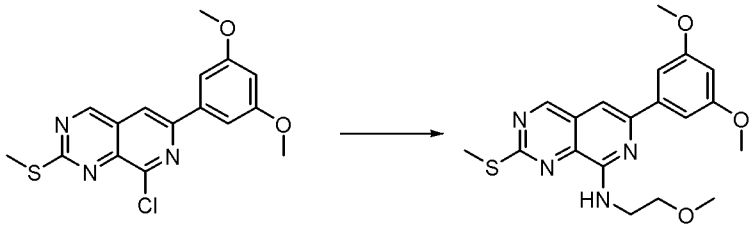
第一步：8-氯-6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备



6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8(7H)-酮（20.0 mg，0.061 mmol）和 N,N-二异丙基乙胺（78 mg，0.610 mmol）加入乙腈（2 mL），再加入 $POCl_3$（0.8 mL）。加热至 90 ℃，搅拌反应过夜。减压蒸发，除去溶剂。加入 EtOAc（10 mL）稀释，用饱和碳酸氢钠溶液洗涤。有机相分离后用饱和食盐水洗涤，无水硫酸钠干燥。过滤，浓缩后柱层析（洗脱剂：PE/EtOAc 0~40%）分离，得到化合物 8-氯-6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（6 mg，收率：28 %）。

MS m/z (ESI): 348.2 $[M+H]^+$.

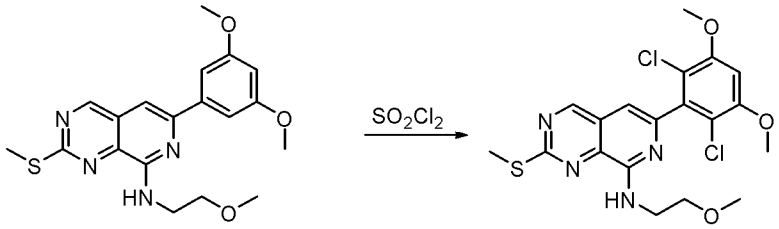
第二步：6-(3,5-二甲氧苯基)-N-(2-甲氧基乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺的制备



8-氯-6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（6 mg，0.017 mmol）和 N,N-二异丙基乙胺（6.5 mg，0.052 mmol）溶于乙腈（1.5 mL），再加入 2-甲氧基乙烷-1-胺（4 mg，0.052 mmol）。加热至 90 ℃，搅拌反应过夜。反应完全，冷却至室温，加入 EtOAc（5 mL）稀释，用饱和食盐水洗涤，无水硫酸钠干燥。过滤，浓缩，柱层析（洗脱剂：PE/EtOAc 0~50%）分离，得到化合物 6-(3,5-二甲氧苯基)-N-(2-甲氧基乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺（4 mg，收率：61 %）。

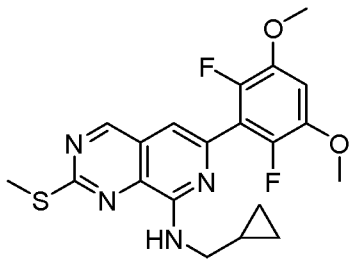
MS m/z (ESI): 387.4 $[M+H]^+$.

第三步：6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-甲氧基乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺的制备

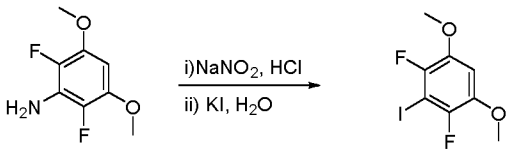


参照中间体 1 的合成方法制备。

中间体 139 4-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)吗啉的制备



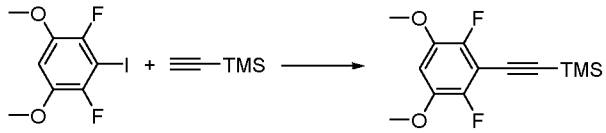
第一步：2,4-二氟-3-碘-1,5-二甲氧基苯的制备



将化合物 2,6-二氟-3,5-二甲氧基苯胺（27.0 g，143 mmol）加入 6.0 M 盐酸溶液（240 mL）中，冰水浴冷却下缓慢滴加 $NaNO_2$ 水溶液（10.35 g，150 mmol，30 mL 水）。25 分钟滴加完，继续反应 15 分钟，产生桔红色悬浊液，将其加入 KI 水溶液（94.9 g，570 mmol，150 mL 水）。升至室温，搅拌反应 30 分钟，析出固体。过滤，水洗，得粗产品。将粗产

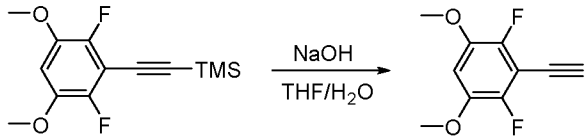
品加入 MeOH（60 mL），室温搅拌 30 分钟。过滤，干燥，得 2,4-二氟-3-碘-1,5-二甲氧基苯（29.3 g，收率：68%）。

第二步：（2,6-二氟-3,5-二甲氧基苯乙炔）基三甲基硅烷的制备



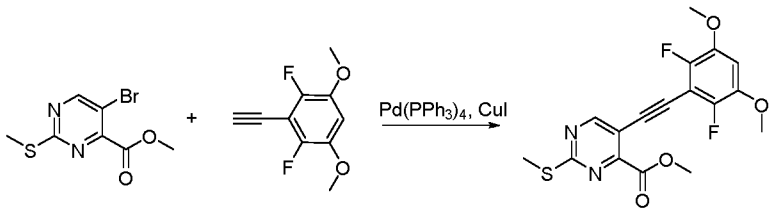
2,4-二氟-3-碘-1,5-二甲氧基苯（25.8 g，86.0 mmol）、三甲基硅基乙炔（36.5 mL，258 mmol）CuI（817 mg，4.3 mmol）以及三乙胺（35.8 mL，258 mmol）加入 DMF（250 mL）。抽换气，氮气保护，然后加入 $Pd(PPh_3)_2Cl_2$（3.15 g，4.3 mmol）。加热 50 度，反应 2 小时。反应完全，加入饱和 NH_4Cl 水溶液淬灭，再入二氯甲烷萃取 3 次。合并有机相，Na_2SO_4 干燥。过滤，浓缩，得粗产品（27.0 g），直接用于下步反应。

第三步：3-乙炔基-2,4-二氟-1,5-二甲氧基苯的制备



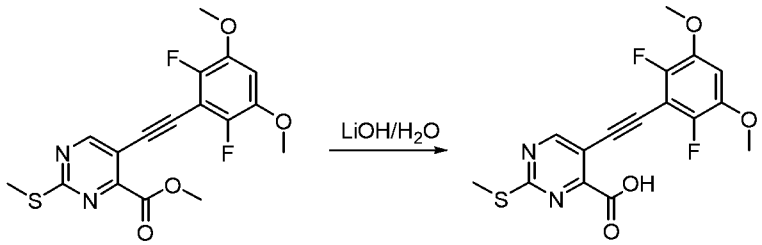
（2,6-二氟-3,5-二甲氧基苯乙炔）基三甲基硅烷（27.0 g，粗品）加入 THF/MeOH（200/200 mL），再加入 NaOH 水溶液（8.6 mL，8.6 mmol，1.0 N）。室温搅拌 15 分钟。反应完全，加入饱和 NH_4Cl 水溶液淬灭，二氯甲烷萃取 3 次。合并有机相，无水 Na_2SO_4 干燥。过滤，浓缩，粗品加入 MeOH（50 mL）打浆，室温搅拌 30 分钟。过滤，得到目标产物（15.0 g，2 步收率：88%）。

第四步：5-((2,6-二氟-3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸甲酯的制备



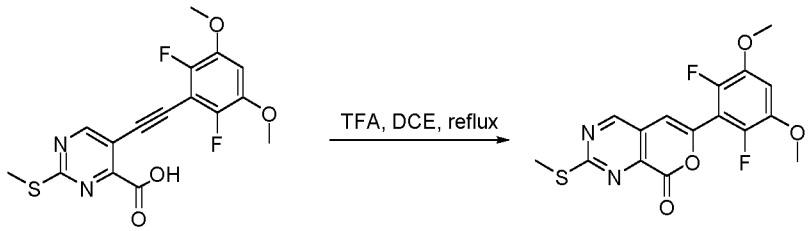
3-乙炔基-2,4-二氟-1,5-二甲氧基苯（10.0 g，50.5 mmol）和 5-溴-2-甲硫基-嘧啶-4-羧酸甲酯（13.0 g，49.5 mmol）溶于 DMF（100 mL），再加入 CuI（479 mg，2.52 mmol）、$Pd(PPh_3)_4$（2.91 g，2.52 mmol）以及 Et_3N（35.0 mL，252.5 mmol），氮气保护。加热 100 度，反应 1.5 小时。反应完全，冷却至室温，加入饱和 NH_4Cl 水溶液淬灭，二氯甲烷萃取 3 次。合并有机相，无水 Na_2SO_4 干燥，过滤，浓缩。粗品经硅胶柱层析分离（PE : EA : DCM = 10 : 2 : 1），纯化得目标产物（15.4 g，收率：82%）。^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 6.69 (t, J = 8.0 Hz, 1H), 4.03 (s, 3H), 3.90 (s, 6H), 2.63 (s, 3H).

第五步：5-((2,6-二氟-3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸的制备



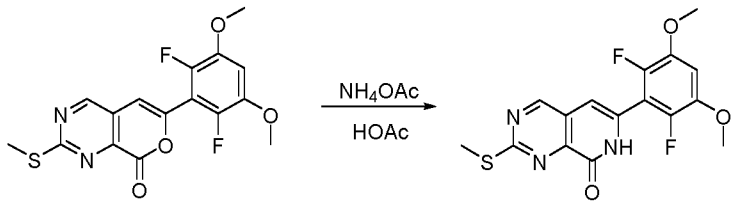
5-((2,6-二氟-3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸甲酯（30.0 g，78.9 mmol）溶于 THF（300 mL），再加入 $LiOH/H_2O$（236.8 mL，236.8 mmol，1 M）。室温搅拌反应 2 小时。反应完全，浓缩除去 THF，再用稀盐酸酸化至 pH 约为 3，析出固体。过滤，水洗，干燥，得目标产物（28.5 g，收率：99%）。

第六步：6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)-8H-吡喃并[3,4-d]嘧啶-8-酮的制备



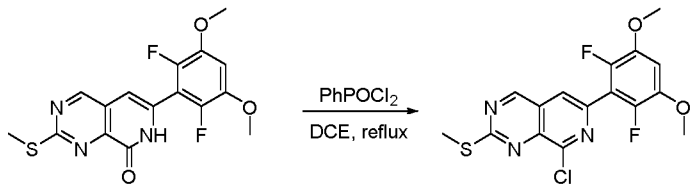
5-((2,6-二氟-3,5-二甲氧苯基)乙炔基)-2-(甲硫基)嘧啶-4-羧酸（2.5 g，6.83 mmol）溶于 DCE（50 mL），再加入 TFA（0.5 mL）。加热回流，反应过夜。反应完全，浓缩，再加入 MeOH（50 mL）打浆，室温搅拌 30 分钟。过滤，固体再用 MeOH（10 mL）洗涤，得目标产物（2.0 g，收率：80%）。^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.22 (t, J = 8.4 Hz, 1H), 7.17 (s, 1H), 3.93 (s, 6H), 2.63 (s, 3H).

第七步：6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8(7H)-酮的制备



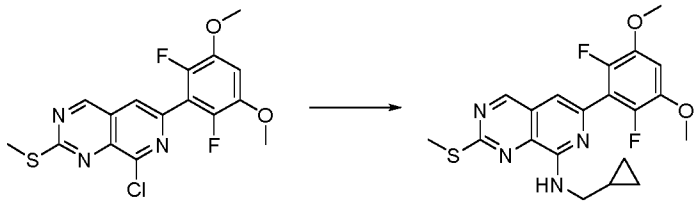
参照中间体 132 第四步操作。

第八步：8-氯-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备



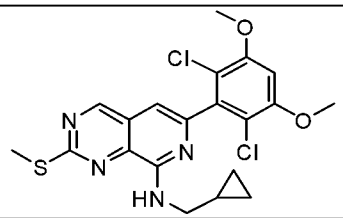
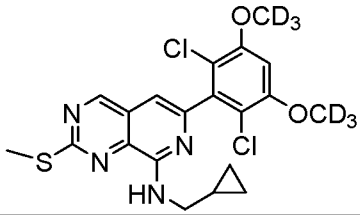
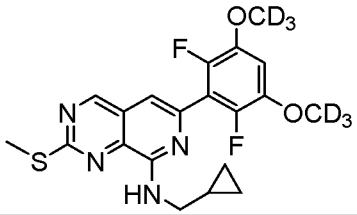
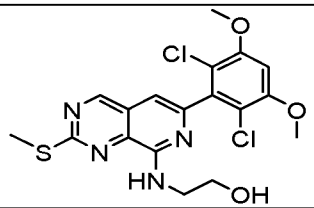
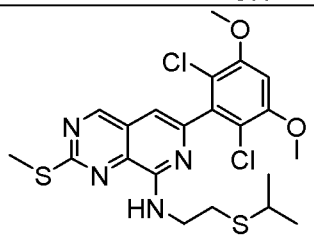
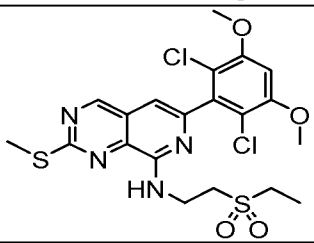
6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8(7H)-酮(1 g, 2.74 mmol)溶于 DCE（80mL），加热至 90 度，然后加入苯膦酰二氯（3.0 mL，21.92 mmol），加热搅拌 16 小时，冷却，在冰浴下调节 pH 至中性，DCM 提取，硅胶柱层析分离（MeOH/DCM 1/20），纯化得到化合物 8-氯-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（930mg，产率 88%）。MS m/z (ESI): 384 $[M+H]^+$。

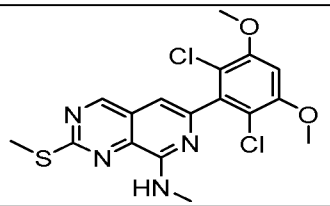
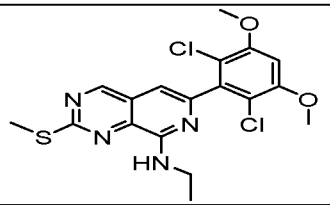
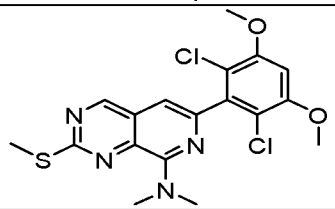
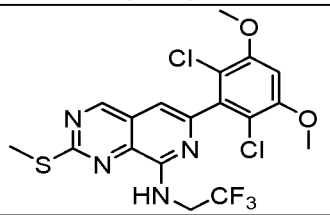
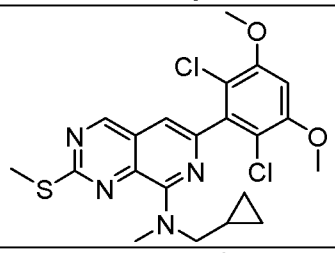
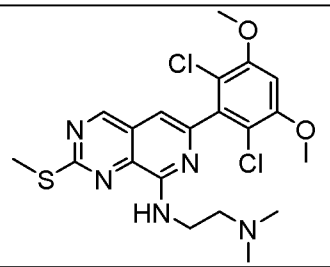
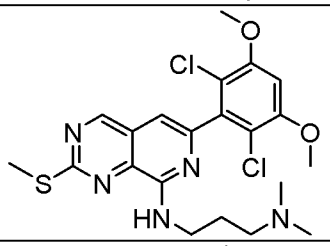
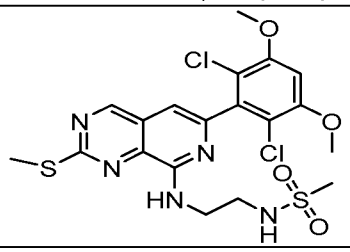
第九步：N-(环丙基甲基)-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺的制备

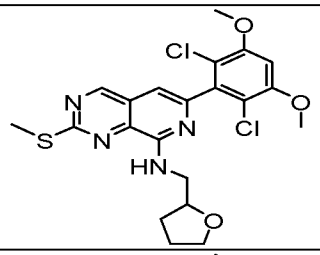
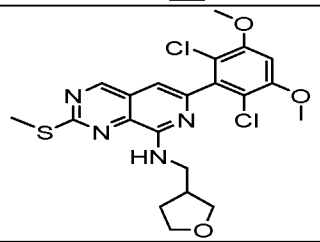
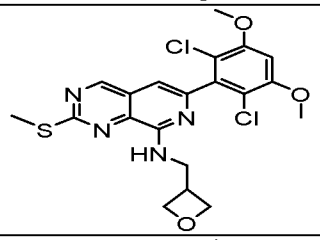
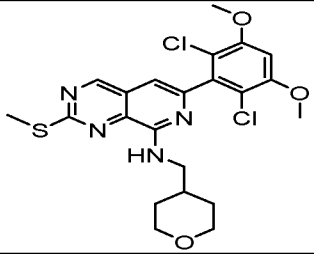
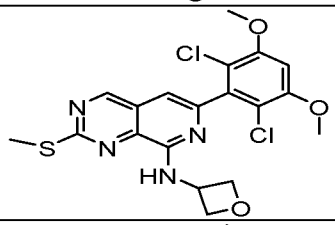
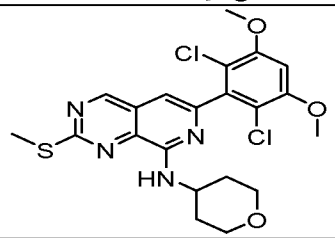
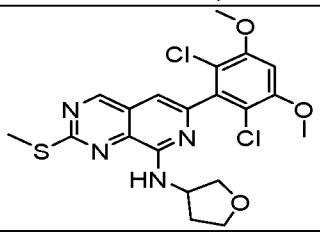


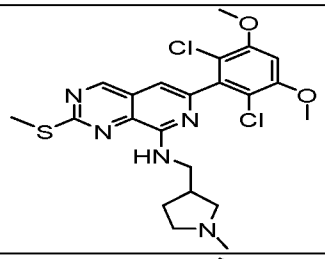
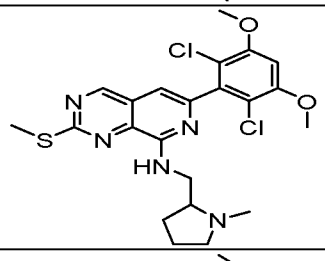
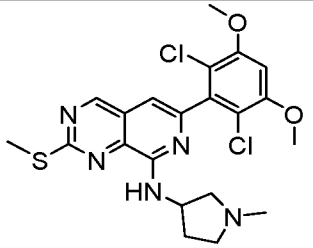
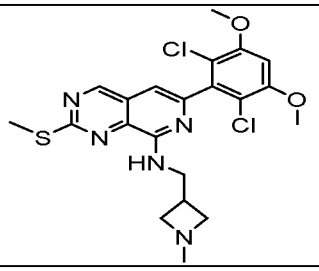
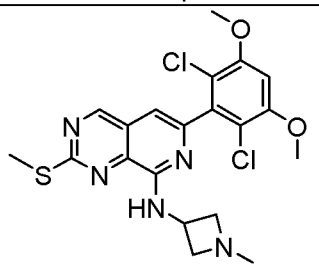
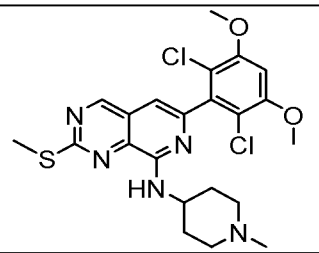
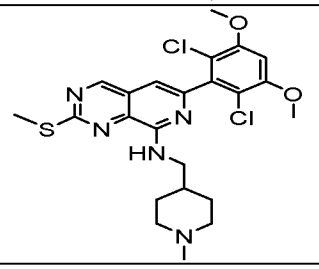
参照中间体 135 第二步操作。

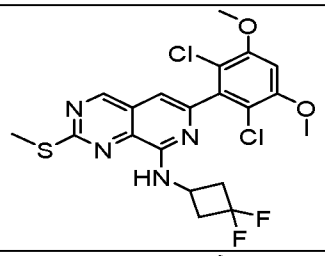
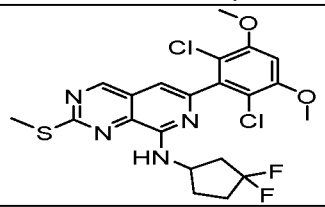
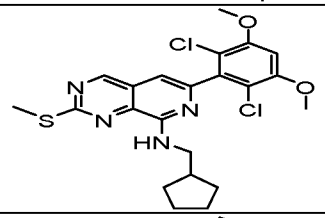
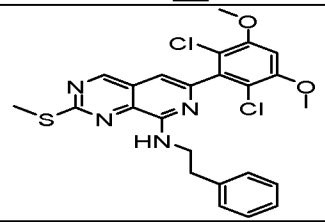
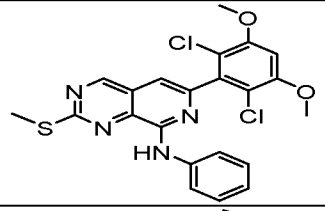
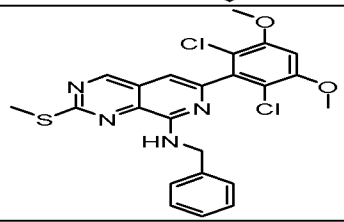
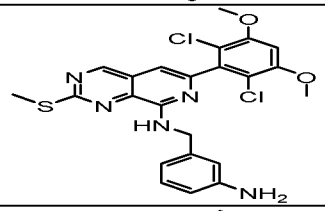
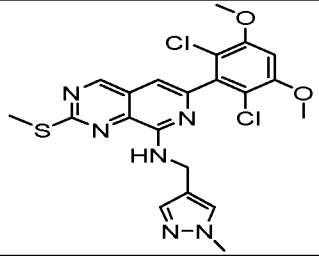
以下中间体 136-330 参照中间体 135 或 139 合成方法制备得到：

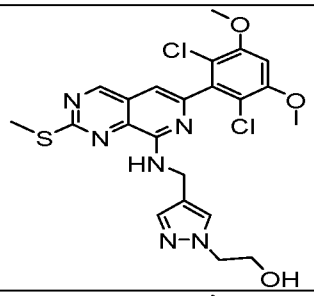
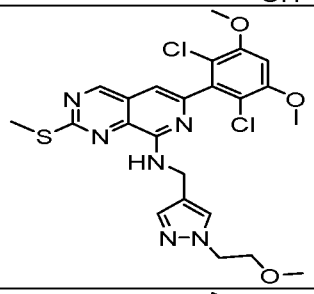
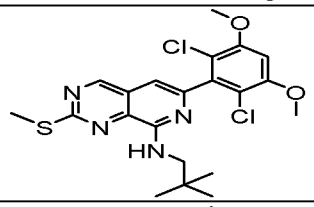
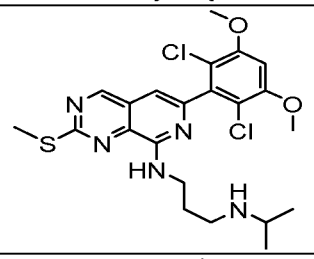
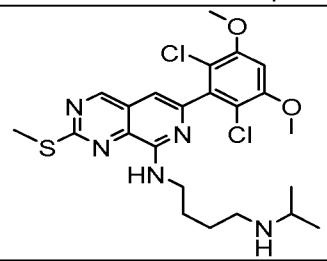
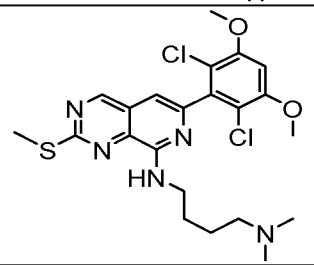
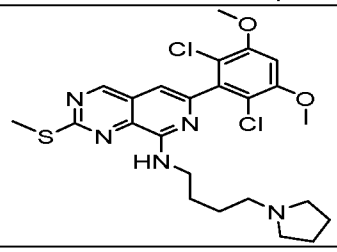
中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
136		N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	451
137		N-(环丙基甲基)-6-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	457
138		N-(环丙基甲基)-6-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	425
140		2-((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)氨基)乙烷-1-醇	441
141		6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(异丙基硫代)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	499
142		6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(乙基磺酰)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	518

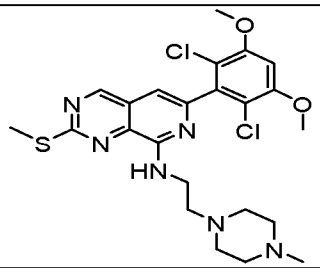
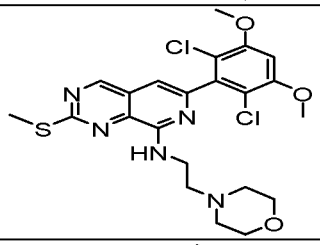
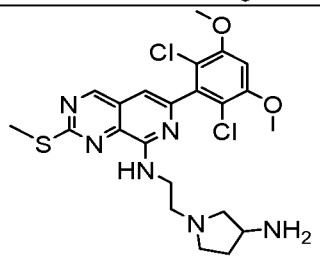
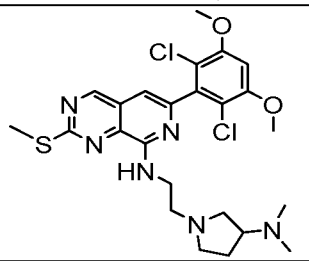
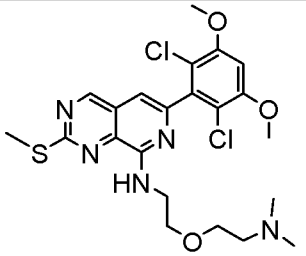
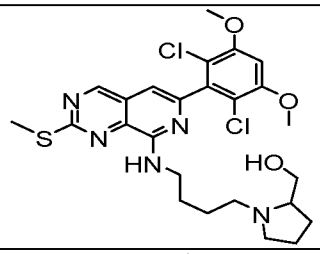
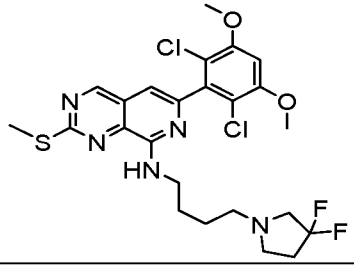
143		6-(2,6-二氯-3,5-二甲氧苯基)-N-甲基-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	411
144		6-(2,6-二氯-3,5-二甲氧苯基)-N-乙基-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	425
145		6-(2,6-二氯-3,5-二甲氧苯基)-N,N-二甲基-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	425
146		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(2,2,2-三氟乙基)吡啶并[3,4-d]嘧啶-8-胺	479
147		N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-N-甲基-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	465
148		N^1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-N^2,N^2-二甲基乙烷-1,2-二胺	468
149		N^1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-N^3,N^3-二甲基丙烷-1,3-二胺	482
150		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)氨基)乙基)甲磺酰胺	518

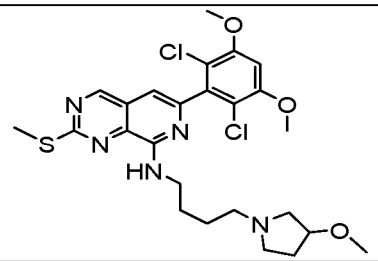
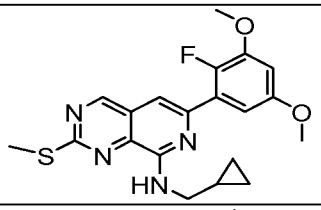
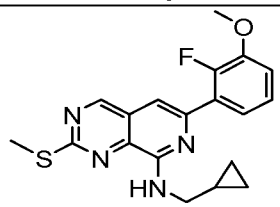
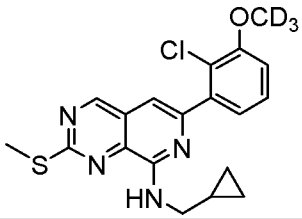
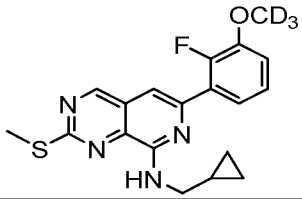
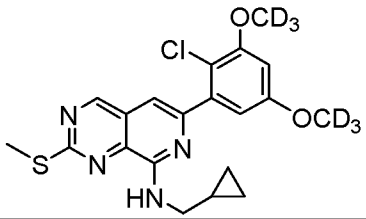
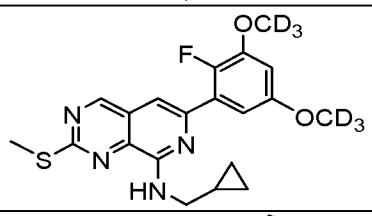
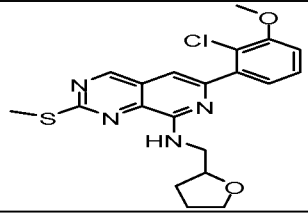
151		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-((四氢呋喃-2-基)甲基)吡啶并[3,4-d]嘧啶-8-胺	481
152		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-((四氢呋喃-3-基)甲基)吡啶并[3,4-d]嘧啶-8-胺	481
153		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(噁丁环-3-基甲基)吡啶并[3,4-d]嘧啶-8-胺	467
154		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-((四氢-2H-吡喃-4-基)甲基)吡啶并[3,4-d]嘧啶-8-胺	495
155		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(噁丁环-3-基)吡啶并[3,4-d]嘧啶-8-胺	453
156		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-8-胺	481
157		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(四氢呋喃-3-基)吡啶并[3,4-d]嘧啶-8-胺	467

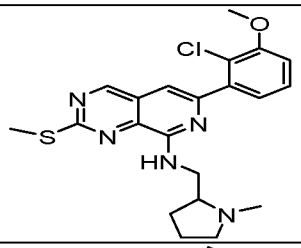
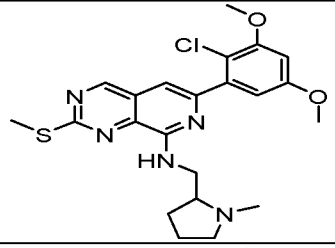
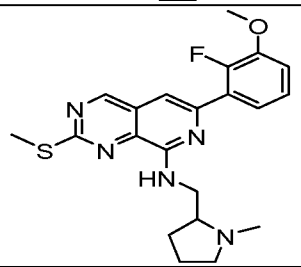
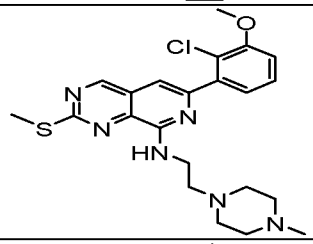
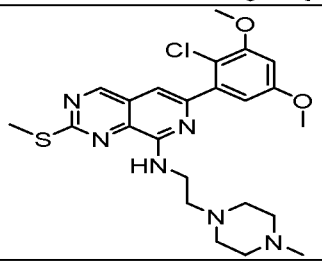
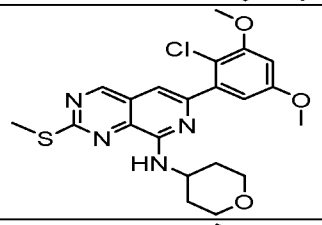
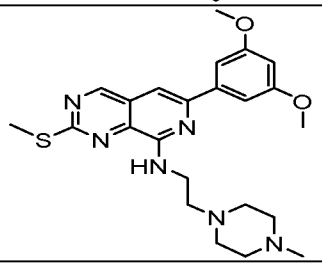
158		6-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-3-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	494
159		6-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-2-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	494
160		6-(2,6-二氯-3,5-二甲氧苯基)-N-(1-甲基吡咯烷-3-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	480
161		6-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基吖丁啶-3-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	480
162		6-(2,6-二氯-3,5-二甲氧苯基)-N-(1-甲基吖丁啶-3-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	466
163		6-(2,6-二氯-3,5-二甲氧苯基)-N-(1-甲基哌啶-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	494
164		6-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基哌啶-4-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	508

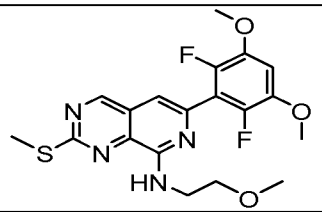
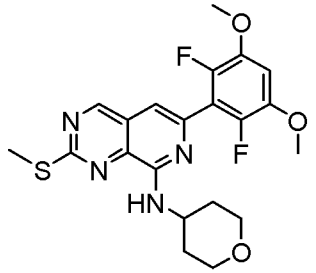
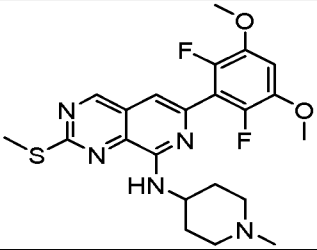
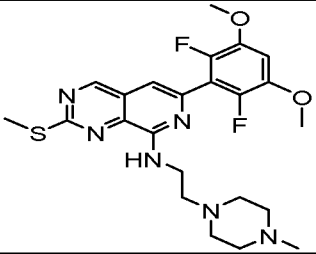
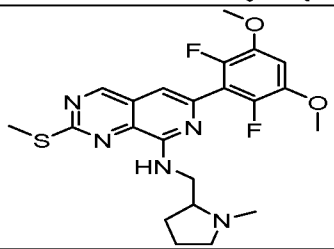
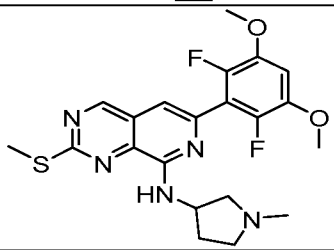
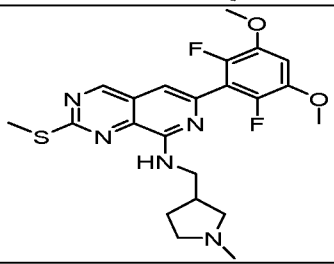
165		6-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二氟环丁基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	487
166		6-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二氟环戊基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	501
167		N-(环戊基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	479
168		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-苯乙基吡啶并[3,4-d]嘧啶-8-胺	501
169		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-苯基吡啶并[3,4-d]嘧啶-8-胺	473
170		N-苯甲基-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	487
171		N-(3-氨基苯甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	502
172		6-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基-1H-吡唑-4-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	491

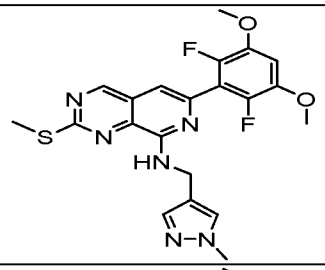
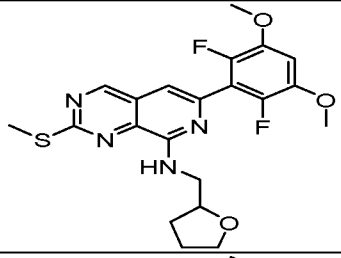
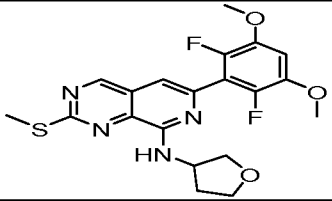
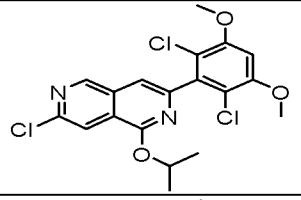
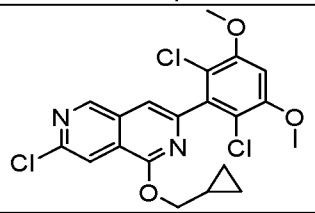
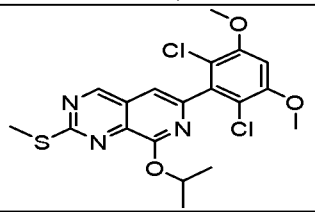
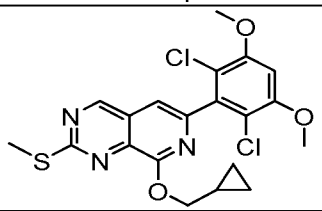
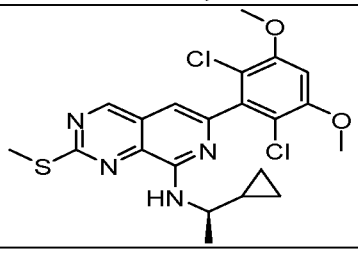
173		2-(4-(((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)氨基)甲基)-1H-吡唑-1-基)乙烷-1-醇	521
174		6-(2,6-二氯-3,5-二甲氧苯基)-N-((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	535
175		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-新戊基吡啶并[3,4-d]嘧啶-8-胺	467
176		N^1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-N^3-异丙基丙烷-1,3-二胺	496
177		N^1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-N^4-异丙基丁烷-1,4-二胺	510
178		N^1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-N^4,N^4-二甲基丁烷-1,4-二胺	496
179		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(4-(吡咯烷-1-基)丁基)吡啶并[3,4-d]嘧啶-8-胺	522

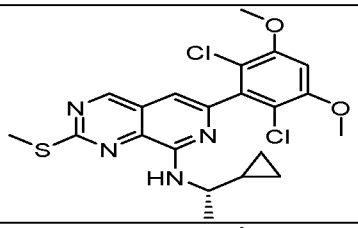
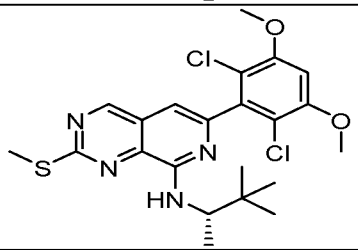
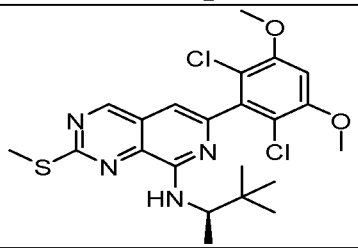
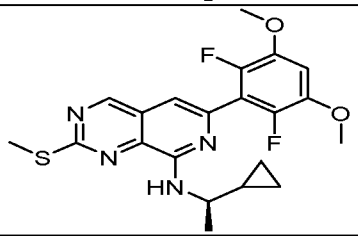
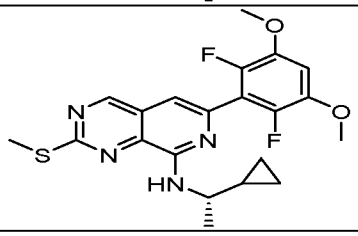
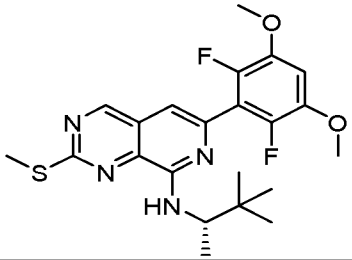
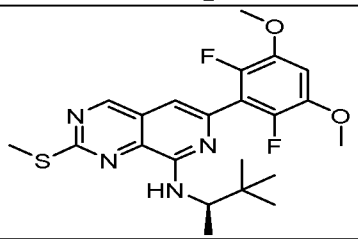
180		6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(4-甲基哌嗪-1-基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	523
181		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(2-吗啉代乙基)吡啶并[3,4-d]嘧啶-8-胺	510
182		N-(2-(3-氨基吡咯烷-1-基)乙基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	509
183		6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(3-(二甲氨基)吡咯烷-1-基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	537
184		6-(2,6-二氯-3,5-二甲氧苯基)-N-(2-(2-(二甲氨基)乙氧基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	512
185		(1-(4-((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)氨基)丁基)吡咯烷-2-基)甲醇	552
186		6-(2,6-二氯-3,5-二甲氧苯基)-N-(4-(3,3-二氟吡咯烷-1-基)丁基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	558

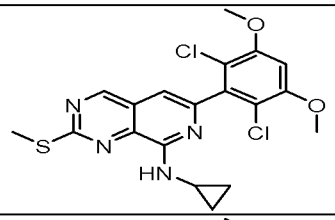
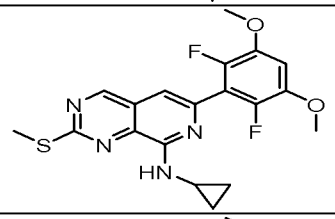
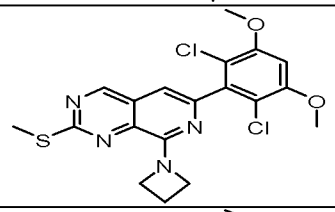
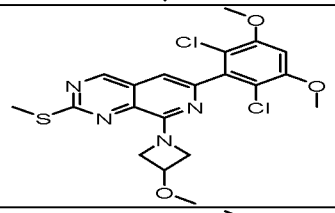
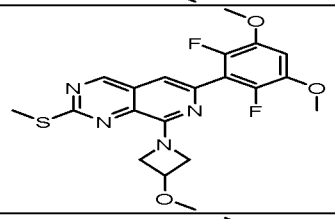
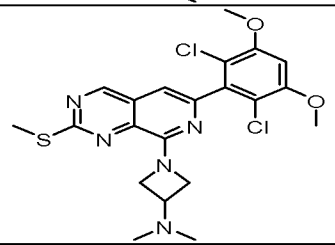
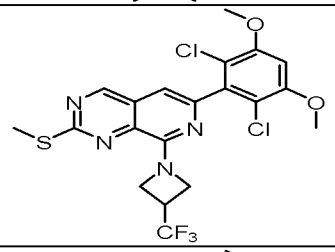
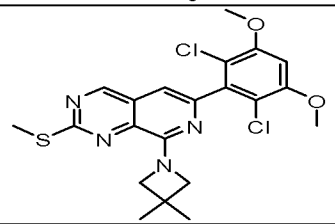
187		6-(2,6-二氯-3,5-二甲氧苯基)-N-(4-(3-甲氧基吡咯烷-1-基)丁基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	552
188		N-(环丙基甲基)-6-(2-氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	401
189		N-(环丙基甲基)-6-(2-氟-3-甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	371
190		6-(2-氯-3-(甲氧基-d_3)苯基)-N-(环丙基甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	390
191		N-(环丙基甲基)-6-(2-氟-3-(甲氧基-d_3)苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	374
192		6-(2-氯-3,5-二(甲氧基-d_3)苯基)-N-(环丙基甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	423
193		N-(环丙基甲基)-6-(2-氟-3,5-二(甲氧基-d_3)苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	407
194		6-(2-氯-3-甲氧苯基)-2-(甲硫基)-N-((四氢呋喃-2-基)甲基)吡啶并[3,4-d]嘧啶-8-胺	417

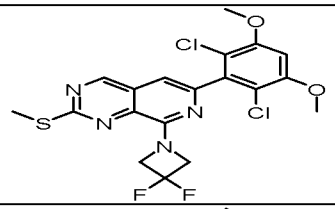
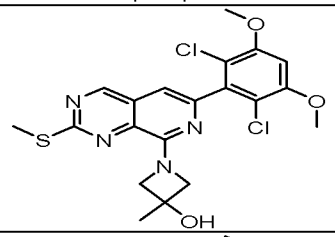
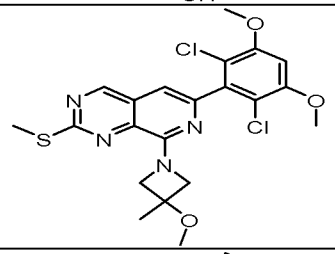
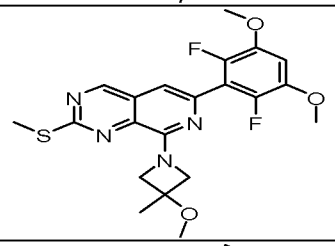
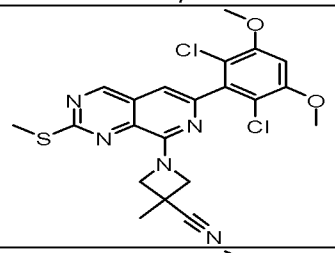
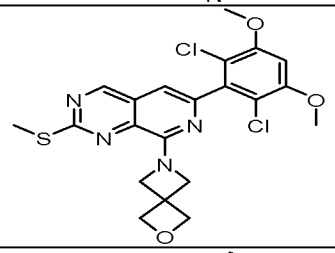
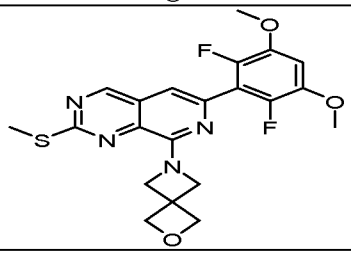
195		6-(2-氯-3-甲氧苯基)-N-((1-甲基吡咯烷-2-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	430
196		6-(2-氯-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-2-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	460
197		6-(2-氟-3-甲氧苯基)-N-((1-甲基吡咯烷-2-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	414
198		6-(2-氯-3-甲氧苯基)-N-(2-(4-甲基哌嗪-1-基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	459
199		6-(2-氯-3,5-二甲氧苯基)-N-(2-(4-甲基哌嗪-1-基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	489
200		6-(2-氯-3,5-二甲氧苯基)-2-(甲硫基)-N-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-8-胺	447
201		6-(3,5-二甲氧苯基)-N-(2-(4-甲基哌嗪-1-基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	455

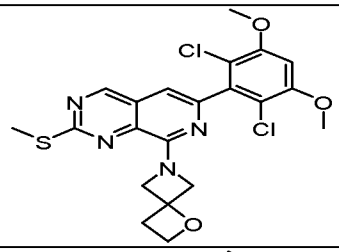
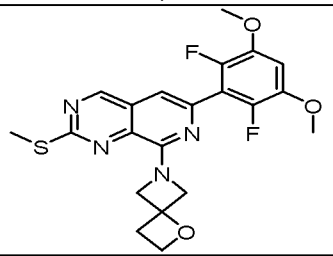
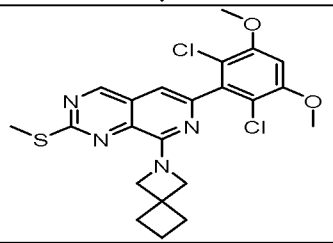
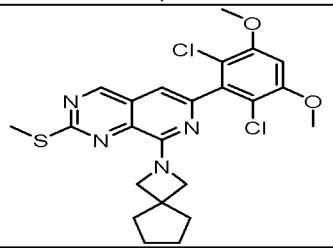
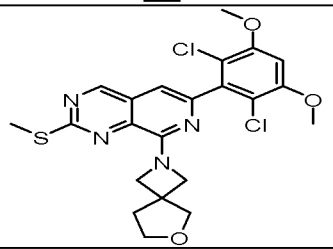
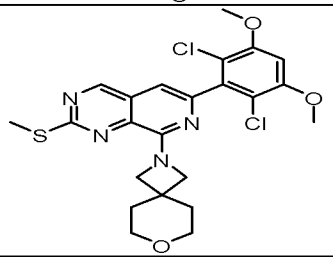
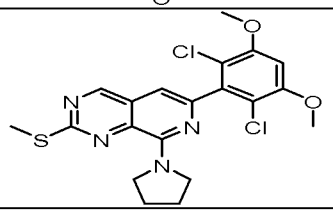
202		6-(2,6-二氟-3,5-二甲氧苯基)-N-(2-甲氧基乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	423
203		6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)-N-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-8-胺	449
204		6-(2,6-二氟-3,5-二甲氧苯基)-N-(1-甲基哌啶-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	462
205		6-(2,6-二氟-3,5-二甲氧苯基)-N-(2-(4-甲基哌嗪-1-基)乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	491
206		6-(2,6-二氟-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-2-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	462
207		6-(2,6-二氟-3,5-二甲氧苯基)-N-(1-甲基吡咯烷-3-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	448
208		6-(2,6-二氟-3,5-二甲氧苯基)-N-((1-甲基吡咯烷-3-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	462

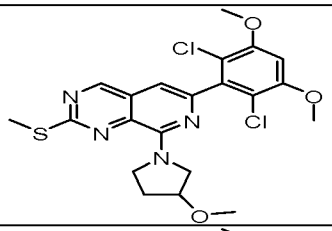
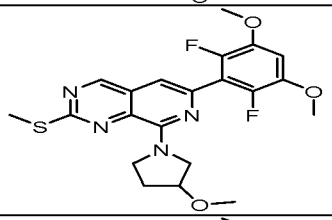
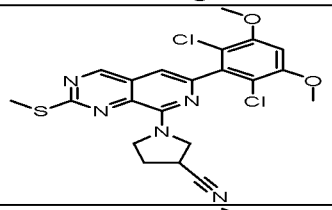
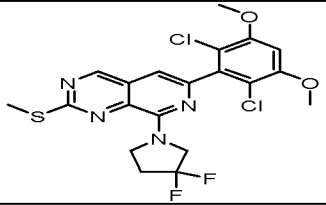
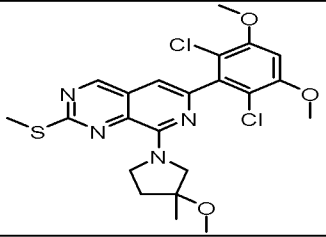
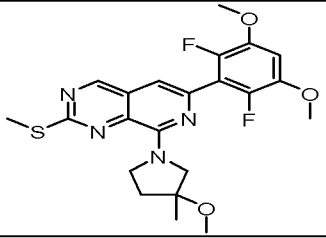
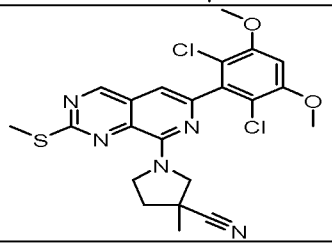
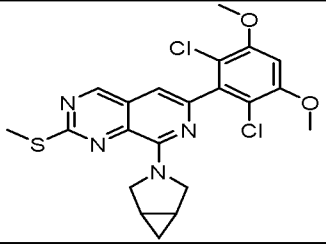
209		6-(2,6-二氟-3,5-二甲氧苯基)-N-((1-甲基-1H-吡唑-4-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	459
210		6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)-N-((四氢呋喃-2-基)甲基)吡啶并[3,4-d]嘧啶-8-胺	449
211		6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)-N-(四氢呋喃-3-基)吡啶并[3,4-d]嘧啶-8-胺	435
212		7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-异丙氧基-2,6-二氮杂萘	427
213		7-氯-1-(环丙基甲氧基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘	439
214		6-(2,6-二氯-3,5-二甲氧苯基)-8-异丙氧基-2-(甲硫基)吡啶并[3,4-d]嘧啶	440
215		8-(环丙基甲氧基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	452
216		(R)-N-(1-环丙基乙基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	465

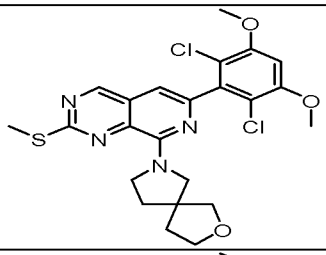
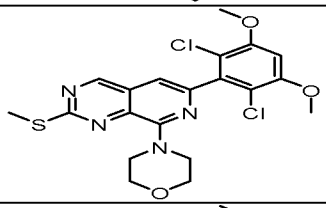
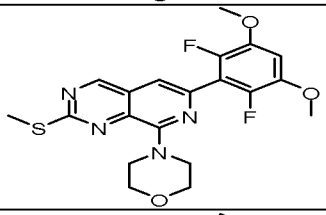
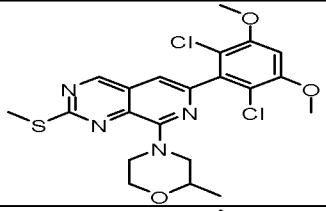
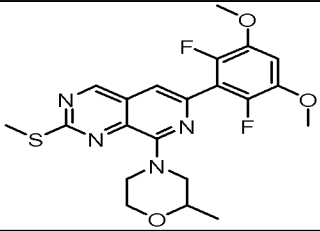
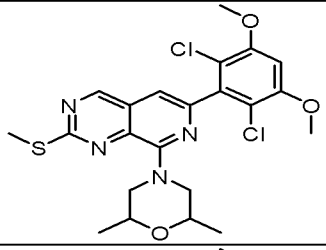
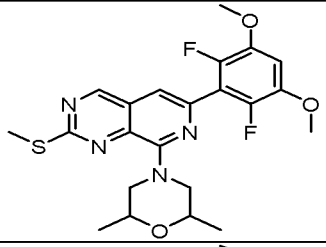
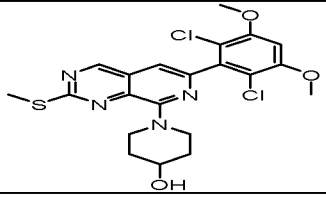
217		(S)-N-(1-环丙基乙基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	465
218		(S)-6-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二甲基丁烷-2-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	481
219		(R)-6-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二甲基丁烷-2-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	481
220		(R)-N-(1-环丙基乙基)-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	433
221		(S)-N-(1-环丙基乙基)-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	433
222		(S)-6-(2,6-二氟-3,5-二甲氧苯基)-N-(3,3-二甲基丁烷-2-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	449
223		(R)-6-(2,6-二氟-3,5-二甲氧苯基)-N-(3,3-二甲基丁烷-2-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	449

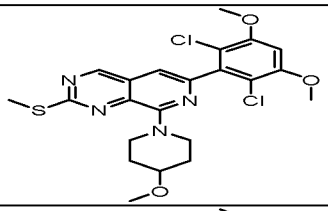
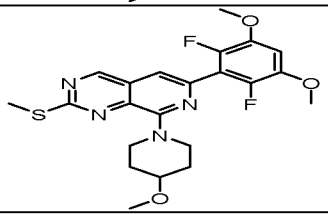
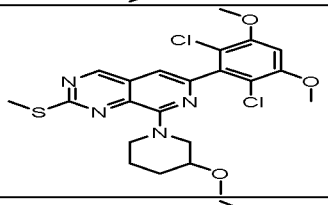
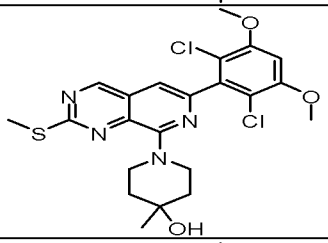
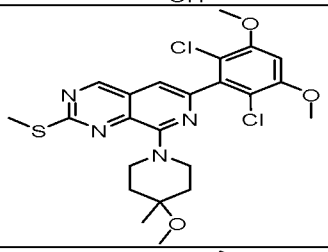
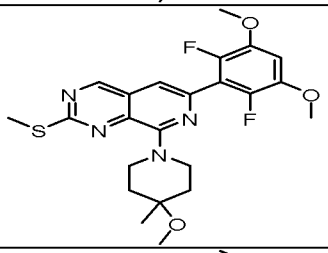
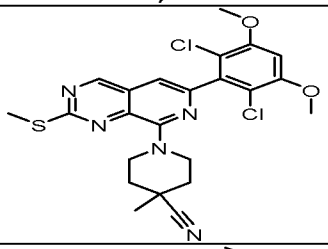
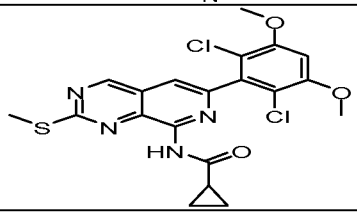
224		N-环丙基-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	437
225		N-环丙基-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺	405
226		8-(吖丁啶-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	437
227		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	467
228		6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	435
229		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-N,N-二甲基吖丁啶-3-胺	480
230		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(3-(三氟甲基)吖丁啶-1-基)吡啶并[3,4-d]嘧啶	505
231		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二甲基吖丁啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	465

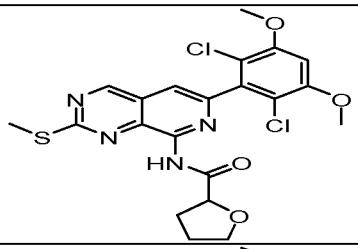
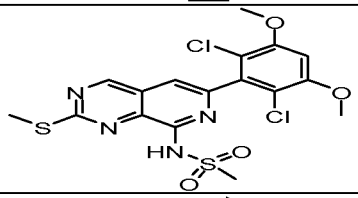
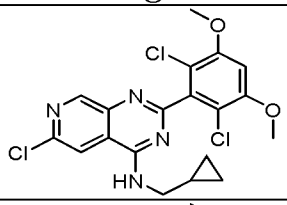
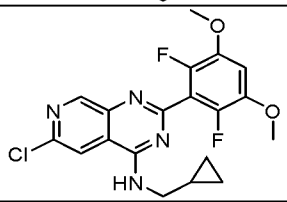
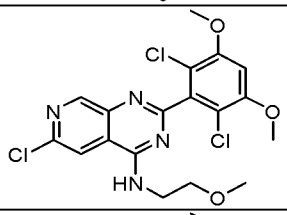
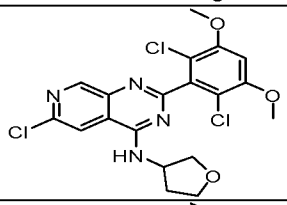
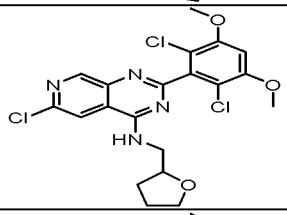
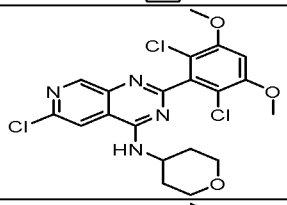
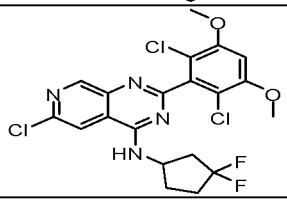
232		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二氟吖丁啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	473
233		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-3-甲基吖丁啶-3-醇	467
234		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吖丁啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	481
235		6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吖丁啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	449
236		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-3-甲基吖丁啶-3-甲腈	476
237		6-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2-氧杂-6-氮杂螺[3.3]庚烷	479
238		6-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2-氧杂-6-氮杂螺[3.3]庚烷	447

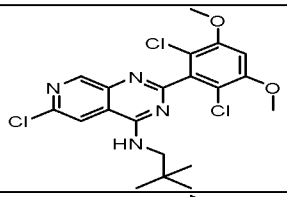
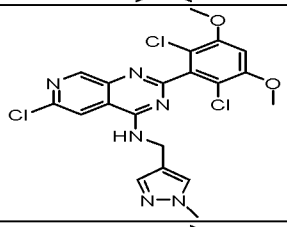
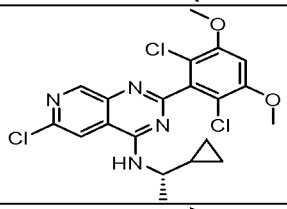
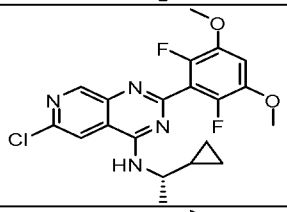
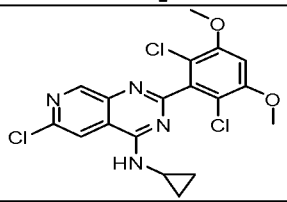
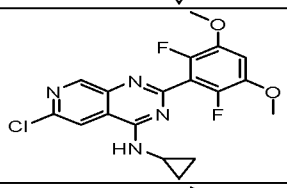
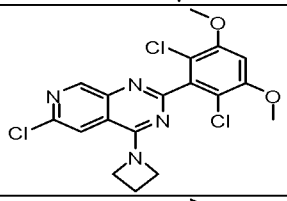
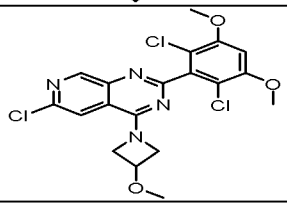
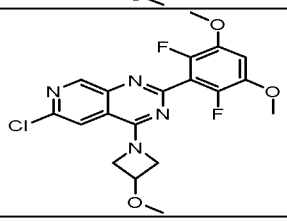
239		6-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-1-氧杂-6-氮杂螺[3.3]庚烷	479
240		6-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-1-氧杂-6-氮杂螺[3.3]庚烷	447
241		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(2-氮杂螺[3.3]庚烷-2-基)吡啶并[3,4-d]嘧啶	477
242		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶	491
243		2-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-6-氧杂-2-氮杂螺[3.4]辛烷	493
244		2-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-7-氧杂-2-氮杂螺[3.5]壬烷	507
245		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(吡咯烷-1-基)吡啶并[3,4-d]嘧啶	451

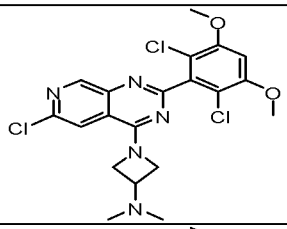
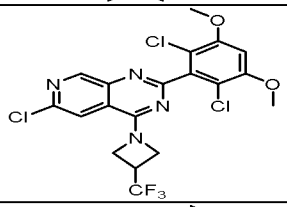
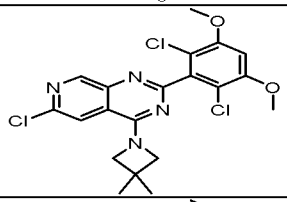
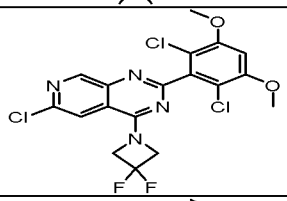
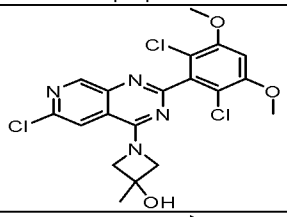
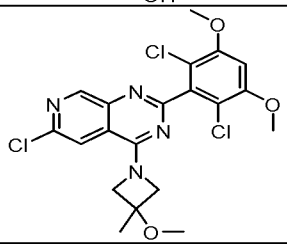
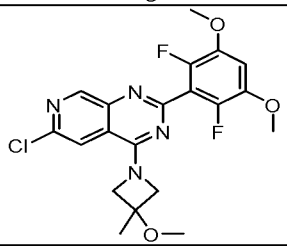
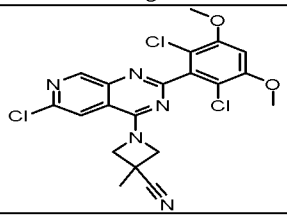
246		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基吡咯烷-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	481
247		6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吡咯烷-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	449
248		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)吡咯烷-3-甲腈	476
249		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二氟吡咯烷-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	487
250		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吡咯烷-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	495
251		6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吡咯烷-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	463
252		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-3-甲基吡咯烷-3-甲腈	490
253		8-(3-氮杂二环[3.1.0]己烷-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	463

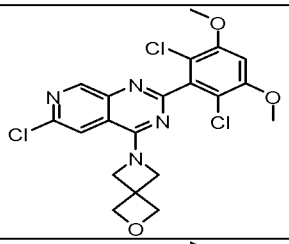
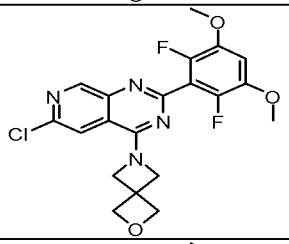
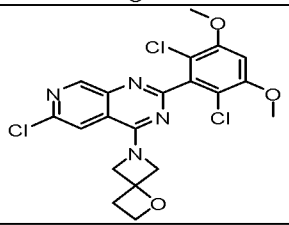
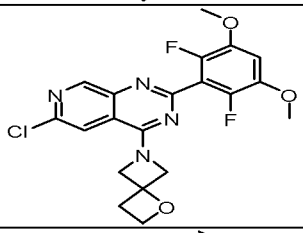
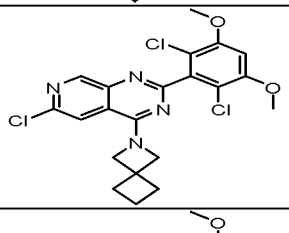
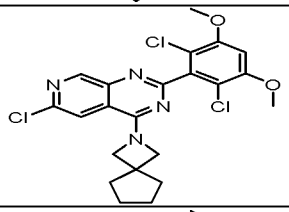
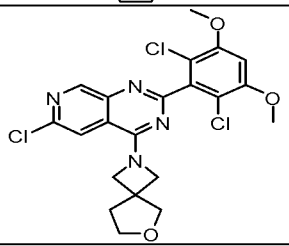
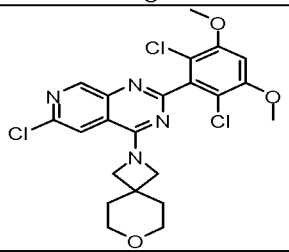
254		7-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2-氧杂-7-氮杂螺[4.4]壬烷	507
255		4-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)吗啉	467
256		4-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)吗啉	435
257		4-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2-甲基吗啉	481
258		4-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2-甲基吗啉	449
259		4-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2,6-二甲基吗啉	495
260		4-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-2,6-二甲基吗啉	463
261		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)哌啶-4-醇	481

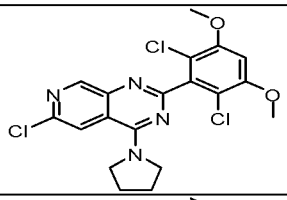
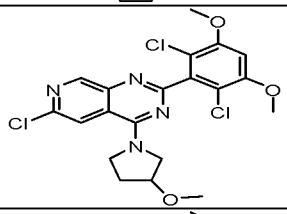
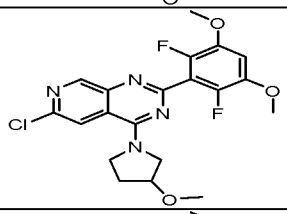
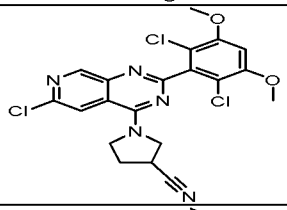
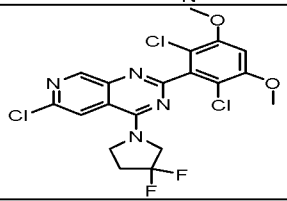
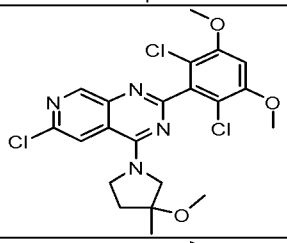
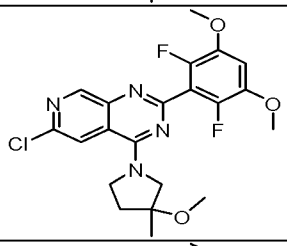
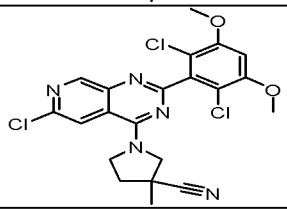
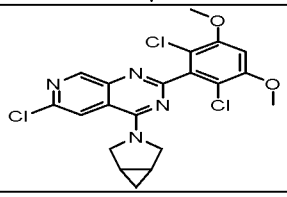
262		6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-甲氧基哌啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	495
263		6-(2,6-二氟-3,5-二甲氧苯基)-8-(4-甲氧基哌啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	463
264		6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基哌啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	495
265		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-4-甲基哌啶-4-醇	495
266		6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-甲氧基-4-甲基哌啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	509
267		6-(2,6-二氟-3,5-二甲氧苯基)-8-(4-甲氧基-4-甲基哌啶-1-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	477
268		1-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-4-甲基哌啶-4-甲腈	504
269		N-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)环丙甲酰胺	465

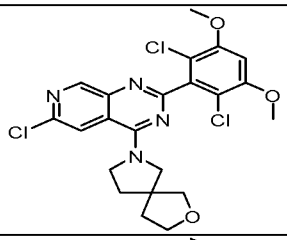
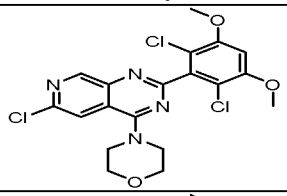
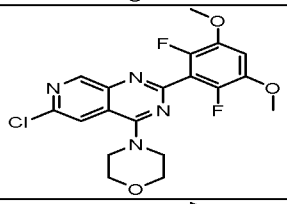
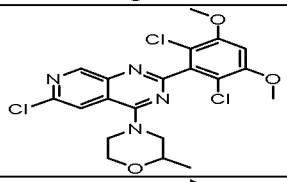
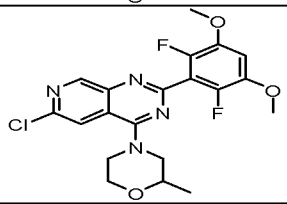
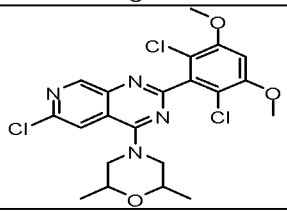
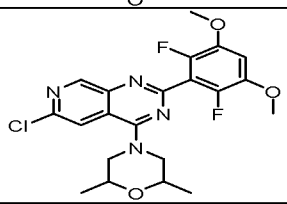
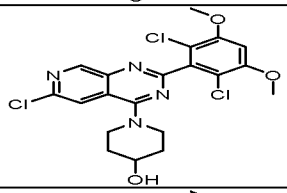
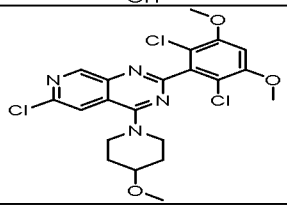
270		N-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)四氢呋喃-2-甲酰胺	495
271		N-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)甲磺酰胺	475
272		6-氯-N-(环丙基甲基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺	439
273		6-氯-N-(环丙基甲基)-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺	407
274		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-(2-甲氧基乙基)吡啶并[3,4-d]嘧啶-4-胺	443
275		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-(四氢呋喃-3-基)吡啶并[3,4-d]嘧啶-4-胺	455
276		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-((四氢呋喃-2-基)甲基)吡啶并[3,4-d]嘧啶-4-胺	469
277		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-4-胺	469
278		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-(3,3-二氟环戊基)吡啶并[3,4-d]嘧啶-4-胺	489

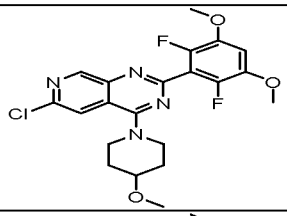
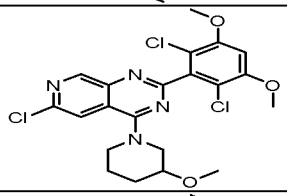
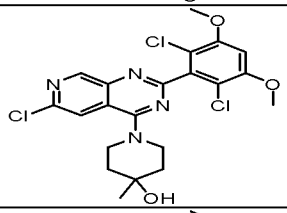
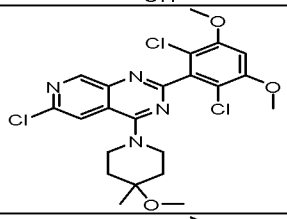
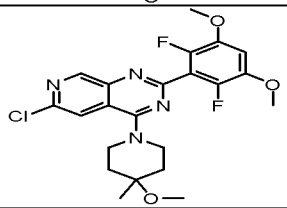
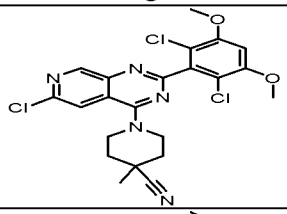
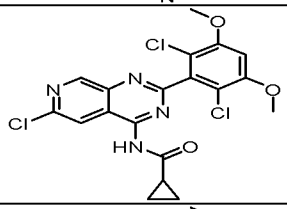
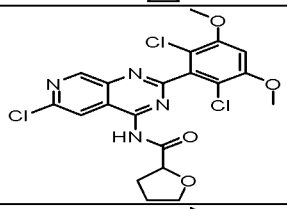
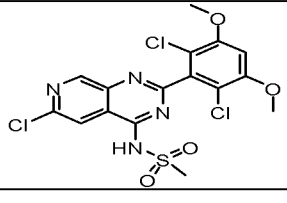
279		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-新戊基吡啶并[3,4-d]嘧啶-4-胺	455
280		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-N-((1-甲基-1H-吡唑-4-基)甲基)吡啶并[3,4-d]嘧啶-4-胺	479
281		(S)-6-氯-N-(1-环丙基乙基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺	453
282		(S)-6-氯-N-(1-环丙基乙基)-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺	421
283		6-氯-N-环丙基-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺	425
284		6-氯-N-环丙基-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-胺	393
285		4-(吖丁啶-1-基)-6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶	425
286		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶	455
287		6-氯-2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶	423

288		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-N,N-二甲基吖丁啶-3-胺	468
289		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-(三氟甲基)吖丁啶-1-基)吡啶并[3,4-d]嘧啶	493
290		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶	453
291		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶	461
292		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-3-甲基吖丁啶-3-醇	455
293		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶	469
294		6-氯-2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶	437
295		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-3-甲基吖丁啶-3-甲腈	464

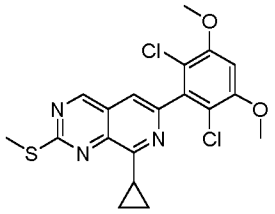
296		6-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2-氧杂-6-氮杂螺[3.3]庚烷	467
297		6-(6-氯-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2-氧杂-6-氮杂螺[3.3]庚烷	435
298		6-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-1-氧杂-6-氮杂螺[3.3]庚烷	467
299		6-(6-氯-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-1-氧杂-6-氮杂螺[3.3]庚烷	435
300		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氮杂螺[3.3]庚烷-2-基)吡啶并[3,4-d]嘧啶	465
301		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶	479
302		2-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-6-氧杂-2-氮杂螺[3.4]辛烷	481
303		2-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-7-氧杂-2-氮杂螺[3.5]壬烷	495

304		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(吡咯烷-1-基)吡啶并[3,4-d]嘧啶	439
305		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶	469
306		6-氯-2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶	437
307		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)吡咯烷-3-甲腈	464
308		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二氟吡咯烷-1-基)吡啶并[3,4-d]嘧啶	475
309		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶	483
310		6-氯-2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶	451
311		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-3-甲基吡咯烷-3-甲腈	478
312		4-(3-氮杂二环[3.1.0]己烷-3-基)-6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶	451

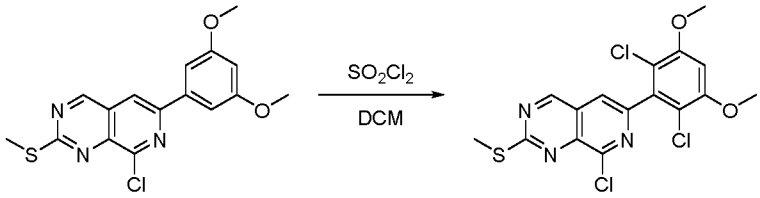
313		7-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2-氧杂-7-氮杂螺[4.4]壬烷	495
314		4-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)吗啉	455
315		4-(6-氯-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)吗啉	423
316		4-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2-甲基吗啉	469
317		4-(6-氯-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2-甲基吗啉	437
318		4-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2,6-二甲基吗啉	483
319		4-(6-氯-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-2,6-二甲基吗啉	451
320		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)哌啶-4-醇	469
321		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶	483

322		6-氯-2-(2,6-二氟-3,5-二甲氧苯基)-4-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶	451
323		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶	483
324		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-4-甲基哌啶-4-醇	483
325		6-氯-2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶	497
326		6-氯-2-(2,6-二氟-3,5-二甲氧苯基)-4-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶	465
327		1-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)-4-甲基哌啶-4-甲腈	492
328		N-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)环丙甲酰胺	453
329		N-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)四氢呋喃-2-甲酰胺	483
330		N-(6-氯-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)甲磺酰胺	463

中间体 331 8-环丙基-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备

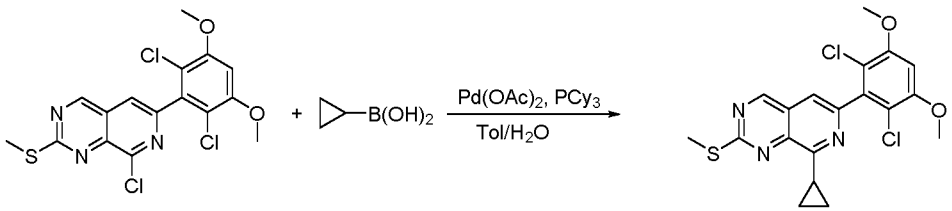


第一步：8-氯-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备



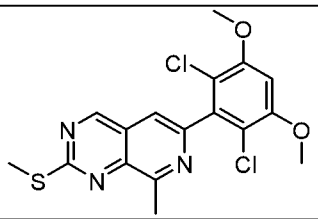
8-氯-6-(3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（500 mg, 1.43 mmol）加入二氯甲烷（30 mL），冷却至零下 30 度。SO_2Cl_2（0.35 mL, 4.31 mmol）溶于二氯甲烷（30 mL），搅拌下，缓慢滴加入反应液中，加完继续搅拌反应半小时。反应完全，加入饱和碳酸氢钠水溶液（50 mL）淬灭。萃取，再依次用水洗涤，饱和食盐水洗涤，无水硫酸钠干燥。过滤，浓缩，柱层析分离，纯化得 8-氯-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（620 mg，88%）。MS m/z (ESI): 416.2 $[M+H]^+$.

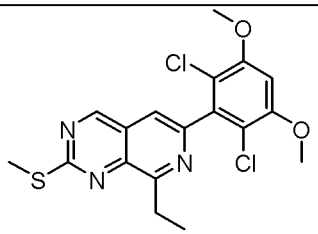
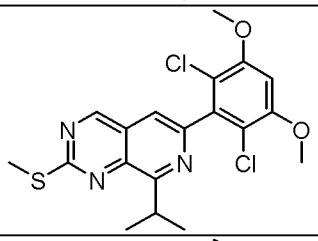
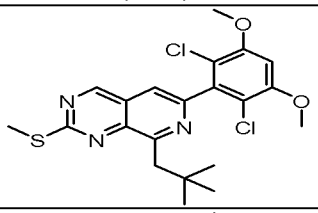
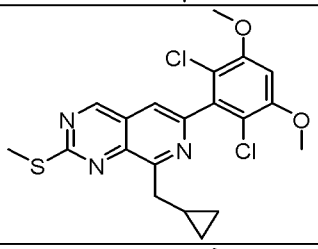
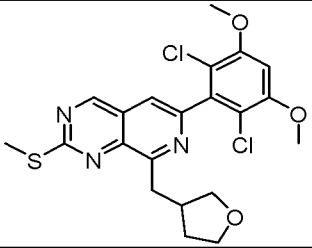
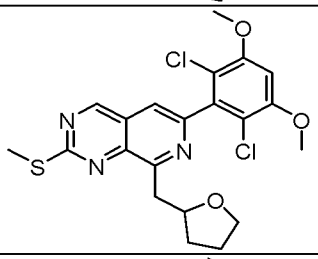
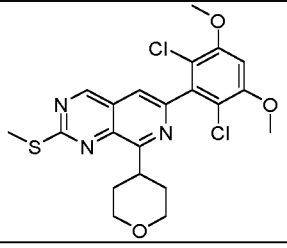
第二步：8-环丙基-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶的制备

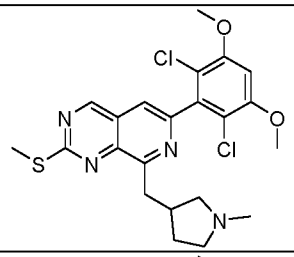
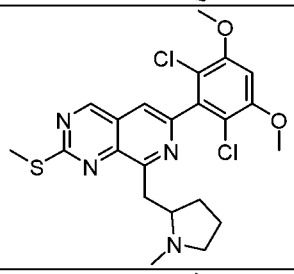
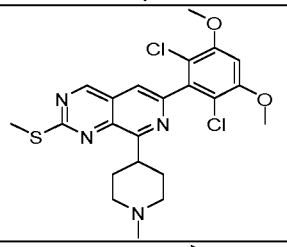
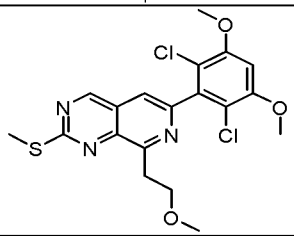
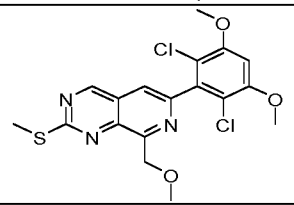
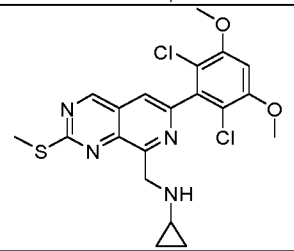
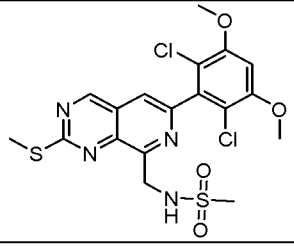


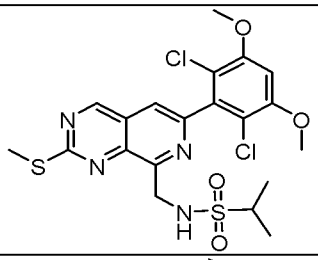
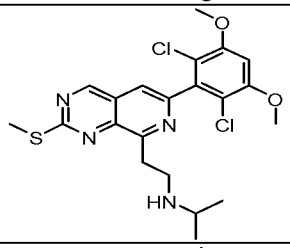
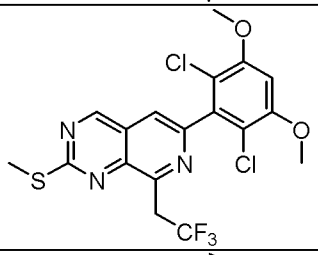
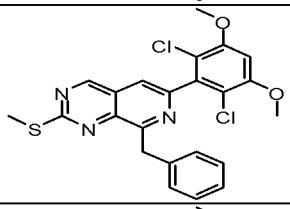
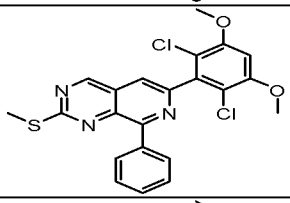
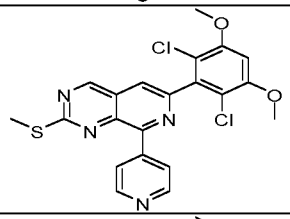
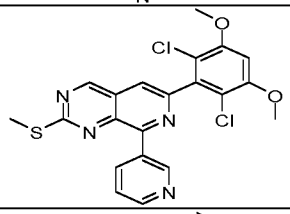
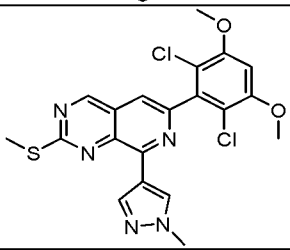
8-氯-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（83 mg，0.20 mmol）、环丙基硼酸（26 mg，0.30 mmol）、$Pd(OAc)_2$（5 mg，0.02 mmol）、PCy_3 （11 mg，0.04 mmol）以及 K_3PO_4（127 mg，0.60 mmol）加入甲苯/水（6:1，5 mL），加热至 100 度，搅拌反应过夜。反应完全，冷却至室温。EtOAc 稀释，饱和食盐水洗涤，无水 Na2SO4 干燥。过滤，浓缩，柱层析分离，得 8-环丙基-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（60 mg，71%）。MS m/z (ESI): 422.2 $[M+H]^+$.

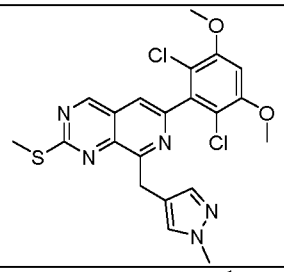
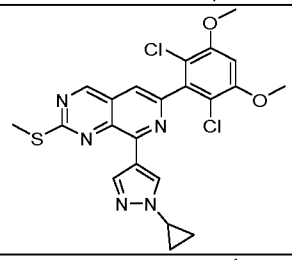
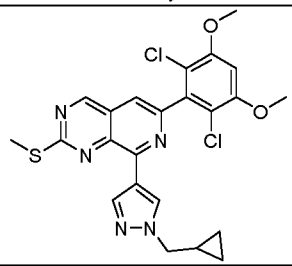
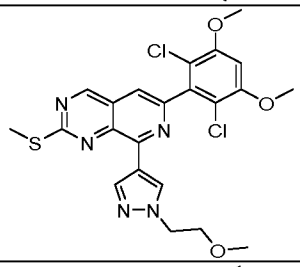
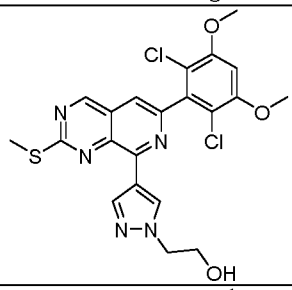
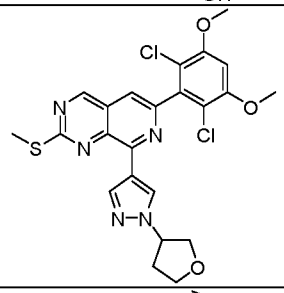
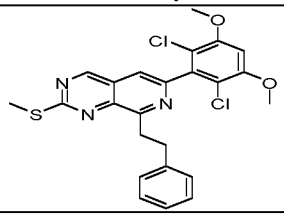
以下中间体 332-364 参照 331 的合成方法制备得到：

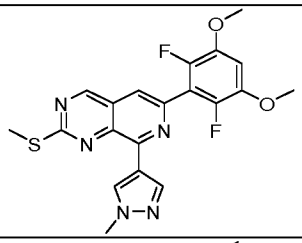
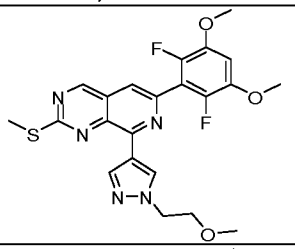
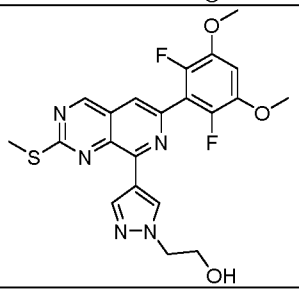
中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
332		6-(2,6-二氯-3,5-二甲氧苯基)-8-甲基-2-(甲硫基)吡啶并[3,4-d]嘧啶	396

333		6-(2,6-二氯-3,5-二甲氧苯基)-8-乙基-2-(甲硫基)吡啶并[3,4-d]嘧啶	410
334		6-(2,6-二氯-3,5-二甲氧苯基)-8-异丙基-2-(甲硫基)吡啶并[3,4-d]嘧啶	424
335		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-新戊基吡啶并[3,4-d]嘧啶	452
336		8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	436
337		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-((四氢呋喃-3-基)甲基)吡啶并[3,4-d]嘧啶	466
338		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-((四氢呋喃-2-基)甲基)吡啶并[3,4-d]嘧啶	466
339		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶	466

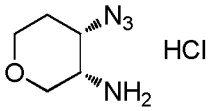
340		6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-3-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	479
341		6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-2-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	479
342		6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-甲基哌啶-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	479
343		6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-甲氧基乙基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	440
344		6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲氧基甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	426
345		N-((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)甲基)环丙胺	451
346		N-((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)甲基)甲磺酰胺	489

347		N-((6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)甲基)丙烷-2-磺酰胺	517
348		N-(2-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)乙基)丙烷-2-胺	467
349		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(2,2,2-三氟乙基)吡啶并[3,4-d]嘧啶	464
350		8-苯甲基-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	472
351		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-苯基吡啶并[3,4-d]嘧啶	458
352		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(吡啶-4-基)吡啶并[3,4-d]嘧啶	459
353		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(吡啶-3-基)吡啶并[3,4-d]嘧啶	459
354		6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	462

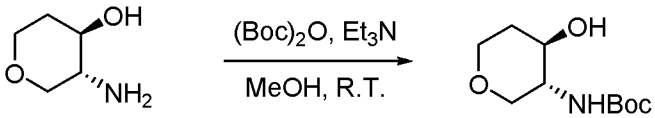
355		6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基-1H-吡唑-4-基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	476
356		8-(1-环丙基-1H-吡唑-4-基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	488
357		8-(1-(环丙基甲基)-1H-吡唑-4-基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	502
358		6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-(2-甲氧基乙基)-1H-吡唑-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	506
359		2-(4-(6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-1H-吡唑-1-基)乙烷-1-醇	492
360		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-(1-(四氢呋喃-3-基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶	518
361		6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)-8-苯乙基吡啶并[3,4-d]嘧啶	486

362		6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	430
363		6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-(2-甲氧基乙基)-1H-吡唑-4-基)-2-(甲硫基)吡啶并[3,4-d]嘧啶	474
364		2-(4-(6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-基)-1H-吡唑-1-基)乙烷-1-醇	460

中间体 365 (3S,4S)-4-叠氮四氢-2H-吡喃-3-胺盐酸的制备



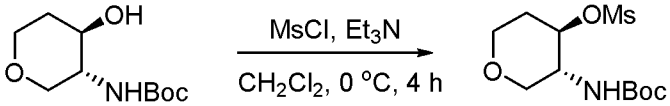
第一步：叔-丁基((3S,4S)-4-羟基四氢-2H-吡喃-3-基)氨基甲酸酯的制备



(3R,4R)-3-氨基四氢-2H-吡喃-4-醇（5.00 g，42.7 mmol）溶于 MeOH（100 mL），再依次加入 Et_3N（4.75 g，47.0 mmol）和 Boc_2O（10.25 g，47.0 mmol），室温搅拌反应过夜。LCMS 监测，反应完全。浓缩除去甲醇，粗产品用石油醚（100 mL）洗涤，过滤，得化合物叔-丁基((3S,4S)-4-羟基四氢-2H-吡喃-3-基)氨基甲酸酯（8.50 g， 收率：92%）。

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 4.68(m, 1H), 4.03(m, 1H). 3.93(m, 1H), 3.63(m, 1H), 3.45(m, 2H), 3.19(m, 1H), 2.81(m, 1H), 2.04(m, 1H), 1.68(m ,1H), 1.61(s, 9H).

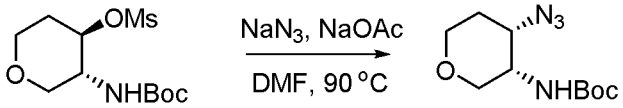
第二步：(3R,4R)-3-((叔-丁氧基羰基)氨基)四氢-2H-吡喃-4-基甲磺酸酯的制备



化合物叔-丁基((3S,4S)-4-羟基四氢-2H-吡喃-3-基)氨基甲酸酯（8.5 g, 39.2 mmol）溶于 CH_2Cl_2（100 mL），冰水浴冷却，依次加入 Et_3N（4.30 g，43.0 mmol）和 MsCl（4.98 g，43.0 mmol）。维持 0 ℃反应 6 小时，反应完全。加水（20 mL）洗涤，有机相用无水 Na_2SO_4 干燥。 过滤，浓缩，得化合物(3R,4R)-3-((叔-丁氧基羰基)氨基)四氢-2H-吡喃-4-基甲磺酸酯（10.2 g，收率：88%）。

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 4.90 (m, 1H), 4.76(m, 1H). 4.03(m, 1H), 3.98(m, 1H), 3.67(m, 2H), 3.47(m, 1H),3.14(s, 3H), 2.18(m, 1H), 1.92(m, 1H), 1.44 (s, 9H).

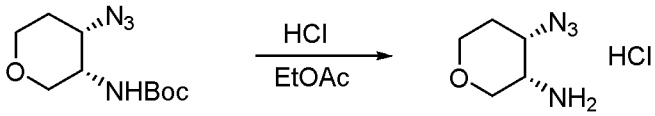
第三步：叔-丁基((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)氨基甲酸酯的制备



(3R,4R)-3-((叔-丁氧基羰基)氨基)四氢-2H-吡喃-4-基甲磺酸酯（10.2 g，34.6 mmol）溶于干燥 DMF（100 mL），再依次加入 NaOAc（9.38 g，69.0 mmol）和 NaN_3（4.49 g, 69.0 mmol ），加热至 90 ℃，反应过夜。反应完全，化合物倒入水（200 mL），再用 EtOAc（50 mL）萃取 2 次。合并有机相，用 LiCl 水溶液（50 mL）洗涤 2 次，无水 Na_2SO_4 干燥，过滤，浓缩，得化合物叔-丁基((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)氨基甲酸酯（6.8 g，收率：81%）。

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 4.85(m, 1H), 3.89(m, 2H). 3.77(m, 1H), 3.63(m, 2H), 3.51(m, 1H), 1.93(m,2H), 1.45(s, 9H).

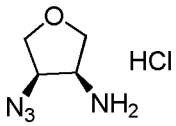
第四步：(3S,4S)-4-叠氮四氢-2H-吡喃-3-胺盐酸的制备



叔-丁基((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)氨基甲酸酯（6.8 g，28.0 mmol）加入 HCl/EtOAc（100 mL），室温搅拌反应 8 小时。LCMS 监测，反应完全。浓缩，得到化合物(3S,4S)-4-叠氮四氢-2H-吡喃-3-胺盐酸（4.0 g，收率：80%）。

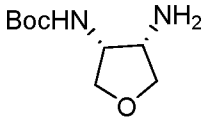
^{1}H NMR (400MHz, DMSO-d6): δ ppm 8.47(m, 3H), 4.36(m, 1H), 3.80(m , 2H), 3.63(m, 3H), 2.0(m , 2H).

中间体 366 (3S,4R)-4-叠氮四氢呋喃-3-胺盐酸的制备

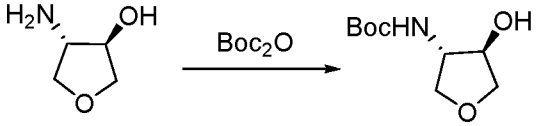


中间体 366 参照中间体 365 的合成方法由(3S,4R)-4-氨基四氢呋喃-3-醇制备。

中间体 367 叔-丁基 ((3R,4S)-4-氨基四氢呋喃-3-基)氨基甲酸酯



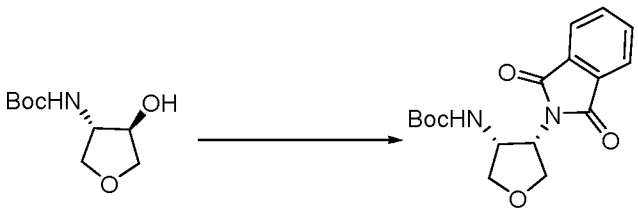
第一步：叔-丁基 ((3S,4R)-4-羟基四氢呋喃-3-基)氨基甲酸酯的制备



(3R,4S)-4-氨基四氢呋喃-3-醇（5.00 g，48.487 mmol）溶于甲醇（100 mL），加入三乙胺(12.24 g, 121.2mmol)，冰水浴冷却，再加入 Boc_2O（11.64 g, 53.34 mmol）。加完后，室温下搅拌反应 24 小时。反应完全，有机相浓缩，除去大部分，加入水（100 mL）搅拌，析出大量白色固体，过滤并用水洗涤，得到化合物叔-丁基 ((3S,4R)-4-羟基四氢呋喃-3-基)氨基甲酸酯（8.00 g，收率：81%）。

^{1}H NMR (400 MHz, Chloroform-d) δ 4.72 (s, 1H), 4.29 (m, 1H), 4.09 (m, 1H), 4.08 – 4.02 (m, 1H), 3.95 (s, 1H), 3.69 (m, 1H), 3.61 (m, 1H), 1.45 (s, 9H).

第二步：叔-丁基((3R,4S)-4-(1,3-二羰基异二氢吲哚-2-基)四氢呋喃-3-基)氨基甲酸酯的制备



叔-丁基 ((3S,4R)-4-羟基四氢呋喃-3-基)氨基甲酸酯 (200 mg, 0.984 mmol)，三苯基磷 (620 mg, 2.364 mmol) 和异二氢吲哚-1,3-二酮 (173 mg, 1.181 mmol) 溶于四氢呋喃（10 mL），冰水浴冷却，再缓慢滴加偶氮二羧酸二异丙酯 (717 mg, 3.546 mmol)。加完后，继续在冰水浴下搅拌反应 1 小时。然后反应液直接浓缩后柱层析（洗脱剂：PE/EA 15 - 30%）分离，得到化合物叔-丁基((3R,4S)-4-(1,3-二羰基异二氢吲哚-2-基)四氢呋喃-3-基)氨基甲酸酯（950 mg）粗品。

^{1}H NMR (400 MHz, Chloroform-d) δ 7.87 (m, 2H), 7.75 (m, 2H), 4.84 (d, J = 9.5 Hz, 1H), 4.51 (t, J = 8.0 Hz, 1H), 4.37 (t, J = 8.3 Hz, 1H), 4.21 – 4.15 (m, 1H), 4.09 (t, J = 8.8 Hz, 1H), 3.85 (m, J = 9.2, 6.4 Hz, 1H), 1.11 (s, 9H).

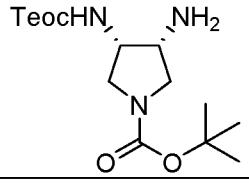
MS m/z (ESI): 559.5 $[M+H]^+$.

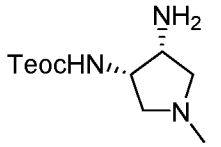
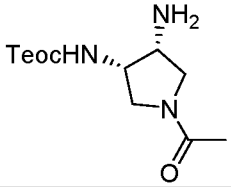
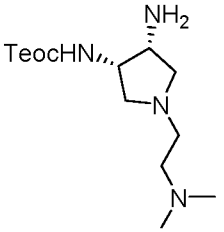
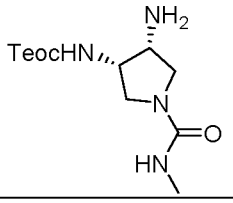
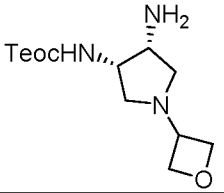
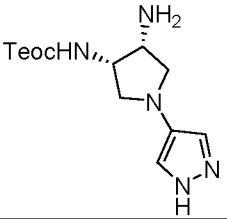
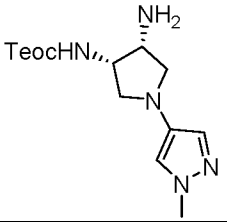
第三步：叔-丁基((3R,4S)-4-氨基四氢呋喃-3-基)氨基甲酸酯的制备

叔-丁基((3R,4S)-4-(1,3-二羰基异二氢吲哚-2-基)四氢呋喃-3-基)氨基甲酸酯 (950 mg, 21%, 0.600 mmol) 溶于乙醇（6 mL），再加入水合肼 (45 mg, 0.900 mmol)。加热至 75 度，搅拌反应 2 小时。反应完全，浓缩，柱层析（洗脱剂：DCM/MeOH 0 ~ 5%）分离，得到化合物叔-丁基((3R,4S)-4-氨基四氢呋喃-3-基)氨基甲酸酯（120 mg, 两步收率：60%)。

^{1}H NMR (400 MHz, Chloroform-d) δ 5.24 (s, 1H), 4.11 (s, 1H), 4.05 (m, 1H), 4.00 (m, 1H), 3.63 – 3.52 (m, 2H), 3.49 (m, 1H), 1.46 (s, 9H).

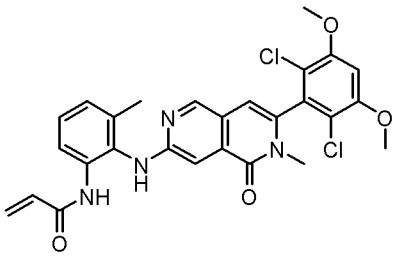
以下中间体 368-375 参照中间体 367 合成方法制备：

中间体编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
368		叔-丁基 (3R,4S)-3-氨基-4-(((2,2,2-三氯乙氧基)羰基)氨基)吡咯烷-1-羧酸酯	377

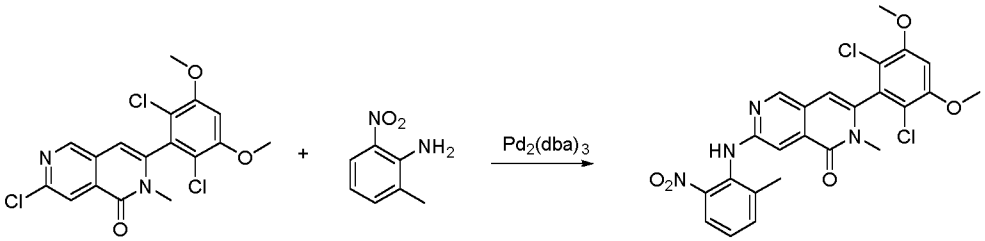
369		2,2,2-三氯乙基((3S,4R)-4-氨基-1-甲基吡咯烷-3-基)氨基甲酸酯	291
370		2,2,2-三氯乙基((3S,4R)-1-乙酰基-4-氨基吡咯烷-3-基)氨基甲酸酯	319
371		2,2,2-三氯乙基((3S,4R)-4-氨基-1-(2-(二甲氨基)乙基)吡咯烷-3-基)氨基甲酸酯	348
372		2,2,2-三氯乙基((3S,4R)-4-氨基-1-(甲基氨基甲酰)吡咯烷-3-基)氨基甲酸酯	334
373		2,2,2-三氯乙基((3S,4R)-4-氨基-1-(噁丁环-3-基)吡咯烷-3-基)氨基甲酸酯	333
374		2,2,2-三氯乙基((3S,4R)-4-氨基-1-(1H-吡唑-4-基)吡咯烷-3-基)氨基甲酸酯	343
375		2,2,2-三氯乙基((3S,4R)-4-氨基-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)氨基甲酸酯	357

具体实施例化合物的制备

实施例 1 N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺的制备

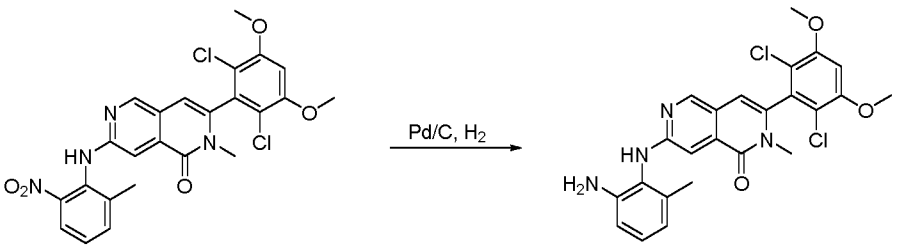


第一步：3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-7-((2-甲基-6-硝基苯基)氨基)-2,6-二氮杂萘-1(2H)-酮的制备



7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮（150 mg, 0.375 mmol）溶于 1,4-二氧六环（20 mL），然后加入 2-甲基-6-硝基苯胺（114 mg, 0.751 mmol），碳酸铯（367 mg, 1.126 mmol），brett-phos (161 mg, 0.3 mmol) 和 $Pd_2(dba)_3$（172 mg, 0.188 mmol）。抽换气，氮气保护。加热至 120 ℃，反应 2 小时。反应完全，浓缩，硅胶柱层析分离（洗脱剂：PE/EtOAc = 2 : 1），得到化合物 3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-7-((2-甲基-6-硝基苯基)氨基)-2,6-二氮杂萘-1(2H)-酮（40 mg, 产率 21%）。MS m/z (ESI): 516 $[M+H]^+$.

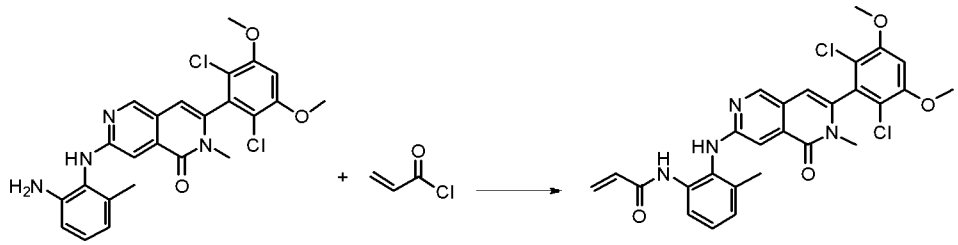
第二步：7-((2-氨基-6-甲基苯基)氨基)-3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮的制备



将 3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-7-((2-甲基-6-硝基苯基)氨基)-2,6-二氮杂萘-1(2H)-酮（40 mg, 0.078 mmol）溶于 10 毫升甲醇，然后加入 10 毫克 Pd-C，反应在氢气下室温搅拌 30 分钟。反应结束后，浓缩，硅胶柱层析分离（洗脱剂：CH_2Cl_2/MeOH = 10:1），得到化合物 7-((2-氨基-6-甲基苯基)氨基)-3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮（9.5 mg, 产率 25%）。

MS m/z (ESI): 486.4 $[M+H]^+$.

第三步：N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺的制备

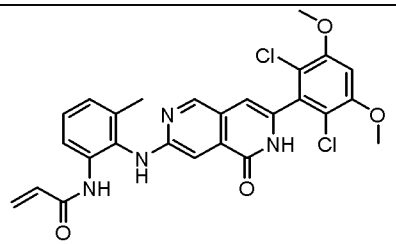
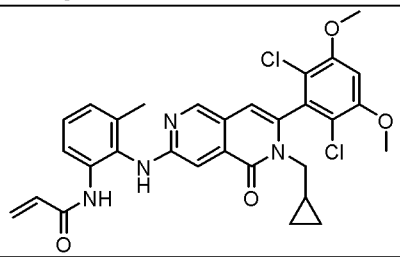
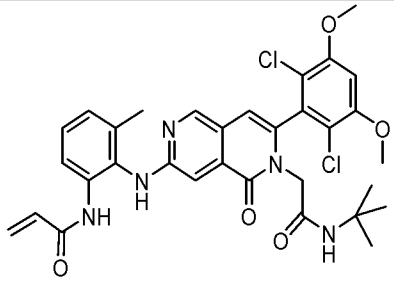


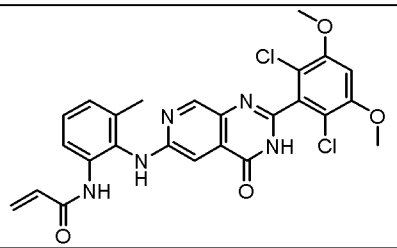
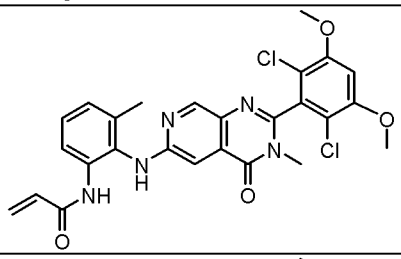
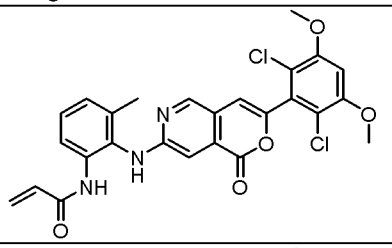
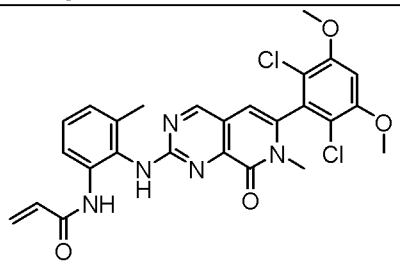
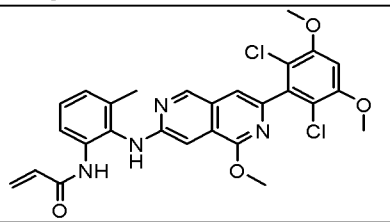
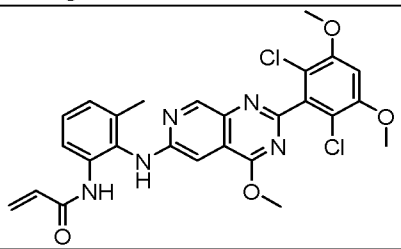
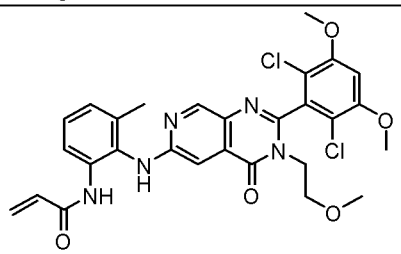
将 7-((2-氨基-6-甲基苯基)氨基)-3-(2,6-二氯-3,5-二甲氧苯基)-2-甲基-2,6-二氮杂萘-1(2H)-酮（9.5 mg，0.02 mmol）溶于 THF/H_2O（4 mL/1 mL），然后加入碳酸氢钠（9 mg, 0.104 mmol），冰水浴冷却，滴加丙烯酰氯/THF 溶液（2 mg/2 mL，0.02 mmol）。0 ℃下搅拌反应 10 分钟。反应完全，二氯甲烷萃取 3 次。合并有机相，再用饱和氯化钠水溶液洗涤，无水硫酸钠干燥。过滤，浓缩，粗品经硅胶柱层析分离，得到化合物 N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺（1 mg，收率：9%）。

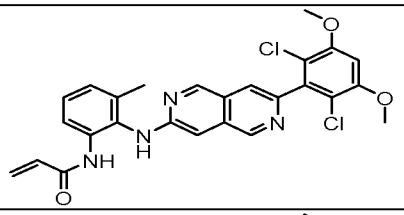
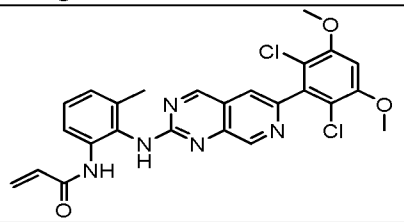
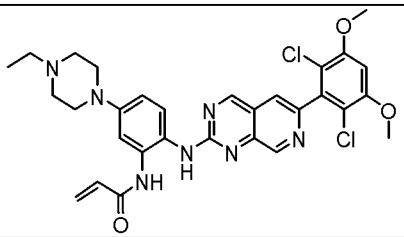
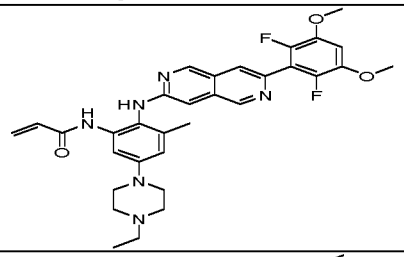
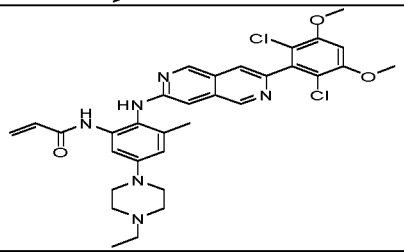
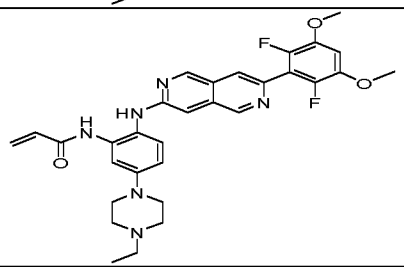
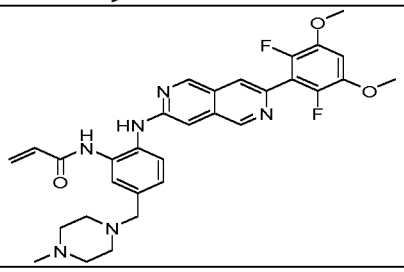
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.10 – 7.05 (m, 2H), 6.68 (s, 1H), 6.52 – 6.48 (m, 1H), 6.44 (s, 1H), 6.39 (s, 1H), 6.33 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 10.2 Hz, 1H), 5.68 (dd, J = 10.2, 1.4 Hz, 1H), 3.99 (s, 6H), 3.25 (s, 3H), 2.21 (s, 3H).

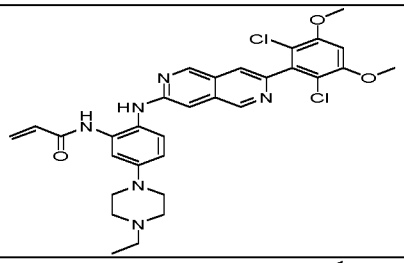
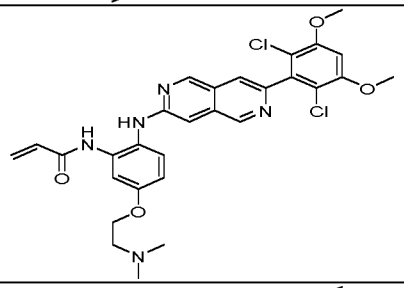
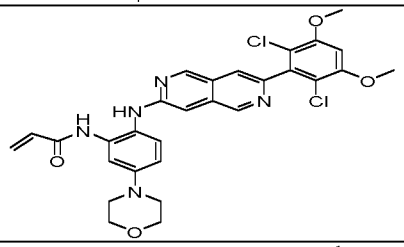
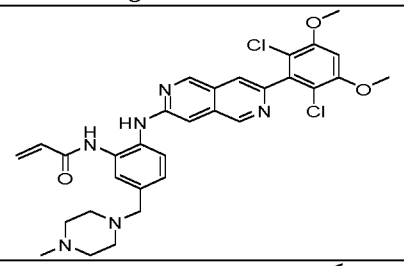
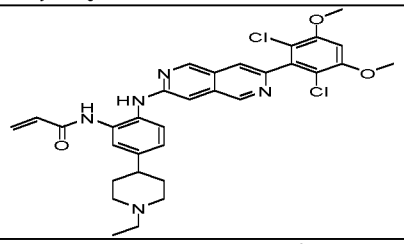
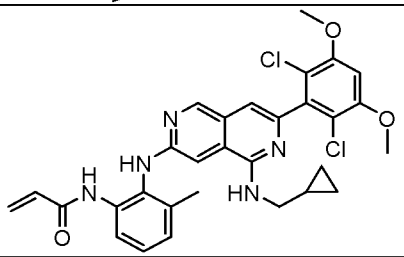
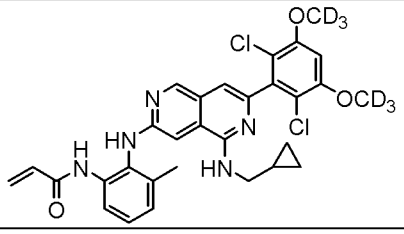
MS m/z (ESI): 541.4 $[M+H]^+$.

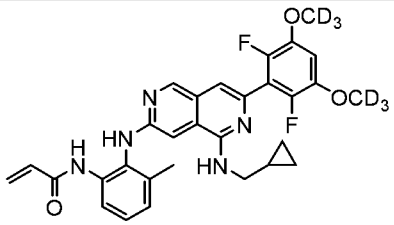
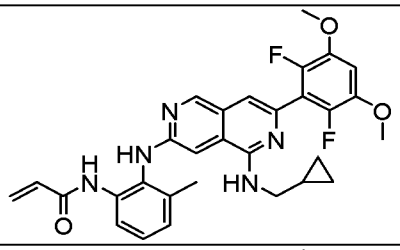
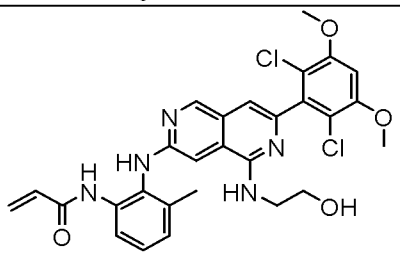
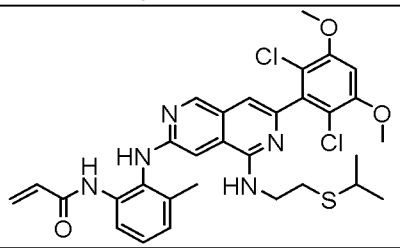
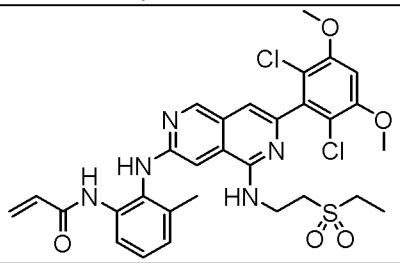
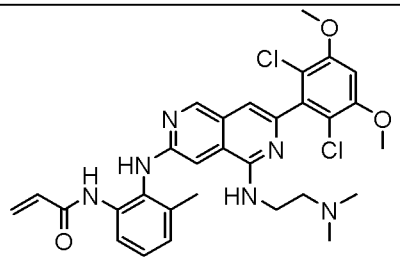
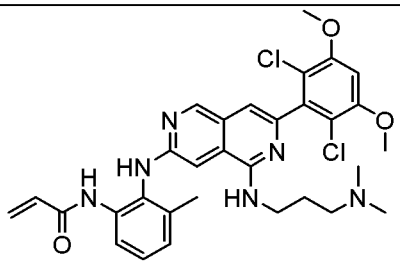
以下实施例 2-75 参照实施例 1 合成方法制备得到：

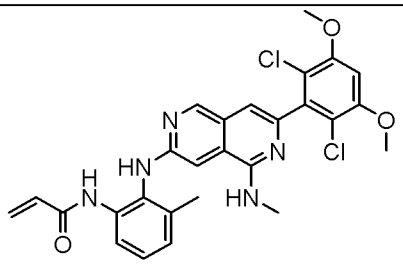
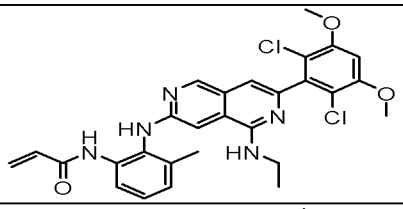
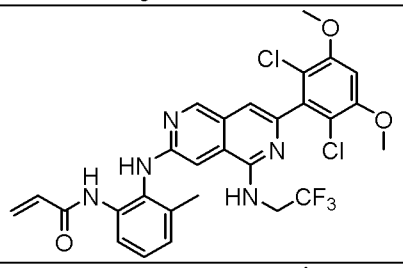
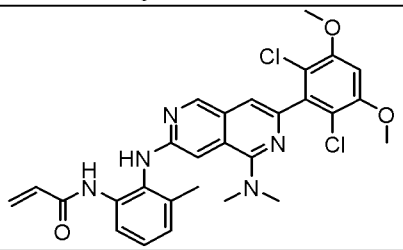
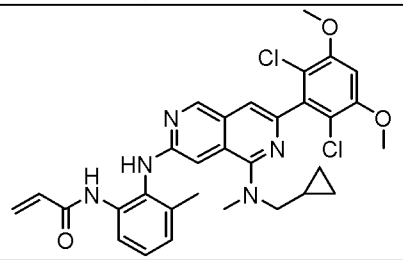
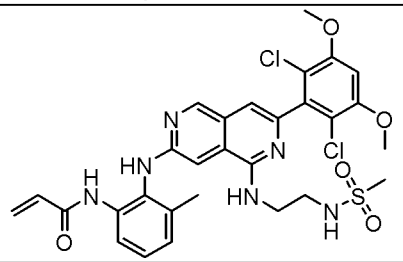
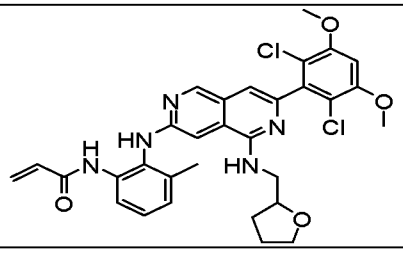
实施例编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
2		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	525
3		N-(2-((6-(环丙基甲基)-7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	579
4		N-(2-((6-(2-(叔-丁基氨基)-2-羰基乙基)-7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	638

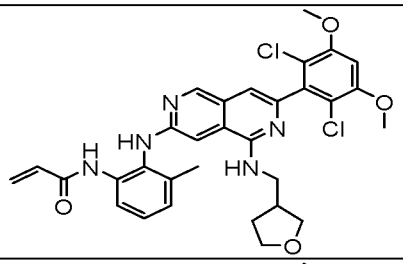
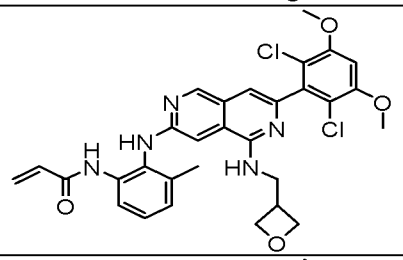
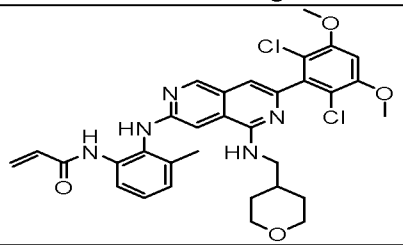
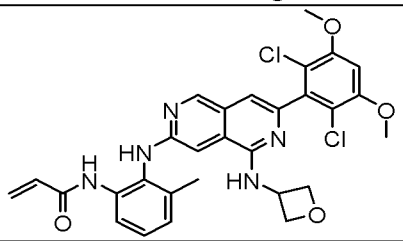
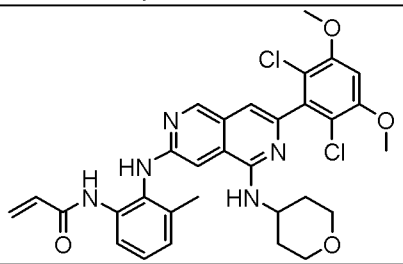
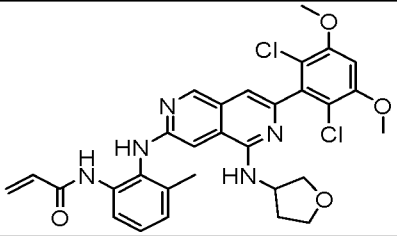
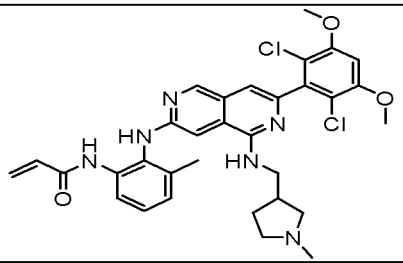
5		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)-4-羰基-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	526
6		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)-3-甲基-4-羰基-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	540
7		N-(2-((3-(2,6-二氯-3,5-二甲氧苯基)-1-羰基-1H-吡喃并[4,3-c]吡啶-7-基)氨基)-3-甲基苯基)丙烯酰基酰胺	526
8		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-7-甲基-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	540
9		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-甲氧基-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	539
10		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)-4-甲氧基吡啶并[3,4-d]嘧啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	540
11		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)-3-(2-甲氧基乙基)-4-羰基-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	584

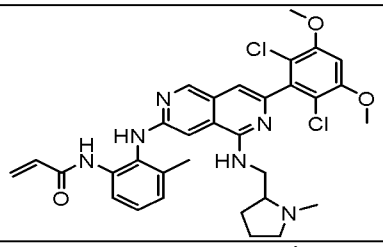
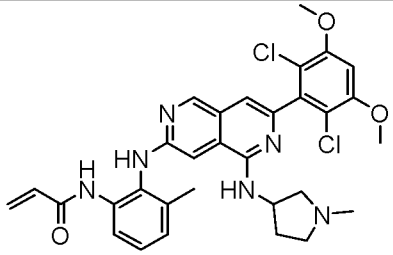
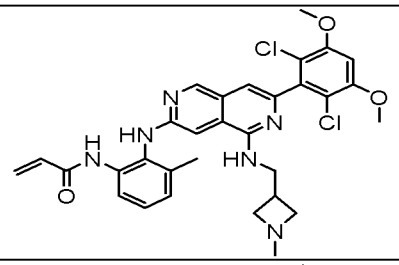
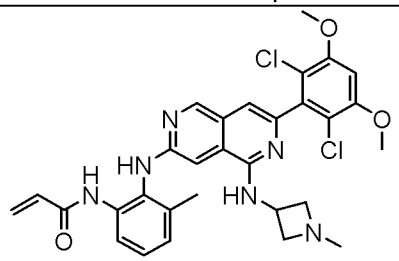
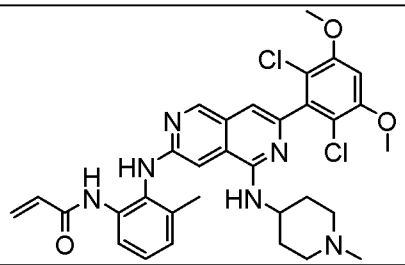
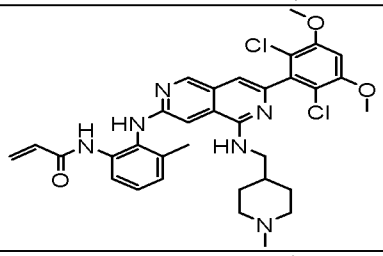
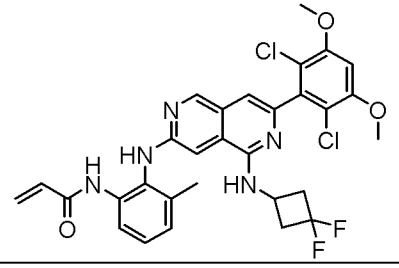
13		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	509
14		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	510
15		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-5-(4-乙基哌嗪-1-基)苯基)丙烯酰基酰胺	608
16		N-(2-((7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-(4-乙基哌嗪-1-基)-3-甲基苯基)丙烯酰基酰胺	589
17		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-(4-乙基哌嗪-1-基)-3-甲基苯基)丙烯酰基酰胺	621
18		N-(2-((7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-(4-乙基哌嗪-1-基)苯基)丙烯酰基酰胺	575
19		N-(2-((7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-((4-甲基哌嗪-1-基)甲基)苯基)丙烯酰基酰胺	575

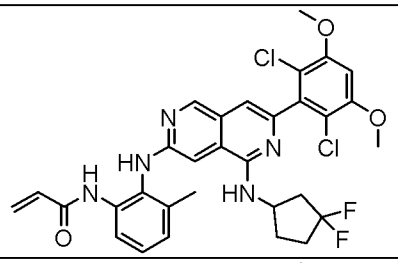
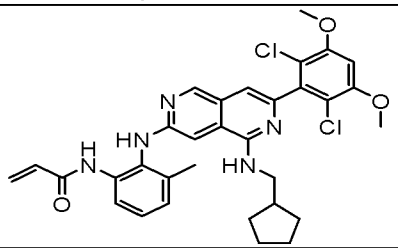
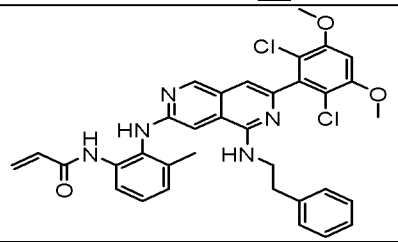
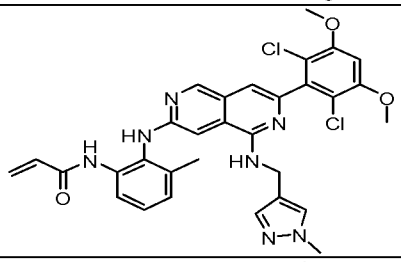
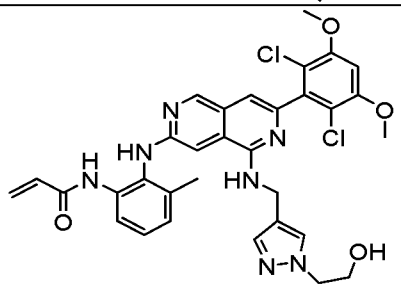
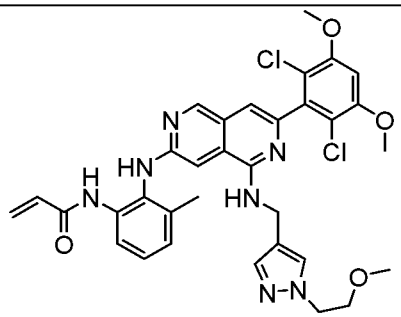
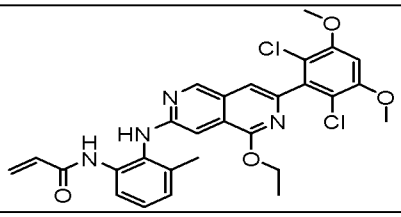
20		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-(4-乙基哌嗪-1-基)苯基)丙烯酰基酰胺	607
21		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-(2-(二甲氨基)乙氧基)苯基)丙烯酰基酰胺	582
22		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-吗啉代苯基)丙烯酰基酰胺	580
23		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-((4-甲基哌嗪-1-基)甲基)苯基)丙烯酰基酰胺	607
24		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-5-(1-乙基哌啶-4-基)苯基)丙烯酰基酰胺	606
25		N-(2-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	578
26		N-(2-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	584

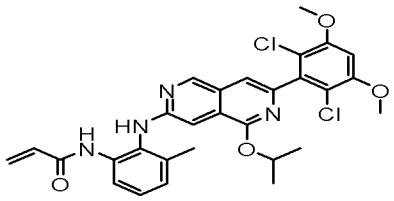
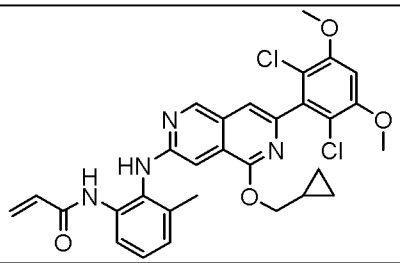
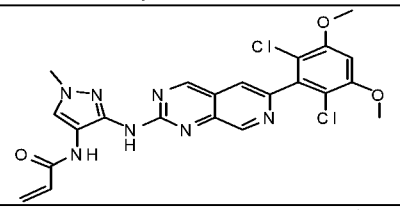
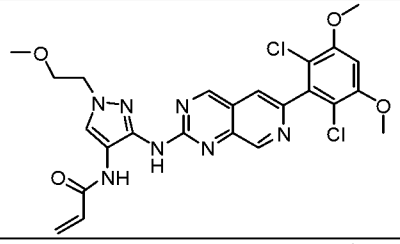
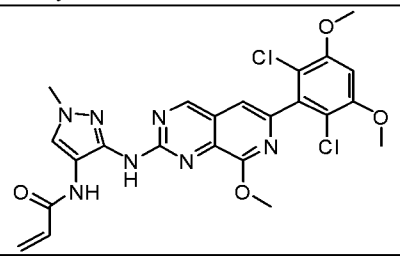
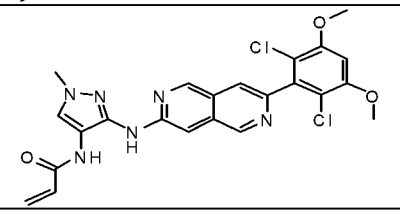
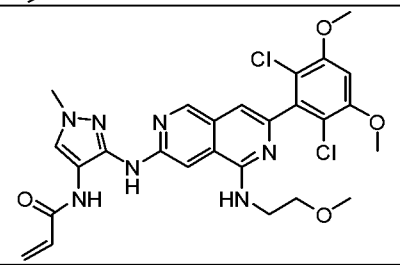
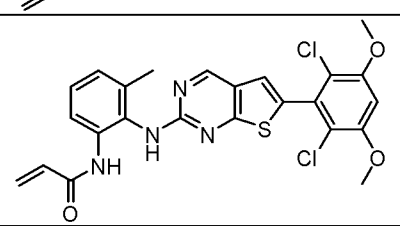
27		N-(2-((5-((环丙基甲基)氨基)-7-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	552
28		N-(2-((5-((环丙基甲基)氨基)-7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	546
29		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-羟基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	568
30		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(异丙基硫代)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	626
31		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(乙基磺酰)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	644
32		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(二甲氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	595
33		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((3-(二甲氨基)丙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	609

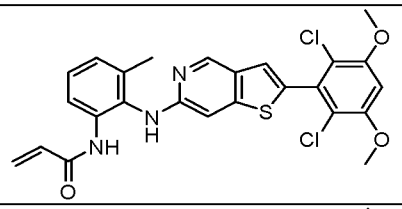
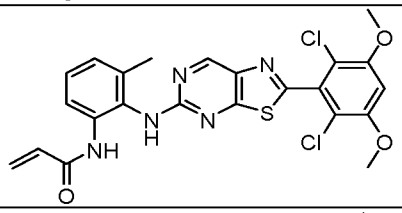
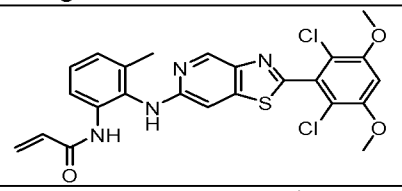
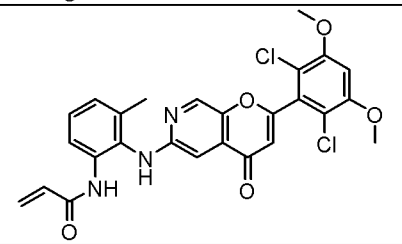
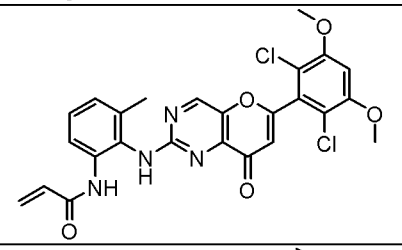
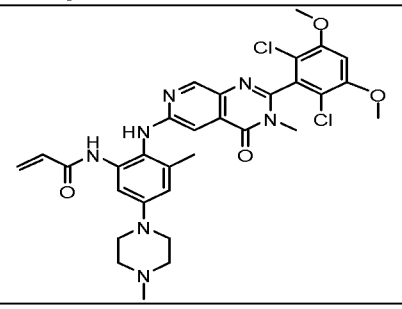
34		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(甲基氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	538
35		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(乙胺基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	552
36		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2,2,2-三氟乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	606
37		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(二甲氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	552
38		N-(2-((5-((环丙基甲基)(甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	592
39		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(甲基磺酰氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	645
40		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	608

41		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-3-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	608
42		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((噁丁环-3-基甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	594
43		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢-2H-吡喃-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	622
44		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	580
45		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢-2H-吡喃-4-基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	608
46		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	594
47		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基吡咯烷-3-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	621

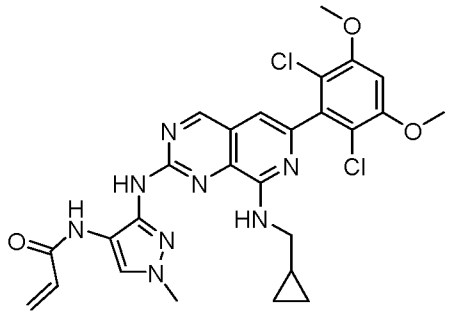
48		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基吡咯烷-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	621
49		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((1-甲基吡咯烷-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	607
50		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基吖丁啶-3-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	607
51		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((1-甲基吖丁啶-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	593
52		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((1-甲基哌啶-4-基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	621
53		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基哌啶-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	635
54		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((3,3-二氟环丁基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	614

55		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((3,3-二氟环戊基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	628
56		N-(2-((5-((环戊基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	606
57		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(苯乙胺基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	628
58		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	618
59		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-(2-羟基乙基)-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	648
60		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	662
61		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-乙氧基-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	553

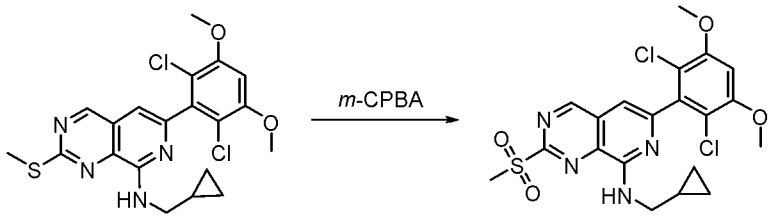
62		N-(2-((7-(2,6-二氯-3,5-二甲氧苯基)-5-异丙氧基-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	567
63		N-(2-((5-(环丙基甲氧基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-3-甲基苯基)丙烯酰基酰胺	579
64		N-(3-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺	500
65		N-(3-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	544
66		N-(3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺	530
67		N-(3-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺	499
68		N-(3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-甲氧基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺	572
69		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)噻吩并[2,3-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	515

70		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)噻吩并[3,2-c]吡啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	515
71		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)噻唑并[5,4-d]嘧啶-5-基)氨基)-3-甲基苯基)丙烯酰基酰胺	516
72		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)噻唑并[4,5-c]吡啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	515
73		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)-4-羰基-4H-吡喃并[2,3-c]吡啶-6-基)氨基)-3-甲基苯基)丙烯酰基酰胺	526
74		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-8H-吡喃并[3,2-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	527
75		N-(2-((2-(2,6-二氯-3,5-二甲氧苯基)-3-甲基-4-羰基-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)氨基)-3-甲基-5-(4-甲基哌嗪-1-基)苯基)丙烯酰基酰胺	638

实施例 76 N-(3-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺的制备



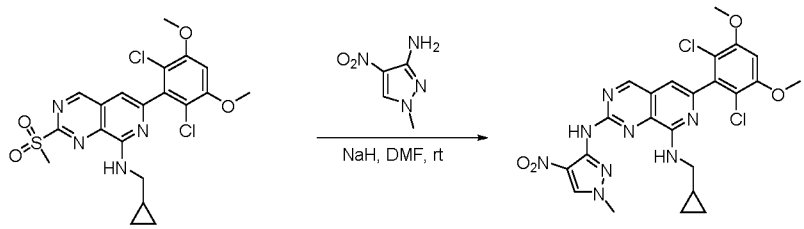
第一步：N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶-8-胺的制备



N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺（210 mg, 0.465 mmol）溶于二氯甲烷（6 mL），再加入间氯过氧苯甲酸（200 mg, 1.163 mmol）。室温下搅拌反应 18 小时。反应完全，加入饱和亚硫酸钠溶液（5 mL），搅拌 5 分钟。二氯甲烷萃取，有机相再分别用饱和碳酸氢钠和饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，柱层析（洗脱剂: PE/EA = 2/1）分离，得到化合物 N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶-8-胺（186 mg，收率：82.7%）。

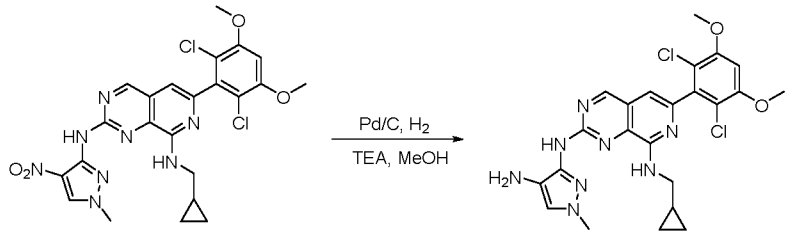
MS m/z (ESI): 483.4 $[M+H]^+$.

第二步：N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-N^2-(1-甲基-4-硝基-1H-吡唑-3-基)吡啶并[3,4-d]嘧啶-2,8-二胺



N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶-8-胺（90 mg, 0.186 mmol）溶于干燥 DMF（5 mL），零度下加入 NaH（15 mg, 0.372 mmol），室温搅拌 10 分钟，然后加入 1-甲基-4-硝基-1H-吡唑-3-胺（32 mg，0.223 mmol），室温搅拌 3 小时。饱和氯化铵水溶液淬灭，乙酸乙酯萃取，硅胶柱层析（PE/EA = 1/1）分离，得到化合物 N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-N^2-(1-甲基-4-硝基-1H-吡唑-3-基)吡啶并[3,4-d]嘧啶-2,8-二胺（100 mg, 产率 98%）。MS m/z (ESI): 545 $[M+H]^+$。

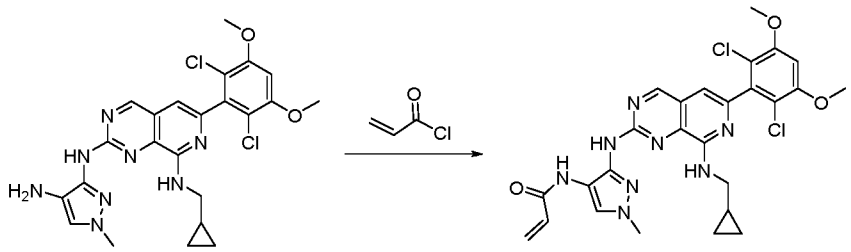
第三步：N^2-(4-氨基-1-甲基-1H-吡唑-3-基)-N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,8-二胺



N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-N^2-(1-甲基-4-硝基-1H-吡唑-3-基)吡啶并[3,4-d]嘧啶-2,8-二胺（40 mg，0.074 mmol）溶于甲醇（10 mL），依次加入三乙胺（3 滴）和 Pd/C（20 mg，10%含量），氢气球下于室温搅拌 45 分钟。反应完全，过滤，硅胶柱层析（DCM/MeOH），得到化合物 N^2-(4-氨基-1-甲基-1H-吡唑-3-基)-N^8-(环丙基甲基)-6-(2,6-

二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,8-二胺（30 mg，产率 80%）。MS m/z (ESI): 515 $[M+H]^+$。

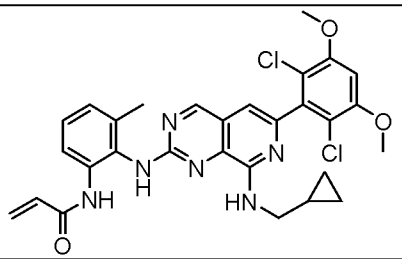
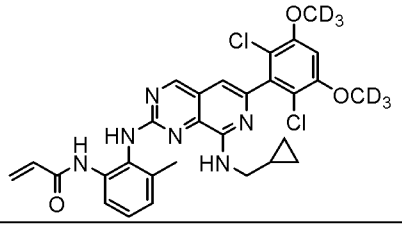
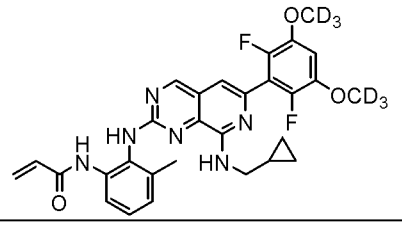
第四步：N-(3-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺

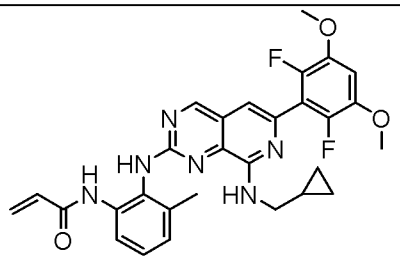
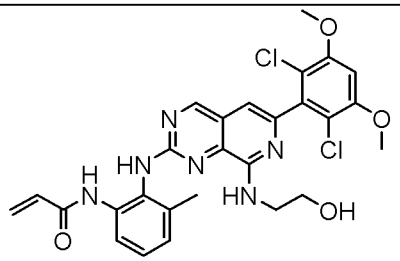
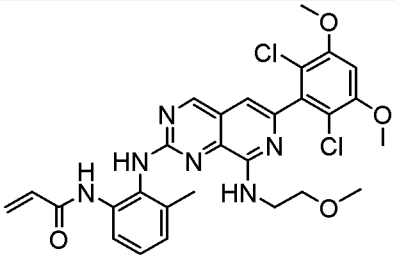
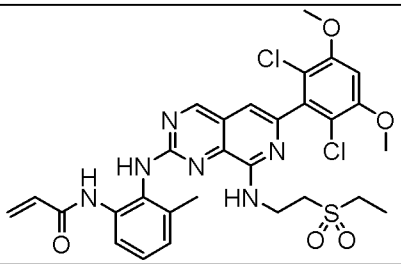
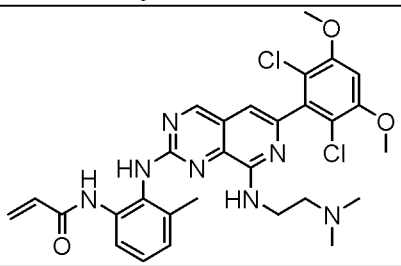
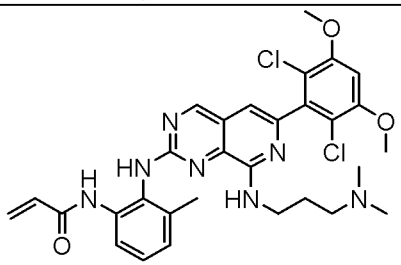
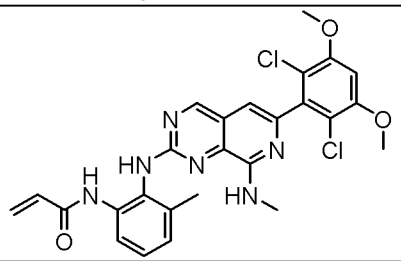


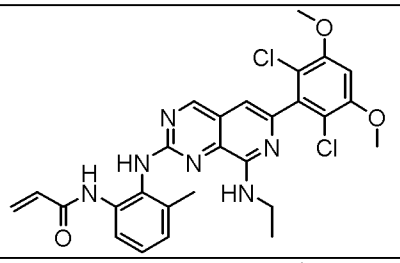
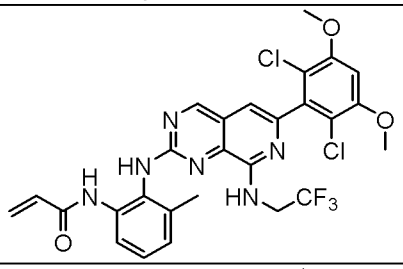
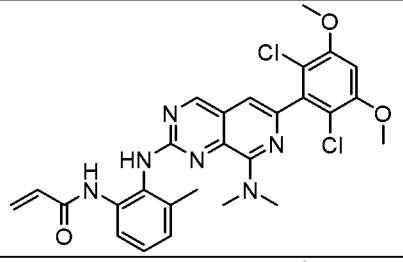
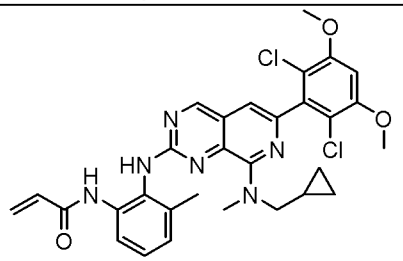
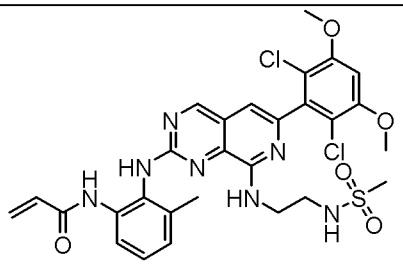
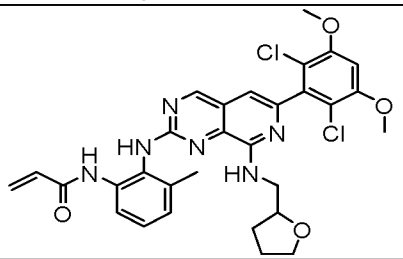
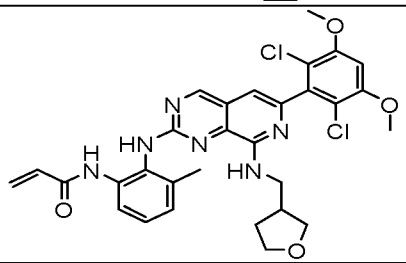
N^2-(4-氨基-1-甲基-1H-吡唑-3-基)-N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,8-二胺（30 mg，0.058 mmol）溶于 THF/H_2O （8 mL/2 mL），加入 $NaHCO_3$（33 mg， 0.39 mmol），冰浴下滴加烯丙酰氯（7 mg，0.078 mmol，溶于 1 mL THF 中）。搅拌 10 分钟，加入 20 mL 饱和碳酸氢钠水溶液，乙酸乙酯提取，硅胶柱层析（PE/EA = 1/1）分离，得到化合物 N-(3-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺（10 mg，产率 22%）。MS m/z (ESI): 569 $[M+H]^+$。

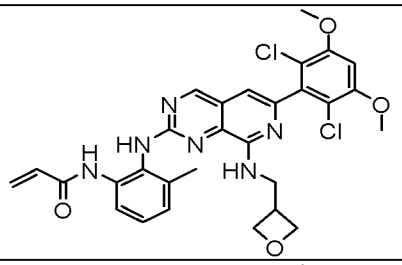
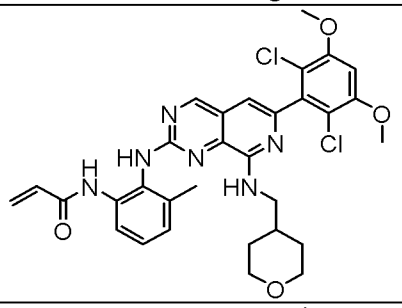
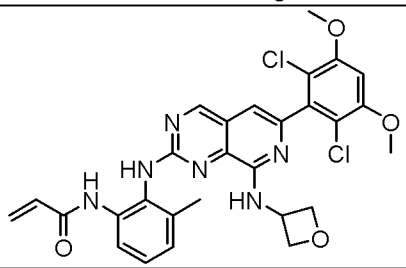
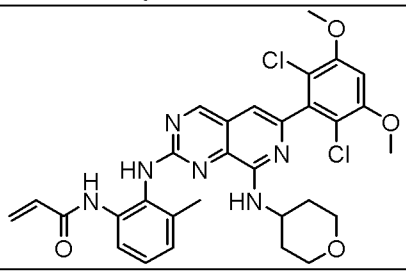
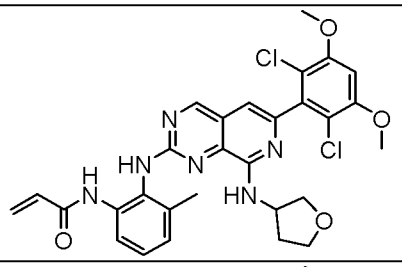
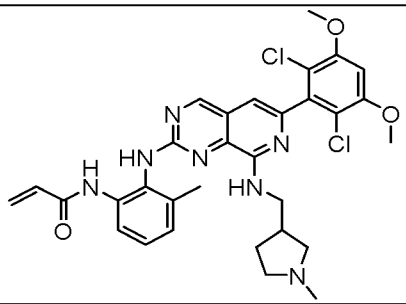
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.17 (s, 1H), 6.77 (s, 1H), 6.63 (s, 1H), 6.38 (d, J = 16.6 Hz, 2H), 6.33 – 6.24 (m, 1H), 5.70 (d, J = 10.1 Hz, 1H), 3.95 (s, 6H), 3.87 (s, 3H), 3.53-3.36(m, 2H), 1.19-1.10 (m, 1H), 0.55-0.41(m, 2H), 0.42-0.29 (m, 2H).

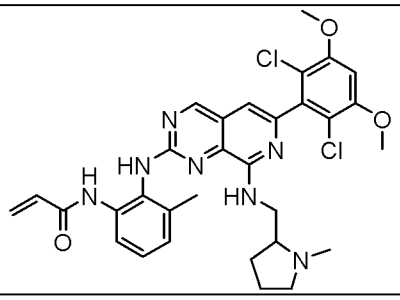
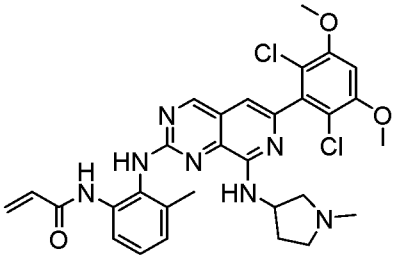
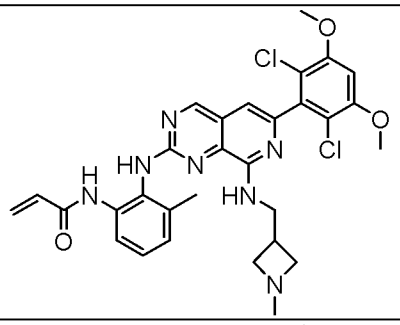
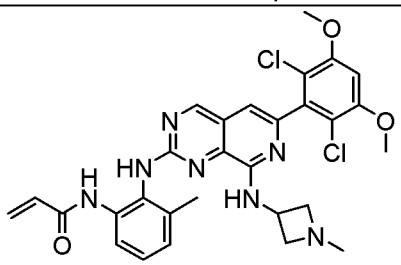
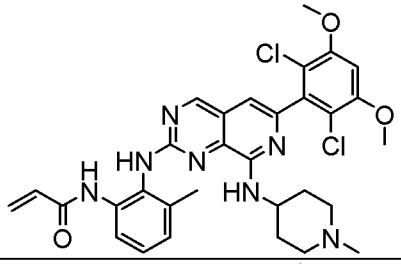
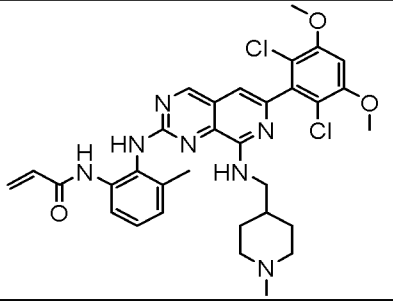
以下实施例 77-117 参照实施例 76 合成方法制备得到：

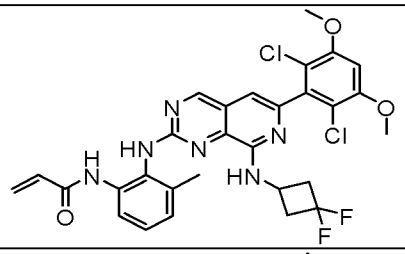
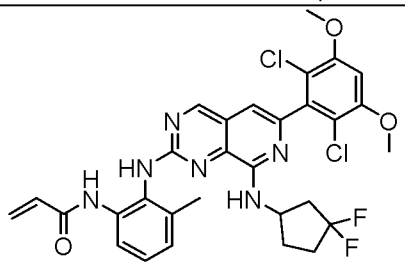
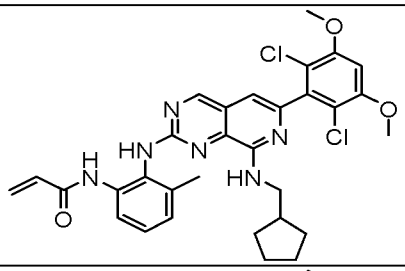
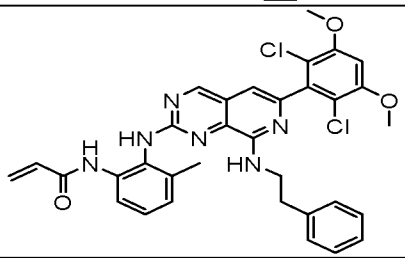
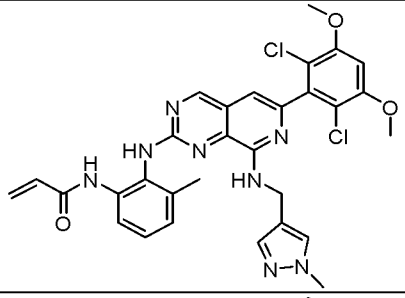
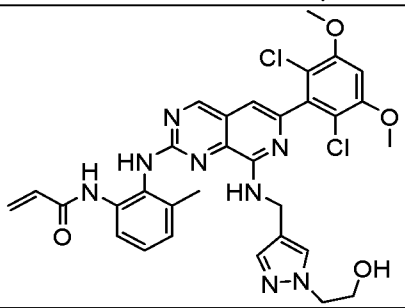
实施例编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
77		N-(2-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	579
78		N-(2-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	585
79		N-(2-((8-((环丙基甲基)氨基)-6-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	553

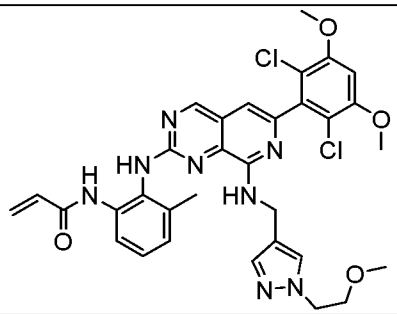
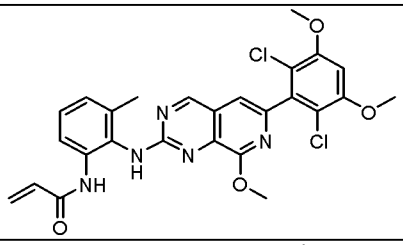
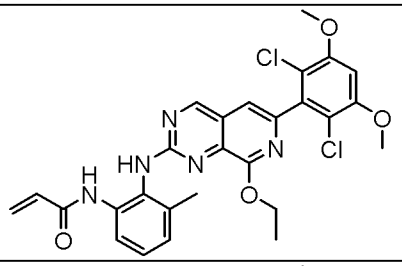
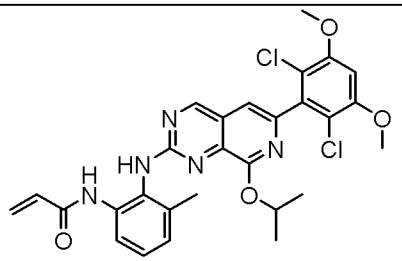
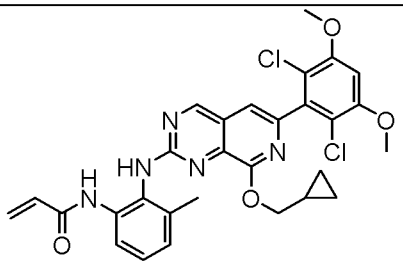
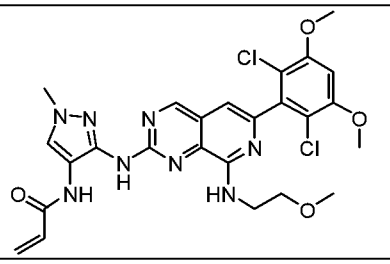
80		N-(2-((8-((环丙基甲基)氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	547
81		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-羟基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	569
82		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	583
83		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(乙基磺酰)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	645
84		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(二甲氨基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	596
85		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3-(二甲氨基)丙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	610
86		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	539

87		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	553
88		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2,2,2-三氟乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	607
89		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(二甲氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	553
90		N-(2-((8-((环丙基甲基)(甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	593
91		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(甲基磺酰氨基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	646
92		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	609
93		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	609

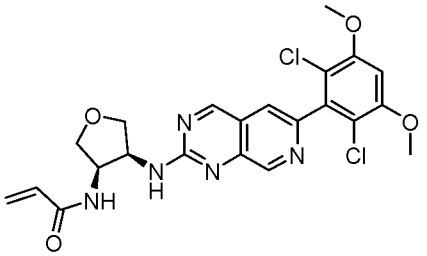
94		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((噁丁环-3-基甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	595
95		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢-2H-吡喃-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	623
96		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	581
97		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	609
98		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	595
99		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	622

100		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	622
101		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	608
102		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吖丁啶-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	608
103		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吖丁啶-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	594
104		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基哌啶-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	622
105		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基哌啶-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	636

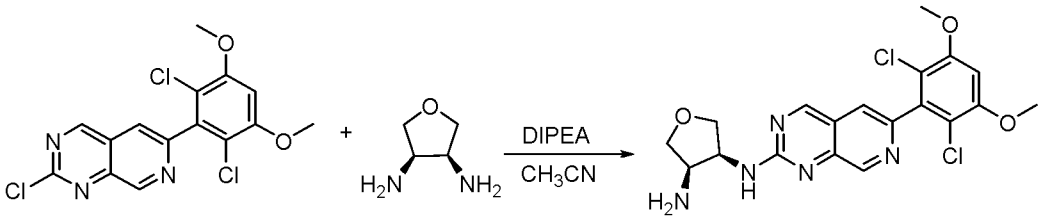
106		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,3-二氟环丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	615
107		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,3-二氟环戊基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	629
108		N-(2-((8-((环戊基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	607
109		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(苯乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	629
110		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	619
111		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-(2-羟基乙基)-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	649

112		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	663
113		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	540
114		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-乙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	554
115		N-(2-((6-(2,6-二氯-3,5-二甲氧苯基)-8-异丙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	568
116		N-(2-((8-(环丙基甲氧基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-3-甲基苯基)丙烯酰基酰胺	
117		N-(3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基-1H-吡唑-4-基)丙烯酰基酰胺	573

实施例 118 (±)-N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备

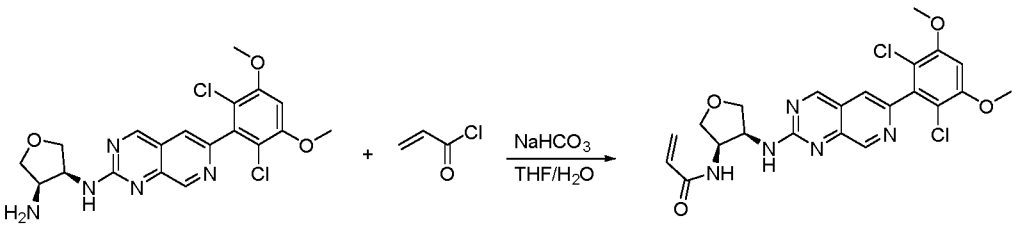


第一步：(±)-(3S,4R)-N^3-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)四氢呋喃-3,4-二胺的制备



2-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶（40.0 mg, 0.108 mmol）和反式-四氢呋喃-3,4-二胺二盐酸（28.3 mg，0.162 mmol）溶于乙腈（2 mL），再加入 N,N-二异丙基乙胺 (70 mg, 0.543 mmol)。加热至回流，反应 16 小时。冷却，反应液加入 EtOAc (10 mL) 稀释，饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，PTLC 分离（展开剂: CH_2Cl_2/MeOH = 10:1），得到化合物(3S,4R)-N^3-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)四氢呋喃-3,4-二胺（30 mg, 收率：64%）。MS m/z (ESI): 436.1 $[M+H]^+$.

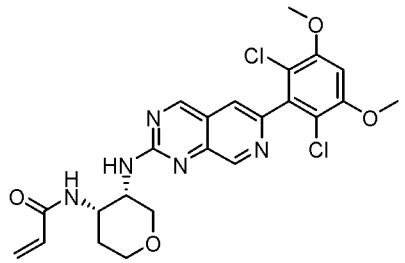
第二步：(±)-N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备



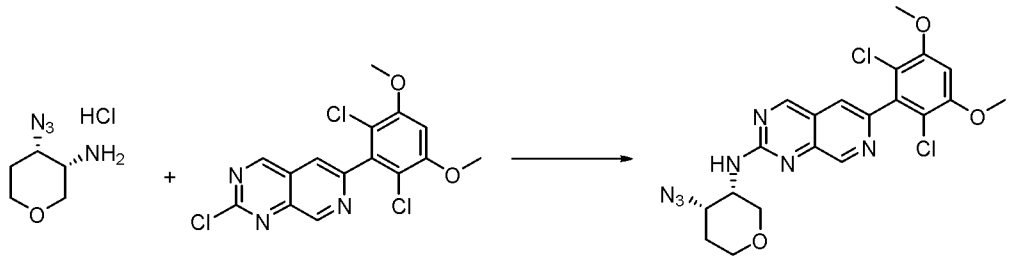
(±)- (3S,4R)-N3-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)四氢呋喃-3,4-二胺（30.0 mg, 0.069 mmol）溶于 THF/H_2O（1.2/0.3 mL），加入 $NaHCO_3$（23.0 mg，0.276 mmol）。冰水浴冷却，加入丙烯酰氯 (6.8 mg, 0.076 mmol)，加完后混合物在 0 ℃下搅拌 10 分钟。反应液加入 EtOAc（5 mL）稀释，饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，粗品经 PTLC 分离纯化（展开剂: CH_2Cl_2/MeOH= 10:1），得到化合物 N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺（17.4 mg, 收率: 52%）。

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 9.16 (s, 1H), 7.55 (s, 1H), 6.68 (s, 1H), 6.45 (d, J = 7.3 Hz, 1H), 6.27 (dd, J = 17.0, 1.4 Hz, 1H), 6.07 (dd, J = 16.9, 10.3 Hz, 1H), 5.63 (dd, J = 10.2, 1.4 Hz, 1H), 4.94 (dd, J = 11.6, 4.9 Hz, 1H), 4.90 – 4.79 (m, 1H), 4.34 – 4.19 (m, 2H), 3.98 (s, 6H), 3.90 – 3.79 (m, 2H).MS m/z (ESI): 490.1 $[M+H]^+$.

实施例 119 N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺的制备

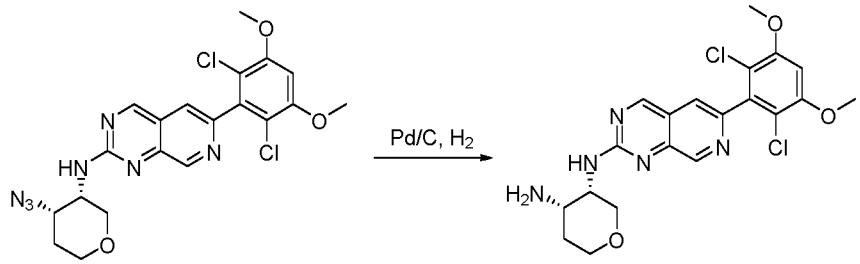


第一步：N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-胺的制备



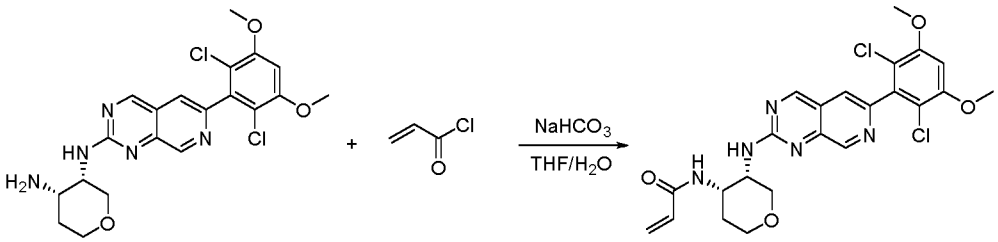
2-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶（100mg, 0.27mmol）溶于 NMP（3 mL），然后加入 Na_2CO_3（143 mg, 1.349 mmol）和(3S,4S)-4-叠氮四氢-2H-吡喃-3-胺的盐酸盐（72 mg, 0.405 mmol）。加热至 120 ℃反应 2 小时。反应完全，冷却至室温，加水，乙酸乙酯萃取三次，合并有机相，无水 Na_2SO_4 干燥。过滤，浓缩，柱层析（洗脱剂：石油醚/乙酸乙酯 2:1）分离，得到化合物 N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-胺(38mg, 产率：29%)。MS m/z (ESI): 478.4 $[M+H]^+$.

第二步：(3S,4S)-N^3-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)四氢-2H-吡喃-3,4-二胺的制备



N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-胺（38mg, 0.08 mmol）溶于 MeOH（8 mL），然后加入 Pd/C（10 mg），氢气球下室温搅拌 30 分钟。反应结束后，浓缩，柱层析（洗脱剂：二氯甲烷/甲醇 10:1）分离，得到化合物(3S,4S)-N^3-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)四氢-2H-吡喃-3,4-二胺（12mg, 产率：33%）。MS m/z (ESI): 451.2 $[M+H]^+$.

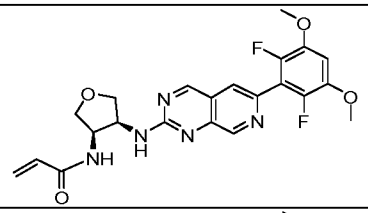
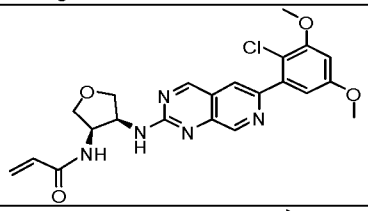
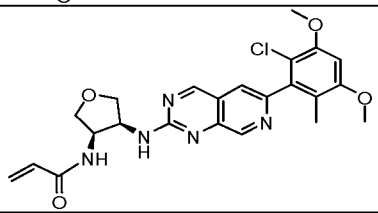
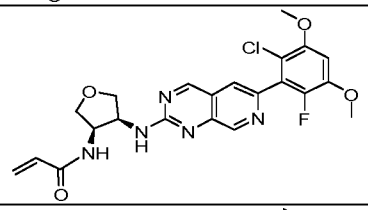
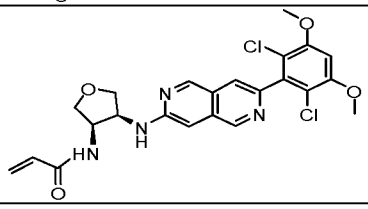
第三步：N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺的制备

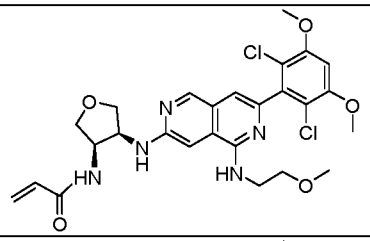
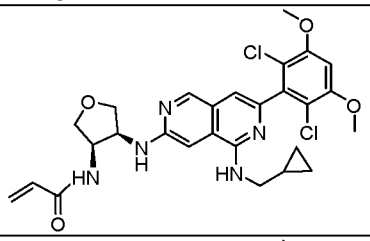
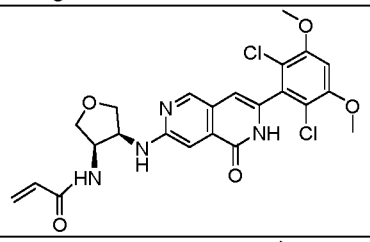
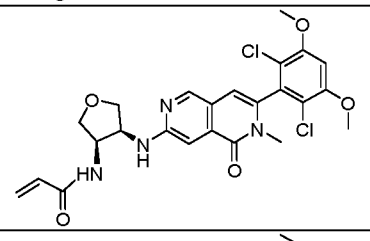
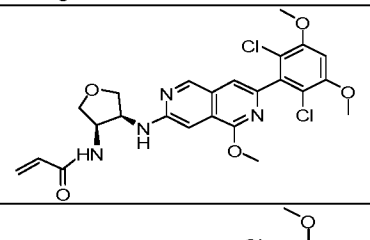
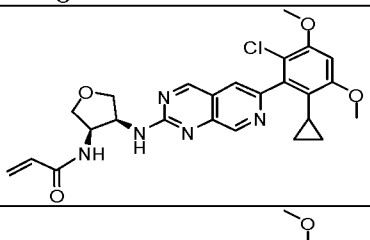
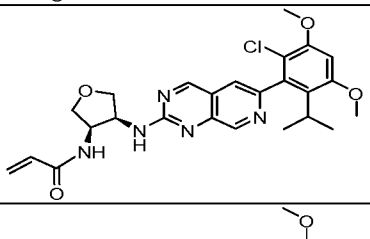
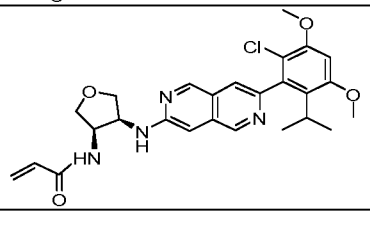


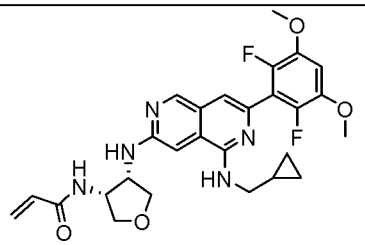
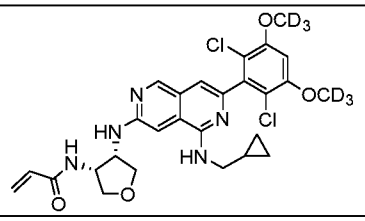
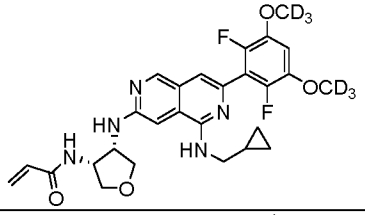
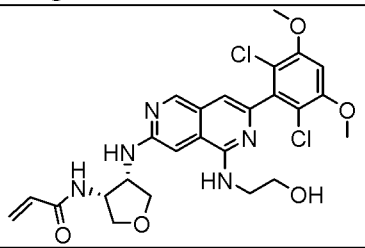
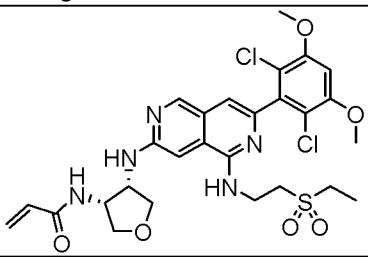
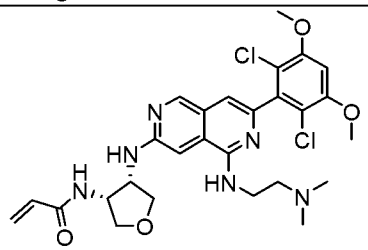
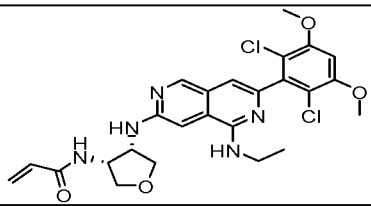
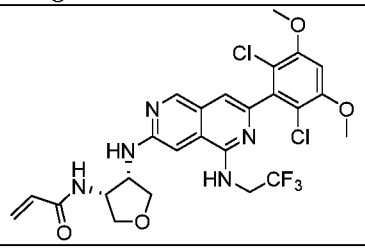
(3S,4S)-N^3-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)四氢-2H-吡喃-3,4-二胺（12mg，0.027mmol) 溶于 THF/H_2O（4 mL/1 mL），然后加入 $NaHCO_3$（12mg, 0.141mmol），冰水浴冷却，滴加丙烯酰氯（3mg, 0.027mmol）的 THF（2 mL）溶液。低温搅拌反应 10 分钟，反应完全。二氯甲烷萃取三次，合并有机相，饱和氯化钠洗，无水硫酸钠干燥，浓缩，柱层析 [洗脱剂: 二氯甲烷/石油醚(10:1)] 得到化合物 N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺（6.3mg，产率：47%)。

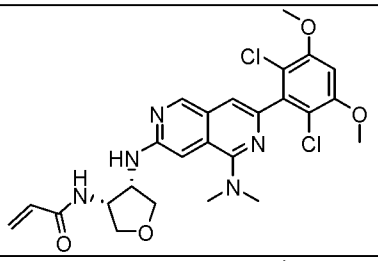
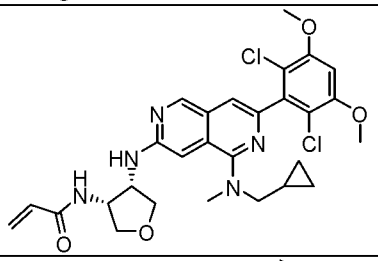
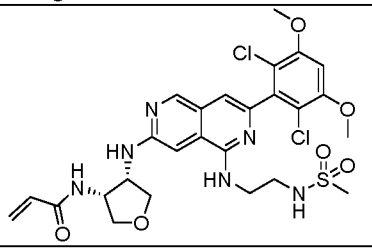
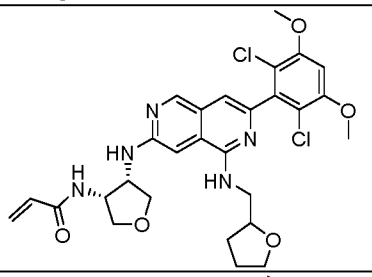
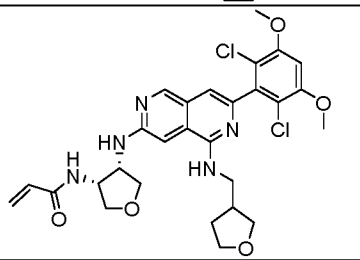
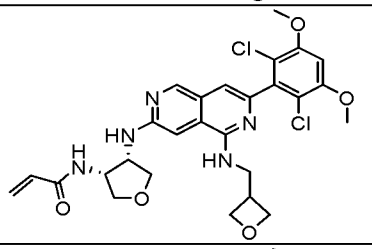
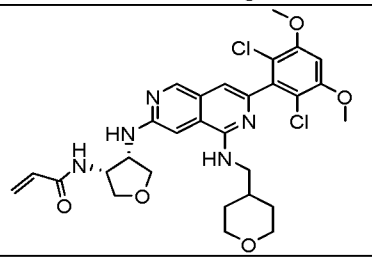
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 2H), 7.56 (s, 1H), 6.68 (s, 1H), 6.25 (dd, J = 16.9, 1.4 Hz, 1H), 6.01 (dd, J = 17.0, 10.3 Hz, 1H), 5.60 (dd, J = 10.3, 1.4 Hz, 1H), 4.55 (s, 1H), 4.35 (s, 1H), 4.11 – 4.00 (m, 2H), 3.98 (s, 6H), 3.78 (d, J = 12.1 Hz, 1H), 3.64 (dd, J = 13.4, 10.9 Hz, 1H), 2.24-2.20 (m, 2H), 2.02-1.99 (m, 2H).MS m/z (ESI): 505.4 $[M+H]^+$.

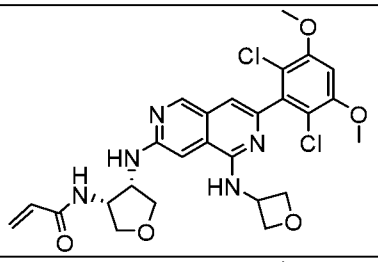
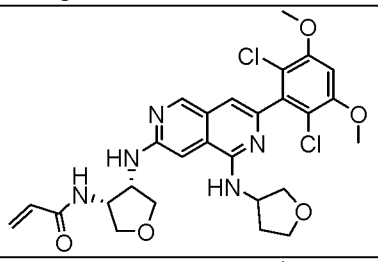
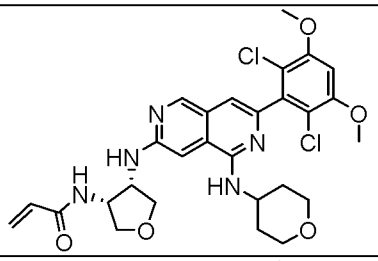
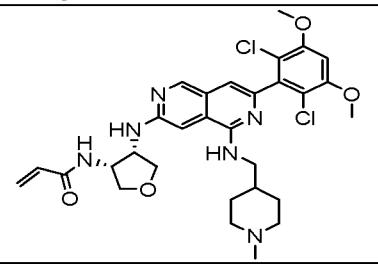
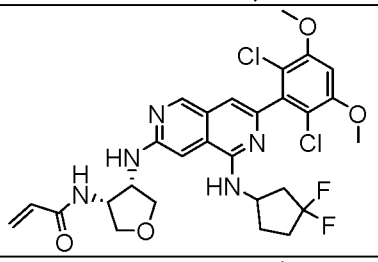
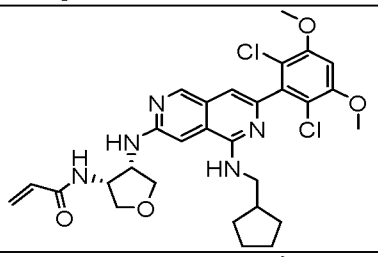
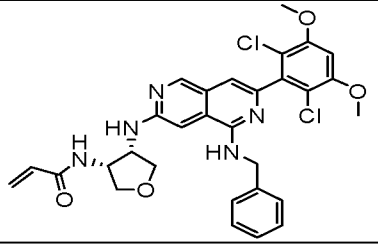
以下实施例 120-420、752 参照实施例 118 或 119 的合成方法制备得到：

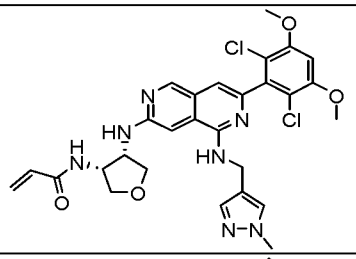
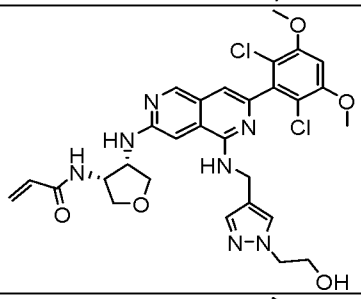
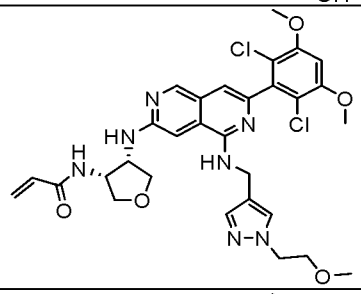
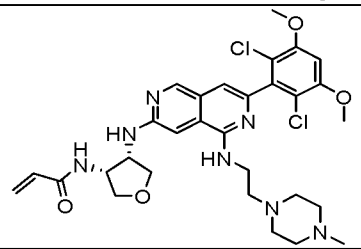
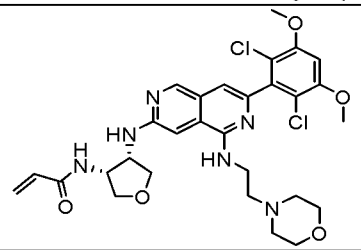
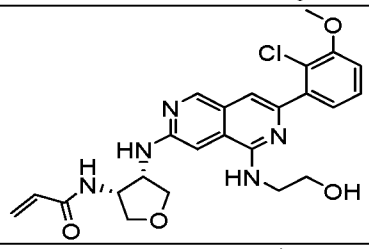
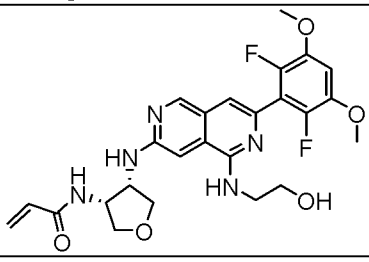
实施例编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
120		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	458
121		N-((3R,4S)-4-((6-(2-氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	456
122		N-((3R,4S)-4-((6-(2-氯-3,5-二甲氧基-6-甲基苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	470
123		N-((3R,4S)-4-((6-(2-氯-6-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	474
124		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	489

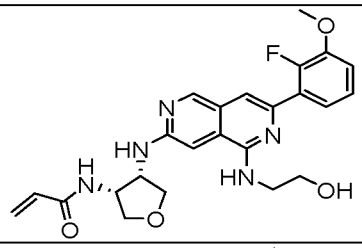
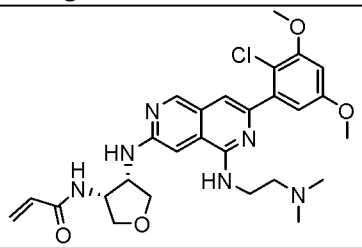
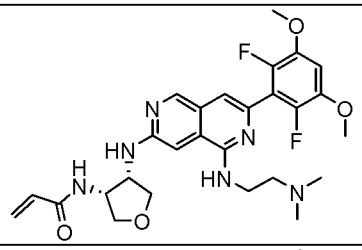
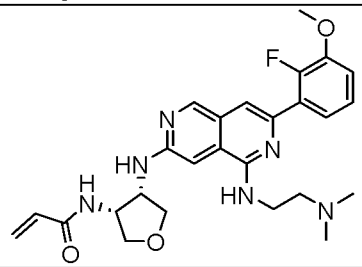
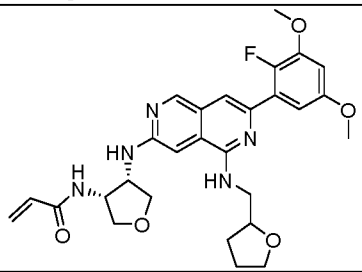
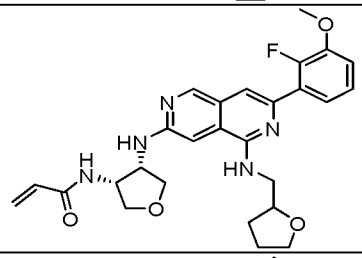
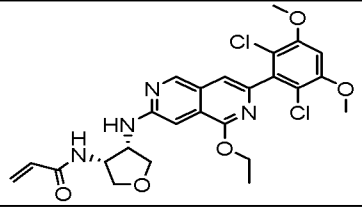
125		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-甲氧基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	562
126		N-((3R,4S)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	558
127		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	505
128		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	519
129		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-甲氧基-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	519
130		N-((3R,4S)-4-((6-(2-氯-6-环丙基-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	496
131		N-((3R,4S)-4-((6-(2-氯-6-异丙基-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	498
132		N-((3R,4S)-4-((7-(2-氯-6-异丙基-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	497

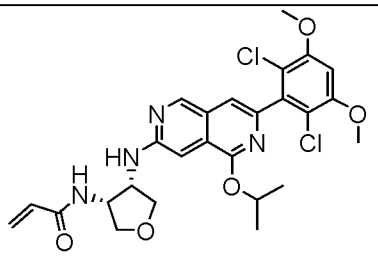
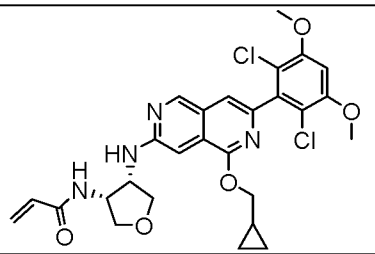
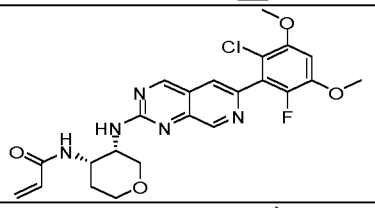
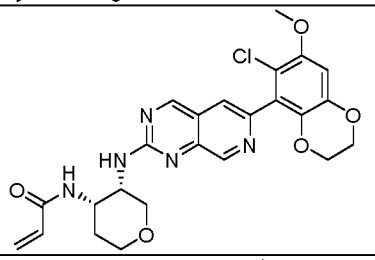
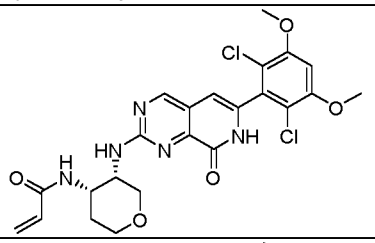
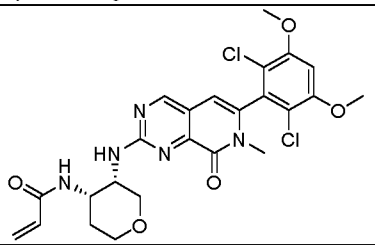
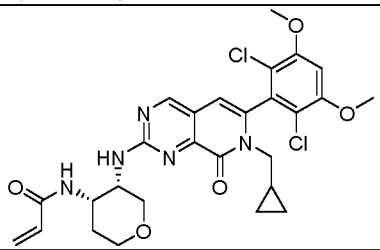
133		N-((3R,4S)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	526
134		N-((3R,4S)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	564
135		N-((3R,4S)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	532
136		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-羟基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	548
137		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(乙基磺酰)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	624
138		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(二甲氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
139		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(乙胺基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	532
140		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2,2,2-三氟乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	586

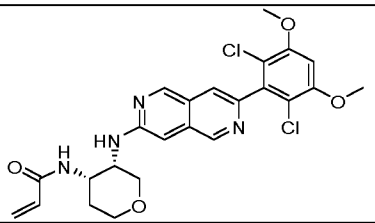
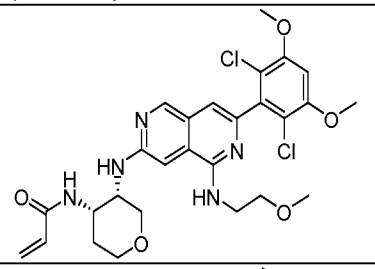
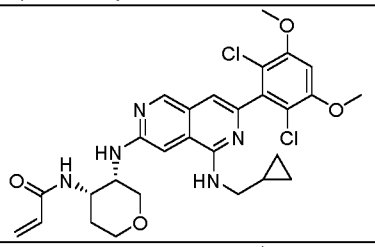
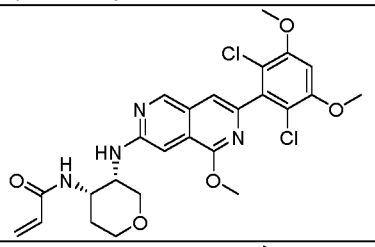
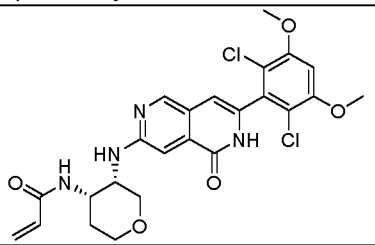
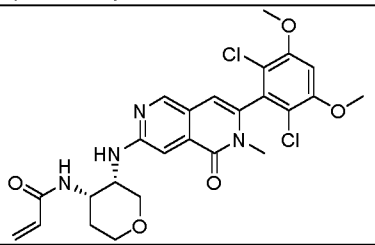
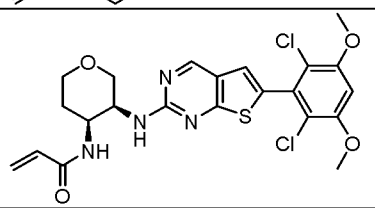
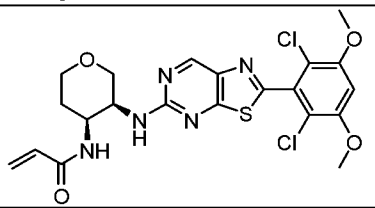
141		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(二甲氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	532
142		N-((3R,4S)-4-((5-((环丙基甲基)(甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	572
143		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(甲基磺酰氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	625
144		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
145		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-3-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
146		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((噁丁环-3-基甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
147		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢-2H-吡喃-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602

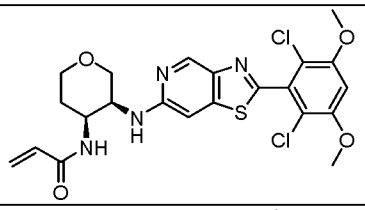
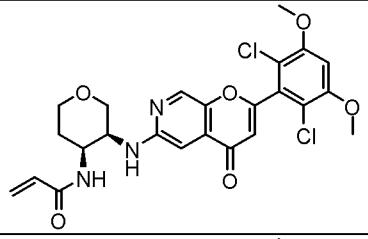
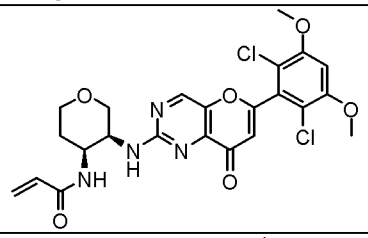
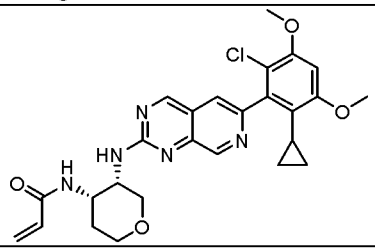
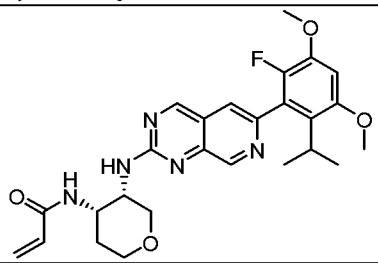
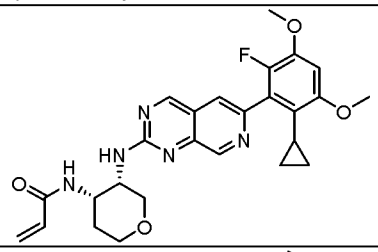
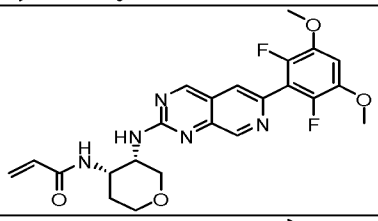
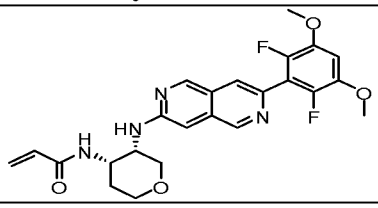
148		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	560
149		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
150		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢-2H-吡喃-4-基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
151		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基哌啶-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	615
152		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((3,3-二氟环戊基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	608
153		N-((3R,4S)-4-((5-((环戊基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	586
154		N-((3R,4S)-4-((5-(苯甲基氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	594

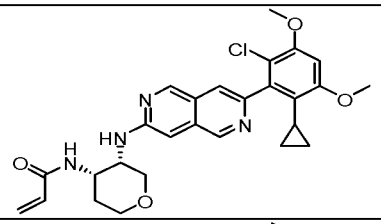
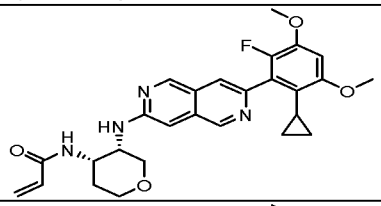
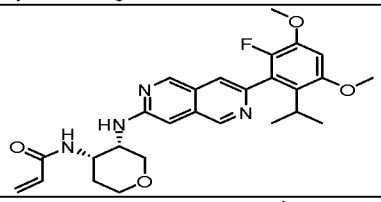
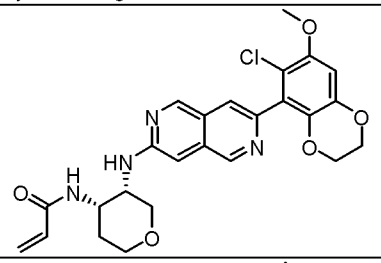
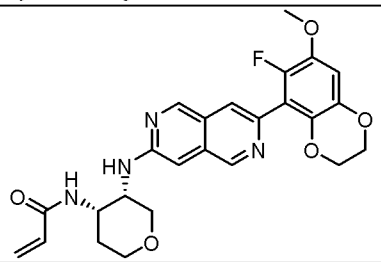
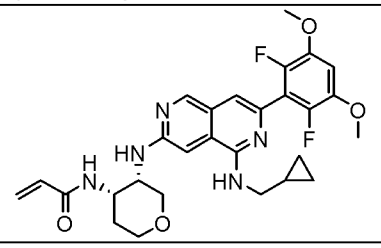
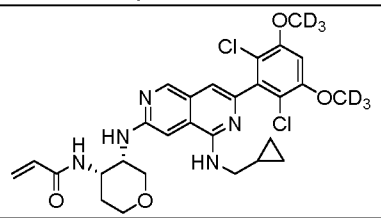
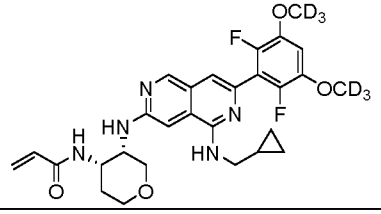
155		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	598
156		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-(2-羟基乙基)-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	628
157		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	642
158		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(4-甲基哌嗪-1-基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	630
159		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-吗啉代乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	617
160		N-((3R,4S)-4-((7-(2-氯-3-甲氧苯基)-5-((2-羟基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	484
161		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-((2-羟基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	516

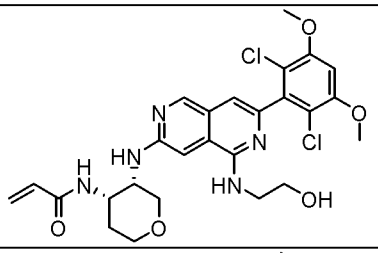
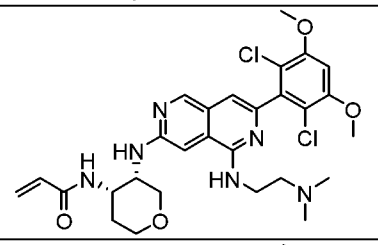
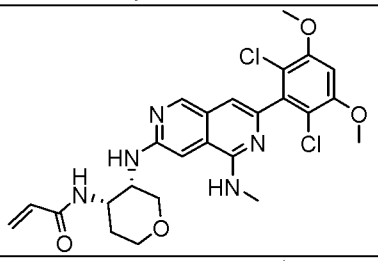
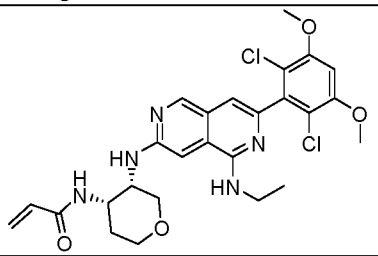
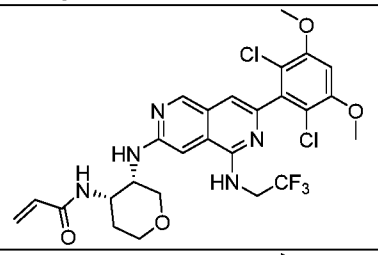
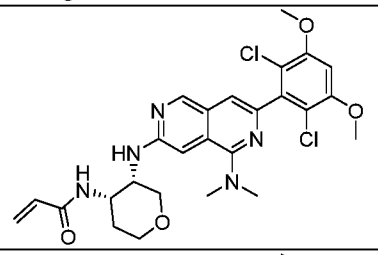
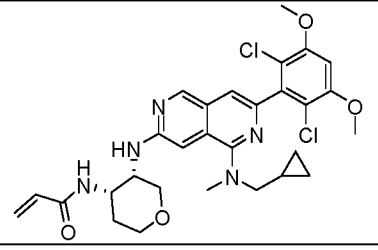
162		N-((3R,4S)-4-((7-(2-氟-3-甲氧苯基)-5-((2-羟基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	468
163		N-((3R,4S)-4-((7-(2-氯-3,5-二甲氧苯基)-5-((2-(二甲氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	541
164		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-((2-(二甲氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	543
165		N-((3R,4S)-4-((5-((2-(二甲氨基)乙基)氨基)-7-(2-氟-3-甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	495
167		N-((3R,4S)-4-((7-(2-氟-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	538
168		N-((3R,4S)-4-((7-(2-氟-3-甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	508
169		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-乙氧基-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	533

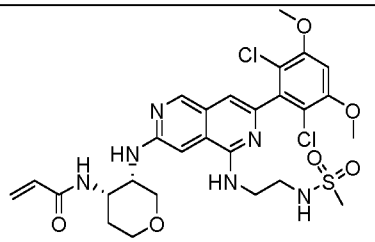
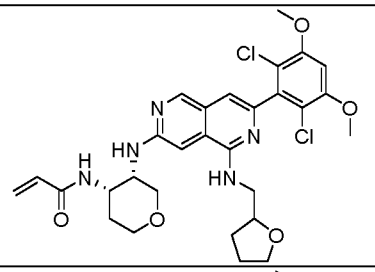
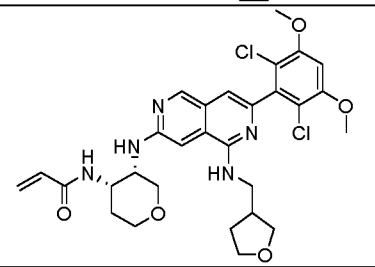
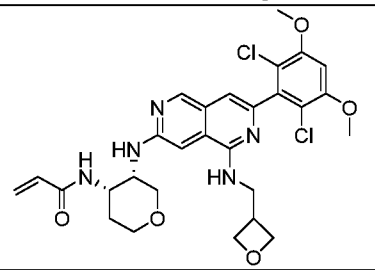
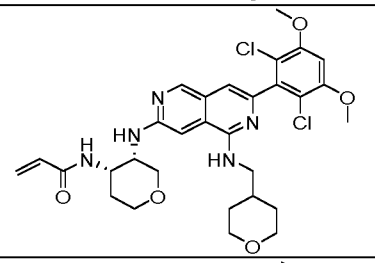
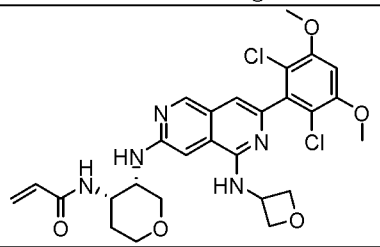
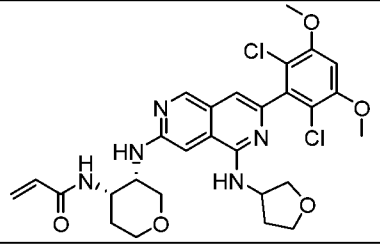
170		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-异丙氧基-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	547
171		N-((3R,4S)-4-((5-(环丙基甲氧基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	559
172		N-((3S,4S)-3-((6-(2-氯-6-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	488
173		N-((3S,4S)-3-((6-(6-氯-7-甲氧基-2,3-二氢苯并[b][1,4]二噁英-5-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	498
174		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	520
175		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-7-甲基-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	534
176		N-((3S,4S)-3-((7-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	574

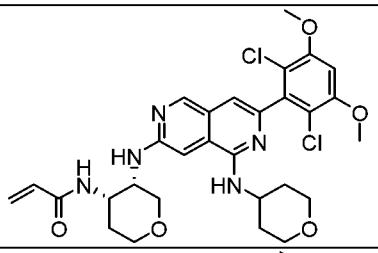
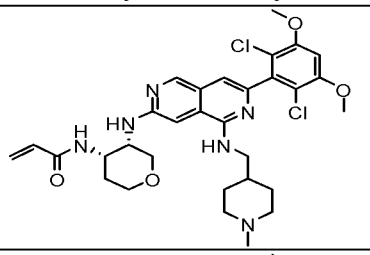
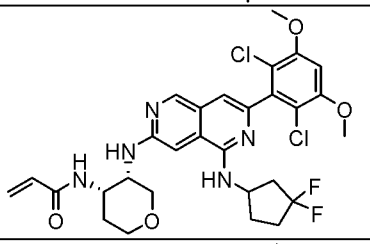
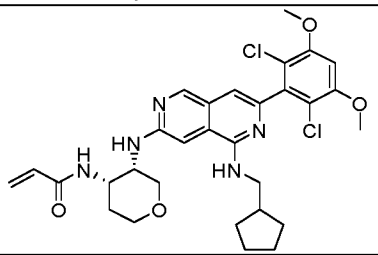
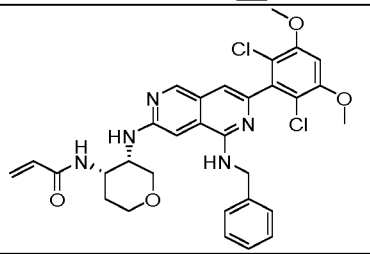
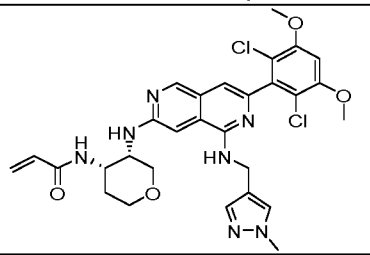
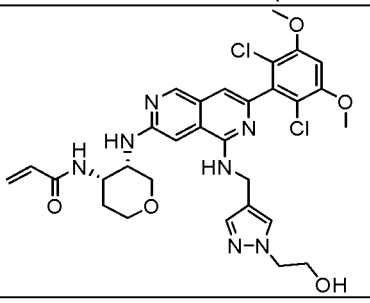
177		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	503
178		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-甲氧基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	576
179		N-((3S,4S)-3-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	572
180		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-甲氧基-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	533
181		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	519
182		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	533
183		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)噻吩并[2,3-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	509
184		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)噻唑并[5,4-d]嘧啶-5-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	510

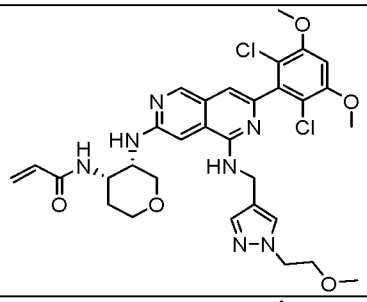
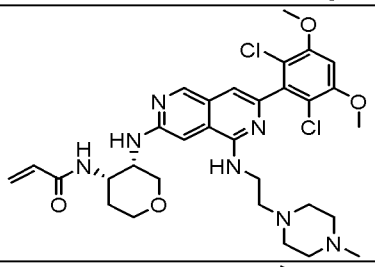
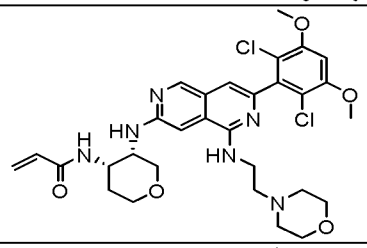
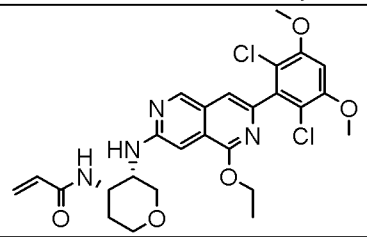
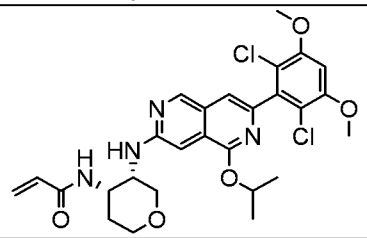
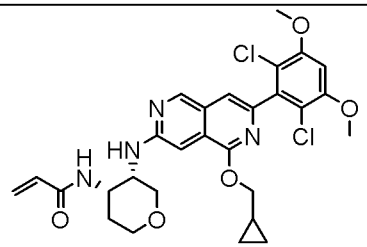
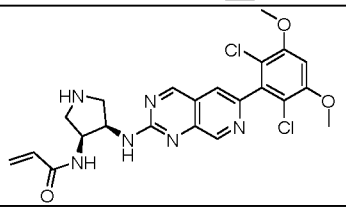
185		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)噻唑并[4,5-c]吡啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	509
186		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-羰基-4H-吡喃并[2,3-c]吡啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	520
187		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-8H-吡喃并[3,2-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	521
188		N-((3S,4S)-3-((6-(2-氯-6-环丙基-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	510
189		N-((3S,4S)-3-((6-(2-氟-6-异丙基-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	496
190		N-((3S,4S)-3-((6-(2-环丙基-6-氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	493
191		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	472
192		N-((3S,4S)-3-((7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	471

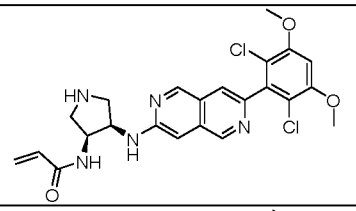
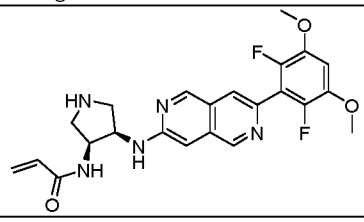
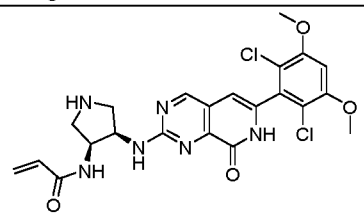
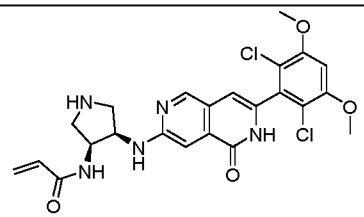
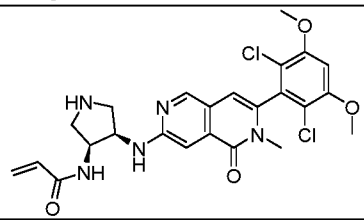
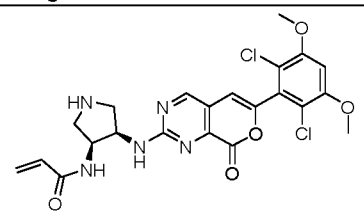
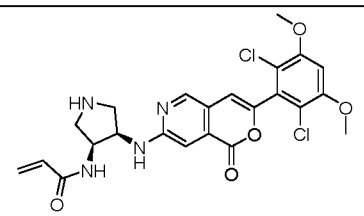
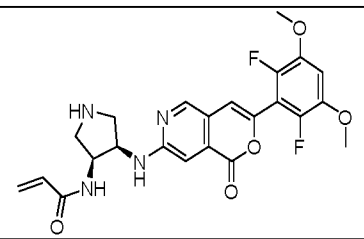
193		N-((3S,4S)-3-((7-(2-氯-6-环丙基-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	509
194		N-((3S,4S)-3-((7-(2-环丙基-6-氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	493
195		N-((3S,4S)-3-((7-(2-氟-6-异丙基-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	495
196		N-((3S,4S)-3-((7-(6-氯-7-甲氧基-2,3-二氢苯并[b][1,4]二噁英-5-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	496
197		N-((3S,4S)-3-((7-(6-氟-7-甲氧基-2,3-二氢苯并[b][1,4]二噁英-5-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	481
198		N-((3S,4S)-3-((5-((环丙基甲基)氨基)-7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	540
199		N-((3S,4S)-3-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	578
200		N-((3S,4S)-3-((5-((环丙基甲基)氨基)-7-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	546

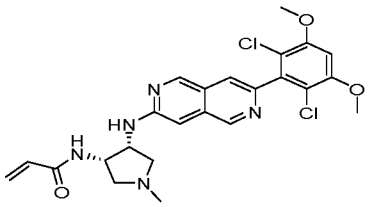
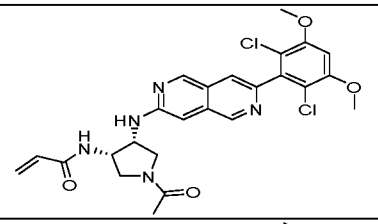
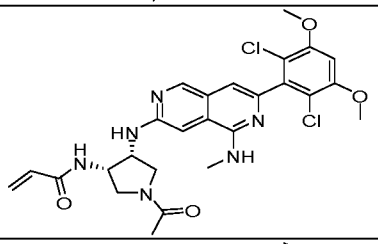
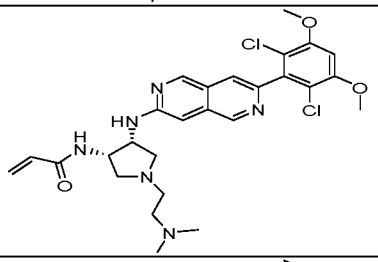
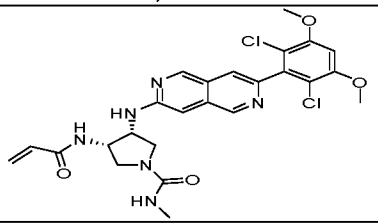
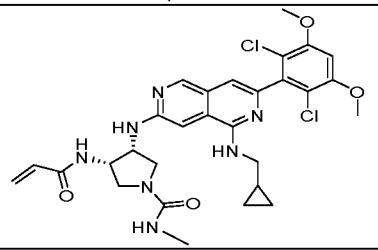
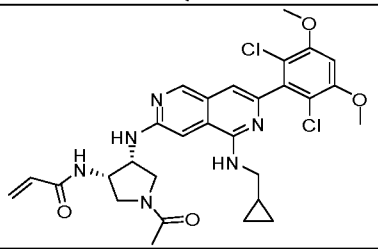
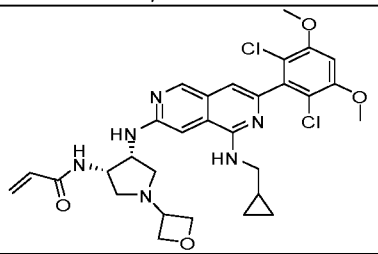
201		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-羟基乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	562
202		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(二甲氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
203		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(甲基氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	532
204		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(乙胺基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	546
205		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2,2,2-三氟乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	600
206		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(二甲氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	546
207		N-((3S,4S)-3-((5-((环丙基甲基)(甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	586

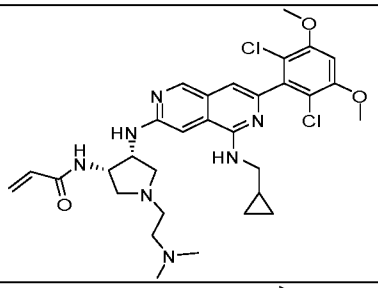
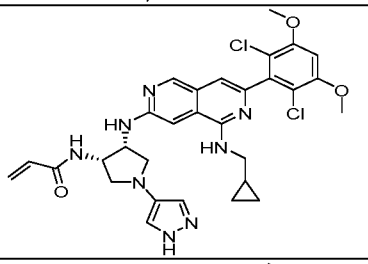
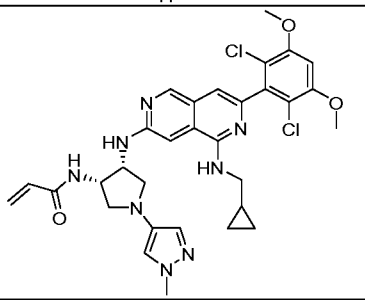
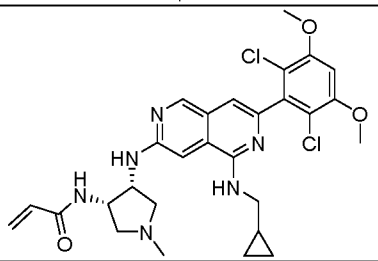
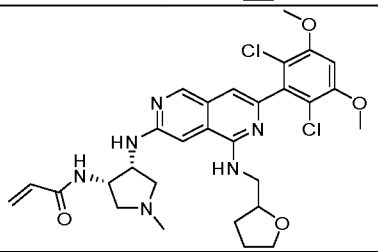
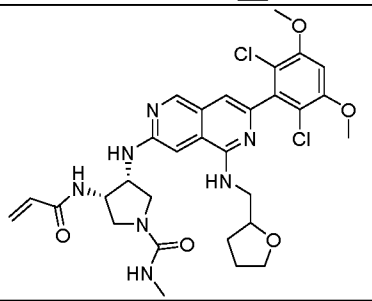
208		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(甲基磺酰氨基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	639
209		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
210		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-3-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
211		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((噁丁环-3-基甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	588
212		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢-2H-吡喃-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
213		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	574
214		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	588

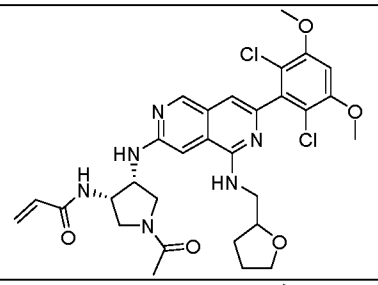
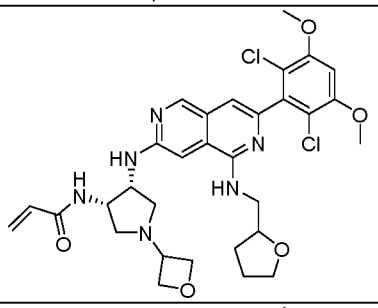
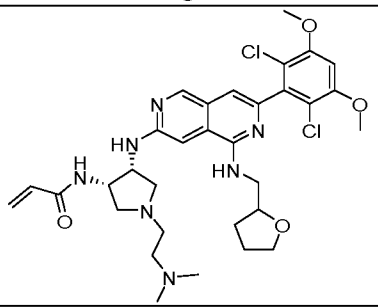
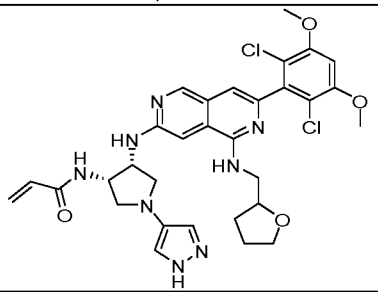
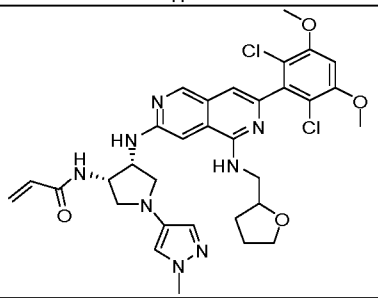
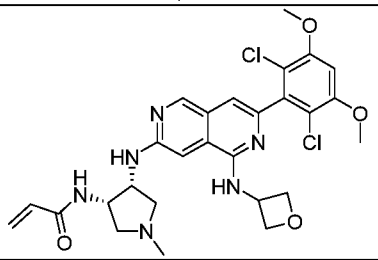
215		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢-2H-吡喃-4-基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
216		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基哌啶-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	629
217		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((3,3-二氟环戊基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	622
218		N-((3S,4S)-3-((5-((环戊基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	600
219		N-((3S,4S)-3-((5-(苯甲基氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	608
220		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-甲基-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	612
221		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-(2-羟基乙基)-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	642

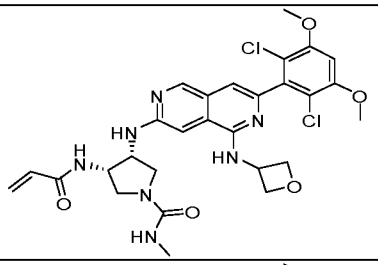
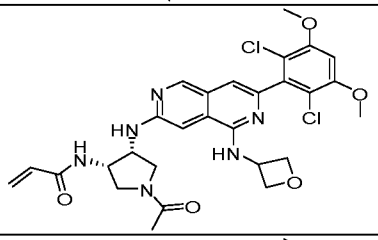
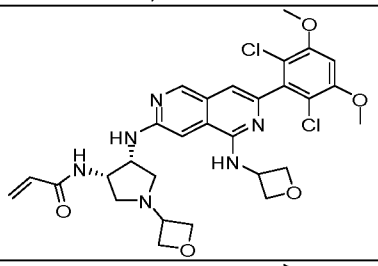
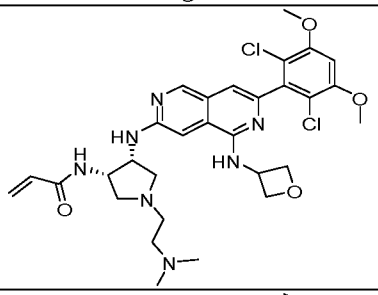
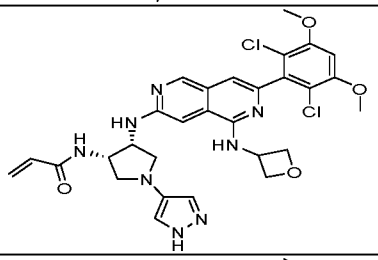
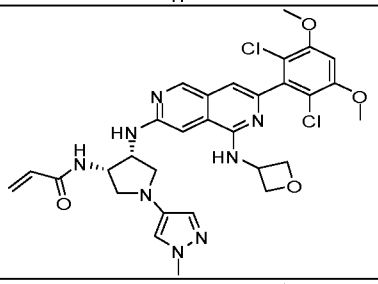
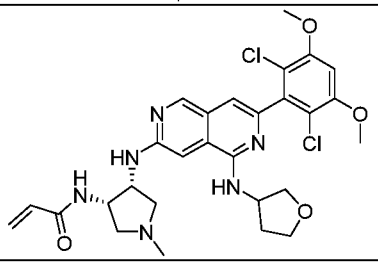
222		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	656
223		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-(4-甲基哌嗪-1-基)乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	644
224		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-吗啉代乙基)氨基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	631
225		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-乙氧基-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	547
226		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-异丙氧基-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	561
227		N-((3S,4S)-3-((5-(环丙基甲氧基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	573
228		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	489

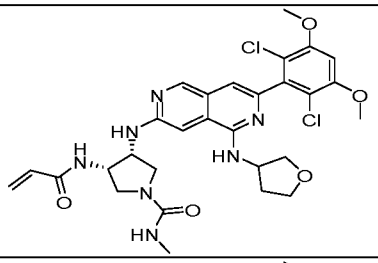
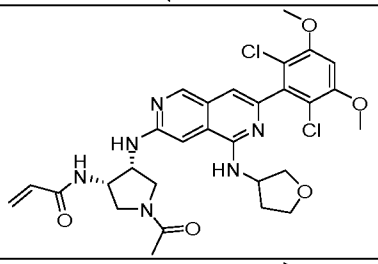
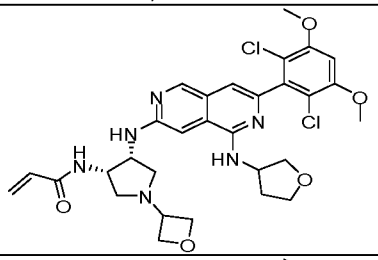
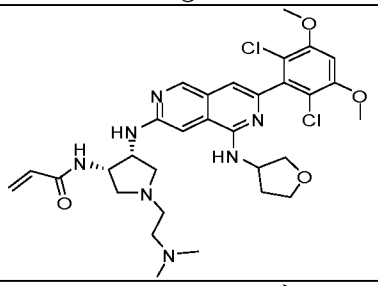
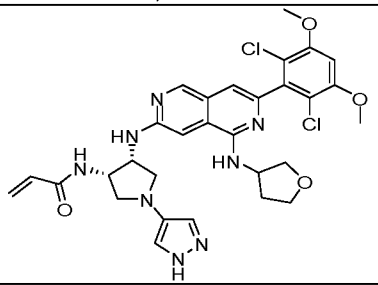
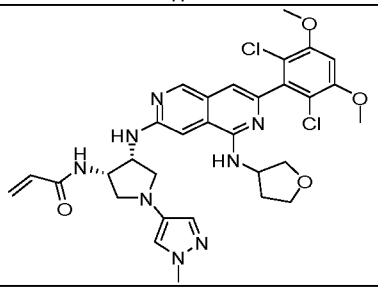
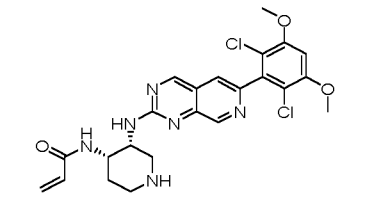
229		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	488
230		N-((3S,4R)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	455
231		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	505
232		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	504
233		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	518
234		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-8H-吡喃并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	506
235		N-((3S,4R)-4-((3-(2,6-二氯-3,5-二甲氧苯基)-1-羰基-1H-吡喃并[4,3-c]吡啶-7-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	505
236		N-((3S,4R)-4-((3-(2,6-二氟-3,5-二甲氧苯基)-1-羰基-1H-吡喃并[4,3-c]吡啶-7-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	472

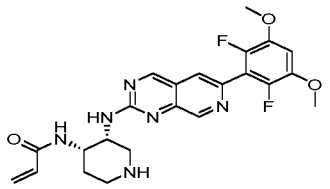
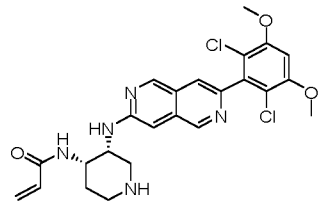
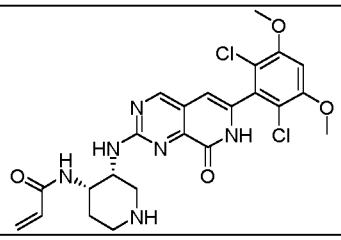
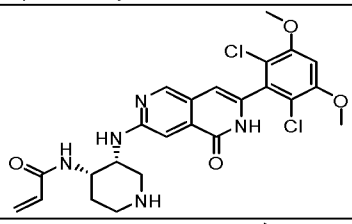
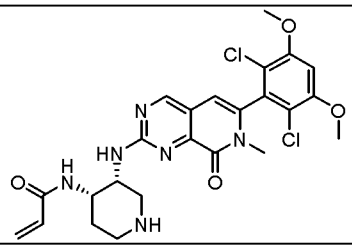
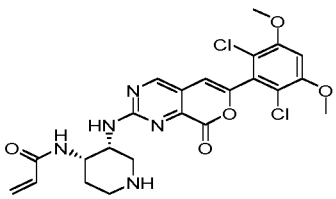
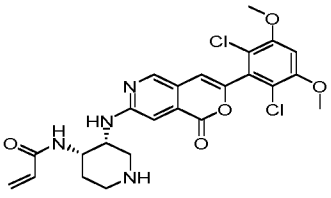
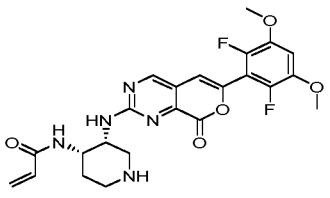
237		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	502
238		N-((3S,4R)-1-乙酰基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	530
239		N-((3S,4R)-1-乙酰基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(甲基氨基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	559
240		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	559
241		(3S,4R)-3-丙烯酰基酰氨基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-N-甲基吡咯烷-1-甲酰胺	545
242		(3S,4R)-3-丙烯酰基酰氨基-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-N-甲基吡咯烷-1-甲酰胺	614
243		N-((3S,4R)-1-乙酰基-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	599
244		N-((3S,4R)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	613

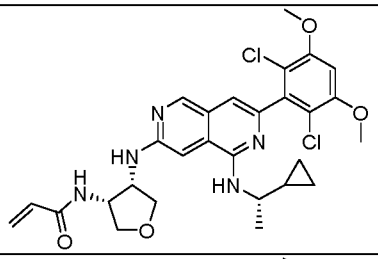
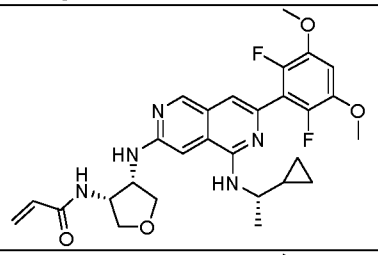
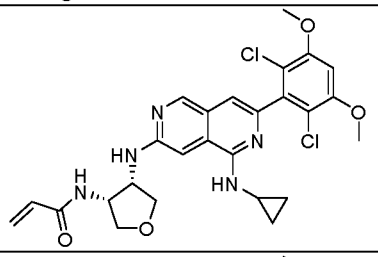
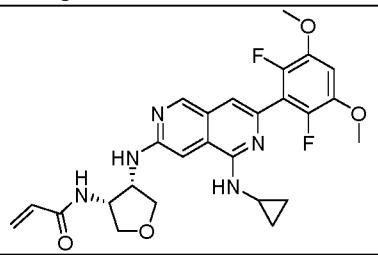
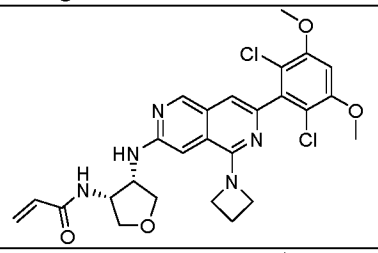
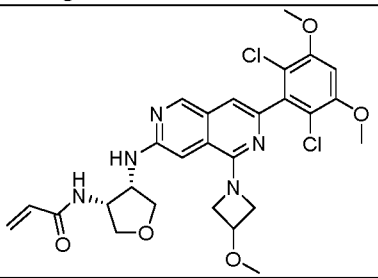
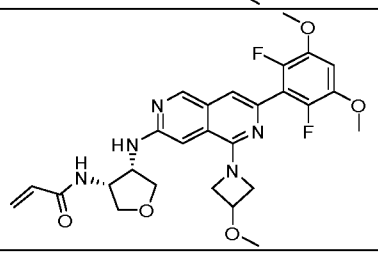
245		N-((3S,4R)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	628
246		N-((3S,4R)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	623
247		N-((3S,4R)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	637
248		N-((3S,4R)-4-((5-((环丙基甲基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	571
249		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	601
250		(3S,4R)-3-丙烯酰基酰氨基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-N-甲基吡咯烷-1-甲酰胺	644

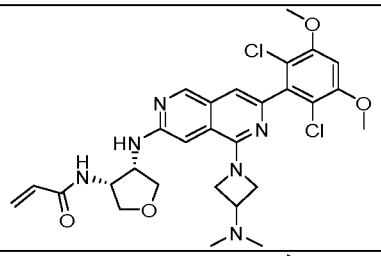
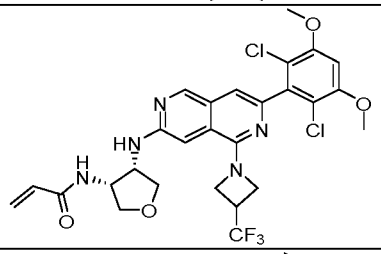
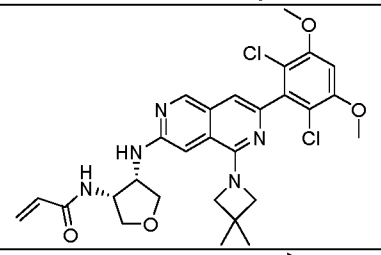
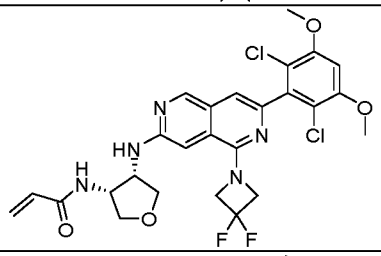
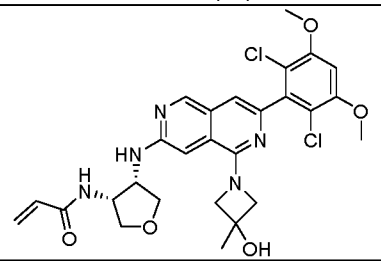
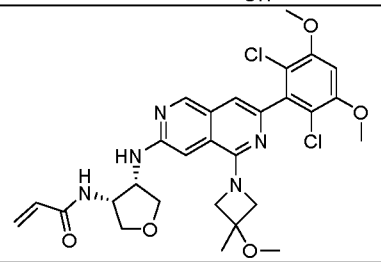
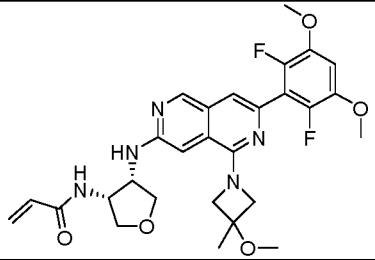
251		N-((3S,4R)-1-乙酰基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	629
252		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	643
253		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	658
254		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	653
255		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(((四氢呋喃-2-基)甲基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	667
256		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	573

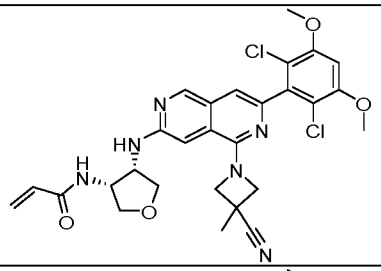
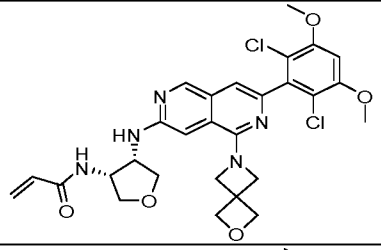
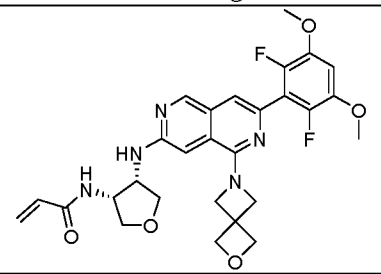
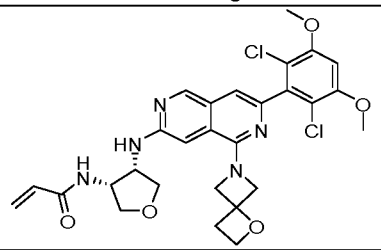
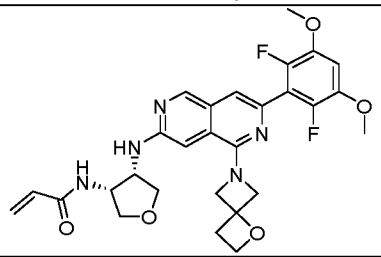
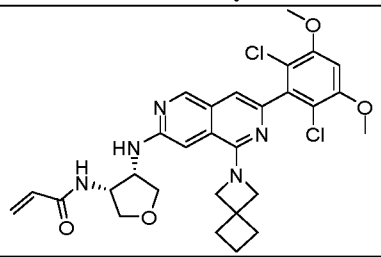
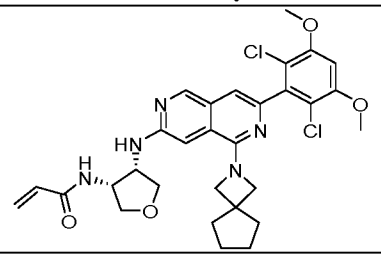
257		(3S,4R)-3-丙烯酰基酰氨基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-N-甲基吡咯烷-1-甲酰胺	616
258		N-((3S,4R)-1-乙酰基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	601
259		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	615
260		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	630
261		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	625
262		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(噁丁环-3-基氨基)-2,6-二氮杂萘-3-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	639
263		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	587

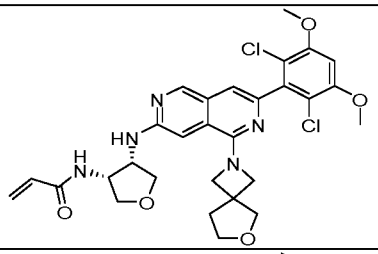
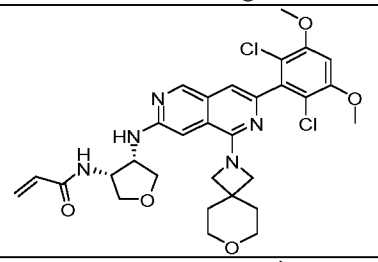
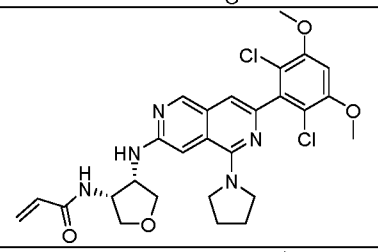
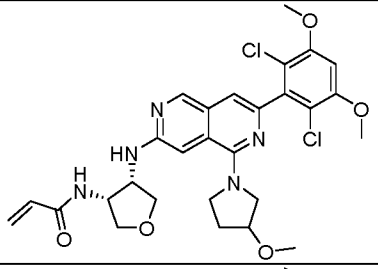
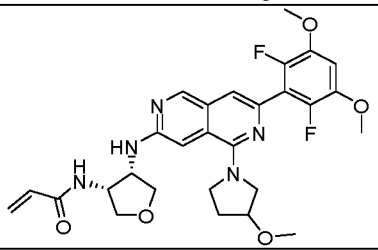
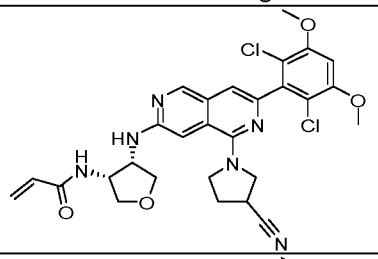
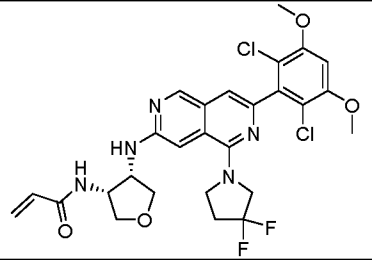
264		(3S,4R)-3-丙烯酰基酰氨基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-N-甲基吡咯烷-1-甲酰胺	630
265		N-((3S,4R)-1-乙酰基-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	615
266		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	629
267		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	644
268		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	639
269		N-((3S,4R)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((四氢呋喃-3-基)氨基)-2,6-二氮杂萘-3-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	653
270		N-((3R,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)哌啶-4-基)丙烯酰基酰胺	503

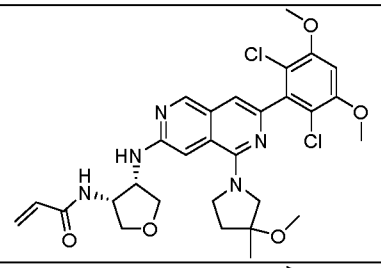
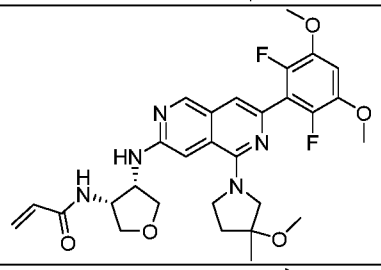
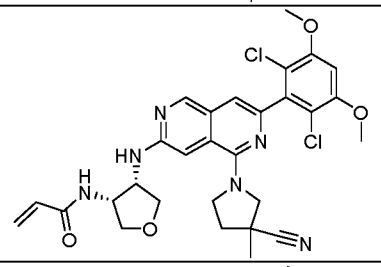
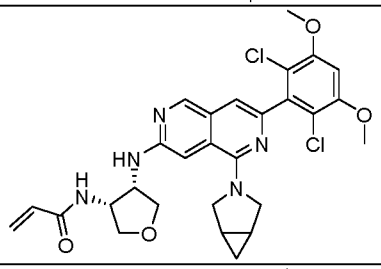
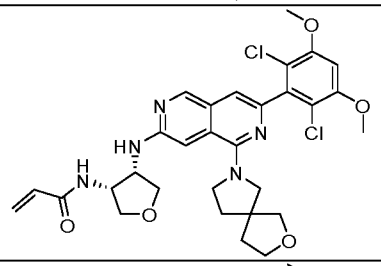
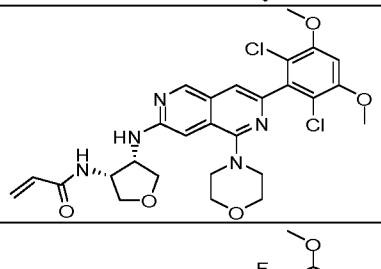
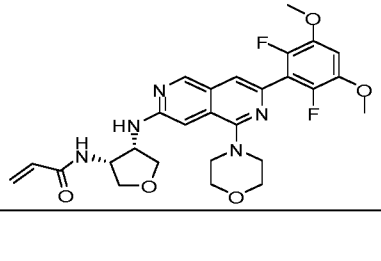
271		N-((3R,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)哌啶-4-基)丙烯酰基酰胺	470
272		N-((3R,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)哌啶-4-基)丙烯酰基酰胺	502
273		N-((3R,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)哌啶-4-基)丙烯酰基酰胺	519
274		N-((3R,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)氨基)哌啶-4-基)丙烯酰基酰胺	518
275		N-((3R,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-7-甲基-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)氨基)哌啶-4-基)丙烯酰基酰胺	533
276		N-((3R,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-8H-吡喃并[3,4-d]嘧啶-2-基)氨基)哌啶-4-基)丙烯酰基酰胺	520
277		N-((3R,4S)-3-((3-(2,6-二氯-3,5-二甲氧苯基)-1-羰基-1H-吡喃并[4,3-c]吡啶-7-基)氨基)哌啶-4-基)丙烯酰基酰胺	519
278		N-((3R,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-羰基-8H-吡喃并[3,4-d]嘧啶-2-基)氨基)哌啶-4-基)丙烯酰基酰胺	487

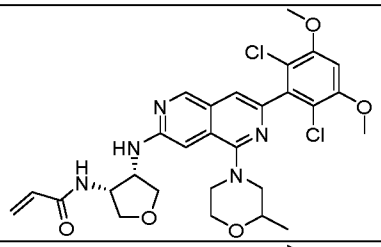
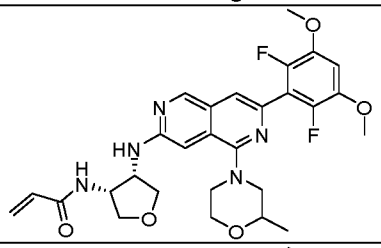
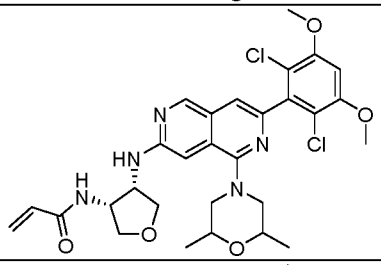
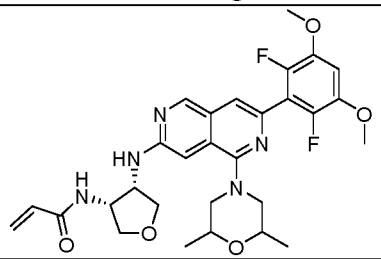
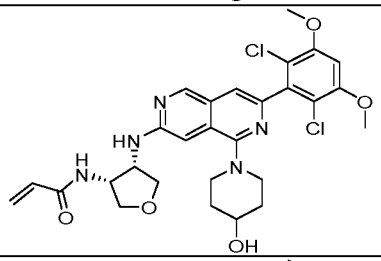
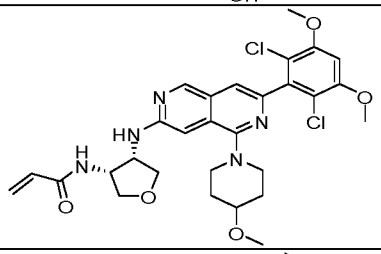
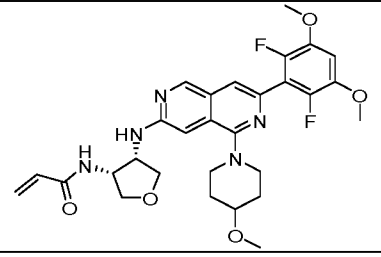
279		N-((3R,4S)-4-((5-(((S)-1-环丙基乙基)氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	572
280		N-((3R,4S)-4-((5-(((S)-1-环丙基乙基)氨基)-7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	540
281		N-((3R,4S)-4-((5-(环丙基氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	544
282		N-((3R,4S)-4-((5-(环丙基氨基)-7-(2,6-二氟-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	512
283		N-((3R,4S)-4-((5-(吖丁啶-1-基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	544
284		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
285		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(3-甲氧基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	542

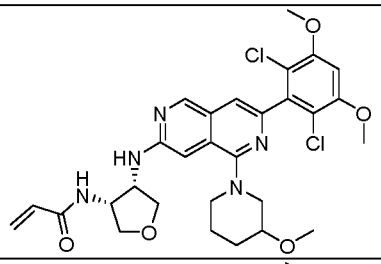
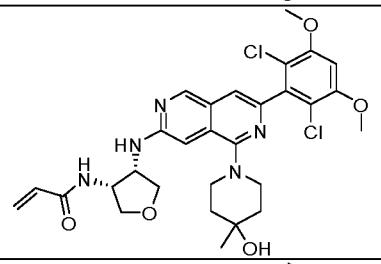
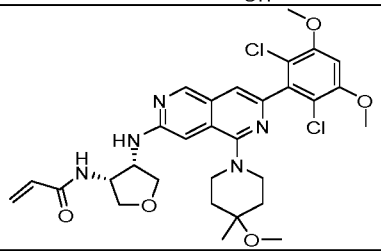
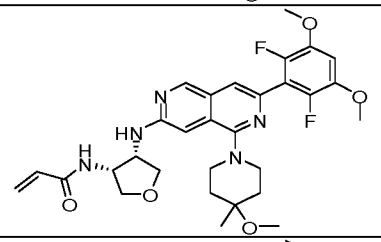
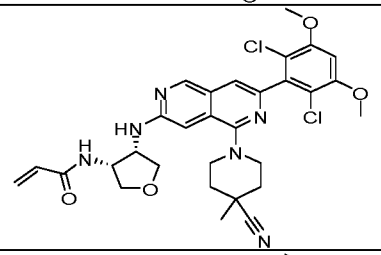
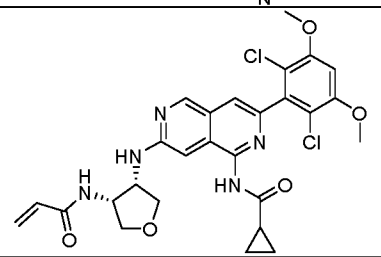
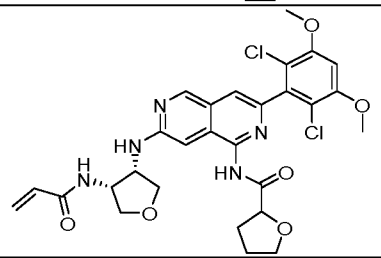
286		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-(二甲氨基)吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
287		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-(三氟甲基)吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	612
288		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3,3-二甲基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	572
289		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3,3-二氟吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	580
290		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-羟基-3-甲基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
291		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基-3-甲基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
292		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(3-甲氧基-3-甲基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	556

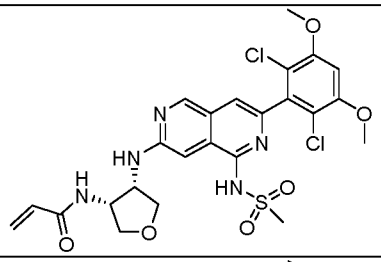
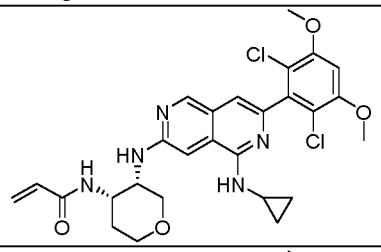
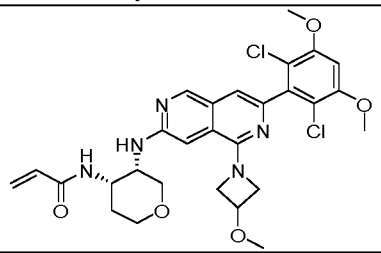
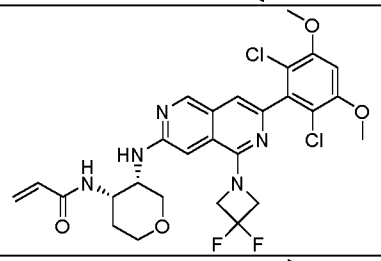
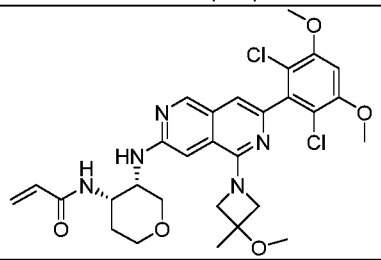
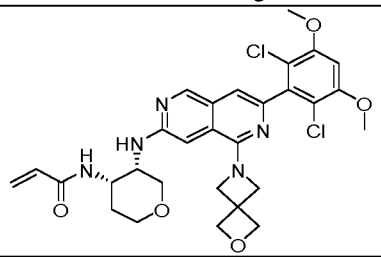
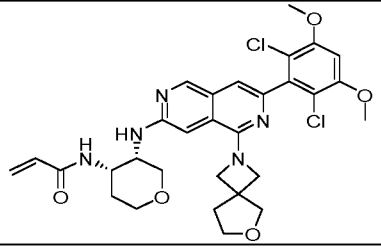
293		N-((3R,4S)-4-((5-(3-氰基-3-甲基吖丁啶-1-基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	583
294		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	586
295		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	554
296		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(1-氧杂-6-氮杂螺[3.3]庚烷-6-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	586
297		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(1-氧杂-6-氮杂螺[3.3]庚烷-6-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	554
298		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2-氮杂螺[3.3]庚烷-2-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584
299		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2-氮杂螺[3.4]辛烷-2-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	598

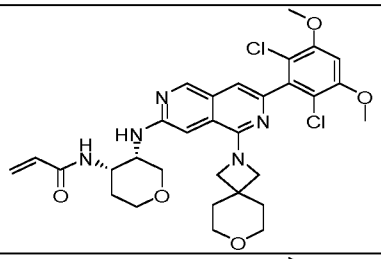
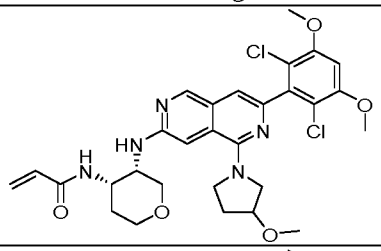
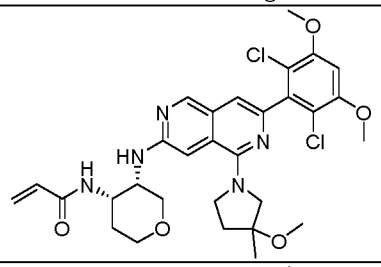
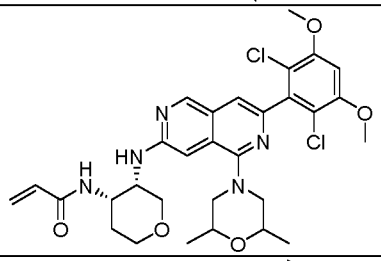
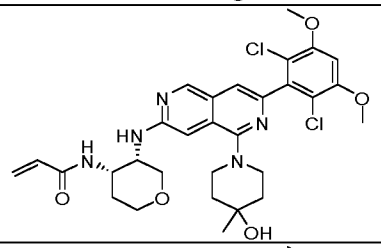
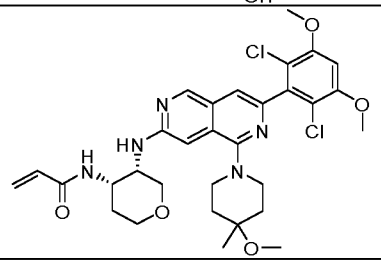
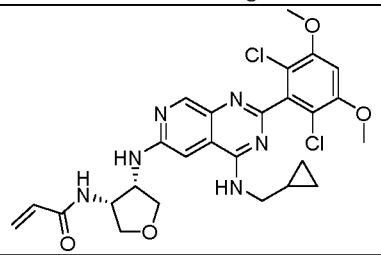
300		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(6-氧杂-2-氮杂螺[3.4]辛烷-2-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	600
301		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	614
302		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	558
303		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
304		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(3-甲氧基吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	556
305		N-((3R,4S)-4-((5-(3-氰基吡咯烷-1-基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	583
306		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3,3-二氟吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	594

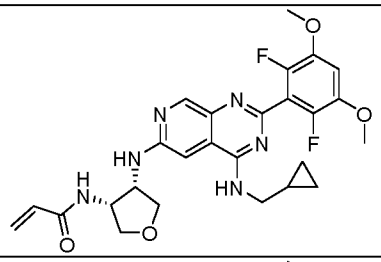
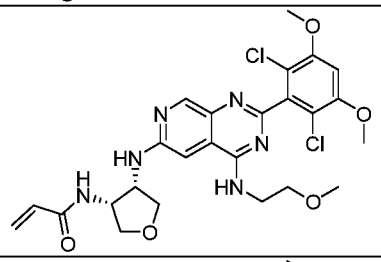
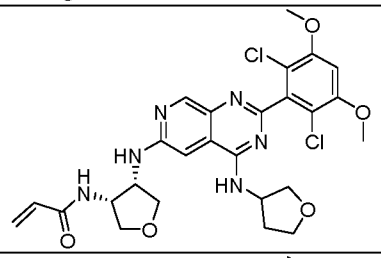
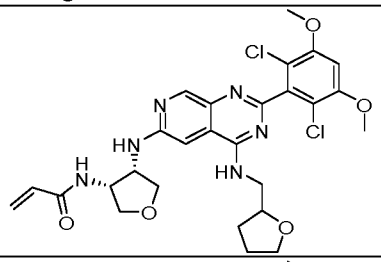
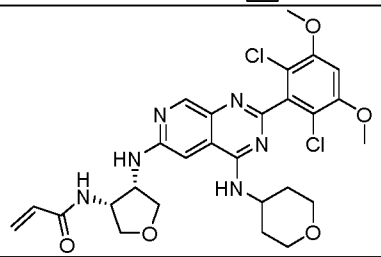
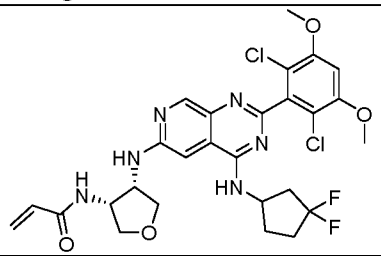
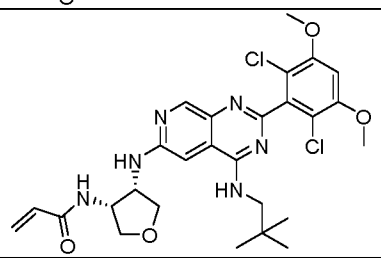
307		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基-3-甲基吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
308		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(3-甲氧基-3-甲基吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570
309		N-((3R,4S)-4-((5-(3-氰基-3-甲基吡咯烷-1-基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	597
310		N-((3R,4S)-4-((5-(3-氮杂二环[3.1.0]己烷-3-基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570
311		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2-氧杂-7-氮杂螺[4.4]壬烷-7-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	614
312		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-吗啉代-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
313		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-吗啉代-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	542

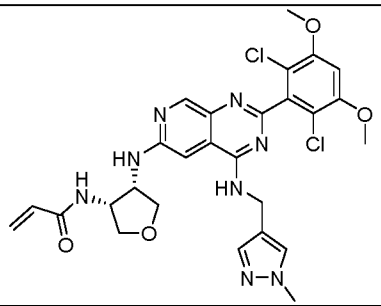
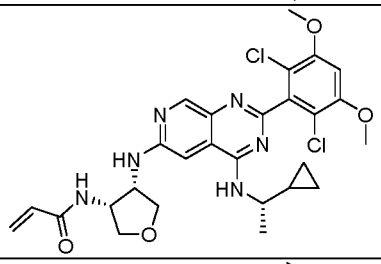
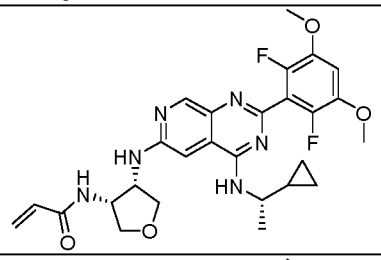
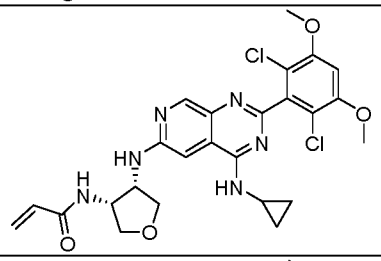
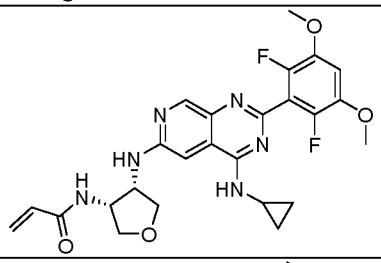
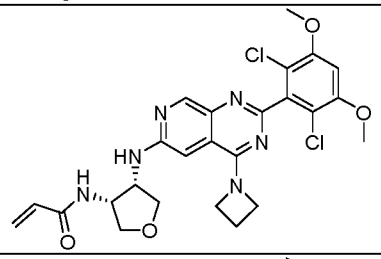
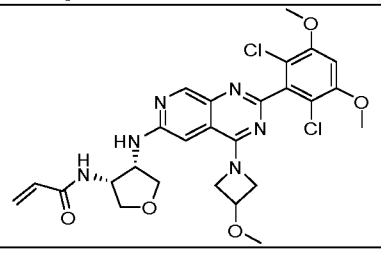
314		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2-甲基吗啉代)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
315		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(2-甲基吗啉代)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	556
316		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2,6-二甲基吗啉代)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
317		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(2,6-二甲基吗啉代)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570
318		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-羟基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
319		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-甲氧基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
320		N-((3R,4S)-4-((7-(2,6-二氟-3,5-二甲氧苯基)-5-(4-甲氧基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570

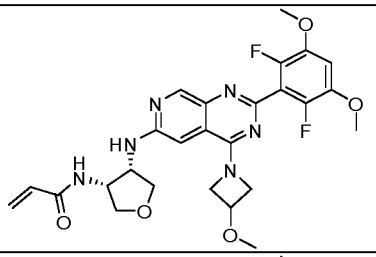
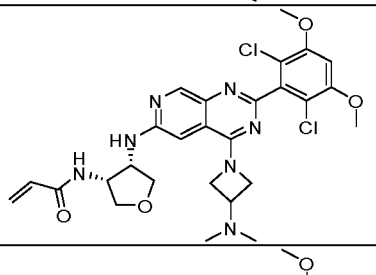
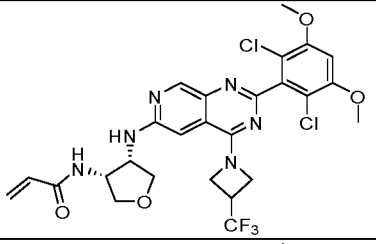
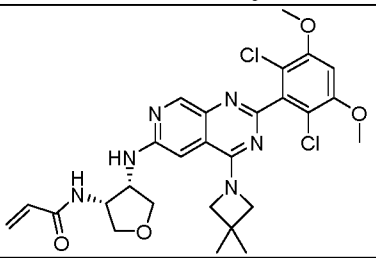
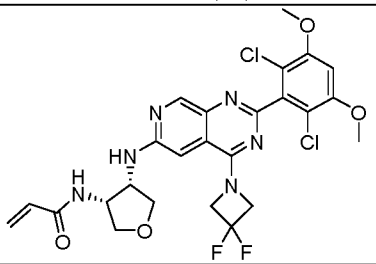
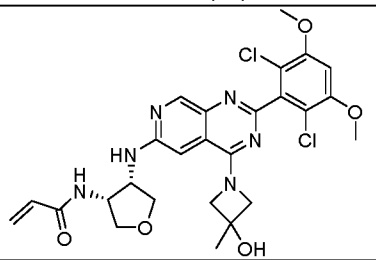
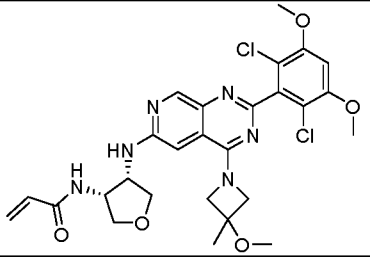
321		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
322		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-羟基-4-甲基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
323		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-甲氧基-4-甲基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	616
324		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-甲氧基-4-甲基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584
325		N-((3R,4S)-4-((5-(4-氰基-4-甲基哌啶-1-基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	611
326		N-(7-(((3S,4R)-4-丙烯酰基酰氨基四氢呋喃-3-基)氨基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)环丙甲酰胺	572
327		N-(7-(((3S,4R)-4-丙烯酰基酰氨基四氢呋喃-3-基)氨基)-3-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-1-基)四氢呋喃-2-甲酰胺	602

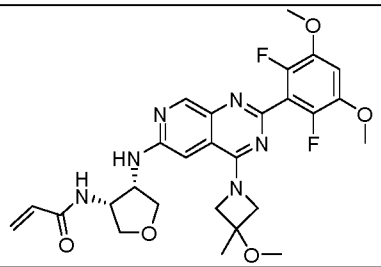
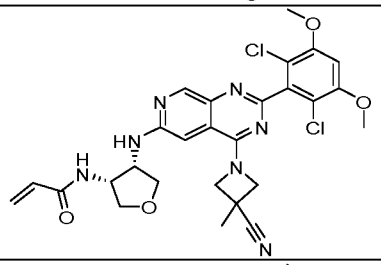
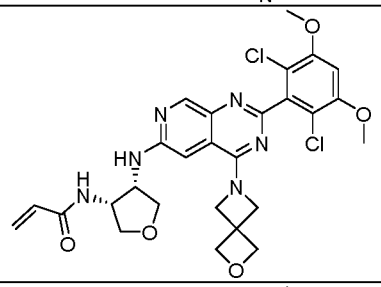
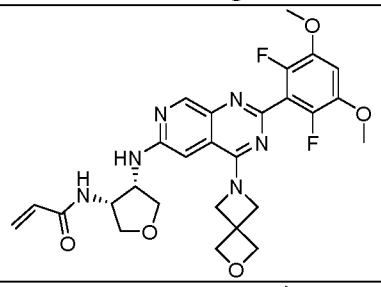
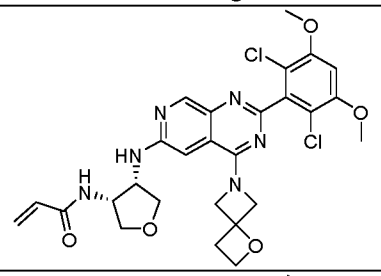
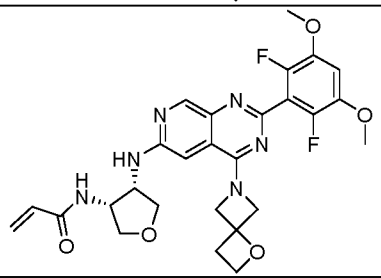
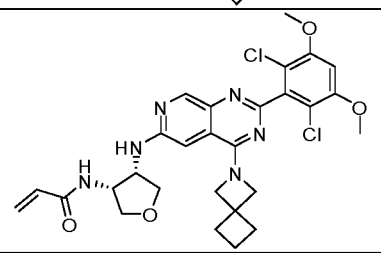
328		N-((3R,4S)-4-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(甲基磺酰氨基)-2,6-二氮杂萘-3-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	582
329		N-((3S,4S)-3-((5-(环丙基氨基)-7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	558
330		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	588
331		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3,3-二氟吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	594
332		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基-3-甲基吖丁啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
333		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	600
334		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(6-氧杂-2-氮杂螺[3.4]辛烷-2-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	614

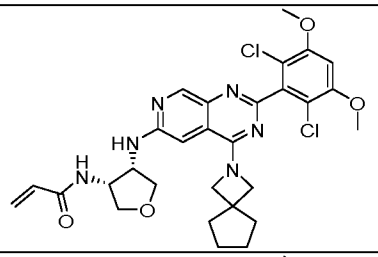
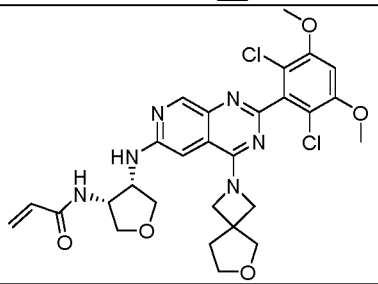
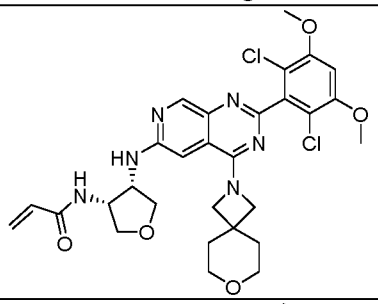
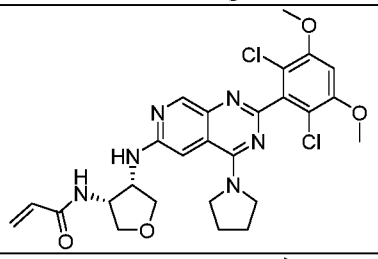
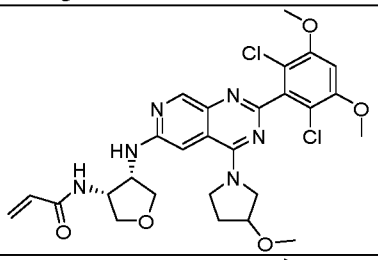
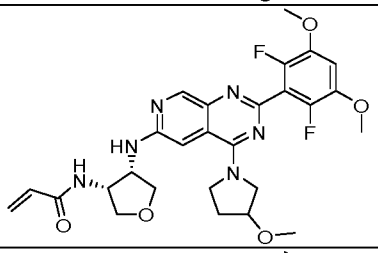
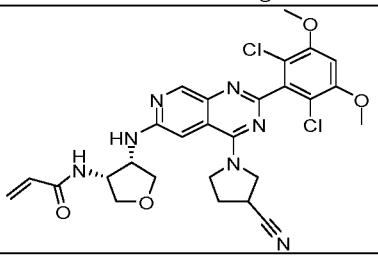
335		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	628
336		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
337		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(3-甲氧基-3-甲基吡咯烷-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
338		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(2,6-二甲基吗啉代)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
339		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-羟基-4-甲基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
340		N-((3S,4S)-3-((7-(2,6-二氯-3,5-二甲氧苯基)-5-(4-甲氧基-4-甲基哌啶-1-基)-2,6-二氮杂萘-3-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	630
341		N-((3R,4S)-4-((4-((环丙基甲基)氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	559

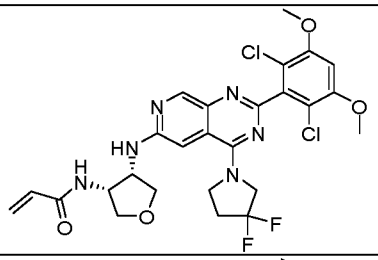
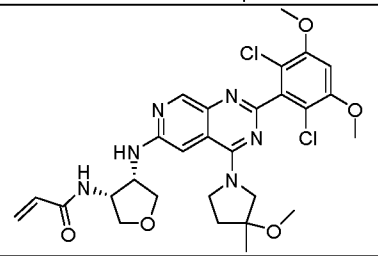
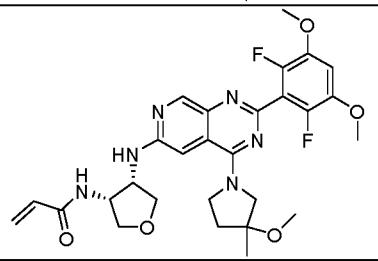
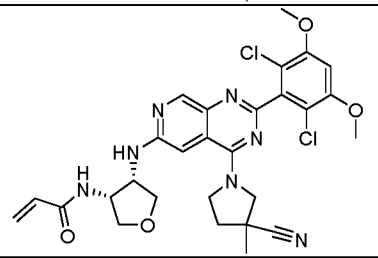
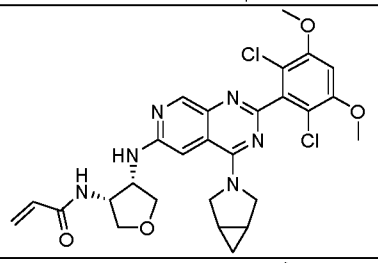
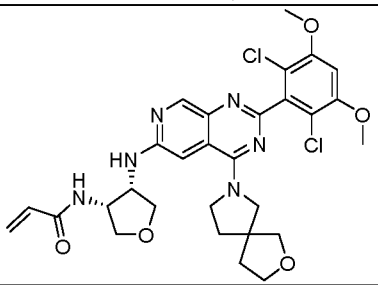
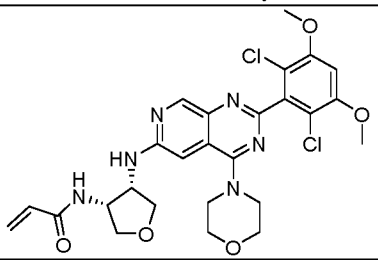
342		N-((3R,4S)-4-((4-((环丙基甲基)氨基)-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	527
343		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	563
344		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
345		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
346		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
347		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((3,3-二氟环戊基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	609
348		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(新戊基氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575

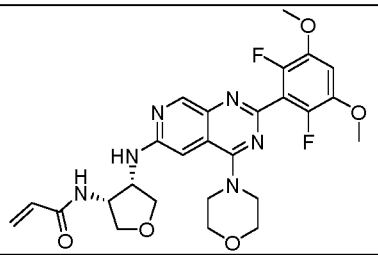
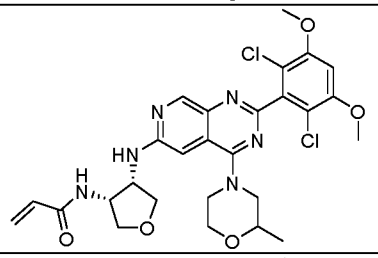
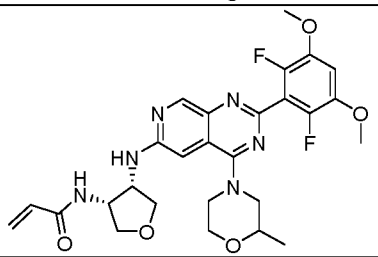
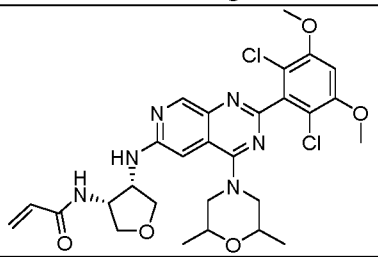
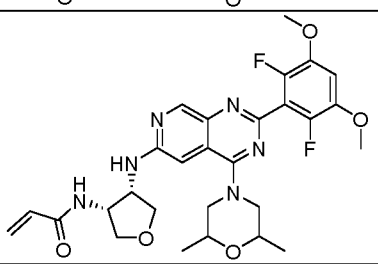
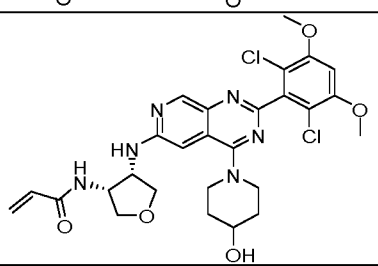
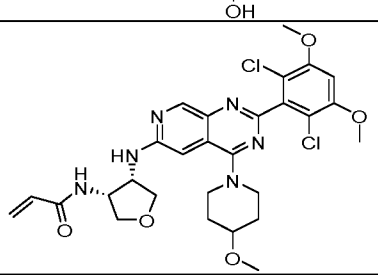
349		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	599
350		N-((3R,4S)-4-((4-(((S)-1-环丙基乙基)氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	573
351		N-((3R,4S)-4-((4-(((S)-1-环丙基乙基)氨基)-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	541
352		N-((3R,4S)-4-((4-(环丙基氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	545
353		N-((3R,4S)-4-((4-(环丙基氨基)-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	513
354		N-((3R,4S)-4-((4-(吖丁啶-1-基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	545
355		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575

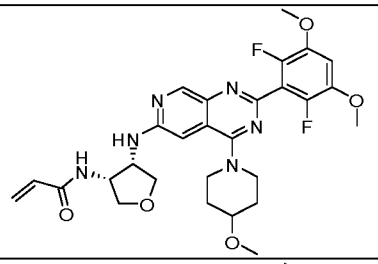
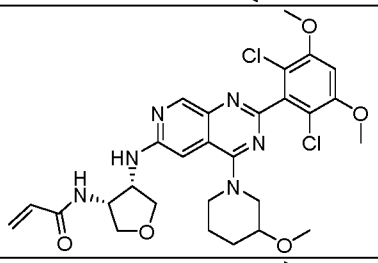
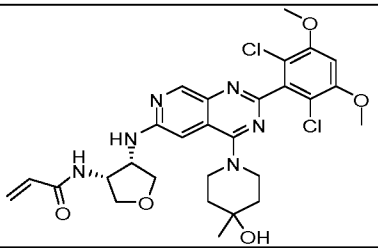
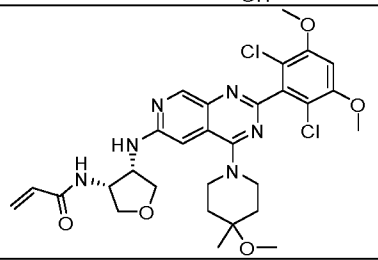
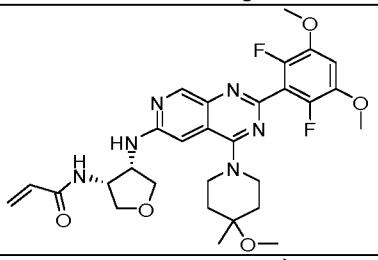
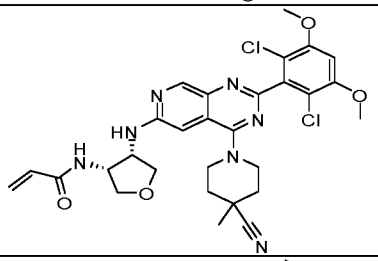
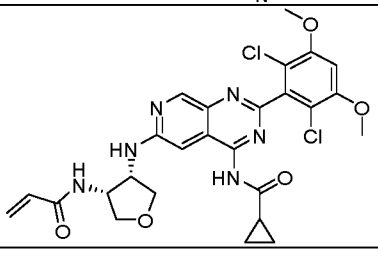
356		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	543
357		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-(二甲氨基)吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
358		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-(三氟甲基)吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	613
359		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	573
360		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	581
361		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-羟基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
362		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589

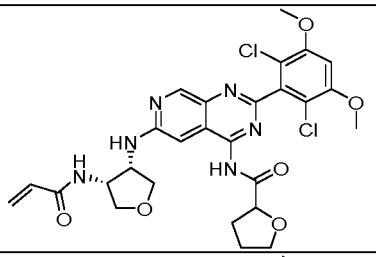
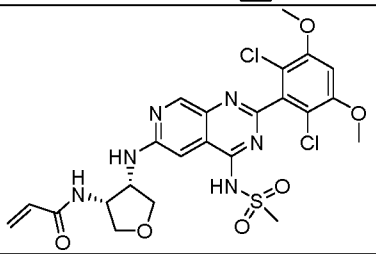
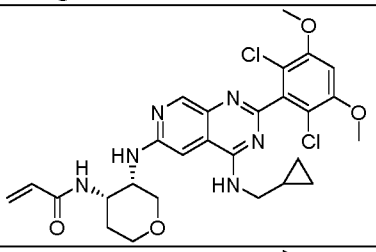
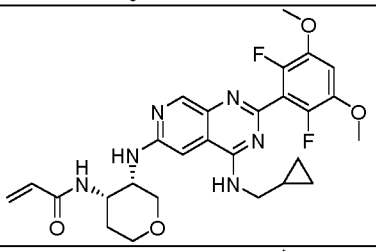
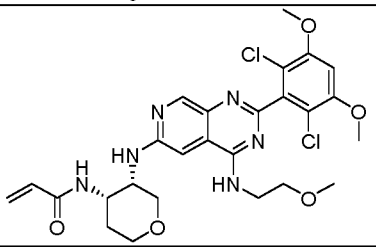
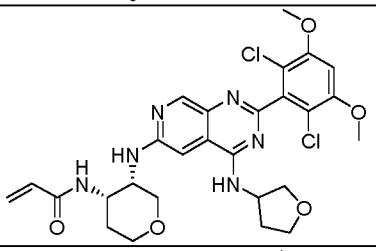
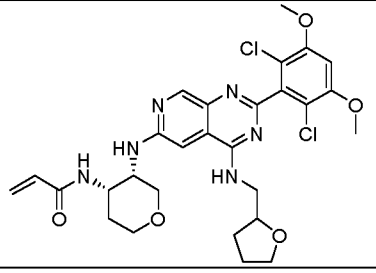
363		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
364		N-((3R,4S)-4-((4-(3-氰基-3-甲基吖丁啶-1-基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584
365		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
366		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	555
367		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(1-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
368		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(1-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	555
369		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氮杂螺[3.3]庚烷-2-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	585

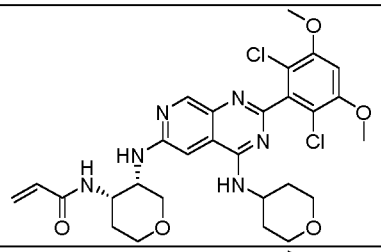
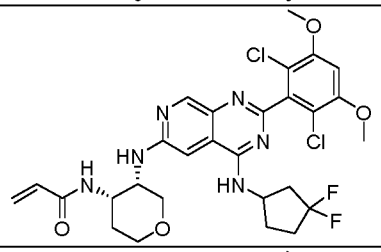
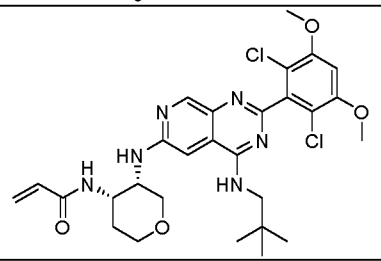
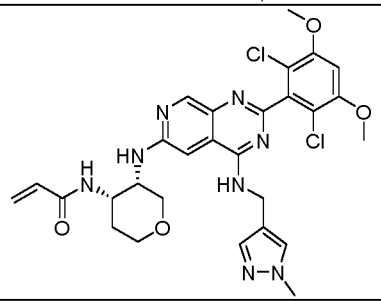
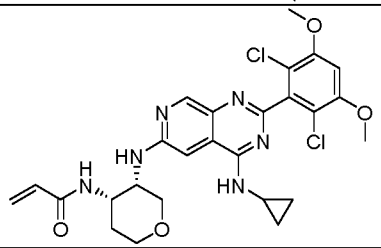
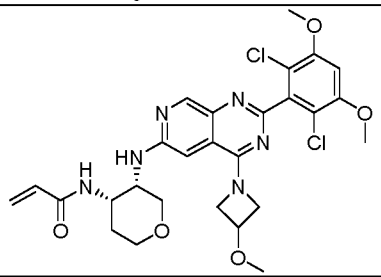
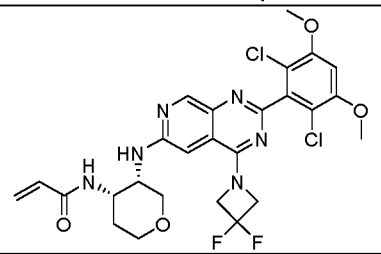
370		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	599
371		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(6-氧杂-2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	601
372		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	615
373		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	559
374		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
375		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
376		N-((3R,4S)-4-((4-(3-氰基吡咯烷-1-基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584

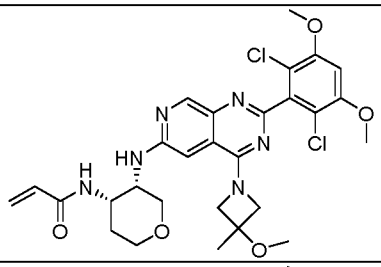
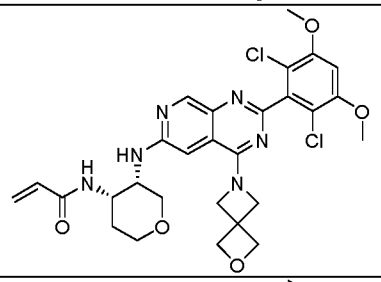
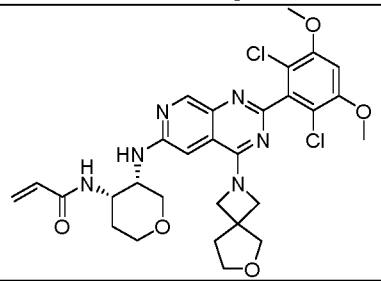
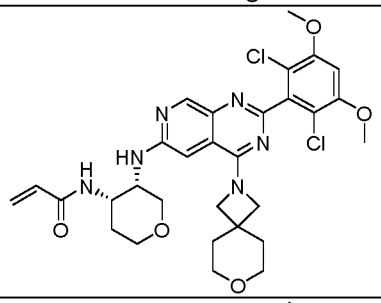
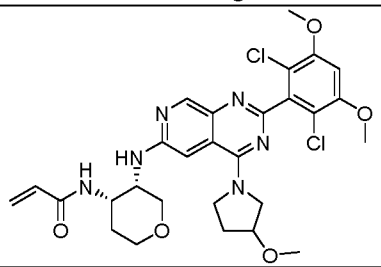
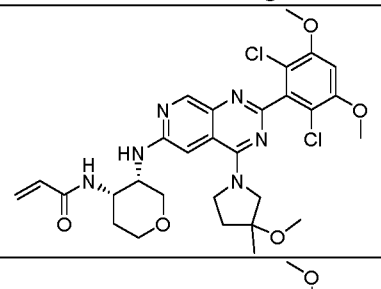
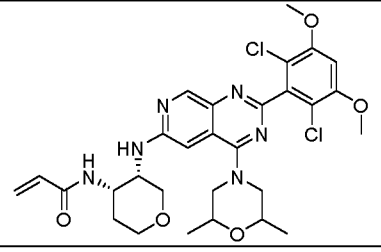
377		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二氟吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	595
378		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
379		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
380		N-((3R,4S)-4-((4-(3-氰基-3-甲基吡咯烷-1-基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	598
381		N-((3R,4S)-4-((4-(3-氮杂二环[3.1.0]己烷-3-基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
382		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氧杂-7-氮杂螺[4.4]壬烷-7-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	615
383		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-吗啉代吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575

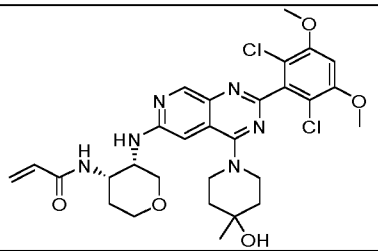
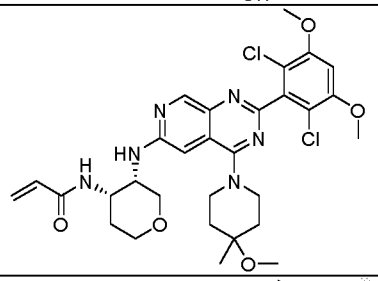
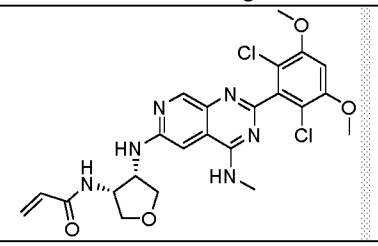
384		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-吗啉代吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	543
385		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-甲基吗啉代)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
386		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(2-甲基吗啉代)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
387		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2,6-二甲基吗啉代)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
388		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(2,6-二甲基吗啉代)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
389		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-羟基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
390		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603

391		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
392		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
393		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-羟基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
394		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	617
395		N-((3R,4S)-4-((2-(2,6-二氟-3,5-二甲氧苯基)-4-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	585
396		N-((3R,4S)-4-((4-(4-氰基-4-甲基哌啶-1-基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	612
397		N-(6-(((3S,4R)-4-丙烯酰基酰氨基四氢呋喃-3-基)氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)环丙甲酰胺	573

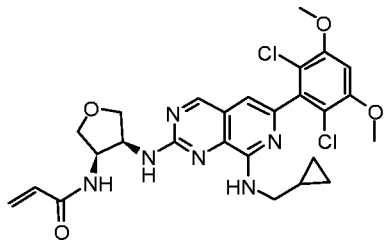
398		N-(6-(((3S,4R)-4-丙烯酰基酰氨基四氢呋喃-3-基)氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-4-基)四氢呋喃-2-甲酰胺	603
399		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(甲基磺酰氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	583
400		N-((3S,4S)-3-((4-((环丙基甲基)氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	573
401		N-((3S,4S)-3-((4-((环丙基甲基)氨基)-2-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	541
402		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	577
403		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
404		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603

405		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
406		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-((3,3-二氟环戊基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	623
407		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(新戊基氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
408		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	613
409		N-((3S,4S)-3-((4-(环丙基氨基)-2-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	559
410		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
411		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	595

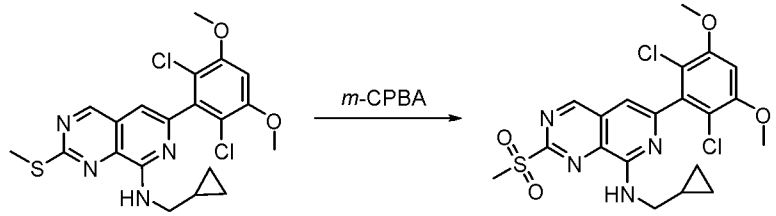
412		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
413		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	601
414		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(6-氧杂-2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	615
415		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	629
416		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
417		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617
418		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(2,6-二甲基吗啉代)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617

419		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-羟基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617
420		N-((3S,4S)-3-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	631
752		N-((3R,4S)-4-((2-(2,6-二氯-3,5-二甲氧苯基)-4-(甲基氨基)吡啶并[3,4-d]嘧啶-6-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	519

实施例 421 N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备



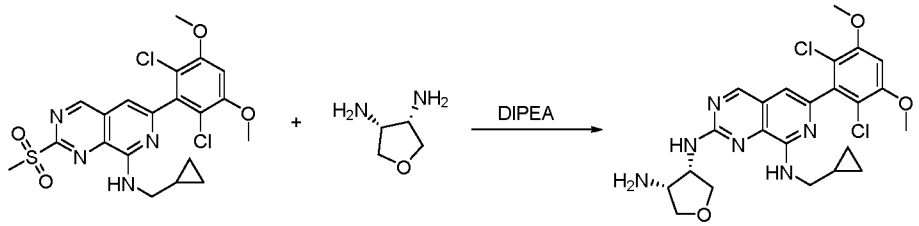
第一步：N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶-8-胺的制备



N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶-8-胺（210 mg, 0.465 mmol）溶于二氯甲烷（6 mL），再加入间氯过氧苯甲酸（200 mg, 1.163 mmol）。室温下搅拌反应 18 小时。反应完全，加入饱和亚硫酸钠溶液（5 mL），搅拌 5 分钟。二氯甲烷萃取，有机相再分别用饱和碳酸氢钠和饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，柱层析（洗脱剂: PE/EA = 2/1）分离，得到化合物 N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶-8-胺（186 mg，收率：82.7%）。

MS m/z (ESI): 483.4 $[M+H]^+$.

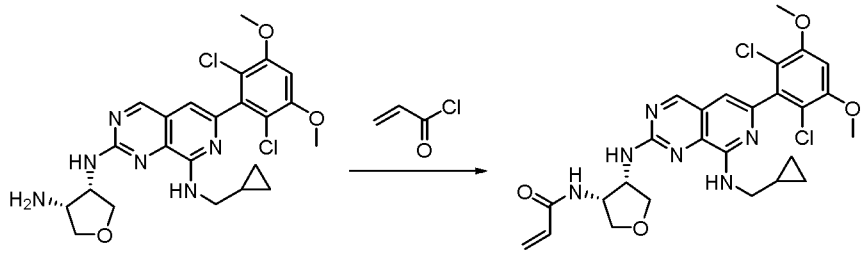
第二步：(±)-N^2-((3S,4R)-4-氨基四氢呋喃-3-基)-N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,8-二胺的制备



N-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶-8-胺(190 mg, 0.393 mmol）和(3R,4S)-四氢呋喃-3,4-二胺二盐酸（206 mg，1.179 mmol）溶于乙腈（6 mL），再加入 N,N-二异丙基乙胺 (507 mg, 3.93 mmol)。加热至回流，搅拌反应 20 小时。反应完全，冷却至室温，反应液用 EtOAc (20 mL) 稀释，饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，制备板（展开剂：CH_2Cl_2/MeOH 10/1）分离，得到化合物(±)-N^2-((3S,4R)-4-氨基四氢呋喃-3-基)-N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,8-二胺（120 mg, 收率：60%）。

MS m/z (ESI): 505.4 $[M+H]^+$.

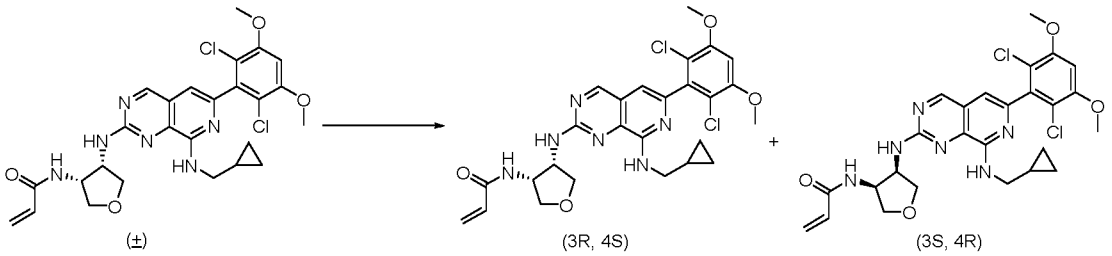
第三步：(±)-N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备



零度下，在(±)-N^2-((3S,4R)-4-氨基四氢呋喃-3-基)-N^8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2,8-二胺 (120 mg, 0.237 mmol)和碳酸氢钠（79.6 mg, 0.948 mmol）的四氢呋喃(6.4 mL) 和水(1.6 mL)的溶液中加入丙烯酰氯 (22.6 mg, 0.249 mmol)。加完后，混合物在零度下搅拌 5 分钟。反应液用 EtOAc (10 mL) 稀释，饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，制备板（展开剂: CH_2Cl_2/MeOH = 20/1）分离，得到化合物(±)-N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺 (93 mg, 收率: 70%）。

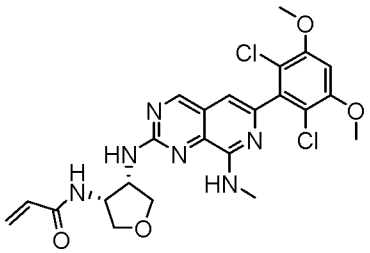
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.80 (brs, 1H), 6.68 (s, 1H), 6.62 (s, 1H), 6.38 (brs, 1H), 6.21 (dd, J = 17.0, 1.5 Hz, 1H), 6.02 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.56 (dd, J = 10.1, 1.5 Hz, 1H), 4.93 – 4.83 (m, 2H), 4.30 – 4.18(m, 2H), 3.96 (s, 6H), 3.90 (dd, J = 9.7, 3.2 Hz, 1H), 3.79 (dd, J = 9.2, 5.2 Hz, 1H), 3.52 – 3.37 (m, 2H), 0.88 (t, J = 6.0 Hz, 1H), 0.57 – 0.48 (m, 2H), 0.36 – 0.26 (m, 2H).MS m/z (ESI): 559.5 $[M+H]^+$.

第四步：N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备

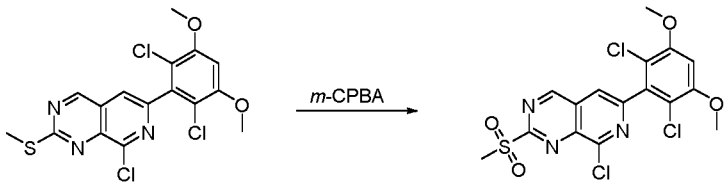


(±)-N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺（93 mg, 0.166mmol）经手性 HPLC 分离，得到 N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺(43.5 mg, ee 值>98%,收率: 46.8%)和 N-((3S,4R)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺(39 mg, ee 值>98%,收率: 41.9%)。

实施例 433 N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备

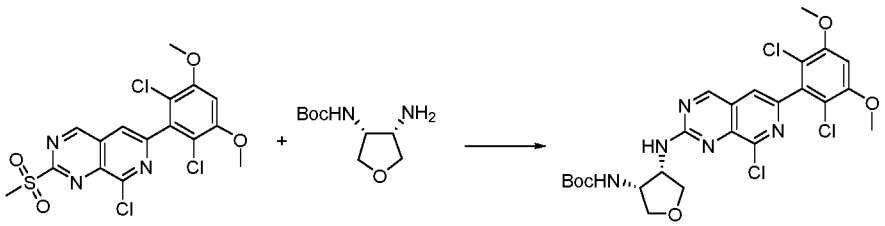


第一步：8-氯-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶的制备



参照实施例 421 第一步操作。

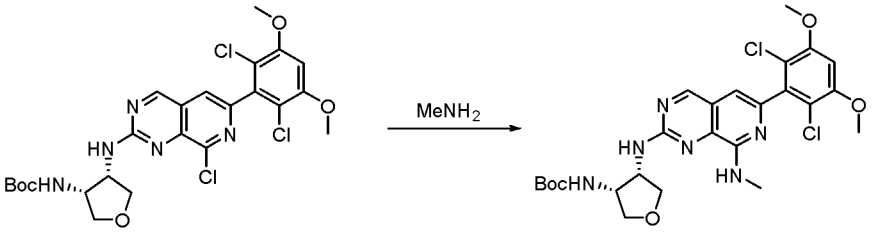
第二步：叔丁基 ((3R,4S)-4-((8-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)氨基甲酸酯的制备



8-氯-6-(2,6-二氯-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶（409 mg, 0.912 mmol）和叔丁基 ((3R,4S)- 4-氨基四氢呋喃-3-基)氨基甲酸酯（553 mg, 2.736 mmol）溶于乙腈（50 mL），再加入三氟乙酸（31 mg，0.274 mmol）。反应液在 95 度下搅拌 4 小时。冷却后，加入乙酸乙酯（50 mL）稀释, 用饱和碳酸氢钠和饱和食盐水洗涤，并用无水硫酸钠干燥，浓缩后柱层析分离（CH_2Cl_2/MeOH 0 ~ 4%）,纯化得到化合物叔丁基 ((3R,4S)-4-((8-氯-6-(2,6-

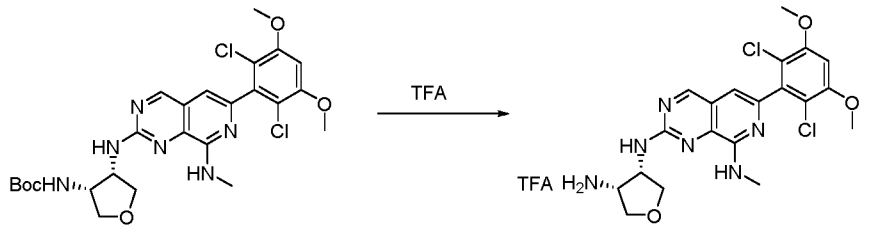
二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)氨基甲酸酯（414 mg，收率：79.6%）。MS m/z (ESI): 570.4,572.4 [M+H]+。

第三步：叔丁基 ((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基) 四氢呋喃-3-基)氨基甲酸酯的制备



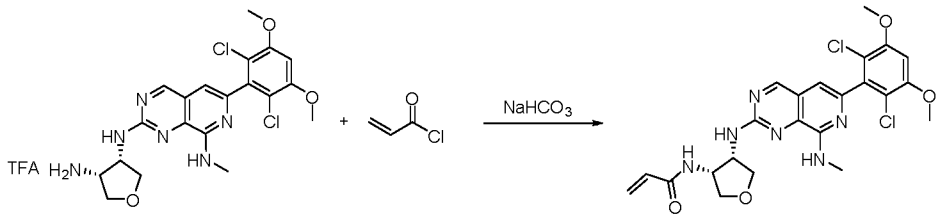
叔丁基 ((3R,4S)-4-((8-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)氨基甲酸酯 (60 mg, 0.105 mmol）和甲胺（1.5 mL , 33%乙醇溶液）的 N-甲基吡咯烷酮（1 mL）溶液在 110 度加热 18 h。反应液用乙酸乙酯（5 mL) 稀释，饱和食盐水洗涤，并用无水硫酸钠干燥，浓缩后用制备板分离（PE/EA = 1:1），纯化得到化合物叔丁基 ((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基) 四氢呋喃-3-基)氨基甲酸酯（32 mg, 收率：54%）。MS m/z (ESI): 565.4, 567.4 [M+H]+。

第四步：N^2-((3S,4R)-4-氨基四氢呋喃-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)-N^8-甲基吡啶并[3,4-d]嘧啶-2,8-二胺的三氟乙酸盐的制备



叔丁基 ((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基) 四氢呋喃-3-基)氨基甲酸酯（32 mg, 0.057 mmol）的三氟乙酸的二氯甲烷（2 mL, 20%）溶液在室温下搅拌 1 h。浓缩后的油状物直接用于下步反应。MS m/z (ESI): 465.4，467.4 [M+H]+。

第五步：N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺的制备

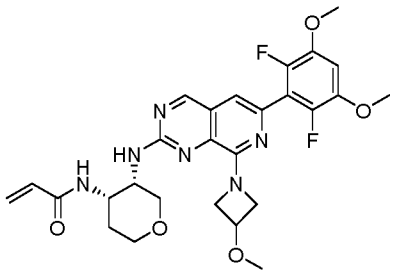


零度下，在 N^2-((3S,4R)-4-氨基四氢呋喃-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)-N^8-甲基吡啶并[3,4-d]嘧啶-2,8-二胺的三氟乙酸盐 (粗品)和 $NaHCO_3$（57 mg，0.684 mmol）的四氢呋喃（3.2 mL）和水（0.8 mL）溶液中加入丙烯酰氯 (5.7 mg，0.063 mmol)。加完后，混合物在零度下搅拌 5 分钟。反应液用 EtOAc (mL) 稀释，饱和碳酸氢钠和饱和食盐水洗涤，并用无水硫酸钠干燥，浓缩后用制备板分离（CH_2Cl_2/MeOH 20:1），纯化得到化合物

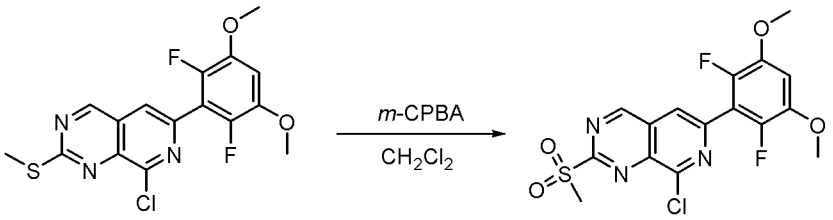
N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺（17.6 mg，收率: 59.5%）。

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.30 (brs, 1H), 6.19 (d, J = 16.9 Hz, 1H), 5.97 (dd, J = 17.0, 10.3 Hz, 1H), 5.88 (brs, 1H), 5.54 (d, J = 10.4 Hz, 1H), 4.95 – 4.83 (m, 2H), 4.29 – 4.18 (m, 2H), 3.95 (s, 6H), 3.89 (dd, J = 9.7, 3.0 Hz, 1H), 3.77 (dd, J = 9.3, 5.5 Hz, 1H), 3.14 (d, J = 4.4 Hz, 3H).MS m/z (ESI): 519.4, 521.4 [M+H]+。

实施例 775 N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺的制备

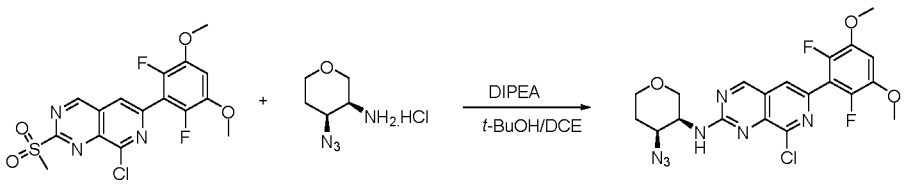


第一步：8-氯-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶的制备



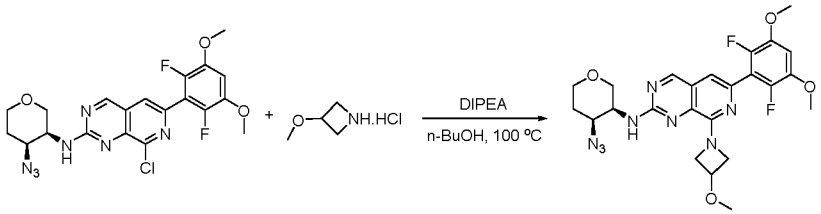
8-氯-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲硫基)吡啶并[3,4-d]嘧啶（930 mg，2.42 mmol）溶于 DCM（50 mL），加入 m-CPBA（1.23g，6.05 mmol），室温下搅拌 2 小时。反应完全，加入硫代硫酸钠淬灭，DCM 提取，硅胶柱层析分离，纯化得到化合物 8-氯-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶（800 mg，产率 79%）。MS m/z (ESI): 416 [M+H]+。

第二步：N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-8-氯-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-胺的制备



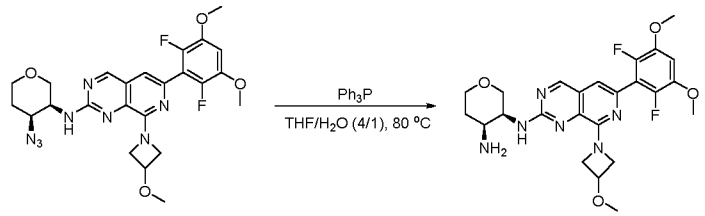
8-氯-6-(2,6-二氟-3,5-二甲氧苯基)-2-(甲磺酰)吡啶并[3,4-d]嘧啶（1g，2.41 mmol）溶于叔丁醇（80 mL）和 DCE（20 mL），再加入 DIPEA（1.55 g，12.05 mmol），加热至 90 度，搅拌反应过夜。DCM 提取，硅胶柱层析分离，得到化合物 N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-8-氯-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-胺（650 mg，产率 56%）。MS m/z (ESI): 478 [M+H]+。

第三步：N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-胺



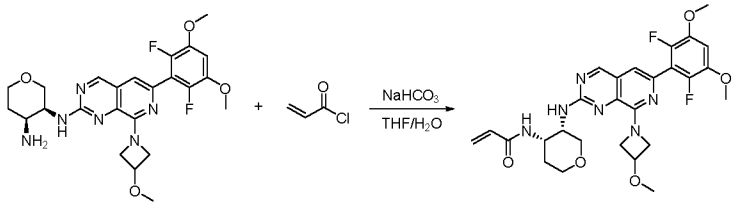
N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-8-氯-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-胺（325 mg，0.68mmol），3-甲氧基吖丁啶盐酸（252 mg，2.04 mmol）和 DIPEA（439 mg，3.4 mmol）溶于正丁醇（15 mL），加热至 100 度，反应 4 小时。浓缩，乙酸乙酯提取，硅胶柱层析分离，得到化合物 N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-胺（350 mg，产率：97%）。MS m/z (ESI): 529 [M+H]+。

第四步：(3S,4S)-N^3-(6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)四氢-2H-吡喃-3,4-二胺的制备



N-((3S,4S)-4-叠氮四氢-2H-吡喃-3-基)-6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-胺（350 mg，0.662 mmol）溶于 THF（10 mL）和水（1 mL）中，加入三苯基磷（521 mg，1.99 mmol），加热至 80 度，搅拌反应 16 小时。冷却，直接加入无水硫酸钠干燥，浓缩，硅胶柱层析分离，得到化合物(3S,4S)-N^3-(6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)四氢-2H-吡喃-3,4-二胺（290 mg，产率 87%）。MS m/z (ESI): 503 [M+H]+。

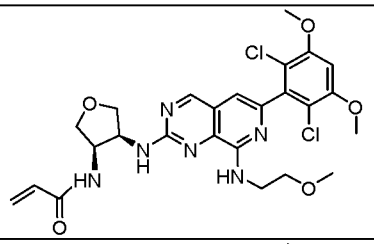
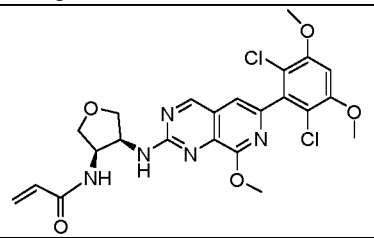
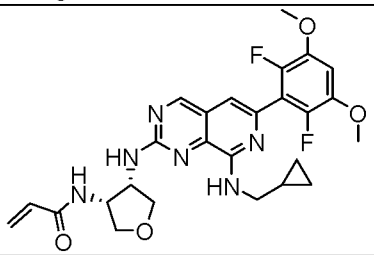
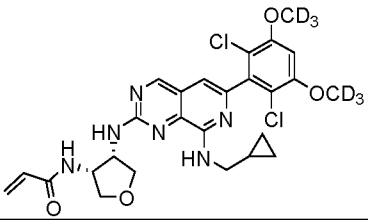
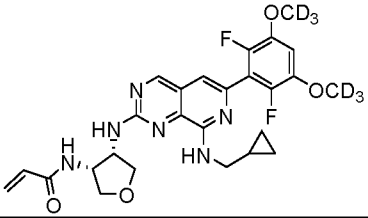
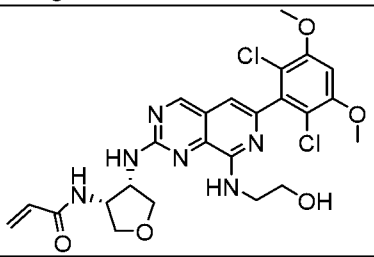
第五步：N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺的制备

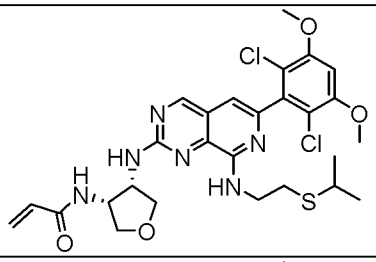
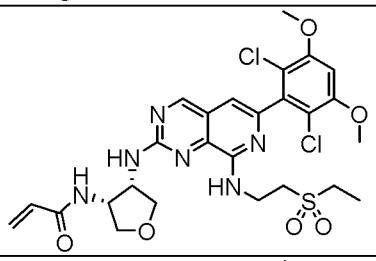
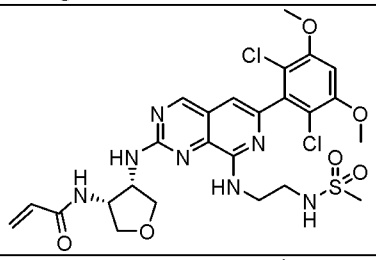
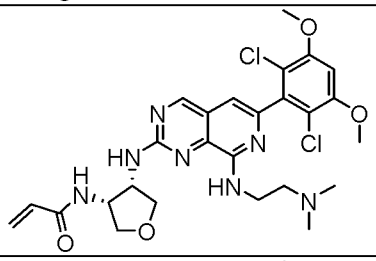
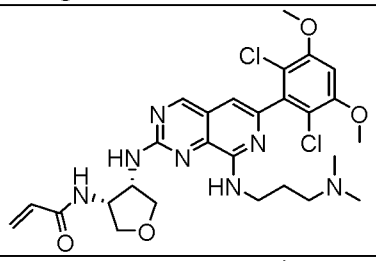
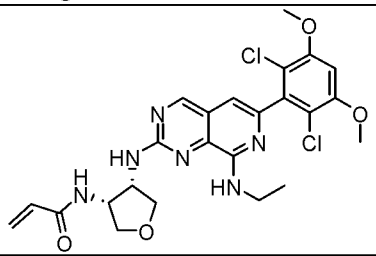
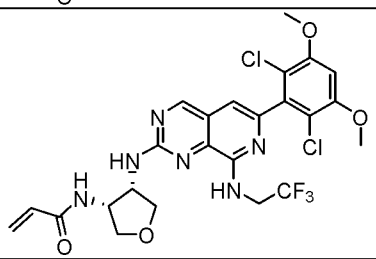


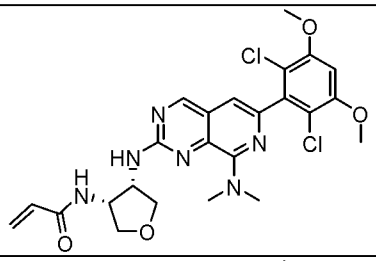
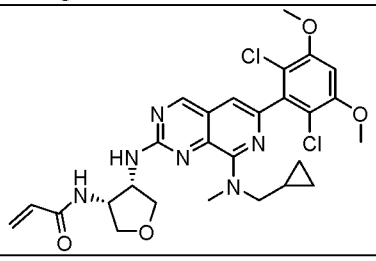
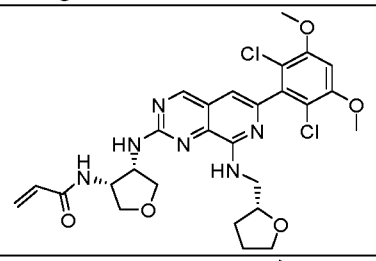
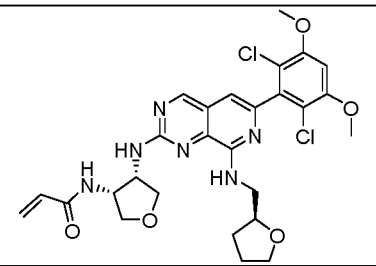
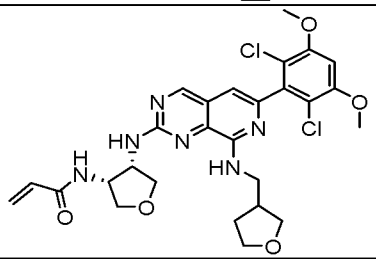
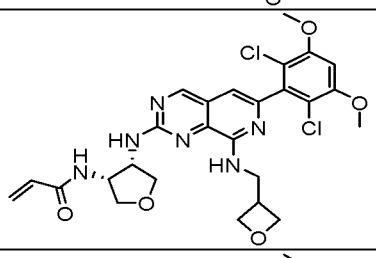
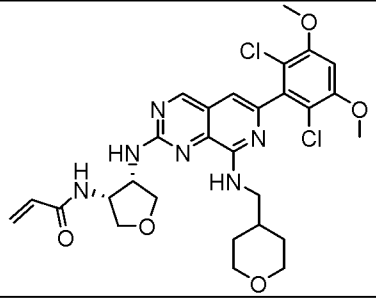
(3S,4S)-N^3-(6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)四氢-2H-吡喃-3,4-二胺（290 mg，0.58 mmol）溶于 THF（20 mL）和水（5 mL），加入 NaHCO3（243 mg，2.89 mmol），室温下滴加丙烯酰氯溶液（63 mg，0.69 mmol，溶于 1 mL THF 中），室温搅拌 10 分钟，TLC 检测，反应完全。加入饱和 NaHCO3 水溶液淬灭，乙酸乙酯提取，浓缩，硅胶柱层析分离，得到化合物 N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺（204 mg，产率 63%）。MS m/z (ESI): 557 [M+H]+。

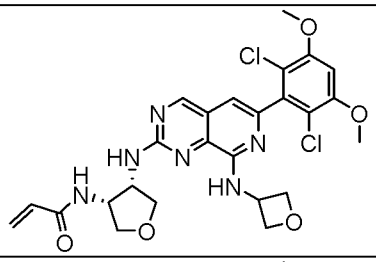
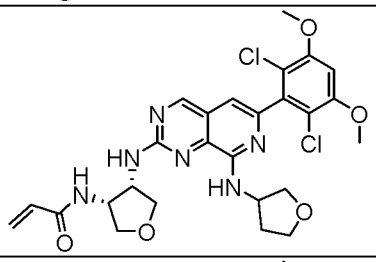
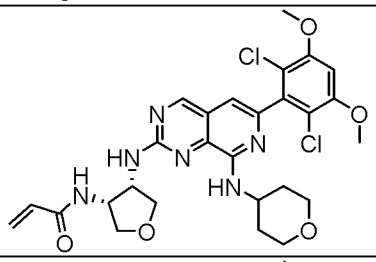
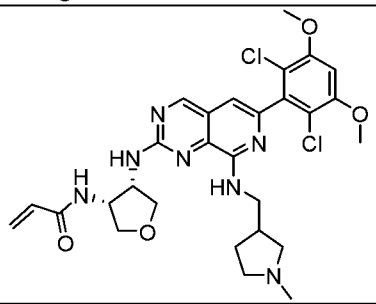
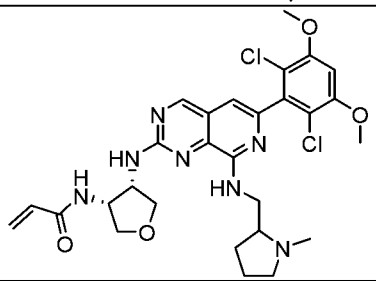
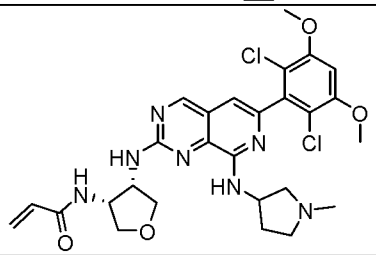
1H NMR (400 MHz, CDCl3) δ 8.92 (s, 1H), 6.96 (s, 1H), 6.69 (t, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.25 (dd, J = 17.0, 1.4 Hz, 1H), 6.08 (s, 1H), 6.02 (dd, J = 16.9, 10.3 Hz, 1H), 5.60 (dd, J = 10.3, 1.4 Hz, 1H), 4.73 (brs, 1H), 4.56 (brs, 1H), 4.42 (d, J = 8.5 Hz, 1H), 4.39 – 4.22 (m, 4H), 4.05 (dd, J = 12.0, 4.5 Hz, 1H), 3.99 (d, J = 11.7 Hz, 1H), 3.92 (s, 6H), 3.75 (dd, J = 11.9, 1.6 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.33 (s, 3H), 2.09 – 2.02 (m, 1H), 1.91 – 1.81 (m, 1H).

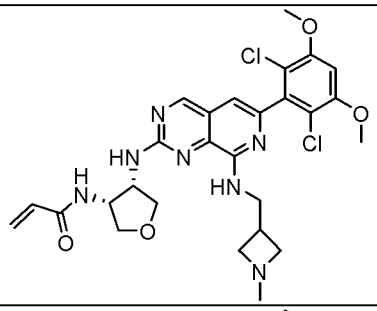
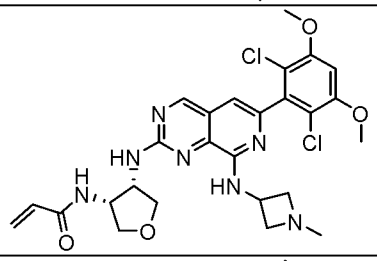
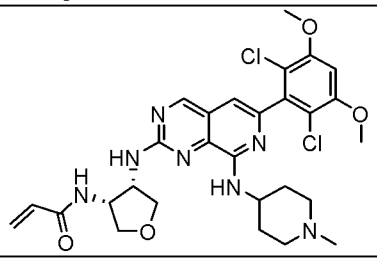
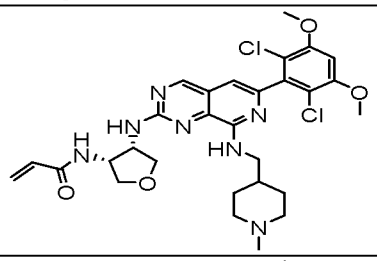
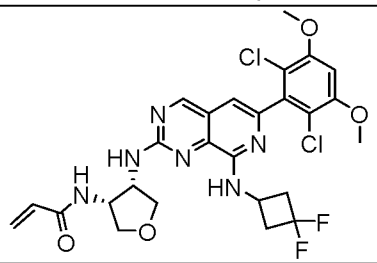
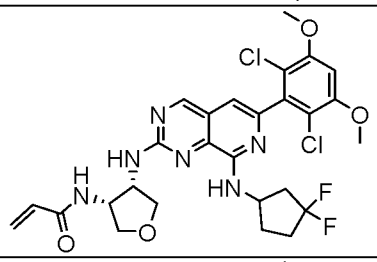
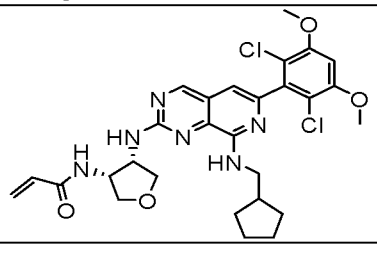
以下实施例 422-714、753-806 参照实施例 433、421 或 775 的合成方法制备得到：

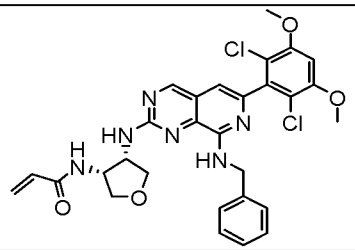
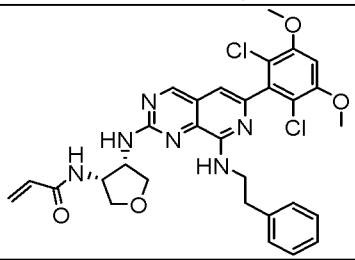
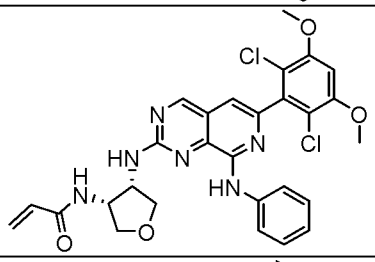
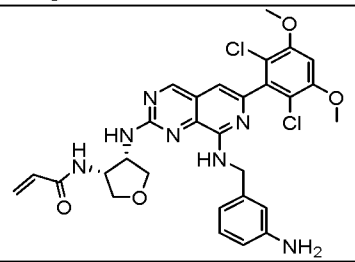
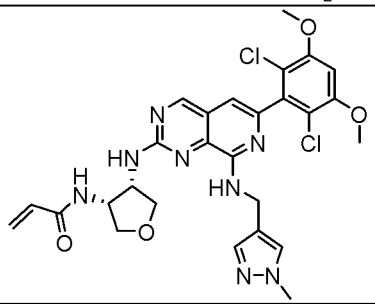
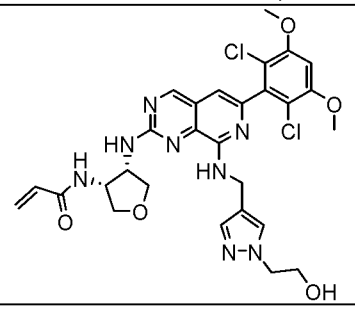
实施例编号	化合物结构	化合物名称	MS:*m/z* $[M+1]^+$
422		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	563
423		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	520
424		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	527
425		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	565
426		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	533
427		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-羟基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	549

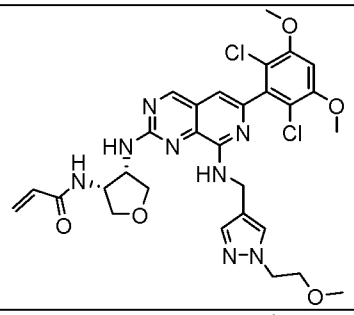
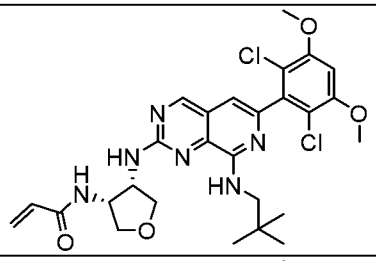
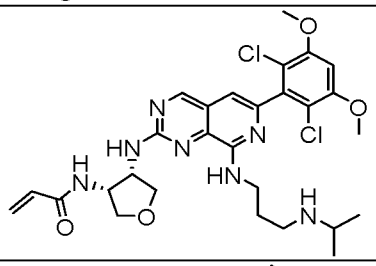
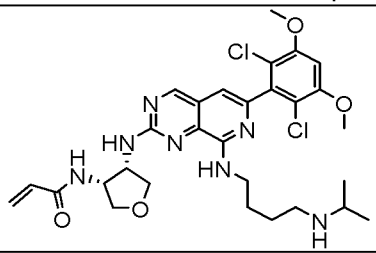
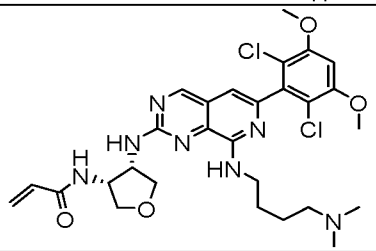
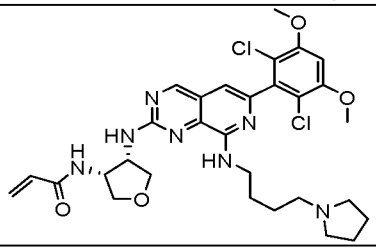
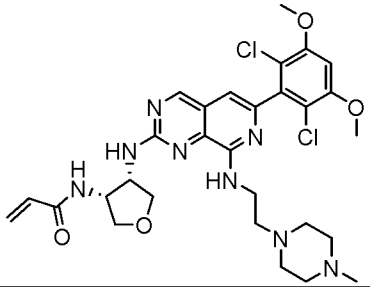
428		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(异丙基硫代)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	607
429		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(乙基磺酰)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	625
430		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(甲基磺酰氨基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	626
431		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(二甲氨基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	576
432		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3-(二甲氨基)丙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	590
434		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	533
435		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2,2,2-三氟乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587

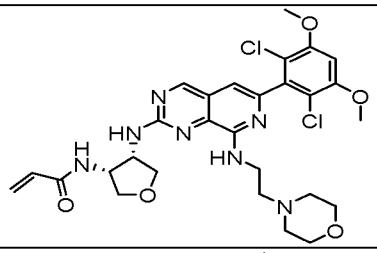
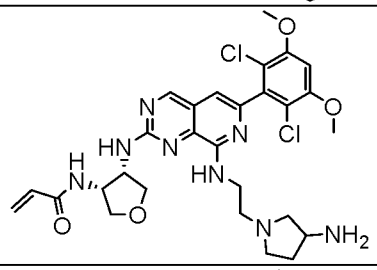
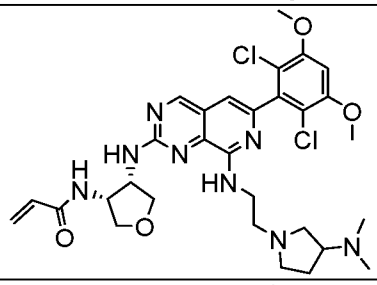
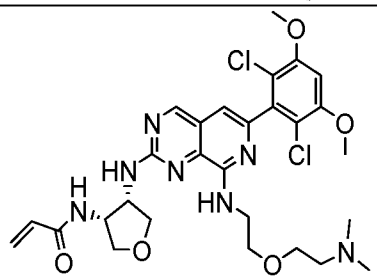
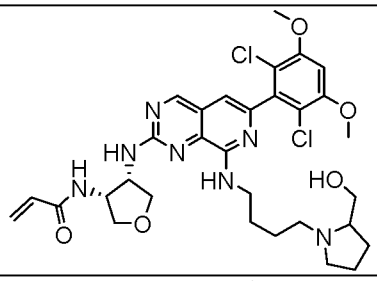
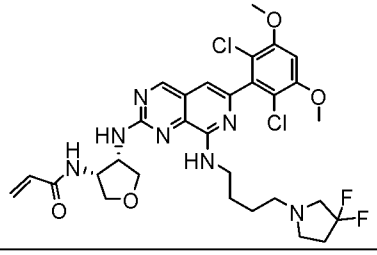
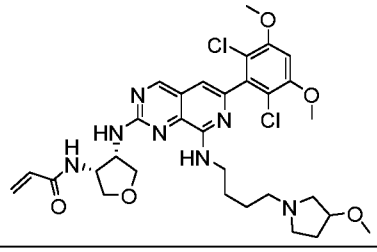
436		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(二甲氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	533
437		N-((3R,4S)-4-((8-((环丙基甲基)(甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	573
438A		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((((R)-四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
438B		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((((S)-四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
439		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
440		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((噁丁环-3-基甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
441		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢-2H-吡喃-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603

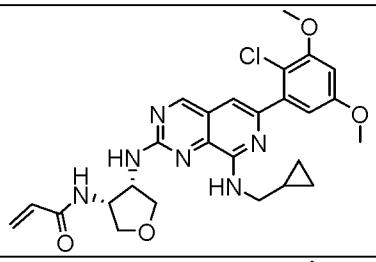
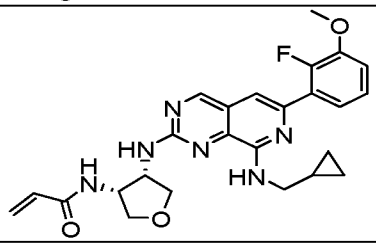
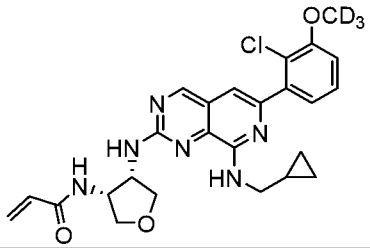
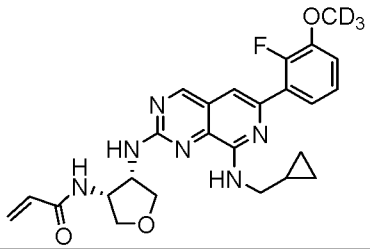
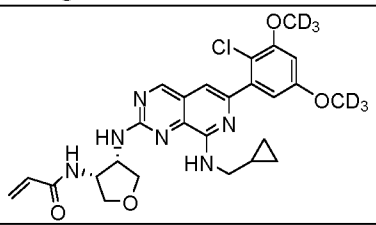
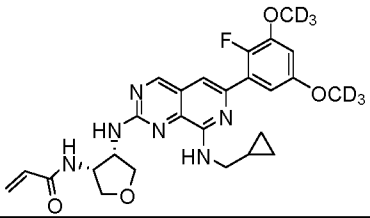
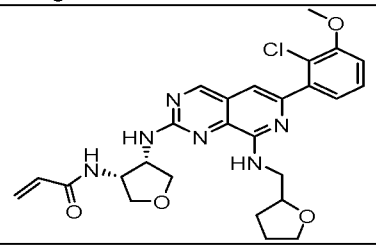
442		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	561
443		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
444		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
445		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
446		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
447		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588

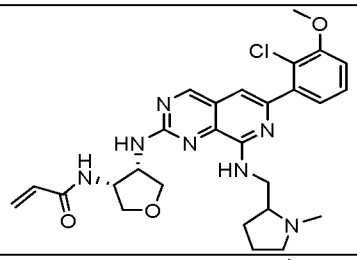
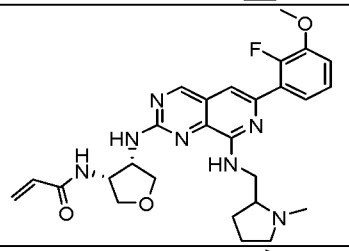
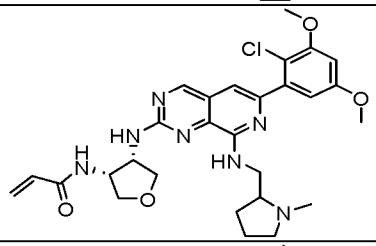
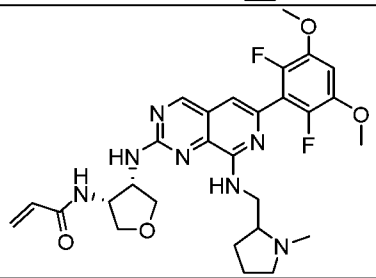
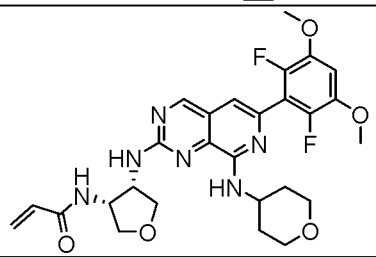
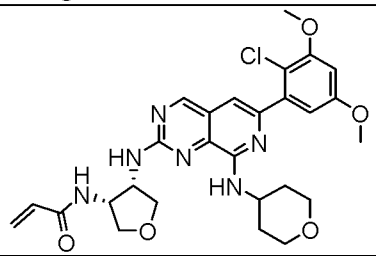
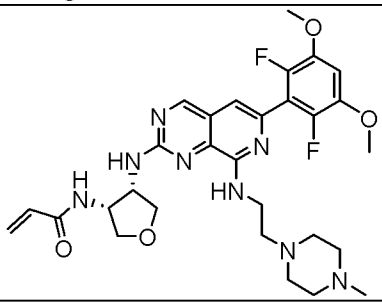
448		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吖丁啶-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
449		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吖丁啶-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
450		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基哌啶-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	602
451		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基哌啶-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	616
452		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,3-二氟环丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	595
453		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,3-二氟环戊基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	609
454		N-((3R,4S)-4-((8-((环戊基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587

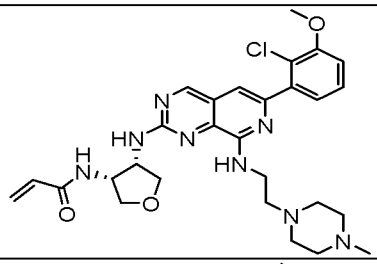
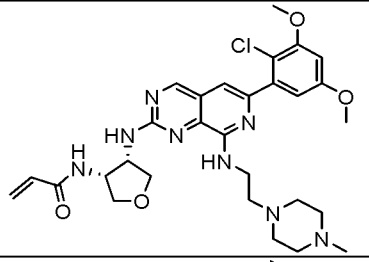
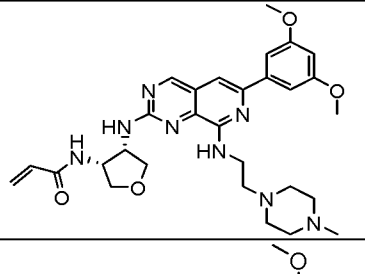
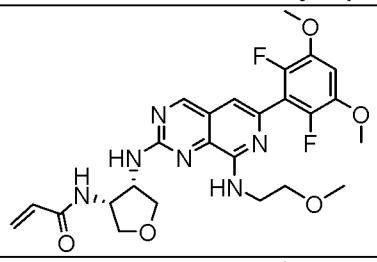
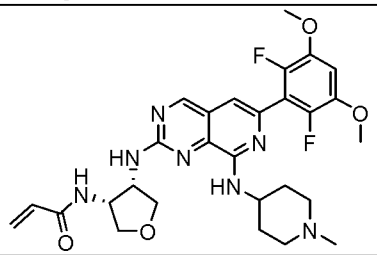
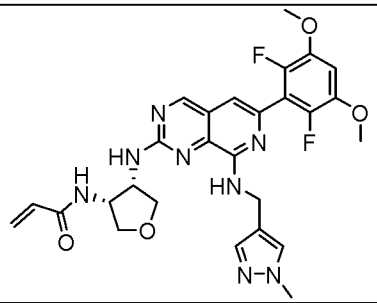
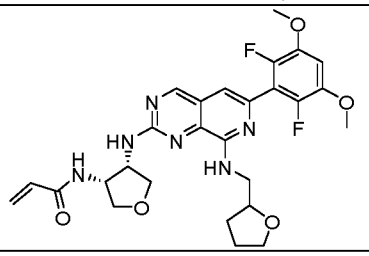
455		N-((3R,4S)-4-((8-(苯甲基氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	595
456		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(苯乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	609
457		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(苯基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	581
458		N-((3R,4S)-4-((8-((3-氨基苯甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	610
459		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	599
460		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-(2-羟基乙基)-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	629

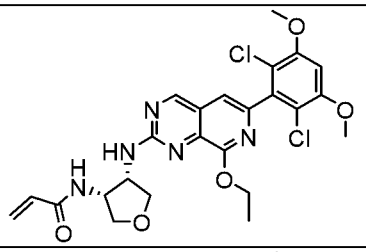
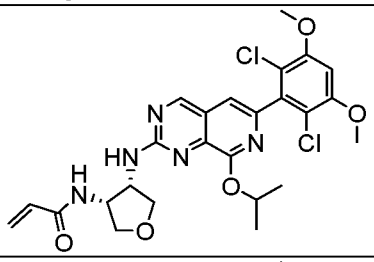
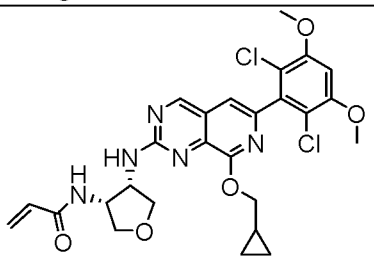
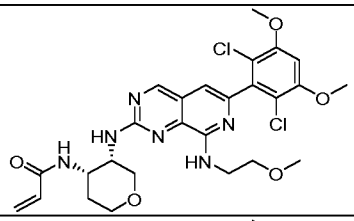
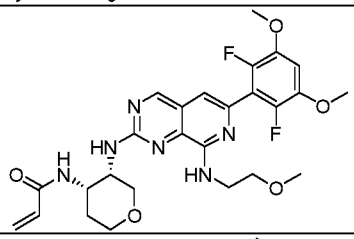
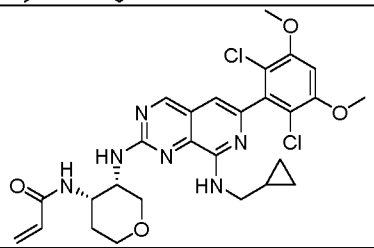
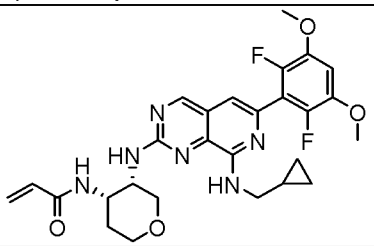
461		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	643
462		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(新戊基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
463		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3-(异丙基氨基)丙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	604
464		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(异丙基氨基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	618
465		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(二甲氨基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	604
466		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	630
467		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(4-甲基哌嗪-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	631

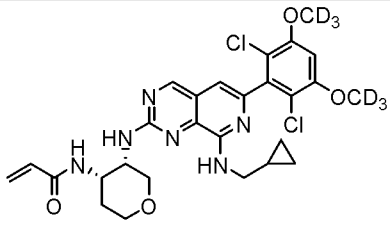
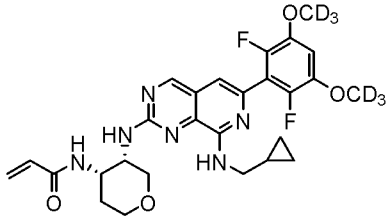
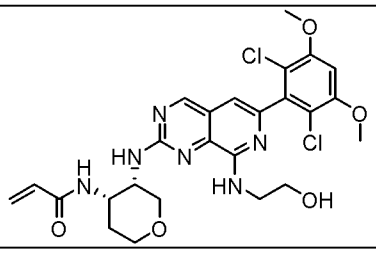
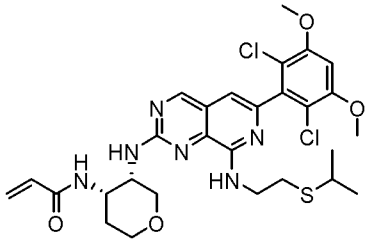
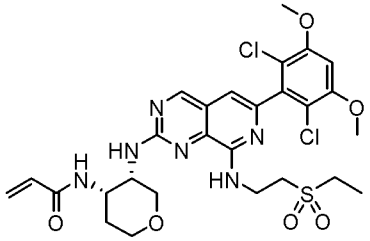
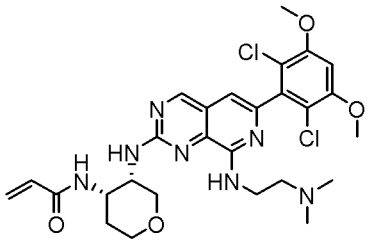
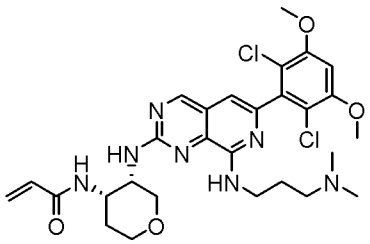
468		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-吗啉代乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	618
469		N-((3R,4S)-4-((8-((2-(3-氨基吡咯烷-1-基)乙基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	617
470		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(3-(二甲氨基)吡咯烷-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	645
471		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(2-(二甲氨基)乙氧基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	620
472		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(2-(羟甲基)吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	660
473		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(3,3-二氟吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	666
474		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(3-甲氧基吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	660

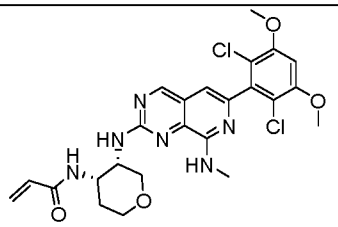
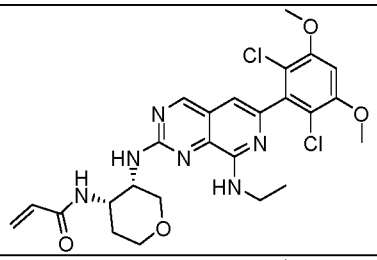
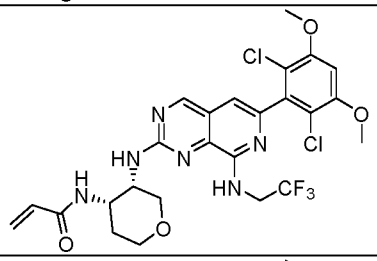
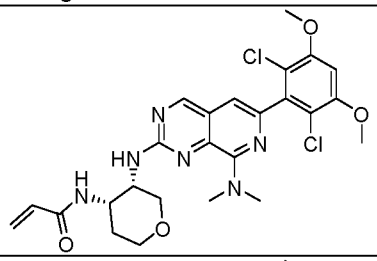
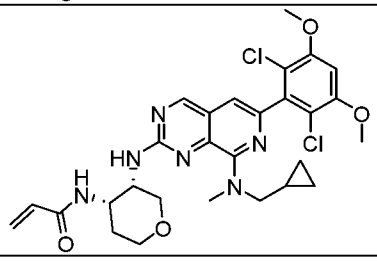
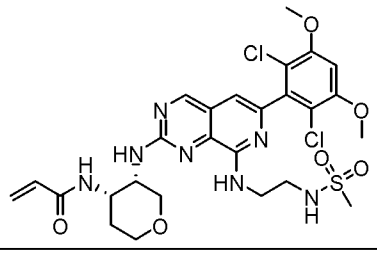
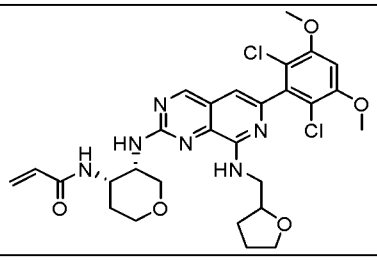
475		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2-氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	525
476		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2-氟-3-甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	479
477		N-((3R,4S)-4-((6-(2-氯-3-(甲氧基-d_3)苯基)-8-((环丙基甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	498
478		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2-氟-3-(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	482
479		N-((3R,4S)-4-((6-(2-氯-3,5-二(甲氧基-d_3)苯基)-8-((环丙基甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	531
480		N-((3R,4S)-4-((8-((环丙基甲基)氨基)-6-(2-氟-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	515
481		N-((3R,4S)-4-((6-(2-氯-3-甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	525

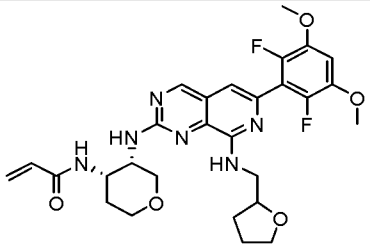
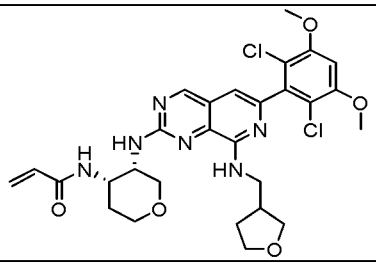
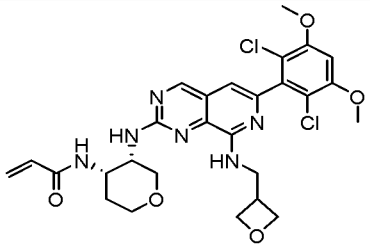
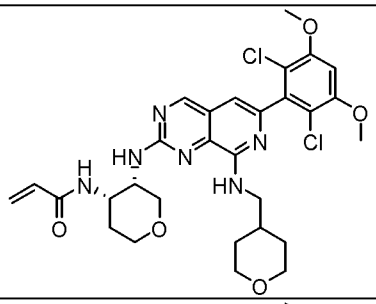
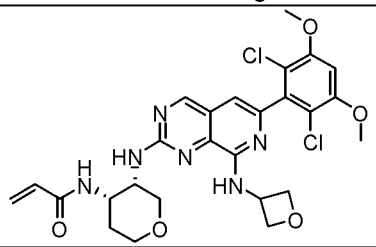
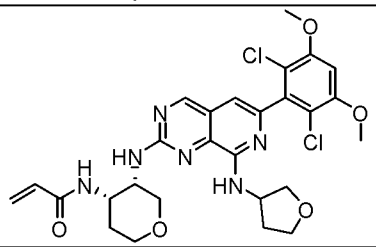
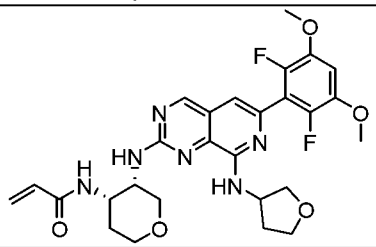
482		N-((3R,4S)-4-((6-(2-氯-3-甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	538
483		N-((3R,4S)-4-((6-(2-氟-3-甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	522
484		N-((3R,4S)-4-((6-(2-氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	568
485		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570
486		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
487		N-((3R,4S)-4-((6-(2-氯-3,5-二甲氧苯基)-8-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	555
488		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((2-(4-甲基哌嗪-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	599

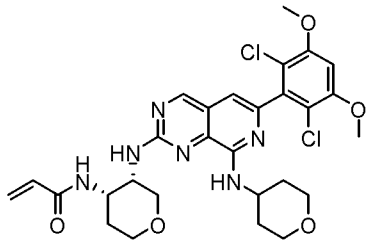
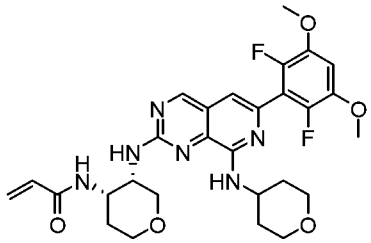
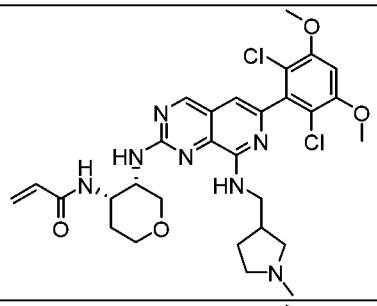
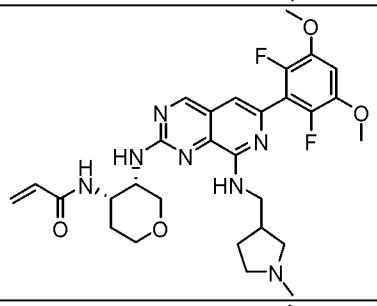
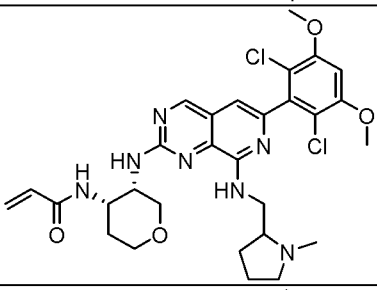
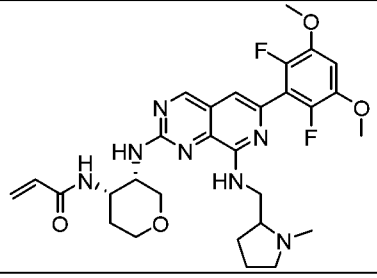
489		N-((3R,4S)-4-((6-(2-氯-3-甲氧苯基)-8-((2-(4-甲基哌嗪-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	567
490		N-((3R,4S)-4-((6-(2-氯-3,5-二甲氧苯基)-8-((2-(4-甲基哌嗪-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	597
491		N-((3R,4S)-4-((6-(3,5-二甲氧苯基)-8-((2-(4-甲基哌嗪-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	563
492		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	531
493		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((1-甲基哌啶-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570
494		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	567
495		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557

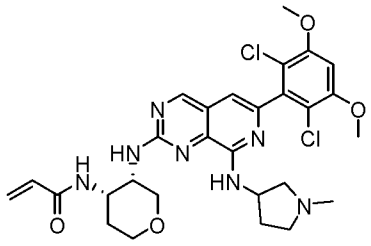
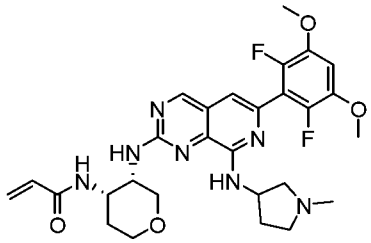
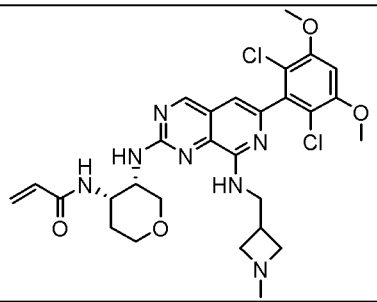
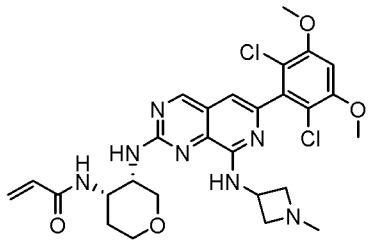
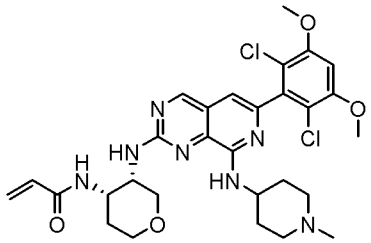
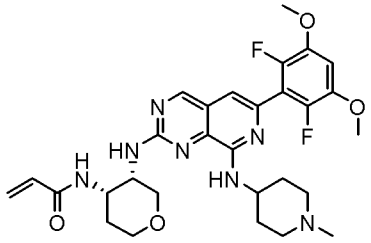
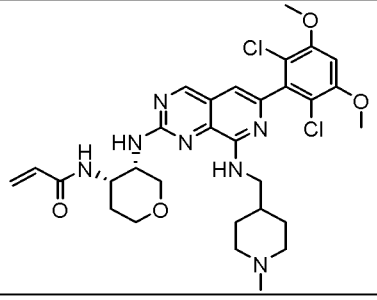
496		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-乙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	534
497		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-异丙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	548
498		N-((3R,4S)-4-((8-(环丙基甲氧基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	560
499		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	577
500		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	545
501		N-((3S,4S)-3-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	573
502		N-((3S,4S)-3-((8-((环丙基甲基)氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	541

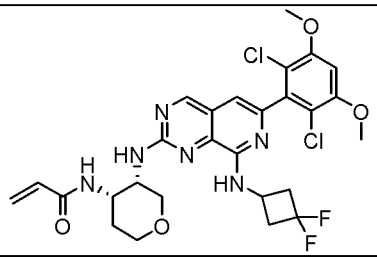
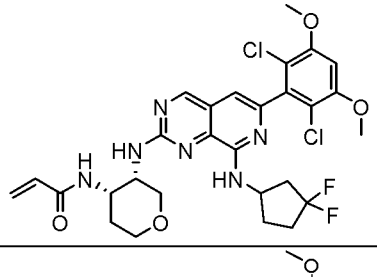
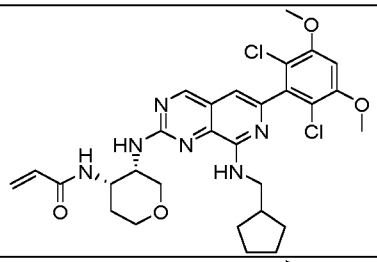
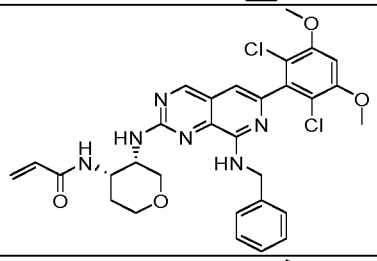
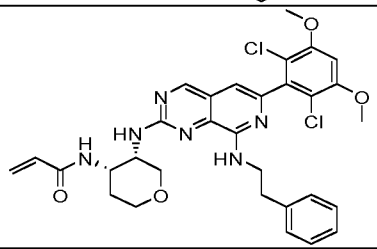
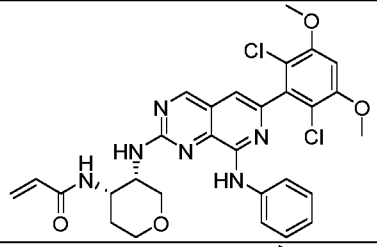
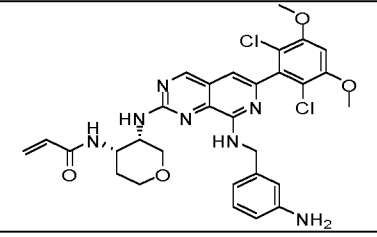
503		N-((3S,4S)-3-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	579
504		N-((3S,4S)-3-((8-((环丙基甲基)氨基)-6-(2,6-二氟-3,5-二(甲氧基-d_3)苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	547
505		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-羟基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	563
506		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(异丙基硫代)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	621
507		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(乙基磺酰)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	639
508		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(二甲氨基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	590
509		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3-(二甲氨基)丙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	604

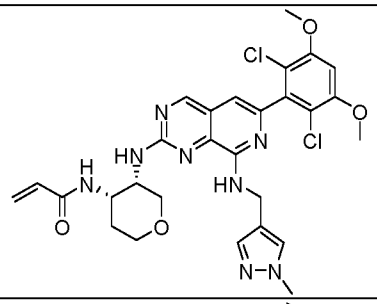
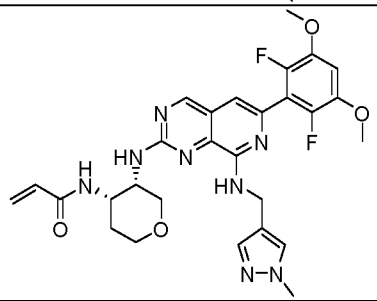
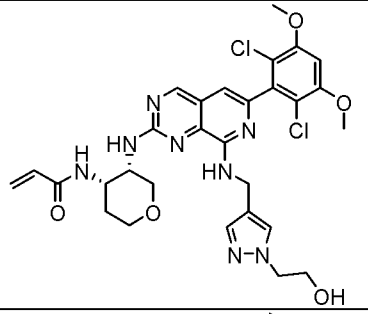
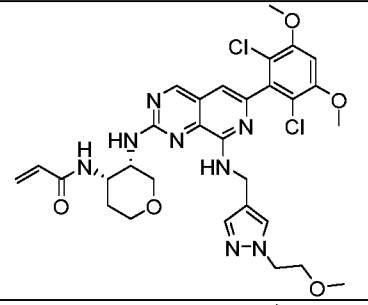
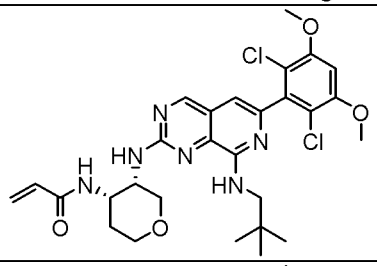
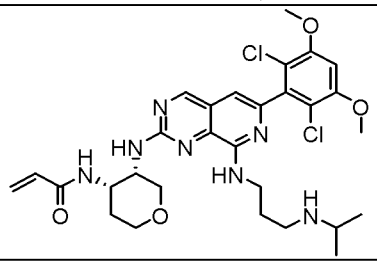
510		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	549
511		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	547
512		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2,2,2-三氟乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	601
513		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(二甲氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	547
514		N-((3S,4S)-3-((8-((环丙基甲基)(甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	587
515		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(甲基磺酰氨基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	640
516		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603

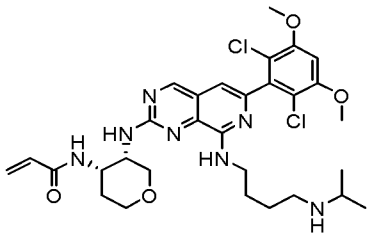
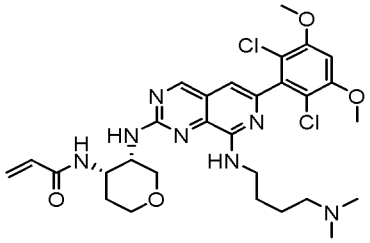
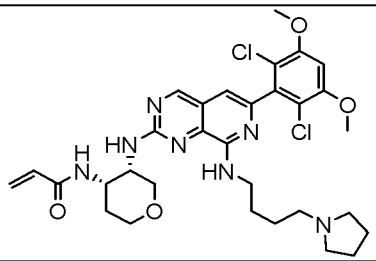
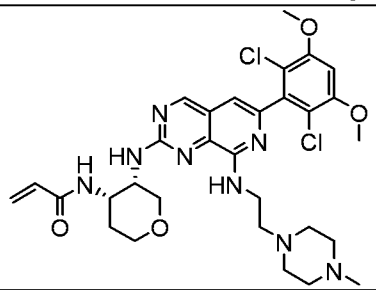
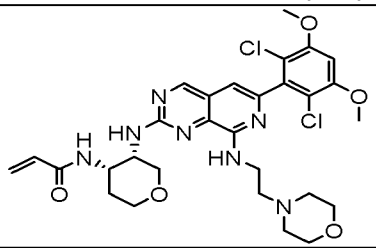
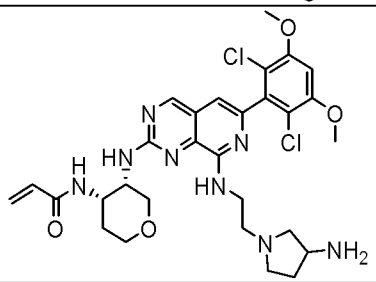
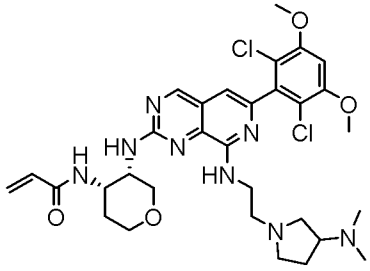
517		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	571
518		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
519		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((噁丁环-3-基甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
520		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢-2H-吡喃-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617
521		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	575
522		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
523		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	557

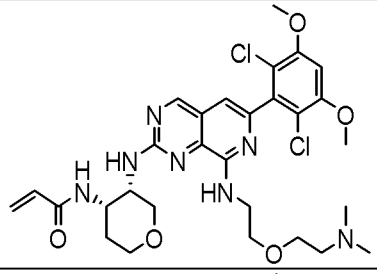
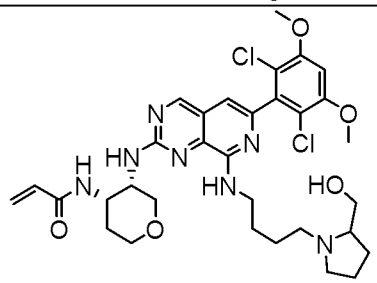
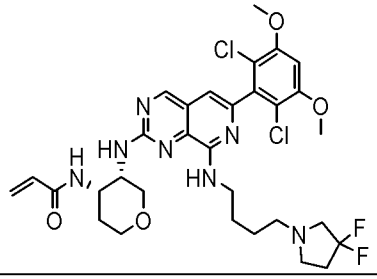
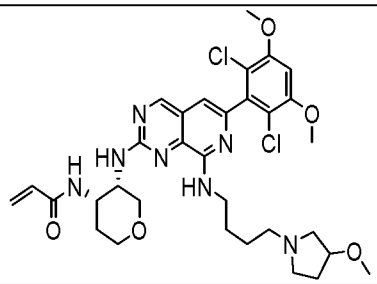
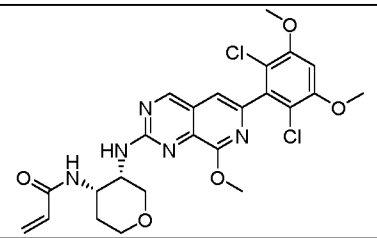
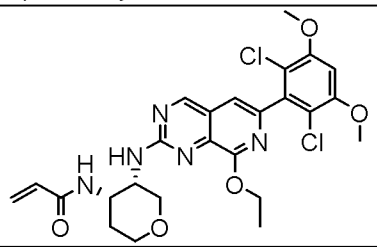
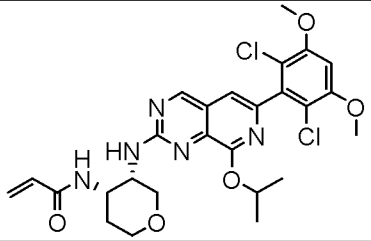
524		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
525		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((四氢-2H-吡喃-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	571
526		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
527		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	584
528		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
529		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((1-甲基吡咯烷-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	584

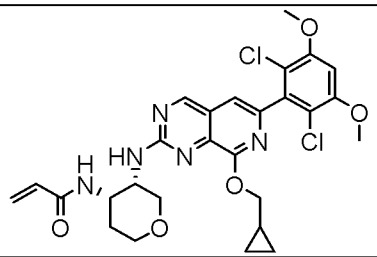
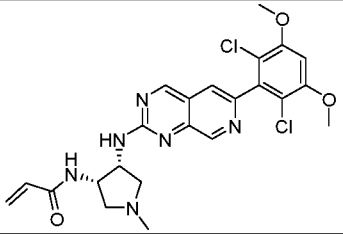
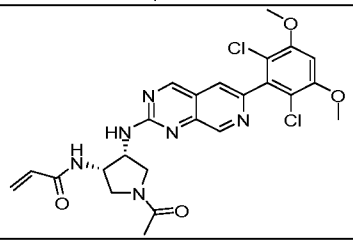
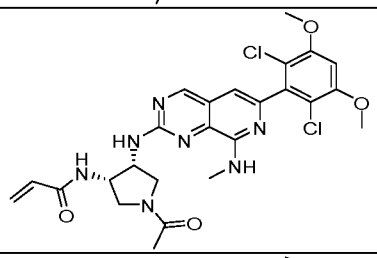
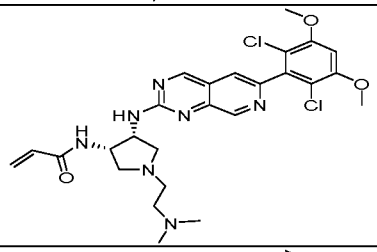
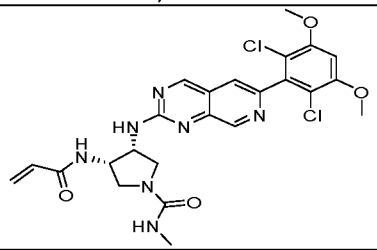
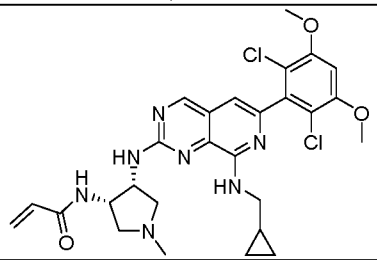
530		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
531		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	570
532		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基吖丁啶-3-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	602
533		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吖丁啶-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	588
534		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基哌啶-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	616
535		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((1-甲基哌啶-4-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	584
536		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基哌啶-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	630

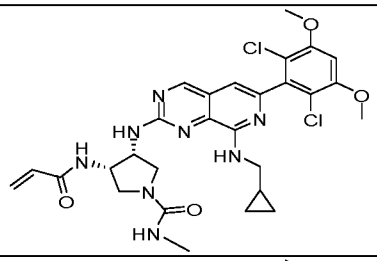
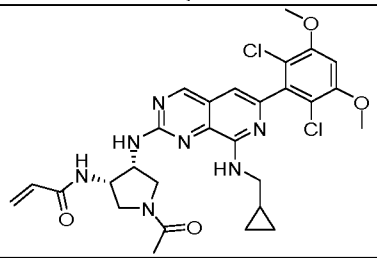
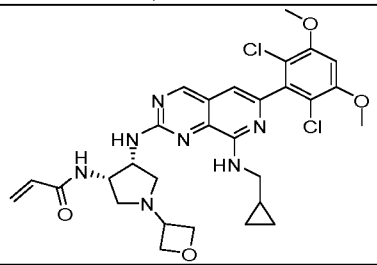
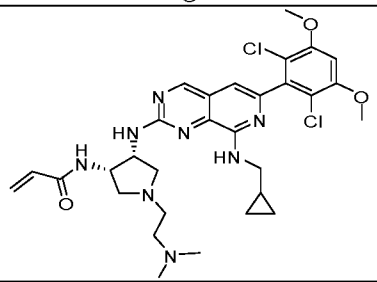
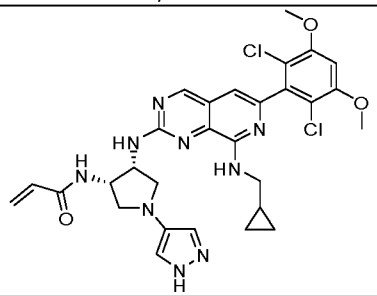
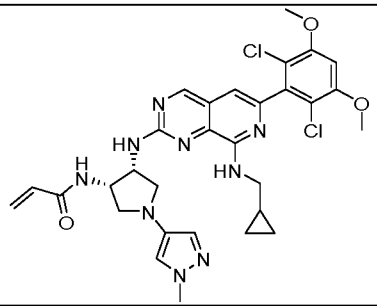
537		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,3-二氟环丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	609
538		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,3-二氟环戊基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	623
539		N-((3S,4S)-3-((8-((环戊基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	601
540		N-((3S,4S)-3-((8-(苯甲基氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	609
541		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(苯乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	623
542		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(苯基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	595
543		N-((3S,4S)-3-((8-((3-氨基苯甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	624

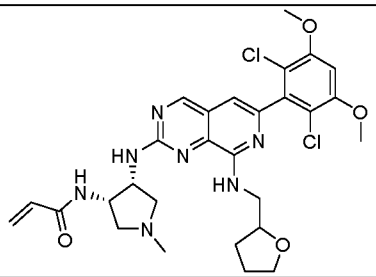
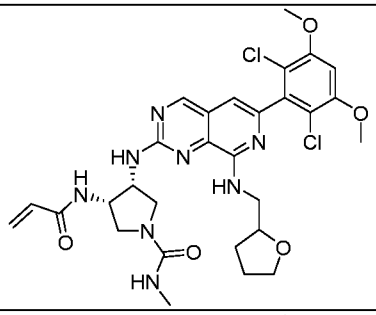
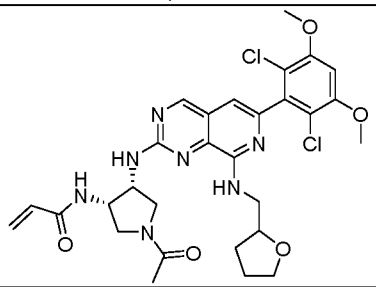
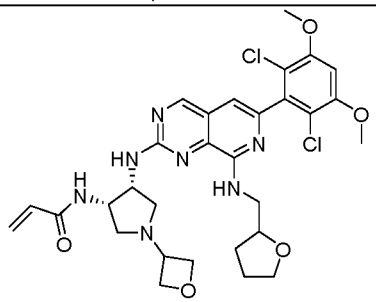
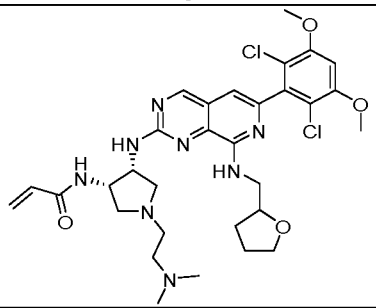
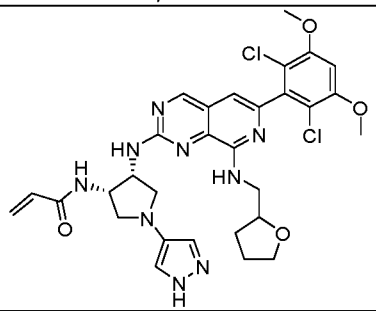
544		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	613
545		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((1-甲基-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	581
546		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-(2-羟基乙基)-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	643
547		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-(2-甲氧基乙基)-1H-吡唑-4-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	657
548		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(新戊基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
549		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3-(异丙基氨基)丙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	618

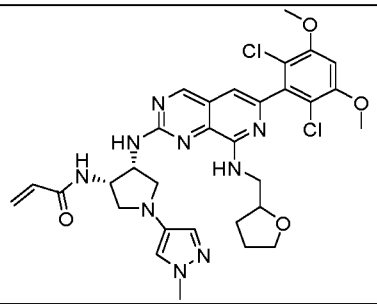
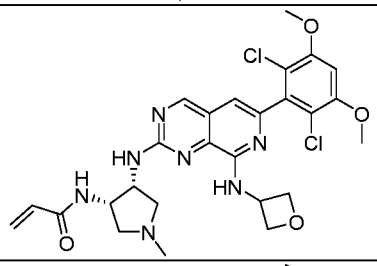
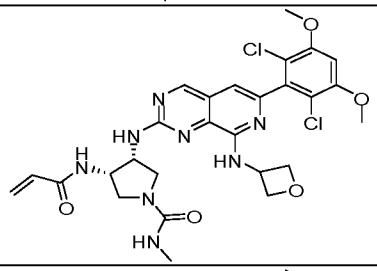
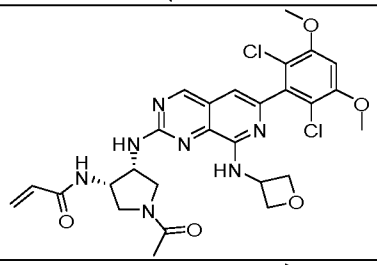
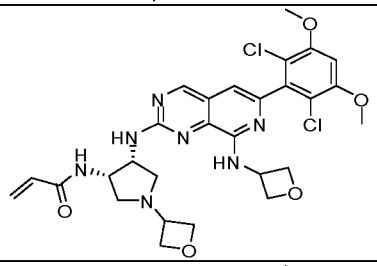
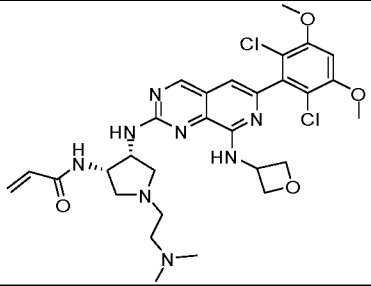
550		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(异丙基氨基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	632
551		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(二甲氨基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	618
552		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	644
553		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(4-甲基哌嗪-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	645
554		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-吗啉代乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	632
555		N-((3S,4S)-3-((8-((2-(3-氨基吡咯烷-1-基)乙基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	631
556		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(3-(二甲氨基)吡咯烷-1-基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	659

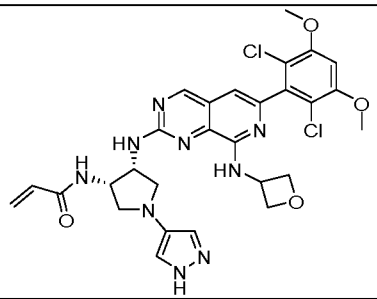
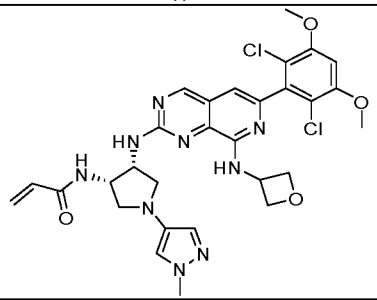
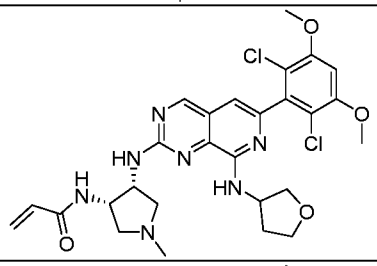
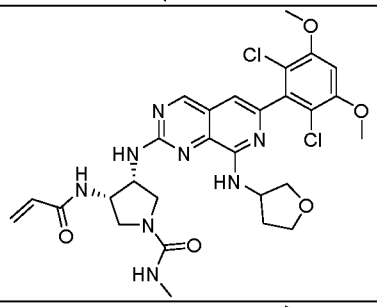
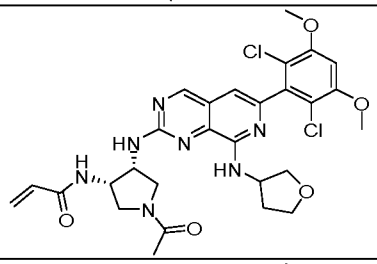
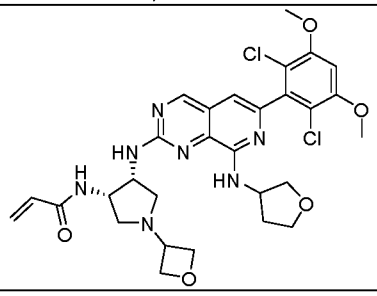
557		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-(2-(二甲氨基)乙氧基)乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	634
558		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(2-(羟甲基)吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	674
559		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(3,3-二氟吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	680
560		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((4-(3-甲氧基吡咯烷-1-基)丁基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	674
561		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	534
562		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-乙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	548
563		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-异丙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	562

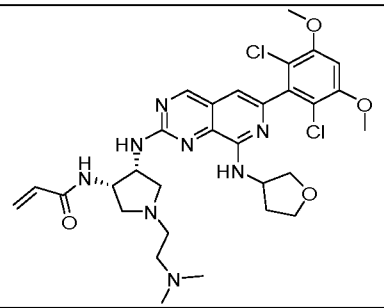
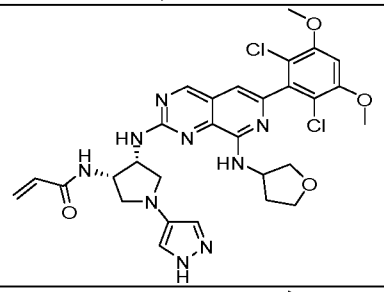
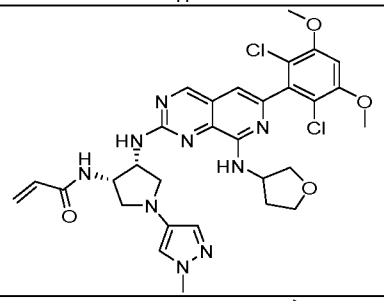
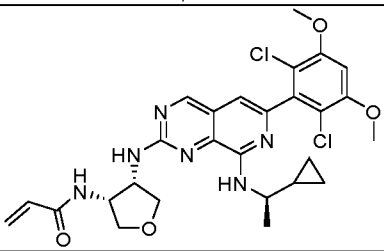
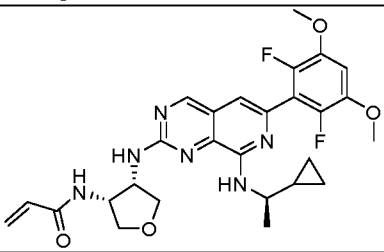
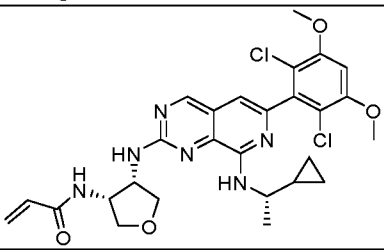
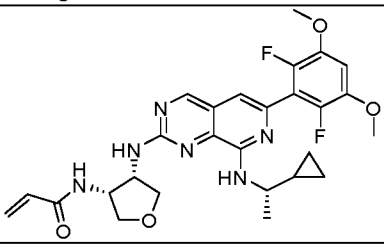
564		N-((3S,4S)-3-((8-(环丙基甲氧基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	574
565		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	503
566		N-((3S,4R)-1-乙酰基-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	531
567		N-((3S,4R)-1-乙酰基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	560
568		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	560
569		(3S,4R)-3-丙烯酰基酰氨基-4-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-N-甲基吡咯烷-1-甲酰胺	546
570		N-((3S,4R)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	572

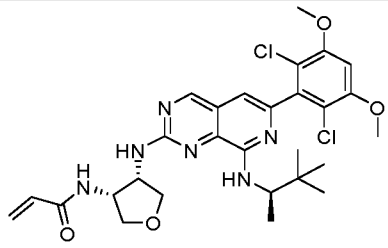
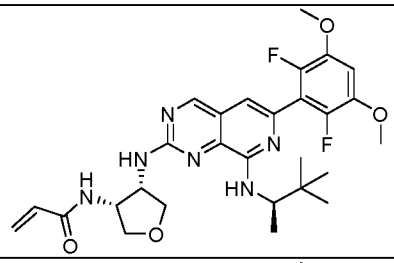
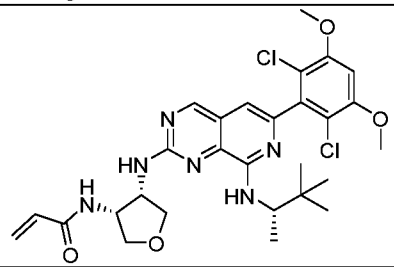
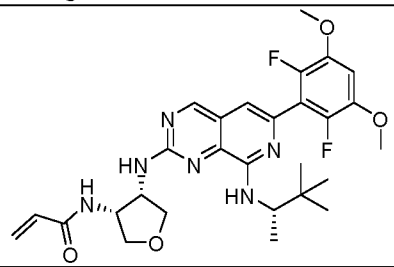
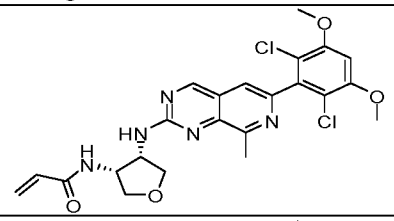
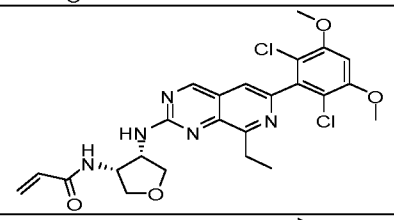
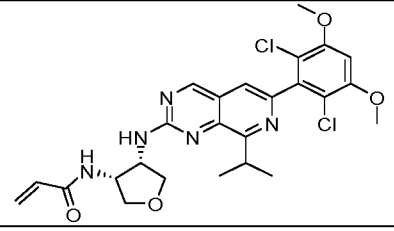
571		(3S,4R)-3-丙烯酰基酰氨基-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-N-甲基吡咯烷-1-甲酰胺	615
572		N-((3S,4R)-1-乙酰基-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	600
573		N-((3S,4R)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	614
574		N-((3S,4R)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	629
575		N-((3S,4R)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	624
576		N-((3S,4R)-4-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	638

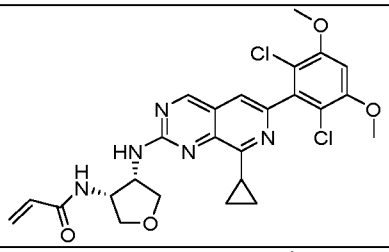
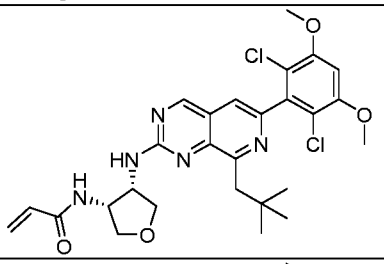
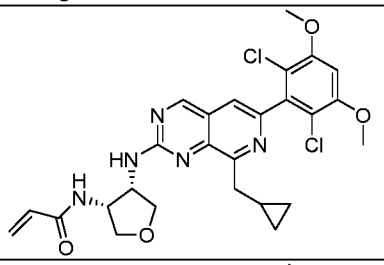
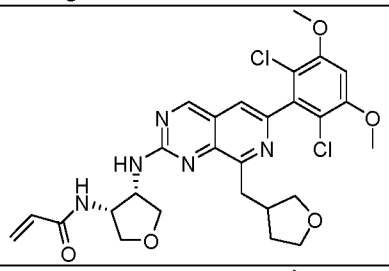
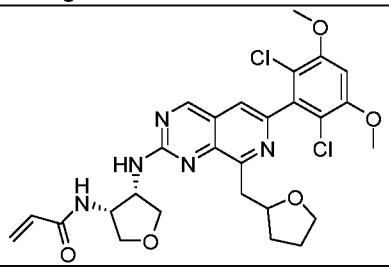
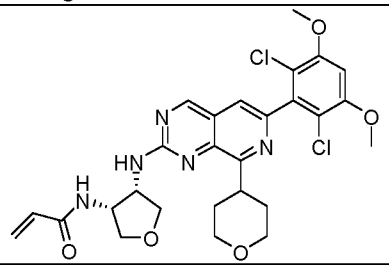
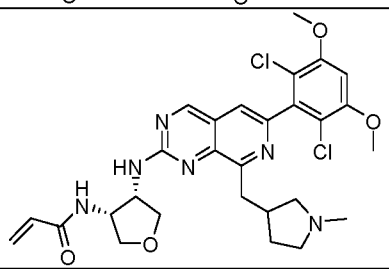
577		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	602
578		(3S,4R)-3-丙烯酰基酰氨基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-N-甲基吡咯烷-1-甲酰胺	645
579		N-((3S,4R)-1-乙酰基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	630
580		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	644
581		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	659
582		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	654

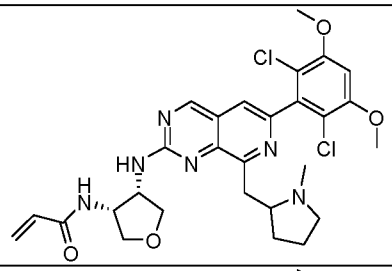
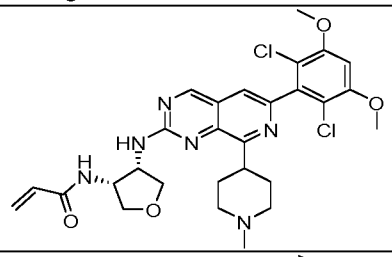
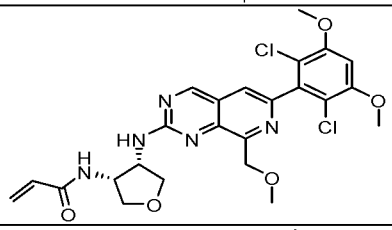
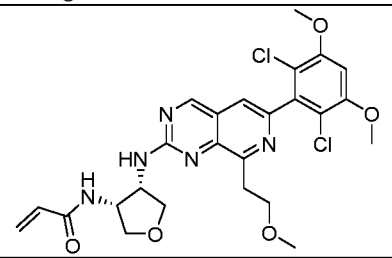
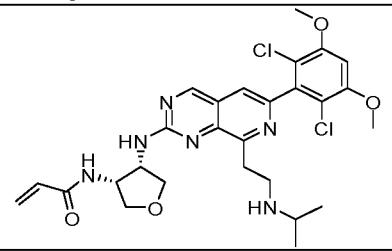
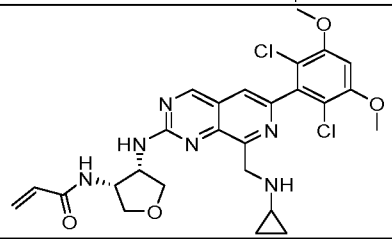
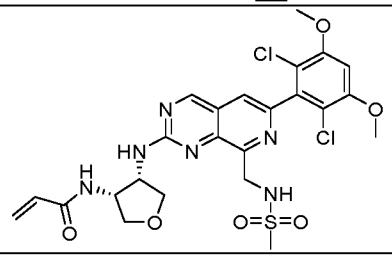
583		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((四氢呋喃-2-基)甲基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	668
584		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	574
585		(3S,4R)-3-丙烯酰基酰氨基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-N-甲基吡咯烷-1-甲酰胺	617
586		N-((3S,4R)-1-乙酰基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	602
587		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	616
588		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	631

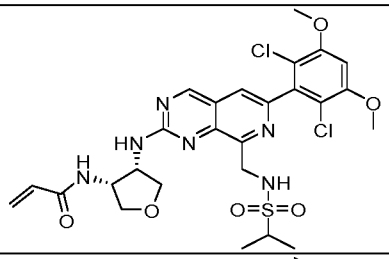
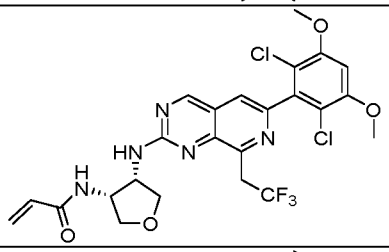
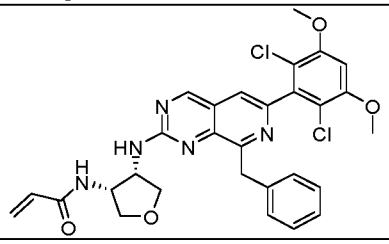
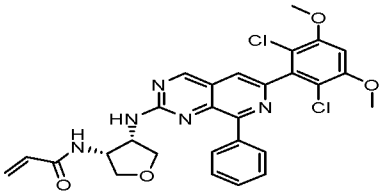
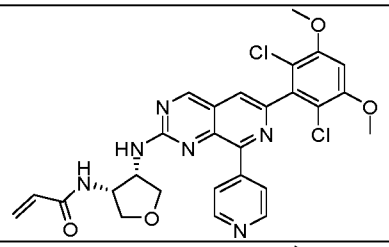
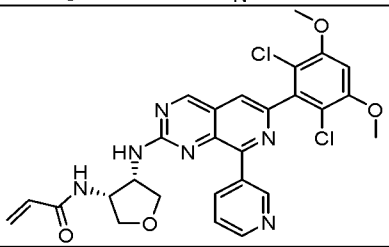
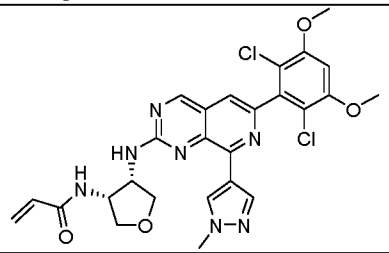
589		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	626
590		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(噁丁环-3-基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	640
591		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-甲基吡咯烷-3-基)丙烯酰基酰胺	588
592		(3S,4R)-3-丙烯酰基酰氨基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-N-甲基吡咯烷-1-甲酰胺	631
593		N-((3S,4R)-1-乙酰基-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡咯烷-3-基)丙烯酰基酰胺	616
594		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(噁丁环-3-基)吡咯烷-3-基)丙烯酰基酰胺	630

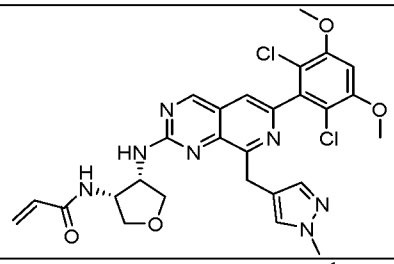
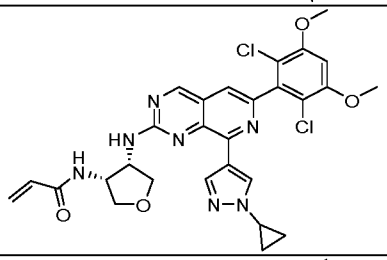
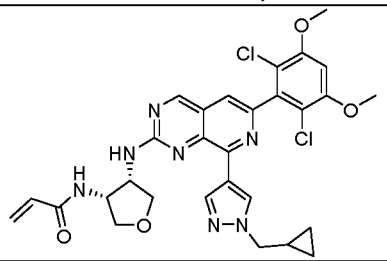
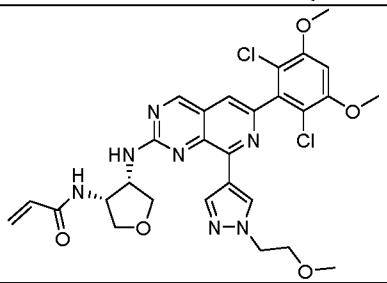
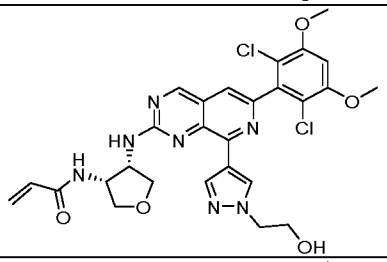
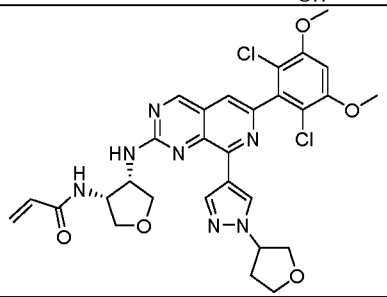
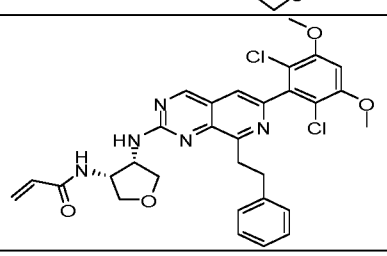
595		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(2-(二甲氨基)乙基)吡咯烷-3-基)丙烯酰基酰胺	645
596		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	640
597		N-((3S,4R)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)-1-(1-甲基-1H-吡唑-4-基)吡咯烷-3-基)丙烯酰基酰胺	654
598		N-((3R,4S)-4-((8-(((R)-1-环丙基乙基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	573
599		N-((3R,4S)-4-((8-(((R)-1-环丙基乙基)氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	541
600		N-((3R,4S)-4-((8-(((S)-1-环丙基乙基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	573
601		N-((3R,4S)-4-((8-(((S)-1-环丙基乙基)氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	541

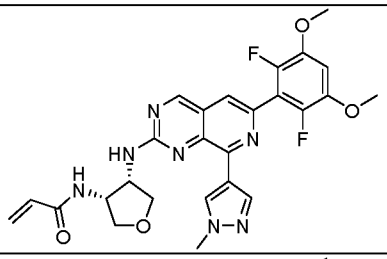
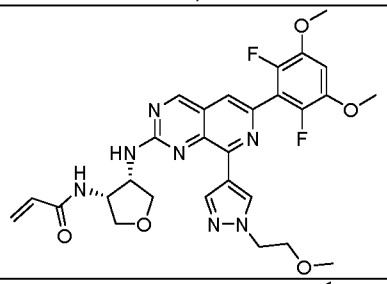
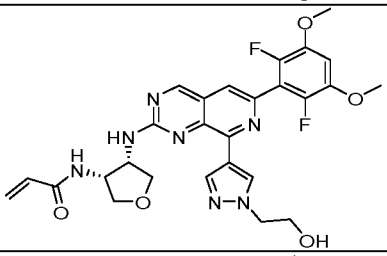
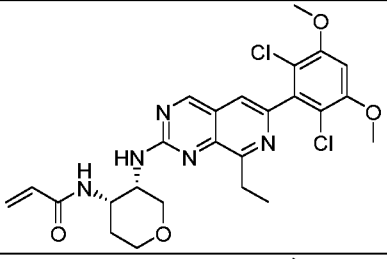
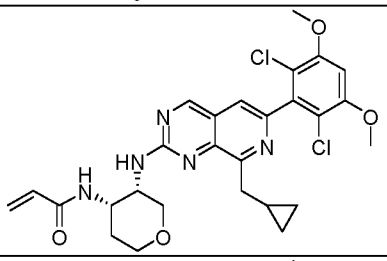
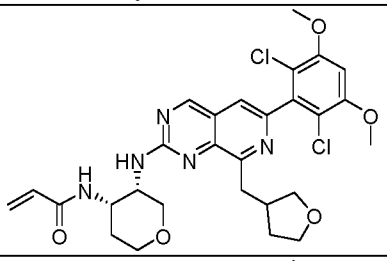
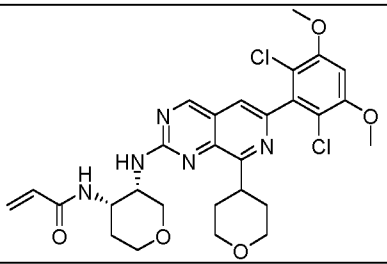
602		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((R)-3,3-二甲基丁烷-2-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
603		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((R)-3,3-二甲基丁烷-2-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
604		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((S)-3,3-二甲基丁烷-2-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
605		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(((S)-3,3-二甲基丁烷-2-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
606		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-甲基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	504
607		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-乙基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	518
608		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-异丙基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	532

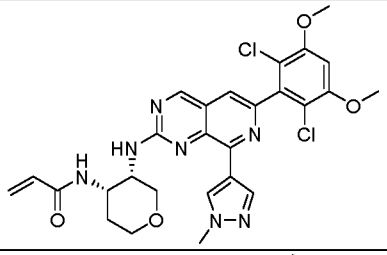
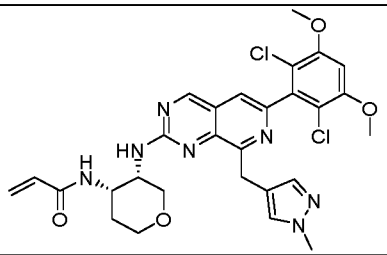
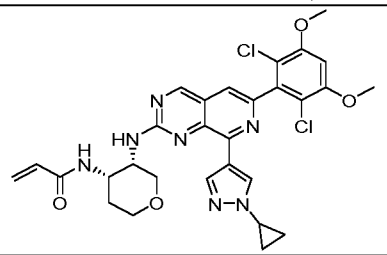
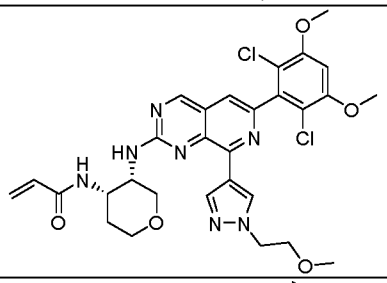
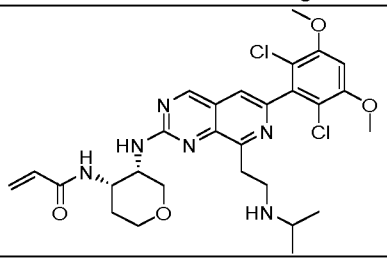
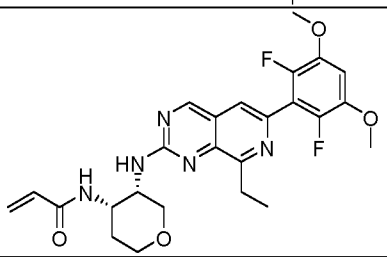
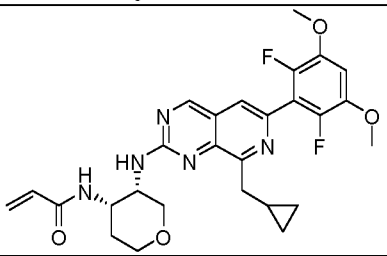
609		N-((3R,4S)-4-((8-环丙基-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	530
610		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-新戊基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	560
611		N-((3R,4S)-4-((8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	544
612		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
613		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-2-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
614		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	574
615		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-3-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587

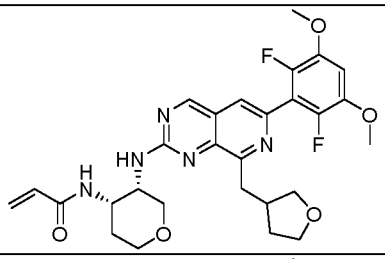
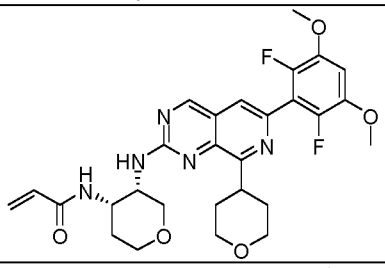
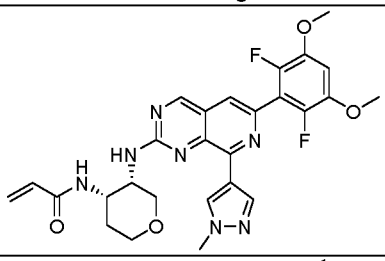
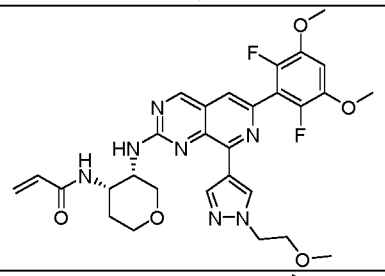
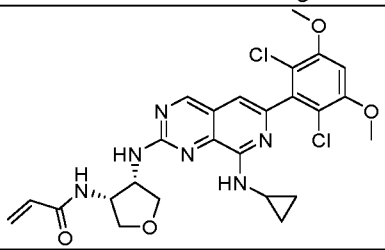
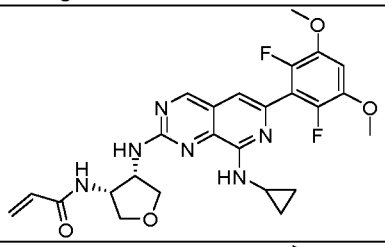
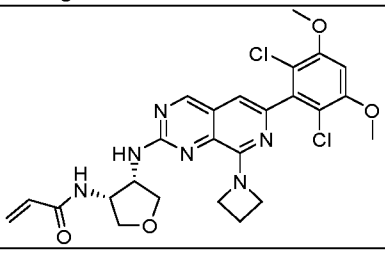
616		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基吡咯烷-2-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
617		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-甲基哌啶-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
618		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲氧基甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	534
619		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-甲氧基乙基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	548
620		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-(异丙基氨基)乙基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
621		N-((3R,4S)-4-((8-((环丙基氨基)甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	559
622		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基磺酰氨基甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	597

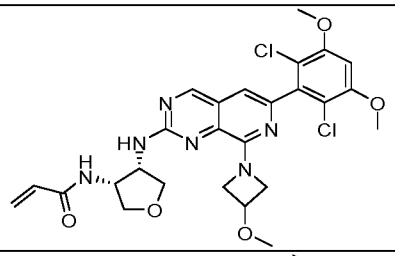
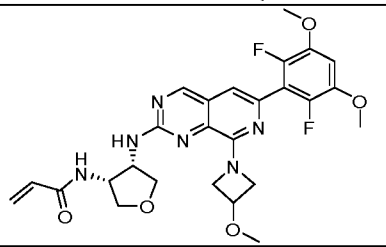
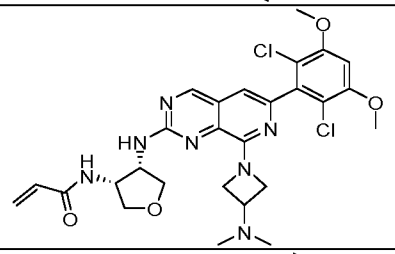
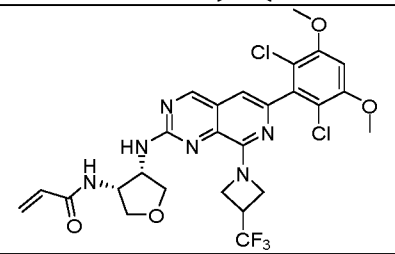
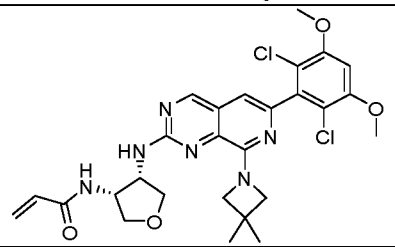
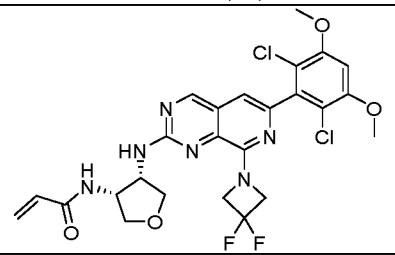
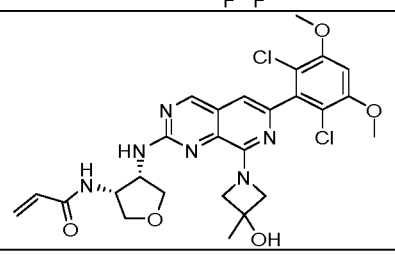
623		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(((1-甲基乙基)磺酰氨基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	625
624		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2,2,2-三氟乙基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	572
625		N-((3R,4S)-4-((8-苯甲基-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	580
626		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-苯基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	566
627		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(吡啶-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	567
628		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(吡啶-3-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	567
629		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	570

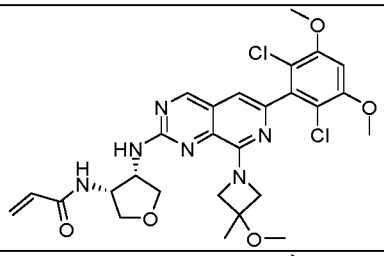
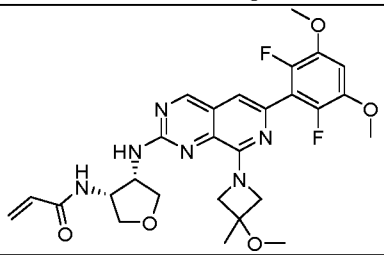
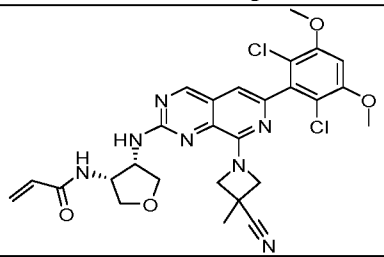
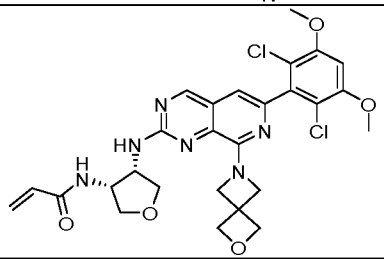
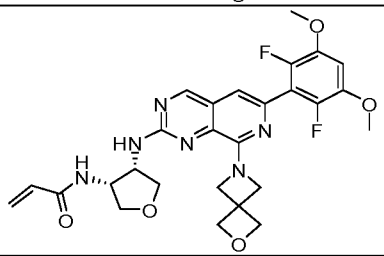
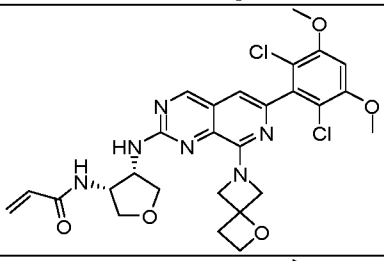
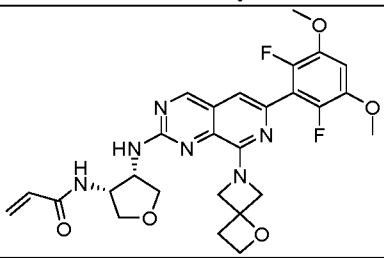
630		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基-1H-吡唑-4-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584
631		N-((3R,4S)-4-((8-(1-环丙基-1H-吡唑-4-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	596
632		N-((3R,4S)-4-((8-(1-(环丙基甲基)-1H-吡唑-4-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	610
633		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-(2-甲氧基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	614
634		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-(2-羟基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	600
635		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-(四氢呋喃-3-基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	626
636		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-苯乙基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	594

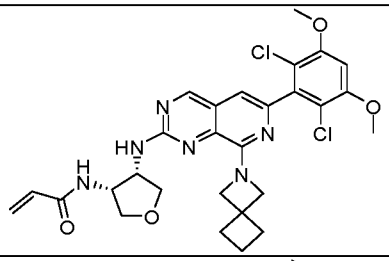
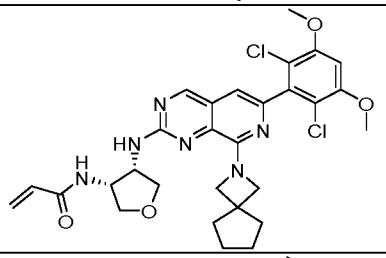
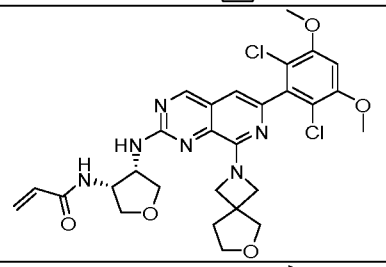
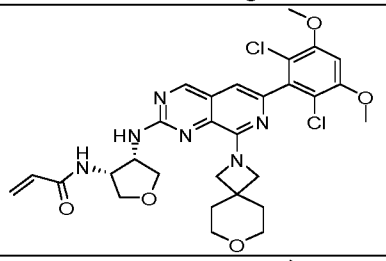
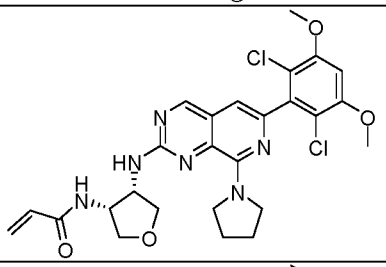
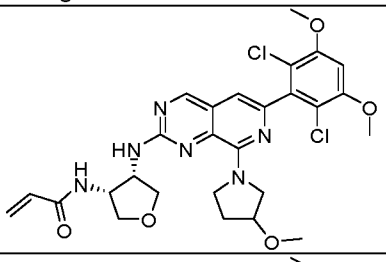
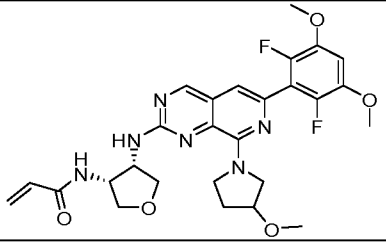
637		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	538
638		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-(2-甲氧基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	582
639		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-(2-羟基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	568
640		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-乙基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	532
641		N-((3S,4S)-3-((8-(环丙基甲基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	558
642		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	588
643		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	588

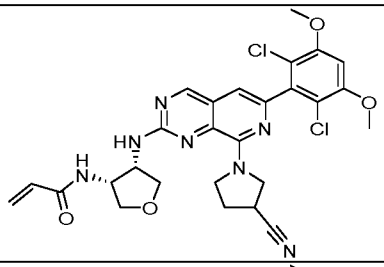
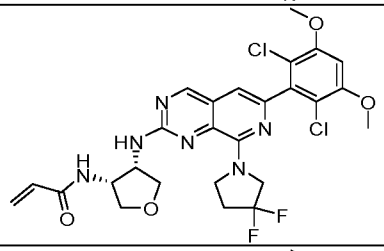
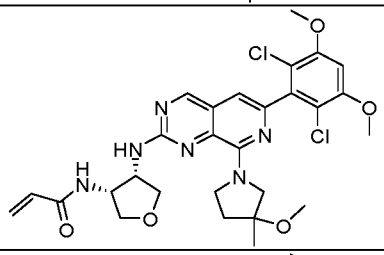
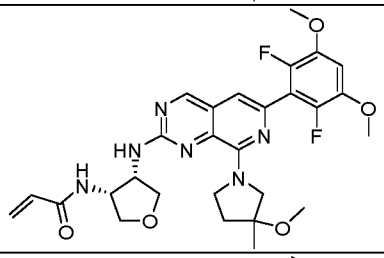
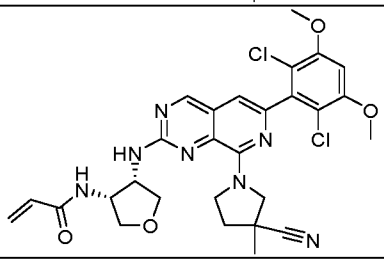
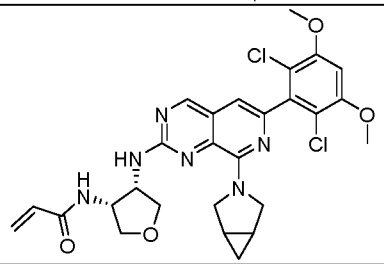
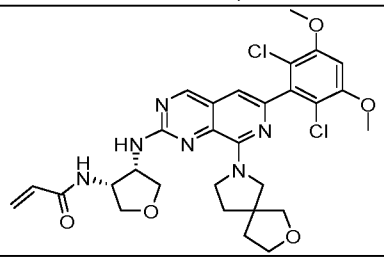
644		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	584
645		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((1-甲基-1H-吡唑-4-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	598
646		N-((3S,4S)-3-((8-(1-环丙基-1H-吡唑-4-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	610
647		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-(2-甲氧基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	628
648		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-(异丙基氨基)乙基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
649		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-乙基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	500
650		N-((3S,4S)-3-((8-(环丙基甲基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	526

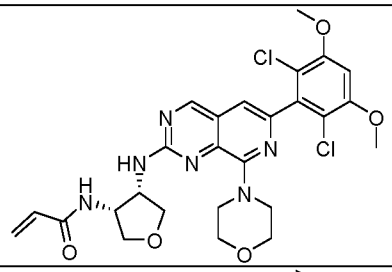
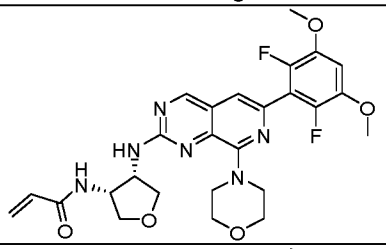
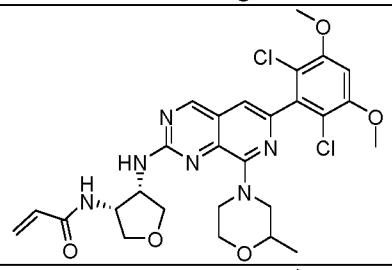
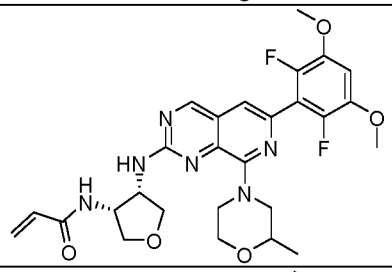
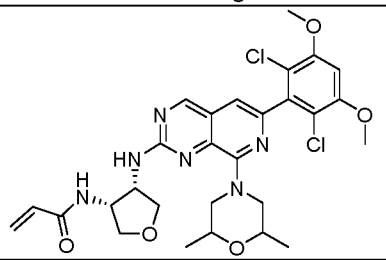
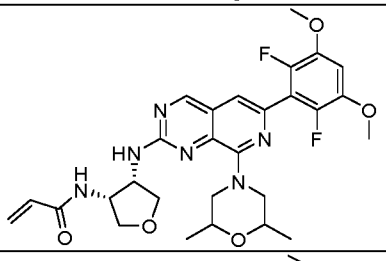
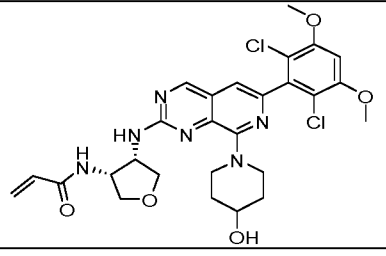
651		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((四氢呋喃-3-基)甲基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	556
652		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(四氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	556
653		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	552
654		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-(2-甲氧基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	596
655		N-((3R,4S)-4-((8-(环丙基氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	545
656		N-((3R,4S)-4-((8-(环丙基氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	513
657		N-((3R,4S)-4-((8-(吖丁啶-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	545

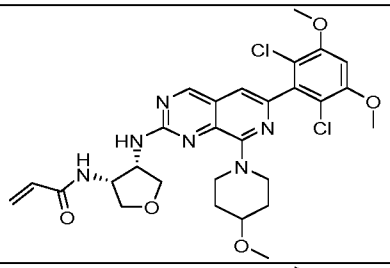
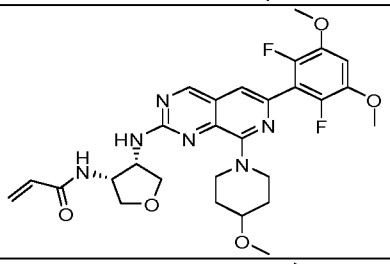
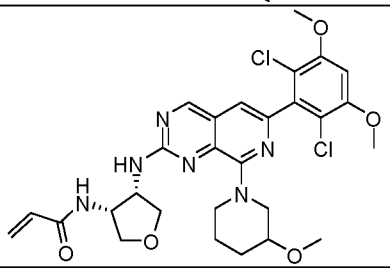
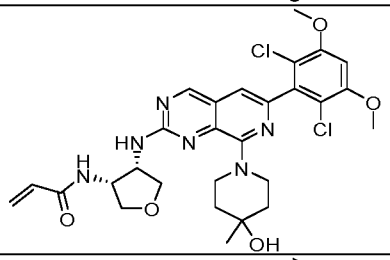
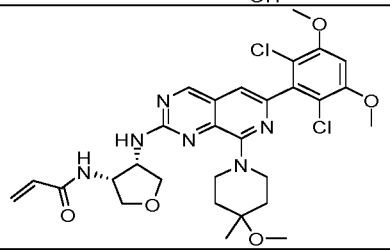
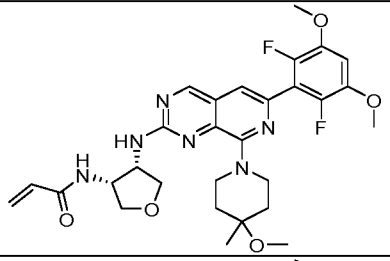
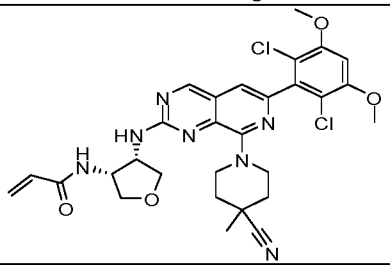
658		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
659		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	543
660		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-(二甲氨基)吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	588
661		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-(三氟甲基)吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	613
662		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	573
663		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	581
664		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575

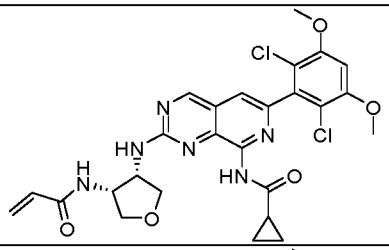
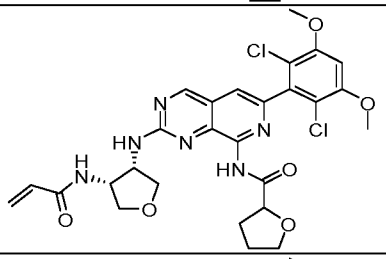
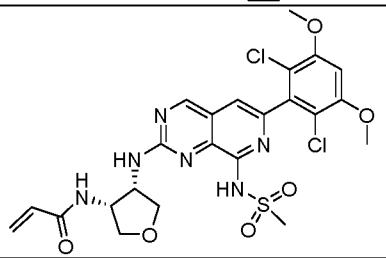
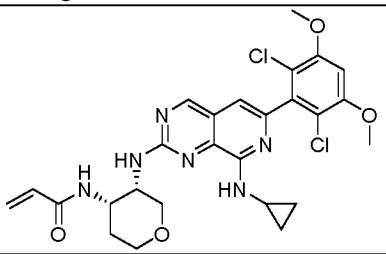
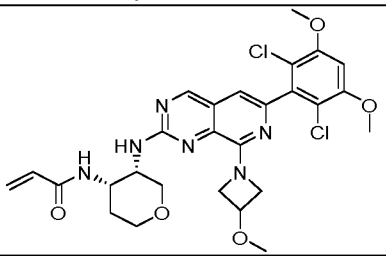
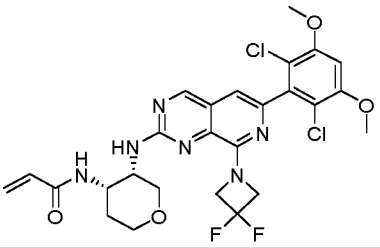
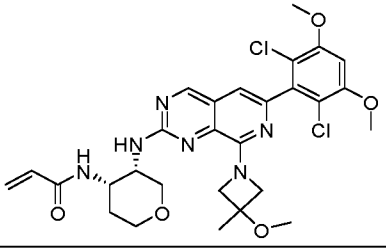
665		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
666		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
667		N-((3R,4S)-4-((8-(3-氰基-3-甲基吖丁啶-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584
668		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
669		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	555
670		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(1-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
671		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	555

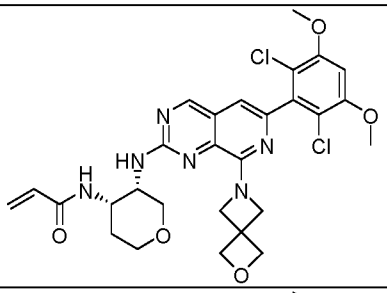
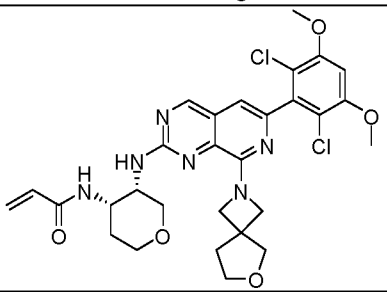
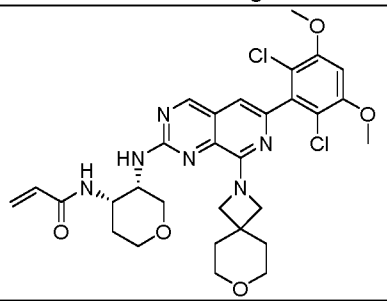
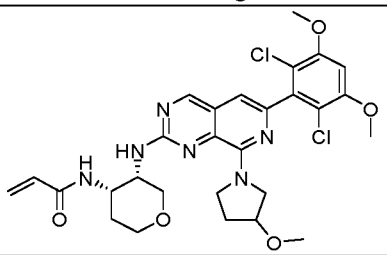
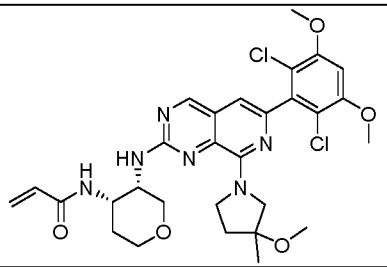
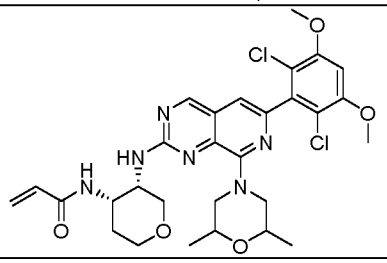
672		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-氮杂螺[3.3]庚烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	585
673		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	599
674		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(6-氧杂-2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	601
675		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	615
676		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	559
677		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
678		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557

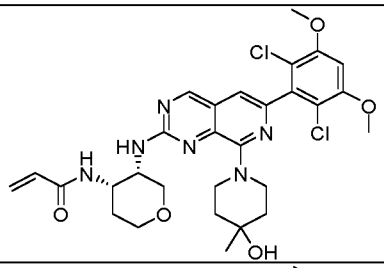
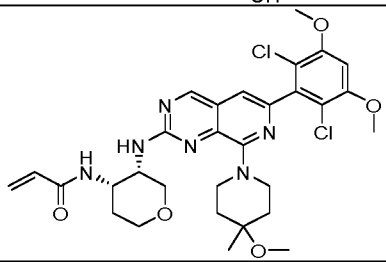
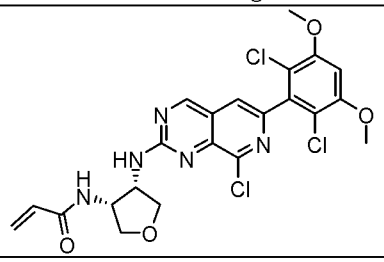
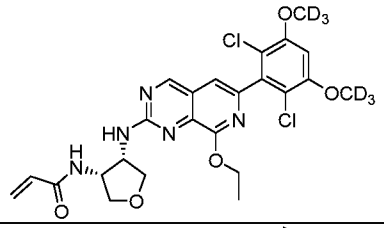
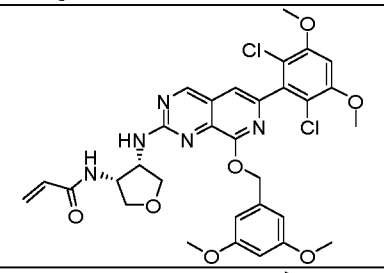
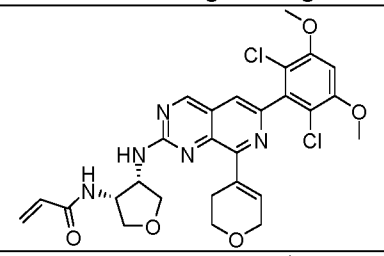
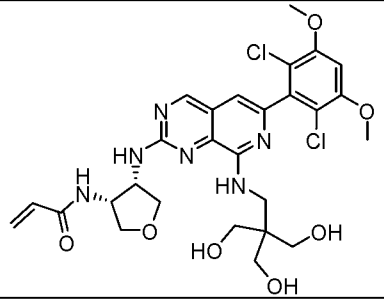
679		N-((3R,4S)-4-((8-(3-氰基吡咯烷-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	584
680		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二氟吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	595
681		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
682		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
683		N-((3R,4S)-4-((8-(3-氰基-3-甲基吡咯烷-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	598
684		N-((3R,4S)-4-((8-(3-氮杂二环[3.1.0]己烷-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
685		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-氧杂-7-氮杂螺[4.4]壬烷-7-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	615

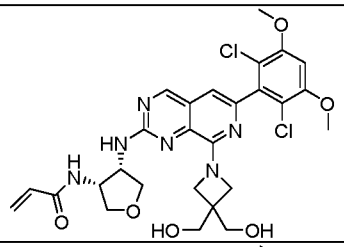
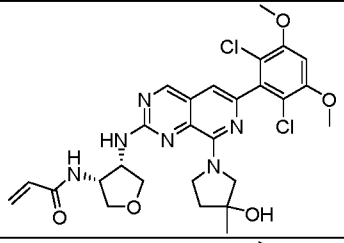
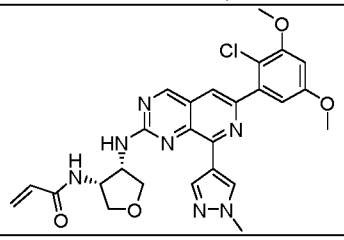
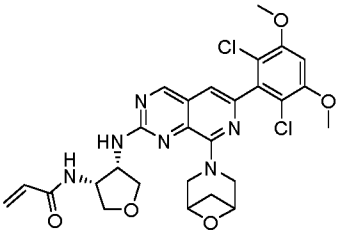
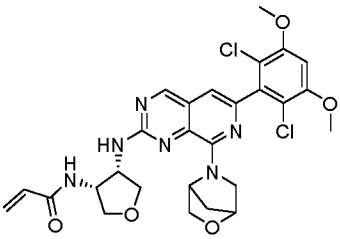
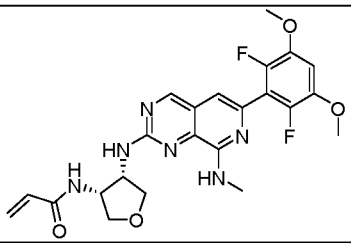
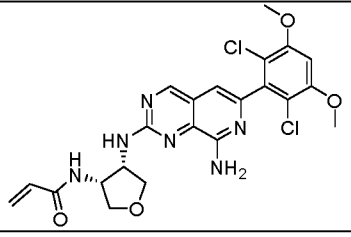
686		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	575
687		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	543
688		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-甲基吗啉代)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
689		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(2-甲基吗啉代)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557
690		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2,6-二甲基吗啉代)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
691		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(2,6-二甲基吗啉代)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
692		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-羟基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589

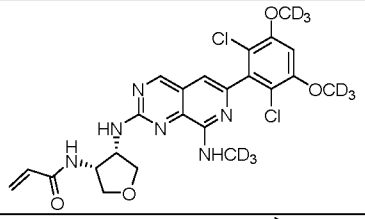
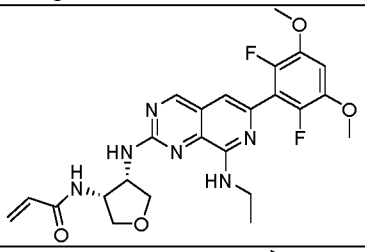
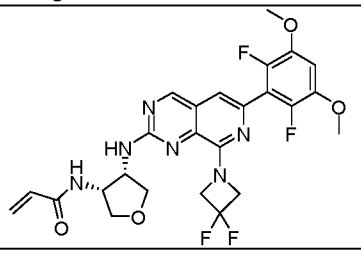
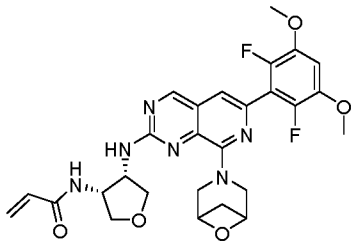
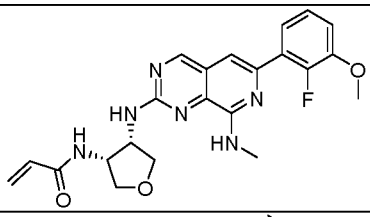
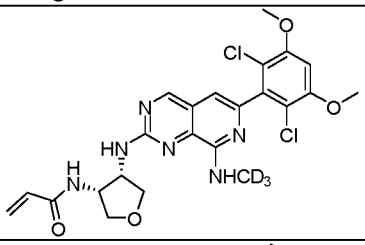
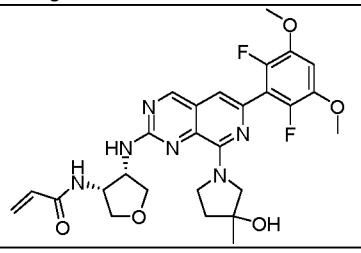
693		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
694		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	571
695		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
696		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-羟基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	603
697		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	617
698		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	585
699		N-((3R,4S)-4-((8-(4-氰基-4-甲基哌啶-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	612

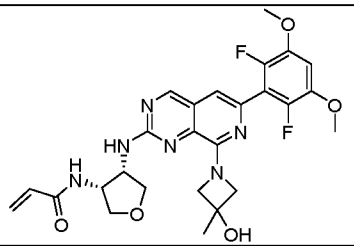
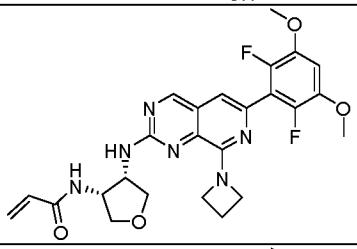
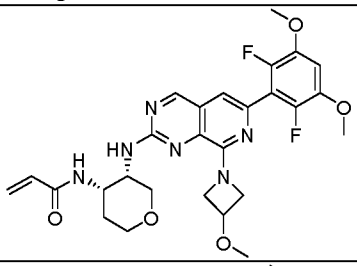
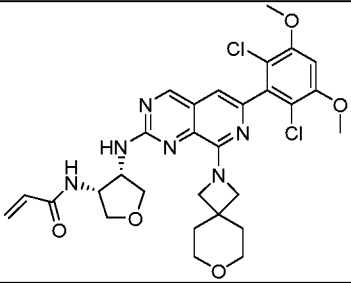
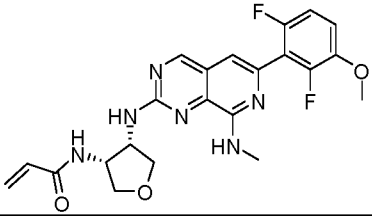
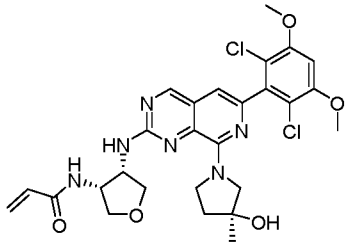
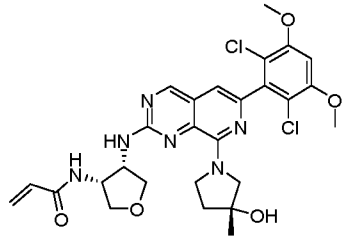
700		N-(2-(((3S,4R)-4-丙烯酰基酰氨基四氢呋喃-3-基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-8-基)环丙甲酰胺	573
701		N-(2-(((3S,4R)-4-丙烯酰基酰氨基四氢呋喃-3-基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-8-基)四氢呋喃-2-甲酰胺	603
702		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(甲基磺酰氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	583
703		N-((3S,4S)-3-((8-(环丙基氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	559
704		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
705		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	595
706		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603

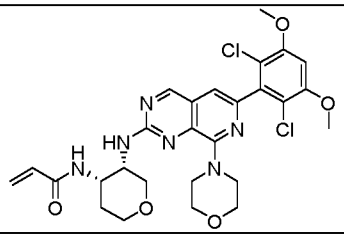
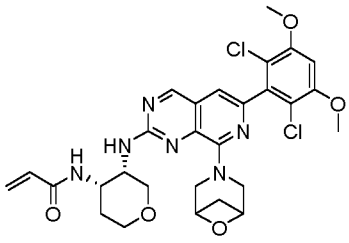
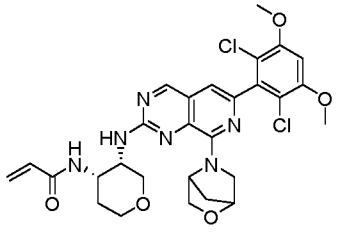
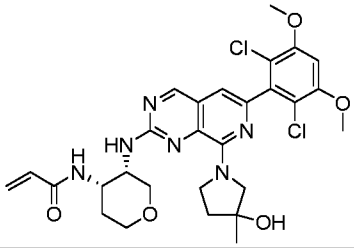
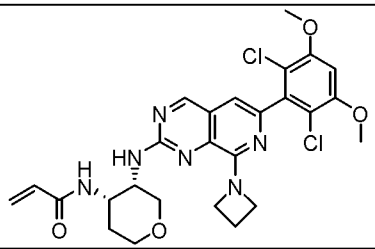
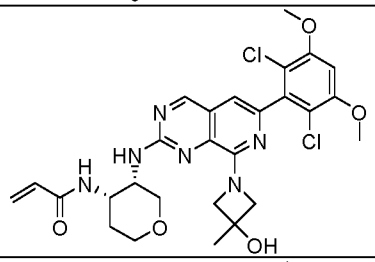
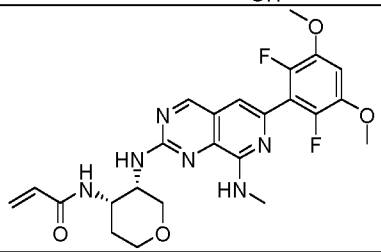
707		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	601
708		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(6-氧杂-2-氮杂螺[3.4]辛烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	615
709		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	629
710		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
711		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617
712		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(2,6-二甲基吗啉代)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617

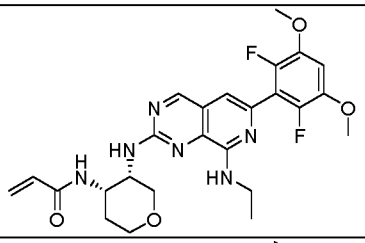
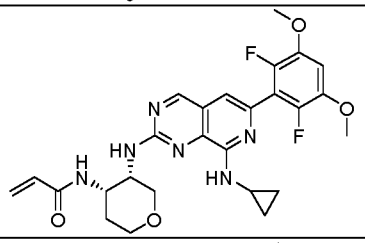
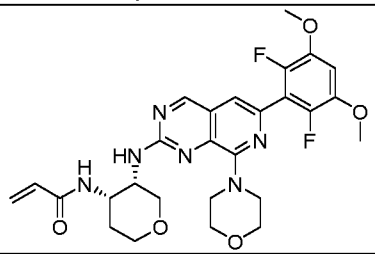
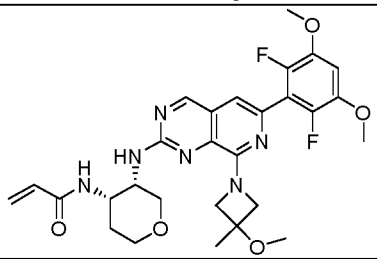
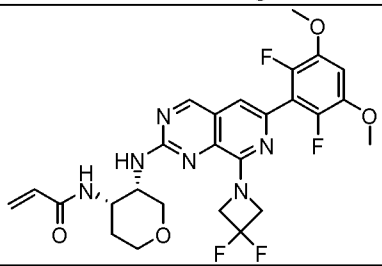
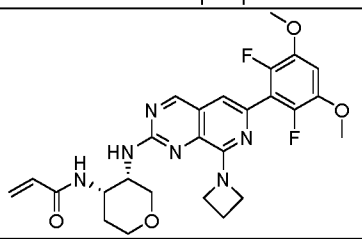
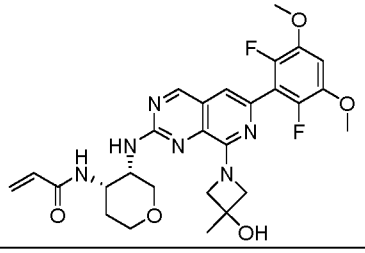
713		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-羟基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	617
714		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(4-甲氧基-4-甲基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	631
753		N-((3R,4S)-4-((8-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	524
754		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-8-乙氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	540
755		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3,5-二甲氧基苄基)氧代)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	656
756		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3,6-二氢-2H-吡喃-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	572
758		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((3-羟基-2,2-二（羟甲基）丙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	623

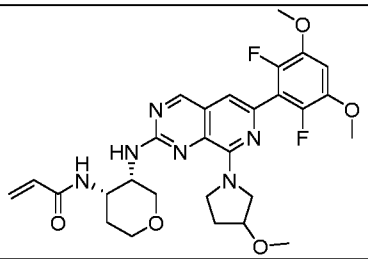
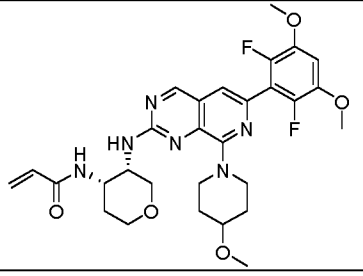
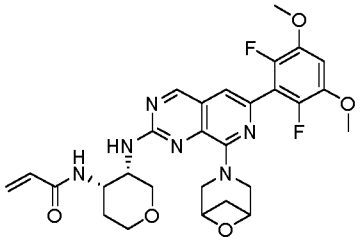
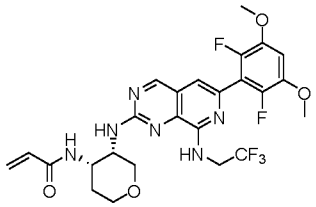
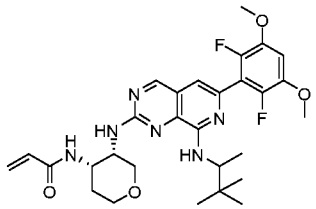
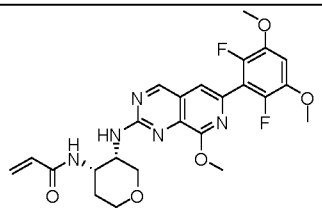
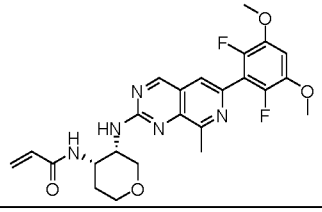
759		N-((3R,4S)-4-((8-(3,3-二(羟甲基)吖丁啶-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	605
760		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
761		N-((3R,4S)-4-((6-(2-氯-3,5-二甲氧苯基)-8-(1-甲基-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	536
762		N-((3R,4S)-4-((8-(6-氧杂-3-氮杂二环[3.1.1]庚烷-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
763		N-((3R,4S)-4-((8-(2-氧杂-5-氮杂二环[2.2.1]庚烷-5-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	587
764		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	487
765		N-((3R,4S)-4-((8-氨基-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	505

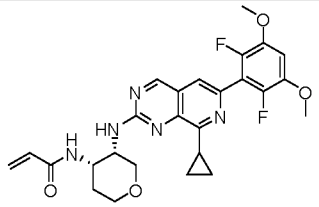
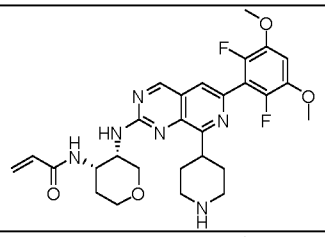
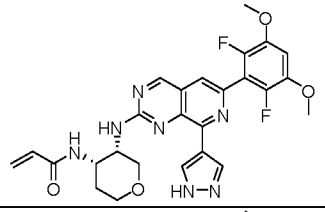
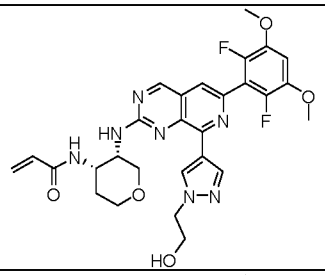
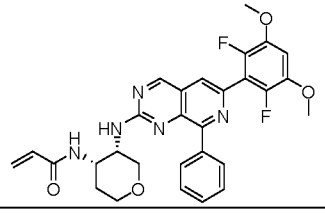
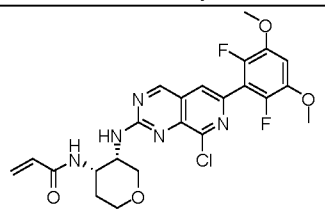
766		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二(甲氧基-d_3)苯基)-8-((甲基-d_3)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	528
767		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	501
768		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	549
769		N-((3R,4S)-4-((8-(6-氧杂-3-氮杂二环[3.1.1]庚烷-3-基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	555
770		N-((3R,4S)-4-((6-(2-氟-3-甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	439
771		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((甲基-d_3)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	522
772		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	557

773		N-((3R,4S)-4-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	543
774		N-((3R,4S)-4-((8-(吖丁啶-1-基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	513
775		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	557
776		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	615
777		N-((3R,4S)-4-((6-(2,6-二氟-3-甲氧苯基)-8-(甲基氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	457
778		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((S)-3-羟基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589
779		N-((3R,4S)-4-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((R)-3-羟基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢呋喃-3-基)丙烯酰基酰胺	589

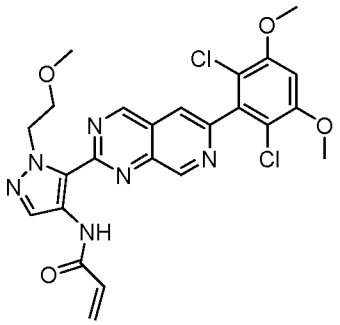
780		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
781		N-((3S,4S)-3-((8-(6-氧杂-3-氮杂二环[3.1.1]庚烷-3-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	601
782		N-((3S,4S)-3-((8-(2-氧杂-5-氮杂二环[2.2.1]庚烷-5-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	601
783		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	603
784		N-((3S,4S)-3-((8-(吖丁啶-1-基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	559
785		N-((3S,4S)-3-((6-(2,6-二氯-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	589
786		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(甲氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	501

787		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(乙胺基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	515
788		N-((3S,4S)-3-((8-(环丙基氨基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	527
789		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	557
790		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	571
791		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3,3-二氟吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	563
792		N-((3S,4S)-3-((8-(吖丁啶-1-基) -6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	527
793		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-羟基-3-甲基吖丁啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	557

794		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(3-甲氧基吡咯烷-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	571
795		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(4-甲氧基哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	585
796		N-((3S,4S)-3-((8-(6-氧杂-3-氮杂二环[3.1.1]庚烷-3-基)-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	569
797		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((2,2,2-三氟乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	569
798		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-((3,3-二甲基丁烷-2-基)氨基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	571
799		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	502
800		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-甲基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	486

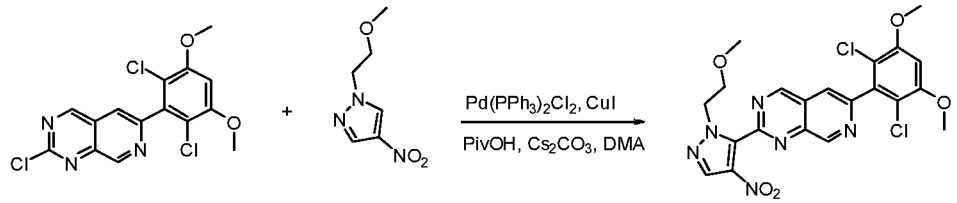
801		N-((3S,4S)-3-((8-环丙基-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	512
802		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(哌啶-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	555
803		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	538
804		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-(1-(2-羟基乙基)-1H-吡唑-4-基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	582
805		N-((3S,4S)-3-((6-(2,6-二氟-3,5-二甲氧苯基)-8-苯基吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	548
806		N-((3S,4S)-3-((8-氯-6-(2,6-二氟-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)氨基)四氢-2H-吡喃-4-基)丙烯酰基酰胺	506

实施例 715 N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺的制备



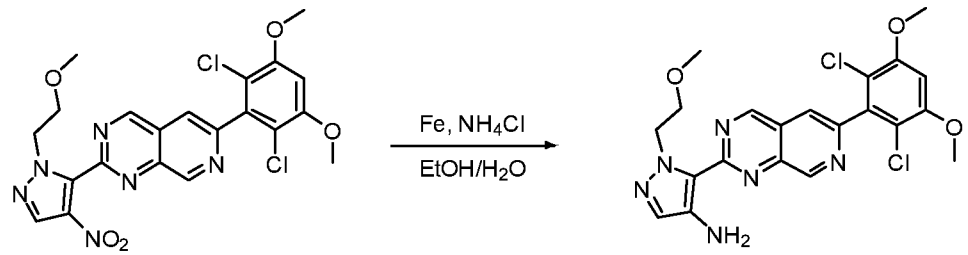
第一步：6-(2,6-二氯-3,5-二甲氧苯基)-2-(1-(2-甲氧基乙基)-4-硝基-1H-吡唑-5-基)吡啶并

[3,4-d]嘧啶的制备



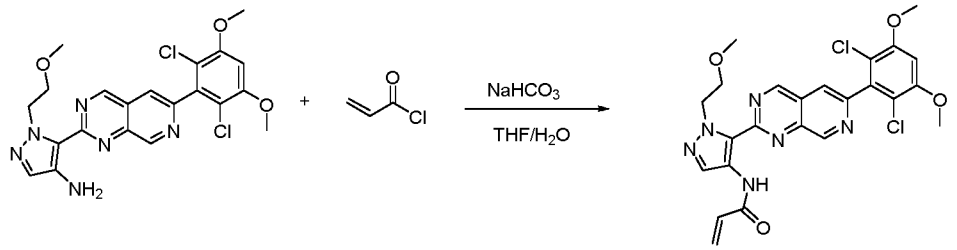
将化合物 1-(2-甲氧基乙基)-4-硝基-1H-吡唑（84 mg，0.49 mmol）和化合物 2-氯-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶（200 mg，0.54 mmol）溶入 DMA（15 mL），然后加入 CuI（112 mg，0.59 mmol），PivOH（15 mg，0.15 mmol），K_2CO_3（88 mg，0.64 mmol）和 $Pd(PPh_3)_2Cl_2$（34 mg，0.05 mmol）。氮气保护下，加热至 140 度反应 1 小时。反应完全，减压浓缩，除去溶剂。快速硅胶柱分离（PE/EA 2:1），纯化得产品 6-(2,6-二氯-3,5-二甲氧苯基)-2-(1-(2-甲氧基乙基)-4-硝基-1H-吡唑-5-基)吡啶并[3,4-d]嘧啶（103 mg，收率 42%）。MS m/z (ESI): 505 $[M+1]^+$.

第二步：5-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-胺的制备



化合物 6-(2,6-二氯-3,5-二甲氧苯基)-2-(1-(2-甲氧基乙基)-4-硝基-1H-吡唑-5-基)吡啶并[3,4-d]嘧啶（103 mg，0.20 mmol）溶于 $EtOH/H_2O$（10/3 mL）混合液，然后加入 Fe 粉（114 mg，2.04 mmol）和 NH_4Cl（109 mg，2.04 mmol）。加热回流反应 2 小时。反应结束后，反应液用二氯甲烷萃取三次，合并有机相依次用水，饱和氯化钠水溶液洗涤。无水硫酸钠干燥，过滤、浓缩。粗产品用快速硅胶柱层析分离（CH_2Cl_2/MeOH 10:1），纯化得产品 5-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-胺（12 mg，收率 12%）。MS m/z (ESI): 476 $[M+1]^+$.

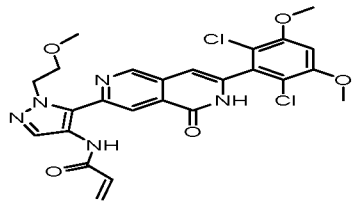
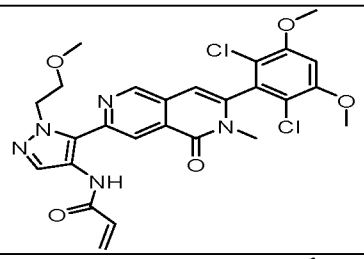
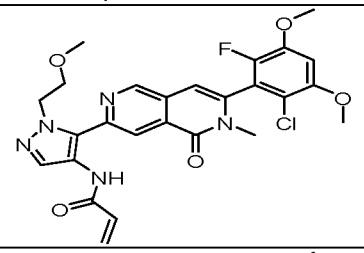
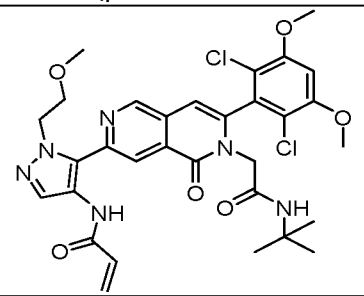
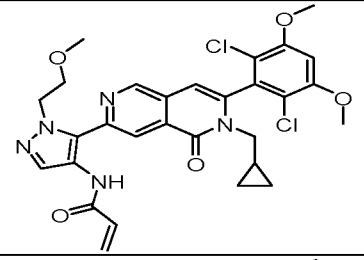
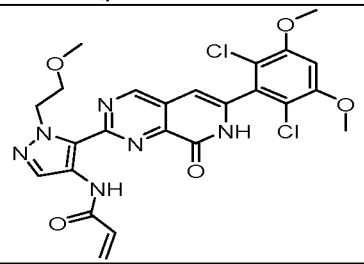
第三步：N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺的制备

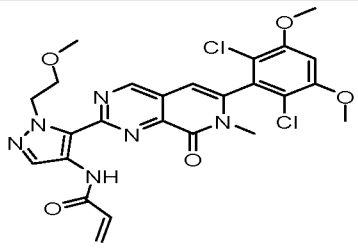
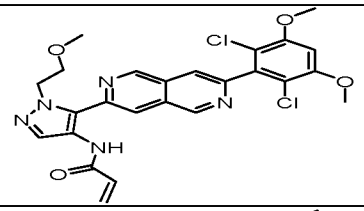
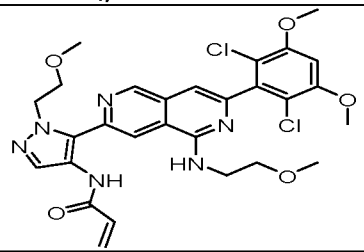
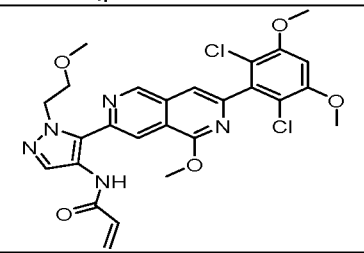
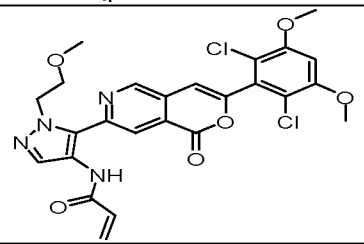
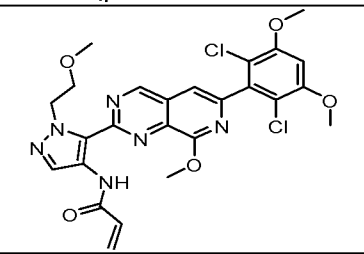
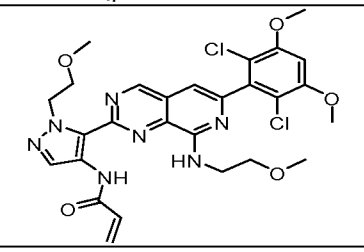


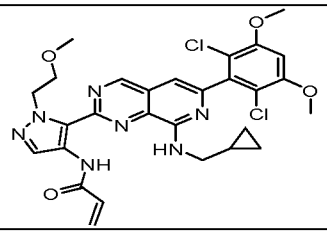
将化合物 5-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-胺（12 mg，0.025 mmol）溶于 THF/H_2O（4:1，4 mL）混合液中，然后加入 $NaHCO_3$（11 mg，0.13 mmol）。冰水浴冷却，加入丙烯酰氯（2.3 mg，0.025 mmol），0 度下搅拌反应 10 分钟。反应结束后，反应液在减压下浓缩，硅胶柱层析分离（CH_2Cl_2/MeOH 10:1），纯化得产品 N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺（4.8 mg，收率 36%）。MS m/z (ESI): 529 $[M+1]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 9.63 (s, 1H), 9.60 (s, 1H), 8.61 (s, 1H), 7.80 (s, 1H), 6.72 (s, 1H), 6.49 (d, *J* = 16.7 Hz, 1H), 6.40 (dd, *J* = 16.9, 9.7 Hz, 1H), 5.84 (d, *J* = 9.7 Hz, 1H), 5.21 (t, *J* = 6.0 Hz, 2H), 4.00 (s, 7H), 3.89 (t, *J* = 5.9 Hz, 2H), 3.35 (s, 3H).

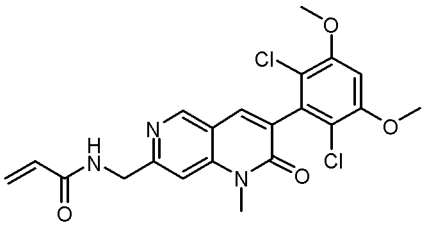
以下实施例 716-729 参照实施例 715 的合成方法制备。

实施例编号	化合物结构	化合物名称	MS:*m/z* $[M+1]^+$
716		N-(5-(7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	544
717		N-(5-(7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	558
718		N-(5-(7-(2-氯-6-氟-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	542
719		N-(5-(6-(2-(叔-丁基氨基)-2-羰基乙基)-7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	657
720		N-(5-(6-(环丙基甲基)-7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	598
721		N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	545

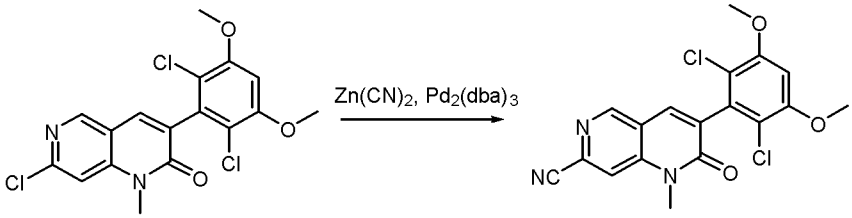
722		N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)-7-甲基-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	559
723		N-(5-(7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	528
724		N-(5-(7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-甲氧基乙基)氨基)-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	601
725		N-(5-(7-(2,6-二氯-3,5-二甲氧苯基)-5-甲氧基-2,6-二氮杂萘-3-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	558
726		N-(5-(3-(2,6-二氯-3,5-二甲氧苯基)-1-羰基-1H-吡喃并[4,3-c]吡啶-7-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	545
727		N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	560
728		N-(5-(6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	602

729		N-(5-(8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)-1-(2-甲氧基乙基)-1H-吡唑-4-基)丙烯酰基酰胺	598

实施例 730 N-((3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-2-羰基-1,2-二氢-1,6-二氮杂萘-7-基)甲基)丙烯酰基酰胺的制备

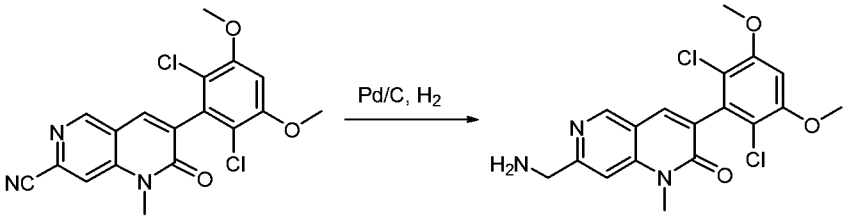


第一步：3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-2-羰基-1,2-二氢-1,6-二氮杂萘-7-甲腈的制备



7-氯-3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-1,6-二氮杂萘-2(1H)-酮（250.0 mg，0.626 mmol），$Zn(CN)_2$（110 mg，0.938 mmol）和 1,1'-双(二苯基膦)二茂铁 (34.7 mg, 0.063 mmol) 加入 DMF /H_2O（5 mL，100:1），再加入 $Pd_2(dba)_3$（28.7 mg，0.031 mmol），氮气保护。加热至 120 ℃，搅拌反应 20 小时。反应完全，冷却至室温，用水稀释并用 EtOAc 萃取，有机相用饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩，硅胶柱层析（展开剂：PE/EtOAc = 10~25%）分离，得到化合物 3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-2-羰基-1,2-二氢-1,6-二氮杂萘-7-甲腈（75 mg, 收率：28%）。MS m/z (ESI): 390.0 $[M+H]^+$.

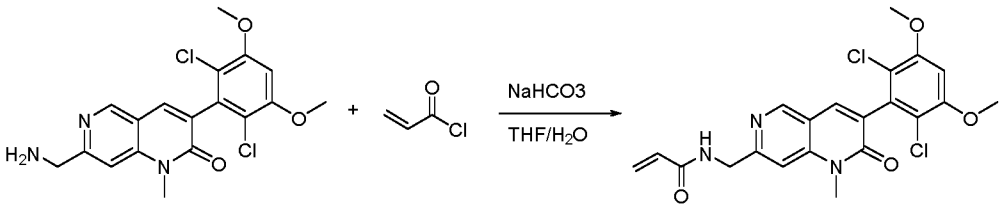
第二步：7-(氨基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-1,6-二氮杂萘-2(1H)-酮的制备



3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-2-羰基-1,2-二氢-1,6-二氮杂萘-7-甲腈（15 mg，0.038 mmol）溶于甲醇（3 mL），加入浓盐酸（15 L）和 10%的 Pd/C（催化量）。氢气球下室温搅拌反应 2 小时，反应完全。过滤，旋干，得到粗品 7-(氨基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-1,6-二氮杂萘-2(1H)-酮，直接用于下步反应。MS m/z (ESI): 394.0 $[M+H]^+$.

第三步：N-((3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-2-羰基-1,2-二氢-1,6-二氮杂萘-7-基)甲

基)丙烯酰基酰胺的制备

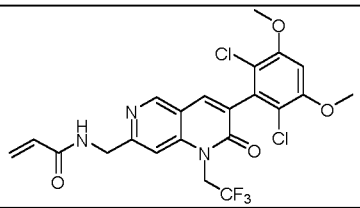
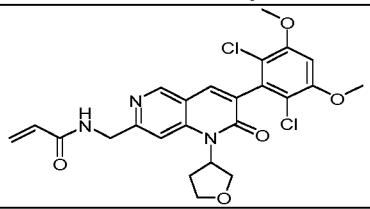
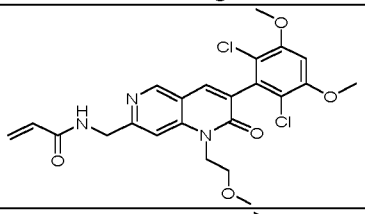
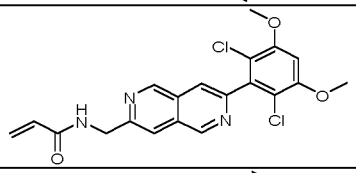
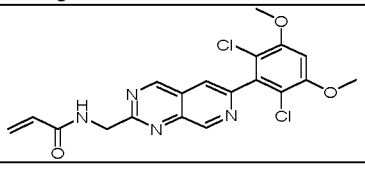


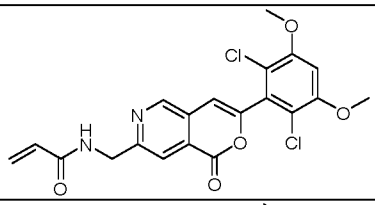
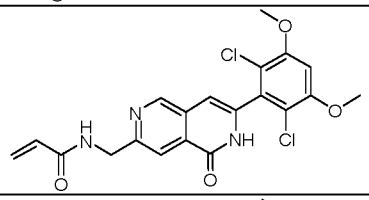
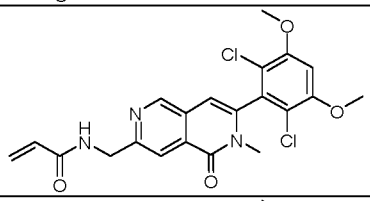
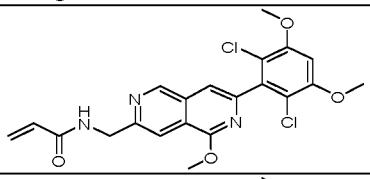
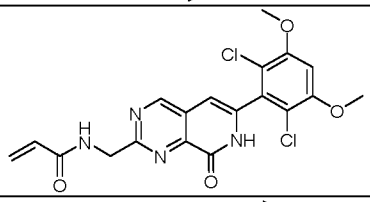
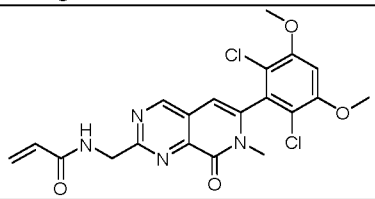
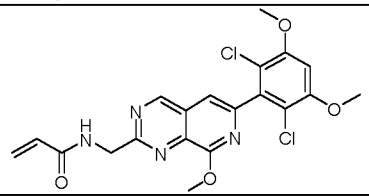
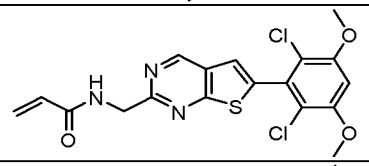
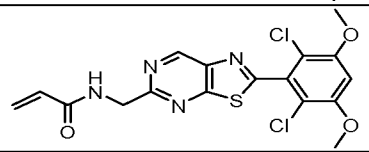
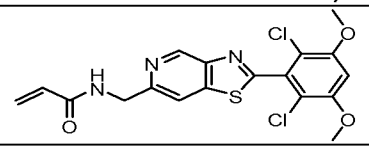
0 ℃下，在 7-(氨基甲基)-3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-1,6-二氮杂萘-2(1H)-酮（粗品，0.038 mmol）和 $NaHCO_3$（19.0 mg，0.230 mmol）的 THF/H_2O（0.8 mL/0.2 mL）溶液中加入丙烯酰氯（3.8 mg，0.042 mmol）。0 ℃下搅拌反应 10 分钟。反应液用 EtOAc（5 mL）稀释，饱和食盐水洗涤，并用无水硫酸钠干燥。过滤，浓缩后用制备板（展开剂：CH_2Cl_2/MeOH= 10:1）分离，得到化合物 N-((3-(2,6-二氯-3,5-二甲氧苯基)-1-甲基-2-羰基-1,2-二氢-1,6-二氮杂萘-7-基)甲基)丙烯酰基酰胺 (1.1 mg，两步收率：6%)。

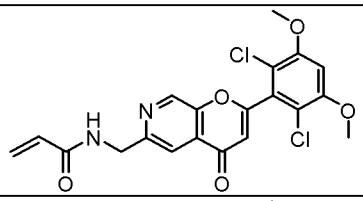
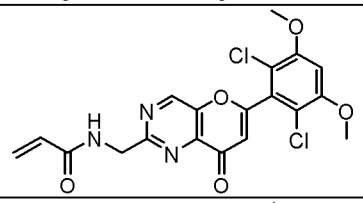
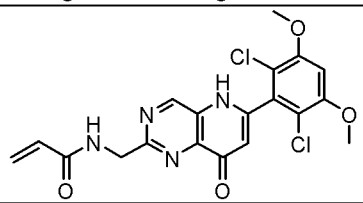
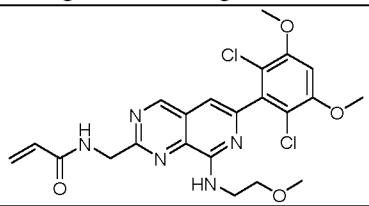
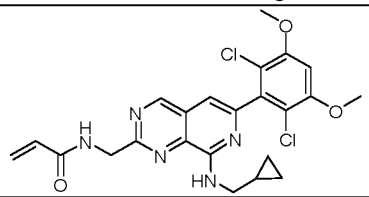
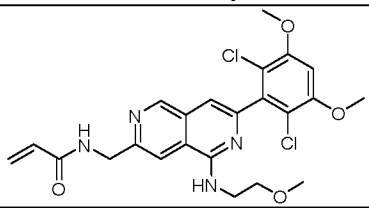
^{1}H NMR (400 MHz, Chloroform-d) δ 8.75 (s, 1H), 7.68 (s, 1H), 7.40 (s, 1H), 6.65 (s, 1H), 6.38 – 6.32 (m, 1H), 6.27 – 6.21 (m, 1H), 5.73 – 5.69 (m, 1H), 5.30 (s, 1H), 4.81 (d, J = 5.6 Hz, 2H), 3.96 (s, 6H), 3.78 (s, 3H);

MS m/z (ESI): 448.0 $[M+H]^+$.

以下实施例 731-751 参照实施例 730 的合成方法制备得到：

实施例编号	化合物结构	化合物名称	MS: *m/z* $[M+1]^+$
731		N-((3-(2,6-二氯-3,5-二甲氧苯基)-2-羰基-1-(2,2,2-三氟乙基)-1,2-二氢-1,6-二氮杂萘-7-基)甲基)丙烯酰基酰胺	516
732		N-((3-(2,6-二氯-3,5-二甲氧苯基)-2-羰基-1-(四氢呋喃-3-基)-1,2-二氢-1,6-二氮杂萘-7-基)甲基)丙烯酰基酰胺	504
733		N-((3-(2,6-二氯-3,5-二甲氧苯基)-1-(2-甲氧基乙基)-2-羰基-1,2-二氢-1,6-二氮杂萘-7-基)甲基)丙烯酰基酰胺	492
734		N-((7-(2,6-二氯-3,5-二甲氧苯基)-2,6-二氮杂萘-3-基)甲基)丙烯酰基酰胺	418
735		N-((6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)甲基)丙烯酰基酰胺	419

736		N-((3-(2,6-二氯-3,5-二甲氧苯基)-1-羰基-1H-吡喃并[4,3-c]吡啶-7-基)甲基)丙烯酰基酰胺	435
737		N-((7-(2,6-二氯-3,5-二甲氧苯基)-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)甲基)丙烯酰基酰胺	434
738		N-((7-(2,6-二氯-3,5-二甲氧苯基)-6-甲基-5-羰基-5,6-二氢-2,6-二氮杂萘-3-基)甲基)丙烯酰基酰胺	448
739		N-((7-(2,6-二氯-3,5-二甲氧苯基)-5-甲氧基-2,6-二氮杂萘-3-基)甲基)丙烯酰基酰胺	448
740		N-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)甲基)丙烯酰基酰胺	435
741		N-((6-(2,6-二氯-3,5-二甲氧苯基)-7-甲基-8-羰基-7,8-二氢吡啶并[3,4-d]嘧啶-2-基)甲基)丙烯酰基酰胺	449
742		N-((6-(2,6-二氯-3,5-二甲氧苯基)-8-甲氧基吡啶并[3,4-d]嘧啶-2-基)甲基)丙烯酰基酰胺	449
743		N-((6-(2,6-二氯-3,5-二甲氧苯基)噻吩并[2,3-d]嘧啶-2-基)甲基)丙烯酰基酰胺	424
744		N-((2-(2,6-二氯-3,5-二甲氧苯基)噻唑并[5,4-d]嘧啶-5-基)甲基)丙烯酰基酰胺	425
745		N-((2-(2,6-二氯-3,5-二甲氧苯基)噻唑并[4,5-c]吡啶-6-基)甲基)丙烯酰基酰胺	424

746		N-((2-(2,6-二氯-3,5-二甲氧苯基)-4-羰基-4H-吡喃并[2,3-c]吡啶-6-基)甲基)丙烯酰基酰胺	435
747		N-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-8H-吡喃并[3,2-d]嘧啶-2-基)甲基)丙烯酰基酰胺	436
748		N-((6-(2,6-二氯-3,5-二甲氧苯基)-8-羰基-5,8-二氢吡啶并[3,2-d]嘧啶-2-基)甲基)丙烯酰基酰胺	435
749		N-((6-(2,6-二氯-3,5-二甲氧苯基)-8-((2-甲氧基乙基)氨基)吡啶并[3,4-d]嘧啶-2-基)甲基)丙烯酰基酰胺	492
750		N-((8-((环丙基甲基)氨基)-6-(2,6-二氯-3,5-二甲氧苯基)吡啶并[3,4-d]嘧啶-2-基)甲基)丙烯酰基酰胺	488
751		N-((7-(2,6-二氯-3,5-二甲氧苯基)-5-((2-甲氧基乙基)氨基)-2,6-二氮杂萘-3-基)甲基)丙烯酰基酰胺	491

生物学测试评价

一、FGFR4 体外生物化学激酶分析

本发明采用 FGFR4 Caliper Assay 测定化合物对 FGFR4 抑制活性的特性。具体实验过程如下：

1、 本发明所进行的激酶反应是在 384 孔板中进行，分别取 12.5 μM 的 FGFR4 和 65 μM 的 ATP 以及 1 μM 的肽（5 Fluo Ahx KKKKEEIYFFFG NH2）；

2、 加入 50 mM HEPES, pH 7.5, 1 mM DTT, 0.02%Tween20, 0.02%BSA, 0.6% DMSO, 10 mM beta 甘油磷酸盐及 10 μM 原钒酸纳，16 mM $MgCl_2$ 的反应体系中；

3、 在 30 ℃下孵育反应 40 分钟；

4、 添加停止溶液（ 100 mM HEPES, pH7. 5, 5% DMSO, 0 .1 % Caliper 涂布试剂，10 mM EDTA 及 0. 015 % Brij35）来终止反应；

5、 取已终止激酶反应的培养盘转移至 Caliper LC 3000 工作站读取数据，使用 Caliper 微流体迁移偏移技术分离磷酸化与未磷酸化的肽，并通过恒定缓冲液流经芯片来转

移分析物，且通过其标记的荧光信号监控底物肽的迁移，利用所形成的磷酸基肽的量计算激酶活性。

6、 最后，通过非线性回归分析不同化合物浓度下的抑制百分比来测定 IC_{50} 值。具体实施例化合物酶学活性检测结果见表 1。

二、FGFR4 细胞增殖实验

本发明采用（Cell Titer Glo(CTG)实验）来评价化合物对细胞增殖的功能性作用。使用来自于中科院细胞库的 Huh7 肝细胞癌细胞（目录号 TChU182）在 DMEM 高葡萄糖(Gibco, cat. No. 1773536)， 10%胎牛血清(Gibco, 10099-141) 中在 37 ℃，5% CO_2 培养箱中培养。细胞增殖/存活的化合物介导的抑制通过对细胞 ATP 水平的定量来评价，使用 CTG 试剂（Promega, #G7573）。具体实验过程如下：

1、 将细胞以 3500 细胞/孔/90 μL 新鲜培养基接种到组织培养基处理的 96 孔板（Costar #3904）；

2、 加入 10 μL 包含以 10 倍其最终所需浓度的化合物稀释液的培养基；

3、 通过测试化合物 5 倍系列稀释来评价剂量效应作用，从 10 μM 开始；

4、 在细胞于 37 ℃5% CO_2 下孵育 3 天后，加入 50 μL CTG 和发光测定后对抑制剂对于细胞存活的影响进行定量；

5、 使用读板器（M1000，Tecan）使用 Graphpad Prism 中四参数曲线拟合来测定导致半数最大生长抑制的化合物浓度（EC_{50}）以及导致绝对半数生长抑制的化合物浓度（Absolute IC_{50}）。具体实施例化合物细胞活性检测结果见表 1：

表 1 酶学及细胞活性检测结果

实施例编号	酶学活性	细胞活性		^{1}H-NMR
	FGFR4 IC_{50}(nM)	HuH-7 EC_{50} (nM)	HuH-7 Absolute IC_{50} (nM)	
实施例 1	13.9	1527	2446	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.10 – 7.05 (m, 2H), 6.68 (s, 1H), 6.52 – 6.48 (m, 1H), 6.44 (s, 1H), 6.39 (s, 1H), 6.33 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 10.2 Hz, 1H), 5.68 (dd, J = 10.2, 1.4 Hz, 1H), 3.99 (s, 6H), 3.25 (s, 3H), 2.21 (s, 3H).
实施例 5	26.1	>10000	>10000	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.72 (s, 1H), 8.23 (s, 3H), 7.34 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.02 (s, 1H), 6.70 (s, 1H), 6.42 – 6.25 (m, 2H), 5.71 (d, J = 9.8 Hz, 1H), 3.97 (s, 6H), 2.25 (s, 3H).
实施例 7	28.9	>10000	>10000	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.75 (s, 1H), 6.67 (s, 1H), 6.54 (s, 1H), 6.39 (d, J = 16.7 Hz, 1H), 6.25 – 6.13 (m, 1H), 5.73 (d, J = 10.0 Hz, 1H), 3.96 (s, 6H), 2.22 (s, 3H).
实施例 9	138	89	1049	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.42 (s, 1H), 8.20 (s, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.20 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.65 (s, 2H), 6.35 (d, J = 15.3 Hz, 2H), 6.16 (dd, J = 17.2, 9.9 Hz, 1H), 5.68 (d, J = 10.2 Hz, 1H), 3.97 (s, 9H), 2.23 (s, 3H).
实施例 10	105.3	3515	4817	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.38 (d, J = 8.2 Hz, 1H), 8.17 (s, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 6.98 (s, 1H), 6.64 (s, 1H), 6.56 (s, 1H), 6.37 (d, J = 16.8 Hz, 1H), 6.20 (dd, J = 16.9, 10.2 Hz, 1H), 5.70 (d, J = 10.2 Hz, 1H), 4.07 (s, 3H), 3.96 (s,

				6H), 2.25 (s, 3H).
实施例 11	100.7	4717	4717	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.14 (s, 1H), 7.49 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.69 (s, 1H), 6.43 – 6.34 (m, 1H), 6.26 (dd, J = 16.9, 10.1 Hz, 1H), 5.72 (dd, J = 10.1, 1.4 Hz, 1H), 3.98 (s, 6H), 3.51 (t, J = 6.4 Hz, 2H), 3.22 (s, 3H), 2.24 (s, 3H), 1.27 (d, J = 7.0 Hz, 2H).
实施例 12	43.8	3352	3352	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.02 (s, 1H), 7.57 (s, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 6.41 (d, J = 16.6 Hz, 1H), 6.26 (dd, J = 16.6, 9.8 Hz, 1H), 6.07 (s, 1H), 5.74 (d, J = 9.8 Hz, 1H), 3.95 (s, 6H), 2.08 (s, 3H).
实施例 13	8.0	181.5	513.1	^{1}H NMR (400 MHz, Methanol-d_4) δ 9.05 (s,1H), 8.98 (s,1H), 7.72 (s,1H),7.68-7.66 (d, J = 8.0Hz, 1H), 7.32-7.24 (m,2H), 6.91 (s, 1H), 6.47(s, 1H), 6.35-6.23 (m, 2H), 5.66-5.63 (dd, J=8Hz,1H),3.97(s,6H), 2.30(s, 3H).
实施例 64	53.3	54.2	268.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.31 – 9.24 (m, 2H), 8.24 (s, 1H), 7.64 (s, 1H), 6.70 (s, 1H), 6.42 – 6.33 (m, 2H), 5.75 (dd, *J* = 9.0, 2.6 Hz, 1H), 5.38 – 5.32 (m, 1H), 3.99 (s, 6H), 3.87 (s, 3H).
实施例 75	246.6	>10000	>10000	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.08 (s, 1H), 7.97 (s, 1H), 6.89 (s, 1H), 6.75 (s, 1H), 6.62 (s, 1H), 6.54 – 6.50 (m, 1H), 6.28 (d, J = 16.6 Hz, 1H), 6.13 – 6.03 (m, 1H), 5.70 – 5.57 (m, 1H), 3.91 (s, 6H), 3.49 – 3.38 (m, 4H), 3.25 (s, 3H), 2.54 – 2.39 (m, 4H), 2.08 (s, 3H), 1.31 (s, 3H).
实施例 76	24.0	23.8	62.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.17 (s, 1H), 6.77 (s, 1H), 6.63 (s, 1H), 6.38 (d, J = 16.6 Hz, 2H), 6.33 – 6.24 (m, 1H), 5.70 (d, J = 10.1 Hz, 1H), 3.95 (s, 6H), 3.87 (s, 3H), 3. 53-3.36(m, 2H), 1.19-1.10 (m, 1H), 0.55-0.41(m, 2H), 0.42-0.29 (m, 2H).
实施例 118	80.5	179.4	332.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 9.16 (s, 1H), 7.55 (s, 1H), 6.68 (s, 1H), 6.45 (d, J = 7.3 Hz, 1H), 6.27 (dd, J = 17.0, 1.4 Hz, 1H), 6.07 (dd, J = 16.9, 10.3 Hz, 1H), 5.63 (dd, J = 10.2, 1.4 Hz, 1H), 4.94 (dd, J = 11.6, 4.9 Hz, 1H), 4.90 – 4.79 (m, 1H), 4.34 – 4.19 (m, 2H), 3.98 (s, 6H), 3.90 – 3.79 (m, 2H).
实施例 119	166.0	78.1	457.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 2H), 7.56 (s, 1H), 6.68 (s, 1H), 6.25 (dd, J = 16.9, 1.4 Hz, 1H), 6.01 (dd, J = 17.0, 10.3 Hz, 1H), 5.60 (dd, J = 10.3, 1.4 Hz, 1H), 4.55 (s, 1H), 4.35 (s, 1H), 4.11 – 4.00 (m, 2H), 3.98 (s, 6H), 3.78 (d, J = 12.1 Hz, 1H), 3.64 (dd, J = 13.4, 10.9 Hz, 1H), 2.24-2.20 (m, 2H), 2.02-1.99 (m, 2H).
实施例 120	303.0	155.6	754.2	1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 9.14 (s, 1H), 7.71 (s, 1H), 6.73 (t, J = 8.0 Hz, 1H), 6.46 (d, J = 7.0 Hz, 1H), 6.26 (d, J = 16.9 Hz, 2H), 6.04 (dd, J = 17.0, 10.3 Hz, 1H), 5.62 (d, J = 10.2 Hz, 1H), 4.93 (d, J = 6.0 Hz, 1H), 4.86 (t, J = 6.2 Hz, 1H), 4.28 (ddd, J = 18.7, 9.4, 6.2 Hz, 2H), 3.93 (s, 6H), 3.85 (ddd, J = 15.4, 9.5, 4.9 Hz, 2H).
实施例 121	182.6	171.9	401.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 9.2 Hz, 2H), 7.94 (s, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 6.48 – 6.43 (m, 1H), 6.24 (t, *J* = 1.9 Hz, 1H), 6.18 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.12 – 6.04 (m, 1H), 5.63 (dt, *J* = 10.3, 1.6 Hz, 1H), 4.97 – 4.85 (m,3H), 4.28 (ddd, *J* = 20.2, 9.5, 6.3 Hz, 3H), 3.98 (s, 3H), 3.94 (s, 3H).
实施例 124	61.6	302.7	556	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 9.02 (s, 1H), 8.11-8.09 (d, J = 8.0Hz, 1H), 7.67 (s, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 6.70-6.68 (dd, J = 8Hz,1H), 6.23-6.16 (dd, J = 16Hz, 1H), 6.01-5.97 (dd, J=16Hz, 1H), 5.52-5.48 (dd, J = 16Hz, 1H), 4.75-4.68 (m, 1H), 4.59-4.52 (m, 1H), 4.15-4.11(m, 1H), 4.06-4.03 (m,

				1H),3.98 (s, 6H), 3.74-3.67 (m, 2H).
实施例 126	22.0	31.5	53.7	^{1}H NMR (400 MHz,$CDCl_3$) δ 8.68(s, 1H),6.82 (s, 1H), 6.76 (s, 1H), 6.62(s, 1H), 6.44 (s, 1H), 6.22-6.18 (dd, J = 16Hz, 1H), 6.00-5.94 (dd, J = 16Hz, 1H), 5.55-5.52(dd, J=8Hz, 1H), 4.92-4.85 (m, 1H), 4.56-4.50 (m,1H), 4.30-4.21 (m, 2H), 3.98 (s, 6H), 3.87-3.84 (dd, J = 12Hz, 1H), 3.77-3.74 (dd, J = 12Hz, 1H), 4.42-4.39 (m, 2H), 1.23-1.19 (m, 1H), 0.59-0.53 (m, 2H), 0.33-0.29 (m, 2H).
实施例 421	12.4	5.4	10.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.80 (brs, 1H), 6.68 (s, 1H), 6.62 (s, 1H), 6.38 (brs, 1H), 6.21 (dd, J = 17.0, 1.5 Hz, 1H), 6.02 (dd, *J* = 17.0, 10.2 Hz, 1H),, 5.56 (dd, J = 10.1, 1.5 Hz, 1H), 4.93 – 4.83 (m, 2H), 4.30 – 4.18(m, 2H), 3.96 (s, 6H), 3.90 (dd, J = 9.7, 3.2 Hz, 1H), 3.79 (dd, J = 9.2, 5.2 Hz, 1H), 3.52 – 3.37 (m, 2H), 0.88 (t, J = 6.0 Hz, 1H), 0.57 – 0.48 (m, 2H), 0.36 – 0.26 (m, 2H).
实施例 422	22.5	47.0	238.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.74 (s, 1H), 6.67 (s, 2H), 6.22 (d, J = 15.4 Hz, 1H), 5.56 (d, J = 10.4 Hz, 1H), 4.89 (s, 2H), 4.29 – 4.17 (m, 2H), 3.98 (s, 6H), 3.96 – 3.80 (m, 4H), 3.76 – 3.65 (m, 2H), 3.35 (s, 3H).
实施例 423	31.7	98.0	347.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.17 (s, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 6.26 (d, J = 16.9 Hz, 1H), 6.12 (dd, J = 17.0, 10.2 Hz, 1H), 5.61 (d, J = 10.2 Hz, 1H), 5.03 – 4.93 (m, 1H), 4.93 – 4.85 (m, 1H), 4.31 – 4.20 (m, 2H), 4.14 (s, 3H), 3.98 (s, 6H), 3.88 (dd, J = 9.8, 4.0 Hz, 1H), 3.82 (dd, J = 9.3, 6.5 Hz, 1H).
实施例 424	11.0	18.5	37.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.85 (s, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.15 (dd, *J* = 17.1, 2.5 Hz, 1H), 6.12 – 6.02 (m, 1H), 5.53 (dd, *J* = 9.5, 2.5 Hz, 1H), 4.99 (td, *J* = 6.3, 4.8 Hz, 1H), 4.87 (q, *J* = 6.5 Hz, 1H), 4.27 (dd, *J* = 9.4, 6.3 Hz, 1H), 4.16 (dd, *J* = 9.0, 6.9 Hz, 1H), 3.92 (m, 7H), 3.80 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.45 (dd, *J* = 13.7, 7.0 Hz, 1H), 3.37 (d, *J* = 6.8 Hz, 1H), 1.33 – 1.24 (m, 1H), 0.55 – 0.41 (m, 2H), 0.42 – 0.29 (m, 2H).
实施例 425	7.7	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 6.68 (s, 1H), 6.61 (s, 1H), 6.22 (d, J = 16.6 Hz, 2H), 6.00 (dd, J = 16.9, 10.2 Hz, 1H), 5.89 (s, 1H), 5.57 (d, J = 10.2 Hz, 1H), 4.89 (s, 2H), 4.30 – 4.20 (m, 2H), 3.90 (d, J = 9.8 Hz, 1H), 3.82 – 3.72 (m, 1H), 3.42 (s, 2H), 1.26 – 1.21 (m, 1H), 0.58 – 0.47 (m, 2H), 0.36 – 0.27 (m, 2H).
实施例 429	22.4	63.2	184.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.06 (s, 1H), 6.78 (s, 1H), 6.64 (s, 1H), 6.18 (d, J = 17.0 Hz, 1H), 6.11 (d, J = 7.2 Hz, 1H), 5.98 (dd, J = 17.0, 10.2 Hz, 1H), 5.81 (s, 1H), 5.56 (d, J = 10.3 Hz, 1H), 4.94 – 4.83 (m, 2H), 4.27 (dd, J = 9.6, 5.8 Hz, 1H), 4.20 (dd, J = 9.4, 6.1 Hz, 1H), 4.10 (s, 2H), 3.97 (s, 6H), 3.87 (dd, J = 9.6, 3.9 Hz, 1H), 3.81 (dd, J = 9.5, 5.0 Hz, 1H), 3.49 – 3.38 (m, 2H), 3.01 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H).
实施例 430	19.1	32.0	93.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.24 (s, 1H), 6.81 (brs, 1H), 6.63 (s, 1H), 6.57 (s, 1H), 6.26 (brs, 1H), 6.16 – 6.03 (m, 2H), 5.53 (d, J = 9.6 Hz, 1H), 5.08 (s, 1H), 4.88 (s, 1H), 4.26 – 4.12 (m, 2H), 3.96 (d, J = 6.0 Hz, 6H), 3.93 – 3.88 (m, 2H), 3.81 (d, J = 10.1 Hz, 2H), 3.60 (d, J = 11.3 Hz, 2H), 3.42 (s, 1H), 2.94 (s, 3H).
实施例 431	519.1	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H), 8.90 (s, 1H), 7.72 (s, 1H), 7.52 (s, 1H), 6.78 (s, 1H), 6.67 (s, 1H), 6.22 – 6.12 (m, 2H), 5.53 (d, J = 9.9 Hz, 1H), 5.00 – 4.88 (m, 2H), 4.33 – 4.27 (m, 2H), 4.26 – 4.19(m, 2H), 3.97 (s, 6H), 3.94 – 3.87 (m, 2H), 3.49 (s, 2H), 2.87 (s, 6H).
实施例 432	105.8	395.8	934.2	^{1}H NMR (400 MHz, $CDCl_3$) δ8.66 (s, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 6.63 (s, 1H), 6.59 (s, 1H), 6.33 (d, J = 6.4

				Hz, 1H), 6.18 (d, J = 5.9 Hz, 2H), 5.59 – 5.49 (m, 1H), 4.99 (s, 2H), 4.30 – 4.23(m, 2H), 3.97 (s, 6H), 3.92 – 3.87 (m, 1H), 3.77 – 3.71 (m, 1H), 3.25 (s, 2H), 2.77 (s, 6H), 2.25 (s, 2H), 1.70 (s, 2H).
实施例 433	7.6	19.3	26.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.30 (brs, 1H), 6.19 (d, J = 16.9 Hz, 1H), 5.97 (dd, J = 17.0, 10.3 Hz, 1H), 5.88 (brs, 1H), 5.54 (d, J = 10.4 Hz, 1H), 4.95 – 4.83 (m, 2H), 4.29 – 4.18 (m, 2H), 3.95 (s, 6H), 3.89 (dd, J = 9.7, 3.0 Hz, 1H), 3.77 (dd, J = 9.3, 5.5 Hz, 1H), 3.14 (d, J = 4.4 Hz, 3H).
实施例 434	8.4	9.6	18.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.51 (s, 1H), 6.27 – 6.15 (m, 2H), 5.97 (dd, J = 16.9, 10.3 Hz, 1H), 5.79 (s, 1H), 5.56 (dd, J = 10.3, 1.4 Hz, 1H), 4.97 – 4.82 (m, 2H), 4.29 – 4.18 (m, 2H), 3.96 (s, 6H), 3.89 (dd, J = 9.6, 3.2 Hz, 1H), 3.76 (dd, J = 9.2, 5.5 Hz, 1H), 3.65 – 3.50 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H).
实施例 435	67.0	80	148.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 6.64 (s, 1H), 6.19 (d, J = 16.9 Hz, 1H), 6.13 (s, 1H), 6.06 (s, 1H), 5.98 (dd, J = 17.0, 10.3 Hz, 1H), 5.56 (d, J = 10.2 Hz, 1H), 4.93 (dd, J = 11.7, 4.8 Hz, 2H), 4.51 – 4.37 (m, 1H), 4.30 – 4.17 (m, 3H), 3.97 (s, 6H), 3.90 (dd, J = 9.7, 2.8 Hz, 1H), 3.78 (dd, J = 9.4, 5.0 Hz, 1H).
实施例 436	>10000	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 6.59 (s, 1H), 6.56 (s, 1H), 6.45 (s, 1H), 6.22 (s, 1H), 6.14 – 6.00 (m, 1H), 5.62 (d, J = 10.2 Hz, 1H), 4.86 (s, 2H), 4.24 (s, 2H), 3.98 – 3.94 (m ,2H), 3.83 (s, 6H), 3.38 (s, 6H).
实施例 438A	3.5	9.9	17.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.84 (brs, 1H), 6.70 (s, 1H), 6.63 (s, 1H), 6.42 (brs, 1H), 6.22 (dd, J = 17.0, 1.5 Hz, 1H), 6.11 – 6.01 (m, 1H), 5.85 (s, 1H), 5.57 (dd, J = 10.1, 1.5 Hz, 1H), 4.93 – 4.81 (m, 2H), 4.30 – 4.16 (m, 3H), 3.96 (s, 6H), 3.92 – 3.82 (m, 3H), 3.82 – 3.74 (m, 2H), 3.58 – 3.45 (m, 1H), 1.95 – 1.85 (m, 2H), 1.70 – 1.64 (m, 2H).
实施例 438B	9.1	15.8	35.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.74 (s, 1H), 6.69 (s, 1H), 6.62 (s, 1H), 6.25 (dd, J = 16.9, 1.4 Hz, 1H), 6.20 (s, 1H), 6.03 (dd, J = 16.9, 10.3 Hz, 1H), 5.81 (s, 1H), 5.61 (d, J = 10.4 Hz, 1H), 4.93 – 4.81 (m, 2H), 4.31 – 4.16 (m, 3H), 3.96 (s, 6H), 3.93 – 3.84 (m, 2H), 3.82 – 3.72 (m, 3H), 3.59 (dd, J = 13.3, 6.7 Hz, 1H), 1.91 – 1.85 (m, 2H), 1.70 – 1.63 (m, 2H).
实施例 439	4.6	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.72 (brs, 1H), 6.69 (s, 1H), 6.63 (s, 1H), 6.35 (brs, 1H), 6.19 (d, J = 17.1 Hz, 1H), 6.00 (dd, J = 17.0, 10.2 Hz, 1H), 5.89 (s, 1H), 5.55 (dd, J = 10.3, 1.5 Hz, 1H), 4.96 – 4.82 (m, 2H), 4.31 – 4.17 (m, 2H), 3.96 (s, 6H), 3.93 – 3.82 (m, 2H), 3.81 – 3.71 (m, 2H), 3.66 (dd, J = 8.9, 5.3 Hz, 1H), 3.63 – 3.51 (m, 2H), 2.82 – 2.69 (m, 1H), 2.13 – 2.00 (m, 1H), 1.77 – 1.72 (m, 1H).
实施例 443	8.2	15.9	70.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.73 (s, 1H), 6.63 (s, 1H), 6.24 – 6.16 (m, 1H), 6.13 (brs, 1H), 5.96 (dd, J = 17.2, 10.3 Hz, 1H), 5.79 (brs, 1H), 5.59 – 5.51 (m, 1H), 4.95 – 4.84 (m, 2H), 4.71 (s, 1H), 4.30 – 4.15 (m, 2H), 4.13 – 4.04 (m, 1H), 4.05 – 3.98 (m, 1H), 3.97 (s, 6H), 3.92 – 3.82 (m, 3H), 3.76 (dd, J = 9.3, 5.7 Hz, 1H), 2.45 – 2.31 (m, 1H), 2.18 – 2.05 (m, 1H).
实施例 444	7.0	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.70 (s, 1H), 6.63 (s, 1H), 6.42 – 6.33 (m, 1H), 6.20 (dd, J = 17.0, 1.4 Hz, 1H), 6.17 – 6.13 (m, 1H), 5.97 (dd, J = 17.0, 10.3 Hz, 1H), 5.75 (d, J = 6.5 Hz, 1H), 5.57 (dd, J = 10.4, 1.4 Hz, 1H), 4.95 – 4.82 (m, 2H), 4.29 – 4.18 (m, 3H), 4.03 – 3.98 (m, 2H), 3.97 (s, 6H), 3.89 (dd, J = 9.6, 3.6 Hz, 1H), 3.76 (dd, J = 9.3, 5.8 Hz, 1H), 3.58 – 3.48 (m, 2H), 2.24 – 2.10 (m, 2H), 1.73 – 1.64 (m, 2H).

实施例 452	42.2	20.3	53.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.88 (brs, 1H), 6.77 (s, 1H), 6.64 (s, 1H), 6.17 (d, J = 16.8 Hz, 1H), 5.95 (m, 2H), 5.55 (d, J = 10.2 Hz, 1H), 5.02 – 4.94 (m, 1H), 4.90 (s, 1H), 4.46 (s, 1H), 4.31 – 4.18 (m, 2H), 3.97 (s, 6H), 3.91 (d, J = 10.8 Hz, 1H), 3.73 (t, J = 8.1 Hz, 1H), 3.11 (s, 2H), 2.80 (s, 1H), 2.69 (s, 1H).
实施例 454	66.9	40.8	89.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 6.21 (d, *J* = 17.0 Hz, 1H), 6.09 – 5.97 (m, 1H), 5.57 (d, *J* = 10.2 Hz, 1H), 4.89 – 4.81 (m ,2H), 4.27 – 4.20 (m ,2H), 3.96 (s, 6H), 3.92 – 3.90 (m, 1H), 3.81 – 3.77 (m, 1H), 3.59 – 3.48 (m, 2H), 2.30 (dd, *J* = 15.2, 7.9 Hz, 1H), 1.83 – 1.76 (m, 2H), 1.59 (brd, *J* = 31.7 Hz, 4H), 1.28 (brs, 3H).
实施例 456	82.4	163	299	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.47 – 7.11 (m, 6H), 6.70 (s, 1H), 6.63 (s, 1H), 6.22 (d, J = 17.1 Hz, 2H), 6.09 – 5.75 (m, 2H), 5.58 (d, J = 10.3 Hz, 1H), 4.89 – 4.60 (m, 2H), 4.22 – 4.15 (m, 2H), 3.96 (s, 6H), 3.83-3.75 (m, 3H), 3.03 (q, J = 6.8 Hz, 2H).
实施例 459	17.3	23.8	58.0	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.58 (s, 1H), 7.38 (s, 1H), 6.98 (s, 1H), 6.71 (s, 1H), 6.14 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.94 (dd, *J* = 17.2, 2.2 Hz, 1H), 5.47 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.86 (s, 1H), 4.67 (q, *J* = 6.1 Hz, 1H), 4.39 (td, *J* = 14.6, 13.6, 5.3 Hz, 2H), 4.12 (t, *J* = 7.9 Hz, 1H), 4.02 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.97 (s, 6H),3.81-3.68 (m, 4H), 3.66 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.33 (s, 3H).
实施例 462	14.5	24.6	38.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 6.30 (s, 1H), 6.23 (dd, J = 16.9, 1.4 Hz, 1H), 6.01 (dd, J = 16.9, 10.3 Hz, 1H), 5.84 (s, 1H), 5.59 (dd, J = 10.3, 1.4 Hz, 1H), 4.93 – 4.77 (m, 2H), 4.29 – 4.19 (m, 2H), 3.96 (s, 6H), 3.91 (dd, J = 9.5, 4.0 Hz, 1H), 3.79 (dd, J = 9.3, 5.5 Hz, 1H), 3.51 (dd, J = 13.1, 6.5 Hz, 1H), 3.36 (dd, J = 13.2, 5.9 Hz, 1H), 0.99 (s, 9H).
实施例 465	46.4	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.18 (d, J = 17.1 Hz, 1H), 6.06 (d, J = 10.1 Hz, 1H), 5.86 (s, 1H), 5.54 (d, J = 10.1 Hz, 1H), 4.96 – 4.83(m, 2H), 4.30 – 4.19 (m, 2H), 3.96 (s, 6H), 3.89 (dd, J = 9.6, 3.7 Hz, 1H), 3.81 (dd, J = 9.2, 5.6 Hz, 1H), 3.59 (s, 2H), 2.76 (s, 2H), 2.53 (s, 6H), 1.26 (s, 4H).
实施例 475	62.0	131.9	677.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.03 (s, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.30 (s, 1H), 6.22 (dd, J = 16.8, 1.4 Hz, 1H), 6.00 (dd, J = 16.9, 10.3 Hz, 1H), 5.82 (s, 1H), 5.61 – 5.53 (m, 1H), 4.88 (q, J = 6.5, 6.0 Hz, 2H), 4.33 – 4.18 (m, 2H), 3.92 (s, 3H), 3.89 (s, 1H), 3.84 (s, 3H), 3.81 – 3.73 (m, 1H), 3.58 – 3.40 (m, 2H), 1.26 (s, 1H), 0.66 – 0.46 (m, 2H), 0.42 – 0.24 (m, 2H).
实施例 498	8797	2393	>10000	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.71 (d, J = 4.2 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 6.67 (s, 1H), 6.17 (d, J = 16.9 Hz, 1H), 6.06 (d, J = 11.2 Hz, 1H), 5.55 (d, J = 10.1 Hz, 1H), 4.95 (s, 1H), 4.63 (s, 1H), 4.39 (s, 2H), 4.31 (t, J = 6.7 Hz, 1H), 4.24 (s, 2H), 3.98 (s, 6H), 3.92 (s, 1H), 0.88 (t, J = 7.0 Hz, 1H), 0.76 – 0.65 (m, 2H), 0.47 (s, 2H).
实施例 501	15.7	17.8	49.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 6.17 (d, J = 16.7 Hz, 1H), 5.96 (d, J = 12.1 Hz, 1H), 5.55 (d, J = 10.5 Hz, 1H), 4.75-4.60 (m, 1H), 4.40-4.25 (m, 1H), 4.10-4.02 (m, 1H), 4.01-3.90 (m, 3H), 3.96 (s, 6H), 3.77 (d, J = 11.9 Hz, 1H), 3.62 (t, J = 12.2 Hz, 2H), 1.98 – 1.86 (m, 2H), 0.88 (s, 1H), 0.55 (s, 2H), 0.35 (s, 2H).
实施例 510	29	75.2	115.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.48 (s, 1H), 6.20 (dd, J = 16.9, 1.4 Hz, 2H), 6.05 (d, J = 8.5 Hz, 1H), 5.91 (dd, J = 16.9, 10.3 Hz, 1H), 5.54 (dd, J = 10.4, 1.4 Hz, 1H), 4.70 (d, J

				= 8.7 Hz, 1H), 4.38 – 4.27 (m, 1H), 4.12 – 4.05 (m, 1H), 3.99 (d, J = 11.2 Hz, 1H), 3.96 (s, 6H), 3.75 (dd, J = 12.0, 1.7 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.09 (d, J = 5.0 Hz, 3H), 1.97 – 1.86 (m, 2H).
实施例 606	23.4	25.7	41.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.44 (s, 1H), 6.67 (s, 1H), 6.30 – 6.24 (m, 1H), 6.17 – 6.08 (m, 1H), 5.63 (d, J = 10.7 Hz, 1H), 4.93 (s, 2H), 4.35 – 4.30 (m, 1H), 4.25 (dd, J = 9.4, 6.1 Hz, 1H), 3.97 (s, 6H), 3.92 (dd, J = 9.6, 3.1 Hz, 1H), 3.87 – 3.82 (m, 1H), 2.98 (s, 3H).
实施例 609	NT	36.6	56.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 6.64 (s, 1H), 6.55 (s, 1H), 6.25 (d, J = 16.8 Hz, 1H), 6.05 (dd, J = 16.9, 10.3 Hz, 1H), 5.86 (brs, 1H), 5.62 (dd, J = 10.3, 1.4 Hz, 1H), 4.90-4.87 (m, 2H), 4.82-4.78 (m,1H), 4.31 (td, J = 10.3, 6.2 Hz, 2H), 3.97 (s, 6H), 3.95 – 3.68 (m, 2H), 3.28-3.24 (m, 1H), 1.27 – 1.21 (m, 2H), 1.10 (dd, J = 8.3, 3.0 Hz, 2H).
实施例 629	2.9	2.6	4.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 7.37 (s, 1H), 6.68 (s, 1H), 6.43 (d, J = 6.2 Hz, 1H), 6.20 (d, J = 16.9 Hz, 1H), 6.09 (s, 1H), 5.98 (dd, J = 17.0, 10.2 Hz, 1H), 5.57 (d, J = 10.3 Hz, 1H), 4.97 – 4.90 (m, 2H), 4.33 – 4.23 (m, 2H), 3.98 (s, 9H), 3.94 (dd, J = 9.8, 3.2 Hz, 1H), 3.82 (dd, J = 9.5, 4.8 Hz, 1H).
实施例 637	4.2	10.1	17.3	^{1}H NMR (400 MHz, Methanol-d_4) δ 9.03 (s, 1H), 8.56 (s, 1H), 8.40 (s, 1H), 7.49 (s, 1H), 6.74 (t, J = 8.0 Hz, 1H), 6.03 (d, J = 5.9 Hz, 2H), 5.46 (t, J = 5.9 Hz, 1H), 4.87 (s, 2H), 4.20 (t, J = 7.8 Hz, 1H), 4.12 (dd, J = 9.1, 6.6 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 6H), 3.83 (d, J = 4.0 Hz, 1H), 3.74 (dd, J = 9.2, 5.4 Hz, 1H).
实施例 655	8.0	28.0	68.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.74 (s, 1H), 6.70 (s, 1H), 6.62 (s, 1H), 6.19 (dd, J = 16.9, 1.4 Hz, 2H), 5.95 (dd, J = 16.9, 10.3 Hz, 1H), 5.79 (s, 1H), 5.55 (dd, J = 10.3, 1.4 Hz, 1H), 4.93 – 4.81 (m, 2H), 4.29 – 4.17 (m, 2H), 3.96 (s, 6H), 3.88 (dd, J = 9.7, 3.3 Hz, 1H), 3.75 (dd, J = 9.2, 5.9 Hz, 1H), 3.01 – 2.84 (m, 1H), 0.87 – 0.79 (m, 2H), 0.76 – 0.69 (m, 1H), 0.68 – 0.58 (m, 1H).
实施例 657	6.5	9.6	13.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.69 (s, 1H), 6.62 (s, 1H), 6.26 (dd, J = 16.8, 1.3 Hz, 2H), 6.06 (dd, J = 17.0, 10.3 Hz, 1H), 5.70 – 5.60 (m, 2H), 4.80-4.70 (m, 3H), 4.60-4.45 (m, 3H), 4.29 – 4.15 (m, 2H), 3.95 (s, 6H), 3.87 – 3.73 (m, 2H), 2.42 (q, J = 7.6 Hz, 2H).
实施例 658	4.8	11.4	15.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.73 (s, 1H), 6.63 (s, 1H), 6.24 (d, J = 16.8 Hz, 1H), 6.13 (d, J = 10.9 Hz, 1H), 5.61 (d, J = 10.1 Hz, 1H), 4.84 – 4.57 (m, 4H), 4.54 – 4.07 (m, 5H), 3.95 (s, 6H), 3.89 – 3.72 (m, 2H), 3.30 (s, 3H).
实施例 659	6.6	18.0	24.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 6.93 (s, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.34 (brs, 1H), 6.24 (dd, J = 16.8, 1.4 Hz, 1H), 6.05 (dd, J = 16.9, 10.3 Hz, 1H), 5.74 (brs, 1H), 5.62 (dd, J = 10.2, 1.4 Hz, 1H), 4.88 – 4.61 (m, 4H), 4.45 – 4.37 (m, 3H), 4.28 – 4.15 (m, 2H), 3.91 (s, 6H), 3.84 (dd, J = 9.5, 3.6 Hz, 1H), 3.77 (dd, J = 9.5, 5.1 Hz, 1H), 3.33 (s, 3H).
实施例 663	4.5	2.3	3.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 6.88 (s, 1H), 6.64 (s, 1H), 6.25 (d, J = 16.9 Hz, 2H), 6.06 (dd, J = 17.0, 10.3 Hz, 1H), 5.93 (s, 1H), 5.63 (d, J = 10.3 Hz, 1H), 4.88 – 4.77 (m, 6H), 4.22 (dd, J = 9.5, 6.2 Hz, 2H), 3.96 (s, 6H), 3.82 (ddd, J = 17.2, 9.6, 5.0 Hz, 2H).
实施例 664	4.9	3.7	4.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.23 (brs, 1H), 6.97 (s, 1H), 6.77 (s, 1H), 6.23 (dd, J = 17.1, 10.2 Hz, 1H), 6.02 (dd, J = 17.1, 2.1 Hz, 1H), 5.57 (d, J = 10.7 Hz, 1H), 5.55 (s, 1H), 4.74 – 4.58 (m, 2H), 4.21 (brs, 4H), 4.12 – 4.01

				(m, 2H), 3.95 (s, 6H), 3.78 – 3.66 (m, 2H), 1.46 (s, 3H).
实施例 665	5.7	9.9	11.8	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.81 (s, 1H), 6.21 (dd, J = 17.1, 10.2 Hz, 1H), 6.00 (dd, J = 17.1, 2.2 Hz, 1H), 5.54 (dd, J = 10.1, 2.2 Hz, 1H), 4.76 – 4.60 (m, 2H), 4.17 (br s, 4H), 4.09 (d, J = 7.4 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.95 (s, 6H), 3.75 (dd, J = 8.7, 5.9 Hz, 1H), 3.67 (dd, J = 9.0, 5.2 Hz, 1H), 3.21 (s, 3H), 1.49 (s, 3H).
实施例 666	4.5	3.2	4.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 6.93 (s, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.37 (s, 1H), 6.24 (d, J = 16.9 Hz, 1H), 6.04 (dd, J = 17.0, 10.3 Hz, 1H), 5.78 (s, 1H), 5.61 (d, J = 10.3 Hz, 1H), 4.84 – 4.73 (m, 2H), 4.56 – 4.41 (m, 2H), 4.41 – 4.26 (m, 2H), 4.26 – 4.17 (m, 2H), 3.91 (s, 6H), 3.85 (dd, J = 9.6, 3.5 Hz, 1H), 3.76 (dd, J = 9.4, 5.1 Hz, 1H), 3.30 (s, 3H), 1.56 (s, 3H).
实施例 668	14.7	16	22.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 6.70 (s, 1H), 6.66 (s, 1H), 6.56 (s, 1H), 6.16 (d, *J* = 17.0 Hz, 1H), 6.01 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 4.80-4.55(m, 8H), 4.18-4.15 (m, 2H), 3.88 (s, 6H), 3.84 – 3.70 (m, 4H).
实施例 675	11.0	6.2	8.7	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.71 (s, 1H), 6.63 (s, 1H), 6.38 (brs, 1H), 6.24 (d, J = 16.9 Hz, 1H), 6.05 (dd, J = 16.9, 10.2 Hz, 1H), 5.78 (brs, 1H), 5.61 (dd, J = 10.2, 1.3 Hz, 1H), 4.87 – 4.75 (m, 2H), 4.42 – 4.15 (m, 6H), 3.95 (s, 6H), 3.86 (dd, J = 9.5, 3.9 Hz, 1H), 3.78 (dd, J = 9.4, 5.4 Hz, 1H), 3.72 – 3.60 (m, 4H), 1.86 (t, J = 5.2 Hz, 4H).
实施例 677	7.4	3.7	5.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 6.41 (brs, 1H), 6.21 (d, *J* = 17.0 Hz, 1H), 5.99 (dd, *J* = 16.6, 10.2 Hz, 1H), 5.71 (brs, 1H), 5.53 (dd, *J* = 10.3, 3.5 Hz, 1H), 4.85-4.70 (m, 2H), 4.28-3.96 (m, 7H), 3.88 (s, 6H), 3.90-3.82 (m, 1H), 3.80-3.72 (m, 1H), 3.29 (d, *J* = 2.8 Hz, 3H), 2.07-1.94 (m, 2H).
实施例 678	6.5	13.3	16.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.94 (s, 1H), 6.56 (s, 1H), 6.50 (d, *J* = 7.4 Hz, 1H), 6.18 (d, *J* = 16.9 Hz, 1H), 5.98 (dd, *J* = 16.9, 10.3 Hz, 2H), 5.54 (d, *J* = 9.7 Hz, 1H), 4.82 – 4.69 (m, 2H), 4.74 – 4.64 (m, 2H), 4.19 – 4.12 (m, 2H), 3.89 (s, 6H), 3.87 – 3.76 (m,7H), 3.76 – 3.67 (m, 1H), 2.20 – 2.10 (m, 1H), 2.08 – 1.95 (m, 1H).
实施例 686	8.2	5.4	8.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.94 (s, 1H), 6.56 (s, 1H), 6.50 (d, *J* = 7.4 Hz, 1H), 6.18 (d, *J* = 16.9 Hz, 1H), 5.98 (dd, *J* = 16.9, 10.3 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 4.81 – 4.73 (m, 1H), 4.70 – 4.67 (m, 1H), 4.20 – 4.12 (m, 2H), 3.89 (s, 6H), 3.88 – 3.67 (m, 10H).
实施例 687	6.3	6.9	10.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.25 (s, 1H), 6.70 (t, J = 7.9 Hz, 1H), 6.47 (brs, 1H), 6.25 (d, J = 16.9 Hz, 1H), 6.06 (dd, J = 16.9, 10.2 Hz, 1H), 5.62 (d, J = 10.3 Hz, 1H), 4.88 – 4.81 (m, 1H), 4.78 (brs, 1H), 4.23 (dd, J = 9.5, 6.2 Hz, 2H), 3.93 (s, 6H), 3.92 – 3.81 (m, 9H), 3.81 – 3.77 (m, 1H).
实施例 690	8.0	8.4	12.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 6.99 (s, 1H), 6.64 (s, 1H), 6.55 (d, J = 7.1 Hz, 1H), 6.26 (dd, J = 17.1, 1.3 Hz, 1H), 6.11 – 6.04 (m, 1H), 6.04 (s, 1H), 5.63 (d, J = 10.2 Hz, 1H), 4.86 – 4.73 (m, 2H), 4.68 (d, J = 12.8 Hz, 1H), 4.61 (d, J = 12.8 Hz, 1H), 4.29 – 4.20 (m, 2H), 3.97 (s, 6H), 3.94 – 3.85 (m, 3H), 3.82 (dd, J = 9.4, 5.0 Hz, 1H), 2.79 – 2.68 (m, 2H), 1.23 (dd, J = 6.3, 2.2 Hz, 6H).
实施例 693	5.6	1.3	2.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 6.99 (s, 1H), 6.63 (s, 1H), 6.53 (s, 1H), 6.23 (d, J = 16.9 Hz, 1H), 6.06 (dd, J = 17.0, 10.2 Hz, 1H), 5.94 (s, 1H), 5.60 (d, J = 10.2 Hz, 1H), 4.87 – 4.77 (m, 2H), 4.39 (d, J =

				8.3 Hz, 1H), 4.30 (d, J = 13.2 Hz, 1H), 4.27 – 4.20 (m, 2H), 3.96 (s, 6H), 3.88 (dd, J = 9.5, 3.5 Hz, 1H), 3.81 (dd, J = 14.4, 5.1 Hz, 1H), 3.51 – 3.39 (m, 3H), 3.38 (s, 3H), 2.15 – 2.01 (m, 2H), 1.79 – 1.74 (m, 2H).
实施例 694	4.8	10.0	12.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 6.70 (t, *J* = 7.9 Hz, 1H), 6.22 (d, *J* = 16.8 Hz, 1H), 6.07 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.59 (d, *J* = 10.2 Hz, 1H), 4.86 – 4.80 (m, 2H), 4.38 – 4.21 (m, 4H), 3.93 (s, 6H), 3.91 – 3.82 (m, 2H), 3.52 – 3.43 (m, 3H), 3.39 (s, 3H), 2.21 – 2.11 (m, 2H).
实施例 704	8.5	17.2	20.2	1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.76 (s, 1H), 6.65 (brs, 1H), 6.62 (s, 1H), 6.25 (d, J = 16.9 Hz, 1H), 6.05 (dd, J = 16.8,10.4 Hz, 1H), 5.61 (d, J = 10.3 Hz, 1H), 4.69 (brs, 1H), 4.55 (brs, 1H), 4.46 – 4.23 (m, 5H), 4.10 – 3.99 (m, 2H), 3.95 (s, 6H), 3.74 (d, J = 11.9 Hz, 1H), 3.61 (t, J = 11.8 Hz, 1H), 3.32 (s, 3H), 2.10 – 1.98 (m, 1H), 1.90 – 1.80 (m, 1H).
实施例 715	62.7	1917.5	1917.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 9.63 (s, 1H), 9.60 (s, 1H), 8.61 (s, 1H), 7.80 (s, 1H), 6.72 (s, 1H), 6.49 (d, *J* = 16.7 Hz, 1H), 6.40 (dd, *J* = 16.9, 9.7 Hz, 1H), 5.84 (d, *J* = 9.7 Hz, 1H), 5.21 (t, *J* = 6.0 Hz, 2H), 4.00 (s, 7H), 3.89 (t, *J* = 5.9 Hz, 2H), 3.35 (s, 3H).
实施例 723	78.5	338.1	1211.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 9.71 (s, 1H), 9.68 (s, 1H), 8.37 (s, 1H), 8.21 (s, 1H), 8.05 (s, 1H), 7.15 (s, 1H), 6.51 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.26 (dd, *J* = 17.1, 2.2 Hz, 1H), 5.75 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.56 (t, *J* = 5.6 Hz, 2H), 4.06 (s, 6H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.14 (s, 3H).
实施例 730	115.0	164	194	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.68 (s, 1H), 7.40 (s, 1H), 6.65 (s, 1H), 6.38 – 6.32 (m, 1H), 6.27 – 6.21 (m, 1H), 5.73 – 5.69 (m, 1H), 5.30 (s, 1H), 4.81 (d, J = 5.6 Hz, 2H), 3.96 (s, 6H), 3.78 (s, 3H).
实施例 752	990.9	1712	2631	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 6.68 (s, 1H), 6.66 (s, 1H), 6.59 (s, 1H), 6.13 (dd, *J* = 16.8, 1.4 Hz, 1H), 5.94 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.51 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.30 (s, 1H), 4.96 – 4.82 (m, 1H), 4.42 (s, 1H), 4.26 (dd, *J* = 9.8, 6.0 Hz, 1H), 4.18 (dd, *J* = 9.3, 7.4 Hz, 1H), 3.92 (s, 6H), 3.88 – 3.81 (m, 1H), 3.74 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.13 (d, *J* = 4.6 Hz, 3H).
实施例 753	19	130	212	^{1}H NMR (400 MHz, Methanol-d_4) δ 9.22 (s, 1H), 7.65 (s, 1H), 6.94 (s, 1H), 6.19 (dd, J = 17.1, 9.9 Hz, 1H), 6.10 (dd, J = 17.1, 2.2 Hz, 1H), 5.56 (dd, J = 9.9, 2.1 Hz, 1H), 5.01 (s, 2H), 4.29 (s, 1H), 4.17 (dd, J = 9.3, 6.2 Hz, 1H), 3.98 (s, 6H), 3.93 – 3.85 (m, 1H), 3.85 – 3.79 (m, 1H).
实施例 754	13.6	18.0	54.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 6.5 Hz, 1H), 7.11 (s, 1H), 6.64 (s, 1H), 6.25 (dd, *J* = 16.9, 1.5 Hz, 1H), 6.05 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.60 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.91 (brs, 1H), 4.79 (t, *J* = 6.5，1H), 4.59 (q, *J* = 7.0，2H), 4.35-4.19 (m, 2H), 3.93-3.68 (m, 2H) 1.48 (t, *J* = 7.1Hz, 3H).
实施例 755	43.0	NT	NT	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 6.84 (s, 1H), 6.67 (s, 1H), 6.58 – 6.49 (m, 3H), 6.30 (d, J = 8.5 Hz, 2H), 6.10 (d, J = 17.0 Hz, 2H), 6.04 – 5.83 (m, 2H), 5.48 (d, J = 10.1 Hz, 1H), 4.72 (s, 3H), 4.63 (d, J = 14.8 Hz, 1H), 4.17 – 4.04 (m, 2H), 3.89 (s, 6H), 3.78 (d, J = 6.2 Hz, 1H), 3.71 (s, 2H), 3.68 (s, 7H).
实施例 756	20.2	19	31	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.43 (s, 1H), 7.13 (s, 1H), 6.66 (s, 1H), 6.36 (s, 1H), 6.26 (dd, J = 16.9, 1.4 Hz, 1H), 6.04 (dd, J = 16.9, 10.3 Hz, 1H), 5.94 (s, 1H), 5.63 (dd, J = 10.3, 1.4 Hz, 1H), 4.89 – 4.78 (m, 2H), 4.45 (d, J = 2.8 Hz, 2H), 4.31 – 4.21 (m, 2H), 3.97 (s, 6H), 3.95 – 3.92 (m, 2H), 3.90 – 3.87 (m, 1H), 3.81 (dd, J = 9.5, 4.8 Hz, 1H), 2.94 – 2.77 (m, 2H).
实施例 758	5.9	5.8	9.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.71 (s, 1H), 6.62 (s, 1H), 6.42 (s, 1H), 6.20 (d, J = 17.0 Hz,

				1H), 6.03 – 5.91 (m, 2H), 5.56 (d, J = 10.3 Hz, 1H), 4.93 (d, J = 7.1 Hz, 1H), 4.81 (s, 1H), 4.67 (s, 1H), 4.41 (s, 1H), 4.25-4.05 (m, 3H), 4.25 – 4.12 (m, 3H), 3.97 – 3.80 (m, 10H), 3.68 (s, 3H).
实施例 759	5.7	42.2	61.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 11.1 Hz, 1H), 6.69 (s, 1H), 6.61 (s, 1H), 6.35 – 6.09 (m, 2H), 5.94 (dd, J = 17.0, 10.3 Hz, 1H), 5.59 (d, J = 10.1 Hz, 2H), 5.00 (p, J = 7.5 Hz, 1H), 4.83 (s, 1H), 4.31 – 4.18 (m, 2H), 4.16 (d, J = 8.1 Hz, 1H), 4.01 – 3.85 (m, 12H), 3.67 (d, J = 14.5 Hz, 2H).
实施例 760	2.9	5.5	6.7	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 5.2 Hz, 1H), 6.68 (d, J = 10.6 Hz, 1H), 6.61 (s, 1H), 6.42 – 6.21 (m, 1H), 6.14 (t, J = 18.1 Hz, 1H), 6.00 – 5.78 (m, 1H), 5.74 (s, 1H), 5.49 (dd, J = 29.1, 10.3 Hz, 1H), 4.91 (t, J = 7.6 Hz, 1H), 4.87 – 4.78 (m, 1H), 4.52 – 4.40 (m, 1H), 4.24 – 4.14 (m, 2H), 4.08 (d, J = 8.7 Hz, 1H), 3.95 (s, 6H), 3.92 – 3.83 (m, 2H), 3.80 – 3.70 (m, 2H), 2.03 – 1.89 (m, 2H), 1.54 – 1.43 (m, 3H).
实施例 761	14.3	20.7	51.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.64 (s, 1H), 8.53 (s, 1H), 7.74 (s, 1H), 6.88 (d, J = 2.7 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 6.20 (d, J = 16.9 Hz, 1H), 6.01 (s, 1H), 5.56 (d, J = 10.3 Hz, 1H), 5.01 – 4.91 (m, 2H), 4.32 – 4.23 (m, 2H), 4.02 (s, 3H), 3.99 – 3.95 (m, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.84 – 3.82 (m, 1H).
实施例 762	5.2	3.2	4.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 6.83 (s, 1H), 6.63 (s, 1H), 6.30 (s, 1H), 6.22 (d, J = 17.1 Hz, 1H), 6.04 (dd, J = 16.9, 10.2 Hz, 1H), 5.81 (s, 1H), 5.60 (d, J = 10.2 Hz, 1H), 4.87 – 4.80 (m, 1H), 4.80 – 4.73 (m, 1H), 4.70 (d, J = 6.4 Hz, 2H), 4.60 (d, J = 13.8 Hz, 2H), 4.27 (d, J = 13.6 Hz, 1H), 4.23 – 4.15 (m, 2H), 4.10 (d, J = 13.7 Hz, 1H), 3.96 (s, 6H), 3.86 (dd, J = 9.6, 4.0 Hz, 1H), 3.75 (dd, J = 9.4, 5.8 Hz, 1H), 3.23 (q, J = 7.2 Hz, 1H), 2.08 (d, J = 8.6 Hz, 1H).
实施例 763	7.9	7.8	11.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 6.79 (s, 1H), 6.63 (s, 1H), 6.25 (dd, *J* = 23.9, 17.1 Hz, 2H), 5.63 (dd, *J* = 19.8, 10.3 Hz, 2H), 4.76 (s, 2H), 4.66 (s, 1H), 4.22 (dd, *J* = 15.1, 7.2 Hz, 3H), 4.14 – 4.10 (m, 1H), 3.97 (d, *J* = 2.0 Hz, 8H), 3.85 (d, *J* = 10.5 Hz, 3H), 3.75 (s, 1H), 2.00 (d, *J* = 9.2 Hz, 1H), 1.93 (s, 1H).
实施例 764	7.0	49.4	60.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 6.84 (brs, 2H), 6.76 (s, 1H), 6.58 (t, *J* = 7.9 Hz, 1H), 6.39 (brs, 1H), 6.08 (d, *J* = 16.9 Hz, 1H), 5.93 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.39 (d, *J* = 10.2 Hz, 1H), 4.81 (p, *J* = 6.6, 5.6 Hz, 2H), 4.15 – 4.05 (m, 2H), 3.85 – 3.81 (m, 1H), 3.81 (s, 6H), 3.71 (dd, *J* = 9.2, 5.8 Hz, 1H), 3.08 (s, 3H).
实施例 765	158	420.8	656.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 6.80 (s, 1H), 6.64 (s, 1H), 6.23 (d, *J* = 16.9 Hz, 1H), 6.08 – 5.91 (m, 4H), 5.75 (s, 1H), 5.58 (d, *J* = 10.4 Hz, 1H), 4.89 (s, 2H), 4.24 (ddd, *J* = 23.7, 9.4, 5.9 Hz, 2H), 3.96 (s, 6H), 3.88 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.76 (dd, *J* = 9.2, 5.5 Hz, 1H).
实施例 766	8.3	19.8	27.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 6.60 (s, 1H), 6.54 (s, 1H), 6.33 (brs, 1H), 6.12 (d, J = 16.9 Hz, 1H), 5.96 (dd, J = 17.0, 10.3 Hz, 1H), 5.48 (dd, J = 10.3, 1.4 Hz, 1H), 4.83-4.78 (m, 2H), 4.17-4.06 (m, 2H), 3.84-3.81 (m,1H), 3.71-3.68 (m,1H).
实施例 767	7	23.9	45.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.87 (s, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.60 (brs, 1H), 6.22 (s, 1H), 6.17 (s, 1H), 5.96 (dd, J = 16.9, 10.3 Hz, 1H), 5.80 (brs, 1H), 5.56 (d, J = 10.3 Hz, 1H), 4.94 – 4.83 (m, 2H), 4.30 – 4.18 (m, 2H), 3.91 (s, 6H), 3.88 (s, 1H), 3.75 (dd, J = 9.3, 5.9 Hz, 1H), 3.65 (s, 2H), 1.36 (t, J = 7.2 Hz, 3H).
实施例 768	4	9.9	12.5	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.09 (s, 1H), 6.69 (t, *J* = 7.9 Hz, 1H), 6.26 (dd, *J* = 17.0, 1.3 Hz, 1H), 6.14 (d, *J* = 7.4 Hz, 1H), 6.03 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.75 (d, *J* = 7.1 Hz, 1H), 5.63 (dd, *J* = 10.3,

				1.3 Hz, 1H), 4.89 – 4.83 (m, 1H), 4.82 – 4.72 (m, 5H), 4.23 (dd, *J* = 9.5, 6.2 Hz, 2H), 3.92 (s, 6H), 3.81 (ddd, *J* = 19.8, 9.5, 4.8 Hz, 2H).
实施例 769	3.7	8.4	10.0	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.04 (s, 1H), 6.69 (t, *J* = 7.8 Hz, 1H), 6.34 (brs, 1H), 6.22 (d, *J* = 16.9 Hz, 1H), 6.04 (dd, *J* = 17.1, 10.1 Hz, 1H), 5.60 (d, *J* = 10.2 Hz, 1H), 4.87 – 4.70 (m, 4H), 4.63 (d, *J* = 13.5 Hz, 2H), 4.30 (d, *J* = 13.6 Hz, 1H), 4.23 – 4.10 (m, 3H), 3.92 (s, 6H), 3.90 – 3.85 (m, 1H), 3.79 – 3.73 (m, 1H), 3.29 – 3.24 (m, 1H), 2.08 – 2.01 (m, 2H).
实施例 770	2413.9	>10000	>10000	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 6,49 (m, 1H), 6.27 (brs, 1H), 6.18 (d, *J* = 16.9 Hz, 1H), 5.93 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.84, (brs, 1H), 5.53 (d, *J* = 10.3 Hz, 1H), 4.91-4.88 (m, 2H), 4.31 – 4.13 (m, 2H), 3.94 (s, 3H), 3.94-3.88(m, 1H), 3.82 – 3.70 (m, 1H), 3.21 (d, *J* = 4.8 Hz, 3H).
实施例 771	7.9	25.5	32.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 6.22, (brs, 1H), 6.20 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.97 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.79 (brs, 1H), 5.55 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.94 – 4.86 (m, 2H), 4.26-4.18 (m, 2H), 3.96 (s, 6H), 3.88 (dd, *J* = 9.8, 3.2 Hz, 1H), 3.81 – 3.72 (m, 1H).
实施例 772	2.9	6.8	8.1	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 6.81 (s, 1H), 6.59 (s,1H), 6.57(brs, 1H), 6.14 (d, *J* = 16.6 Hz, 1H), 5.96 (m, 1H), 5.85 (brs, 1H), 5.53 (d, *J* = 10.4 Hz, 1H), 4.87 – 4.66 (m, 2H), 4.53 – 4.23 (m, 4H), 4.18-4.08 (m, 2H), 3.83 (s, 6H), 3.82-3.69 (m, 2H), 1.95-1.75 (m, 2H), 1.51 (s, 3H).
实施例 773	1.8	2.0	2.3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 6.87 (d, *J* = 5.2 Hz, 1H), 6.66 (t, *J* = 8.1 Hz, 1H), 6.45 (brs, 1H), 6.14 (dd, *J* = 16.9, 12.4 Hz, 1H), 5.96 (dd, *J* = 16.9, 10.3 Hz, 1H), 5.82 (brs, 1H), 5.50 (dd, *J* = 20.2, 10.3 Hz, 1H), 4.93-4.85 (m, 1H), 4.84-4.78 (m, 1H), 4.43-4.34 (m, 2H), 4.19-3.77 (m, 5H), 3.90 (s, 6H), 3.72 – 3.69 (m, 1H), 1.49 (d, *J* = 23.8 Hz, 3H).
实施例 774	3.2	6.9	8.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.88 (s, 1H), 6.67 (t, *J* = 7.9 Hz, 1H), 6.52 (brs, 1H), 6.24 (dd, *J* = 17.0, 1.5 Hz, 1H), 6.08 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.96 (brs, 1H), 5.61 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.82 – 4.72 (m, 2H), 4.57 (brs, 4H), 4.26 – 4.16 (m, 2H), 3.91 (s, 6H), 3.85 (dd, J = 9.4, 3.9 Hz, 1H), 3.78 (dd, J= 9.4, 5.0 Hz, 1H), 2.42 (p, *J* = 7.6 Hz, 2H).
实施例 775	8.9	20.8	27.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.96 (s, 1H), 6.69 (t, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.25 (dd, J = 17.0, 1.4 Hz, 1H), 6.08 (s, 1H), 6.02 (dd, J = 16.9, 10.3 Hz, 1H), 5.60 (dd, J = 10.3, 1.4 Hz, 1H), 4.73 (brs, 1H), 4.56 (brs, 1H), 4.42 (d, J = 8.5 Hz, 1H), 4.39 – 4.22 (m, 4H), 4.05 (dd, J = 12.0, 4.5 Hz, 1H), 3.99 (d, J = 11.7 Hz, 1H), 3.92 (s, 6H), 3.75 (dd, J = 11.9, 1.6 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.33 (s, 3H), 2.09 – 2.02 (m, 1H), 1.91 – 1.81 (m, 1H).
实施例 776	4.9	7.9	9.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 6.92 (s, 1H), 6.67 (t, *J* = 7.9 Hz, 1H), 6.38 (brs, 1H), 6.23 (dd, *J* = 17.0, 1.4 Hz, 1H), 6.03 (dd, *J* = 16.9, 10.3 Hz, 1H), 5.80 (brs, 1H), 5.61 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.86 – 4.77 (m, 2H), 4.27 – 4.19 (m, 6H), 3.91 (s, 6H), 3.89 – 3.86 (m, 1H), 3.76 (dd, *J* = 9.3, 5.7 Hz, 1H), 3.69 – 3.66 (m, 4H), 1.86 (t, *J* = 5.2 Hz, 4H).
实施例 777	NT	650.8	660	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 6.86-6.81 (m, 3H), 6.45 (brs, 1H), 6.13 (d, *J* = 16.9 Hz, 1H), 6.06 (brs, 1H), 5.86 (dd, *J* = 16.9, 10.3 Hz, 1H), 5.67 (brs, 1H), 5.49 (d, *J* = 10.4 Hz, 1H), 4.98 – 4.68 (m, 2H), 4.28-4.07 (m, 2H), 3.84 (s, 3H), 3.84-3.71 (m, 1H), 3.67 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.08 (d, *J* = 4.8 Hz, 3H).
实施例 778	NT	9.5	11.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 6.29 (brs, 1H), 6.11 (d, J = 17.1 Hz,

				1H), 5.81 (m, 2H), 5.45 (d, J = 10.2 Hz, 1H), 5.07-4.84 (m, 2H), 4.55-4.40 (m, 1H), 4.22-4.15 (m, 2H), 4.05-3.75 (m, 3H), 3.95 (s, 6H), 3.91-3.71 (m, 2H), 2.05-1.96 (m, 2H), 1.44 (s, 3H).
实施例 779	NT	7.5	8.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.70 (s, 1H), 6.61 (s, 1H), 6.43 (brs, 1H), 6.11 (d, *J* = 17.1 Hz, 1H), 5.97 (dd, *J* = 16.9, 10.3 Hz, 1H), 5.79 (brs, 1H), 5.45 (d, *J* = 10.2 Hz, 1H), 5.01-4.75 (m, 2H), 4.55-4.40 (m, 1H), 4.25-4.00 (m, 4H), 3.95 (s, 6H), 3.94-4.80 (m, 2H), 3.79-3.72 (m, 1H), 2.03-1.93 (m, 2H), 1.53 (s, 3H).
实施例 786	17.0	38.4	47.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.86 (s, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.49 (s, 1H), 6.20 (dd, J = 16.9, 1.3 Hz, 1H), 6.11 (s, 1H), 6.02 (d, J = 8.6 Hz, 1H), 5.88 (dd, J = 17.0, 10.3 Hz, 1H), 5.53 (dd, J = 10.4, 1.4 Hz, 1H), 4.73 (d, J = 8.5 Hz, 1H), 4.38 – 4.26 (m, 1H), 4.08 (d, J = 12.1 Hz, 1H), 3.99 (d, J = 12.1 Hz, 1H), 3.92 (s, 6H), 3.75 (dd, J = 12.0, 1.7 Hz, 1H), 3.61 (m, 1H), 3.13 (s, 3H), 1.91 (m, 2H).
实施例 787	45.0	86.0	102.8	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.89 (s, 1H), 6.90 (t, J = 8.1 Hz, 1H), 6.81 (s, 1H), 6.13 (dd, J = 17.1, 1.9 Hz, 1H), 5.96 (dd, J = 17.0, 10.3 Hz, 1H), 5.47 (dd, J = 10.2, 1.9 Hz, 1H), 4.24 (dt, J = 12.4, 4.2 Hz, 1H), 4.07 (dd, J = 11.9, 4.4 Hz, 1H), 3.99 – 3.93 (m, 1H), 3.90 (s, 6H), 3.78 (dd, J = 12.0, 2.0 Hz, 1H), 3.67 – 3.52 (m, 2H), 3.47 – 3.33 (m, 1H), 2.06 (qd, J = 12.5, 4.8 Hz, 1H), 1.77 – 1.66 (m, 1H), 1.46 – 1.26 (m, 5H).
实施例 789	7.8	12.6	15.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.24 (s, 1H), 7.00 (brs, 1H), 6.70 (t, J = 8.0 Hz, 1H), 6.25 (dd, J = 16.9, 1.3 Hz, 1H), 6.02 (dd, J = 17.0, 10.3 Hz, 1H), 5.57 (d, J = 10.3 Hz, 1H), 4.50 – 4.30 (m, 2H), 4.19 – 3.76 (m, 11H), 3.97 (s, 6H), 3.63 (t, J = 10.2 Hz, 1H), 2.32 – 1.75 (m, 2H).
实施例 790	8.5	11.4	13.6	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 6.97 (s, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.24 (dd, J = 17.1, 1.4 Hz, 1H), 6.04 (brs, 1H), 6.01 (dd, J = 16.9, 10.3 Hz, 1H), 5.63 – 5.53 (m, 1H), 4.62 – 4.31 (m, 4H), 4.22 – 3.95 (m, 4H), 3.92 (s, 6H), 3.78 – 3.72 (m, 1H), 3.66 – 3.57 (m, 1H), 3.28 (s, 3H), 2.13 – 2.05 (m, 1H), 1.90 – 1.78 (m, 1H), 1.53 (s, 3H).
实施例 791	3.7	6.4	8.4	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.10 (s, 1H), 6.70 (t, J = 7.9 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.27 (dd, J = 17.0, 1.4 Hz, 1H), 6.18 – 6.08 (m, 1H), 5.98 (dd, J = 16.9, 10.3 Hz, 1H), 5.59 (dd, J = 10.3, 1.3 Hz, 1H), 4.80 (q, J = 12.0 Hz, 2H), 4.68 (q, J = 11.9 Hz, 2H), 4.44 (d, J = 10.0 Hz, 1H), 4.41 – 4.34 (m, 1H), 4.06 (dd, J = 11.9, 4.6 Hz, 1H), 3.99 (d, J = 11.8 Hz, 1H), 3.92 (s, 6H), 3.76 (dd, J = 11.9, 1.6 Hz, 1H), 3.62 (td, J = 12.0, 2.5 Hz, 1H), 2.02 (s, 1H), 1.92 – 1.81 (m, 1H).
实施例 792	3.1	4.8	6.2	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 6.92 (s, 1H), 6.83 (d, J = 6.8 Hz, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.26 (dd, J = 16.9, 1.5 Hz, 1H), 6.07 (dd, J = 17.0, 10.2 Hz, 1H), 6.02 (brs, 1H), , 5.61 (dd, J = 10.3, 1.5 Hz, 1H), 4.53 (s, 2H), 4.48 – 4.36 (m, 3H), 4.35 – 4.29 (m, 1H), 4.05 (dd, J = 11.9, 4.6 Hz, 1H), 3.99 (d, J = 11.7 Hz, 1H), 3.91 (s, 6H), 3.74 (dd, J = 11.8, 1.6 Hz, 1H), 3.61 (td, J = 12.0, 2.5 Hz, 1H), 2.41 – 2.32 (m, 2H), 2.12 – 2.04 (m, 1H), 1.91 – 1.80 (m, 1H).
实施例 793	5.3	7.9	9.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 6.97 (s, 1H), 6.67 (t, J = 7.9 Hz, 1H), 6.63 (brs, 1H), 6.23 (dd, J = 17.0, 1.3 Hz, 1H), 6.04 (d, J = 8.8 Hz, 1H), 5.99 (dd, J = 17.1, 10.4 Hz, 1H), 5.57 (dd, J = 10.2, 1.4 Hz, 1H), 4.51 –4.39 (m, 3H), 4.38 – 4.31 (m, 1H), 4.30 – 4.20 (m, 2H), 4.07 – 3.96 (m, 2H), 3.91 (s, 6H), 3.75 (dd, J = 11.8, 1.6 Hz, 1H), 3.65 – 3.56 (m, 1H), 2.05 – 1.98 (m, 1H), 1.91 – 1.80 (m, 1H), 1.56 (s, 3H).

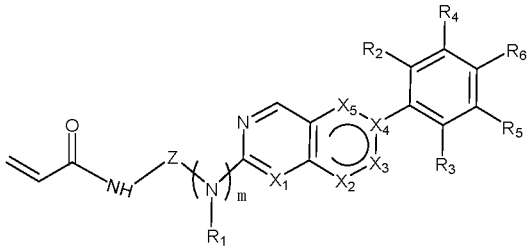
实施例 794	4.8	5.5	6.9	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 3.0 Hz, 1H), 6.93 (d, J = 4.0 Hz, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.36 (brs, 1H), 6.26 – 6.15 (m, 1H), 6.05-5.90 (m, 2H), 5.60-5.50 (m, 1H), 4.50-4.30 (m, 2H), 3.92 (s, 6H), 4.23-3.80 (m, 7H), 3.70-3.65 (m, 1H), 3.60-3.55 (m, 1H), 3.34 (d, J = 7.0 Hz, 3H), 2.02-1.90 (m, 2H), 1.87-1.78 (m, 2H).
实施例 795	7.5	9.5	11.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.20 (s, 1H), 6.69 (t, J = 7.9 Hz, 1H), 6.22 (dd, J = 17.0, 1.5 Hz, 1H), 6.02 (dd, J = 17.0, 10.3 Hz, 1H), 5.55 (d, J = 10.8 Hz, 1H), 4.54 – 4.15 (m, 4H), 4.13-4.00 (m, 2H), 3.93 (s, 6H), 3.77 (d, J = 12.0 Hz, 1H), 3.70 – 3.57 (m, 1H), 3.52-3.38 (m, 3H), 3.37 (s, 3H), 2.07-1.85 (m, 2H), 1.65 – 1.46 (m, 4H).
实施例 796	23.0	38.0	47.8	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.04 (s, 1H), 6.68 (t, J = 7.9 Hz, 1H), 6.25 (s, 1H), 6.20 (dd, J = 17.0, 1.4 Hz, 1H), 6.07 (s, 1H), 5.93 (dd, J = 16.9, 10.3 Hz, 1H), 5.56 (dd, J = 10.2, 1.4 Hz, 1H), 4.71 (d, J = 6.4 Hz, 2H), 4.61 (d, J = 13.6 Hz, 1H), 4.55 (d, J = 13.6 Hz, 1H), 4.45 (d, J = 8.9 Hz, 1H), 4.41 – 4.34 (m, 1H), 4.17 (d, J = 13.7 Hz, 1H), 4.07 (d, J = 13.5 Hz, 2H), 3.99 (d, J = 11.9 Hz, 1H), 3.92 (s, 6H), 3.73 (d, J = 11.6 Hz, 1H), 3.67 – 3.64 (m, 1H), 3.59 (td, J = 11.9, 2.6 Hz, 1H), 3.22 (q, J = 7.1 Hz, 1H), 1.97 (d, J = 13.7 Hz, 1H), 1.92 – 1.81 (m, 1H).
BLU-9931	24.7	549	1362	
BLU-554	18.0	22	126	
备注	“NT”是“Not Tested”，指暂未测试。BLU-9931、 BLU-554 为阳性化合物。			

从具体实施例化合物酶学活性数据来看，本发明系列化合物对 FGFR4 激酶活性具有很强的抑制作用。从具体实施例化合物细胞活性数据来看，本发明系列化合物对 FGFR4 高表达的 HuH-7 细胞增殖活性具有很强的抑制作用。

在本发明提及的所有文献都在本申请中引用作为参考，就如同每一篇文献被单独引用作为参考那样。此外应理解，在阅读了本发明的上述讲授内容之后，本领域技术人员可以对本发明作各种改动或修改，这些等价形式同样落于本申请所附权利要求书所限定的范围。

权 利 要 求 书

1.式(I)化合物、其立体异构体或其药学上可接受盐：



（I）

其中，

X_1选自-C(R_7)-或N；

X_2、X_3、X_5各自独立的选自-(CR_8)$_n$-、-C(O)-、-N(R_9)-、N、O或S；

X_4选自C或N；

Z选自C_{1-8}亚烷基、C_{2-8}亚链烯基、C_{2-8}亚链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基或5-10元杂芳基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-8}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-8}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代；

R_1选自氢、氘、C_{1-8}烷基、C_{1-8}烷氧C_{1-8}烷基、C_{3-8}环烷氧基C_{1-8}烷基、C_{3-8}环烷基C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基或C_{1-8}烷酰基；

R_2、R_3、R_4、R_5、R_6、R_7各自独立的选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-S(O)(N$R_9$)$R_{10}$、-$C_{0-8}$-P(O)($R_{10}$)$_2$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-$C_{0-8}$-N$R_{13}R_{14}$、-$C_{0-8}$-C(O)N$R_{13}R_{14}$、-$C_{0-8}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-8}$-N($R_{13}$)-C(O)O$R_{11}$，或者，$R_2$与$R_4$、$R_3$与$R_5$、$R_4$与$R_6$、$R_5$与$R_6$和其直接相连的碳原子一起形成$C_{5-10}$环烷基、5-10元杂环基、5-10元芳基或5-10元杂芳基，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-S(O)$_r$$R_{10}$、-$C_{0-8}$-O-$R_{11}$、-$C_{0-8}$-C(O)O$R_{11}$、-$C_{0-8}$-C(O)$R_{12}$、-$C_{0-8}$-O-C(O)$R_{12}$、-

C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$C(O)NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代；

R_8选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-$S(O)_rR_{10}$、-C_{0-8}-$S(O)(NR_9)R_{10}$、-C_{0-8}-$P(O)(R_{10})_2$、-C_{0-8}-O-R_{11}、-C_{0-8}-$C(O)OR_{11}$、-C_{0-8}-$C(O)R_{12}$、-C_{0-8}-O-$C(O)R_{12}$、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$C(O)NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-$S(O)_rR_{10}$、-C_{0-8}-O-R_{11}、-C_{0-8}-$C(O)OR_{11}$、-C_{0-8}-$C(O)R_{12}$、-C_{0-8}-O-$C(O)R_{12}$、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$C(O)NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-$S(O)_rR_{10}$、-C_{0-8}-O-R_{11}、-C_{0-8}-$C(O)OR_{11}$、-C_{0-8}-$C(O)R_{12}$、-C_{0-8}-O-$C(O)R_{12}$、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$C(O)NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代；

R_9选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基或C_{1-8}烷酰基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、卤取代C_{1-8}烷基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-$S(O)_rR_{10}$、-C_{0-8}-O-R_{11}、-C_{0-8}-$C(O)OR_{11}$、-C_{0-8}-$C(O)R_{12}$、-C_{0-8}-O-$C(O)R_{12}$、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$C(O)NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代；

R_{10}选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{3-8}环烷基、3-10元杂环基、卤取代C_{1-8}烷基、C_{5-10}芳基、5-10元杂芳基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基或C_{1-8}烷酰氨基；

R_{11}选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基或5-10元杂芳基，上述基团任选地被以下基团单取代或多取代：氘、卤素、氰基、C_{1-8}烷基、C_{1-8}烷氧基、C_{1-8}烷硫基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基、C_{1-8}烷基磺酰胺基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基、=O或羟基；

R_{12}选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{1-8}烷氧基、C_{3-8}环烷基、C_{3-8}环烷氧基、3-10元杂环基、3-10元杂环氧基、C_{5-10}芳基、5-10元杂芳基、C_{5-10}芳氧基或5-10元杂芳氧基，上述基团任选地被以下基团单取代或多取代：氘、卤素、氰基、C_{1-8}烷基、C_{1-8}烷氧基、C_{1-8}烷硫基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基、C_{1-8}烷基磺酰胺基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基、=O或羟基；

R_{13}、R_{14}各自独立的选自氢、氘、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基或C_{1-8}烷酰基，或者，R_{13}、R_{14}和其直接相连的氮原子一起形成4-10元杂环基，

上述基团任选地被以下基团单取代或多取代：氘、卤素、C_{1-8}烷基、C_{1-8}烷氧基、C_{1-8}烷硫基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、C_{1-8}烷基磺酰基、C_{1-8}烷基磺酰胺基、氨基、单C_{1-8}烷基氨基、二C_{1-8}烷基氨基、=O或羟基；

m为0或1；

n为0、1或2；

r为0、1或2；

条件是，当X_3选自-$(CR_8)_n$-时，X_2选自-C(O)-，X_4选自C，X_5选自-$N(R_9)$-、N、O或S；当X_3选自-C(O)-时，X_2选自-$N(R_9)$-，且Z选自C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基或苯基。

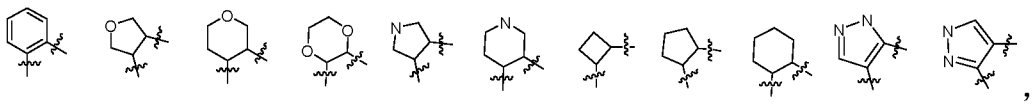
2.根据权利要求1所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，Z选自C_{1-4}亚烷基、C_{2-4}亚链烯基、C_{2-4}亚链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基或5-8元杂芳基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-C(O)OR_{11}、-C_{0-4}-C(O)R_{12}、-C_{0-4}-O-C(O)R_{12}、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-C(O)$NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-C(O)R_{12}或-C_{0-4}-$N(R_{13})$-C(O)OR_{11}的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-C(O)OR_{11}、-C_{0-4}-C(O)R_{12}、-C_{0-4}-O-C(O)R_{12}、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-C(O)$NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-C(O)R_{12}或-C_{0-4}-$N(R_{13})$-C(O)OR_{11}的取代基所取代；

R_1选自氢、氘、C_{1-4}烷基、C_{1-4}烷氧C_{1-4}烷基、C_{3-6}环烷氧基C_{1-4}烷基、C_{3-6}环烷基C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基或C_{1-4}烷酰基；

R_2、R_3、R_4、R_5、R_6、R_7各自独立的选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-$S(O)(NR_9)R_{10}$、-C_{0-4}-$P(O)(R_{10})_2$、-C_{0-4}-O-R_{11}、-C_{0-4}-C(O)OR_{11}、-C_{0-4}-C(O)R_{12}、-C_{0-4}-O-C(O)R_{12}、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-C(O)$NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-C(O)R_{12}或-C_{0-4}-$N(R_{13})$-C(O)OR_{11}，或者，R_2与R_4、R_3与R_5、R_4与R_6、R_5与R_6和其直接相连的碳原子一起形成C_{5-8}环烷基、5-8元杂环基、5-8元芳基或5-8元杂芳基，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-4}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

3.根据权利要求 1 所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，Z选自C_{1-2}亚烷基或如下结构：



上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代。

4.根据权利要求 1 所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，

R_1选自氢、氘、甲基、异丙基、甲氧乙基、环丙氧甲基、环丙甲基、烯丙基、环丙基或乙酰基；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、卤素、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、$-C_{0-4}-O-R_{11}$或$-C_{0-4}-NR_{13}R_{14}$，或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成C_{5-8}环烷基、5-8元杂环基、5-8元芳基或5-8元杂芳基，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-4}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$或$-C_{0-4}-N(R_{13})-C(O)OR_{11}$的取代基所取代；

R_6选自氢或氘。

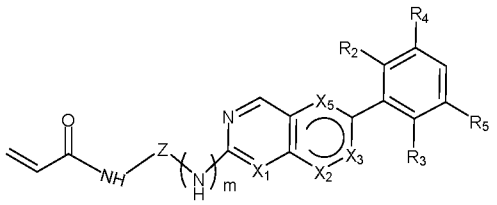
5.根据权利要求 1 所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，R_1选自氢、氘、甲基或环丙甲基；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、甲基、异丙基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、-C_{0-4}-O-R_{11}或-C_{0-4}-$NR_{13}R_{14}$，

或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮，所述5-8元杂环基任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-4}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代；

R_6选自氢或氘。

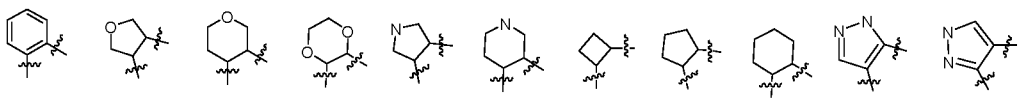
6.根据权利要求1所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自如下式(Ⅱa)化合物：



(Ⅱa)，

其中，X_3选自-N(R_9)-、N、O或S；

Z选自C_{1-2}亚烷基或如下结构：



，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-$NR_{13}R_{14}$、-$C_{0-4}$-C(O)$NR_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、甲基、异丙基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、-C_{0-4}-O-R_{11}或-C_{0-4}-$NR_{13}R_{14}$，

或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮，所述5-8元杂环基任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠

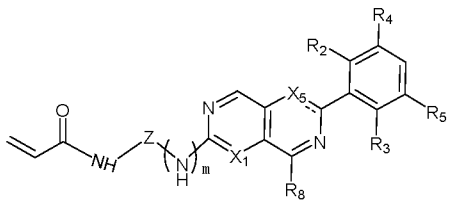
氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-4}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-N$R_{13}R_{14}$、-$C_{0-4}$-C(O)N$R_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代；

R_7选自氢、氘、氯、氟、羟基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、-C_{0-4}-O-R_{11}或-C_{0-4}-N$R_{13}R_{14}$；

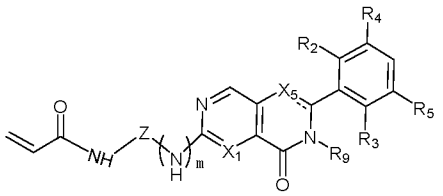
R_9选自氢、氘、C_{1-4}烷基、C_{3-6}环烷基或3-8元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-N$R_{13}R_{14}$、-$C_{0-4}$-C(O)N$R_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代；

X_1、X_2、X_5、R_8、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r如权利要求1所述。

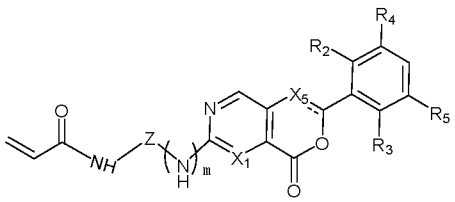
7.根据权利要求6所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自如下式(IIIa-1)、(IIIa-2)、(IIIa-3)或(IIIa-4)化合物：



(IIIa-1)

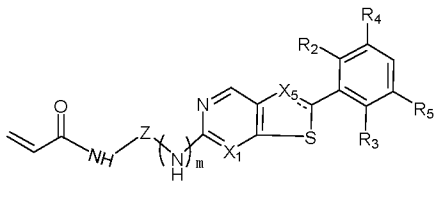


(IIIa-2)



(IIIa-3)

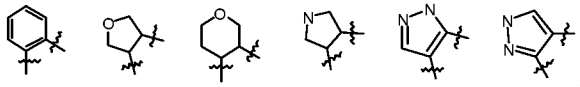
或



(IIIa-4)

，

其中，Z选自C_{1-2}亚烷基或如下结构：



，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-S(O)$_r$$R_{10}$、-$C_{0-4}$-O-$R_{11}$、-$C_{0-4}$-C(O)O$R_{11}$、-$C_{0-4}$-C(O)$R_{12}$、-$C_{0-4}$-O-C(O)$R_{12}$、-$C_{0-4}$-N$R_{13}R_{14}$、-$C_{0-4}$-C(O)N$R_{13}R_{14}$、-$C_{0-4}$-N($R_{13}$)-C(O)$R_{12}$或-$C_{0-4}$-N($R_{13}$)-C(O)O$R_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、

-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或-O-R_{11}，

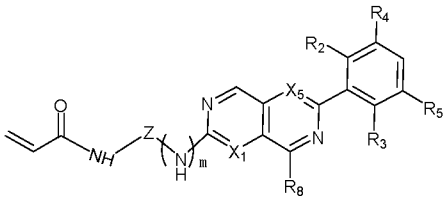
或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮；

R_7选自氢、氘、氯、氟、羟基、环丙基或-O-R_{11}；

R_9选自氢、氘、C_{1-4}烷基、C_{3-6}环烷基或3-8元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、C_{1-4}烷基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、-C_{0-4}-O-R_{11}、-C_{0-4}-$NR_{13}R_{14}$或-C_{0-4}-$C(O)NR_{13}R_{14}$的取代基所取代；

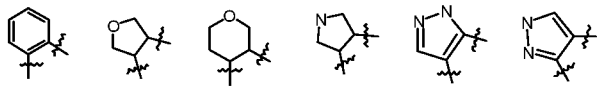
X_1、X_5、R_8、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r如权利要求1所述。

8.根据权利要求7所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自式(Ⅳa-1)化合物：



(Ⅳa-1)

其中，X_5选自-CH-或N；

Z选自C_{1-2}亚烷基或如下结构：  ，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代；

R_2、R_3、R_4、R_5各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或-O-R_{11}，

或者，R_2与R_4、R_3与R_5和其直接相连的碳原子一起形成5-8元杂环基，所述杂原子选自氧或氮；

R_7选自氢、氘、氯、氟、羟基、环丙基或-O-R_{11}；

R_8选自氢、氘、卤素、氰基、硝基、叠氮基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-$S(O)_rR_{10}$、-C_{0-4}-$S(O)(NR_9)R_{10}$、-C_{0-8}-$P(O)(R_{10})_2$、-C_{0-8}-O-R_{11}、-C_{0-8}-$C(O)OR_{11}$、-C_{0-8}-$C(O)R_{12}$、-C_{0-8}-O-$C(O)R_{12}$、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$C(O)NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代；

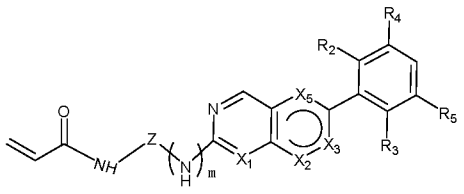
X_1、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r如权利要求1所述。

9.根据权利要求8所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，

R_8选自氢、氘、卤素、氰基、C_{1-8}烷基、C_{2-8}链烯基、C_{2-8}链炔基、C_{3-8}环烷基、3-10元杂环基、C_{5-10}芳基、5-10元杂芳基、-C_{0-8}-O-R_{11}、-C_{0-8}-$NR_{13}R_{14}$、-C_{0-8}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-8}-$N(R_{13})$-$C(O)OR_{11}$，

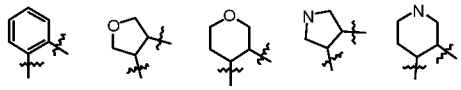
上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代，上述基团再任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4}烷基、C_{2-4}链烯基、C_{2-4}链炔基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、C_{5-8}芳基、5-8元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-$C(O)OR_{11}$、-C_{0-4}-$C(O)R_{12}$、-C_{0-4}-O-$C(O)R_{12}$、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-$C(O)NR_{13}R_{14}$、-C_{0-4}-$N(R_{13})$-$C(O)R_{12}$或-C_{0-4}-$N(R_{13})$-$C(O)OR_{11}$的取代基所取代。

10.根据权利要求1所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自如下式（IIb)化合物：



（IIb），

其中，X_3 选自-$(CR_8)_n$-或-C(O)-；

Z 选自 C_{1-2} 亚烷基或如下结构：  ，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-C(O)OR_{11}、-C_{0-4}-C(O)R_{12}、-C_{0-4}-O-C(O)R_{12}、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-C(O)$NR_{13}R_{14}$、-C_{0-4}-N(R_{13})-C(O)R_{12} 或-C_{0-4}-N(R_{13})-C(O)OR_{11} 的取代基所取代；

R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、甲基、异丙基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、-C_{0-4}-O-R_{11} 或-C_{0-4}-$NR_{13}R_{14}$，

或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮，所述 5-8 元杂环基任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-4} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-C(O)OR_{11}、-C_{0-4}-C(O)R_{12}、-C_{0-4}-O-C(O)R_{12}、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-C(O)$NR_{13}R_{14}$、-C_{0-4}-N(R_{13})-C(O)R_{12} 或-C_{0-4}-N(R_{13})-C(O)OR_{11} 的取代基所取代；

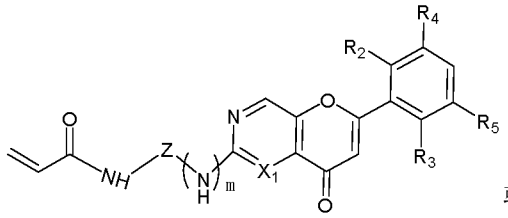
R_7 选自氢、氘、氯、氟、羟基、烯丙基、乙炔基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基、-C_{0-4}-O-R_{11} 或-C_{0-4}-$NR_{13}R_{14}$；

R_9 选自氢、氘、C_{1-4} 烷基、C_{3-6} 环烷基或 3-8 元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、卤取代 C_{1-4} 烷基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、-C_{0-4}-$S(O)_rR_{10}$、-C_{0-4}-O-R_{11}、-C_{0-4}-C(O)OR_{11}、-C_{0-4}-C(O)R_{12}、-C_{0-4}-O-C(O)R_{12}、-C_{0-4}-$NR_{13}R_{14}$、-C_{0-4}-C(O)$NR_{13}R_{14}$、-C_{0-4}-N(R_{13})-C(O)R_{12} 或-C_{0-4}-N(R_{13})-C(O)OR_{11} 的取代基所取代；

X_1、X_2、X_5、R_8、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r 如权利要求 1 所述；

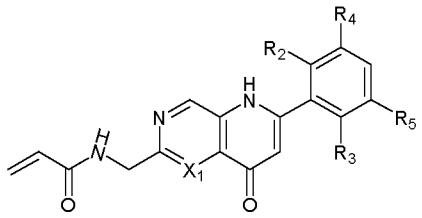
条件是，当 X_3 选自-$(CR_8)_n$-时，X_2 选自-C(O)-，X_5 选自-N(R_9)-、N、O 或 S；当 X_3 选自-C(O)-时，X_2 选自-N(R_9)-，且 Z 选自 C_{1-4} 烷基或苯基。

11.根据权利要求 10 所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自如下式(IIIb-1)或(IIIb-2)化合物：

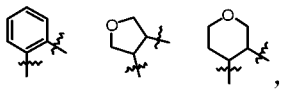


（IIIb-1）

或



（IIIb-2），

其中，Z 选自 C_{1-2} 亚烷基或如下结构：  ，

上述基团任选进一步被一个或多个选自氘、卤素、氰基、硝基、叠氮基、C_{1-4} 烷基、C_{2-4} 链烯基、C_{2-4} 链炔基、C_{3-6} 环烷基、3-8 元杂环基、C_{5-8} 芳基、5-8 元杂芳基、$-C_{0-4}-S(O)_rR_{10}$、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-C(O)OR_{11}$、$-C_{0-4}-C(O)R_{12}$、$-C_{0-4}-O-C(O)R_{12}$、$-C_{0-4}-NR_{13}R_{14}$、$-C_{0-4}-C(O)NR_{13}R_{14}$、$-C_{0-4}-N(R_{13})-C(O)R_{12}$ 或 $-C_{0-4}-N(R_{13})-C(O)OR_{11}$ 的取代基所取代；

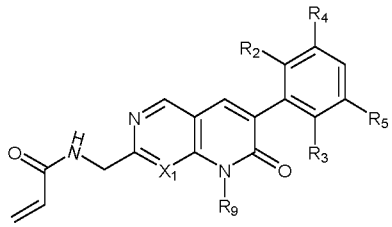
R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或 $-O-R_{11}$，

或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮；

R_7 选自氢、氘、氯、氟、羟基、环丙基或 $-O-R_{11}$；

X_1、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、r 如权利要求 1 所述。

12.根据权利要求 10 所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自如下式(IIIb-3)化合物：



（IIIb-3），

其中，R_2、R_3、R_4、R_5 各自独立的选自氢、氘、氯、氟、羟基、甲基、异丙基、环丙基、3-氧杂环丁基、三氟甲基、三氘甲基或 $-O-R_{11}$，

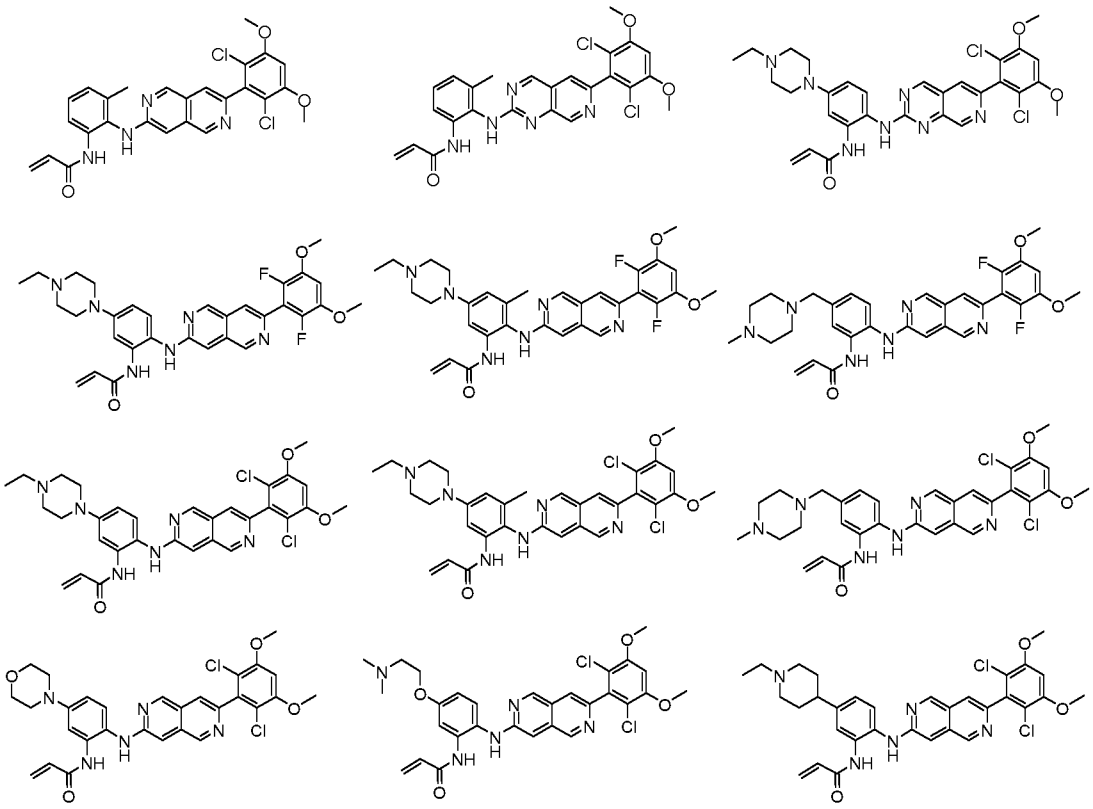
或者，R_2 与 R_4、R_3 与 R_5 和其直接相连的碳原子一起形成 5-8 元杂环基，所述杂原子选自氧或氮；

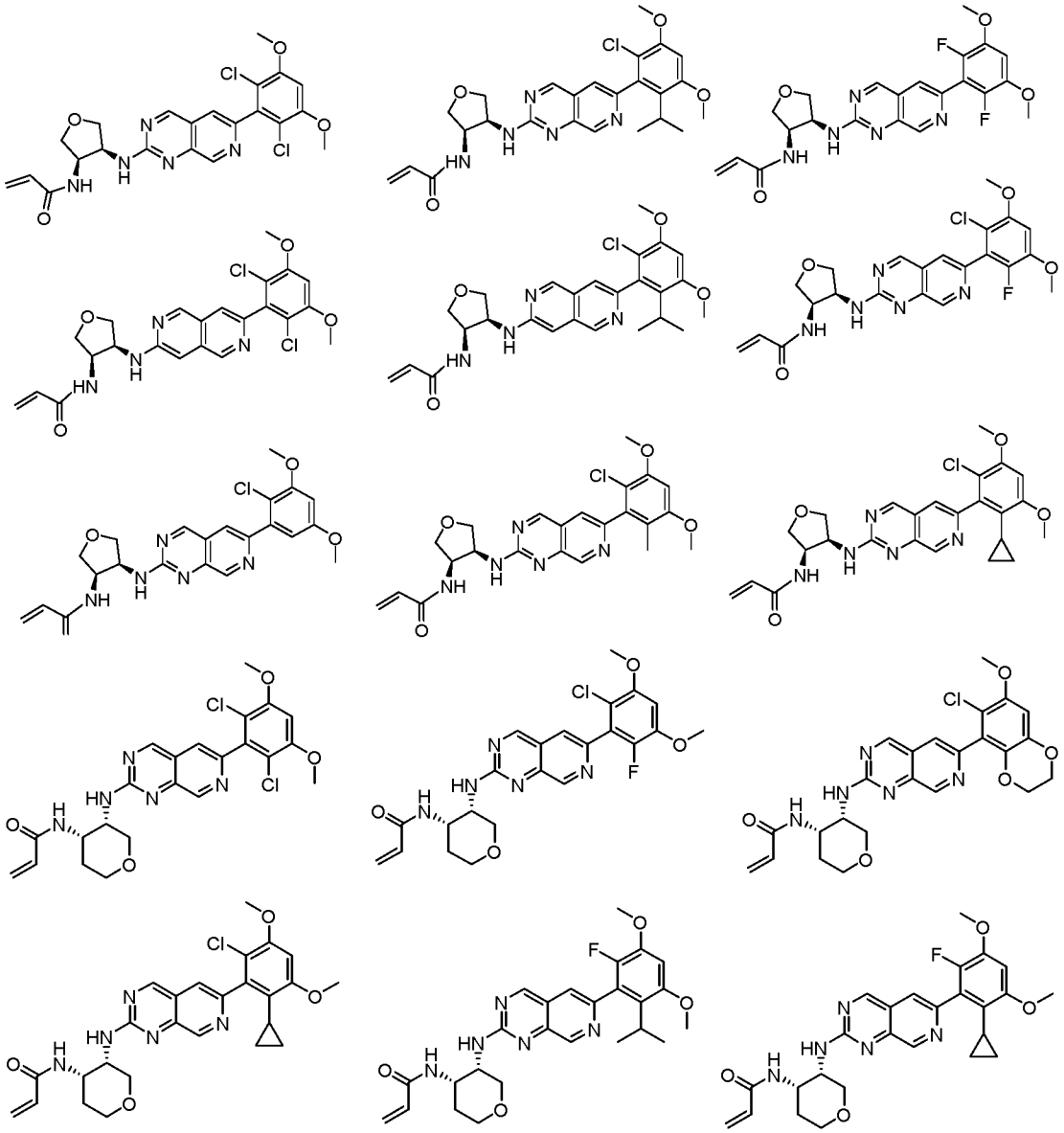
R_7 选自氢、氘、氯、氟、羟基、环丙基或 $-O-R_{11}$；

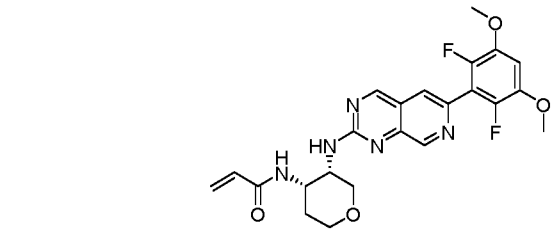
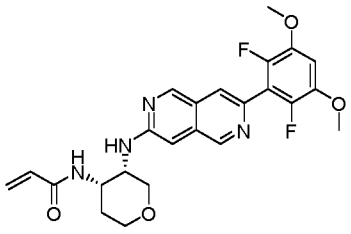
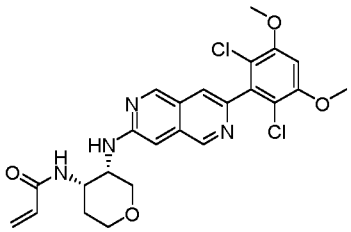
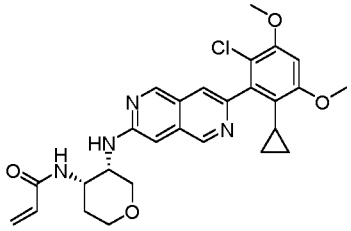
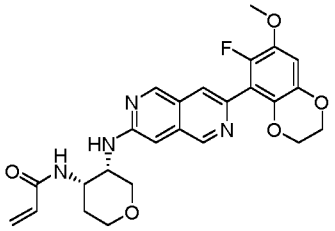
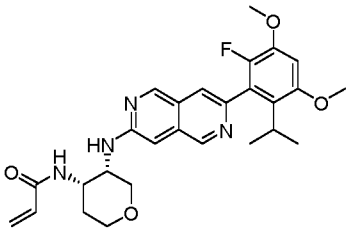
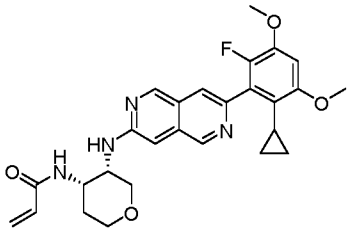
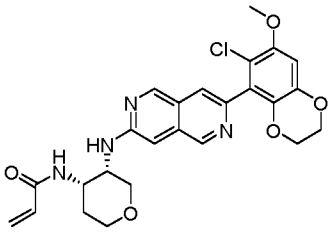
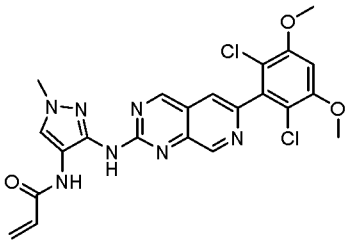
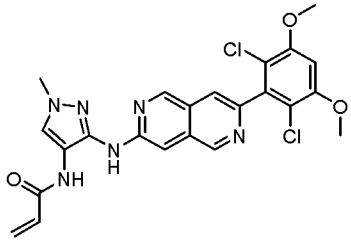
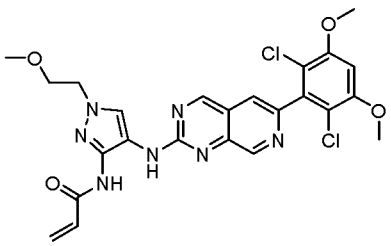
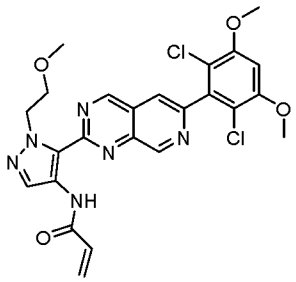
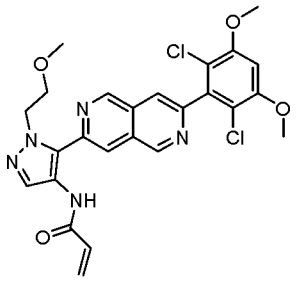
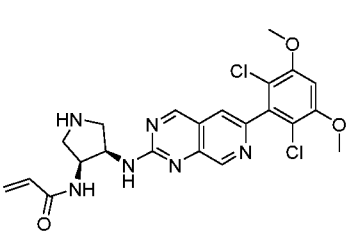
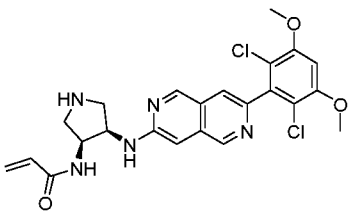
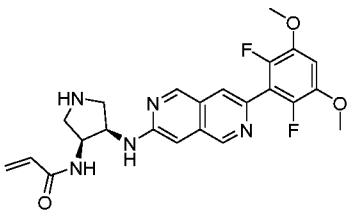
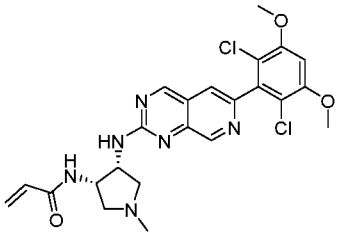
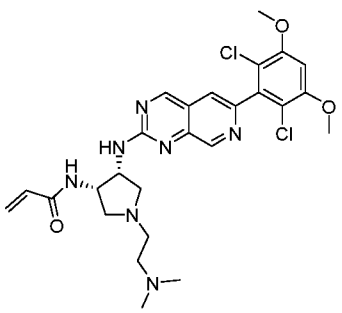
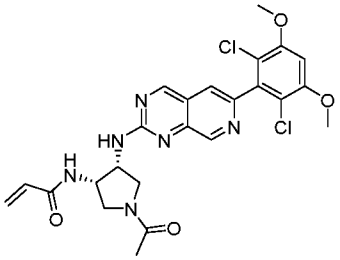
R_9选自氢、氘、C_{1-4}烷基、C_{3-6}环烷基或3-8元杂环基，上述基团任选进一步被一个或多个选自氘、卤素、C_{1-4}烷基、卤取代C_{1-4}烷基、C_{3-6}环烷基、3-8元杂环基、$-C_{0-4}-O-R_{11}$、$-C_{0-4}-NR_{13}R_{14}$或$-C_{0-4}-C(O)NR_{13}R_{14}$的取代基所取代；

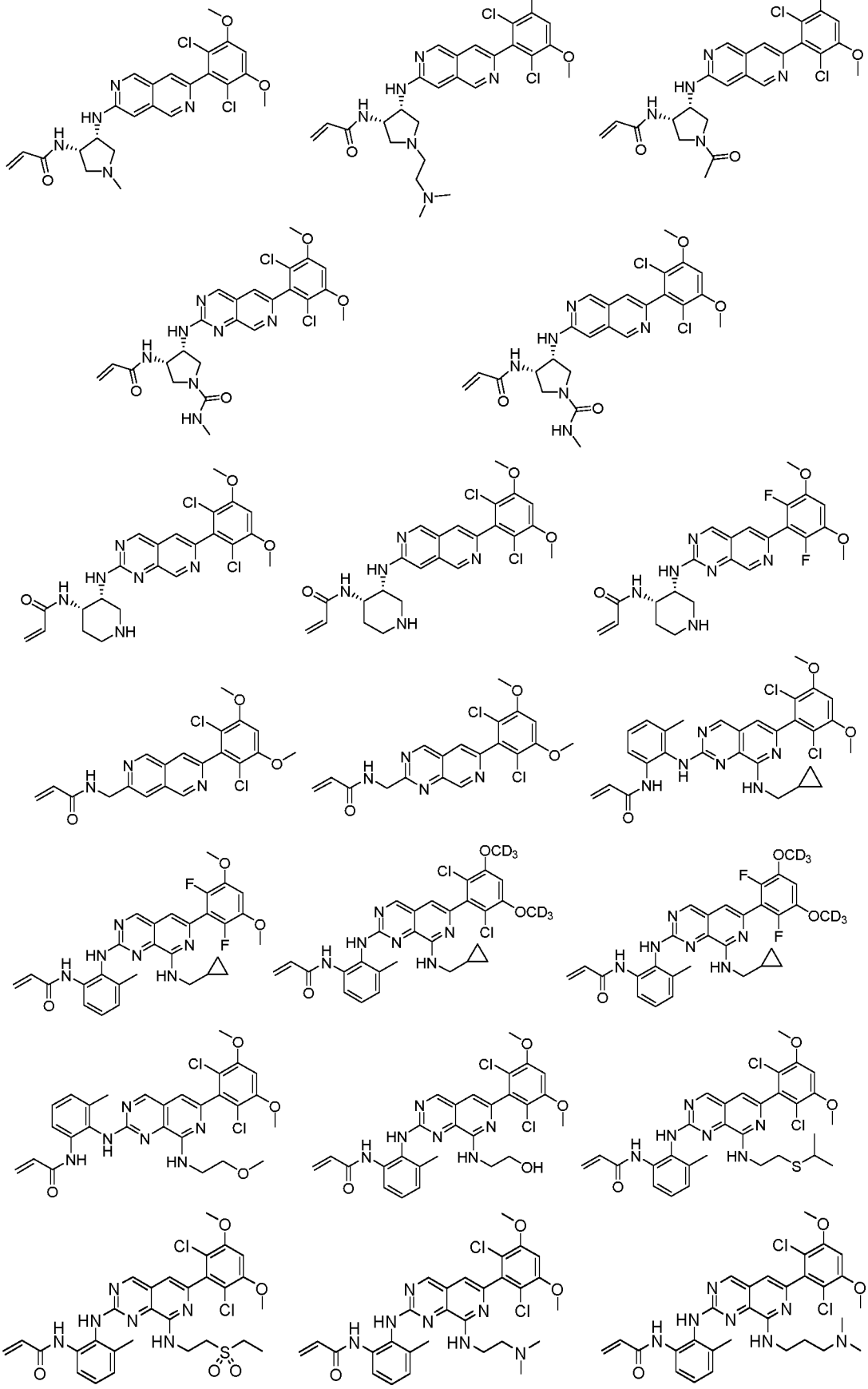
X_1、R_8、R_{10}、R_{11}、R_{13}、R_{14}、n如权利要求1所述。

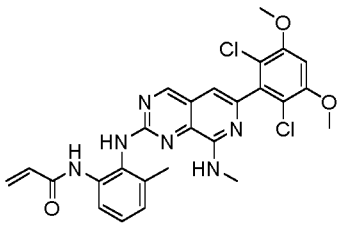
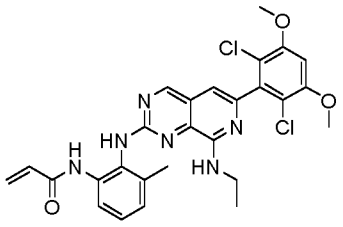
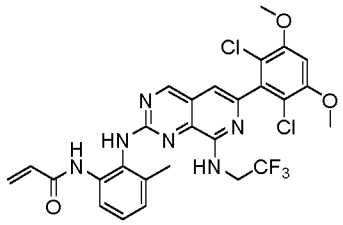
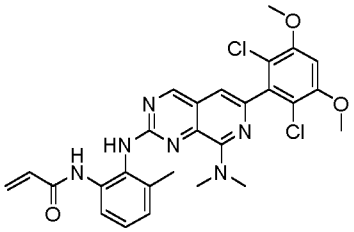
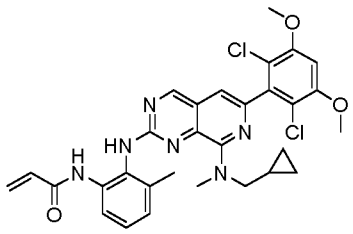
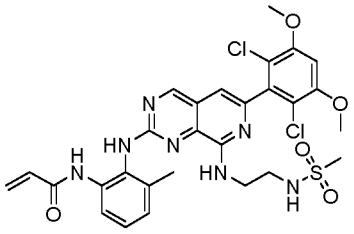
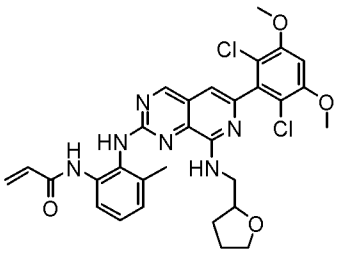
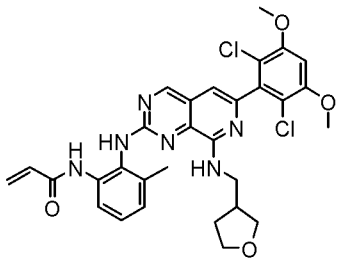
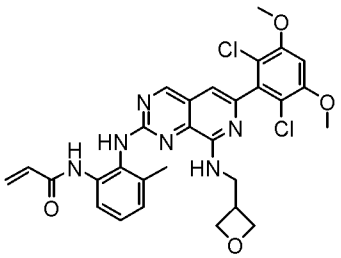
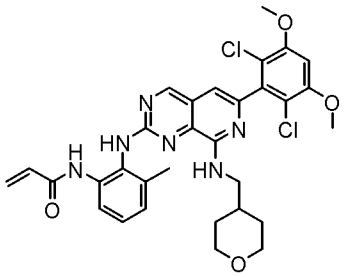
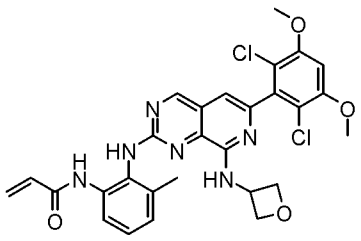
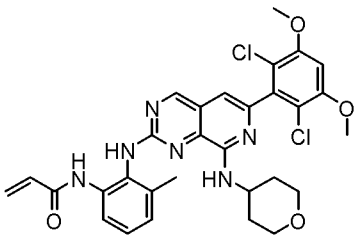
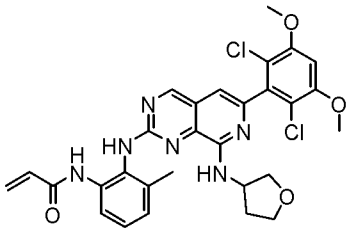
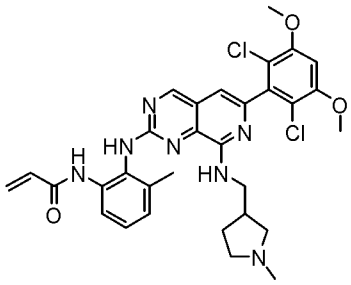
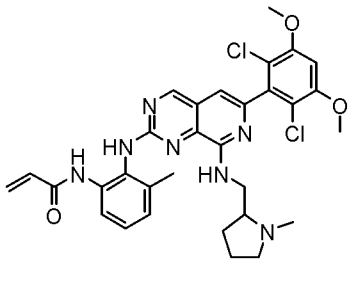
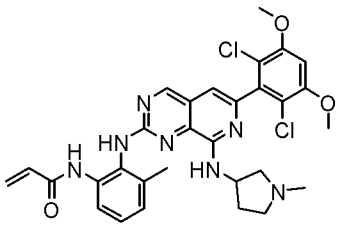
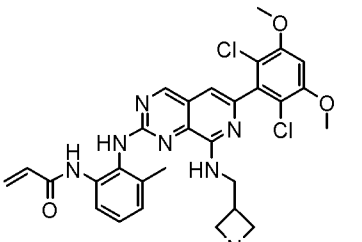
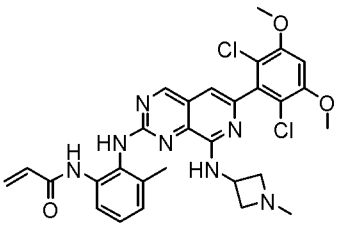
13. 根据权利要求1-12任一所述的式(I)化合物、其立体异构体或其药学上可接受盐，其特征在于，选自如下化合物：

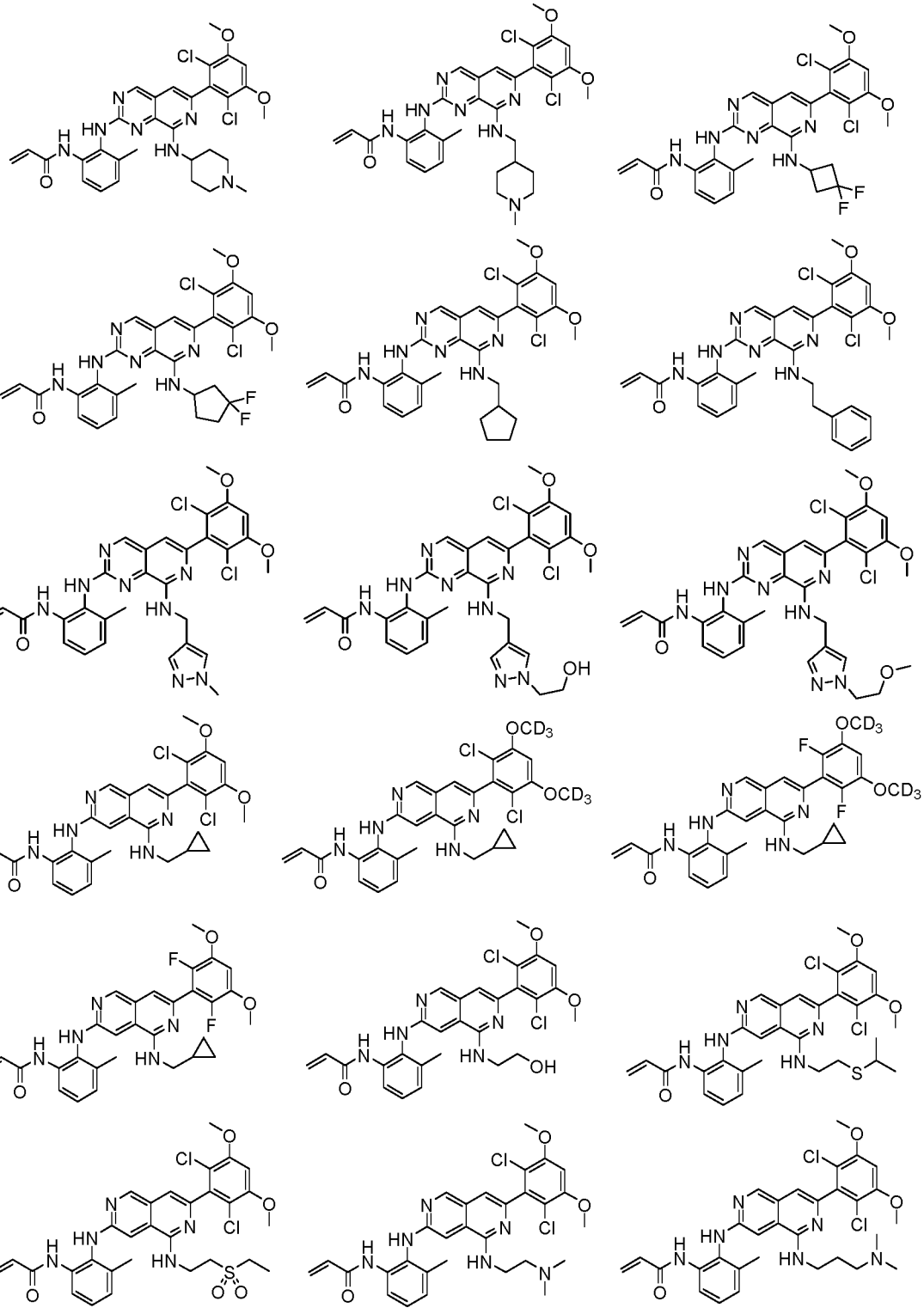


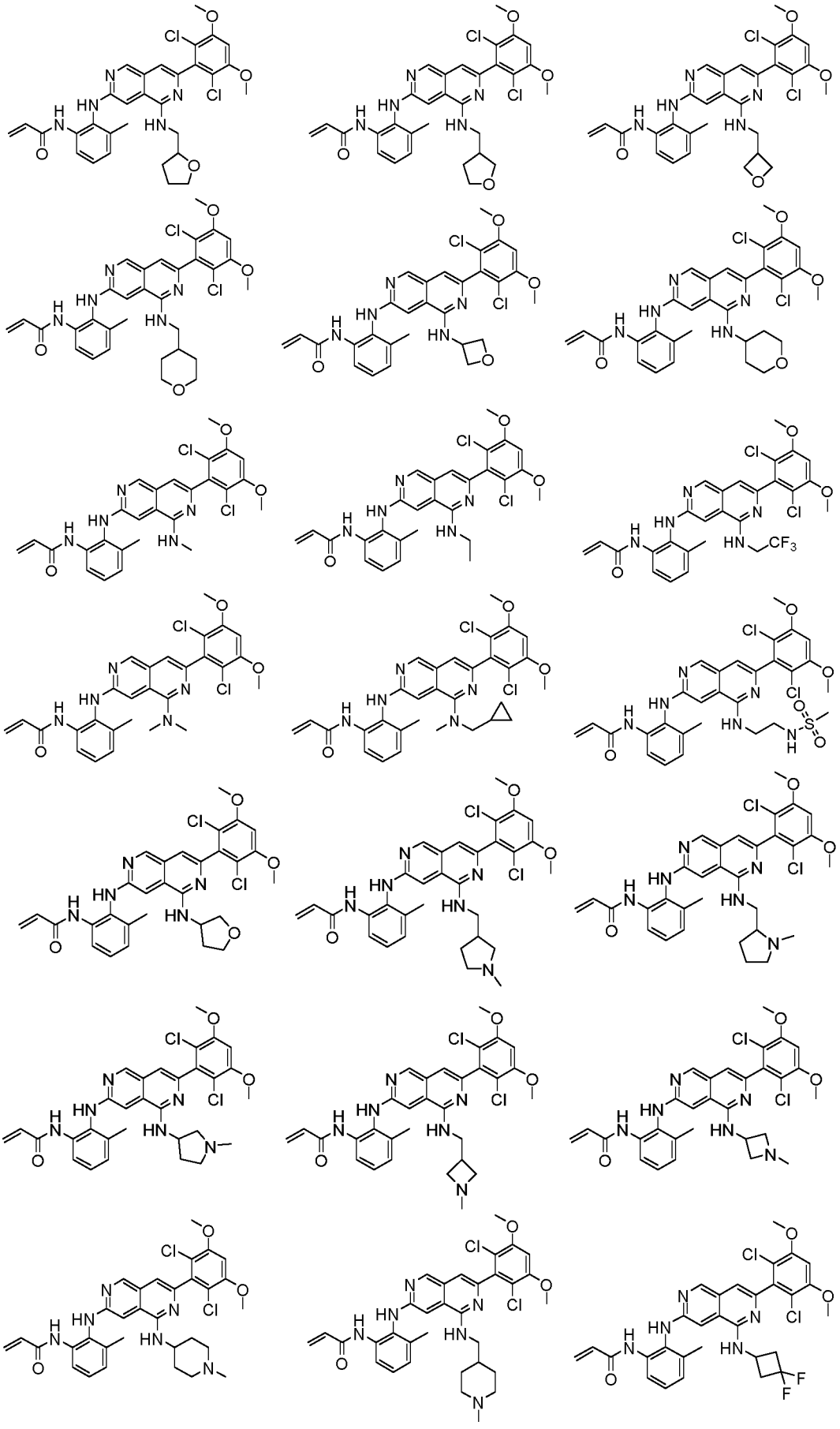


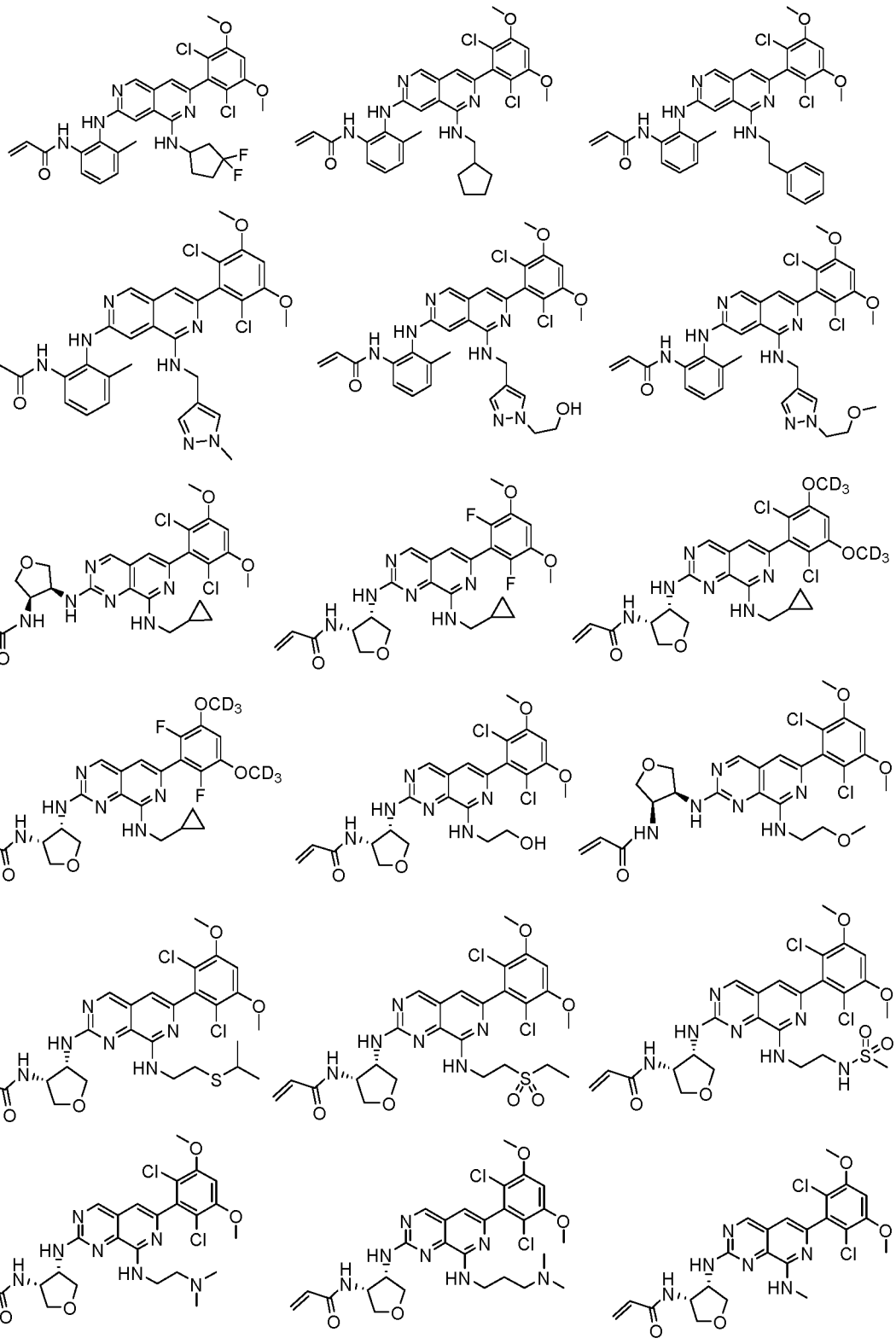




















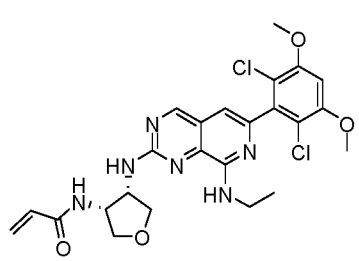
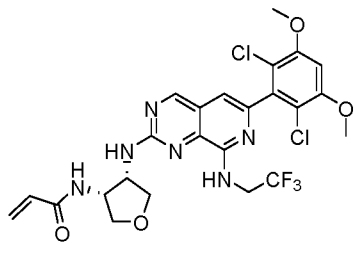
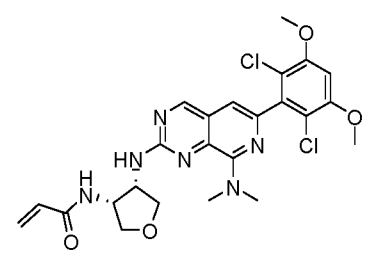
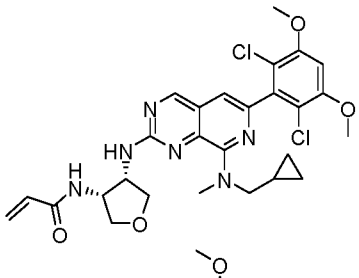
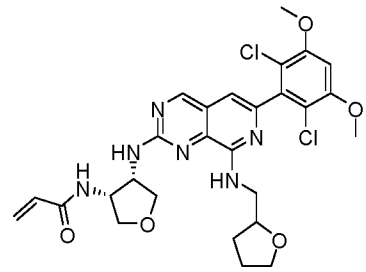
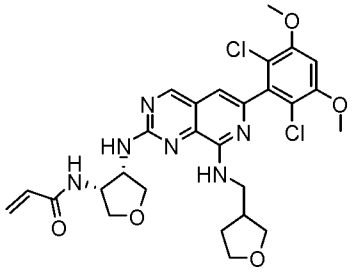
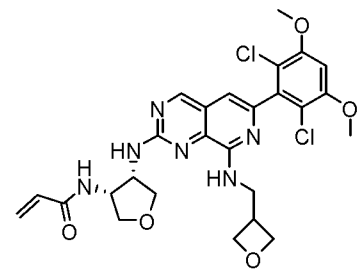
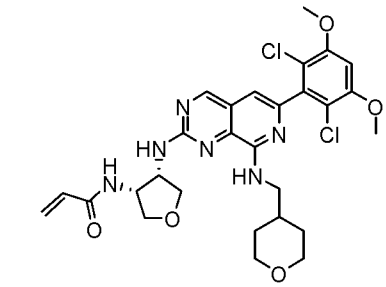
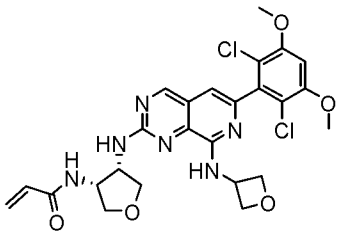
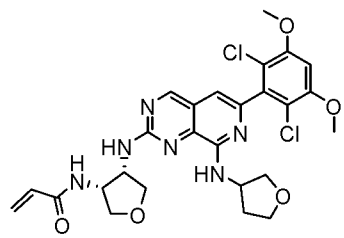
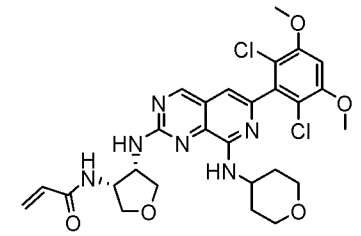
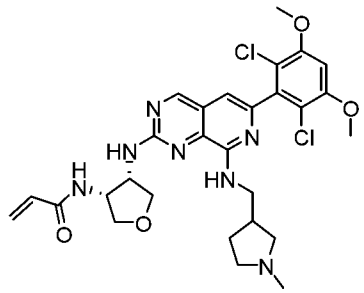
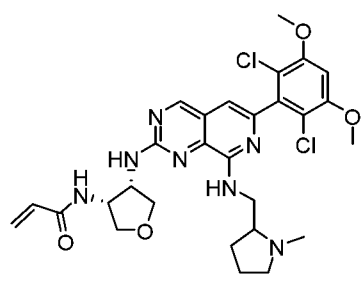
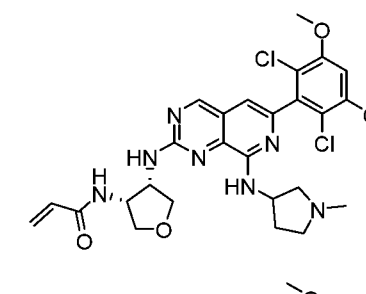
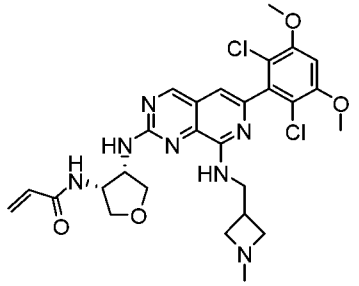
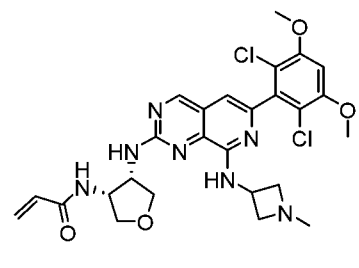
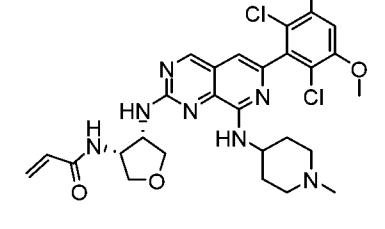


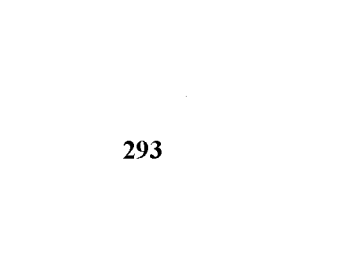



















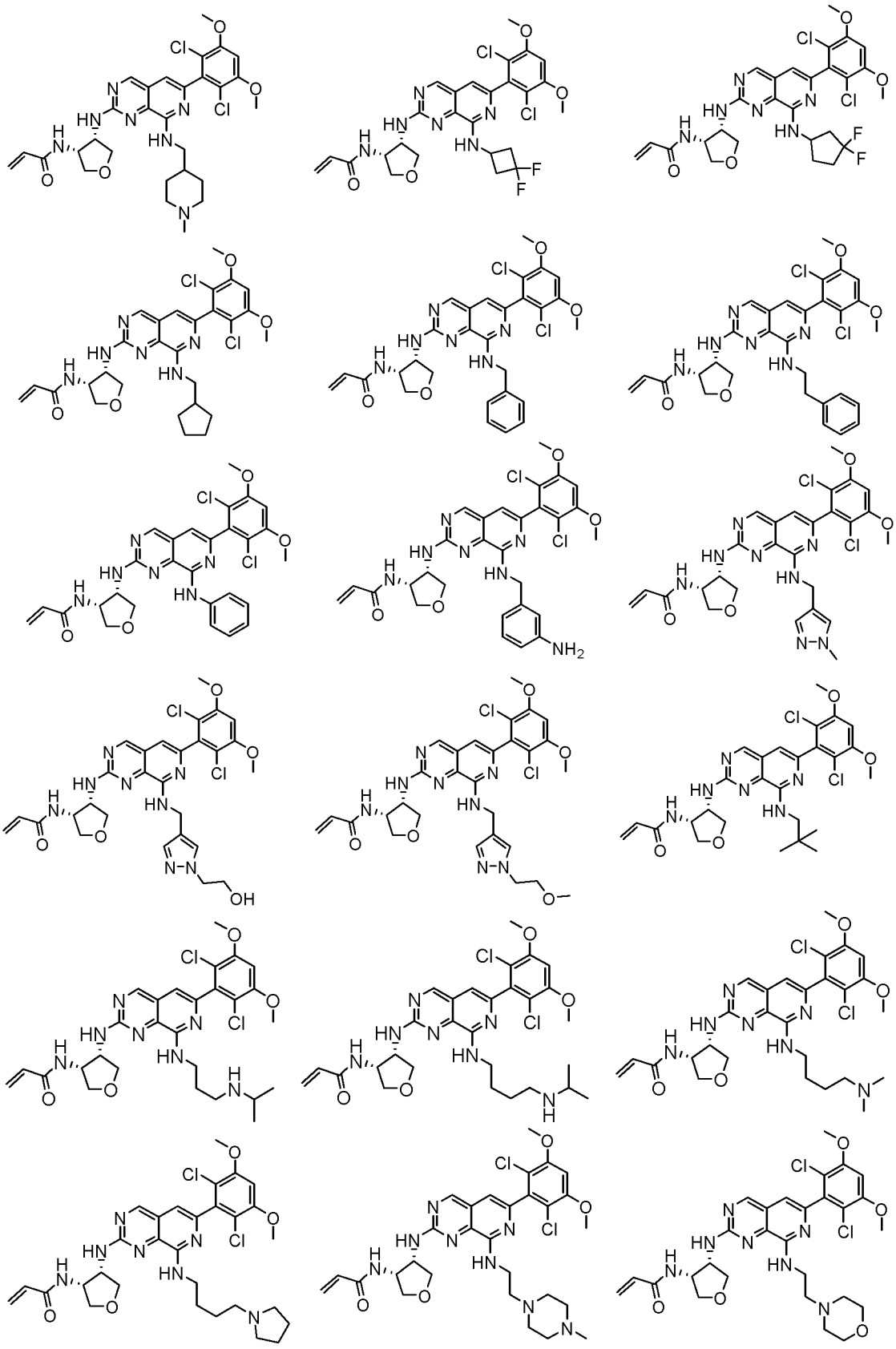


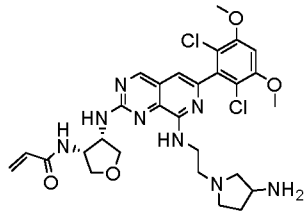
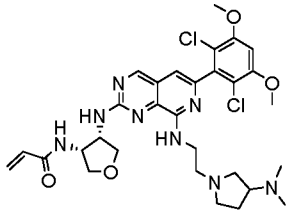
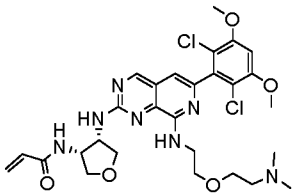
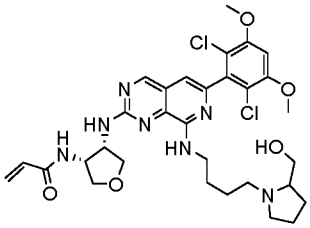
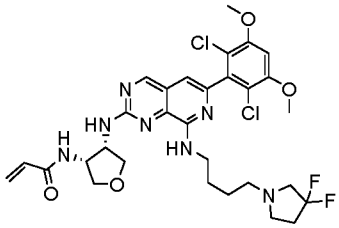
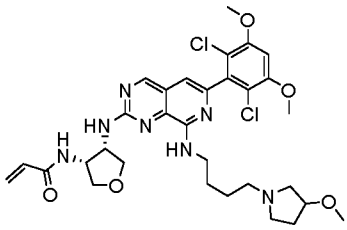
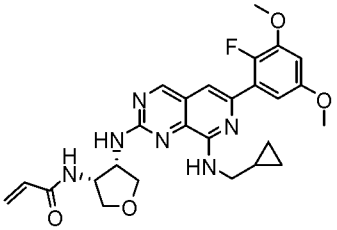
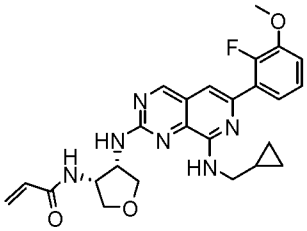
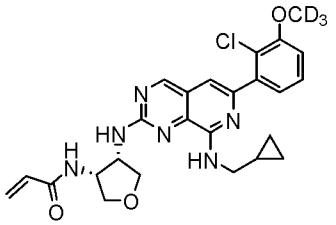
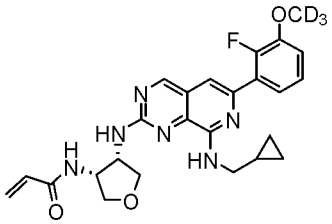
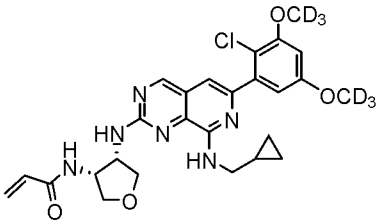
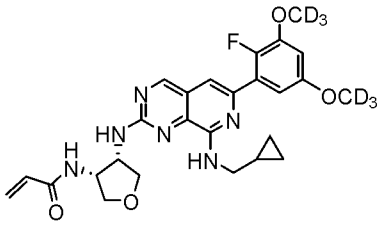
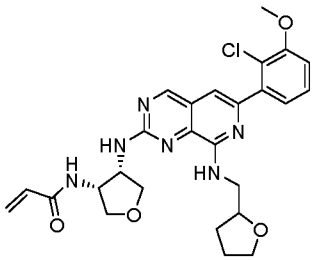
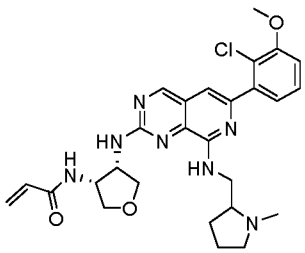
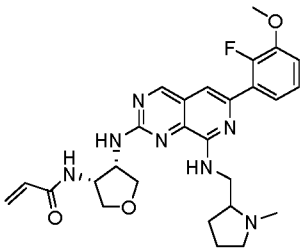
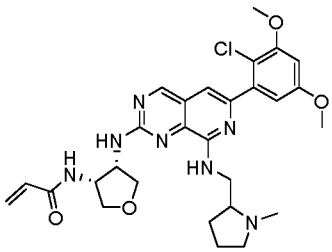
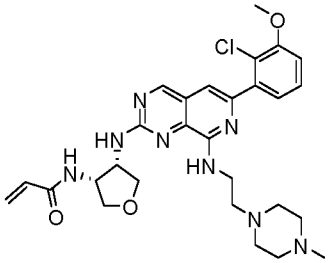
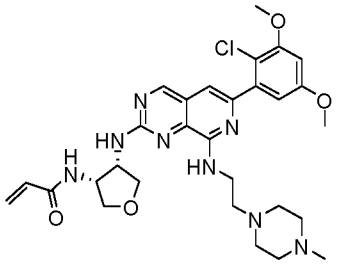
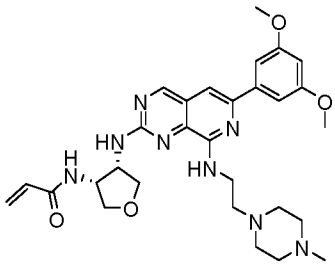


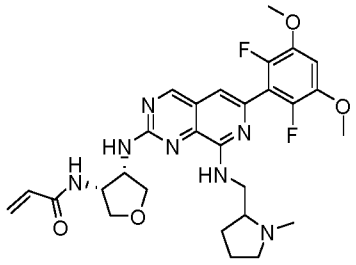
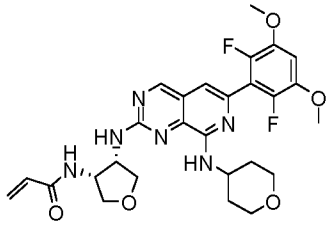
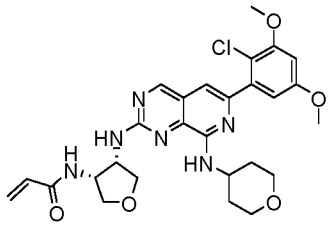
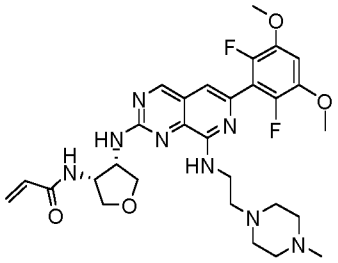
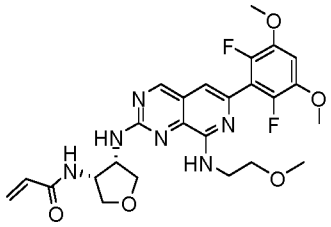
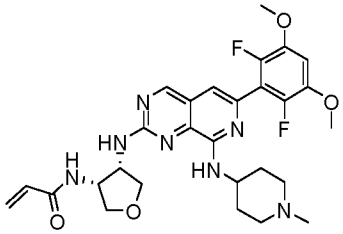
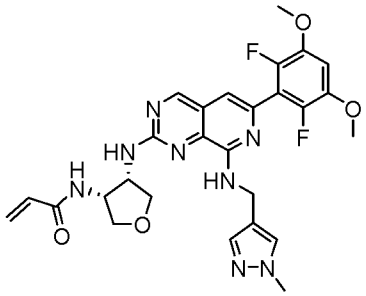
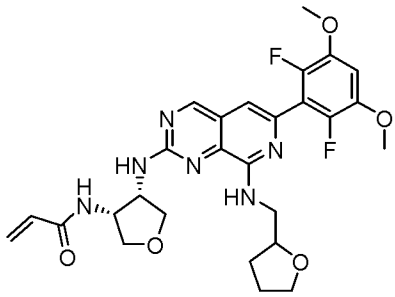
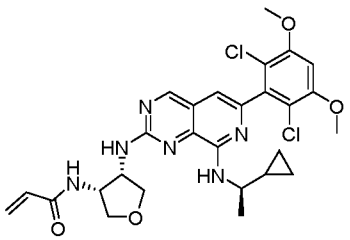
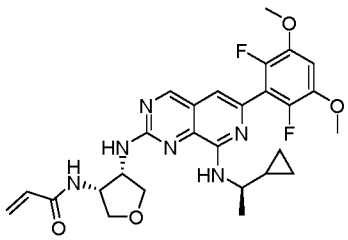
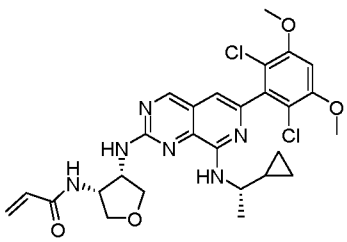
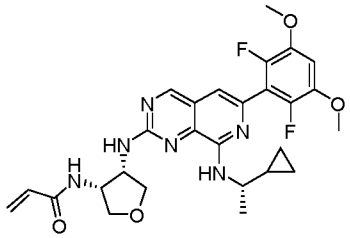
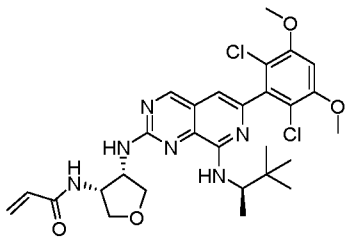
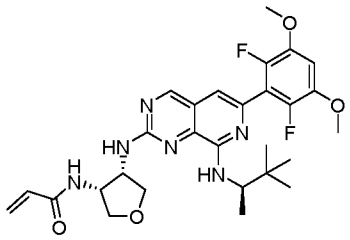
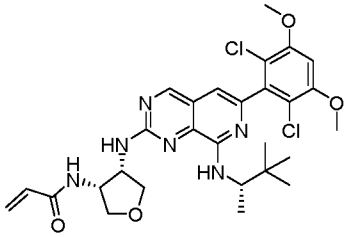
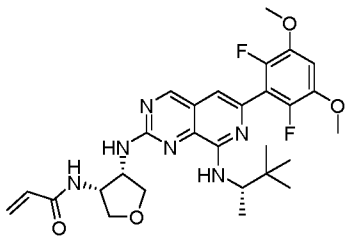


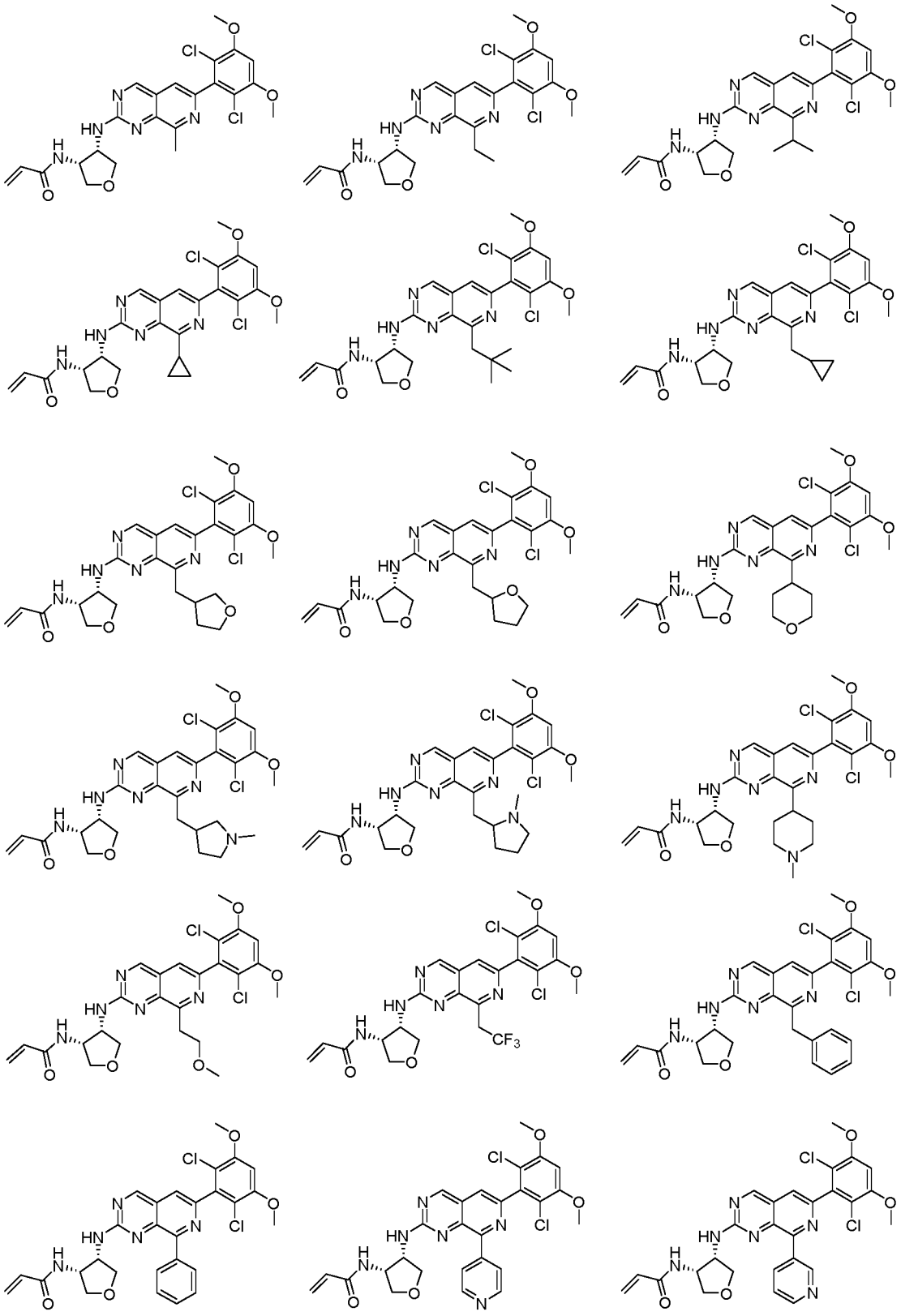


















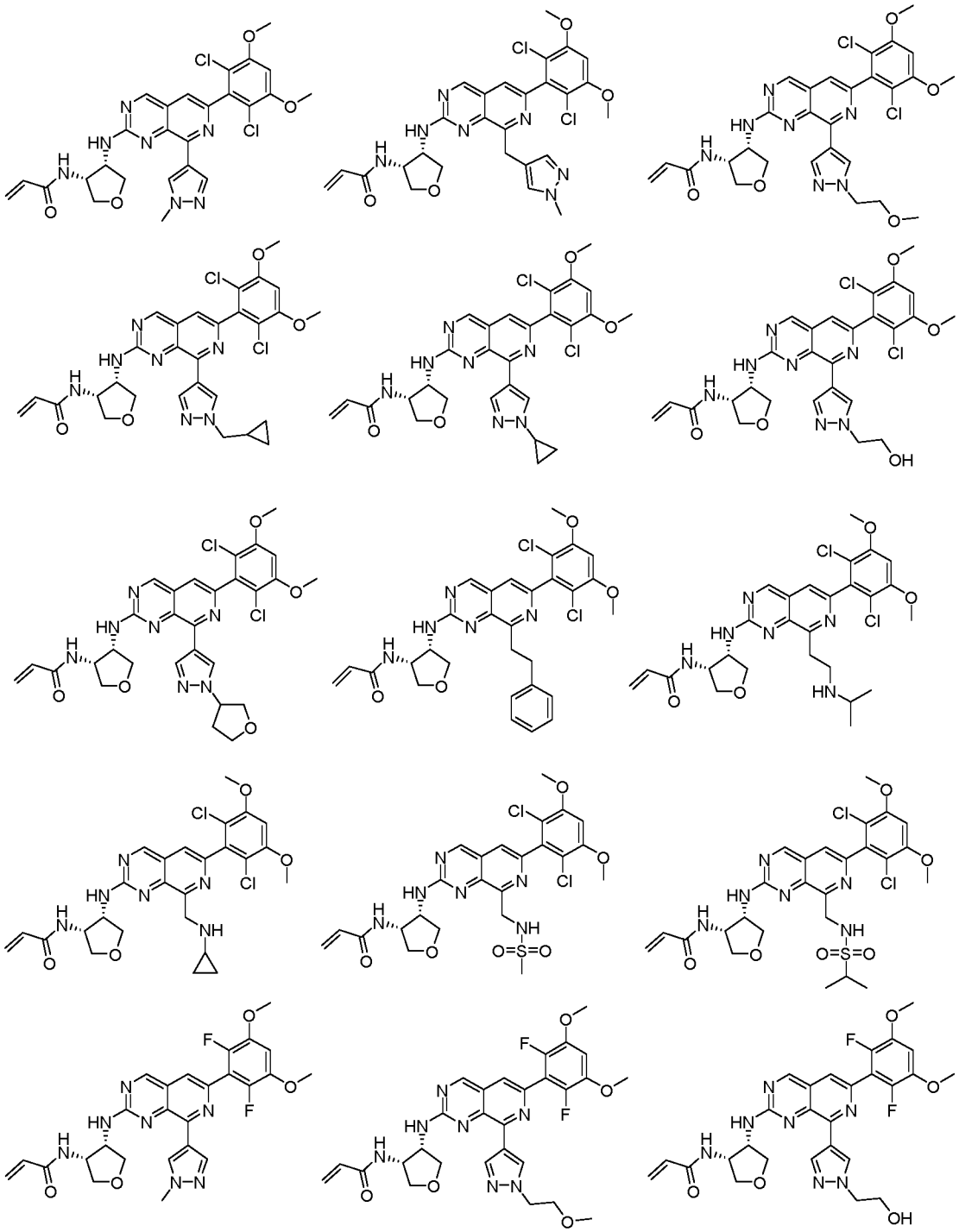


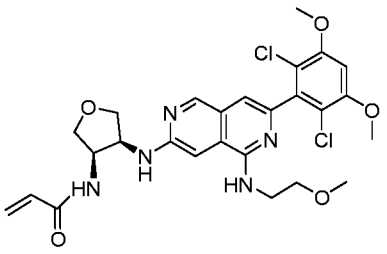
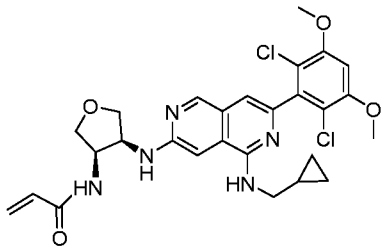
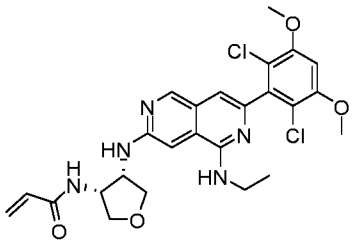
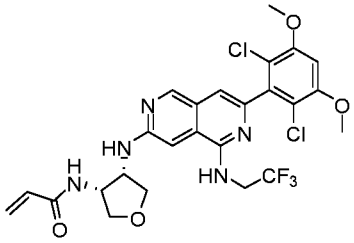
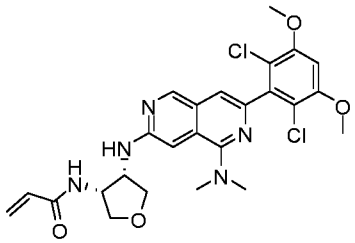
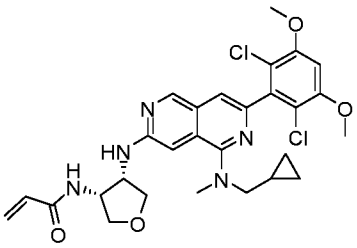
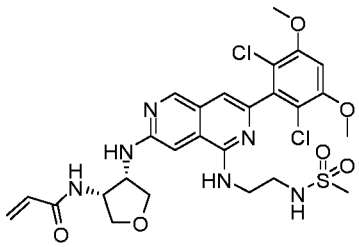
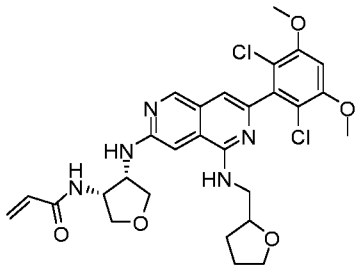
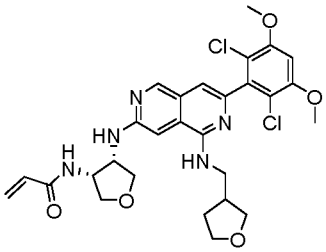
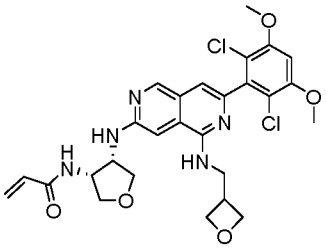
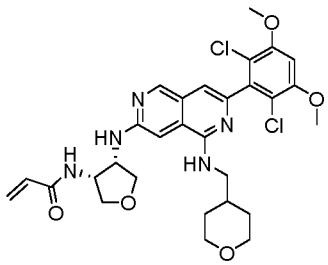
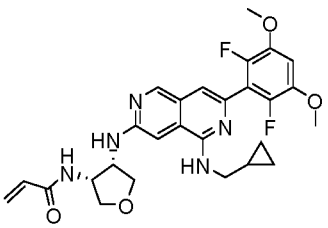
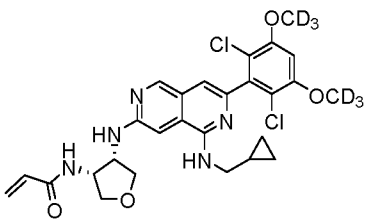
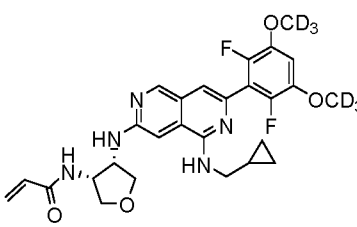
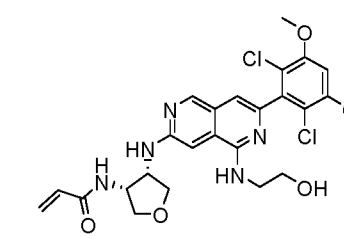
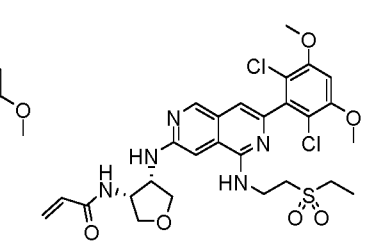
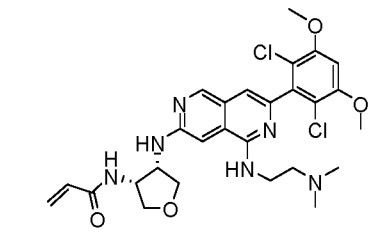


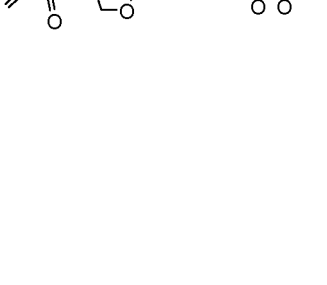




















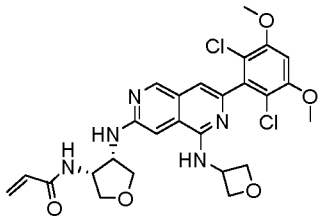
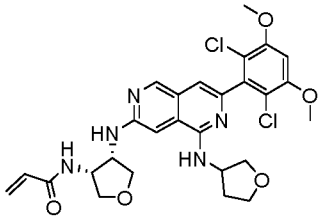
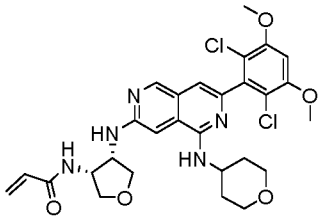
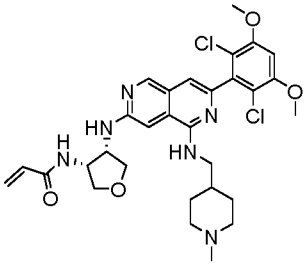
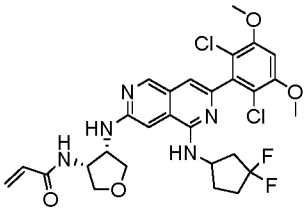
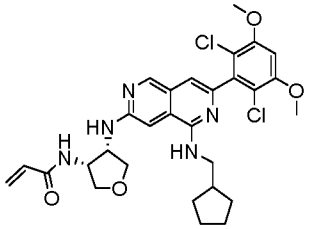
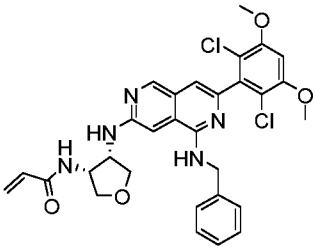
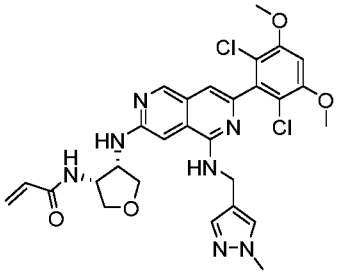
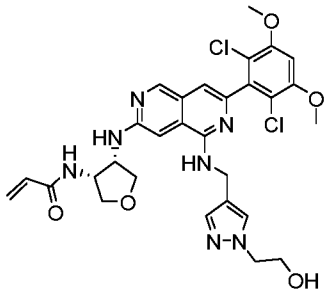
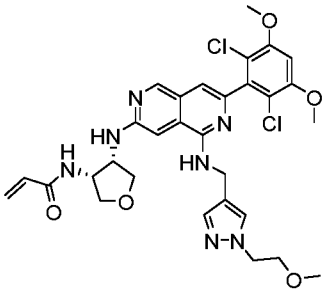
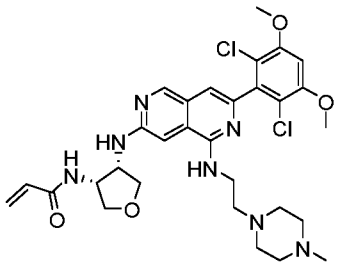
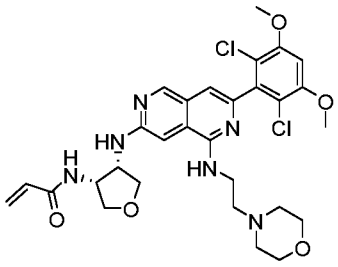
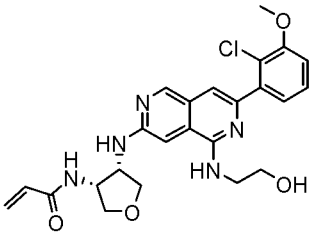
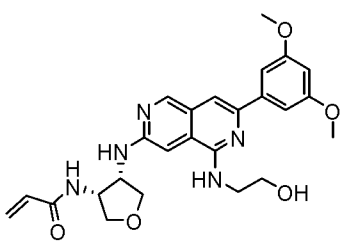
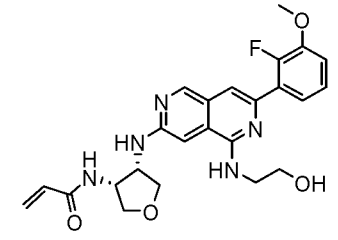
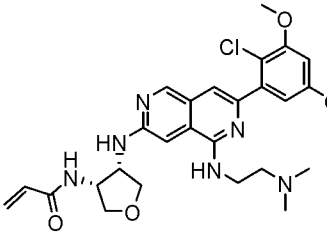
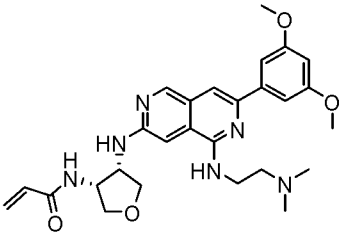

















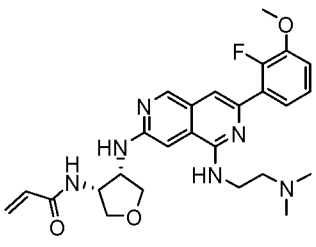


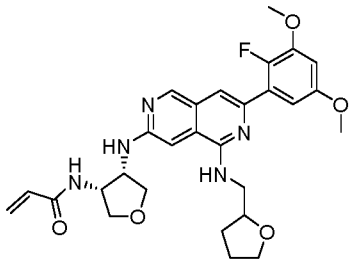
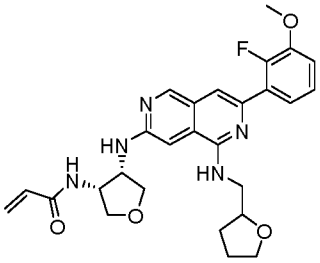
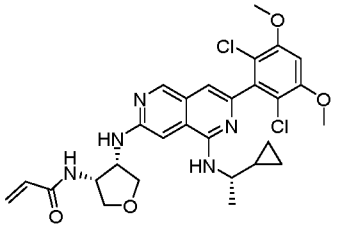
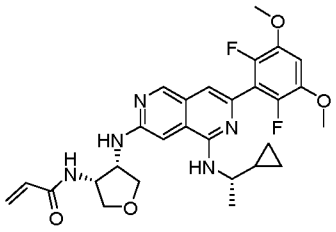
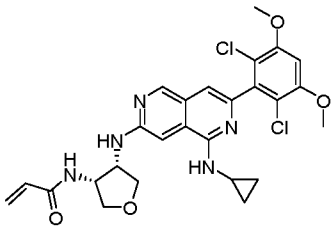
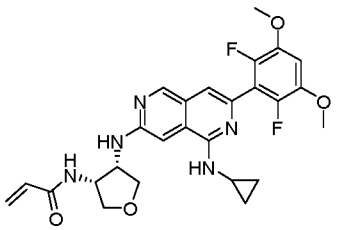
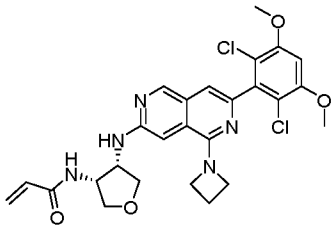
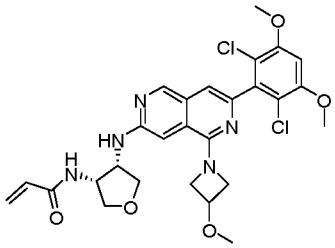
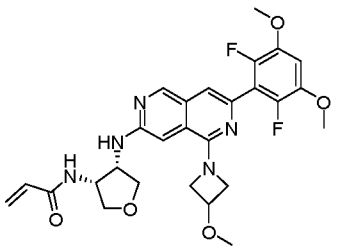
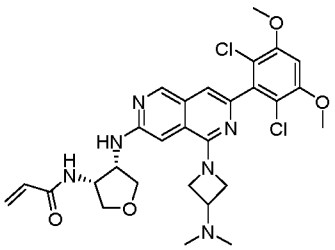
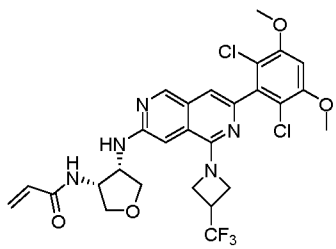
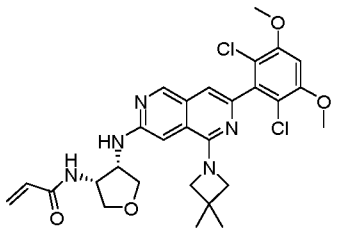
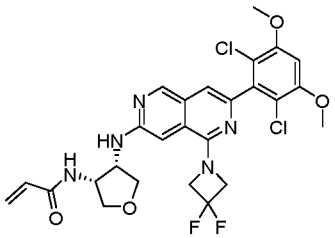
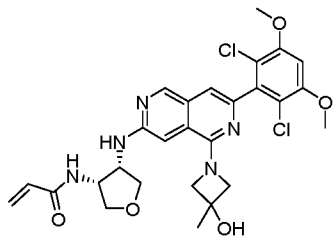
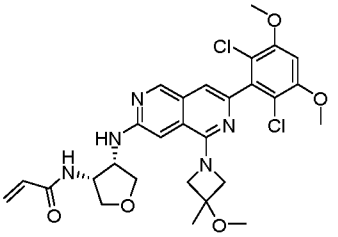
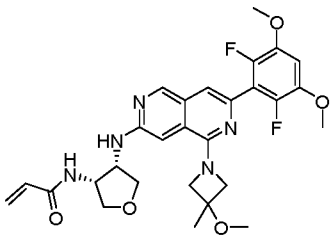
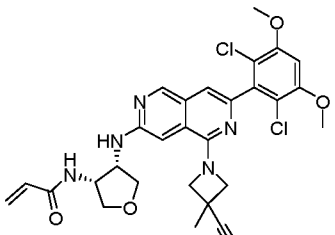


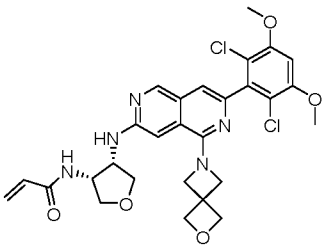
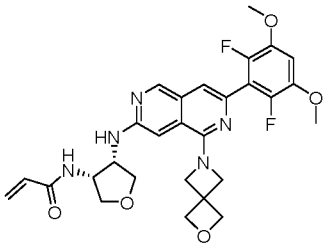
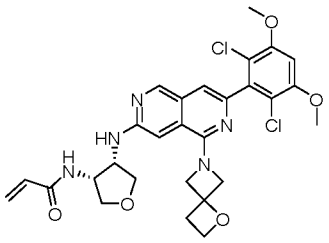
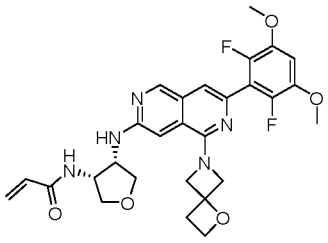
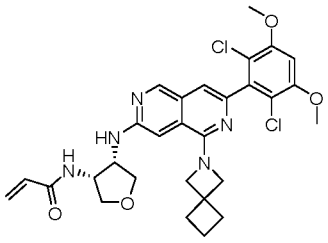
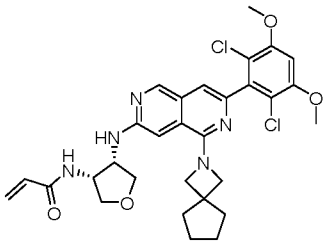
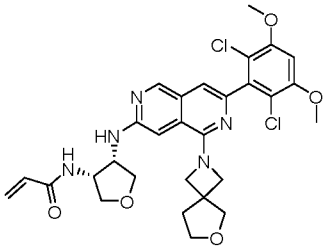
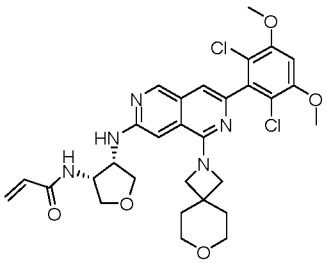
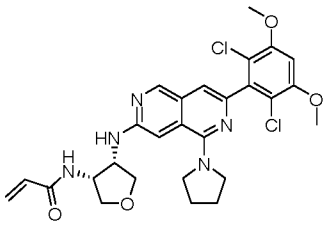
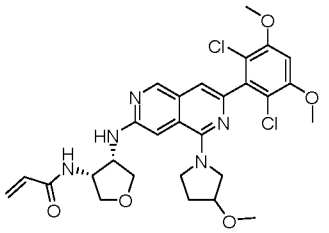
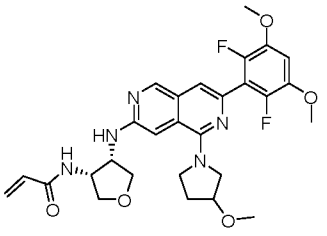
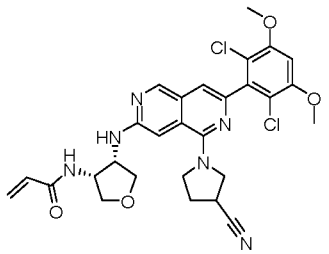
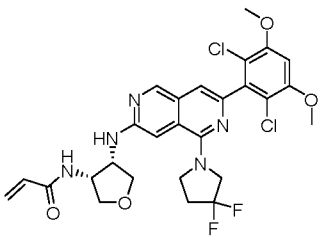
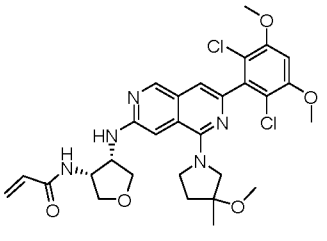
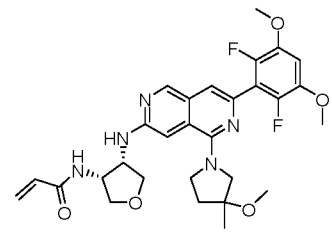
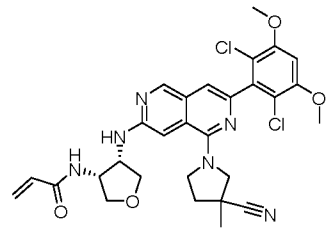
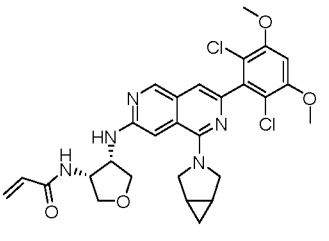


















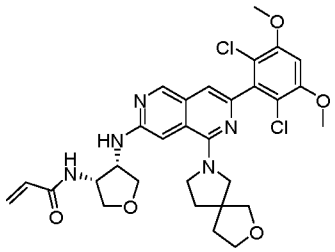
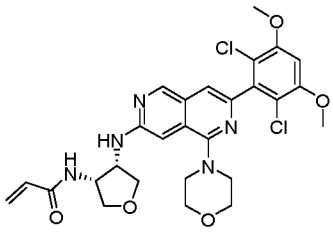
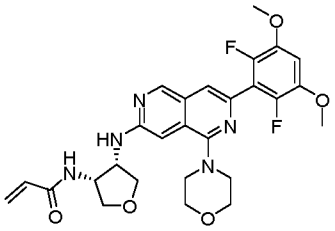
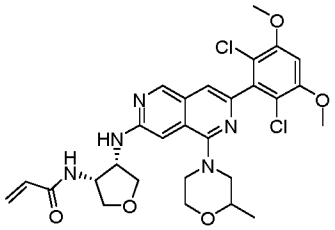
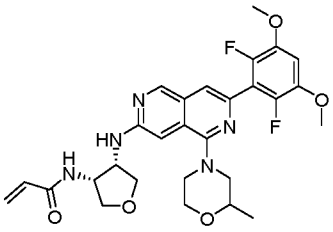
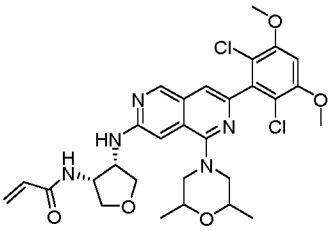
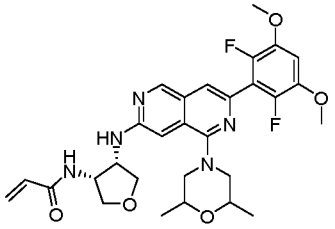
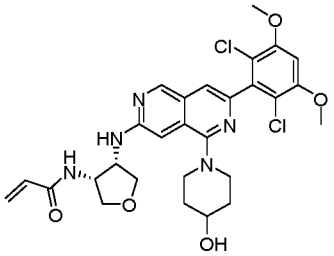
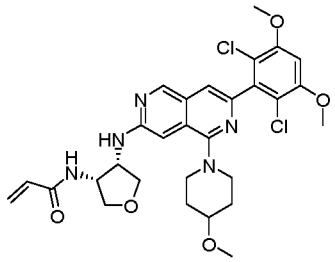
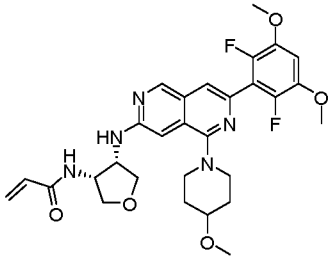
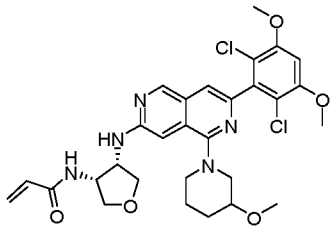
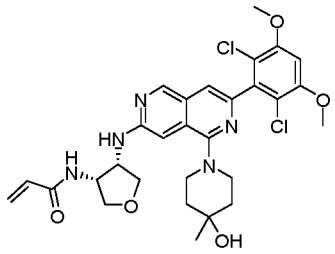
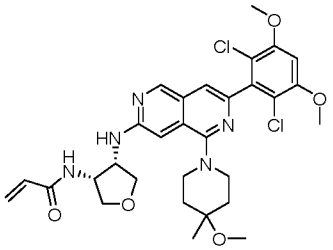
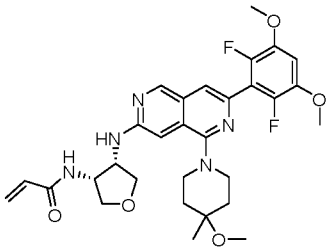
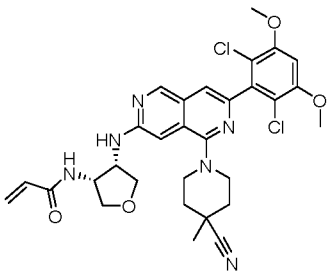
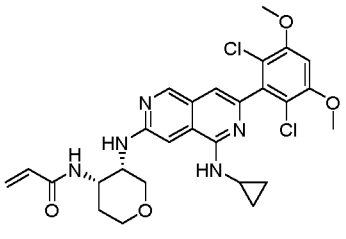
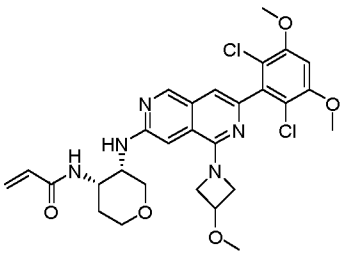
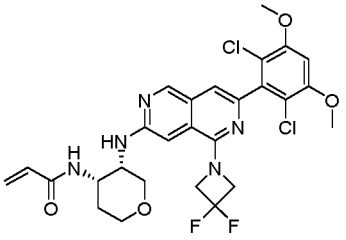


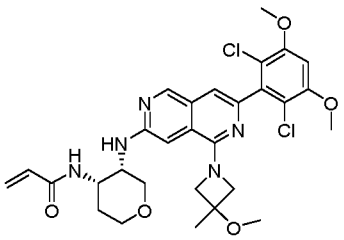
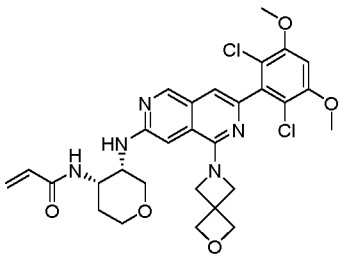
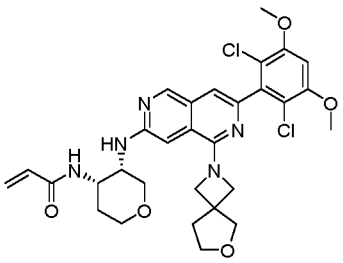
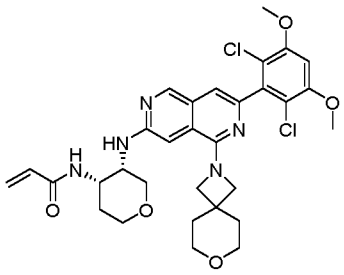
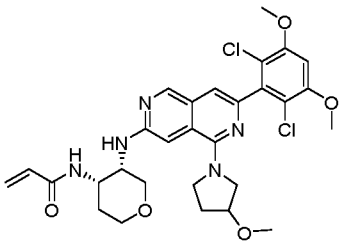
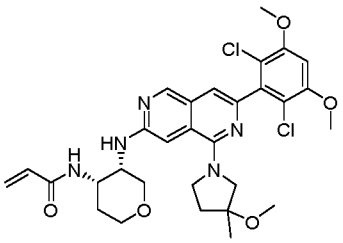
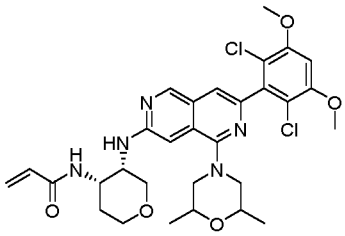
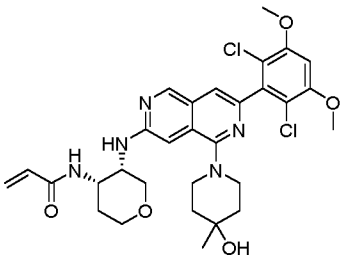
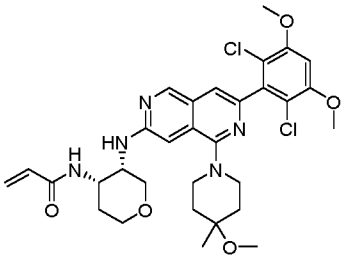
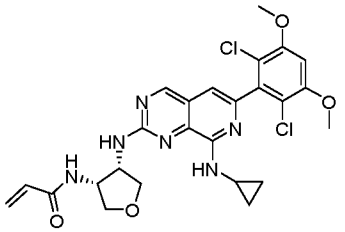
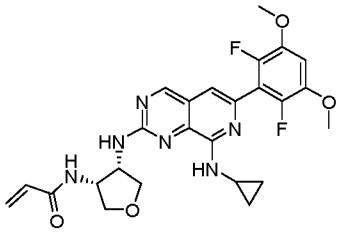
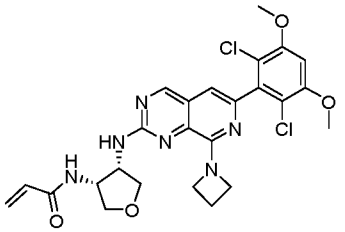
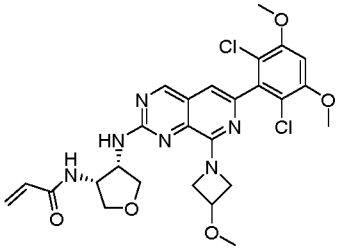
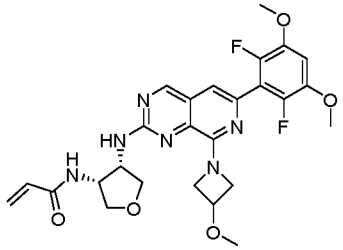
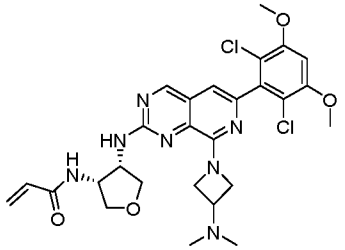
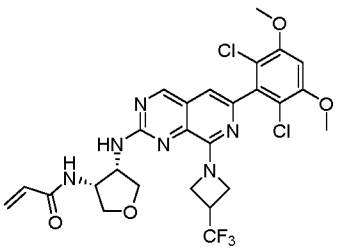
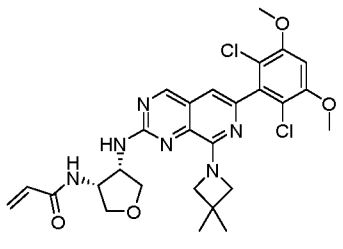
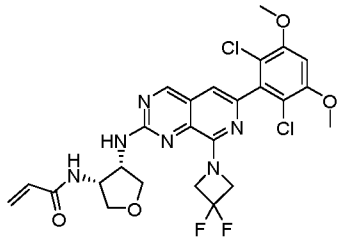


















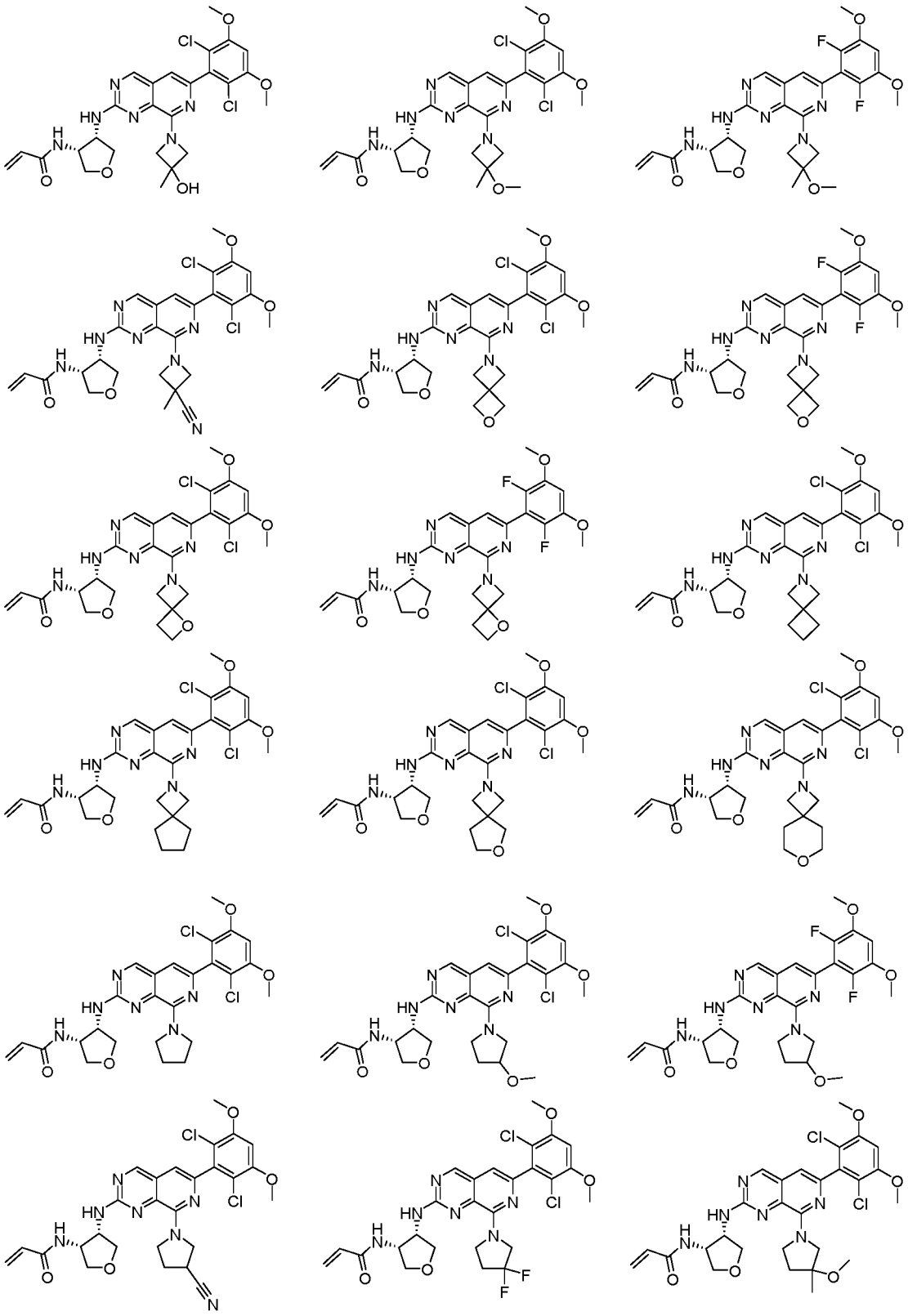


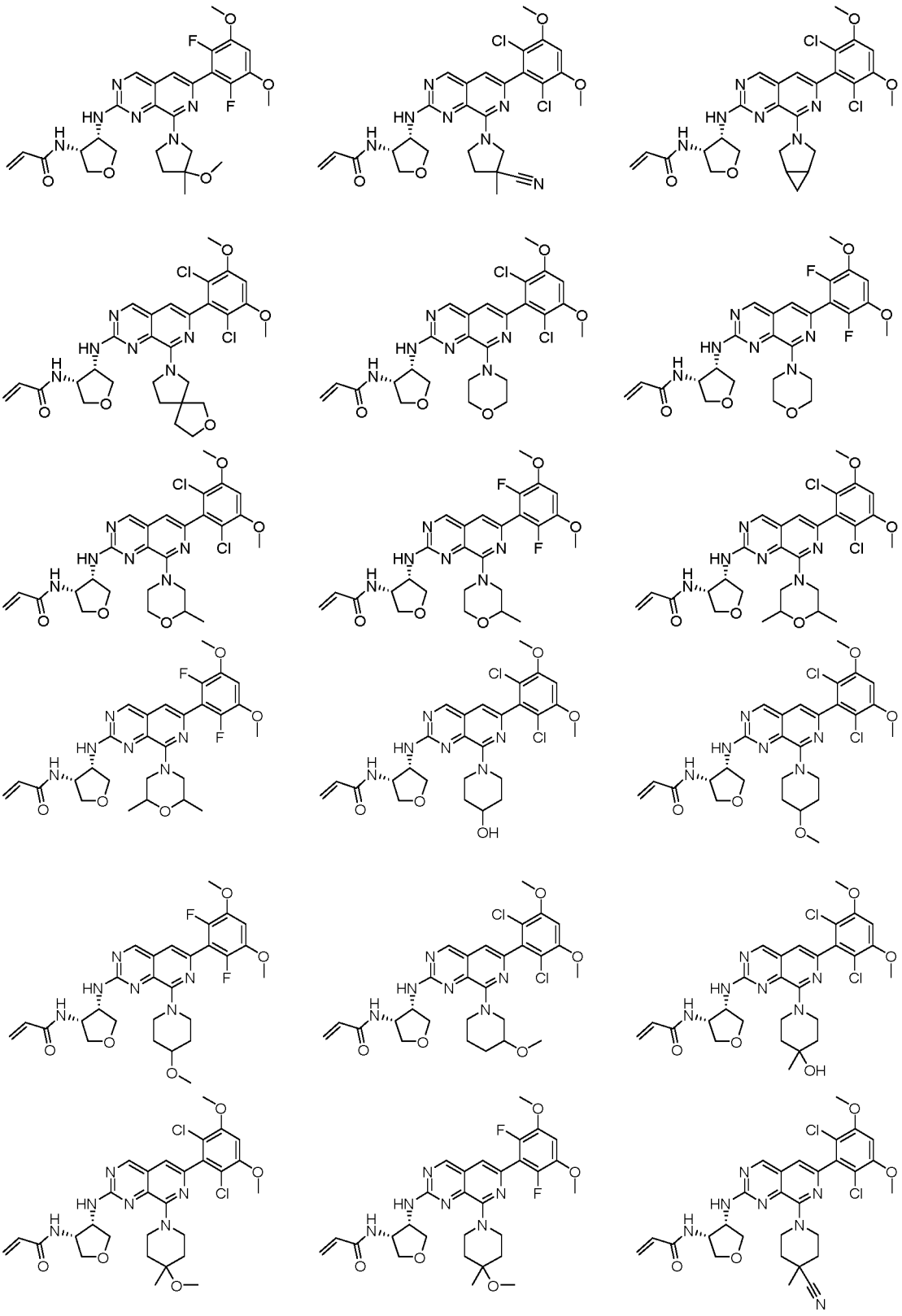


















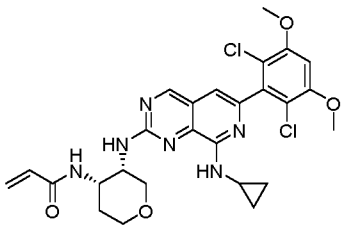
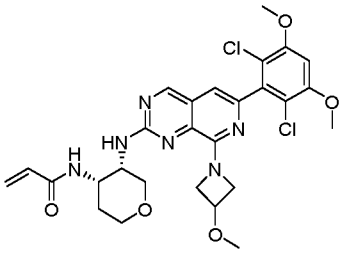
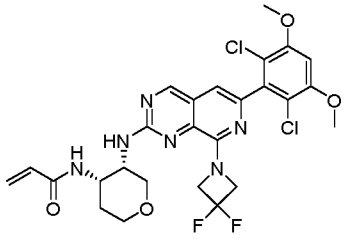
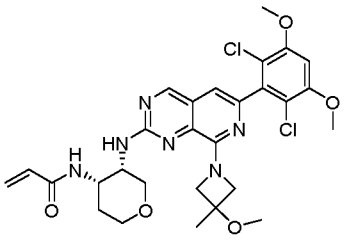
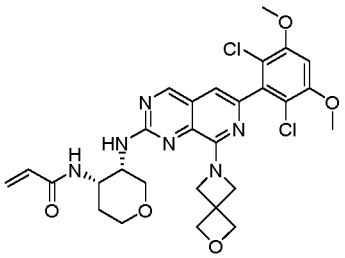
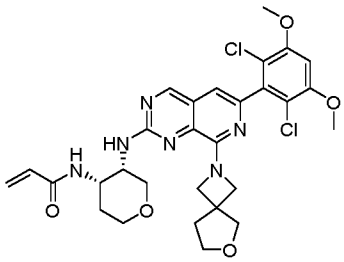
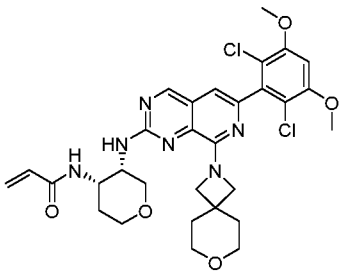
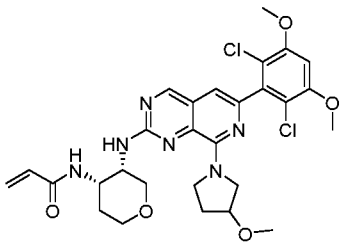
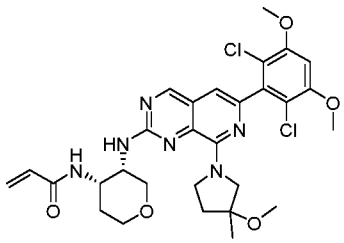
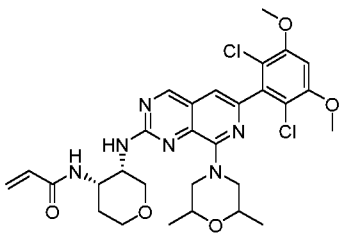
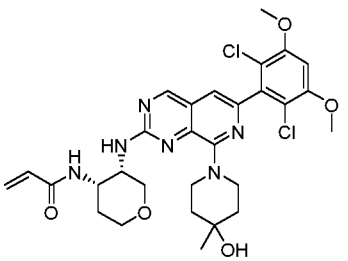
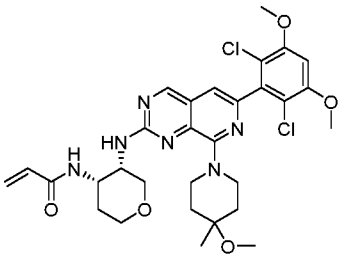


















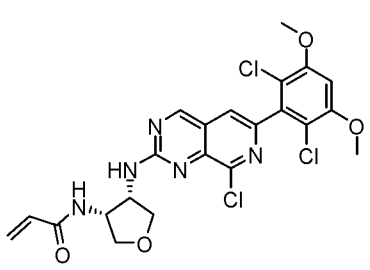
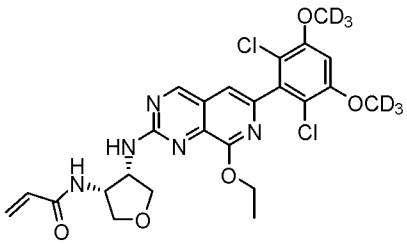
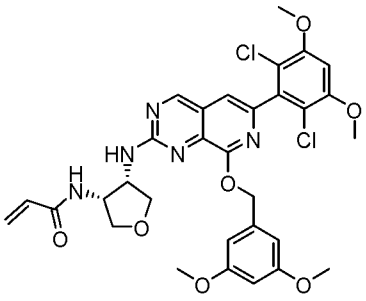
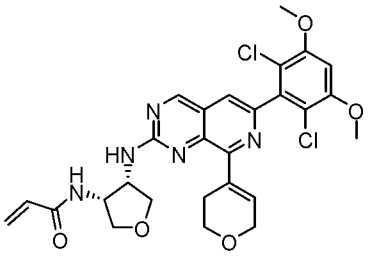
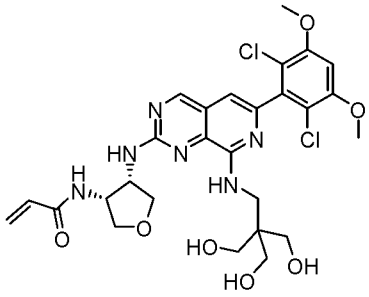
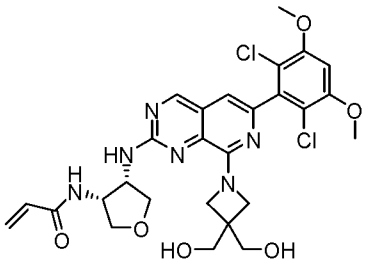
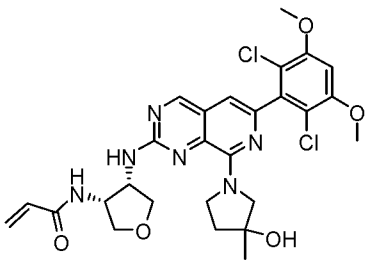
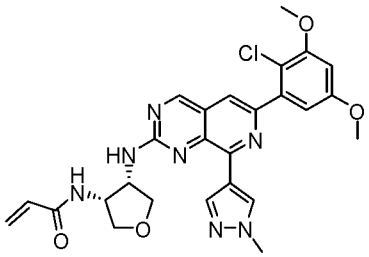
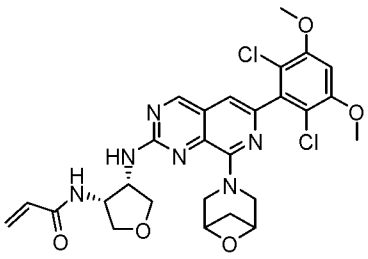
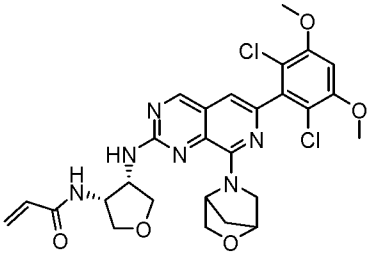
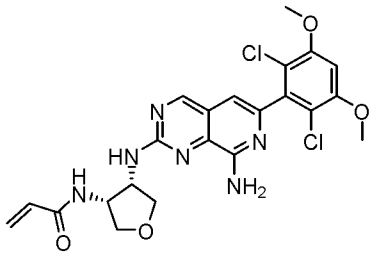
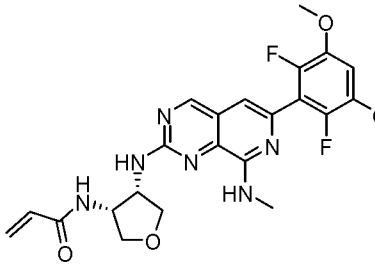
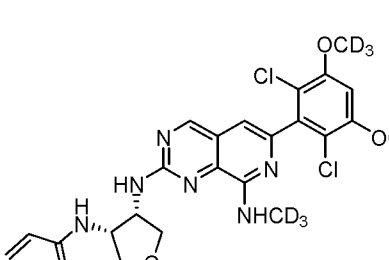
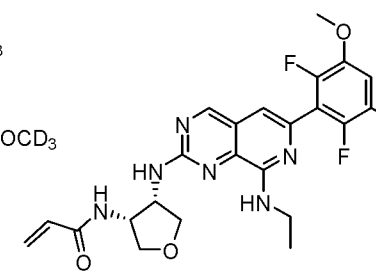
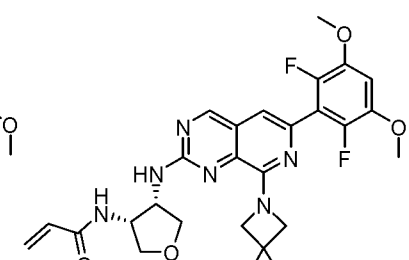



















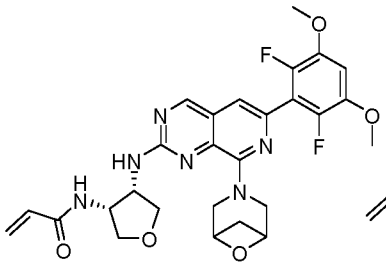
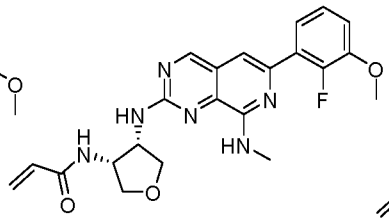
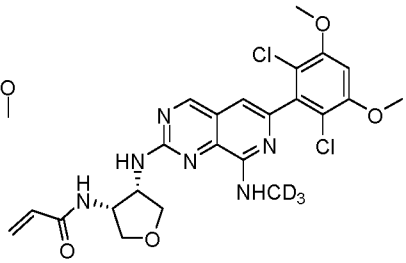
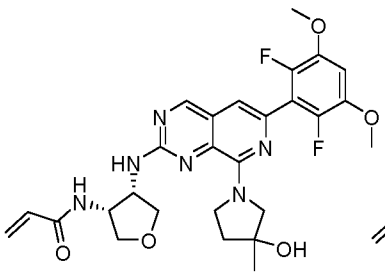
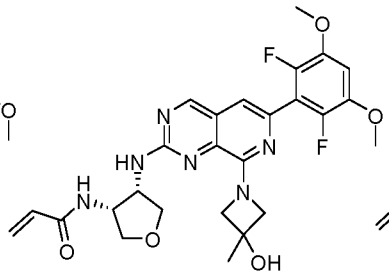
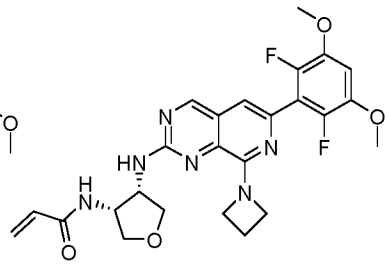
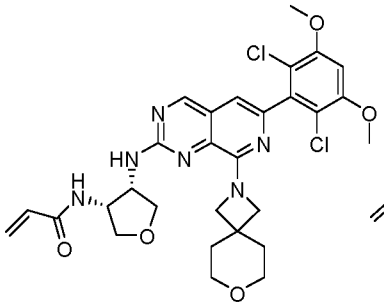
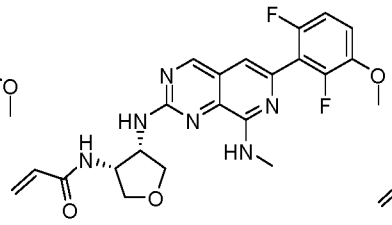
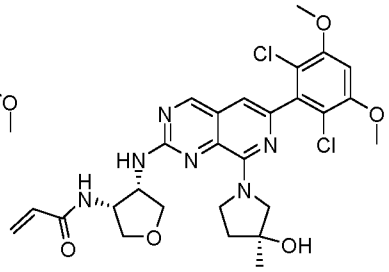
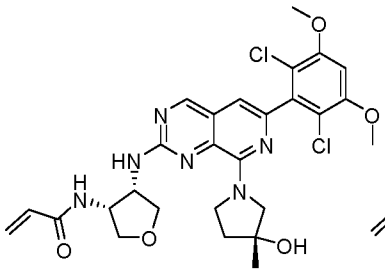
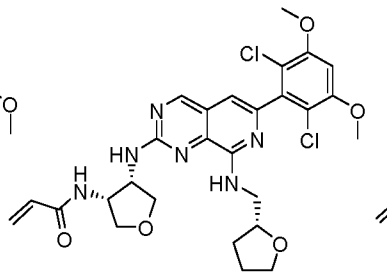
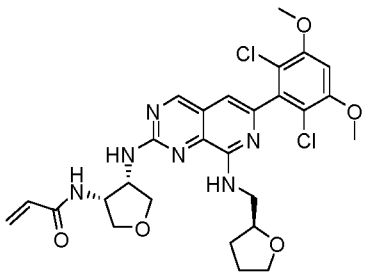
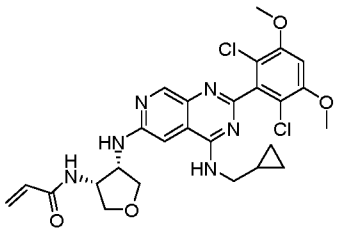
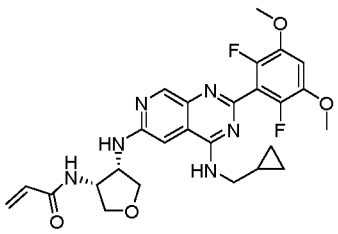
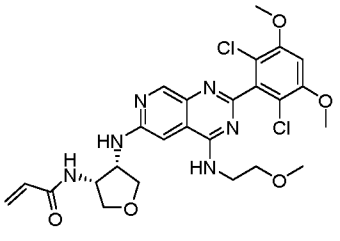



















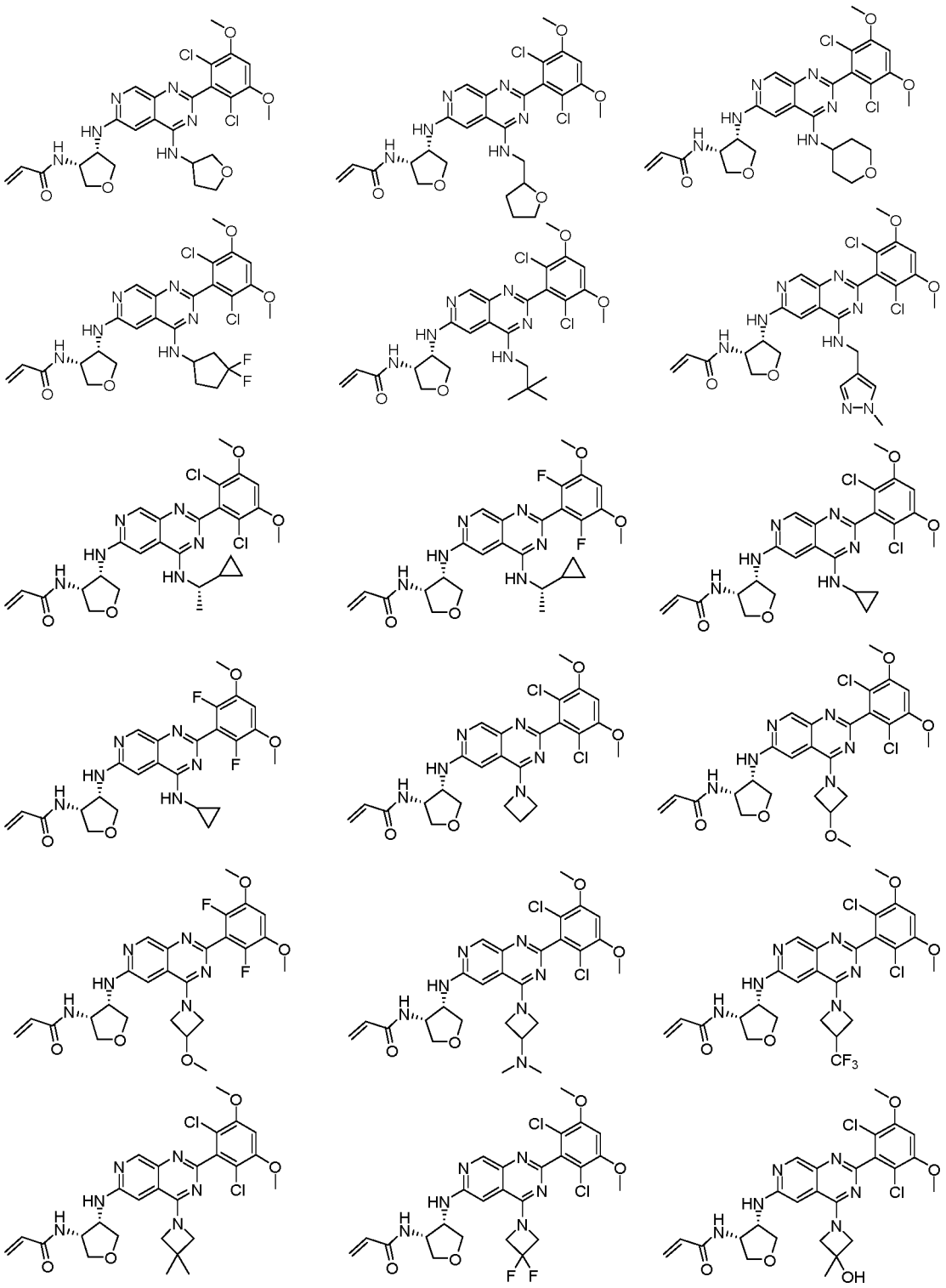


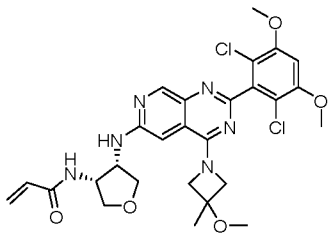
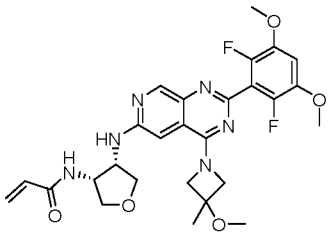
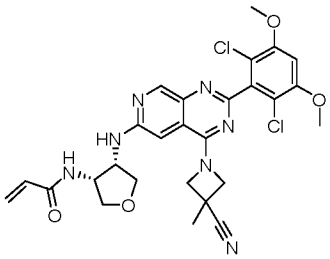
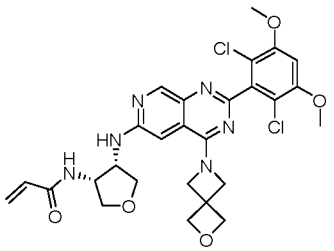
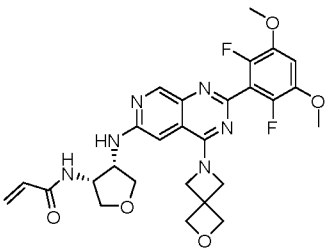
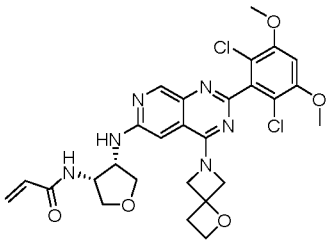
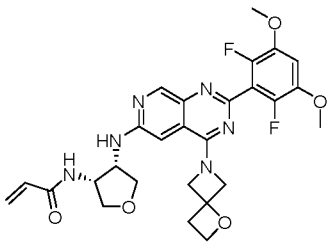
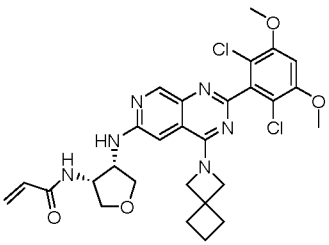
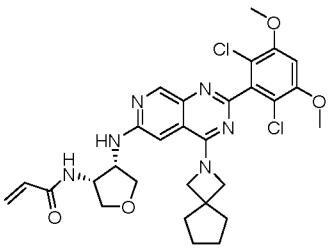
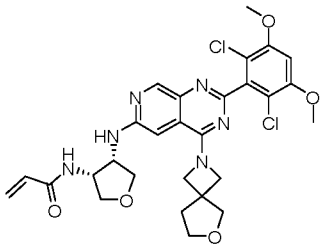
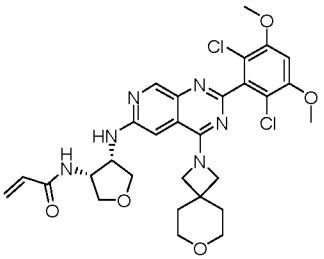
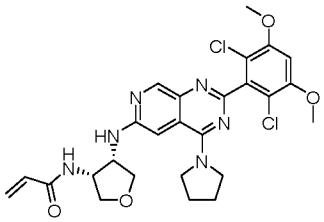
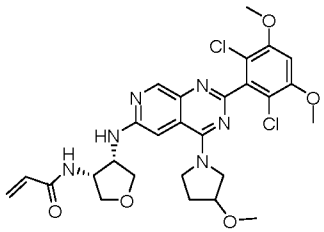
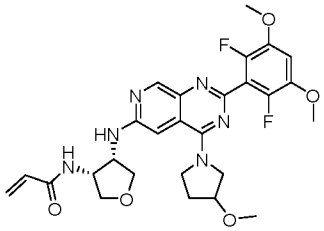
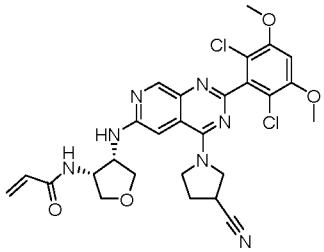
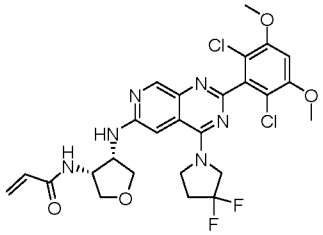
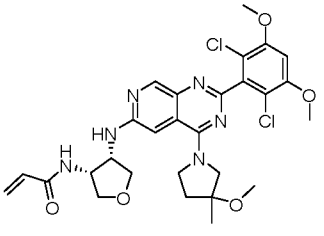
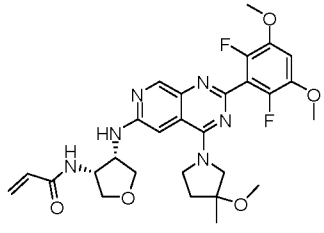
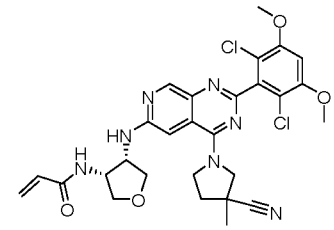
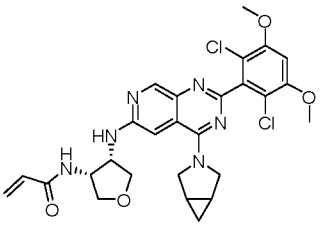


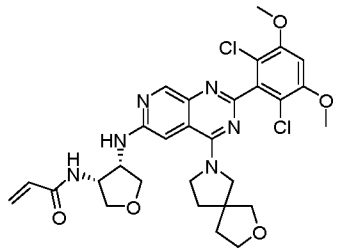
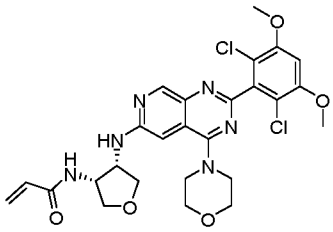
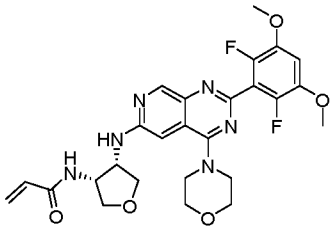
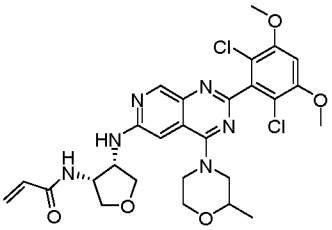
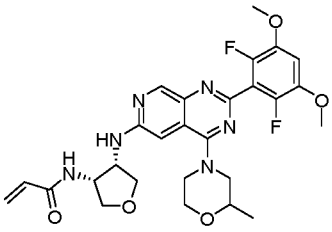
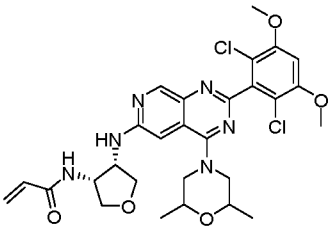
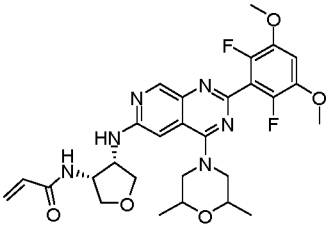
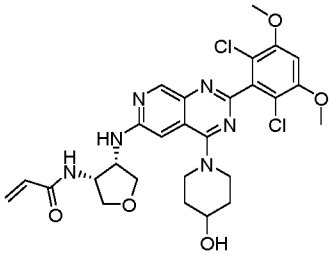
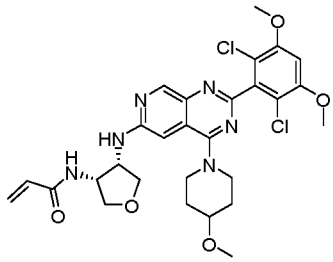
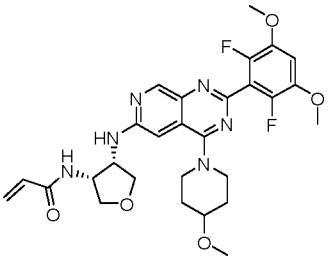
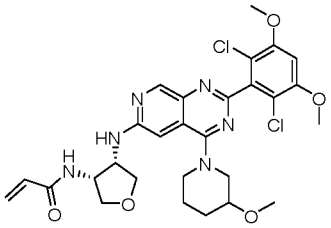
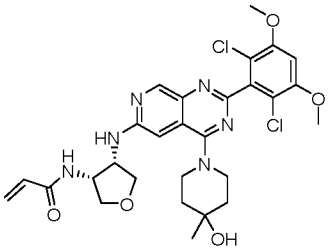
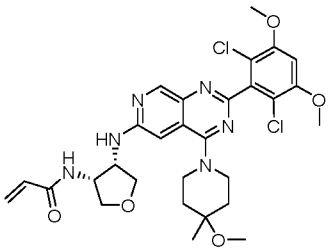
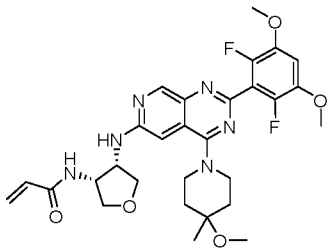
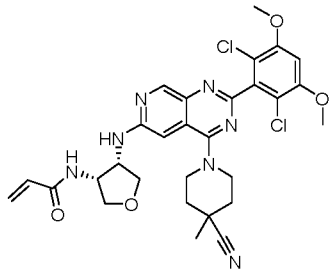
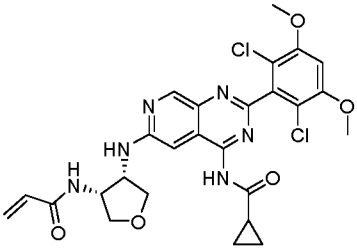
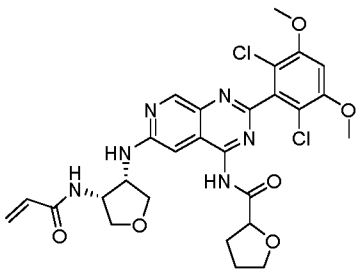
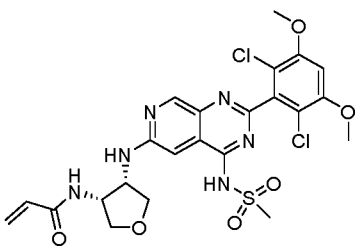













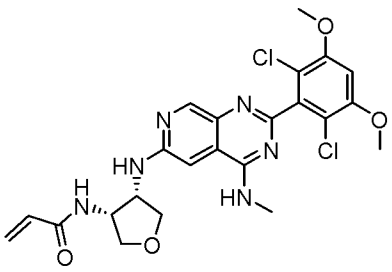
















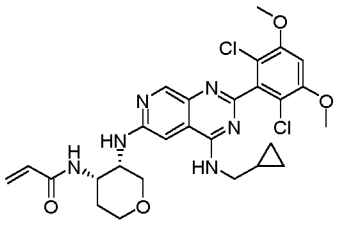
















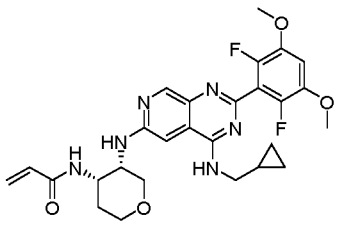


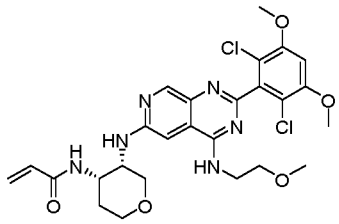





















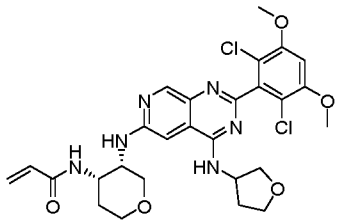



















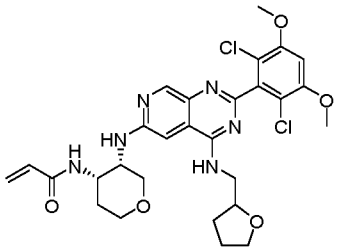


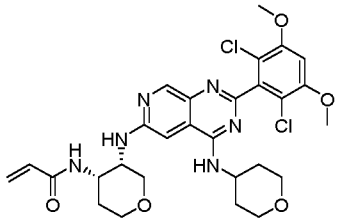


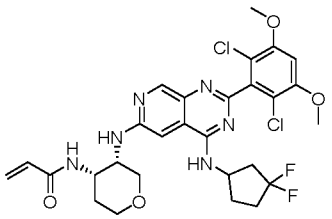


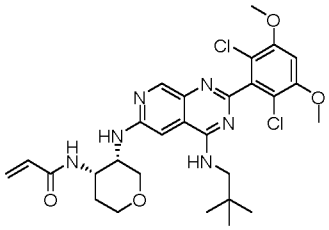


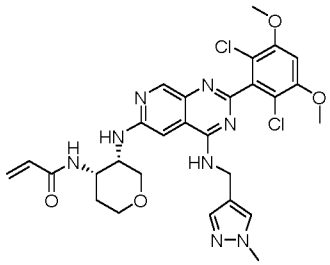


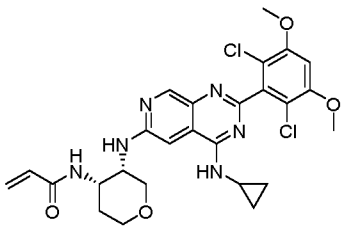


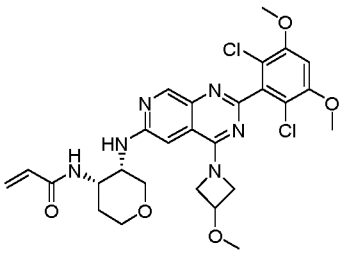


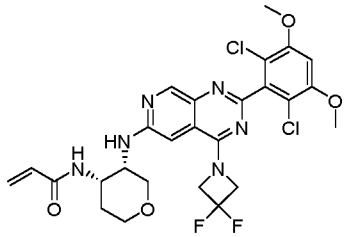


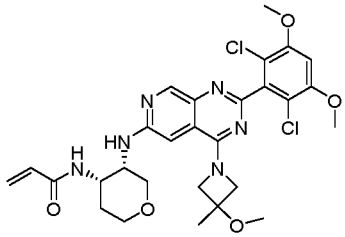


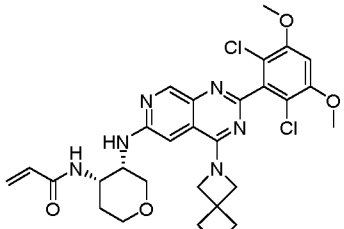


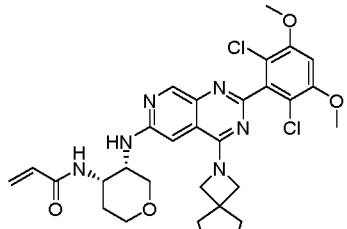


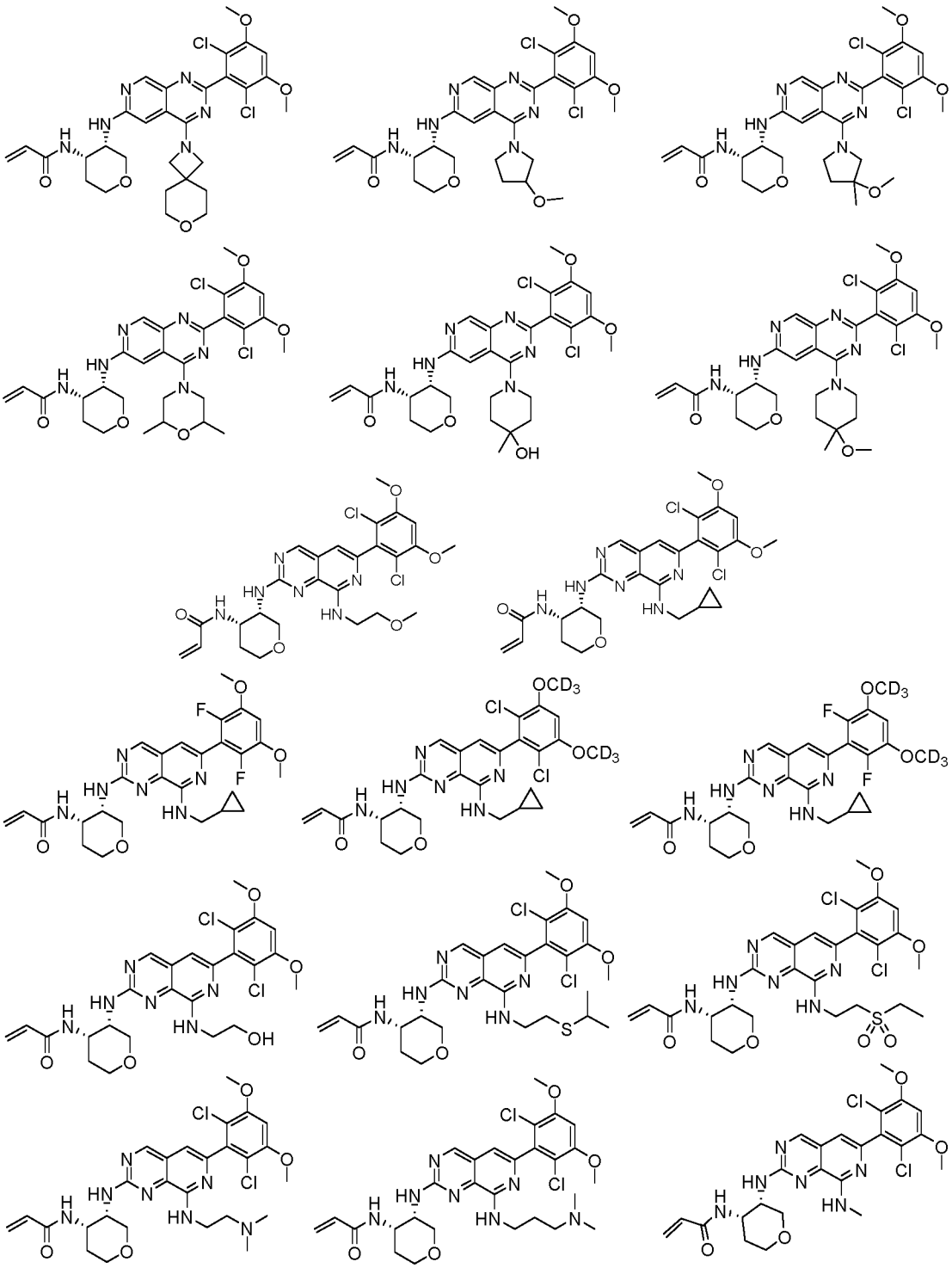


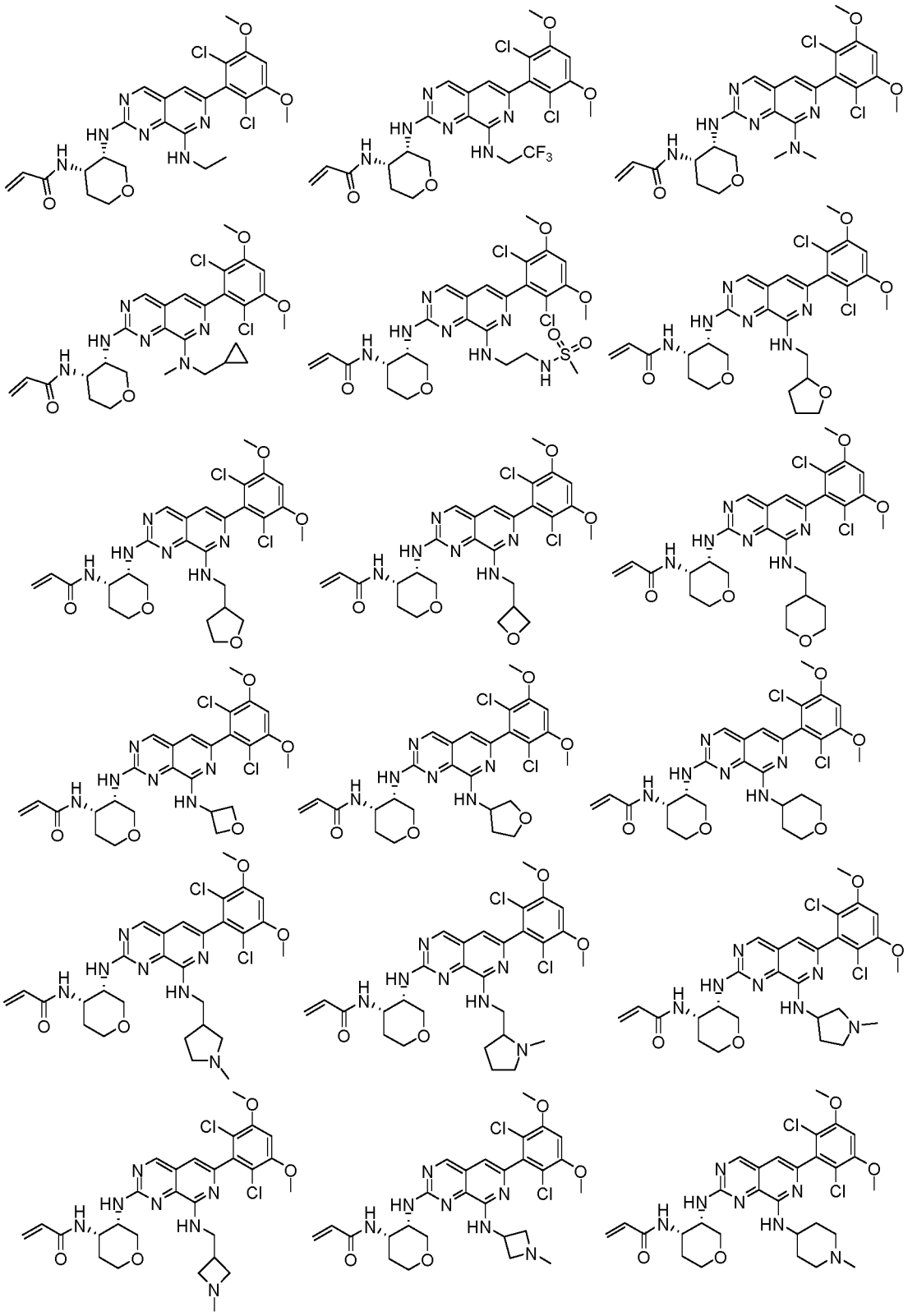


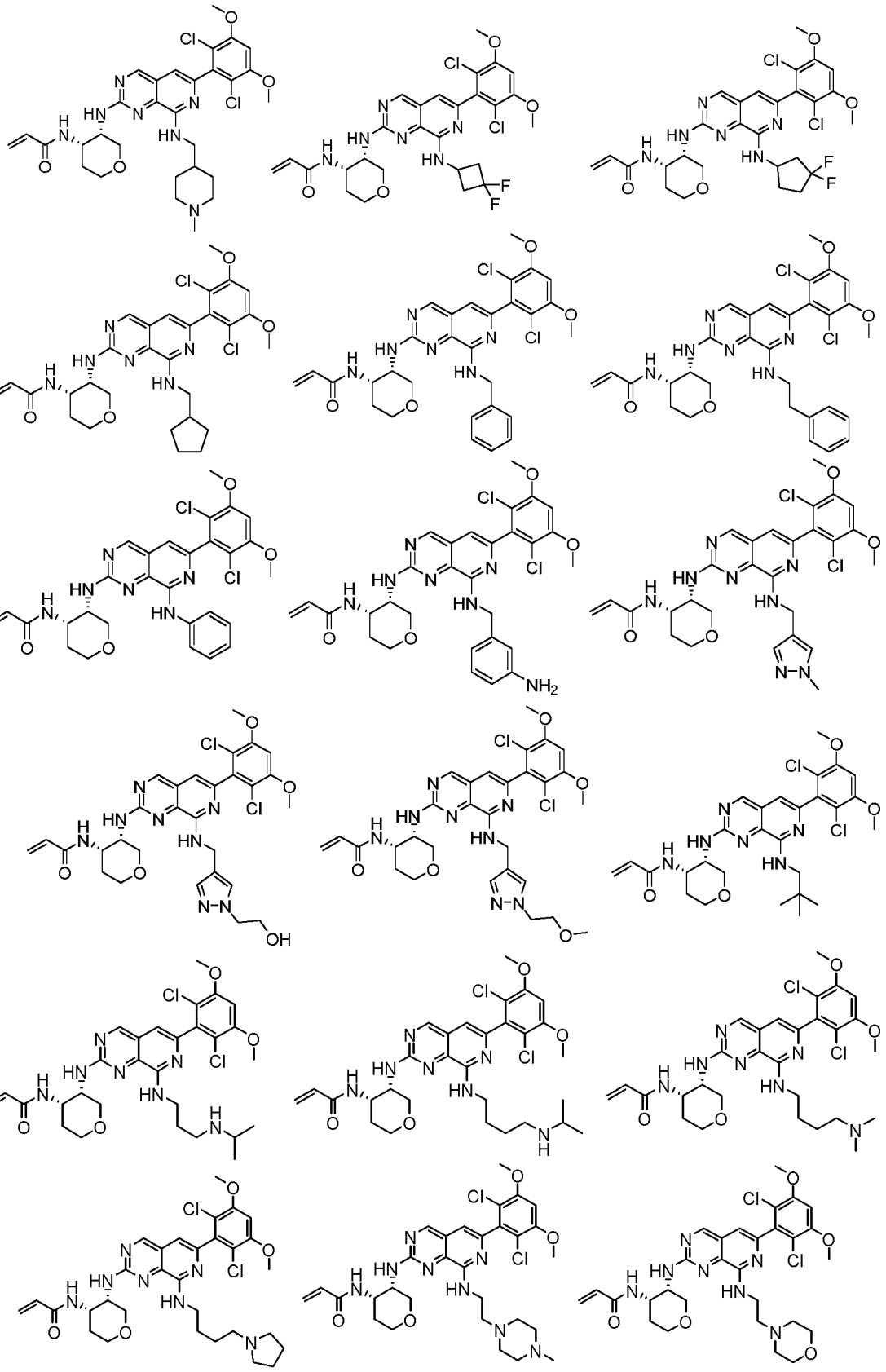


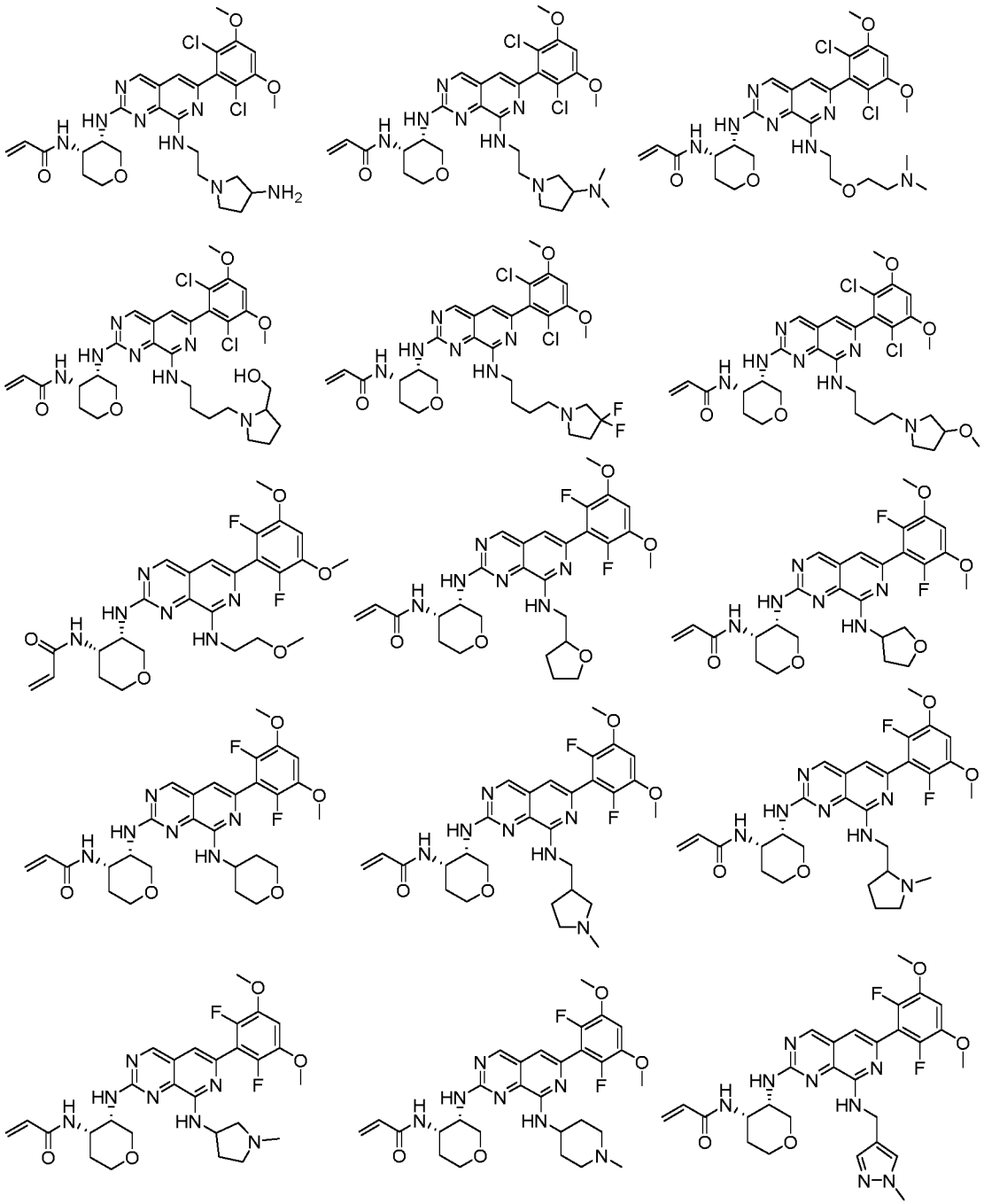


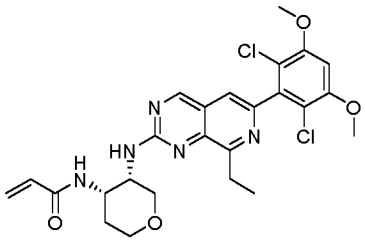
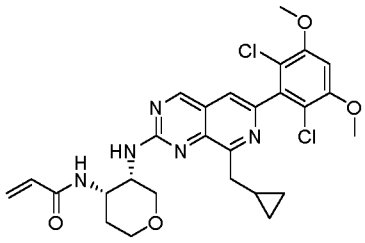
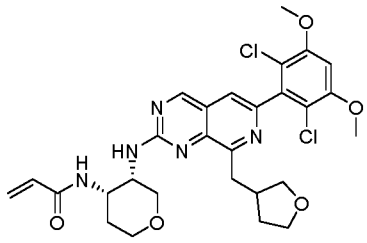
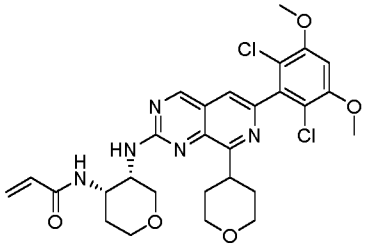
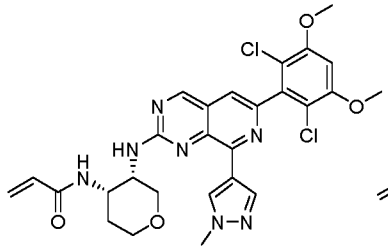
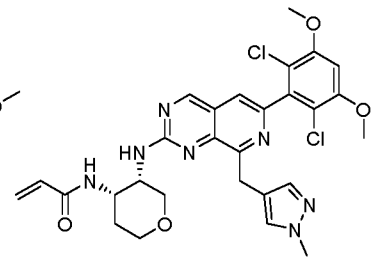
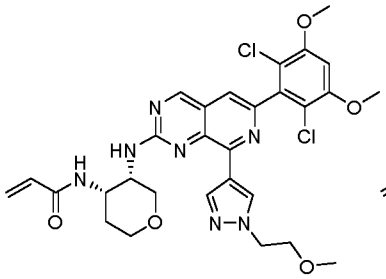
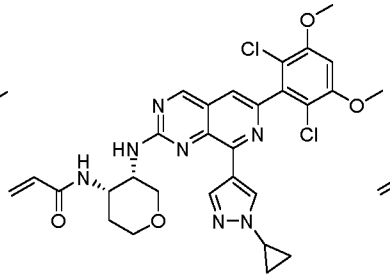
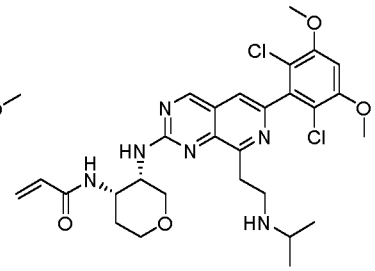
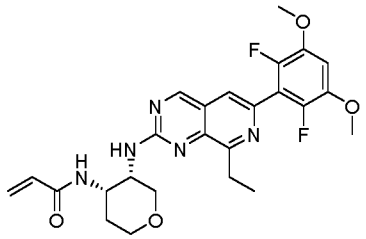
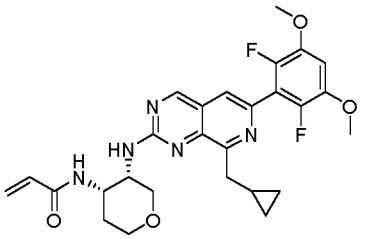
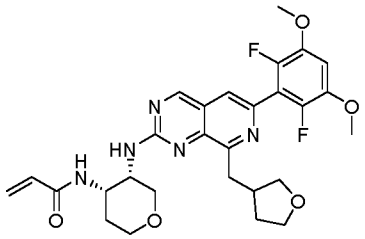
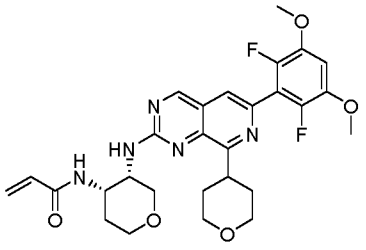
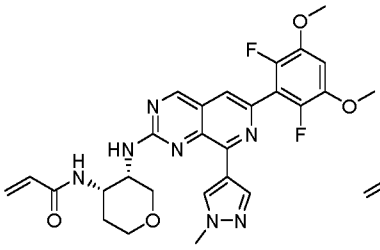
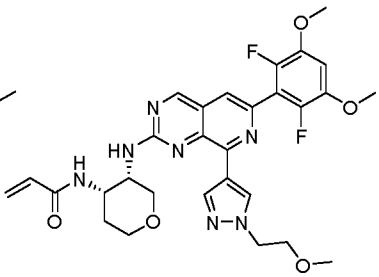


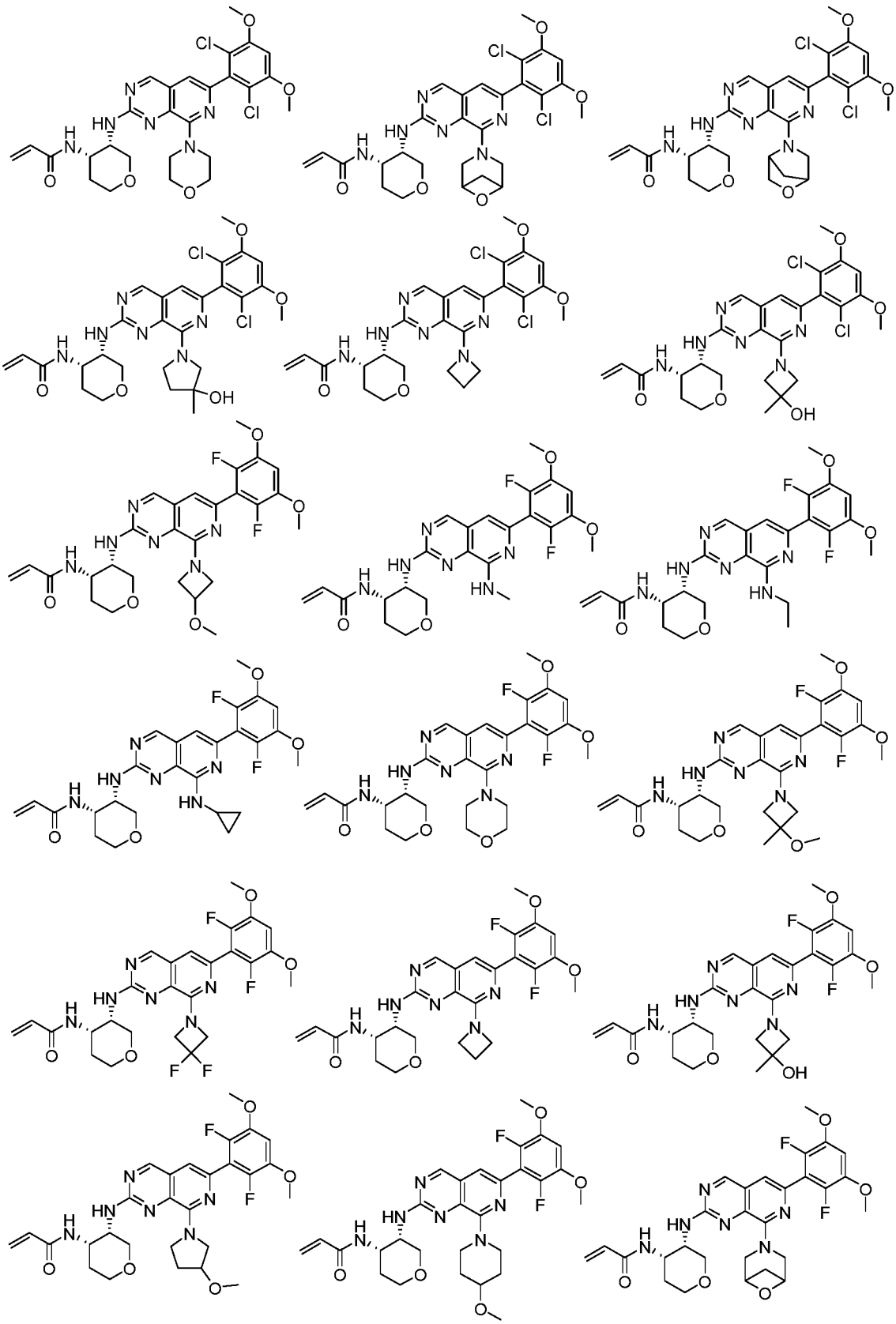


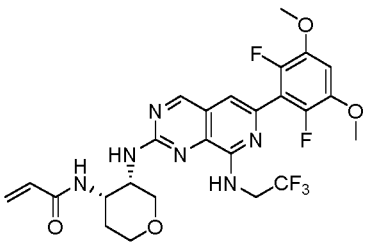


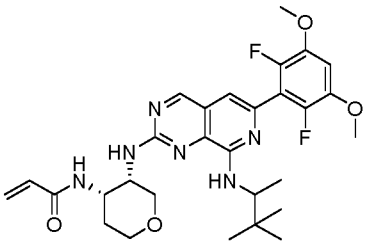


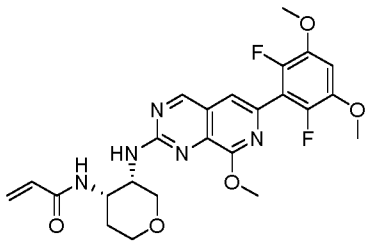


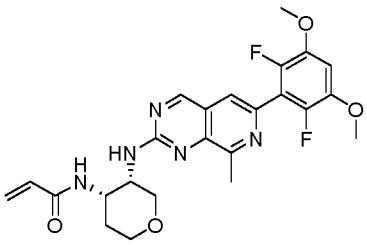
















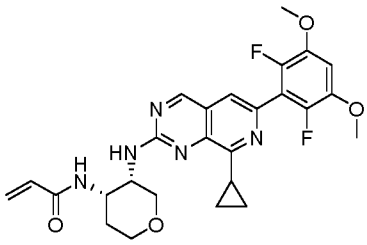


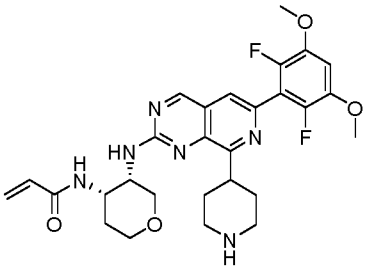


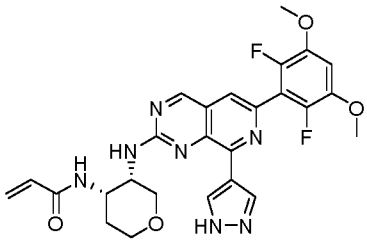


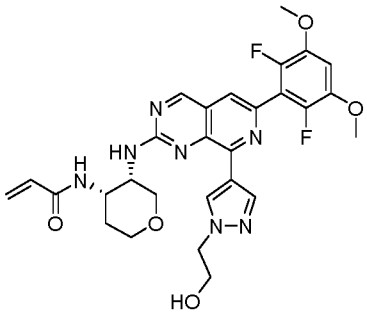


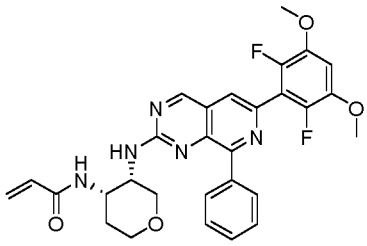


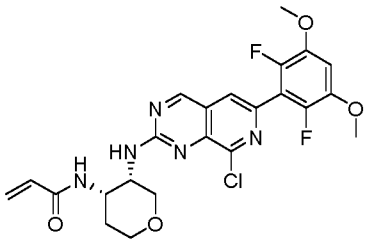


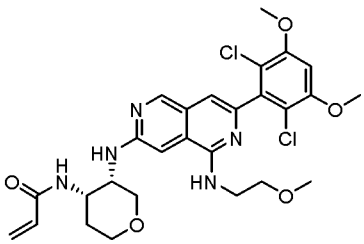


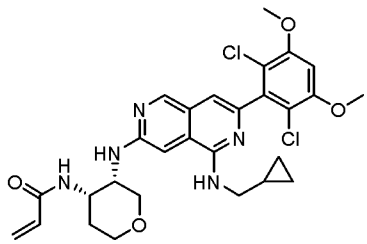


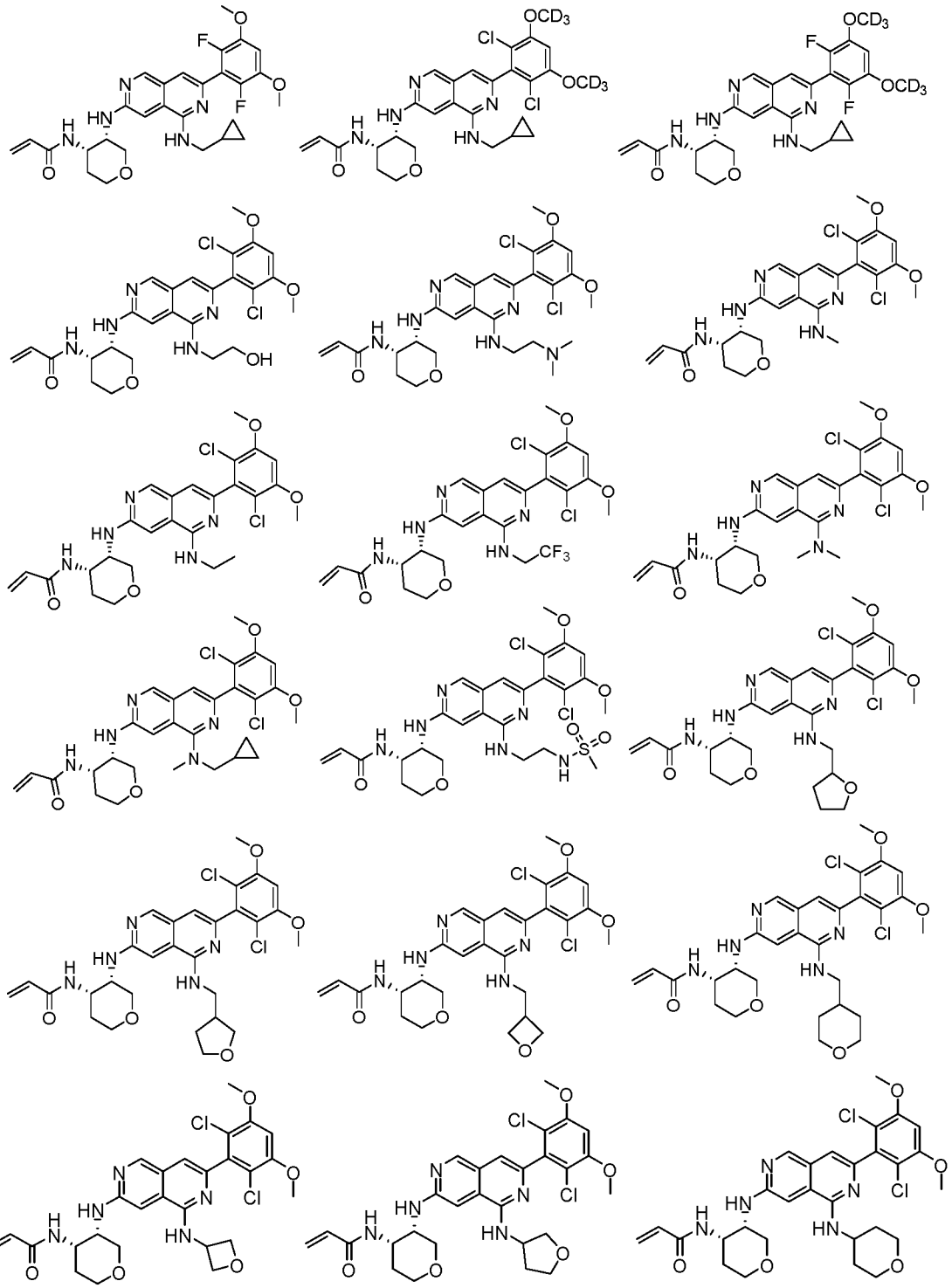


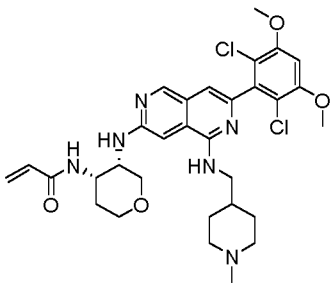
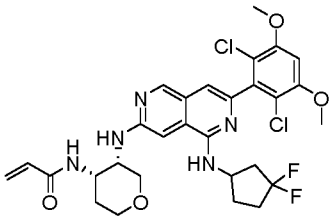
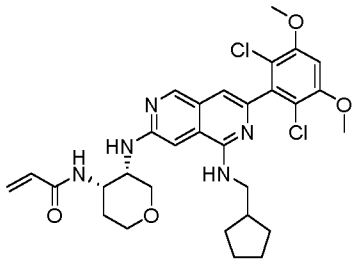
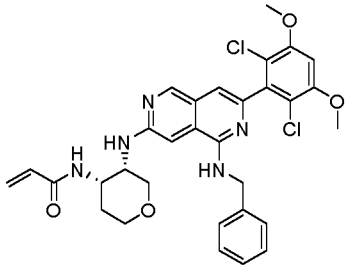
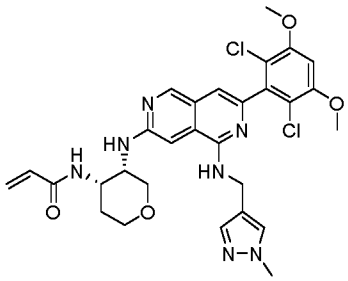
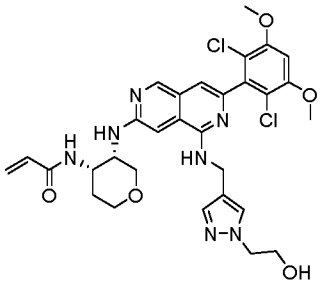
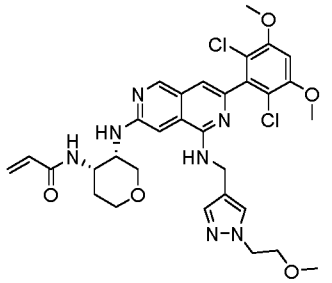
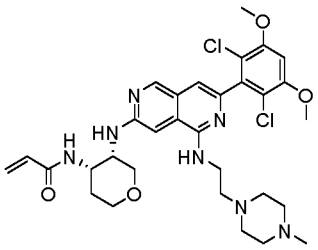
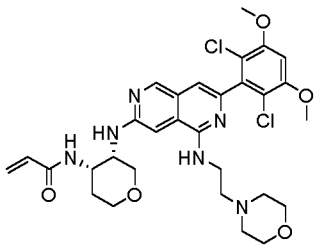
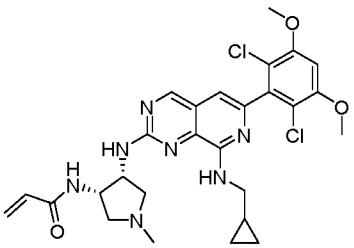
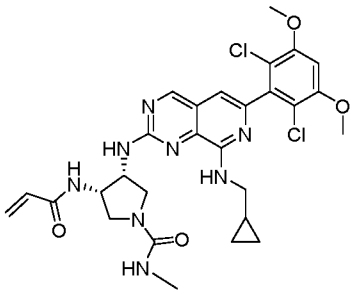
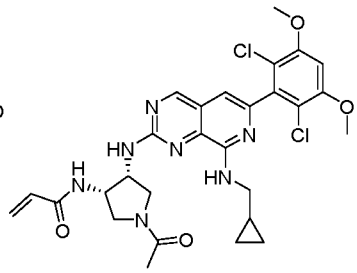
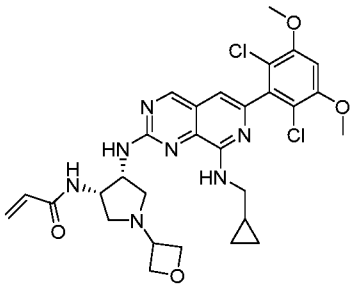
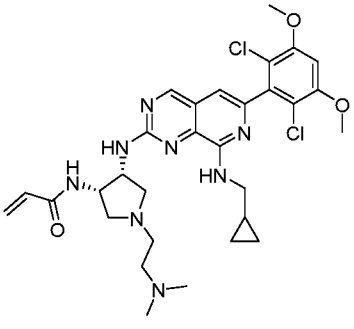
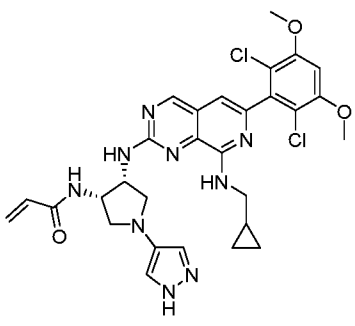
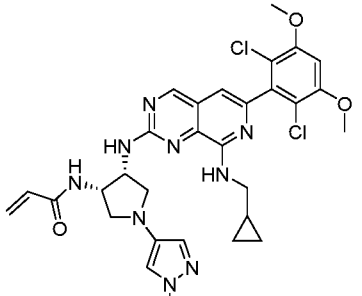
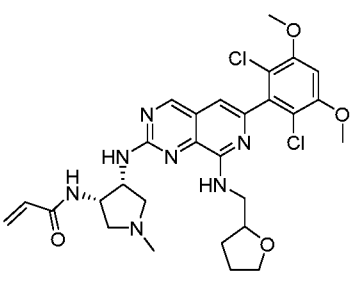
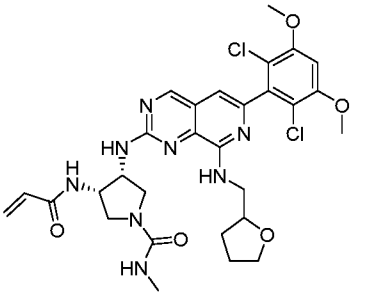


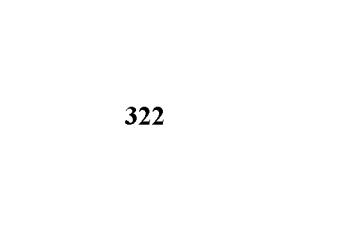


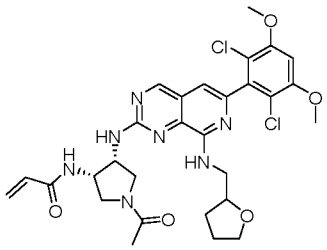
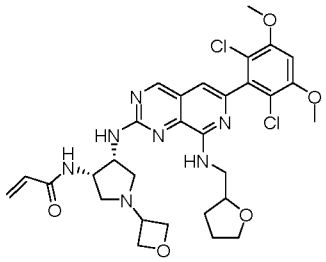
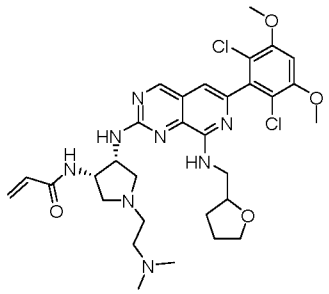
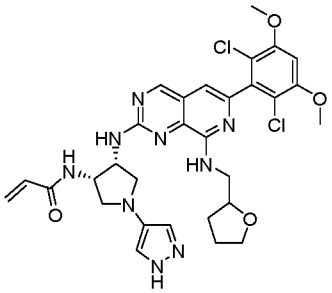
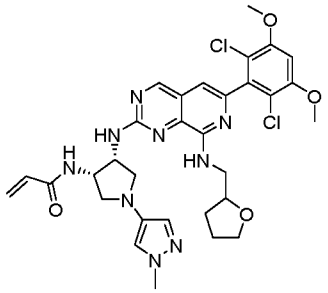
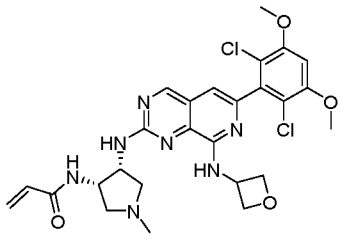
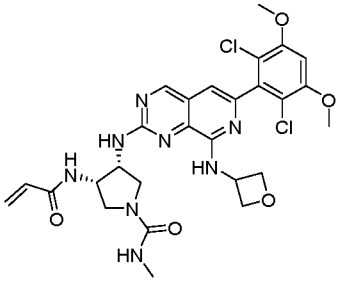
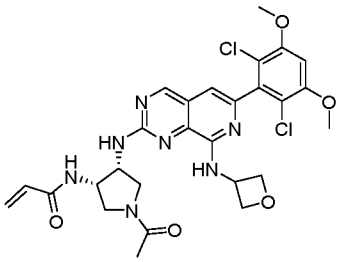
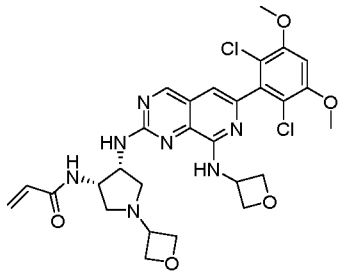
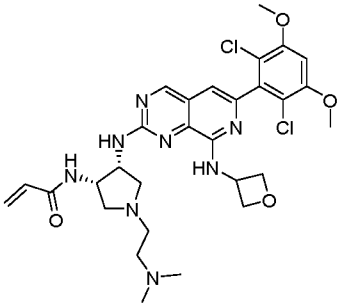
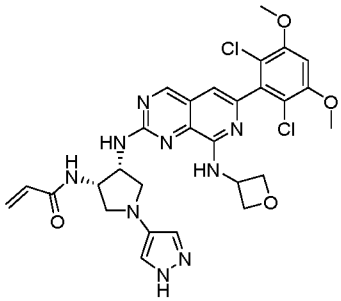
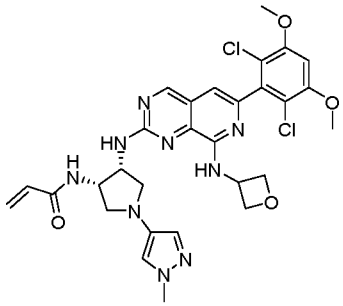
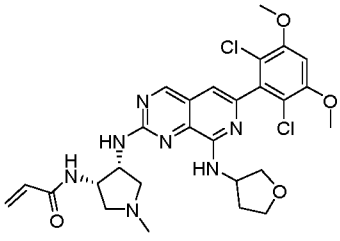
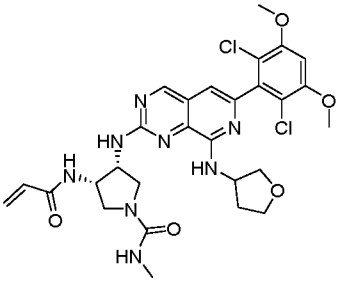
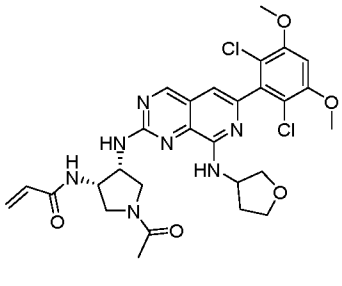
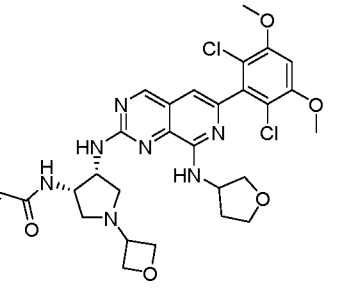
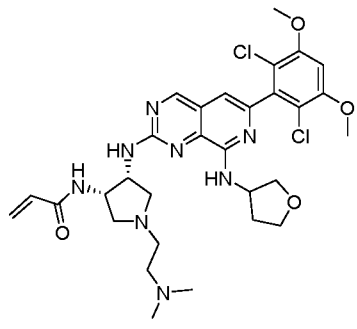
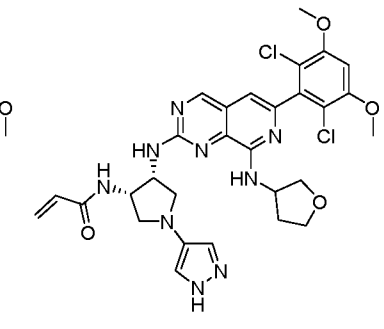


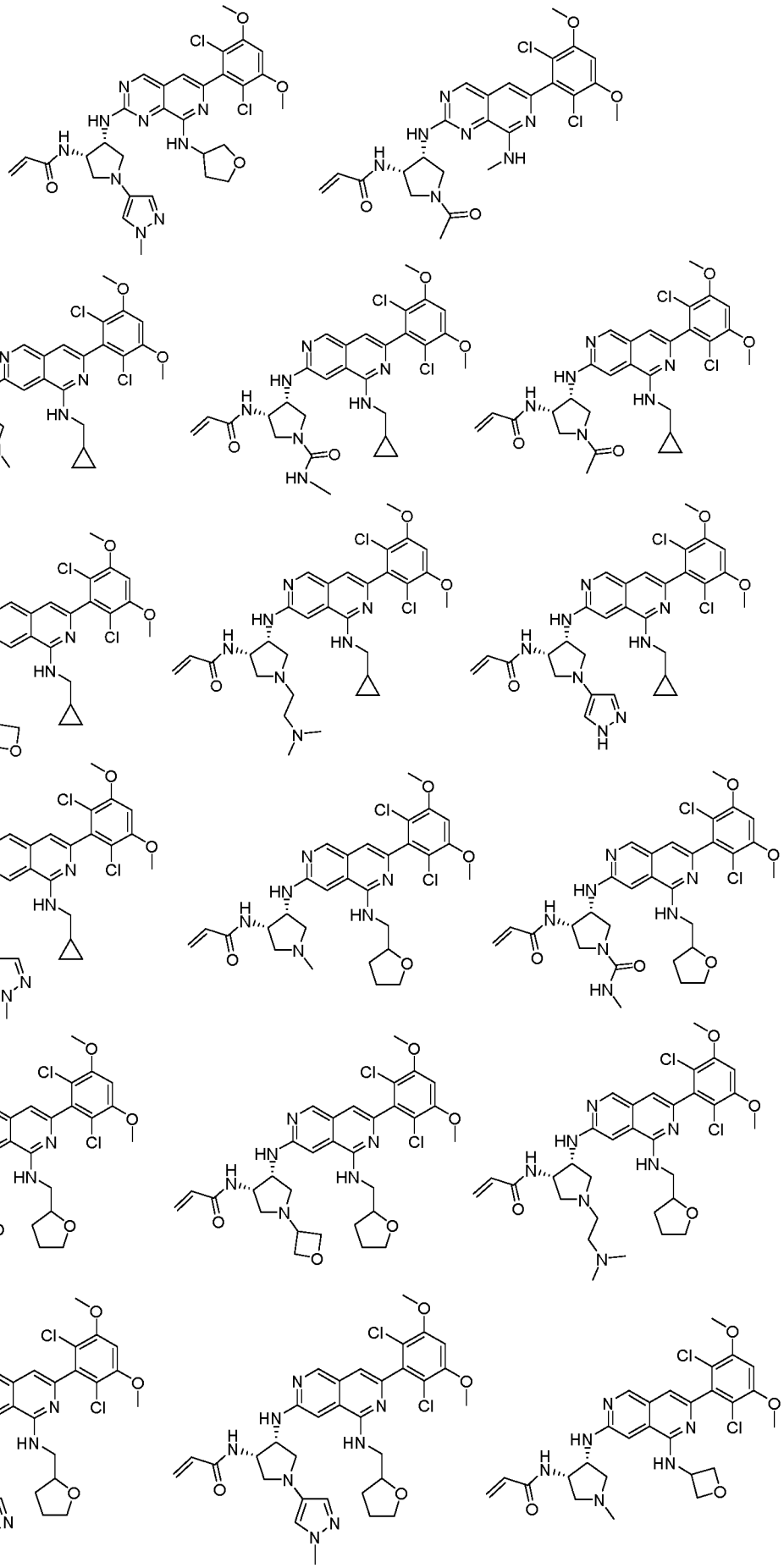


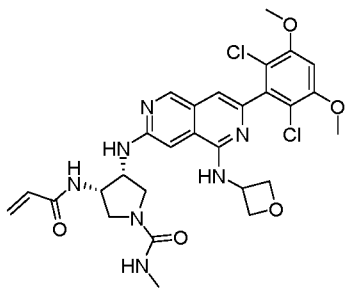
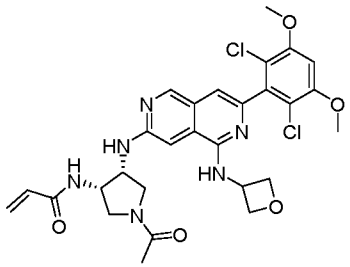
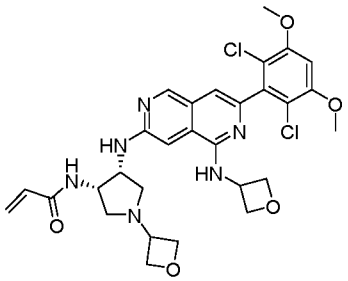
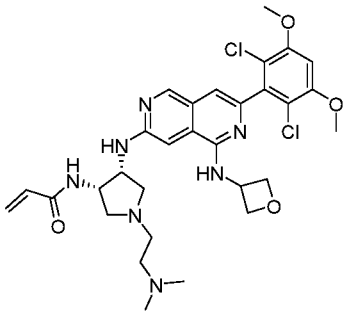
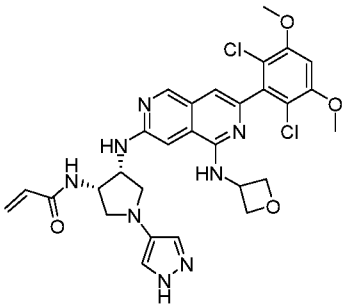
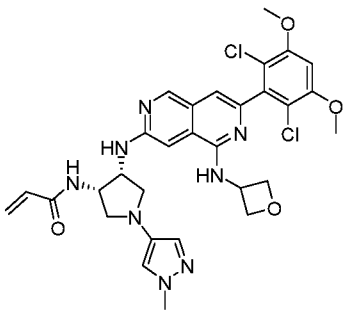
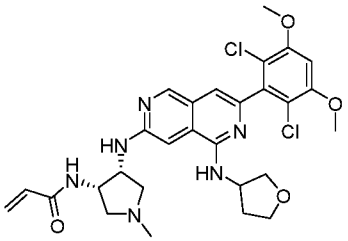
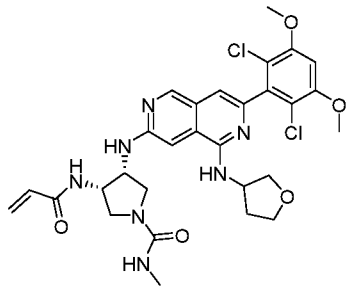
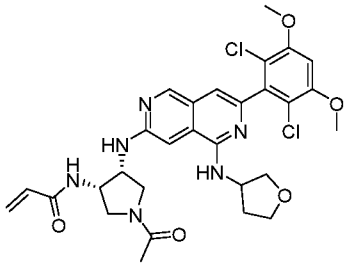
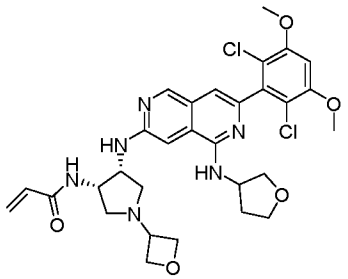
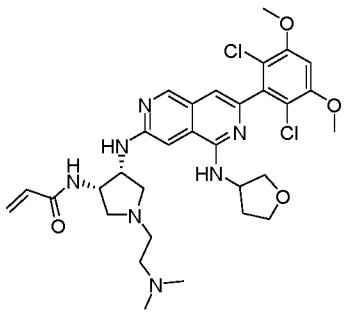
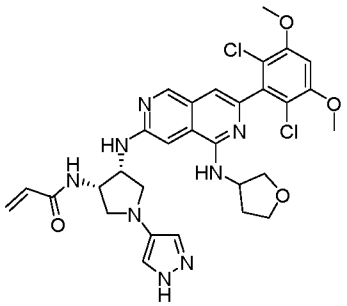
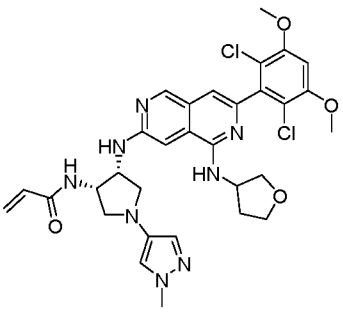
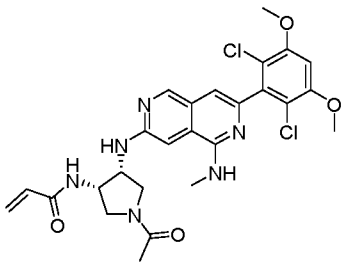
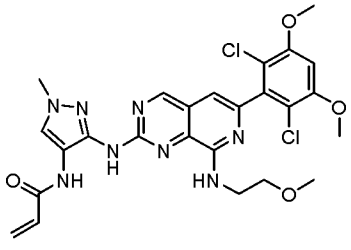
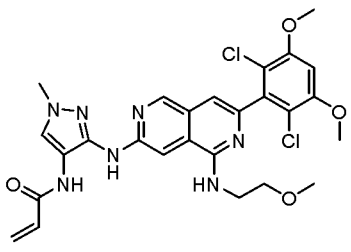


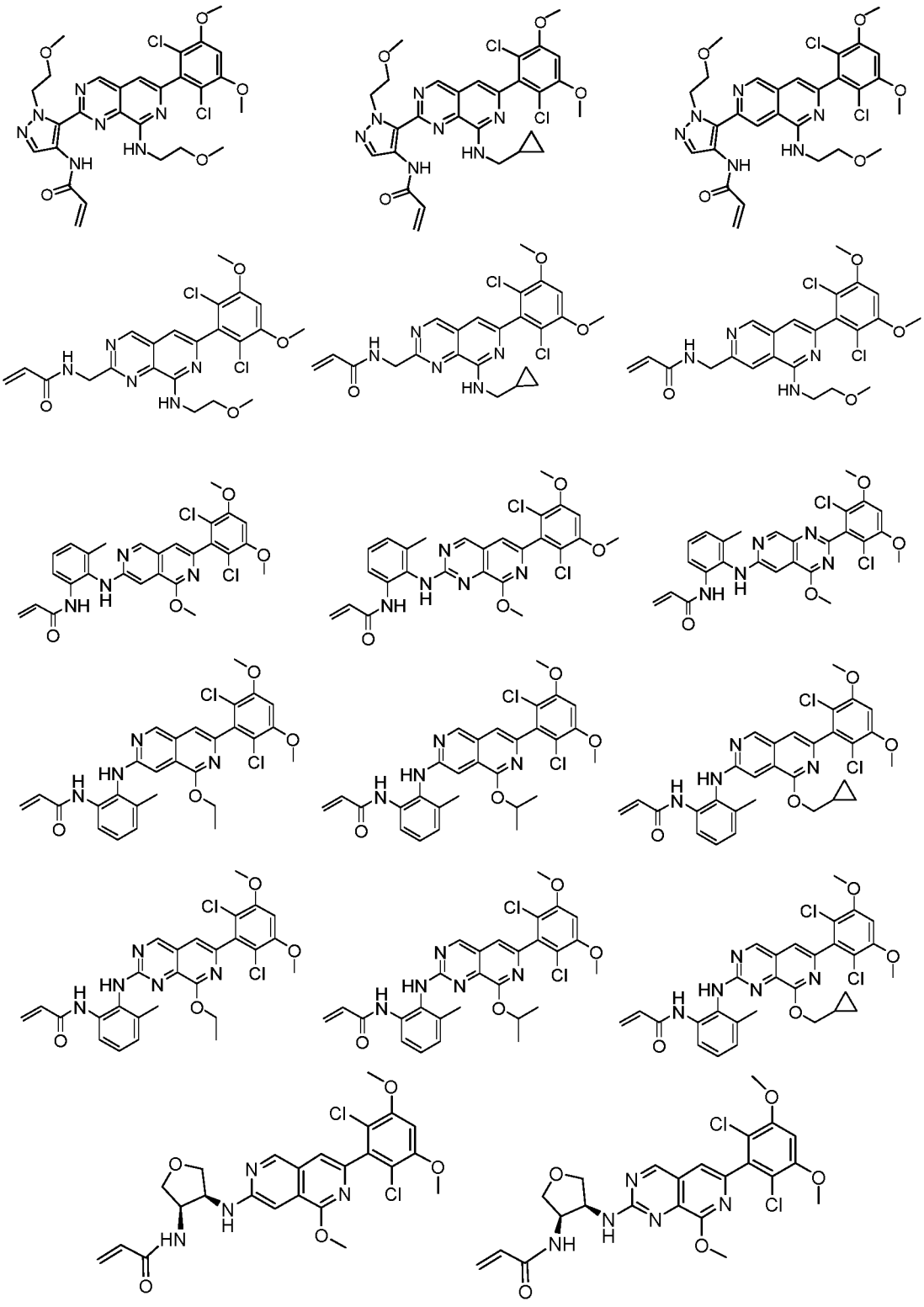



















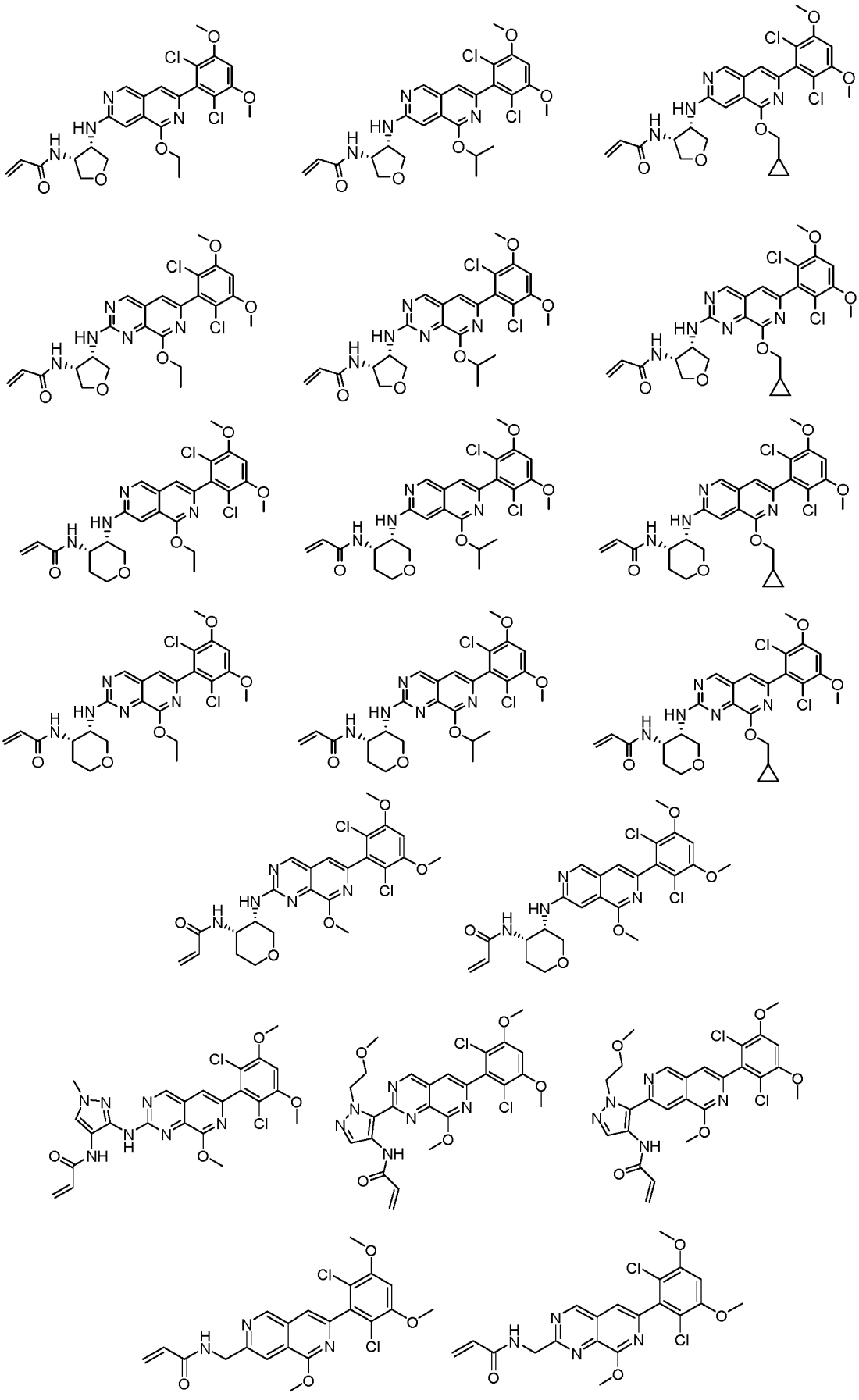


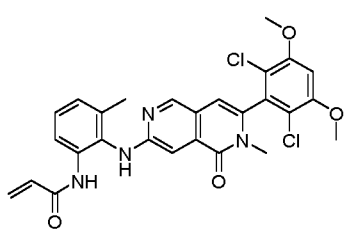
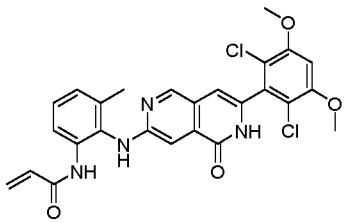
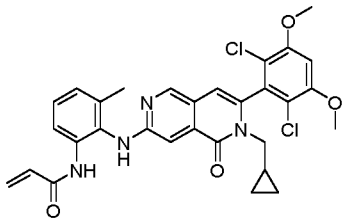
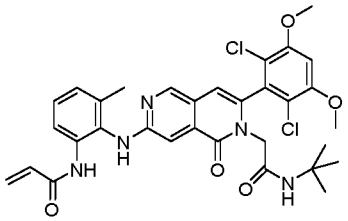
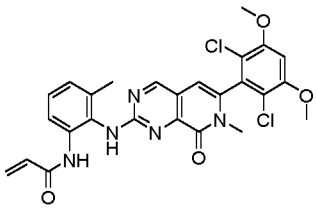
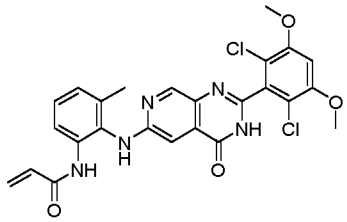
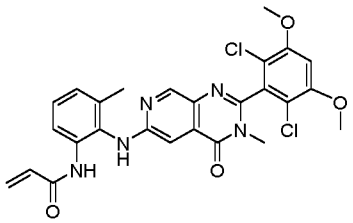
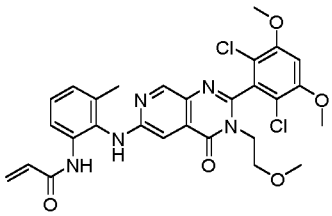
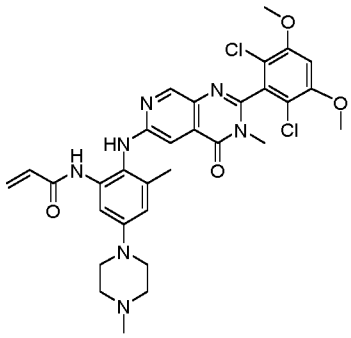
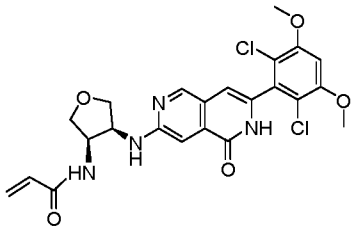
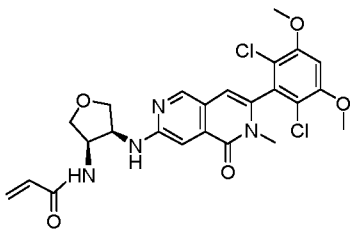
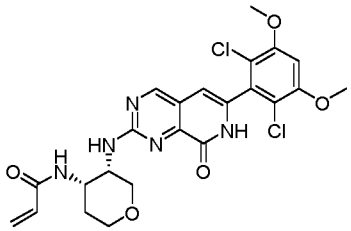
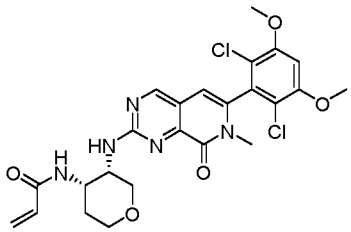
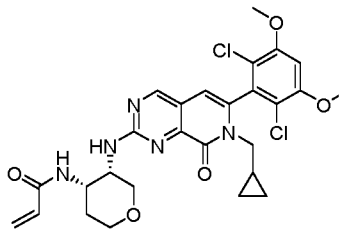
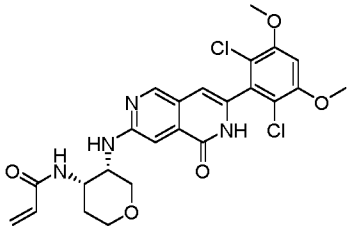
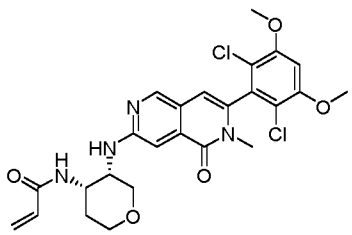
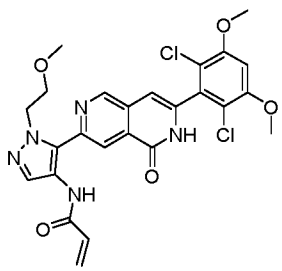
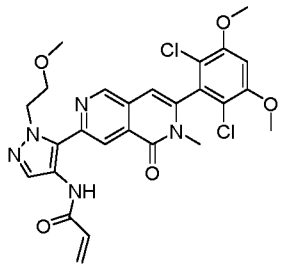



















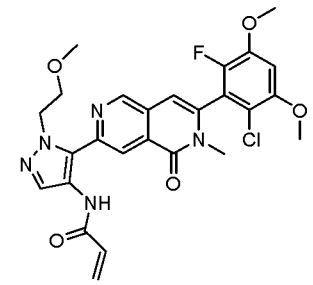
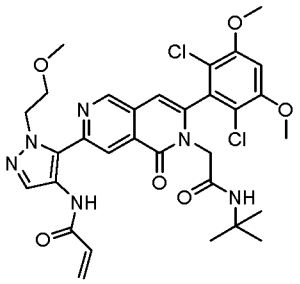
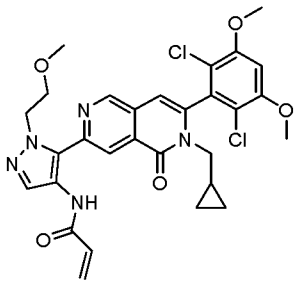
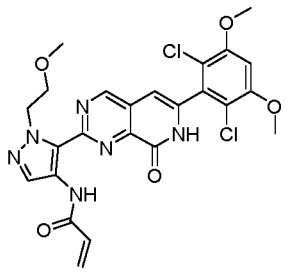
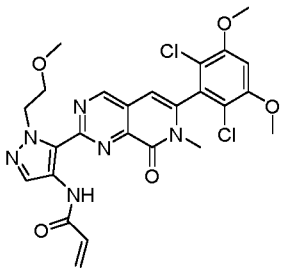
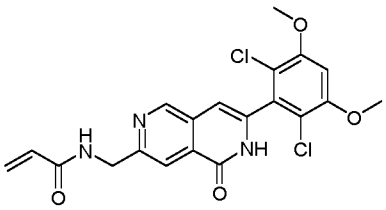
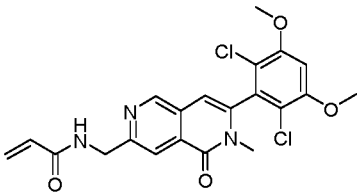
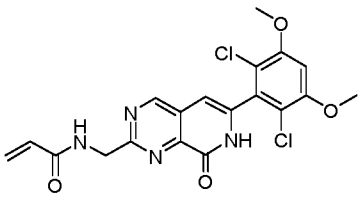
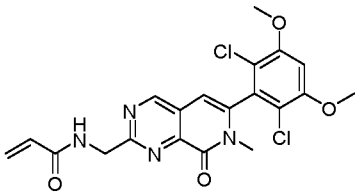
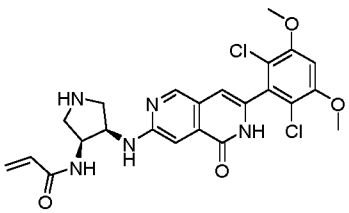
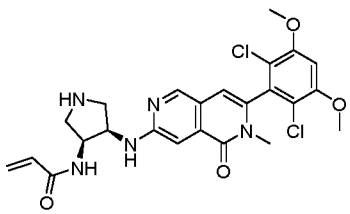
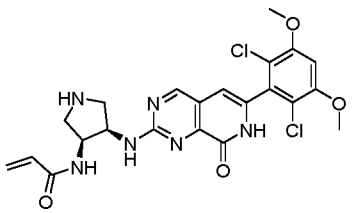
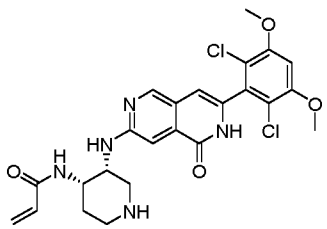
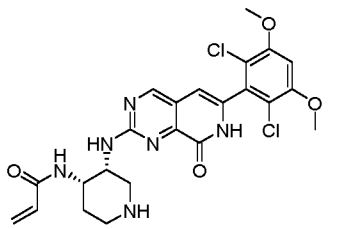
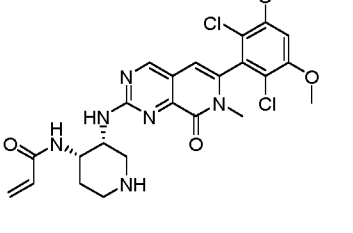
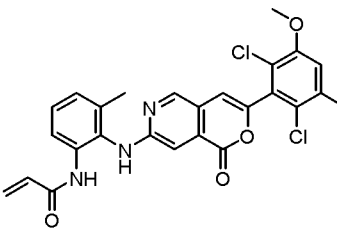
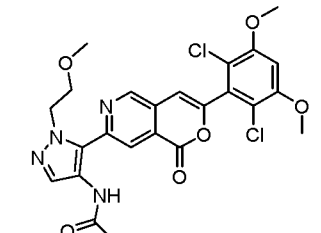
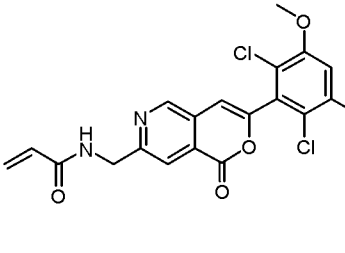


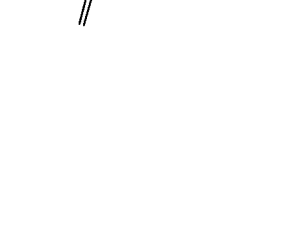

















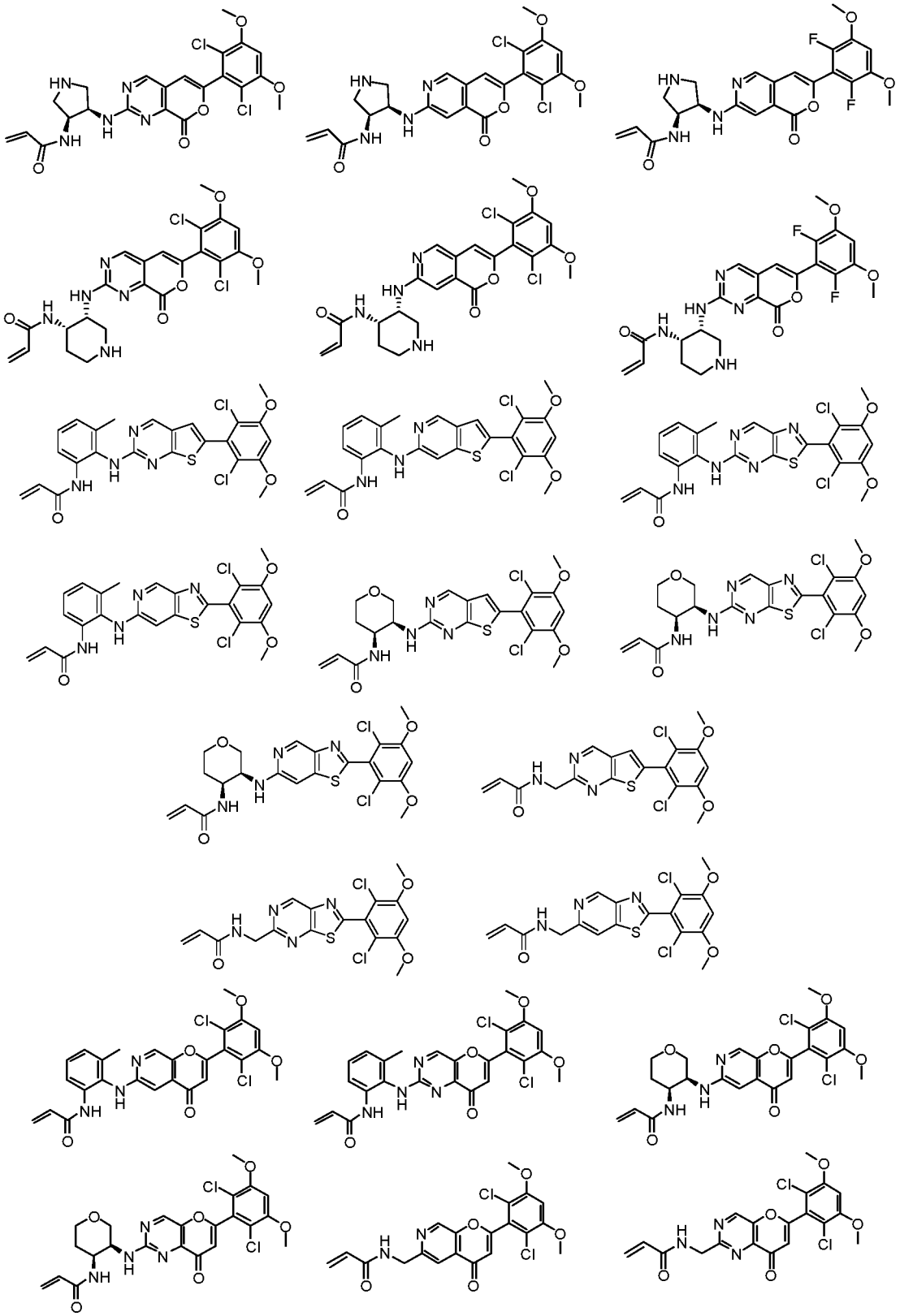


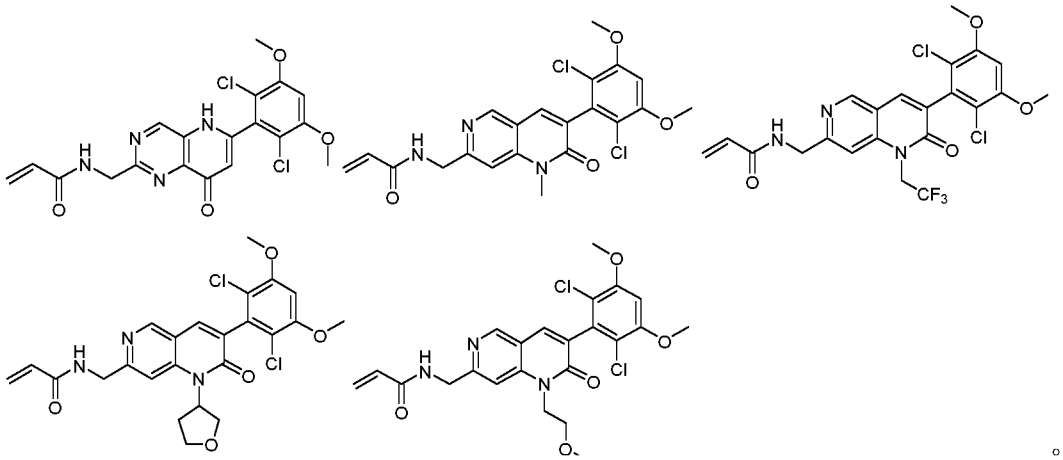


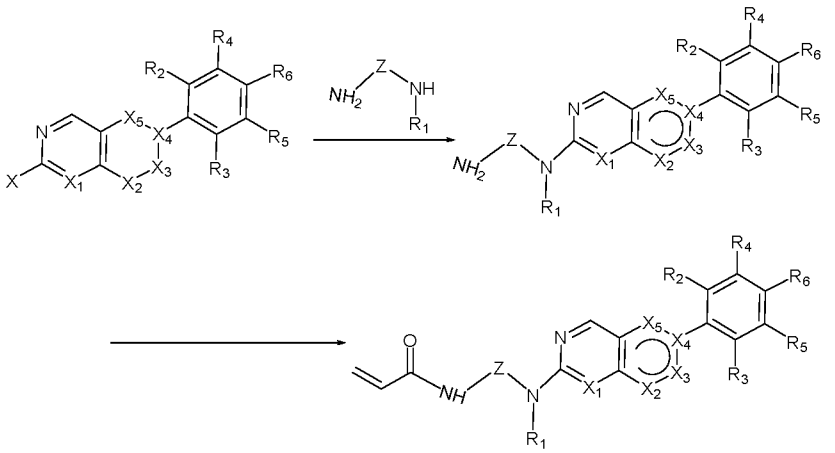























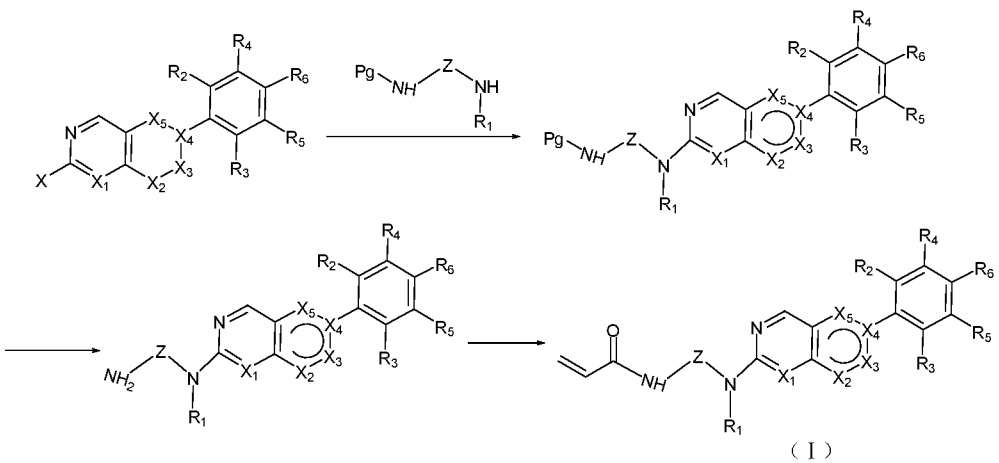


14. 权利要求 1-13 任一所述的式(I)化合物、其立体异构体或其药学上可接受盐的制备方法，当 m=1 时，包括如下步骤：



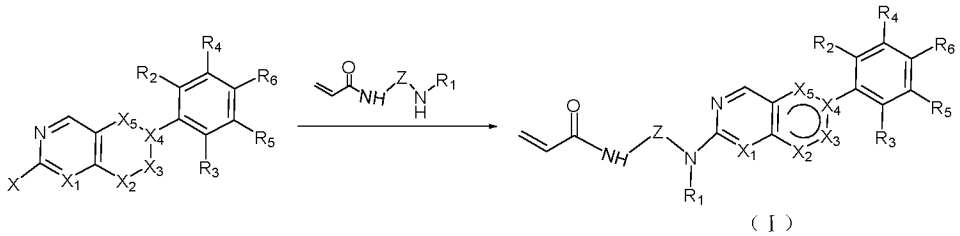
（I），

或者，



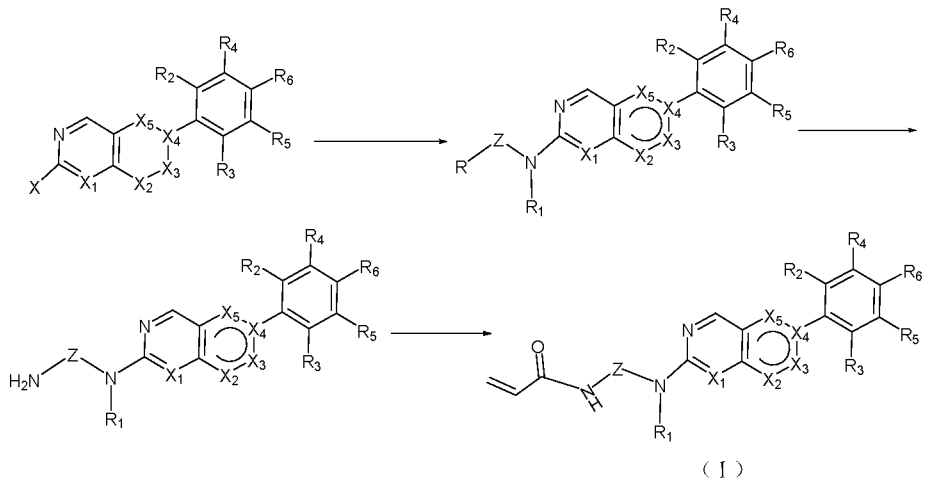
（I）

或者，



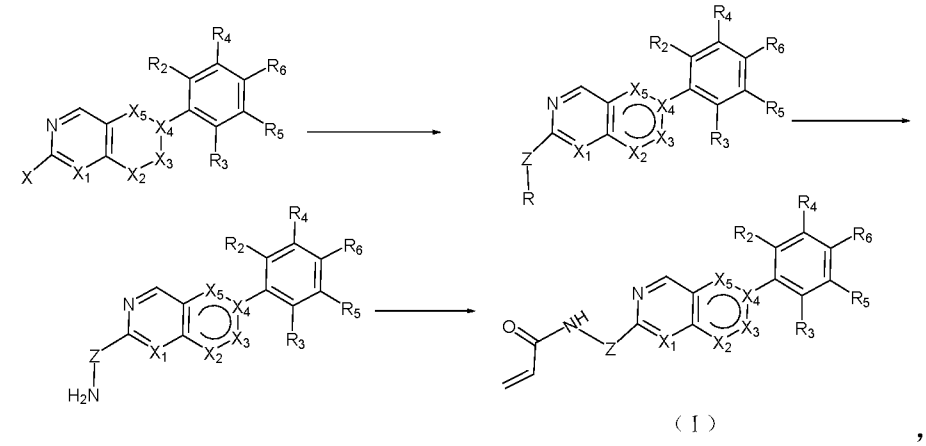
（I）

或者，



（I）；

或者，当 m=0 时，包括如下步骤：



（I），

任选的，根据取代基的不同，在不同的取代基之间进行转换反应；

其中：X 为离去基团，优选自氯、溴、甲硫基、甲磺酰基或甲氧基；R 选自硝基、氰基或叠氮基；Pg 为氨基保护基，优选自叔丁氧羰基、苄氧羰基、2-联苯基-2-丙氧羰基或对甲苯磺酰基；X_1、X_2、X_3、X_4、X_5、R_1、R_2、R_3、R_4、R_5、R_6、R_7、R_8、R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、m、n、r 如权利要求 1 所定义。

15. 一种药物组合物，其包括治疗有效剂量的权利要求 1-13 任一所述的式(I)化合物、其立体异构体或其药学上可接受盐及可药用的载体。

16. 权利要求 1-13 任一所述的式(I)化合物、其立体异构体或其药学上可接受盐，或权利要求 15 所述的药物组合物在制备 FGFR4 抑制剂药物中的应用。

17. 根据权利要求 1-13 任一所述的式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或权利要求 15 所述的药物组合物在制备治疗癌症的药物中的应用；优选的，所述癌症是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤。

18. 根据权利要求 1-13 任一所述的式(I)化合物、其立体异构体或其药学上可接受盐，或权利要求 15 所述的药物组合物，其用作 FGFR4 抑制剂。

19. 根据权利要求 1-13 任一所述的式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或权利要求 15 所述的药物组合物，其用于治疗癌症；优选的，所述癌症是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤。

20. 一种抑制 FGFR4 的方法，所述方法包括给予需要治疗的患者有效治疗量的权利要求 1-13 任一所述的式(I)化合物、其立体异构体或其药学上可接受盐，或权利要求 15 所述的药物组合物。

21. 一种治疗癌症的方法，所述方法包括给予需要治疗的患者有效治疗量的权利要求 1-13 任一所述的式（I）所示的化合物、其立体异构体或其药学上可接受的盐，或权利要求 15 所述的药物组合物。

22. 根据权利要求 21 所述的方法，其特征在于，所述癌症是前列腺癌、肝癌、胰腺癌、食管癌、胃癌、肺癌、乳腺癌、卵巢癌、结肠癌、皮肤癌、神经胶质母细胞瘤或横纹肌肉瘤。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/116186

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04 (2006.01) i; C07D 239/84 (2006.01) i; C07D 475/00 (2006.01) i; A61K 31/437 (2006.01) i; A61K 31/505 (2006.01) i; A61K 31/506 (2006.01) i; A61K 31/517 (2006.01) i; A61K 31/519 (2006.01) i; A61P 35/00 (2006.01) i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 471/-; C07D 239/-; C07D 475/-; A61K 31/-; A61P 35/-

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, CNKI, REGISTRY, CAPLUS: FGFR4 抑制剂, FGFR4, inhibitor, 结构式检索

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 105307657 A (CELGENE AVILOMICS RESEARCH INC. et al.), 03 February 2016 (03.02.2016), description, paragraph [0018], embodiments, and claims 1 and 54-60	1-22
X	CN 104540809 A (BLUEPRINT MEDICINES), 22 April 2015 (22.04.2015), description, paragraph [0006], and claims 1 and 34	1-22
X	CN 105658642 A (BLUEPRINT MEDICINES CORPORATION), 08 June 2016 (08.06.2016), description, paragraph [0010], and claims 1 and 10	1-22

☐ 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
31 January 2018	26 February 2018
Name and mailing address of the ISA State Intellectual Property Office of the P. R. China No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, China Facsimile No. (86-10) 62019451	Authorized officer LOU, Xinglong Telephone No. (86-10) 010-53962160

INTERNATIONAL SEARCH REPORT

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PCT/CN2017/116186

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.: 20-22
because they relate to subject matter not required to be searched by this Authority, namely:
[1] claims 20-22 relate to a method for treatment of a human body by therapy; however, the examiner still carried out a search based on the application of compounds or stereoisomers thereof, pharmaceutically acceptable salts and drug combination in preparing drugs for treating the corresponding diseases.

2. ☐ Claims Nos.:
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:

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/CN2017/116186

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 105307657 A	03 February 2016	MX 2015011514 A	11 August 2016
		WO 2014144737 A1	18 September 2014
		EP 2968337 A1	20 January 2016
		SG 11201507478V A	29 October 2015
		EP 2968337 A4	19 October 2016
		EA 201591420 A1	29 February 2016
		PE 17762015 A1	11 December 2015
		JP 2016519673 A	07 July 2016
		CA 2907243 A1	18 September 2014
		US 2016046634 A1	18 February 2016
		AU 2014228746 A1	10 September 2015
		US 9663524 B2	30 May 2017
		KR 20150131237 A	24 November 2015
CN 104540809 A	22 April 2015	US 2014378481 A1	25 December 2014
		RU 2015104342 A	27 August 2016
		AU 2017272281 A1	04 January 2018
		MX 2015000405 A	14 July 2015
		US 9126951 B2	08 September 2015
		US 2015210694 A1	30 July 2015
		IL 236611 D0	26 February 2015
		WO 2014011900 A3	27 February 2014
		CA 2878412 A1	16 January 2014
		AU 2013290074 A1	29 January 2015
		US 9340514 B2	17 May 2016
		WO 2014011900 A2	16 January 2014
		JP 2015523383 A	13 August 2015
		JP 6104377 B2	29 March 2017
		US 2017066812 A1	09 March 2017
		HK 1206023 A1	31 December 2015
		EP 2872491 A2	20 May 2015
		IL 236611 A	26 February 2015
		US 2014088100 A1	27 March 2014
		US 8802697 B2	12 August 2014
		KR 20150029030 A	17 March 2015
		SG 11201500125Q A	27 February 2015
CN 105658642 A	08 June 2016	US 2015119405 A1	30 April 2015
		PH 12016500739 A1	30 May 2016
		AU 2014339972 A1	07 April 2016
		HK 1221460 A1	02 June 2017
		US 2017174652 A1	22 June 2017
		CA 2928042 A1	30 April 2015
		JP 2016534059 A	04 November 2016
		WO 2015061572 A8	02 July 2015
		EP 3060560 A1	31 August 2016
		KR 20160070118 A	17 June 2016
		MX 2016005297 A	12 August 2016
		TW 201602084 A	16 January 2016
		UY 35798 A	29 May 2015
		IL 244738 D0	31 May 2016
		WO 2015061572 A1	30 April 2015

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2017/116186

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		RU 2016120012 A	01 December 2017
		US 9434700 B2	06 September 2016

国际检索报告

国际申请号
PCT/CN2017/116186

A. 主题的分类

C07D 471/04(2006.01)i; C07D 239/84(2006.01)i; C07D 475/00(2006.01)i; A61K 31/437(2006.01)i; A61K 31/505(2006.01)i; A61K 31/506(2006.01)i; A61K 31/517(2006.01)i; A61K 31/519(2006.01)i; A61P 35/00(2006.01)i

按照国际专利分类(IPC)或者同时按照国家分类和IPC两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

C07D471/-; C07D239/-; C07D475/-; A61K31/-; A61P35/-

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, CNKI, REGISTRY, CAPLUS: FGFR4抑制剂，FGFR4，inhibitor，结构式检索

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
X	CN 105307657 A (西建阿维拉米斯研究公司等) 2016年 2月 3日 (2016-02-03) 说明书第[0018]段，实施例，权利要求1、54-60	1-22
X	CN 104540809 A (蓝印药品公司) 2015年 4月 22日 (2015-04-22) 说明书第[0006]段，权利要求1、34	1-22
X	CN 105658642 A (蓝图药品公司) 2016年 6月 8日 (2016-06-08) 说明书第[0010]段，权利要求1、10	1-22

☐ 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
2018年 1月 31日	2018年 2月 26日

ISA/CN的名称和邮寄地址	受权官员
中华人民共和国国家知识产权局(ISA/CN) 中国北京市海淀区蓟门桥西土城路6号 100088	楼兴隆
传真号 (86-10)62019451	电话号码 (86-10)010-53962160

国际检索报告

国际申请号
PCT/CN2017/116186

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： 20-22
因为它们涉及不要求本单位进行检索的主题，即：

[1] 权利要求20-22涉及对人体实施的治疗方法，但审查员基于化合物或其立体异构体、药学上可接受的盐以及药物组合物在制备治疗相应疾病的药物中的应用仍然进行了检索。

2. ☐ 权利要求：
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：

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/CN2017/116186

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）
CN	105307657	A	2016年 2月 3日	MX	2015011514	A	2016年 8月 11日
				WO	2014144737	A1	2014年 9月 18日
				EP	2968337	A1	2016年 1月 20日
				SG	11201507478V	A	2015年 10月 29日
				EP	2968337	A4	2016年 10月 19日
				EA	201591420	A1	2016年 2月 29日
				PE	17762015	A1	2015年 12月 11日
				JP	2016519673	A	2016年 7月 7日
				CA	2907243	A1	2014年 9月 18日
				US	2016046634	A1	2016年 2月 18日
				AU	2014228746	A1	2015年 9月 10日
				US	9663524	B2	2017年 5月 30日
				KR	20150131237	A	2015年 11月 24日
CN	104540809	A	2015年 4月 22日	US	2014378481	A1	2014年 12月 25日
				RU	2015104342	A	2016年 8月 27日
				AU	2017272281	A1	2018年 1月 4日
				MX	2015000405	A	2015年 7月 14日
				US	9126951	B2	2015年 9月 8日
				US	2015210694	A1	2015年 7月 30日
				IL	236611	D0	2015年 2月 26日
				WO	2014011900	A3	2014年 2月 27日
				CA	2878412	A1	2014年 1月 16日
				AU	2013290074	A1	2015年 1月 29日
				US	9340514	B2	2016年 5月 17日
				WO	2014011900	A2	2014年 1月 16日
				JP	2015523383	A	2015年 8月 13日
				JP	6104377	B2	2017年 3月 29日
				US	2017066812	A1	2017年 3月 9日
				HK	1206023	A1	2015年 12月 31日
				EP	2872491	A2	2015年 5月 20日
				IL	236611	A	2015年 2月 26日
				US	2014088100	A1	2014年 3月 27日
				US	8802697	B2	2014年 8月 12日
				KR	20150029030	A	2015年 3月 17日
				SG	112015001250	A	2015年 2月 27日
CN	105658642	A	2016年 6月 8日	US	2015119405	A1	2015年 4月 30日
				PH	12016500739	A1	2016年 5月 30日
				AU	2014339972	A1	2016年 4月 7日
				HK	1221460	A1	2017年 6月 2日
				US	2017174652	A1	2017年 6月 22日
				CA	2928042	A1	2015年 4月 30日
				JP	2016534059	A	2016年 11月 4日
				WO	2015061572	A8	2015年 7月 2日
				EP	3060560	A1	2016年 8月 31日
				KR	20160070118	A	2016年 6月 17日
				MX	2016005297	A	2016年 8月 12日
				TW	201602084	A	2016年 1月 16日
				UY	35798	A	2015年 5月 29日
				IL	244738	D0	2016年 5月 31日
				WO	2015061572	A1	2015年 4月 30日

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2017/116186

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）
		RU	2016120012	A	2017年 12月 1日
		US	9434700	B2	2016年 9月 6日